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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 of CO₂ as the pyruvate molecules are processed..
 - *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 of CO₂ as the pyruvate molecules are processed. 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 microarrays:** 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 ⇨

- ▷ **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 H₂O will tend to lower osmotic pressure, dilute ions, and increase volume.

7 Nutrition, Feeding, and Digestion

Fundamentals of Animal Energetics

- ▷ **Energy metabolism:** the sum of the processes by which animals acquire energy, channel energy into useful functions, and dissipate energy.
 - Catabolic processes: breaking down of organic molecules to release energy.
 - Anabolic processes: use of energy to construct molecules.
- ▷ **Second law of thermodynamics:** the total entropy of an isolated system can never decrease over time.
 - **Isolate systems:** part of the material universe that does not exchange matter or energy with its surroundings.
 - Energy can be thought of both the capacity to do work, of the capacity to **increase order**.
 - **Thermodynamic equilibrium:** the state of maximum entropy; the state isolated systems spontaneously evolve towards.
- ▷ Animals require energy from the outside because energy is necessary to create and maintain their essential internal organization.

Forms of Energy

- **Chemical Energy:** energy liberated or required when atoms are rearranged into new configurations.
- **Electrical Energy:** energy that a system possesses by virtue of separation of electrical charges.
- **Mechanical Energy:** energy of organized motion in which many molecules move simultaneously in the same direction.
- **Molecular kinetic energy (heat):** energy of random atomic-molecular motion.
- ▷ **Physiological work:** any process carried out by an animal that increases order.
 - All forms of energy are capable of doing work, though not equally capable of doing physiological work.
 - Chemical energy can be used by animals, directly or indirectly, to do **all forms** of physiological work (totipotent).
 - Electrical and mechanical energy are both heavily used in animals, though cannot be used for everything.

- E.g., electrical energy used to set ions in motion and mechanical energy to pump blood, but neither can synthesis proteins.
- Animals **cannot use heat to do any form of physiological work.**
- ▷ **High-grade energy:** energy that can do physiological work; chemical, electrical, and mechanical.
- ▷ **Low-grade energy:** heat, which cannot do physiological work.
- ▷ **Degrade:** when the use energy to perform a function and downgrade it to form heat.
- ▷ Transformations of high-grade energy are **always inefficient.**
 - **Efficiency of energy transformation:** a ratio between output and input of high-grade energy.
 - Typically much less than a 1:1 ration.
 - ATP at most uses about 70% of the energy released from glucose into bonds of ATP.
 - Only a maximum of 25%-30% of energy is liberated and used for muscular motion.
- ▷ **Ingested chemical energy:** energy in the chemical bonds of food that animals use to do physiological work.
 - **Fecal chemical energy:** chemical-bond energy in compounds that are unable to be digested or absorbed.
 - **Absorbed energy:** portions of chemical-bonds that are able to assimilated and used

Major Functions of Physiological Work

- **Biosynthesis:** the process that synthesizes body constituents, such as proteins and lipids, by the use of absorbed energy.
 - Some absorbed energy remains in chemical form since products are often organic molecules themselves.
 - During growth, chemical energy accumulates in the form of biosynthesized products.
 - Also produces organic compounds that are exported from the body during ht animals life.
 - All steps are inefficient, thus Biosynthesis produces heat and products.
- **Maintenance:** all the processes that maintain the integrity of the animal's system.

- e.g., circulation, respiration, nervous coordination, gut motility, and tissue repair.
- Energy used for Maintenance is degraded entirely to heat within the body in majority of cases.
- **Internal work:** mechanical work that takes place inside an animal's body.
 - Many forms of maintenance, such as blood circulation and gut motility, are types of internal work.
- **External work:** application of mechanical forces on objects outside of an animal's body.
 - Much of absorbed chemical energy is used to fuel external work.
 - Some energy leaves the body as mechanical energy transmitted to the environment.
 - Energy of external work is stored if it is converted into increased potential energy of position.

Metabolic Rate

- ▷ **Metabolic rate:** the rate at which an animal consumes energy.
 - Heat is always the dominant component of the metabolic rate.
 - Knowing average metabolic rates of animals allows for calculations of chemical energy usage.
- ▷ calorie (cal): the amount of heat needed to raise the temperature of 1g of water by 1 °C.
 - kilocalorie (kcal): 1000 cal, often written as Calorie.
 - One calorie is equivalent to 4.186 J (joule).
 - Watts: joules/second.
 - Metabolic rates are often expressed as calories per unit of time or watts.

Principal Significance of Metabolic Rates

- The metabolic rate is one of the most important determinants of how much food it needs.
 - Adults' food needs depend almost entirely on metabolic rates.
- The total rate of heat production provides a quantitative measure of the total activity of all its physiological mechanisms.
 - Metabolic rate typically correlates with the intensity of living.
- Ecologically the metabolic rate measures the drain the animal places on the physiologically useful supplies of the ecosystem.

Calorimetry

- **Direct calorimeter:** a device that measures the rate at which heat leaves the animal's body.
 - Not all work energy is converted to heat; some energy converted to mechanical or potential energy can be measured inaccurately.
- **Indirect calorimetry:** measures of an animal's metabolic rate by means other than quantifying heat and work.
 - Indirect methods are often cheaper and easier.
- **Respirometry:** metabolic rate measured indirectly through respiratory gas exchange with the environment.
 - Rate of oxygen consumption provides a convenient and readily measured estimate of metabolic rate.
 - $C_6H_{12}O_6 + 6 O_2 \rightarrow 6 CO_2 + 6 H_2O + 2820 \text{ kJ/mol}$
 - Glucose + Oxygen \rightarrow Carbon Dioxide + Water + Energy
 - Oxidization of an unknown quantity of glucose, but with known measurements of O_2 used or CO_2 produced, then you can calculate exact heat produced.
 - Different food sources require different amounts of O_2 and produce different amounts of CO_2 during catabolism, which causes issues with identifying correct conversion factor
 - **Respiratory quotient (RQ):** the metabolic signature that reveals particular food sources being oxidized.
 - $$\frac{\text{moles of } CO_2 \text{ produced per unit of time}}{\text{moles of } O_2 \text{ consumed per unit of time}}$$
 - $RQ \approx 0.7 = \text{lipids.}$
 - $RQ \approx 0.83 = \text{proteins.}$

- $RQ \approx 1$ = carbohydrate.
- The most common approach used today is measuring rate of O_2 and accepting relatively small potential errors ($\pm 5\%$ - 8%).
 - External work does not have to be measured in most cases.
 - Excludes anaerobic metabolism of the gut microbiome.
 - Does not work well for measurement of metabolic rate during anaerobically fueled exercise.
- **Material Balance:** the measurement of the chemical-energy content of organic materials entering and leaving the animal's body.
 - Assumes that any energy that an animal ingests as chemical energy, but does not void as chemical energy, must be consumed.
 - If animal is currently gaining or losing biomass, then calculations will be off.
 - Animals can lose chemical energy in other ways than food, feces, or urine.
 - Best suited for **long term** measurements of average metabolic rates.

Factors of Metabolic Rates

- **Physical activity** and **temperature of the environment** are often the most influential factors.
- Other factors include: ingestion of food, age, gender, time, body size, reproductive condition, hormonal states, psychological stress, and salinity of ambient water.
- **Specific dynamic action (SDA):** the increase in the metabolic rate caused by ingestion of food.
 - Not the greatest factor, but almost always must be taken into account.
 - Under many circumstances, if an animal has not eaten for a while, then consumes food, then metabolic rates will rise despite all other factors kept constant.
 - The **magnitude** of SDA represents the total excess metabolic heat production induced by the meal.
 - Roughly proportional to the amount of food eaten.
 - Protein foods exhibit relatively much higher SDA than other macromolecules.

- **Diet-induced thermogenesis (DIT):** long-term increase in metabolic rate induced by persistent overeating.

Basal vs Standard Rates

- **Basal metabolic rate (BMR):** a standardized measure of metabolic rate that applies to **homeotherms**.
 - **Thermoneutral zone:** the range of environmental temperatures which the basal metabolic rate is minimal.
 - **Fasting:** when SDA effects of meal have ended.
 - Represents an animal that is in the thermoneutral zone, fasting, and resting.
- **Standard metabolic rate (SMR):** a standardized measure of metabolic rate that applies to **poikilotherms (ectotherms)**.
 - Represents metabolic rate of an animal is at rest and fasting.
 - A single animal may have many SMRs due to conformity of body temperatures.
- **Routine metabolic rate:** refer to metabolic rates of animals exhibiting regular, typically minimal, movements or behaviors.

Metabolic Scaling

- ▷ **Metabolic scaling:** the relation between metabolic rate and body size.
 - Energy needs of the species are not proportional to their respective body sizes.
 - Increases as a whole, but less significantly.
- ▷ **Weight-specific metabolic rate:** metabolic rate calculated per unit of body weight.
 - Decreases as weight increases, though it's not indirectly proportional.
- ▷ **Kleiber's law:** $M = aW^b$ ($B = B_o M^{3/4}$)
 - M (B): whole-body metabolic rates, unit of power—watts typically.
 - W (M): body weight, unit of mass—kg typically.
 - a (B_o): mass-independent-normalization constant, unit of power/unit of mass.
 - b ($3/4$): mean observed allometric scaling factor.
 - **Allometric equation:** when b is not equal to 1, meaning a lack of proportionality.

- Weight specific: $M/W = aW^{b-1}$
- Logarithmic: $\log M = \log a + b \log W$, useful for comparing a wide range of species in a linear representation.
- ▷ Resting heart rate varies in functionally similar way as weight-specific BMR.
 - Small species tend to have higher heart rate than large ones.
 - However, heart weight per unit of body weight shows little relation to body size.
- ▷ Physiologists are not in consensus for the explanation to why we see consistent observed allometric relations.
 - Runer's law is based on heat loss on animal, but it predicts a lower rate ($b = 2/3$) and does not account for poikilotherms.
 - Fractal geometry of scaled circulatory systems may give rise to more concrete answer.

8 Aerobic and Anaerobic Metabolism

Mechanisms of ATP Production

- ▷ **Burst exercise:** sudden intense exercise, generally leading to quick exhaustion.
- ▷ **Sustained exercise:** exercise that can be sustained at a steady rate for long periods of time.
- ▷ ATP is not transported from one cell to another.
 - Each cell must make its own ATP.
 - ATP is not stored by cells to any substantial extent.
- ▷ The rate at which a cell can do muscular work depends on the rate the cell can produce ATP at the given moment.
 - $\text{ADP} + \text{P}_i + \text{energy from foodstuff molecules} \rightarrow \text{ATP}$
 - $\text{ATP} \rightarrow \text{ADP} + \text{P}_i + \text{usable energy by cell processes}$
 - P_i : inorganic phosphate ions, HPO_4^{2-}
 - Energy-demanding processes are dependent on the cellular mechanisms that drive this equation and can only happen as fast as such mechanisms.

Aerobic Catabolism

- **Aerobic catabolic pathways:** pathways that use O_2 to completely oxidize foodstuff molecules to CO_2 and H_2O in order to capture released energy into ATP bonds.
- Subdivided into four major reactions:
 - Glycolysis (in cytoplasm)
 - Krebs cycle (in mitochondrial matrix)
 - Electron transport chain (inner mitochondrial membrane)
 - Oxidative Phosphorylation (inner mitochondrial membrane)
- **Glycolysis:** the series of enzymatically catalyzed reactions in which glucose (or glycogen) is converted to pyruvic acid.
 - Occurs in the cytosol and is an oxygen-independent metabolic pathway.
 - Each molecule of glucose is converted into 2 pyruvate ($\text{C}_3\text{H}_3\text{O}_3^-$) molecules.

- **NAD**: small non-protein molecule that undergoes reversible oxidation and reduction; synthesized from niacin.
- 2 NADs are reduced into 2 NADH_2 per molecule of glucose catabolized.
- 2 ATPs are used and 4 are formed from each glucose processed, providing net yield of 2 APT per glucose.
- **Krebs (citric acid) cycle**: when pyruvic acid is oxidized in the mitochondria by cyclic series of enzymatic reactions.
 - The 2 pyruvate molecules from glycolysis enter the mitochondria matrix by facilitated diffusion to start the cycle.
 - Each pyruvate is oxidatively decarboxylated, forming CO_2 and a two-carbon acetyl group that is combined with coenzyme A to form acetyl coenzyme A (acetyl-CoA).
 - Acetyl-CoA is the starting point for the citric acid cycle; can be obtained from oxidation of fatty acids too.
 - Overall outcomes:
 - 6 carbons of each glucose molecule catabolized emerge in the form of 6 molecules of CO_2 as the pyruvate molecules are processed.
 - 8 molecules of NADH_2 and 2 molecules of FADH_2 are produced for each glucose molecule. (4/1 per pyruvate)
 - 2 molecules of ATP are produced for each glucose catabolized.
 - $\text{C}_6\text{H}_{12}\text{O}_6 + 6 \text{O}_2 \longrightarrow 6 \text{CO}_2 + 6 \text{H}_2\text{O} + 2820 \text{ kJ/mol}$.
- O_2 is not a direct participant of glycolysis or the Krebs cycle, though it is essential.
 - NADH_2 and FADH_2 are intermediate electron acceptors, but cannot serve as the final resting places for electrons due to limited quantity in cell.
 - O_2 is required for the continuation of aerobic catabolism by acting as the final electron acceptor in the remaining steps, which generates the majority of ATP produced.
- **Electron Transport (respiratory) chain**: a series of complexes that transfer electrons via redox (reduction+oxidation) across a membrane that drives synthesis of ATP.
 - The chain takes electrons from NADH_2 (complex I) and FADH_2 (complex II) and passes them through redox reactions by the use of accompanying H^+ ions, via ubiquinone/cytochrome ($b - c_1$ and c).

- The electrons are passed along to cytochrome oxidase, which reduces the O_2 to H_2O , acting as the **final electron acceptor**.
- An adult human produces about 0.8 L of metabolic water per day in the process of voiding electrons from cells.
- Pumps **10 H^+** for **1 oxygen** (pair of electrons) reduced.
- **Oxidative phosphorylation:** the process of forming ATP from ADP via the energy released in the transport of electrons through the electron-transport chain.
 - **Chemiosmotic hypothesis:** the indirect two-step process that pumps protons across the inner mitochondrial membrane, creating an electrochemical gradient far from equilibrium.
 - The proton motive energy (back-diffusion) is used by ATP-synthase to generate ATP from ADP.
 - **P/O ratio:** ratio between phosphate and oxygen; defined as the number of ATP formed per atom of oxygen reduced to water.
 - Current estimates in mammalian mitochondria: 1 ATP : 4.3 H^+ .
 - Results in 2.3 ATP per oxygen, i.e., a **P/O ratio of 2.3**.
 - 2.3 represents the current maximum P/O ratio observed.
 - **Coupling:** the linkage of electron transport with oxidative phosphorylation.
 - Capable of being graded in its efficiency, ranging from 0 to 2.3.
 - Tightly coupled = P/O of 2.3
 - Uncoupled = P/O of 0.
 - **Uncoupling protein 1 (UCP1):** can use back-diffusion protons to generate much greater degree of heat rather than ATP.
- **Net yield of ATP from aerobic catabolism:**
 - **Substrate level phosphorylation:** phosphorylations that occur in glycolysis and the Krebs cycle:
 - Altogether, 6 ATP molecules are formed.
 - Together, the electron transport chain and oxidative phosphorylation produce per molecular of glucose:
 - 2.3 ATP/ $NADH_2$ and 1.4 ATP/ $FADH_2$
 - With a max of 25 ATP.
 - 31 total generated, with 2 used at start of glycolysis.
 - Actual **net yield: 29 ATP per glucose**.

- **Energetic efficiency:** assuming tight coupling, is estimated to be $\approx 60\%$ -70%.
 - I.e., 60%-70% of chemical energy released by oxidizing glucose to CO_2 and H_2O is captured into chemical-bond energy of ATP.

Anaerobic Catabolism

- **Redox balance:** the inability of the electron transport chain to regenerate NAD and FAD from NADH_2 and FADH_2 in the absence of O_2 .
 - Describes the cell's ability to remove electrons from a given compound as fast as electrons are added to it.
 - Without a balance, the cell will not be able to generate any ATP due to substrate level phosphorylation breakdown.
- Some tissues can produce ATP at a substantial rate without O_2 , however, the mammalian brain lacks such ability.
- **Anaerobic glycolysis:** the sequence of reactions that converts glucose to lactic acid.
 - **Lactate dehydrogenase (LDH):** the enzyme that catalyzes the reduction of pyruvic acid and produces lactic acid.
 - The rate limiter of anaerobic glycolysis.
 - Lactic acid is used as the final electron acceptor.
 - Only about 7% of free energy is released by the conversion of glucose to lactic acid; yielding vastly lower amounts of ATP compared to aerobic catabolism.
 - A cell must synthesize significant amounts of LDH for the intracellular process that must prevail during O_2 deprivation.
- Anaerobic glycolysis is not the only mechanism of anaerobic catabolism.
- When vertebrates use anaerobic glycolysis they must deal with the lactic acid once O_2 becomes available.
 - **Gluconeogenesis:** the conversion of lactic or pyruvic acid to glucose or glycogen; represents one path of lactic acid metabolism.
 - The second path is for the carbon chains to be fully oxidized by the way of Krebs cycle and electron-transport chain, which makes 27 (requires already functioning electron transport chain).
- Often tissues that generate lactic acid export it to tissues that are better supplied with O_2 .
- **Steady state:** a state at which a reaction can go on indefinitely, free of intrinsic limitations. In terms of ATP production:

- Can produce ATP as fast as it is used.
 - Uses raw materials (foodstuff molecules) no faster than they are replenished.
 - Chemical by-products (not ATP) are voided or destroyed as fast as they are made.
 - Does not cause other changes in cell function that progress to the point of disruption.
 - Nonsteady-state mechanisms violate one or more of the above, resulting in short lived processes.
- **Phosphagens:** Compounds that serve as temporary stores of high-energy phosphate bonds.
 - Occurs in skeletal muscles of vertebrates and muscles of many invertebrates.
 - Creatine phosphate is the phosphagen of vertebrate muscle, and some invertebrates.
 - Arginine phosphate is most common for invertebrates.
 - Synthesized by use of ATP to store energy, allowing for donate bonds back to ADP later.

Comparative Properties of the Mechanisms of ATP Production

▷

Themes in Exercise Physiology

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9 Thermal Biology

