ANTI- ARRYTHMIC DRRUGS:

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•*Physiology of heart beat:*

•Antiarrhythmic drugs suppress arrhythmias by blocking specific ionic flow. The ion channels are trans-membrane proteins possessing two important features:

•*(1)* An ion selective pore that allows the passage of a specific ion

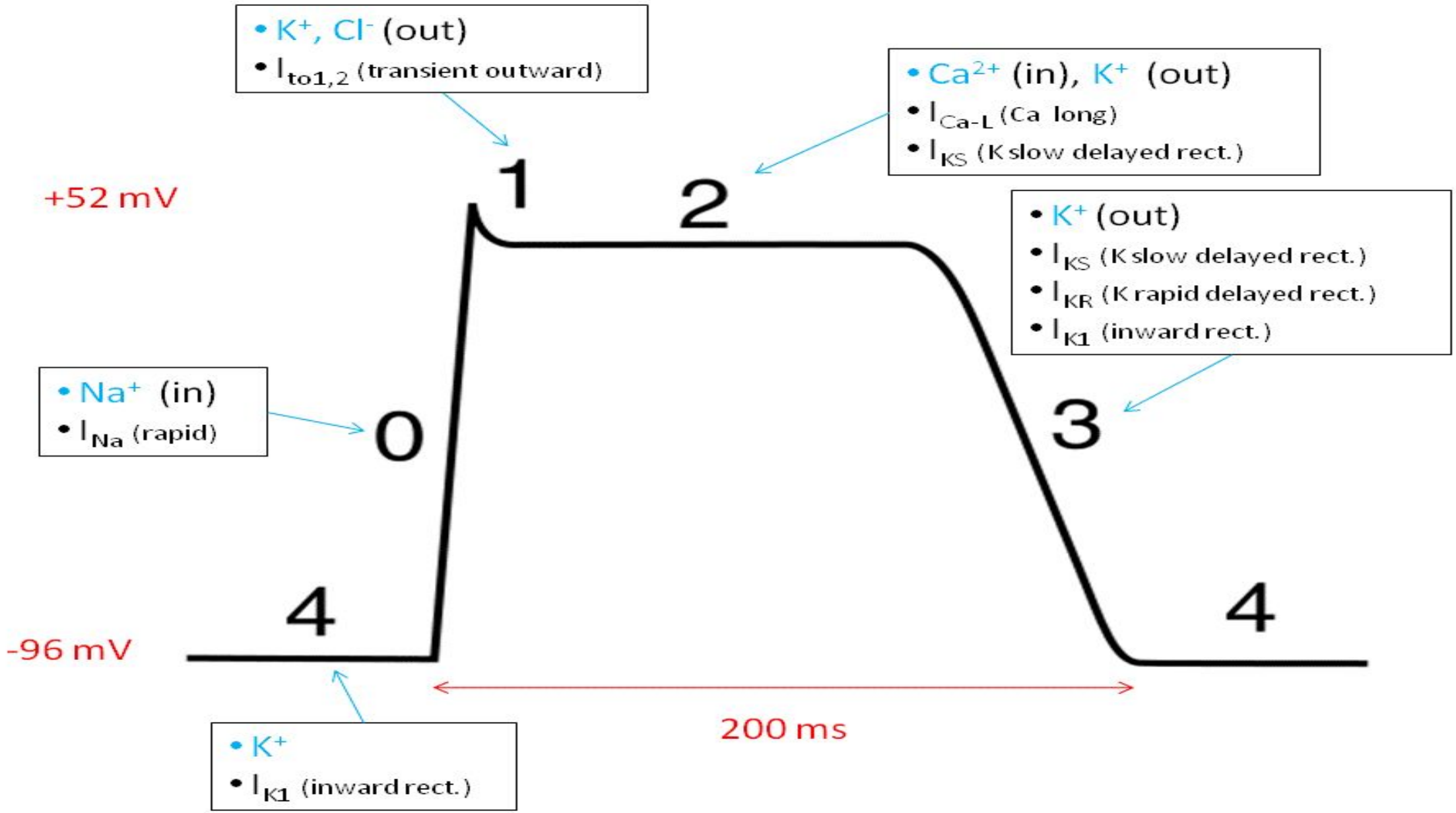
•*(2)* Regulatory components that respond to chemical stimulation or changes in the trans-membrane potential by opening or closing through specific ion channels or by altering autonomic function.

- ***Phase 0 (rapid depolarization):*** occurs when the membrane potential reaches a critical firing threshold (about -90mV), at which the inward current of Na^+ flowing through the voltage-dependent sodium channels becomes large enough to produce a depolarization.
- ***Phase 1, partial repolarization***, occurs as the Na^+ current is inactivated. There may also be a transient voltage-sensitive outward current.
- ***Phase 2,*** **the** ***plateau***, results from an inward Ca^{2+} current.
- ***Phase 3, repolarization***, occurs as the Ca^{2+} current inactivates and a delayed outwardly rectifying K^+ current.

•***Phase 4,*** **the** ***pacemaker potential***, is a gradual depolarization during diastole.

- ***Refractory Period***
  - Depolarized cardiac cells are transiently unresponsive to any activation stimuli. During this interval, most Na and some Ca channels are inactivated, and the cardiac myocytes are said to be refractory.
- ***MECHANISMS OF ARRHYTHMIAS:***

1. ***Disturbances of Impulse Formation.***
2. ***Disturbances of Impulse Conduction.***


• K+, Cl- (out)
• Ito1,2 (transient outward)
• Ca2+ (in), K+ (out)
• ICa-L (Ca long)
• IKS (K slow delayed rect.)
+52 mV
1
2
• K+ (out)
• IKS (K slow delayed rect.)
• IKR (K rapid delayed rect.)
• IK1 (inward rect.)
• Na+ (in)
• INa (rapid)
0
3
4
4
-96 mV
200 ms
• K+
• IK1 (inward rect.)

•Dysrhythmias arise because of:

- Delayed after-depolarization, which triggers ectopic beats
- Re-entry, resulting from partial conduction block
- Ectopic pacemaker activity
- Heart block.

•*Clinically, dysrhythmias are divided:*

a. According to their site of origin (supraventricular and ventricular)
b. According to whether the heart rate is increased or decreased (tachycardia or bradycardia).

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•***Vaughan Williams Classification of anti-arrhythmic drugs***

•The antiarrhythmic drugs can be classified according to their predominant effects on the action potential but this classification is not convenient because many of the drugs have actions relating to more than one class or may have active metabolites with a different class of action.

•1)) Class I (sodium channel blockers):

•*Generally cause a decrease in excitability and conduction velocity.*

•Class I drugs bind more rapidly to the open or inactivated sodium channels than to channels that are fully repolarized (resting) following recovery from the previous depolarization cycle. Therefore, these drugs show a greater degree of blockade in tissues that are frequently depolarizing (for example, during tachycardia, when the sodium channels open often). This property is called ***use-dependence*** (or state-dependence), and it enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal, low-frequency beating of the heart.

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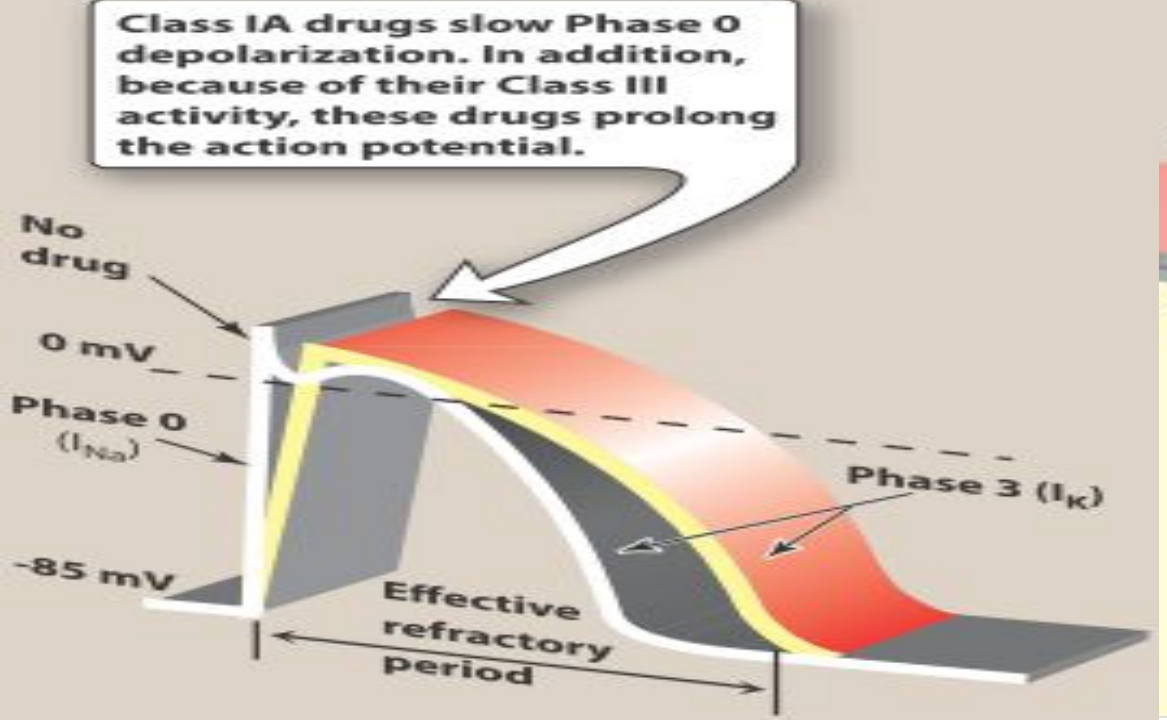
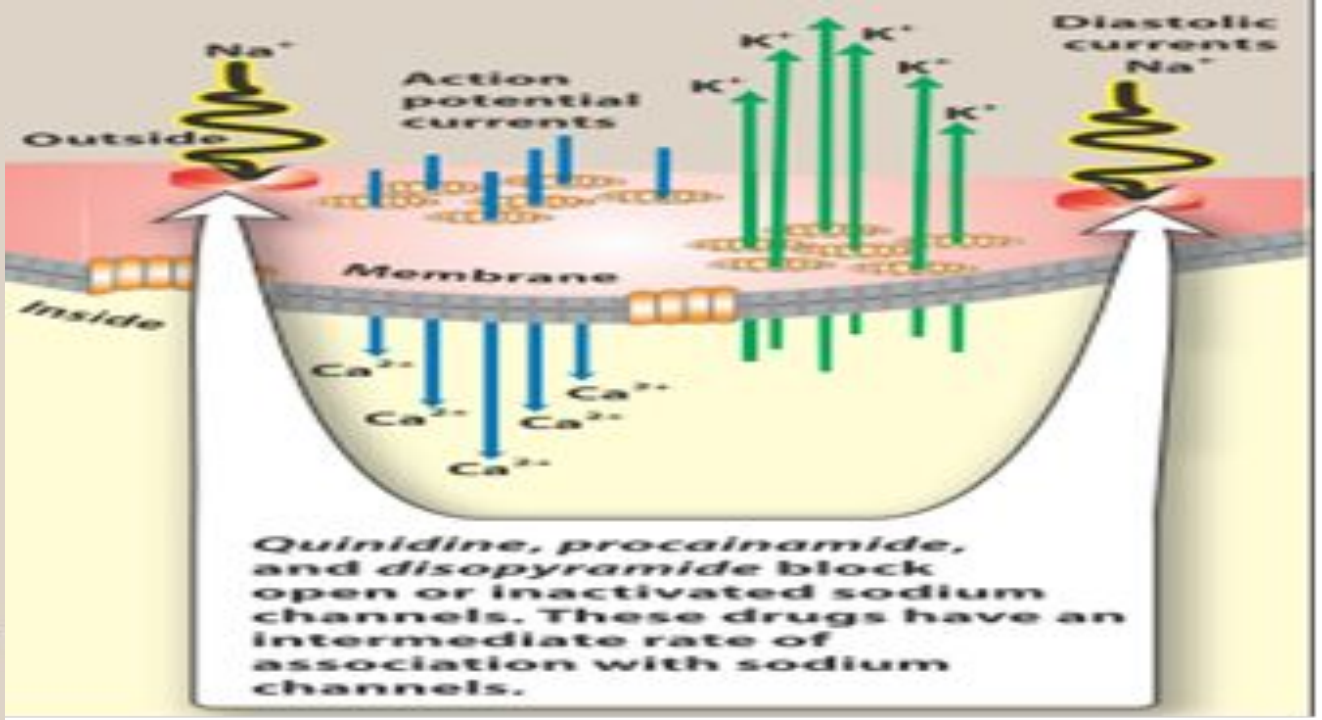
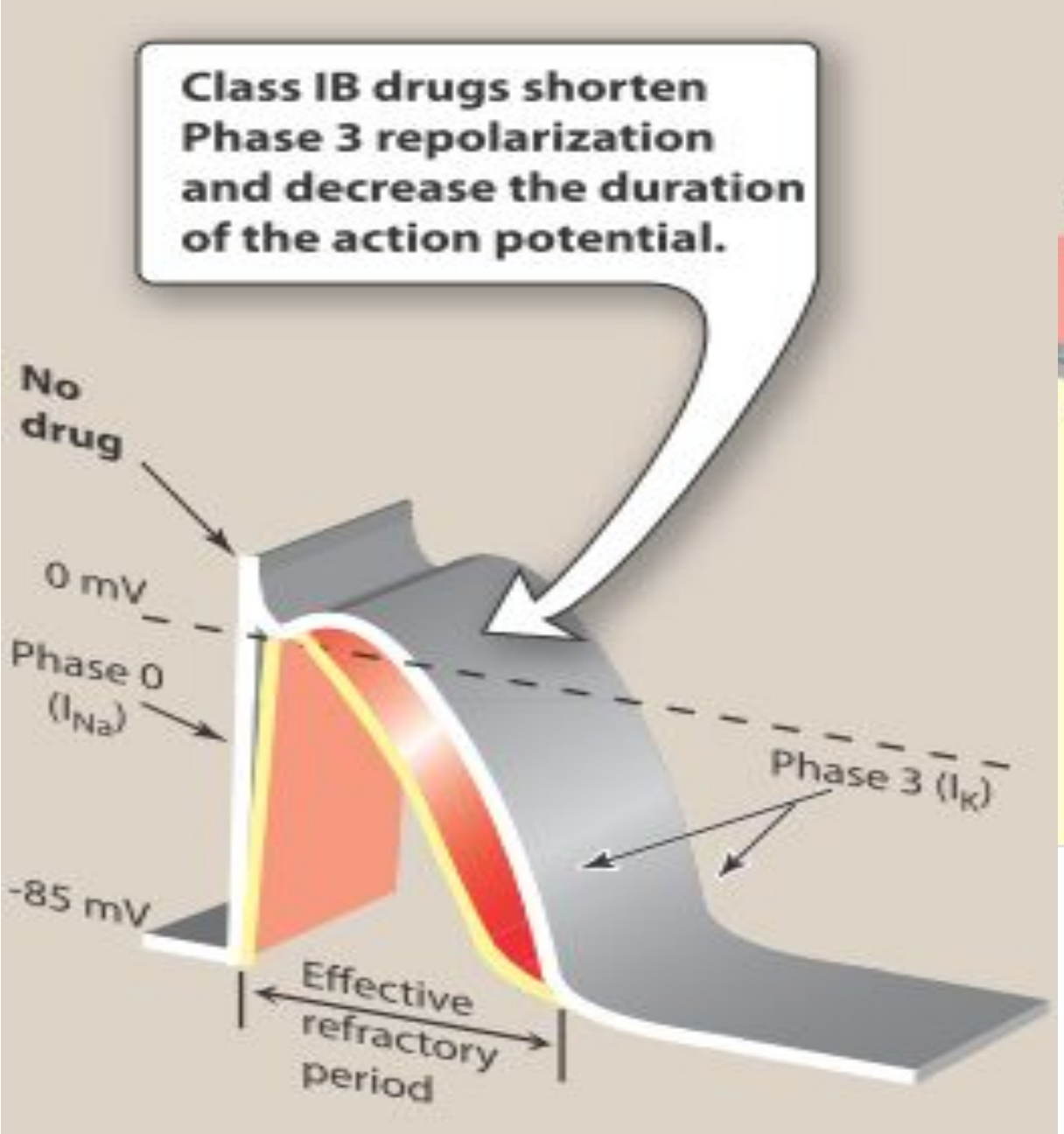
•*Class 1A*

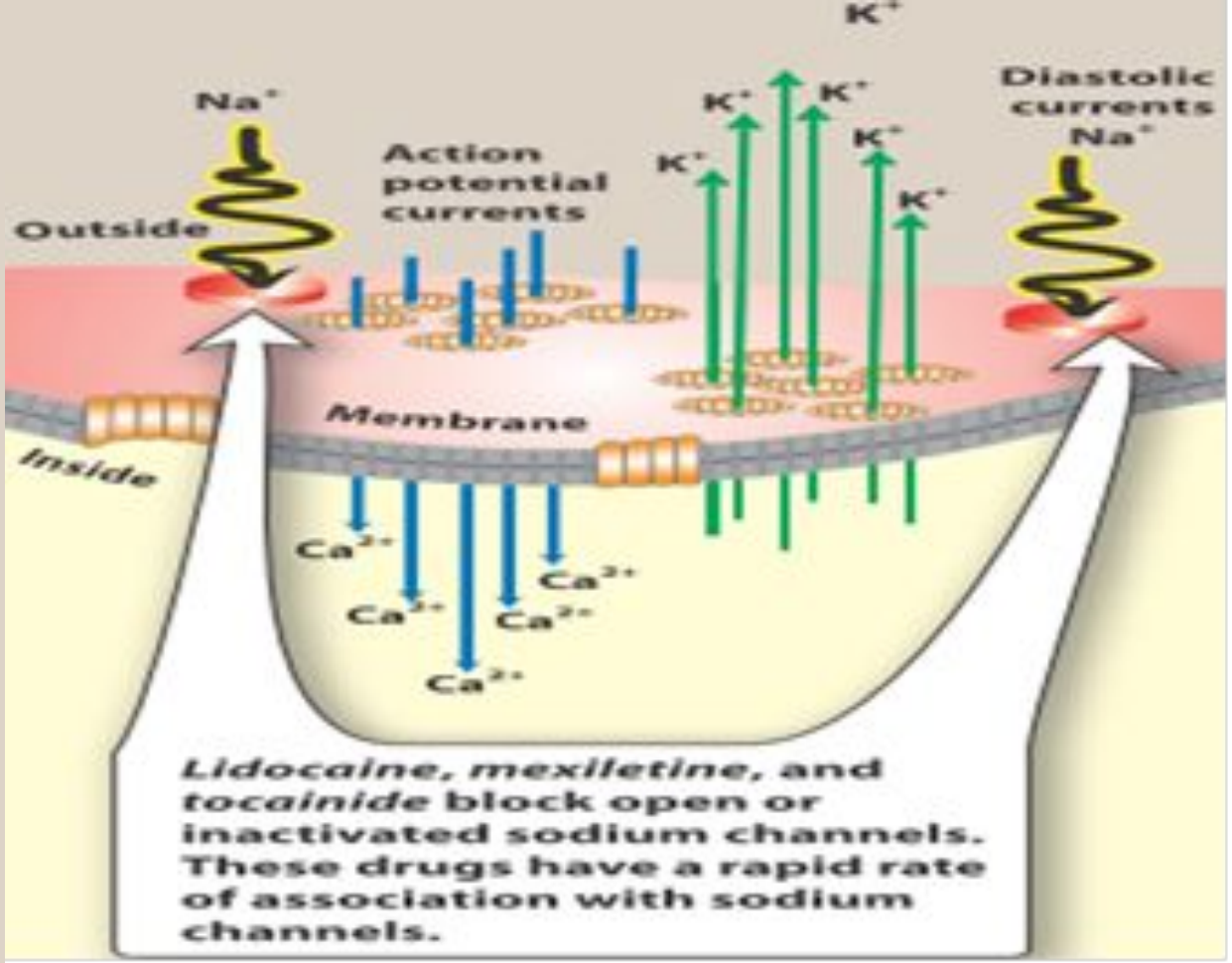
•They prolong the APD (i.e. prolong refractory period). They have an intermediate speed of association and then dissociation with activated/inactivated sodium-channels.





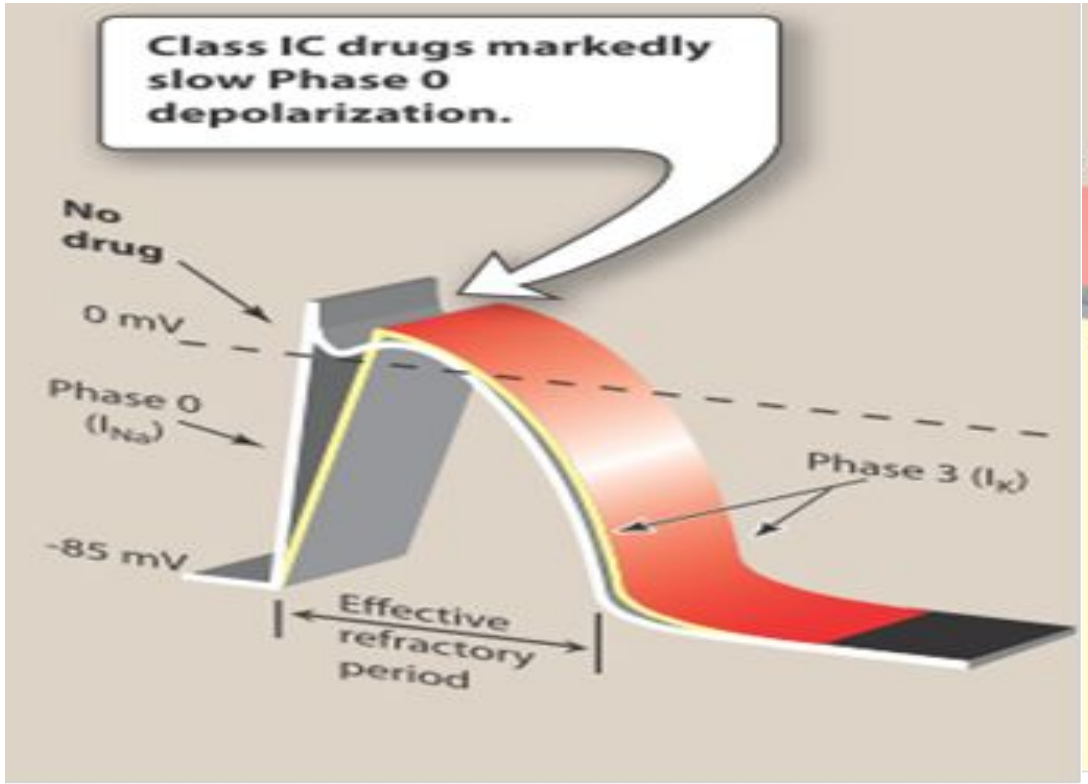
- ***Class 1A***
- They prolong the APD (i.e. prolong refractory period). They have an intermediate speed of association and then dissociation with activated/inactivated sodium-channels.

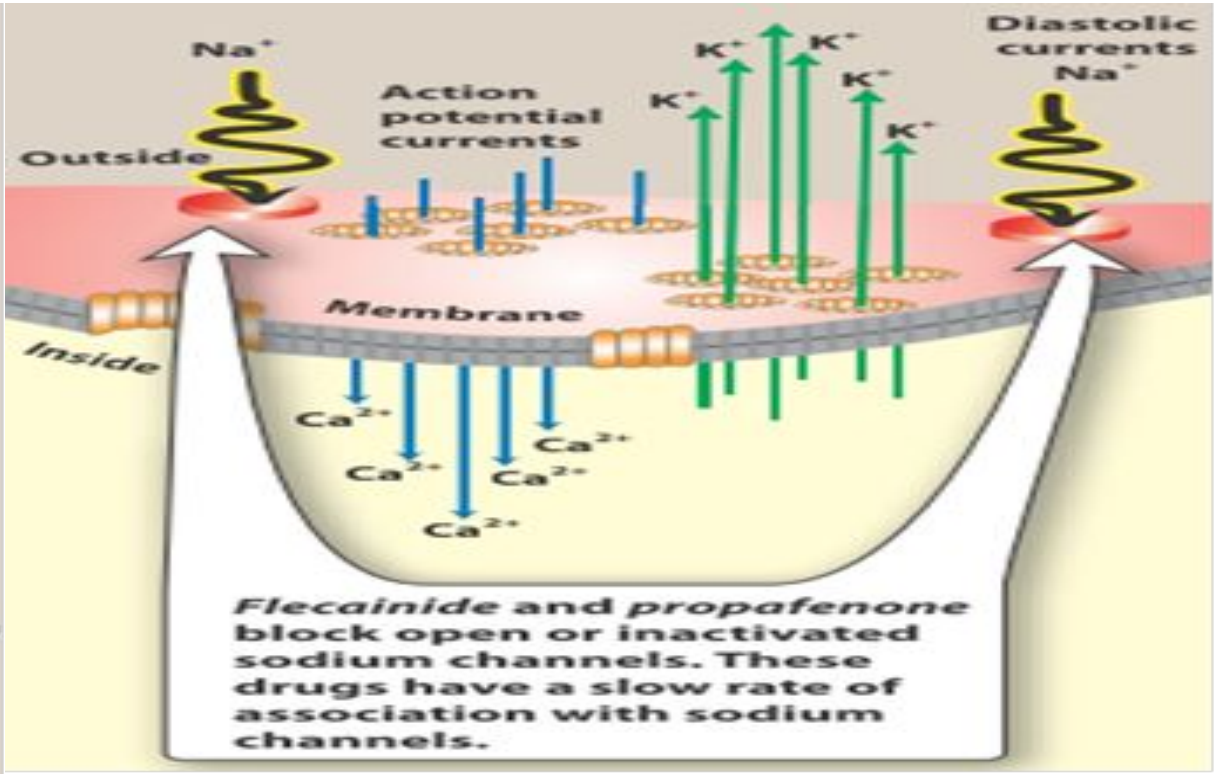

Class IB drugs shorten Phase 3 repolarization and decrease the duration of the action potential.
No drug
0 mV
Phase 0 (I_{Na})
Phase 3 (I_K)
-85 mV
Effective refractory period


Na+
Action potential currents
K+
Diastolic currents
Na+
Outside
Membrane
Inside
Ca2+
Lidocaine, mexiletine, and tocainide block open or inactivated sodium channels. These drugs have a rapid rate of association with sodium channels.

•***Class 1B***: they shorten the APD and The Class IB agents rapidly associate and dissociate from sodium channels. (i.e. shorten refractory period).

•***Class 1C***: they have minimal effects on the APD and refractory period. These drugs slowly dissociate from resting sodium channels.

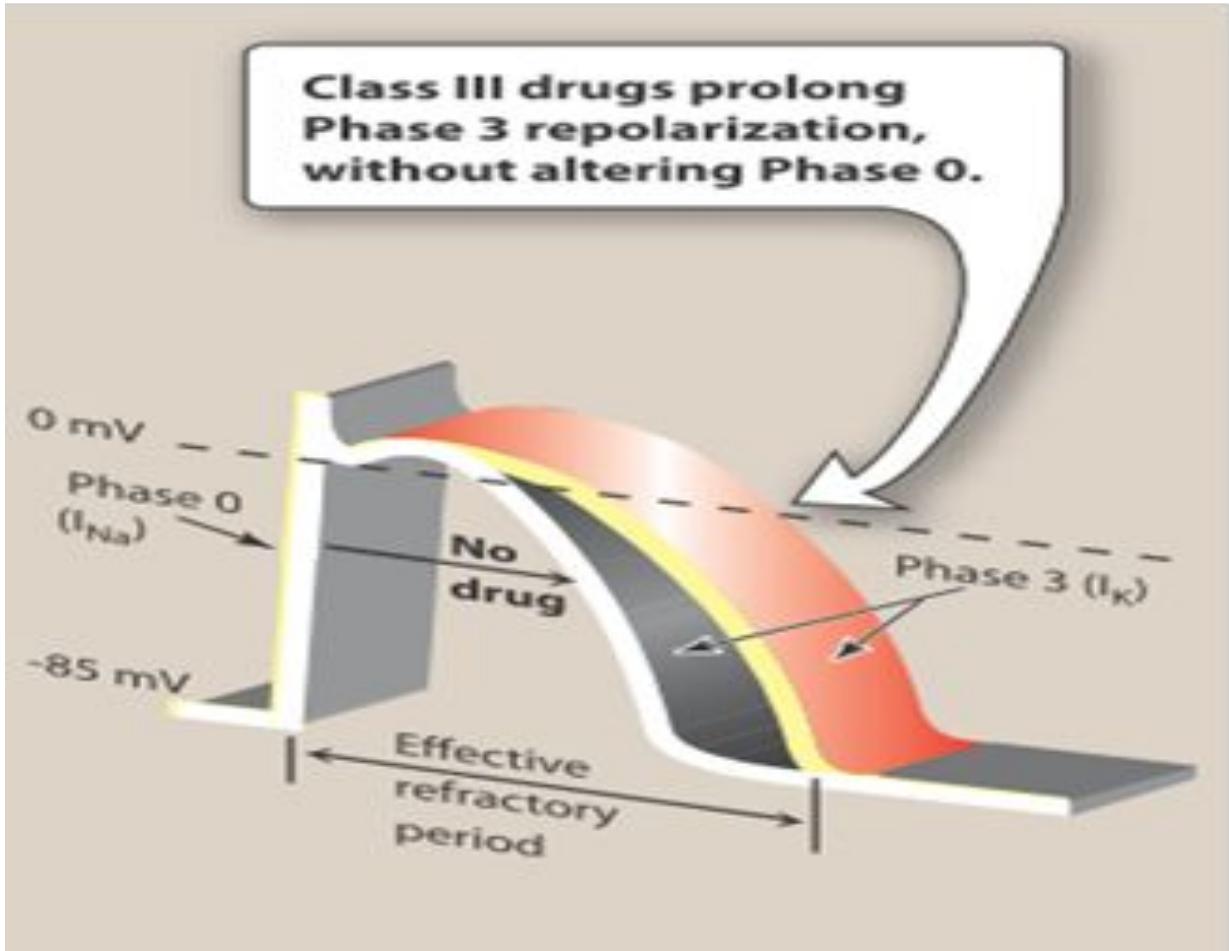


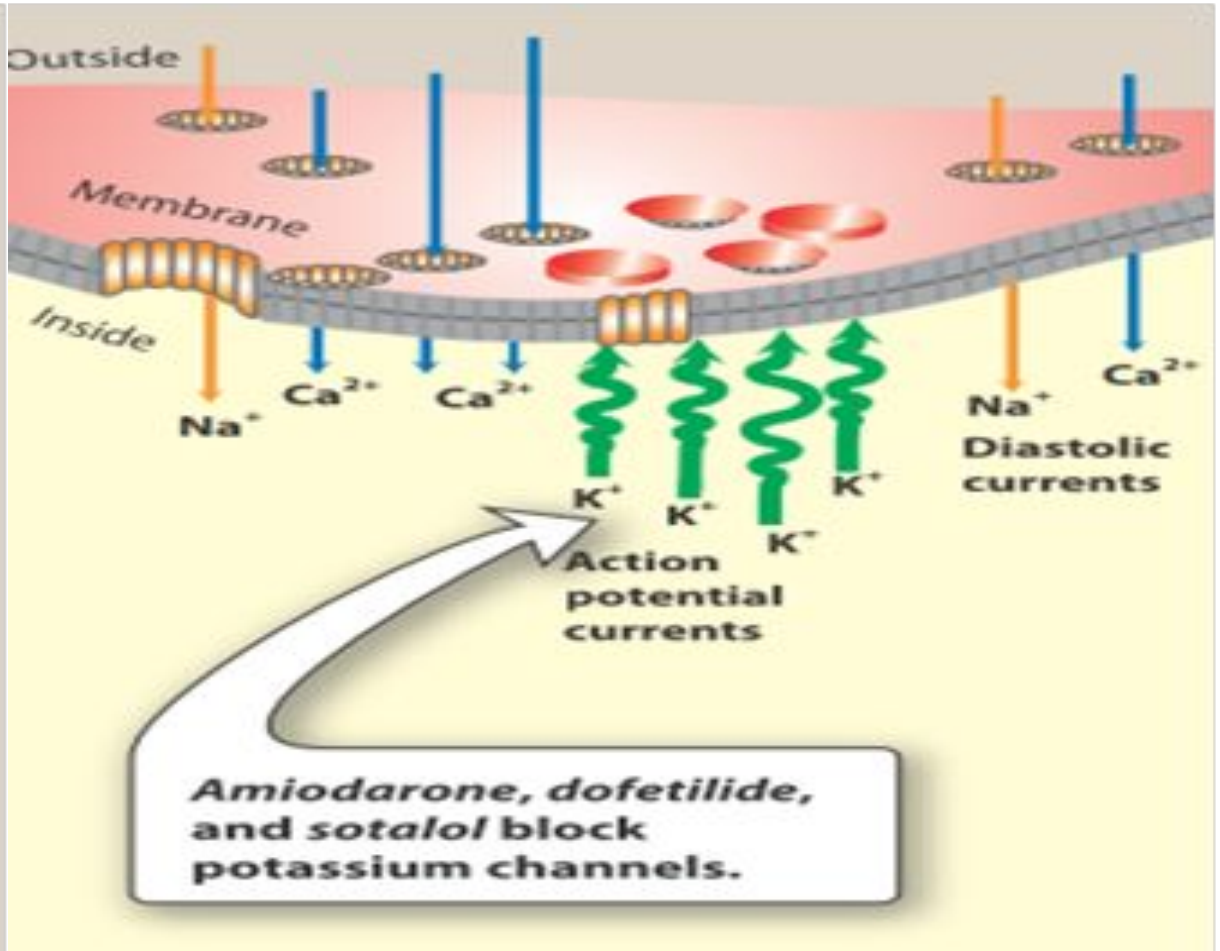


- ***2)) Class II action is sympatholytic***: Drugs with this action reduce β-adrenergic activity in the heart by decreasing the sympathetic out flow.

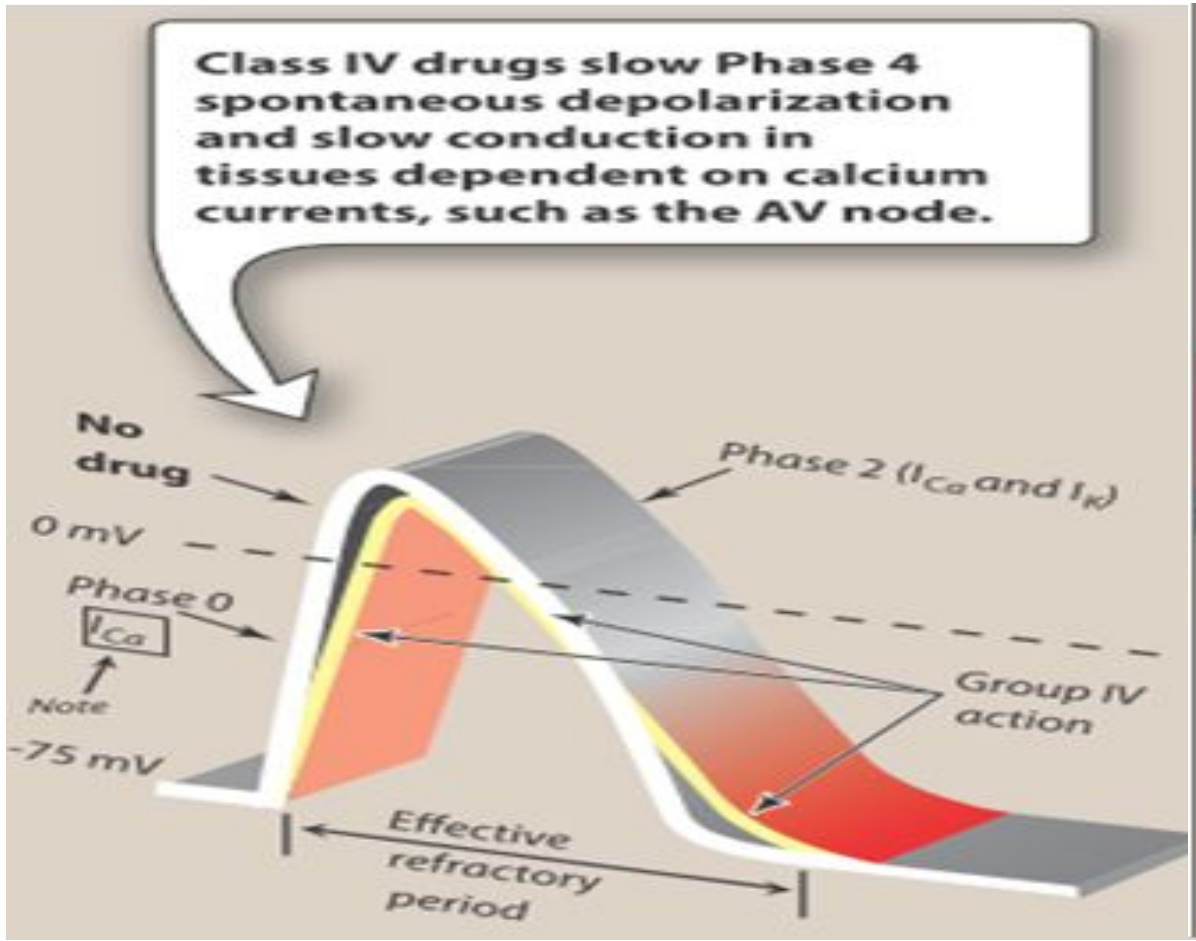
3)) Class III : action is manifest by prolongation of the APD. Most drugs with this action block the rapid component of the delayed rectifier potassium current. Inhibition of potassium channels (Class III activity) widens the action potential, leading to a prolonged QT interval

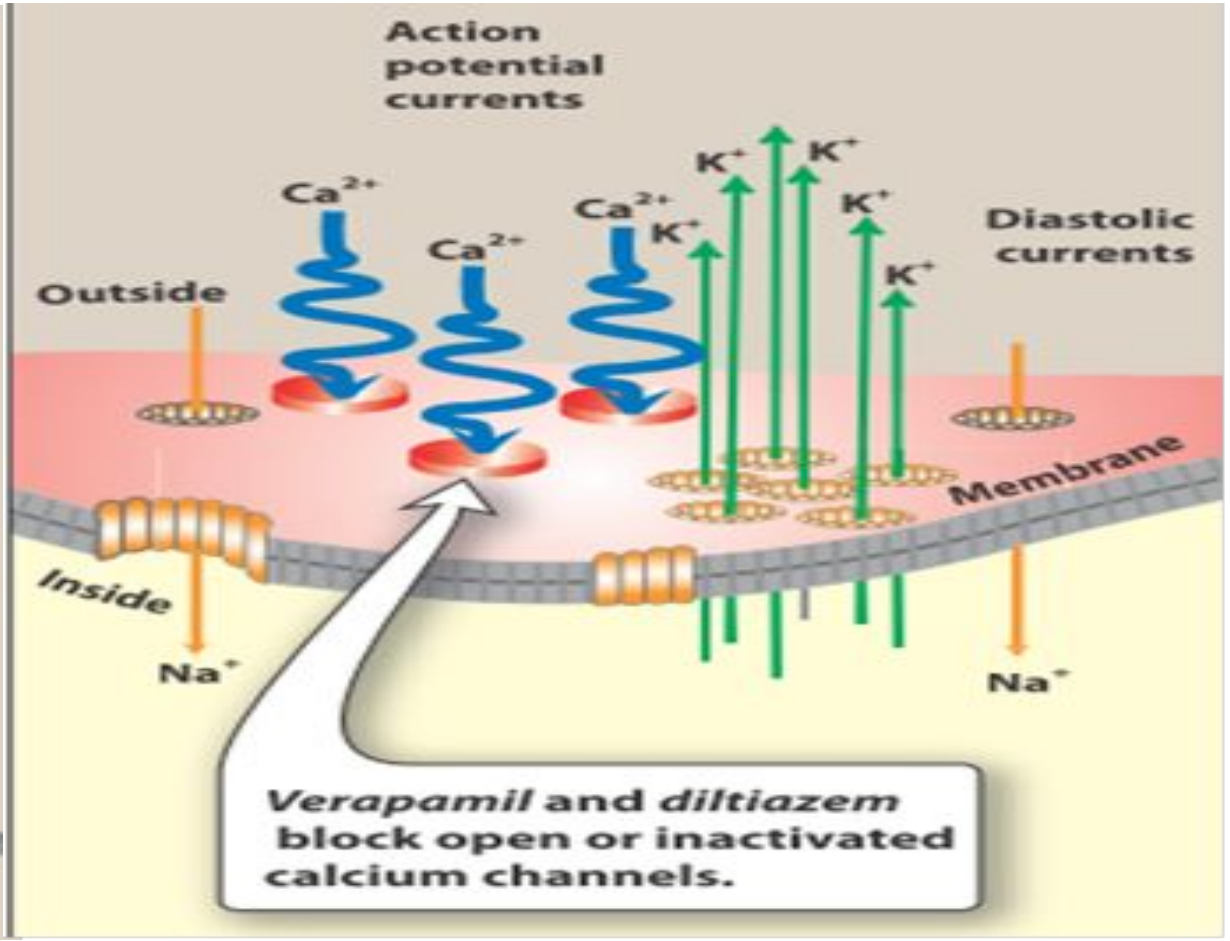
- ***4. Class 4 action is blockade of the cardiac calcium current***
- *5- Others*: adenosine, digoxin and magnesium


Class III drugs prolong Phase 3 repolarization, without altering Phase 0.
0 mV
Phase 0 (I_{Na})
No drug
Phase 3 (I_K)
-85 mV
Effective refractory period


Outside
Membrane
Inside
Na^+
Ca^{2+}
Ca^{2+}
K^+
K^+
K^+
K^+
Action potential currents
Na^+
Diastolic currents
Ca^{2+}
Amiodarone, dofetilide, and sotalol block potassium channels.

4. *Class 4 action is blockade of the cardiac calcium current*





•***SODIUM CHANNELS BLOCKERS***

• *A- SODIUM CHANNEL-BLOCKING DRUGS (CLASS I-A):*

•QUINIDINE

- Quinidine has pronounced cardiac **anti-muscarinic effects** than procainamide. Quinidine absorbed orally. It undergoes metabolism by the hepatic cytochrome P450 enzymes

❖ Quinidine is drug of choice to maintain normal sinus rhythm in patients with atrial flutter/fibrillation.

•Side effects:

1. *QT interval prolongation* and of torsade de pointes arrhythmia.
2. *GIT side effects*: diarrhea, nausea, and vomiting.
3. ***Cinchonism****:* A syndrome of headache, dizziness, and tinnitus.
4. Quinidine can increase the plasma concentrations of digoxin which may in turn lead to signs and symptoms of *digitalis toxicity.*

•Procainamide:

- The drug also is nonspecific blocker of potassium channels. It is given orally. Intravenous route is rarely used, because hypotension occurs if the drug is infused too rapidly.
- Procainamide has a relatively short half-life of 2 to 3 hours, acetylated in the liver &eliminated via the kidneys.
- Procainamide is of choice against most atrial and ventricular arrhythmias, digitalis-induced arrhythmias and atrial fibrillation of recent onset.
- Procainamide has *ganglion-blocking properties*. This action reduces peripheral vascular resistance and can cause hypotension.

•Side effect:

1. Torsade de pointes arrhythmia and syncope.
2. lupus erythematosus, pleuritis, pericarditis,
3. Others include nausea and diarrhea rash, fever
4. Patients receiving cimetidine and procainamide may exhibit signs of procainamide toxicity as cimetidine inhibits the metabolism of procainamide

•DISOPYRAMIDE

- Its cardiac anti muscarinic effects are even more marked than those of quinidine but it causes peripheral vasoconstriction

- Approximately half of the orally ingested drug is excreted unchanged by the kidneys.
- Disopyramide can precipitate all of the electro-physiologic disturbances described for quinidine.

Side effects:

- Atropine-like effect accounts for most of its symptomatic adverse effects: urinary retention, dry mouth, blurred vision, constipation, and worsening of pre-existing glaucoma.
- Disopyramide is used in a variety of supraventricular arrhythmias.

B. SODIUM CHANNEL-BLOCKING DRUGS (CLASS IB):(shorten APD)

•Lidocaine

•Acts mainly on damaged tissues.

❖ It drug of choice for arrhythmias during with acute myocardial infarction. It is used only by the intravenous route because of extensive first-pass transformation by the liver.

•Side effects:

- Lidocaine is one of the least cardiotoxic.
- Local anasthstic effects include paresthesias, tremor, nausea of central origin, hearing disturbances, slurred speech, and convulsions may occur.
-

•Phenytoin

•It appears to be particularly effective in treating digitalis -induced arrhythmias Phenytoin shortens the action potential duration of ventricular myocardium.

•Side effects:

- It may decrease the QT intervals.
- The rapid IV administration of phenytoin can present a hazard. Respiratory arrest, arrhythmias and hypotension have been reported.

•MEXILETINE

•Mexiletine is an orally **active congener of lidocaine**. The elimination half-life is 8-20 hours.

❖ Mexiletine is used in the treatment of ventricular arrhythmias.

❖ Mexiletine has also shown significant efficacy in relieving chronic pain, especially pain due to diabetic neuropathy and nerve injury.

•Adverse effects:

- Neurologic, like tremor, blurred vision, and lethargy.
- Nausea is also a common effect.

•***C- SODIUM CHANNEL-BLOCKING DRUGS (CLASS IC)(Na,K,Ca blockers on conducting system cells)***

•**Flecainide and Encainide**

•**Decrease the slope of phase 4 depolarization of S.A. node.**

- Flecainide is absorbed orally, undergoes minimal biotransformation, and has a half-life of 16to 20 hours.
- They are approved for refractory ventricular arrhythmias and for the prevention of paroxysmal atrial fibrillation/flutter associated with disabling symptoms and paroxysmal supraventricular tachycardia. It has no anti muscarinic effects.

•Side effects:

- Exacerbation of arrhythmia even when normal doses.
- **Contraindicated in heart failure and I.H.D (may cause sudden death)**

•**PROPAFENONE**

•It possesses weak β-blocking activity. It metabolized in the liver, with an average half-life of 5-7 hours.

•The drug is used primarily for:

- supraventricular arrhythmias and life-threatening ventricular arrhythmias in the absence of structural heart disease..

•The adverse effects: A metallic taste, constipation and arrhythmia

•**MORICIZINE**

Moricizine is is used for treatment of ventricular arrhythmias.

1. BETA-ADRENOCEPTOR-BLOCKING DRUGS (CLASS II)

- **Propranolol: (with MSA)** is used for
  - *Patients who have survived AMI to prolong life in this situation.*
  - *Inappropriate sinus tachycardia (e.g. in association with panic attacks).*
  - *Paroxysmal SVT that are precipitated by emotion or exercise.*
  - *Rapid atrial fibrillation that is inadequately controlled by digoxin.*
  - *Tachydysrhythmias of thyrotoxicosis (they decrease the conversion of T4 to T3 (Cardiotoxic).*
  - *Tachydysrhythmias of phaeochromocytoma, after adequate α-receptor blockade.*

- **Acebutolol:** cardio-selective β_1- blocking agent that also has some minor membrane stabilizing effects on the action potential.
  Esmolol is a shortest -acting β blocker used primarily as an antiarrhythmic drug for intraoperative and other acute arrhythmias.

•*DRUGS THAT PROLONG EFFECTIVE REFRACTORY (CLASS III)*

•*K channel blockers*

•These drugs prolong action potentials, usually by blocking potassium channels in cardiac muscle(also block Na and Ca channels). (**broad spectrum** anti arrythmic drug:all types of arrythmias)

•**Amiodarone(40% iodine) and Dronedarone(less iodine)**

- Amiodarone has anti-anginal as well as antiarrhythmic activity. Amiodarone is incompletely absorbed after oral administration.
- Full clinical effects may not be achieved until 6 weeks after initiation of treatment.
- Amiodarone is metalized by liver cytochrome CYP3A4 and its levels are increased by drugs that inhibit this enzyme, e.g. cimetidine.
- Drugs that induce CYP3A4, e.g. rifampin, decrease Amiodarone concentration when co-administered.

•It has low incidence of torsade de pointes despite significant QT interval prolongation. Amiodarone causes **coronary** and peripheral vasodilation.

•Indications:

- Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias.
- In Wolff-Parkinson-White syndrome (it is a disorder of the heart in which the ventricles of the heart contract prematurely due to an accessory pathway known as the *bundle of Kent*. This accessory pathway is an abnormal electrical communication from the atria to the ventricles).

• Side effects:

- Dose-related pulmonary fibrosis (chronic cough)may be observed in 1% of patients.
- Abnormal liver function tests and hepatitis(fibrosis) may develop,
- Photodermatitis, corneal microdeposits(reversible) and visual halos Rarely.

• Amiodarone blocks the peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) (toxic)results in hypothyroidism or hyperthyroidism.

• Contraindicated in arrythmia due to thyrotoxicosis.

•VERNAKALANT:

•It prolongs the atrial effective refractory period and slows conduction over the AV node. Ventricular effective refractory period is unchanged produces less APD prolongation in the ventricle (does not change the QT interval).

•SOTALOL

Sotalol has both (class II) and (class III) actions. It has a modest ability to suppress ectopic beats

•DOFETILIDE

- Dofetilide causes a dose-dependent blockade of potassium current. The half-life is 10 hours. Excretion is in the urine, with 80 percent as unchanged
- Used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease with impaired left ventricular function.

•IBUTILIDE

- Ibutilide appears to be more effective in terminating atrial flutter than atrial fibrillation. It may cause QT interval prolongation and torsade de pointes.

1. CALCIUM CHANNEL-BLOCKING DRUGS (CLASS 4)

- Verapamil and Diltiazem bind only to open, depolarized channels, thus preventing repolarization until the drug dissociates from the channel.
- They slow conduction and prolong the effective refractory period.
- They are absorbed after oral administration. Verapamil is extensively metabolized by the liver.

•VERAPAMIL and DILTIAZEM

•Verapamil blocks both activated and inactivated L-type calcium channels. Atrio- ventricular nodal conduction time and effective refractory period are invariably prolonged.

- SVT is the major arrhythmia indication for verapamil. Contraindicated in VT (sudden death).
- To retain sinus rhythm after using digoxin for AF(since digoxin can't bring sinus rhythm).

•5- MISCELLANEOUS ANTIARRHYTHMIC AGENTS:

ADENOSINE

Adenosine is a nucleoside. Its half-life in the blood is less than 10 seconds. It inhibits the pacemaker current through its action as agonist on the A receptors in the conducting system ,which **decreases the slope of phase 4 of** the pacemaker action potential (-ve chronotropic effect).

- It **is the drug of choice for emergency prompt conversion of paroxysmal SVT to sinus rhythm**. (given i.v) (rapid onset of action within 4 seconds)
- It causes flushing and shortness of breath or chest burning.
- Ineffective if its taken with theophylin.
- Contraindicated in asthmatic patients.

•MAGNESIUM

- It used for digitalis-induced arrhythmias with hypomagnesaemia.
- It influence Na^+/K^+ ATPase, sodium channels, certain potassium channels, and calcium channels.

•Digoxin:

- It **increases vagal activity (parasympathetic stimulation),** thereby decreasing heart rate by slowing depolarization of pacemaker cells in the AV node, so The principal antiarrhythmic effect is achieved via prominent vagotonic actions .

Thank you