

Module: physiology

Cours 1. Bioenergetics

Bioenergetics, also known as biochemical energetics, is the study of energy transformation in living cells. Energy is being transformed within cells, from one energy-rich compound to another (e.g. from ATP to ADP). Energy transformation is important because all living things require a continuous supply of energy to stay alive, grow and reproduce.

Thermodynamics is a branch of science that deals with the transformation of different forms of energy, and how the energy is utilized. **Laws of Thermodynamics:**

The first law of thermodynamics : Principle of energy conservation

states that energy can neither be created nor destroyed but can be transformed from one form to another

-Example: the hydrolysis of ATP (chemical energy) is necessary for muscular contraction (mechanical energy) transformation from one form of energy to another

The second law of thermodynamics : Increase in entropy

During energy production, the systems involved evolve from an ordered state to a less ordered state. The resulting disorder is called entropy (S): energy degrades as it transforms. For example, when cells perform their functions, they convert some of the energy into heat.

1. Components of total daily energy expenditure (TDEE):

1.1 Resting Energy Expenditure (REE): Basal or resting metabolic rate (BMR or RMR) is the amount of energy per minute the body uses to maintain a quiet resting state. This is approximately 60% of the energy used every day is needed to maintain the essential body functions that sustain life. These functions include nervous system activity, breathing, heart function, maintenance of body temperature (thermoregulation), and hormone activity.

1.2 Physical Activity Energy Expenditure (PAEE): Physical activity can be parsed into exercise and nonexercise activities. Exercise represents a physical activity that is planned, structured, and repetitive, aimed at maintaining or improving physical fitness. Nonexercise physical activity includes all remaining activities, such as activities in leisure, work, household, and transportation also unconscious activities (30% of TDEE).

1.3 Thermic Effect of Food (TEF): represent approximately **10%** of TDEE, TEF or DIT represents the energy used for the ingestion and digestion of food, along with the absorption, transport, and storage of nutrients

2. thermogenesis and thermolysis

In the absence of thermoneutrality, humans expend energy to maintain body temperature. Thermogenesis is the process of heat production in the human body, while thermolysis is the process of heat loss. Both are crucial for thermoregulation, the body's ability to maintain a stable internal temperature. Thermogenesis occurs through metabolic activity, muscle contractions, and the action of adipose tissue, which dissipates energy as heat. Thermolysis involves various methods of heat exchange, including radiation, convection, conduction, and evaporation (sweating).

3. Available methods for determination of energy expenditure

Direct calorimetry:

The direct determination of EE represents the measurement of heat exchange between body and environment. This method measures the sensible heat released by the body ($T^{\circ}_{\text{out}} - T^{\circ}_{\text{in}}$), as well as the water steam released through respiration and skin. It requires an isolation chamber, hermetically sealed, highly sophisticated and large enough to allow some degree of activity. Although it is considered a gold standard method, it is not widely used due to its high complexity and cost.

Indirect calorimetry :

Food calorimetry allows us to determine the number of calories per gram of food. In this activity, a piece of food is burned, and the released energy is used to heat a known quantity of water. The temperature change of the water is then used to determine the amount of energy in the food.

Theoretical value – biological value = energy losses (digestive losses (5% of energy intake), non-metabolizable waste mainly urea eliminated in the urine for proteins.

Respiratory calorimetry

- It requires the subject to be in a stable state and at rest for at least 15 to 30 minutes.
- It is based on the measurement of **the volume of oxygen consumed per unit of time in l/min by spirometry: $V \cdot O_2$** and on knowledge of the **thermal coefficient of oxygen kcal/l of O_2 : C**

The energy expenditure kcal/h or Q is: $Q = C \times V \cdot O_2$

Cours 2. Food ration

Dietary intake is the amount of food needed to ensure the metabolic function of a healthy individual. It must be quantitatively sufficient to meet energy expenditure and qualitatively balanced to ensure optimal intakes of essential amino acids and fatty acids, water, mineral salts, and vitamins.

1. Estimated Energy Requirement: The EER is an estimate of how many calories a person needs to consume, on average, each day to stay healthy, based on their age, sex, height, weight, and physical activity level.

Basal Metabolic Rate (BMR):

► **For Men:** $BMR = 66.5 + (13.75 \times \text{weight in kg}) + (5 \times \text{height in cm}) - (6.75 \times \text{age in years})$

► **For Women:** $BMR = 655.1 + (9.563 \times \text{weight in kg}) + (1.85 \times \text{height in cm}) - (4.676 \times \text{age in years})$

To calculate Total Daily Energy Expenditure (Cal/day), you multiply the BMR by an activity factor representing the individual's daily physical activity level **TDEE = BMR × DAL**

Physical activity level (DAL)	
Sedentary	1,2
Lightly active	1,37
Moderately active	1,55
active	1,72
Very active	1,9

2. Acceptable Macronutrient Distribution Ranges (AMDR) : The AMDR is the calculated range of how much energy from carbohydrate, fat, and protein is recommended for a healthy diet. The AMDRs are as follows: Carbohydrate 45-65%, 1 gram of carbohydrate contains 4 kcal of energy., Fat 20-35% One gram of fat contains 9 kcal of energy, and Protein 10-35% 1 gram of protein contains 4 kcal of energy. People who do not meet the AMDR may have increased risk of developing health complications

3. Nitrogen balance: Nitrogen balance can be described as a measure of the net change in total body protein. 1 gram of nitrogen represents 6.25 grams of protein.

► **Nitrogen Balance (g/day) = (Protein intake in g/day / 6.25) - (Urinary Urea Nitrogen in g/day + 4)**

the 4 accounts for nitrogen lost in other forms, such as fecal losses, sweat...

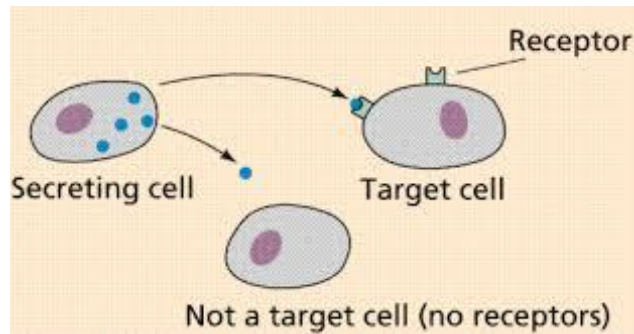
Normal, healthy adults are in neutral balance with a nitrogen balance that is equal to about + 0.5 g/d; During neutral nitrogen balance, whole body protein synthesis is equal to whole body protein degradation. If nitrogen balance is positive, the subject is in a net anabolic state, There is an increase in total body protein. This is the normal state in growth (including pregnancy), or recovery from injury or illness. whereas if the nitrogen balance is negative, the subject is in a net catabolic state. This is never normal, It is often a sign of nutritional risk or poor health, seen in conditions like trauma, infection, severe injury (such as burns), starvation...etc.

Carbohydrates are essential macronutrients that are the primary source of energy for humans. 1 gram of carbohydrate contains 4 kcal of energy. Carbohydrates are present in plant-based foods like grains, fruits, vegetables, and milk. Carbohydrates are ingested in the form of simple carbohydrates, like monosaccharides include glucose, fructose, and galactose and disaccharides lactose, sucrose, and maltose., or complex carbohydrates, like oligosaccharides raffinose and polysaccharides include greater than ten sugar units and consist of starches, glycogen, and fibers are plant polysaccharides like pectin and cellulose found in whole grains, fruits, vegetables, and legumes but are not digestible by humans. However, they play a major role in gut health and function which can be digested by microbiota in the large intestine. For healthy children and adults, carbohydrates should make up approximately 45 to 65% of energy. The recommended fiber intake is greater than 38 g for men and 25 g for women

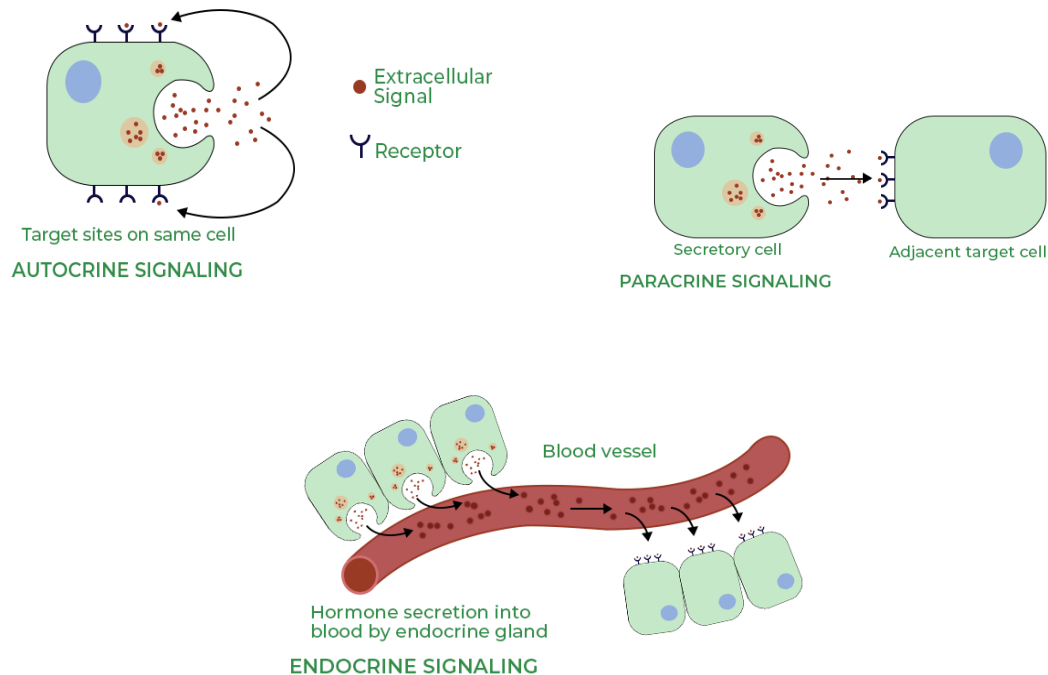
Lipids are essential macronutrients that are the main source of stored energy in the body, contribute to cellular structure and function, regulate temperature, and protect body organs. Lipids are found in fats, oils, meats, dairy, and plants. Consumed mostly in the form of triglycerides. One gram of fat contains 9 kcal of energy. For healthy children ages 1 to 3, ages 4 to 18, and adults, approximately 30 to 40%, 25 to 15%, and 20 to 35% of daily energy intake should come from fat, respectively. Approximately 5 to 10% and 0.6 to 1.2% of the daily fat energy intake should consist of omega 6 polyunsaturated fatty acids (linoleic acid) and omega 3 polyunsaturated fatty acids (α -linolenic acid), respectively.

Cours 3. Ligand-receptor Interaction

Intercellular communication is one of the characteristics of multicellular organisms, is done by the secretion of chemical signals or ligands released by secretory cell to target cell has ligand-specific receptors. Allows cell survival, proliferation, and/or differentiation. The absence of signals leads to cell death.



1. type of communication



2. ligand:

water-soluble: e.g. Neurotransmitters, Peptide hormones or Growth factors bind to cell surface receptors

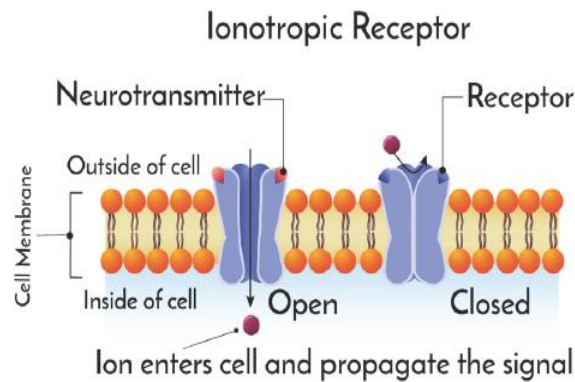
Fat-soluble: e.g. steroid hormone binds to intracellular receptors

3. Receptors

3.1 Surface receptors

3.1.1 Ionotropic receptor: These are polymeric receptors, generally pentameric, formed of 5 distinct protein subunits (α , β , γ , δ) which surround an ion channel, one or more of which have sites capable of binding the ligand, generally the α subunit.

The binding of a mediator molecule to its site causes a change in the conformation of the channel protein, and the opening of the ion channel and diffusion of ions across the membrane. Ionotropic receptors are involved in both excitatory and inhibitory synapses e.g. acetylcholine receptor channel.



3.1.2 G protein-coupled receptors (Metabotropic receptor)

G protein-coupled receptors (GPCRs) are integral membrane proteins containing an extracellular amino terminus, seven transmembrane α -helical domains, and an intracellular carboxy terminus; GPCRs were named for their common ability to associate with heterotrimeric G proteins ($G\alpha\beta\gamma$). The α subunit has a GDP/GTP binding site

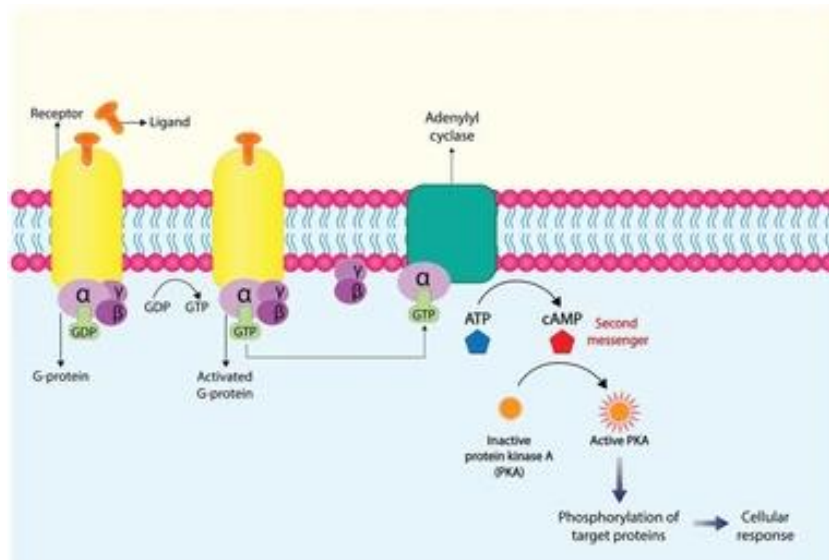
The binding of the ligand (first messenger) to its specific GPCR triggers a series of reactions:

- The receptor changes its three-dimensional conformation and activates the G protein;
 - when a GPCR is activated, it induces the α subunit to release GDP and instead binds to guanosine triphosphate (GTP).
 - The α subunit is activated by binding to GTP and detaches from the β,γ dimer of the G protein;
 - The α subunit GTP activates an effector (an ion channel or an enzyme)

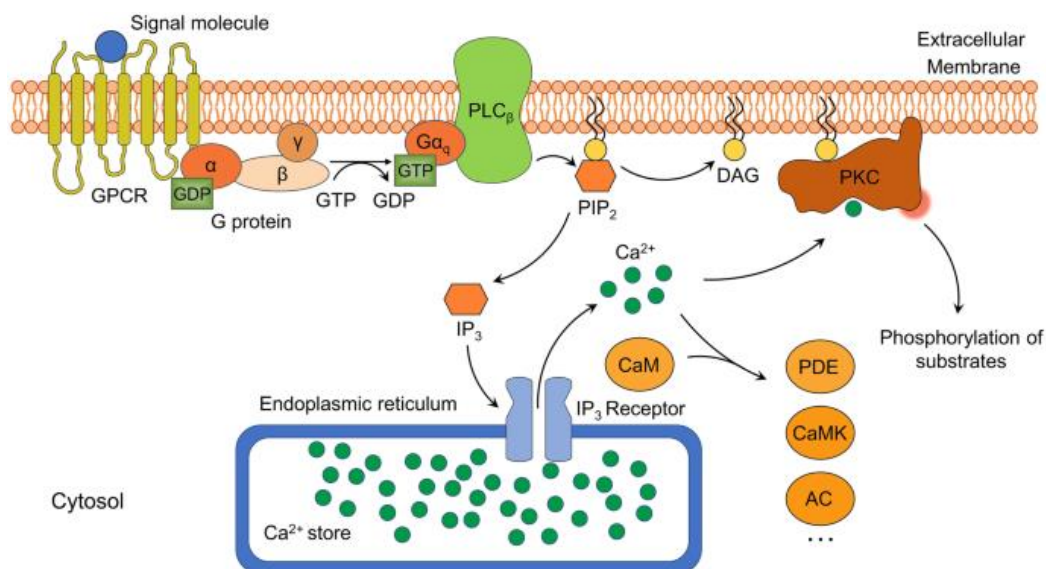
The α subunit of G protein has a GTPase activity, and once it hydrolyzes GTP to GDP, the α GDP molecule reassociates with the β - γ dimer and becomes inactive

In some cells, the G protein directly activates an ion channel, causing the passage of ions. In other cells, the activated G protein activates a membrane enzyme, such as adenylate cyclase (effector), which forms small molecules called cAMP (cyclic adenosine monophosphate), which act as a second messenger. The cAMP activates a second intracellular enzyme called protein kinase A (PKA), which amplified phosphorylation cascade leads to the regulation of gene expression or opening of the ion channel

in the case of the αi -GTP complex the result will be the inhibition of the formation of the second messenger



Many GPCRs elicit their physiological function by activating an inositol phospholipid signaling pathway via phospholipase C- β (effector) (PLC β). This particular pathway is mediated by a sub-class of GPCRs often coupled to a G protein α_q ($G\alpha_q$) that leads to the activation of PLC β . Activated PLC β can hydrolyze phosphoinositol bisphosphate (PIP₂) to form-diacylglycerol (DAG) and inositol trisphosphate (IP₃) (second messenger) While IP₃ is known to interact with the IP₃ receptors at the endoplasmic reticulum (ER) and results in intracellular calcium release, DAG is best known for its role in the activation of protein kinase C (PKC).



Enzyme receptors (tyrosine kinase receptors)

The receptor itself has an enzymatic activity. Its activation by the primary messenger this activity which is of the kinase or phosphatase type. Most of them are receptor tyrosine kinases(RTK), one of the best known being the insulin receptor

The insulin receptor is composed of two α subunits and two β subunits.

2 extracellular α subunits: These are involved in the binding and recognition of insulin. 2 transmembrane β subunits: These carry the catalytic activity generated by the hormone/receptor binding.

A disulfide bridge links each α unit to a β

This process begins when insulin binds to the receptor alpha subunit in the extracellular domain. The conformational change of the receptor, the monomeric units of receptors come together and dimerises. Dimerization activates tyrosine kinase in the intracellular domain of the receptor undergoes autophosphorylation (an -OH group carried by a tyrosyl residue becomes -O-P) and phosphorylation of the IRS (insulin receptor substrate) adjacent to the receptor (R-OH R-O-P) which transmit the hormonal message through a cascade of phosphorylation/dephosphorylation reactions that will cause the observed biological effects (formation of glucose transporters)

3.2 Intracellular receptors: Intracellular receptors, also known as nuclear receptors, regulate cellular functions by altering gene expression. These receptors are classified into 2 types type I intranuclear receptors and type II extranuclear receptors activated by lipophilic hormones such as: thyroid hormone, estrogen and progestin...

Type I intracellular receptors: In the inactive state, type I nuclear receptors are found in the cytoplasm and are usually bound to a chaperone protein. Following the binding of a ligand, the receptor undergoes a conformational change that releases the chaperone protein and allows the receptor to translocate to the nucleus. Once in the nucleus, the ligand-receptor complex binds to a specific DNA sequence and acts as a transcription factor to modulate the transcription of one or more genes. Type I intracellular receptors include the glucocorticoid, androgen, and progesterone receptors.

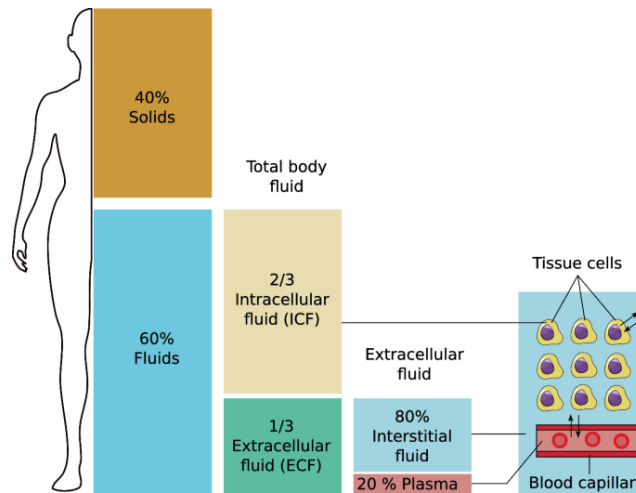
Type II intracellular receptors: Type II intracellular receptors are located in the nucleus regardless of ligand-binding status. In the inactive state, these receptors are bound to co-repressor proteins. The co-repressor proteins are released upon ligand binding, allowing the receptor to bind to DNA and modulate gene expression. Type II intracellular receptors include retinoic acid and thyroid hormone receptors

Cours 4. Liquid compartments

The human body contains two major fluid compartments:

The extracellular fluid compartment (ECF), which represents about **one-third** of total body water.

The intracellular fluid compartment (ICF), which represents about **two-thirds** of total body water; It includes all the water contained within the cells.



1. The extracellular fluid compartment

1.1 Blood: is a vital biological fluid that circulates continuously through the blood vessels and the heart, driven especially by the heart's pumping action. It consists of a liquid component, the plasma, and billions of cells mainly red blood cells, which give blood its characteristic color. Blood transports oxygen (O_2) and nutrients essential for the survival and functioning of all body tissues and carries waste products such as carbon dioxide (CO_2) and nitrogenous wastes to the organs responsible for their elimination (kidneys, lungs, liver, and intestines).

1.2 Lymph: is a clear, yellowish fluid that circulates through the lymphatic vessels and lymph nodes. It contains white blood cells, especially lymphocytes which play a major role in the immune response by producing antibodies to fight bacteria, viruses, and fungi. Lymph also transports antibodies that neutralize or destroy foreign substances (antigens) that enter the body, as well as nutrients throughout the organism.

1.3 Interstitial fluid: also called the interstitium, has an ionic composition similar to that of blood plasma. It fills the space between blood capillaries and cells, allowing the exchange of nutrients, gases, and waste products between them.

2. Measuring the volume of liquid compartments

The volume of a fluid compartment is measured **indirectly** by diluting a known quantity of tracer (= indicator = marker). Once the tracer reaches **equilibrium** meaning it has been distributed uniformly throughout the compartment being studied the volume can be calculated using the dilution formula:

$$\text{Volume} = \frac{\text{Amount of indicator}}{\text{Final concentration}}$$

The tracer must have certain properties:

- Homogeneous distribution within the compartment being studied
- It must not diffuse into other compartments
- It must not be metabolized or synthesized
- It must not be toxic
- Its measurement must be rapid.

3. The comparative ionic composition of ECF and ICF

Intracellular and extracellular fluids do not have the same composition. The intracellular fluid is rich in potassium (K^+) and phosphorus (mainly as phosphate ions, PO_4^{3-}), which are crucial for energy exchange. It is poor in sodium (Na^+), chloride (Cl^-) and calcium (Ca^{2+}). Because calcium tends to precipitate in the presence of phosphate, only a small amount of calcium is found in the cytosol; most of it is stored in organelles such as the mitochondria and endoplasmic reticulum. The unequal distribution of Na^+ and K^+ across the plasma membrane is maintained by the Na^+/K^+ -ATPase pump.

4. Comparative ionic composition of plasma and Interstitial fluid

The ionic composition of plasma and interstitial fluid is almost identical, except that plasma contains approximately 70 g/L of proteins compared to about 7 g/L (almost none) in interstitial fluid. Plasma also contains slightly more Na^+ and slightly less Cl^- and HCO_3^- . This distribution is due to the balance of Gibbs-Donnan

When two compartments are separated by a membrane semi permeable that allows small ions (Na^+ , K^+ , Cl^-) to pass but not large, charged molecules like proteins⁻, an unequal distribution of ions occurs. On the plasma side, negatively charged proteins that cannot cross the membrane attract positive ions and repel negative ones. This leads to a small difference in ion concentrations between plasma and interstitial fluid, a phenomenon known as the Gibbs–Donnan effect.

5. Exchanges between fluid compartments

5.1 Exchanges between plasma and interstitial fluid

5.1.1 Exchange by diffusion: This process is continuous and bidirectional. It allows the rapid and balanced exchange of blood gases and small molecules between plasma and interstitial fluid.

5.1.2 Exchange by filtration and reabsorption:

Oncotic pressure is the pressure in the blood plasma that is generated by plasma proteins, mainly albumin. These proteins are too large to cross capillary walls, so they attract water and help keep it inside the blood vessels. This process is known as reabsorption

Hydrostatic pressure is the pressure that blood or interstitial fluid exerts on the capillary walls.

Capillary hydrostatic pressure (P_c):

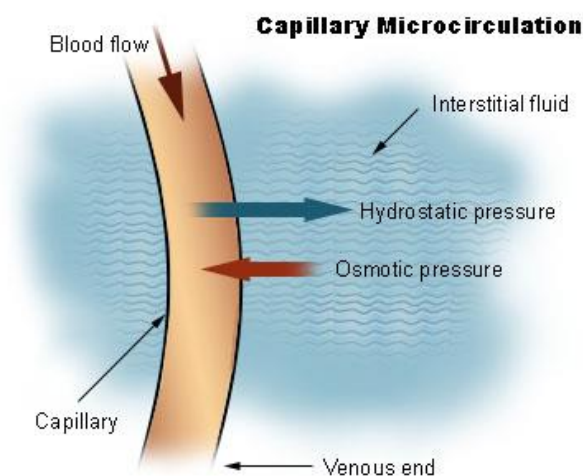
The pressure exerted by the blood inside the capillaries. It pushes water out of the capillaries into the interstitial space.

Interstitial hydrostatic pressure (P_i):

The pressure in the interstitial fluid surrounding the capillaries. Pushes fluid into the capillary

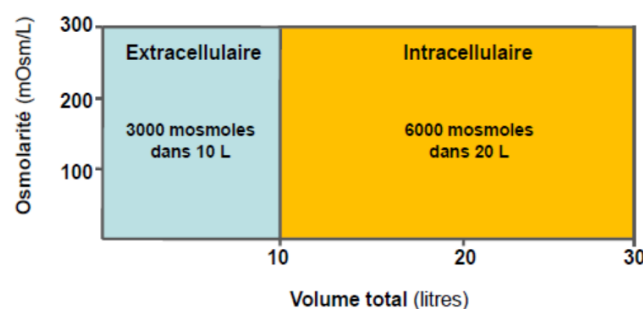
Capillary hydrostatic pressure is typically much higher than interstitial hydrostatic pressure, which causes a net movement of fluid from the capillaries into the tissues.

This process is known as filtration



5.2 Exchanges between the intracellular and extracellular compartments

The intracellular fluid volume is approximately twice that of the extracellular fluid volume.



Passive Transport by Diffusion

Ions move down their chemical or electrical gradients without energy expenditure.

Simple diffusion: occurs directly across the plasma membrane for blood gases (O_2 , CO_2) and some small lipid-soluble molecules.

Ion diffusion: takes place through selective ion channels that allow specific ions (e.g., Na^+ , K^+ , Cl^-) to pass.

Facilitated diffusion: uses membrane transporters (carriers or permeases) to move larger or polar molecules such as glucose down their concentration gradient.

Active Transport

Active transport moves substances against their concentration or electrical gradients and requires energy.

Primary active transport uses ATP directly, as in the Na^+/K^+ -ATPase pump, which maintains the ionic difference between the intracellular and extracellular environments.

Secondary active transport uses the energy stored in ionic gradients to drive the co-transport of other substances (e.g., glucose– Na^+ cotransport).

6. EDEMA

Edema is the abnormal accumulation of fluid in the interstitial spaces. It occurs when filtration exceeds reabsorption across capillary walls, disturbing the balance between hydrostatic and oncotic pressures.

Edema due to decreased plasma oncotic pressure (liver disease) :

Most plasma proteins, especially albumin, are synthesized in the liver. In alcoholic cirrhosis or severe liver disease, protein synthesis decreases, leading to a reduction in plasma oncotic pressure. As a result, more fluid leaves the capillaries than is reabsorbed, causing water accumulation in the interstitial space, and hence edema.

Edema due to decreased plasma oncotic pressure (malnutrition)

In cases of severe malnutrition (e.g., kwashiorkor), the diet lacks essential amino acids required for plasma protein synthesis. This leads to hypoproteinemia (low serum protein), decreased oncotic pressure, and generalized edema.

Edema due to kidney damage

In nephrotic syndrome or glomerular damage, the kidneys lose large amounts of albumin in the urine (proteinuria). Although protein synthesis is normal, the loss of plasma proteins causes a drop in oncotic pressure, leading to edema, often first visible in the face or around the eyes.

Edema due to lymphatic obstruction

Normally, the lymphatic system drains excess interstitial fluid. If the lymphatic vessels are obstructed, fluid accumulates locally, causing lymphedema. A classic example is elephantiasis, common in intertropical regions, caused by parasitic filarial worms transmitted by mosquito bites. The lymphatic blockage leads to massive swelling of affected limbs or genitals.

Cours 5. Electrophysiology

All cells have an intracellular chemical composition that differs from the extracellular environment, creating a potential difference across the membrane. In most cells (non-excitabile cells), this transmembrane potential difference remains relatively stable. However, in excitable cells (such as nerve and muscle cells), this potential can change rapidly, shifting from a resting state (resting potential) to an active state characterized by an action potential (AP), before quickly returning to its equilibrium state..

1. The resting potential (RP) corresponds to a potential difference (PD) or voltage difference, expressed in millivolts (mV), across the cell membrane. The RP establishes an electrical polarity in which the extracellular environment is positive (+) and the intracellular environment is negative (-). The RP results from the unequal distribution of ions on either side of the cell membrane, particularly Na^+ and K^+ . This distribution is maintained by the semi-permeable nature of the membrane, which allows limited diffusion of K^+ and Na^+ through leak channels. The activity of the Na^+/K^+ ATPase pump also helps preserve this imbalance by counteracting the passive diffusion of Na^+ and K^+ .

The measurement of the resting potential is performed using the intracellular **microelectrode technique**. The objective is to record the potential difference that exists across the plasma membrane ; therefore, it is necessary to measure and compare the intracellular potential with the extracellular potential.

To measure the resting membrane potential of a cell, the two terminals of a voltmeter are connected: one to a reference electrode and the other to a micropipette. The tip of the micropipette is brought close to the cell surface, and the reference electrode is placed in the extracellular solution. The signal is amplified and transmitted to an oscilloscope. At this stage, the voltmeter shows no potential difference (0 mV), then the tip of the micropipette penetrates the cell, the voltmeter displays the potential difference between the intracellular and extracellular environments. The measured value corresponds to the resting potential (e.g., -75 mV), meaning that the intracellular potential is 75 mV lower than the extracellular potential.

The resting potential varies depending on the cell type:

- Smooth muscle cells: -60 to -40 mV
- Skeletal muscle cells: -90 mV
- Cardiac cells: -80 mV

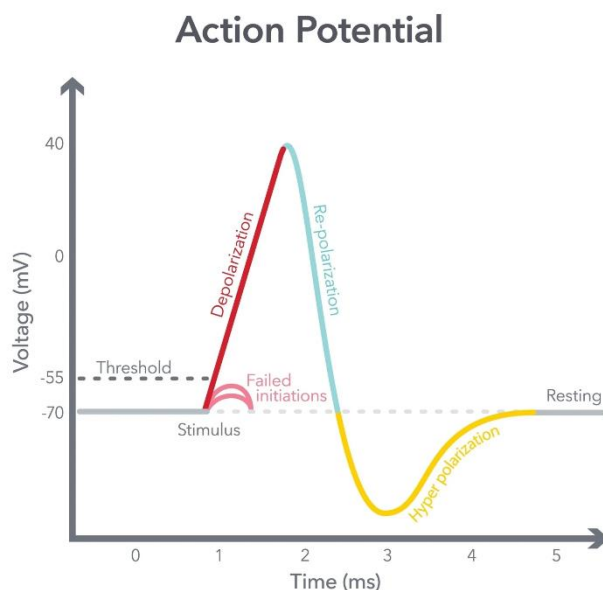
2. Action potential : The basic unit of information transmission at the neuronal level is a brief electrical impulse that travels along the axon, called an action potential. This is a temporary reversal of the membrane potential, generated by the opening and closing of various voltage-gated ion channels.

This potential, which corresponds to a temporary change in membrane polarity, consists of three phases:

Depolarization: Extremely brief, lasting only a fraction of a millisecond, it results from an increase in sodium (Na^+) permeability, allowing an influx of positive charges. Consequently, the membrane potential becomes less negative, typically changing from about -60 mV to $+40 \text{ mV}$.

Repolarization: Slightly slower, this phase allows the membrane potential to return toward its resting level. It corresponds to the closure of sodium channels and the opening of potassium channels.

Hyperpolarization: Even slower (lasting several milliseconds) and of low amplitude, this phase corresponds to an excessive efflux of potassium during repolarization, making the membrane potential more negative than the resting potential.



The time between hyperpolarization and the resting state:

potassium channels are not immediately inactivated when the fiber returns to its resting potential, potassium ions continue to leave the cell, causing a slight hyperpolarization until potassium permeability returns to its resting value K^+ (channels will close progressively). At the same time, the Na^+/K^+ pump becomes active and expels the sodium ions that entered during the depolarization phase.

Imposed potential:

Two microelectrodes are implanted in a cell. One is used to measure the membrane potential relative to a third, indifferent electrode placed in the extracellular environment. The other intracellular electrode is used to inject an electric current.

If an electric current is passed through the cell, adding positive charges, the membrane potential becomes less negative (depolarization). Conversely, if the electric current flows in the opposite direction, the membrane potential becomes more negative (hyperpolarization)

Patch Clamp:

This technique allows the study of ion channel function at the single-channel level. A patch of membrane is isolated inside a glass micropipette with a tip diameter of approximately 1 μm . Using appropriate electronic equipment, a controlled potential is applied to the membrane patch, and the resulting ionic currents flowing through the isolated channel(s) are recorded.

Ion channel inhibitor method:

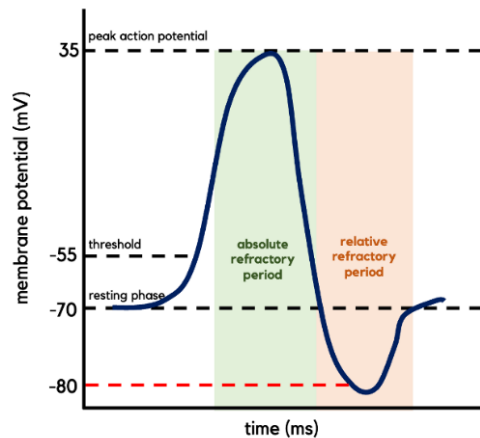
Adding tetrodotoxin (TTX) to the preparation prevents an action potential from occurring. TTX has the unique property of blocking sodium channels, thereby preventing depolarization.

Conversely, adding tetraethylammonium (TEA) to the preparation causes repolarization to occur much later once the fiber has depolarized. This is because TEA blocks potassium channels, so the fiber must wait until the sodium channels are completely inactivated and the Na^+/K^+ pump restores the initial ionic concentrations before repolarization can take place.

Excitability and conductivity are two inseparable properties of the neuron. The former allows it to generate an action potential following a suprathreshold stimulation, and the latter allows it to propagate. However, at the moment the action potential is generated, the fiber is depolarized, making it impossible to depolarize it again. It is therefore necessary to wait until the membrane potential returns to a value below the critical threshold before the neuron can be excited again. This leads us to distinguish two periods that characterize its excitability:

An absolute refractory period (ARP) during which any stimulation, even suprathreshold, is ineffective because the fiber is already depolarized.

- **A relative refractory period (RRP)** during which a second action potential can be generated, provided that the depolarization produced by the stimulus reaches the critical threshold. This requires a stronger stimulus, as the resting potential has not yet been fully restored.



Continuous Conduction: It refers to the non-myelinated conduction, where the flow of nerve-impulse is slower (0.1 m/s). It occurs in unmyelinated axons, where the ions flow throughout the axon segment via voltage-gated channels.

Saltatory Conduction: It refers to the myelinated conduction, where the action potential plunges much faster (100 m/s) from one node to another. It occurs in myelinated axons, where the flow of ions is discontinuous because of the uneven distribution of voltage-gated channels

3. synaptic transmission:

Synapses are specialized areas of contact between neurons, between sensory cells and neurons, or between neurons and effector cells. Synapses mediate communication between cells. Synaptic transmission refers to the process in which a chemical signal is released from one neuron and diffuses to other neurons or target cells, generating a signal that excites, inhibits, or modulates cellular activity.

A synapse has a tripartite structure consisting of a presynaptic compartment, synaptic cleft, and postsynaptic compartment. The presynaptic terminal contains vesicles filled with neurotransmitters, which are released into the synaptic cleft, a tiny gap between the two neurons. The neurotransmitters then diffuse across the cleft to bind to receptors on the postsynaptic membrane, transmitting the signal.

4. synaptic transmission at Neuromuscular Junction

Motor end plate, or neuromuscular junction, is defined as the specialized attachment site where a motor nerve fiber connects to the skeletal muscle fiber, characterized by unmyelinated axon terminals that release the neurotransmitter acetylcholine into synaptic clefts.

Action Potential Propagation to the Nerve Terminal: An action potential travels down the motor neuron and reaches the nerve terminal. The voltage change causes the voltage-gated calcium channels in the nerve terminal membrane to open.

Calcium Influx and Vesicle Fusion: Calcium enters the nerve terminal, causing interaction between synaptic vesicles with the presynaptic membrane via SNARE proteins and releasing acetylcholine into the synaptic cleft by exocytosis.

Acetylcholine Binding to Receptors: ACh then diffuses across the synaptic cleft and binds to the nAChRs located on the motor end plate of the muscle fiber. ACh binding opens the receptor channels, allowing sodium ions to enter the muscle cell, thus depolarizing the membrane.

Generation of Endplate Potential: The influx of sodium ions depolarizes the postsynaptic membrane, shifting the potential from -90 mV to -40 mV and creating a local depolarization known as the endplate potential (EPP). A single EPP is sufficient to reach the threshold and generate an action potential that propagates along the muscle fiber

Muscle Contraction: The action potential travels deep into the muscle fiber through the transverse tubules (T-tubules), which are invaginations of the sarcolemma. The dihydropyridine (DHP) receptor, located in the T-tubule membrane, detects the depolarization of the sarcolemma, producing a conformational change in the DHP receptor. The DHP receptor is mechanically coupled to the ryanodine receptor located on the sarcoplasmic reticulum membrane. The conformational change in the DHP receptor triggers the opening of the ryanodine receptor, allowing calcium ions to be released from the sarcoplasmic reticulum into the muscle cell's cytoplasm. The released calcium causes muscle contraction.

excitatory and inhibitory postsynaptic potential

An excitatory postsynaptic potential (EPSP) is the change in membrane voltage of a postsynaptic cell following the influx of positively charged ions into a cell (typically Na^+) because of the activation of ligand-sensitive channels. This results in a depolarization of the postsynaptic cell, thus increasing the likelihood of action potential propagation. These excitatory synapses serve to increase excitability in neurones. Conversely, inhibitory postsynaptic potentials (IPSP) result from the influx of negative ions (e.g., Cl^-) into, or the efflux of positive ions (e.g., K^+), out of the postsynaptic cell. This results in cell hyperpolarization and thus decreases the likelihood of action potential propagation, and therefore represent inhibitory synapses.

Depolarization or Hyperpolarization of postsynaptic membrane.

Localized: EPSPs and IPSPs occur at the postsynaptic membrane, usually on dendrites or the soma (the depolarization or hyperpolarization is not generated everywhere, only in the small region of membrane where the ligand-gated channels open)

Passive decay: EPSPs and IPSPs are electrotonic potentials that decay over both time and distance. The further a synapse is from the cell body, the smaller the EPSP/ IPSPs will be at the axon hillock

Duration : depends on the type of receptor for example: AMPA receptors (Ionotropic) for glutamate lasts only a few milliseconds which produce fast synaptic transmission. However metabotropic glutamate receptors, open channels indirectly last hundreds of milliseconds to seconds which produce slow synaptic transmission.

Graded potentials are changes in the electrical charge across a neuron's membrane that vary in size, rather than being all-or-none events (for EPSP), depends on the amount of neurotransmitter released and the number of channels that open.

Summation : the process by which a postsynaptic neuron integrates several EPSPs in a temporal or spatial manner to reach the threshold of an action potential. The EPSP signal is propagated down the dendrite and is summed with other inputs at the axon hillock.

Temporal Summation: occurs when a single synapse releases neurotransmitter several times in rapid succession. Each EPSP adds to the next before the previous one has fully dissipated. If these successive depolarizations accumulate sufficiently, they can bring the membrane potential to threshold and trigger an action potential.

Spatial summation: occurs when stimuli are applied at the same time, but in different areas (different synapses on the same neuron) , with a cumulative effect upon membrane potential.

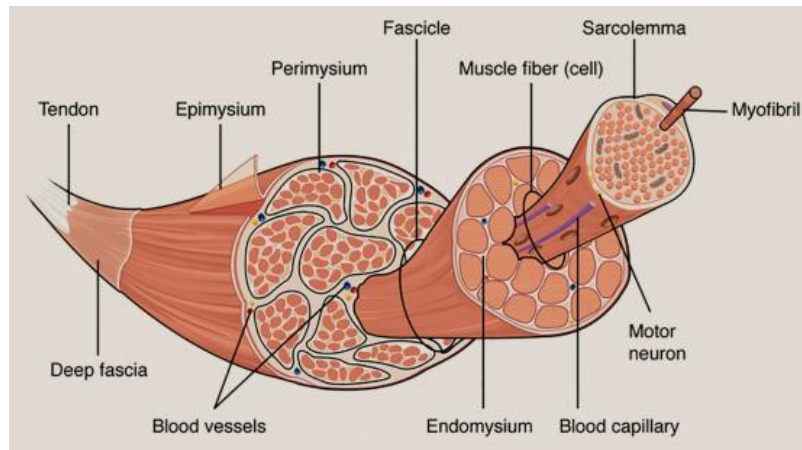
Cancellation : occurs when EPSP and IPSP reach the postsynaptic neuron at the same time. EPSPs depolarize the membrane, while IPSPs hyperpolarize it. As a result, an IPSP can partially or completely cancel the depolarizing effect of an EPSP, preventing the membrane from reaching the threshold and stopping the generation of an action potential.

Cours 6. skeletal muscle

Skeletal muscle is found throughout the body and functions to contract in response to a stimulus. Skeletal muscle serves many purposes, including producing movement, sustaining body posture and position, maintaining body temperature, storing nutrients, and stabilizing joints. In contrast to smooth and cardiac muscle contraction, most skeletal muscle contraction is under voluntary control, receiving neural inputs allowing conscious control of muscles. Skeletal striated muscle is the most abundant type (over 400 distinct muscles), represents approximately 40% of the human body weight and contains 50 to 75% of all body proteins

1. Macroscopic anatomy of a skeletal muscle

skeletal muscle fibers are made up of endomysium, perimysium, and epimysium, covering the sarcolemma; each muscle fiber is a layer of connective tissue called the endomysium. Capillaries and nerve tissue are present within the endomysium to supply the individual muscle fibers. Multiple muscle fibers join to form fascicles encased by another connective tissue covering known as the perimysium. The perimysium may surround anywhere from 10 to 100 fascicles. Muscle fascicles are further grouped to form a muscle encased by a fibrous tissue envelope called the epimysium.



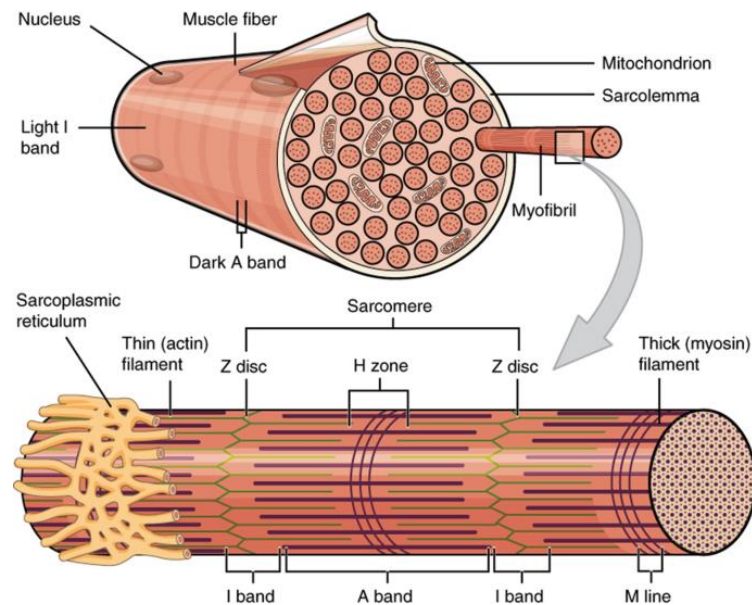
2. Microscopic anatomy of a skeletal muscle

Skeletal muscle is a highly organized tissue composed of bundles of muscle fibers called myofibers which are striated, multinucleated cells ranging from 10 to 100 micrometers in diameter and many centimeters long. The oval nuclei are located in the cell's periphery, adjacent to the sarcolemma

The sarcolemma is a tubular sheath that encases and defines each muscle fiber, forming a barrier between extracellular and intracellular compartments. The sarcolemma is comprised of a plasma membrane and a polysaccharide coating . Invaginations within the sarcolemma are termed transverse tubules (T tubules), which function as a major location for ion exchange.

The sarcoplasm of a muscle fiber is comparable to the cytoplasm of other cells, but it contains significant reserves of glycogen as well as myoglobin, a protein (red pigment) that constitutes an oxygen reservoir inside the muscle cell and does not exist in any other type of cell. Muscle cells contain the usual organelles as well as highly modified organelles, namely the myofibrils and the sarcoplasmic reticulum.

Each muscle fiber is composed of several hundred to several thousand myofibrils. Myofibrils are composed of actin (thin filaments), myosin (thick filaments), and support proteins. The arrangement of actin and myosin gives skeletal muscle its microscopic striated appearance and creates functional units called sarcomeres. When viewed under electron microscopy, sarcomeres are arranged longitudinally and include the M line, Z disk, H band, A band, and I band.



The Z line, or Z disk, is the terminal boundary of the sarcomere, where alpha-actinin acts as an anchor for the actin filaments. The M line is the central-most line of the sarcomere, where myosin filaments are anchored together through binding sites within the myosin filament. The H band contains the M line and is the central region of the sarcomere that contains only myosin filaments. The A band is a larger portion of the sarcomere that contains the entirety of the myosin fibers and includes regions of actin and myosin overlap. The I band covers the terminal regions of two adjacent sarcomeres and contains only actin filaments. The H and I bands shorten with muscle contraction, while the A band remains a constant length.

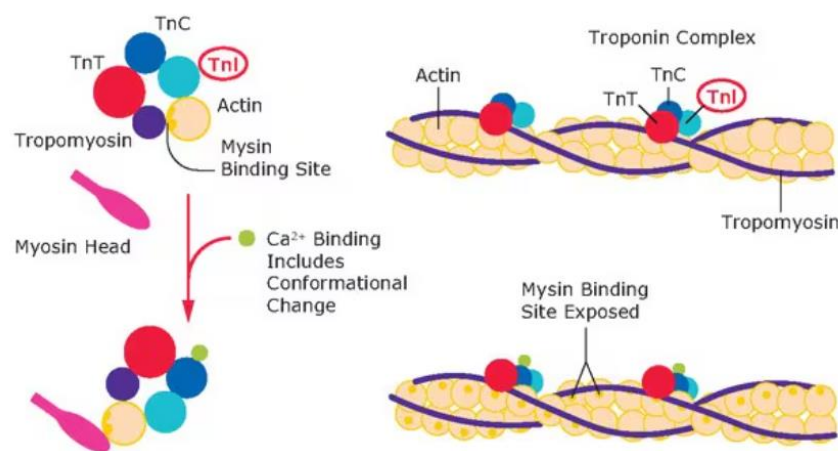
Actin filaments are double-helical structures, known as filamentous-actin (F-actin), composed of monomeric G-actin units. G-actin exhibits polarity and creates a positive and negative end within the sarcomere, with the positive end situated toward the terminal end of the sarcomere. Tropomyosin is a helical protein that runs along the actin double helix within its groove. Troponin binds tropomyosin by a troponin complex at every seven-actin monomer and is composed of troponin-C (Tn-C), troponin-I (Tn-I), and troponin-T (Tn-T). Tn-T binds tropomyosin, Tn-I inhibits actin and myosin binding, and Tn-C binds calcium.

Myosin proteins are composed of two regions: light meromyosin and heavy meromyosin. Light meromyosin (LMM) binds other light meromyosin regions to anchor myosin at the M line. Heavy meromyosin (HMM) is further subdivided into two regions; the S-1 portion, or the myosin head, binds actin and contains an ATPase portion, while the S-2 portion is the location of the power stroke.

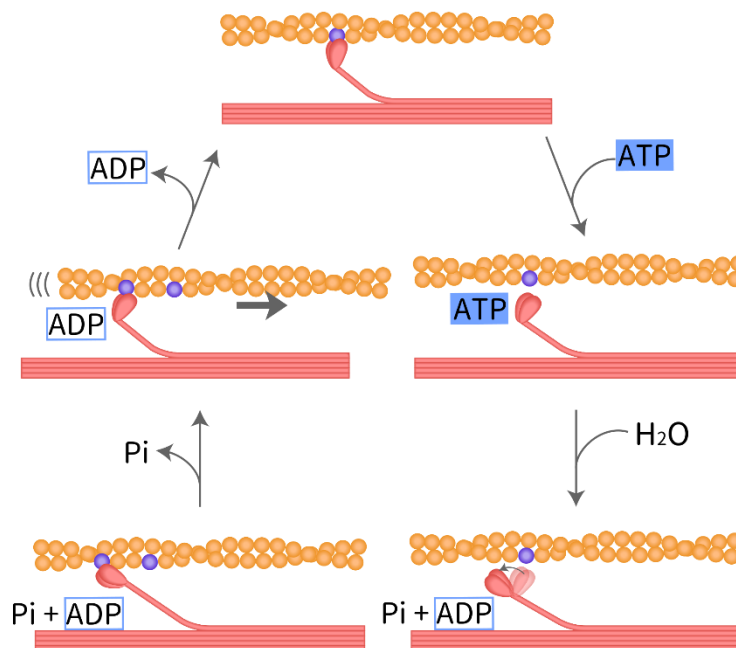
3. Mechanism of muscle contraction

- When a significant motor end plate depolarizing potential overcomes the threshold of the skeletal myocyte, the cell fires an action potential.

- This depolarizing potential is propagated to T tubules, causing a conformational change in the dihydropyridine receptors.
- This conformational change opens ryanodine receptors on the terminal cisternae of the sarcoplasmic reticulum to release Ca from its storage site in the sarcoplasmic reticulum into the intracellular fluid
- Ca^{2+} binds to troponin C, causing a conformational change in troponin that moves tropomyosin from the myosin binding site on actin. Note: in the presence of Ca^{2+} , troponin C remains in this configuration, leaving the myosin binding site on actin available for myosin interactions.



- ATP then binds myosin causes the release of the actin-myosin cross-link (=myosin disassociated with actin).
- Hydrolysis of this bound ATP to ADP plus inorganic phosphate induces a change in myosin to the “cocked position.” Note: only ADP remains attached to myosin.
- The myosin head then interacts with actin at another binding and moving the myosin head toward the positive end of actin (closer to the ends of the sarcomere).
- ADP is released from myosin causing another change that results in the “power stroke.” At this time, myosin is bound to actin and will remain bound without more ATP.
- Another ATP molecule binds myosin. The cycle continues, shortening the sarcomere as myosin slides along the actin.



The force of contraction is a summation of the number of motor units recruited and the frequency of action potentials that reach those motor units. The motor unit is defined as a single motor neuron and all the muscle fibers it innervates, with multiple motor units stimulating a single muscle. The number of muscle fibers comprising a motor unit depends on the function of the muscle. Muscles that require fine motor control will involve fewer fibers, whereas larger muscle groups will involve significantly more muscle fibers. Muscles that function over a prolonged period, such as lower back muscles, will asynchronously recruit fibers so that fatigue of individual fibers is spread out over time and space.

Muscle metabolism is driven by the need to produce ATP for contraction. Muscles first use their small store of ATP, then rely on creatine phosphate for about 15 seconds of extra energy. After this, they obtain ATP from breaking down glycogen and lipids. Without oxygen, glucose undergoes anaerobic glycolysis, producing only 2 ATP and lactic acid, which supports activity for about a minute. With oxygen, aerobic respiration in mitochondria produces up to 36 ATP per glucose and can sustain activity much longer, relying first on muscle glycogen and then on nutrients delivered by the blood. During intense exercise, the heart and lungs must boost oxygen supply. Anaerobic metabolism is fast but inefficient, while aerobic metabolism is slow to start but produces much more ATP.

Course7. physiology of the autonomic nervous system

The autonomic nervous system (ANS) also known as the visceral or involuntary nervous system is made up of pathways of neurons that control various organ systems inside the body, using many diverse chemicals and signals to maintain homeostasis. It divides into the sympathetic and parasympathetic systems. It functions without conscious control throughout the lifespan of an organism to control cardiac muscle, smooth muscle, and exocrine and endocrine glands, which in turn regulate blood pressure, urination, bowel movements, and thermoregulation

The autonomic nervous system exerts influence over the organ systems of the body to upregulate and downregulate various functions. The two aspects of the ANS operate as opposing functions that act to achieve homeostasis.

The sympathetic nervous system, also known as the “fight or flight” system, increases energy expenditure and inhibits digestion. The following changes take place on activation of the sympathetic nervous system:

- Heart rate and cardiac muscle contractility increase
- The ciliary muscle relaxes, and the pupil becomes dilated for the betterment of far vision.
- Bronchodilation of the lungs
- Decreased GI motility
- Decreased urine output
- Relaxation of the detrusor muscle of the bladder and contraction of urethral sphincters
- Increased secretions from sweat glands
- Increased blood flow to muscles because of relaxation of arterioles
- Constriction of large arteries and large veins
- Increased metabolism, increased glucose production and mobilization by the liver
- Increased lipolysis within fat tissue
- Suppression of the immune system

The parasympathetic nervous system, also known as “rest and digest,” can be thought of as functioning in opposition to the sympathetic nervous system. Its functions include:

- A decrease in heart rate and contractility of cardiac muscle
- Constriction of the ciliary muscle and the pupil for near vision
- Increased secretion by lacrimal glands and salivary glands
- Increased gut motility, bronchoconstriction of the lungs
- Contraction of the detrusor muscle with the relaxation of urethral sphincters

- Glycogen synthesis by the liver
- Swelling of the clitoris and erection of the penis
- Activation of the immune system

the neurotransmitters of the autonomic ganglion

The neurotransmitters involved in the ANS are acetylcholine, norepinephrine, and epinephrine. Preganglionic neurons of the sympathetic and parasympathetic and postganglionic neurons of the parasympathetic nervous system utilize acetylcholine (ACh) (cholinergic synapses). Postganglionic neurons of the sympathetic nervous system use norepinephrine and epinephrine (adrenergic synapses)

Postsynaptic receptors of ANS

ACh is released by all preganglionic neurons, regardless of their involvement in the parasympathetic or sympathetic nervous system. ACh binds to nicotinic acetylcholine receptors, a ligand-gated ion channel, on postganglionic neurons. Once ACh binds, the ion channel is open to allow the flow of ions, specifically sodium and calcium, which induces an excitatory postsynaptic potential, and results in the propagation of a neuronal signal down the axon. ACh also gets released by postganglionic neurons of the parasympathetic nervous system. Here, ACh binds to muscarinic acetylcholine receptors on the target site, which are G-protein-coupled receptors. . It is important to note that ACh also gets released by postganglionic neurons of sweat glands and binds to and activates muscarinic receptors. This activity is an exception to the sympathetic nervous system, which normally involves norepinephrine as its chemical messenger released from postganglionic neurons

Norepinephrine gets released by postganglionic neurons of the sympathetic nervous system, which binds to and activates adrenergic receptors, which are G-protein-coupled receptors

Epinephrine is released into systemic circulation by chromaffin cells within the adrenal gland, specifically the adrenal medulla. The sympathetic nervous system splanchnic nerves synapse on chromaffin cells and stimulate them to release epinephrine using the signal messenger acetylcholine. This feature of the adrenal gland is an important component of the sympathetic nervous system as it allows systemic effects to occur on major organ systems

Acetylcholine receptors:

There are two subtypes of nicotinic receptors, the muscular type (N1) and the neuronal type (N2).. The N1 receptor is present on skeletal muscle at the neuromuscular junction. N2 is within the peripheral and central nervous systems. N2 receptors are on the cell bodies of postganglionic neurons within the parasympathetic and sympathetic nervous systems. They are also on the adrenal medulla as a component of the sympathetic nervous system.

There are five different types of muscarinic receptors, M1, M2, M3, M4, and M5. Furthermore, each subtype is either stimulatory or inhibitory. Subtypes M1, M3, and M5 are stimulatory function through the phospholipase C second messenger pathway, while M2 and M4 function through a second messenger pathway that inhibits adenylate cyclase and prevents the formation of cAMP from ATP. The M1 muscarinic receptor is in the cerebral cortex, salivary, and gastric glands. M2 receptors are present in smooth muscle as well as cardiac tissue. M3 receptors are in smooth muscle cells, particularly of the bronchioles, iris, bladder, and small intestines. M4 and M5 receptors have a less clear distribution but have been found in the hippocampus, substantia nigra, and other locations within the brain

adrenergic receptors

The two major categories of adrenergic receptors (AR) are designated alpha and beta. Each has sub types: Receptor α_1 involves a Gq protein that elevates C^{++} , resulting in smooth muscle contraction. Receptor α_2 involves a Gi protein that decreases cAMP and C^{++} influx which inhibits neurotransmission. Receptors β_1 , β_2 & β_3 involve a Gs protein and cAMP elevation that increases C^{++} for smooth muscle contraction (β_2 & β_3 can be linked to a Gi protein that decreases cAMP resulting in smooth muscle relaxation). Thus, the effect of ACh and NE can be either excitory or inhibitory, based on the receptor distribution within visceral organs.

Adrenal Medulla

A mass sympathetic discharge, which typically occurs during the “fight-or-flight” response and during exercise, involves the simultaneous stimulation of organs and tissues throughout the body. Included among these tissues are the adrenal medullae which release epinephrine and norepinephrine into the blood. In large part, the indirect effects of these catecholamines are similar to and, therefore, reinforce those of direct sympathetic stimulation. However, there are some important differences in the effects of the circulating catecholamines and those of norepinephrine released from sympathetic nerves.

The duration of activity of the catecholamines is significantly longer than that of neuronally released norepinephrine. Therefore, the effects on the tissues are more prolonged. This difference has to do with the mechanism of inactivation of these substances. Norepinephrine is immediately removed from the neuroeffector synapse by way of reuptake into the postganglionic neuron. This rapid removal limits the duration of the effect of this neurotransmitter. In contrast, there are no enzymes in the blood to degrade the catecholamines. Instead, the catecholamines are inactivated by COMT in the liver. As one might expect, the hepatic clearance of these hormones from the blood would require several passes through the

circulation. Therefore, the catecholamines are available to cause their effects for a comparatively longer period of time (up to 1-2 minutes as opposed to milliseconds).

Because they travel in the blood, organs and tissues throughout the body are exposed to the catecholamines. Therefore, they are capable of stimulating tissues that are not directly innervated by sympathetic nerve fibers: airway smooth muscle, hepatocytes, and adipose tissue, in particular. As a result, the catecholamines have a much wider breadth of activity compared to norepinephrine released from sympathetic nerves.

The other important feature that distinguishes the catecholamines from neuronally released norepinephrine involves epinephrine's affinity for β_2 receptors. Norepinephrine has a very limited affinity for these receptors. Therefore, circulating epinephrine causes effects that differ from those of direct sympathetic innervation including a greater stimulatory effect on the heart and relaxation of smooth muscle (vascular, bronchial, gastrointestinal, and genitourinary). Epinephrine and norepinephrine have equal affinity for β_1 receptors, the predominant adrenergic receptor on the heart. However, the human heart also contains a small percentage of β_2 receptors which, like β_1 receptors are excitatory. Therefore, epinephrine is capable of stimulating a greater number of receptors and of causing a greater stimulatory effect on the myocardium.

Beta two adrenergic receptors are also found on smooth muscle in several organ systems. These receptors tend to be inhibitory and cause relaxation of the smooth muscle. Vascular smooth muscle in skeletal muscle contains both α_1 and β_2 receptors. Norepinephrine, which stimulates only the excitatory α_1 receptors, causes strong vasoconstriction. However, epinephrine, which stimulates both types of receptors, causes only weak vasoconstriction. The vasodilation resulting from β_2 receptor stimulation opposes and, therefore, weakens the vasoconstriction resulting from α_1 receptor stimulation.

Another noteworthy example of the relaxation of smooth muscle by way of β_2 receptor stimulation involves the airways. Bronchodilation, or the opening of the airways, facilitates airflow in the lungs. Any direct sympathetic innervation to the lungs is irrelevant in this respect, as only circulating epinephrine is capable of stimulating these receptors on airway smooth muscle.