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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 celluar 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 memberane structures:
  - **Glycoproteins**: carbohydrate chain attached to a protein.
  - **Glycolipids**: similar to glycoproteins, but attached to lipid molecues.
  - *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**: whey hydrocarbon tails contain double bonds (less hydrogen).
  - Increase membrane fluidity due to extra space created.
- The fluidity of the cell membrane allows proteins to from 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 stabalized by non-covalent bonds.
  - The substrate is converted to a product by first becomeing 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**:
  - $\mathbf{V_{max}}$: the maximum velocity of a reaction and is determined by:
    - The number of active enzyme molecues 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 coverted 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.
  - Stabalized 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 our proteins are called *dimeric, trimeric*, or *tetrameric* respectively.

▷ Enzymes catalyze reversible reactions in both directions.

- This is because they accelrate 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 gen 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.
- Metods 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 disurbing 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 tranlasted, 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 metabolmics 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 of 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 that can make DNA more or less accessbile 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 extracelluar signaling.
- **Permeability**: the ease at which the solute can move through the membrane by diffusion.
  - Changed by use and quantity of ion channels
- **Faciliated 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 biding 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 differnet 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 solevent 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 mantained 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 thorugh 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 componenets across semipermable membranes.

- Plays a 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 mean 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 ↦

- **Osmoregulation**: the active regulation of the osmotic pressure of an organism's body fluids.
  - Detected by osmoreceptors, primarily found in the hypothalamus.
  - Acts to maintain homeostasis of the water content and electrolyte concentration.
- **Osmoconformers**: match their body osmolarity to their environment actively or passively.
  - Most marine invertebrates are osmoconformers.
- **Osmoregulators**: tightly regulate their body osmolarity through internal conditions.
  - More common in animals.
- **Volume conformity**: passive changes in body-fluid volume.
- **Volume regulation**: regulation of the total amount of water in a body fluid.
- There is also ionic regulation and conformity that are subject to ion-specific physiological controls.
- Influx of H_2O will tend to lower osmotic pressure, dilute ions, and increase volume.

7 Nutrition, Feeding, and Digestion

▷