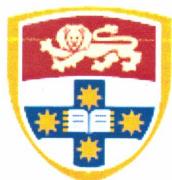


The University of Sydney Discipline of Physiology



THE UNIVERSITY OF
SYDNEY

INTEGRATED PHYSIOLOGY A PHSI2005 & 2905

LECTURE OUTLINES AND LEARNING OBJECTIVES

SEMESTER 1, 2016

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CONCEPTS IN PHYSIOLOGY – Dr Michael Morris



Dr Morris's research interests include understanding the molecular mechanisms controlling the pluripotency and directed differentiation of embryonic stem cells and early embryos. His lab uses ES cells as a model for human development to the early stages of the nervous system, and also looks at improving the development of cultured embryos for use in assisted reproduction.

2015 was the first year that we started off with a series of lectures covering basic concepts in Physiology. These basic concepts highlight the unique and special qualities of this branch of science. Though the examples given will largely be of a general nature, they will be drawn from material that you will encounter in more detail later in this semester and, in some cases, material that will be covered in PHSI2006 in second semester.

A critical aspect of these basic concepts is that while they can and should be understood individually, it is their integration with one another that lies at the heart of Physiology. If you can get to grips with these basic concepts – even at the qualitative level – you should be able to apply them meaningfully to any physiological problem and gain significant insight regardless of whether those problems are encountered in 2nd year or 3rd year or beyond that to Honours and postgraduate research.

Put simply, life is a complex system with many levels of control and in which each level of control talks to and responds to all the others either directly or indirectly. Physiology is the science of that integrated communication and response that keeps life ticking over. On the other hand, pathophysiology is the breakdown within and between the various integrated control mechanisms resulting in acute or chronic morbidity and, in some cases, death.

Lecture 1 Physiology and Homeostasis

(Silverthorn, Chapter 1)

- Homeostasis defined
- General concepts of steady state, equilibrium and disequilibrium, and feedback regulation
- The coordinated (physiological) integration of various organs and tissues involved in exercise – a brief overview

At the end of this lecture you should understand what homeostasis is and understand the general properties of feedback regulation that control homeostasis in humans

Lecture 2 Membranes, gradients and transporters (Silverthorn, Chapter 5)

- The plasma membrane (and other membranes) – a selectively permeable barrier
- Lipid composition of the plasma membrane – phospholipids, cholesterol, the bilayer
- Protein composition of the plasma membrane – structural proteins, transporters, receptors
- The extracellular and intracellular compartments

- Control of entry and exit of substances to and from the cell – small lipid molecules, small polar and charged molecules, large molecules like proteins, and water
- Water and osmotic equilibrium
- Chemical gradients of uncharged molecules
- Membrane potential and electrochemical gradients of charged molecules
- Active and passive transport and homeostasis

At the end of this lecture you should be able to:

1. Draw and label a diagram of the plasma membrane showing its lipid and proteinaceous components
2. Qualitatively explain and give examples of water and osmotic equilibrium, chemical gradients of polar molecules, membrane potential and electrochemical gradients of ions
3. Use this information to explain homeostasis as a steady state at the molecular/cellular level
4. Provide examples of transporters and transport processes that work passively and actively

Lecture 3 Cell communication and signalling **(Silverthorn, Chapter 6)**

- Sensing incoming signals (autocrine, paracrine and endocrine) – ligands and receptors
- Processing incoming signals – cell signaling pathways, including second messengers
- Cellular response to signaling – the emergent properties of the system
- Cell-to-cell contact
- The body in harmony – cells, tissues and organs working together

At the end of this lecture you should be able to:

1. Define ligands and receptors, and give examples of each
2. Understand qualitatively how information is passed from the outside of the cell to the inside via a plasma membrane receptor
3. Draw various types of cell signalling pathways, including those that use second messengers and/or phosphorylation
4. Understand that the cell integrates all the information that it receives and responds accordingly (emergent properties)
5. Give examples of emergent properties of a cell

Lecture 4 Oxygen transport and use **(Silverthorn, Chapters 4 & 18)**

- Partial pressure of oxygen in the lungs and in tissues
- Oxygen in the lungs meets deoxygenated blood
- Red blood cells (erythrocytes), haemoglobin, porphyrin and iron
- A brief overview of oxygen transport through the cardiovascular system
- Oxygen in the blood meets deoxygenated tissue
- Glucose and aerobic metabolism
 - Citric acid cycle and production of carbon dioxide
 - Mitochondria and electrochemical gradient of H⁺
 - ATP production and the fate of oxygen

At the end of this lecture you should be able to:

1. Trace the path of oxygen from the lungs to the tissues where it is used, including how it is transported in red blood cells
2. Explain oxygen partial pressure and gradients and the uptake and release of oxygen
3. Explain qualitatively the fate of glucose in aerobic metabolism, including the production of carbon dioxide
4. Explain qualitatively the electrochemical gradient of H⁺ produced in the mitochondria and the production of ATP
5. Explain the fate of oxygen

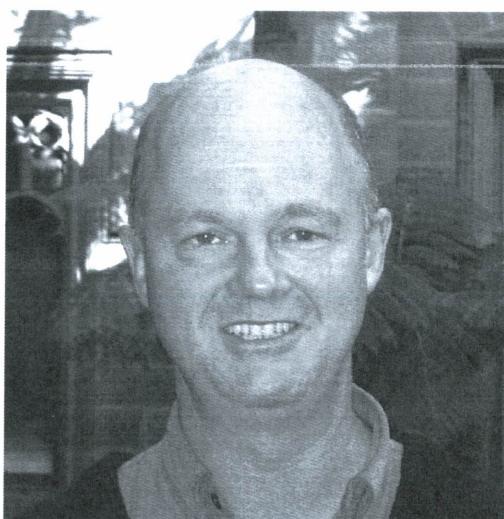
Lecture 5 Pathophysiology – what happens when things go wrong

- The body as a series of complex integrated ‘circuits’
- Examples of defective switches and the consequences – local and systemic effects

At the end of this lecture you should be able to:

1. Qualitatively understand that molecular circuitry is integrated across cell, tissues, organs and the whole organism
2. That these molecular circuits often contain key components that can be defective through genetic abnormality, disease or injury
3. That defective circuits can undermine the homeostasis of the whole organism leading to morbidity and mortality

CELLULAR NEUROPHYSIOLOGY – A/Prof. Bill Phillips



A/Prof. Phillips is head of the Molecular Neuroscience Laboratory. The laboratory is concerned with the synaptic connections between nerve cells and their targets: how they form, how they are maintained through life and how they may be modified in disease states.

A major challenge for neuroscientists is to understand the loss of synapses in neurological diseases and in ‘normal aging’: what are the circumstances in which synapses are lost, what molecular and cellular pathways are involved and how might synapse loss might be slowed or prevented. We focus on the neuromuscular junction, because it is a large, easily accessible synapse with profound importance to human wellbeing.

Physiology is about us developing a mental model (theory) for how a particular body system works. A good physiological model allows us to predict precisely how mutations or other changes that modify one component of a cellular signalling system will affect the system as a whole. My aim in this block of lectures is for you to develop your own mechanistic understanding of how electrical signals are generated and propagated along nerves, and how such signals can be transmitted via chemical synapses to target cells.

We will focus on the example of the motor neuron and its target, the skeletal muscle fibre. In these lectures, I don’t ask you to memorize a lot of facts but I do ask you to apply your mind to understanding how the system works. By the end of these lectures you should, for instance, be able to predict from theory how a rise or fall in the concentration of a particular ion in the blood will modify the resting membrane potential of a neuron, how blockage of potassium-selective channels would be expected to influence action potential signalling etc. In the exam I might ask you to explain in your own words why you predict this.

To do well in my section of the mid-semester quiz and final exam you should attend my lectures, and I suggest making some notes as you go. The PDF of my slides might be something useful to annotate. I won’t give you lots and lots of details to remember but I will expect you to critically ask yourself, “Do I really understand this?” Making a note here or two is a way of reinforcing your memory of a lecture. Reading over your lecture notes within 12 h of the lecture notes is a powerful way of reinforcing what you have learnt.

If you have trouble grasping the mechanisms as I describe them, the ‘Supplementary Notes’ might also help to clarify these issues. I’ve written my Learning Objectives in the form of short answer questions. Test yourself after each lecture by treating the learning objectives like a practice exam. Spend 5 min attempting to answer each question. If you can’t confidently answer the relevant questions after reading over the Supplementary Notes then put up your hand in the next lecture or come down the front to ask me about it. In general, we lecturers really appreciate such questions at the end of the lecture. It shows you care.

Lecture 1 Resting Membrane Potential

- Balance of electrical charge
- Active transport creates concentration gradients
- Ion channels
- Chemical driving forces
- Electrical forces on ions
- Ionic currents across the membrane
- The Smarties game / Nernst Potentials
- Relative permeability to ions
- The Goldman Equation

Lecture 2 The Action Potential

- Need for amplified signalling
- Depolarisation initiates neuronal signalling
- Voltage gated sodium channels & the Hodgkin Cycle
- Voltage gated potassium channels and repolarisation
- Ratio of permeability: potassium and sodium ions
- Na^+ Channel inactivation and the refractory period
- Information is encoded in by AP frequency
- Role of the Na^+/K^+ Pump in nerve signalling

Lecture 3 Action Potential Propagation

- Cable theory allows us to understand the limitations on signal transmission in axons
- Passive electrical properties of axons slow action potential propagation
- Continuous Propagation of action potentials
- Saltatory Propagation
- Damage to the myelin sheath modifies saltatory propagation in predictable ways

Lecture 4 Neuromuscular Synaptic Transmission

- Recording postsynaptic electrical potentials
- The nicotinic acetylcholine receptor: example of a ligand-gated cation channel
- Pre-synaptic neurotransmitter release is controlled by calcium influx to the nerve terminal
- Quantal synaptic transmission
- Recycling of acetylcholine at the neuromuscular junction

Lecture 5 Central Nervous System Transmission

- Fast glutamatergic synapses on neurons: similarities and differences from the NMJ
- Fast inhibitory synapses on neurons
- Inhibitory chloride channels moderate the effect of depolarising currents upon depolarisation of the soma
- Summation of postsynaptic currents in neurons: cable properties revisited
- Diversity of neurotransmitters and their postsynaptic receptors
- Neuromodulation: producing changes in neuron excitability

Review session

The purpose of this session is for me to try to answer your questions about my lectures (and the nerve prac). Try to answer each of the learning objectives in no more than 5 lines. Please email me any remaining questions before the review sessions. I'm not very good at trying to explain physiological mechanisms and concepts in an email, so please don't put such questions off till the end of semester.

CELLULAR NEUROPHYSIOLOGY LEARNING OBJECTIVES

Membrane Potential

- 1.1 Describe the characteristic arrangement of the soma, axon, dendrites and axon terminal of a somatic motor neuron and explain the roles that these structures play in the function of the neuron.
- 1.2 Explain what is meant by the electrochemical (Nernst) equilibrium for an ion. What forces contribute to it?
- 1.3 If the temperature were to rise how would this affect the magnitude of the Nernst Potential for potassium?
- 1.4 Referring to the concentration gradient and the forces that act on K^+ under different conditions, explain why the Nernst potential for K^+ is normally negative.
- 1.5 Referring to the concentration gradient and the forces that act on Na^+ under different conditions, explain why the Nernst potential for Na^+ is normally positive.
- 1.6 Referring to the concentration gradient and the forces that act on Cl^- under different conditions, explain why the Nernst potential for Cl^- is normally negative.
- 1.7 Suppose that in an animal from the planet Zeta the neurons contain a much higher concentration of Ba^{2+} ions in their cytosol than in the extracellular fluid. Suppose there are also Ba^{2+} -selective channels in the neuron membrane. Will the Nernst Potential for Ba^{2+} be positive, negative or zero? What if the membranes had no permeability to Ba^{2+} ?
- 1.8 In what way would a doubling of the density of potassium leakage channels be expected to affect the Resting membrane potential for potassium of the cell in question? Would it alter the Nernst Potential?
- 1.9 Considering what we have learnt about the Nernst Potentials for Na^+ and K^+ , and assuming the membrane contains ion channels that are permeable to both of them, explain how ongoing diffusion of each of these ions would collectively help maintain the Resting membrane potential.

The Action Potential

- 2.1 Considering the role of ion-selective channels, explain why the resting membrane potential for most neurons is in the negative range of about -50mV to -80mV. Why isn't it positive? What factors might explain why electrophysiologists find differences among neurons in their resting membrane potentials?
- 2.2 If Na^+/K^+ -pump is inhibited with a drug, the resting membrane potential of the neuron decays only very slowly (over a period of about 20min) during which time action potentials can still be propagated in the neuron. What does this tell us about the role of the Na^+/K^+ -pump in neuronal signalling?
- 2.3 Describe the functional differences between non-gated, ligand-gated and voltage-gated ion channels.
- 2.4 What is meant by Depolarised? Hyperpolarised? Threshold potential?
- 2.5 Describe the changes in membrane permeability that occur when the membrane of a neuron is depolarised to threshold, and how they produce the subsequent changes in membrane potential that we refer to as the action potential.
- 2.6 What are the two types of gates on the voltage-gated sodium channel in the axon membrane? Under what circumstances do each of these gates open?
- 2.7 Describe what is meant by the term Hodgkin Cycle. Precisely how would a small reduction in the density of voltage-gated sodium channels in the axon membrane be expected to affect membrane depolarisation during the Hodgkin cycle?
- 2.8 What are the ion conductive and gating properties of the voltage-gated potassium channel in the axon membrane? How does its properties as a channel differ to those of the voltage-gated sodium channel?

Action Potential Propagation

- 3.1 What is meant by the term *local circuit current*? Explain how local circuit currents spread the action potential along the axon membrane.
- 3.2 What is meant by the *axoplasmic resistance*? Why does the diameter of the axon affect the axoplasmic resistance? Are all axons the same diameter? If an axon is very thin, how would the spread of an action potential along it compare to a very large diameter axon?

- 3.3** What is meant by the membrane *conductance*? What does it measure? What are the structures within the membrane that determines the membrane conductance? If an axon has a high membrane conductance, how would the spread of the action potential be affected, compared to an axon with low membrane conductance? Why?
- 3.4** What do we mean by the electronics term “*capacitance*”? How does electrical charge get stored on a membrane?
- 3.5** In what way does the capacitance property of the lipid bilayer affect the rate of change of the membrane potential during electrical signalling in neurons?
- 3.6** Describe with the aid of a drawing how myelination modifies the structure of an axon. Label the *Nodes of Ranvier*, the *internode* regions and the location of voltage-gated sodium channels.
- 3.7** How is the capacitance per square cm of membrane affected by myelination of the membrane? Why is this?
- 3.8** Describe two ways in which axons can become specialized in order to propagate action potentials more rapidly. In each case, which passive electrical properties of the axon are modified: axoplasmic resistance? membrane conductance? membrane capacitance? How do these changes, in turn, speed up signalling?
- 3.9** With the aid of arrows on a diagram describe the differing paths taken by currents involved in the spread of an action potential along a myelinated axon and an unmyelinated axon.
- 3.10** Why is propagation of the action potential slowed down when axon tracts become demyelinated? Refer to the changes that occur in basic electrical properties and how these, in turn, affect action potential propagation.
- 3.11** Dendrites, where synaptic inputs to a motor neuron arise, are also very thin, tube-like structures, like axons. How would you expect this to affect the total amount of charge stored on the membranes of the dendritic tree? How would this affect the time-course of depolarising synaptic potentials arising from synapses on the dendrites?

Neuromuscular Synaptic Transmission

- 4.1** What are meant by the “*presynaptic*” and “*postsynaptic*” parts of the synapse? What are their respective roles?
- 4.2** List the sequence of events in neuromuscular synaptic transmission: from the nerve action potential till the muscle action potential.
- 4.3** Draw a cross-section through a neuromuscular synapse, labelling the location of voltage-gated Ca^{2+} channels, synaptic vesicles, acetylcholine, nicotinic acetylcholine receptors, acetylcholinesterase and voltage-gated Na^+ channels.
- 4.4** Describe the function of each of these components in the process of synaptic transmission.
- 4.5** Describe three features that make the *nicotinic acetylcholine receptor* an example of a *ligand-gated cation channel*.
- 4.6** What are *synaptic vesicles* and how are they affected by calcium influx into the nerve terminal?
- 4.7** What is the *endplate potential* (EPP) and how is it recorded?
- 4.8** What is a *spontaneous miniature endplate potential* (mEPP) and what phenomenon is it thought to represent?
- 4.9** What is meant by “*the probabilistic nature of transmitter release*” and why do changes in the extracellular concentration of Ca^{2+} influence it?
- 4.10** What are meant by *quantal amplitude* and *quantal content*? What factors influence each of these parameters at the NMJ?
- 4.11** What is the relationship between the endplate potential amplitude, quantal amplitude and quantal content?
- 4.12** If the concentration of calcium ions in the extracellular fluid ($[\text{Ca}^{2+}]_o$) was raised from 0.5mM to 2mM, in what way would this effect synaptic transmission? What is the mechanism?
- 4.12** What terminates the action of acetylcholine on the acetylcholine receptors? How does it do so?
- 4.13** Describe the processes by which acetylcholine is recycled at the neuromuscular junction and why this recycling is important.

Central Nervous System (CNS) Transmission

- 5.1** What are the similarities in structure and function between the neuromuscular junction and the fast, *glutamatergic* synapses on the dendrites of the motor neuron? Identify three differences.
- 5.2** In what respects are fast *glycinergic* and *GABAergic* synapses similar to glutamatergic synapses and in what ways are they different? Refer to the driving forces and charges for the particular ions involved.
- 5.3** With the aid of a drawing, explain the way in which depolarising inward currents at synapses on the dendrites of a motor neuron can depolarize the cell soma (body) and axon hillock.
- 5.4** Describe the influence of *glycinergic* and *GABAergic* synaptic activity upon the excitability of the motor neuron.
- 5.5** Using a drawing of a motor neuron, explain how chloride channels at inhibitory synapses moderate the depolarising currents during EPSPs.
- 5.6** Outline ways in which different neurotransmitters and multiple receptor types can work together to shape the firing activity of a neuron.
- 5.7** In what sorts of ways can *neuromodulators* act on cells? What is meant by the term *second messenger*, and how can they influence neuron excitability?

MUSCLE PHYSIOLOGY – Dr Atomu Sawatari



Dr. Sawatari is head of the Systems Neurosciences Laboratory. He is interested in understanding the layout and function of the neural circuits that underlie perception and complex behaviours. By employing a combination of novel anatomical and physiological methods, his research team hopes to reveal the actual functional connections of neurons forming the circuits that give rise to these higher functions.

Dr. Sawatari is coordinator of the Advanced stream of Integrated Physiology.

This series of four lectures describes the structure and function of skeletal, smooth and cardiac muscle cells, with a particular focus on the cellular mechanisms of contraction and relaxation. The lecture series lays the foundation for a deeper understanding of how different levels of force can be achieved at the level of individual muscle fibres, and how the coordinated activation of these cells can affect the function of entire muscle systems and organs. The knowledge developed in these lectures provides the background for further study of the role of some of these cells in 3rd year Units of Study.

Theory lectures focus on the cellular and molecular structures of muscle cells and the mechanisms leading to muscle force production, shortening, and movement. These mechanisms are further explored for skeletal muscle in the “Skeletal Muscle Mechanics” practical class, which is supported by a programmed text explaining difficult theoretical concepts.

Topics, methods, and experiments covered in the “Skeletal Muscle Mechanics” practical class will also be covered. An emphasis will be placed on linking the conceptual understanding of the other lectures to the specific experiments which will be conducted in the practical.

Lectures 1-4

Structure and function of muscle cells (with a focus on skeletal muscle)

Different types of muscle (how other muscle types differ from skeletal muscle)

- Gross, cellular and molecular structure
- The molecular basis of muscle contraction
 - The role of calcium
 - The cross-bridge cycle
 - Sliding filament theory of muscle contraction
 - Excitation-contraction coupling
 - Relaxation

Cardiac muscle

- Cellular structure
- Molecular mechanisms of contraction
- Excitation - contraction coupling
- Factors affecting force production

Smooth muscle

- Cellular structure
- Molecular mechanisms of contraction
- Excitation (activation) - contraction coupling

Skeletal Muscle Mechanics

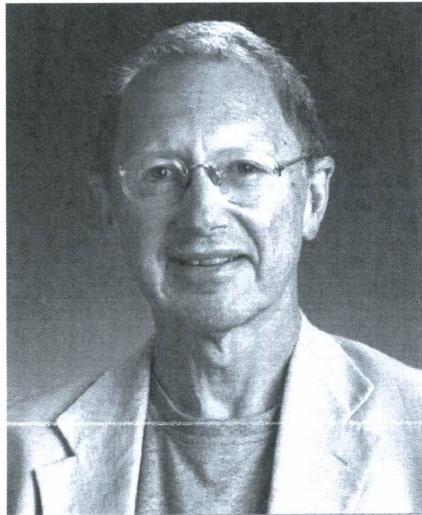
- Twitch *vs* tetanic contractions: effect of stimulation frequency
- Length-tension relationship
- Isometric and isotonic contractions
- Motor unit recruitment

MUSCLE LEARNING OBJECTIVES

By the end of the four lectures you should be able to:

1. Describe the structure and understand the function of skeletal, cardiac and smooth muscle at:
 - a) The gross level (whole muscle--muscle bundle--muscle cell--myofibril)
 - the cellular level (sarcomere, A- and I-bands, Z-line (or disc), H-zone, thick and thin filaments, myosin and actin).
 - the molecular level (myosin, actin, tropomyosin, troponin-1, -T, -C).
 - b) Highlight the differences between the three cell types with respect to structure and function.
2. Skeletal muscle:
 - a) Describe the structure and function of T-tubules and explain how they interact with the sarcoplasmic reticulum to release calcium (Ca^{2+}). Relate your understanding of this process to the mechanisms of muscle relaxation.
 - b) Describe the role of calcium in initiating myosin and actin interaction via regulatory proteins troponin and tropomyosin. Explain the role of ATP in this interaction and its importance in powering the process of cross-bridge cycling and force production.
 - c) Relate your understanding of the cross-bridge cycle to the “sliding-filament theory” of muscle contraction and list the evidence that supports this theory.
 - d) Use your understanding of nerve action potential to define graphically the time course between motoneurone activation, neuromuscular junction activation, muscle activation and muscle force production.
 - e) Predict the relative amount of force produced by a muscle under different physical and chemical conditions by drawing on your understanding of the sliding filament theory and the cross-bridge cycle.
3. Cardiac muscle:
 - a) In addition to 2a), b) and c), describe the function of intercalated disks in the excitation process.
 - b) Define graphically the time course between the cardiac cell action potential and the contraction and explain the significance of the long refractory period for heart function.
4. Smooth muscle:
 - a) In addition to 2a), b) and c), describe the function of dense bodies, intermediate filaments and caveoli.
 - b) List the two main types of smooth muscles, the organs whose function they support, and compare their different modes of excitation.
 - c) Describe the different ways that intracellular calcium levels can be increased and the mechanisms which result in cross bridge cycling and force production.

NERVOUS SYSTEM: EXECUTIVE AND MOTOR CONTROL
Prof. Max Bennett



Professor Bennett is head of the Neurobiology Laboratory. The Neurobiology Laboratory conducts research into the molecular mechanisms underlying synaptic transmission in the nervous system, with specific emphasis on the phenomena known as *Synaptic Plasticity*; that is, the ability of the brain to alter the structure of its own circuitry over seconds to minutes. Currently research in the lab is concentrating on signal transduction in glial cells, communication between neurons and glial cells and their applications to neuronal disorders both in central and peripheral nervous systems.

Lecture 1 Overview of the Nervous System

(Silverthorn, pp. 291–308)

- Functions of the nervous system
- Main divisions of the central nervous system (CNS):
 - spinal cord
 - brain stem
 - thalamus
 - cerebral cortex
- Reflex pathway

Lecture 2 General Properties of Sensory Systems

(Silverthorn, pp. 326–340)

- Different receptors and modalities e.g. the skin, proprioceptors
- Transduction mechanisms
- Phasic and tonic receptors,
- Receptive fields (including in the skin)
- Sensory acuity
- Coding for modality, location and intensity

Lectures 3 Volition and the Motor System

(Silverthorn, pp. 358–367)

- Extensor and flexor movements
- The stretch reflex
- The muscle spindle
- Reciprocal inhibition
- Cortical control of movement
- Organisation of motor cortices
- Descending pathways for movement
- Pyramidal and extrapyramidal pathways
- Feedback and error correction

NERVOUS SYSTEM: EXECUTIVE AND MOTOR CONTROL

Overview of the Nervous System

1. To list the major parts of the brain and state the dominant function of each part
2. To understand the organisation of the major sensory and motor pathways
3. To describe the sequence of events that take place in a simple reflex (e.g. withdrawal reflex)

General Properties of Sensory systems

1. Classify sensory receptors by adequate stimulus, and discuss cutaneous receptors
2. Describe the sequence of events that leads from a stimulus to its perception
3. Distinguish between phasic and tonic receptors
4. Explain the concept of receptive field for various sensory systems (include the skin)
5. Describe how action potentials are generated in sensory neurons in response to stimuli
6. Explain, for the skin senses, the basis of acuity
7. Explain coding of modality, location and intensity
8. Describe the central projections of these neural pathways, in general terms only

Reflexes

1. List the components of a reflex arc
2. Describe the components of the stretch reflex from stimulus to response and know the function of this reflex
3. Recognise that where there are antagonistic muscles, it is usual for excitation of one to be accompanied by relaxation of the other, i.e., there is reciprocal inhibition
4. Describe the components of the withdrawal reflex and know the function of this reflex

Voluntary Movement

1. Understand the three hierarchical levels of motor control
2. Recall that at the lowest level, the spinal cord, there are reflexes and stereotyped sequences of motor activity that originate in the central pattern generators
3. Understand the differences between the direct (pyramidal) projection system and the indirect (extrapyramidal) system, which muscle groups and movements each system controls
4. Understand the basis of the homunculus in the primary motor cortex
5. Recall the feedback pathway via the cerebellum that regulates movement

NERVOUS SYSTEM: SENSORY AND AUTONOMIC PATHWAYS

Dr Atomu Sawatari



Dr Sawatari is head of the Systems Neurosciences Laboratory. He is interested in understanding the layout and function of the neural circuits that underlie perception and complex behaviours. By employing a combination of novel anatomical and physiological methods, his research team hopes to reveal the actual functional connections of neurons forming the circuits that give rise to these higher functions.

Dr Sawatari is coordinator of the Advanced stream of Integrated Physiology.

Lectures 1 & 2 Vision and Sensory Systems

(*Silverthorn, pp. 442–451*)

- Review of sensory systems and relevant concepts, focusing on vision
- Ganglion cell receptive fields
- Visual pathway, retinotopic organisation
- Visual thalamus and its proposed function
- Visual cortex and its receptive fields

Lecture 3 Overview of Autonomic Nervous System (ANS) functions

- Where does the ANS fit into the rest of nervous system?
- Structure of the ANS, comparison to somatic nervous system
- Sympathetic and Parasympathetic divisions: similarities and differences in anatomy, function, transmitters and receptors
- Clinically important agonists and antagonists (e.g., atropine and salbutamol)
- The adrenal gland: a special case
- Dual innervation and sympathetic *vs* parasympathetic dominance: relevance to “fight or flight” *vs* “rest and digest” and effect on major organ systems
- Hierarchical control of ANS
- Example of an autonomic circuit and reflexes: pupillary light reflex

VISION AND SENSORY SYSTEM OBJECTIVES

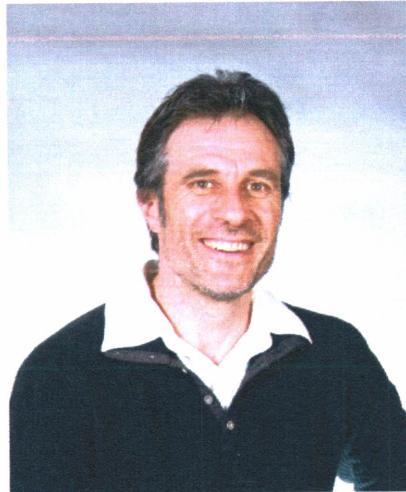
1. Describe the function of the fovea and relate resolving power to receptor density
2. Describe the electrical responses of retinal ganglion cells and their receptive field features
3. Describe the central visual pathway, understanding its retinotopic organisation
4. Discuss a proposed function of the visual thalamus
5. Contrast the receptive field properties of visual cortical cells with those of retinal ganglion cells and interpret the neural connections that could account for the differences

AUTONOMIC NERVOUS SYSTEM LEARNING OBJECTIVES

1. Describe the structure and functions of the ANS noting similarities and differences with the somatic nervous system

2. Describe structural and functional features of sympathetic and parasympathetic divisions of ANS
3. Describe the physiological significance of cholinergic and adrenergic receptors and their major subtypes (Explain how they relate to the clinical importance of atropine and salbutamol)
4. Outline the function of the adrenal gland
5. Explain the physiological significance of dual innervation, and relate this to sympathetic *vs* parasympathetic dominance on major organ systems during flight-or-fight *vs* resting states
6. Describe the hierarchical central control of the ANS
7. Explain the pupillary reflexes in terms of the autonomic innervation of the circular and radial muscles of the iris

REPORT WRITING AND ACADEMIC HONESTY – Dr Michael Morris



Dr Morris's research interests include understanding the molecular mechanisms controlling the pluripotency and directed differentiation of embryonic stem cells and early embryos. His lab uses ES cells as a model for human development to the early stages of the nervous system, and also looks at improving the development of cultured embryos for use in assisted reproduction.

Lecture Overview

1. Being able to write well, in scientific language, is a very important graduate attribute. Many of you will have had little if any training and guidance in this regard.

This lecture provides an overview of the scientific writing style, with particular respect to writing up a practical report, which in many ways is similar to a published manuscript found in a scientific journal.

The material presented here is intended to complement the following information:

- The tutorial on Key Practical Learning Concepts, which will provide worked examples and class exercises on the theory underpinning the scientific process and how to present and write about data.
- A detailed set of guidelines for writing up the assessable prac report for PHSI2005.
- The marking rubric that can be used to guide you in writing up the PHSI2005 prac report, and that will be used as a guide by the markers to assess your report.
- [The Write Site](#), which provides online support to help you develop your academic and professional writing skills.

2. All Students, and Academics, must adhere to strict standards of academic honesty. This includes, but is not limited to, plagiarism and collusion. The University has recently strengthened and tightened its regulations and policies regarding Academic Honesty.

This lecture will provide some guidelines into what is, and isn't, acceptable practice regarding plagiarism and collusion, with particular respect to an assessable prac report.

Note that the material covered here is certainly not exhaustive! The onus is on students to engage with and understand the University's policies. The Unit of Study Outline, accessible through Blackboard, provides links to policy documents. The Library also has an excellent video tutorial at <http://www.library.usyd.edu.au.skills/elearning/learn/plagiarism/index.php>

Learning Objectives

Report writing

- Recognise that scientific writing is a very important graduate attribute
- Understand what a professional scientific report is, and what it is intended to convey
- Gain insight into aspects of scientific writing style
- Recognise that the prac report is broken up into sections similar in terms of order and scope to a published scientific paper
- Understand the rationale behind each of the sections and what content should be included in each – and what content should be excluded
- Learn what to avoid (i.e., common mistakes often made by students, and often academics!) and what to pay close attention to (to produce a well-rounded, superior product)
- Recognise that the information in this lecture is complementary to other sources of information (e.g., see list above under Lecture Overview), which can be used collectively to help you write better

Academic honesty – plagiarism and collusion

- Recognise that academic honesty in all forms is a critical graduate attribute
- Recognise that collusion and plagiarism (and other forms of academic dishonesty and student misconduct) constitute cheating and is completely unacceptable practice at this University and in any professional setting
- Understand the definitions of collusion and plagiarism, including through the examples given
- Understand some of the penalties that can be imposed in cases of collusion and plagiarism
- Understand that the information presented here is a brief guide and not exhaustive and that the emphasis is on students to understand University policy
- Recognise where to seek further information, explanation, and help

CARDIOVASCULAR PHYSIOLOGY – Dr Sharon Herkes



Dr Sharon Herkes is a teaching-focused lecturer in Physiology with an interest in pedagogical research: the development of blended-learning courseware and strategies for improved student engagement. She has developed a generic Blackboard site – the PLAIGround (**P**hysiology **L**earning **A**ctivities and **I**nformation) – which encourages students to learn core physiology concepts through game playing. Past research interests include mucosal transport and motility of the small intestine. In addition, Sharon has worked for several multinational pharmaceutical companies managing early stage clinical research trials of drugs in development.

For this topic, see Silverthorn Chapters 14 and 15.

Lecture 1: Introduction and haemodynamics

- Overview of the cardiovascular system
- Flow, resistance and pressure gradients
- Arterial and venous capacitance
- Regulation of vascular resistance

Lecture 2: Mechanical events of the cardiac cycle

- The heart as a pump
- Unidirectional blood flow
- Phases of the cardiac cycle

Lecture 3: Electrical events of the cardiac cycle

- Pacemaker activity in the heart
- Spread of excitation through the heart
- Excitation contraction coupling
- Properties of cardiac muscle
- Absolute refractory period of cardiac muscle cells
- The electrocardiogram (ECG)

Lecture 4: Venous return and cardiac output

- Venous return and its regulation
- Frank-Starling law of the heart
- Cardiac output and its regulation
- Redistribution of cardiac output during exercise

Lecture 5: The microcirculation and specialized circulations

- Overview of microcirculation
- Movement of substances across the capillary wall
- The lymphatic system and oedema
- Effect of posture changes and exercise on capillary exchange
- The coronary circulation
- The cerebral circulation

Lecture 6: Regulation of arterial blood pressure

- Why is the regulation of blood pressure important?
- Short-term regulation of blood pressure - baroreceptor reflex
- Longer term regulation of blood pressure

CARDIOVASCULAR SYSTEM OBJECTIVES

General Objectives

1. To understand the mechanisms by which blood is pumped throughout the body.
2. To understand how blood flow to all regions of the body is regulated.

Specific Objectives

Lecture 1: Introduction and haemodynamics

At the end of this lecture you should understand:

1. The general circuitry of the cardiovascular system
2. The relationships between flow, resistance and pressure as related to the cardiovascular system
3. The regulation of flow in the blood vessels

At the end of the lecture you should be able to:

1. Define resistance, by reference to Ohm's law
2. Derive the relationship between mean arterial pressure, cardiac output and total peripheral resistance
3. State Poiseuille's law, and explain its significance in relation to blood flow through resistance vessels
4. Explain why the pressure gradient across capillaries is less than that across arterioles, despite the fact that the former have a smaller calibre
5. Define vascular capacitance
6. Explain how the relative capacitances of the arterial and venous systems determine how a change in blood volume is distributed between the arterial and venous compartments
7. Recall typical ranges for normal human systolic and diastolic pressures
8. Compare the anatomical distribution and functions of sympathetic vasoconstrictor and dilator vasomotor nerves
9. Illustrate, by means of a graph, autoregulation of blood flow to a vascular bed.
10. Explain the physiological importance of metabolic autoregulation

Lecture 2: Mechanical events of the cardiac cycle

At the end of this lecture you should understand:

1. The function of the heart valves and their role in the unidirectional flow of blood through the heart
2. The phases of the cardiac cycle

3. The changes in pressure and volume which occur in the atria, ventricles and aorta at different times in the cardiac cycle

At the end of the lecture you should be able to:

1. Draw a scaled and labelled diagram illustrating the typical changes in pressure in the left atrium, left ventricle and aorta during the cardiac cycle in the human heart, and correlate these with left ventricular volume, ECG, heart sounds and opening and closing of the cardiac valves
2. Define the following terms: systole, diastole, stroke volume, ejection fraction, preload, afterload, inotropic effect, chronotropic effect, bradycardia, tachycardia

Lecture 3: Electrical events of the cardiac cycle

At the end of this lecture you should understand:

1. How the pacemaker and contractile cells of the heart contribute to heart function
2. The mechanism for neural control of heart rate
3. The basic properties of cardiac muscle
4. The cardiac conduction system
5. The normal waveforms of the ECG and what they represent

At the end of the lecture you should be able to:

1. Explain how the structural properties of cardiac muscle permit the rapid spread of action potentials throughout the heart
2. Explain the changes in transmembrane potential in (i) a typical myocardial cell (ii) a sino-atrial nodal cell before, during and after an action potential, in terms of the opening and closing of membrane channels and consequent movement of ions
3. Draw a simple diagram illustrating the main features of the cardiac conduction system
4. Describe the spread of depolarisation from the sino-atrial node through the atrial myocardium, atrio-ventricular node, specialised conducting pathways and ventricular myocardium, with reference to the time taken for the depolarisation to reach the different parts of the heart
5. Explain why conduction through the A-V node is relatively slow, and the physiological significance of this fact
6. Explain, in terms of membrane properties, why the absolute refractory period of cardiac cells is so long, and the physiological advantage of this fact

Lecture 4: Venous return and cardiac output

At the end of this lecture you should understand:

1. The factors which regulate venous return
2. The action of the skeletal muscle pump
3. The factors which regulate cardiac output
4. Mechanisms by which cardiac output can be redistributed
5. The concepts of cardiac preload and afterload

At the end of the lecture you should be able to:

1. Explain the relationship between end-diastolic ventricular volume and cardiac output (the Frank-Starling law)
2. Show how the Frank-Starling relationship can be altered by sympathetic or parasympathetic stimulation
3. Describe the autonomic innervation of the heart

4. Describe the effects of excitation of autonomic nerves on heart rate and myocardial contractility
5. Describe the effects of dynamic exercise on heart rate, myocardial contractility, total peripheral resistance, and venomotor tone
6. Briefly explain the underlying mechanisms causing each of these effects
7. Explain how all of these effects combine to increase cardiac output

Lecture 5: The microcirculation and specialized circulations

At the end of this lecture you should understand:

1. The forces involved in the movement of substances cross the capillary membrane
2. The function of the lymphatic system as it relates to the circulation
3. Mechanisms involved in redistribution of blood flow
4. Features of specialized circulations

At the end of the lecture you should be able to:

1. List the various components of the microcirculation, and briefly describe the structure and function of each
2. Compare the microcirculation in the skin with that in skeletal muscle, and explain the physiological significance of any differences between the two vascular beds
3. Contrast the properties of capillaries in the liver with those in the brain
4. Explain the difference between diffusion and filtration in the exchange of water and solutes between capillary plasma and interstitial fluid
5. Explain how in a given region the total capillary flow, and the total surface area available for exchange, can be independently controlled
6. Recall the equation which relates the rate of diffusion of any molecule or ion across the capillary endothelium to the variables which determine it
7. Recall the equation which relates bulk fluid flow across the endothelium to the forces which determine it
8. By means of this equation, and by recalling typical average values for the relevant hydrostatic and osmotic forces, explain why filtration would normally occur at the arterial end of a capillary, while re-absorption normally occurs at the venous end
9. Predict the effect of a change in pre-capillary resistance, post-capillary resistance, and arterial blood pressure on the bulk fluid flow across the capillary endothelium

Lecture 6: Regulation of blood pressure.

At the end of this lecture you should understand:

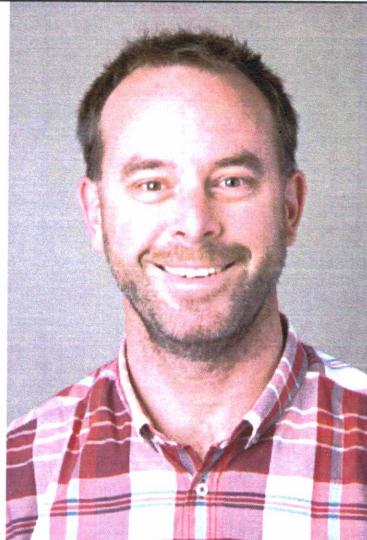
1. How mean arterial pressure is controlled
2. The baroreceptor reflex
3. Sympathetic influences on the heart and circulation
4. Hormonal influences on the heart and circulation

At the end of the lecture you should be able to:

1. Briefly describe the afferent and efferent pathways subserving the baroreceptor reflex
2. Draw a block diagram summarising the effects on autonomic nerve activity and the subsequent effects on cardiovascular variables reflexly evoked by a change in baroreceptor firing rate

3. Provide examples which demonstrate the importance of the baroreceptor reflex as a buffering system
4. Describe the sequence of steps by which a reduction in mean arterial blood pressure leads to an increased production of angiotensin II
5. Describe the role of the renin-angiotensin-aldosterone system in blood pressure regulation.

EXERCISE PHYSIOLOGY – Dr Andrew Hoy



Dr Hoy is a Senior Research Fellow and Head of the Lipid Metabolism Laboratory. His research interests are in understanding how the inability to safely sort excess calories leads to diseases such as insulin resistance and type 2 diabetes. Likewise, the lab is focused on elucidating the metabolic interaction between obesity with breast and prostate cancer.

This series of three lectures integrates the preceding content in PHSI2005 and describes how the physiology of each of the systems – nervous, muscle and cardiovascular – work together to support exercise performance. Exercise is an example of an external stimulus which requires a coordinated response by several internal systems to maintain homeostasis. The key physiological core concepts this series of lectures will present examples of homeostasis, cell-cell communication, interdependence between systems, gradients and mass balance, and causality. This content is a platform for further exploration of metabolic physiology in Senior Physiology Units of Study.

Lecture 1 will focus on skeletal and cardiac muscle metabolism and the different metabolic substrates for ATP generation, which are essential to support muscle activity. Different substrates are involved depending on the intensity, duration and type of exercise and this will be explored in this lecture.

In Lecture 2 the steps involved in the supply of oxygen to support aerobic exercise will be examined, as will the roles that the nervous and cardiovascular systems play as complementary units during this form of exercise.

In Lecture 3, adaptations to exercise training in the cardiovascular system and skeletal muscle metabolism pathways will be discussed.

EXERCISE PHYSIOLOGY OBJECTIVES

General Objectives

1. To understand the metabolism of various substrates including glucose, fatty acids, oxygen that support exercise performance.
2. To understand the roles that the nervous and cardiovascular systems play in aerobic exercise.
3. To learn and/or reinforce the following core Concepts in Physiology that underpin the above objectives:
 - a. Homeostasis
 - b. Cell-cell communications such as between myocytes and endothelial cells for local vasodilation
 - c. Interdependence between cells, organs and organ systems
 - d. Flow down gradients such as oxygen diffusion at the lung and glucose and fatty acid transport into the myocyte

- e. Energy including the generation and expenditure of ATP and the acquisition, transformation and transportation of substrates to sites of demand
- f. Mass balance which is the result of input and output of a system/pool
- g. Causality where changes in one system induce a response in another system; e.g., the increase in oxygen by working muscle causes an increase ventilation and cardiac output

Specific Objectives

Lecture 1: Energetic Pathways in Muscle During Exercise

At the end of this lecture you should understand:

- 1. The metabolic differences between skeletal and cardiac muscle as well as the different fibre types of skeletal muscle. This is an extension of the content delivered by Dr Sawatari in his lectures on Muscle Physiology.
- 2. The processes that consume ATP during muscle activity and the main pathways for regenerating ATP inside skeletal muscle fibres. This is an extension of the content delivered by Dr Sawatari in his lectures on Muscle Physiology.
- 3. The different energy pathways utilized in anaerobic *vs* aerobic exercise.
- 4. How the different energy pathways utilized in aerobic exercise are influenced by work rate and duration.
- 5. What happens to the main metabolic substrate pools in skeletal muscle, cardiac muscle and liver during and following exercise.

Lecture 2: Aerobic Exercise

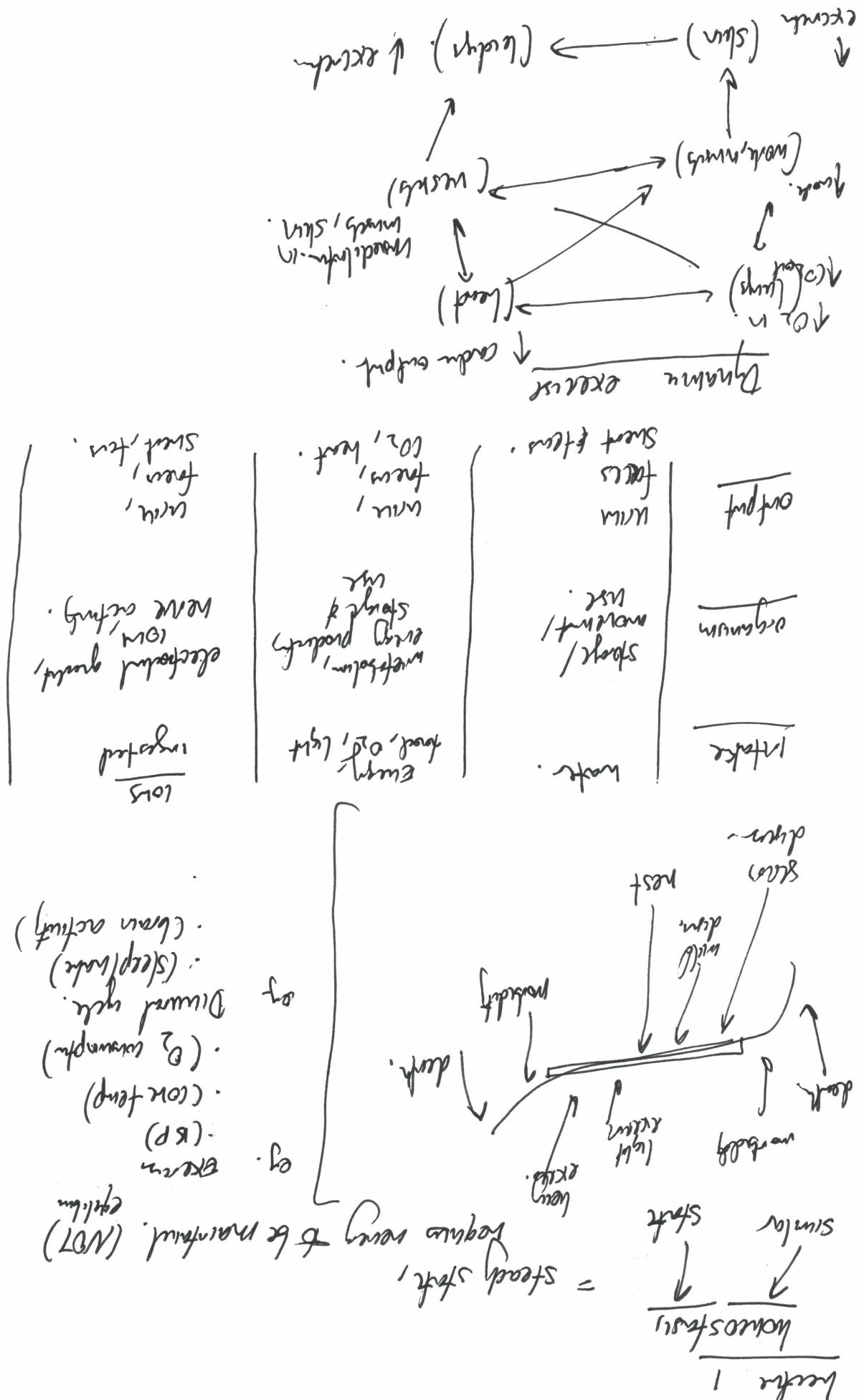
At the end of this lecture you should understand:

- 1. Exercise is a disruption to oxygen balance that requires a coordinated response to maintain homeostasis.
- 2. The delivery of oxygen to working muscle involves 5 steps: ventilation, diffusion, transport of O₂ to the tissues, increased blood flow, uptake of O₂ by muscle cells.
- 3. The role that the nervous system plays in delivering oxygen to working muscle.
- 4. The role that the nervous system plays in mobilising stored substrates during aerobic exercise.
- 5. What fatigue is and potential sources of fatigue including changes in pH, substrate availability and calcium availability.
- 6.

Lecture 3: Cardiovascular and Metabolic Adaptations to Exercise Training and review

At the end of this lecture you should understand:

- 1. The adaptations in the cardiovascular system and metabolic pathways in skeletal muscle to aerobic exercise training.
- 2. The adaptations in the anatomy of skeletal muscle to aerobic exercise training.



metabolism passes lipid bilayer by:

poor leishmania which includes Leishmania and -

more in the beginning - displayed in upper

Red blood cells

- *laryngeal phonetic* : block;
- *voiced* (*sust./gliss.*) - *sharpen* (*1013*) - *soften* (*profusion*)

reform - expect to pay high
taxes -
inflation -
(incomes) stand

morfologi

semantika

makna kata

makna kalimat

B E

A C D F

Lec 2 Lipid bilayer 

left group will follow - independent / final

$\text{Na}^+ - \text{K}^+ - \text{ATPase}$ - active transport

glucose - phosphate, water, sodium K⁺



(LUTI) - example of facilitated diffusion

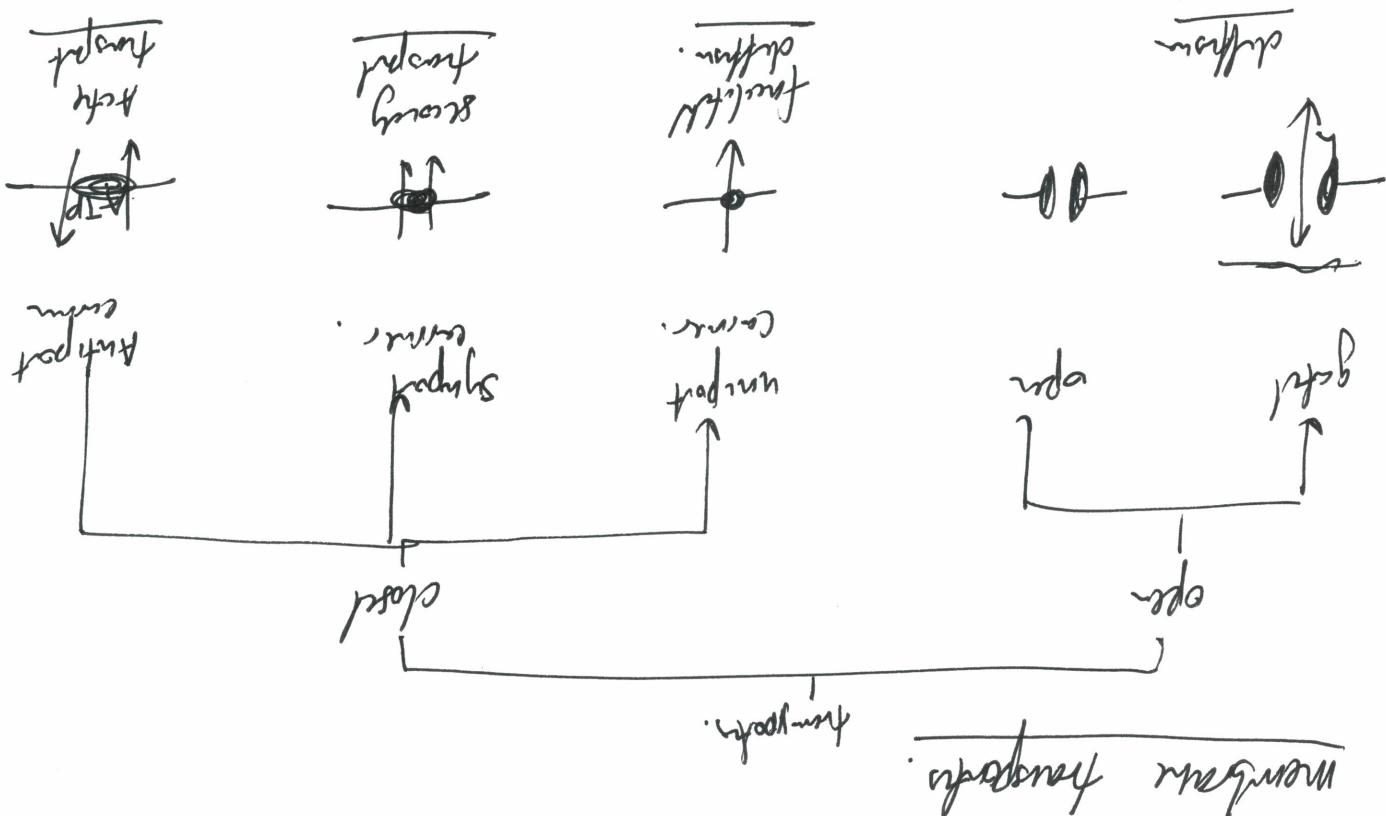
PLS

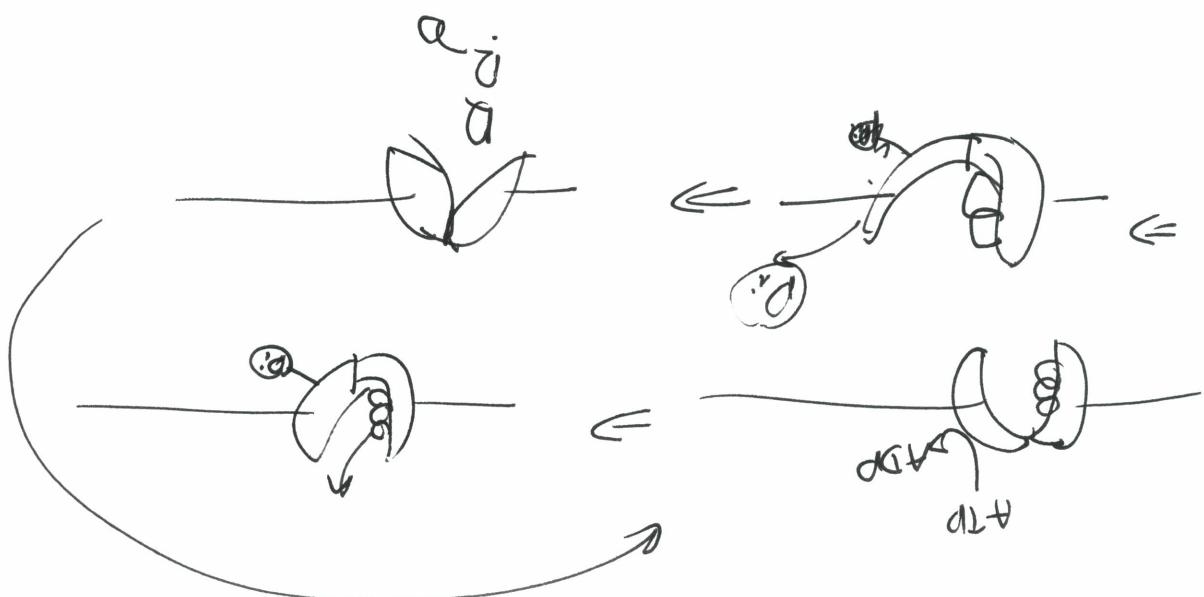
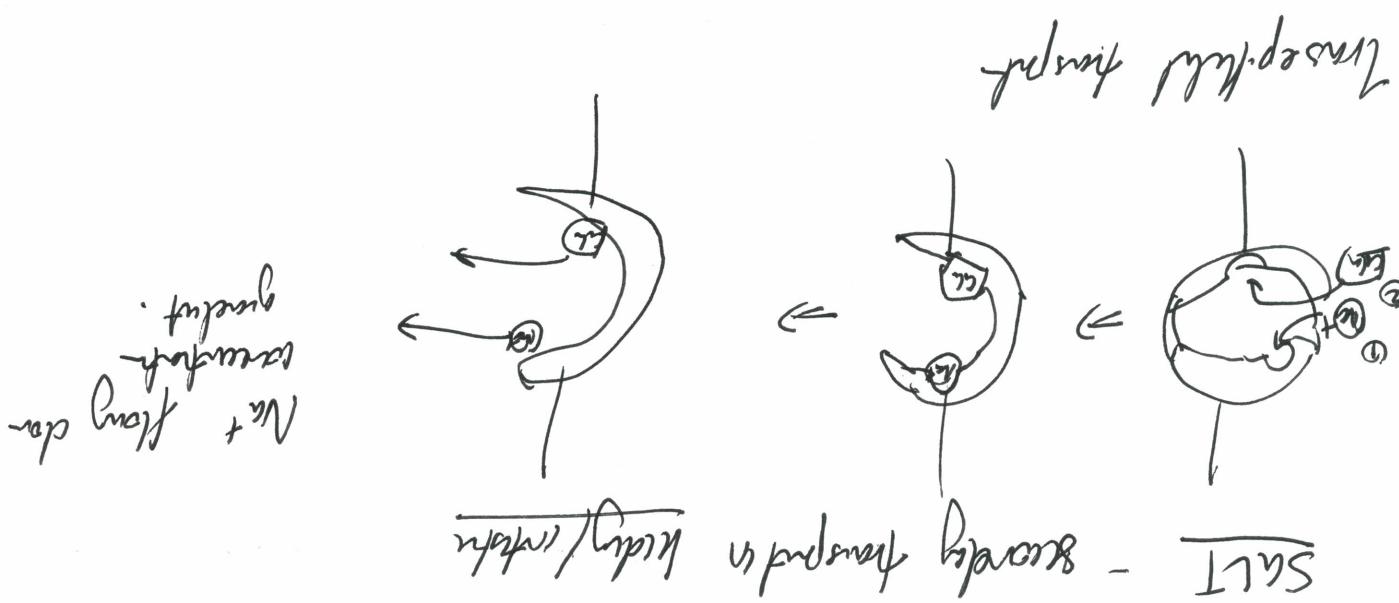
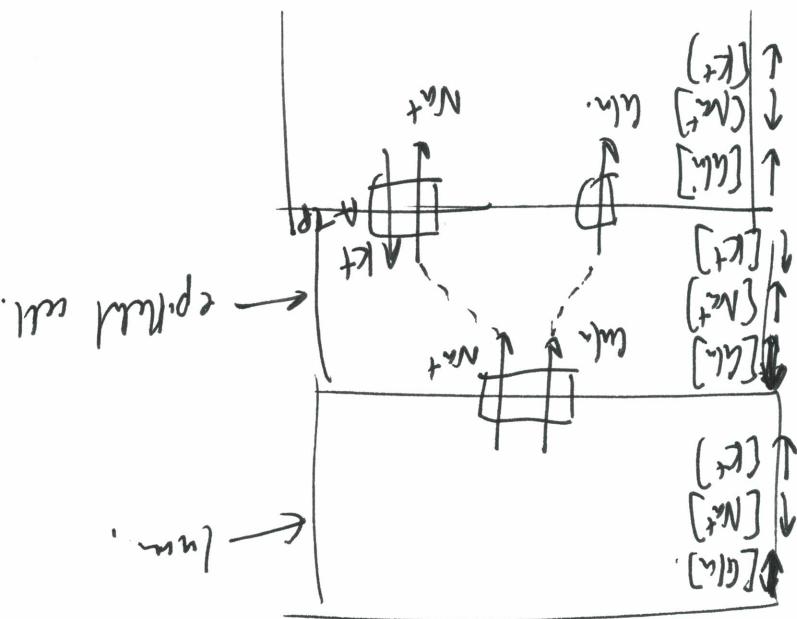
hypotonic [in] < [out] → water enters cell

isotonic [in] = [out]

hypertonic [in] > [out] → water leaves cell

example of facilitated diffusion - water channels

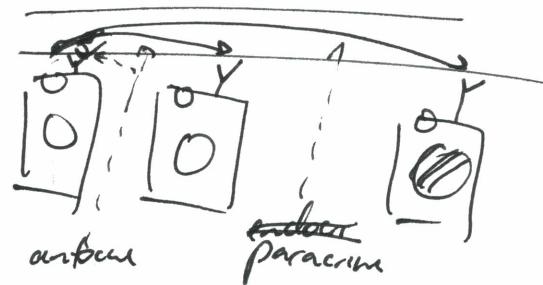
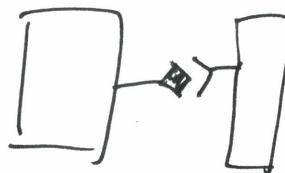
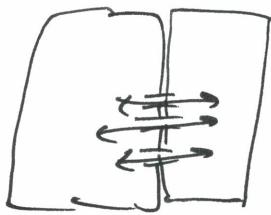




hauter 3

Types of sixty b/w cell.

- (I) gap juncs. (II) contact-dependent. (III) auto cone/paracrine



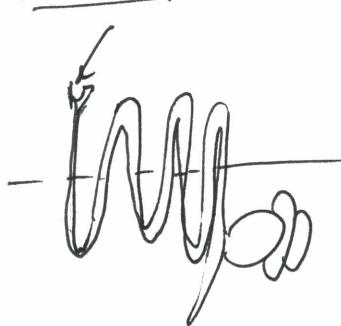
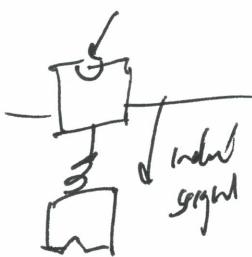
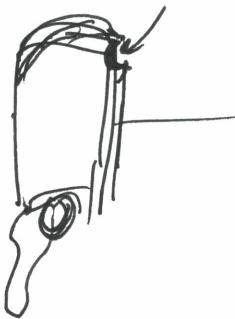
e.g. insulin & glucagon

Types of membrane receptors

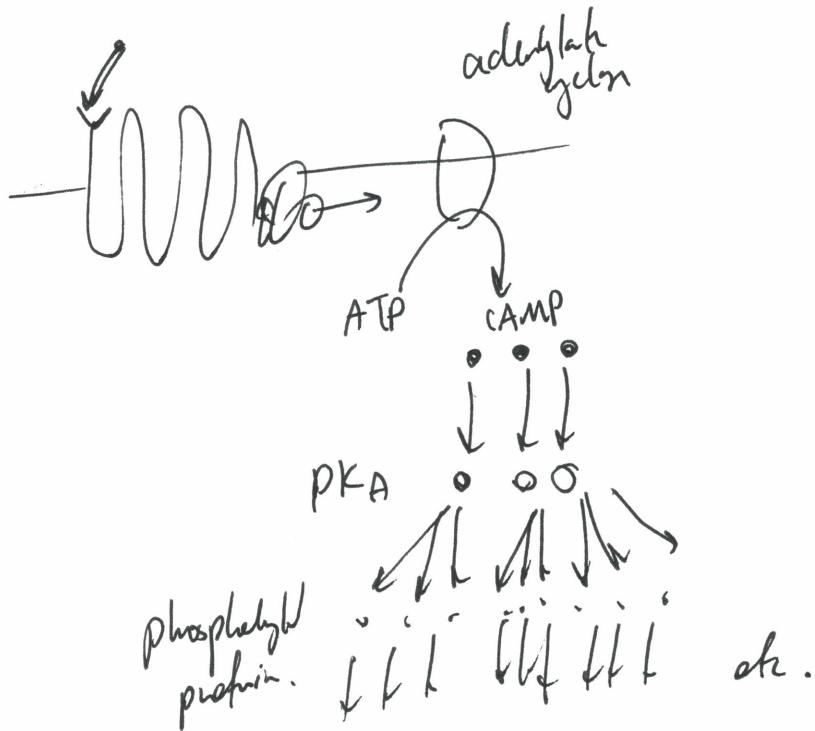
- (I) receptor channel (II) receptor-enzyme.

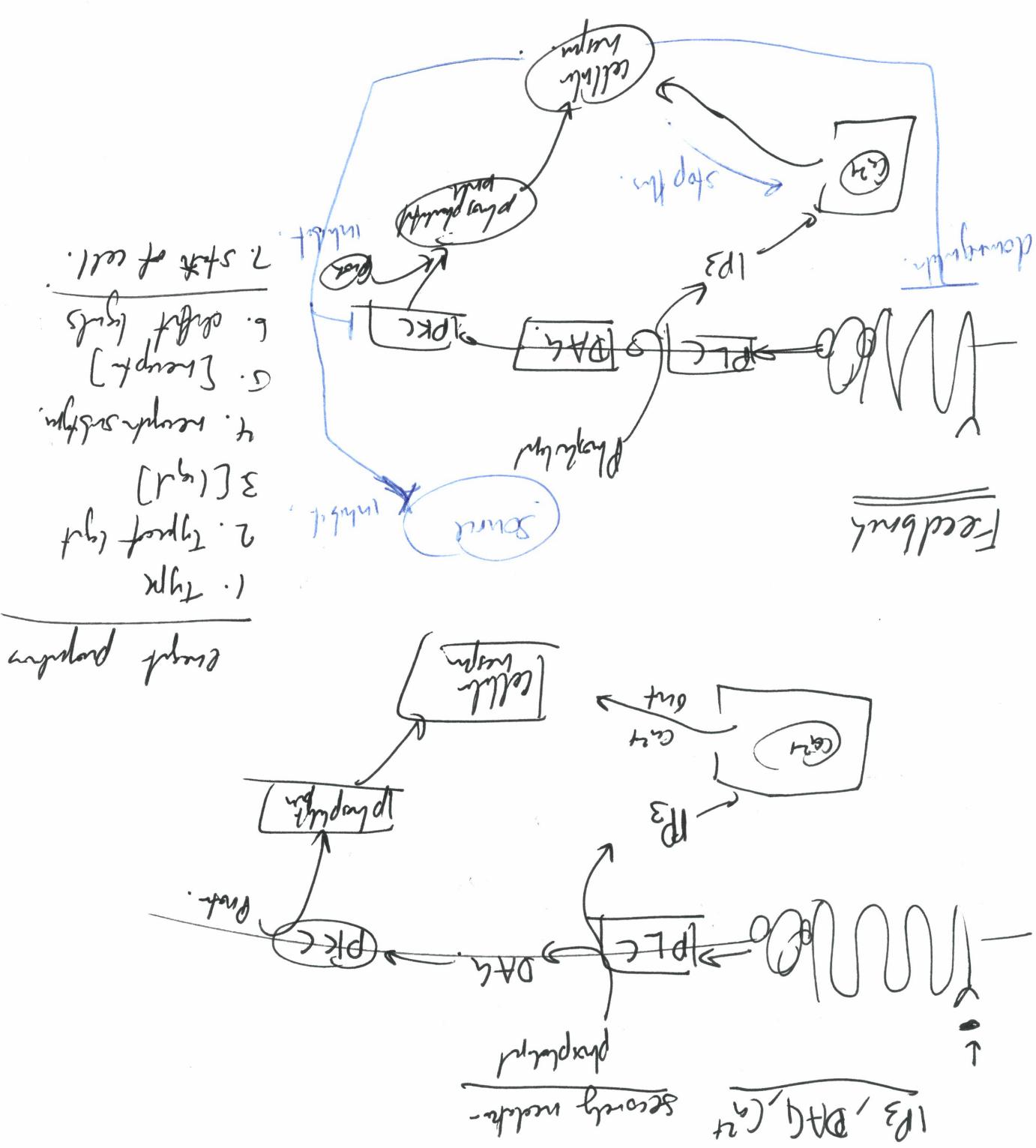
- (III) G-protein coupled receptor

- (IV) integrin receptor.



cAMP GPCR

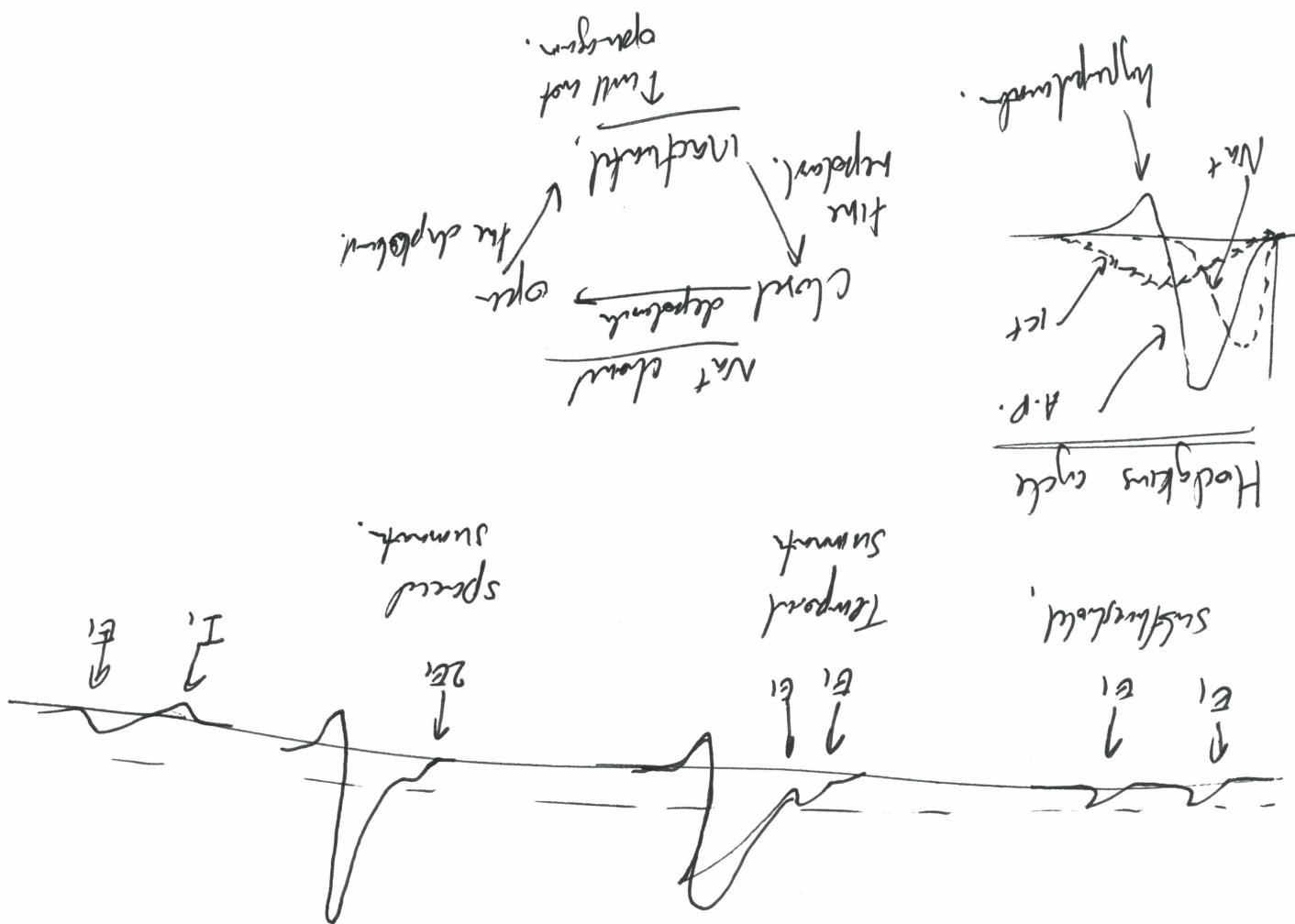




1.6

1.7
C₂H₅OH + HCl → C₂H₅Cl + H₂O

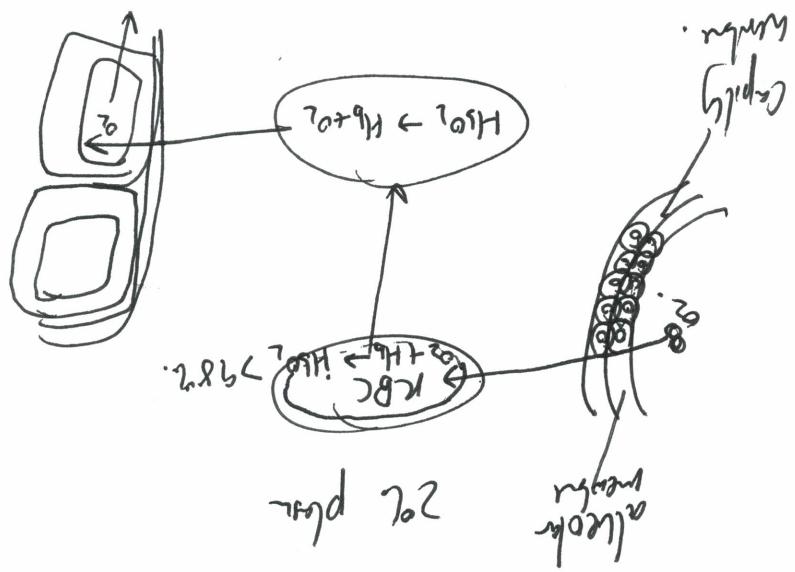
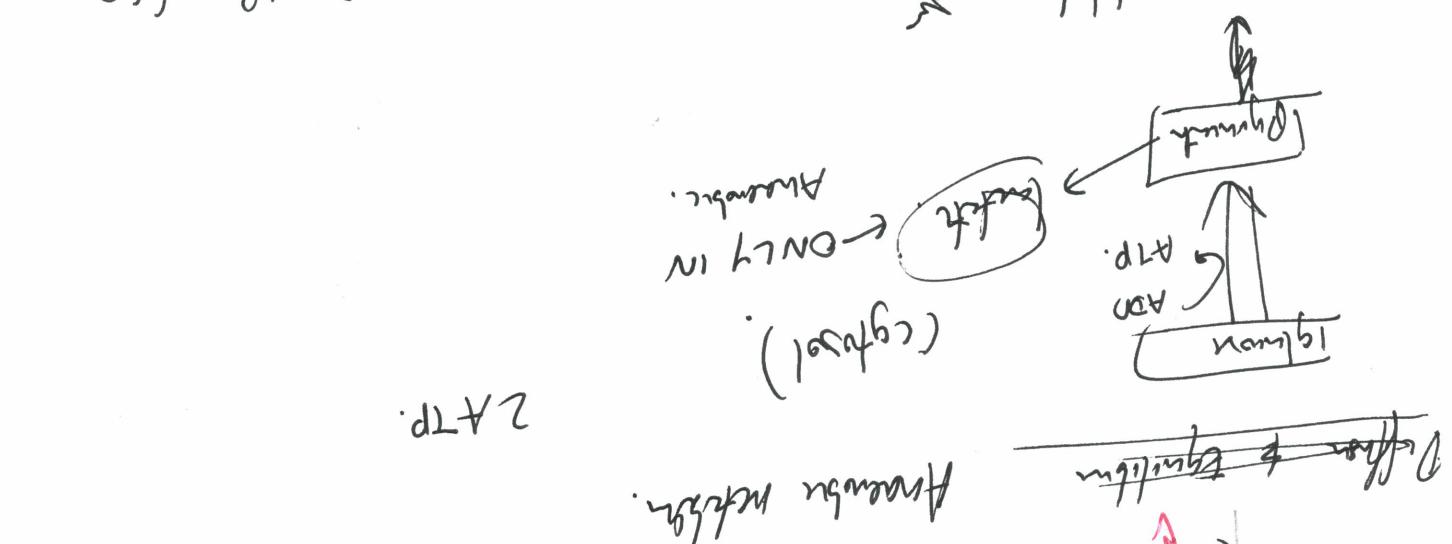
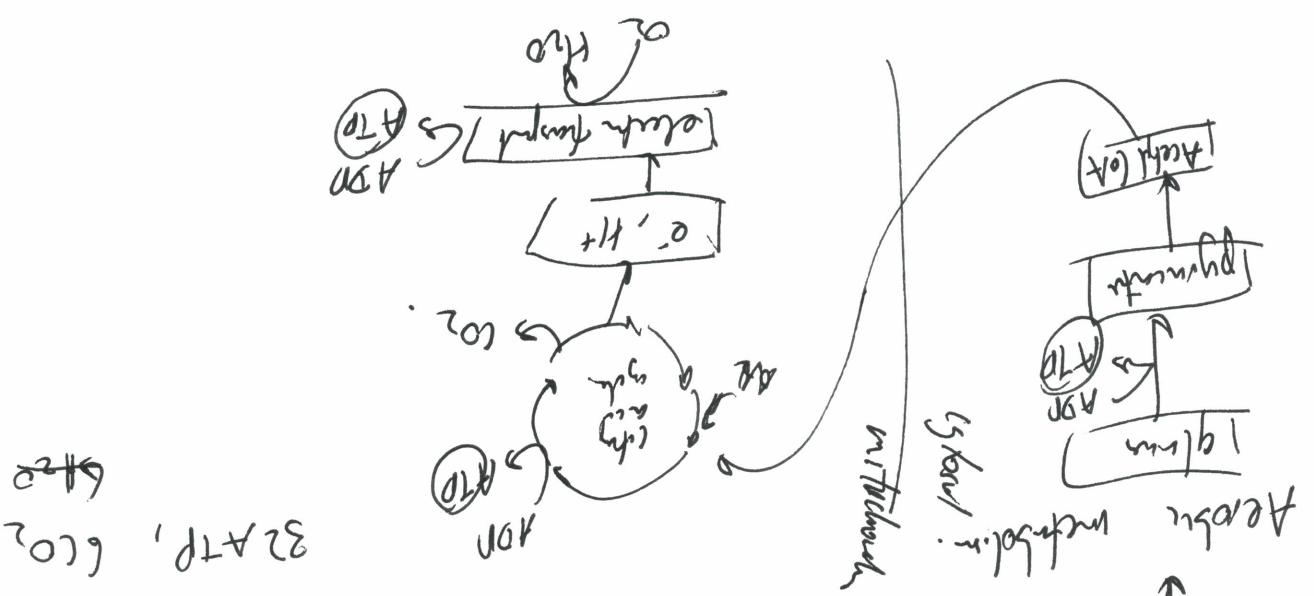
1.8
CH₃COOH + NaOH → CH₃COONa + H₂O



$$V_m = \frac{RT}{F} \ln \left[P_{\text{ex}} [K^+] + P_{\text{in}} [Na^+] + P_{\text{ex}} [Cl^-] \right]$$

addition of

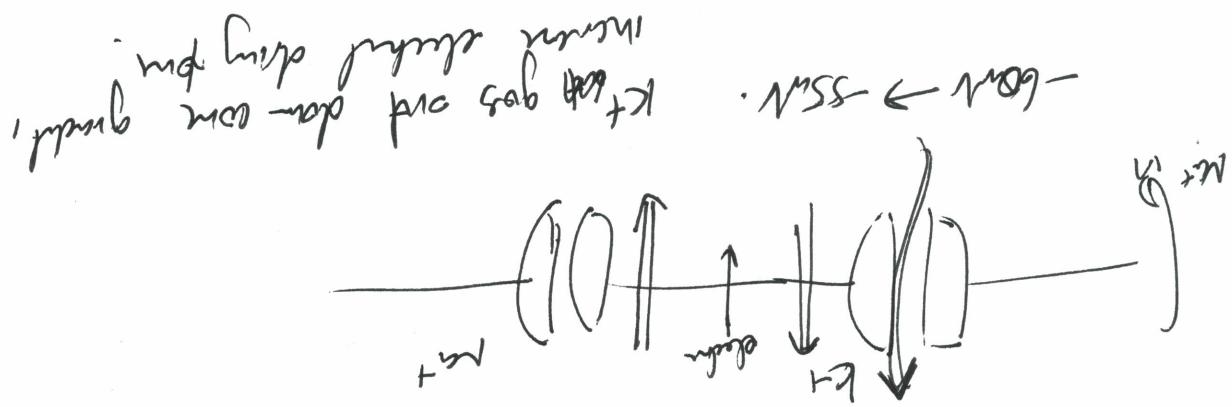
substance - AP



Pulmonary & systemic circuit

- 2% plasma
- 98% haemoglobin
- oxygen transport

(1)



* Number of Zener series parallel to E_a is N_{st} .

$$E_a = -60\text{mV}$$

$$E_a = +35\text{mV}$$

$$N_{st} = \frac{(-) \left[\begin{array}{c} (+) \\ (-) \end{array} \right]}{\left[\begin{array}{c} (+) \\ (-) \end{array} \right] \times \frac{+2}{-2}} = \frac{-2}{2} = 1$$

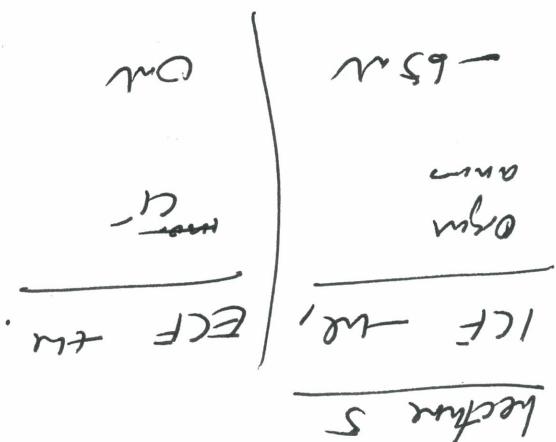
When $f_{dn} = f_{eu}$, we have equilibrium point (Vbias point).

$\frac{\text{Forward steady state}}{\text{Reverse steady state}} = \frac{10^{13}}{10^{13}}$

$\frac{\text{diffusion down channel}}{\text{diffusion up channel}} \approx k_t$

$(+) (10^{13})$

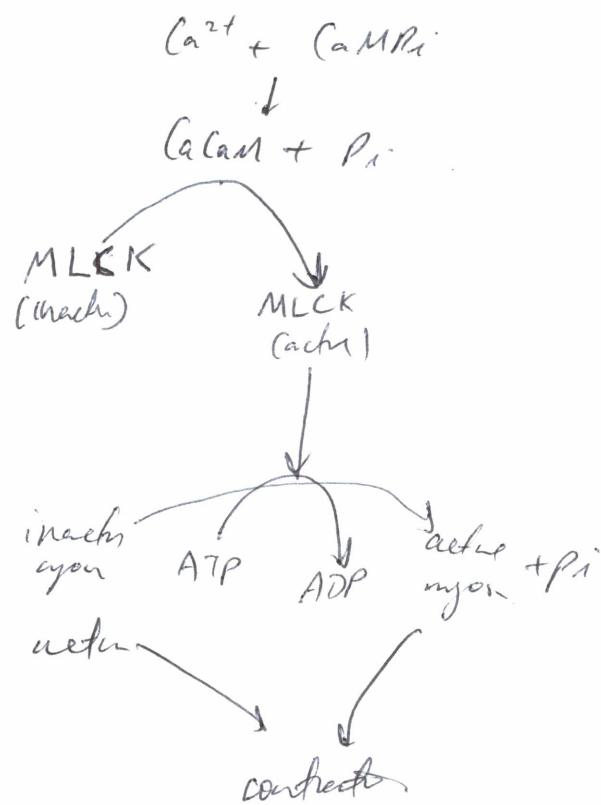
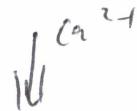
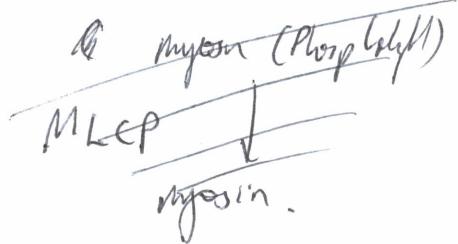
$(-) (10^{13})$



Saltatory propagation

smooth muscle tone loss

1.



Integrated Physiology – an overview

Systems in PHSI2005/2905

- Nervous (CNS and PNS)
- Musculoskeletal (but largely skeletal muscle)
- Cardiovascular

Combined Systems

- Cellular Neurophysiology – Nervous & Skeletal Muscle
- CV & Nervous system & Endocrine system
- Exercise Physiology – CV, Skeletal Muscle & Nervous

Systems in PHSI2006/2906

- Respiratory
- Endocrine
- Gastrointestinal
- Renal
- Reproductive

Concepts in Physiology

PHSI2005

Michael Morris

5 lectures

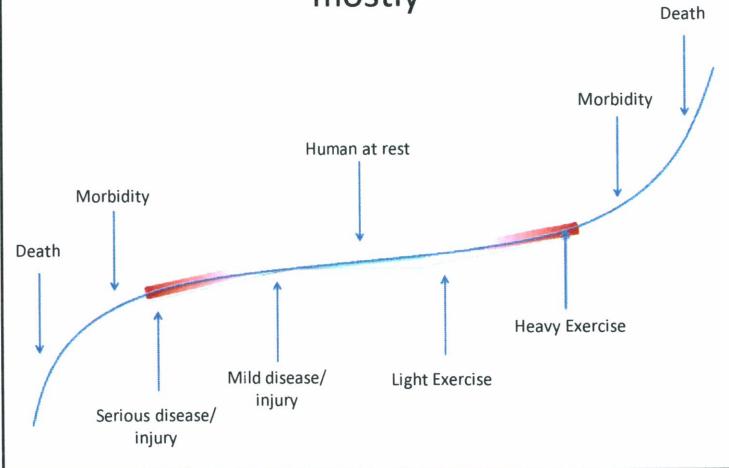
- **Physiology & Homeostasis**
- Membranes, gradients & transporters
- Cell communication and signalling
- Oxygen transport and use
- Pathophysiology – what goes wrong

Definition of homeostasis

- **Homeo** – like or similar
- **Stasis** – condition of state
- I.e., similar conditions
- Effectively a **steady state** or **set of steady states**
- Requires **energy** to be maintained
–not like a simple equilibrium.

L allansone give, in a little bit
of ways to maintain that zone.

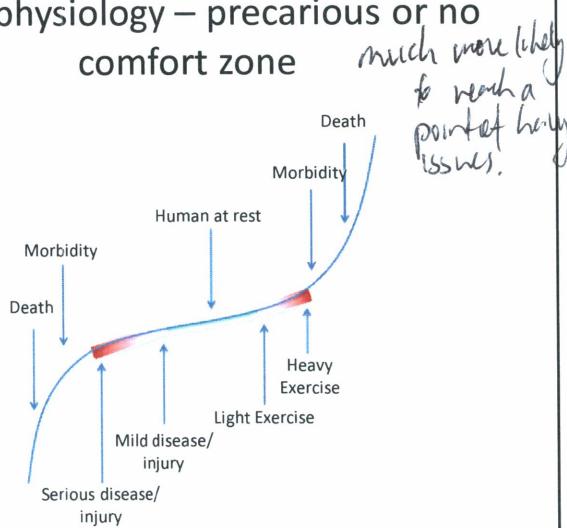
Homeostasis: Life in the comfort zone - mostly



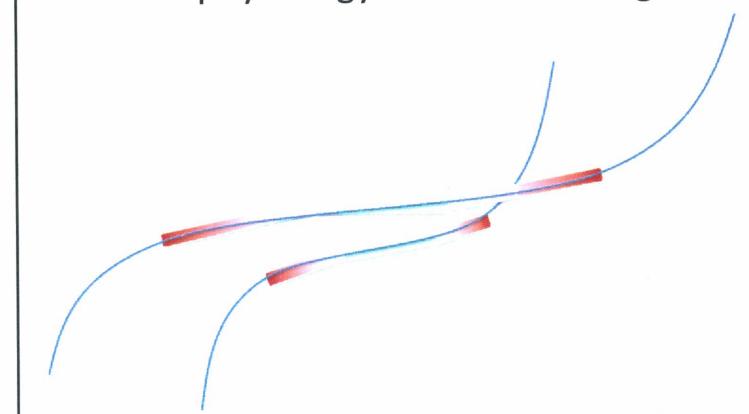
Video: Athletes pushed to the red zone

Video: Parkinson's Disease

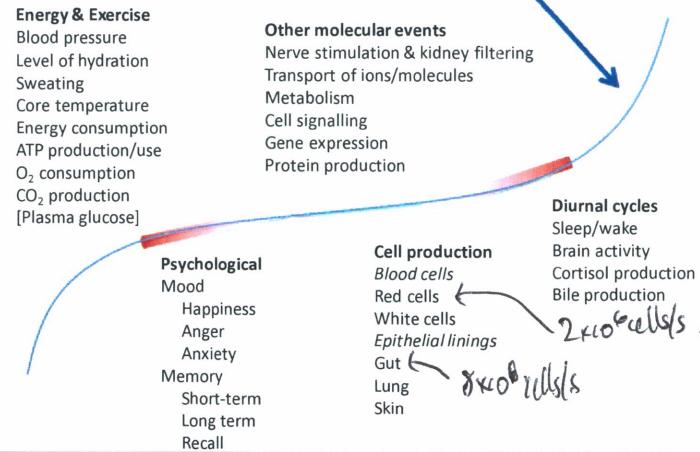
Pathophysiology – precarious or no comfort zone



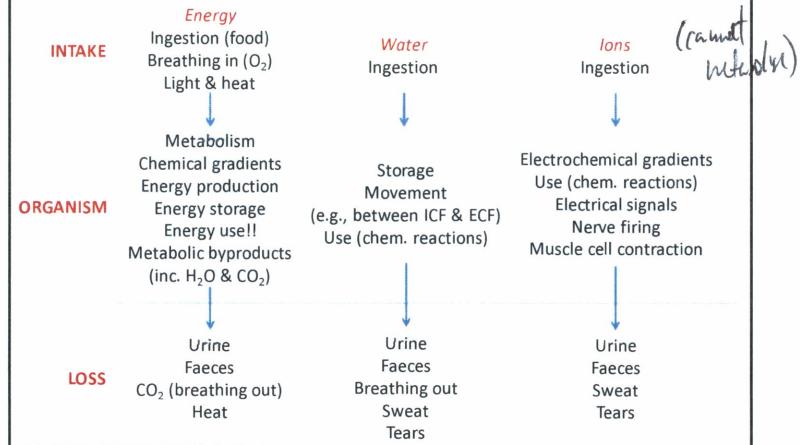
Normal Physiology – a comfortable life
vs
Pathophysiology – life on the edge



What might this line represent?



Homeostasis: Steady states require intakes and losses



Other types of loss

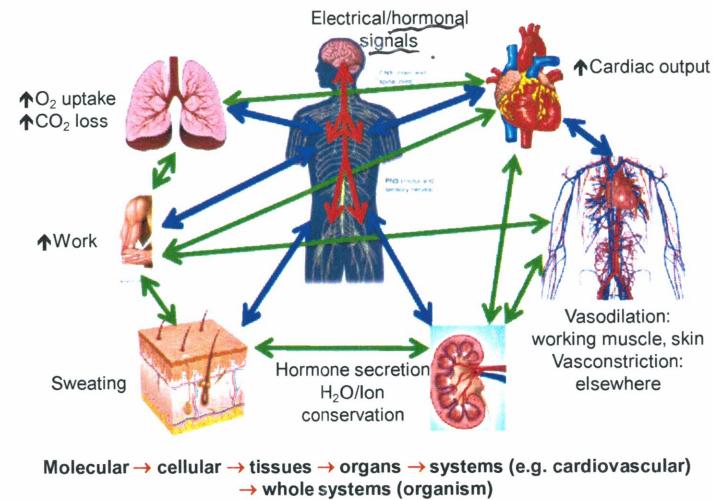
- **Diarrhoea**
- **Vomiting**
- **Feeding your gut flora**
- **Diuresis** (e.g., diuretics, cholera)
-
- **Blood/tissue loss**
 - Menstruation, ejaculation
 - Donation
 - Injury, amputation
-
- **Disease**
 - Muscle wasting (DMD, ALS)
 - Cachexia (cancer)
 - Nerve loss (Parkinson's, Alzheimer's, stroke)
 - Cardiomyopathy

After heart attack,
capacity to regenerate
heart tissue is 0-
in other experiments
this is not the case.

↑ (learn regeneration of other species) → apply to humans
→ (learn how humans operate) ↗ looking at how other species operate

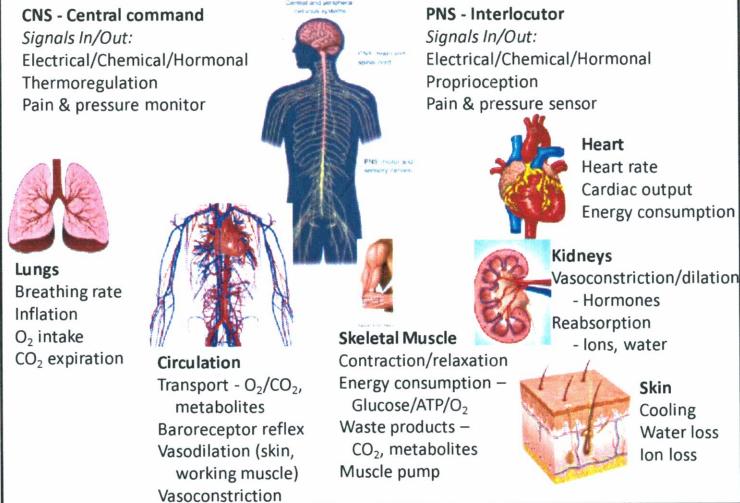
Physiology & Homeostasis: The interconnectedness of all things

An example – Dynamic Exercise



any organ in body respond to each other organ

An example – Dynamic Exercise



5 lectures

Concepts in Physiology

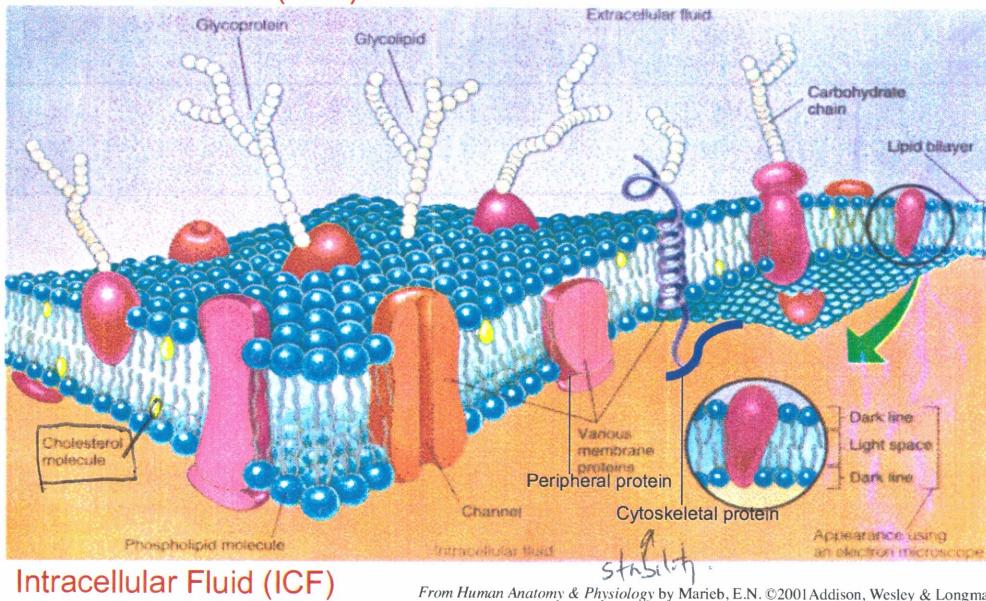
PHSI2005

Michael Morris

- Physiology & Homeostasis
- Membranes, gradients & transporters
- Cell communication and signalling
- Oxygen transport and use
- Pathophysiology – what goes wrong

The Plasma Membrane

Extracellular Fluid (ECF)



Intracellular Fluid (ICF)

From Human Anatomy & Physiology by Marieb, E.N. ©2001 Addison, Wesley & Longman

selective barrier
separating ECF & ICF (cytoplasm)

Plasma membrane: Lipid bilayer

- Phospholipids & cholesterol
- Hydrophilic head groups (face water)
- Long hydrophobic tails (oily interaction)
- Self assembling, **very little stability**
- Permeable to small hydrophobic molecules
 - Naturally occurring, clinical drugs, toxins
- Barrier to:
 - Large hydrophobic molecules
 - Large molecules (e.g., proteins)
 - Atomic ions (e.g., Na^+ , K^+ , Cl^-)
 - Charged molecules (e.g., amino acids, sulphates)
 - Polar molecules (e.g., glucose, water)

cannot get through only barrier

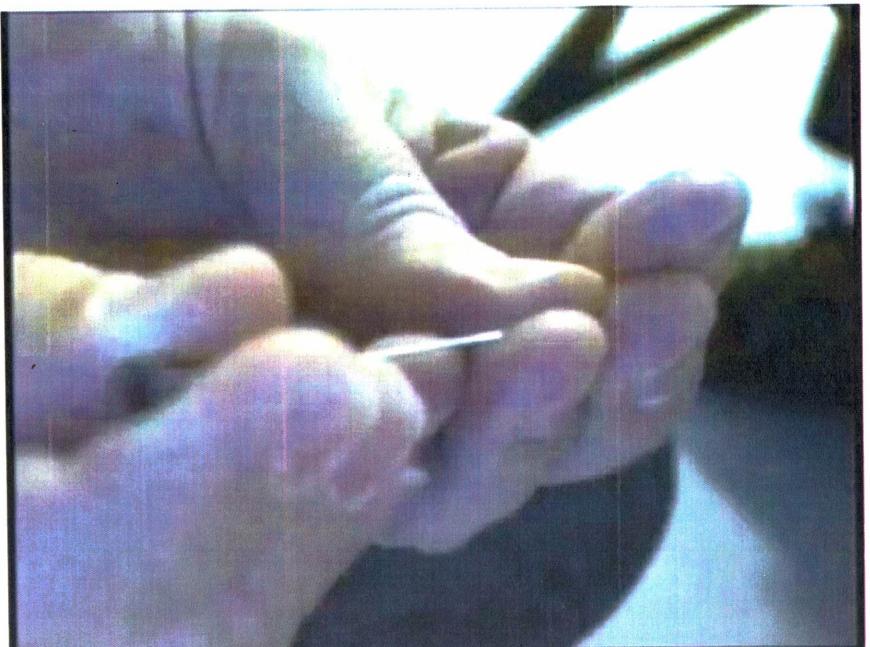
go through very slowly

Plasma membrane - Fluid mosaic

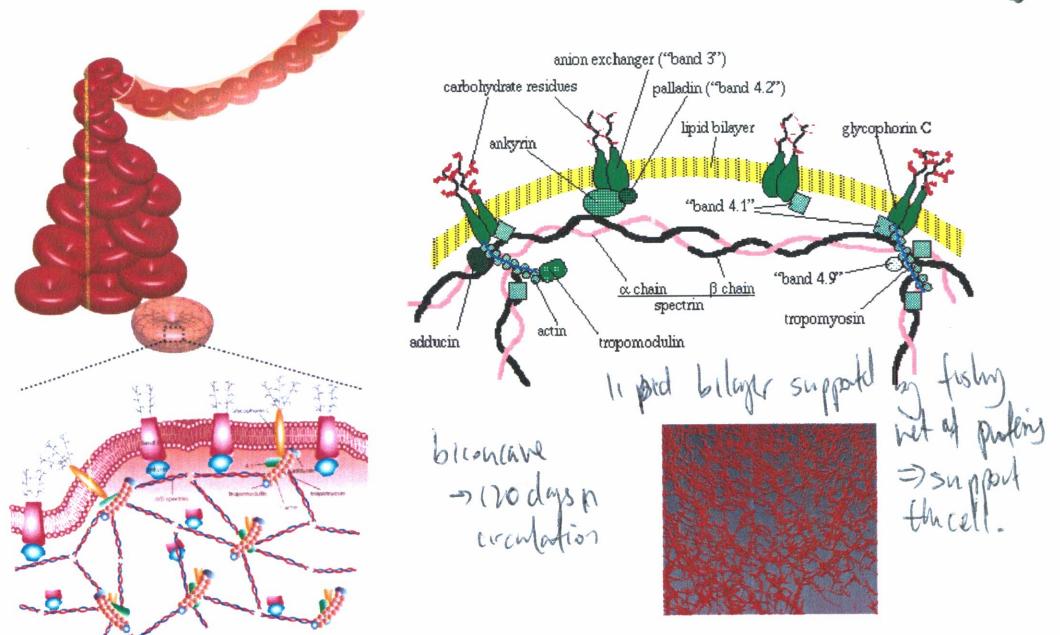
Lipid bilayer is modified by addition of:

- Membrane-attached proteins *hooked onto lipid bilayer*
 - e.g., cytoskeletal proteins, which provide stability
- Specialised lipids & glycolipids, which alter permeability of small hydrophobic molecules
- Transmembrane proteins
 - Transporters, which greatly and selectively modify barrier permeability *↔ movement of matter*
 - Receptors, which receive and interpret signals (communication between cells near and far) *↔ movement of information.*

Video: Red Cells in Circulation



Cytoskeletons: Essential Support for Lipid Bilayers



→ Gmade in bone marrow
is destroyed in spleen.
connects b/w spleen & bone marrow.



What are the physiological advantages? *⇒ hydrodynamic shapes.*

slow movement to allow

greater diffusion b/w cell & tissue.

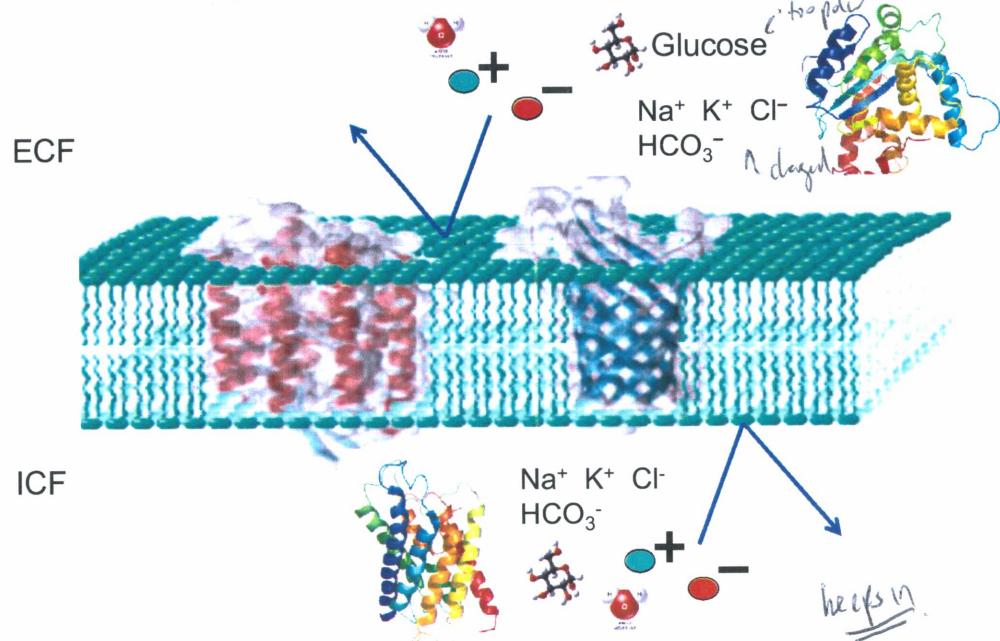
→ (is) work heart less do.

Every cell needs a cytoskeleton!

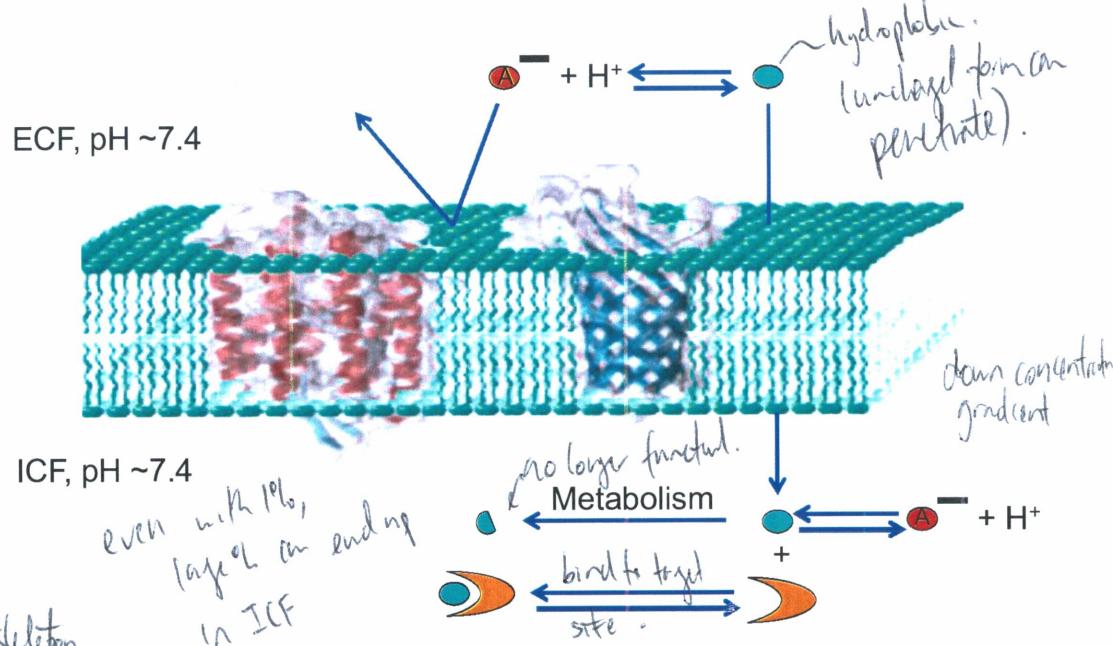
- Even cells at rest are unstable without a cytoskeleton
- Specialised shapes
- High shear stress
 - Red and white cells in circulation
- Motility and shape change
 - Red cells squeezing through capillaries
 - White cells squeezing between cells
 - Movement to sites of infection
 - Swallowing invaders (phagocytosis)
- Contraction and relaxation
 - Skeletal, cardiac and smooth muscle
- Stretching and relaxation
 - Vasculature, heart, lungs, bladder, GIT, skin

↑ support shape of cell.

Polar & Large Molecules Don't Penetrate Lipid Bilayer



Small Hydrophobic Molecules Penetrate Lipid Bilayer



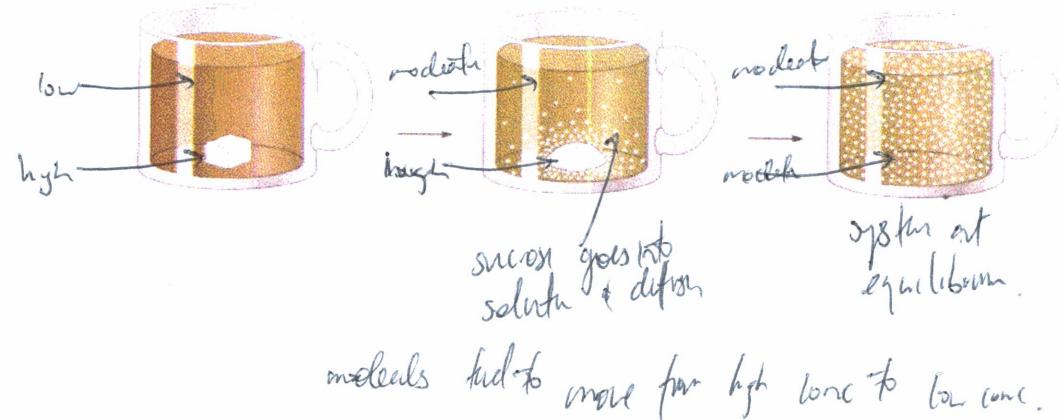
So, how do these other molecules cross biological membranes?

Keys are:

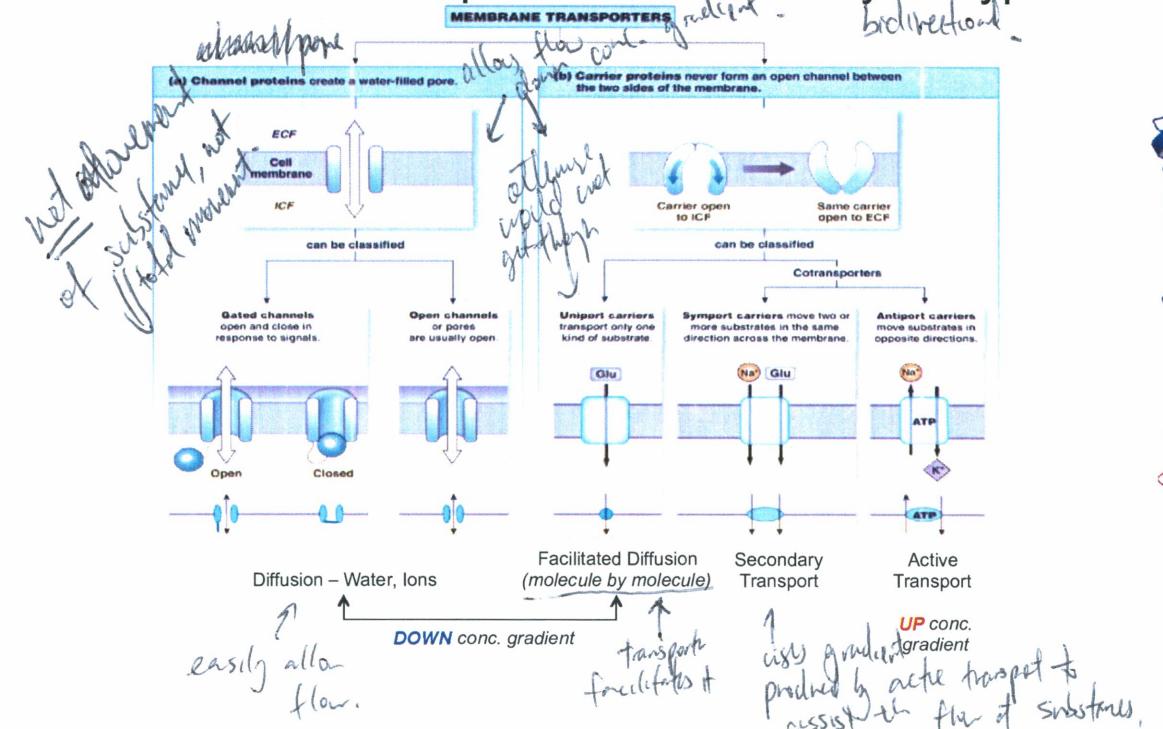
- Osmosis (water)
- Diffusion (solutes and water)
- Concentration (chemical) gradients
- Electrochemical gradients (for ions)
- Selective transporters *(bypass the lipids.)*
- Energy (usually ATP; movement against gradients)

↑ can pump for low [J] to high [J].

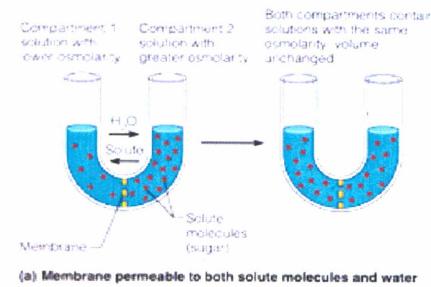
Concentration gradients and diffusion



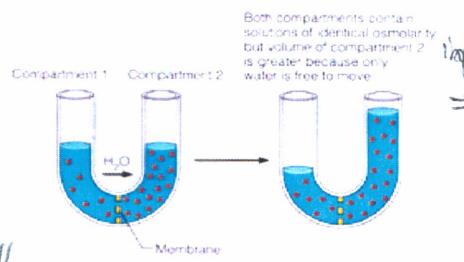
Membrane Transporters: A Summary of Types



Selective permeability and osmosis

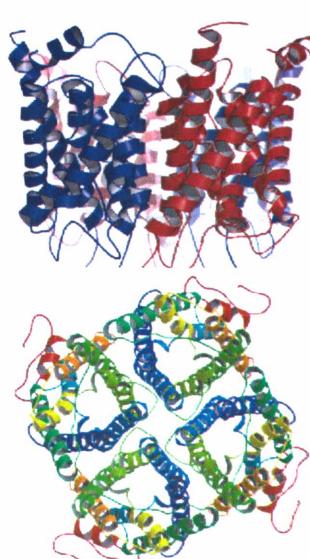


Osmolarity = the concentration of all dissolved particles in solution
 $K^+ + Cl^-$
 $1M KCl = 2 \text{ osmoly/L}$
 $= 20 \text{ osm/L}$.

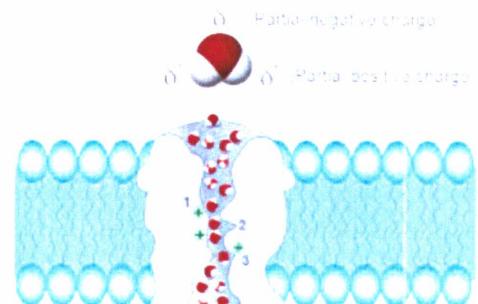


From Human Anatomy & Physiology by Marieb, E.N. ©2001 Addison, Wesley & Longman

Aquaporin: The Water Channel/Pore

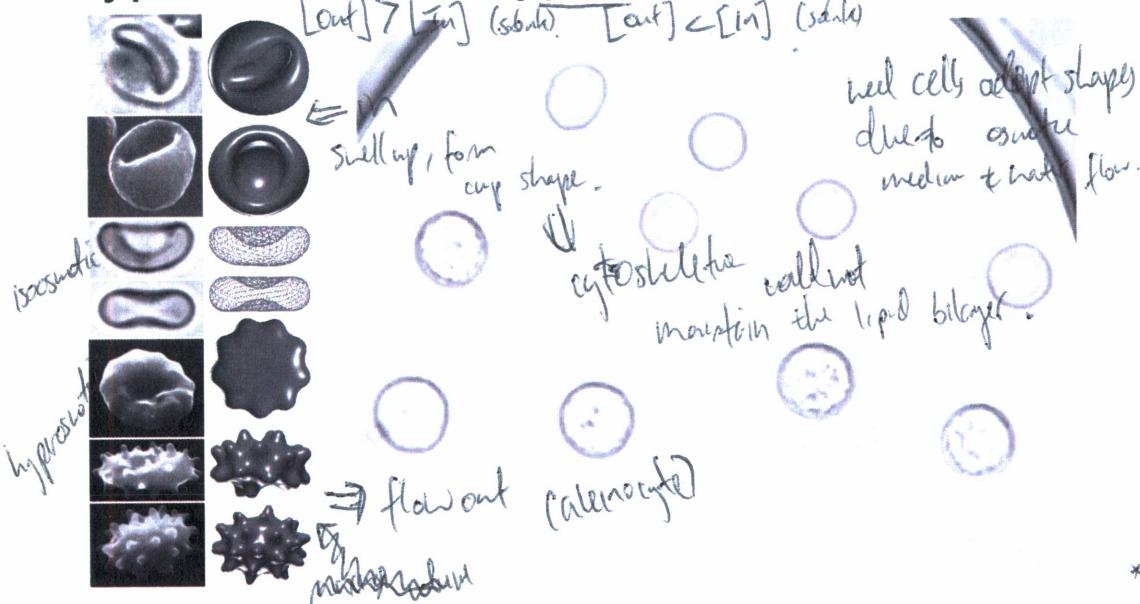


Top view

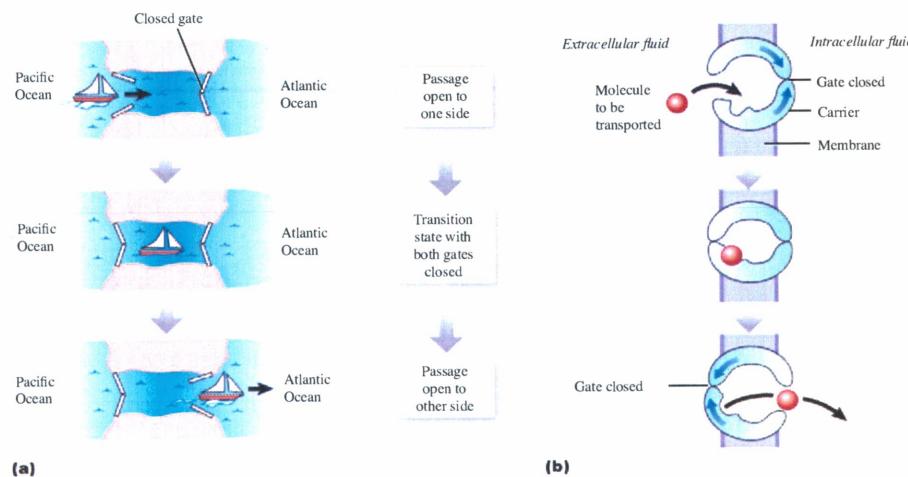


water & small
but polar so can't get though membrane easily.

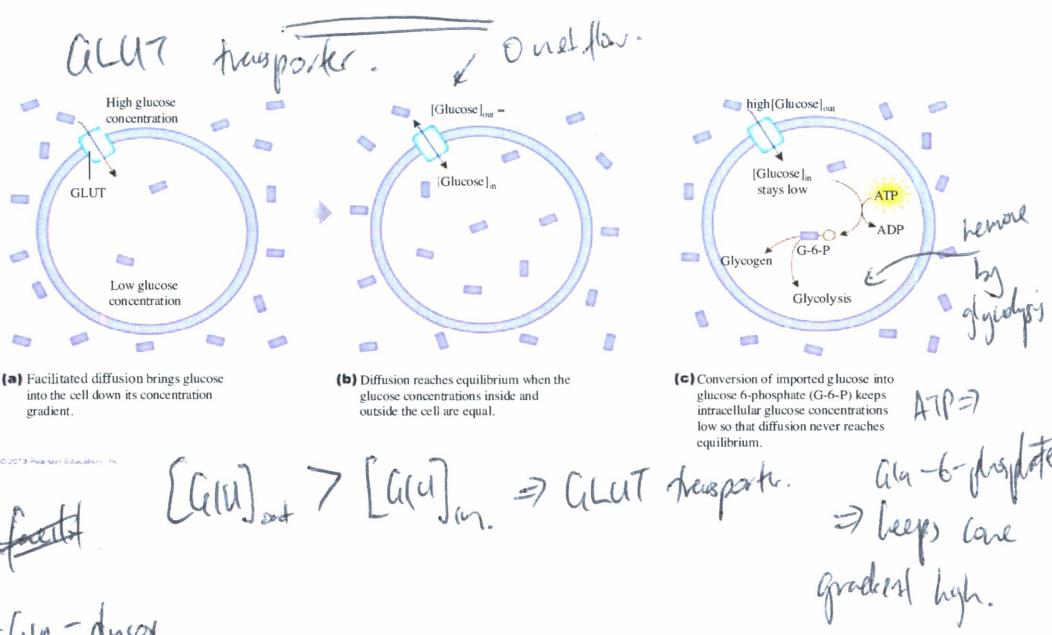
Video: Red Cells in Isosmotic, hyperosmotic & hypodsmotic solutions



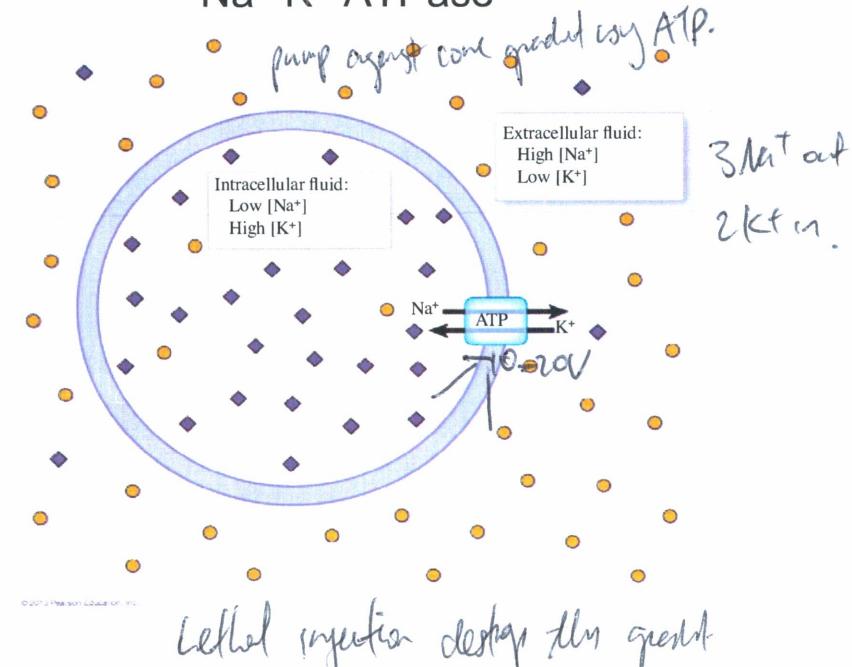
Facilitated diffusion is molecule by molecule



Facilitated Diffusion: Glucose into Cells

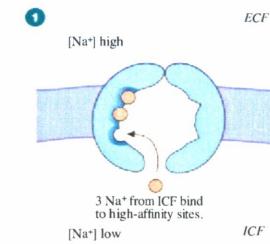
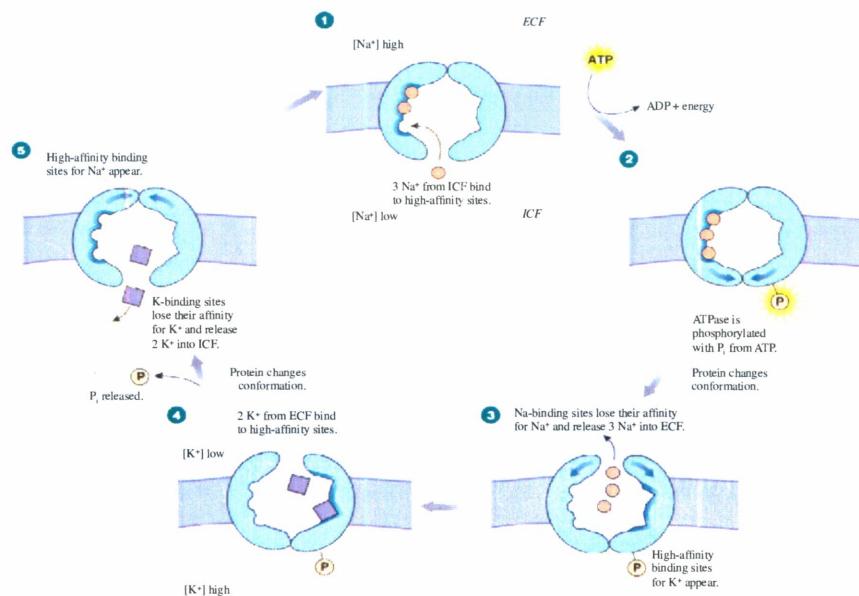


Active Transport: The sodium-potassium pump, Na^+-K^+ -ATPase

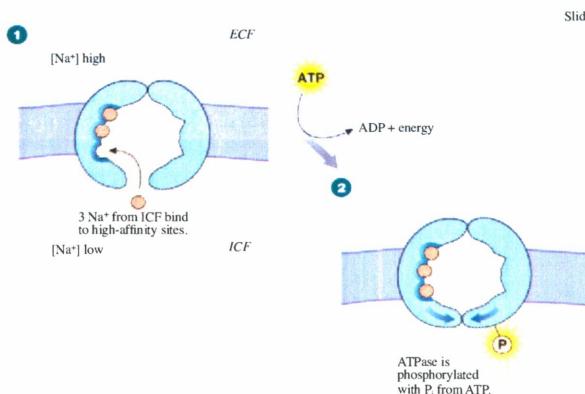


Mechanism of the Na^+-K^+ -ATPase

Slide 1



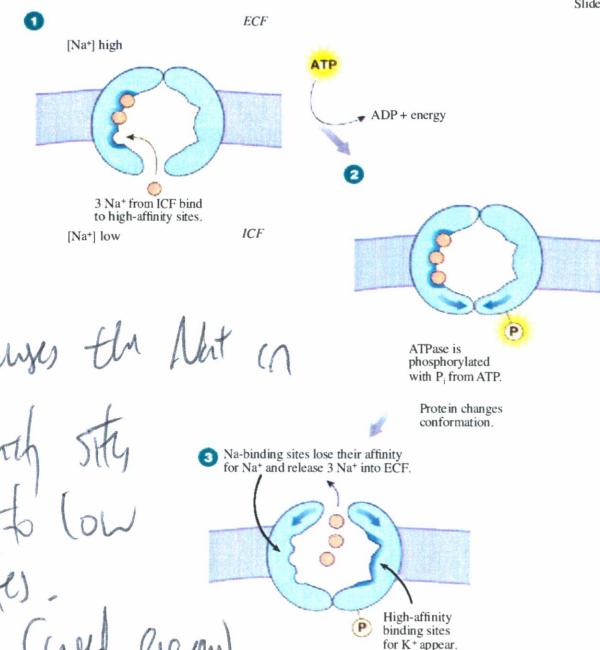
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ATP
diss carrier

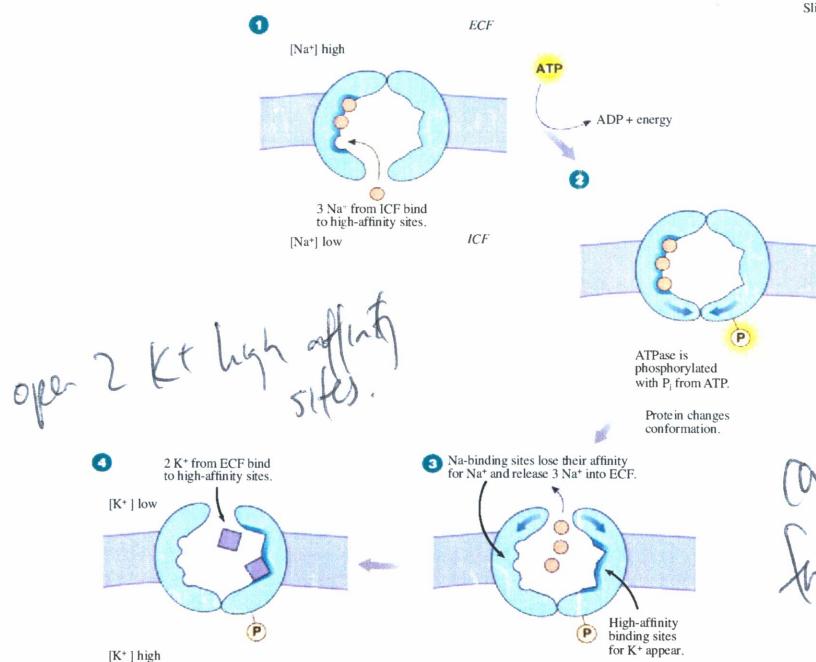
Slide 2

causes the Net in
high affinity sites
to move to low
affinity sites.
(used energy)

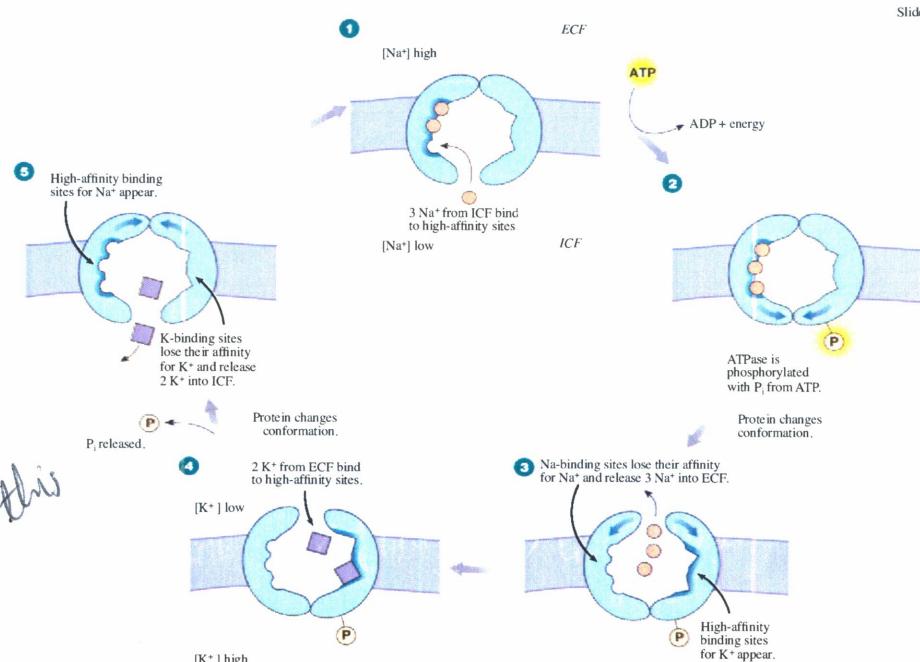


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Slide 3

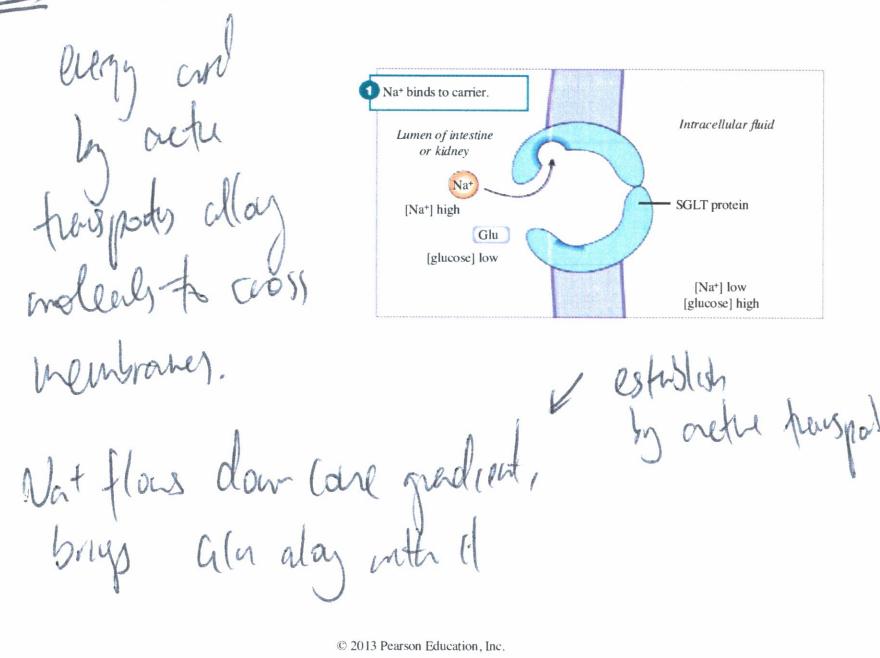
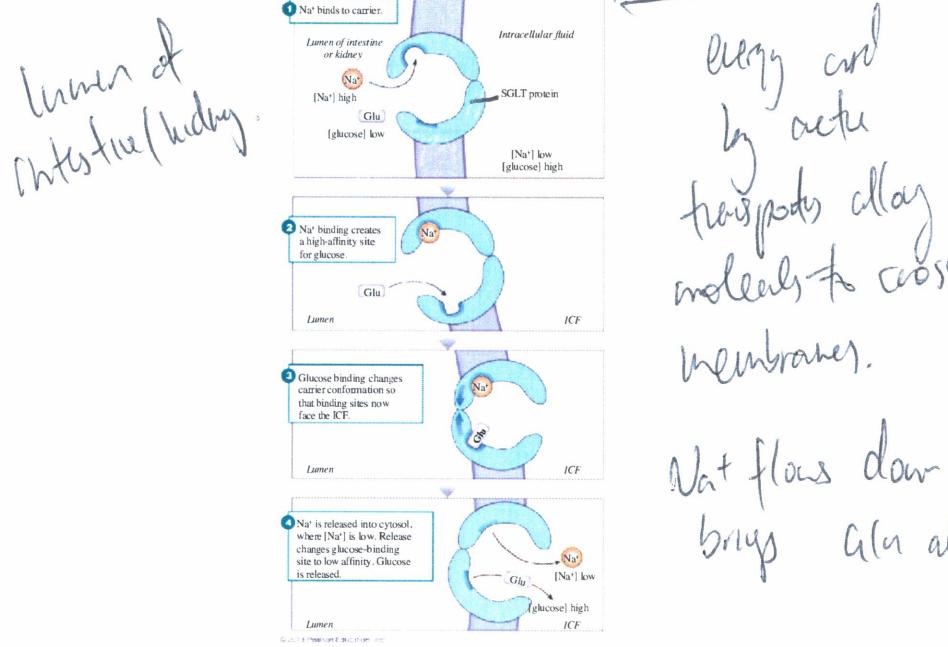


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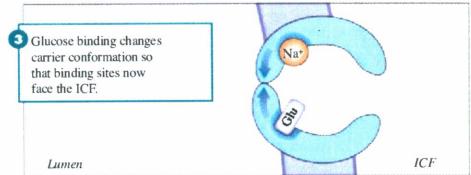
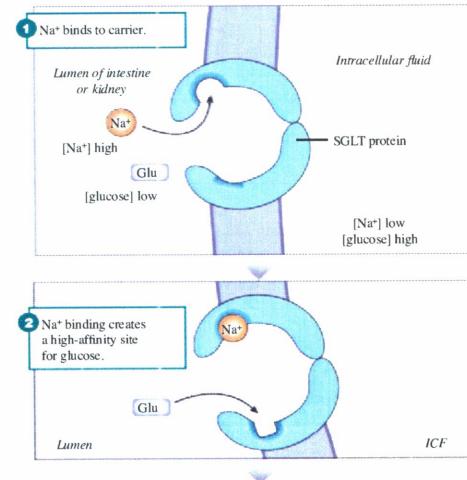
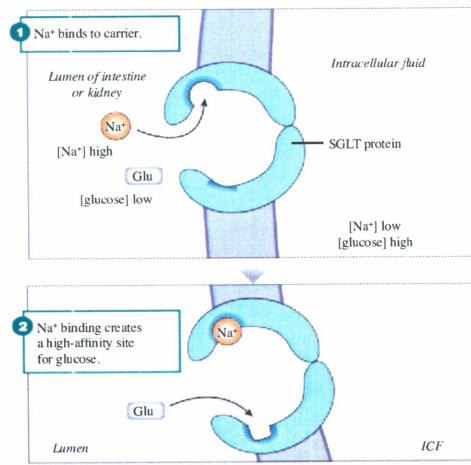


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Secondary Transport: Mechanism of the SGLT transporter

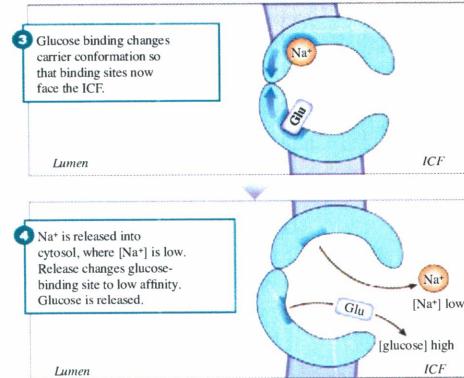
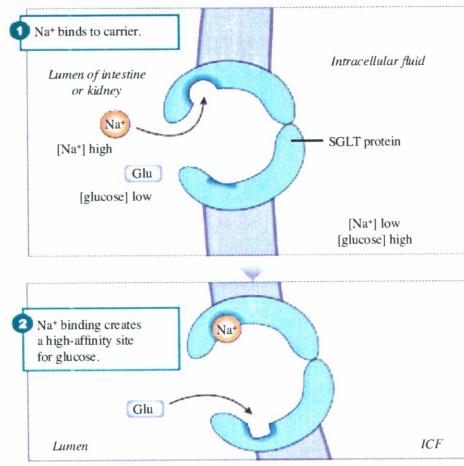


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Putting Them Together: Transepithelial transport of glucose

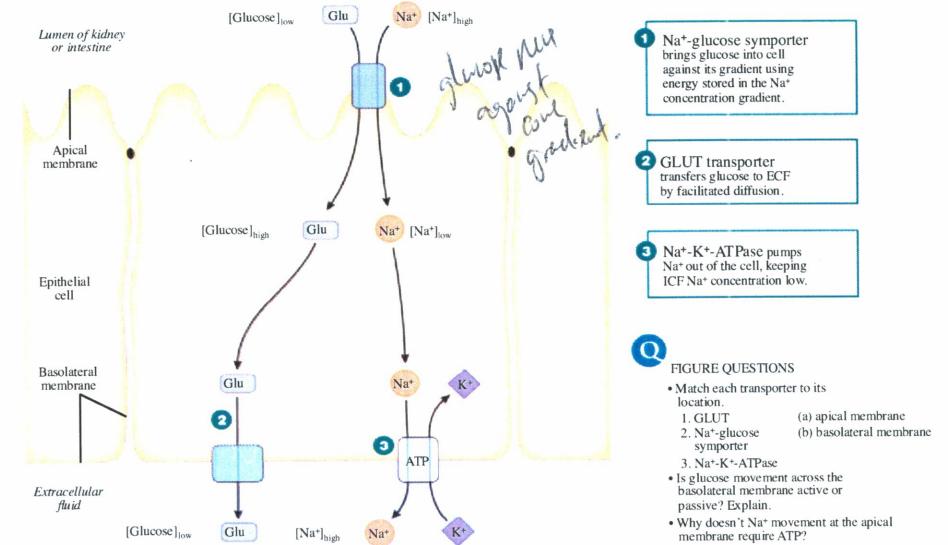
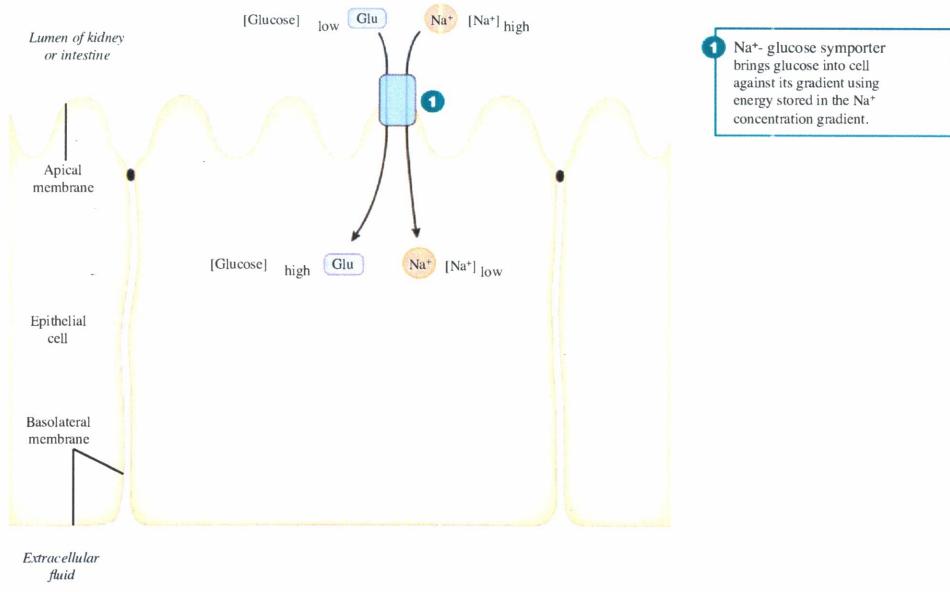
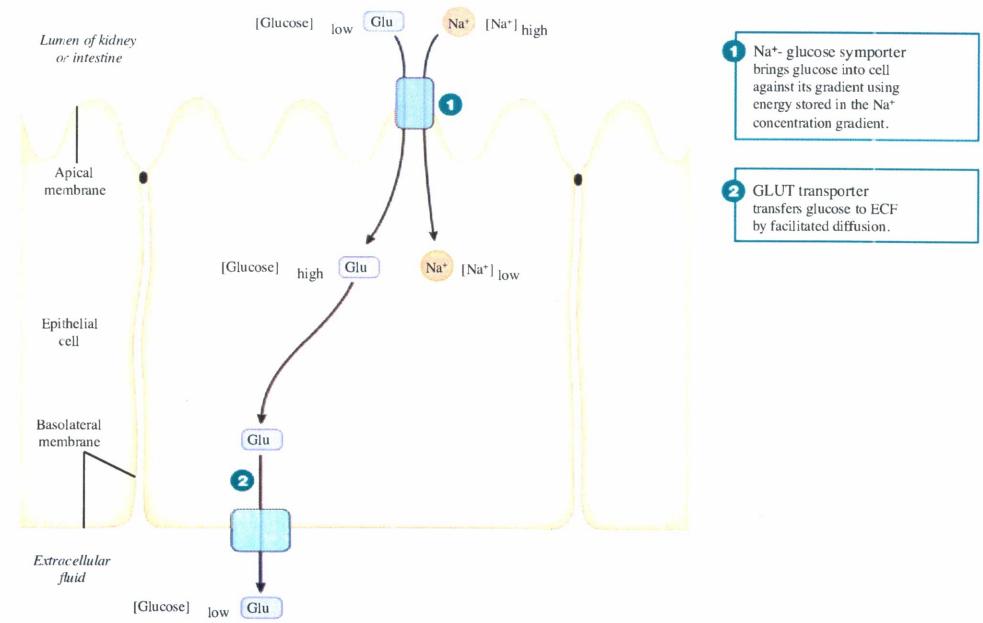


FIGURE QUESTIONS

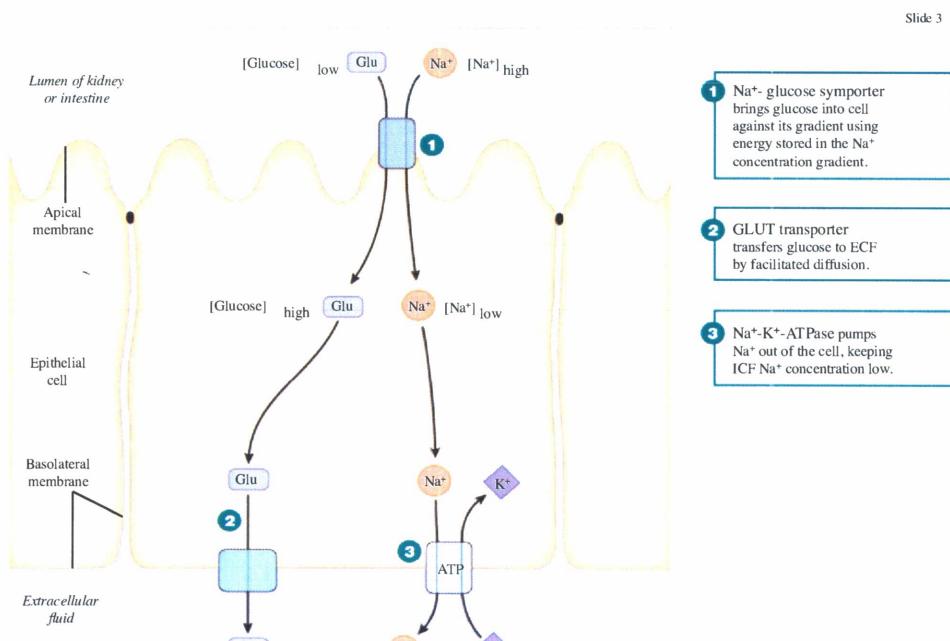
- Match each transporter to its location.
 - 1. GLUT (a) apical membrane
 - 2. Na^+ -glucose symporter (b) basolateral membrane
 - 3. Na^+-K^+ -ATPase
- Is glucose movement across the basolateral membrane active or passive? Explain.
- Why doesn't Na^+ movement at the apical membrane require ATP?



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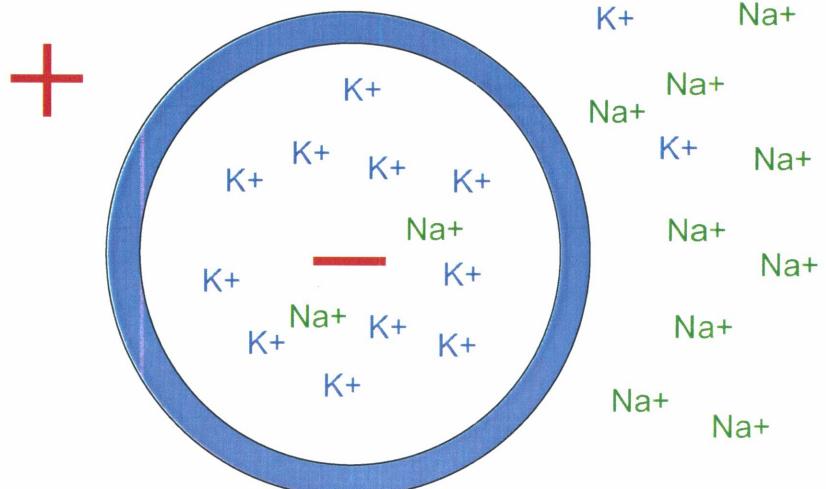


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The Electrochemical Gradient of Ions



- ICF more negative than ECF = *Negative Membrane Potential*
- If Na^+ moves in: *With conc. Gradient; With electrical gradient*
- If K^+ moves out: *With conc. Gradient; Against electrical gradient*

Concepts in Physiology

PHSI2005

Michael Morris

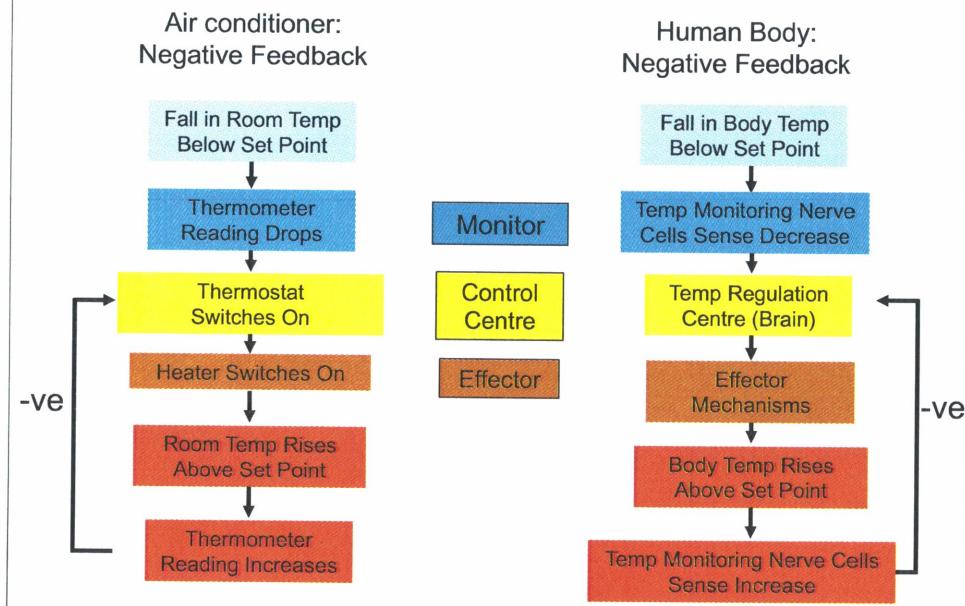
Integrated circuits control life/homeostasis

- Types of circuits:
 - Negative feedback
 - Positive feedforward
 - Many more!
- Operating at **all** levels:
 - System
 - Organ
 - Tissue
 - Cellular
 - Molecular
- Circuits must be:
 - Robust → cannot break down in real life easily
 - Responsive → react to environmental changes.
 - Yet a little noisy!

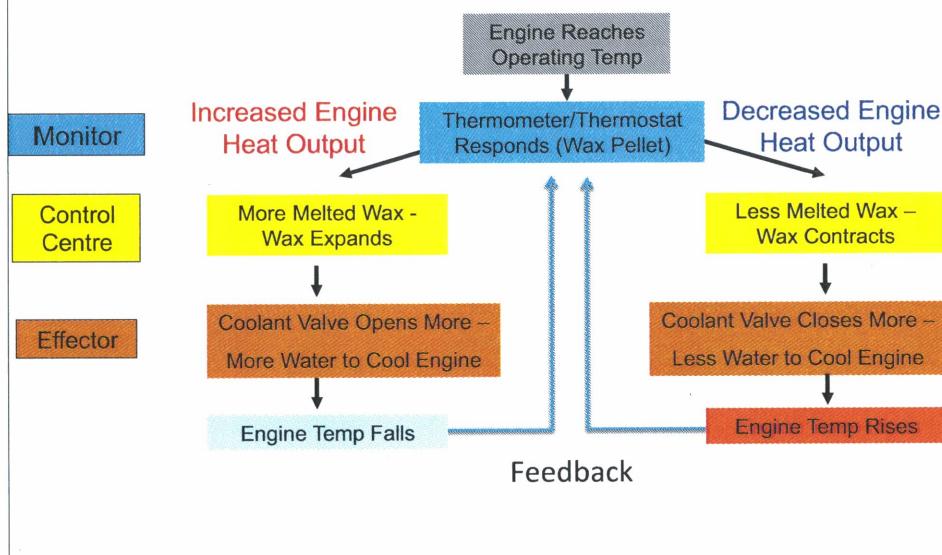
5 lectures

- Physiology & Homeostasis
- Membranes, gradients & transporters
- **Cell communication and signalling**
- Oxygen transport and use
- Pathophysiology – what goes wrong

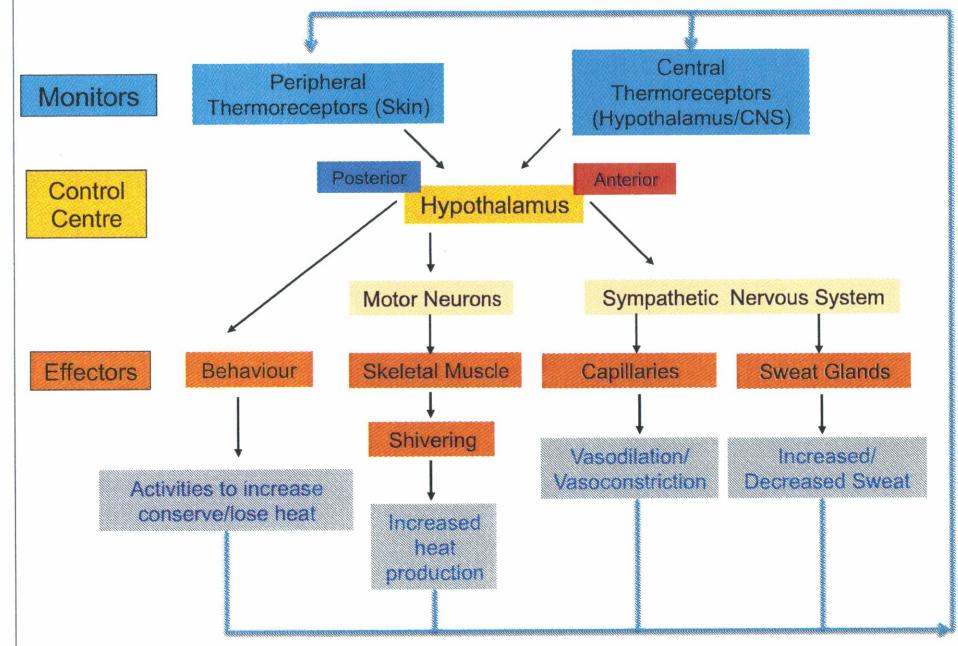
Feedback Control



Car Engine: Dynamically Regulated Feedback



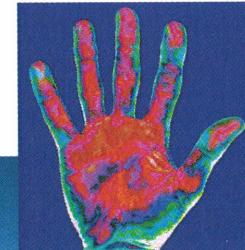
Major Thermoregulatory Pathways – Dynamic Regulation



Thermoregulation: Homeothermy

"A pattern of temperature regulation in which the cyclic variation in core temperature is maintained within $\pm 2^{\circ}\text{C}$ despite much larger variations in ambient temperature"

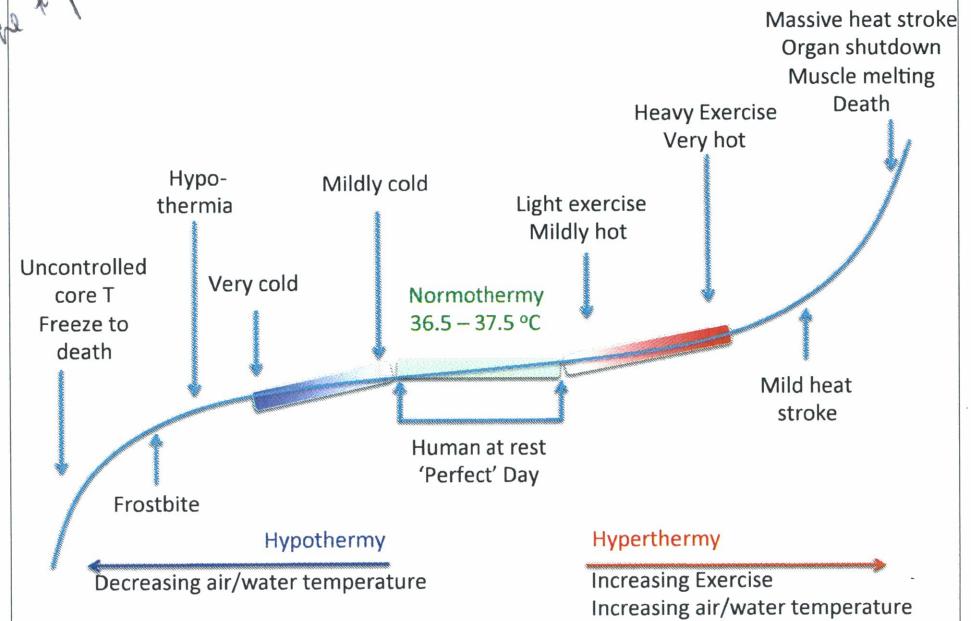
- 2 important compartments: Peripheral (cutaneous) and Core
- Sometimes large gradients to protect core



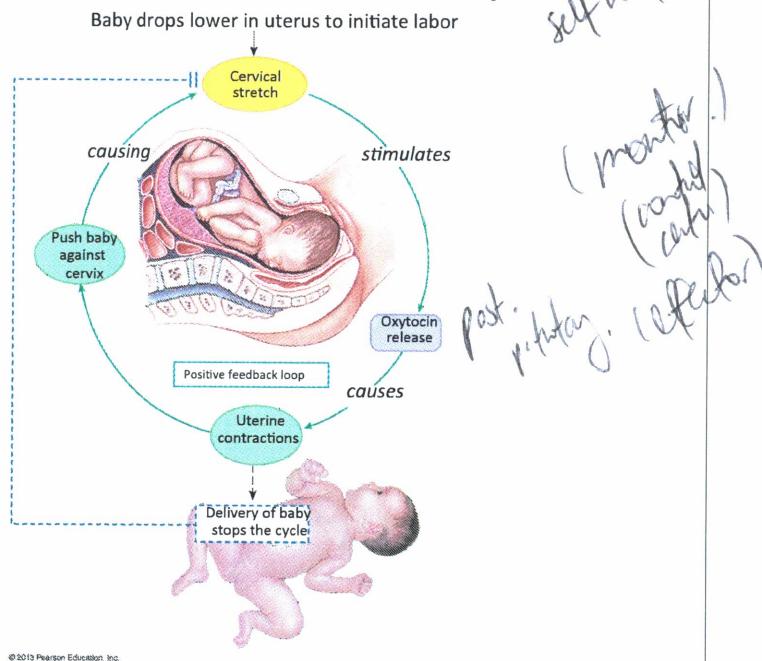
carlosdaman.wordpress.com

*Starting
body will
still attempt to
maintain homeo
temp*

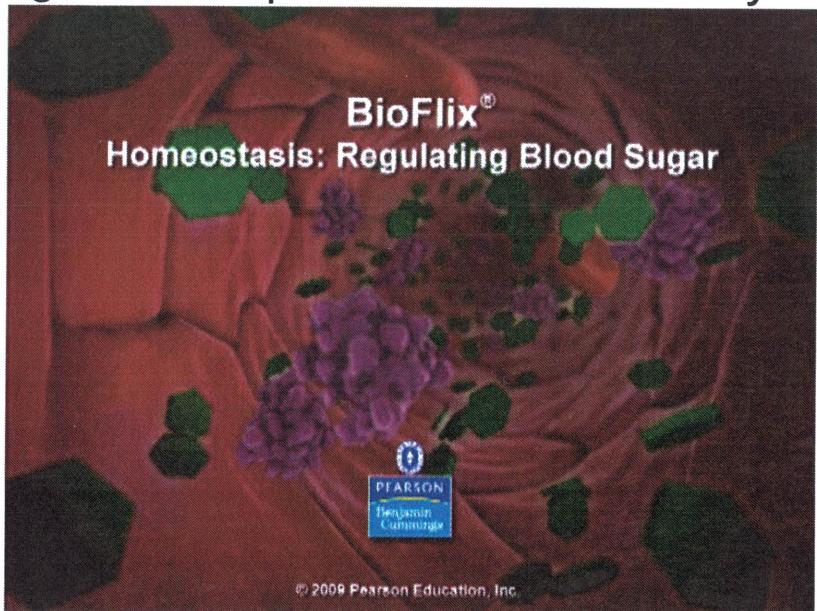
Homeothermy: Life in the comfort zone



Positive Feedforward Loop



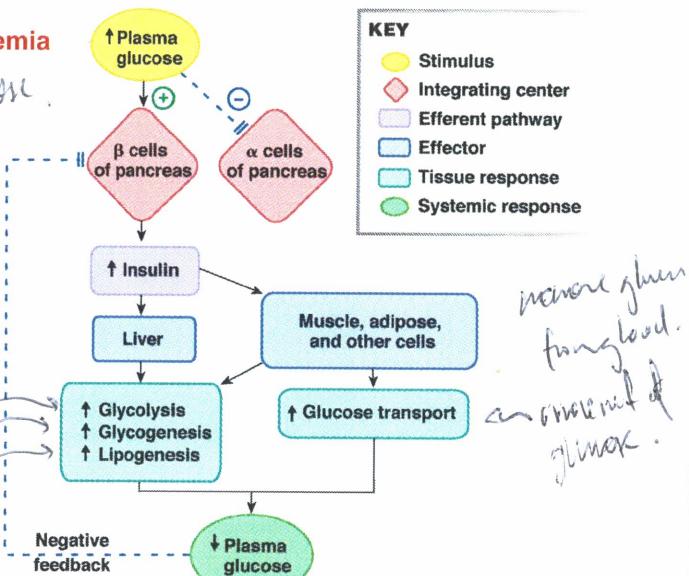
Video: Plasma Glucose Homeostasis – A good example of feedback circuitry



Feedback Regulation and Blood Glucose

Feast: hyperglycemia

high blood glucose

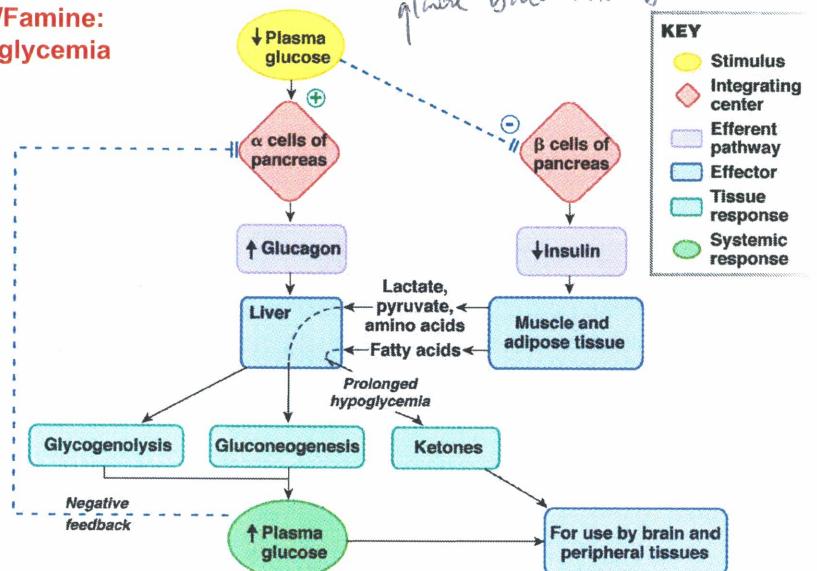


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Feedback regulation and blood glucose

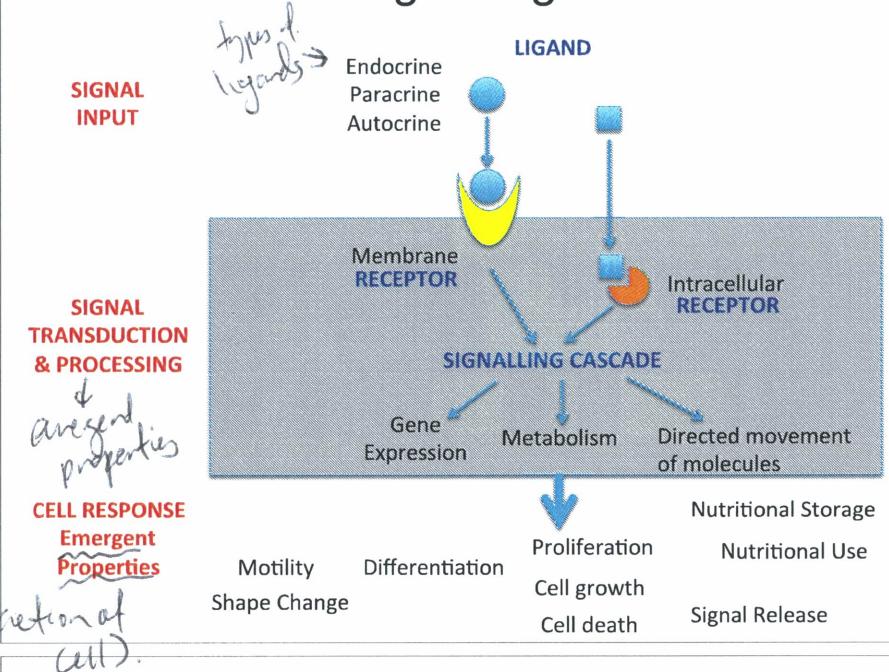
Fast/Famine: hypoglycemia

glucose back into blood stream.

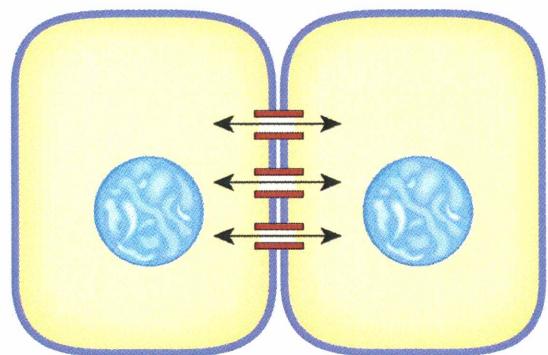


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Chemical Signalling: The Basics



Gap Junctions



(a) Direct cytoplasmic connections between adjacent cells.

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Emergent Properties of the Cell

Depends on:

- Type of cell
- State of cell (e.g., low/high nutrition available, cell division)
- Type of ligand
- [Ligand]
- Receptor and receptor subtype
- [Receptor]
- Number of different ligands

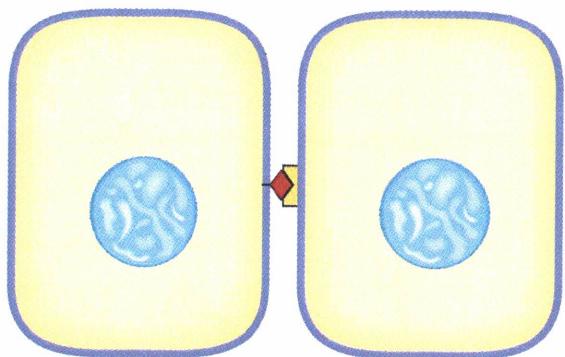
*cell needs a receptor
many circuitry pathways - cell must make use of this bombardment of information.*

Video: Connexins & Cardiomyocytes



*cells connected through gap junction.
⇒ synchronous beating.*

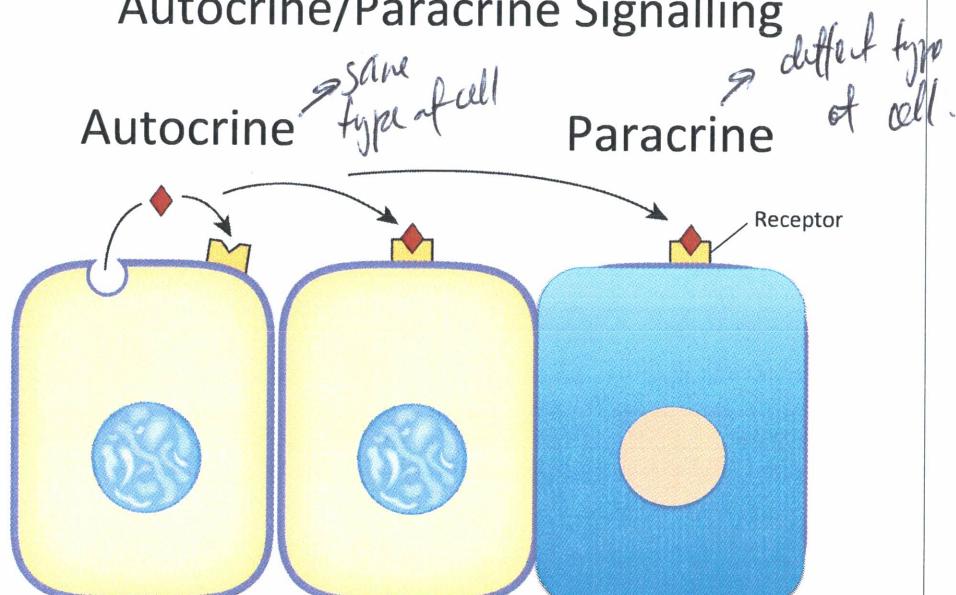
Contact-Dependent Signalling



(b) Interaction between membrane molecules on two cells.

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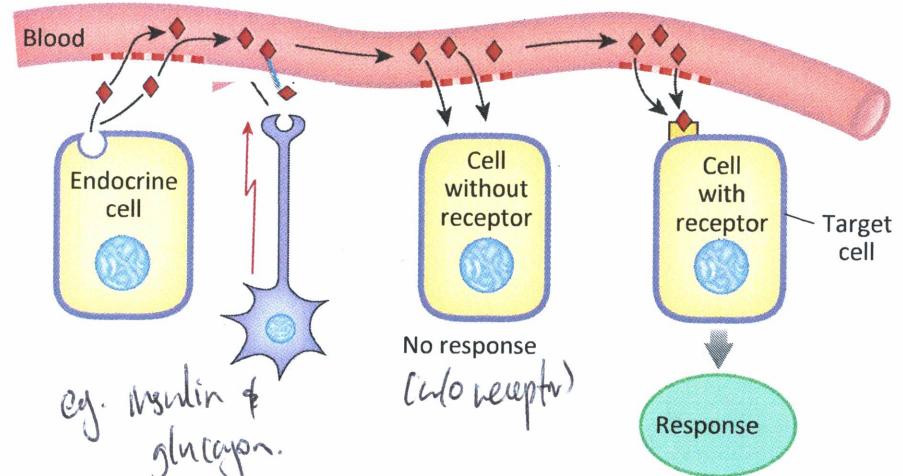
Autocrine/Paracrine Signalling



Autocrine = Acts on same cell type

Paracrine = Acts on different cell type

Endocrine Signalling

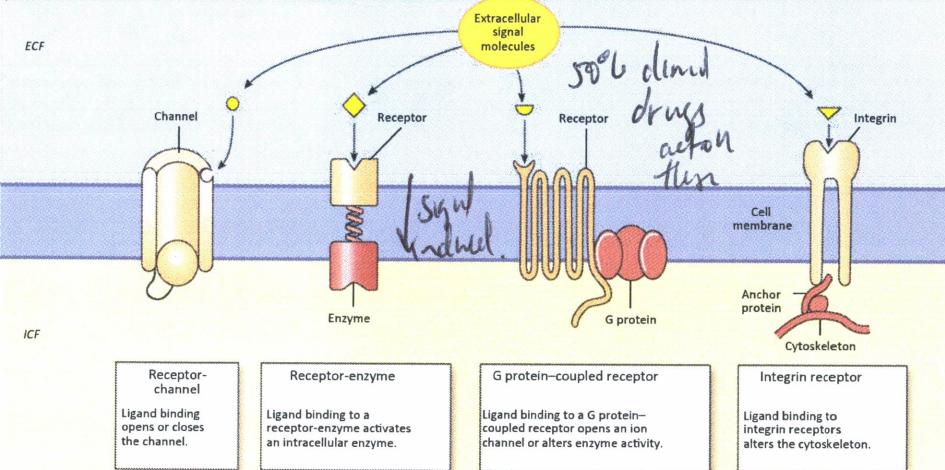


(d)

Hormones are secreted by endocrine glands or cells into the blood. Only target cells with receptors for the hormone respond to the signal.

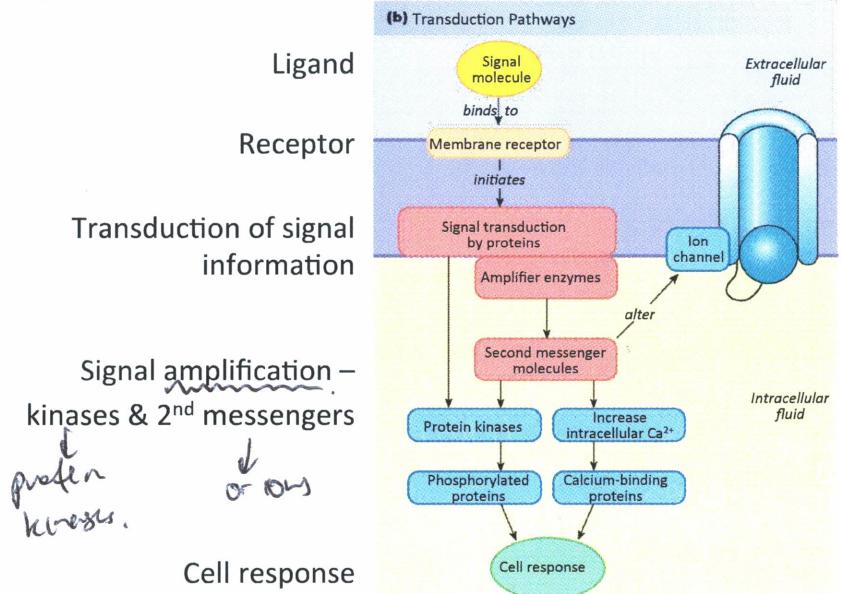
Types of Membrane Receptor

(e) Four Categories of Membrane Receptors



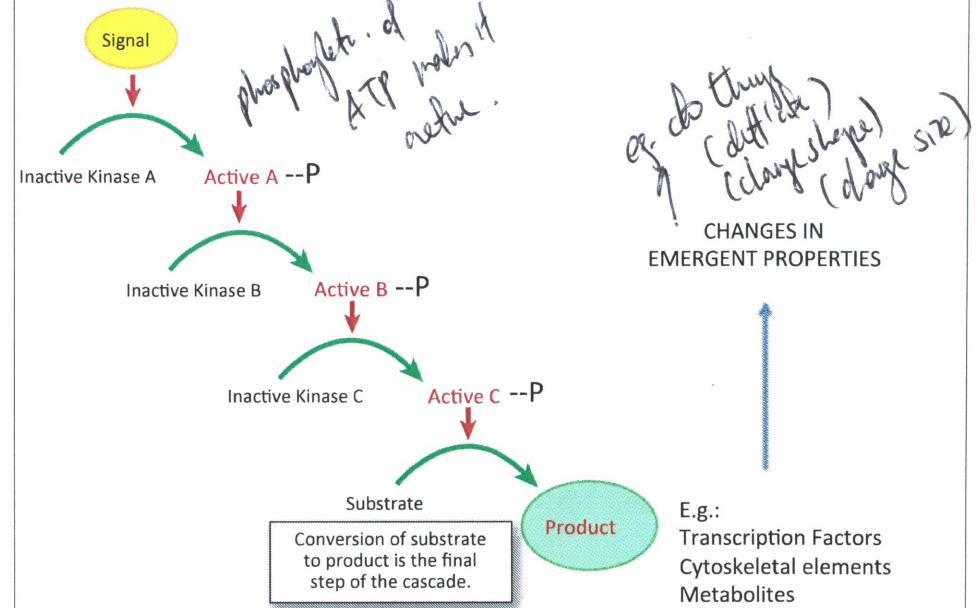
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Signalling Pathways Come in Many Forms



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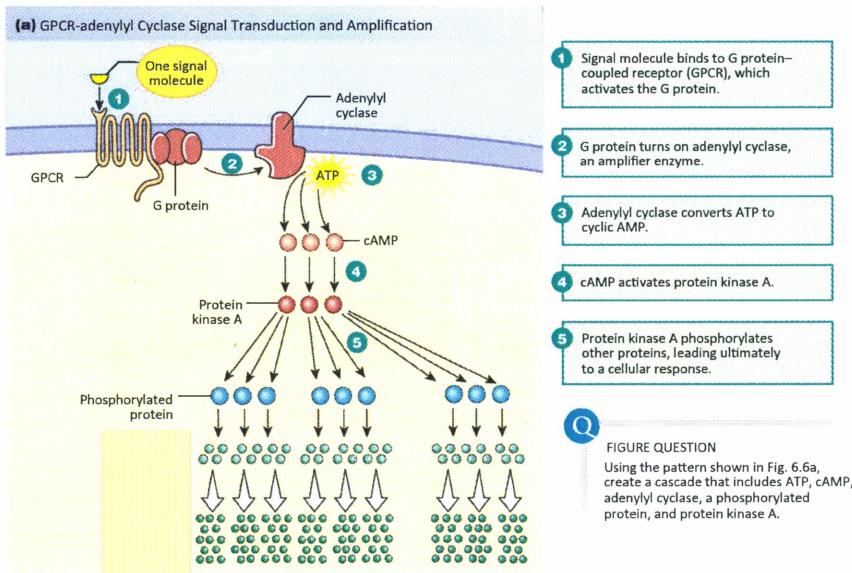
Protein Kinase Pathways Work by Successive Phosphorylation



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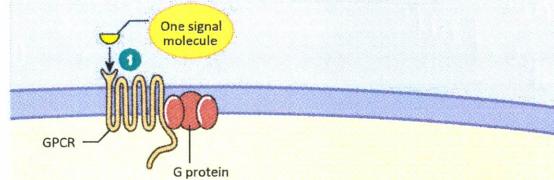
Slide 1

GPCRs & Second Messenger Signalling: cAMP



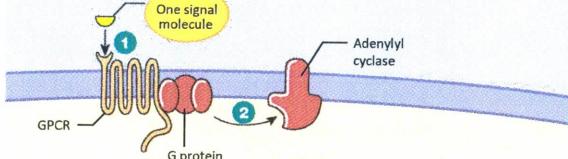
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(a) GPCR-adenylyl Cyclase Signal Transduction and Amplification



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(a) GPCR-adenylyl Cyclase Signal Transduction and Amplification



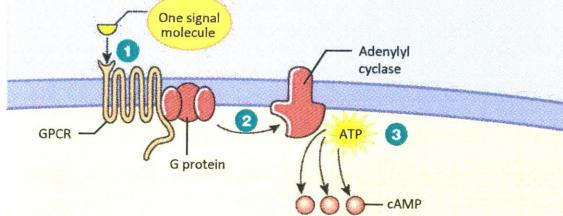
Signal forwarded
Slide 2

- 1 Signal molecule binds to G protein-coupled receptor (GPCR), which activates the G protein.
- 2 G protein turns on adenyl cyclase, an amplifier enzyme.

(Activates)
→ converts ATP
to cAMP

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(a) GPCR-adenylyl Cyclase Signal Transduction and Amplification



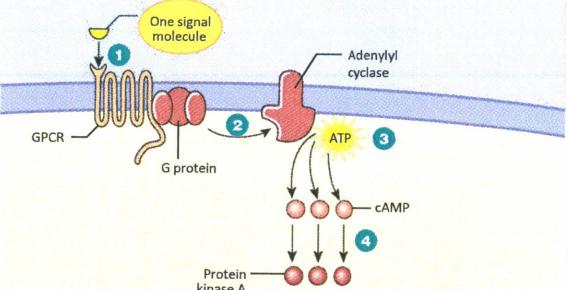
- 1 Signal molecule binds to G protein-coupled receptor (GPCR), which activates the G protein.
- 2 G protein turns on adenyl cyclase, an amplifier enzyme.

- 3 Adenyl cyclase converts ATP to cyclic AMP.

*ATP is substrate
in this reaction*

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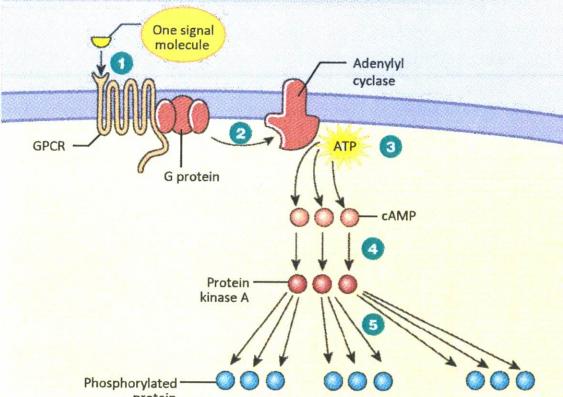
(a) GPCR-adenylyl Cyclase Signal Transduction and Amplification



- 1 Signal molecule binds to G protein-coupled receptor (GPCR), which activates the G protein.
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- 3 Adenyl cyclase converts ATP to cyclic AMP.
- 4 cAMP activates protein kinase A.

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(a) GPCR-adenylyl Cyclase Signal Transduction and Amplification



- 1 Signal molecule binds to G protein-coupled receptor (GPCR), which activates the G protein.
- 2 G protein turns on adenyl cyclase, an amplifier enzyme.

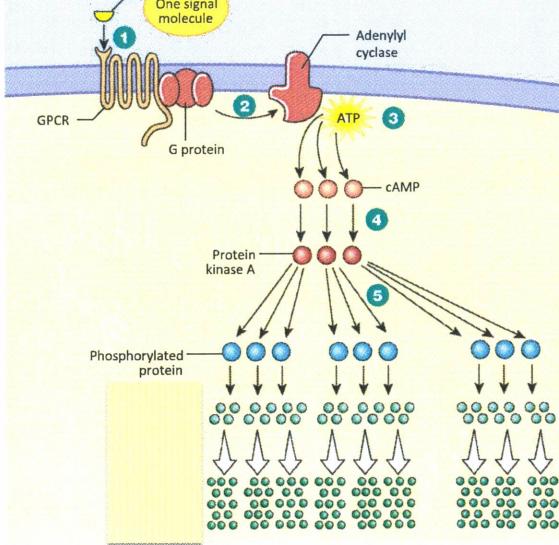
- 3 Adenyl cyclase converts ATP to cyclic AMP.

- 4 cAMP activates protein kinase A.

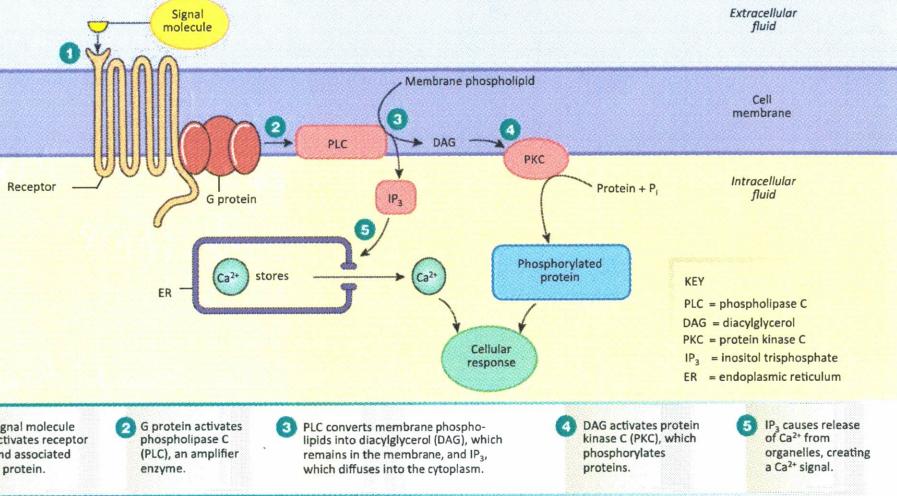
- 5 Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

*cascade
amplification*

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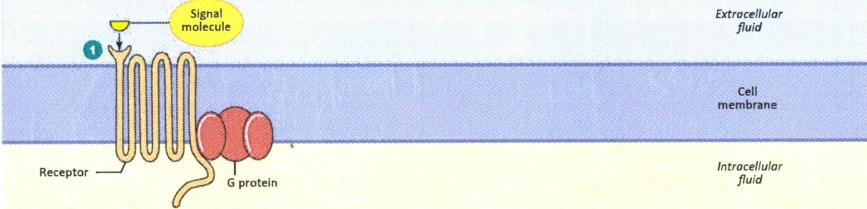
(a) GPCR-adenylyl Cyclase Signal Transduction and Amplification

- 1 Signal molecule binds to G protein-coupled receptor (GPCR), which activates the G protein.
- 2 G protein turns on adenyl cyclase, an amplifier enzyme.
- 3 Adenyl cyclase converts ATP to cyclic AMP.
- 4 cAMP activates protein kinase A.
- 5 Protein kinase A phosphorylates other proteins, leading ultimately to a cellular response.

GPCRs & Second Messenger Signalling: IP₃, DAG, Ca²⁺**(b) GPCR-phospholipase C Signal Transduction**

- 1 Signal molecule activates receptor and associated G protein.
- 2 G protein activates phospholipase C (PLC), an amplifier enzyme.
- 3 PLC converts membrane phospholipid into diacylglycerol (DAG), which remains in the membrane, and IP₃, which diffuses into the cytoplasm.
- 4 DAG activates protein kinase C (PKC), which phosphorylates proteins.
- 5 IP₃ causes release of Ca²⁺ from organelles, creating a Ca²⁺ signal.

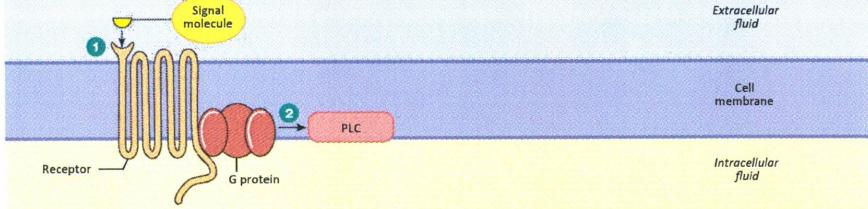
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(b) GPCR-phospholipase C Signal Transduction

KEY
 PLC = phospholipase C
 DAG = diacylglycerol
 PKC = protein kinase C
 IP₃ = inositol triphosphate
 ER = endoplasmic reticulum

- 1 Signal molecule activates receptor and associated G protein.

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(b) GPCR-phospholipase C Signal Transduction

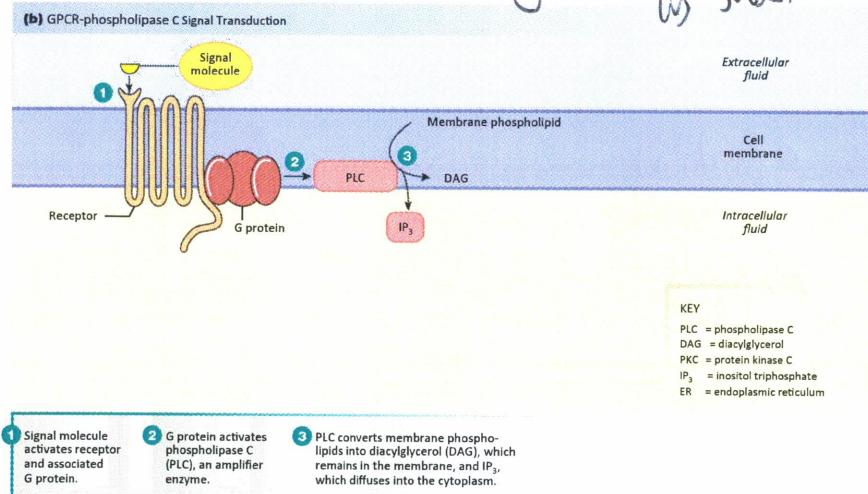
- 1 Signal molecule activates receptor and associated G protein.
- 2 G protein activates phospholipase C (PLC), an amplifier enzyme.

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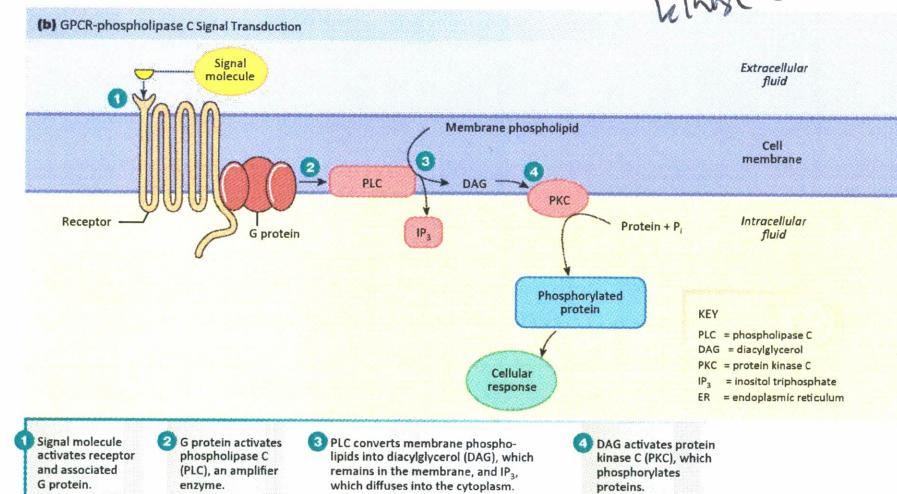
Auges goes & amplifies.

KEY
 PLC = phospholipase C
 DAG = diacylglycerol
 PKC = protein kinase C
 IP₃ = inositol triphosphate
 ER = endoplasmic reticulum

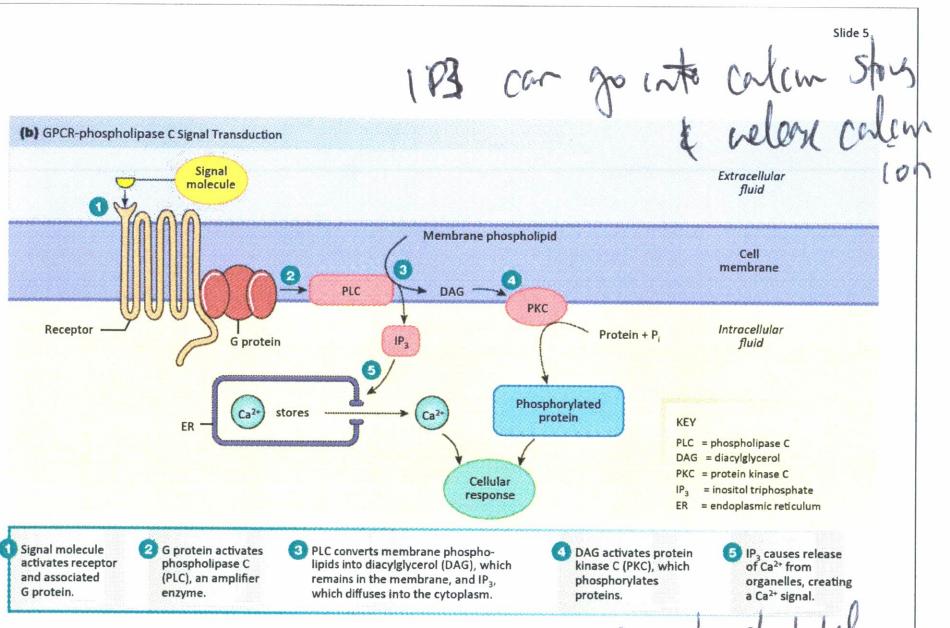
using membrane phospholipid substrate



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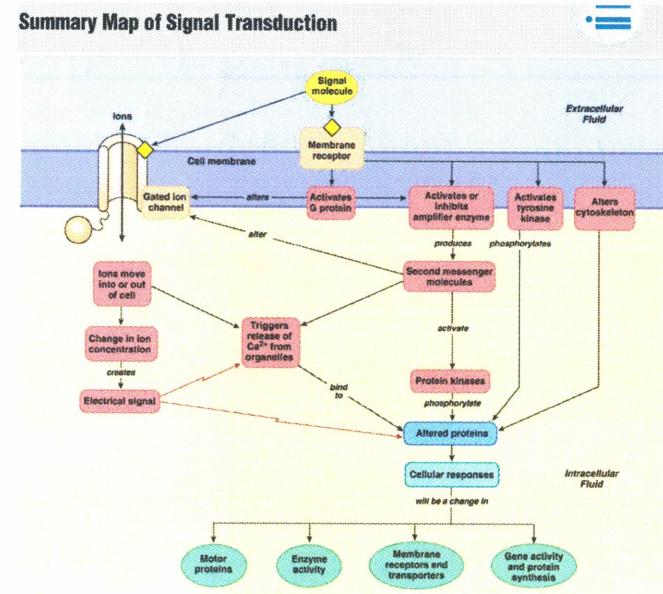
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both Ca²⁺ & phosphorylated protein modulates the cellular response

DAG activates protein kinase C.

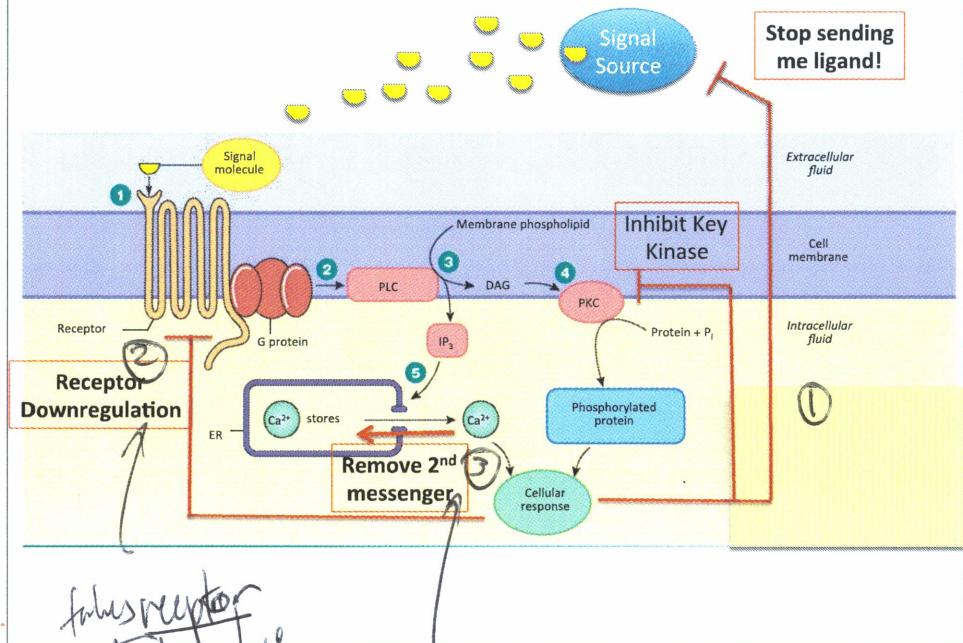
Combination Signalling

Summary Map of Signal Transduction



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But what about feedback?!



↑ ~~Receptor
out of membrane~~
false receptor
(turn neepkoff)
no longer exposed
to ligand.

↑ ~~key~~ key
key turned switch off,
→ pump Ca²⁺ back
into stores

• abstract of this
place
→ sketch of a
few minutes.

lecture 4

Concepts in Physiology

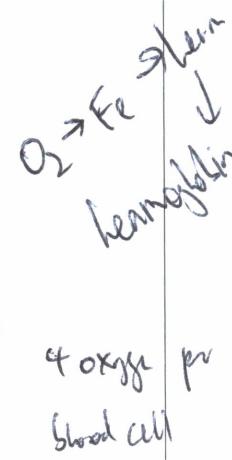
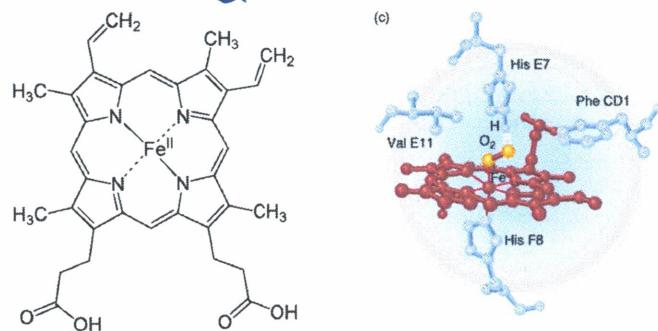
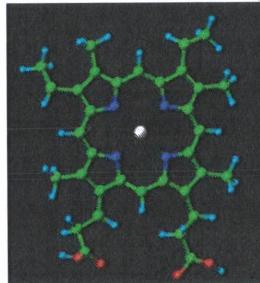
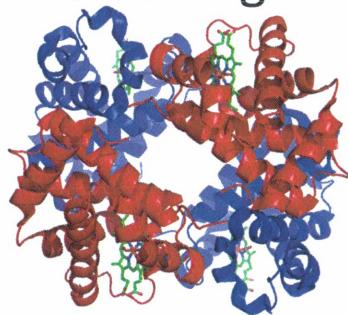
PHSI2005

Michael Morris

5 lectures

- Physiology & Homeostasis
- Membranes, gradients & transporters
- Cell communication and signalling
- **Oxygen transport and use**
- Pathophysiology – what goes wrong

Haemoglobin, Haem & O₂



Collected Properties of O₂ transport

Oxygen: Small, uncharged and non-polar gas

- Easily crosses cell membranes
- Diffuses rapidly over short distances
- Net flow always down concentration gradient

High O₂ partial pressure in lungs

- Must cross membranes of:
 - Epithelial lung cells
 - Cells lining capillaries
 - Red blood cell membrane

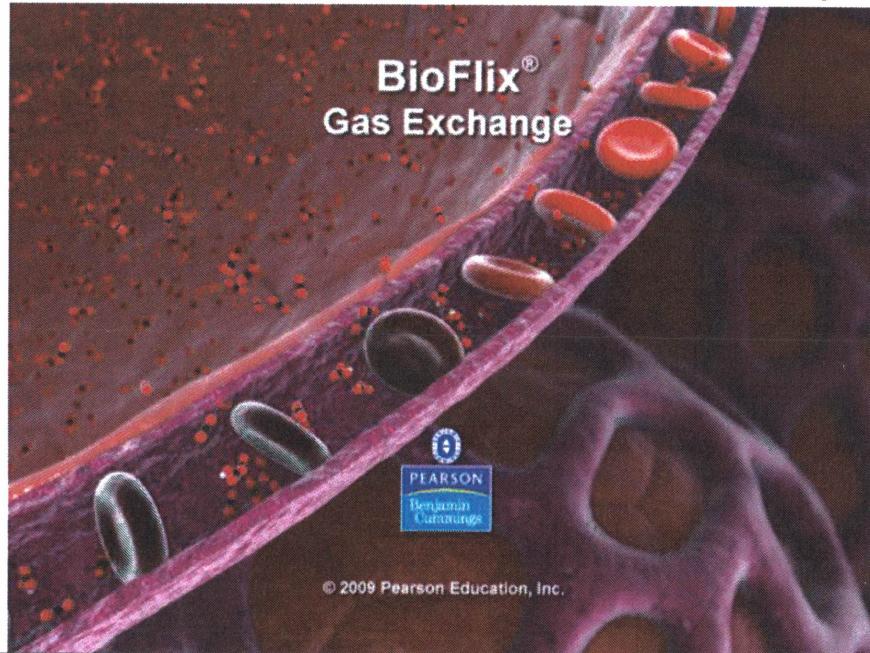
Transport

- Only 2% dissolves in plasma
- 98% attaches to haemoglobin/haem/Fe²⁺
- Chemical equilibrium very rapid
- Without haemoglobin – far too little O₂ would be carried to tissues

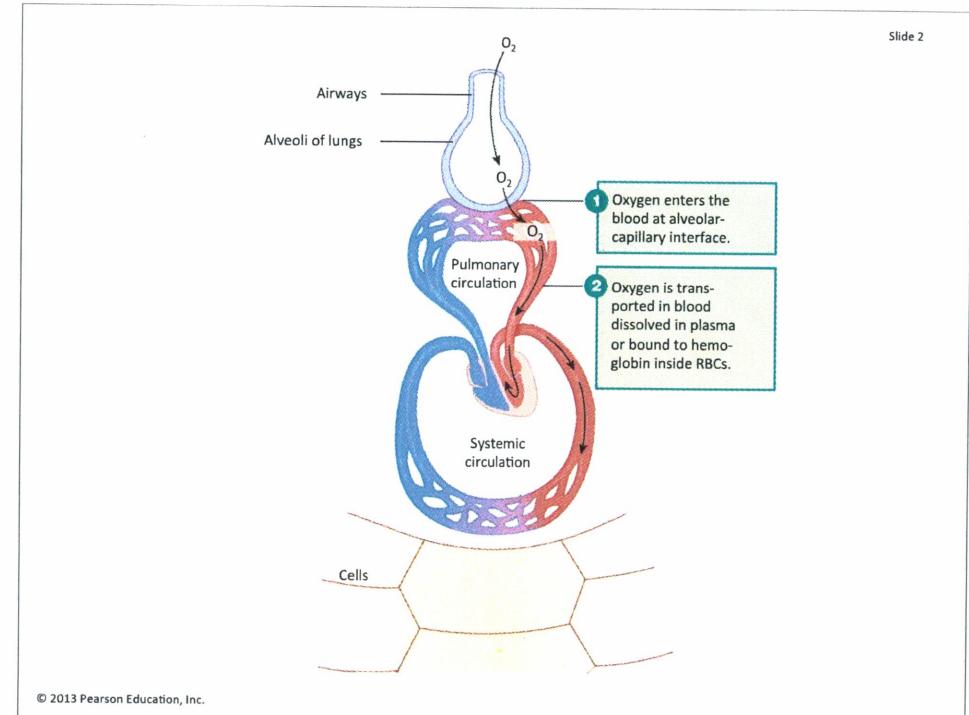
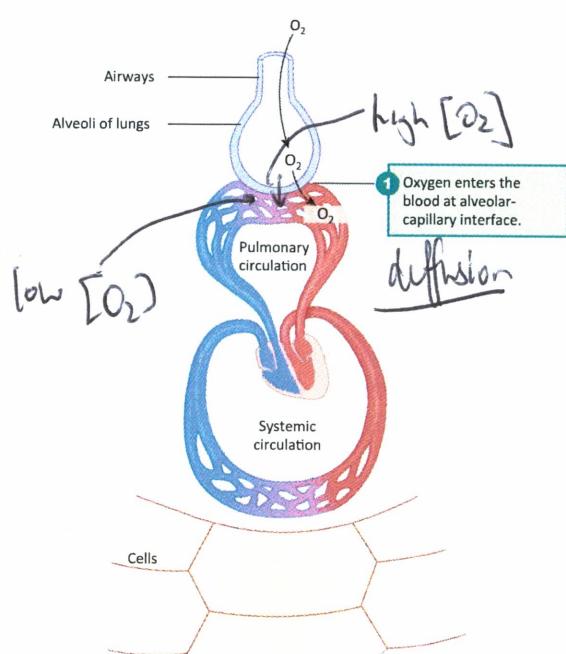
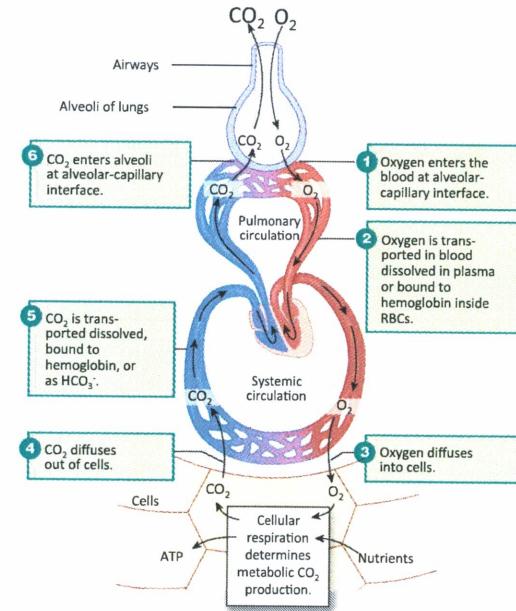
Low O₂ partial pressure at tissues

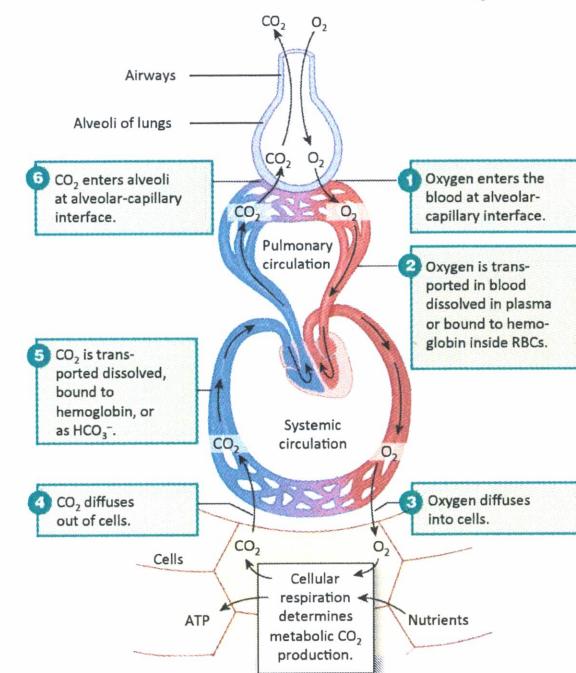
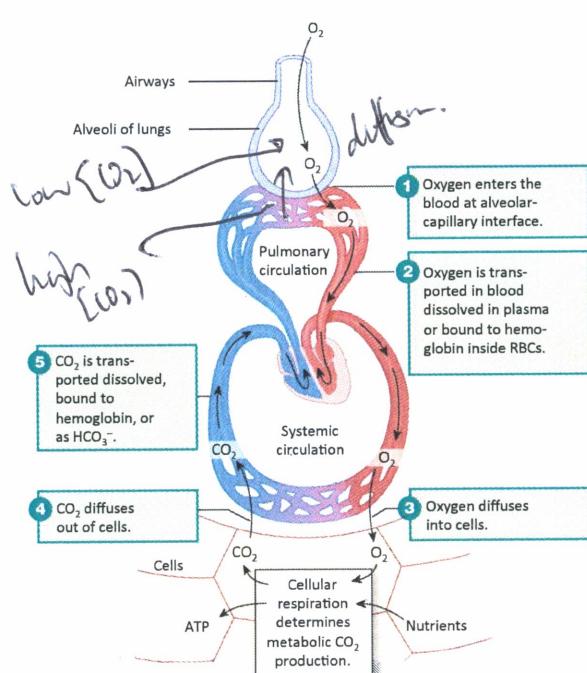
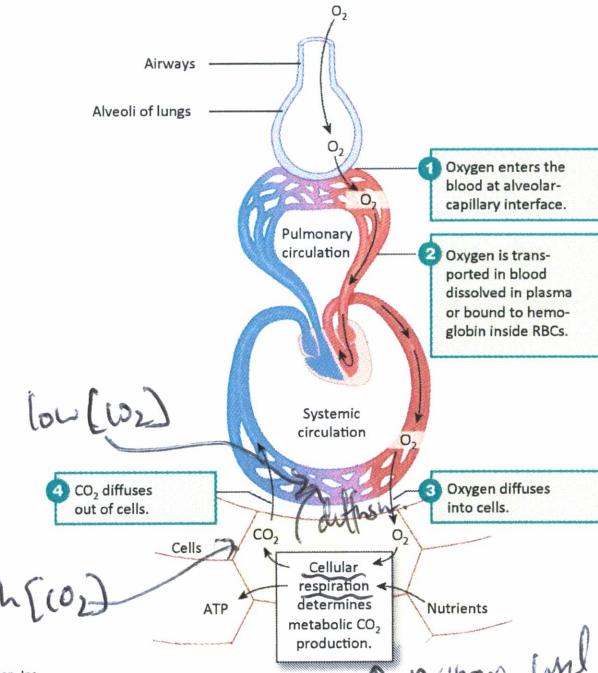
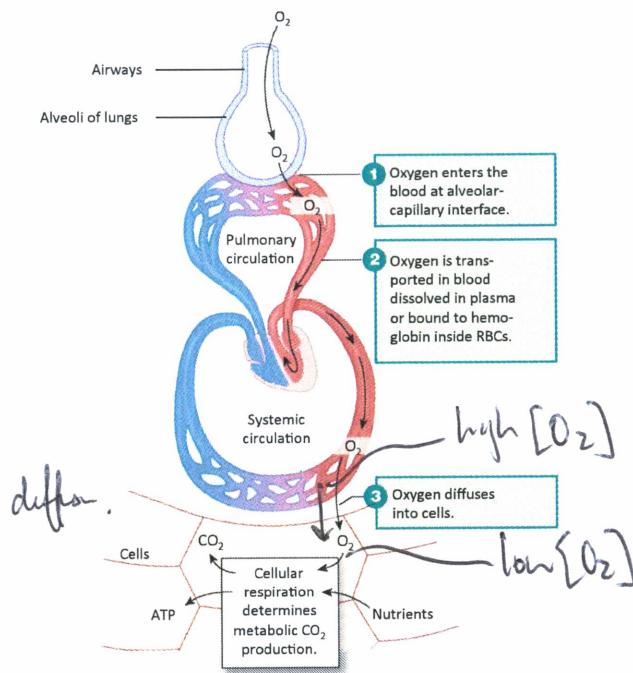
- Chemical reactions reverse
- Rapid diffusion of O₂ out of red blood cells and plasma into cells

Video: Pulmonary Gas Exchange & Transport

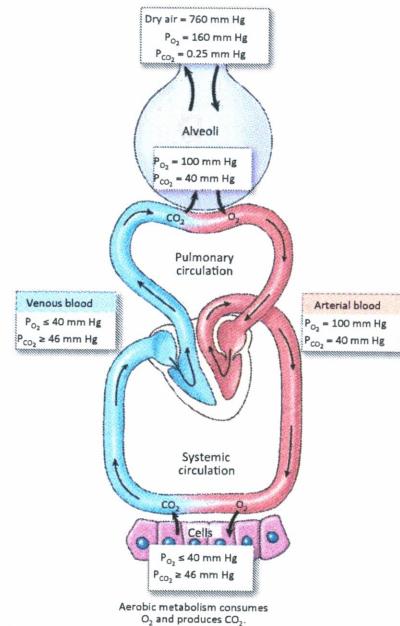


Pulmonary Gas Exchange & Transport

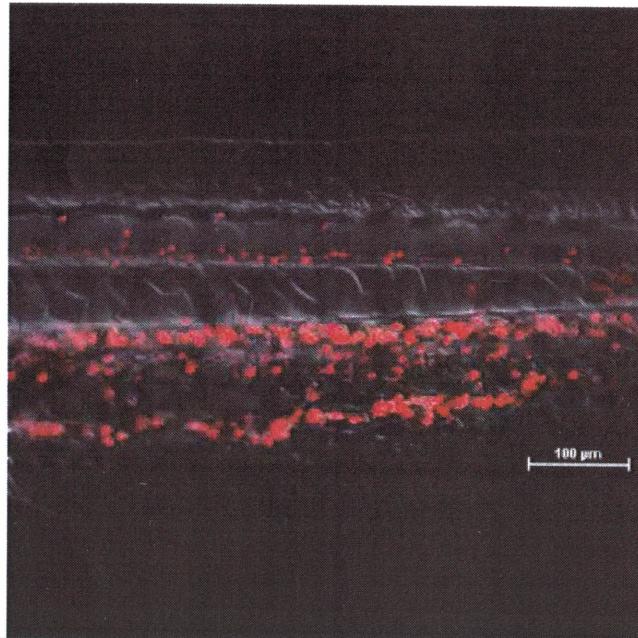




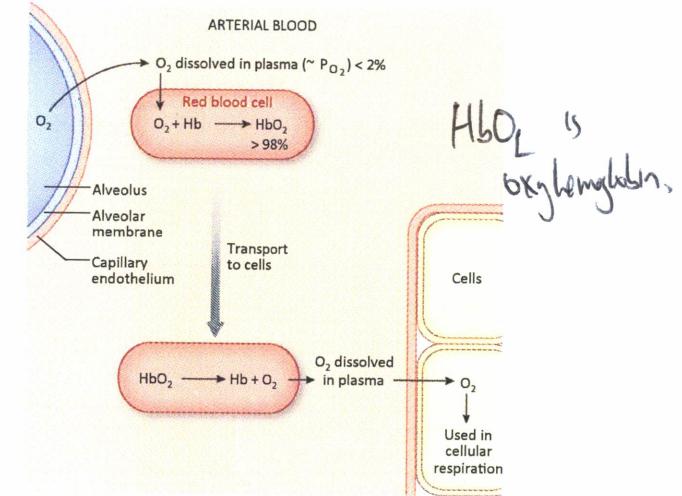
O₂ & CO₂: Net Diffusion Down Conc. Gradient



Video: Blood Flow in Zebra Fish



O₂: Diffusion and Equilibria Are Rapid

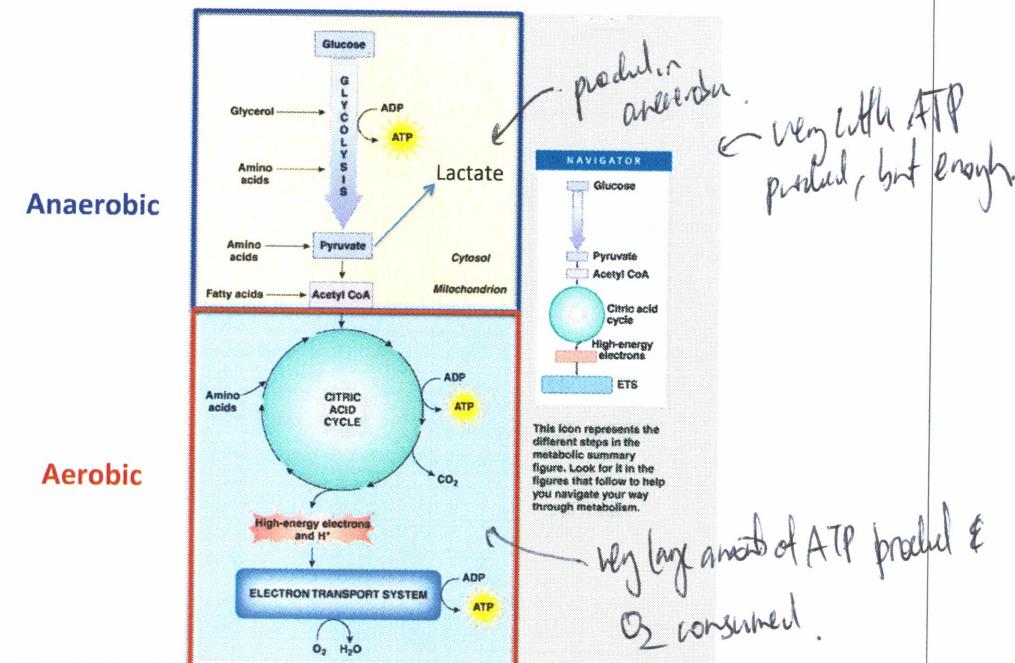


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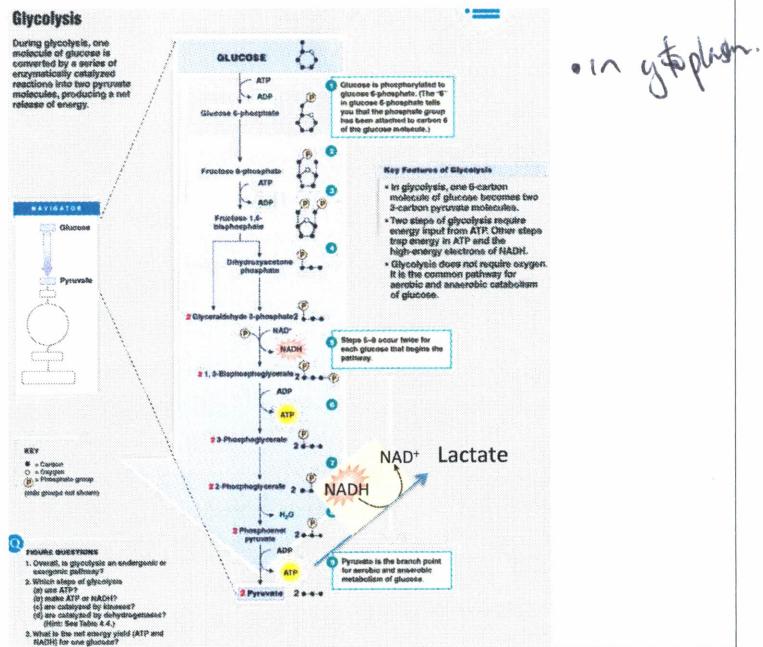
Q

FIGURE QUESTION
How many cell membranes will O₂ cross in its passage between the airspace of the alveolus and binding to hemoglobin?

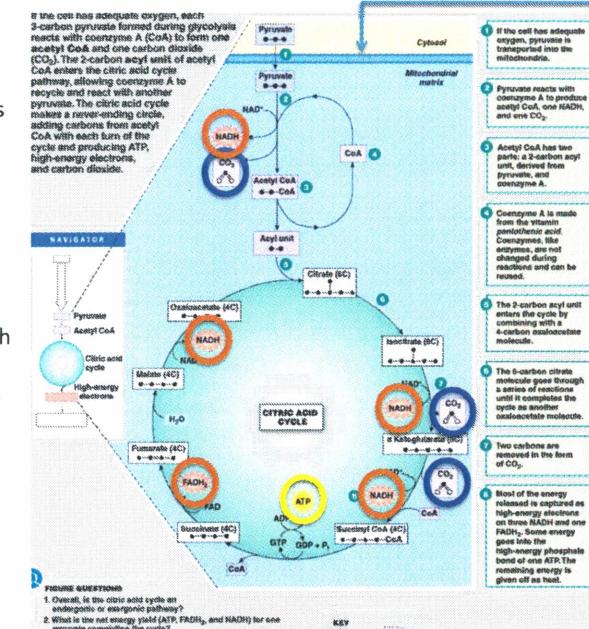
Anaerobic vs Aerobic Glucose Metabolism



Anaerobic Metabolism: A little bit of ATP



Aerobic Metabolism: Starts in mitochondria with citric acid cycle



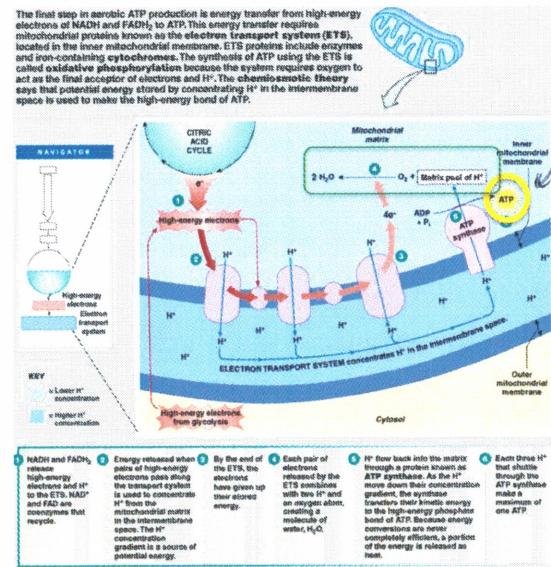
Double membrane of mitochondria

- different compartments in cell.

O_2 is greater than
greater just outside
inside in O_2 .

~~NADH & FADH₂~~ ^{reduces}
high energy electrons

Electron Transport System: Lots of ATP



- of ATP
- secretly transport product across cell membrane.
- two lipid bilayers.
- high energy electrons used to pump H⁺ it across against gradient.

Anaerobic vs Aerobic Metabolism

[a] Anaerobic Metabolism		$\text{C}_6\text{H}_{12}\text{O}_6 \rightarrow 2 \text{C}_3\text{H}_5\text{O}_3^- + 2 \text{H}^+$			
		NADH	FADH ₂	ATP	CO ₂
1 Glucose					
	G L Y C O L Y S I S	2		4 -2	
	↓				
2 Pyruvate					
2 Lactate		-2			
TOTALS		0	NADH	2	ATP

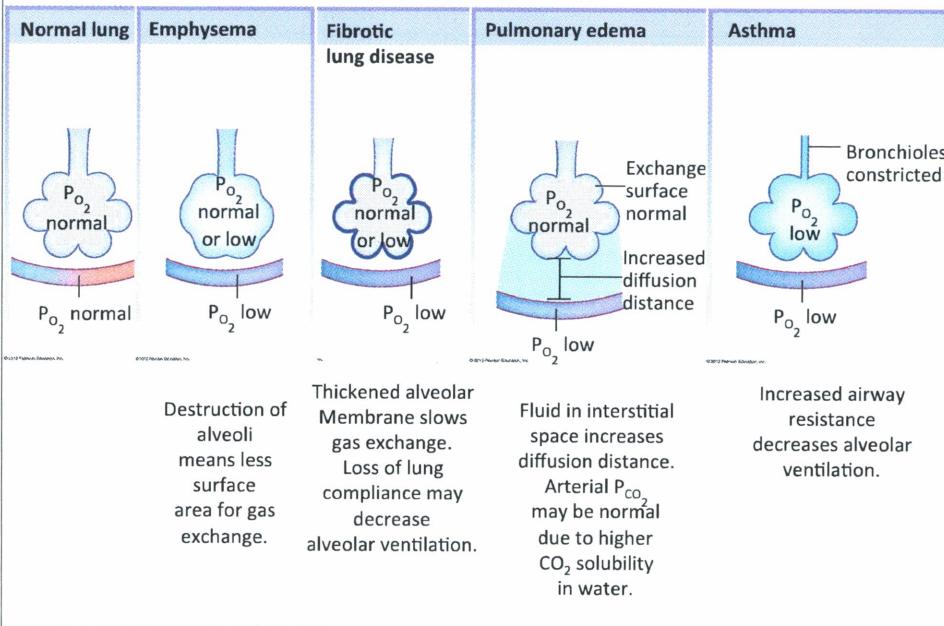
(b) Aerobic Metabolism

$$\text{C}_6\text{H}_{12}\text{O}_6 + 6 \text{ O}_2 \longrightarrow 6 \text{ CO}_2 + 6 \text{ H}_2\text{O}$$

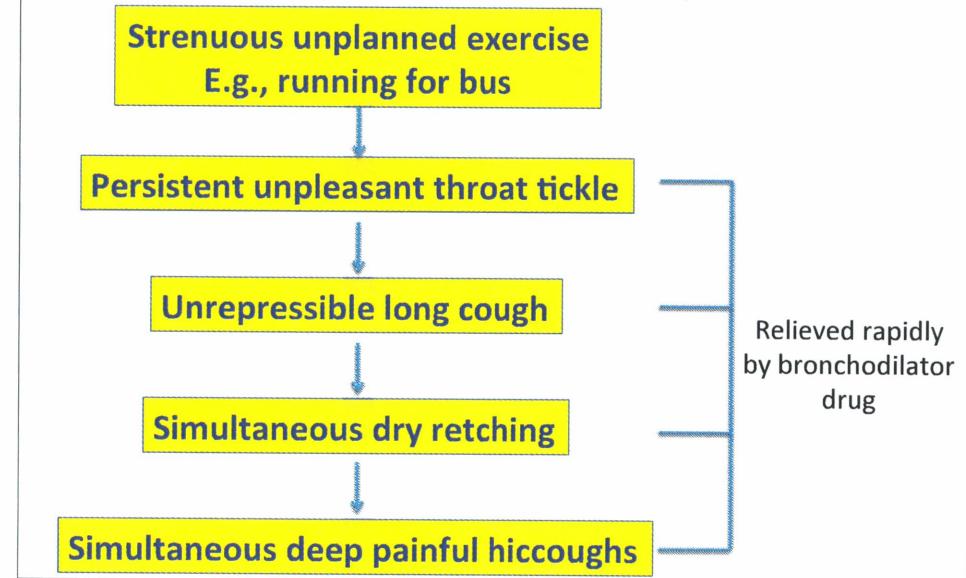
1 Glucose	NADH	FADH₂	ATP	CO₂
Glycolysis	2*		+4 -2	
2 Pyruvate	2			
2 Acetyl CoA				2
Citric acid cycle	6	2	2	4
High-energy electrons and H ⁺				
ELECTRON TRANSPORT SYSTEM	26-28			
TOTALS	6 H ₂ O	30-32 ATP	6 CO ₂	

* Cytoplasmic NADH sometimes yields only 1.5 ATP/NADH instead of 2.5 ATP/NADH.

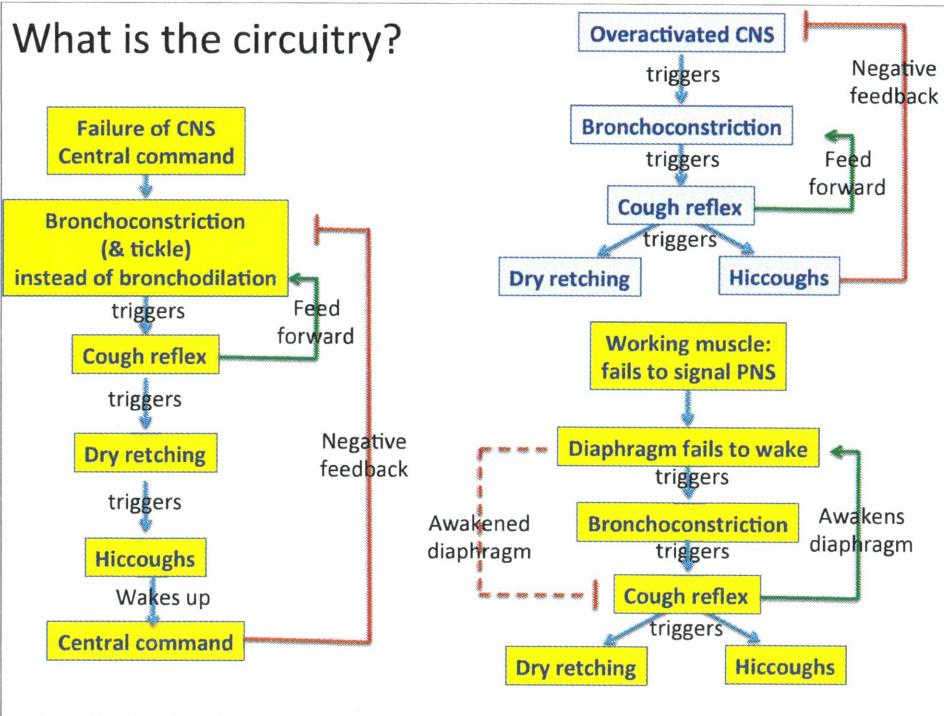
Pulmonary pathophysiology



Case study: A series of unfortunate events Temporal sequence



What is the circuitry?



COMMONWEALTH OF AUSTRALIA

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PHSI2005/2905: Cellular Neurophysiology

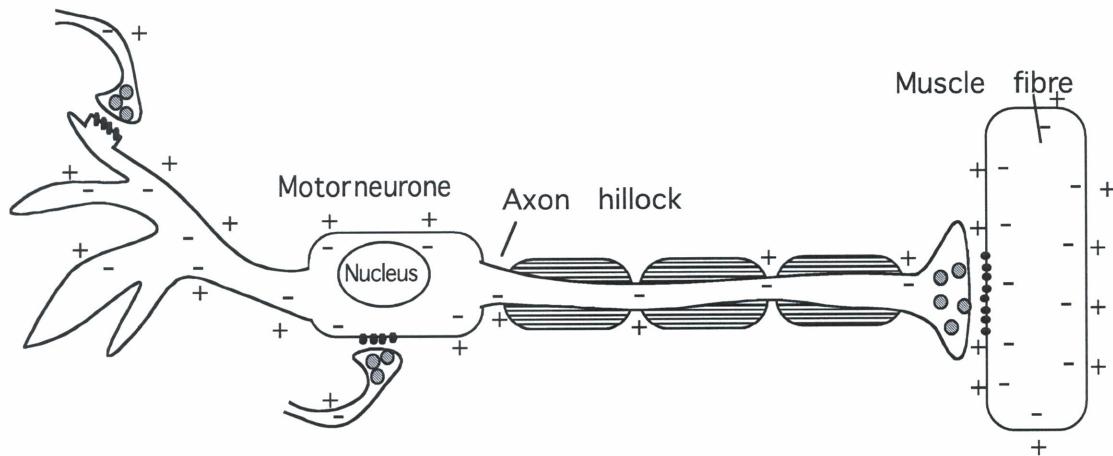
Lect. 1 Resting Membrane Potential

28/3/15

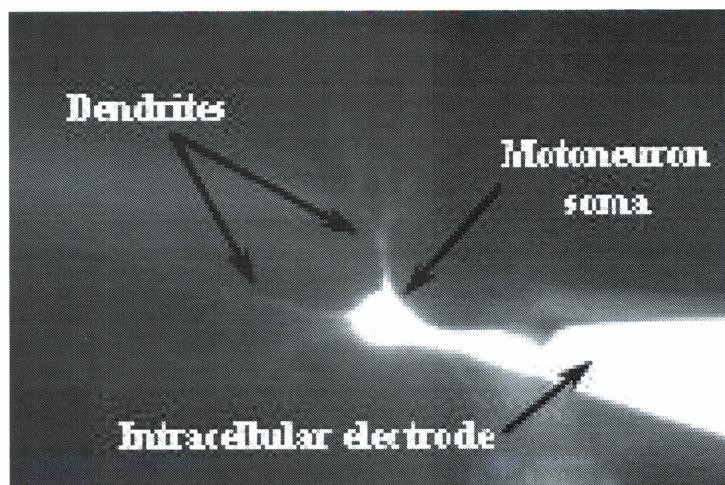
Bill Phillips, Physiology

- Balance of electrical charge
- Active transport creates concentration gradients
- Ion channels
- Chemical driving forces
- Electrical forces on ions
- Ionic currents across the membrane
- The Smarties game / Nernst Potentials
- Relative permeability to ions
- The Goldman Equation

Most cells have an electrical potential across their membrane
What does this mean and how does it come about?

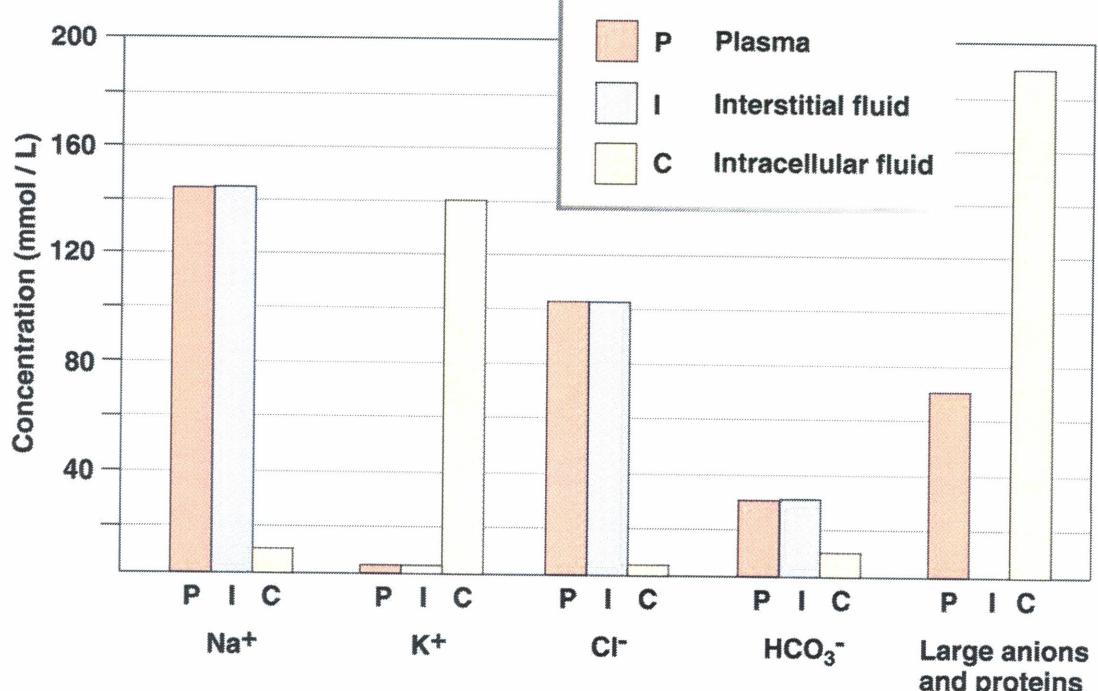


Measuring the membrane potential (imbalance of charge)
across the plasma membrane of a motor neuron



Resting membrane potential (typically about -60 millivolts)

(b) Distribution of solutes



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Figure 5-3b

Extracellular fluid (conductor)

High concentration of sodium ions

Na⁺ Cl⁻

Balanced by chloride ions

} salt solution

Lipid bilayer (insulator)

K⁺ Org⁻

Cytoplasm (conductor)

High concentration potassium ions

Balanced by organic anions

} salt solution

Only a tiny imbalance of anions vs cations is needed to generate physiological membrane potentials

INSIDE	OUTSIDE
200,000	200,000
cations +	cations +
200,001	200,000
anions	anions
-65mV (compared to outside)	zero mV (by convention)

Balance of electrical charge

- For membrane potential to change cations or anions must **SELECTIVELY** cross the membrane
- Only a tiny movement of ions is needed
- Diffusion force (chemical driving force) drives ions across the membrane
- Ion channels permit ionic currents

Types of ion channels

Permeable to:	Non-gated	Voltage-gated	Ligand-gated
Na^+	+	+	+
K^+	+	+	+
Cl^-	-	+	+
Ca^{2+}	-	+	+

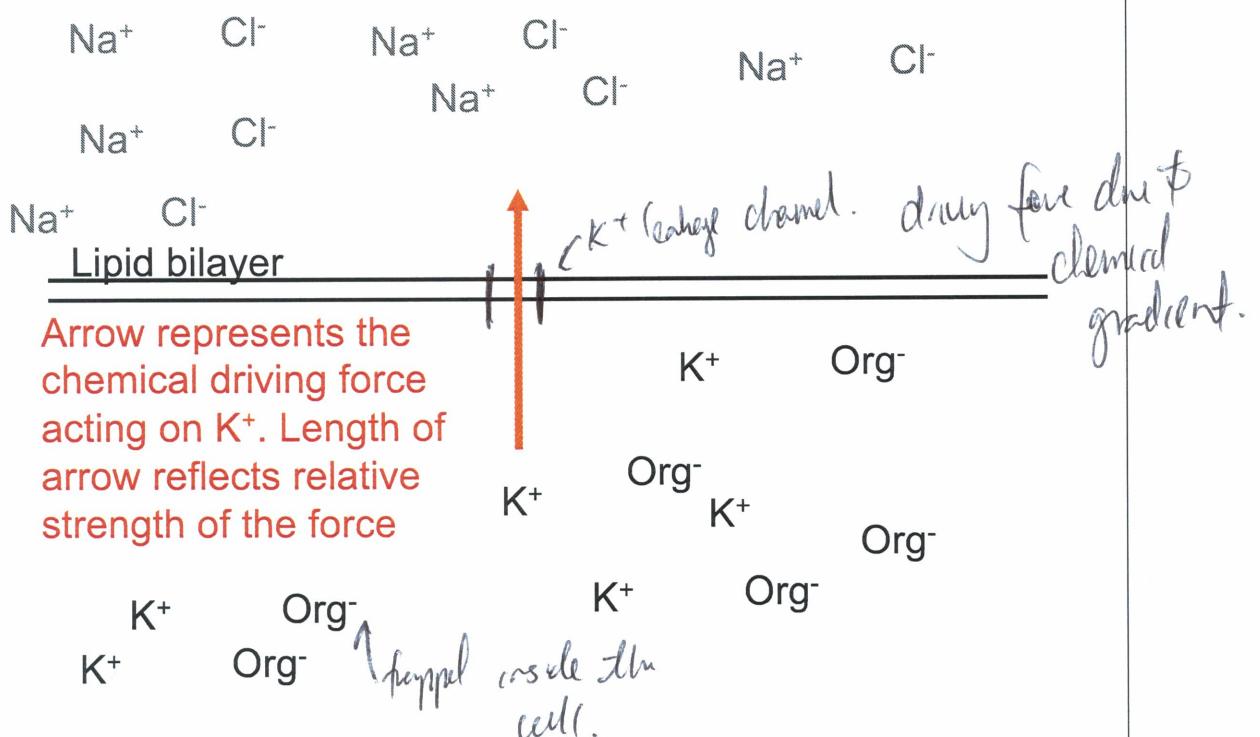
Electrical forces on ions

- Cations attracted to areas of net negative charge
- Anions attracted to areas of net positive charge
- In a resting (not signalling) neuron, the inside is more negative than outside. We say the membrane potential is negative or polarised. Resting membrane potential.

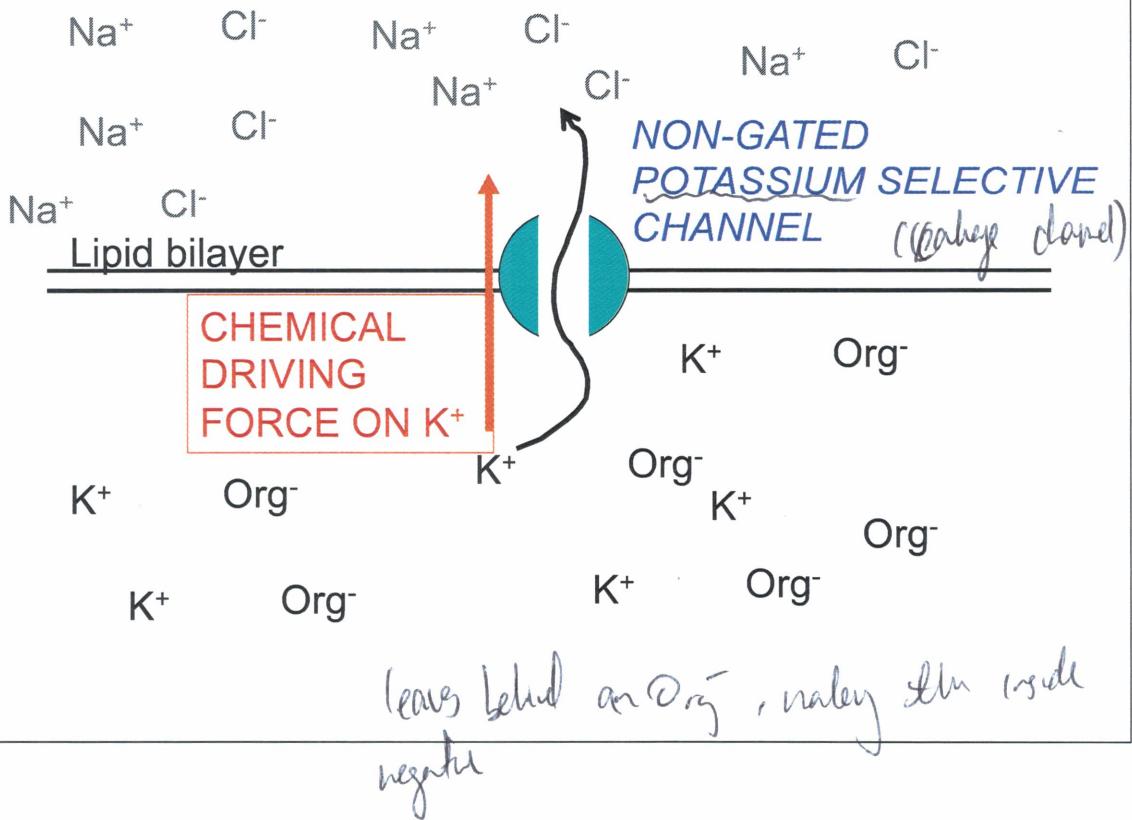
potassium and sodium both contribute to the resting membrane potential

- First we consider just the forces acting on potassium, as defined by the Nernst Potential for Potassium
- Then we consider just the forces acting on sodium, as defined by the Nernst Potential for Potassium
- Finally we need to think about the relative permeability of the membrane to potassium vs sodium and how this determines the resting membrane potential when both ions are moving across the membrane

Vector diagrams can help us to understand the forces Acting on ions across a membrane

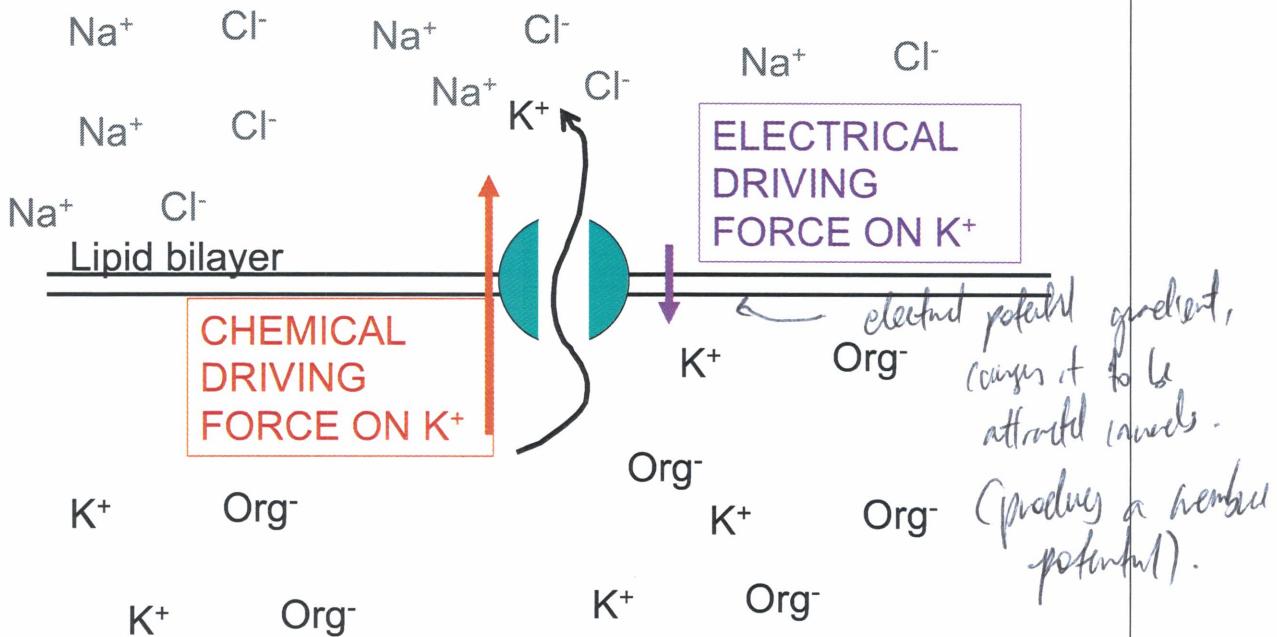


K^+ -selective channels make it possible for potassium to cross the membrane, driven by its chemical driving force



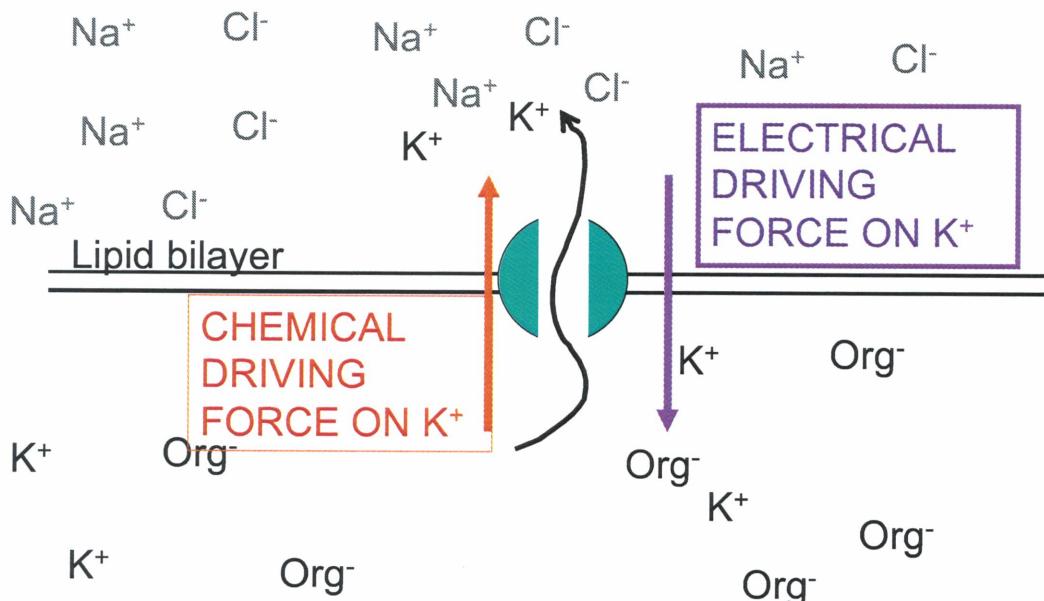
size of
concentration
gradient
affects chem
driving force.

Selective efflux of potassium ions creates an electrical potential difference and an opposing electrical driving force



EXCESS -VE CHARGE = MEMBRANE BECOMES POLARIZED

Ongoing diffusion of K^+ would eventually result in an equilibrium Potential being reached



**ELECTRICAL DRIVING FORCE = CHEMICAL DRIVING FORCE
= EQUILIBRIUM POTENTIAL / NERNST POTENTIAL**

more difficult, means the same in membrane physiology, so
 $F_{K^+}^{(chan)} = F_{K^+}^{(elec)}$ \Rightarrow Nernst potential.

Nernst/equilibrium Potential

T=temperature in Kelvin
R= the Gas Constant

$$E_K = \frac{RT}{ZF} \ln \frac{[K^+]_o}{[K^+]_i}$$

$\frac{T_K \propto T}{}$

concentrations
of K^+ on the
outside/inside

equilibrium potential
for K^+ ions.

\ln = natural logarithm (log to base e)

F = Faraday constant

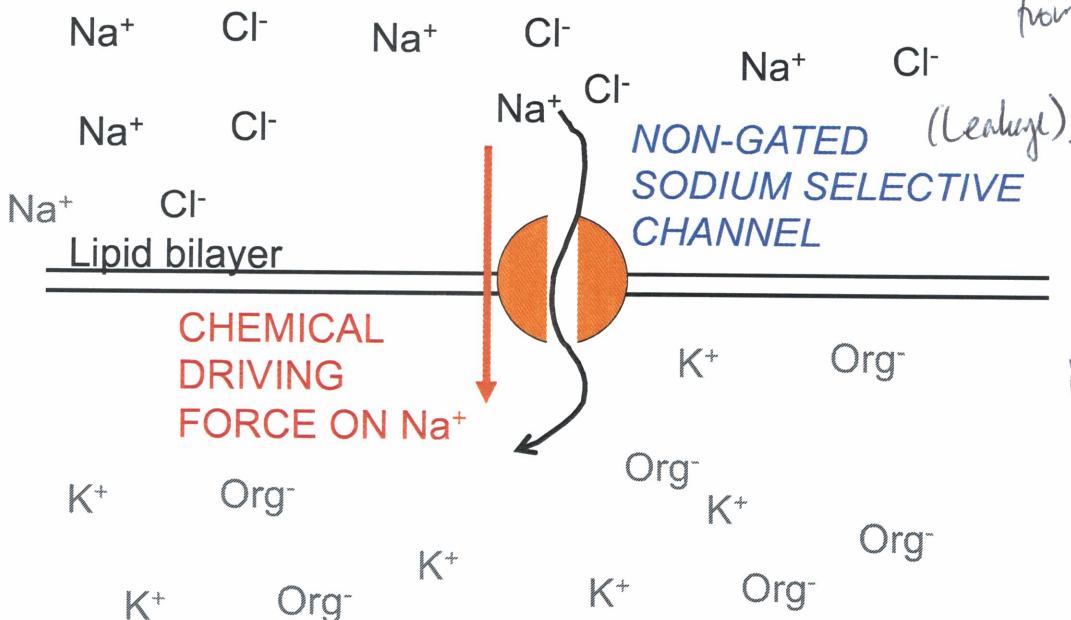
Z= valence of the ion

In a typical healthy neuron, the K^+ concentration gradient yields $E_K = -75mV$.

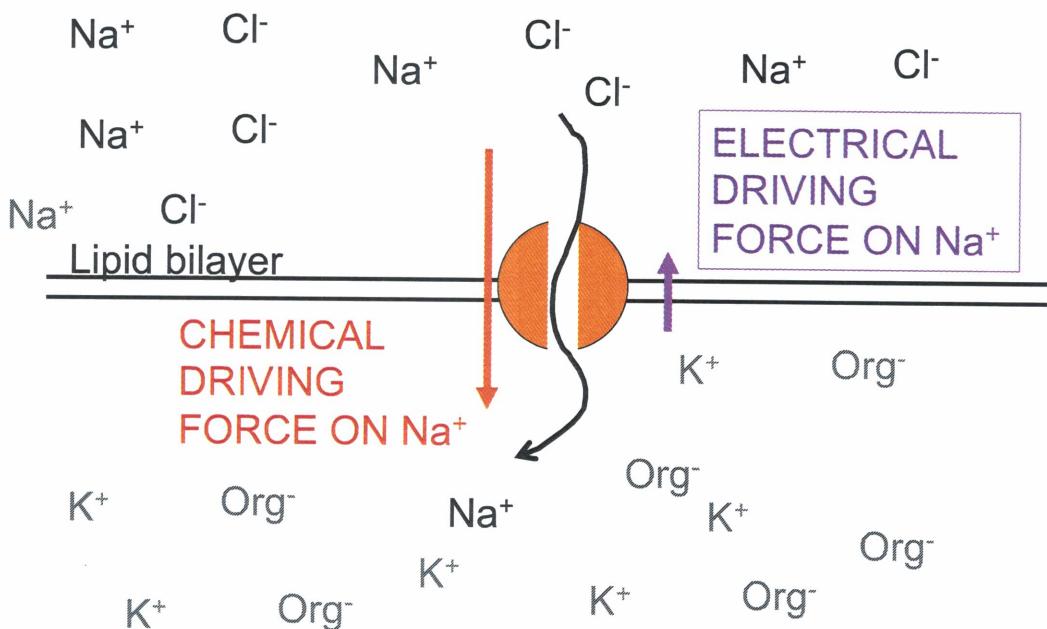
TAKES number potential to $-65mV$.

few Na^+ channels

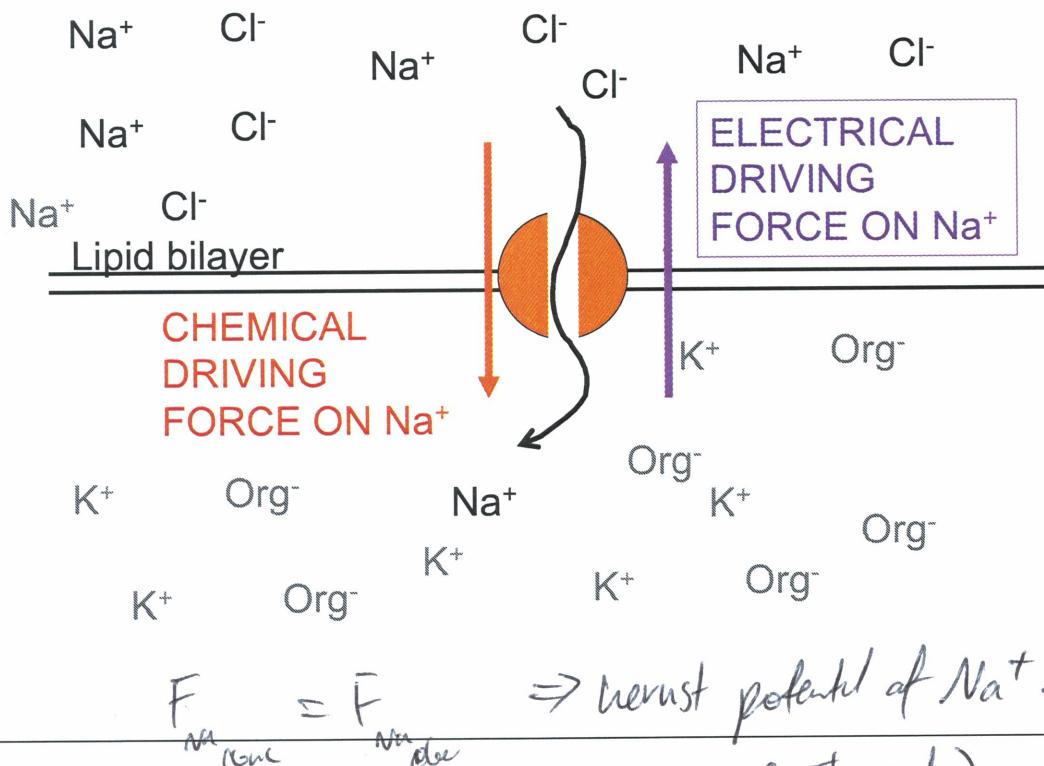
The chemical driving force on sodium ions is inward



→ prevent the membrane from becoming too negative.
↓ raise the membrane potential.



NERNST POTENTIAL FOR SODIUM



Nernst/equilibrium Potential

T=temperature in Kelvin

R= the Gas Constant

$$E_{\text{Na}} = \frac{RT}{ZF} \ln \frac{[\text{Na}^+]_o}{[\text{Na}^+]_i}$$

concentrations
of Na^+ on the
outside/inside

\ln = natural logarithm (log to base e)

F = Faraday constant

Z= valence of the ion =+1 for Na^+

In a typical healthy neuron, the Na^+ concentration gradient yields $E_{\text{Na}} = +55\text{mV}$.

the nernst potential.