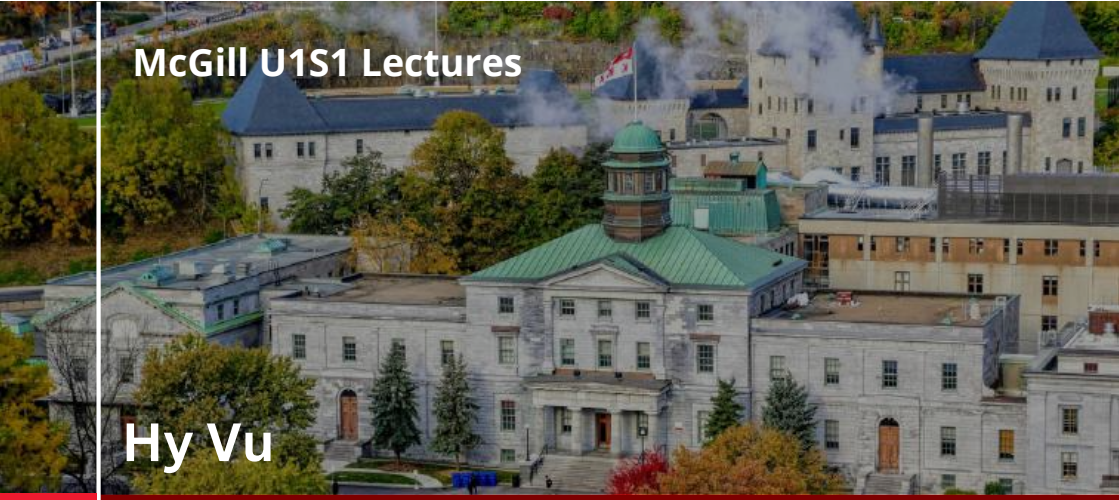

McGill U1S1 Lectures

Hy Vu

Mammalian Physiology I

Lecture Notes

Prof: Dr. Vollrath, et al.

McGill

McGill Mammalian Physiology I Lectures (PHGY 209)

Hy Vu

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Foreword

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Prerequisites: General Biology I + II, adequate knowledge of general and organic chemistry.

Chapter 1

Introduction

1.1 A Brief History of Physiology

The word physiology derived from the Greek word: *Physis* (which means “nature" or “origin") and *logos* (which means “the study of"). The origin of physiology can be traced and developped back in the 5^{th} century BC in ancient Greece, by **Hippocrates.** Later on around the 16^{th} century AD, French physician **Jean Fernel** coined the term *physiology*.

Definition 1.0 Nowaday, **Physiology** is known as the study of functions and mechanisms of a healthy biological (living) system, namely *organism*.

1.2 An Overview of Physiology

Every living organism will be made up of the smallest unit of life called **cells**. When an organism is composed of only 1 cell, we call it a *single cellular organism*, like an amoeba; otherwise if > 2 cell, we call it a *multicellular organism*, like human.

The hierarchy of multicellular system (called *levels of organisation*) often follow this scheme:

1. **Organs:** A group of mostly identical cells work together for a specific functions.

2. **System:** A group of organs work together for a specific functions.

3. **Organism:** A group of system work together for a specific functions.

The main functions that they all do is to maintain the survival of cells since they need a specific environment to live in.

Definition 1.1 The action/mechanism of dynamically maintaining a constant internal environment/condition of a biological system, regardless of the external environmental changes, is called **homeostasis**.

Theorem 1.0 (Fundamental Law of Biology) *At all levels of organisation, the functional activities are mainly directed at maintain an optimal and constant internal condition i.e. maintaining homeostasis.*

The entirety of organism's system is simply a feedback loop to keep the internal body in homeostasis. In general, homeostasis control: concentration of molecules (nutrients, O_2, waste, etc.), pH, temperature, volume and pressure.

Definition 1.2 A failure to maintain homeostasis that cause a disruption in the biological system is called a **disease**.

When a disease lead to a complete disruption of the biological system, the biological system is **dead**.

Chapter 2

The Bodily Fluids and Transport

As we said before, the body has its own internal environment that are kept at a constant level by homeostasis. One of the many composition of this internal environment is our bodily fluids.

Definition 2.0 **Bodily Fluid** or **biofluids** are liquids that are found within the human body.

2.1 Water

Water is the most abundant component of the body which make up around 45% – 75% of the total weight. Although why would there be such a wide range for water content for each individual? To answer this, we would need to understand the percentage of water as compared to the total body mass vs lean body mass.

Water Content Taken From Total Body Mass: When looking for water content for each tissues of the body, we can come of with the following table:

Tissues	Percentage as compared to the tissue mass
Skin	75%
Muscle	75%
Heart, Liver, Brain, etc.	70 – 80%
Bone	25%
Fat (adipose tissue)	10%

As you can see, for both bone and fat, they are somewhat dry compared to the rest of the other tissues. Therefore, water content as a percentage of total body mass has a greater variation because each individual can have a greater fat content within them and since water does not make up fat that much, the total water content would drop. For lighter individuals with lower body fat content, it would seem as though their water content is much higher.

Water Content From Lean Body Mass: When we take water content as a percentage of the total lean body mass (the total mass exclude your weight), then the variation would decrease since looking at the table above, the percentage of water within each tissue that is not adipose does not vary much.

More Variations for Water Content

Water content view above varies by the individual's weight but it can also vary depending on the individual's age and sex.

Note 2.0 The following water content will be measured as a percentage to total body mass. Assuming ideal conditions that all individual have the same weight in a certain group of age and sex.

As infants, they typically has a higher water content regardless of sex. When they reach around 10-18 years old, the water content would drop and we begin to see the different between male and female. As females, they would have a lower water content after puberty due to the production of estrogen which subsequently increase the fat content in the breast and buttocks region.

Age	Male	Female
Infancy	65%	65%
10 – 18	59%	57%
18 – 40	61%	51%
40 – 60	55%	47%
> 60	52%	46%

Then after is male puberty which lead them to have an increase in lean body mass therefore increase the water content. Then the water content decrease for both overtime as they will be losing mostly muscles.

Now that we understand the water content variation with each individuals, it is also important to know how much water in the body for drug dosage. To calculte the total amount of water, we use the following equation

$$V_{H_2O} = \frac{\%_{H_2O} \cdot M}{\rho_{H_2O}}$$

where V_{H_2O} is the volume of water in litre (L), $\%_{H_2O}$ is the percentage of water compared to the total body mass, M is the mass of the individual measured in kg and ρ_{H_2O} is the water density which is approximately $1.00\frac{kg}{L}$. We can see that this equation does in fact yield the volume of water in litre by doing dimensional analysis:

$$V = \frac{[\ ] \cdot [kg]}{\frac{[kg]}{[L]}} = [kg] \cdot \frac{[L]}{[kg]} = [L]$$

Remark 2.0 *Percentage is a numerical value and has no unit thus dimensionless (represented as empty in dimensional analysis).*

Example 2.0 For a 70-kg male individual with water percentage of 65% and a female 70-kg female individual with water percentage of 60%, their water content respectively would be

$$V_{H_2O \text{ of male}} = \frac{65\% \cdot 70kg}{1.0\frac{kg}{L}} = 45.50L\ H_2O$$

$$V_{H_2O \text{ of female}} = \frac{60\% \cdot 70kg}{1.0\frac{kg}{L}} = 42.0L\ H_2O$$

Remark 2.1 *For sake of simplicity, we won't need to divide by the concentration since it is ideally 1.*

Example 2.1 Dosage...

2.1.1 Water Balance

The main idea behind water balance is that the amount of water the body consume must be equal to the amount of water excreted under normal healthy condition (later on we will see if water balance is not conserved there would be malignant conditions that arises).

If supposed that the total input of water for a 20-year-old individual was 3.0L. There are 2 ways such individual can have make the fluid intake: **oral intake** which is when water enter the body via consumption through food or directly drinking water (assuming 1.5L for drinking and 1.0L for food), and **metabolic intake** which is when water is produce by the mitochondria via aerobic cellular respiration (assuming 0.5L).

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If this individual consume 3.0L of water, then the total output must also be 3.0L from the body. We can categorize this water output/loss into: **obligatory loss** which is the amount of water loss regardless of the hydration state of the body, and **facultative loss** which is the amount of water loss depending on the hydration state of the body (controlled mostly through urination). We can even divided each of these loss into their sensibility forms: **sensible loss** which are any water loss that can be sense by the body (e.g. urinating, defecating, sweating, etc.) and **insensible loss** which are any water loss that cannot be sense by the body (e.g. cutaneous transpiration, breathing, etc.)

Remark 2.2 *Cutaneous transpiration is simply pure water evaporate from the skin pores. It leaves the pores through passive diffusion (no energy required), occurs continuously everywhere on the skin surface. Sweating on the other hand, evaporate electrolytic solution via sweat glands through active diffusion (required energy), occurs only at the sweat gland and is temperature dependent (neither obligatory nor facultative).*

We can use the same sort of assumption that 0.5L is loss through breathing, 0.5L through cutaneous transpiration, 0.5L from urine and 0.1L from feces. The rest 1.4L can be thought of as facultative loss (the individual may have more water inside the body) that can be eliminated by the kidney.

Definition 2.1 **Water turnover** is the amount of replaced loss water over a period of time. Normally, over a 24h period, an adult would have a water

turnover of 3 – 4% and an infant of 10% of the total body mass.

Although it seems that water turnover implies the water gain but it also reveal the amount of water loss too (considering such individual has a normal water balance) i.e. if an individual has a water turn over of 2% then that individual must has lost water content of 2% the total body mass.

Observation 2.0 We can see that infants have a greater water turnover than adult which also link with greater water loss. This is due to the small volume (the infant) that the water is occupying thus giving it a higher chance of transpire than a larger volume (an adult). This is also a reason that infants are very susceptible to overheating.

When water balance is no longer in equilibrium, then certain conditions arise. If the body experience a **negative water balance**, then there is more water loss than intake which means the body is experiencing *dehydration*. The cause to negative water balance could be: reduce in water intake, excessive loss in water from sweating, the gut, urine and respiration (at high altitude).
The other extremity is not good as well, if there is an extreme positive water balance i.e. **water intoxication (water toxemia)**, then the body is experiencing *overhydration*. The cause to water intoxication is mainly: overconsumption of water, renal failure.

2.2 Compartment of Water in The Body

Water, which made up of around 60% of the total body weight can be divided into 2 major compartment: **intracellular fluid (ICF)** that takes up around 40% of the body mass and is located inside cells; and **extracellular fluid (ECF)** that takes up 20% of the body mass and is located outside of the cell.

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We can further divide ECF into a major and a minor compartment. The major compartment consists of **plasma** and **interstitial fluid (ISF)**. Plasma is the liquid medium of blood that allow RBCs and WBCs to suspend in, it takes up 5% of the total body weight.

Definition 2.2 The percentage of blood volume that is occupied by RBCs is called **hematocrit** and is given as the following equation

$$Ht = 100\left(\frac{\text{Volume of RBCs}}{\text{Total Volume}}\right) = 100\left(\frac{V_{\text{RBCs}}}{V_{\text{TT}}}\right) \tag{2.1}$$

Hematocrit is also called by some as **packed cell volume (PCV)**

Example 2.2 If the hematocrit of a person is 45% and given the total volume of blood extracted for donation as $1L$; then then volume of RBCs would be

$$V_{\text{RBCs}} = Ht \cdot V_{\text{TT}} = 45\% \cdot 400mL = 180mL \text{ RBCs}$$

ISF is considered the "true" internal environment as it is the fluid that filled the gaps of tissues, cells, etc. It allows for nutrient and waste to be transported in and out of the body. It made up of 15% of the total body mass. ISF and plasma are common in many ways, however the main different between them is that $[\text{protein}]_{\text{plasma}} > [\text{protein}]$

Finally, the minor compartment of the ECF consists of: **lymph** which takes up $1-2\%$ of the ECF volume and **transcellular fluid** which takes up $> 1-2\%$ of the ECF volume.
The lymphatic system is a 1 way circuit consists of lymphatic fluid, tubules, vessels and ducts which would then drain to the vena cava. Transcellular fluids are fluids that small fluid volumes that secrete by specialized epithelial cells and because it contributes such a small percentage of the total body fluid, any local changes wouldn't let into significant water off-balance.

Example 2.3 Intra-ocular fluid is a transcellular fluid that fills the anterior and posterior chamber of the eyes. This fluid is made by the ciliary body; when there's too much of this fluid, the pressure of the eyes, called **intraocular pressure (IOP)**, increases which can lead to **glaucoma**. A common treatment is using *prostaglandins* that can help with fluid drainage from the eye.

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Remark 2.3 *Although truly we did divided body fluids into different compartmet however, these compartments are not entirely and rigidly separated from one another.*

In general, body fluids must satisfies the following conditions: 1. the total volume should remain constant (can differs from individual to individual), 2. the relative distribution of fluids in each compartment should be constant and 3. each compartment are in dynamic equilibrium.

2.2.1 Methodology to Measure Compartment Volume

Before measuring the fluid volume of each compartment, we first have to know how to measure the total fluid in the body.

Method 1.1 (Direct) The simplest method (not specifically ideal and ethically questionable) is directly measuring the total body water. In this method, we measure the mass of the sample M then subjected it to dehydration such that it removes all of the water in the body. Then we measure its weight again $M_{\emptyset\ H_20}$ and the total water volume of this method is

$$V_{H_2O} = \frac{M - M_{\emptyset\ H_20}}{\rho_{H_2O}}$$

As we said, this is not the best method since it can lead the sample to dead which is the last thing we would want to do in a laboratory. There is another method that is much better although its accuracy is relatively fine.

Method 1.2 (Indirect) In this method, we introduce a known solution with a volume Q. We then inject this solution into the subject's body and let it dilute for a while. After the fluid has theoretically distributed all over the body, we then take a sample fluid from the subject and determine the concentration of the known solution in the subject's body fluid c. Finally, the total fluid volume V of that individual would be

$$V = \frac{Q}{c}$$

This method is also cal;ed **indicator dilution method**.

This known solution is called an **indicator** and it has to be non-toxic, diffuse readily and evenly to all of the different compartment of the body, as well as introduce no changes. Some known indicator that we tend to use are antipyrine, D_2O or T_2O.

Example 2.4 A person is injected with 50mL of D_2O into their vein and after a while, blood was drawn and the concentration of D_2O was measured in

plasma to be $0.001 mL\ D_2O/mL$ plasma. Then the total body water of this person is

$$V_{H_2O} = \frac{Q}{c} = \frac{50}{0.001} = 50000 mL = 50L\ H_2O$$

Now supposed that we want to measure only the volume in the ECF, then we must make sure that our indicator cannot pass through the cell membrane. Some of these indicators are radioactively labelled inulin, sucrose and mannitol. For an average person, the ECF volume should be around $14L$.

Like the ECF, to measure the plasma volume, we need indicators that cannot pass through the capillary wall. 1 very well known indicator for this is **Evan's blue** or I^{131}–albumin. An average person would have plasma volume of around $3.5L$.

Finally, for the rest of the body fluid such as ICF and ISF, we only need to do simple arithmetic to find out their volume

$$V_{\text{ICF}} = V_{\text{TT}} - V_{\text{ECF}}$$
$$V_{\text{ISF}} = V_{\text{ECF}} - V_{\text{plasma}}$$

2.2.2 Ionic Composition

Body fluids are simply aqueous solution with inorganic ions and variable [proteins]. When we look at the composition of the ICF, we can see that it has $[K^+] \uparrow$ and $[Na^+]$, $[Cl^-] \downarrow$ while the ECF is the opposite $[K^+] \downarrow$ and $[Na^+]$, $[Cl^-] \uparrow$. This understanding can help us with making artificial physiological solution such as *saline*.
Saline is a 0.9% $NaCl$ solution which means that for every $1L$ of the solution (usually water), there will be $9g\ NaCl$. There are also many other types of physiological solution that can mimics almost the same as the internal environment of the body. e.g **Ringer's solution** is a solution such that for every $1L$ of solution, there will be $8.6g\ NaCl + 0.3g\ KCl + 0.3g\ CaCl_2$.

2.3 Transport Mechanism

Even though we said that these compartment are not rigidly separated; however they still have some sort of passable barrier so that not all of the

fluid get mixed up together. With that in mind, in this section, we will learn about the mechanism that fluids or even material can pass through these barriers. We will mainly focus on the cell barrier that is the *cell (plasma) membrane*.

Ever notice how substances like O_2, H_2O and other can just pass through the cell membrane with ease while others can't? well that's because cell membrane is selective permeable.

Definition 2.3 A material is said to be **selective permeable** if it is permeable to some substances while impermeable for others.

Cell membrane is highly permeable for water, gases, small uncharged molecules and lipid-soluble substances. It is only slightly permeable to large molecules and ions but is impermeable to very large molecules. One would ask that how can cell membrane perform such task? well we simply look at the composition of cell membrane.

2.3.1 Composition of Plasma Membrane

The plasma membrane is approximately $6-10nm$ thick. It is made up of a *bilayer of phospholipid* of which made up $40-50\%$ of the membrane total weight.

Definition 2.4 A **phospholipid bilayer** is 2 layer of phospholipids with their hydrophobic tail (non-polar, made up of fatty acid chains) pointing toward each other, while the hydrophilic head (polar, made up of glycerol and phosphate) pointing away (see Figure 2.1).

This bilayer is tightly packed together (especially the tails) thus making it difficult or even impossible for large molecules to enter. Non-polar molecules such as O_2 and CO_2 has no problem passing through compared to polar molecules (ions) that would be deflected by the hydrophobic tail.

Remark 2.4 *Because phosphoslipids have a hydrophobic and hydrophilic sides, we call it **amphipathic** (inherit both properties).*

Nevertheless, having tightly bound phospholipids are not necessarily good since it will be very solid like. To fix this problem, molecules called **cholesterol** (a slightly amphipathic molecule) are inserted between phos-

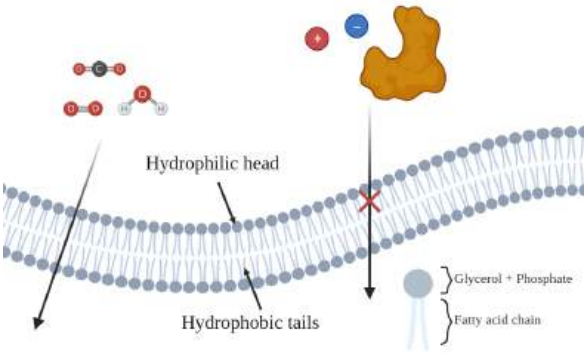

Figure 2.1: Visual Represenation of phospholipid bilayer

pholipid, making it more spaced out therefore more fluid-like. At high T^o, it stabilizes and create firmness to the cell and at low T^o, it prevents phospholipids to aggregate maintaining the fluidity.

It is good to have a good structure but if a cell cannot communicate to each other, then it is sort of useless; and this is where proteins come into play. Protein made up of $25-75\%$ of the membrane mass, it mainly functions as transport channel, enzyme, receptor, identity marker, adhesions and cytoskeletal attachment sites for cells. There are 2 types of protein that make up the membrane: **integral proteins**, which are proteins that are closely attached to phospholipids, and are mostly *transmembrane*; and **peripheral protein**, which are proteins that are loosely attached on its surface (mostly cytoplasmic surface) (see Figure 2.2).

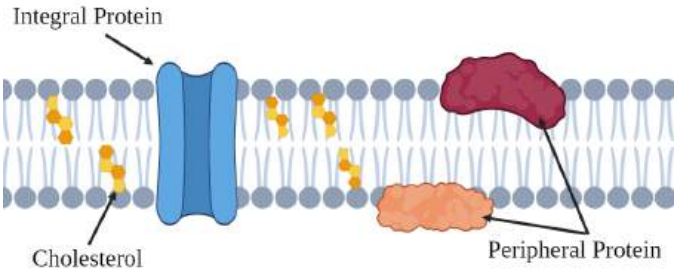

Figure 2.2: Cholesterols, integral and peripheral proteins as components of the membrane.

The final components of plasma membrane is called **glycocalyx** which is long polysaccharide chain that extend out of the membrane on the extracellular surface and also are held by proteins. Together, they're called *glycoproteins*. Glycocalyx serves mainly as protector of infection and helps in cellular recognition.

Molecules and substances can be transported into/out of the cell via directly pass through the phospholipid bilayer or via integral proteins (channels or carrier). We can classify the transport mechanism across the plasma membrane into its requirement of energy, that are: passive and active transport.

2.3.2 Passive Transport

Definition 2.5 A transport mechanism is that isn't dependent on energy i.e. doesn't require energy and the movement of substances/molecules is dependent on the existence of a concentration gradient is called **passive transport**.

There exists 3 types of passive transport: simple diffusion, facilitated and osmosis (kind of like simple diffusion). For facilitated, we can further divide it into 2 types: ions channels and carrier proteins.

Simple Diffusion

Have you ever noticed when you drop some salt in a large bath, eventually the entire pool will be salty instead of 1 volume that you drop the salt in? That's because of diffusion, where solute will move from a [high] to [low].

Definition 2.6 **Simple diffusion** is a passive diffusion where substances (solute) can cross the plasma membrane (or any permeable barrier) directly from high concentration to low concentration. At equilibrium (equal concentration for both), the net movement is 0.

Example 2.5 When there is a build up of CO_2 inside the cell, simple diffusion would cause the CO_2 to diffuse out of the cell where there's less CO_2.

Definition 2.7 A **flux (Φ)** is the amount of particles or substances cross a

surface per unit of time. Mathematically it is defined as

$$\Phi = \frac{I}{A} \text{ where } I = \frac{dq}{dt} \tag{2.2}$$

where dq is a small change in a physical quantity (could be solute, etc.) passing though an area A and dt is a small change in time.

Remark 2.5 *Even though solute would move from high to low in diffusion they move in fact in both way, however the movement from high to low is more significant than the other way, hence the* Φ_{net} *is from high to low.*

Definition 2.3 A **concentration gradient** (∇C) is the measurement of change in concentration from 1 region to the next. Mathematically it is given as

$$\nabla C = \frac{dC}{dx} \tag{2.3}$$

where dC is a small change in concentration and dx is a small change in distance.

Example 2.6 If there is a ∇C between the extracellular and intracellular space of a cell, then the Φ_{net} is from [high] to [low]. Once $\nabla C = 0 \iff \Phi_{\text{net}} = 0 \iff$ net movement = 0.

Notice that the higher the gradient, the more solute there is to pass through the membrane thus the higher the flux and the inverse is also true! We can then draw a conclusion that they're proportional to each other

$$\Phi_{\text{net}} \propto \nabla C$$

We can assume a constant D that when multiply with ∇C, it would be equivalent to the Φ_{net}

$$\Phi_{\text{net}} = D \cdot \nabla C \tag{2.4}$$

Using definition of gradient and flux: equation (2.2) and (2.1), we can say that

$$\frac{I}{A} = D\frac{dC}{dx} \iff \frac{dq}{dt}\frac{1}{A} = D\frac{dC}{dx}$$
$$\frac{dq}{dt} = DA\frac{dC}{dx}$$

We can given redefine $\frac{dq}{dt}$ as $\mathbf{J}$ which is also a flux. Furthermore, we can approximate $\frac{dC}{dx}$ into its simpler form

$$\begin{aligned}\frac{dq}{dt} = DA\frac{dC}{dx} \iff \mathbf{J} &= DA\frac{C_1 - C_2}{\Delta x} \\ \mathbf{J} &= \frac{DA}{\Delta x}(C_1 - C_2) \\ \mathbf{J} &= PA(C_1 - C_2)\end{aligned}$$

where P is the permeability coefficient that is different for each cells. This is in fact Fick's Law of Diffusion!

Law 2.0 (Fick's Law of Diffusion) When a cell is submerge in a concentrated solution, then the rate of diffusion for that cell would be given as

$$\mathbf{J} = PA(C_1 - C_2) \tag{2.5}$$

Where $\mathbf{J}$ is the rate of diffusion, P is the permeability constant, A is the surface area of the cell, C_1 and C_2 are the intracellular and extracellular concentration respectively.

Although not shown explicitly in the equation but the diffusion time would increase proportionally to the square of the distance.

Facilitated Diffusion: Ion Channels

Ion channels are protein channels that faciliate the movement of ions. These channel can be made of 1 to a cluster of protein. Ions channels is also selective on which ions it allows through depending on the channels' distribution of charge as well as size.

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Defintion 2.4 A **electrical gradient** ∇E is the measurement of the change in charges from 1 region to the next. Mathematically it is given as

$$\nabla E = \frac{dQ}{dx}$$

where dQ is a small change in eletric charge over a small change in distance dx.

The movement of ions through the channels is affected by ∇E also. When there exists both ∇C and ∇E, we call it an **electrochemical gradient**. Cell naturally has ∇E where their intracellular space is more negatively charged than their extracellular space

Example 2.7 When there is a high $[K^+]$ in the intracellular space than the intracellular space then the ∇C would cause K^+ to move inside of the cell. And because of ∇E, K^+ would tend to move into the negatively charged intracellular space.

We will reach an electrochemical equilibrium when the concentration is in balanced with the electric force.

$$\nabla E = \nabla C$$

in such case, their is no ionic movement across the channel.

Ion channels has 2 states that they can be in: *closed or opened*. The closeness and openess of ion channels also depend on the type of channel but in general, they can either have a **conformational change** ,where the inside can morph and block the channel, or have an **occlusion of the channel pore**, where the channel "fold into itself" thus closing off the pore.

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When channels can be closed and opened, we call such mechanism **gating**. There are 3 types of gating that a channel can have: ligand-gated, voltage-gated and mechanically gated.

Definition 2.5 A **ligand-gated ion channel** is an ion channel that when a *ligands* (molecules that bind to receptors) bind to the channel, it will open. e.g. acetylcholine is a ligand that when bind to the **nicotinic receptor**, the channel open allowing K^+ to flow in.

Definition 2.6 A **voltage-gated ion channel** is an ion channel that when a there is an *electrical membrane potential (action potential)*, it will open. e.g. when cardiac action potential reaches its peak at around $52mV$, the cardiac ion channel specifically for K^+ and Cl^- open allowing their respective ions to flow out.

Definition 2.7 A **mechanically-gated ion channe;** or **mechanosensitve channel** is an ion channel that can open when there is an applied stretch on to

the channel. e.g. when skin are damage through an impact, that impact will directly transfer to the pair receptor which allow ions to flow in, create an action potential and send back to the neural network.

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We will not go through too much of ion channel since it would be out of our course scope. Nevertheless, we would end this ion channel section by realizing that there are 4 main ions that the cells are dealing with: K^+, Na^+, Ca^{+2} and Cl^- thus there would be specific channels for each of these types.
All and all, the number of ions that would flow through these channels depend on 3 main factors

1. Channel conductance
2. Duration of opening
3. Frequency of opening

Facilitated Diffusion: Transport Proteins

In general, **facilitated diffusion by transport protein** is the movement of molecules and ions through the plasma membrane via integral membrane called **transporters**.

Remark 2.6 *Ions moving through transport protein is much slower than those that uses ion channels.*

This when a transport required a transporter, it is also called the **mediated transport system** (common for both passive and active transport). For this system, their transporters all share the following characteristics:

I. **Specificity:** Each transporters only have a specific molecule that it will transport.

II. **Saturation:** The higher concentration of molecules there are, the Φ into the cell also increases **however** at a certain concentration, it will eventually hit a plateau or a limit (*transport limit* T_m) since there could only be a finite amount of transporter to get all of the increasing molecule in .(theoretically, for diffusion, it can goes linearly forever).

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III. **Competition:** When structurally similar molecules compete for the same binding site.

The above characteristics also reveal factors that can affect the Φ: [solute], solute's affinity to transporter, [transporter], transporter's conformational change frequency.

Now...going back specifically for facilitated diffusion, like we said above, it is a type of diffusion where transport proteins are involved, because there are larger molecules that cannot diffuse through the membrane. The general mechanism of facilitated diffusion is as follow

1. Molecule bind to binding site.
2. Transporter change its conformation.
3. Molecule is transported to the other side.
4. Transporter return to its original conformation.

INSERT IMAGE HERE

Example 2.8 Hormones can increase the affinity and/or the number of transporter in some membrane, such as, Glut-4 transport glucose in muscle and can be increase via insulin.

Osmosis

Water can diffuse easily through the majority of membrane and this diffusion is faciliated by a group of protein that create a water permeable channel called **aquaporins**. The net diffusion of water through a semipermeable (permeable to water but not anything else) is called **osmosis**.

In osmosis, water will flow against the ∇C i.e. it will flow from [low] to [high]. This is because when water flow to the higher concentrated section, it will dilute the portion.

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Supposed now given a beaker contain an amount of water, we then divide the beaker into half by a semipermeable membrane. On one side we add high amount of solute while the otherside we add nothing. Theoretically, if there was an infinite amount of water, all of the water will flow to the solute side to dilute it until it reaches the same concentration of the otherside (which is 0). In reality however, the water will move over but it will stop at a point, the reason it stops is due to the air pressure as well as hydrostatic pressure; This pressure which stop osmosis is called *osmotic pressure*.

Definition 2.8 The minimum pressure required to stop the movement of water through a semipermeable membrane via osmosis is called **osmotic pressure**.

Derived from the ideal gas law, osmotic pressure Π is given as

$$\Pi = MRT \tag{2.6}$$

Where $M = \frac{n}{V}$ (n is the number of mole of particle, V is the volume), R is the ideal gas constant, T is the temperature. From the equation we can see that osmotic pressure is proportional to n (number of mol) and not their size or charge.

An important concept when it comes to osmosis is **Osmolarity** which is the total solute concentration of a solution. For context, we begins with osmol which is the amount of solute particles i.e. 1osmol = $1mol$ solute particles.

Remark 2.7 *The number of solute particles correspond to the amount it would dissociate in water.*

Example 2.9 When we add $NaCl$ into water, it would dissociate to Na^+ and Cl^- while glucose wouldn't dissociate. So, if there was 1 mol $NaCl$ it would correspond to 1 mol Na^+ and 1 mol Cl^- therefore totaling 2 osmol $NaCl$. And for glucose, 1 mol glucose is the same as 1 osmol glucose.

Using osmol, we defined osmolarity as

$$\Theta = \frac{\text{amount of solute in osmol}}{\text{total volume in liter}} = \frac{n_{\text{osmol}}}{V} \tag{2.7}$$

The unit for this equation is osmol/L or “Osm" (read as osmolar).

Example 2.10 For a liter of water with 1 mol of $NaCl$, the osmolarity would be

$$\Theta = \frac{2\text{osmol } NaCl}{1L} = 2 \text{ Osm}$$

Looking back at equation (2.5), we realized that osmotic pressure is proportional to the number of mol which is proportional to osmolarity therefore

$$\Pi \propto \text{Osm}$$

Assuming the condition is at room temperature 25^oC or $298.15K$, the osmotic pressure in term of Osmolarity is defined as

$$\Pi = MRT \longrightarrow \Pi = \text{Osm} \cdot RT$$
$$\Pi = 22.4\Theta$$

Example 2.11 The typical salinity of the body and saline solution used in hospitals have almost the same salinity content that is 0.9% $NaCl$. The molarity of this solution would be

$$M = \frac{9g\ NaCl}{L\ H_2O} \cdot \frac{1\text{mol } NaCl}{58.5g\ NaCl} = 0.15M\ NaCl$$

The osmolarity would be

$$\Theta = \frac{9g\ NaCl}{L\ H_2O} \cdot \frac{1\text{mol } NaCl}{58.5g\ NaCl} \cdot \frac{(0.15\text{osmol } Na^+ + 0.15\text{osmol } Cl^-)}{0.15\text{mol } NaCl} = 300mOsm$$

The osmotic pressure would then be

$$\Pi = 22.4(0.30\text{Osm}) = 6.7atm$$

For any solution that has the same osmolarity as the normal extracellular osmolarity (300mOsm), such solution is called, **isoosmotic**; if $\Theta <$ 300mOsm, the solution is called **hypoosmotic**; and if $\Theta >$ 300mOsm, it is called **hyperosmotic**.

In order for any solution to exert osmotic pressure to or from a cell, particles in the solution cannot pass the membrane (or else it can pass and change the concentration thus stopping osmosis); such particles are said to be **nonpenetrating**. In fact, Na^+can act like a nonpenetrating solute since any Na^+moves into the cell will be pumped out again by Na^+/K^+ATPase.

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Supposedly, we drop a blood cell into a mixed solution of a specific concentration of nonpenetrating solutes. Then, if the solution has a concentration of nonpenetrating solute particles of 300mOsm, no water will flow in or out of the cell, thus it's called **Isotonic**. For concentration < 300mOsm, water will move into the cell, and it's called **hypotonic**; and for concentration > 300mOsm, water will move out of the cell and the solution is called **hypertonic**.

2.3.3 Active Transport

Definition 2.7 A transport mechanism that is energy dependent i.e. required energy and does not care about the ∇C is called **active transport**. There are types of active transport: primary, secondary active transport, endocytosis and exocytosis

Remark 2.8 *The energy that is used by active transport is through hydrolyze ATP by the transporter.*

Primary Active Transport

In **primary active transport**, phosphorylation of the transporter will change its conformation and thus its binding affinity i.e. ATP will bind to the transporter and via hydrolysis, the transporter become phosphorylated and transport whatever it has in its binding site. Then it will return to its original conformation via dephosphorylation.

INSERT IMAGE HERE

Example 2.12 Na^+/K^+–ATPase is a primary transporter that can transport 3 Na^+ ions and 2 K^+ ions in opposing direction. First, 3 Na^+ ions will bind to the transporter's binding site, then ATP will be hydrolyze thus phosphorylating it. After, the transporter changes its conformation and transport 3 Na^+ ions out of the cell; the transporter will stay at this conformation till 2 K^+ ions bind to its binding site; the transporter dephosphorylate, returning to its original conformation thus bringing the 2 K^+ ions into the cell.

Some other primary active transporter are Ca^{2+}**–ATPase** (maintain low intracellular Ca^{2+}level), H^+**-ATPase** (maintain low lysosomal pH) and H^+/K^+**-ATPase** (acidify the stomach).

Secondary Active Transport

In **secondary active transport**, the transporter utilizes energy from the electrochemical gradient by moving an Na^+ that is coupled with another solutes (can be ions, glucose, etc.) that needed to be transported against the concentration gradient. Nevertheless the creation and maintenance of the electrochemical gradient is maintained by primary active transport which technically means secondary active transport **indirectly** uses ATP.

The general mechanism of secondary active transport is as follow: Na^+ bind to the transporter which allow another solute to bind along side it; the transporter changes conformation and the Na^+ and solute is delivered inside of the cell. Na^+ will then be excreted out via primary active transport namely Na^+/K^+-ATPase.

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Definition 2.10 When the solute is transported in the same direction as Na^+, we call that a **cotransport** also known as **symport**.

Definition 2.11 When the solute is transported in opposite direction to Na^+, we call that an **countertransport** also known as **antiport**.

Example 2.13 Na^+/amino acid transporter acts as a symport as it brings amino acid and Na^+ intracellularly.

Example 2.14 H^+/Na^+ exchanger (maintain pH) is an antiport that transport Na^+ into the cell and H^+ out of the cell. Na^+Ca^{2+} exchanger is also an antiport the transports Na^+ into the cell and Ca^{2+} out of the cell.

Now we move to the last 2 active transport mechanism that involves the cell membrane.

Exocytosis

Exocytosis is the process that a cell release waste or materials extracellularly by the fusion of vesicle to the membrane. In this mechanisms, a vesicle, made from a phospholipid bilayer, form around the material that is transported; once the vesicle reaches the plasma membrane, it will merge and turning itself inside out thus transporting the material extracellularly.

There are 2 types of exocytosis: constitutive and regulated.

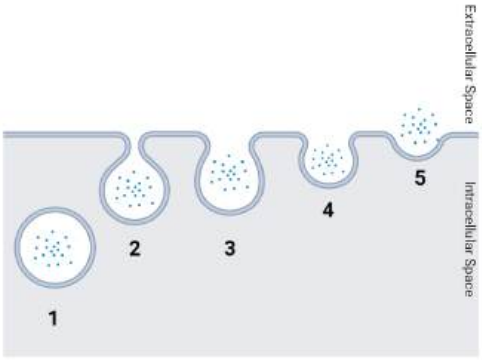


Figure 2.3: General mechanism of exocytosis

Definition 2.12 When a cell undergoes a non-regulated endocytosis for the purpose of incorporating the vesicle to the membrane or getting rid of waste product, the process is called **constitutive exocytosis** i.e. it doesn't require a specific signal to release a vesicle.

Definition 2.13 When a cell undergoes a regulated endocytosis, driven mostly by the build of cystolic Ca^{2+}or from extracellular signals, to secrete hormones, digestive enzymes or neurotransmitters is called **regulated exocytosis**.

Endocytosis

Endocytosis is the process that a cell takes in materials by engulfing and pinching of the membrane thus form a vesicle around those materials. One could think that the mechanism of endocytosis is the reverse of exocytosis: cell membrane first engulf materials and surrouding them with its membrane; the membrane with fuse from both side and pinch off leaving a vesicle containing those materials in the intracellular space.

Endocytosis can be divided into 3 categories: phagocytosis, pinocytosis and receptor-mediated endocytosis. Receptor-mediated endocytosis can be further subdivided into 2 sub-categories: clathrin-dependent receptor-mediated endocytosis and potocytosis

I. **Phagocytosis** or "cell-eating" is a process of endocytosis where engulfed materials are small dust particles, cell debris and microorgan-

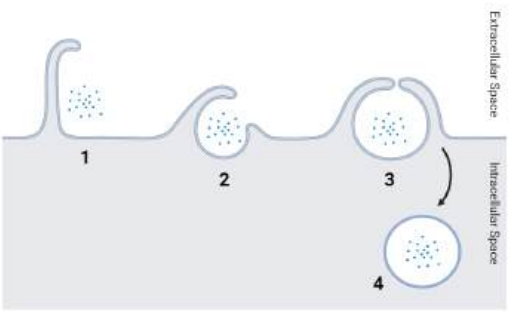


Figure 2.4: General mechanism of endocytosis

isms. The formation of the endocytotic vesicle for the particles are specific and is triggered by them. There's one special structure during phagocytosis: the **pseudopodia** which are cell's membrane extension to reach the particle. Once the pseudopodia fully merged and engulfed the particle the vesicle it forms is called *phagosomes*. The content of phagsomes will be degraded once it fuses with lysosomes.

II. **Pinocytosis** or *fluid endocytosis* or even "cell-drinking" is a process of endocytosis where the engulfed materials are mainly extracellular fluid (and solutes if presented). The formation of the endocytotic vesicle for these materials is unspecific, unregulated and once it is in the cytoplasm, it can fuse with other vesicles e.g. endosomes and lysosomes.

III. **Receptor-mediated endocytosis (RME)** is a process of endocytosis where extracellular particles (ligands) bind to a receptor site which triggers endocytosis at that receptor site.

- **Clathrin-dependent receptor mediated endocytosis (CME)** is a type of RME such that when ligands bind to the receptor, the receptor site begins to "sink" into the intracellular space thus forming a vesicle. An adaptor protein, coupled with the ligand-receptor complex, activates **clathrin** (a protein). Clathrin will then coat the exterior of the vesicle forming a *clathrin-coated vesicle*. The vesicle will shed its clathrin coat once it fuses to other vesicles or it can travel to the other side and fuse with the

membrane (process is called **transcytosis**). At the end, the receptor and the clathrin will be recycled to the membrane.

- **Potocytosis** is a type of RME with the same mechanism as CME however it does not involved a clathrin coat. When particles during this process will be isolated and transported by tiny vesicles called **Caveolae**. These caveolae and directly transport in the cytoplasm, fuse to the endoplasmic reticulum, other organelles or even perform transcytosis. Because of these small caveolae, potocytosis can only transport small particles such as vitamins.

INSERT IMAGES HERE

extra: Cholesterol is transported in the blood as lipid-rotein particles known as low-density lipproteins (LDL). lipoprotein is recognized by PM receptors and endocytosis follows.

2.4 A Brief Look at Capillaries

To create a better transition to the next topics, we would like to look at transport and some capillaries actions (since many exchanges happen at the capillary site).

Definition 2.14 **Capillaries** are the smallest blood (around 1mm in length and 8μm in diameter) vessel, made from a single layer of squamous endothelial cell. They are also the intermediate transition between arteries and veins.

An average adult has around 40km of capillaries network, 5% of which actually contains blood. There are mainly 3 types of transport across the capillary wall

1. **Diffusion:** Most molecules that the capillary carry can diffuse easily through it. Some actually diffuse through water-filled channels.
2. **Transcytosis:** For larger molecules, a coupled process of endo and exocytosis through the endothelial cell is required.
3. **Bulk Flow:** Extracellular fluid can pass through the endothelial via hydrostatic pressure to distribute to the plasma and ISF (which also determine magnitude of bulk flow). Capillary walls act as a filter for protein free plasma to move from capillaries to ISF.

Chapter 3

Hematology

As a branch of medicine, **hematology** is the study of the functions, compositions and diseases of *blood* etc. It can be seen as the sub-discipline of internal medicine.

Definition 3.1. **Blood** is a body fluid that is used mainly in the circulatory system. It is considered as highly dynamic tissue.

Blood has been theorized and used symbolically throughout history, however in the modern day, we view blood as “carrier of disease". Even then, it has a really good function in the body such as transport nutrients, waste, hormones and regulate T^o. Not only that it has a slightly neutral environment of pH $7.30 - 7.45$ and has WBCs and plasma proteins. Blood accounts for around 7% of the total body mass (5L).

3.1 Blood and Transcapillaries Transport

When blood drawn out of the body, it would have a uniform red-ish colour however to get to the know the true composition, we would have to centrifuge it so that heavier tissues would fall to the bottom (for separation).

3.1.1 Blood Composition

When we centrifuged blood, it would be divided into 3 layers: yellow-ish layer (consists of plasma), buffy layer (consists of white blood cells, platelets) and red-ish layer (consists of red blood cells)

Remark 3.1. *We will be using some abbreviation for blood composition: red blood cells would be RBCs, white blood cells would be WBCs.*

Figure 3.1: Blood before and after centrifugation.

In term of bodily fluid, blood can be divided into the extracellular fluid, which is plasma, and intracellular fluid, which is fluid inside each RBCs. When talking about blood, we tend to look at its total volume thus some terminology would be useful.

Definition 3.2. A normal blood volume of around 5L is called **normovolemia**. If $V < 5L$, it is called **hypovolemia** and if $V > 5L$ it's called **hypervolemia**.

Hematocrit is also a good measurement for blood volume [review Definition 2.2, equation (2.1)]

Example 3.1.1. For a 70kg male with an approximate blood volume of 5L, if his hematocrit of around 45%, then $V_{\text{RBCs}} = 2.25L$ and $V_{\text{plasma}} = 2.75L$.

3.1.2 Composition of Plasma

The composition of plasma is similar to that of ISF. It composes of > 90% H_2O, consists of lots of ions especially Na^+ and Cl^- (which is why we can approximate saline fluid to be 0.9% $NaCl$); nutrients, gases and wastes. And the main composition that differentiate it from the ISF is high protein concentration (around 7%), these proteins are albumins, globulins and fibrinogen. These proteins are what we'll be focusing next since other composition although are important, it is not as appealing as these proteins.

Composition: Plasma Proteins and Separation

In order to learn these plasma proteins, we must first isolate them from the rest of the plasma composition. There are many way to characterized it such as: differential precipitation by salts, sedimentation in ultracentrifuge, immunological characteristics and **electrophoretic mobility**. Out of all of these method, we would be focusing on electrophoretic mobility.

Definition 3.3. **Electrophoresis** is a fractionation method (separate different molecules/substances in a mixture) that based on movement of charged particles along a voltage gradient.

Essentially, we will put the mixture in this permeable gel and send a voltage gradient across it. The rate of migration (of each proteins in the mixture) is influenced by the number, charge distribution and molecular weight of each proteins.

INSERT FIGURE OF ELECTROPHORESIS OF ALL PROTEIN

When we actually perform the experiment, we find that we couldn't find the peak of fibrinogen - but why? This is because we were using serum (plasma without the clotting factors aka fibrinogen).
We can use this to see what some of disease that a patient can potentially have.

Example 3.1.2. When there's a drop in albumin peak (as compared to the control), it tells us that the patient would have **renal diseases**. When there's is a high peak in gamma globulin, the patient would have some bacterial infections.

Not only for detecting diseases, we can use electrophoresis to come up with some properties of these plasma proteins

INSERT PLASMA PROTEINS PROPERTIES TABLE HERE.

Most plasma proteins is made from the liver hence if there is liver disease, the plasma protein would decrease. Another type of plasma proteins called **gamma globulins** were derived from the **lymphoid tissues** instead of the liver.

3.2 Transcapillaries Dynamics

Plasma proteins are important in the distribution between the plasma and ISF by controlling the **transcapillary dynamics**, which is the process of fluid and molecules enter and exiting the plasma or ISF through the capillaries.

Looking back at previous chapter, we figured out the osmolarity of the ECF is rougly 300mOsm, which means that in equilibrium, the osmolarity of the plasma and ISF is also 300mOsm. To keep going to transcapillary dynamics, we would have to convert osmolarity to pressure (ideally using mmHg); Assuming at room T^o, then the osmotic pressure would be

$$\Pi = (22.4)(300) = 6700mPa = 6.7Pa \cdot \frac{760\text{mmHg}}{1Pa} \approx 5100\text{mmHg}$$

At equilibrium, the osmotic pressure from both plasma and ISF is the same hence no net movement. The majority of other solute found in the plasma and ISF can easily diffuse through the capillary wall. Plasma proteins however are big and bulky thus they cannot cross the capillary wall, making them **non-penetrating/diffusible solutes**; and because of that, they can exert osmotic effects.

Definition 3.4. An osmotic pressure that is exerted by the presence plasma proteins is called the **colloidal osmotic pressure (COP) of plasma** or **colloidal oncotic pressure (COP) of plasma**. And it is measured to be around 25mmHg.

So now, the osmotic pressure would no longer be 5100mmHg for each of them since in the plasma, the osmotic pressure is increased causing liquid from ISF to flow into plasma, this movement would eventually reach equilibrium again. One thing to remind ourselves is that as the concentration of plasma change, COP also change which means the net movement of water will change:

- If COP↑, water flows from ISF into the plasma.
- If COP↓, water flows from plasma into the ISF.

This dynamical system lead other smaller solutes and liquid to be able to cross the capillary walls. There are mainly 2 types of this transport: filtration and osmotic flow.

Filtration is essential and extended version of *bulk flow* which we briefly looked upon but shall give it a proper definition.

Definition 3.5. **Bulk flow** or **mass flow** is the flow of fluid and/or solutes down the concentration gradient. The main cause to bulk flow is hydrostatic pressure which also determines its magnitude α

$$\alpha \propto P_{\text{H-static}}$$

When bulk flow passes through a porous membrane such that small particles can goes through and “filtrates" all other larger ones is called **filtration**. Typically filtration pushes plasma’s contents out to the ISF and the capillary walls act like a filter.

Definition 3.6. **Osmotic flow** is the flow of liquid into the plasma membrane that is caused by plasma proteins and its exerted osmotic pressure (COP).

The movement of fluids and solutes that is caused by the osmotic flow and filtration is called **Starling forces** theorized by Ernest Starling. A balance of Starling forces is important for the distribution of bodily fluids of the ECF. Before moving into how Starling’s view on transcapillaries transport, we first have to have a brief look at the circulatory system. In layman’s term, the circulatory system consists of the heart which pump blood through series of blood vessels called *veins* and *arteries*. Oxygenated blood

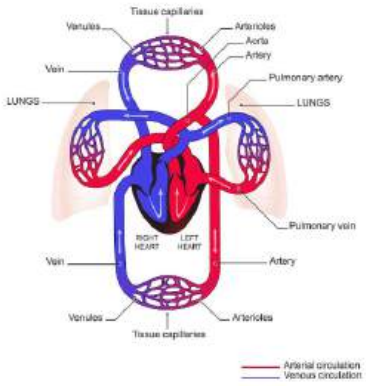


Figure 3.2: A simplified version of the cadiovascular system

is pumped out of the heart through the aorta to the arteries then passes through the capillaries which loop back into veins and return to the heart by the vena cava.

The **capillaries bed** is where the exchanges between the plasma and ISF occurs. They can perform this exchange because the capillaries are made up of 1 layer of endothelial cells. First, we can measure the blood pressure (BP) on the arterial and venous side of the capillary bed to be 35mmHg and 15mmHg respectively, These 2 pressures would force fluid out. We can then measure the COP of plasma across the entirety of the capillary bed to be 25mmHg, this pressure would pull fluid in.

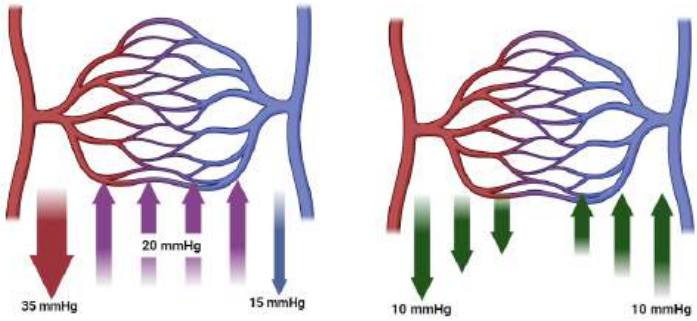


Figure 3.3: Starling's transcapillary dynamics. Red arrow represents the arterial capillaries BP, blue is the venous capillaries BP and violet arrows are COP. The second diagram shows the net movement of Starling's transcapillary dynamics.

When we take the net force and net movement across the capillary bed, We would have a gradient of net fluid filtration out to ISF at the arterial end of 10 mmHg and net fluid absorption into the plasma at the venous end of 10 mmHg.

Remark 3.2. *This filtration and absorption is called an **exchange** and happens on the entire length of the capillary bed, not just the 2 ends.*

Remark 3.3. *At the middle of the capillary bed, the absorption pressure will be equal to the filtration pressure thus net movement of 0.*

All in All, transcapillary transport is built upon Starling's transcapillary dynamics which are made up of filtration and osmotic flow. They mainly transport O_2, CO_2, nutrients and cellular waste.

3.2.1 Lymphatic System and Its Effects

Only around 90% of fluid filtered out by the capillary bed would be brought back via venous return. The remainder of fluid will be brought into the *lymphatic system*

Definition 3.7. **lymphtic system** is a network of organs and vessels which protect your body from infection as well as maintain a water balance.

The lymphatic system consists of connected blind-ended terminal tubules which coalesce to form large lymphatic vessels which converge to form the lymphatic ducts which then ultimately drain to the vena cava. Lymphatic vessels are made from a single layer of endothelial cell which are highly permeable to all ISF constituents (including proteins leaked from plasma to ISF).

Like we've said above, only 90% of plasma fluid is reabsorbed via venous return, the remainder will be brought back by the lymphatic system. On average, the body circulate around 6000L of blood, around 20L is filter into the ISF and only 17L is reabsorbed; the rest 3L is absorbed by the lymphatic system which will be brought back into the blood vessels.

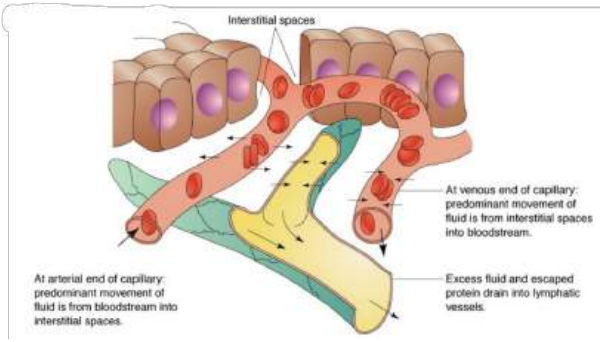


Figure 3.4: Exchange between the lymphatic system and blood vessels and ISF.

3.2.2 Plasma Proteins Contributions of Colloidal Osmotic Pressure

We now want to look back at the plasma proteins and figure out which one of them has the biggest effect when it comes to COP. Remember! COP does not depending on any property of plasma proteins, only its abundance is count i.e. the amount of the plasma protein there are. For optimizing weight and size, COP of each proteins is directly proportional to its concentration and inversely proportional to its weight.

Since the body loves to optimize things, it would choose the proteins with the lowest molecular weight to make the highest contribution...and indeed that proteins is **albumin**. Albumin with molecular weight of $\approx 69kDa$ contributes around $20mmHg$ (of the COP) as compared to fibrinogen with molecular weight of $\approx 350kDa$ and contributes $> 1mmHg$.

INSERT TABLE HERE

As we can see, plasma proteins in general play an important role when it comes to the transcapillary dynamics by determining the distribution of fluid between the plasma and ISF. Not only that, it also contributes to the plasma viscosity (directly related to BP), contribute to pH range of plasma. Each of the plasma proteins also play an important role in itself: fibrinogen and some globulins can help with clotting, $\gamma-$globulins (immunoglobulins) can provide some resistance for infection and albumins with some globulins are for mineral, lipids and hormones transport.

3.2.3 Factors in Transcapillary Dynamics

To end transcapillary dynamics, we will be looking at some factors that can effect it. The factors that make up the transcapillary dynamcis are

1. **Hydrostatic Pressure**
2. **Colloidal Osmotic Pressure**
3. **Capillary Permeability**
4. **Lymphatic Drainage**

When some of these factors are unbalanced/disrupted, it can lead to some bad side effects.

Example 3.2.1. **Edema** is a term to describe the accumulation of excess fluid in the interstitial space. Conditions that could lead to edema is increase in hydrostatic pressure, decrease in COP, increased in capillary permeability and blocked lymphatic drainage. When hydrostatic pressure increases, the amount of plasma fluid will be filtered out also increases and a decrease in COP will lead to a decrease in net absorption.

An extreme case of edema, due to a decrease in COP is *Kwashiorkor*. This disease is cause by the liver inability to produce plasma proteins hence lower plasma protein level; which also corresponds to lower COP. These conditions are often found in baby in tropical regions.

Increase in capillary permeability would also allow some plasma proteins pass through which in turn, can exerts their own COP on the to plasma.

Example 3.2.2. **Elephantiasis** is another extreme condition of edema where the lymphatic system is blocked, probably due to parasitic infection. When there is no lymphatic return, almost all of the extra fluid will stay within the ISF and will continually build up if there is no drainage.

3.3 Classification of Blood Cells

Previously we've looked at the composition of the plasma, now we will look blood cells i.e. we will look at the red and buffy part when centrifuged blood. It is important to note too that we'll be looking mostly at red blood cells.

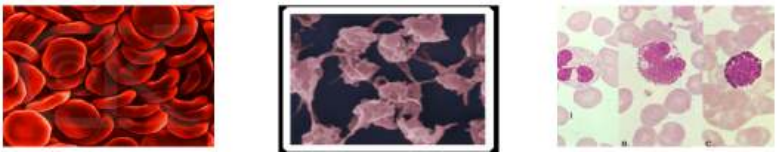


Figure 3.5: Different types of blood cells (from left to right:) RBCs, platelets and WBCs.

Blood cells are general divided into 3 types: erythrocytes (or red blood cells), thrombocytes (or platelets) and leukocytes (or white blood cells). Here are some general description of them:

- **Erythrocytes (RBCs)** is the most concentrated in our body of around 5×10^6 RBCs/μL. Their size on average is $7.5 \mu m$ in diameter and typically last for 120 days ($\sim$ 4 months).
- **Thrombocytes (Platelets)** is the second most abundant with concentration around $250,000 - 400,000$ Platelets/μL. Their size ranges from $2 - 3 \mu m$ and last from $7 - 8$ days.
- **Leukocytes (WBCs)** has the concentration of $8,000 - 10,000/\mu L$. They're the biggest of the 3 with diameter range from $10 - 12 \mu m$ and can last for hours (WBCs that destroy infection right away) to years (memory WBCs that need to be maintained).

All of the mentioned cells above all came from the same stem cells.

Definition 3.8. **Hematopoietic stem cells (HSCs)** are stem cells that can mature and become different kind of blood cells. They're located in the bone marrow and umbilical cord (for babies). They're also called **pluripotential** which mean they can become several types of cells and **multipotential** which means they can become different cells of the same lineage.

The process of making blood cell, as a whole, is called **hematopoiesis**; this can be further divided into the process of making RBCs, platelets and WBCs: **eruthropoiesis**, **thrombopoiesis** and **leukopoiesis**. The general pattern of hematopoiesis is as follows:

1. HSCs will start self-replication thus making more HSCs (division or proliferation process)

2. HSCs will become **committed hemapoietic stem cells (CHSCs)**.

3. CHSCs will receive *stimulant* and goes through any of the specific routes to become 1 specific blood cell (differentiation process).

The stimulant the kick start differentiation and proliferation is called **cytokines** or **hematopoietic growth factors (HGFs)**. This stimulant is released by 1 cell which effect an entire group of cells.

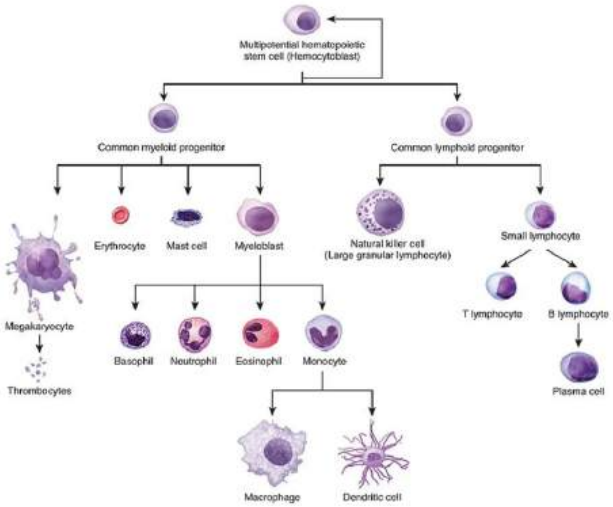


Figure 3.6: Hematopoiesis

The site at which hematopoiesis takes place differs from prenatal to natal. Prenatally, babies' hematopoiesis take place in the yolk sac in the first month (diminish in the third), then it would be made by the liver and spleen.

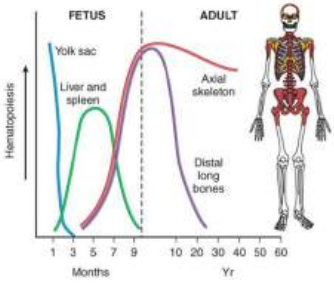


Figure 3.7: Different site of hematopoiesis in the human body

Once the baby is born and reach adulthood, most of hematopoiesis will take place in the axial skeleton and less at the distal bone (move toward proximal site). This site are mainly: flat bones of skull, shoulder blades, sternum, vertebrae, ribs, pelvis and proximal epiphysis of long bones (such as femur).

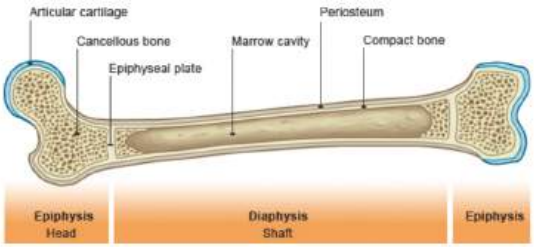


Figure 3.8: Epiphysis and diaphysis of long bones.

As we've said before, in adults, this happens specifically in the bone marrow. This is also the reason why ppl with conditions where their HSCs malfunctions will be given bone marrow, which is for the reintroduction of a new population of HSCs into the body.

3.3.1 Red Blood Cells: Characteristics

The main function of RBCs is to transport respiratory gases such as O_2 and CO_2 to different compartment of the body. As usual, the body loves to optimize everything so the RBCs is shape like a **biconcave disc** which are held together by a fibrous protein called **spectrin**.

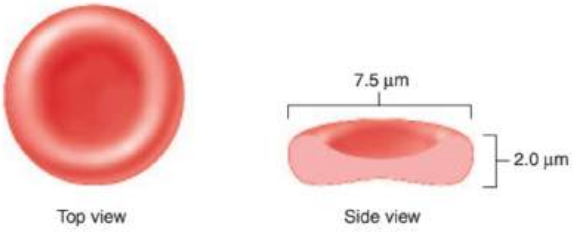


Figure 3.9: Shape of RBCs

This shape allow RBCs to maximize surface area, minimize the diffusion distance and increase flexibility (allow RBCs to squeeze through narrow blood vessels).

Numerical and Morphological Values for Blood and RBCs

When doing a complete blood check, it is important for medical professional to not leave any minute details about the blood out. The blood test that measure all possible value it can find given a blood sample is called **complete blood count (CBC)** and it measures: the amount of RBCs, WBCs, platelets, hematocrit (Ht), and hemoglobin (Hb) concentration.
Not only that, it can also look at the cell size (micro-, normo- or marcocytic) and shape (round, sickle, etc.).

Important Structures and Values of RBCs

The RBCs counts in men and woman are different (which will be explained later on) with male RBCs counts to be $5.1-5.0\times10^6$ RBCs/μL where as with female to be $4.5-4.8\times10^6$ RBCs/μL. For a total $5L$ of blood, on average (counted for both male and female), the total RBCs count is $20-30\times10^{12}$. Nevertheless, the rate of RBCs production and destruction is the same of around 2×10^6 RBCs/s (same for both sex too).

RBCs mainly composed of water, 33% of it is *hemoglobin* and the rest is lipids, proteins and ions. It does not have subcellular organelles, nucleus nor mitochondria. Even when missing these important organelles, it has an important enzyme system for replacement: **glycolytic enzymes** which can generate energy anaerobically, and **carbonic anhydrase** for CO_2 transport. The most important structure out of all of them is the **hemoglobin (Hb)**. Hb, weigh around $64kDa$, is made from 4 subunits of $\alpha-$ and β chain in each of this unit is a *heme* group (precursor to Hb) that hold an iron ion. Each of the Hb can hold 4 O_2 atoms and each RBCs is made from $200-300\times 10^6$ Hb. When Hb is combined with oxygen, we call it **oxy-hemoglobin** (HbO_2) otherwise it is called **deoxyHb**.

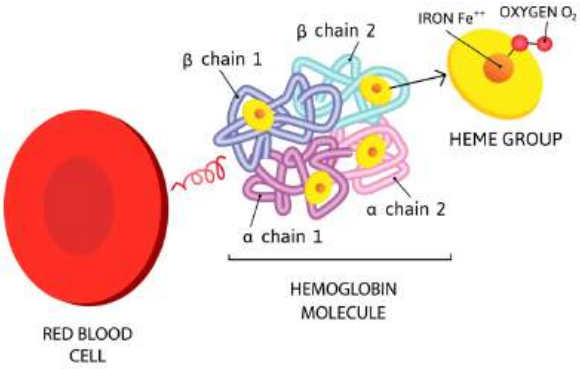


Figure 3.10: Structure of hemoglobin

The colour of Hb also depend on where it is; in the lung, Hb is saturated with O_2 forming HbO_2 and will give a bright red colour, while in tissues, O_2 is dissociated from Hb forming deoxyHb and will give a dark red colour.

Hbs are also good as a buffer and are good for CO_2 and O_2 transport. We can see this by comparing the solubility of O_2 in blood with plasma and with Hb. With plasma only, O_2 solubility is low at $0.3mL\ O_2/100mL$ plasma but with Hb the number increase to $20mL\ O_2/100mL$ blood.

Proof. The average of amount of Hb found in blood is $15g/100mL$ blood and when Hb is full saturated with O_2, each gram of Hb hold around $1.34mL\ O_2$. The O_2**-carrying capacity** of blood is

$$\frac{15g\ \text{Hb}}{100mL\ \text{blood}} \cdot \frac{1.34mL\ O_2}{1g\ \text{Hb}} = \boxed{20\frac{mL\ O_2}{100mL\ \text{blood}}}$$

□

As you can see it is much more efficient with Hb. One could raise the question that is **If Hbs increase oxygen solubility then why don't they dissolve in the plasma?**...Well, to put it simply, there is a lot of Hb and letting them flow around in the plasma would change its viscosity and COP; we can also potentially lose then via the kidney circulation.
Nevertheless, the binding of O_2 to Hb is under the influence of to body's T^o, ionic composition, pH, pCO_2 and intracellular enzyme concentration.

3.3.2 Red Blood Cells: Erythropoiesis

During erythropoiesis, RBC myeloid progenitor cells proliferation and differentiation is activated via HGFs called **erythropoietin (EPO)**. During proliferation and differentiation, the RBC myeloid progenitor will begin to lose its nucleus (and organelles), decrease in size ($18\mu m$-$7\mu m$) and most importantly synthesize and accumulate Hb.

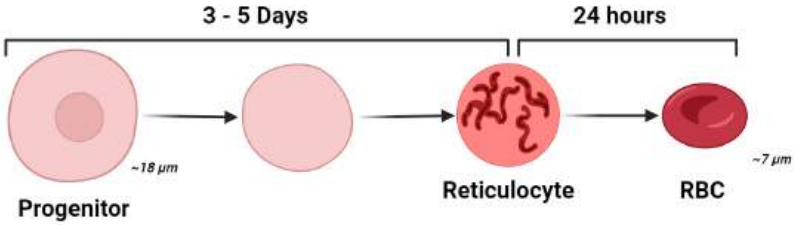


Figure 3.11: Process of Erythropoiesis

Remark 3.4. *EPO acts only to the RBCs myeloid progenitor cells and not the HSCs or any other pluripotent cells.*

This process of differentiation and proliferation will take around $3-5$ days, after which, immature RBCs called **reticulocyte** will be released into circulation which can mature to become RBCs. Within a 24 hours period, we can still identify RBCs from reticulocytes. For an average person, the reticulocyte count would be $< 1\%$ (of the total RBCs count), we use an index called **reticulocyte index** to see the amount of effective erythropoiesis in the bone marrow which is given as follow

$$RI = \frac{R\% \times \frac{\text{Ht}}{45}}{MF} \tag{3.1}$$

where RI is the reticulocyte index, $R\%$ is the reticulocyte count, Ht is the hematocrit and MF is the maturation factor (you do not need to know this equation for this course).

The 2 main factors that can change erythorpoiesis RBCs production (hence the total amount of RBCs too) is O_2 requirement and availability. When the body need more oxygen in the case of vigorous aerobic exercise, the brain would release more EPO in order to make RBCs to carry O_2 to muscle tissues. One the other hand, when O_2 level decreases, the body also experience a low O_2 level thus the kidney will release EPO to increase RBCs level to capture as much O_2 as possible.

Example 3.3.1. The condition when the body is not getting enough oxygen is called **hypoxia** which is a result from decrease in RBCs count or O_2 availability (probably from being in higher altitude). When the kidney senses hypoxia, it release EPO which would increase EPO concentration in the plasma. This would also increase the rate of erythropoiesis in the bone marrow and maturation of reticulocytes. This would then caused an increase in O_2 level. When there's an increase in O_2 level, the body stop experiencing hypoxia, the kidney stop releasing EPO, and then so on returning to normality (this is an example of **negative feedback loop**)

Remark 3.5. *Typically, the hypoxia negative feedback loop is transient unless there is a certain chronic conditions.*

Example 3.3.2. This also relates to human's acclimatization to higher altitude. Take Everest mountain climbers, they typically have to stay at a certain altitude for $2-3$ weeks so that the body would experience mild hypoxia in order to increase the total RBCs count.
Not only for climbers but athletes who trained at higher altitude performs better than those who trained at a lower altitude, due to their high RBCs counts, there'll be more O_2 transport to tissues.

Remark 3.6. *It is important to note that high RBCs count is beneficial however having too much RBCs can decrease blood flow due to higher viscosity and friction which would lead to clotting.*

Not only EPO can perform regulation but there are hormones that can also indirectly affect the RBCs production. The hormone **testosterone** can increase the release of EPO, not only that, it can also increase RBC myeloid progenitor sensitivity to EPO i.e. making them more susceptible to turning

into RBCs. On the contrary, Estrogen do the opposite. This is also why male has a higher RBCs count than female because male tend to produce more testosterone than female.

3.3.3 Red Blood Cells: Regulation and Control

RBCs don't have nucleus and other organelles thus its life span is limited to 120 days. With our current understanding, there is no pharmacological tool to prolong RBCs. After 120 days, the RBCs is degraded and damage thus can not provide any useful output for the body hence we need to get rid of it by any mean.

Remark 3.7. *On average, RBCs travel around 300mi (in the circulatory system) through out their lifespan.*

Destruction and Recycle of RBCs

When RBCs reach their final stages of their lifespan, they're removed from circulation and brought to the liver to be destroyed by **macrophage** via phagocytosis. Even so, RBCs have lots of useful components in it thus after macrophage phagocytose the RBCs, it will release its content back to the plasma. These components are heme group, globin molecule and iron.

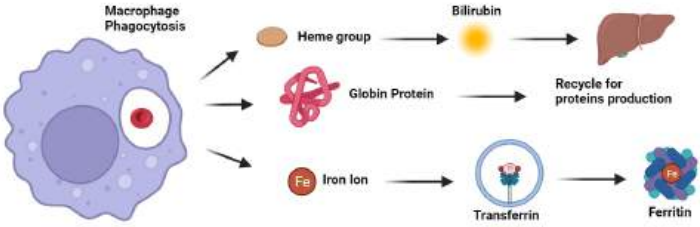


Figure 3.12: Components of RBCs after phagocytosis by macrophage.

Globin proteins are amino acid pool which can be reuse to make other proteins This component are organic and don't create much harm. Iron, on the other hand, is toxic so it will be picked up by a blood plasma glycoprotein called **transferrin** and deliver to liver, spleen and gut. At the site of storage, it will be bound to protein called **ferritin** (will be kept their for RBCs production later on). Then finally, the heme group will be degraded into **bilirubin** and further degraded by the liver and excreted from the intestinal tract. Bilirubin is the component with concentration of $1mg/dL$

that make the plasma have a yellow-ish hue to it.

Sometimes, bilirubin concentration increases which is caused mainly by excessive hemolysis, liver damage and even obstruction of bile duct. The condition for this increase is called **jaundice**. For new born, this is more common and is called **neonatal jaundice** which is cause by their liver unability to process bilirubin yet (condition will go away by itself).

3.3.4 Red Blood Cells: Abnormal Dynamics

In normal RBC dynamic, the amount of RBCs produce is equal to the amount of RBC destroyed (roughly the same). Nevertheless, sometimes we may develop certain condition that can tip the balance of this process.
When there is more production of RBCs than destruction, it is called **polycythemia** and the inverse would be **anemia**.

Before getting into these condition, it is important to have certain indices to evaluate or else the conditions could be different, we use the following indices: number of RBCs, hematocrit (Ht) and number of hemoglobin (Hb).

Example 3.3.3. When not enough indices, we won't be able to know what the true condition: RBCs count is higher than normal, is it polycythemia or dehydration? there is less RBCs, is it anemia or fluid retention?

The normal RBCs count is around $5-5.5\times10^6$ RBCs/μL, Ht level varies from $41-50\%$ for male and $36-48\%$ for female, and Hb level is around $16g\%$ Hb.

Polycythemia: General Outline

In polycythemia, there is an overproduction of RBCs which means that we expect Hb and RBCs count to go up, which is $>6\times10^6$ RBCs/μL and $>18g\%$ Hb.
Polycythemia is divided into 2 kind: relative and absolute. For relative polycythemia, the condition is related toward a decrease/low plasma volume i.e. it seems like the Ht level is high but it's because of lower plasma. For absolute, this conditions is more related to the actual production of RBCs.

We can in fact, divide absolute polycythemia into 2 types: physiological and pathological

Polycythemia: Absolute and Physiological

For **Physiological Absolute Polycythemia**, it is a secondary effect that arise from living in high altitude, which would decrease the O_2 availability, turn on hypoxia cycle and produce more RBCs; and increase physical activity, which would increase O_2 requirement thus increase EPO release and produce more RBCs; and other conditions. In these situation, the increase in production of RBCs is not a "malware" in the bone marrow.

Example 3.3.4. A disease called **emphysema** which can chronically obstruct the lung airway. If a person has emphysema, they would also have physiological absolute polycythemia, since the air availability is lowered (due to obstruction) thus increase in production of RBCs.

Polycythemia: Absolute and Pathological

For **Pathological absolute polycythemia**, it is a primary effect caused by a possible tumor of the RBC myeloid progenitor or unregulated RBC production by bone marrow.

Example 3.3.5. **Polycythemia vera** is a type of blood cancer where the stem cells are dysfunctional. The RBCs count of this disease is around $7-8\times10^6$ RBC/μL and Ht level of 70%.

All in all, polycythemia is bad since as mentioned in Remark 3.6, an increase in RBCs production can lead to blood clotting.

Anemia: General Outline

In **anemia**, there is a decrease in the O_2-carrying capacity of blood, sometimes we relate it with overdestruction of RBCs but it's not always true. Even so, in anemia, there is still a lower RBCs and Hb level than normal; that is, for male: $< 4\times10^6$ RBC/μL and $< 11g\%$ Hb, for female: $< 3.2\times10^6$ RBC/μL and $< 9g\%$ Hb .

Anemia can be classify into 2 types: morphology and etiology

Anemia: Morphological Classification

We now need to classify individual RBC based on their shape and size thus morphology. This would be useful later on as we study etiological side.

When it comes to size, we divide into 3: microcytotic (smaller than normal, $V < 80\mu m^3$), normocytotic (normal, $V = 80 - 94\mu m^3$) and macrocytotic (bigger than normal, $V > 94\mu m^3$).
Colouration of RBCs is also taken into account (it is measured with Hb level): hypochromic (paller than normal, < 33% Hb), normochromic (~ 33% Hb) and hyperchromic (redder than normal, > 33% Hb).

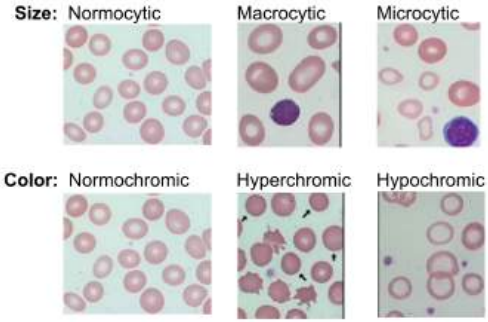


Figure 3.13: Morphological classification of anemias

Anemia: Etiological Classification, Dimished Return

We can then to classify anemia is through etiology which is the cause of disease, there are 3 main subclassificaiton of etiology but we will begin with **diminished return**. Some probable causes for diminished return could be abnormality of site of production, not enough EPO or raw materials.

Example 3.3.6. **Aplastic (hypoplastic) anemia** is rare blood conditions that is caused by the failure of RBC production in the bone marrow (abnormality at production site). The RBCs produced from this condition are normocytotic and -chromic however there is not enough of this RBCs.

Example 3.3.7. **Renal disease** is a disease that can cause a gradual loss of function in the kidney. When this happens, kidney will not be able to produce EPO to stimulate the production of RBCs (inadequate stimulant). The RBCs produced from this disease are also normal but again, not enough of them.

Example 3.3.8. **Iron deficiency anemia** (the most common type) is the inadequate amount of iron for an increase requirement for iron (during pregnancy, puberty etc.). Inadequate amount of iron can be due to dietary

deficiency, failure to absorb and loss of iron during hemorrhage. Because there's not enough iron, the heme group will lose its iron thus decrease in size and look paler thus microcytotic and hypochromic.

There are in total 4g of iron in the body, and the entire process of erythropoiesis require around 25mg of iron per day the typical intake of iron needed in male around 1mg/day for males and 2mg/day for females.

Proof. Destruction and production of RBCs release and require the same 25mg Fe. Out of 25mg released, 24mg is recycled and 1mg is lost (hence why male need to intake 1mg Fe). As for females, during menstruation, they lose 50mL blood/month, which is around 25mg Fe. Therefore they will need 50mg Fe/month to replenish the loss and potential loss which is 2mg Fe/day □

Anemia: Etiological Classification, Ineffective Maturation

For ineffective maturation (sometimes called **megaloblastic anemia**), a probable caused is deficiencies of Vit-B12 and folic acid or even inadequate of Fe. Low level of Vit-B12 and folic acid could lead to a normal RBC to grow in size thus RBCs with ineffective maturation are often macrocytotic and normochromic. We will digress a little and look at Vit-B12.

The absorption of Vit-B12 is peculiar because it needs an intrinsic factor to bind to it to be absorbed in the ileum of the intestinal tract. If there is a failure in one of these step, there would be no absorption of Vit-B12.

Example 3.3.9. **Pernicious anemia** is a blood condition where there is a deficient in Vit-B12 intrinsic factor, leading to no absorption of Vit-B12 thus create macrocytotic RBCs.

Anemia: Etiological Classification, Reduced RBC Survival

A **reduced RBC survival** anemia is caused by an could be due to an overdestruction of RBC as compared to production.

Example 3.3.10. **hemolytic anemia** is a blood condition where the rate of RBC destruction is higher than production. This can be acquired through medication or congenital, that is present from birth. RBCs in such conditions would have abnormal membrane structure (spherocytosis, condition where the overall RBC shape looks like a sphere), enzymes systems and Hb structure (such as sickle cell anemia)

3.4 Hemorrhage and Hemostasis

Hemorrhage is blood loss which can be external or internal (in the tissues). When blood stays inside tissues, it is called **hematoma**. The process of stopping blood is **Hemostasis**

Remark 3.8. *It is important to not mix up hemostasis (the process of stopping blood) with homeostasis (the balance in our body).*

3.4.1 Hemostasis

Hemostasis is the response right after hemorrhage. There are several mechanism that contribute to hemostasis: vascular response, platelet response (critical for stopping bleeding) and clot formation (the only part the is physical). With these types of response, we can divide them into 2 types: primary (rapidly but last only minutes) and secondary hemostasis (last until the wound is healed). Even when secondary is very effective, majority small wounds only require the primary activation.

Let's take an example of a vascular injury. At the beginning, when the blood vessel rupture, its content will be poured into the ISF. Then the vessel will contract at the damage site to lower the amount of loss.

Definition 3.9. The process of a blood vessel contract to lower its diameter is called **vasoconstriction** while the opposite would be **vasodilation**

After vasoconstriction happens, platelets will accumulate and aggregate at the injured site to form a plug (white thrombus).As time goes on, this plug will harden and become blood clot (for larger injuries) or if the site of damage is smaller, a blood clot is not needed.
Essentially, primary hemostasis is activated with vascular and platelet response while blood clot formation is formed from secondary hemostasis. (see Figure 3.14)

3.4.2 Primary Hemostasis

Vasoconstriction

The blood vessel is made from endothelial cells lines with smooth muscles. Typically, to avoid opposing endothelial cells from sticking with each other, they release vasodilating factor (such as prostacycline or NO) that would increase the diameter. When the blood vessel is damaged however,

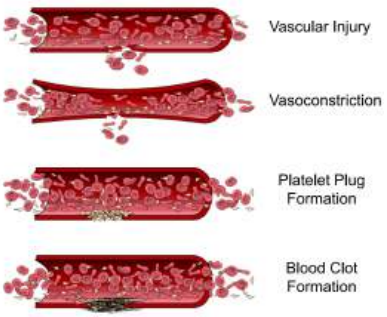


Figure 3.14: Stages of hemostasis for a damaged blood vessel.

the smooth muscle will contract thus brought opposing endothelial cells closer and stick on to each other.

Platelet Response

Platelet are very small in size of around $2-4\mu m$. They're not "cell" but cell fragments. They're filled with different granules and lots of other organelles like ER and mitochondria but they don't have a nucleus. These granules contain factors for vasoconstriction as well as **platelet aggregation factors (PF)** or **Thrombin**.
We only have around $250,000$ platelet/μL blood. The hematopoiesis of platelets (or thrombopoiesis) is the same as RBCs however the myeloid progenitor cell (receiving stimulus from thrombopoietin) will differentiate and become **megakaryocyte** which would fragments into platelets as it goes into systemic circulation.

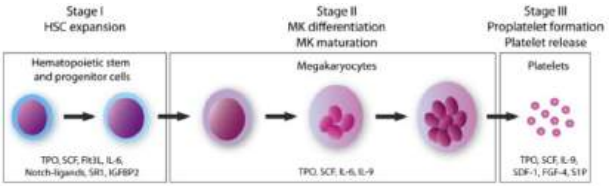


Figure 3.15: Formation of platelet

For a platelet plug formation, The collagen of damaged endotelial cells is exposed which allow platelets to bind with it. **Von Willebrand factors (VWF)** found in the plasma as well as released from endothelial cells will

form a stronger link between the endothelial cells with the platelet (adhesion). During this time, platelets will release **thromboxane A2 (TXA2)** which would cause more platelets to produce and helps in the consolidation of platelet plug. TXA2 is also partially produce by **adenosine diphosphate (ADP)** which would cause platelet aggregation. **Platelet factor (PF)** is also released which can cause blood coagulation and further platelet recruitment;
When endothelial cells are damaged, it also leads to another pathway called **coagulation pathway** which release thrombin that is important for the secondary hemostasis.

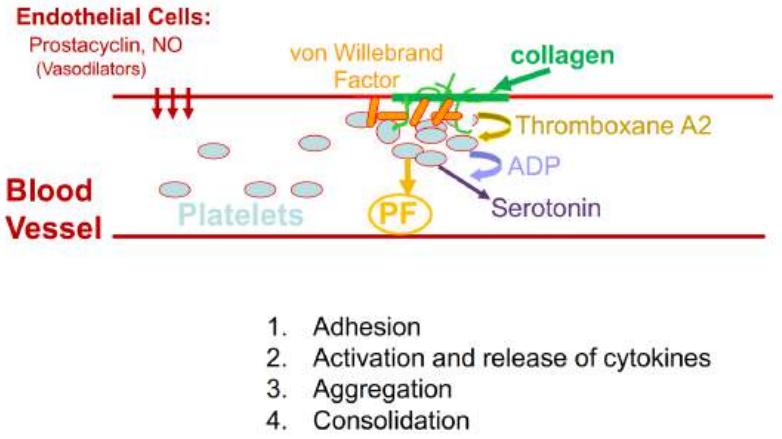


Figure 3.16: Primary hemostasis pathway.

Abnormalities of Primary Hemostasis

Abnormalities of the primary hemostasis response can lead to prolonged bleeding. These conditions can caused by the blood vessel failure to constrict or simply the deficiency in platelets. This deficiency can be numerical (how much platelet there are) or functional (congenital or acquired) .

Example 3.4.1. **Thrombocytopenia** is a condition where the body have a low platelet count ($< 75{,}000$ platelets/μL). The secondary effect that this condition lead to is having round reddish spot on the skin called **petechia** which are formed by an accumulation of blood below the skin.

Remark 3.9. *Aspirin inhibits the synthesis of TXA2 helps with consolidation of platelet which is good for unclogging and lower risk of a heart attack.*

3.4.3 Secondary Hemostasis

A blood clot or a **thrombus** is initiated by the injury to the blood vessel wall which result in a sequential activation/interaction of groups of proteins and clotting factors. When looking at an thrombus, we see that there are lots of RBCs but they're not required, they got stuck when travel around. An important aspect of clotting is the release of phospholipid agents and calcium that can help that helps with clot formation.

Remark 3.10. *The naming of protein factors (PrF) are named in Roman numerals in the order they were discovered.*

There are 3 stages to blood blot formation: vessel injury, intermediate stage and clot formation (only visible stage). When we look at the intermediate step that lead to clot formation, there are 2 pathways to consider intrinsic (3-6min) and extrinsic pathway (15-20s). The intrinsic pathway takes longer to build up however it will sustain for the entire duration while extrinsic create the first respond which would coupled to the intrinsic pathway i.e. these 2 pathways are connected.

Remark 3.11. *Extrinsic pathway is anything outside of the blood vessels while intrinsic is the inverse.*

The main "ingredient" we'll be looking at is **fibrin** which is a tough fibrous protein substance that can hold the clot together. The entirety of secondary hemostasis (include both pathway) is to make more fibrin and even, its most strong stable form (less susceptible to lysis) **cross-linked fibrin**.

Extrinsic Pathway

When endothelial cells are damaged, tissues factors are release which will convert PrF **VII** to **VIIa**. In the presence of VIIa, PrF **X** is converted to **Xa**, **IX** is converted to **IXa** which would cause **X** to convert to **Xa** too. Xa along with Ca^{2+}, Va, PF and other enzyme create the enzyme **prothrombinase**, which would turn **prothrombin** into **thrombin**. In the presence of thrombin, **fibrinogen** is converted to **fibrin**, PrF **XIII** is converted to **XIIIa** which can then convert fibrin to **cross-linked fibrin**.

Remark 3.12. *The creation of prothrombinase and prothrombin (in small amount) via extrinsic pathway kick start the intrinsic pathway.*

Intrinsic Pathway

When the endothelial cells are damaged, their exposed collagen will convert PrF **XII** to **XIIa**. In the presence of XIIa, PrF **XI** is converted to **XIa**, which along with Ca^{2+}will convert **IX** to **IXa**. PrF **VIII** is converted to **VIIIa** in the presence of thrombin (from previous pathway). Under the presence of Ca^{2+}, PF, VIIIa and IXa, PrF **X** is converted to **Xa**. The presence of thrombin also convert **V** to **Va**. Xa along with Ca^{2+}, Va, PF and other enzyme create the enzyme **prothrombinase**, which would turn **prothrombin** into **thrombin**. In the presence of thrombin, **fibrinogen** is converted to **fibrin**, PrF **XIII** is converted to **XIIIa** which can then convert fibrin to **cross-linked fibrin**.

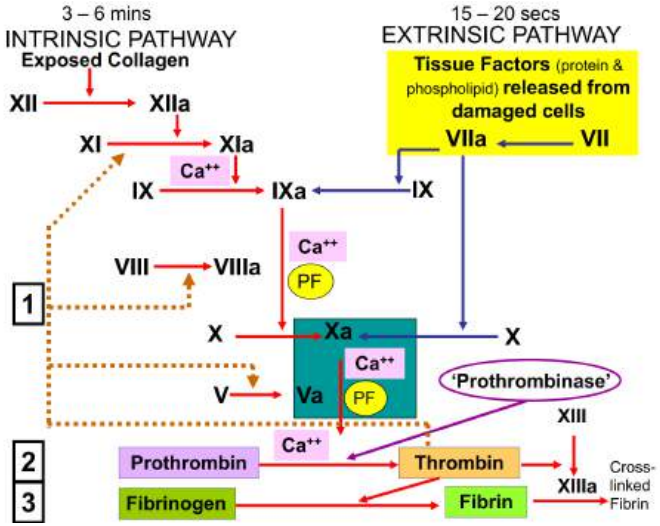


Figure 3.17: Extrinsic and intrinsic pathway. Dotted arrow extended from thrombin shows its positive feedback to make more PrF.

Remark 3.13. *These 2 pathways happen at the same time but extrinsic is faster.*

Remark 3.14. *The production of thrombin create a positive feedback loop to the intrinsic pathway, making more PrF for the making of thrombin.*

Abnormalities of Secondary Hemostasis

Looking back, we can sum up all the factors that control coagulation are: calcium, phospholipids and protein (plasma) factors. When there are problems with these factors, our body would have poor control over hemorrhage or incomplete hemostasis.

Example 3.4.2. **Hemophilia** is a congenital (inherited) bleeding disorder where blood cannot clot properly. The main cause behind hemophilia is the missing of factor VIII.

Example 3.4.3. **Vitamin K deficiency** is an acquired condition where the body does not get enough vitamin K (an important cofactor for the synthesis of prothrombin) which can lead to uncontrolled bleeding.

3.4.4 Regulation of Blood Clot

Positive feedback loop is never ideal since the clot could grow bigger without control. The body's measure to counter this problem is with **clot retraction**, where the clot size is reduced but its density stay relatively the same or higher. This process requires contractile proteins called **thrombosthenin** (released by platelets). These proteins along with other factors would create a contractile force onto the fibrin network, making it reduce in size.

Fibrinolysis

Another way to prevent blood clots to keep growing, the body activates **fibrinolysis** or **thrombolysis**, which is the process of breaking down fibrin network.

A plasma protein called **Plasminogen** in the presence of **plasminogen activator** (released by the intrinsic proactivator such as PrF XIIa and extrinsic factors) will become plasmin. In the presence of plasmin fibrin will breakdown into fibrin fragments. The clotting of blood vessels is kept in check by inhibitors of platelet adhesion and anticoagulants. These substances can be naturally occuring in the body or as drugs.

Example 3.4.4. **Aspirin** as we mentioned above that can lower the adhesion of platelets acts as an inhibitor of platelet adhesion.

Example 3.4.5. **Anticoagulants** are a class of drug that disrupt clot formation. **Coumarin** is an anticoagulant that can block the synthesis of prothrombin, PrF VII, IX and X. **Heparin** is a anticoagulant that can inhibits thrombin activation and actions.

Example 3.4.6. **Thrombolytic drugs** are a class of drug that can cause clot lysis. Tissue plasminogen activator (tPA) is a drug that can activates plasminogen which consequently create fibrinolysis. **Streptokinase** is a thrombolytic agent (drug) that can lyse clots and fibrin networks.

Chapter 4

Immunology

Definition 4.1. **Immunology** is the study of the immune system; which is a complex of organs and cells that are used to protect the body from foreign substances.

The immune system diffuses all over the body and its role is to protect the entire body hence why it needs to extend everywhere. It protects us from pathogens and even cancers.

Definition 4.2. **Pathogens** are organisms that can cause a disease to the host (our body).

Remark 4.1. *Everything in the body is under the immunue system's surveillance however this can be dangerous as it can potentially harm us such as autoimmune disorders, immunity against transplants, etc.*

There are 2 different branches of immune system and they are non-specific (innate) and specific (adaptive). Innate is the first line of defense of the immune system; it does not require to recognizing the pathogen i.e. it attacks all pathogens the same ways thus is fast and constant. Adaptive, on the other hand, requires pathogenic recognition and takes time to develop cells to respond against them; even so, it would be much faster when that pathogen is presented in the body again.
In this chapter, we will mainly look at **How does the immune system recognize "foreign" cells? How is the immune system organized? And what types of cells are involved?**

Before doing this, we would like to present they ways scientist make discoveries. Generally, scientific breakthrough is mainly by 3 ways: accidental, genelization hypothesis, serendipity (happy accidents).
Sometimes, scientific discoveries are accidental such as the *discovery of quinine as medication for Malaria.* A man from the Andes suffers from malarial fever and while in the middle of the forest, he was very thirsty. He decided to drink from a pond near by the tree called "Quinoa-Quinoa" and his fever is miraculously cured. Turns out the chemical in the pond from the tree is Quinine.
Discoveries can also stem from generalize and push a hypothesis further, such as in the case of Alexander Fleming. He was a biologist whom found a fungus growing on his agar plate where the bacteria cannot grow. He looked at this further can develop penicillin.

The first **vaccination** for smallpox comes from the cowpox (vaccination is the same as *immunization* but the later is more scientifically correct).

4.1 Components of the Immune System

Although it is true that the immune system diffuse through every where in the body however, we still have a localize place where the immune system would develop. We can divide the components that make up the immune system into 2 part: lymphoid organs and immune cells.

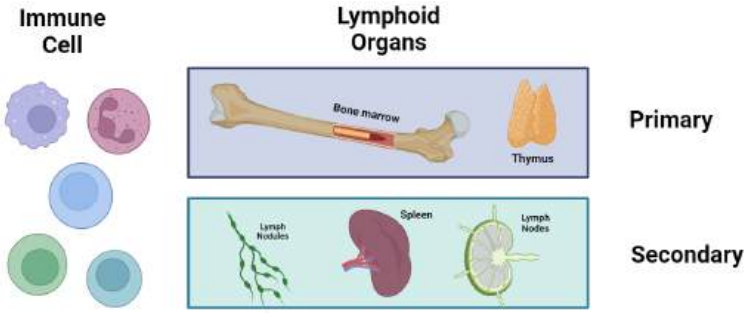


Figure 4.1: Components of the immune system.

4.1.1 Lymphoid Organs

The **lymphoid organs** are organs that made up the lymphatic system. They are also divided into primary and secondary.

The **primary lymphoid organs** are where the immune stem cells divide and develop which consists of the bone marrow and the thymus. We begin with the **bone marrow** where the hematopoiesis of immune cells such as **B-cells** and **immature T-cells** happens. This is also where the maturation of B-cell happens too.
The **thymus**, located superior to the heart, is where the T-cells mature. It also contains dendritic, epithelial cells and macrophage. This is also the site of T-cell maturation.

The **secondary lymphoid organs** are the site where most immune responses occurs and it consists of the lymph nodes, spleen and lymphoid nodules. **Lymph nodes** scatter all around the body and are the sites where microbes are filtered and phagocytize by macrophages. The **spleen** is the largest lymphoid organ, located next to the pancreas, its main job is to remove microbes and old RBCs. **Lymphoid nodules** locate in the tonsils, as well as every mucus-filled place that has contact with the external environment. It also contains lymphocytes.

Remark 4.2. *The lymphatic system is much more permeable than blood vessels hence bacteria and pathogens would be able to move into it and gets trap.*

4.1.2 Immune Cells

The **immune cells** are essentially WBCs or leukocytes. When looking at the development of the pluripotent stem cell into WBCs, we can trace into 2 lineages: the lymphoid and the myeloid.

When the pluripotents develop into lymphoid progenitor cells, the progenitor will then become **lymphocytes**. These lymphocytes are **B-lymphocytes (B-cells)**, which can initiate antibody-mediated immune responses; T-lymphocytes, which can be further classify into **helper T cells (AKA CD4+ cells)** and **cytotoxic T cells (AKA CD8+ cells)**. There are also **natural killer cells (NK cells)** which can kill other cells.

When the pluripotents develop into myeloid progenitor cells, the progenitor will then become **eosinophils**, which can destroy particles; **basophils** along with **mast cells** which can produced various signalling chemicals; **neutrophils**, which can phagocytizes other cells; **monocytes**, which can become macrophages and dendritic cells.

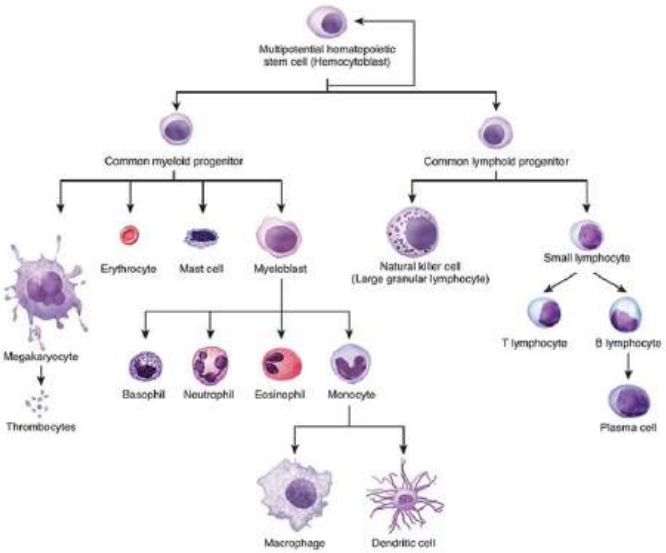


Figure 4.2: lymphoid and myeloid lineage.

The following page will be the table of all the immune cells along with their site of production and functions.

Name	Site Produced	Functions
Leukocytes (white blood cells)		
Neutrophils	Bone marrow	Phagocytosis Release chemicals involved in inflammation (vasodilators, chemotaxins, etc.)
Basophils	Bone marrow	Carry out functions in blood similar to those of mast cells in tissues (see below)
Eosinophils	Bone marrow	Destroy multicellular parasites Participate in immediate hypersensitivity reactions
Monocytes	Bone marrow	Carry out functions in blood similar to those of macrophages in tissues (see below) Enter tissues and transform into macrophages
Lymphocytes	Mature in bone marrow (B cells and NK cells) and thymus (T cells); activated in peripheral lymphoid organs	Serve as recognition cells in specific immune responses and are essential for all aspects of these responses
B cells		Initiate antibody-mediated immune responses by binding specific antigens to the B cell's plasma membrane receptors, which are immunoglobulins Upon activation, are transformed into plasma cells, which secrete antibodies Present antigen to helper T cells

Name	Site Produced	Functions
Leukocytes (white blood cells)		
Cytotoxic T cells (CD8 + cells)		Bind to antigens on plasma membrane of target cells (virus-infected cells, cancer cells, and tissue transplants) and directly destroy the cells
Helper T cells (CD4 + cells)		Secrete cytokines that help to activate B cells, cytotoxic T cells, NK cells, and macrophages
NK cells		Bind directly and nonspecifically to virus-infected cells and cancer cells and kill them
		Function as killer cells in antibody-dependent cellular cytotoxicity (ADCC)
Plasma cells	Peripheral lymphoid organs; differentiate from B cells during immune responses	Secrete antibodies
Macrophages	Bone marrow; reside in almost all tissues and organs; differentiate from monocytes	Phagocytosis Extracellular killing via secretion of toxic chemicals Process and present antigens to helper T cells Secrete cytokines involved in inflammation, activation and differentiation of helper T cells, and systemic responses to infection or injury (the acute phase response)
Dendritic cells	Almost all tissues and organs; microglia in the central nervous system	Phagocytosis, antigen presentation – PROFESSIONAL APCs
Mast cells	Bone marrow; reside in almost all tissues and organs; differentiate from bone marrow cells	Release histamine and other chemicals involved in inflammation

Now that we've got all the components of the immune system, we will now be looking at them in action.

4.2 Innate Immune Response

The **innate (non-specific) immunity** is the body's ability to defend against microbes and pathogens without the need to recognize them (hence non-specific and much faster). We can divide innate immunity into the first line and second line of defense.

Remark 4.3. *The second line of defense can also be divided into cell-mediated and humoral-mediated.*

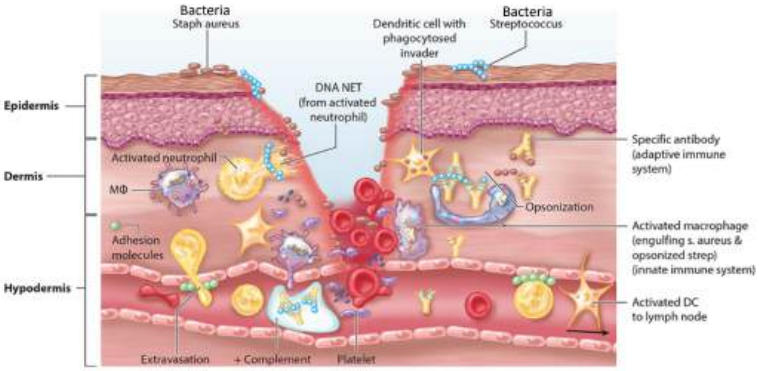


Figure 4.3: First line of defense is breach activated the second line of defense against infections.

4.2.1 First Line of Defense

The first line of defense for the innate immunity is the **physical barrier** of the body. This barrier is the most apparent with the skin. It is water resistant, prevents entry of foreign substances. There are also tight junctions in epithelial cells, mucus, hair and celia that made it difficult for pathogen to go further. These cells can release chemicals and secretion (such as sebum, lysozyme, gastric juice etc.) that create an unpleasant environment for microbes.

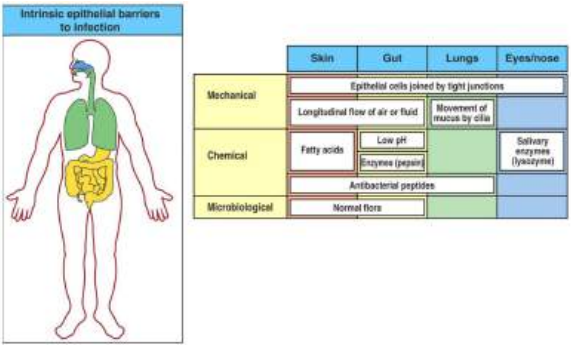


Figure 4.4: Different mechanism for the first line of defense

Even when we have a system of physical barrier, there are still many ways that this barrier can be broken which allow pathogen to enter and infect.

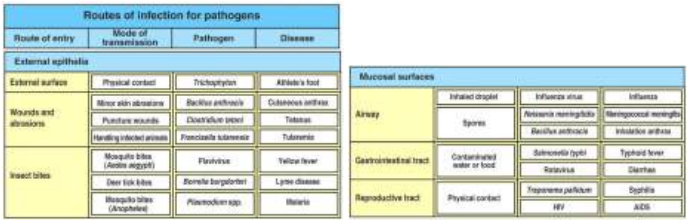


Figure 4.5: These are the route of infection that pathogens used (not on the exam)

If the first line of defense is breached, the second line of defense will be activated.

4.2.2 Second Line of Defense: Humoral-Mediated Immunity

The humoral mediated immunity depends mostly on the humoral factors.

Definition 4.3. **Humoral factors** are factors (macromolecules such as proteins) and antimicrobial substances (such as C-reactive proteins, complements and cytokines) that are transported by the circulatory system that can help with the innate immune response.

When there is damage to the tissue that pass through the first line of defense, the humoral mediated immunity will be activated via the process of **inflammation** and/or fever. Inflammation can be recognized by the following signs and symptoms: redness, heat, pain and swelling. As for the process of inflammation, it follows 3 stages:

1. **Vasodilation:** The blood vessel diameter will widen increasing the permeability of capillaries (allowing more plasma to pass through thus causes *swelling*).

   Remark 4.4. *This is where the cell mediated response begins and humoral response stop since it will involve mostly the neutrophil! (explain in the next lecture)*

2. **Emigration of Phagocytes**

3. **Tissue Repair**

Humoral substances such as interferons, complements and Fe-binding proteins are substances that would discourage the growth and spread of pathogen (antiviral, antimicrobial, etc.)

Interferons

Interferons are cytokines that are released in response of a viral infection. They are made up of 2 group: type I and II interferons (we will only look at type I). Type I interferons are proteins that can bind non-specifically inhibit the replication of virus in host cells. Its mechanism is as follows:

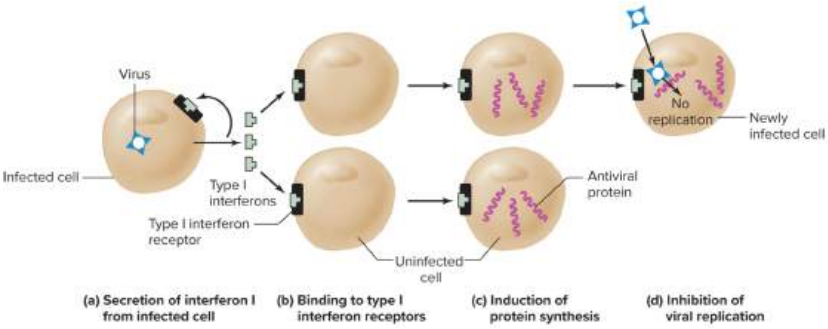


Figure 4.6: Mechanism of interferons

1. At first when host cells will be infected and the viral genome will use the host machinery to replicate itself. The infected host will release type I interferons will be release to bind to other cells.

2. These interferons will go and bind to the membrane receptors infected host cells and even other non-infected cells.

3. The binding of interferons will lead to the cell mass-producing **antiviral proteins**.

4. If the cell is already infected, antiviral proteins will inhibit the further viral replication; if the cell isn't then it would inhibit any viral genome if they enter.

Remark 4.5. *Type I interferons are also responsible for killing tumor cells and causing fever.*

Complement

Definition 4.4. A **complement** is a family of 30 plasma proteins with different functions. They activate each other through a large cascade.

Complement is another mean of killing pathogens prior to phagocytosis. Because complement is activated is a cascade, once 1 complement is activated, the signal will be amplified large scale to many other unactivated complements. Due to the amount of plasma proteins involved, they will create a complex system however we will look at 1 of them that is the $C3$ central protein.

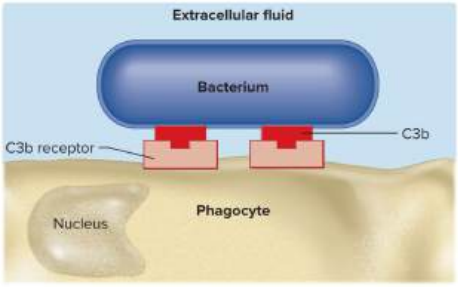


Figure 4.7: C3b is released as opsonin

Definition 4.5. **Opsonin** is an antibody or a substance that can bind to the pathogen which could facilitate the process of phagocytosis.

When C3 is activated, it can decompose to **C3b** which can have many function. Firstly, it can act as an opsonin by *non-specifically* binding to bacterial surface on 1 side and leaving the other side free for the receptor of phagocytes to bind to (activate phagocytosis). C3b is also part of a proteolytic enzyme that can initiate a cascade creating a **membrane attack complex (MAC)** that can "poke holes" in pathogens making water and other molecules enter them.

All in all, the complement system has 3 different pathway that it can takes (2 of them is either innate or adaptive, 1 of the we will not look at) which would result in the activation of complement leading to either recruitment inflammatory cells, opsonization or lysis of pathogens.

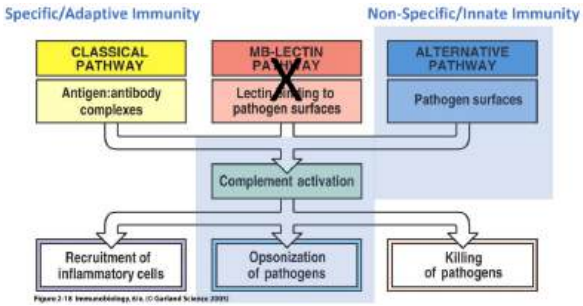


Figure 4.8: Different pathway of the complement system.

Iron Binding Proteins

Last but not least are the iron binding protein that can help out with our body immunity such as **transferrin**, **hepcidin**, etc.

4.2.3 Second Line of Defense: Cell-Mediated Immunity

Cell-mediated immunity is a type of innate immunity carried out directly by specific types of cell. These cells we'll be looking at is the **natural killer cells** and **phagocytes**.

Natual Killer Cells

Natural killer cells (or NK cells) are lymphocytes that are similar to cytotoxic T cells. They target and kill viral-infected and cancerous cells by directly bind to them and release chemical which can lead to the death of infected cells.

Remark 4.6. *They're part of the innate immune response so still target cell indiscriminately.*

If they target cell indescriminately like that...**how would they know which is the infected which isn't?** Well, there is a type of membrane protein called the **membrane histocompatibility complex (MHC)** that NK used for recognition (more later on MHC).

Remark 4.7. *All cells (except a few) would have a type of MHC called MHC I on their membrane surface.*

Using the above remark, NK cells will bind to this MHC I of cells. If the cell isn't infected, MHC I is expressed and when NK cells bind to it, they won't be activated. If the cell is infected, MHC I will be altered or absent and when there isn't a correct binding of MHC I, NK cells will be activated and kill the cell.

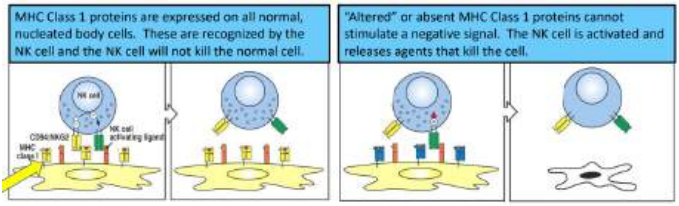


Figure 4.9: NK cells activation and MHC binding.

Phagocytes

The next cell to look at are phagocytes (cells that can perform phagocytosis). There are 2 main types of phagocytes: **fixed-tissue macrophages**, which already present at a tissue site and **neutrophils**, which has to be recruited to the site. Macrophages along with dendritic cells are derived from **monocytes**.

We've seen phagocytosis before so we'll summarize its process of digesting bacteria. First, bacteria will be recognized and captured by the pseudopodia of the phagocytes. This forms a vesicle as the bacteria is brought into the phagocytes. **Lysozyme** (vesicle digestive substances) inside the phagocytes will merge to the bacteria which will form a **phagolysosome**. The digestive substance will breakdown the bacteria; and any useful component will stay in the phagocytes while the rest will be released.

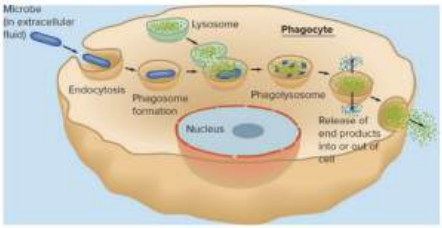


Figure 4.10: Mechanism of phagocytosis.

Once again, this types phagocytes attack indiscriminately so...**how can phagocytes recognize bacteria?** Well, phagocytes will look or unique structures that human cells do not have but microbes do, these structure are called the **molecular signature of infections**.
When looking at bacteria, molecular signatures are the **pathogen-associated molecular patterns (PAMPs)**. For 2 main strains of bacteria: positive and negative, we found the PAMPs as **lipopolyssacharide (LPS)** and **peptidoglycan (PGN)** respectively.

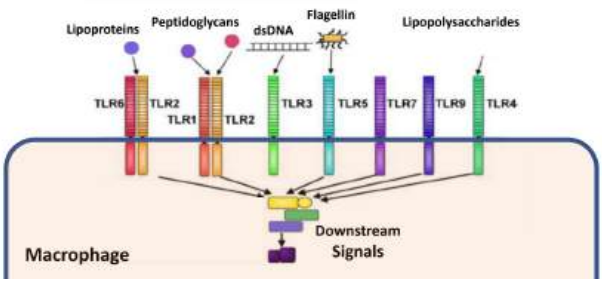


Figure 4.11: Different TLRs of macrophage.

When looking at the macrophages, they have surface receptors called **pattern recognition receptors (PRRs)** or **toll-like receptors (TLRs)** that

can recognize the PAMPs. Once macrophages recognize PAMPs it will sends signals for neutrophils and other macrophages to come and start inflammation.

Inflammation

Although we did mentioned inflammation before, we will now take a deeper look at it. Supposed that the first line of defense is breached (maybe by a splinter), then bacteria and microbes will enter the tissue which would be phagocytize by macrophage. These macrophages will send signals and inflammation begins:

1. **Vasodilation:** The blood vessel diameter will widen increasing the permeability of capillaries (allowing more plasma to pass through thus causes *swelling*).

2. **Emigration of Phagocytes:** This step consists of smaller intermediate steps. We begin with chemotaxis) where signals (from the macrophage), such as **chemokines/chemoattractants**, stimulate the movement of phagocytes (specifically neutrophils) and attract them to the site of injury. **Margination** happens when these neutrophils adhere to the surface of the endothelial cell. Then **diapedesis** happens when the neutrophils squeeze through the pores between 2 endothelial cells (possible thanks to vasodilation).

3. **Tissue Repair:** Cells will be recruited to repair the damaged tissue (won't be looked at in this course).

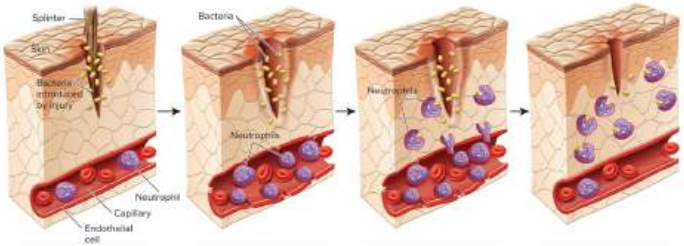


Figure 4.12: Steps of inflammation

One thing to know that during inflammation and phagocytosis, the neutrophils can die. Once they're dead, they form a **neutrophils extracellular**

traps (NETs) which are made from granular bound chromatin and selected cytoplasmic proteins. The NETs would trap the bacteria in place. The combination of dead bacteria and neutrophils would form a **pus** that the body tend to get rid of externally.

Now, when our body has an infection, we don't only stop at this point (even though for smaller infection, innate is all needed) but ask ourselves ... **what if the infection happens again?** Or **would it be better to have a system to keep track of all the infection so when the next happens, it will be more efficient?** Well...this is where we shift ourselves to the *adaptive immune response*.

4.3 Adaptive Immune Response

Before getting to the adaptive immunity, let's estabilish certain terms

Definition 4.6. **antigens** are substance that would cause a release and binding of antibody: **anti**body **gen**erator.

Other definition of antigens would be *substances that can induce immune responses* but we would consider this as **immunogen** (more broad). When an immunogen produce a vigourous immune response (allergic reaction) would be an **allergen**.
Antigens can be a cell or just part of a cell. It does not have to be a microbe e.g. pollen, incompatible blood transfuse, transplants etc. On each antigen, there are regions called **epitode** that immune cells can recognize. This epitode also lay the development of the adaptive immune system.

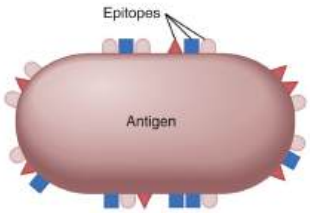


Figure 4.13: Antigens and their epitodes

Recognition of these epitode is mediated by the **major histocompatibility complex (MHC)** (like that of the NK cells). There 2 molecular classes of MHC: **MHC-I** are MHC expressed on all nucleated cells e.g. in humans

we have **human leukocytes antigen complex** HLC-A, B and C; and **MHC-II** are MHC expressed on **antigen presenting cells** (macrophages, dendritic and B-cells) e.g. HLA-DP, DQ and DR.

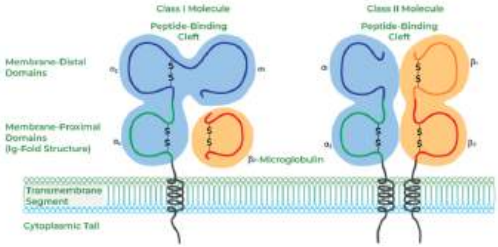


Figure 4.14: MHC I and MHC II

Remark 4.8. *Only twins would have the same MHCs on their cells, otherwise the MHCs are different from each individuals.*

Remark 4.9. *T-cell receptors recognize antigens only when they're associated with the MHC II.*

Now we can get into the adaptive immune response. The **adaptive immune response** are the body's ability to protect itself from **specific microbes/substances** that involves in keeping memory of previously encountered antigens. Like the innate, the adaptive is classified into 2 types: humoral (antibody-mediated) immunity and cell-mediated immunity. In order for any of these immunity to be activated, B and T-cells must be able to recognize the antigens then be activated and launch an attack on them.

4.3.1 Functions and Origins of B and T lymphocytes

Although we've previously discussed about B and T lymphocytes, we will know look deeper at their origins. The pluripotent stem cell will divide into the B and T lineage
On the B lineage, the stem cell will develop and matured into B-cells in the bone marrow. After it will travel to the secondary lymphoid organs. Once B-cells are activated by antigens, it will become plasma cells which releases antibody.
On the T lineage however, the stem cell will develop into immature T-cells in the bone marrow. They will travel to the thymus to mature into either cytotoxic T cell (T_C) or helper T cells (T_H). They can travel to the secondary lymphoid organs and be activated by antigens.

Remark 4.10. *The maturation of NK cells once leave the bone marrow is unknown*

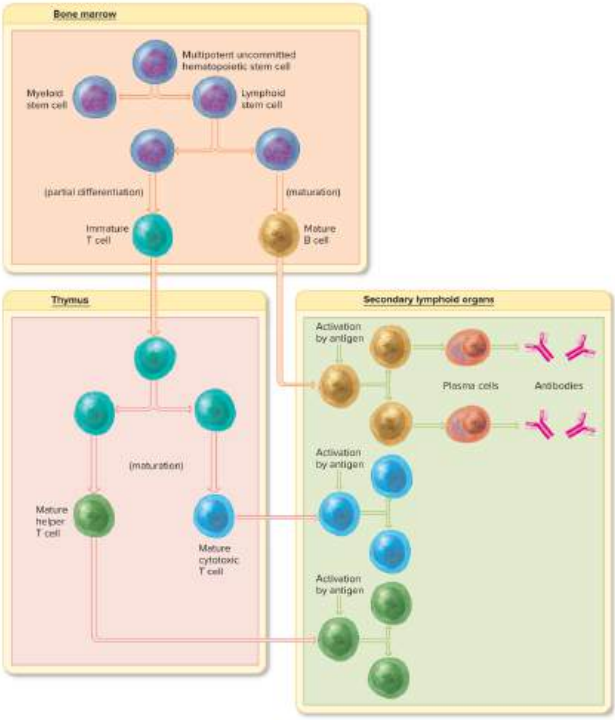


Figure 4.15: Origin of B and T cells and their development

When activated, B-cells would differentiate into plasma cells and release antibodies that can bind to antigen at their epitodes. This is essentially the antibodies-mediated response. These antibodies can guide phagocytes, NK cells, etc. to attack the antigens. On the other hand, T-cells, which make up the cell-mediated immunity, is divided into 3 types: T_C, T_H and regulatory T cell T_R. Upon activation, T_C can directly target specific antigen, T_H can release chemokines that can induce the function of T_C and even B-cells; and T_R which can stop the adaptive immune system from going "rogue" and overproduce.

Remark 4.11. *T_R suppress the immune system from attack its own proteins. If this suppression fail, the immune system can go against itself creating a*

*disease known as **autoimmune disease**.*

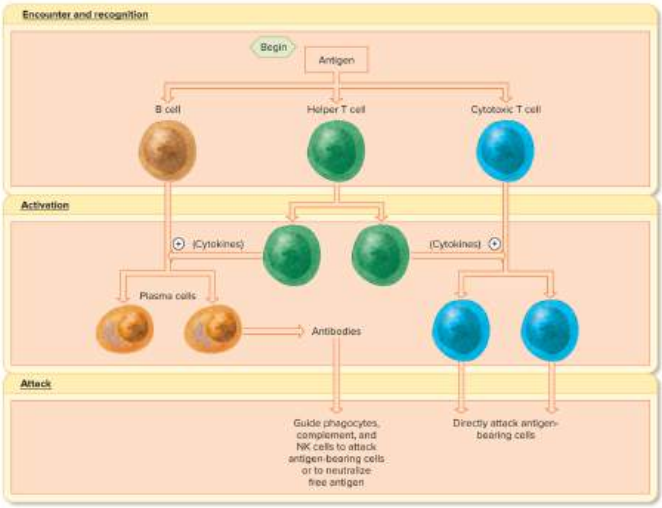


Figure 4.16: Activation of B and T cells

We've repeatedly said many time "activation of B or T-cells" but the real question is **how do we activate B-cell or T-cell?**...Well, this is where we make the shift from the innate to the immune response using **antigen presenting cells (APCs)**

Remark 4.12. *Activation of T_H can also activate the rest of B-cells and T-cells.*

4.3.2 Antigen Presenting Cells and Adaptive Activation

APCs are cells that can ingest antigens then presents its constituents to adaptive immune cells to activate them. Most of APCs are **interdigitating dendritic cells ("professional" APC)**, macrophages and even B cells.

The steps to present the bacteria constituents is as follows:

1. APC will ingest and breakdown antigens into peptide fragments.
2. APC will synthesize and package MHC II.

3. Antigens peptide fragments will be bounded to the MHC II.
4. MHC II peptide complex will be brought to the surface of the APC for recognition by T_H

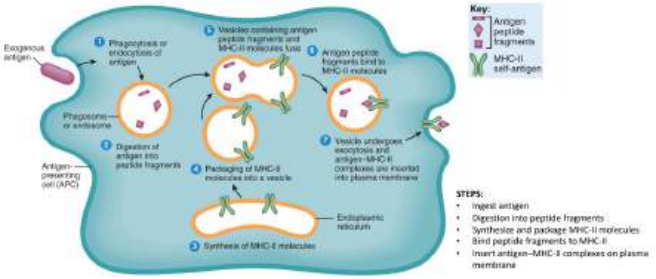


Figure 4.17: Mechanism of APCs

This process happens usually at the site of injury (tissue). After which, APCs will travel to the lymph nodes where B and T-cells are present. At the lymph node, the APCs will present its MHC II antigen peptide complex to the receptor of a T_H (abbreviated TCR).

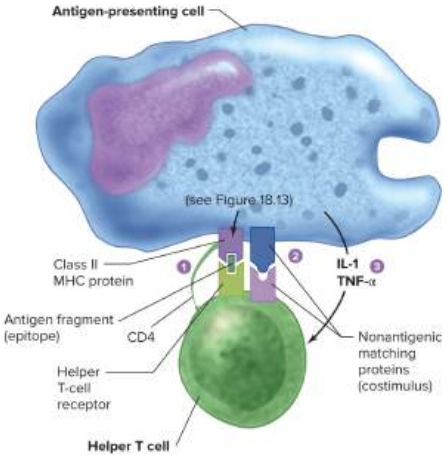


Figure 4.18: APC bind with T_H at the TCR as well as a co-reception site.

However, in order for T_H to not activated by a random APCs, the APCs must have **co-reception**. Co-reception is simply another receptor (B7) from

the APCs to bind with another receptor (CD28) from the T_H making sure that its a good match. Lastly, to activate other T_Hs, APC will release cytokines (IL-1, TNF-α, etc.) to stimulate them. Thus T_H will be fully activated when B7 bind with CD28, MHC II peptide complex bind with TCR and cytokines release of APCs.

Checkpoint Inhibition

All biological processes need to be able to shut down. Similarly, we cannot have the APCs bind and activate T_H indefinitely. This is where checkpoint inhibition comes to play.

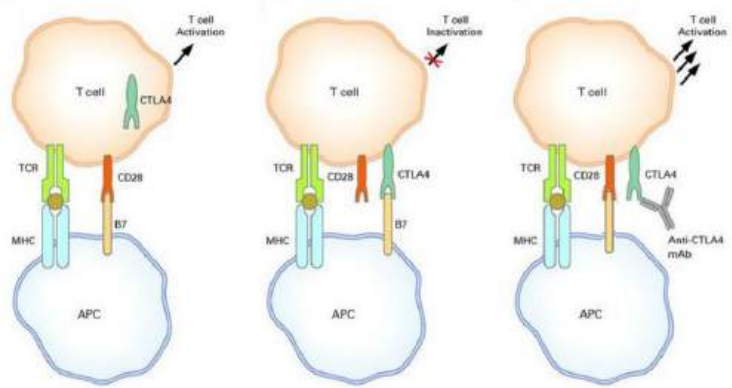


Figure 4.19: Checkpoint inhibition and immunotherapy (antibody: anti-CTLA4)

T_H will present another receptor called CTLA4 or PD-1 which would displace the binding of B7 to CD28. When B7 is displaced to bind with CTLA4, CD28 unbinded thus T_H is deactivated.

Remark 4.13. *Some cancer cells used checkpoint inhibition to "hide" from the immune system by not activating the T_H. To combat this, scientist introduce immunotherapy where an antibody (Anti-CTLA4) will bind to CTLA4 thus disabling the displacement of B7 $\Longrightarrow$ T_H activation.*

4.3.3 Antibodies-Mediated Immune Response

Like we've said before, B-cells can also acts as an APC by presenting the antigen peptide to T_H. Once T_H is activated (by direct activation from the B-cells peptide presentation or other APCs), one of its receptors called

CD40L will bind with the **CD40** of the B-cell. Cytokines such as IL-4, 5 and 6 will be release from the T_H to the B-cell. This amount of stimuli will cause B-cells to undergo rapid differentiation and maturation into **plasma cells.** These plasma will produce specific antibodies to the epitode of that antigen. Or the differentiation will become memory B-cells.

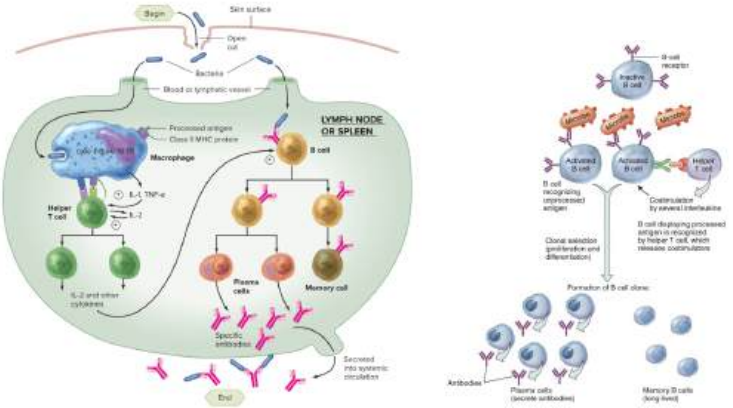


Figure 4.20: T_H cell and activation of B-cells.

This process of B-cells differentiation is known as **clonal selection**. Clonal selection would produce plasma cells (which then produce specific antibodies) and memory cells which can remember these antigen and will rapidly produce them if the infection happens again.

Antibodies: General Structures

An infected and normal patient serum is put under protein electrophoresis. As usual, we see the spike for the plasma proteins albumin is high for both individual however...for the reading of the infected patient, we see there is another spike for $\gamma-$globulins. (see Figure 4.21)

Essentially, **antibodies** that plasma cells released to counter infections (and in generals) are these $\gamma-$globulins, which are also called **immunoglobulins (Ig)**. They're made from 2 pairs of identical polypeptide heavy chain and light chain (4 polypeptide chain in total). Within the light and heavy chain, there are 2 regions: variable and constant region.

The **variable region** also known as the **antigen fragment binding (FAB) region** is where the antigen will bind to. The **constant region** or **frag-**

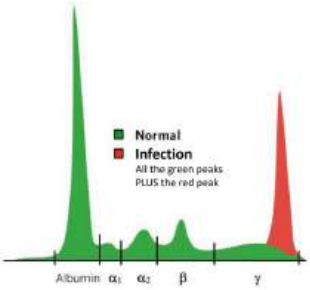


Figure 4.21: Protein electrophoresis of infected and normal serum.

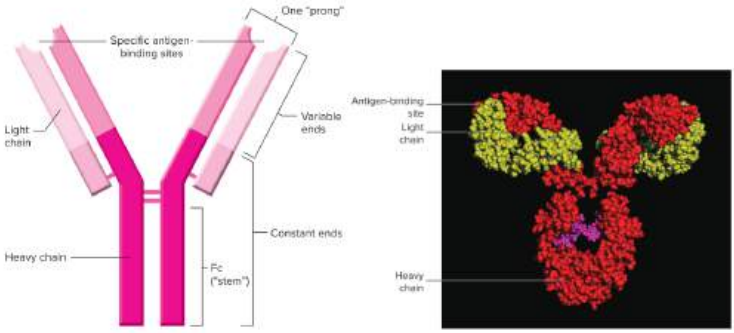


Figure 4.22: "Anatomy" of antibodies.

ment crystallize (F_C) region is the same for all antibodies of the same family/class.

Remark 4.14. *The FAB region is highly variable and is made up of lots of peptide combination which means that can change to be specific for a type of antigen.*

Remark 4.15. *Antibodies can also be receptors of B-cells.*

Now the question arise is that **how can an antibody become specific?** Well, first the B or T cell must be in a state of **immunocompetence**, which simply means mature, can recognize antigen and activate immune response. Once this is established, we will now look at the molecular level when making antibody with specificity.

Both heavy and light chain of the antibody has genes to encode it in B-cells; specifically the FAB region has multiple gene to code for it. We divide the multiple gene that encodes for it as V, D and J "section" and the last gene encodes for the F_C region (C section). Each of these section will have their own genetic segment that RNA polymerase can transcribe: V section has ~ 50 segments (V1-50), D has ~ 26 segments (D1-25) and J has ~ 7 segments (J1-6). The antibody is made up from combining 1 segment of each of these 3 sections together + the F_C region gene. A special genes call **recombination activating genes (RAGs)** encode for a protein complex which would recognize these genes segments, splice them and recombine them for transcription and ultimately translate into their respective polypeptide chains.

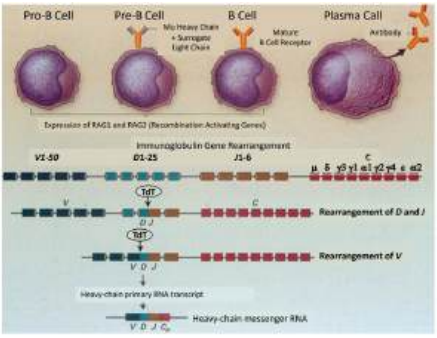


Figure 4.23: The process of making specific antibody. It says that this is for the heavy chain but the same would be the light chain and its FAB region.

Remark 4.16. *With this amount of VDJ segments, we can only make around 10,000 different antibody combination.*

To make the number of possible antibody combination increase, a specialized DNA polymerase called **terminal deoxynucleotide transferase (TDT)** would come and add 1 or multiple nucleotide to the end of any of these segments (beside F_C). When TDT add nucleotides like this, it will cause a **frame shift mutation** thus creating a different reading frame for transcriptase each time $\Longrightarrow$ drive up the amount of antibody combination to "theoretically infinite". Thanks to this enormous amount of possible antibody, creating an antibody specific to any antigen epitode is possible.

Although FAB region is important for antigen specificity, its F_C region

also make contribution. The F_C region will be different from classes of antibodies thus we can divide the antibodies according to their F_C region: IgG, IgA, IgM, IgD and IgE. **IgG** are the most abundant type of antibody in the serum, **IgA** are found in **mucosa associated lymphoid tissue (MALT)** and from breastmilk.

Remark 4.17. *Mothers provide additional antibody (IgA) for their babies by breast feeding.*

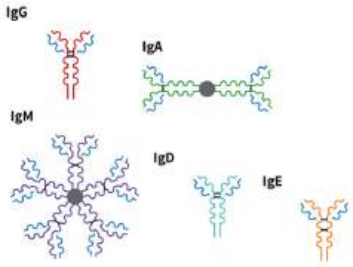


Figure 4.24: Different antibodies classes according to their F_C region.

IgM are antibodies that first formed against infection and can activate complement, **IgD** are antibodies for prenatal babies and **IgE** are antibodies for allergies.

Antibodies: Functions

Antibodies has a variety of functions when it comes to counter an infection. First, it can neutralize antigen by binding to bacteria or toxins. Once bound, the antibody will prevent it to bind somewhere else or propagate. Second, it can agglutinate antigen; once bind to antigen, it can use its other FAB region to bind to a different antigen thus clumping them together.

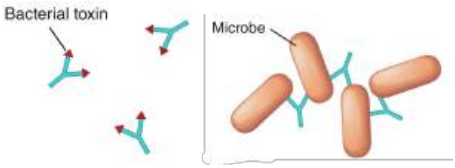


Figure 4.25: Antibodies neutralize and agglutinate antigens

Third, it can precipitate antigens. In this case, antibodies will bind to soluble antigens and these antibodies-antigens complex will form a *lattice* together making them insoluble thus precipitate. Fourth, it can activate the classical complement pathway. Once bind to the antigen, it can recruit/activate complement proteins and form MAC, or it can mediate the process of opsonization by phagocytes.

Figure 4.26: Antibody recruit complement protein and mediate opsonization

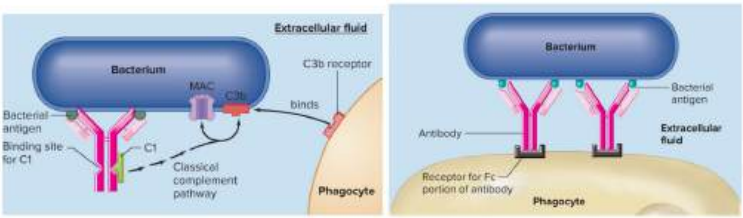


Figure 4.27: Antibody activate MAC, C3b receptors and enhance phagocytosis.

Last but not least, antibodies create a direct connection to the activation of cytotoxic T-cells (CD4+) which will be the beginning of the cell-mediated response (we'll be looking at in the next lecture).

Antibodies: Response and Production

Now we will look at the production of antibodies according to antigen response. When our body first got infected with an antigen, the body will try its best to produce a specific antibody in a short amount of time. This will result in an increase of antibody but then these amount of specific antibody would be enough to fight of the infection. Once infection is over, memory B-cells will remember these antigen and prepare for a potential future attack. If the body is infected the second time with the same antigen, there will be an immediate spike in antibody production since memory B-cells

already know how to make them to counter the antigen.

We can see this experimentally by tracking the concentration of antibody after the first and second injection of the same antigen. At first there would be a small spike then after the second, there will be a large production of antibody.

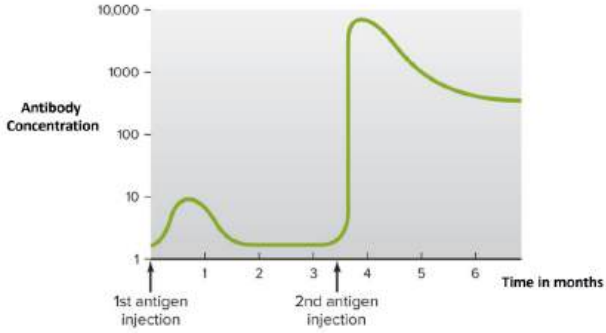


Figure 4.28: Antibody concentration after the first and second antigen injection.

Not only that, we can also see antibody specificity as it being produced during infection. When we look at the antibody titer in the first time of infection, we can see that the body production first response antibodies (IgM) will increase similar to that of specific antibodies (IgA).

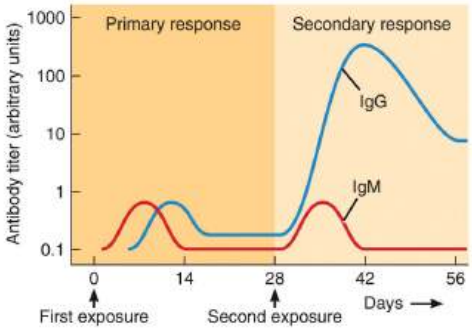


Figure 4.29: Changes in specific antibodies production in first and second response.

On the second infection however, the amount of IgM produce will be

the same but because we have memory B-cells for this infection, the production of specific antibodies IgA will spike much higher.

Remark 4.18. *The immune response when the body encounter antigens for the first time is called* ***primary response*** *while the immune response for the second time is called* ***secondary response***

Active and Passive Antibody Immunity

Antibody-mediated immunity can be divided into 2 types according to their response: active and passive and each of these can be further subdivide into natural and artificial.
An **active immunity** is when the body's immune system has a long-lasting protection against foreign substances, it's due to the involvement of memory B-cells. We can induce active immunity naturally by exposing the body to antigen by chance; we can also induce this artificially by purposely exposing the body to antigens, this process is known as **vaccination** or **immunization**.

Example 4.3.1. A person who is exposed to the flu virus by accident would develop active immunity "naturally" while a person who purposely exposed themselves to the flu virus by injecting flu vaccine would develop active immunity "artificially".

Remark 4.19. *Majority of vaccine is a modified and sometimes less potent version of the antigen. It can be a small quantities of dead pathogens, toxins or derived antigenic molecules from the original antigens.*

A **passive immunity** is when the body receive antibody from others for temporary protection, thus require no memory B-cells. Passive immunity can be achieved naturally such as the transfer of IgG from the placenta to the fetus or IgA found in breast milk. It can also be achieved artificially by injecting the body with serum containing antibodies from an organism already has immunity.

4.3.4 Cell-Mediated Immune Response

The major tissues that play the main role in the cell-mediated immune response is the T-cells. But before getting into its mechanism, let's revisit some of the previous concepts of which we will have a different outlook to them.

Just like antibodies, T-cells would recognize antigens to eliminate them, but then **how can our body make sure that antibodies or in this case T-cells will not attack our owns cell?** Well, under normal circumstances, antibodies are not produced to attack or bind to self-cell receptors (AKA **self-antigens**).

As our body matures, we will develop **immune tolarence** which is the immune system's ability to not attack certain antigens (self-antigens). The process of immune tolerance would able clonal deletion and inactivation of T-cells if they were to recognize and attack self-antigens.

Example 4.3.2. Normally, T-cells must be able to recognize MHC II molecules (of APCs and others) and cannot recognize MHC I or protein cells. If T-cells cannot recognize MHC II or able to recognize MHC I of protein cells, it will be **negatively selected** (eliminated).

Remark 4.20. *Typically, our body destroy around* 95% *of the produced T-cells. This is because of the enormous combination of possible T-cells receptor (similar to antibodies), it's much more efficient to just to kill them off instead otherwise.*

Even when the body kill most of produced T-cells, the rest is still over billions of other T-cells in secondary lymphoid organs to detect foreign substances.

Remark 4.21. *Cytotoxic T-cells has glycoproteins called CD8+ so some would called it CD8+ cells while helper T-cells would have CD4+ therefore CD4+ cells.*

With our knowledge so far about infection and fighting of antigens, we can in fact classify antigen into 2 types

Definition 4.7. **Endogenous antigens** are antigens that is produced by the self-cells i.e. foreign substance "hijacked" the self-cells (host) machinery to make themselves.

Definition 4.8. **Exogeneous antigens** are antigens that are foreign to the body.

Most of the time, T_C target infected by endogenous antigen. Cytotoxic T-cells or cell-mediated immunity can be activated by 2 mechanism follow one another.

Activation of Cytotoxic T-cells

In this mechanism, the after APCs has present the antigen peptide via MHC-II to helper T-cell, it will release cytokines such as IL2 or INF that can partially activate T_C. T_C's receptors will bind to the MHC-I of an infected cell where the antigen fragment is presented. After this binding, T_C is fully activated and release granzymes and perforins which cause the infected cells' apoptosis.

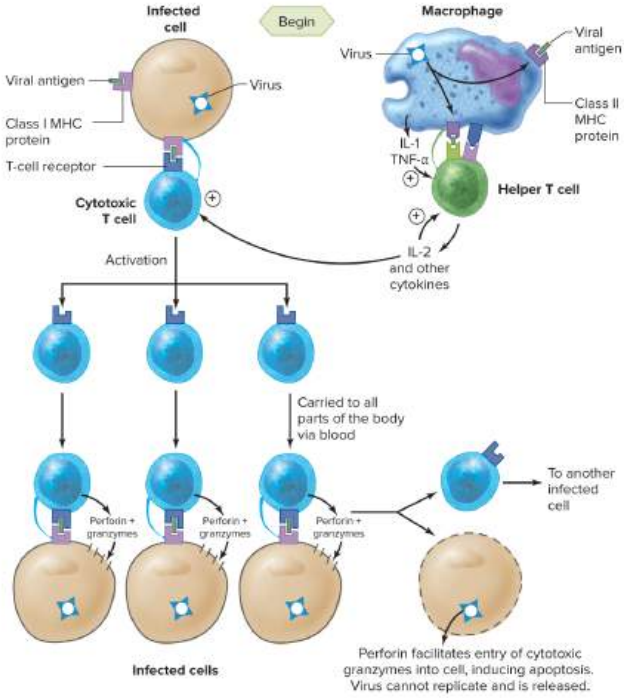


Figure 4.30: Complemetary activation of T_C.

Then like B-cells that create memory B-cells, T_C will create memory T-cells for future attack.

Remark 4.22. *Activation and de-activation of T_C also dependent on the check point inhibition i.e. displacement of B7 to CTLA4 instead of CD28 will inactivate T-cells.*

Factors That Alter Infection Resistance

Protein-calorie malnutrition, **stress and negative state of mind** can cause a decrease in resistance to infection; **sleep deprivation** can also decrease immune function while **pre-existing disease** can make the body more susceptible for infection.
Best way to counter these are through modest exercises/condition and balance diet.

4.4 Disruption of the Normal Immunity

We will now look at certain disease/disorder that would disrupt the normal immune response. There are mainly 2 cases: under-active (or **immunodeficiency disease**) and over-active immune response.

4.4.1 Immunodeficiency Diseases

Immunodeficiency Diseases are diseases where the immune system is weakened and is not as active as before.
Certain example would be **acquired immunodeficiency syndrome (AIDS)** which is the result when the body is infected with HIV virus. This lentivirus is very perculiar as it does not infect normal cells but directly go for vitals immune cells such as T_H, macrophages and dendritics. AS HIV infect more T_H, there won't be any immune cells to even combat against simple infection thus patient developped AIDS.
The more deadly immunodeficiency disease is **severe combined immunodeficiency disease (SCID)**. This disease is rare and is caused by a genetic mutation where there is a malfunction or even absence of B and T cells or even NK cells.

4.4.2 Overactive Immune Responses

There are many cause to an overactive immune response that would be harmful for the body. We begin with a tissue or graft transplantation.

Tissue Graft and Transplantation Reaction

Although having a tissue graft or transplantation is good for the body (probably certain tissue or organ is damaged), the immune system doesn't care. The immune system cannot recognize what is "good" or "bad" for the body,

it only sees what is foreign or not foreign to the body.
In such scenario, the MHC-I proteins on the grafts cells would be different from that of the recipient. The recipient's T_H will see this as foreign cells, and start an immune response which would damage the transplantation. A way to counter this is to: **use radiation to destroy new dividing cells**, **drugs that decrease T-cells population/division** and **drugs that can block T_H's cytokines production** (such as cyclosporine).

Blood Transfusion Reaction

Prior to the discovery of blood group, doctor would transfuse blood to patients without testing. This led to many patient not recover from the transfusion but would get worst. This is because blood from 1 person doesn't necessarily the same to another.

Although blood lacks MHC, they have carbohydrates and proteins. With this, we divide blood into group correspond to the **surface antigen** (on the RBCs) and **antibodies** found in the plasma. For a **type A blood**, the RBCs have A antigen and the plasma has B antibodies; **type B blood** would be the inverse. For **type AB blood**, they would have both A and B surface antigen and have no antibodies. As for **type O blood**, the RBCs has no surface antigens but has both A and B antibodies.

Remark 4.23. *Another proteins can be found in certain individual are **Rh factor**. Individual have Rh factors are "Rh positive" otherwise it is "Rh negative".*

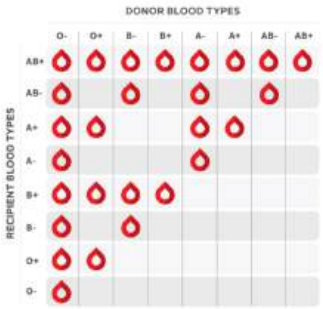


Figure 4.31: Blood compatibility chart including Rh factor.

The above is all of the different combination blood types and their compatibility

Remark 4.24. *Type O (specifically O^-) are called **universal donor** while type AB (specifically AB^+) is called **universal recipient**.*

Allergic Reactions

Allergic reaction is the body immune response over-reactivity to a substance that wouldn't activate the immune response to the majority of other individual. Because of this, the immune system is said to be "hypersensitive" to such substance (called **allergens**). Allergic reaction is divided into 2 types: immediate (reaction happens right away) and delayed hypersensitivity (reaction happens 12-72h after).

When this allergen enters the body, mast cells will secrete a large quantity of chemicals including IgE antibodies that will attack them. Typically, allergic reaction would occurs at the site of allergens entry; however, when mast cells produce a large quantity of these chemicals, it can get into the systemic circulation. Once in the system circulation, it can cause severe hypotension and bronchiolar constriction. This series of events are called **anaphylaxis** or **anaphylactic shock** that can be cause death due to respiratory or circulatory failure.

Autoimmune Diseases

autoimmune diseases are diseases that cause the immune system to attack the body's proteins as antigens. In such situation, "auto"-antibodies and self-reactive T-cells attack self-cells having these proteins. Some known autoimmune diseases are the following

1. **Type I diabetes mellitus** is an autoimmune disease where the immune system attack the $\beta-$cell that produce *insulin*.
2. **Rheumatoid arthritis** is an autoimmune disease where the immune system releases autoantibondy *rheumatoid factor* that attack the joints.
3. **Multiple sclerosis** is an autoimmune disease where the immune system attack the myeline sheath of the neurons of the nervous system.
4. **Myasthenia gravis** is an autoimmune disease where the immune system cause a weakened in the neuromuscular junctions which would also weaken the skeletal muscle.

Chapter 5

Neurology I

The mind isn't the same as the brain but it requires a brain. This could mean that the brain is an information processing machine. **Computational theory of mind** states that the mind is an "information processing system" and that cognition combined with consciousness is part of computation.

"The information processing is all the way down and all the way up". This meant that the nervous system is connected via specialized cells called neurons. Then these neurons would form networks around the entire body.

To motivate ourselves to study about the nervous system, we first will take a look at the processor of thought itself: the brain.

5.1 Nervous System

Definition 5.1. The **brain** is a complex organ that is the center of the nervous system.

Definition 5.2. The **nervous system** is a complex system of organs that work together for the coordination, sensory information of an organism.

The nervous system is dispersed all through out the body and is divided into 2 part: central (CNS) and peripheral nervous system (PNS).
The CNS control all of the bodily/voluntarily movements, while the PNS connects the CNS to the rest of the distal organs and limbs.

The PNS is made up of 2 fibers: **afferent fibers** which are sensory neurons that allow us to have a sense of "touch"; and **efferent fibers** which are sensory neurons allow us to control our muscles. The afferent and efferent fibers make up the **somatic nervous system (SNS)** (also subdivision of PNS).
Along side the SNS that make up the PNS is the **autonomic nervous system (ANS)** that monitor our internal environment and the rest of the body without our own input using **autonomic fibers**.
Another type subclass of ANS is the **enteric nervous system** that controls the **GI (gastrointestinal)-tract**.

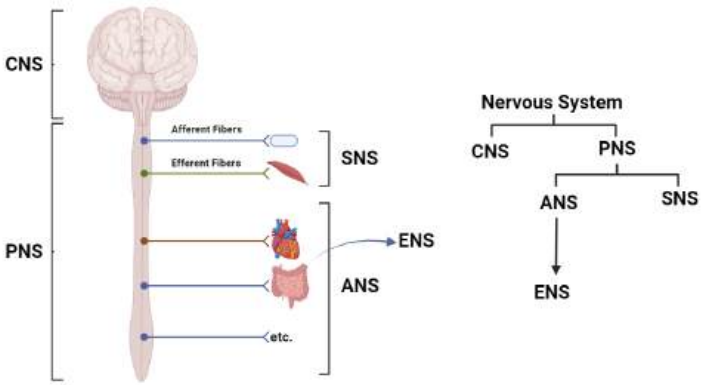


Figure 5.1: Different sub-system in the nervous system.

5.2 Neurons

We cannot talk about the nervous system without the neurons

Definition 5.3. **Neurons** are specialized cells that make up the nervous system. These cells can receive and transmit information in the form of electricity.

There is around 100 billion neurons in our body. In the 1900s, Santiago Ramon y Cajal, a famous neuro-anatomist, and was able to theorize and draw out the neurons within the hippocampus! As we've said in the definition, neurons are electrical cells which uses electricity.

Remark 5.1. *This is not special since every cells would have electrical properties in 1 way or another.*

The special thing about the electrical properties of neurons is its complex electrical system that can be tune or amplify.

5.2.1 Neuronal Communication and Morphology

Neuronal communication is much more complex than the any other cellular system in the body. They communicate at junctions separating 2 neurons called **synapses** and each neurons has a myriad of different synapses. We can compare neuronal network (NN) to a computer network (CN) and ... surprisingly NN is much slower (frequency of 100impulse/s ($100Hz$)) than CN (can reach up to $10GHz$). However...even if the brain isn't as fast as the PC, the neurons can do multiple task at the same time while the PC would take much more time.

Like its communication system, neurons also have very complex **morphology** (shape). When we look at other cells, majority of the time, we can see a round shape while neurons can have different shape depending on the location and function i.e. There no 1 type of neurons but many types.

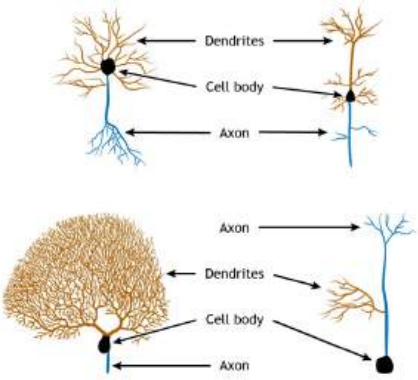


Figure 5.2: Neurons with different morphology but has the homologous anatomical part.

Despite the numerous amount of neuron types, "anatomically" they're similar. They all have: the **soma (cell body)**, which has the nucleus (like other cells), and the **extensions**, which are segments to reach other neurons.

Remark 5.2. *If we were to remove all of the neuron's extensions, it can still*

survive but the antithesis is wrong.

The extensions are divided into 2 types: **dendrites**, which would receive information [input] coming in form other neurons *think of antenna*) and 1 **axon**, which is able to communicate to other neurons. The axons can be very short or extremely long depending on the neurons it has to transmit the information.

Remark 5.3. *The more dendrites there are the more input/information it can have. Look at the purkinje neurons with its highly branched dendrites.*

The flow of neuronal information is unidirectional, that is it goes 1 direction (infos are sent down the axons but not the opposite). The reason that neurons can do this is thanks to polarization (talk about later on). Furthermore, when inputs are sent to a neuron, it can process them at the soma which allow it to send (or not) the processed information down the axon and create an input to another neurons then etc.

5.2.2 Electrical Properties of Neurons: Resting Membrane Potential

To understand the electrical properties of neurons, we have to know what is the resting membrane potential is.(starting line of all of what neurons do).

Definition 5.4. A neuron's (or cell's) **resting membrane potential** is the *stable* difference in the *electric potential* (voltage) between the intracellular space and extracellular space. A resting membrane potential of neuron is around $-70mV$.

There are 2 terms were need to tackle and understand for this: electric potential and stable, as in **what does it means to have a stable electric potential?** Let's begin with the first *electric potential.*

Definition 5.5. An **electric potential energy** is the total amount of energy stored in a system of charges. An **electric potential** is the electric potential energy per total charges.

Remark 5.4. *We'll be using ICS for "intracellular space" and ECS for "extracellular space".*

When we measure the **difference** between the electric potential of the ECS and ICS of the cell, we get around $-70mV$. This must mean that there

is a different in electric potential (if not then it would've been 0mV) and because electric potential energy is relatively constant for charges, the amount of charge in ICS and ECS is different.

What is the charge distribution between the ICS and ECS?

The ICS and ECS are made from aqueous solution with ions diffuse into them, these ions are: Na^+, K^+, Cl^- and A^- (other ions). Normally, the negative and positive charge is evenly distributed through out ICS and ECS. However, there is a tiny fraction of more negative charge in the ICS than ECS. In fact, this tiny imbalance create a **concentration gradient of physiological ions** across the membrane which create that membrane potential.

Remark 5.5. *This gradient is cause by having more ions$^-$ in the ICS but the concentration of total ions (regardless of charge) is the same for both spaces.*

we can demonstrate this remark by seeing the concentration of these ions.

Theorizing: There is a high concentration of Na^+ and Cl^- in the ECS (with $[Na^+]>[Cl^-]$) while there is a high concentration of K^+ and A^- in the ICS (with $[A^-]>[K^+]$).

Ions	Intracellular Space	Extracellular Space
Na^+	10 mM	145 mM
K^+	140 mM	5 mM
Cl^-	5mM	100mM
A^-	145mM	50mM

Table 5.1: Concentration of different physiological ions in the body.

Their concentration sum is equal as well as the charges within them also add up to 0. But if the charges sum up to 0, we wouldn't be able to measure the electric potential difference. This is contradictory since it said above that the ICS is more negative than the ECS so **why is it neutral?**...well for the simple fact that we're assuming the neuron has no ionic dynamic. Nevertheless, the concentration and charge distribution would change if we allow the normal ionic movement across the membrane.

What is causing ICS to have more negative charge than positive charge? i.e. What is causing a difference in charge distribution?

It is important to know that the membrane of the cell is impermeable to all ions **but** is highly permeable to K^+ at rest, which mean it could create a concentration gradient.

Definition 5.6. A **leak channel** is an ion channel that allow only K^+ to go to the ECS.

Mechanism of Action: At equilibrium, there is a higher $[K^+]$ in the ECS than ICS, so K^+ will move toward the ECS which is mediated by leak channels. This creates a concentration gradient. As more K^+ leaves, the ICS becomes more charge$^-$ (since it is lacking charge$^+$) thus creates an electric gradient. This also creates an electric force pulling the K^+ back in (- attracts +) but the concentration gradient by diffusion also force the K^+ back out. This tug of war will go on till the 2 forces equal and we reach **electrochemical equilibrium**.

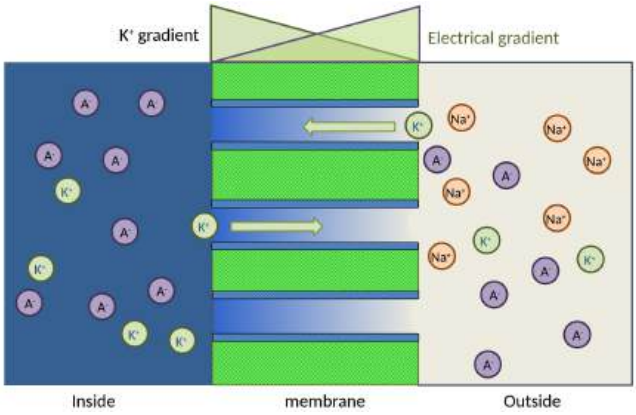


Figure 5.3: Summary of K^+ movement across the membrane creating a negatively charged ICS.

As you can see, there is a higher concentration of negative charge in the ICS as to the ECS which is why there is a membrane potential difference. Now we understand where this small imbalance in charge is, why is it specifically at around -70mV. (see Table 5.2)

Remark 5.6. *You would expect that the $[K^+]$ in the ECS to be equal to the ICS since the K^+ was moving out but this is not the case. The reason for this is that*

Ions	Intracellular Space	Extracellular Space
Na^+	10 mM	145 mM
K^+	150 mM	5 mM
Cl^-	5mM	100mM
A^-	155mM	50mM

Table 5.2: Measurement of different physiological ions in the body after electrochemical equilibrium.

at electrochemical equilibrium, there is still a concentration gradient which would create a force opposing to the electric force. If there's no concentration gradient ($[K^+]$ is equal in ICS and ECS) then the electric force would be at full power instead of in balance.

Why is the resting membrane is -70mV?

Back to the original finding, we also define this resting membrane to be *stable* which simply means the neuron is at rest.

Now, the membrane potential at the electrochemical equilibrium is described by **Nernst equation** which would give the neuron's resting membrane potential.

$$E_{\text{ion}} = \frac{2.3RT}{zF} \log \frac{[ion]_{\text{ECS}}}{[ion]_{\text{ICS}}} \tag{5.1}$$

When we applied this equation to the concentration K^+, we get that

$$E_{K^+} = \frac{2.3RT}{zF} \log \frac{150mM}{5mM} \approx -90mV$$

Well...once applied the equation, we get -90mV which is not equal to our measured resting membrane of -70mV, but we're too negative...**why is that?** Well...this is because we're stating that the membrane is exclusively permeable to K^+; if this is the case then the membrane potential is -90mV

Remark 5.7. *In fact, -90mV is called the eletrical potential of K^+ leak channel at equilibrium.*

It's not -70mV because we haven't taken in counter other physiological ions. If Na^+ can pass through the membrane, the Na^+ will flow in until the potential difference is +70 same thing with Cl^- which is -80mV. Not only that, we sort of assuming idealized condition that Na^+ cannot enter the cell

at all; however, that's not true since there would be Na^+ leak into the cell, which makes the theoretical membrane potential (-90mV) more positive (since membrane potential by Na^+ is +70mV). There's a mechanism that causes the leakiness but we won't talk about it in this course. Because of this, the net potential difference when taking in the movement of Na^+ and K^+ is roughly around -70mV.

Remark 5.8. *It is not -10mV as we expected when taking the average of the 2. The reason for this is when it comes to the contribution of membrane potential, K^+ contributes more than Na^+ therefore the membrane potential leans more toward that of K^+'s.*

Remark 5.9. *When we're talking about voltage, we're looking at 2 regions in space so we're taking the inside relative to the outside.*

Remark 5.10 (Very Important)**.** *Even when there is a change in concentration of these ions, the change is VERY MINISCULE. Nevertheless, this small change is enough to create a somewhat large potential difference.*

Coming back into the making of the concentration gradient, we realize that the concentration of K^+ and Na^+ will change overtime because of their movement. We need a mechanism to bring the concentration back to original.

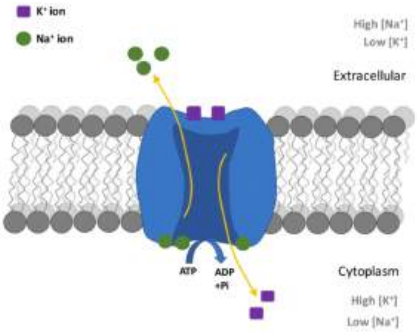


Figure 5.4: Na^+-K^+ pump

The main structure to mediate this process is called the Na^+-K^+ **pump**, that bring K^+ in and release Na^+ out. This pump uses ATP to transport Na^+ and K^+ against their concentration gradient.

5.2.3 Electrical Properties of Neurons: Action Potential

Neurons send information as an impulse down the axons. These brief impulses are called action potentials and they usually begin at the **initial segment** of the axon.

Definition 5.7. An **action potential** is a transient event at which the neuron's membrane potential goes under rapid changing i.e. The membrane will go from its resting potential (-70mV) all the way up to 30-40mV then drop immediately back down to -70mV.

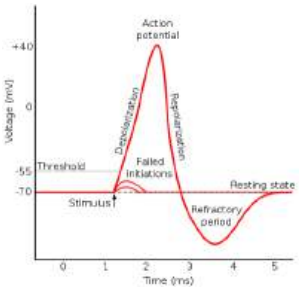


Figure 5.5: Action potential

After it begins from the initial segment, the impulse will move down the axon to the presynaptic terminals. What's interesting about action potential is that we can initiate it as long as we pass the neuron's "threshold potential".

Definition 5.8. A neuron's **threshold potential** is the membrane potential where it will trigger action potential.

Experimentation: Supposed that we take a stimulating electrode and stick it inside the axon's initial segment; then we attach it to a stimulator. This stimulator can inject current to the axon which change its membrane potential. We inject charge$^+$ which makes the resting membrane potential more positive. The action of many the membrane potential more positive is called **depolarization** (opposite is hyperpolarize).

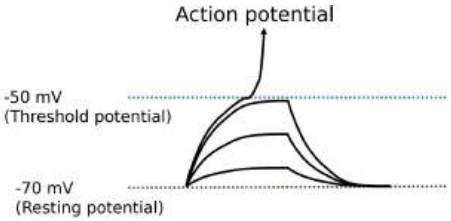


Figure 5.6: Threshold Potential Experiment.

We start inject slowly charge$^+$: at -65mV and -60mV, membrane potential will get to those respective point then drop down when we turn off the stimulator. At around -50mV however, an action potential is generated and

does not stop when we remove the electrode. The neuron's membrane potential at -50mV is called the threshold potential. From this we can think of action potential as an all or another event i.e. it either happens or not, nothing in between. But we need to ask ourselves what really happens at -50mV so that it can create a big spike in membrane potential?

Why is there an action potential produced when the resting membrane potential reach its threshold potential (-50mV)?

To answer this, we need to understand another kind of channel: **Voltage - gated Na^+ channels (VGNCs)** and they're very concentrated (more than leak channels) in the axon which enable it to propagate action potential. VGNCs are made from selectively permeable pore for Na^+ and have 1 gate that is closed at the resting membrane potential. Lastly, VGNCs open as the membrane potential depolarize, typically at around the threshold potential. Once opened, they will immediately (1ms) be shut off/inactivated (cannot be opened unless is reactivated). VGNCs serve an important role in the creation of an action potential.

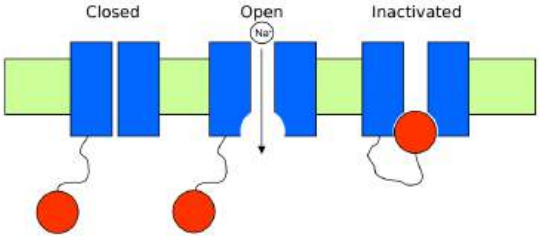


Figure 5.7: The activation and inactivation of VGNCs.

Mechanism of Action (Pre-action potential): At -50mV, only a critical fraction of VGNCs will open (it open at a feedback loop). As the membrane depolarize to higher potential, more VGNCs will open up, creates a positive feedback loop that drives the membrane potential higher. Then at 30mV, action potential reaches its maximum and VGNCs inactivates making the membrane relax and return to resting state. At the same maximal time, K^+ start flowing through leaky channels, which brings the entire membrane potential back down to -70mV. (see Figure 5.8)

One addition element we're adding are **voltage - gated K^+ channels (VGKCs)** which can contributes also to the falling of action potential.

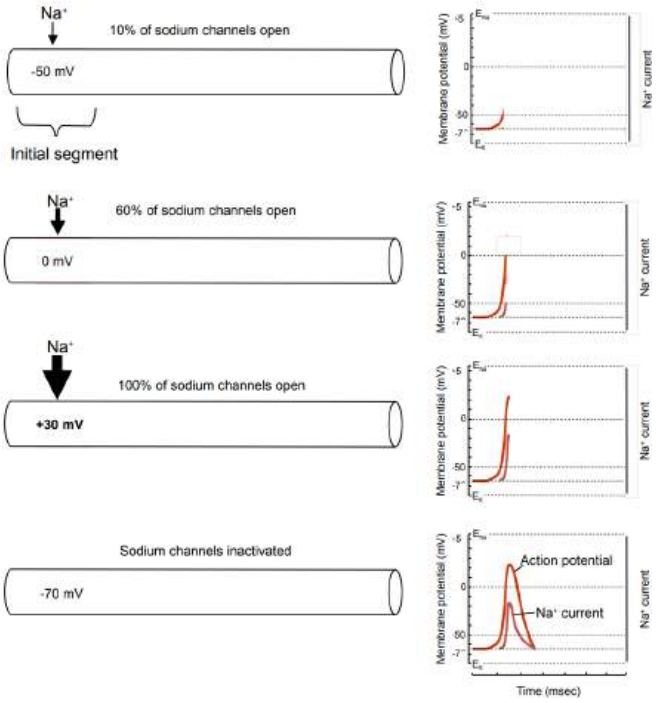


Figure 5.8: VGNCs activation and creation of action potential. Neurons communicate by the pattern and frequency of these action potentials.

Mechanism of Action (Post-action potential): VGKCs are generally slower than the VGNCs, which means that they open when the VGNC is already inactivated (at peak of action potential). This means that during the falling of action potential, there are more pores for $K^+$to flow back out which allows the membrane potential to repolarize (returning to back to). The VGKCs and leak channel will in fact open a bit longer, creating an overshoot to lower than the resting potential (hyperpolarization). After this, both channels will close and returning back to the resting membrane

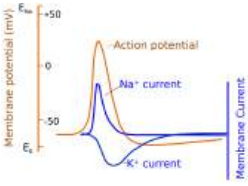


Figure 5.9: VGCKs and leak channels' contribution in action potential falling

Even without VGKC, the action potential we still be able to repolarize however it would takes a longer period of time. The shorter the action potential, the more action potential you can send.

Remark 5.11. *Both hyperpolarization and repolarization means to make the membrane potential more negative. The main difference is that repolarization is caused by closing of VGNCs and opening of VGKCs while hyperpolarization is caused by the prolonged opening of VGKCs and leak channels.*

The influx of $Na^+$is not in 1 step (i.e. it's not like 1mM Na^+immediately change to 100mM) but it's a fast and gradual build up but also this build up doesn't change concentration much (look at **remark 5.10**). Once again, the restoration of these ions distribution after action potential events is carried out by the Na^+- K^+pump.

If neurons can make an action potential, how can it propagate down the axon?

Action potential needs to propagate down the axon since we need to transfer it to another neurons at the presynaptic terminals.
Observation: If we were to triggers an action potential at the initial segments, the rest of the segment will still be -70mV while the initial segment will be at around +30mV peak. Action potential of the initial segment is positive, which would attract the negative and therefore causing the depolarization of the adjacent segment of the initial segment. Then at threshold, that segment initiate action potential which would then depolarize the next segment, so on and so forth.

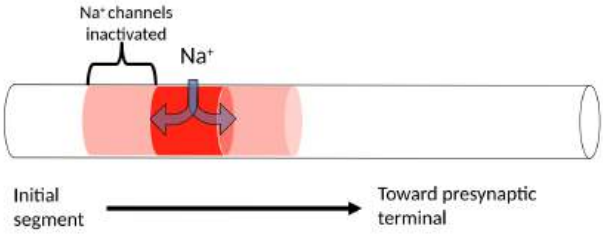


Figure 5.10: Action potential propagates in a uni-directional manner.

There comes a problem though...**how can the neuron make sure that the action potential won't depolarize the previous segment**? Well...after the initial segment reached action potential peak and starts to repolarizes, the VGNCs are inactivated and unexcitable creating a period called

the **absolute refractory period** which disable the adjacent action potential to have any effect. The period where prolonged opening of VGKCs and leak channels, which caused hyperpolarization, is called **relative refractory period** and is also less excitable.

Remark 5.12. *Although in Figure 5.10, it is shown segment as actual individual segment but in actuality, it is 1 continuous fashion instead of discrete.*

There's not only the change electric potential that can cause a production of an action potential, other method such as **transdunction of pressure on the skin** can also activate neuronal activity.

Toxicological and Pharmacological Effects of Chemicals on the VGCNs

Definition 5.9. **neurotoxins** are toxins that are dangerous for nerve tissues.

There are neurotoxins that are naturally occuring! and are produced by animals too. We'll look at some of these neurotoxins and see its effect on the body.

Example 5.2.1. **tetrodotoxin** is a type of extremely potent neurotoxin produced by pufferfish that can block the VGNCs (or sodium channels in general). This prevents the firing of action potential which can lead to inability of using muscle (both autonomic and somatic).

Example 5.2.2. **Batrachotoxin** is a type of potent neurotoxin produced by poison dart frogs that can open irreversibly the VGNCs. (opposite to the tetradotoxin).

Example 5.2.3. Other chemicals in pesticides such as **pyrethroid** or scorpion's and anemonae's toxin can alter/modulate the VGNCs.

Although not all chemicals that is have some effects on the VGNCs are all toxic. Certain chemicals and compound are injected to patient on purpose supposedly for a surgical procedure.

Definition 5.10. **Local anesthetics (LA)** are drugs that can cause an absence of sensation in specific regions of the body.

Local anesthetics is essential for surgery since it allows surgeon to perform an operation without the patient being in pain.

Example 5.2.4. **Lidocaine, benzocaine, tetracaine and cocaine** are drugs under the class of LA. They work by binding and inhibiting the VGNCs.

We can even go further to see that drugs that block the VGNCs can be vital for certain condition too.

Definition 5.11. **Antiepileptics** or **anticonvulsants** are drugs that can treat *epileptic seizures.*

Example 5.2.5. **Phenytoin and carbamazepine** are anticonvulsants that works as a VGNCs inhibitors.

5.2.4 Myelination and Saltatory Conduction

Fast propagation of action potential is vital for survival. The faster your action potential can propagate down the axon, the faster your reflex would be. Different animals would have different way to boost the propagation speed.

Example 5.2.6. Through evolution, the axons of squids are really big/think (1000x ours). The reason squid does this is because the propagation speed is directly proportional to the axons diameter (reason for this is complex and we won't get into it). This is not just for squid but most of invertebrates animals.

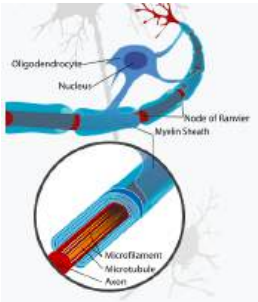


Figure 5.11: Insulation of Axons

For **vertebrates animals** (like us), we have a different structure to increase the propagation speed. The main problem with our axons is that it is small and thin so and we cannot make them bigger (we have more axons that typical invertebrates) **how would we solve such problem?** Well...the evolutionary strategy for this is by insulating the axon. The layer of insulation that neurons used to wrap around their axons is called the **myelin (sheath)**. Depending on where the neuron located, the myelin would be made from a different cell.

Example 5.2.7. The myelin in the CNS is made from **oligodendrocytes** while that from the PNS is made from **Schwann cells**.

Remark 5.13. *The slowest axon in the body is the **group C nerve fiber** which travel at around 0.2-0.5m/s. This type of axon is unmyelinated.*

The wrapping of the myelin is not 1 continuous fashion along the length of the axon. We would be able to spot short gaps ($\sim 1mm$) between 2 myelins on the axon. These gaps are called **nodes of Ranvier** and this structure is the main way to help action potential to propagate faster. This mechanism is also called the **saltatory conduction**.

Mechanism of Action: We first look at the concentration of of VGNCs along the axons with myelin. As we can see, the concentration of them will be greats at the initial segment and the nodes of Ranvier and almost none between the myelin.

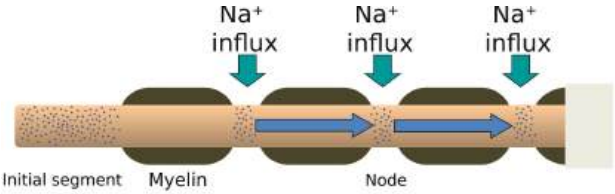


Figure 5.12: Myelin and their increase of action potential propagation.

When action potential is generated in the initial segment, the signal will propagate down to the next segment (between the myelin) but because there's no VGNCs, the signals will slowly dies down. It is not completely lost, thanks to the insulation of myelin, the action potential reaches just enough to depolarize the first node of Ranvier (that has VGNCs). Once this happens, the node will generate an action potential that can go through the segment of myelin again, then it is repeated till the action potential reaches the terminal.

Turns out this types of propagation is much faster than the typical continuous streamline fashion we've thought of before (explanation is complicated but think of a runner vs a speed skater).

Remark 5.14. *Myelination of axons is especially important for the neurological well being of the individual.*

Example 5.2.8. A loss of myelination on axons could lead to **multiple sclerosis** which is a disease where it is hard for an individual to control their own muscle, lose the ability to see clearly, write, speak, or walk etc.

Another thing to know is that 60% of the brain is made up of **white matter** which consists of mostly myelinated axons (also found in the spinal

cord) while the rest 40% is made up of **grey matter** which are soma, dendrites and synapses.

5.3 Synapses

Definition 5.12. **Synapses** are points of contact between 2 neurons to exchange information. They can communicate through these synapses chemically or electrically.

On a neuron, there are 3 types of synapses: axodendritic, axosomatic and axo-axonic. Axodendritic synapses are synapses between dendrites if 1 neurons with the axons of another neuron; in such case, the neurons with dendrites will form protrusion that extend to the axons of other neurons called **dendritic spine** and the size of the spine correlate to learning process. Axosomatic synapses are synapses between the soma and the axon and the axo-axonic synapses are between axons and axons.

Remark 5.15. *A single neuron can branch out to make multiple synapses with different neurons.*

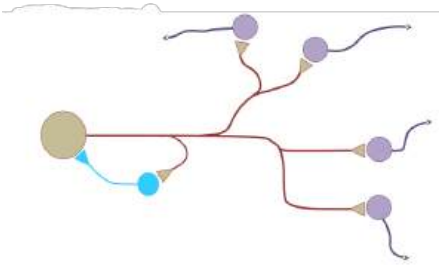


Figure 5.13: A single neurons with different synapses from branching

5.3.1 Structure of Synapses

The swelling of the axons terminal is called the **presynaptic terminal**. The regions of another neuron that the presynaptic terminal will communicate is called the **postsynaptic spine (membrane)**. The space separating the presynaptic terminal and postsynaptic spine is the **synaptic cleft**.

Definition 5.13. **Neurotransmitters** are chemical (endogenous) that allows neurons to communicate with each other.

Within the presynaptic terminal, there are vesicles which have neurotramsitters. These synaptic vesicle can either be free flow or concentrated at the edge of the presynaptic terminal forming the **active zone**. Neurotransmitters can then be released through the synaptic cleft to the postsynaptic membrane.

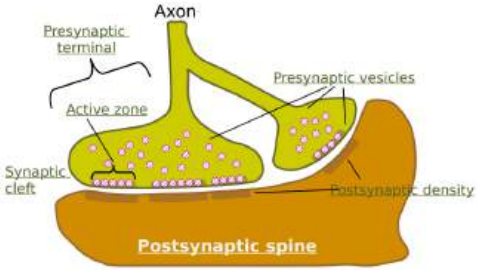


Figure 5.14: Structure of a synapse.

On the postsynaptic membrane, near the synaptic cleft, there are regions with high receptor concentration called **postsynaptic density**, where neurotransmitter can bind to.

Ions Channels

There are 2 types of channel we need to look at: voltage-gated Ca^{2+} channels (VGCCs) and ligand-gated ion channels (LICs)

Remark 5.16. *LICs also have other names such as neurotransmitter receptor or ionotropic receptors.*

VGCCs are found in the presynaptic terminal at the active site while LICs are found in the postsynaptic membrane at the postsynaptic density.

> **Mechanism of Action (Ions Channels):** The action potential propagates down the axons and "invade" the axons terminals. This would depolarize the presynaptic terminals causing VGCCs to turn on and allow an influx of Ca^{2+} into the terminal. Ca^{2+} is a **biochemical signalling molecule** which means it will bind to proteins and cause a cascade which lead to the release of the vesicles. These

vesicles have signalling molecules which would be released to the synaptic cleft then travel toward postsynaptic membrane, where they will bind LICs which allow ions to flow in.

Remark 5.17. *Ca^{2+}'s concentration is lower (very) in the ICS and relatively high in the ECS which means that if VGCCs open, Ca^{2+} has a natural tendency to flow down the concentration gradient.*

5.3.2 Excitatory and Inhibitory Synapses

The majority of synapses are either **excitatory** (mostly dendritic spine) or **inhibitory**. Neurotransmitter would either depolarize the postsynaptic membrane or hyperpolarize it. The depolarization event (postsynaptic membrane's response) is very brief, small and is called the **excitatory postsynaptic potential (EPSP)** while and same with the hyperpolarization even which is called **inhibitory postsynaptic potential (IPSP)**.

Excitatory Post Synaptic Potential (EPSP)

The main excitatory neurotransmitter that mediate EPSP is **glutamate (GLU)**. When released, glutamate can bind to 2 different types of receptor in the postsynaptic membrane which are: AMPA receptor and NMDA receptor. Their name is correspond to endogenous agonist that can bind to the receptor.

Example 5.3.1. For AMPA receptor, the endogenous agonist can bind to it is AMPA or *α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid* while NMDA receptor would have *N-methyl-d-aspartate*.

They're both LICs. When they're activated, they will allow ions to flow in and cause an EPSP.

Mechanism of Action (AMPA receptor): GLUs are released from the presynaptic vesicles and will bind to the AMPA receptor which allow $Na^{+}$to flow in and creates an EPSP. The EPSP is very small, it depolarize only around -2mV (to get to threshold need -20mV) and last around 20ms. However, these neurons have multiple AMPA that are getting bind by GLU at the same time. When these EPSP happens at roughly the same time, they will spread in the soma but begin to converge with each other at the initial segments. The de-

polarization then sum up and drives the postsynaptic potential to its threshold to create an action potential.

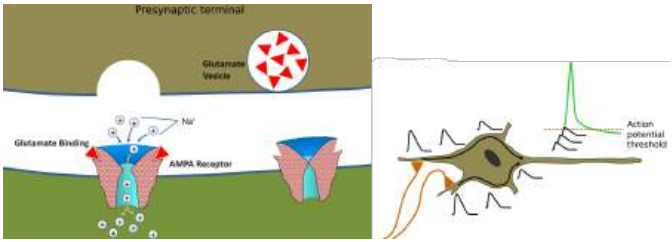


Figure 5.15: Mechanism of AMPA Receptor and depolarization addng up.

NMDA receptor, on the other hand, is a little different from AMPA. Not only GLU can bind to them but also Lycine. What's more interesting is that it allow the influx of Ca^{2+}instead of Na^{+}therefore it would trigger a biochemical events instead of depolarization. Not only beging a LICs but its full activation is also dependent on the membrane potential of the postsynapse.

Mechanism of Action (NMDA receptor): At its closed conformation (resting membrane), they have Mg^{2+} blocking the channel. Even with the binding of GLU, the Mg^{2+} still blocks it. Once the postsynaptic membrane depolarizes to -50mV (carried out by AMP), Mg^{2+} will displace and allow $Ca^{2+}$to flow in and initiate biochemical events.

Remark 5.18. *NMDA receptor involves in **synaptic plasticity**, which are neurons' ability to strengthen more frequently used synapses (strengthening connections is the basis of learning).*

Synaptic plasticity is represented by a model called **long term potentiation (LTP)**. First, we will fire a single action potential to the presynapse terminal and record the EPSP (control). Then, we will stimulate the presynaptic neurons with multiple action potential. Once this happens, GLU will get released so much and causing the series of EPSP in the postsynaptic membrane. At this time too, Mg^{2+} will unbind from the NMDA and allow $Ca^{2+}$to flow in and create a chain of biochemical events. What we found from the LTP model is that the Ca^{2+}cause the neuron to produce

and insert more AMPA receptors. Now we were to stop for a while, then come back and fire an action potential, the EPSP will be much bigger than the control test.

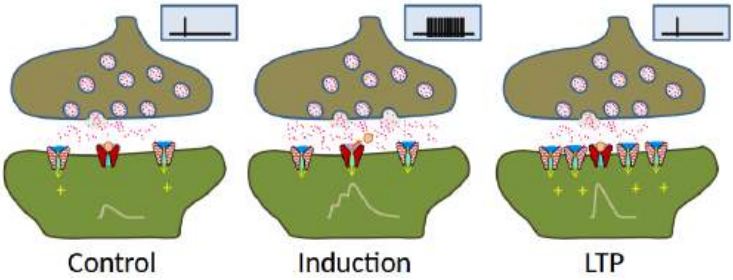


Figure 5.16: Long term potentiation.

Remark 5.19. *Although GLU is important, when [GLU] is higher, it can acts as* ***neurotoxin****. The reason for this is that there will be too much EPSP happens as well as a high influx of* Ca^{2+}*. If* $[Ca^{2+}]$ *stays at that level in the ICS, the neuron will die. This death is called* ***excitotoxicity****. Excitotoxicity is contributed after stroke of those with neurodegenerative disease.*

Example 5.3.2. During a stroke, neurons dies and release of high amount of GLU to the **penumbra** (area around a stroke event). This high level of GLU could then lead to once again, excitotoxicity.

Example 5.3.3. Monosodium glutamate is a common chemical in food to enhance its taste. Monosodium GLU doesn't have high effectiveness on adult since they have blood-brain barrier which disable the passage of monosodium GLU. Babies on the other hand do not have this barrier which makes them susceptible to excitotoxicity.

Inhibitory Post Synaptic Potential (IPSP)

IPSP will bring action potential away from the threshold. The main inhibitory neurotransmitter that mediate IPSP is **γ-aminobutyric acid (GABA)**. GABAs will bind to the **$GABA_A$ receptor** which opens ion channel and allows Cl^- to flow in thereby hyperpolarize the postsynaptic membrane. This channel is the main target for certain pharmaceutical drugs

Example 5.3.4. **Benzodiazepine** is a drug that can bind to the $GABA_A$ receptor and enhance the effectiveness of GABA. Barbitrurate has the same

mechanism but more easily overdosed because it has a much bigger effect. Another compound that can do this is ethanol (alcohol).

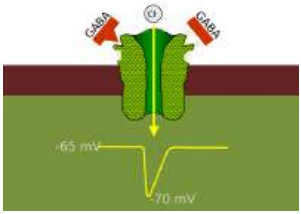


Figure 5.17: IPSP mediated by GABA.

Synaptic Integration

Synaptic integration is a neuronal process of integrating multiple signals of EPSP and IPSP (essentially adding them up). It would fire action potential if the sum of EPSP is higher than the IPSP i.e. synaptic integration is mainly EPSP than IPSP. The excitation and inhibition signals will shape the neurons and drive them to fire action potential or not.

Remark 5.20. *Any given neurons are excitatory neurons or inhibitory neurons i.e. at its presynptic terminals, it would either release only GABA or Glut e.g.Purkinje neurons are inhibitory and always release GABA.*

Interestingly enough, an inhibitory neuron can fire action potential, and release GABA... but in order to fire action potential, it needs excitatory synapses to activate them. (A paradoxical circle of activation and inhibition). Our body should always have a balance in excitation and inhibition (leaning more to excitation) and when this is out of balance, certain condition can arise.

Example 5.3.5. **Seizure** is the result where neurons fire too many action potential (too much excitatory) and almost no inhibition (inhibition is essential since it acts like a "break" for excitation).

5.3.3 Metabotropic receptors

All of the above are fast synaptic transmission carried out by fast ionotrophics channels. Nevertheless, there is another type of receptor: **Metabotropic**

glutamate receptors (mGluRs). They're activated by GLU but are not ion channels. They also belongs to the excitatory receptors family (NMDA, AMPA, etc.).

> **Mechanism of Action (mGluRs):** When neurotransmiter bind to Glut receptor, it changes its conformation but does not allow ions in but would initiates the synthesis small molecules called **2nd messenger** in the cell that can cause biochemical events. These 2nd messenger can build up and activate proteins inside the cell. They could also activate **protein kinase** (can catalyze phosphate onto proteins), transcription factor and even other ion channels.

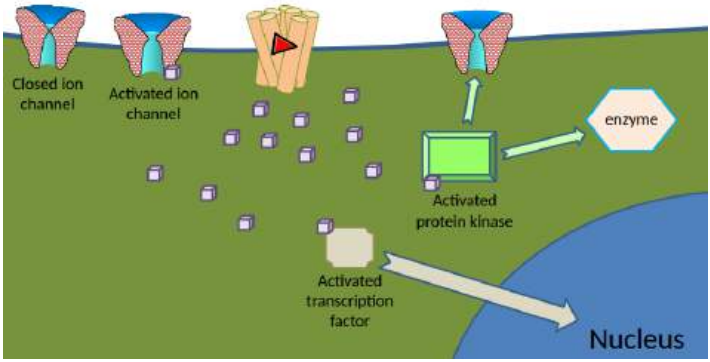


Figure 5.18: Mechanism of mGluRs.

Ionotrophic receptor acts very quickly, however the mGluRs take a long time because these 2nd messenger would take time to diffuse into the cell (long time). They're slow to turn on but also slow to turn off.

Not only that mGluRs are found in the excitatory but they're also found in inhibitory synapses alongside $GABA_B$ receptors.

Neuromodulator

Both GABA and GLU can activate ionotropic and metabotropic receptors but there are neurotransmitters that act specifically to metabotropic receptors, which are called **neuromodulator**. Neuromodulators include: dopamine

(DA), serotonin (5-HT), norepinephrines (NE), neuropeptides (e.g. endorphin). They're not involved on fast transmission however they can shape the entire global functioning of the brain.

Example 5.3.6. The sleep wake cycle as well as attention can be affected by the release of NE. 5-HT has influences in mood and are the precrusor for antidepressant drugs. DA is the main neurotransmitter involved in the *brain-reward system* which has stimulating and reinforcing effects.

The neurons that release neuromodulators are most concentrated in the brain stem, such as DA neurons that are mostly found in the *substatia nigra* and *ventral tegmental area.* They have axons that spread around the brain and can release their respective neurotramsitter to any regions hence why they have a significant effects on the global brain function.

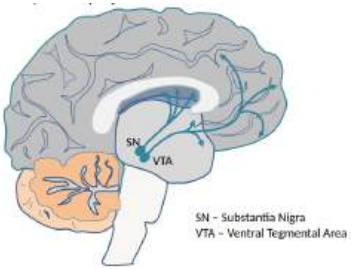


Figure 5.19: Regions where "DAnergic neurons" are found.

These neuromodulators are the main precursor to some pharmaceutical drugs i.e. They use these neuromodulator to create drugs with similar structure which then apply almost similar effect. Or they can design drugs that bind to the receptors that release these neuromodulators (since they have such a big role to the entire brain). However, it is important to know that some of these drugs do not 100% mimic the effect of endogenous neurotransmitter.

Example 5.3.7. Cocaine inhibits dopamine transporter which disable it from re-uptakes DA released in the synaptic cleft. This would lead to higher concentration of DA and therefore stimulate the rewarding system and reinforce the abuse of cocaine.

Chapter 6

Neurology II

Previously, we've talked about the main component of the nervous system: neurons and synapses. Today, We'll touch on cognitive, sensory topics, and the central nervous system.

6.1 Brief Overview of CNS Anatomy

Like we've said before, the nervous system is divided into 2 parts: central and peripheral (CNS and PNS). We can use the PNS to receive external input to send to the CNS, this mechanism is known as **afferent** (sensory input, soma is out of CNS). In turn, the CNS can send signals to creates movement of the body against the external environment, this mechanism is known as **efferent** (motor output, soma is in the CNS). we also have another mechanism called the **visceral input** which is afferent that are only for the internal environment.
In the following lectures we'll be focusing mainly on the efferent mechanism. Efferent mechanism can be carried out by either the **somatic nervous system** (SNS, a PNS that we can control) that are carried out by efferent (motor) neurons that can innervates skeletal muscles or **autonomic nervous system** (ANS, a PNS that we cannot control) that are carried out also by motor neurons but can only innervates skeletal muscles.

6.1.1 CNS Anatomy

Now, we'll focus more on the CNS itself. The CNS consists of mostly the **brain** and the **spinal cord**.

Definition 6.1. **Nerve** is a collection of neuronal axon. Spinal nerve will send axons down to the PNS around the body while the cranial nerves are axons located mainly in the brain.

The Brain

In the brains, **cranial nerves** mainly provide the visual, olfactory, vestibular functions etc.
When the spinal cord enter the crane it merge to the **brain stem**, which consists of medulla, pons and midbrain. Superior to the brain stem is the **cerebrum** (this is what people imagine to be the brain). Deep inside it are structure such as the **corpus callosum** and **thalamus**. Inferior and posterior to the cerebrum is the **cerebellum**. The exterior layer (surface) of the cerebrum, made from grey matter, is called the **cerebral cortex**. The cortex is divided into different area called: frontal, parietal, occipital and temporal lobe.

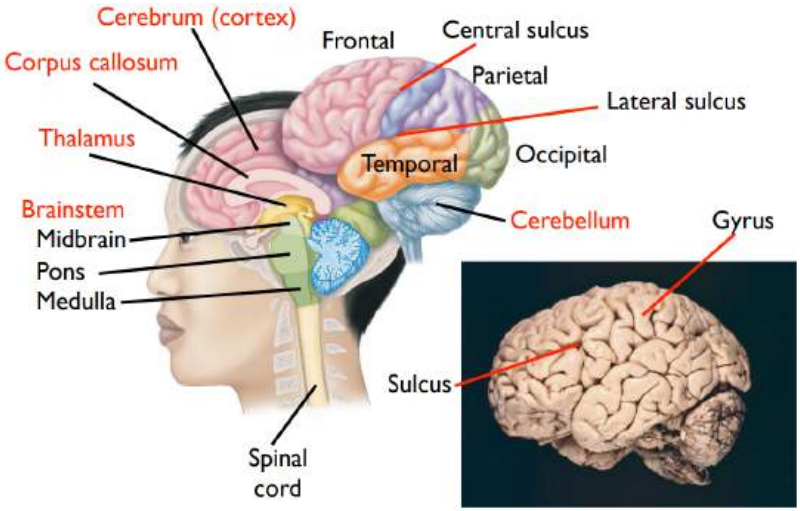


Figure 6.1: Anatomy of the brain.

The brain is folded into sections called **gyri** to increase the surface area of the cerebrum allow more packing of neurons and nerves. Between each gyri are grooves called **Sulcus**. Dividing the frontal and temporal lobe is largest sulcus called the **central sulcus**.

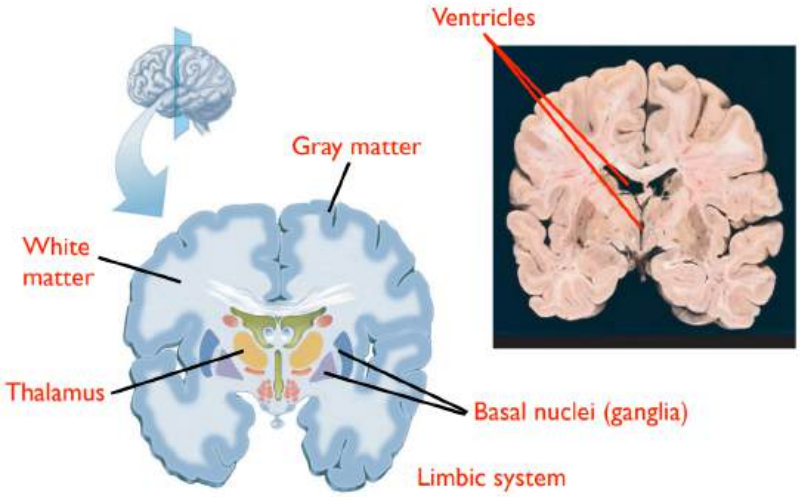


Figure 6.2: Coronal slice of the brain.

When we slice the brain on the coronal (front) plane, we found more internal structure.
Grey matter (occupied the external) are somas while **white matters** (occupied the internal) are myelinated axons. We can also see some of the previous structure such as thalamus but also 1 more structure that is the **basal ganglia (nuclei)**

Definition 6.2. A **ganglion** is a group of neuron cell bodies in the PNS. For CNS it's **nucleus**

The basal ganglia, thalamus and along with other major brain structure will make up the **limbic system**, which is important for memories and emotions. Finally we can see an empty cavity in the middle of the brain called **ventricles**. As we will see that there are many other ventricles in the CNS and they all can produce **cerebral spinal fluid (CSF)**.

The Spinal Cord and Segment

The **spinal cord** is a long vertical extension inferior to the brain, made from nervous tissues. From the spinal cord, **spinal nerves** can branch out and make up the SNS (sensation, muscle control, etc.)

The entire spinal cord is divided into 31 **spinal segment** and each of them would have 1 pair of spinal nerves branch from the left and right. Each of the 31 spinal segment would innervate different part of the body. From the top we have 8 pair of **cervical nerves**, 12 pairs of **thoracic nerves**, 5 pairs of **lumbar nerves**, 5 pairs of **sacral nerves** and 1 pair of **coccygeal nerves**.

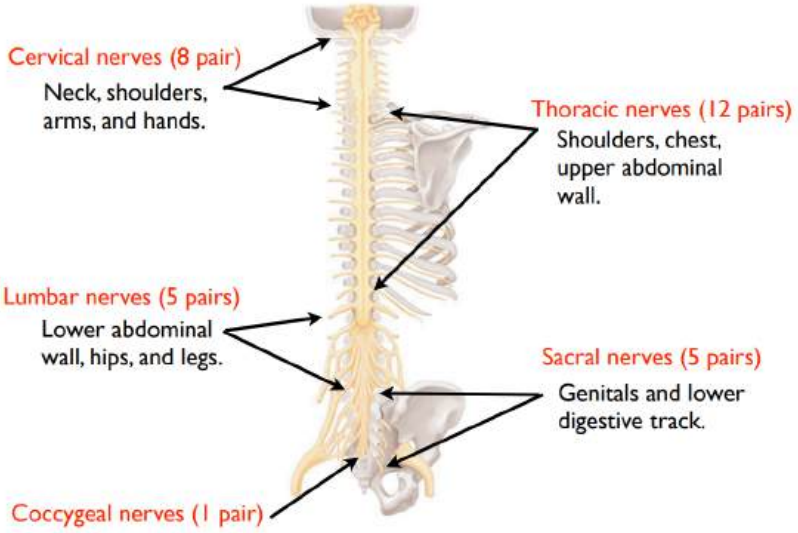


Figure 6.3: Division of the spinal cord.

The spinal cord lies between a bone structure called the **vertebral column**. Each of these column are made by 1 **vertebrate**.
In the middle of the spinal cord, we can find grey matter in a butterfly shape, which is surrounded by white matter. The butterfly shape has the **dorsal horn** (sensory information can enter) and **ventral horn** (motor information can exit). In the middle of the butterfly grey matter is the **central canal** where CSF can flow up or down from the brain.
Each spinal nerve (1 of each pair) is made from a dorsal and ventral root

that do sensory or motor infos respectively. One special thing about the dorsal root is that it has ganglion unlike the ventral root.

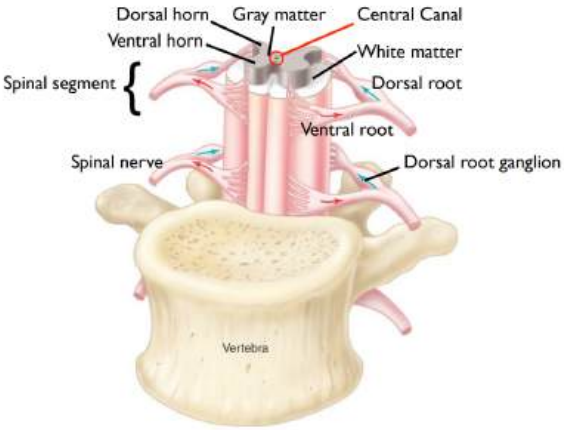


Figure 6.4: Anatomy of spinal cord.

6.1.2 Cranial Nerves

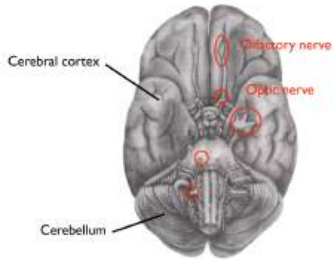


Figure 6.5: Olfactory and optic nerves.

We have a total of 12 cranial nerves, 10 of which project toward the brain stem while the other 2 projects directly to specific part of the brain (optic and olfactory).

Remark 6.1. *Concussion can cause brain edema which increase* ***intercranial pressure****. This pressure can compress the brainstem and cranial nerves that regulate pupillary response (reflex).*

6.1.3 Development of the Nervous System

We all start as an **ovum**, then it starts to differentiate into a **blastocyst** (within a week). By week 2, we can observe a **cell mass** within that blastocyst. On week 3, the **embryonic disk** is formed.

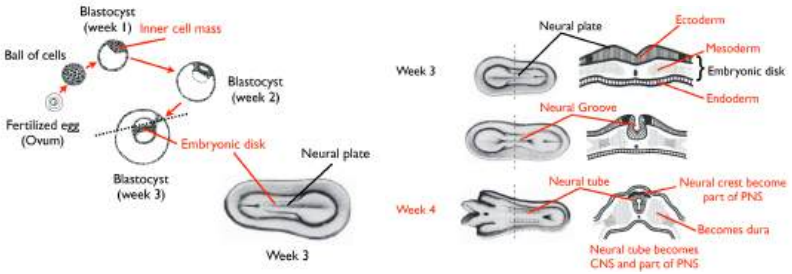


Figure 6.6: Development of the nervous system.

The top of the embryonic disk is the **neural plates**. The top layer of the plate is called **ectoderm** (will become nervous system) then **mesoderm** (will become muscles) and **endoderm** (will become GI tract). To each side of then neural plate is the **neural plate border**. From week 3 to 4, the ectoderm will begin to fold into itself creating a **neural groove** which develop into the **neural tube**, while part of the mesoderm integrated to become the dura (explain later). This folding also allow the neural tube border to fold into themsevles creating the **neural crest** which will become the PNS. The neural tube will become the CNS and part of the PNS (see Figure 6.6, right).

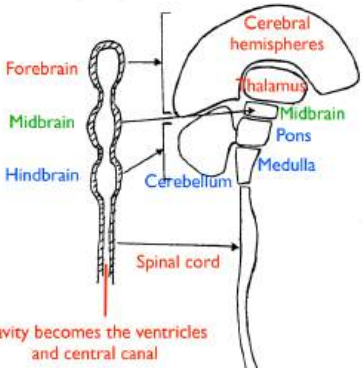


Figure 6.7: Development of the neural tube to CNS.

Remark 6.2. *Neural tube defect is a birth defect condition where the closing of neural tube is improper.*

On week 4, neuronal tube will form vesicles that is the forebrain, midbrain and hindbrain. The forebrain bulge (or **proencephelone**) will become the cereral hemisphere and thalamus, the midbrain (or **mesencephelon**) becomes the midbrain, the hindbrain (or **telecephelon**) becomes the cerebellum, pons and medulla. The hollow cavities of the neuronal tube will become the ventricles and central canal(see Figure 6.7).

6.1.4 Circulation of the CNS

There are mainly 2 types of fluid circulation we'll be looking at: cerebral spinal fluid and blood

CSF circulation

Ventricles are openings in the brain, it contains 150mL of **cerebral spinal fluid (CSF)**. The largest ventricles in the brain is the **lateral ventricle**, which is divided into the left and right. The lateral ventricle. The lateral ventricle connects to the **third ventricle** via the **foramen of Monro**. The third ventricle connects to the **fourth ventricle** (between brainstem and cerebellum) via the **cerebral aquaduct**. The fourth ventricle can also drain to the **central canal** of the spinal cord.

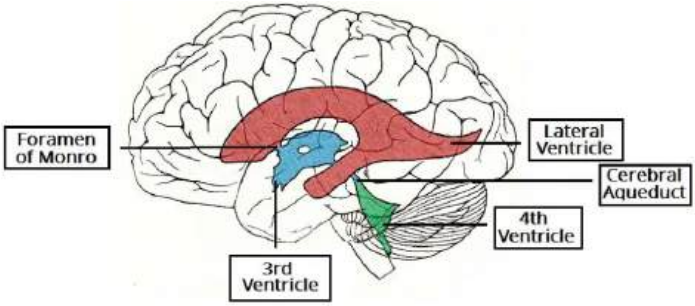


Figure 6.8: Ventricles and connections in the brain

Instead of going to the central canal, the CSF can be drain into the **subarachnoid space** via the **foramens of Lushka and Magendie** at the 4th ventrice. From the subarachnoid space, the **arachnoid vili** collects CSF which can be circulate back into the venous blood supply for recycle.

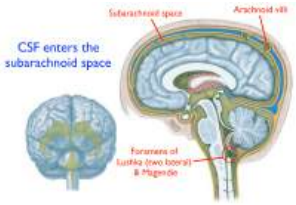


Figure 6.9: Subarachnoid spaces and recycle of CSF.

The ventricles are lined by the **choroid plexus** which produces CSF. CSF is produced at a rate of 500mL/day in the 4 ventricles. It acts a support and cushions the CNS, it can gives nourishment to the brain and removes waste through absorption of arachnoid villi (cells that take CSF out of the brain). When there is too much CSF, it would cause certain condition

Example 6.1.1. **Hydrocephalus** is a condition where there's a build of CSF due to the inability to absorb it. It can be further divided into 2 types: **communicating hydrocephalus**, which is the blocking of CSF as it leaves the ventricle (failure of arachnoid vili or subarachnoid space); and **non-communicating hydrocephalus**, which is the blocking of the passages between ventricles.

Remark 6.3. *Unlike blood, CSF isn't pumped around, it simply circulate according to whichever flow there is.*

The subarachnoid space is made from the **meninges** (membrane). The first layer of the meninges is called the **dura mater** (strongest layer), then it is the **arachnoid membrane** then the **pia mater** (very thin) that covers the cerebral cortex. Between the arachnoid membrane and pia mater is the subarachnoid space which consists of CSF and blood vessels.

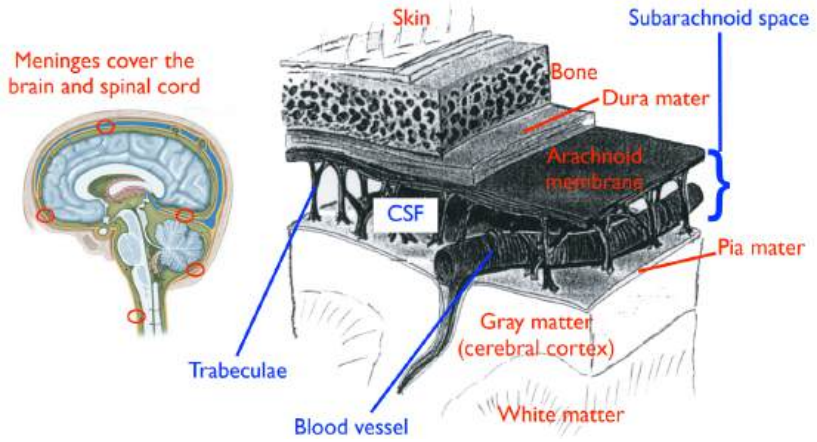


Figure 6.10: Meninges of the brain.

On the midline of the brain (division between the left and right lobe of the brain), there is a **dural venous sinus** where CSF, collected by the arachnoid villi from the subarachnoid space, will drain into.

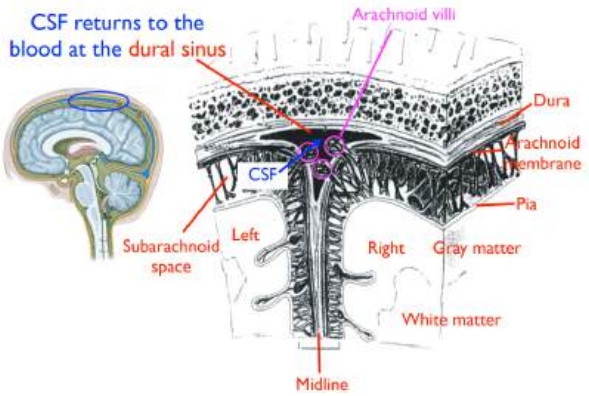


Figure 6.11: Dural venous sinus drainage.

Blood Circulation

The brain requires constant supplies of glycogen and oxygen. The transport of blood to the brain do not require insulin. This is why too much insulin would make the body absorb too much glucose which leave none left for the brain. During fasting/starvation, your body will do everything to keep the glucose supply to the brain high.

Remark 6.4. *Neuronal tissues requires lots of glucose. When there is an inadequate nutrient supplies, neurons can die which is a stroke.*

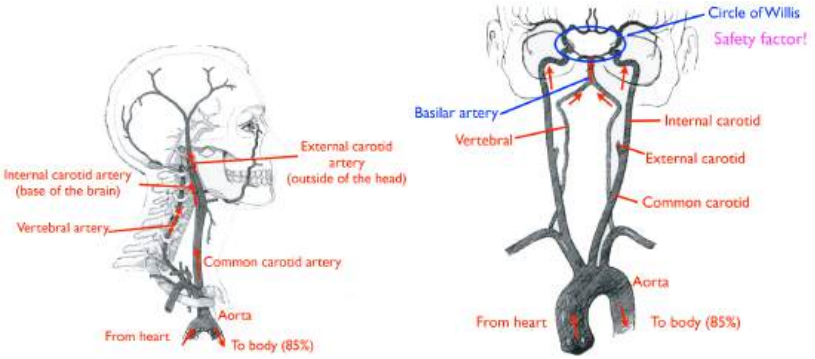


Figure 6.12: Artieries to the brain.

The brain receives 15% of the total blood supply hence it would be evident to have major blood vessel up to the brain.
From the aorta, it branches to the brain mainly by the **common carotid artery** (left and right) as well as **vertebral artery** (left and right). As it reaches the skull, the common carotid artery branches out to the **external** and **internal carotid artery**. The left and right vertebral arteries will merge near the skull forming the **basillar artery**. The basillar artery will marge with the carotid arteries forming a loop called the **circle of Willis**.

Remark 6.5. *This structure could provide a safety factor since if there was some problem arise to other arteries, the circle of Willis allow a full circulation to the brain.*

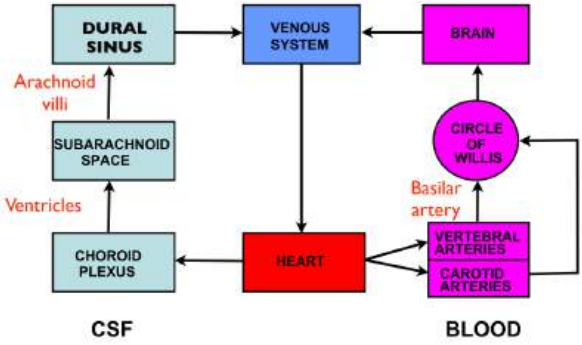


Figure 6.13: Summary of cerebral circulation.

Lastly and also important is the **blood brain barrier**. This barrier helps regulate the brain internal composition. The capillaries made up this barrier has endothelial cells as the lining but it has tight junctions between them (unlike the normal capillary). To get anything from the capillary to the brain, the substance must either passively diffuse through the endothelial cells or actively transport through. Surroudning the endothelial cells are foot processes of **astrocytes**, which can maintain the cerebral environment, take excess neurotransmitter, regulate ions concentration and takes up waste and debris. (see Figure 6.13)

Opiate drugs (e.g. morphine) typically doesn't cross the blood brain barrier because it isn't lipid soluble. Howeer we were able to do that by convert morphine to heroin which can cross it. Heroin cannot interact with

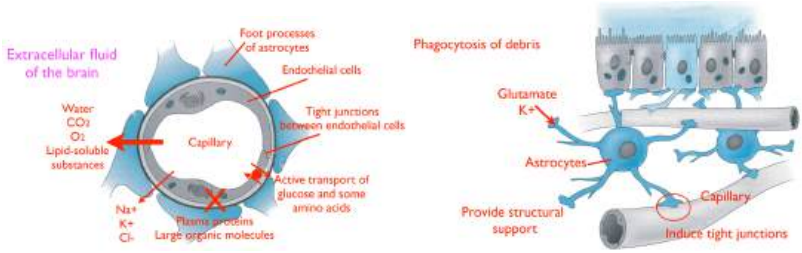


Figure 6.14: Blood brain barrier and astrocytes.

opiate receptors so there are enzymes that can reconvert it back into morphine which allow it to interact. The problem is that the newly re-formed morphine cannot cross the blood brain barrier which mean it stay in the brain system for a long time.

6.2 Sensory and Perception

Definition 6.3. A **sensation** is the active awareness of a sensory stimulation (e.g. you can sense pain etc.) while **perception** is the understanding of a sensation means (e.g. you can sense pain and know it's because you hit your hand on the table).

You don't really perceive the stimulus energy from the external world but what you're perceiving is neural activity produced by that stimulus. This concept is best described by the following 2 law or aspects

Theorem 6.1 (Law of Specific Nerve Energies)**.** *Regardless of how a sensory neuron is activated, the sensation would corresponds to that "speciality" of that neuron.*

Example 6.2.1. By rubbing your eyes, you're applying pressure onto the eye thus increasing its intraoccular pressure. This change would lead to the activation of neurons in the eyes via mechanical energy. At the end, you would see a flash of light while rubbing your eyes.

Theorem 6.2 (Law of Projection)**.** *Regardless of where in the brain the sensory pathway is stimulated, the sensation is felt at the sensory receptors location.*

Example 6.2.2. The signal of touch will be sent from the receptor site to the hippothalamus of the brain but you do not feel touch in your hippothalamus, you feel it at the receptor site where the touch signal originated.

Definition 6.4. A **modality** is a class of stimulus

Essentially, to sum up the 2 theorem above, the brain "knows" the modality and location of every sensory afferent. This is referred as **labeled-line code** i.e. it is a coding label on each stimulus' types and location.

Remark 6.6. *There's an exception to this that is pain stimulus which is caused by a miswiring.*

Remark 6.7. *We will mostly use "afferent" for sensory signals but also as a description for any component of the sensory e.g. afferent neurons.*

6.2.1 General Properties of Transduction and Neural Activities

Definition 6.5. **Transduction** is a process where stimulus energy is converted into neural activities via opening or closing or ions channels (located on/in sensory receptors).

We have **sensory receptors** that can receive stimulus by itself i.e. these receptors located on axons that directly sends afferent to the CNS. Usually they will lay in a specialized receptor membrane called specialized **intermediate neurons** to transmit afferent to another neurons which would relay it to the CNS.

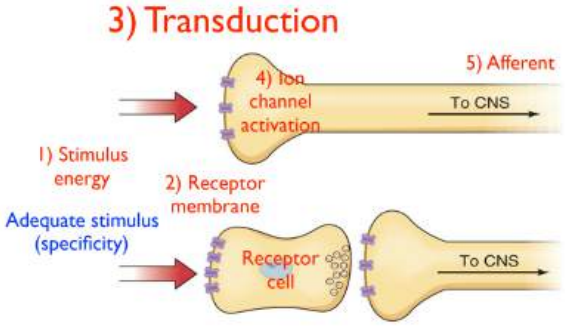


Figure 6.15: Step of turning stimulus to neural activity.

These receptors can be activated or respond to a stimulus energy which is called **adequate stimulus**. We can induced these stimulus energy through various ways but some receptors requires specific stimulus.

Example 6.2.3. *mechanoreceptors* are receptors that responds mainly to mechanical energies.

Once that specific stimulus energy acts on the receptors, the ions channels will open or close which lead to afferent sending information to the CNS via action potentials

If we were to probe different part of the axon that was activated by the stimulus energy, we wuld be able to see how the stimulus energy is transducted. First we see stimulus energy coming in, this would lead to the depolarization of the membrane.

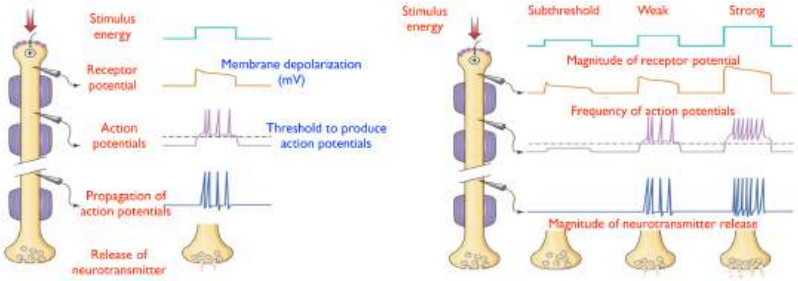


Figure 6.16: Probing the axons to see how stimulus energy is transducted. Stimulus intensity is also directly proportional to afferent response

If the depolarizaion reaches threshold then action potentials are produced. These action potentials will propagate toward the presynaptic terminal and allow the release of neurotransmitter.
Interestingly enough, different amount of stimulus energy would lead to different afferent activity. If we does the same probing as before, we will see that the stronger the stimulus energy, the larger the afferent activity which would lead to high release of neurotransmitter. (see Figure 6.16, right)

6.2.2 Adaptation of Afferent response

Most afferent neuron tends to adapt to stimuli overtime and such process is called **adapting response**. Certain afferent would be non-adapting i.e. stays the same regardless, slowly adapting i.e response to some stimulus intensity, or rapidly adapting i.e. response to only fast stimulus change.

To see this we will perform a little experiment. Using square wave stimulus we can look at different afferent and its adaptation. The purpose of

a square is that it would have a rapid stimulus change then stay at that level for a while the drop down. We can see that the non-adapting afferent would encode for the entire stimulus. For slowly adapting afferent, it would encode for mostly when the stimulus change and some of the stimulus intensity. Rapidly adapting afferent would ignore all the stimulus intensity and encode only where the stimulus changes.

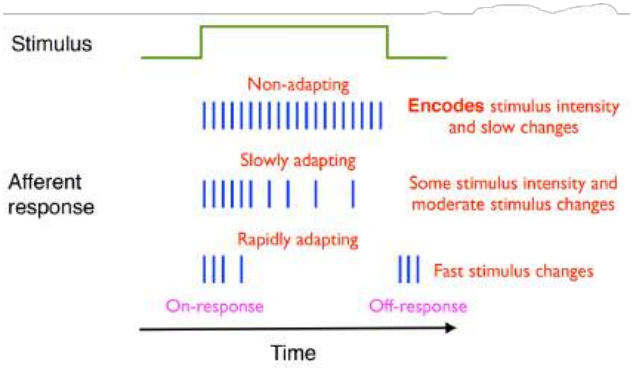


Figure 6.17: Different afferent and adaptation to stimulus.

One question may arise from this is **why would most neurons adapt to stimuli instead to sending all of the stimulus intensity?** On a behaviour point of view, it is best to know the change in environment than just having the stimulus. that's why during the square-wave stimulus, the neuron tends to fire at each end of the wave after adaptation since it's much more beneficial to detect changes than constant.

6.2.3 Receptive Field

Definition 6.6. **Receptive field (RF)** is a region that activates sensory receptors or neurons.

Somatosensory neurons is localized at a specific region of space. These neurons do not see perceive the entire world around it but only part of it which is the receptive field. You can think an afferent neuron have branches that is at a specific location on the skin. Depending on the where the stimulus is on the receptive field, it would induce different neural activity.

Example 6.2.4. A stimulus near the RF would lead to a high afferent response (corresponds to amount of action potential) while far away would lower the afferent response.

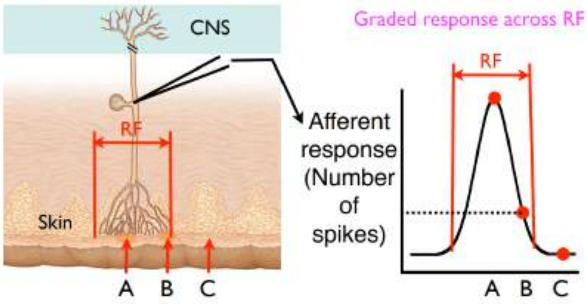


Figure 6.18: Receptive field and afferent response.

The problem is that the brain does not know how strong is each stimulus from the receptive field. Remember, the brain only perceive the neural activity and intensity of stimulus can change the afferent response itself. This also means the brain will not know the **difference between a light stimulus in the middle of the RF or a strong stimulus to the edge of the RF.**

To solve this problem, RFs tend to overlap such that a single stimulus will produce a large response (maybe at the RF) but also produce smaller response of neighbouring RF. This mechanism of presenting 1 stimulus as afferent response by different neurons (RF) is called **population coding**. This allows the brain to detect the strength and location of stimulus.

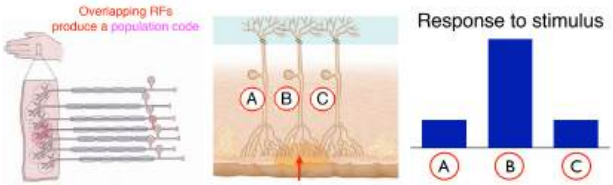


Figure 6.19: Overlapping RFs

Definition 6.7. **Acuity** is the ability to differentiate 1 stimulus from another.

The smaller the RF, the higher your acuity would be; while the larger it is the smaller your acuity would be. The reason for this is with smaller RF, you'd have a higher "concentration" of overlapping RF at that spot which

increase acuity since stimuli that are not so far apart can still be differentiate by the high amount of overlapping RFs. On the other hand, larger RF would have a lower concentration of overlapping RF at that spot which decrease acuity

Remark 6.8. *We can test acuity on different part of the body. Prepare 2 needle and poke them at a test spot on the body at the same time. Begins by having the 2 needles very close then increase the distance between then until you can differentiate the 2 needle, that would roughly be the distance between 2 RFs.*

Lateral inhibition is the process of 1 strong afferent response inhibiting smaller afferent response which would sharpen sensory acuity.
There are **inhibitory interneurons** that can shape and change the neighbouring afferent. What happened is that afferent response will come in and excite the interneuron which would lead it to inhibit the rest of the around it. Whichever RFs create a bigger afferent response i.e. receive a bigger stimulus, the more its interneurons inhibit the others leading that afferent response to be larger than the rest.

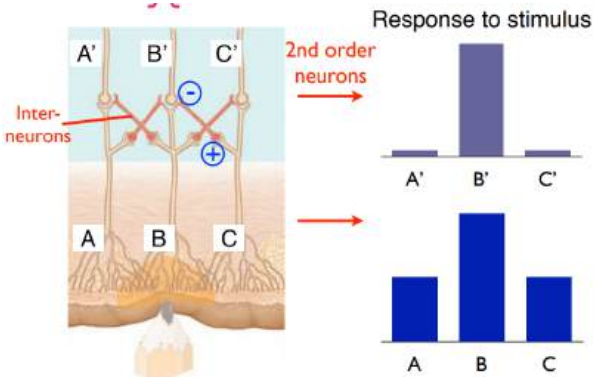


Figure 6.20: Lateral inhibition and increase in acuity.

6.2.4 Sensory Inputs Modulation

The brain can inhibit and shape sensory information going up the spinal cord. This inhibition and reshaping can be done by the **descending pathway** (top down) or **ascending pathway** (bottom up). We've seen the ascending pathway and modulation with the lateral inhibition of inhibitory

interneurons. Now we'll look at the descending pathway where the brain does the modulation

Example 6.2.5. Supposed you were trying to find your friends who is wearing a bright red shirt in a large crowd. You'd notice that immediately all of the people wearing red is more distinguished than others. This is because of the descending pathway where the visual cortex of the colour red become enhanced.

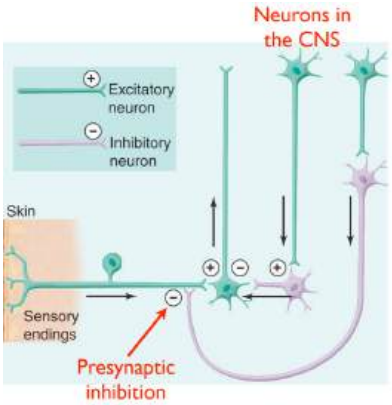


Figure 6.21: Mechanism of descending pathway.

Example 6.2.6. Pain are highly modulated and can be shut down by the brain. The brain can sends signals down to the neurons carring the pain signal and inhibit them from relaying that signal from synapsing in the spinal cord. Furthermore, the synapses have opiate receptors which is why opiates like morphine is used a lot as pain reliever in clinical conditions.

Remark 6.9. *The ascending pathway is automatic but the descending pathway is somatic i.e. you have control of your descending pathway.*

6.3 Somatosensory System

The **somatosensory system** is a system that can transduce external stimulus in form of somatic senses such as touch, pain, thermal, etc. The somatosensory system made up of many different receptors that can response to different stimulus such as mechanical (touch), thermal (temperature) and chemical energy.

6.3.1 Mechanoreceptors

Definition 6.8. **Mechanoreceptors** are sensory receptors that can open or close its ion channel in response to mechanical energy. Their structure are generally specialized end organs that surrounds nerve terminals.

There are different types of mechanoreceptors depending on the location which can be superficial or deep.

In the superficial layer, we can find the **Meissner's corpuscle** which are fluid-filled structure with nerve terminal that can rapidly adapt (to stimulus). They can sense light touch and flutter. The **Merkel's disk (nerve ending)** is a supreficial mechanoreceptor, whose structure consists of small epithelial cells surround the nerve terminal that can slowly adapt. They can sense pressure and texture.

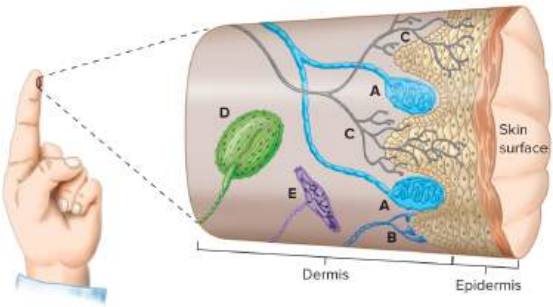


Figure 6.22: A: Meissner's corpuscle, B: Merkel's disk, C: Free neuron endings, D: Pacinian corpuscle and E: Ruffini endings.

In the deep layer, we can find the **Pacinian corpuscle** which are large concentric of connective tissue surround the the nerve terminals that can rapidly adapt. They can sense strong vibration. The **Ruffini endings** are deep mechanoreceptors whose structure consists of nerve endings, that can slowly adapt, wrap around a spindle-like structure. They can detect stretching and bending of the skin allowing you to feel the shape of an object.

The somatosystem also encodes for **proprioception**, which consists of muscle spindles that provide a sense of static position and movement of limbs and body i.e. allow us to "know" where each if our body part is.

Mechanism of Mechanoreceptors

Mechanoreceptors are ions channels that can be opened by the stretch of cytosleketal strands. These strands interconnect with all of the mechanoreceptors so that when there's a deformation, they pull onto each of the receptor.

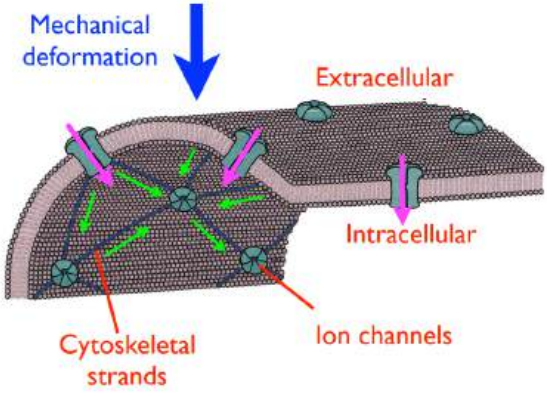


Figure 6.23: Mechanism of mechanoreceptors

This pulling will lead to an open conformation of the ion channel which allow ions to flow.

6.3.2 Thermoreceptors

Definition 6.9. **Thermoreceptors** are sensory receptors that has similar general structure like mechanoreceptors but respond to a range of temperature.

They made up of a family called **transient receptor potential proteins**. They consists of 2 afferents: cold $(0-35^oC)$ or warm $(35-50^oC)$. Not only temperature change can activate thermoreceptors but chemicals can also do that.

Example 6.3.1. Menthol can activate cold afferent of the thermoreceptors while capsaicin and ethanol can activate the warm afferent.

Remark 6.10. *Any temperature below or above these range of the thermoreceptors will activate pain receptors.*

6.3.3 Nociceptors

Definition 6.10. **Nociceptors** are sensory receptors same as mechano and thermoreceptors (free nerve ending it ion channels). They mainly response to intense mechanical deformation, excessive temperature and chemicals.

The pain afferent produced by the no are high modulated i.e. can be suppressed or enhanced. We also have visceral pain receptors that are activated by inflammation.

Mechanism and Enhancement of Nociceptors

Once an extreme pressure is sensed by nociceptors, they will fire afferent to the spinal cord which allow substance P to be released thus allow you to feel pain (initiation). Substance P will be released to mast cells which in turn release histamine, and to blood vessel which cause dilation. Histamine, along with other substance like 5-HT and prostaglandin (released by cells in the lesion), can act as an agonist to the nociceptor. This would lead to an increase sensitivity to that nociceptors i.e. increase sensitivity at the injured site. This increase in sensitivity is called **hyperalgesia** using the ascending pathway.

6.3.4 Neural Pathway of the Somatosensory System

Somatic sensory information can be sent to the brain via 2 neural pathways depending on the modalities: dorsal column and anterolateral pathway.

The **dorsal column pathway** will transduct touch and propriocetion toward the brain.

Definition 6.11. When an afferent is **ipsilateral**, it means means afferent on the same side; on the contrary, **contralateral** means on opposite sides.

> **Mechanism of Action (dorsal column pathway):** After touching something, mechanoreceptors are activated which sends *ipsilateral* afferent through the spinal nerve including the dorsal ganglion. Afferent will cross the dorsal horn of the grey matter then travel up the spinal cord via the dorsal column (white matter). Afferent enter the brainstem then branches at the level of the medulla which will cross the midline and sends toward the **reticular formation**. In turn, **medial lemniscus** will send this *contralateral* signal across

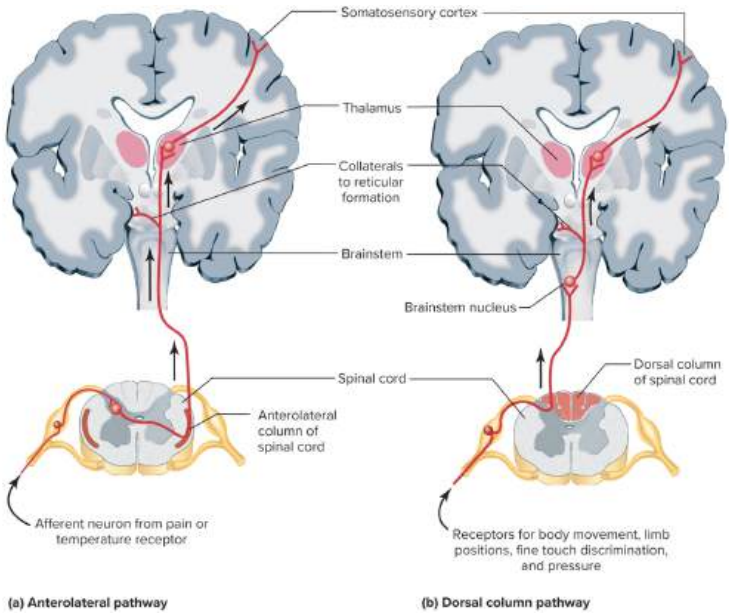


Figure 6.24: Mechanism of the anterolateral and dorsal column pathway

the midline of the body, to the thalamus then to the snesory cortex

On the other hand, **anterolateral pathway** will transduct temperature and pain to the somatosensory cortex. This pathway is different from that of dorsal column.

Mechanism of Action: Signals will be sents through the spinal nerves as usual. It will then be sent to the dorsal horn where it would synapses *ipsilaterally*. This signal will travel across the grey matter, central canal which cross the midline. This *contralateral* signal will be sent through the spinal cord via the **anterolateral column (or spinothalamic)**. Afferent enter the brainstem then branches at the level of the medulla which will cross the midline and sends toward the **reticular formation**. In turn, **medial lemniscus** will send this *contralateral* signal across the midline of the body, to the thalamus then to the snesory cortex

Remark 6.11. *Spinal injury could cause a loss in touch, temperature or even pain sensation.*

Your brain know the modality and location of each afferent however...this is not the same as pain. Visceral and somatic pain afferent commonly synapse on the same neurons in the spinal cord (via the anterolateral column pathway). **What's the problem here?** It does not know which afferent is driving which pain because they share the same neurons. Usually, these pains would be "assigned" to the skin by the brain and it is called **referred pain** i.e. the pain of a region is actually the cause of another region due to the brain using the same synapsing neurons.

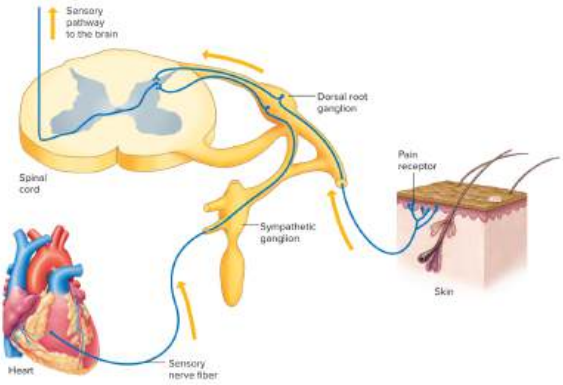


Figure 6.25: Referred pain

Example 6.3.2. Heart attack typically produced pain and numbness on the left arm.

We could technically block pain by ourselves. The second neurons in the ascending pain pathway will be inhibit by the periaqueductal grey matter in the midbrain. It will send inhibitory signals down to the reticular formation, then through the **dorsolateral funiculus** which then will synapse with the second neuron in the dorsal horn thereby inhibit it. This process of pain inhibition is called **analgesia**.

Remark 6.12. *This is also the why there's a class of drug called analgesic which is pain reliever.*

Remark 6.13. *These neurons in the pain pathway have opiate receptors which would create presynaptic inhibition and also can be inhibit by opiate drugs such as morphine.*

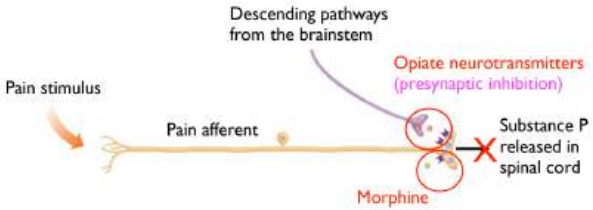


Figure 6.26: Opiate receptors and morphine

6.3.5 Somatosensory Cortex

In the somatosensory cortex, ganglions are grouped according to the location of the receptors that sent the afferent. e.g. ganglions that carry afferent from the hand would be group together into a quasi-discrete section on the somatosensory cortex.
The somatosensory mapping area for each section correlates (proportional) to the amount of innervation, acuity at that location.

Example 6.3.3. The tip of the finger is highly innvervated as well as has high acuity therefore on the somatosensory cortex, it would occupy a large regions.

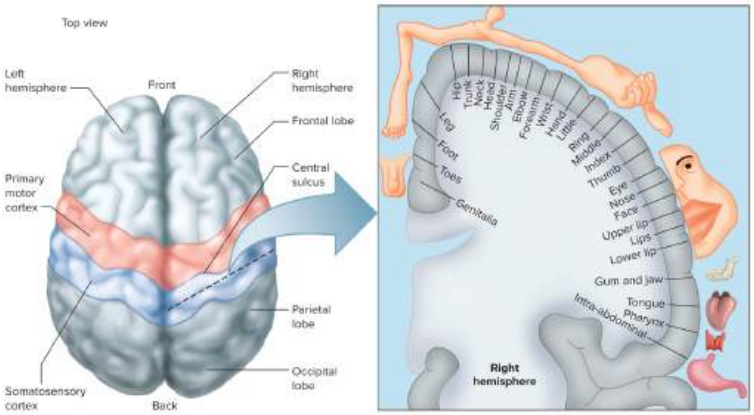


Figure 6.27: Mapping of the somatosensory cortex.

Remark 6.14. *This is a contralateral representation i.e. if this is the right hemisphere of the somatosensory cortex, then it would correlates to the left side of the body*

Example 6.3.4. If there was a lateral damage on the somatosensory cortex, we would lose all contralateral somatosensory on the face.

6.3.6 Lesions and Somatosensory findings

We'll be looking at some example and apply what we've known into clinical setting (similar but not really) that is to find the lesions on the spinal cord according to the somatosensory lost on the body or *v.v.*

Example 6.3.5. A spinal segment has a lesion on the left dorsal column. What would be the somatosensory findings (lost) for this patient?
Answer: Because it's a lesion on the dorsal column, we would expect a left lost of touch and proprioception at and below this spinal segment.
We can generalize this problem, that is, if there's a lesion on 1 side of the dorsal column, there will be an ipsilateral loss of touch and proprioception at and below the spinal segment.

Example 6.3.6. A patient present to the hospital with loss of touch and proprioception (TaP) from the left hand to the toe. Everything is normal on the left rightside. The patient pain and temperature perception is intact for both side. Where's the lesion?
Answer: If T^o and pain is normal for both side then we can rule out the anterolateral column. The patient lost TaP hence it has to be a lesion on the dorsal column and since it is from the hand down, we can be more specific that it is the cervical dorsal column. Now, the patient only lost TaP on the left therefore there's a lesion on left cervical dorsal column.

Example 6.3.7. A patient present to the hospital with bilateral loss of touch and proprioception from the bellybutton to the toes. Pain and temperature is still intact.
Answer: Like before, T^o and pain is intact therefore it is not the anterolateral column. Patient experienced a loss of TaP which means it is the dorsal lateral column and because it is from the belly button, it would be the lumbar dorsal lateral column. If the. It's a loss on both side therefore it's a lesion on the entire lumbar dorsal lateral column.

Example 6.3.8. A patient present to the hospital with bilateral loss of pain and temperature in a thin strip at the level below the chest. Their TaP are

intact. Where's the lesion?
Answer: TaP are intact while there's a loss of pain and temperature could potentially mean a lesion on the anterolateral column. However, the loss is localized to a thin strips which means it is a lesion elsewhere. If the patient lost pain and T^o on both side, it's a possibility that the place where the second neuron crosses is damage which is the central canal

Example 6.3.9. A patient present to the hospital with loss of TaP, temperature and pain on the left side along a thin strip at the level of the belly button (no loss on the right). Furthermore, there's also a loss of TaP from the below button down to the toe of the left side while on the right side from the belly button down (not including the right thin strip), there's also a loss of pain and temperature.
Answer: If there's a loss of TaP on the left at and below the belly button, we would expect as before that there's a lesion on the left lumbar dorsal lateral column. In addition to that, there's also a loss of temperature and pain on the left while the right is intact which means that there's a lesion where the first neuron synapses i.e. left dorsal horn of the grey matter. But there's also a loss of pain and T^o on the right side from bellybutton to the toe which means that there's a lesion on the left lumbar anterolateral column.
In summary, there's a lesion on the left hemisphere of the lumbar spinal segment.

Remark 6.15. *The condition in example 6.3.9 is also known as* ***Brown-Sequard syndrome***

6.4 Visual System

The main stimulus for the visual system is light which are picked up by photoreceptors. Visual perception is dependent on context i.e. the brain tends to "fill up" gaps in whatever you see or relate it to sth.

6.4.1 Anatomy and Physiology of the Eyes

The white part of your eyes is the **sclera**. When it becomes transparent at the front of is the **cornea**. Behind the cornea is the **pupil** whose size can be changed by the **iris**. Behind it is the **lens** and the **intraoccular space** which is filled with **vitrous humour**. The second layer to the sclera is the **retina** whose internal surface is made up of **retinal pigment epithelium**.

The retina has lots of feature but mainly are the **fovea centralis**, which is a region of high photoreceptor density (cones) thereby deliver the highest visual acuity; and **optic disc** which is a circular regions where visual afferent converges and exit the eyes as the optic nerve (this is also where our blind spot is).

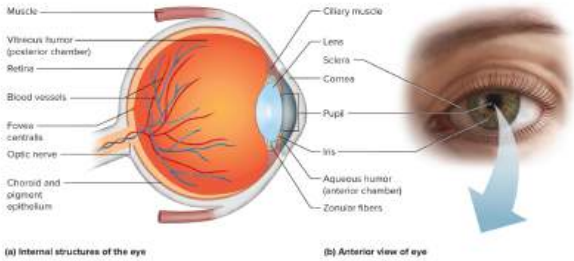


Figure 6.28: Anatomy of the eyes.

Light tends to scatter all through out from an object. When light passes through a medium such as lens or water, it will change the angle of incident; such phenomenon is called *refraction*. Refraction is also the main mechanism that allow light to focus on the retina.
We've always thought that the lens of our eyes does the refraction but actually the majority of refraction is carried out by the cornea while the lens is more for adjustment. The process of adjustment is called *accommodation*.

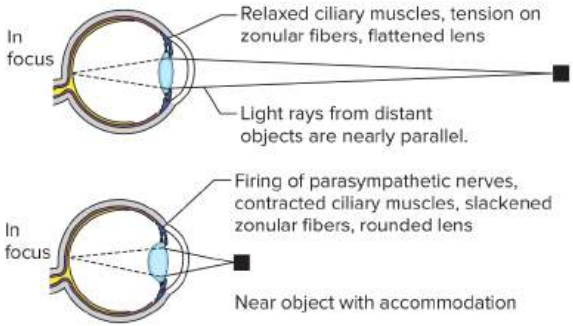


Figure 6.29: Accommodation of lens.

When the object is far away, the ciliary body (muscle that control the shape of the lens) will relax and allow the lens to flattened. On the other

hand, when the object is closer, the ciliary body will contract and round the lens.

Common Visual Defects

The most common visual defect is **nearsighted (myopia)** where the eyeballs is too "long" or *myopic*. On the contrary, **farsighted (hyperopia)** is a condition where the eyeballs is too "short" or *hyperopic*. **Astigmatism** is a visual defect where the lens or cornea is not spherical; **Presbyopia** is a condition where the lens cannot accommodate; and **cataract** is when the lens change colour or becomes cloudy.

6.4.2 Phototransduction

Retina is a complicate circuit of photoreceptors neuronal cells. The organization of the retina is quite peculiar since it is "backward". From the retinal pigment epithelium, as we move *outward* (into the intraoccular space), we first will begin with photoreceptors which are cones and rods. They're connected to **horizontal cells** which also connect to the bipolar and amacrine cells which then finally converge to **ganglion cells**. The axons of ganglion cells will make up the optic nerve that exit the eyes.

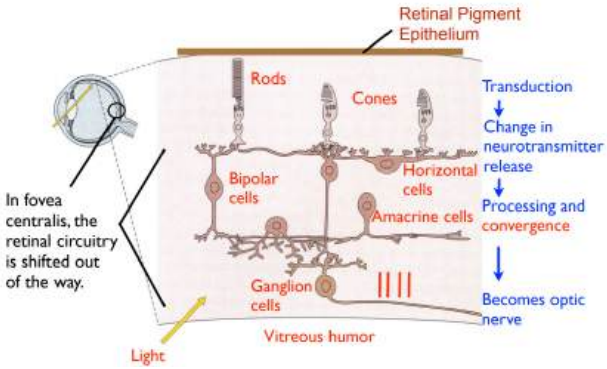


Figure 6.30: Organization of the retina.

Remark 6.16. *It seems inefficient to have photoreceptors to the back of the eyes instead of the front but actually this arrangement minimize distortion and maximize absorption.*

This idea of retinal convergence is basically when multiple photoreceptors send signals to a ganglion cell. Cones are actually less convergent than rods because if you were to look at the peripheral retina (far away from the fovea), there would be a larger area of more rods which which all converge to 1 ganglion. The down side is the acuity would decrease (still high RF). On the other hand, at the fovea, it is exclusively for cones at a single point (low RF but high acuity) but they all will converge to their own ganglion hence lower convergence.

Now let's get into the transduction pathway from light stimulus to action potentials.
Light can change the ion channels on cones and rods which lead to neutrotransmitter release. Signals are then processed and converges at the ganglion cell which will send afferent. Then **how does light closes ions channels?** To answer this, need to to take a closer look at the photoreceptors (rods or cones doesn't matter since they have the same mechanism).

There are 2 portion to them: inner segment and outer segment. The inner segment consists of the nucleus while the outer segment consists of stacked membrane disc. The reason that the disc are stacked is because photons are hard to catch so this would increases the likely hood. Inside each disc is the **chromophore** which is a molecule that sits in a protein called **opsin** that can capture photon.

Remark 6.17. *If it was rod there's 1 kind of opsin called rhodopsin while for cones there are 3 different opsin molecules (for each red green blue).*

The outer segments also has lots of cGMP in the ICS and the lining the outer segment also has many cGMP-gated Na^+ channel. When this channel open due to the presence of cGMP, Na^+ will flow in and photoreceptor is depolarized. When it's depolarized neurotransmitter are released into the previous circuitry of horizontal, amacrine cells, etc.

Remark 6.18. *This depolarization events happens when there's no light (in the dark) for rods. Therefore photon (in the presence of light) reduce neurotransmitter through hyperpolarization (mechanism shown below).*

> **Mechanism of Action:** The disc have tons of opsin proteins which can capture photon. Once photon is capture by the opsin, literally the photon smash into the opsin protein. The chromophore and opsin separate which lead to conformational change. Opsin will

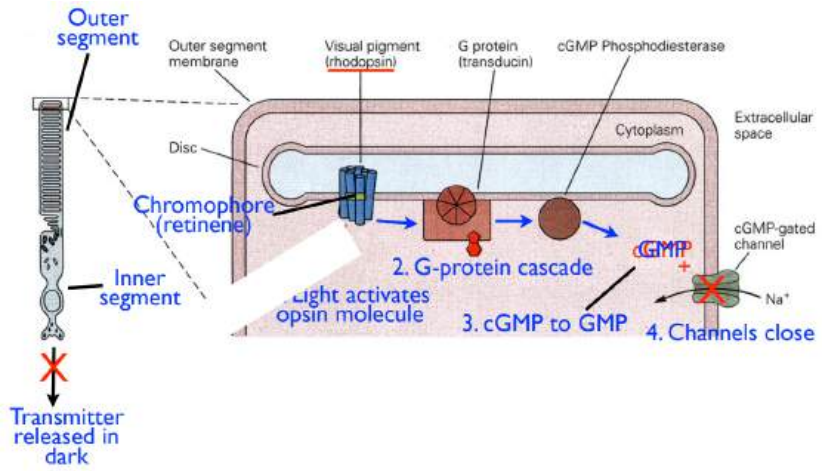


Figure 6.31: Mechanism of action for photoreceptors

> trigger G-protein cascade, which is a motor. The motor can run for a while, which convert cGMP to GMP. Because of there are more GMP than cGMP, the cGMP-gated Na^+ channel closes which lead to hyperpolarization of the photoreceptor which reduce transmitter. (see Figure 6.31)

You might ask yourself that **if neurotransmitter is reduced, how can ganglion at the end can fire action potential?** Well...this is due to the middle circuitry with amacrine, bipolar and horizontal cells. They process and invert the signal coming for ganglion cells.

Rods and Cones

Although there are many similarities of function between these 2 photoreceptors, they also have some differences on their own. (see table below)

All in all, rods are photoreceptors used for mostly during the night, they're more sensitive and can capture more light. Nevertheless, they're achromatic consisting of only 1 opsin; not present in the fovea therefore lower acuity but is more convergent. On the other hand, cones are photoreceptors used mostly during the day, they're less sensitive and and have

Rods	Cones
High sensitivity, night vision	Low sensitivity, day vision
More rhodopsin, captures more light	Less opsin
High amplification, single photon closes many Na+ channels	Lower amplification
Slow response time	Faster response time
More sensitivity to scattered light	Most sensitive to direct axial rays

Rod system	Cone system
Low acuity: not present in central fovea, highly convergent	High acuity: concentrated in fovea, less convergent
Achromatic: one type opsin	Chromatic: three types of opsin

less opsin. Nevertheless, they're main concentrated in the fovea making them high in acuity but is less convergent.

6.4.3 Dark and Light Adaptation

When you're out in bright lid room, the rods are inactivated because photons will break all the bond between the chromophore and the opsin. If you immediately turn the to a minimal, you'll get a temporary blindness. This is because there's not enough photons for the cones to work while the rods were inactivated previously because the chromophore and opsin's bond are broken. After around 15-20min you'll regain the ability to see since your rods will be reactivated again.

the reciprocal would happen when you're in a dark room and immediately turn the light on. Initially, your cones are inactive since there's not enough light while your rod is completely activated. Once light are immediately turn on, your rod will be saturated with photons and chromophore and opsin's bond start breaking extremely fast which make ganglion fires a lot of action potential. At the same time, cones are also activated as well; so the combination of all of the photoreceptor activated at the same time will render you temporary blind (you may experience this blindness by an extreme bright flash). After a bit, the rods will be deactivated and cones take over.

6.4.4 Ganglions and Receptive Field

Retina reports relative intensity of light. i.e. retina does't report how much photon is coming off from an object but it's comparing the differences between the object and its surrounding.

Example 6.4.1. Take the following figure Many would say at the grey ring to

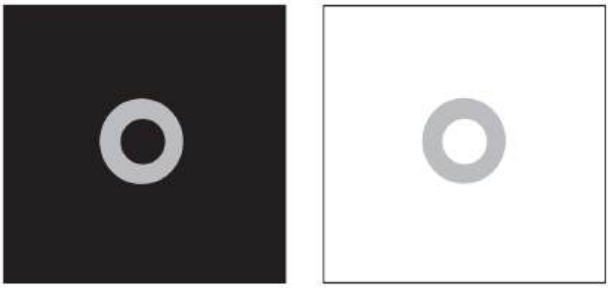


Figure 6.32: Same grey color ring with different background.

the left is darker than that on the left. In fact, these 2 have the same colour. The reason many of us perceive this is the retina would compare the grey right to the dark or light back ground. If the grey ring is presented in a dark background. they're less photon firing out thus it gives an illusion that the right is lighter.

How does this work? Well, the internal circuitry of the retina is doing this computation of the differences in photon between the visual input (what you're looking at) and what's neighbouring to it (what you can see but not looking at directly). These comparison is also carried out by ganglion cells.

If we're classifying ganglion in accordance with their center-surround RFs, then there are 2 types: excitatory center + inhibitory surrounding (ECIS), inhibitory center + excitatory surrounding (ICES). Essentially, the ECIS ganglions love to have their RF's center receiving bright stimulus while its surrounding is dark and the antithesis is true for ICES ganglions

Example 6.4.2. THe ECIS ganglion would fire lots of action potential when it's looking at a image with a bright center and dark surrounding since it matches with the ganglion's "preference".

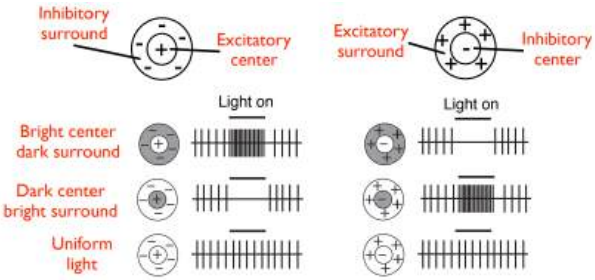


Figure 6.33: ECIS and ICES ganglions and action potential when exposed to different images.

But then you might ask yourself **but images that we see are not these center and surrounding things no?** Well...no it isn't but remember that the vision that we have doesn't stop at just the ganglions. All of the action potential of the ganglions will be sent to the visual cortex to be put together as an image that you'd typically see.

6.4.5 Colour Vision

Like we've prevsiously known, rods general send information about dark and light due to it having 1 opsin molecules. Cones on the other hand has 3 opsin molecules that can interact with photon of different wavelength which allow us to see colour. Our colour vision and opsin molecules from the cones can detect light wavelength from 400 to 700 nm which makes up the colour spectrum.

Remark 6.19. *Other animal like bats or rodents can see ranges below 400 (toward the UV light) and mosquitoes can see ranges above 700 (toward the infrared).*

Ganglion cells sends information about colour depending on which colour receptors is activated. Colour is highly influenced by its neighbouring the same mechanism that caused contrasting of light intensity.

Looking at Figure 6.34 (left), many would perceive that the 2 X would have different colour even though they're the same. This is the same way as before where the ganglion would take the differences between the center and the surrounding. Therefore the output of the retina only encodes for *relative* amount of brightness and colour.

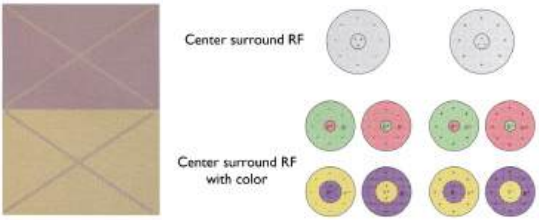


Figure 6.34: X of same colour but different background (left). Different type of center-surround RF of ganglion.

Colour Blindness

Colour blindness is a genetic condition where opsin molecules are not functioning correctly or not at all; which leave individuals to have different colour perception than a normal person does.

Remark 6.20. *More that* 5% *of the population experience colour blindness. Of them, the majority is male.*

6.4.6 The Neural Pathway of Visions

If you imagine a midline in the visual world, we have a **left and right visual field**. Refraction of the cornea and lense will invert the image coming in which means that the right or left visual field will be project to the opposite side on the retina. We divide the retina's side into the **temporal** (the side closer to the temporal lobe) and **nasal** (closer to the nose).

After, optic nerves from each eyes will sends signals from the visual input of both visual field down to the **optic chiasm**. At the optic chiasm, some of the axons will cross and some doesn't, then **How do we know which axons will or won't cross?** Well...fibers or axons that receives visual inputs from the nasal retina are the one that will cross the optic chiasm (midline). Then, from the optic chiasm, it will branch out to become the left and right **optic tract**. The optic tract will only carry visual input of the *contralateral visual field.* Then the optic tract will synapse at the **lateral geniculate nucleus** , in the thalamus, which would go to the visual cortex via the a projection called the **optic radiations**. The **visual cortex** made from the left and right **occipital lobe** which would also receive input from both eyes with contralateral visual field.

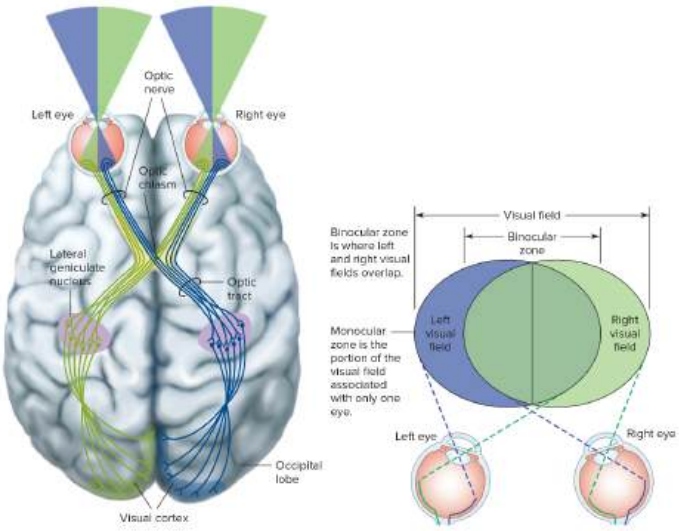


Figure 6.35: Pathway of visual information to the visual cortex.

Remark 6.21. *Further finding shows that, almost* 50% *of the entire cortex contains neurons that respond to visual inputs.*

If this is the case then visual information and how we perceive it isn't localized only at the visual cortex but at other part as well. Then, **how does the flow of visual information through the cortex has been studied over the past years?**

Examining neurons in the **primary visual corves** shows that they have small RFs no center-surround structure. It can detect edges, changes in colour and contrast (oriented line segment).
There are around 20 labelled visual area in your brain. Of the approximate 20, they're divided into 2 streams: parietal visual and temporal visual stream.

Remark 6.22. *They're called stream since you always begin at the visual cortex of the occipital lobe then you can stream out to the temporal and parietal lobe*

The parietal visual stream's neurons large RFs which can see almost the entire visual field. They're more spatial selective (where things are)

and responded to motion (how things are moving through space). This visual information would then be mixed with the somatosensory information to form the **polymodal visual** and other sensory modalities combined together i.e. what you touch is where you see it.
In contrast to that, the temporal visual stream has large RFs and can recognize complex features such as faces.

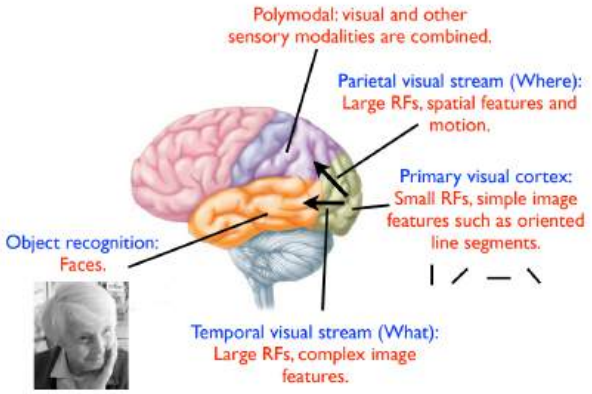


Figure 6.36: Visual information flow from the occipiatal lobe to the frontal lobe.

Then finally, the 2 stream will all merge together in the frontal lobe, and we finally see a grand unified visual perception of the external world.

6.4.7 Lesion and Visual Findings

We'll be looking at some example and apply what we've known into clinical setting (similar but not really) that is to find the lesions on visual system according to the visual lost or v.v.

Example 6.4.3. A patient present to the hospital with a lesion of on 1 of the optic nerve, what would be the visual loss?
Answer: If it's the optic nerve then they must have an ipsilatral loss of vision i.e. loss of vision in 1 eye where the optic nerve is carrying inputs.

Example 6.4.4. A patient present to the hospital with Loss of vision in the contralateral vision field. Where is the lesion?
Answer: Since it is a contralateral loss as well as half of the vision field is still intact, then the optic nerve is not damaged. A contralateral loss of vi-

sion field meaning that the contralateral inputs were loss therefore there's a lesion on the optic tract...

Remark 6.23. *Contralateral loss of vision can also be a damage on 1 hemisphere of the visual cortex or a lesion on the optic radiations.*

Example 6.4.5. A patient present to the hospital with a lesion on the optic chiasm, what would be the visual loss?
Answer: Well, if optic chiasm is damaged there would be some visual loss in both visual field hence bilateral. Rememer, optic chiasm is the place where the nasal optic nerve would cross which means we would lose any nasal retinal visual input. The visual input was inverted from the cornea which means that we would lose temporal visual input. Putting all of them together, we get a a bilateral loss of temporal visual hemifield (left or right visual field).

6.5 Auditory System

Definition 6.12. **Sounds** are vibrations that propagates in the air that causes a change in pressure of the air.

we're only sensitive to sounds of frequency at around 10Hz to 20kHz. Other animal may have a higher frequency percetion. Not only frequency of sound play a role but also the loudness/amplitude of it. Sounds are measure is decibel which is a logarithmic scale i.e. a 20dB sound would be 100x times more powerful than that of 10dB. Normally, we the safe range for us is $0- \leq 80$dB. Sounds from 100-140dB would cause some discomfort and anything above would be painful.

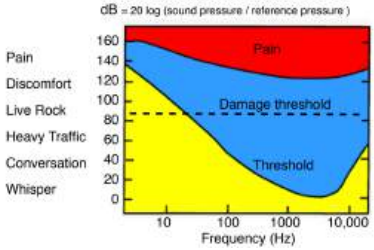


Figure 6.37: Normal audibility curve.

Remark 6.24. *Even though the pain and discomfort start around 100dB, the damage sound threshold is roughly in the high 80s i.e. You can listen to a sound of 90dB and not feel pain nor discomfort however...you would be damaging your ear without knowing it.*

Note: if you're using your earbuds, a volume level of 50% or below is generally safe for an indefinite amount of time. At 80% you only can listen for 30min per day and at 100% it's reduced down to 5min.

Definition 6.13. **Presbecusis** is a natural hearing loss condition where an advancing in age would lead to a gradual hearing loss (mostly is high frequency loss).

6.5.1 Anatomy of the ear

The ear as observe from the outside consists of the earlobe with folds called pina and a hole where sound can go through.

Remark 6.25. *The ear is shaped that way is because it can reflect certain frequency.*

Remark 6.26. *When you're young, you can detect stuff that slightly above the Brownian motion of air in your ear; it's also the quietest sound you can detect.*

When we move deeper in, we can go through the **external auditory canal** then to the **tympanic membrane**. The tympanic membrane would connect to the smallest bones structures called **malleus**, **incus** and **stapes** (abbreviated to MIS) in the **middle ear**. The middle of the ear cavity got its air from the **Eustachian tube** that would connect to the nasal cavity.

Behind the middle ear, embedded in your skull is the **inner ear** which hold the **osseous labyrinth**, a bony shell of the inner ear. The osseous labyrith consists of the the cochlea, semicircular canals, oval and round window. The cochlea is the main organ for sound detection, semicircular canals are mainly for the vestibular system, oval and round windows are membranes to transmitter auditory signal to the cochlea.
If we cut away the bony shell, we can see sensory epithelia that can transduce auditory or vestibular signals. There are also 2 other organs called the **utricle** and **saccule** which is important for detection of horizontal and verticle acceleration of your head.

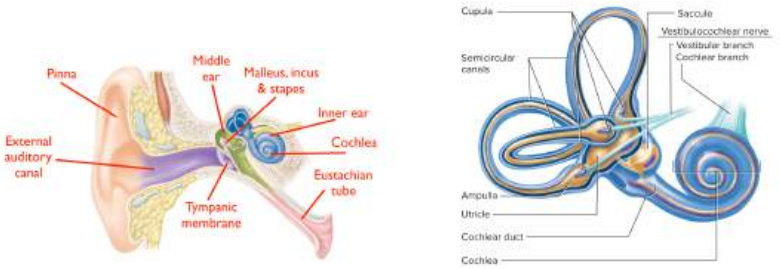


Figure 6.38: Anatomy of the ear and the osseous labyrinth.

> **Mechanism of action:** First, sound will be deflected from the pinna to the external auditory canal. It will then reach to the tympanic membrane. High pressure cause the tympanic membrane to move inward and low pressure is the opposite. The movement of the tympanic membrane is connected to the MIS. The MIS is modulated by skeletal muscle which reduce the amount of movement for loud sounds. The sound is also amplified by the oval window (smaller area than tympanic membrane). The oval window transmit this through fluid filled canals in the cochlea which would circulate to the tip (*helicotrema*) and return back at the round window to equalize the pressure.

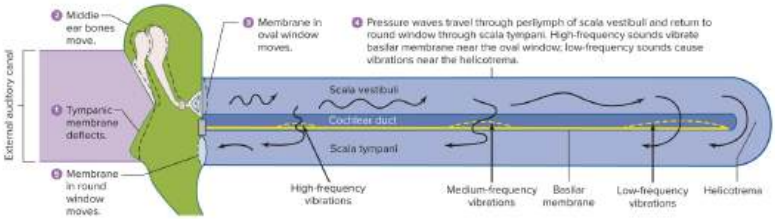


Figure 6.39: Helicotrema

The cochlea has 2 fluid filled membrane which is the scala vestibuli (tympani) and cochlear duct

The cochlear duct is lined with the flexible **basilar membrane** that can move up and down in response to the pressure wave of the other duct. The

basilar membrane isn't uniform and vibrates differently from each other along the cochlear duct. Depending on the frequency of the wave, the basilar membrane would vibrates at the regions that was designated to such frequency i.e. the basilar membrane encodes different frequencies.

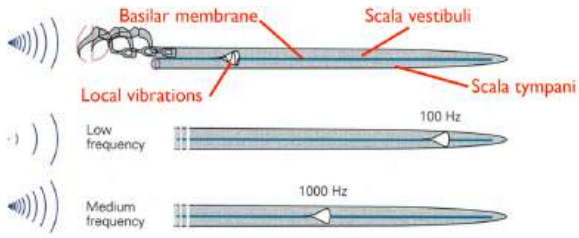


Figure 6.40: Basilar membrane in response to different frequency

6.5.2 Hair Cells and Auditory Transduction

Looking at the cross section is cochlea, we can see, sitting on the basilar membrane, the **organ of corti** which is also where the afferent is. It has 4 rows of specialized cells called **hair cells** and that's where the transduction process and afferent comes from. We can divide them into the outer and inner hair cells where majority of afferent comes from the inner while the outer is efferent.

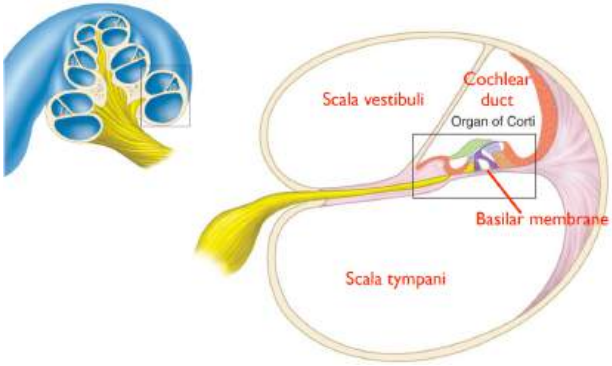


Figure 6.41: Cross section of the cochlea.

The outer hair cells have *electromotility* which shorten them when depolarized and lengthened when hyperpolarized. The outer hair cells is

thought to amplify the motion of the basilar membrane. The outer hair cells actually make a clicking noise due to its electromotility and these noise can be capture. Using this understand clinicians have developped the **otoacoustic emission test** which allow them to know if the auditory system of a baby is working properly.

Remark 6.27. *Quebec is the last place in Canada that required auditory screening.*

Atop the hair cells are bundles of hair called **stereocilia**. As the basilar membrane move up or down, there's a shearing force applied upon the stereocilia. This shear force is due to the fact that stereocilia is connected to a surface called the tectorial membrane. The shear force would then cause the stereocilia to bend 1 way other the other.

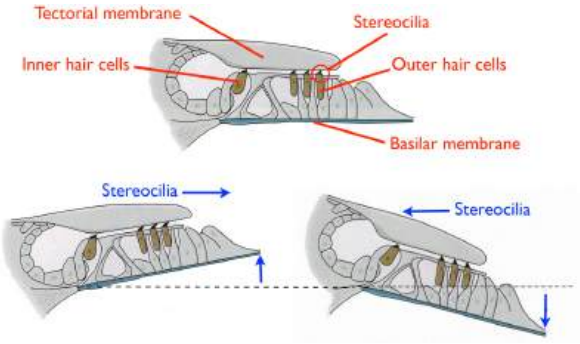


Figure 6.42: Movement of stereociliar when the basilar membrane move

Why does moving stereocilia causes transduction? Well...we theorize that there are ion channels on these stereociliar that lead to depolarization but**Where?** well...What we found is that as the stereocilia moves, its tip getting bigger then smaller and v.v. With the advancement of electromicroscope, we can see a very small fragment called **tip link** that connect each stereocilia together. There are around 15,000 hair cells in each cochlea, each hair cells there are 10-20 cilia and each of them 1 tip link and if they break, it is problematic. It also turns out that ion channels are located on each side of the tip links. When the cilia move in 1 direction, the tip links is pulled which open the ion channels.
The ion channels allow K^+ to come in thus depolarize the cell which lead to the released of neurotransmitter to neuron dendrites. Now you might find

it weird...**Why is it K^+ but not Na^+ like usual?** Well...It's because the composition of the fluid in the couchlear duct is different from all other fluid in the body that is it has a high $[K^+]$ in it.

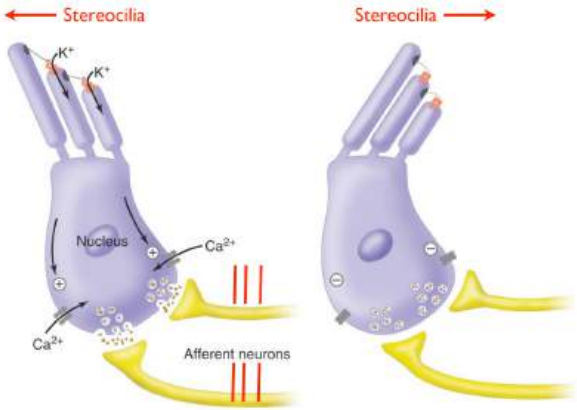


Figure 6.43: Tip link connect stereocilia together at the ion channel.

This is a fragile system and can break. One of the most serious is **Tinnitus** which is ringing of the ear. Tinnitus can be transient or chronic. Transient tinnitus is main caused by the loud sounds, which create mechanical stresses on stereocilia and break the tiplink. However it would grows back eventually (ringing stops).
Chronic tinnitus has multiple causes but mainly because of loud noises. It's originated mainly in the inner ear, nerve or central pathway. The ringing does not stop for this condition.

6.5.3 The Neural Pathway of Auditions

Afferents coming from the cochlea form the **8th cranial nerve** which go to the medulla. From the medulla, signals are sent bilaterally to the midbrain then thalamus, then finally the **auditory cortex** i.e. the afferent is sent both ipsilaterally and contralaterally to the auditory cortex. This bilateral pathway also allow us to localize where the sound is.

Cochlear Implants

The **cochlear implant** is an implant that would re-estabilishing hearing for hearing loss individual. Deafness can be due to problems with the hair cells but the afferent are still there which means that we can still stimulate it with electrodes. Electrodes of the implant will figure out what frequency and where to stimulate those afferent.

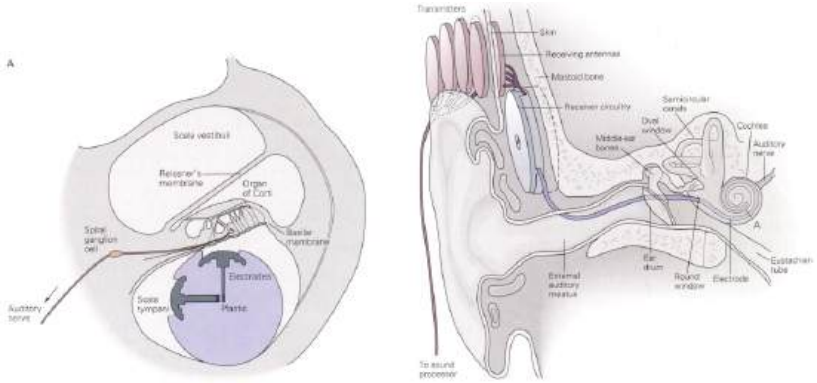


Figure 6.44: Cochlear implants and electrodes.

6.6 Vestibular system

The vestibular organs consists of mainly the semicircular canals, utricle and saccule (Described in the anatomy of the ear). It can detect how your head is moving through space. Both utricle and saccule would detect linear acceleration, more specifically, horizontal and verticle respectively. The semicircular canals (3) on the other hand would detect 3 angular rotation of the head (pitch, yaw and roll). Not only that, they also help you to be balance but also help with the visual system.

Have you ever noticed that when you focus your eyes an object, you can turn your head and still have your gaze on that object. This is due to the **vestibular ocular reflex**. This reflex makes sure that as you move your head in 1 direction, the vestibular organs will "lock" your gaze on what you're looking at.

6.6.1 Angular rotation

The afferent of the vestibular system is similar to that of the auditory system i.e. they all use hair cells and stereocilia to depolarize and release neurotransmitter.

We begins with the detection of angular rotation with the semicircular canals.
In the semicircular cannals, there are structure called ampula and cupula. The cupula is a structure connected to hair cells and stereociliar. It's also held in place at the tip by the ampula [wall]. When you rotate your head, the cupula moves with your head but the fluid doesn't move right away due to momentum which cause the cupula to bend thereby bend your stereocilia.

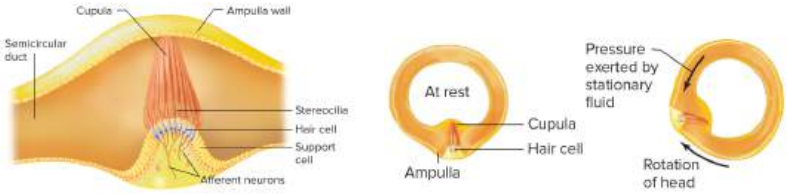


Figure 6.45: Ampula and cupula structure and movement.

6.6.2 Linear Acceleration

The utricle and saccule detect linear acceleration (forward backward, up and down). They have hair cells that stick into the a gelatinous substance with **otolith** embedded in it. The otolith are calcium carbonate crystals and the gelatinous substance is slightly heavier than the fluid.

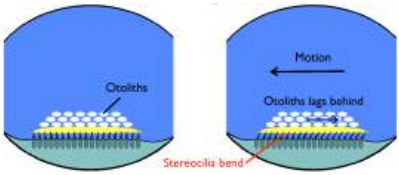


Figure 6.46: Otolith and the mechanism of detect linear acceleration.

When there's a linear acceleration, the fluid will move in 1 direction while the heavier otolith (gelatin) will move in the opposing direction because it's heavier then slowly it will get back to the same direction (lagging behind). This movement of the otolith in the other direction would directly bend the stereocilia and release neurotransmitter.

6.7 Gustatory System

For gustation, the main organ that mediate it is the **tongue**. It has bumps called **papillae**, to the side of it are **taste bud** which consists of **taste pores** where dissolved chemicals can enter and interact wirth **gustatory (taste) cells**. Once this interaction is established, afferent is create for gustation.

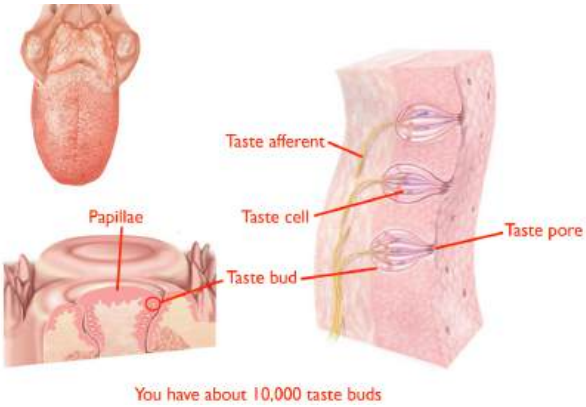


Figure 6.47: Brief anatomy of the tongue.

6.7.1 Gustatory Transduction and Neural Pathway

We have around 10,000 taste buds but we can only distinguish only a few tastes and each of these tastes are mediated in different ways. The **sensation of salty** is due to Na^+passing through the ions channels of the taste cells which depolarize it and create an afferent. The **sense of sour** is due to H^+ ions entering ions channels.
We develop the sense of bitter as a protection mechanism. The **sensation of bitter** is tranduced by many way such as blocking ion channels or trigger G-proteins. The **sensation of sweet** is transduced by the binding of glucose

to the G-protein. Finally, the **sensation of sumami** is transduced by the activation of glutamate receptors which then activate G-protein cascade.

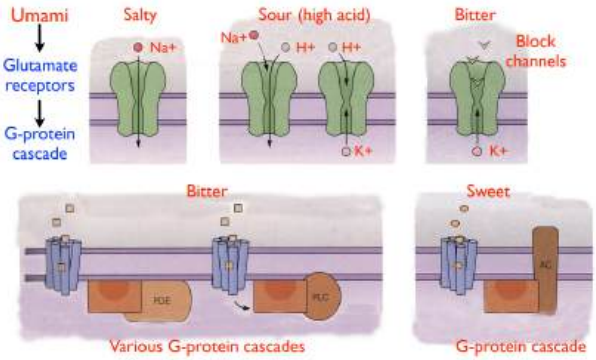


Figure 6.48: 6 transduction pathway of different tastes.

Remember...In order for the cell to differentiate all of these tastes, chemicals must dissolve in the saliva then its constituents can interact with the cell which then produce an afferent.

Gustatory afferent can travel through the cranial nerve where it first synapses at the level of the medula where it will then travel and synapse in the thalamus. From the thalamus, it will then go to the gustatory cortex

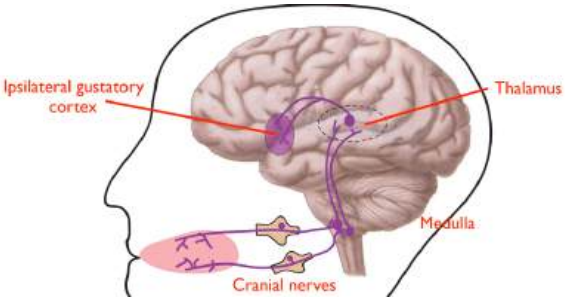


Figure 6.49: Neural pathway of gustation.

Remark 6.28. *Unlike other afferent going their respective cortex, the gustatory afferent doesn't cross the midline thus all of the afferent is ipsilateral.*

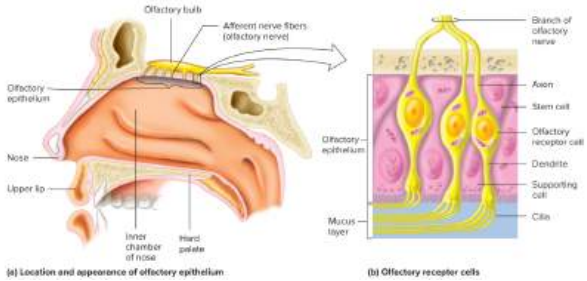


Figure 6.50: Brief anatomy of the nose.

6.8 Olfactory System

The main organ that mediate olfaction is the nose. Inside the nose is the nasal cavity. The nasal cavity's "ceiling" or the lining that sits near the brain is called the **olfactory epithelium**. Protruding from the olfactory epithelium (suspend in mucus) is the cilia of **olfactory receptor cells**. From the olfactory cells, it will branch toward the brain via the **olfactory nerve**. Many olfactory nerves will merge to make the **olfactory bulb** which would go to the brain as the **olfactory tract**.

6.8.1 Olfactory Transduction and Neural Pathway

Odourant molecules will move into the nasal cavity of your noce which would bind to the olfactory epithulium. They will dissolve to the mucus which can then bind to the cilia of olfactory receptors cells. The molecule will interact with the component on the cilia which activate a G-protein cascade that open ion channel and depolarize the olfactory receptor cell.

We're have 1000 odour receptors that respond to many chemicals

Remark 6.29. *Some odour chemicals can bind to the receptors very well while other won't be that much.*

Because of this, it sets up a population code for that odour. That means that even if you have 1000 odour receptors, it can encode for over 10,000 chemicals. In fact, most of the enjoyment in eating food comes from olfactory system instead of the gustatory.

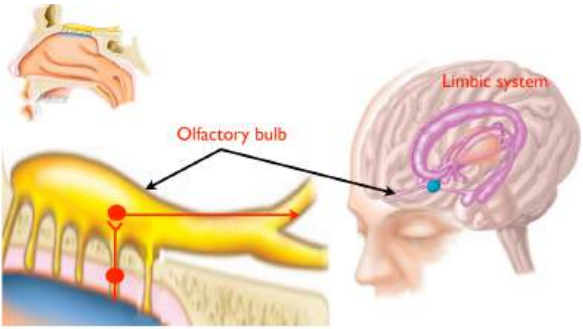


Figure 6.51: Projection of the olfactory system to the limbic system.

Unlike the rest of the sensory systems, the olfactory system projects directly to the limbic system which is the emotional and memory system of the brain. This is also why certain odour may trigger a certain memory, feeling or give you a sense of nostalgia.

We'll now deviate from the topic of the sensory system (as we've finished all of it) and turn to a new topic that is **consciousness**.

Consciousness can be thought of as either the state of consciousness or conscious experience.

Definition 6.14. The **state of consciousness** is associated with the level of arousal (awake, asleep, etc.) This can be measured by behaviour or brain activity.

If that is the case is a machine conscious? Technically, in a way, it has some sens of consciousness but not like that of a human hence why we have the second definition

Definition 6.15. The **conscious experience** are thoughts, life, desires and ideas.

So then **what's the different then between machine and us with consciousness?** Well, a machine doesn't have thought nor desire. It does not have ideas or invention, it can certain create stuff only through the thought of a human. Human, on the other hand, has the need to reproduce due to evolution. Then as we gain that thought and ability to control, we call those desires.

6.9 States of Consciousness

We can measure one's brain activity or state of conscious through the **electroencephalograph (EEG)**. EEG has surface electrodes that attached to the skull and they measure the activity of neurons closest to it. The size of electrodes are big compared to neurons (really small), this also means that 1 electrode can be affected by millions of neurons at the same time.

Remark 6.30. *EEG only tell us its activity but it does not tell us what the neurons are doing.*

EEG measure very tiny signal, in order of microvolts.
The way we interpret these signals is that the frequency correlates to the responsiveness.

Example 6.9.1. When you're alert and awake, you tend to have high frequency signal because you're more responsive (as compared to sleep with lower frequency).

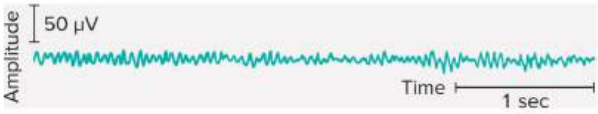


Figure 6.52: EEG of an awake and alert patient.

Example 6.9.2. **Epilepsy** is a common neurological disease characterized the repetition of seizures. It's associated with an abnormal synchronization of neuronal discharge (neurons gets excited all together). The EEG of a typical epileptic patient is through these big amplitude which correlates to synchronous neural activity. (see Figure 6.53)

Remark 6.31. *It's hard to correlate amplitude to a specific neural activity since it varies according to the brain state, activity, and frequency specific-wave.*

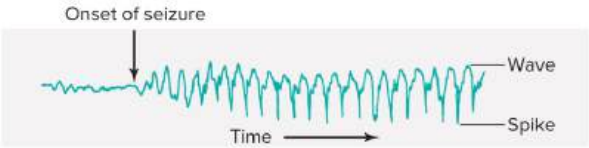


Figure 6.53: EEG of an epileptic patient experiencing a seizure.

Researchers gave these frequency-specific waves different names which are α, β and γ rhythms. α rhythm is characterized by slow frequencies signal with high amplitude which is when you're alert but relaxed with eyes closed. β wave is characterized by higher frequency and lower amplitude when you're fully alert.

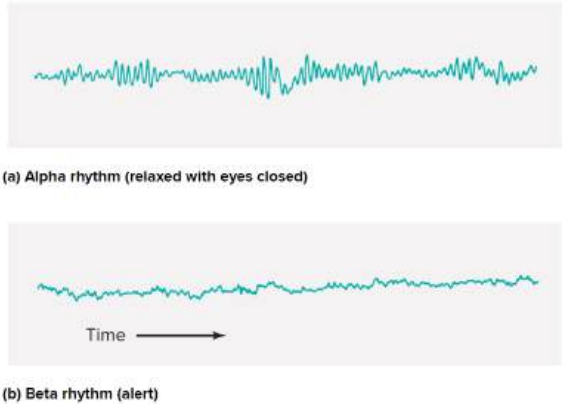


Figure 6.54: EEG of α and β rhythm.

γ rhythm is characterized by very high frequency (30-100Hz) which correlates to the combination of stimuli together (e.g. hearing and seeing at the same time.)

6.9.1 Sleep

When you're awake, you can have different rhythm that are low amplitude and high in frequency. When you go to sleep, the amplitude will be bigger and lower in frequency. Your sleeping cycle are typically divided into 2 phase which we will see below:

The phase of building up in bigger of amplitude and lower in frequency is called **non-rapid eyes movement sleep (NREM sleep)**. This phase are divided into 4 stages where each stage will have higher in amplitude as compared to the previous. The build up from stage 1 to 4 takes around 30-45 minutes.

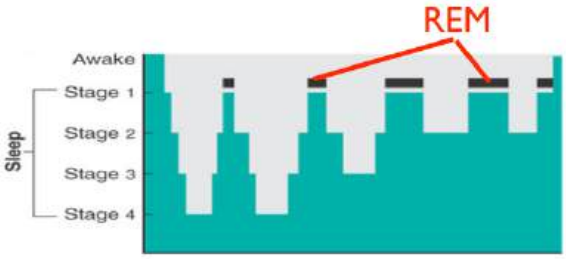


Figure 6.55: The sleep cycle

After reaching stage 4, you would eventually jump into the next phase which is the **rapid-eye movement (REM) sleep**. REM sleep is interesting because even though you are sleeping the EEG pattern is the same as when you're awake and alert. During REM sleep, your eyes are moving rapidly while the skeletal muscle is relaxed or even inhibited. This stage of sleep also increase heart rate and respiration.

Remark 6.32. ***Sleep apnea*** *is a condition where the tongue fall back to the throat which reduce respiration or even worst block it entirely. Sleep apnea share the same sign as snoring (falling back of the tongue).*

Through out the entire sleep, if undisturbed, you would jump from NREM to REM then back to REM (this completes 1 sleeping cycles which takes around 90-100min) and v.v. You also tend to dream a lot through out

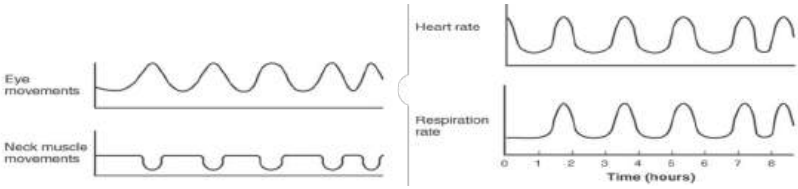


Figure 6.56: Physiological changes during REM sleep.

these but you only remember some of that are close to when you're about to wake up.

Why do we sleep?

Well...firstly, we haven't given the formal definition of sleep yet so we will now

Definition 6.16. **Sleep** is a natural phenomenon where an organism enter a state that is characterized by decrease in consciousness, sensory activity and muscle activity (almost none).

Sleep is a consolidation process that changes the brain. This consolidation process can be see a lot through memory consolidation; that is, sleep helps the brain to consolidate short-term memory to long-term. It's also for general health which allow the body to recover if we have any sickness; this is also why you tend to feel more sleepy when you're sick.

Regulation of Sleep

Circardian rhythm is the period of wake and sleep. Your circadian rhythm is mediated by the **reticular activating system** as well as the hypothalamus, to be more specific: **preoptic area** and **suprachiasmatic nucleus** (central pacemaker of the circadian rhythm).

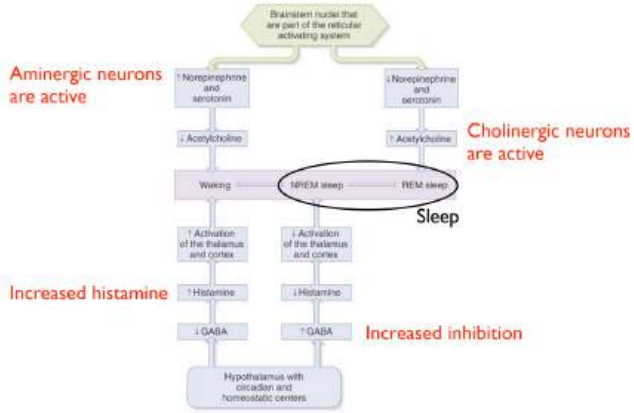


Figure 6.57: Regulation of sleep.

RAS and its associate structures release a variety of neurotransmitter for the sense of awakeness or sleep. When you're awake, the released of norEPI and 5-HT is increased while that of ACh is decreased this would make aminergic neurons active. At the same time, the hypothalamus also inhibit the release of GABA and increase in the release of histamine. The opposite effect of would happen when you're asleep (norEPI and 5-HT↓, ACh ↑ which makes Cholinergic neurons active; GABA ↑, Hist ↓).

6.9.2 The Motivation and Emotion Pathway

Your motivation is what produce goal directed behaviour while emotion is what accompany our conscious experience.

Motivation is made by the **mesolimbic** and **mesocortical dopamine pathway** where *dopamine* is the main neurotransmitter. This pathway consists of neurons that synapse with each other which will then release dopamine to the prefrontal cortex where emotions are processed. The release of dopamine via this pathway would create a positive reinforcement for your actions (things that you do, e.g. you like swimming and going swimming or even winning in a swimming competition would cause a release of dopamine telling you to do more.)

Figure 6.58: Mesolimbic and mesocortical dopamine pathway (motivation) and limbic system (emotion).

Not only that it is used for motivation, understanding this pathway is important for drug addiction. Drugs (such as heroin, amphetamine) can mimic the effect of dopamine which is why injecting them they can cause a positive reinforcement effect thereby lead to addiction.
This understanding of drug addiction was through experimentation of mouse and *brain self-stimulation*. In such experiment, a mouse is placed in a box with a lever that if pressed, it would give an electrical stimulation to the mouse brain that trigger the rewarding sites. What they found is that if

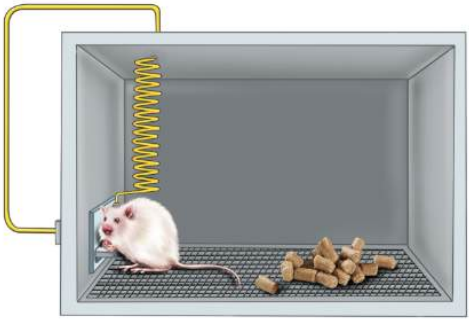


Figure 6.59: Brain self-stimulation by rats.

the lever deliver no stimulus, the mouse would press it at random interval; however, if the lever deliver the stimulus, the mouse would constantly press it. This pressing action can lead up to 2000 times in a day until they collapse from exhaustion. It also seems that the stimulation of such pathway is more rewarding than any external needs (food given to the mouse was left by it).

Now we move to the emotion pathway. One could think of our emotion as the brain's mechanism to *rate a conscious experience or action.*

Example 6.9.3. Swimming is something you like and by going to swim, you'd feel happy. In this case, happy is a positive rating for such experience or action. If you were forced to stop swimming, you'd feel sad hence it is a negative rating for this experience.

Emotional response is mediated by the **limbic system**. It consists of the amygala and the hippocampus (memory) (see Figure 6.58, right). Certain smell can general an emotional response since the olfactory bulb is connected directly. As integrated to emotion is the hippocampus which we would be discussing next since it has a very important role in the development of memory.

6.9.3 Learning and Memories

Through many studies of both structures and functions, researchers divide memory into 2 types: declarative and procedural memories. **Declarative memories** are retention and recalls of a conscious experienced i.e. memorized facts or events. **Procedural memories** are memory used to know how to do certain things i.e. muscle memories.

Example 6.9.4. Remembering that when I was young, I went to the beach in florida is declarative memory (you can "declare" or say out loud such memory). Remembering how to ride a bike or cook a meal is a procedural memory (I can physically carry out the task in order).

These 2 memories also have a further classification to them, which are short-term (STM) and long-term memories (LTM). Typically, at the beginning, both procedural and declarative memories are ST since you've just learned it. Procedural STM are typically distributed through out the brain while that of declarative STL are located mainly in the hippocampus and other limbic structure.

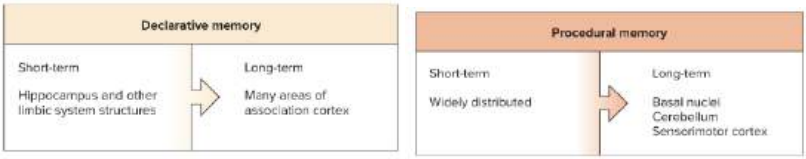


Figure 6.60: Declarative and procedural STM and LTM.

The process of turning STM to LTM is called **consolidation** which is facilitated by sleep. Procedural LTM is stored mainly in the basal nuclei, cerebellum and the somatosensory cortex. Declarative LTM, on the other hand, is stored all through out their associated cortex.

Patient HM and STM

This is a very famous example when studying neurology. In summary, patient HM suffers from severe epilepsy which was treated by the partial removal of his hippocampus.
Post-operation checkup found that his ability to retain or consolidate declarative STM is no longer available while both LTM is still intact i.e. he can still recall who he is and his past but is unable to form new LTM. However, his procedural STM is still available as the researchers can still teach him skills but he will was never able to recall when they've taught him. This really drive home that the hippocampus is important for the storage of declarative STM.

6.9.4 Language

Language is usually specialized in the left cortex (90% of the population). There are 2 main identified areas that relate to language: Wernicke's and

Broca's area. **Wernicke's area** is associated to the comprehension of written and spoken language i.e. you can listen and read a language. The **Broca's area** is associated to the articulation of language i.e. you can speak a language

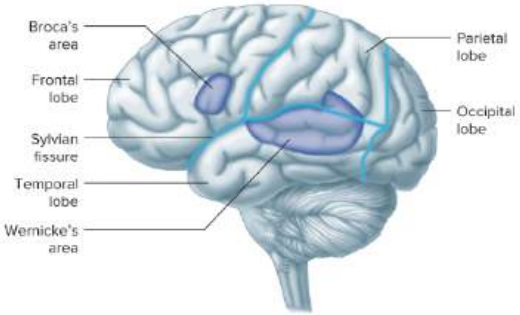


Figure 6.61: Broca's and Wernicke's area on the left cortex.

Aphasia is a language deficit which is caused by the damage of either Broca's or Wernicke's. Aphasia due to the damage of the Broca's area would lead to the inability to articulate language while still comprehend. Aphasia due to the damage of the **Wernicke's area** would lead to inability to comprehending the language and production of language are often senseless.

6.9.5 Parietal Damage

Parietal damage is common complication by individuals who went through a stroke. This condition is characterized by a syndrome called **sensory neglect** whereby they lose contralateral input

Example 6.9.5. A patient experienced a stroke which lead to parietal damage. When given her an image to draw, she could only draw only half of the picture since according to her, she could not perceive the latter half. This is as if her visual field just ignore its existence.

6.9.6 Altered State of Consciousness

Our state of consciousness typically varies from 1 to the next however, it still have some level of normality to it. When this normality is radically shifted, we call it the **altered state of consciousness**. There are many reason that can lead up to this alternation e.g. drugs, hynosis, disease; today,

Figure 6.62: Lois Wain's' cat painting through out his descending into schizophrenia

we will look at 2 psychiatric illnesses: schizophrenia and bipolar.

Schizophrenia is a disease that lead to information in the brain not properly regulated. Its symptoms covers a wide range which can include hallucination, delusion, immobilization. The cause of this disease is unclear though researchers suggested that it has something to do with abnormal neuron's development from infancy to adulthood. The most widely accepted theory is that there are overactivity in the mesocortical dopamine pathway.
This disease can affect 1 out of 100 people and has no prevention nor cure however there are drugs that could alleviate some of the symptoms.

There are also mood disorder which are **depressive (depression)** and **bipolar disorder**.
Depression is characterized by the loss of energy, interest, the feeling of aggravated sadness and emptiness, disturbed sleep and even lead to suicidal thoughts.

There are usually not much treatment but mainly there are drugs that modulate the release of neurotransmitters.

Example 6.9.6. Lithium is a neurotransmitter modulator for schizophrenia

Interestingly some famous artists experience altered state of consciousness and we can see the changes their artistic output. Louis Wain is a famous artist that suffers from Schizophrenia, his art changes radically as his

conditions worsen, the same way with William Utermohlen's self portraits.

Bipolar Disorder is a neurological condition that lead to a radical changes in mood, 1 person can go from depressive to mania and v.v.

Chapter 7

Myology I

Definition 7.1. **Myology** is the study of muscle.

In this chapter, we will mainly look at the muscle control in the body AKA *motor behaviour*. Although the chapter name's is *myology*, it does have some connection with the nervous system.

7.1 Motor Behaviour

Most living things on earth can moves have a brain. There are 2 types of motor behaviour that is voluntary and reflexive motor behaviour. We won't talk much of the voluntary (or **autonomic**) motor behaviour but mostly reflexive in this chapter (the next chapter is dedicated for the voluntary).

Before that, we need to understand certain terminology as for muscles and motor movement.

Definition 7.2. **Flexion** refers to the action of bending of a limb at a join i.e. decreasing the angle around the joint. The opposite, increasing the angle around the joint, is called **extension**.

Definition 7.3. Muscles that mediate flexion are called **flexor** while that of extension is called **extensor**

Definition 7.4. Muscles that acts opposite to the movement of the at a joint is called **antagonists** while those that acts in the direction of the movement is called **agonists**.

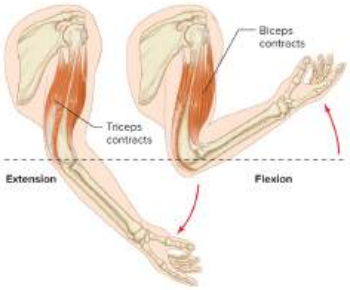


Figure 7.1: Extension and flexion of the arm.

Example 7.1.1. When you bring your arm toward your shoulder, this action is flexion since you're decreasing the angle around the joint at your elbow. During this flexion, the flexor muscle (bicep) acts as the agonist and contracts while the extensor muscle (tricep) acts as the antagonist and relaxs.
When you do the opposite movement of open up your arm, it's extension. The flexor muscle (bicep) acts as the antagonist and relaxs while the extensor muscle (tricep) acts as the agonist and contracts.

Remark 7.1. *When you hold your limb at a fixed position, you're balancing between the forces of flexion and extension.*

7.1.1 Motor Neurons

Motor behaviours are controled by **motor neurons**. They are excitatory and release **Acetylcholine (ACh)** at the junction of the muscle. They're classified into 2 types: α and γ motor neurons. The α motor neurons innervate skeletal muscle while the γ innervates muscle spindle. The cell bodies of these neurons are located in either the ventral horn of the grey matter (which forms the spinal nerves) or the brainstem (which forms the cranial nerves).

7.1.2 Efferent Neural Pathway

The neural pathway of efferent can be coupled by the CNS with its descending pathway or coupled with the afferent of the somatosensory system.

Definition 7.5. **Interneurons** are neurons that make the connection between the motor and the sensory pathway.

Some afferent will go up the spinal cord to the brain, but some can synapse with interneurons at the dorsal horn. These interneurons then synapse with the **motor neurons** in the ventral horn creating motor efferent. There can also be descending efferent coming directly from the brain to synapse with interneurons and subsequently the motor neurons. The pathway from afferent to interneurons would be

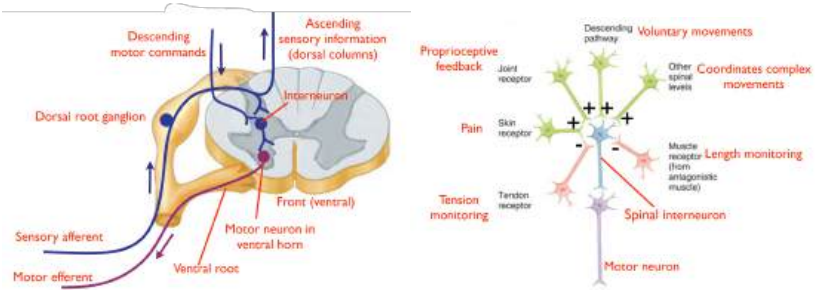


Figure 7.2: Efferent neural pathway.

involuntary while the pathway from the brain down to the interneurons (descending) would be **voluntary**.

These interneurons in the spinal cord is high important because they can receive lots of signals at the same time. The interneurons' soma are connected to multiple pathway that are pain, proprioception, descending pathway, complex movement coordination, tension and length monitoring (both inhibitory). Its axon is connected to the motor neuron which depending on the signals it receive can excite the motor neurons or not.

7.1.3 Spinal Reflexes

Spinal reflexes are defined as simple motor behaviours produced by the CNS that lie along the spinal cord. As the name suggested, this motor behaviour is not voluntary and it's mostly much faster (since it travels to the spinal cord then efferent is sent out immediately). There are mainly 3 types of spinal reflexes: withdrawal, stretch and inverse stretch reflex.

Withdrawal reflex is a reflex that protect limbs from injury. *Stretch reflex* is a reflex that control the muscle lengthening. *Inverse stretch reflex* is a reflex that control muscle tensioning.

Remark 7.2. *Stretch reflex can change due to some aspect of the nervous system (will discussed in later section)*

Remark 7.3. *Reflex can be modified as most spinal reflexes can be overridden.*

7.2 Spinal Reflexes: Withdrawal Reflexes

In short, we can define **withdrawal reflex** is a rapid coordinated contraction of muscles to protect the limb from injuries. We will now look at the mechanism of action of the withdrawal reflexes.

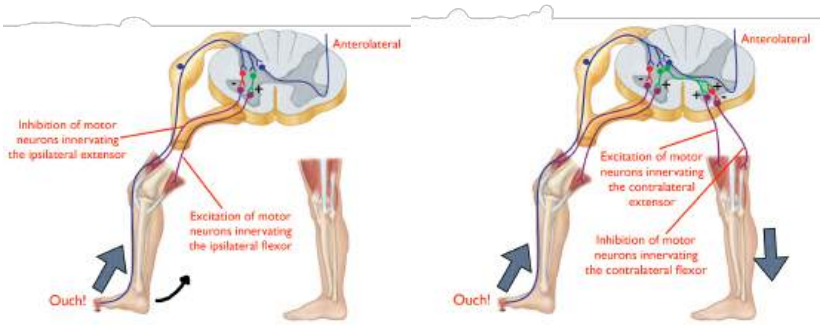


Figure 7.3: Mechanism of withdrawal reflex and cross extensor reflex.

Mechanism of Action (Withdrawal Reflex): Supposed that you accidentally step on a pin.
1. The nociceptors will be activated which send afferent through the anterolateral column to the brain. At the same time, this afferent would synapse with interneurons which in turn synapse or excite the motor neuron at the ventral horn. The motor neurons will innervate the *ipsilateral* flexor (hamstring) while inhibit the *ipsilateral* extensor (quadricep) around the knee joint.
2. At the same time, if you lift 1 foot up, the other foot automatically planted solid on the ground. The afferent of the nociceptors will synapse to the interneurons which then cross the midline and excite *contralateral* motor neurons. They will innervate the *contralateral* extensor (quad) and inhibit *contralateral* flexor (hamstring). [cross-extensor reflex]

Remark 7.4. *Quadricep and hamstring can be either flexor or extensor depending on the joints in reference e.g. hamstring is an extensor around the hip joint but is a flexor around the knee joint.*

Remark 7.5. *This reflex is **polysynaptic** which means there are more than 1 synapse between the input (afferent) and the output (efferent).*

7.2.1 Magnitude of Withdrawal Reflex Variation

Through many testing and experimentation, we found that the more painful the stimulus, the stronger the withdrawal reflex shown in the graph below

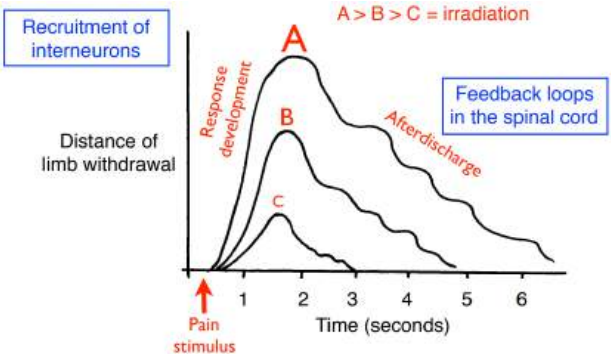


Figure 7.4: Variation of withdrawal reflex as the magnitude of pain stimulus increase.

There are 2 main interval that let us to this understanding response development and after-discharge.
Response development refers to to the withdrawal reflex response. After-discharge refers to the time interval when the limb keep withdrew even after the pain stimulus is removed. As the pain stimulus grew the response development also grew with it and the after-discharge will be extended (limb kept withdrew longer).

The reasoning for a higher response development is due to a larger recruitment of interneurons when the pain stimulus is larger. The after-discharge length is due to feedback loop in the spinal cord that keep the withdrawal effect longer.

7.2.2 Summmary: Withdrawal Reflex

All in all, during withdrawal reflex, the ipsilateral flexor muscle contracts and extensor muscle relaxes while the opposite happens for the contralateral flexor and extensor muscle. The system is polysynaptic which is when there's many synapses between the output and the input.

7.3 Spinal Reflexes: Stretch Reflex

The **stretch reflex** is the reflex that involve in lengthening muscles. Stretch reflex have a monosynaptic and polysnaptic component. We won't look into the polysynaptic since it will be similar for all reflexes.

The monosynaptic stretch reflex is also known as the **knee-jerk reflex** since it's most prominent and easily observed in the knee.

> **Mechanism of Action (Knee-Jerk Reflex):** First, we begin by supposedly stretch the extensor muscle. This stretching would lead to the activation of the stretch receptor in the muscle that send afferent to the spinal cord and up the dorsal lateral column to the brain. Some of this afferent will synapse the motor neuron in the ventral horn lead to the excitation of the *ipsilateral extensor* and the inhibition of *ipsilateral flexor*.

Example 7.3.1. Monosynaptic stretch reflex (knee-jerk reflex) can be tested in the doctor office by tapping the reflex hammer on the patellar tendon. This examination is used to check for muscle tone.

Definition 7.6. **Muscle tone** is a muscle's resistance to stretch i.e. amount of tension. (discussed later on)

7.3.1 Stretch Receptors, Muscle Spindles and More

Stretch receptors are important for the stretch reflex, hence the name, as well as modulation of muscle lengthening. The stretch receptors are made from afferent nerve fibers wrapped around **intrafusal muscle fiber** that are encapsulated by connective tissues. This entire structure is called a **muscle spindle**. The main skeletal muscle fibers that give the outer layer and produce the necessary force for movement are called the **extrafusal muscle fibers**.

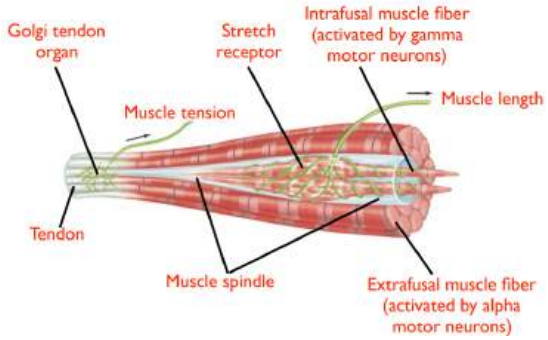


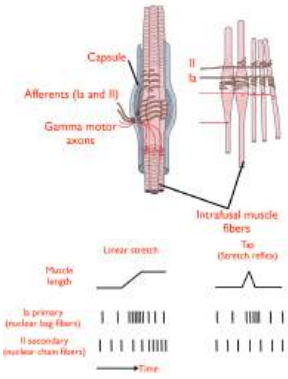
Figure 7.5: Muscle spindle and extrafusal fibers.

Remark 7.6. *Muscle spindles will sit parallel to the extrafusal muscle fibers.*

These muscle fibers will then converges as they reach a joint to form the **tendon** which is where the proprioceptor that can sense tension called **Golgi tendon organ** resides.

Let's remind ourselves that there are 2 types of motor neurons: α and γ. We can be more specific than before as α motor neurons can innervate the extrafusal fibers while the γ can innervate the spindle (intrafusal).

There are 2 afferents that comes out of the intrafusal fibers are afferent Ia and II. The Ia afferent is rapidly adapting i.e. it fires lots of AP when there's an immediate change in stimulus. The II one is non-adapting i.e. it fires lots of AP when the stimulus build up to another level. Because of this, Ia afferents can detect when there's a length change in the muscle fiber, they report dynamical change signals. Afferent can then detect when there's no change in length, they report static signals.



Now because the muscle spindle is parallel with the extrafusal fibers, when the extrafusal fibers stretch, it will stretch with it. The stretching of muscle spindle would cause the afferent I to fires action potential. The problem arises when the opposing action happens. The voluntary contrac-

tion of the muscle, mediated by α motor neurons, will lead to a decrease in the muscle spindle tension thereby decrease its sensitivity.
To counter this, muscle spindles have γ motor neurons will innervate the 2 intrafusal ends and maintain the tension. This mechanism is called **α-γ coactivation**.

7.3.2 Summary: Stretch Reflex and Muscle Spindles

All in all, the stretch reflex would lead to the resists of muscular changes that lead to the idea of muscle tone. It has a monosynaptic and polysynaptic component. This reflex has a positive feedback by muscle spindles.

Muscle spindles is the main structure of the stretch receptor. They do not contribute to the force produced by muscles (made by extrafusal fibers). They have 2 main afferent coming from it that is Ia (detect dynamical changes in muscle length) and II (detect static muscle length). Their sensitivity is maintained by $\alpha - \gamma$ coactivation.

7.4 Spinal Reflexes: Inverse Stretch Reflex

The **inverse stretch reflex** is a reflex that cause a prolonged stretched muscle to relax.

> **Mechanism of Action (Inverse Stretch Reflex):** When you contract your extensor muscle, the Golgi tendon organs will be but under tension and give off afferent. This afferent will travel up the Ib to the spinal cord where it can travel up the dorsal lateral column. Some of these afferent will synapse with interneurons that can lead to the inhibition of ipsilateral extensor muscle and excitation of ipsilateral flexor

Wait a minute...isn't this counter-intuitive, if you're contracting your muscle, why would the body inhibit that exact muscle? Well...there's no definite answer to this, it's simply a control system. The best explanation so far is that your muscle is really powerful, to the point that it can hurt themselves (ripped off tendons or even break bones), so to lower this strength, the body inhibit it a little.

Remark 7.7. *These reflexes can be overridden by the emotional response. If you ever heard news of mothers that can lift extreme heavy objects that they could never before, this is due to their emotional response override the inverse stretch reflex from overcontracting.*

The stretch reflex is mediated by the Golgi tendon organs which we will be talking next.

7.4.1 Golgi Tendon Organs

The **Golgi tendon organs** is lined parallel with the muscle at the tendon. It's role is to detect the force produced by the muscle. If we were to record the afferent at different condition of the Golgi tendon organs, we found that during rest, there will be no afferent; when there's a slight stretch (stretch reflex), it will fire some afferent; and when there's a strong muscle contract, the Golgi tendon organs will fires lots of afferent. (see Figure 7.6, left)

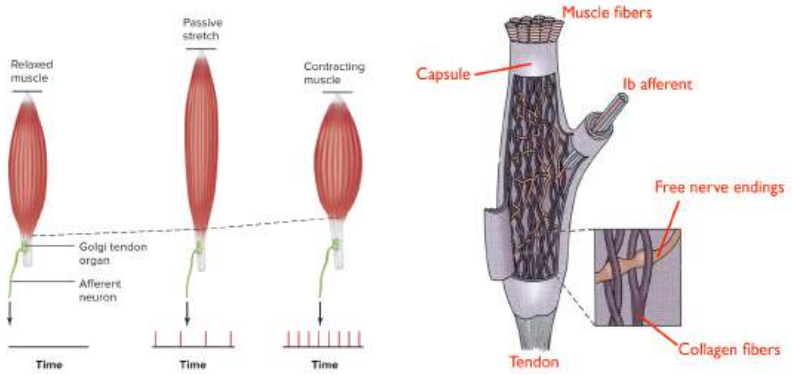


Figure 7.6: Golgi tendon organs structure and afferent at different condition.

The Golgi tendon organs are made up of collagen fibers that intertwine with free nerves ending which converge to form the **Ib afferent**. These collagen fiber and nerves endings are encapsulated at the tendons connecting directly to the muscle fibers. (see Figure 7.6, right)
When the muscle contract, the collagen fiber will be pulled apart thus pinch in the free nerves endings. These nerves endings have mechanoreceptor which would be activated due to this pinching action.

7.4.2 Summary:Inverse Stretch Reflex and Golgi Tendon Organs

All in all, the inverse stretch reflex is a way for your body to modulate the amount of muscle contraction you're able to produced to no damage yourself.

The stretch reflex is mediated by the Golgi tendon organs that lies parallel to the extrafusal fibers and can report muscle contraction. The signal of muscle contraction from the Golgi tendon organs will be sent by the Ib afferent.

7.5 Motor Cortex and Movement Control

The main cortex that mediate voluntary movement is the **motor cortex** (or somatomotor cortex). It's believed that the *wanting* of motor behaviour and movement originate from the prefrontal cortex which is the *highest center control*. Signals from this center will travel down to the motor cortex then other brain structures such as basal nuclei, brainstem, etc. These **middle level** mainly execute the contraction of muscle and makes corrections based on sensory information.
At the base level there are receptors that can send afferent and muscles fibers that can receive efferent.

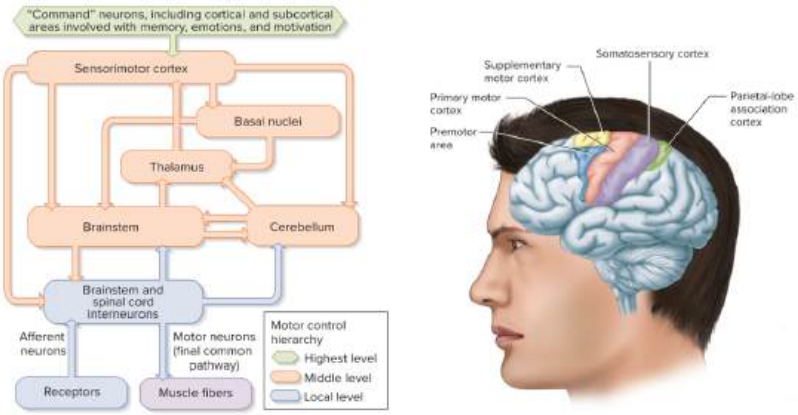


Figure 7.7: Hierarchy of motor control and motor cortex.

There are 2 major descending pathway for motor control: corticospinal and extrapyramidal tract.
The **corticospinal tract** is a direct connection from the motor cortex to the spinal cord. It sends efferent that direct skilled movements to the motor neurons which will contracts muscle fibers. On the other hand, **extrpyrimidal tract** originate from the brainstem to the spinal cord to direct posture movement e.g. if you were to bend reach something, your extrapyrimidal tract will send efferent to your trunk so that it can stabilize the posture and center of gravity.

7.5.1 Motor Cortex

Looking back at the motor cortex, we can see that it's divided into many areas. Starting near the prefrontal cortex are the **premotor area** and **supplementary motor cortex**. Then moving toward the back we would find the **primary motor cortex** sitting anterior to the somatosensory cortex separated by the *central sulcus*.

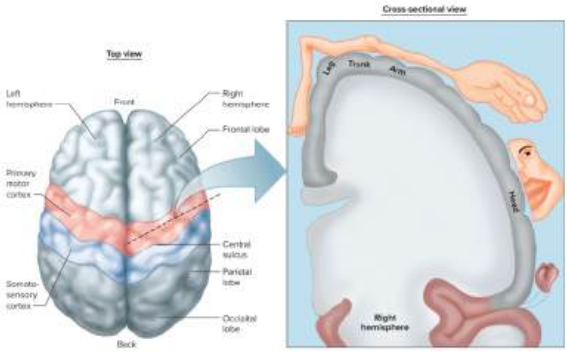


Figure 7.8: Somatotopic mapping of the motor cortex.

Like the somatosensory cortex, we can create a **somatotopic map** due to the anatomical arrangement of motor neurons in the motor cortex. Each of the area correlates to body part that will be moved by the motor cortex and its size (on the map) is proportional to how many neurons is controlling it as well as the complexity of the control too.

We can now put all of what we've known together to see how voluntary

movement is mediated in the body

Mechanism of Action (Voluntary Movement): We begin in the prefontal cortex where we consciously initiate an efferent. This efferent travels to the premotor area and reaches the primary motor cortex.
1. From the primary motor cortex, efferent is sent down the corticospinal tract where it crosses the midline in the medulla. The efferent then synapses and excites the *contralateral* α and γ motor neurons which then contract the appriopriate *contralateral* skeletal muscles.
2. At the same time, efferent is sent from the brainstem down the extrapyrimidal tract. This tract is dispersed and can cross the midline. This means the efferent can synapse with both *contralateral* and *ipsilateral* interneurons which then synapse with the α and γ motor neurons of the trunks for correct posture and centre of gravity control.

Corticospinal vs Extrapyrimidal Tract

In summary, corticospinal tract originates from the primary motor cortex (specifically precentral gyrus). It's a compact discrete fiber tract that branch to the spinal cord. It mainly controls the *contralatera* muscles, mainly the extremeties such as feet and hands for skilled voluntary movement.

The extrapyrimidal tract originates from neurons in the brainstem. It's diffused and non-discrete tract with multiple pathway. The extrapyrimidal tract control both *contralateral* and *ispislateral* muscles, mainly trunks and muscles involved with posture and balance.

Muscle Tone

Muscle tone is the resistance to stretch (see Definition 7.6). Muscle tone can change due to damage of the descending pathway (corticospinal or extrapyrimidal) or the motor neuron.

These descending pathways activate interneurons and somehow most of these interneurons in their circuitry are inhibitory. So if the descending pathway is damaged, interneurons are less inhibited which lead to an

overactive motor reflexes called **spasicity** thereby lead to a higher muscle tone which is called **hypertonia**. It also causes **rigidity** which is constant muscle contraction.

On the other hand, damages to the motor neurons can lead to **hypotonia** where muscle tone is abnormally low which means the stretch reflex will decrease or even loss completely. It can also lead to **atrophy** which is the decrease in muscle mass.

7.5.2 Basal Nuclei

The **basal nuclei** determine the specific sequences of movment needed to make an action. It made up of a clusters of cell bodies, hence nuclei, that likes to the interior of the brain near the thalamus. We won't look at the circuitry and mechanism of the basal nuclei but we will see some common disorder that's associated with it.

Parkinson's disease is the most common movement disorder which effect the basal nuclei. It reduces the dopamine level in the basal nuclei. This lead to it not work properly and when the basal nuclei doesn't work correctly, it will lead to **akinesia** where movements are reduced and **bradykinesia**, where movement is slowed. It also causes muscle rigidity and resting tremor.

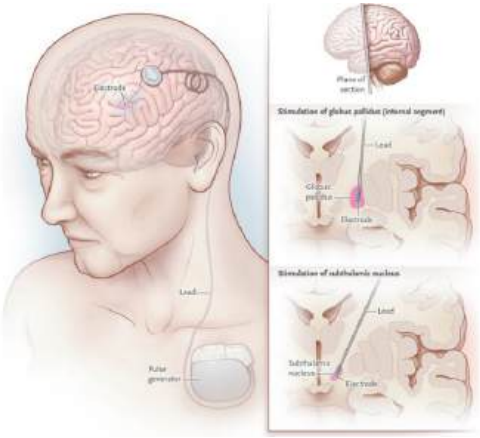


Figure 7.9: Deep brain stimulation

There are no cure but there are some available treatment such as L-DOPA and deep brain stimulation. L-DOPA is a dopamine precursor that can increase the dopamine level in the brain. Deep brain stimulation is a method that connects electrodes to the basal nucei and stimulate it.

Remark 7.8. *Deep brain stimulation is the best treatment we've found however it does not work for everyone.*

Huntington disease is a genetic mutation where a widespread of neurons begin to die in the brain later on in life. The neurons in the basal nuclei will be lost [die] as well. While Parkinson's lead to reduced movement, this disease lead to **hyperkinetic disorder** characterized by an excessive motor movement. These movements are typically **choreiformic** which means that it's jerky, random involuntary movement (of limbs and even faces).

7.5.3 Cerebellum

The **cerebellum** determines the movement timing, planning and errors corrections; it's also the place that mediate the learning of motor skills. The cerebellum has almost 50% of the total cranial neurons. The reason that it holds so much neurons is because it receives lots of sensory information. Not only that it's constantly making adjustments in the sensory information and interacting with the extrapyramidal tract originates at the brainstem.

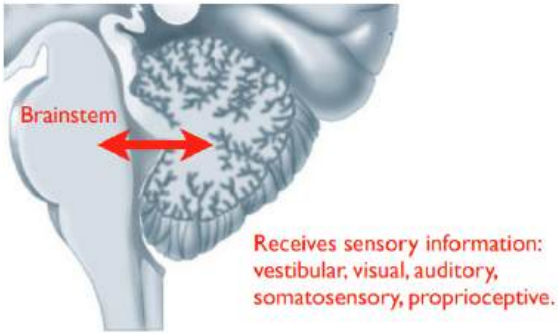


Figure 7.10: Cerebellum and its interaction with brainstem, and sensory information reception.

Because cerebellum is important for the correction, timing and etc. of movement, damages to it can lead to the potential loss of those mecha-

nism.

Cerebellar disease is a disease characterized by the dysfunction of the cerebellum. It tends to lead to **asynergia**, where a smooth movement is divided into their components; **dysmetria**, where patient cannot control distance, speed or range of motion; **ataisa**, where muscle coordiation is loss; and intention tremor. These individuals will not have highly skilled motor control and lose the ability to learn new motor skills.

Chapter 8

Myology II

The main output that create movement in the body is the **muscle**. We'll look briefly at the physiology of muscle then more specifically the physiology of the muscle cells. After talking about the physiology of muscles, we'll touch on a very much related subject, that is the autonomous system which technically brings us back to neurology.

8.1 General Structure of Skeletal Muscles

There are 3 kinds of muscle that make up the human body: skeletal, cardiac and smooth muscle.
The **skeletal muscles** involve in voluntary movement; as the name suggested, they connect to your skeleton allow you to consciously control movement. The heart is made from *cardiac muscle* which can contract and relax via cardiac cells which is similar to that of skeletal muscles. The *smooth muscle* is all of the rest of the muscles found in your body that involved in involuntary movements. There are many types of involuntary muscles but they all share the same characteristic hence we grouped them under smooth muscles.
We won't get much into cardiac and smooth muscle (reserved for Physiology 210) but we will look mainly at skeletal.

Remark 8.1. *Even so, 1 important thing to note is that you can control skeletal muscle but you cannot control skeletal nor smooth muscles.*

It's quite fascinating that you're able to perform these complex bodily movement, such as running or even something seemingly simple as con-

trolling a single thread through a needle, yet the only thing your muscles do is contract or relax. This gives us our first question is that

How can muscles perform these complex movement? Or even simpler how does it allow you to move in the first place?

Well...The reason that you're able to do complex movement is thanks to the way muscle are connected with each other on the body.

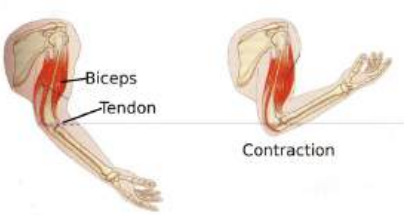


Figure 8.1: Muscles Contraction lead to joint flexion.

As for the second part, the reason muscle can move your body is because the muscle connects to a strong connective tissue called **tendons** which is connected to the joint of your body "framework" or **bones**. Because of this, when you contract your muscle, it gets shorter which pull on your tendon which then pull back across your joint and ultimately pull the bone toward it.

8.1.1 Anatomy of Muscle Fibers

When we look at the cross section of a skeletal muscle, We can see that it is made up of these muscles cells called **muscle fibers**, they're called fibers is because they're long and thin like a fiber or filaments. These muscle fibers can bundle up into a **fasciscle** which can further bundles with other fascicles to make a muscle. (see Figure 8.2)

Histological slides of muscles shows these muscle fibers have distinctive stripes going perpendicular to their length. These stripes are indicative and underlay the mechanism of the muscle fibers of which we will look at later on.
Because of these stripes, skeletal muscle is also referred as **striated muscles**. Not only these stripes that are unique, we can also spot these black

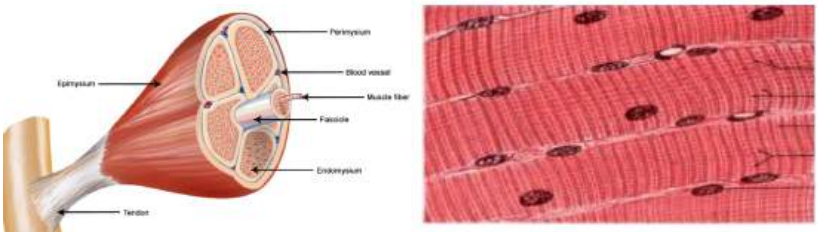


Figure 8.2: General structure of skeletal muscle and muscle fibers histological slide.

dots that appear on the whole length of the fiber. These black dots are **nuclei** of the muscles.

Remark 8.2. *Muscle fibers are unusual because they are* ***multinucleated*** *where as the majority of cells is mononucleated.*

how did they get this much nuclei?

Well...It has to do with how fibers are formed. A muscle fiber originate from many mononucleated cells called **myoblasts**. Later to development, these myoblasts fuse into each other thus create the length of the fiber as well as having it multinucleated.

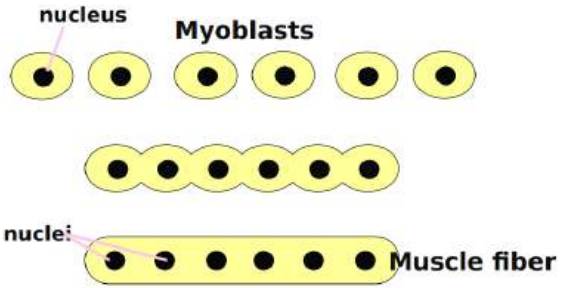


Figure 8.3: Fusion of myoblasts to create multinucleated muscle fibers.

Why do they have this much nuclei?

The first reason is that the muscle is long and thin and make a lot of protein. These proteins are translated from mRNA which is transcribed in the gene,

hence the amount of proteins you can make dependent on the amount of mRNA you can make more proteins. Therefore having many nuclei lead to higher proteins production.
The second reason is that if there's only 1 nucleus, the proteins will be transported very far and wide through out the length. But if you have many nucleus, you would have proteins synthesis and proximal transportation all along the length.

Then **why aren't neurons like that if this is much ore efficient?** Well...This is not the way neurons have evolved as well as neuron deal with proteins transport in a different way.

8.1.2 Anatomy of Myofibrils, sarcomere and Filaments

The interior of a skeletal muscle fiber is packed full with cylindrical bundes called **myofibrils** which are made from proteins.

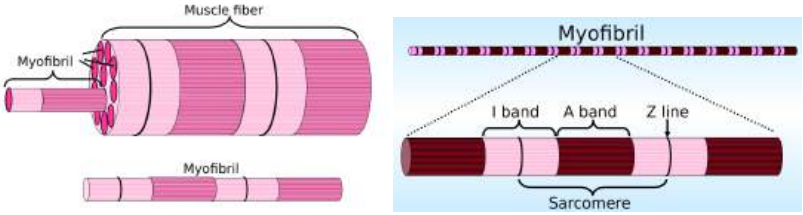


Figure 8.4: Structure of myofibrils and bands.

Going back to the histological slide of Figure 8.2, we will notice that these striations have alternating dark and light band (divided in half by a dark line). So then **why does the fibers has the bands?** well...this is because myfibrils have stripes and because myofibrils made up the muscle fibers, it also make them have stripes.

Remark 8.3. *If the stripes of the fibers is similar to that of the myofibrils this must mean that these bands are perfectly lined up with each other.*

It would makes sense for them to line up because they're part of the contractile machine. By having all of these machinery lined up, it will be much more efficient during contraction that all the machinery contract as 1 single unit which maximize the force. This lining up happens at all level of a muscle.

We name bands that made up the striation as A-band (dark), I band (light) and separating the middle of the I band is the Z-line (because it's 3D it's more like a disk instead of a line). The portion (distance) between 2 Z-line is called a **sarcomere**. The sarcomere is the smallest unit of contraction. i.e. muscle contraction happens because of fibers contraction which is caused by myofibrils contraction which is caused sarcomere contraction.

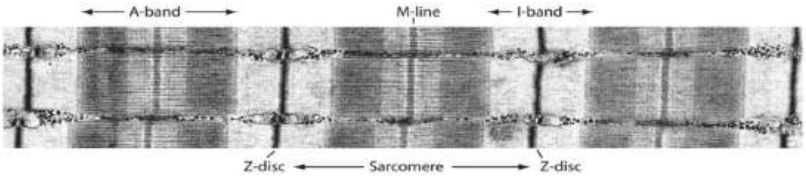


Figure 8.5: Electron micrograph of sarcomere. The image seems like it's flat due to perspective but it's cylinderical.

Looking at the sarcomere through the electronmicroscope (see Figure 6.8), we can see some pre-defined structure such as the A, I-band and Z-line. Not only that, there are newer regions such as **H-zone** (middle of the A band) and a dark line running through it called **M-line**. The electron micrograph also reveal more about these bands. If we look closely, we can see these thin thread extends from the Z-line reaching the width of the I-band called **thin filament**; the same way happened in the M-line, where thick thread extend the width of the A-band called **thick filaments**.

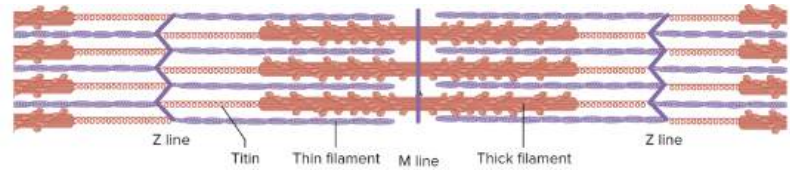


Figure 8.6: Cartoon's structure of sarcomere for better visualization. Although not mentioned, the cross-bridges are theb bulb extending from the thick filaments. Once again...this is a 2D image but in fact these are 3D.

Going from the Z-line, it's the light I-band then goes the A band which is separated into a very dark region and a slightly dark region. The reason that these band looks different is because they corresponds to different filaments. The I-band is made from thin filament which gives its light contrast while the A-band is made from thick filament that gives the dark contrast.

The region of very dark contrast is the 2 filaments overlap.
Thsi overlapping is mediated by thick filament's **cross-bridges**.

Remark 8.4. *It's the interaction between the cross-bridges and the thick filament that lead to contraction.*

If we were to look at the cross section of the A-band where the overlapping section is, we can see a matrix of thick and thin filaments in a *crystalline arrangement*. That is, each thick filament is surrounded by 6 thin filaments while each thin filament is surrounded by 3 thick filaments. As the cross section move toward the Z-line or the M-line, we would see only thin or thick filament respectively.

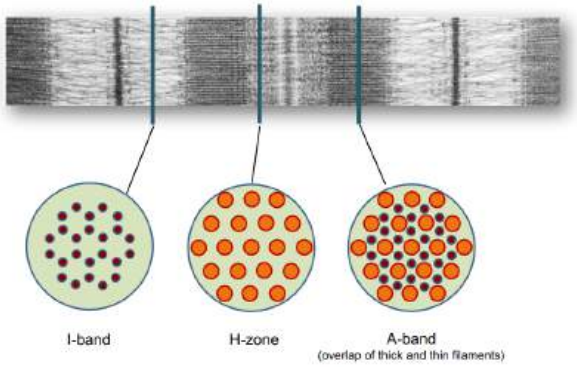


Figure 8.7: Cross section of sarcomere and the crystalline arrangement of thick/thin filament.

What are the thick and thin made up?

Well...the thin filament is made from **actin** which is an important proteins that has many function in normal cells. Actin itself is not fibrous, it's a *globular proteins* but what's special about it is that it can glue together and form a long thin thread. 2 of these actin subunit thread can then spiral onto each other, in a double helix conformation, to make the thin filament

The thick filament is made from **myosin** which actually forms a fibrous (filament-like) structure. It has a long thin part and has a globular section that extends out. These myosins will bundle with each other to form the thick filament.

Remark 8.5. *The M-line is an anchor point that these myosin can grasp onto and form the thick filament.*

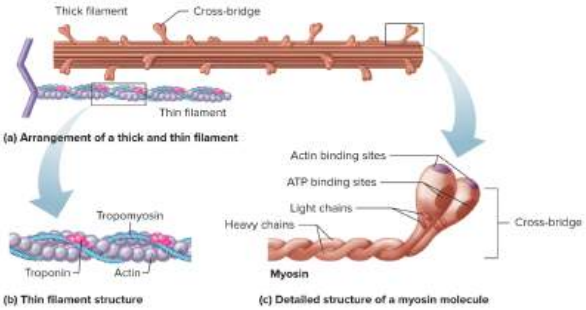


Figure 8.8: Actin and Myosin that makes up the thin and thick filament. Some of those named structures we will look at later on.

Here's the summary image of the electron micrograph and cartoon representation

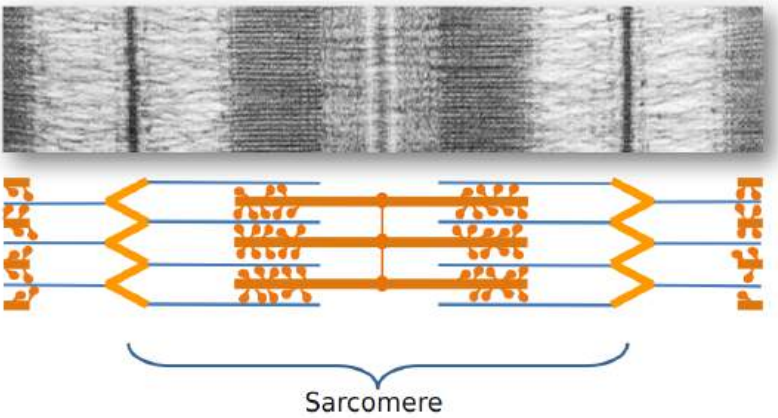


Figure 8.9: Summary image of a sarcomere.

8.2 Physiology of Muscle Contraction

Now that we've covered majority of the anatomy of muscle and its constituent, the main thing the wonder is **how does contraction of sarcomere work?** Well...the sarcomere contraction follows the **sliding filament model**.

> **Mechanism of Action (Sliding Filament Model):** When the muscle fibers contract, the head groups (cross-brdiges) of the thick filament will reach and pull the thin filament toward the M-line, which make it move over the thick filament. After they will let go then grasp and pull the thin filament again then v.v. Essentially bringing the Z-line closer together. This contraction happens to all the sarcomere thus shorten the entire myofibril.

Remark 8.6. *the length of the thick nor thin changed, they only overlap more and Z-line gets pulled closer and shorten the sarcomere.*

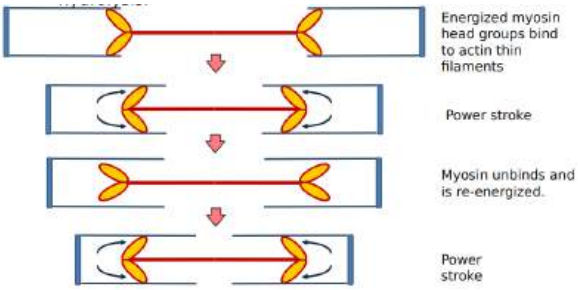


Figure 8.10: Sliding filament model.

Remark 8.7. *Although, they're all line up as a unit, each head group is acting independently or else if they let go at the same time, we'll lose muscle contraction. Nevertheless, the net effort is still result contraction.*

If we can measure the force or tension of a single fiber in relation with its length, we find that there's an optimal length that it works best.

If you go over this range, you're pulling the thick and thin filament which lead to no overlap i.e. The thick filament cannot grasp the thin filament. If we go under this range, the thick filament will run into the the Z-line and cannot contract i.e. The muscle fiber is too short and cram up which disable contraction.

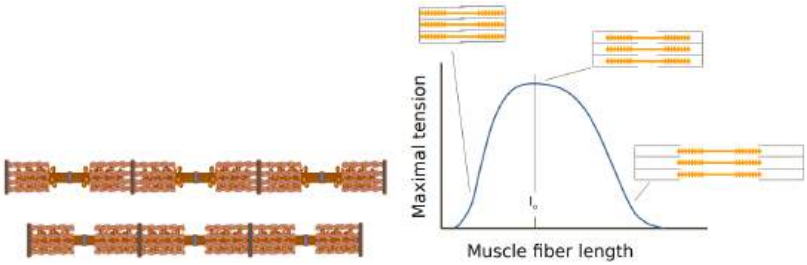


Figure 8.11: sarcomere pre- and post-contraction.

Then how does this explain static tension (stationary holding an object)?

If you need an optimal length to make contraction but in stationary contraction, there's no length involved...Well, the thick filament will try to pull the thin filament like normal but the thin filament will not move. After, it will release and then try pulling again, then the cycle continue but there's no length change.

8.2.1 Cross-Bridge Cycle

We know that muscle contraction is caused by the shortening of sarcomeres via the sliding filament model but **How can the head group can grasp on?** Well...Obviously it's due to energy which is why when you use your muscle for a long time, your body heat up due to enegy usage.
Well then how is energy fed into this process? Well...it's coming from the hydrolysis of ATP. The full cycle of using ATP to cause a muscle contraction is called **cross-bridge cycle**.

> **Mechanism of Action (Cross-Bridge Cycle):** We begin with the head group of the myosin which can bind and hydrolyze ATP.
> **1.** Myosin headgroup is bound with ATP, hydrolyzes it to ADP and phosphate group which generate energy.
> **2.** This changes the conformation to the head group into a "cocked" position, like the hammer of a pistol.
> **3.** The myosin headgroup then bind to the actin. The binding trigger a conformational change that return to the relaxed position. This change in conformation, called **power stroke**, is how the head group can pull the thin filament toward the M-line. **4.** ADP and

phosphate group are released which allow ATP to bind and trigger the cycle again.

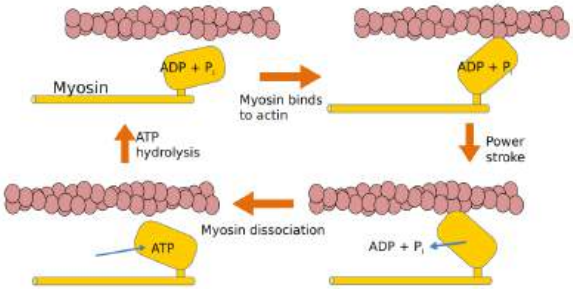


Figure 8.12: Cross-brdige cycle mechanism

Remark 8.8. *ATP is important for the contraction of muscle. This importance is shown through the evolution of muscle to maintain concentration of ATP at a constant level regardless of level of fatigue.*

If some how the [ATP] level decreases, we won't be able to contract our muscle which also underlies the reason that corpses tend to be stiff.
The term that describes this phenomenon is called *rigor mortis*. When an animal (us included) dies, [ATP] level is at minimum (or 0) which means that there's no ATP for the head group to bind hence it does not let go of the thin filament which then stiffens the muscle at a fixed position.

8.2.2 Neuromuscular Connection

So now we know that muscle contraction is caused by the contraction of muscle fiber which is caused by the contraction of myofibrils which is caused by the contration of sarcomere. The contraction is mediated by the thick and thin filament pull on each other via the cross-bridge cycle. Even then, in order to cause a muscle fiber to contract, there must be some external stimulus as it doesn't simply contract on its own so...

What causes the muscle fiber to contract?

Well...we need to go back to the nervous system. In the brain, you consciously activate a movement, in the proximity of the prefrontal cortex.

This efferent then goes to the motor cortex which then send it down the spinal cord to the motor neurons at the ventral horn. The motor neurons then send action potential to activate these muscle fibers. This connection between motor neuron and muscle fiber lead to a concept developed by *Charles Scott Sherrington*:

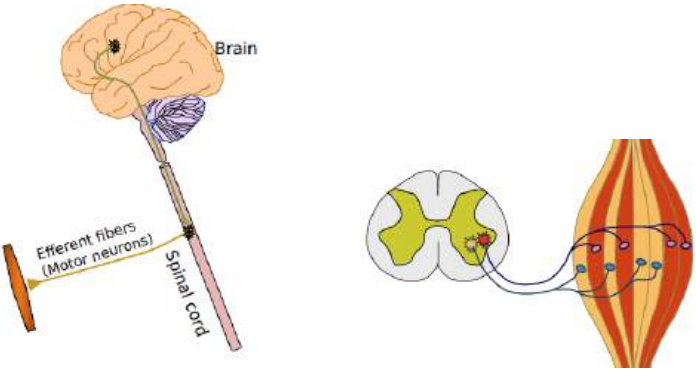


Figure 8.13: General pathway of efferent and motor unit schematic.

Definition 8.1. A **motor unit** consists of a motor neuron and muscle fibers that it will innervate.

Remark 8.9. *A single motor neurons can innervate anywhere from a few muscle fibers (such as occular muscles) to hundred thousands (such as large muscles like quad).*

A motor unit represent the smallest unit muscle fibers work altogether with its respective motor neuron. As the remark points out, the amount of muscle fibers innervates can vary however this variation can be determined by location and complexity of the motion.

Example 8.2.1. Muscles located in the eyes requires complex adjustment hence the motor unit would be smaller allowing more motor neurons to control muscle fibers. On the other hand, large muscle like the quadriceps do not require such fine tune and complicate adjustment hence its motor unit is much larger.

When talking about communication between neurons and cells, we cannot NOT talk about the *synapse*. Synapses are especially important as it is the place where the action potential (AP) is transferred from 1 neuron

to another neuron, cell or, in this case, muscle fibers. There are synapses, called **neuromuscular junction**, from the motor neuron and the muscle fiber and it is approximately in the middle of the muscle fiber. These synapses are very large showing a very high affinity toward the muscle i.e. strong synapse.

Remark 8.10. *Few neurology terminology is changed such as post synaptic membrane is changed to **end plate**.*

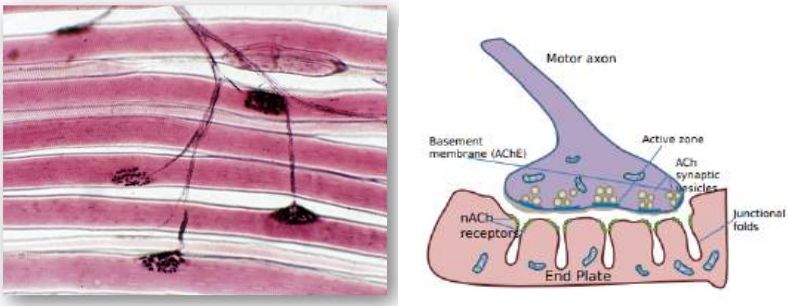


Figure 8.14: Structure of neuromuscular junction.

These end plates has folds on them called **junctional folds** that help with maximizing the area in contact with presynaptic membrane. Along the end plates are ligand-gated ion channels called **nicotinic-acetylcholine receptor (nAChR)** which when bound by acetylcholine (ACh) or nicotine will allow the influx of $Na^+$to the muscle fiber. Nicotine is not so important for our understanding of muscles however **acetylcholine (ACh)** is as it is the main neurontramsitter, stored in presynaptic vesicles, that relay AP of motor neurons to the muscle fiber.

Mechanism of Action (Neuromuscular Transmission): Following from the transmission of efferent down to the motor neurons, it will fires AP that travel to its presynaptic terminals.
At the presynaptic terminal, vesicles will merge to its membrane and release ACh to the synaptic space. ACh will bind to the nAChRs which will open and allow $Na^+$to flow into the muscle fiber. This influx will locally (proximal to the junction) depolarize the muscle fiber. Due to the large area of the synapse, lots of nAChRs will open creating a large influx and subsequently a large EPSP, called **end**

plate potential of around 30-40mV (much higher than neuron's). This potential will reach the threshold and lead to AP. The AP then rapidly propagates the entire length (both side) of the fiber at the same time and then the whole fiber contract as a unit.

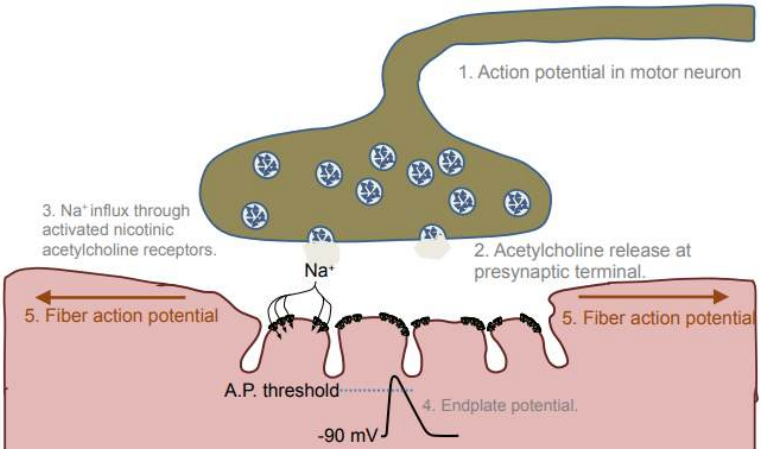


Figure 8.15: Neuromuscular transmission mechanism

But how does AP actually trigger contraction?

Well...from what we know, this AP is happening on the membrane of the fiber that somehow get into the cellular interior which lead to contraction. To know this contractile mechanism, we need to introduce a few more structures.

The **sarcoplasmic reticulum (SR)** is an intracellular storage site that is separated (has its own membrane) from all of the intracellular organelles. It acts as the main storage site of Ca^{2+}.
The **T-tubules** are tubes that extend to the myofibrils and connects directly to the muscle fiber's membrane, called **sacrolemma**. Another way of seeing T-tubules is that they're continuous with the membrane but will invaginate in toward the myofibrils. The T-tubules allow a direct interaction of the ECS with what's in the muscle fiber.

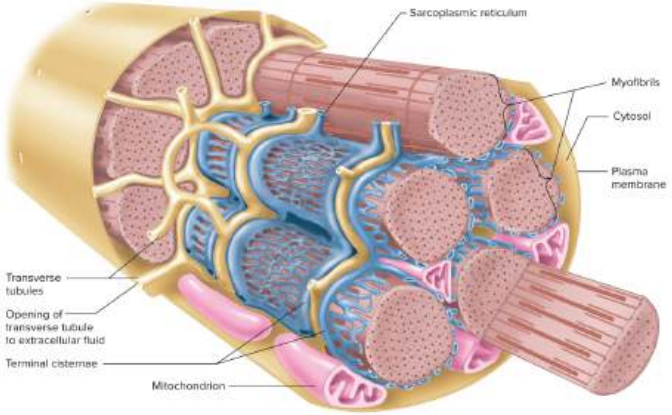


Figure 8.16: SR and T-tubules structure.

Along side these 2 structure are 2 important ion channels: voltage-gated Ca^{2+} channels and ryanodine receptor. The voltage-gated Ca^{2+} channels (VGCC), also called **dihydropyridine (DHP) receptors**, can be found on the T-tubules' membrane and is used to transport Ca^{2+} from the ECS to the ICS of muscle cells. **Ryanodine receptors (RyRs)**, also are ion channels, are found on the SR's membrane that also used to transport Ca^{2+} from SR's interior to the ICS of muscle fiber (or *sarcoplasm*).

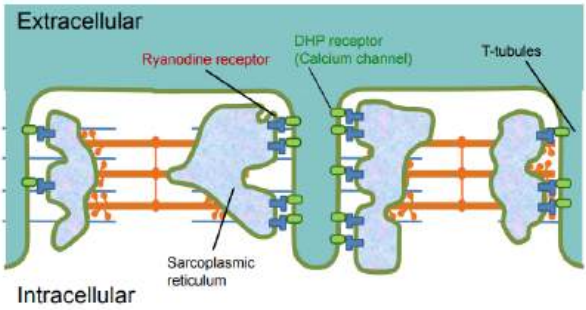


Figure 8.17: Cartoon structures required for the mechanism of excitation-contraction coupling.

Remark 8.11. *The majority, if not all of the receptors are named in accordance to the molecules that can bind to it*

Example 8.2.2. DHP is a compound that can bind to VGCC (DHP receptor) and inhibit it which disable the influx of Ca^{2+} to the ICS. On the other hand, ryanodine is a toxin from a plant that at different concentration can inhibit ryanodine receptor (lead to paralysis) or partially opens it (potentially lead to painful transient muscle contraction).

Now that we've got the structures, we can start to describe the mechanism by which AP is translated into muscle contraction, which is called *excitation-contraction coupling*.

Mechanism of Action (Excitation-Contraction Coupling): AChs are released to the end-plate and trigger an AP to travels along the outside of the membrane. As the AP reach T-tubules, its membrane is depolarized which activated VGCC that lead to an influx Ca^{2+}. However this influx of Ca^{2+} is insignificant and does not cause contraction.
Instead, the VGCC is coupled with RyRs via direct mechanism interaction i.e. when the VGCC open, it will mechanically interact and lead to the opening of RyRs. The opening of RyRs will lead to a massive efflux of Ca^{2+} (much larger than VGCC) from the SR to the sarcoplasm and cause contraction.

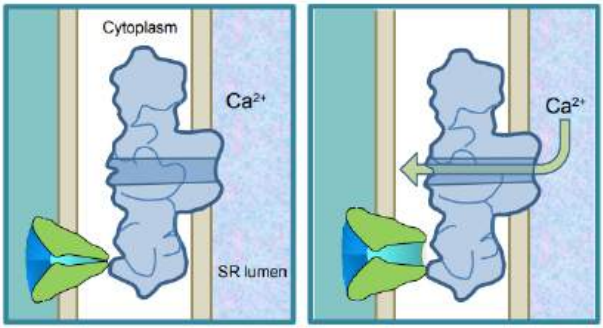


Figure 8.18: Mechanical coupling of DHP receptor (VGCC) and RyRs.

Remark 8.12. *Think of VGCC as a "voltage-sensor" and it can detect when there's a voltage difference between the ICS and ECS but its Ca^{2+} contribution is negligible.*

But how does Ca^{2+} trigger contraction?

Well...to answer this, we need to once again look at the structure of the thin and thick filament. As mentioned in Figure 8.8, some structures are not yet mentioned which are: troponin and tropomyosin. Troponins are receptor-like molecules that are coupled with tropomyosin, which is a rod-shaped molecules that cover the entire length of the thin filament.

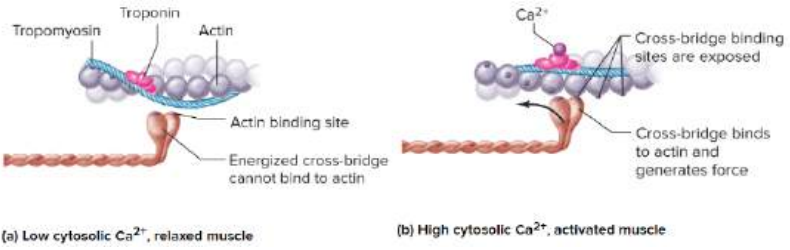


Figure 8.19: Binding of Ca^{2+} to troponin which cause tropomyosin to open the head group binding site.

When there a low $[Ca^{2+}]$ in the sarcoplasm (relaxation), the tropomyosin will cover the binding of the thick filaments' head groups which disable the cross-bridge cycle from happening. As the $[Ca^{2+}]$ reaches a higher level (contraction), Ca^{2+} will bind to the troponin which will cause a conformational change and since troponin is coupled to the tropomyosin, it also cause tropomyosin to change position and opens the head group binding sites. Then cross-bridge cycle can start.

8.3 Single-Fiber Contraction

Before looking further into the mechanics and a muscle fiber's contraction, we need to define some terms

Definition 8.2. The force exerted on an object through contraction of muscle is called **tension** while an object exerting force on a muscle is called **load**.

Remark 8.13. *In order to have static muscle contraction, tension must be equal to load. In order to move an object, tension must be higher than the load etc.*

Definition 8.3. The contraction of a single muscle fiber in response to AP of a motor neuron is called a **twitch**.

Essentially, if we can stimulate an AP to a muscle fiber to record it, we would spot a distinct twitch. At first, we can see that the fiber will yet to contract when there's an AP, then after a brief period it will contract i.e. there's a **latent period** where muscle is not yet contracting when AP is presented. The latent period makes sense since it corresponds to the excitation-contraction coupling (building up of sufficient Ca^{2+} that can cause contraction).
After this, tension begins to rise till it reaches the maximum tension can produced by a muscle fiber (this period is called **contraction time**). The contraction time, takes around 30-40ms, is related to the cross-bridge cycle where the thick pull onto the thin filament inducing tension.
Then, tension at the peak will drop back down to its original state (this period is called **relaxation time**). During this time interval, which is around 150ms, Ca^{2+} will be released back to the SR which brings the sarcoplasmic $[Ca^{2+}]$ back to baseline.

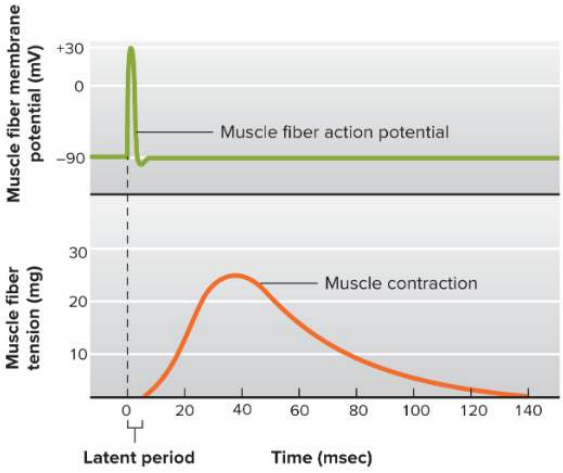


Figure 8.20: Recording of a twitch

But twitching action isn't very helpful...**how can muscle work with just a twitch?** Well...their twitching actions would sum up into a transient tensioning.

We perform the same experiment as before. That is, if we stimulate 1 single motor neuron with 1 AP, we would expect the same twitch. Now, we will change the stimulus according to frequency i.e. we will fire AP at a rate of 1 every 100ms. What we found is that as the muscle fiber reaches maximal contraction and begins to relax; however, it will not relax all the way to the baseline but begins another tension development (due to AP applied at a frequency shorter than a twitch [around 150ms]). This also caused the peaked tension of the second twitch to be higher than the first's. Then, at some point, it will reaches a steady-state where the muscle would oscillate between tensioning and relaxation.

Definition 8.4. When a muscle contraction is maintained in response to repetitive stimulation, it is called a **tetanus**.

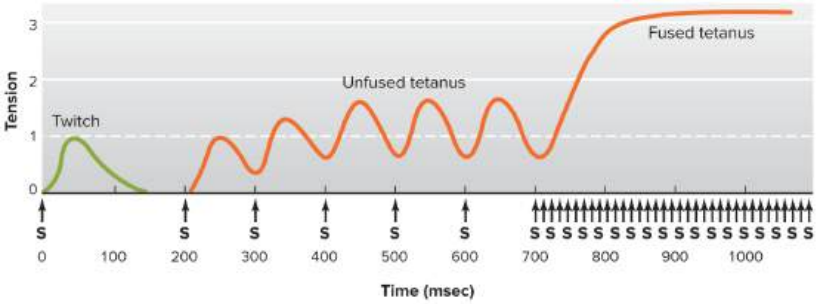


Figure 8.21: Unfused and fused tetanus.

What we've done above is called an **unfused tetanus**. If we did the same experiment as above but now with a higher frequency of action potential induced of around 10,000 every 100ms, we would find that the oscillating steady state will not occur but instead the level of tension will increase much larger than before (called **maximal tetanic tension**, higher frequency will not increase this tension anymore). This tension is a stable steady state instead of an oscillating one and this is called a **fused tetanus**. The fused tetanus is the true muscle contraction happens in your body since motor neurons don't fire a single AP and multiple in frequency.

Remark 8.14. *What we can conclude through these experiment is that muscle tension and frequency of AP is related to each other. Nevertheless, this direct correlation will reach a plateau once tension has reached maximal tentatnic tension.*

It is important to produce the maximal tension against a load but it's also important to have control over that tension i.e. We vary how much force produced by muscles. To do this, we need to vary the number of activated fibers which is dependent on 2 other factors size of motor unit and number of active motor units.
As we remember from before, a larger motor unit corresponds with a control of larger amount of muscle fiber. By varying the amount of active motor unit (activate some, inhibit some), we can also vary the tension output. The process of increase the amount of active motor unit is called **recruitment** and this process is also good for fine control (complex motion) of muscle too.

8.4 Muscle Energy Metabolism and Fiber Types

Muscle can use a lot of energy and this energy consumption is quite different from other cells. Essentially, the energy consumption of other cells are fairly stable however it is not in muscle because muscle won't use a lot of energy unless it's activated (contracted).
Not only that, muscle fibers have evolved their own special mechanism of managing energy since they need lots of ATP (energy) to contract and this [ATP] cannot drop or else the same locking in rigor mortis can happen.

There are mainly 3 ways that muscle can generate its ATP supply depending on the intensity of muscle usage: creatine phosphate, oxidative phosphorylation and glycolysis.

Remark 8.15. *1 common molecules we'll be mentioning is glycogen which is a long chain of glucose connected together.*

> **Mechanims of Action (ATP Generation):** The generation of ATP in muscle can vary by the intensity of muscle usage.
> **1.** At low level of muscle activity (contraction), ATP that pre-exist in the body will be broken down into ADP. This ADP will then be phosphorylated, by **creatine kinase** with **creatin phosphate** as a substract, to ATP again.
> **2.** At moderate level of muscle activity, during the first 5-10min, an *aerobic process*, called **oxidative phosphorylation**, converts glucose, glycogen (stored in muscle) and oxygen to ATP. For the next 30min, it will then begin to use glucose and fatty acid in the blood

stream as fuel. Beyond this point, fatty acid will be the main fuel.
3. At maximal level of muscle activity, oxidative phosphorylation is at its maximum and the main contribution now is glycolysis. This *anaerobic process* will use glucose (from the blood stream) and glycogen to make ATP.

Remark 8.16. *A waste product from glycolysis is* ***lactic acid*** *which is the molecule that cause the burning sensation during exercise.*

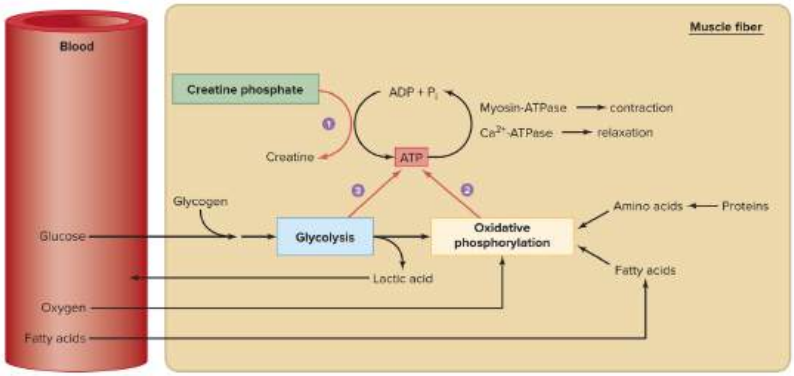


Figure 8.22: ATP generation via 3 pathways.

8.4.1 Types of Muscle Fibers

There are different fibers and they are classified according to their ATP generation/usage, strength and velocity: fast glycolytic, slow and fast oxidative fibers.

As the name suggested, **fast glycolytic fiber** uses glycolysis to generate its ATP very quickly. This fiber is used for very quick short yet large burst of tension i.e. fast glycolytic fiber can produce a large amount of force but only for a short amount of time. This is mainly due to the ineffiency of glycolysis as well as muscle fatigue related to the release of lactic acid.

Remark 8.17. *fast glycolytic's myosin has high ATPase activity.*

Slow oxidative fiber on the other hand uses oxidative phosphorylation to generate its ATP through a long period of time. Not only that the myosin's

ATPase activity is lower which means contraction happens at a lower rate hence it does not generate much tension i.e. slow oxidative fiber can sustain a long period of time but only produce minimal tension.
Because they're using oxidative phosphorylation, they will have a protein called **myoglobin** to carry oxygen in. This also contributes to a longer period hence it is slow. At the same time, it uses glucose and fatty acids in the blood stream meaning that it has "limitless" fuel which is why it can sustain for a long time.

Remark 8.18. *Due to a high amount of myoglobin in slow oxidative fiber it would have a red (dark red) colouration while fast glycolytic would be paler.*

Finally, the third is the **fast oxidative fiber** which is in fact similar in metabolic action with the slow oxidative fiber however its component are much faster and generate a little more force. i.e. fast oxidative fiber can sustain an intermediate amount of time and produce an intermediate amount of tension.

Remark 8.19. *Fibers can be either fast or slow and cannot switch between the 2.*

This clear distinction would lead to fiber taking dominant in a muscle depending of the activity you were training it to develop

Example 8.4.1. If you are a powerlifter, your muscle would develop and consists of mostly fast glycolytic fiber as compared to a marathon runner's muscle which consists of mostly slow oxidative fiber.

Essentially, by training to be a powerlifter your slow oxidative will not switch into fast glycolytic instead you're making the ratio of you slow oxidative fiber to be larger.

8.4.2 Muscle Fatigue and Exercise Response

Definition 8.5. A decline in muscle tension due to repeated stimulation is called **muscle fatigue**.

Muscle fatigue can be characterized by its lower contraction and relaxation rate and is not caused by muscle damage nor the depletion of ATP. Our understanding of muscle fatigue is still quite incomplete however there are some ruled out causes depending on the level of stimulation and duration

1. **High-intensity + short-duration muscle fatigue:** this type of fatigueness was found to be related to changes in [ion] (due to K^+ efflux) but also a reduction of pH due to the release of lactic acid.

2. **Low-intensity + high-duration muscle fatigue:** this type of muscle fatigue was found to be related to the depletion of glycogen or glucose.

3. **Central command fatigue:** This is more on the neuro-psychological side of fatigue. In this case, the brain cannot communicate properly to the muscle due to increase distress sensations.

Like we've discussed, muscle would response differently depending on the exercise you're doing. Going back to example 8.4.1, we would expect that the powerlifter to have a larger muscle profile than the marathon runner...**why is that the case?** Well...for the powerlifter, they will develop mainly the fast glycolytic fiber and this development is characterized by an increase in myofibrils in the fiber. Because of this increase, the fiber themselves would be bigger hance generate more force.
On the other hand, for the marathon runner, they will develop mainly the slow oxidative fiber that is characterized by a more efficient energy usage. The muscle does not get bigger, instead it can learn to use glucose and glycogen more efficiently to produce ATP.

After a long exercise, you would feel that burning sensation due to the release of lactic acid but you will also feel soreness later on...**so what happened here?** Well...the soreness is caused by inflammation of muscle damage. This damage is not necessarily a bad thing since a rebuild of muscle fiber will be done and strengthen it more.

8.5 Smooth Muscle

We'll now look briefly at smooth muscle as it would be the main muscle that take part of the autonomous nervous system which we would be looking in the next chapter.

Smooth muscle are involuntary muscle (we cannot control) and is characterized by its "smooth" body i.e. it lacks striation like the skeletal muscle but **why doesn't it have striation?** Well...to put it simple, striation is an evolutionary morphological approach of muscle in order to produce a large amount of tension. Smooth muscle, on the other hand, does not need

to produce large amount of tension; it only requires an amount that can maintain homeostasis.

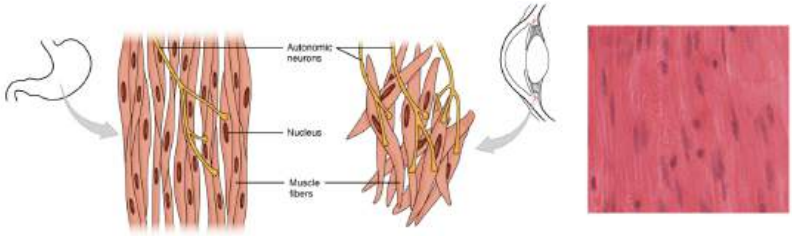


Figure 8.23: Smooth muscle

Morphologically, smooth muscle cell looks more like a typical cells as compared to the rod-like morphology of a skeletal mucle fiber.

8.5.1 Smooth Muscle Contraction

Similar to skeletal muscle, smooth muscle cells uses myosin and actin to contract. Unlike skeletal muscle however, its arrangement of myosin and actin isn't as "organized" or unit-like.

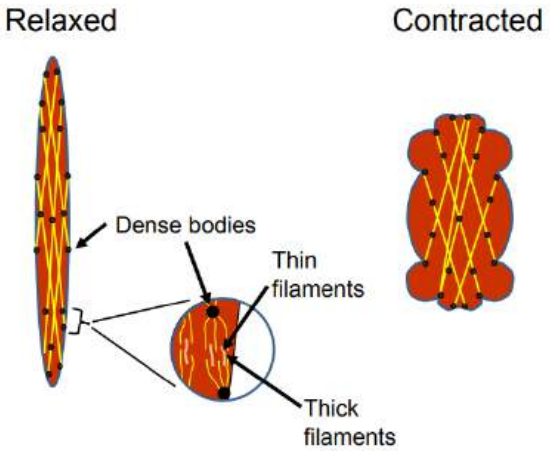


Figure 8.24: Thick and thin filament arrangment on smooth muscle.

The thin filaments are anchored to either the plasma membrane or a structure called the **dense body** that can be found all through out the cell.

Thick filament in the middle of 2 thin filament would perform the same mechanism of pulling in the 2 thin filament closer to its middle. This would result in a contraction.

Remark 8.20. *Nevertheless, the mechanism of how it contract is quite different than that of skeletal muscle.*

We won't get into the differences nor the underlying biochemical event, however we can briefly look at how the muscle contract.

> **Mechanism of Action:** Ca^{2+} either flow in from the ECS or from the SR would bind to **calmodulin**. This binding would activate *myosin light chain kinase* that phosphorylate and thereby activate myosin of the thick filament which lead to contraction.

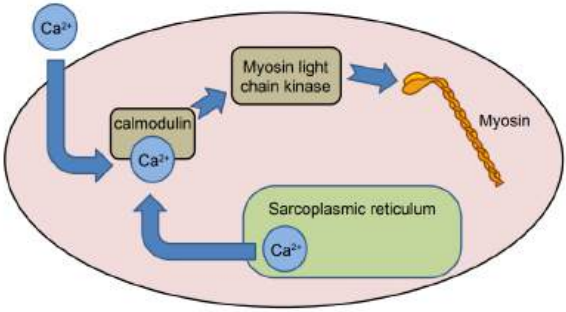


Figure 8.25: Smooth muscle contraction mechanism.

Remark 8.21. *Smooth muscle, depending on location, would also have its main source of Ca^{2+} different i.e. smooth muscle from 1 place would primarily use ECS' Ca^{2+} as compared to another place that uses SR's Ca^{2+}.*

8.5.2 Activation of Smooth Muscle

Unlike skeletal muscle, they're not activated by ACh nor do they have nAChRs. They instead have **metobotropic neurotransmitter receptors** and *hormone receptors*. These metobotropic neurotransmitter and hormones are delivered directly by the autonomous nervous system.

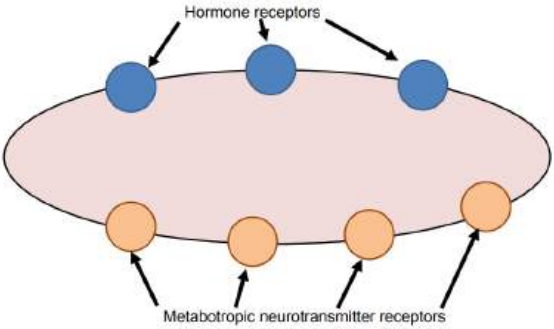


Figure 8.26: Different ways to activate smooth muscle.

Example 8.5.1. **Oxytocin** is a hormone released and bind to the hormone receptor of uterus' muscle lining (smooth muscle) which lead to its contraction during childbirth.

Chapter 9

Neurology III

In this chapter, we will look at the **autonomic nervous system (ANS)**.

Definition 9.1. The **autonomic nervous system (ANS)** is part of the peripheral nervous system that control physiological processes such as heart rate, blood pressure, digestion etc.

The ANS plays an important role in maintaining homeostasis in the body. It's divided into 3 main divisions: sympathetic, parasympathetic and enteric division. We won't talk much about the enteric division but for you information, it is the division can control the gastrointestinal tract.

The *sympathetic division* is the division of the ANS that has to do mostly of regulating the level of arousal, it is also considered our **fight-or-flight response**.

Example 9.0.1. If you get into a dangerous situation, you sympathetic division will take over. It will increase you heart rate, dilate your pupils and increase breathing rate.

Essentially what the sympathetic division is doing in preparing your body in an optimal condition to either face the danger (fight) or run away from it (flight). Sometimes...your emotion could override the sympathetic division and what ended happening is that you'll be frozen at 1 spot due to shock (this is why it's also called fight-flight-freeze response).

The *parasympathetic division* is the division of the ANS that as the opposing effect to sympathetic. It's also called the **rest-and-digest response**.

Example 9.0.2. When you're relaxed, your heart rate will decrease, you breathing will decrease and your digestion increase.

Essentially, the parasympathetic division is making your body relax and "refuel" itself via digestion.

Remark 9.1. *The sympathetic and the parasympathetic division are said to have antagonistic complementary effect i.e. they act on the same process but in opposing manner (see example 9.0.1 and 9.0.2).*

Remark 9.2. *It's misleading to think that the sympathetic division is activated only in emergency situation (same with parasympathetic). In fact, both division are activated to maintain homeostasis however during their respective situation, like danger, the sympathetic division will predominate.*

9.1 Pharmacology of the Sympathetic and Parasympathetic Divisions

If we remember back, we see that sensory neurons' cell bodies are located in the dorsal horns of the spinal cord while those of motor neurons are located in the ventral horn. For neurons that drive autonomic system, their cell bodies are mainly located in the middle between the dorsal and ventral. Unlike the somatic nervous system, the ANS is made up of 2 neurons (or clusters of neurons) connecting the CNS to the effector cells.

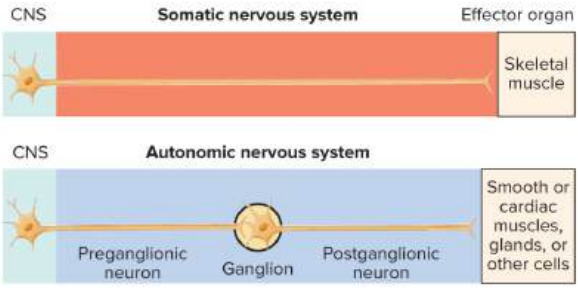


Figure 9.1: Differences in neuronal pathway between SNS and ANS.

We typically these clusters **ganglion**. The first cluster of neuronal cell bodies located in the near middle of the spinal cord is called **preganglionic**

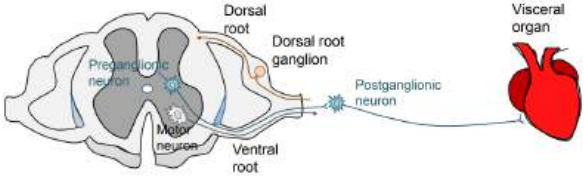


Figure 9.2: Preganglionic neurons synapse to postganglionic neurons which then synapse to target (effector) cells.

neurons. The second cluster of neuronal cells that will be excited by the preganglionic neurons' axons are called **postganglionic neurons**.

> **Mechanism of Action (General Pathway of ANS):** Preganglionic neurons will fire APs which would travel through its axon and synapse with the postganglionic neurons. The postganglionic neurons will the relay this signal to the target cell by releasing neurontransmitter which are usually ACh or NorEPI.

Remark 9.3. *The sympathetic ganglion are interconnected and has its length parallel with the spinal cord. This ganglionic structure is called **sympathetic trunks***

9.1.1 Sympathetic Division

The sympathetic division of ANS has its preganglionic neurons mostly located in the lumbar and thoracic section of the spinal cord.

The sympathetic division follows the same pathway as the general pathway described above. However, we can more specific as the preganglionic neurons (much shorter as well) would release ACh to the nAChRs of postganglionic neurons thereby depolarize them and fires an AP. The AP will travel to effector cells and postganglionic neurons (much longer) will release norEPI which would bind to the cells' *metabotropic receptors* that can be α or β-adrenergic receptors and cause some physiological changes to the cell.

Remark 9.4. *These metabotropic receptors are not necessarily ion channels but can still induce physiological changes. Not only that, these receptors have specific biology to the cell/organs they're found on.*

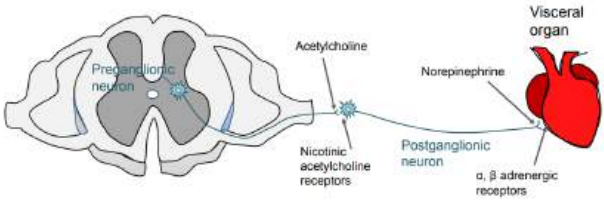


Figure 9.3: Sympathetic Division

Example 9.1.1. Once activated, the sympathetic division can lead to increase heart rate (HR) due to norEPI binds to metabotropic receptors of the heart.
β-blockers are common family of medicine that can reduce blood pressure. They function by binding to the β-adrenergic receptors of the heart which lead to HR↓ and BP↓

Example 9.1.2. Released norEPI would lead to an increase in HR of the heart by increasing the amount of contraction it performs. On the other hand, norEPI that release to the α-adrenergic receptors of the smooth muscle of bronchial tube would lead to its relaxation. Because of this, the biology of these receptors are tissue specific

9.1.2 Parasympathetic Division

The parasympathetic division is a little different from the sympathetic. First, its preganglionic neurons are much longer and isn't located in the spinal cord. In fact, the preganglionic neurons come from the brainstem and their axons are group together to form **some of** the **cranial nerves**.

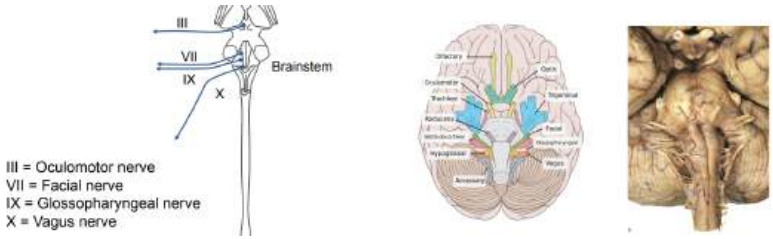


Figure 9.4: Different cranial nerves and vagus nerve

There are many regions in the brain stem that are made up of pregan-

glionic neurons which make up some of the cranial nerves such as: oculomotor, facial, glossopharyngeal and vagus nerve etc. All of the described nerves are important however the main nerve we will look at is the **vagus nerve** which is important for autonomic control of the visceral organs.

Its pathway are general is the same where the preganglionic neurons would fires AP and then release ACh to the postganglionic neurons, that are sitting close to the target cells, thus depolarize it through the mechanism of nAChRs. The postganglionic neurons would transmit the AP and release ACh to the target cell's **muscarinic ACh receptors**.

Remark 9.5. *Like metabotropic receptors, muscarinic ACh receptors are also tissue-specific.*

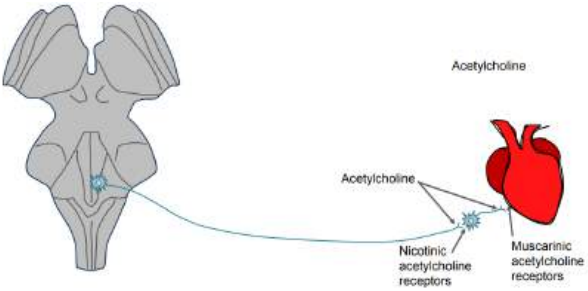


Figure 9.5: Pathway of the parasympathetic division.

Example 9.1.3. Release ACh to the muscarinic ACh receptors of the heart would lower its contraction rate while the same release in to those of the bronchial tubes would increase its contraction.

From many observation, we can see a sort of antagonistic behaviour between these 2 division as described above.

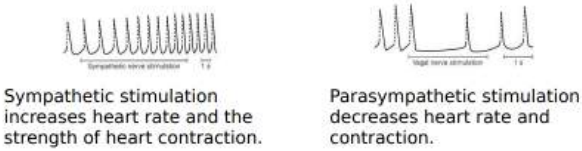


Figure 9.6: Stimulation of the sympathetic vs parasympathetic division.

If we to look at the HR between stimulation of sympathetic and parasympathetic division, we would see sympathetic increase HR while parasympathetic decrease HR v.v.

9.2 Enteric Nervous System

The **enteric nervous system (ENS)** is a complex nervous system that line the entire digestive tract. One of the main thing the ENS does is regulating the contraction of the digestive tract (GI tract).

Remark 9.6. *It is an independent system on itself and only required to receive input from maybe the sympathetic and parasympathetic ANS.*

Example 9.2.1. If the sympathetic division is activated, it would release ACh to the ENS which then inhibit contraction. On the other hand, if parasympathetic division is activated, norEPI would be release to the ENS which activate contraction.

We were to look at a simple diagram that is representative of the GI tract, we can see it has 2 different layers of muscle lining it: longitudinal and circular smooth muscle. These 2 layers would be innervated by neurons found in a layer called the **myenteric plexus** (in between the 2 smooth muscle). The neurons would coordinate with each other in a timely matter so that the food traveling through would be like a wave motion.

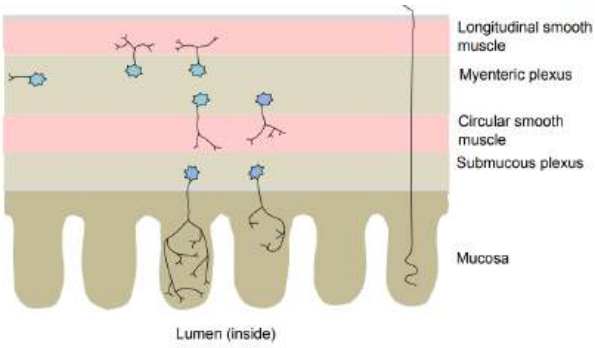


Figure 9.7: Layers of the GI tract and the ENS that innervate them.

Another layer called **submucosus plexus** holds neurons that help with the release of important substances for digestion.

9.3 Autonomic System Sensory Input

The ANS needs to have sensory input in order to activate the sympathetic or the parasympathetic division. There are 2 way sensory input (afferent) can reach the brain: traveling from the spinal cord up to the brain or directly travel from cranial nerves. This cranial nerve that carry sensory input to the brain for the ANS is once again the *vagus nerve*. **But isn't the vagus nerve for parasympathetic division to send signals?** Well...yes but remember that the axons that made up these nerves are not just from the preganglionic neurons but also from axons that would relay sensory input back to the brain. This is homologous to how the peripheral nerves that both transmit efferent and relay afferent.

This sensory input would be integrated to in the brain in a hierarchical fashion i.e. it would have some level of integration that is connected to higher of level and etc.

9.3.1 Brainstem

Sensory inputs coming from the spinal cord and vagus nerves would converge at a point called **periaqueductal gray** in the brainstem. Here the brainstem would integrate and the relay an autonomic response to the rest of the body.

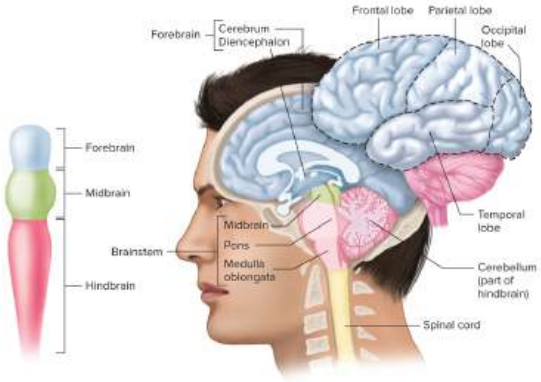


Figure 9.8: Brainstem

Example 9.3.1. When a cat is being threatened, its brainstem would activate its defensive response (automatically and autonomously) where it would arch up its back, point its tail up, dilate its pupils, and even hissing.

Remark 9.7. *These automatic and autonomous responses would varies from 1 species to the next.*

Example 9.3.2. If we (human) was to be threatened or placed in a situation of danger, our pupils dilate, our heart beats faster, our muscle tense up, our palm sweat and our breathing rate increases.

Essentially, this is the first level of sensory input integration made that lead to an autonomic output.

9.3.2 Hypothalamus

The next level of integration is the hypothalamus which can control and modulate the actions or ouputs produced by the brainstem.
The **hypothalamus** is located deep in the brain just superior from the optic chiasm. Hanging below it and posterior to the optic chiasm is the **pituitary gland** which is an important gland for the endocrine system.

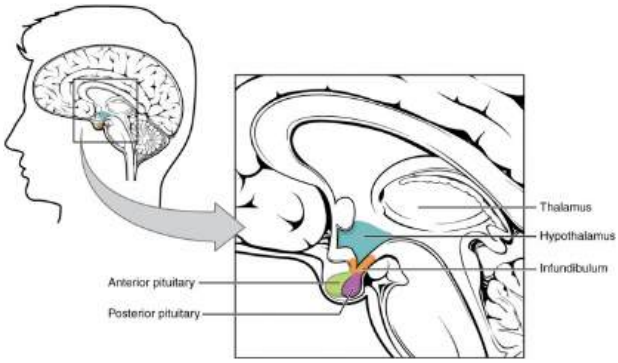


Figure 9.9: Hypothalamus and the pituitary gland.

The hypothalamus is really important as it's the "master coordinator" of output responses that are involved in maintaining homeostasis. It regulates 5 physiological functions/aspects

1. Blood pressure and electrolyte
2. Body temperature

3. Energy metabolism
4. Reproduction
5. Emergency responses to stress

The hypothalamus can communicates to different brain area that can illicit and homeostatic balance in the body. It can communicate with the brainstem to modulate autonomic output responses, or with the pituitary gland to modulate hormonal output, or with the specific regions of cerebral cortex to illicit emotional or motivational responses.

Example 9.3.3. Supposed that your body temperature drop below 37^oC, neurons that can sense the changes in temperature would report back, via afferent, to the brain especially the hypothalamus. The hypothalamus would detect deviation from this set point and start communicating. First, autonomic responses by the brainstem would generate where your body begins to shiver, blood flow is more directed to the body instead of the limb. Next, it communicates with the pituitary gland lead to thyroxin release and drive up metabolism and increase temperature. Lastly, it would communicate to those regions of the cerebral cortex which tells the cognitive mind, "you", to maybe put on a jacket or turn on the heater.

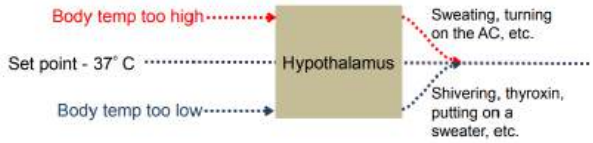


Figure 9.10: Changes in body temperature and the hypothalamus responses.

wait...then what happened when you have a fever? Well...when you're having a fever, the immune system would change the set point of the hypothalamus from 37^oC to a higher one. Then the hypothalamus would detect that your body is at 37^oC which would then communicate with previously shown brain area and drive up temperature.

9.3.3 Amygdala

The **amygdala** is an important part of the brain that deals with aggression and fear. The amygdala is located deep in the brain from the temporal lobe,

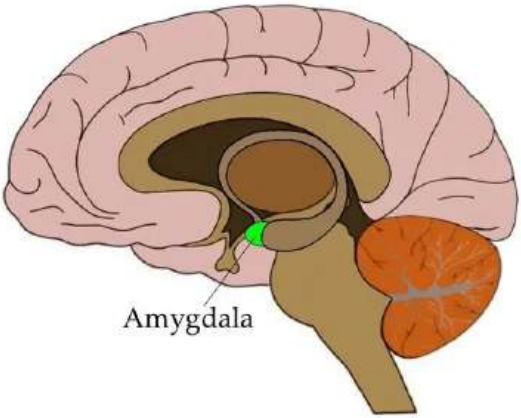


Figure 9.11: Amygdala.

is posterior from the hypothalamus and is located next to the hippocampus.

The amydala is a very strange regions since damages to it could lead patients to lose cognitive recognition of fear. Sometimes ago, researchers gather patient with bilateral lose of the amygdala (very rare) and studied them. They then shows them pictures where normal people would have normal responses to it and it indeed their responses was normal. However, once they shown horrific images that would increase the arousal level of normal patient, they has the same arousal level as all the other images. This is why it's part of regulating fear and aggression.
What's more peculiar is that the experiment was done again with a new set of image but now and then researcher would put back those horrific images that were previously seen by the subjects. They found that patient with functional amygdala would be able to recall these images and its illicit frightful responses; however, for bilateral amygdala deficits individuals, they could not recall ever seeing the image. This lead to the understanding that emotional responses (in this case fear) have is directly connected memory system.

All in all, the amygdala is important for emotionally tag memories so that it becomes more and more vivid.

9.3.4 Cerebral Cortex

Finally is the **cerebral cortex** which is especially important to mediate between the hypothalamus and the amygdala.

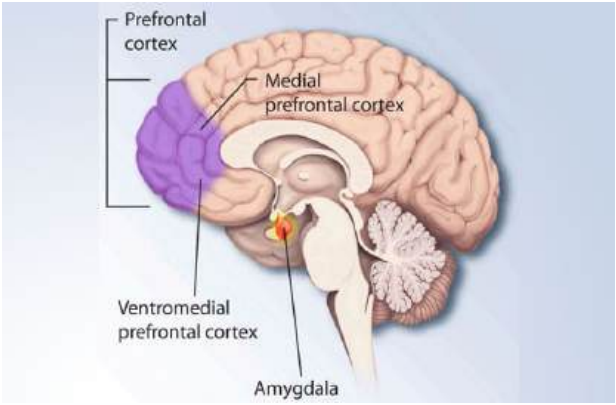


Figure 9.12: Medial frontal region of the cerebral cotex.

The main part that facilitate this is the *medial frontal region* of the brain. It basically connects illicit feeling with a cognitive states i.e. you're feeling afraid and your heart beating fast well why are you afraid well you might answer yourself that probably because of the estrange environment that you're in.

So in short, you have these emotional physiological responses that are mediated by the amygdala and you have these bodily physiological responses by the hypothalamus and brainstem; and those 2 responses are connected and "talking" by the cerebral cortex which allow you to assign meanings to the feelings you're having.

Note to Author: *Good luck on your final exam on December* 12^{th}*, 2023!!!*

Good luck!

Hopefully this notebook can help you!

This notebook contains all of PHGY 209 lecture: physiology of body fluids, blood, body defense mechanisms, muscle, peripheral, central, and autonomic nervous systems.

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