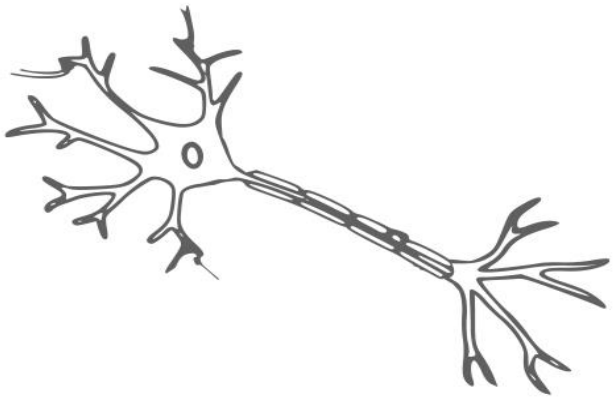
Sheet no.

17

Physiology



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The first two lectures with Dr. Yanal will be about cells excitability

There are two types of cells excitable and non-excitable cells

Excitable cells: are cells that are not capable of performing their function unless it is activated(excited) with a stimuli example nerves and muscular cells

Non-Excitable cells: cells that are capable of performing their function without an electrical stimulus or excitation example RBCs and endocrine cells (hormones are secreted from endocrine cells through signal transduction that doesn't involve action potential)

What does excitation mean?

Excitation: Reversal of membrane potential where we inverse the membrane potential from negative inside relative to the outside to positive inside relative to the outside (depolarization)

How cells can be excited: -

1. Entry of Na^+ ions
2. Entry of Ca^{2+} ions
3. Entry of both ions

All cells (Excitable and Non-Excitable) have resting membrane potential and all have the same concentration of sodium ions inside and outside of the cell,**140** milliequivalents per liter (mEq/L) outside the cell and**14** mEq/L inside of the cell (10 folds)

Calcium concentration outside the cell is 1 millimole per liter (M/L = Eq/L) whereas is inside the cell is 10^{-7} M/L (10000 folds difference)

Potassium concentration inside the cell 150mM and outside the cell 4mM (35 folds)

Resting membrane potential varies between cells like RBCs -7mv, muscle cells -30mv, spinal cord neurons -65mv, skeletal muscle cells -90mv and in ventricular cells (cardiac) -90mv.

When opening the sodium channels the Na^+ ion will diffuse from **outside the cell to the inside** down the concentration gradient changing the membrane potential from the resting membrane potential -90mv to +30mv but the concentration of Na^+ ions at the end of depolarization inside and outside the cell won't be considerably affected due to the fact a very small amount of Na^+ ions are needed to diffuse to reach the +30mv membrane potential. The concentration almost remains the same 140mM/L outside the cell and 14mM/L inside but still, sodium must be pumped outside to return to resting membrane potential

When sodium entered the cell the membrane potential inside the cell became positive which resulted in an electrical force opposing the entry of Na^+ ions therefore at that moment there are two forces applied to the sodium ions, **chemical force** as a result of the concentration gradient pushes the sodium inside and **electrical forces** resulted from the electrical charges of ions between the membrane.

So how much positive charge is needed to generate enough electrical force to resist and counteract sodium ion entry due to the chemical force?

To find the solution Nernst equation must be used to calculate the sodium equilibrium potential (how many positive charges are needed inside the cell to prevent the entry of Na^+ ions from the chemical force)

$$E_K = \frac{RT}{ZF} \log \frac{[K^+]_o}{[K^+]_i}$$

Nernst calculation for Na =+61mv

$$E_K = -61 \log \frac{Na_i}{Na_o}$$

Example: If Na_o = 140 mM and Na_i = 14 mM

E_K = -61 log(14/140)

E_K = -61 log(0.1)

E_K = +61 mV

At +61mv the net movement of Na^+ ions equal zero as the number of sodium ions leaving the cells matches the number of ions entering

important

But the membrane potential won't reach +61mv as cells after depolarization reaches a positive membrane potential that varies between cells ranging from 0mv to +30mv but not +61mv and this range depends on the speed the sodium channels will close after being activated that differs from one cell to another (the slower it closes the more positive membrane potential it will reach)

Nernst equation for Ca = +122mv

Nernst equation for k = -90mv

The results of the Nernst equation of the ions must be memorized

When finding the resting membrane potential of ventricular cells is -90mv we must conclude that positive currents are entering and leaving the cell

Current (I) is the flow of electrons (The driving force) that is opposed by resistance

Current (I)= Driving force (DF) / Resistance(R)

$I = \Delta V/R$

$G\ (conductance) = 1/R$

$I = G.\ \Delta V$

(Current is directly proportional to the driving force and inverse to the resistance)

Resistance: How difficult this process to occur (the ions moving inward or outward)

➔ Conductance (g) = 1/R so, I=DF*g

The flow of sodium =inward current

The flow of potassium =outward current

what is the driving force?

How far is the membrane potential from the equilibrium potential for each ion?

Potassium current (I_{ion}) = (E for membrane – E for the ion) * g for the ion

At membrane potential -90 (at rest) → current for potassium = (-90 – (-90)) * g = Zero

It means no NET movement for potassium ions

Current for sodium= (-90-61) * g Na^+ but the conductance for Na^+ at rest = ZERO

- The resting membrane potential (RMP) varies between the cells either excitable or non-excitable, why?

  important

  Because of different conductance for each ion in each different cell.

  (NOTE: Nernst equation calculates the equilibrium potential for one ion without considering the effect on other ions' potential) so we have to include other ions that's why we use other equations like Cords conductance eq. and Goldman Hodgkin Katz (dr. Khatatbeh's material)

Eg: for cells with RMP-90 the conductance for potassium is the highest with a slight contribution of sodium.

And for RMP -65 the potassium is still dominant but with a higher contribution for sodium

And if RMP -7 the conductance for sodium is close to the potassium

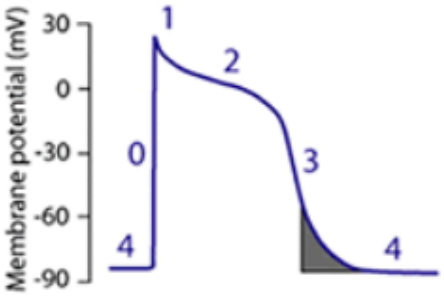
- Drugs may be inhibitory or excitatory:

Inhibitory drugs (that calm you down) open the chloride channels in the spinal cord neurons that have the RMP=-65 (NOTE: E_{cl^-}=-70), so chloride ions will move inward which **increases** the negativity inside (more negative potential), thus, the potential will be further from the threshold, that makes it difficult to reach the threshold and cause an action potential.

While the **excitatory drugs**, open the sodium channels (E_{Na+}=+61) so sodium will move inward and negativity inside will **decrease,** so it is easier to reach the threshold

- Sodium channels in the membrane are classified into two fast sodium channels and slow sodium channels

At -90 there are channels called fast sodium channels they are closed and active (ready to open) (they cause a large amount of sodium to enter the cell in no time), and the depolarization will be at an angle of 90



look at period 0 (this is fast sodium channels)

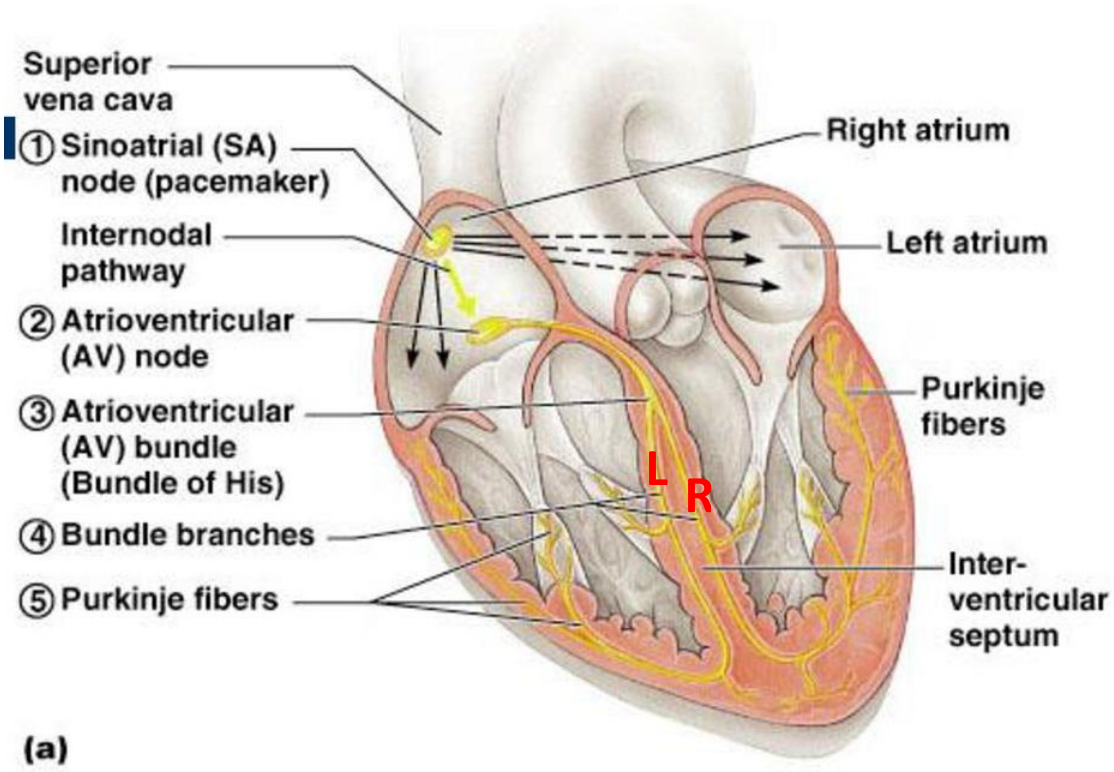
this will be taken later

while at -65 (the threshold) they are closed and inactive, so only the slow sodium channels will be opened, and the depolarization will be curved and take more time.

This is the importance of the threshold, which inactivates the fast channels so the depolarization will be curved not right-angled.

Fast channels will bring the potential to the threshold then they will be inactivated and the rest voltage channels will make the depolarization, Threshold activates all the voltage-gated channels.

→Conducting System of the Heart



There are 3 important regions in the heart

1. SA node
2. AV node
3. Intraventricular bundle including AV bundles, left (**L**) and right (**R**) bundle branches, and Purkinje cells

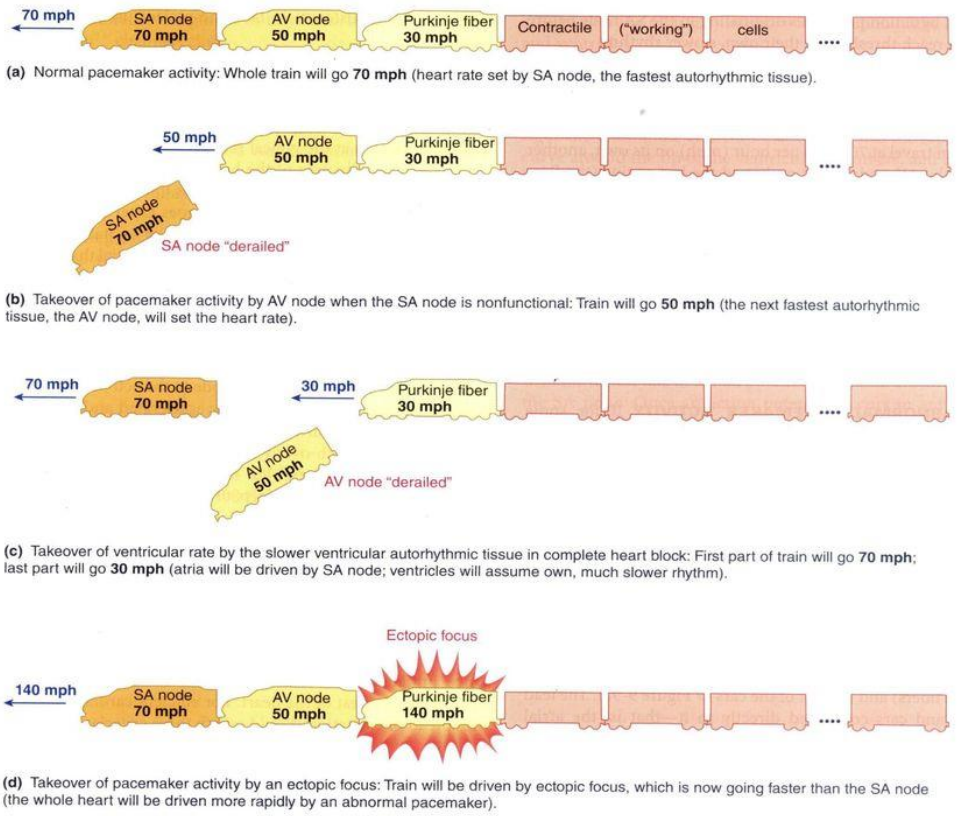
SA nodal cells **do not** contain actin and myosin filament hence they are not contractile cells. Purkinje cells contain actin and myosin filament but they are not used for contraction instead it is used for electrical purposes.

SA Node

The plasma membrane in these cells contains a channel that is leaky to **sodium** at a rest membrane potential.

Sinoatrial cells are called the pacemaker cells and they are responsible for making approx. 70-80 beat per minute bpm. when the SA node is abnormal (Sick Sinus Syndrome (SSS)) and it is not functioning the AV node will become the pacemaker and it will be called *Latent Pacemaker* as it will be responsible for 40-60bpm.

If the Purkinje cells become the pacemaker (Latent) by cutting the connection between the atrium and the ventricle (atrioventricular block) then the beats will be between 15-40 bpm **which is not enough** and an artificial pacemaker will be needed in that case.



(a) Normal pacemaker activity: Whole train will go **70 mph** (heart rate set by SA node, the fastest autorhythmic tissue).

(b) Takeover of pacemaker activity by AV node when the SA node is nonfunctional: Train will go **50 mph** (the next fastest autorhythmic tissue, the AV node, will set the heart rate).

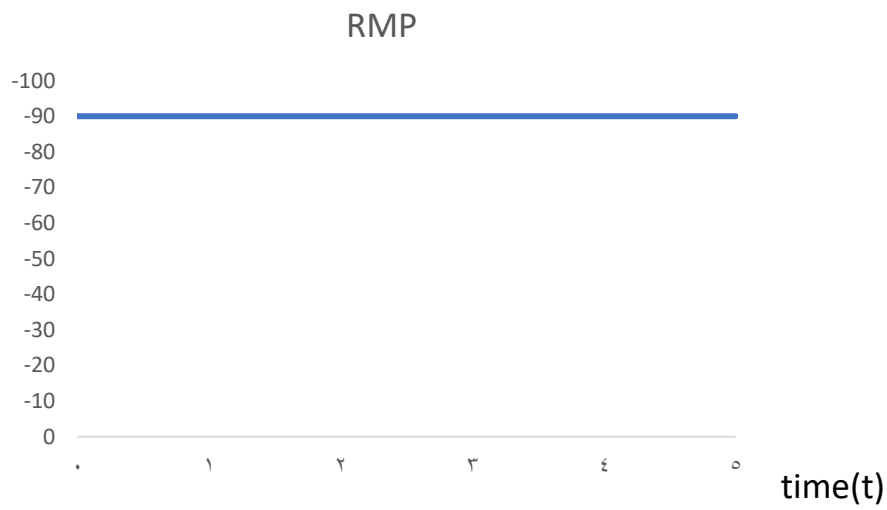
(c) Takeover of ventricular rate by the slower ventricular autorhythmic tissue in complete heart block: First part of train will go **70 mph**; last part will go **30 mph** (atria will be driven by SA node; ventricles will assume own, much slower rhythm).

(d) Takeover of pacemaker activity by an ectopic focus: Train will be driven by ectopic focus, which is now going faster than the SA node (the whole heart will be driven more rapidly by an abnormal pacemaker).

The figure shows that whenever the SA nose is functioning the rest of the cardiac muscle will follow the same beats rate of the SA node but if it started malfunctioning then the cardiac muscle will follow the rate of the AV node and if none of them were functioning then it will follow the beating rate of Purkinje fibers.

(latent means that the beats from them are hidden by the SA node's beats, so they are not the main pacemaker)

A Latent pacemaker (AV node, AV bundle, Purkinje Fibers, Left and Right bundles) can't be faster than the active pacemaker else it will be called *Ectopic Focus* (abnormal) and it is life-threatening. And their membrane potential is considered unstable.



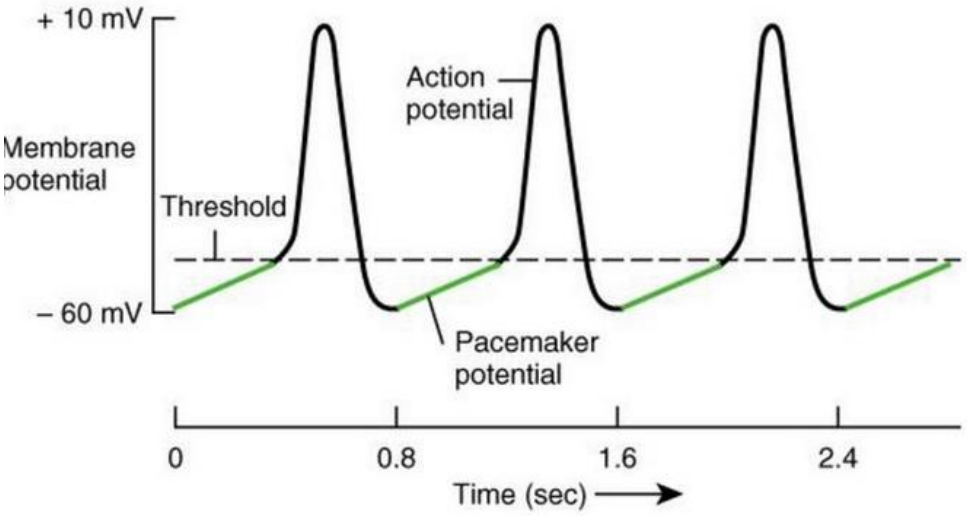
This figure shows :

- No change in voltage for each second (slope = delta V/ delta t =0)
- Highest deriving force for sodium, and highest conductance for potassium
- It is Stable RMP (will never ascend to the threshold unless it is excited by an external stimulus), stable means there is no change in voltage by the time (slope=0)
- The positive currents entering (Na^{+}, Ca^{+2}) equal positive currents leaving(K^{+}), NET current is zero.

RMP for Ventricular cells is -90

So, VA cells will never bring themselves to the threshold

→cardiac membrane potential at SA nodes



(b) Pacemaker potentials and action potentials in autorhythmic fibers of SA node

SA nodal cells have unstable membrane potential (delta v/ delta t >0) the slope between -65 and -50(the threshold) is ascending

This means SA cells can bring themselves to the threshold without any external stimulus, they have leaky sodium channels in their membrane so SA cells have the intrinsic ability to bring membrane potential by themselves to the threshold (without external effects from the nervous and endocrine systems)

Assume that each beat occurs in 0.8 Min and there are 60 more beats

The heart rate would be 60/0.8 min= 75 beats per min (bpm)

In sympathetic stimulation (which increases the heart rate) the sodium and calcium will diffuse inward faster so the slope between voltage -65 and -50 will be bigger (reach the threshold -50 faster)

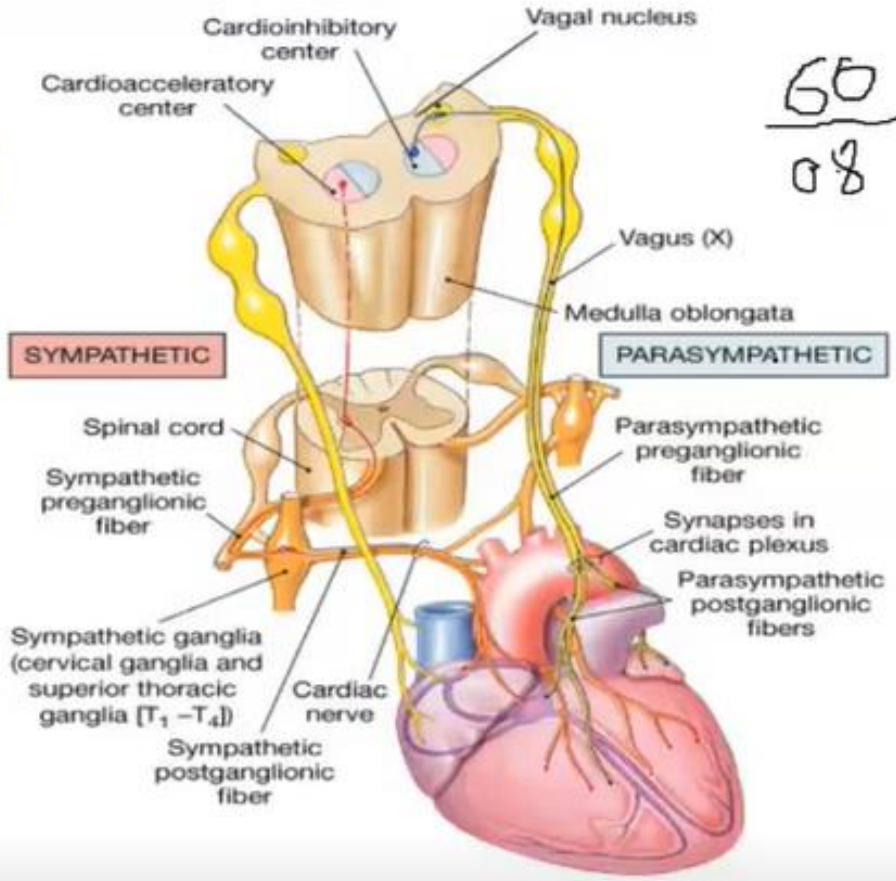
Heart rate = 60 beat / 0.2 min =300 bpm

In parasympathetic (which decreases heart rate) sodium will get inside slower and the angle will be less and less heart rate

Heart rate = 60 beat/1 min= 60 bpm

These stimulations will affect the SA nodes and AV nodes

Autonomic Innervation of the Heart



60 = 75
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