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1 Animals and Environments

Introduction

- ▷ What is physiology?
 - Form and function of organisms; the study of how organisms work.
- ▷ Central questions of physiology: **mechanism** and **origin**.
 - Mechanism:
 - Refers to the **components** of living organisms and understanding **how** components interact to enable the organism to function.
 - Origin:
 - Asks why a mechanism exists, or **what** is the mechanistic **adaptive significance** of the mechanism.
 - Mechanism and adaptive significance are distinct concepts; knowing about one doesn't necessarily mean you know anything about the other.
- ▷ Krogh's principle:

"For such a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied."

 - This idea is central to disciplines that rely on the *comparative method*.
 - Other key concepts:
 - There is unity in diversity; many organisms are very much alike at the most fundamental levels.
 - The differences are subject to particular niches and often highly specialized that allow for biologist to study more complex systems.
 - The similarities allow us overcome technical limitations via animals that are easier to study.
- ▷ Physiology subdisciplines:
 - Mechanistic: emphasizes the mechanisms by which organisms perform their life functions.
 - Evolutionary: emphasizes evolutionary origins and the adaptive significance of traits.
 - Comparative: emphasizes the way in which diverse phylogenetic groups resemble and differ from each other.

- Environmental: emphasizes the ways in which physiology and ecology interact.
- Integrative: emphasizes the importance of all levels of organization, from genes to proteins and tissues to organs in order to better understand whole physiological systems.

Homeostasis

- ▷ Important ideas to remember:
 - Organisms are structurally dynamic; form stays relatively static while individual cells recycle frequently.
 - Most cells are exposed to the **internal** environment, not external.
 - Internal cells may vary or kept constant with the environment.
- ▷ Temperature regulation:
 - **Conformity**: organism's internal temperature **correlates** with external temperature in a particular range of temperatures.
 - **Regulation**: internal environment is held mostly **constant** using cellular mechanisms.
- ▷ **Homeostasis**: the coordinated physiological processes that maintain a relatively constant state in the organism.
 - **Positive feedback**: less common in homeostasis due difficulty in regulation; leads to runaway effect easily.
 - **Negative feedback**: more common in homeostasis due to self correcting nature.
 - **Effector**: executes the change in action that produces an effect, e.g. signals to increase temperature.
 - **Sensor**: sense changes in environment and sends information to the effector.

Physiology and Time

- ▷ Timeframes of physiological change:
 - **Acute**: short-term, reversible, and quick to adapt to changes in environment. Usually minutes to hours.
 - **Chronic**: long-term after prolonged exposure to new environments. Changes are usually reversible, but often slower.

- Chronic can be termed acclimation, or phenotypic plasticity/flexibility.
- Repetitive acute responses usually lead to chronic responses.
- **Evolutionary:** changes due to alteration in gene frequencies in **populations** exposed to new environments.
- ▷ Acclimation is **not the same** as adaption.
 - *Adaption* is an evolutionary trait present at high frequency in a population due to survival/reproductive advantages.
 - Not all traits are adaptations.
 - The amount of natural variation in a trait must be considered across populations, species etc.

2 Molecules and Cells in Animal Physiology

Cell Membrane Review

- ▷ Major cell membrane structures:
 - **Glycoproteins**: carbohydrate chain attached to a protein.
 - **Glycolipids**: similar to glycoproteins, but attached to lipid molecules.
 - *Glycocalyx*: combination of glycoproteins and glycolipids on the surface of cell.
 - **Integral proteins**: embedded in phospholipid bilayer.
 - **Peripheral proteins**: associated with one side of the bilayer.
- ▷ **Unsaturated phospholipid**: when hydrocarbon tails contain double bonds (less hydrogen).
 - Increase membrane fluidity due to extra space created.
- ▷ The fluidity of the cell membrane allows proteins to form complexes and dynamically change shape.

Enzyme Fundamentals

- ▷ **Enzymes**: a protein catalyst that plays two primary roles: **accelerating** and **regulating** chemical reactions.
- ▷ *Substrates*: the initial reactants of the reaction that an enzyme catalyzes.
- ▷ **Enzyme-substrate-complex (E-S)**: a combination of enzyme (E) with a molecule of substrate (S) that starts a reaction.
 - Usually stabilized by **non-covalent** bonds.
 - The substrate is converted to a product by first becoming an *enzyme-product complex (E-P)*, then dissociates to yield free product and free enzyme.
 - $E + S \rightleftharpoons E-S \rightleftharpoons E-P \rightleftharpoons E + P$
- ▷ **Saturation kinetics**:
 - **V_{max}**: the maximum velocity of a reaction and is determined by:
 - The **number** of active enzyme molecules present relative to substrate.
 - The catalytic **effectiveness** of each enzyme molecule.
 - These properties usually undergo heavy selection pressure.

- *Saturated*: all enzymes are occupied by a substrate molecule nearly all the time and now unable to increase reaction velocity.
- **Hyperbolic**: asymptotically approaches V_{\max}
 - Tends to happen when enzymes have just one substrate binding site.
 - Or when substrate sites behave independently
- **Sigmodal**: approaches V_{\max} with a sigmodal trajectory.
 - When multiple sites influence each other.
- **Turnover number (k_{cat})**: the **total effectiveness**, expressed as the number of substrate molecules converted to product per second by each enzyme molecule when saturated.
 - Depends partly on the *activation energy* of the enzyme-catalyzed reaction.
 - **Activation energy**: the energy required for the substrate to enter the *transition state*.
 - **Transition state**: the intermediate chemical state between substrate and product.
 - Enzymes **lower the activation energy** required to enter transition state.
- ▷ **Enzyme-substrate affinity**: The proclivity of the enzyme to form a complex with the substrate when they meet.
 - **Likely** complex formation results in **high-affinity**.
 - **Unlikely** complex formation results in **low-affinity**.
 - Affinity affects the shape of the reaction velocity.
 - **Higher** affinity produces a **steeper** velocity, and a **lower** affinity produces a more **linear** result.
 - Enzyme concentration is not changed.
 - **Half-saturation constant, K_m** : the substrate concentration required to attain one-half maximum reaction velocity.
 - K_m and enzyme-substrate affinity are **inversely related**.
 - i.e. **low-affinity** enzyme has a **greater K_m** .
- ▷ **Molecular Flexibility**:
 - **Conformation**: the three-dimensional shape of a protein.

- Stabilized mostly by **weak, noncovalent bonds**—hydrogen, van der Waals, hydrophobic, electrostatic, etc.
- Weak interactions allow for easy yet stable conformational changes.
- Enzyme molecules composed of two, three or four proteins are called *dimeric*, *trimeric*, or *tetrameric* respectively.
- ▷ Enzymes catalyze reversible reactions in both directions.
 - This is because they accelerate the approach towards equilibrium (principles of mass action).
- ▷ **Ligand**: any molecule that selectively binds by noncovalent bonds to structurally and complementary sites on a specific protein.
- ▷ **Cooperativity**: the interactions between multiple binding sites that may facilitate or inhibit the binding of other sites.
 - Can either **positive** or **negative**; **facilitating** or **inhibiting** binding on the same molecule.
 - **Homotropic cooperativity**: facilitation or inhibition of the **same ligand**.
 - **Heterotropic cooperativity**: influences on the binding of **other ligands**.
 - Interactions occur **at a distance**, resulting in delayed, or rippling responses.
 - **Allosteric modulation**: the modulation of the **catalytic properties**.
 - **Allosteric sites**: nonsubstrate-binding regulatory sites for **nonsubstrate ligands** that modulate the catalytic properties.
 - *Allosteric modulators*: the nonsubstrate ligands.
 - Allosteric **activation**: **increases** and **inhibition**: **impairs** affinity, thus the **catalytic activity**.
- ▷ **Isozymes**: enzymes that catalyze the same chemical reaction but differ in amino acid sequence.
- ▷ **Interspecific enzyme homologs**: different molecular forms of an enzyme coded by homologous gene loci in different species.
 - Isozymes and interspecific enzyme homologs often **differ** in their **catalytic** and **regulatory** properties.
 - Functional differences often prove to be adaptive in different environments.

3 Genomics

Genomics

- ▷ **Genomics:** study of the genomes—the full set of genetic material—of organisms.
- ▷ Methods of genomics:
 - Computational biology and bioinformatics use various computational methods to process large amount of genomic data.
 - **High-throughput:** methods of analyzing large data with out much human attention and mostly computation.
 - **Annotation:** laborious direct human interpretation.
- ▷ The **overarching goals** of genomics is to elucidate the **evolution** and the **current functioning** of genes and genomes.
- ▷ **Gene families:** genes that share distinctive DNA base sequences and *tend* to code for functionally similar proteins.
- ▷ **Postgenomic era:** the study of species after genome is sequenced.

Transcriptomics

- ▷ **Transcriptomics:** the study of which genes are transcribed to make mRNA and the rates at which they are transcribed.
 - aka transcription profiling.
 - Implies the study of great numbers of mRNAs.
- ▷ **Transcriptome:** a species full set set of mRNA molecules. It represents the full complement of genes being transcribed at any given time.
 - Time is emphasized; it's a snapshot transcription activity during the observed period.
 - Very useful in comparative methods.
- ▷ Methods of transcriptomics:
 - **DNA midroarrays:** aka gene chips; a high throughput method tht allows simultaneous analysis of large number of mRNAs.
 - **mRNA sequencing:** aka RNA-Seq; similar to microarrays, but can identify both known and **novel** transcripts.
 - More sensitive than microarrays.

- Readily applicable across wide range of species.
- **Gene manipulation:** studies that permit the direct assessment of gene function by directly altering its expression.
 - **Gene deletion:** aka gene knockout; breaking or disturbing function of an animal's gene to interfere with proteins, creating deficient or inferior phenotypic traits.
 - **Forced overexpression:** inverse of gene deletion; experimentally increasing synthesis of the mRNA.
 - **Compensation:** phenotypic alterations of that tend to make up for the manipulation done by forced expression or gene deletion.
 - **RNA interference (RNAi):** allows specific mRNA targets to be silenced in animals with *normal* genomes.
 - **Normal genomes:** wild type that is not artificially manipulated.
 - RNAi is reversible.
 - **CRISPR/Cas:** used to edit nuclear DNA in eukaryotic cells.
 - Can be used to insert sequences that then can be transcribed and translated, providing insights on protein function.

Proteomics

- ▷ **Proteomics:** the study of proteins being synthesized by cells and tissues.
 - Implies simultaneous study of large numbers of proteins.
 - Predicting proteins from gene transcription is still very difficult; transcription, translation, and post-translational processing are all regulated dynamically and independently.
- ▷ **Two-dimensional gel electrophoresis:** the primary proteomics method that separates complex mixtures of samples using two different protein properties.
 - Separated by **isoelectric points** and then **molecular weights**.

Metabolomics

- ▷ **Metabolomics:** study of organic compounds in the cells and tissues other than macromolecules coded by the genome.
 - **Metabolites:** compounds currently being processed by metabolism and the majority of metabolomics focus of study.

- e.g. sugars, amino acids, and fatty acids.
- ▷ **Nuclear magnetic resonance (NMR)**: primary method of metabolomics that is capable of detecting and quantifying a large variety of compounds through identification of unique signatures in the NMR spectrum.

4 Physiological Development

Epigenetics

- ▷ **Epigenetics:** modifications in gene expression with **no change in DNA sequence** that are transmitted when genes replicate.
- ▷ **Marked:** aka tagged; when DNA is modified in way to alter expression.

Mechanisms of Epigenetic Marking

- **DNA methylation:** addition of methyl groups to cytosine residues in DNA.
 - Generally represses or silences the gene.
 - **DNA methyltransferase 1 (DNMT1):** an enzyme acts to perpetuate the pattern of methylation in daughter cells.
 - **Methylome:** the set of all methylated sites.
- **Histone modification:** modified histones that can make DNA more or less accessible for transcription.
 - Can be modified by methylation, acetylation, phosphorylation, or other covalent bonding of chemical groups at specific sites.
 - Also has mechanisms for perpetuation, e.g. small RNA molecules play a role.
- ▷ **Epigenome:** the global summary of marks or a set of epigenetic marks in a cell.

Epigenetic Inheritance

- **Mitotic inheritance:** aka somatic; perpetuation of marks during the process of cell division by mitosis within an **individual**.
- **Meiotic inheritance:** aka transgenerational; perpetuation of marks during meiosis that results in passing of marks to **offspring**.
- ▷ Research is continuing to provide strong evidence that epigenetics can radically alter physiology.
- ▷ Epigenetic marking may also play large roles in lifelong effects due early-life and prenatal environments.

5 Transport of Solutes and Water

Passive Transport

- ▷ **Equilibrium:** the state at which a of minimum capacity to do work under locally prevailing conditions.
 - A change toward equilibrium is always in the direction of decreasing work potential.

Concentration gradients

- ▷ General definition: the difference in concentration between two solutions or regions.
- ▷ More accurately: $\frac{C_1 - C_2}{X}$ where X is the distance separating (boundary layer) the regions of concentration of solute particles, making it a colligative property.
- ▷ **Fick diffusion equation:** $J = D \frac{C_1 - C_2}{X}$
 - J is the net number of solute molecules passing into the low-concentration region from the high-concentration of solute particles, making it a colligative property.
 - **Diffusion coefficient (D):** proportionality factor determined by the permeability of the membrane or epithelium as well as the temperature.
- ▷ Each solute diffuses according to its own concentration of solute particles.
- ▷ **Simple diffusion:** aka diffusion; moves solute from an area of high solute concentration to an area of low solution concentration.
 - Does not use energy as it can only move material in the direction of the concentration gradient and towards equilibrium.

Electrical gradients

- ▷ **Electrical gradient:** difference in charge across a membrane.
- ▷ Many solutes bear electrical charge that affects the diffusion of such solutes.
- ▷ **Bulk solution:** solution not in contact with with a membrane.
 - Has a net charge of zero, this regions do not differe in charge.
 - Lack of net charge does not affect diffusion in the bulk solution, though does affect diffusion across the cell membranes of epithelia.
 - *Bulk flow:* physical kinetic movement of fluid, typically due to pressure.

- ▷ **Electrochemical gradient:** gradient consisting of the chemical gradient (concentration gradient) and the electrical gradient.

Biological Aspects of Diffusion

- ▷ **Ion channels:** integral membrane protein that permits the passive transport of inorganic ions by diffusion through the membrane.
 - Some can be selective for certain ions, such as Na^+ , Cl^- , and K^+
 - Even the least selective discriminate between **anions** and **cations**
 - **Gated channels:** ion channels that can open and close due to the proteins allowing for conformational changes.
 - **Voltage-gated:** responds to voltage change.
 - **Stretch-gated:** aka tension gated: responds to physical tensions.
 - **Phosphorylation-gated:** responds due to changes in protein phosphorylation.
 - **Ligan-gated:** responds due to extracellular signaling.
- ▷ **Permeability:** the ease at which the solute can move through the membrane by diffusion.
 - Changed by use and quantity of ion channels
- ▷ **Facilitated diffusion:** the process of spontaneous passive transport of molecules of ions across a biological membrane via transmembrane integral proteins.
 - Always occurs in the direction of electrochemical equilibrium.
 - Solutes are transported faster than they are in simple diffusion.
 - Solutes must bind reversibly with binding sites on transporter proteins.
 - Temperature dependence is substantially different due to presence of an activated binding event.

Active Transport

- ▷ **Active Transport:** the movement of molecules across a cell membrane that is **against** the concentration gradient.
- ▷ **Primary active transport:** uses protein pumps that normally use ATP.
 - Often transports metal ions such as Na^+ , K^+ , Mg^{2+} , and Ca^{2+}

- Most enzymes used are transmembrane ATPases, such as the sodium-potassium pump, which moves three Na^+ ions out of the cell for every two K^+ moved into the cell.
- ▷ **Secondary active transport:** uses potential energy derived through movement of ions (using transporter proteins and ATP) across the electrochemical gradient.
 - **Antiporter:** one substrate is transported across the membrane while the other is contransported in the opposite direction.
 - **Symporter:** two substrates are transported in the same direction across the membrane.
 - Na^+ , K^+ , or H^+ ions are usually the ones moving down the gradient and used to transport the desired ion up the relative gradient.

Diversity and Modulation of Channels and Transporters

- ▷ **Multiple molecular forms:** many forms of a channel and transporter proteins are common.
 - Different species have evolved different molecular forms, which can modulate function and efficiency.
 - Allows for opportunities for adaptation.
- ▷ **Modulation by gene expression:** common channels and transporters can be modulated throughout a lifetime via gene expression responses to environmental circumstances.
- ▷ **Noncovalent and covalent modulation:** both ligand (often noncovalent) binding and phosphorylation (covalent) allow for rapid regulation of channels and transporters.
- ▷ **Insertion-and-retrieval modulation:** the location of proteins in the membrane allow for another way of regulating activity.
 - Some proteins are held in reserve, and inserted into the membrane when necessary.
 - Inverse is also true, some proteins can be retrieved from the membrane in order to modulate usage.
 - Often only takes minutes for modulation to occur.

Colligative Properties of Aqueous Solutions

- ▷ **Colligative properties:** the properties of solutions that depend on the ratio between solute particles and solvent molecules.

- Not dependent on the nature of the chemical species present.
- Effects include: relative lowering of vapour pressure, elevation of boiling point, depression of freezing point, and *osmotic pressure*.
- ▷ **Vapour pressure:** the pressure of the vapour which is in equilibrium with that liquid.
 - Vapour pressure of a solvent is lowered when a non-volatile solute is dissolved in it to form a solution.
- ▷ **Boiling and freezing points:** additions of solute help stabilize the solvent in the liquid phase, lowering chemical potential, and thus a lower tendency to move to gas phase or solid.
 - **Freezing point depression:** lowering of freezing point of a solvent with the addition of a solute that is insoluble in the solid solvent.
 - **Boiling point elevation:** increased by the by the addition of a non-volatile solute.
 - Both are proportional to the lowering of vapour pressure in a dilute solution.

Osmosis

- ▷ **Osmosis:** the spontaneous net movement of solvent molecules through a selectively permeable membrane into a region of higher solute concentration.
 - Can be made to do work.
 - The primary means by which **water** is transported into and out of cells.
 - **Turgor:** the force and which the cell pushes the plasma membrane against the cell wall.
 - Turgor is largely maintained by osmosis across the cell membrane between the interior and its relatively hypotonic environment.
- ▷ **Osmotic pressure:** the external pressure required to be applied so that there is no net movement of a solvent across the membrane.
 - The semipermeable membrane allows the passage of solvent molecules but not the solute particles.
 - Also defined as the measure of tendency of a solution to take in pure solvent by osmosis. "Water wants to go where solutes are"
 - **Osmotic gradient:** the difference in pressure between the solution and the pure liquid solvent when the two are in equilibrium across a semipermeable membrane.

- Formula: $K \frac{\Pi_1 - \Pi_2}{X}$
- i.e., the **rate** at which water crosses the membrane by osmosis.
- Similar to the Fick equation for concentration gradient, except $\Pi_{1\&2}$ are the osmotic pressures of the solutions on each side of the membrane, and K is the osmotic permeability of the membrane + temperature.
- Proportional to the concentration of solute particles, making it a colligative property.
- **Isosmotic**: when two solutions have the same osmotic pressure.
- When solution $A < B$ in terms of osmotic pressure then:
 - A is **hyposmotic** to B — A has less solutes than B
 - B is **hyperosmotic** to A — B has more solutes than A.
 - The direction of net water movement by osmosis is from hyposmotic solution into the hyperosmotic one, i.e., $A \rightarrow B$
- ▷ Water is still capable of diffusing directly through lipid membranes.
- ▷ **Aquaporins**: water-channel proteins that greatly increase water transport.
 - Water transport through aquaporins is strictly passive.
- ▷ Nonpermeating solutes often create persistent osmotic-gradient components across semipermeable membranes.
 - Plays an important role in blood, as blood pressure forces water out, but proteins create persistent tendency to take up water; termed **colloid osmotic pressure** of the blood.
- ▷ Passive solute transport and osmosis interact.
 - **Solvent drag**: when solute moves with water crossing the membrane.
 - Tends to alter electrochemical gradients which plays a continuous role in rates of passive transport of both water and solutes.
- ▷ Active solute transport provides a means to control passive water transport.
 - Water transport is strictly passive, though control of solutes indirectly allows for metabolic water transport.

Osmoregulation

Excerpt from Chapter 27: Water and Salt in Physiology ⇨

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7 Nutrition, Feeding, and Digestion

