Lectures 7-9

NERVE & MUSCLE

Functions of nerve fibers

Nerve cell is called **neuron**. There are 100 billion neurons (give or take 100 million) differ based on their structure, chemistry and function. Neurons confer the unique functions of the nervous system which are generation and transmission of impulse. **Glia** are the supporting elements which are 10 times as many as neurons**.**

According to physioanatomic basis, neurons are classified into **afferent** (**sensory**) and **efferent** (**motor**). Each is subdivided into **somatic** and **visceral** neurons. They are further subdivided into **general** and **special** neurons.

Another classification is according to **conduction velocity** and **caliber** (diameter) of nerve fiber. From larger to lower caliber they are:

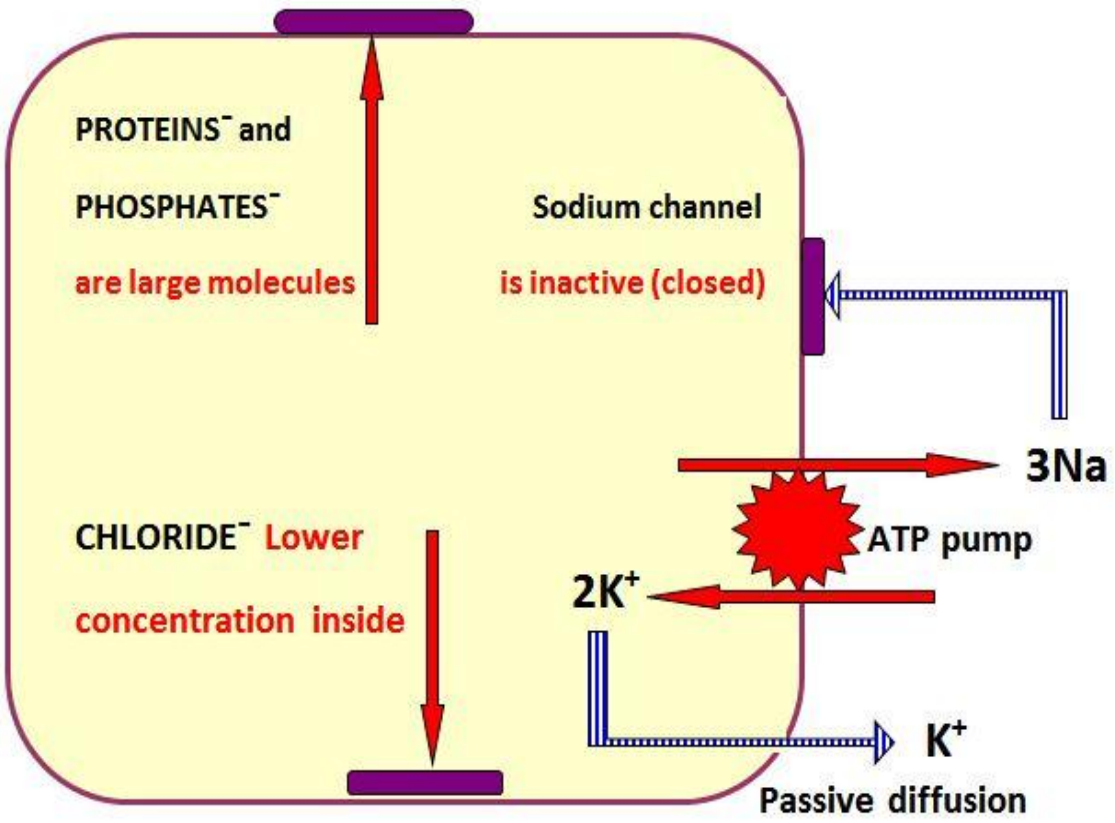
Nerve type Aα has the largest diameter and fastest conduction velocity e.g. somatic motor and proprioceptive nerve fibers.
Nerve type Aβ e.g. sensory fibers of fine touch and fine pressure.
Nerve type Aγ e.g. motor fibers to muscle spindle.
Nerve type Aδ e.g. sensory fibers of acute pain, crude touch and cold.
Nerve type B e.g. preganglionic autonomic nerve fibers.
Nerve type C has the smallest diameter unmyelinated fibers e.g. sensory fibers of chronic pain, heat, gross pressure and postganglionic sympathetic fibers.

Types of glia in central nervous system:
a. Astrocytes: They support the neurons, provide nutrient supply, guide migration of young neurons and regulate extracellular space
b. Microglia: Transform into special type of macrophages to get rid of microorganisms and debris.
c. Ependymal cells: Line the central cavities of brain and spinal cord.
d. Oligodendrocytes: Form myelin sheath to function in insulation.
Types of glia in peripheral nervous system:
a. Schwann Cells: Produce myelin sheath and neurilemma
b. Satellite cells: The same functions as astrocytes
Resting membrane potential

All living cell membrane interior is negative in relation to the membrane exterior. This is called resting membrane potential (**RMP**) and it is due to uneven distribution of ions inside and outside the membrane.
RMP of nerve cell is **–**70 mV
RMP of skeletal muscle is **–**70 to **–**90 mV
RMP of cardiac muscle is **–**85 to **–**95 mV
RMP of smooth muscle is variable but nearly about **–**50 mV.

The following ionic fluxes (movements) are responsible for the **electric phenomenon** of resting membrane potential:

1. Sodium-Potassium pump: This is called Na^+-K^+ ATPase pump which extrudes (expels) three sodium ions outside the cell and intrudes two potassium ions inside. This results in much positive ions outside plasma membrane.
2. Sodium channels are inactive at rest. Sodium ions cannot enter to the cell.
3. Potassium channels allow continuous passive diffusion of K^+ outside the cell due to concentration gradient. This K^+ **efflux** results in **diffusion potential**.
4. Chloride ions stand still inside the cell due to their higher concentration outside the cell.
5. Anionic proteins and phosphates cannot leave the cell due to their large size



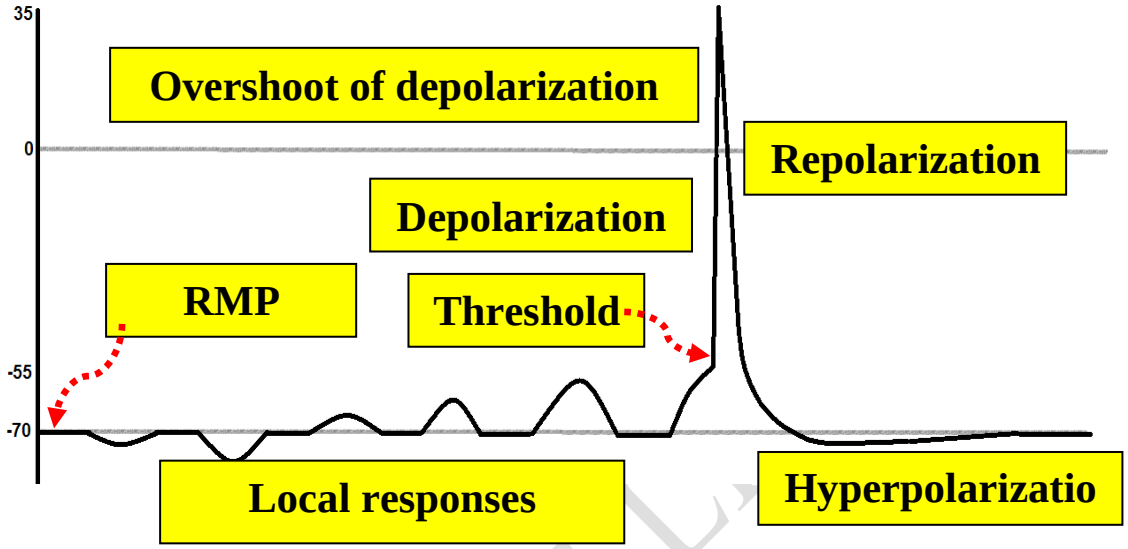
Action potential

Nerve and muscle cells are excitable cells i.e. they have the ability to reverse the negativity of their membrane potential in **response** to a sufficient external **stimulus**. The external stimulus may be electrical, chemical, physical or other types of stimuli. This change in membrane potential (from negative to positive) is called **action potential (AP)**. The response in nerve cell is **transmission** of action potential (nerve **impulse**) while the response in muscle cell is **contraction**.

Phases of action potential curve in neurons

1-Depolarization phase: Sharp rise of curve from -70mV toward zeromV membrane potential which **overshoot**s to reach about +35 mV. This phase is due to activation of all fast Na^+ channels with inrush (entrance) of huge number of Na^+ ions.

2-Repolarization phase: Rapid fall of the curve toward the previous negative potential which occurs due to fast inactivation of Na+ channels and continuous pumping of Na^+ and passive diffusion of K^+ outside the cell.
3-Hyperpolarization phase: Decline of the curve to a more negative potential than RMP which is here about –72 mV due to slow closure of K^+ channels. After that, the membrane regains its RMP.



Propagation of action potential (transmission of impulse)

Action potential is transmitted along the axon as **electrotonic flow of current** which is very fast (like in the solid electricity wire). Myelin sheath provides insulation to prevent leakage of ions and the impulse is jumping from node to node of Ranvier. This is called **saltatory conduction**.

Neuromuscular junction

Neuromuscular junction is a synaptic junction between motor neuron and skeletal muscle fiber. The first is called **presynaptic** membrane and the other is called **postsynaptic** membrane (or motor end plate). Between them is the synaptic **cleft**. A chemical substance called **acetylcholine (Ach)** which is a **neurotransmitter (NT)** synthesized and stored in **synaptic vesicles**.

Acetylcholine is synthesized from *acetyl coenzyme A* and *choline*. The reaction is catalyzed by choline acetyl **transferase enzyme** (**CAT**). ACh receptors are **nicotinic** receptors (either alpha or beta) and **muscarinic** receptors. Nicotinic receptors are present in **neuromuscular junction**, **sympathetic ganglia** and many parts of **CNS**. Muscarinic receptors are present in **smooth muscles** and **glands**. After stimulation of postsynaptic membrane, acetylcholine must be degraded in the synaptic cleft by **acetylcholinesterase** enzyme **(ACE)**.

Function of skeletal muscle

General functions of skeletal muscle are movement, maintenance of posture, stabilization of joints and temperature homeostasis. The muscle is composed of fibers (cells) and each cell is composed of fibrils. The myofibrils are composed of

thick and thin filaments. **Thick myofilaments** are formed from myosin. **Thin myofilaments** are formed from actin, tropomyosin and troponin

Initiation of contraction: Excitation – contraction coupling

1- Nerve impulse from motor neuron reaches axon terminal
2- Calcium ions enter the axon terminal.
3- Calcium ions attract the synaptic vesicles to the axon terminal.
4- The vesicular membrane fuses with presynaptic membrane.
5- Acetylcholine is released into the synaptic cleft.
6- Acetylcholine binds its nicotinic receptor on post synaptic membrane.
7- Na^+ channels are opened and Na^+ ions enter to the postsynaptic membrane. This depolarization fires action potential (AP) in muscle fiber membrane (sarcolemma).
8- AP propagates along sarcolemma and down through T tubules resulting in release of Ca^{2+} from sarcoplasmic reticulum to the myofibrils.
9- Myosin ATPase on myosin head is activated and ATP splits resulting in high energy myosin-ADP complex.
10- Ca^{2+} binds to troponin of thin filaments resulting in changes in molecular shape of troponin.
11- Troponin with tropomyosin are removed from binding site on the actin filament and so, myosin immediately attaches actin (actin-myosin cross bridge).
12- Myosin head bends and pulls on actin.
13- New ATP attached to myosin head and cross bridge simultaneously detaches. So, ATP causes muscle relaxation in addition to contraction.
14- If no new impulse, Ca^{2+} is pumped back into sarcoplasmic reticulum (SR) and relaxation occurs. If Ca^{2+} present from additional impulse, cycle repeats and myosin head "steps" to next binding site on actin.

Types of skeletal muscle contraction

Most real-life movements involve both isometric and isotonic contraction.
Isotonic contraction: Muscle changes in length and moves load.
Isometric contraction: Tension increases but the muscle length stays constant. The load is greater than force e.g. maintenance of posture.

Clinical considerations: Abnormal contractions

Spasm: A sudden involuntary contraction of short duration.
Cramps: Painful spasmodic contraction of muscle fibers.
Rigor mortis: Inability of muscle fibers to relax after death (there is no ATP).
Convulsion: Violent tetanic contraction of entire muscle groups.
Fibrillation: Asynchronous contraction of individual muscle fibers resulting in flutter with no effective movement.
Tic: Spasmodic twitching common in eyelid and facial muscles.
Myalgia: Pain in one or more muscles.
Myositis: Inflammation of muscle tissue.
Poliomyelitis: Viral destruction of motor neurons in the anterior horn of spinal cord.
Contracture: Abnormal sustained contraction resultant from continuous availability of Ca^{2+} near myofibrils due to lack of Ca^{2+} pump back to sarcoplasmic reticulum.

Cardiac Muscle

It is branched and interdigitated and functions as **syncytium** due to presence of **intercalated discs** and **gap junctions**. Its RMP is about -85 mV and its AP is slow and characterized by presence of plateau.

The AP phases are:

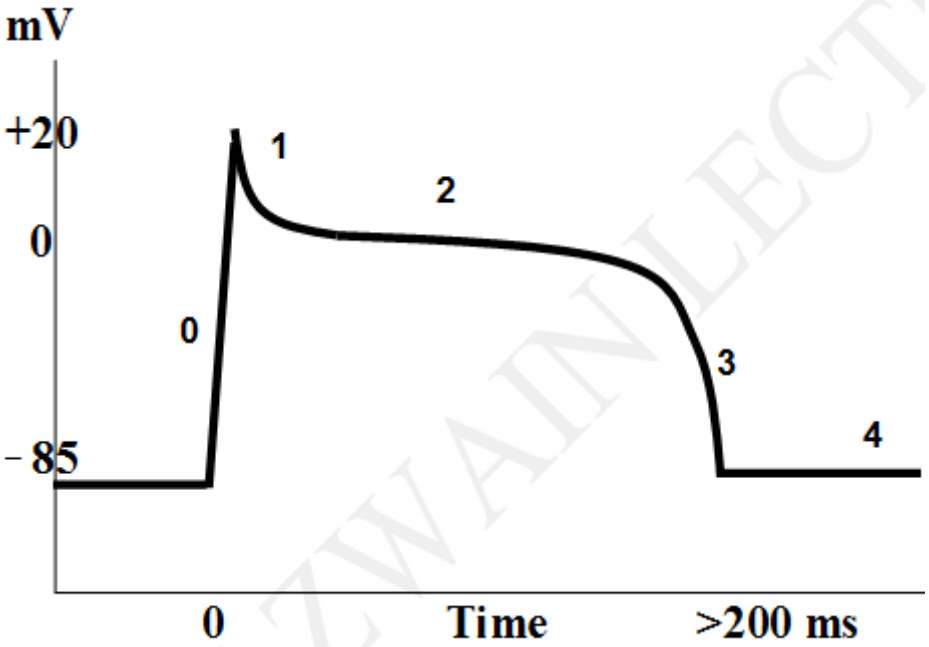
Phase 0: Depolarization lasts about 2 ms and occurs due activation of all Na^+ channels with huge influx of Na^+ ions.

Phase 1: Initial rapid repolarization occurs due fast inactivation of Na^+ channels.

Phase 2: plateau (200 ms) and occurs due to opening of Ca^{2+} channels and influx of Ca^{2+} ions. Cardiac muscle never tetanized due to the plateau phase**.**

Phase 3: Late rapid repolarization occurs due to closure of Ca^{2+} channels.

Phase 4: Base line (RMP)



Pacemaker potential

Cardiac muscle contraction is **myogenic** (originated inside the muscle) not **neurogenic** (initiated by nerve) and the nerve supply is only regulatory. This due to the presence of specialized conductive tissue in the heart called **pacemaker tissue**. This tissue has unstable low membrane potential called prepotential or pacemaker potential which declines and depolarizes continuously and steadily (due to slow decrease in K^+ efflux) which spreads the impulses all over the heart. Steeper prepotentials result in **tachycardia**, while lower prepotentials result in **bradycardia**.

Smooth muscle

Small, spindle-shaped cells arranged in sheets of opposing fibers. Generally there are two sheets *longitudinal and circular* sheets with fibers at right angles to each other. The alternating contraction of layers results in **peristalsis**. It has no structured neuromuscular junction and has lower myosin to actin ratio. It has no troponin complex and no sarcomeres. There is electrical communication between individual smooth muscle cells due to **gap junctions**. This makes the entire sheet responds to a single stimulus (Syncytium). There may be pacemaker cells and some are **self-excitatory**. Ca^{2+} interacts with regulatory molecules called **calmodulin** (not troponin). Contraction is slow, sustained and resistant to fatigue. Smooth muscle has a unique property of depolarization and contraction in response to stretch.

Smooth muscle also has the property of **stress-relaxation** (**plasticity**) which means that with gradual increase in stretch; tension at first increases and then decrease even below its initial level. This property is of benefit especially in uterus in order to adapt to the continuous increase in fetal size and in urinary bladder to adapt to the continuous increase in urine volume.

Smooth muscles are in continuous state of partial contraction (tone). Different types of nerve supply with multiple neurotransmitters are found in smooth muscles but their role is only to modify that muscle tone. Smooth muscle is also affected by other factors like chemicals, pH, temperature, CO_2, O_2 ....etc

Comparison of skeletal, cardiac and smooth Muscle

Characteristic	Skeletal	Cardiac	Smooth
Sarcomere	Present	Present	None
T Tubules	at each end	Present at one end	None
Gap Junctions	None	Intercalated discs	present
NM Junctions	Present	None	present
Regulation	voluntary	hormones, involuntary	involuntary,hormones, local
Ca^{2+} Source	SR	SR, extracellular fluid	SR, extracellular fluid
Role of Ca^{2+}	Via troponin	Via troponin	Via calmodulin
Pacemakers	None	Present	In single-unit
Nervous effects	Excitation	Excitation or inhibition	Excitation or inhibition
Speed	Varies: slow to fast	Slow	Very slow
Rhythm	None	Yes	present
With stretch	increases strength	increases strength	plasticity
Respiration	Aerobic, anaerobic	Aerobic	Primarily anaerobic