ELECTRO-PHYSIOLOGY OF HEART

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MYOCARDIAL CELLS

There are two types of myocardium:

1. Specialized myocardium
    a. SA node
    b. AV node
    c. Purkinje fibers
2. Contractile myocardium
    a. Atrial myocardium
    b. Ventricular myocardium

PRODUCTION OF RESTING MEMBRANE POTENTIAL

Resting membrane potential in myocardial cell is produced by:

1. Na-K ATPases
2. Opening of potassium channels

Certain genes produce mRNA which activate Na-K ATPases. These channels allow 3 Na^+ ions to efflux out of the cell while two K^+ ions to enter inside the cell. Like all cells in the body myocardial cells are also rich in Na-K ATPases.

Net loss of Na^+ ions is greater than net gain of K^+ ions. So inside of membrane will become slightly negative (-5mV). Electrically this pump contributes very little to RMP but it causes imbalance of concentration of sodium and potassium ions across the membrane.

Ions move along their concentration grandient.

Concentration gradient of Na^+ ions is directed inward. Interior electronegativity also attract Na^+ ions inward. When cells are electrically resting, sodium channels are closed so sodium cannot go inside the cell.

Concentration of K^+ ions is directed outside the cell. As electrically the cell is negative so electrical gradient of K^+ ions is small but directed inside the cell. The net electrochemical gradient is directed outside the cell.

In resting cell, there are potassium-leakage channels due to which resting cell membrane is highly permeable to potassium. As K^+ ions keep moving out of cell, cell keeps becoming more electronegative.

A time comes when concentration gradient and electrical gradient for K+ ions becomes equal and net movement of K+ ions will stop and this is called equilibrium potential for potassium. Normally equilibrium potential for potassium is -85mV.

So mainly K+ influx is responsible for Resting Membrane Potential (-90mV).

ACTION POTENTIAL IN CONTRACTILE MYOCARDIUM

When cell is stimulated by loading cations inside cell, the electronegativity of the cell decrease. When it reaches to **-70mV (threshold potential),** specialized **voltage sensitive sodium channels** open. These channels have two gates. The activation gate which is closed at RMP and the inactivation gate which is open at RMP. At -70mV, activation gate starts to open while inactivation gate begins to close. Activation gate is quick to open while inactivation gate takes some time.

Na^+ ions move inside the cell with opening of sodium channels and depolarization in cell takes place.

As the membrane is depolarized, some other channels also open up including **Voltage Gated Potassium Channels** and **Votage Gated Calcium Channels.**

Voltage Gated Potassium Channels efflux potassium ions out of cell and cell starts to regain electronegativity.

Ca^{+2} ions are normally present in high concentration outside the cell. Calcium channels open after depolarization and a time come when number of cations moving out as K^+ ions become equal to number of cations moving in as Ca^{+2} ions and a plateau phase is seen on graph.

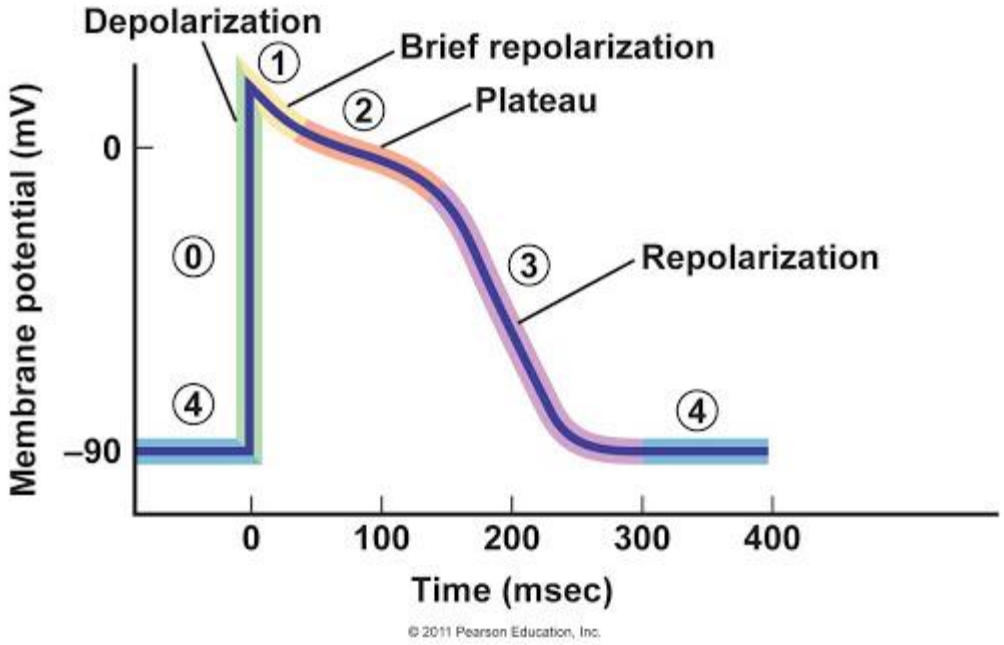
After some time Calcium channels close. As more and more potassium is going out, voltage inside cell progressively becomes negative until RMP is established and the cell is said to be repolarized.

When the opening of sodium channels allow influx of Na^+ ions, some Na^+ ions move to neighboring area and increase the RMP to threshold potential in that area. Hence action potential travels to adjacent area in this manner.

Repolarizing plateau of atria is shorter than ventricles and purkinje fibers.

Action potential travels from cell to cell through gap junctions. Gap Junction is the area between to cells which is filled with filled with fluid and hence carry electrical impulses from one cell to another.

GRAPHICAL REPRESENTATION



- -90mV is resting membrane potential
- Depolarization is due to opening of voltage gated sodium channels
- Brief repolarization is due to opening of Voltage Gated potassium channels
- The plateau phase is due to simultaneous opening of Voltage Gated calcium channels in addition to voltage gated potassium channels
- The repolarization is due to closure of voltage gated calcium channels while voltage gated potassium channels are kept open

ACTION POTENTIAL IN SA NODE

SA Node is specialized in automaticity, meaning it undergoes depolarization spontaneously. Every minute it undergoes spontaneous depolarization 72 times.

Like all other cells these cells have Na-K ATPases and potassium leakage channels. The distinguishing character of SA node is presence of **sodium leakage channels**. Sodium leakage channels allows sodium ions to move inside cell and hence its **RMP remains at -60mV**.

All voltage gated sodium channels in the membrane remains permanently closed as these channels are designed to open at -70mV in usual cells.

Due to the sodium leakage channels, the cell cannot remain at RMP and gradually shifts towards **threshold potential (-40mV)**

At threshold potential, voltage gated calcium channels open and calcium ions start moving in. these Ca^{+2} ions leads to depolarization.

As soon as it completes depolarization, voltage gated potassium channels open and allows efflux of potassium ions. K^+ efflux leads to repolarization.

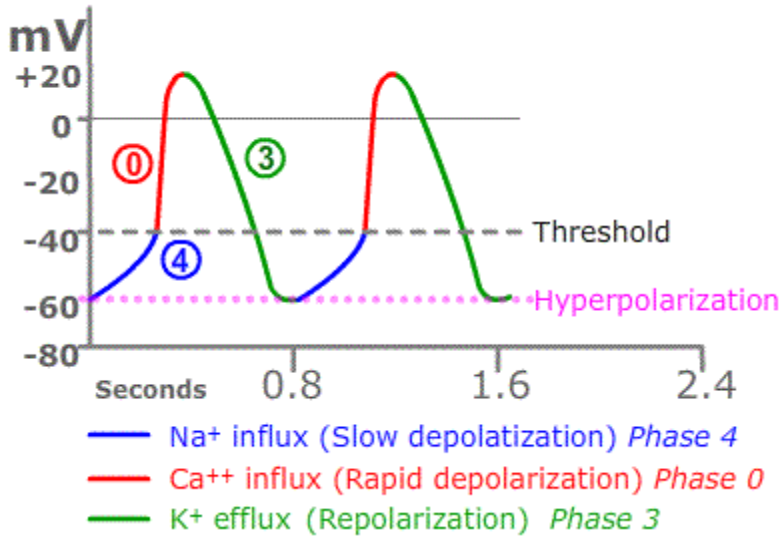
SA node produces depolarizing currents after every 0.8 second.

Depolarization in SA node and AV node is due to voltage gated calcium channels.

Depolarization of atrial cells, ventricular cells and purkinje fibers is due to voltage gated sodium channels.

Ca^{+2} ions move through gap junctions from SA node to atrial cell and activate action potential in atrial cells.

Simple SA Depolarization Model *(Fig.1)*



ACTION POTENTIAL IN AV NODE

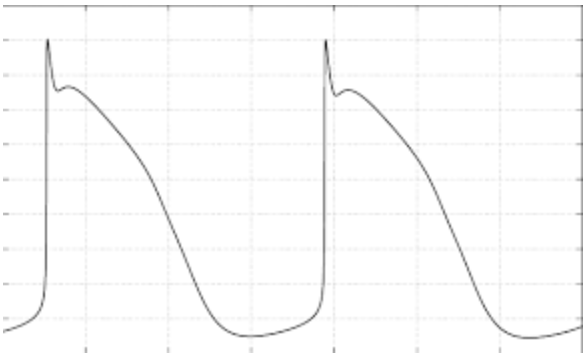
AV node cells have similar action potential graphs but AV node has lesser automaticity as compared to SA node.

ACTION POTENTIAL IN PURKINJE CELLS

Purkinje cells have some amount of sodium leakage channels so Na^+ ions leak inside cell and hence these cells have a tendency of automaticity.

The depolarization of pukinje cells is due to voltage gated sodium gates.

The repolarizing events of purkinje cells are similar to those of atrial action potential.



AUTONOMIC NERVOUS SYSTEM + CARDIAC ELECTRICAL AND MECHANICAL ACTIVITY

Autonomic nervous system is of two types:

1. Sympathetic nervous system (SNS)
2. Parasympathetic nervous system (PNS)

Sympathetic nervous system supply heart through sympathetic cardiac nerves (norepinephrine) and circulating epinephrine. Epinephrine and norepinephrine stimulate **Beta-1** receptors on cardiac tissue. These receptors are found on all myocardium including specialized and contractile myocardium.

Parasympathetic supply mainly comes from vagus nerves. Right vagus usually found on SA node while left vagus on AV node. Both vagus nerves release acetylcholine. Acetylcholine works on parasympathetic receptors on heart called **M_2 muscarinic receptors**. These receptors are not distributed as freely as beta-1 receptors. These receptors are especially concentrated on SA node and AV node. A few of these receptors are found on atrial contractile myocardium. Ventricular myocardium lack M_2 receptors.

STIMULATION OF BETA1-ADRENERGIC RECEPTORS

Stimulation of beta-1 receptors in the heart results in

- Inotropic effect – increased contractility
- Chronotropic effect – increased heart rate
- Dromotropic effect – increased rate of conduction through AV node
- Lusitropic effect – increased relaxation of heart during diastole

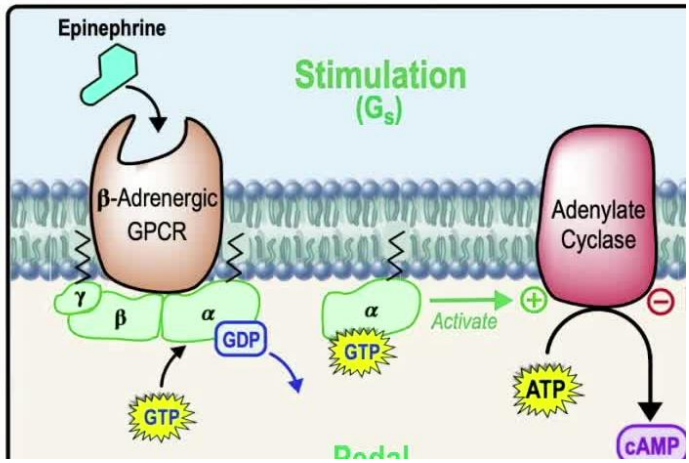
How sympathetic activity alters electrical properties of SA nodal cell?

Beta-1 receptors are basically long peptide chain which passes through cell membrane seven times. These receptors are also called serpentine receptors. It has one extracellular domain to which epinephrine binds, and one intracellular domain which gives signals to the cell.

Beta-1 receptor is coupled intracellularly with special G-protein which is called **G-stimulatory protein**. G-stimulatory protein is a trimeric protein having three subunits; alpha stimulatory, beta stimulatory and gamma stimulatory.

When epinephrine or norepinephrine binds to extracellular domain of beta receptors, its extracellular domain stimulates alpha stimulatory unit of G-stimulatory protein. As soon as alpha stimulatory unit is stimulated, it loses GDP molecule previously attached to it and acquire GTP due to which alpha-stimulatory unit becomes active and detach from beta and gamma units.

The detached alpha-stimulatory protein moves to target effector protein called **adenylyl cyclase** attached to membrane. The alpha-stimulatory unit will stimulate adenylyl cyclase and adenylyl cyclase will convert ATP into cyclic AMP thereby increasing intracellular levels of cAMP. cAMP is intracellular second messenger and stimulate **protein kinase A**. Protein Kinase A is an enzyme and have a capability to phosphorylate target proteins. It can phosphorylate many proteins including calcium channels. When calcium channels are phosphorylated, they become active and calcium enters into cell. Thus calcium ion concentration is increased in SA node and RMP become more near to threshold. RMP achieve threshold more rapidly and total number of depolarization will increase when stimulated by SNS due to which heart rate will increase and this action is called positive chronotropic action.



How parasympathetic activity slows down heart rate by inhibiting SA node

M_2 receptors are present on SA node where acetylcholine binds. Acetylcholine stimulates M_2 receptor which thereby give signal to a different type of G-protein called **G-inhibitory protein**. The three subunits of G-inhibitory protein are alpha inhibitory subunit, beta inhibitory subunit and gamma inhibitory subunit.

Alpha inhibitory subunit is stimulated by M_2 receptors and moves towards adenylyl cyclase. Adenylyl cyclase sends inhibitory signals to its active part which in turn decrease protein kinase A activity, thereby reducing the phosphorylation of calcium channels.

The beta-inhibitory and gamma-inhibitory units interact with special potassium channels and efflux of potassium takes place. Total number of action potentials produced by SA node is inhibited and hence heart rate slows down.

All these activities are observed in AV node as well since AV node is concentrated with beta-1 receptors as well.

Sympathetic effects on contractile myocardium

Stimulation by SNS causes an elevation in intracellular Ca+2 ions and thus an increase in contraction of both atria and ventricles. This is done by electromechanical coupling or excitation-contraction coupling.

Electromechanical coupling or excitation-contraction coupling refers to the series of events that link the action potential (excitation) of the muscle cell membrane to muscular contraction.

Stimulating cells, through gap junctions, load cations into target cells. These cations lead to depolarization of the cells. After depolarization, plateau phase develops. During plateau phase some extracellular Ca^{+2} ions enter the cell which leads to stimulation of sarcoplasmic reticulum. Sarcoplasmic reticulum are stores of calcium and massive amount of calcium is released which help actin myosin to interact and cause contraction. This is called positive inotropic action.

As soon as cell repolarize completely, special proteins called calcium-sodium exchangers are activated in the membrane. These exchanges will export the calcium (which has entered the cell) out of the cell in exchange for Na^+ ions. In this way calcium ions efflux out, while Na^+ ion influx takes place. This sodium will in turn go out through sodium-potassium ATPases.

The calcium released from sarcoplasmic reticulum is re-absorbed and contraction of muscle ceases.