◉Sheet ○Slides

Number

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- Last lecture we talked about types of Na+ channels briefly, and we mentioned the Na+ leak channels that solely characterize the heart, and are also present in self-excitable cells (SA nodal cells)
  Now, we are going to talk about SA Node (Sino Atrial Node) which is the pacemaker of the heart.
  → SA nodal cells are self-excitable due to Na+ leak channels (it's the site where Action Potential is born).

How does Action Potential arise in the heart?

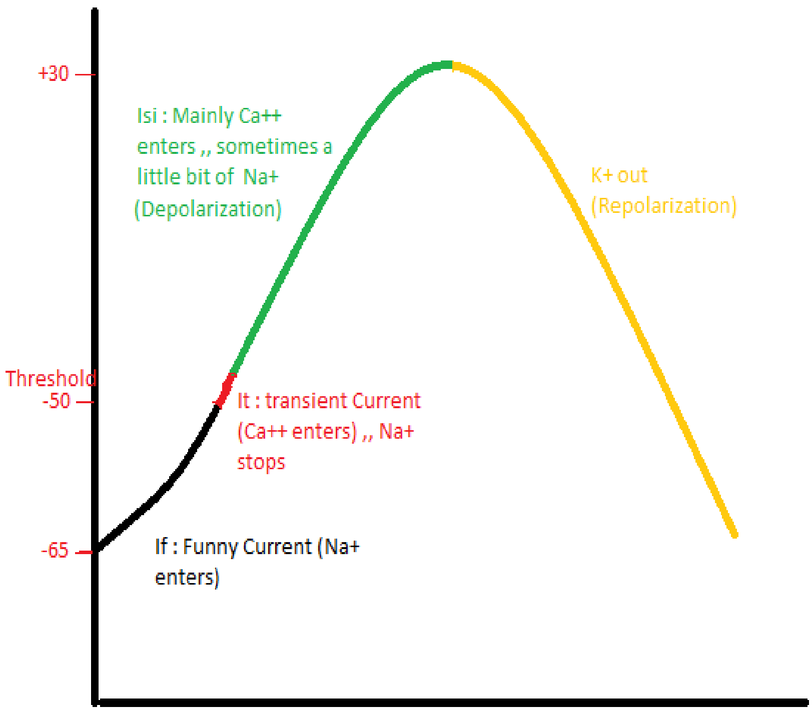
1. SA nodal cells make the Action Potential.
2. This Action Potential is carried to 3 structures: Left Atrium, Right Atrium and AV Nodal cells (AtrioVentricular Node).
3. AV Node is a collection of cells that receives this impulse from SA Node and takes it down through bundle of fibers (called Bundle of His).
4. Bundle of His then branches left and right, and goes down to the Apex.
5. Impulse is carried then by purkinje cells to reach Ventricular Muscle fibers.

> **Note that: Purkinje cells are specialized in Conduction (not contraction) →They are conducting pathways.**

- As SA nodal cells have Na+ leakage channels at rest, they bring themselves to threshold.

What does If means??

Funny Current: it means that at -65 mV, Na+ channels are opened (Leaky), but when it reaches -50 mV (threshold), they are shut off.



Action Potential in SA Node (Slow Response)

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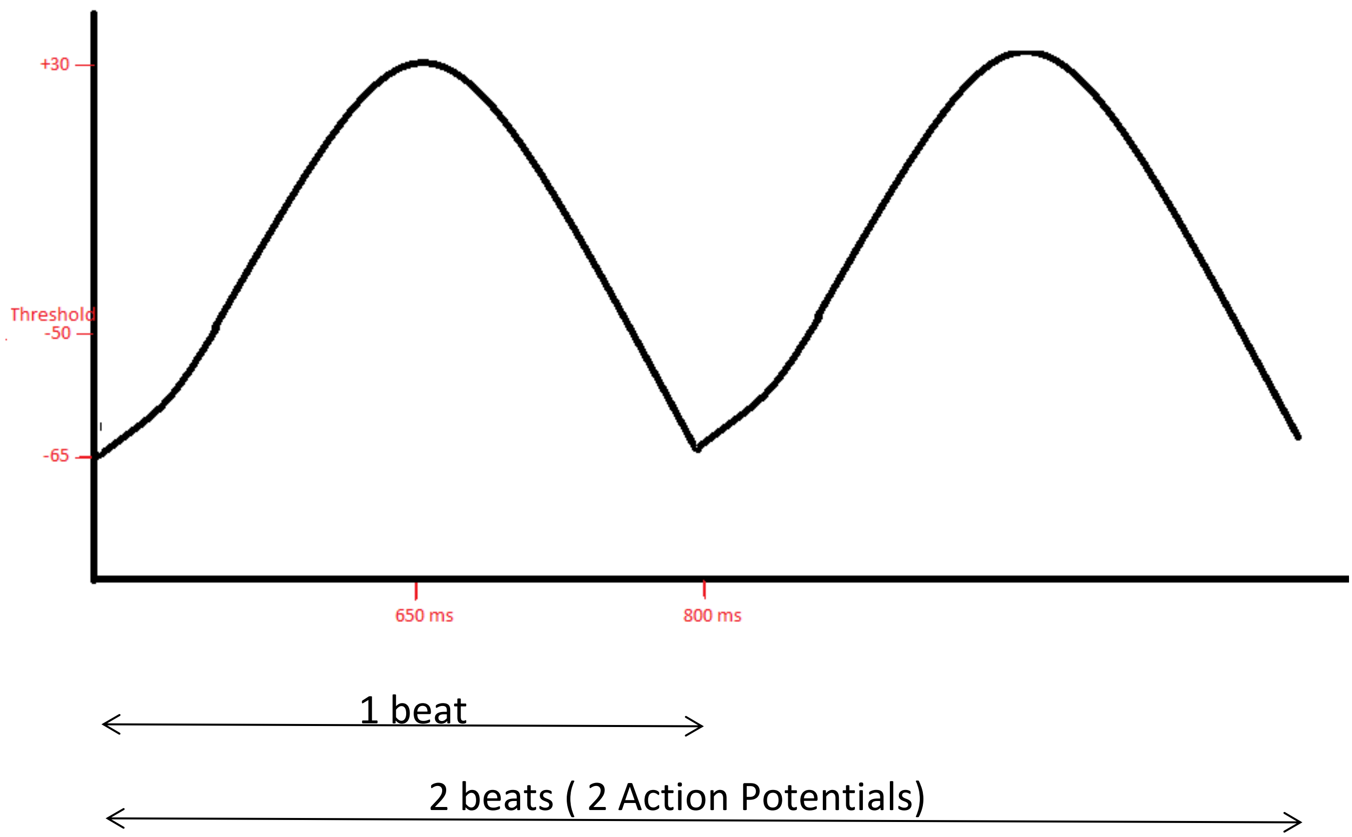
→ Another closer look for Action Potential in SA Node:



→ Every 0.8 second, we have 1 beat (one cardiac cycle)

→ A single cycle of cardiac activity can be divided into two basic phases:

1) Diastole (relaxation): when the ventricles are relaxed and expanded while refilling with blood returning from the circulatory system (after contraction).
2) Systole: represents the contraction of ventricles, happens right after Diastole.

What is the Heart Rate ?

It's the speed at which the heart beats.

Heart rate = 1min/0.8sec = 60/0.8 = 75 bpm (beats per minute)

SA Node is called Pacemaker because it's the structure that determines the Pace (rhythm) of the heart (Heart Rate).

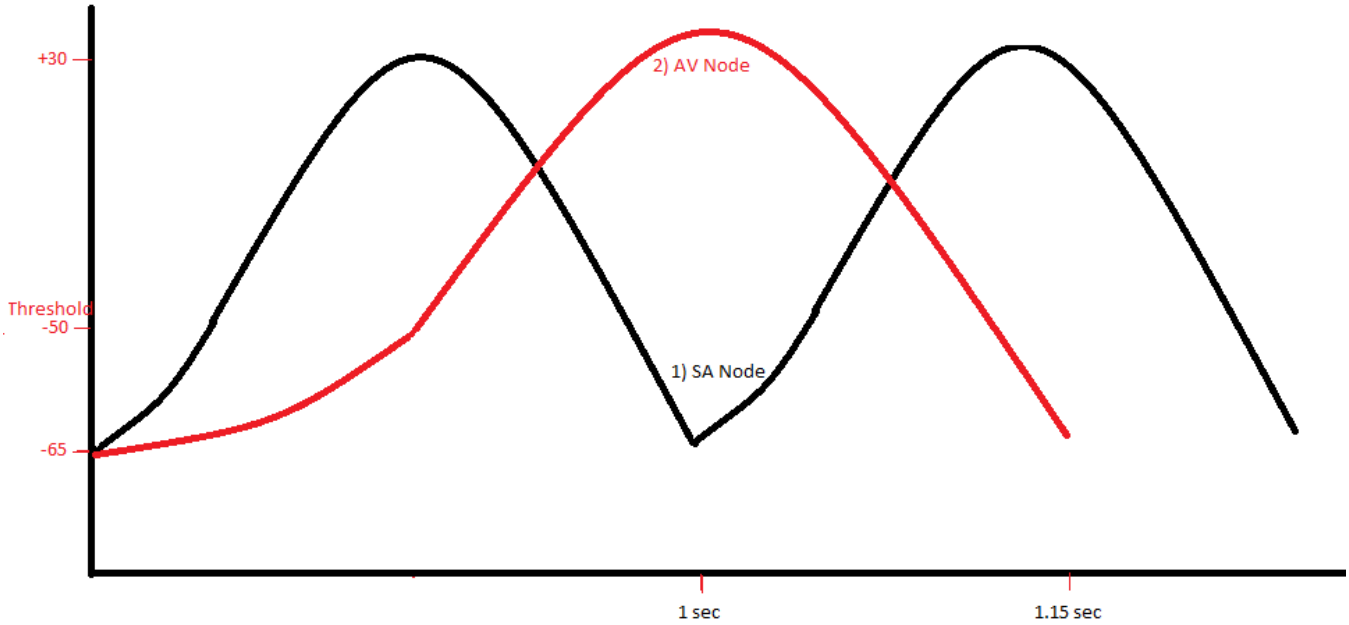
What if SA Node can't function because of infection, inflammation, destruction…etc ??

Ans: AV Node must play its role and become the Pacemaker of the heart.

AV Node is also leaky to Na+, but **less leaky** than SA → then it takes longer to reach the threshold.

→ When AV Node is the pacemaker then it is called "Latent Pacemaker", due to ***Over-driving Suppression***".

- **Over-driving Suppression** means that SA Node overdrives (leads) the heart and masks SA Node, so AV Node becomes suppressed and can't lead the heart because of the higher rhythm of SA Node.



"Both SA & AV are Slow Response action potentials"

→Heart Rate when AV Node is the pacemaker = 60/1.15 = 52 bpm

AVG heart rate (AV) = 40-60 "almost 55 bpm".

While AVG heart rate (SA) = 60-100 "almost 75 bpm".

What if AV Node is destructed ??

If AV Node is damaged, there will be no connection between left atrium and left ventricle (Dissociation), so Purkinje cells & bundle of His will become "**Latent Pacemaker**" → They are leaky to Na+, but **less leaky** than AV Node.

→ So, Atrium will beat as normal (70-80 bpm). On the other hand, Ventricle will beat around 15-40 bpm which is Not enough. **(How do we solve this issue)**?

Ans: The medical solution is an external artificial pacemaker, connected by wires to the ventricle, and gives impulse every 0.8 second→ Normal Heart Rate is recovered.

What makes SA Node the Pacemaker of the heart?

High leakage to Na+, so it reaches the threshold faster (Purkinje , bundle of His, and AV are also leaky to Na+ but **less** than SA).

- SA: Pacemaker.
- AV: Latent Pacemaker.
- Bundle of His: Latent Pacemaker.
- Purkinje: Latent Pacemaker.
- Ventricular cells (Muscle cells): they aren't leaky to Na+ and suppressed by SA Node then AV Node. Therefore, they will never become the Pacemaker.(**What if all of the mentioned above are ruined**??)

  Ans: Ventricular cells must be the Pacemaker and called "**ectopic pacemaker**".

  → Ectopic pacemaker is life threatening. **WHY?**

  1. Normal duration of Systole (contraction) is 0.3 sec, Diastole (filling) is 0.5 sec, and our heart pump 5L/min of blood.
  2. When Ventricular cells function: they generate abnormal electrical impulses.
  3. Chambers contract in a rapid and unsynchronized way (filling duration is significantly reduced → 0.1 sec for example).
  4. The ventricles "fibrillate" rather than beat.
  5. No cardiac output (The heart pumps little or no blood, for ex: 0.5-1L/min).

  → This causes "**Ventricular fibrillation**" which leads to **DEATH!**

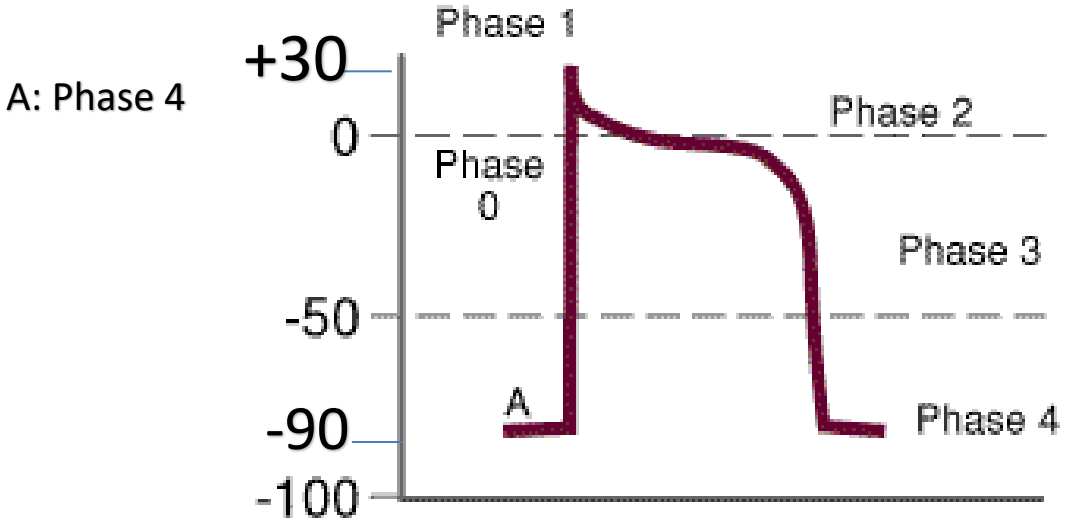
Action Potentials in SA, AV, Atrial cells are ***slow*** response action potential,

While in Ventricle, it's ***fast*** action potential.

What is the difference between Slow and Fast response action potential ?

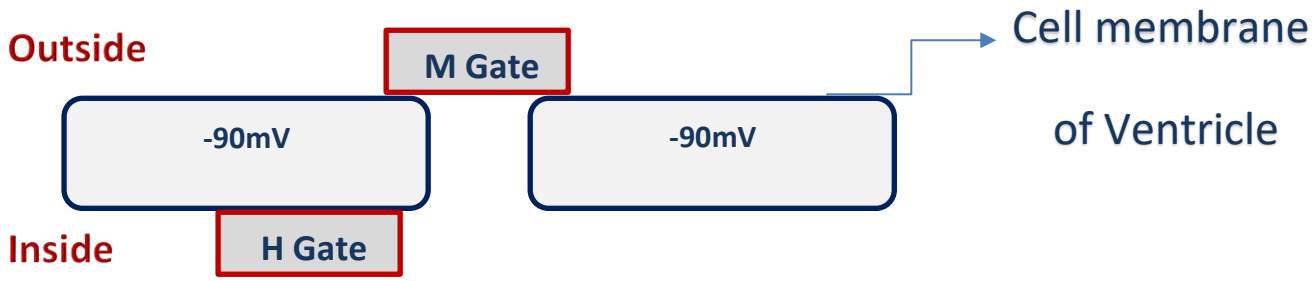
1- Fast response resting membrane potential = -90mV, while slow response resting membrane potential = -65mV.
2- (Study the figure of fast response action potential below (we have already drawn the slow response one)).

Fast Response AP



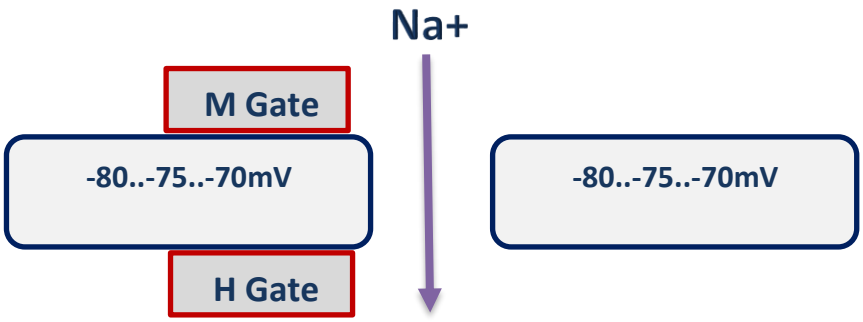
- Phase 4 (Resting Membrane Potential): Stable with respect to time ΔV/Δt = Zero : (# of +Ve charges entering the cell = # of +Ve charges exiting the cell "Net movement of +Ve charges = 0".Therefore, it will remain -90mV forever).
- Phase 0: ΔV/Δt is extremely high (reaching the extent of AP in 1-2 ms, almost No time).
- Phase 1: Initial entry of K+ (transient out).
- Phase 2 (Plateau Phase): Ca++ enters and K+ exits.
- Phase 3: Ca++ stops entering the cell, but K+ continues exiting the cell (Fast Repolarization).

→ Before stimulation:

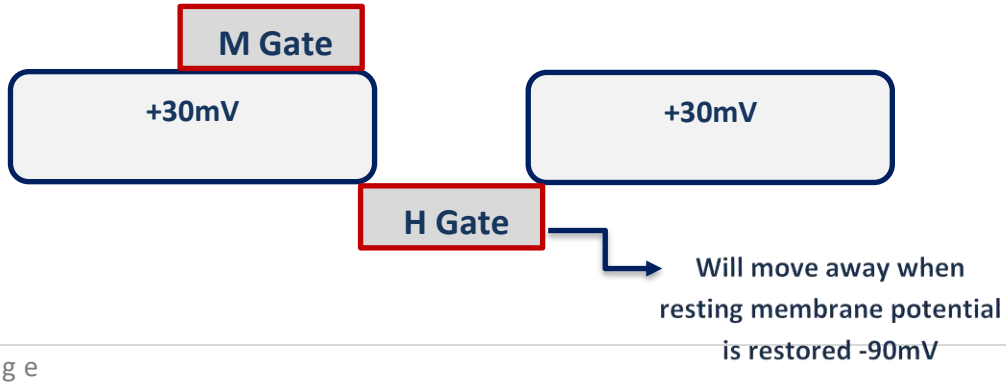


- Fast Na+ channel is **closed** but **active** (ready to open).
- **M Gate**: external gate closing the channel (Activation gate), we can remove it away upon stimulus, fast: it takes 0.2 millisecond.
- **H Gate**: internal gate (inactivation gate), slow: it takes 1 millisecond.

→ After stimulation:

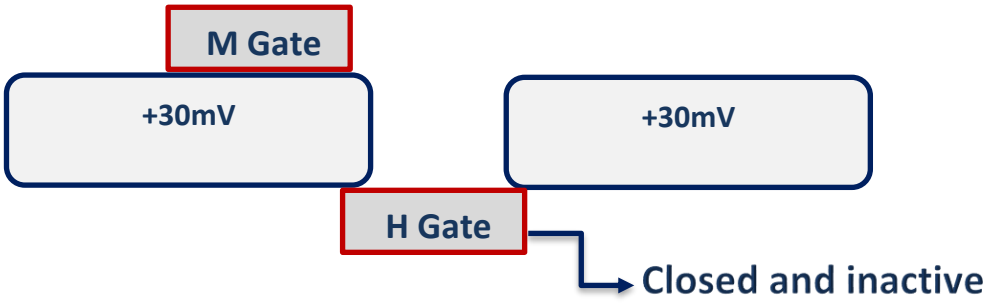


- Na+ channel is opened → Na+ enters the cell.
- M Gate is away from the channel.
- H Gate starts closing at -60mV but it's a slow gate. before it's completely closed: Na+ will enter and make the membrane potential +30mV.



➢ By injection of positive charges inside the cell and stop this process at -60mV:

H Gate closes and becomes inactive.. then you cancelled the fast Na+ channels.



How do we reach the extent of Action Potential very fast(Phase 0)??

Electrical stimulus arrives, mechanical contraction occurs then ventricle pumps blood (ejection). The contraction must be efficient, so all of ventricular cells will contract together simultaneously → This is called **Syncytium.**

➢ **Syncytium: ventricular cells act and behave as a single cell (cells together).**

What makes the ventricular cells act as a single cell?!

Ans: between these cells there are gap junctions. And these junctions allow sequential depolarization (Once the 1st cell is depolarized, the 2nd cell will be depolarized immediately).

→ In SA & AV Nodes: Phase 0 takes time and each cell is depolarized and contracted before Action Potential reaches the 2nd one.

In Contrast to Fast Response AP:

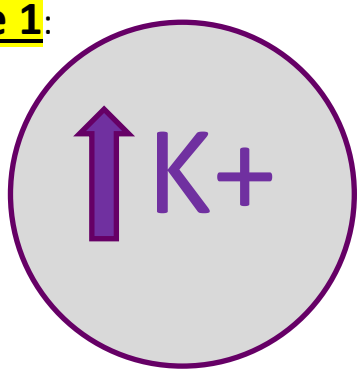
- Phase 4 (Resting Membrane Potential) in Slow Response AP is not stable.
- Phase 4 "Depolarization Wave" is Slow & Ascending because of +Ve charges entering the cell > +Ve charges exiting the cell.

Positive & Negative current determines the direction not type of ions:

→Negative Current: entering the cell

→Positive Current: exiting the cell

Phase 1:



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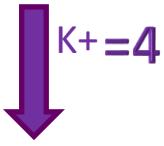


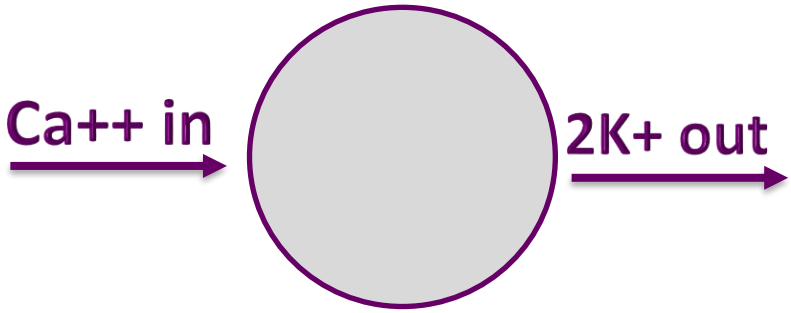
→ Chemical and Electrical Forces favor the exit of K+

→ I_{k+} = DF*Gk+ = (Em-Ek+)*Gk+ =+120*Gk+

→ In cardiac cells: we have ***8 different types of K+*** channels: some of them opens at -90mV, others at +30mV, transient channels …etc.

Phase 2 (Plateau):

- ✓ Ca++ channels open.
- ✓ K+ channels are still open too.
- ✓ Fast Na+ channels are closed and inactive (refractory period).
- ✓ Membrane potential (+10 mV) is stable for 250 millisecond.



→ one calcium ion enters with charge of = two potassium ions exit the cell

1*+2 in = 2*+1 out

+2 in = +2 out

Tetanization: sustained muscle contraction when the motor nerve that innervates a muscle emits action potentials at a very high rate.

→ In skeletal muscles, action potential occurs every 2 millisecond. Tetanization in skeletal muscles is a sustained contraction without relaxation (Summation), athletes are more prone to Tetanus than others.
It's painful but not serious condition in skeletal muscles.

Summation: If a skeletal muscle is stimulated and a second stimulus is applied before relaxation is completed, a second contraction which develops a greater tension is fused to the first one. A possible explanation may be that Ca++ remains from the previous contraction with additional Ca++ from the second stimulus constitutes more Ca++ than it should be available.
→ If the stimulus is repeated at a sufficiently high rate, the muscle will not relax between each stimulus but rather will remain in a contracted state.

In Cardiac Muscle, in order to stimulate it again: membrane potential must go back to -90mV. So, when the 2nd stimulus arrives, the muscle is already relaxed → There is **no Summation** of contraction in Cardiac Muscle. Therefore, **no Tetanization** will be presented **in the heart** ➔ And this is the importance of Plateau.

➔ If Tetanization occurs in the heart, there will be no relaxation, no filling ➔**DEATH**.

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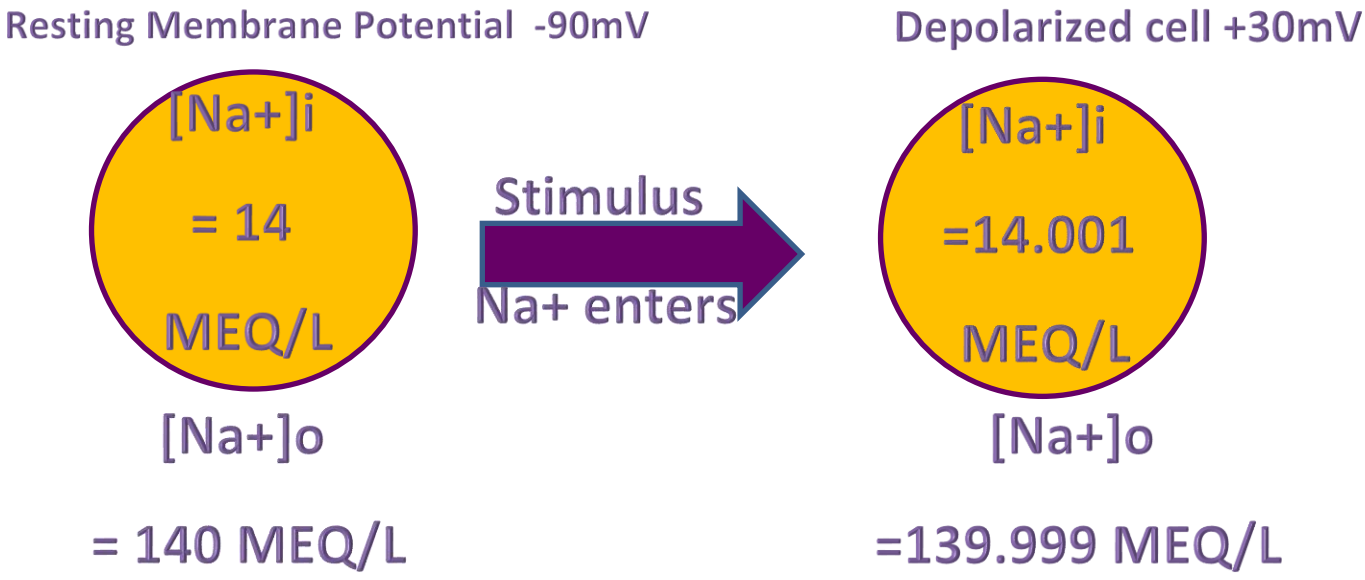

- The Data above tells us that to make [Na+] the same at both sides of the membrane:

We need ***500,000*** stimuli. So, one stimulus won't make a big and measurable difference in the concentration gradient of Na+.