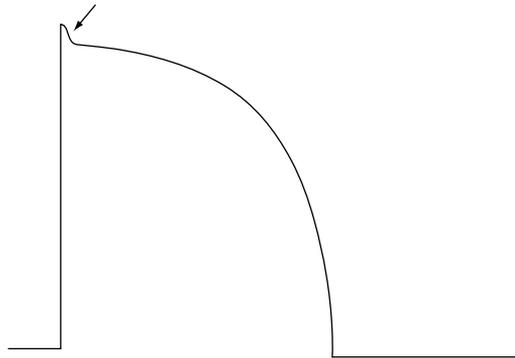


# 1 Ions, Channels, and Currents

## Self-Assessment Questions

### 1.1 POTASSIUM CHANNELS AND CURRENTS

- 1 In a diagram of AP shown below, which one of the following currents is active where arrow is pointing?



- A  $I_{to}$   
B  $I_{K1}$   
C  $I_{Na}$   
D  $I_{Ca}$
- 2 Which one of the following genes controls the expression of  $I_{Kr}$ ?
- A KCNQ1 (KvLQT1)  
B KCNH2 (HERG)  
C SCN5A  
D MinK
- 3 Which one of the following actions is likely to activate  $I_{K_{atp}}$  current?
- A Rise in intracellular ATP  
B Rise in intracellular calcium  
C Fall of intracellular ATP  
D Fall of intracellular calcium

## 2 Essential Cardiac Electrophysiology

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- 4 How does congestive heart failure affect depolarizing/repolarizing currents?
- A Outward repolarizing currents are reduced
  - B Inward depolarizing currents are reduced
  - C Outward repolarizing currents are increased
  - D APD is decreased
- 5 Which one of the following is least likely to occur with prolongation of the plateau phase of the AP?
- A Increase in strength of contraction
  - B Increase in conduction velocity
  - C Increase in the duration of contraction
  - D Increase in refractoriness
- 6 Which one of the following is likely to increase the activity of  $I_{Kr}$ ?
- A Increased extracellular potassium
  - B Exposure to Sotalol
  - C Decreased extracellular potassium
  - D Increase in chloride current
- 7 Which one of the following agents is likely to block  $I_{Ks}$ ?
- A Aminophylline
  - B Indapamide
  - C Activation of protein Kinase C
  - D Erythromycin
- 8 When does the reverse use dependent block occur?
- A It occurs with repeated activation of the channel
  - B It occurs when the sodium channel is blocked
  - C It occurs at a slow heart rate but not at a fast heart rate
  - D It occurs in the presence of catecholamines
- 9 Which one of the following is the least likely attribute of  $I_{to}$ ?
- A It is present in ventricular epicardium but not in endocardium
  - B It is responsible for the spike and dome characteristic
  - C It is a chloride current
  - D It is also present in the human atrium
- 10 Which one of the following is associated with Brugada syndrome?
- A Defect in the SCN5A gene
  - B Loss of  $I_{Kr}$
  - C ST segment depression in precordial leads
  - D Deafness

## 1.2 SODIUM CHANNELS AND CURRENTS

- 1 Which one of the following currents is likely to occur when the Na moves across the cell membrane and into the cell?
  - A Inward current
  - B Outward current
  - C Repolarizing current
  - D No change in current
  
- 2 A patient receiving a Na channel blocker develops AF with rapid ventricular response. What changes on ECG can be anticipated to occur?
  - A Narrowing of the QRS complex during tachycardia
  - B Widening of the QRS complex during tachycardia
  - C Prolongation of the QT interval
  - D Shortening of the QT interval
  
- 3 What is likely to happen when a Na channel is blocked?
  - A Increase in intracellular Ca and increased contractility
  - B Increase in EAD and DAD
  - C Decrease in contractility
  - D Increase in extracellular Na
  
- 4 Which one of the following is not associated with Brugada syndrome?
  - A Mutation in SCN5A resulting in loss of function
  - B Increase in  $I_{to}$  current
  - C Inhibition of  $I_{Ca}$  during the plateau phase
  - D Mutation in SCN5A, resulting in gain of function
  
- 5 What type of channel block, by lidocaine, results in effective suppression of arrhythmias during myocardial ischemia?
  - A Inactivated state block
  - B Resting state block
  - C Open state block
  - D Closed state block
  
- 6 Which one of the following agents is likely to be effective in treating Flecainide-induced VT?
  - A IV magnesium
  - B IV lidocaine
  - C IV amiodarone
  - D IV digoxin

- 7 Which one of the following metabolic abnormalities is likely to decrease lidocaine dissociation from the channel sites?
- A Acidosis
  - B Ischemia
  - C Hyperkalemia
  - D Hyponatremia
- 8 What electrophysiologic manifestations can be expected when  $I_{NaB}$  (the slow component of the background Na current) is blocked?
- A Lengthening of the QT interval
  - B Positive inotropy
  - C Occurrence of EAD
  - D Bradycardia
- 9 Which one of the following interventions is likely to promote occurrence of TDP in patients with LQT3?
- A Beta blocker induced bradycardia
  - B Permanent pacemaker
  - C Mexiletine
  - D Exercise-induced sinus tachycardia

### 1.3 CALCIUM CHANNELS AND CURRENTS

- 1 In which one of the following is there no contribution from Calcium current  $I_{CaL}$ ?
- A EAD
  - B Electrical remodeling of the atrium during AF
  - C DAD
  - D Depolarization of the SA and AV nodes
- 2 Which of the following statements is incorrect?
- A  $\beta$ -Adrenergic agonists increase  $I_{CaL}$  channel activity
  - B  $\beta$  Blockers act as Ca channel blockers
  - C Parasympathetic stimulation decreases  $I_{CaL}$  activity
  - D T-type Ca channel density is increased by growth hormone, endothelin, and pressure overload
- 3 Which of the following agents has no effect on T-type Ca channel?
- A Amiloride
  - B Flunarizine
  - C Mibefradil
  - D Digoxin

- 4 Which of the following statements for the sarcoplasmic Ca release channel (SCRC) is incorrect?
- A Caffeine releases Ca from SCRC
  - B Doxorubicin depletes sarcoplasmic reticulum Ca
  - C It is blocked by verapamil
  - D Ischemia decreases Ca release from the sarcoplasmic reticulum
- 5 Which of the following agents does not block Ca channel?
- A Terfenadine
  - B Magnesium
  - C Diltiazem
  - D Sotalol
- 6 Which of the following statements is incorrect?
- A  $I_{CaL}$  participates in the occurrence of DAD
  - B Phase-3 EAD shares the mechanisms of DAD
  - C EAD is associated with bradycardia and prolongation of APD
  - D DAD is associated with increased heart rate and Ca overload

## 1.1 POTASSIUM CHANNELS AND CURRENTS<sup>1-4</sup>

- There are more than eight types of potassium currents.
- The plateau phase of the action potential (AP) depends on the balance between inward (depolarizing) and outward (repolarizing) currents.
- Potassium currents (outward movement of the K through the potassium channels) are the main contributors to repolarization.

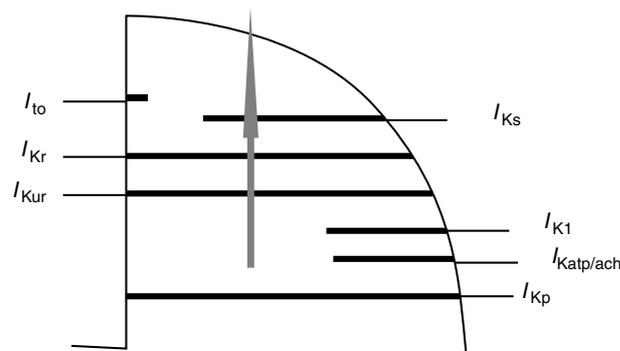
### Classification of potassium currents

Voltage gated currents	Inwardly rectifying currents	Background currents
$I_{to}$	$I_{K1}$	$I_{Kp}$
$I_{Kur}$	$I_{Kach}$	
$I_{Kr}$	$I_{Katp}$	
$I_{Ks}$		

- AP duration (APD) determines the amount of calcium influx and tissue refractoriness. It is inversely related to heart rate. Prolongation of AP plateau increases the strength and duration of contraction. It also increases refractoriness.
- In congestive heart failure (CHF) and in left ventricular hypertrophy (LVH), repolarizing outward currents are reduced by 50%. This increases APD and results in early after depolarization (EAD) and arrhythmias. Use of class III drugs in patients with CHF needs reevaluation as the intended target (K channels) is down regulated or absent.
- In atrial fibrillation (AF) repolarizing outward currents ( $I_K$ ,  $I_{to}$ ) are reduced. Reduction of these currents may exacerbate the arrhythmic effect of hypokalemia and hypomagnesemia.
- Potassium channel expression is decreased in hypothyroid and hypoadrenal states.

### Delayed and inwardly rectifying voltage sensitive potassium channels

- Rectification is a diode-like property of unidirectional current flow, which could be inwards or outwards. It limits the outward flow of potassium through  $I_{Kr}$  and  $I_{Ks}$  during a plateau. Delayed rectifier potassium channels have slow onset of action.
- Voltage gated potassium channels are activated during an upstroke of AP.
- Rapidly activating and inactivating voltage-sensitive transient outward current produces phase 1 of repolarization.
- Slowly activating delayed rectifier potassium current, and inward rectifier  $I_{K1}$ , which includes fast inactivating rapid component  $I_{Kr}$  and slow component  $I_{Ks}$ , contributes to plateau and phase 3 of AP.



**Fig 1.1** Outward currents.

- K channels carry a positive charge, which acts as a voltage sensor.
- Potassium channels are closed at resting potential and open after depolarization.
- Two types of voltage-gated channels play a major role in repolarization.
  - i Transient outward current ( $I_{to}$ ), which is characterized by rapid activation and inactivation.
  - ii Delayed rectifier  $I_K$ , which has several components (Fig. 1.1):
    - $I_{Kr}$  is a rapidly activating current with inward rectification.
    - $I_{Ks}$  is a slowly activating current.
    - $I_{Kp}$  is a time independent background plateau current.
    - $I_{Kur}$  is an ultra rapid current.

#### Transient outward potassium current ( $I_{to}$ )<sup>5</sup>

- There are two types of  $I_{to}$  currents:  $I_{to1}$  and  $I_{to2}$ .
- $I_{to}$  is present in ventricular epicardium but not in endocardium. It is responsible for spike and dome morphology of AP in epicardium.
- In human atrium it recovers rapidly from inactivation, thus allowing rapid repolarization at a fast heart rate.
- Flecainide, Quinidine, and Ambasilide inhibit  $I_{to}$ . Flecainide binds to inactivated  $I_{to1}$ . It also demonstrates fast unbinding. Quinidine binds to open channel; its slow recovery from block causes a rate dependent effect.
- Inhibition of  $I_{to}$  prolongs repolarization in diseased human ventricle.
- $I_{to2}$  is calcium activated.

#### $I_{to}$ and J wave

- J wave (Osborn wave), elevated J point and T wave alternans may be due to a transmural gradient between epicardium and endocardium as a result of uneven distribution of  $I_{to}$ .
- Prominent J waves are often seen in the presence of hypothermia and hypercalcemia.

**Rapidly activating delayed rectifier  $I_{Kr}$** 

- It is blocked by methane sulfonamide, class III agents (D-Sotalol).
- Inward rectification of  $I_{Kr}$  results in a small outward current.
- It plays an important role in atrial pacemaker cells. It rapidly recovers from inactivation and it peaks at  $-40$  mV.
- KCNH2 (HERG, Human Ether Related-a-go-go gene protein) encodes  $I_{Kr}$  channel.
- $I_{Kr}$  is increased in the presence of elevated extracellular potassium. Normally, increased extracellular potassium will decrease the outward potassium current by decreasing the chemical gradient, but the activity of  $I_{Kr}$  is increased.
- Increase in serum potassium by 1.4 mEq/L decreases QTc by 24% and decreases QT dispersion.
- The efficacy of  $I_{Kr}$  blockers is limited by inverse rate dependency. The drug is more effective at a slower heart rate. A high heart rate increases the prevalence of  $I_{Ks}$ , which is insensitive to  $I_{Kr}$  blocker. This offsets the  $k$  blocking effects of the  $I_{Kr}$  blockers.
- The effect of  $I_{Ks}$  but not of  $I_{Kr}$  is enhanced by  $\beta$ -adrenergic stimulation. Thus, the effects of pure  $I_{Kr}$  blockers will be antagonized by sympathetic stimulation.
- Selective  $I_{Kr}$  blockers (D-Sotalol) lose efficiency at high rates and during sympathetic stimulation.
- $I_{Kr}$  and  $I_{Ks}$  are present in the human atrium and ventricle.

**Slowly activating delayed rectifier  $I_{Ks}$** 

- $I_{Ks}$  is controlled by the gene KvLQT1 (voltage-dependent potassium controlling protein) and MinK (minimal potassium current controlling protein). MinK combined with protein of KvLQT1 induces  $I_{Ks}$ . Expression of both these proteins is necessary for normal function of  $I_{Ks}^1$ .
- MinK, a protein, acts as a function altering  $\beta$  subunit of KvLQT1. MinK modifies KvLQT1 gating and pharmacology.
- Mutation in MinK and KvLQT1 causes congenital long QT syndrome (LQTS).
- MinK suppression leads to inner ear abnormalities and deafness, seen in the Jarvell Lange-Nielson syndrome.
- Reduced activity of  $I_{Ks}$  in M cells prolongs APD.
- Bradycardia and class III drugs, which reduce  $I_{Ks}$  in M cells, prolong APD and predispose to arrhythmias.
- Slow deactivation of  $I_{Ks}$  is important for rate dependent shortening of AP. As the heart rate increases,  $I_{Ks}$  has less time to deactivate during shortened diastole, it accumulates in an open state, and contributes to faster repolarization.
- Increase in intracellular magnesium decreases and increase in intracellular calcium increases  $I_{Ks}$ .

- Indapamide (Diuretic), Thiopental, Propafol (Anesthetics) Benzodiazepine, and chromanol block  $I_{K_S}$ .
- Increasing cAMP either by  $\beta$ -adrenergic stimulation or by phosphodiesterase inhibitors increases  $I_{K_S}$ .
- Activation of protein kinase C increases  $I_{K_S}$ .

### **$I_{K_{UR}}$ current**

- It is responsible for atrial repolarization. It is a potassium selective outwardly rectifying current. Short APD of the atria is due to  $I_{K_{UR}}$ .
- $I_{K_{UR}}$  is also found in intercalated disks.
- $I_{K_{UR}}$  is absent from the human ventricular myocardium.
- It is enhanced by  $\beta$ -adrenergic agonists and is inhibited by  $\alpha$ -adrenergic agonists.
- Drugs inhibiting  $I_{K_S}$  (Amiodarone, Ambasilide) or  $I_{K_{UR}}$  (Ambasilide) will be therapeutically superior.
- The presence of  $I_{K_{UR}}$  in the human atrium makes atrial repolarization relatively insensitive to agents that fail to inhibit this current (D-Sotalol and Flecainide). Quinidine and Ambasilide block  $I_{K_{UR}}$  in a rate independent fashion.
- $I_{K_{UR}}$  decreases with increasing heart rate.

## **Inwardly rectifying currents**

### **Inward rectifier $I_{K1}$**

- $I_{K1}$  rectification allows it to carry substantial current at negative potentials which maintains the resting potential.
- Resting potassium conductance is produced by voltage independent inwardly rectifying potassium channels.
- These channels permit inward potassium flux on membrane hyperpolarization but resist outward potassium flux on depolarization. It prevents potassium ion leak during prolonged depolarization. In addition to  $I_{K1}$ ,  $I_{K_{atp}}$  and  $I_{K_{ach}}$  are also inward rectifiers.
- Intracellular magnesium, calcium, and polyamines block  $I_{K1}$ . Increase in intracellular pH inactivates  $I_{K1}$ . Increase in extracellular potassium depolarizes the resting membrane.
- Inwardly rectifying potassium channels (K1) produce less outward currents than inward currents. They stabilize the resting membrane potential by high resting potassium conductance, but during depolarization produce little outward current.

### **ATP sensitive potassium channel (K<sub>atp</sub>)<sup>6,7</sup>**

- $K_{atp}$  channel opens when the intracellular ATP level falls and closes when the ATP levels rise. ATP produced by the glycolytic pathway is preferentially sensed by the  $K_{atp}$  channel.
- $I_{K_{atp}}$  is a weak inward rectifier but produces a large outward current during depolarization and its activation decreases APD.

- It is responsible for ischemia preconditioning where brief episodes of ischemia protect the myocardium from prolonged episodes of ischemia.
- During ischemia, intracellular magnesium and sodium levels increase,  $I_{K_{atp}}$  current decreases, and extracellular potassium increases.
- Protons, lactates, oxygen free radicals, adenosine, and muscarinic receptor stimulation desensitize the  $K_{atp}$  channel to the effects of the ATP level.
- Sodium and potassium pump and other ATPases degrade ATP.
- Cromakalim, Bimakalim, Aprikalim, Nicorandil, Adenosine, and protein kinase C open the  $K_{atp}$  channel and mimic preconditioning. Sulfonylureas such as Glipizide and Tolbutamide block  $K_{atp}$  and abolish preconditioning.
- During ischemia there is loss of intracellular potassium and increase in extracellular potassium resulting in membrane depolarization, slow conduction, and altered refractoriness resulting in reentrant arrhythmias.  $K_{atp}$  counteracts these effects by shortening APD, decreasing workload, promoting inexcitability, and increasing potassium conductance during ischemia and hypoxia. Increased potassium conductance is a result of an increased level of intracellular sodium that occurs during ischemia.
- $I_{K_{atp}}$  decreases APD and calcium influx. It preserves high-energy phosphates.
- Diazoxide does not activate  $I_{K_{atp}}$  in sarcolemma but mimics preconditioning. This suggests that there may be other pathways involved in preconditioning.
- $I_{K_{atp}}$  causes coronary vasodilatation.

#### **$I_{K_{ach}}$ (Acetylcholine-dependent K current)**

- Stimulation of muscarinic receptors activates this current. It is mediated by acetylcholine.  $I_{K_{ach}}$  is inwardly rectifying potassium current.
- Parasympathetic stimulation slows heart rate by activating muscarinic receptors, which reduces  $I_f$  (hyperpolarizing cation current; f stands for funny) in pacemaker cells.
- The effect of potassium channel blockers on atrial repolarization depends on their ability to counteract cholinergic activation of  $I_{K_{ach}}$ , either by direct blocking of the channel (Quinidine) or by muscarinic receptor antagonism (Ambasilide, Disopyramide).

#### **Background K currents $I_{Kp}$**

- These currents contribute to repolarization and resting membrane potential.
- These currents are inhibited by decreasing intracellular pH.
- Arachidonic acid and polyunsaturated fatty acids modulate these channels.

#### **Characteristics of potassium channel block<sup>5,8,9</sup>**

- Voltage gated potassium channels are activated during upstroke of AP.
- Rapidly activating and inactivating voltage sensitive transient outward current produces phase 1 of repolarization.

- Slowly activating delayed rectifier potassium current, and inward rectifier  $I_{K1}$ , which includes fast inactivating rapid component  $I_{Kr}$  and slow component  $I_{Ks}$ , contributes to plateau and phase 3 of AP.
- Potassium channel blockers prolong APD. This is characteristic of Class III action.
- Some potassium channel blockers produce less block at a fast heart rate and more blocks at a slower heart rate. This phenomenon is called reverse use dependence.
- Potassium channels contribute to repolarization; therefore, reverse use dependent block will manifest itself during repolarization at the channel level.
- Blocking of K channel may not consistently affect repolarization because of the following:
  - i Many potassium channels are involved in repolarization.
  - ii Blocking of potassium channels (outward currents) may be counterbalanced by inward currents  $I_{Ca}$ ,  $I_{Na}$ , and  $I_{Na/Ca}$ . Thus no one current dominates repolarization.
  - iii Nonspecific effects of potassium channel blockers.
  - iv Extracellular potassium level may affect K currents.
  - v Potassium channel distribution may be variable. Potassium channel expression varies within different layers of myocardium.  $I_{Kur}$  is found in the atria but not in the ventricles.
  - vi  $I_{Kr}$  block could shift repolarization to  $I_{Ks}$  at rapid rates. Inability of  $I_{Ks}$  to deactivate rapidly and fully will produce less of an increase in APD.
  - vii Many antiarrhythmics are capable of causing potassium channel block and other ion channel blocks simultaneously.
  - viii Drugs that need a long plateau phase to work will be more effective in the ventricle than the atrium.
- Open channel block occurs when the drug is present during activated or open state.
- Trapping block occurs when the channel closes around the drug without need for the drug to unbind. Activation is required to remove the drug from the binding site.
- The drug may bind the channel during the inactive state, but cannot bind it during the resting state.

#### **Effect of pharmacologic agents on action potential**

- Acetylcholine in low concentration prolongs and in high concentration produces abbreviation of epicardial AP. These effects are as follows:
  - i Reversed by atropine.
  - ii Do not occur when  $I_{to}$  is blocked.
  - iii Accentuated by isoproterenol.
  - iv Persist in the presence of Propranolol.
  - v Caused by inhibition of  $I_{Ca}$  or activation of  $I_{Kach}$ .

- Isoproterenol causes epicardial AP abbreviation more than endocardial. It influences  $I_{to}$ ,  $I_{Ca}$ ,  $I_K$ , and  $I_{Cl}$ . These currents contribute to phase 1 and phase 3 of AP.
- Organic calcium channel blockers (Verapamil) and inorganic calcium channel blocker  $MnCl_2$  decreases the  $I_{Ca}$  (inward current) and leaves the outward currents unopposed, resulting in decrease of APD and loss of dome in epicardium and not in endocardium.
- $I_{to}$  block may establish electrical homogeneity and abolish arrhythmias due to dispersion of repolarization caused by drugs and ischemia.
- Quinidine inhibits  $I_{to}$ .
- Amiloride, a potassium sparing diuretic, prolongs APD and refractoriness.
- Antiarrhythmics, Antimicrobial, Antihistamine, Psychotropic, GI prokinetic, and a host of other pharmacologic agents may alter repolarization.

### **M cells, potassium currents, and APD**

- M cells are found in the mid-myocardium of anterior, lateral wall, and outflow tract.
- Electrophysiologically they resemble Purkinje cells.
- M cells show disproportional AP prolongation in response to slow heart rate. This may be due to weaker  $I_{Ks}$  and stronger late  $I_{Na}$ .
- M cells may enforce pump efficiency at slow rates. Long depolarization permits longer efficient contraction.
- Epicardium and endocardium electrically stabilize and abbreviate APD of M cells.
- Loss of either layer by infarction will lead to prolongation of APD. This may be the mechanism of increase in QT interval and QT dispersion seen in non-Q wave myocardial infarction (MI). These differences could be aggravated by drugs that prolong QT interval or in patients with LQTS.
- M cells play an important role in the inscription of T waves by producing a gradient between epicardium, endocardium, and M cells.
- U waves are due to repolarization of His Purkinje cells.
- Amiodarone prolongs APD in epicardium and endocardium and to a lesser extent in M cells; this may prevent transmural dispersion of refractoriness.

## **1.2 SODIUM CHANNELS AND CURRENTS<sup>10-13</sup>**

- Inward movement of the Na or Ca across the cell membrane through the specific channels produces inward current. Na current depolarizes the cell membrane and is voltage dependent (Fig. 1.2).
- The process of channel opening is called activation and the process of closing is called inactivation. During inactivation phase channel enters a nonconducting state while depolarization is maintained.
- The gating process measures current movement rather than ion movement.
- Channels flip between conducting and non-conducting states.

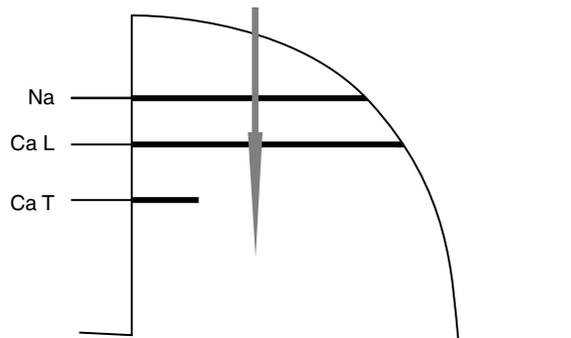


Fig 1.2 Inward currents.

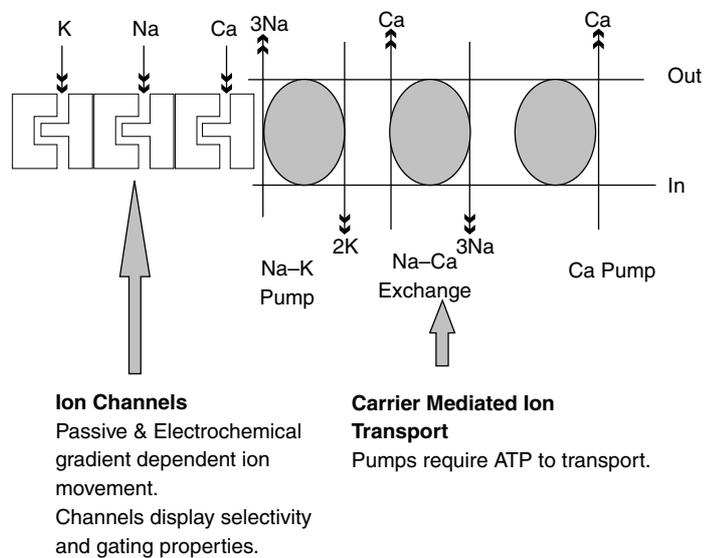


Fig 1.3 Ion pumps and channels.

- When all the gates (active or inactive) are open would a channel allow the passage of the ions.
- During the early part of repolarization Na channels become inactive. On completion of repolarization the Na channel returns from the inactive to the closed state. During resting potential the sodium channel is closed. Na ion conduction through the channel occurs when the channel is in the open state and not during the resting state.
- Movement of the sodium occurs through channels and pumps (Fig. 1.3).
- Repolarization occurs due to outward K currents. It will be delayed if the K currents are blocked as in LQT1 and LQT2 or when inward depolarizing currents

persist during repolarization as in LQT3. In LQT3 SCN5A, an Na channel remains open during repolarization resulting in continued inward current. This causes prolongation of the QT interval.

- Voltage-dependent opening of Na channel occurs as voltage decreases and conformational change in channel protein occurs (activation).
- There are no  $\beta_2$  subunits of sodium channel in cardiac myocytes. Both  $\beta_1$  and  $\beta_2$  subunits are expressed in the Na channels of the brain neurons.
- Lidocaine inhibits the inactivated state of the sodium channel.
- Chronic exposure to Na channel blocking antiarrhythmic drugs increases the sodium channel messenger RNA which counteracts the effects of channel blockade.

#### **Sodium channel block**

- There are two types of Na channel block:
  - i **Tonic** block results in a reduction of the peak current with the first pulse of the train of pulses. It is seen in drug-induced reduction of current during infrequent stimulation.
  - ii **Phasic** block occurs when there is a sequential decline in the peak current from beat to beat. It is also called use dependent or frequency dependent block. It decreases AP upstroke and slows conduction velocity. This type of block increases with repetitive stimulation. If the interval between AP is less than four times the recovery constant of the channel, block accumulates.
- During phase 0 Na channels open (open state) for less than 1 millisecond and then become inactive.
- During phase 2 and phase 3 (plateau phase) less than 1% of sodium channels remain open (inactivated state).
- Most depressants of conduction such as elevated extracellular potassium (as may occur in ischemia) produce membrane depolarization and increase the fraction of inactivated Na channels. Lidocaine produces inactivated state block; thus, it is effective in ischemic zones. The fraction of channels available in the open state is reduced during ischemia.
- Quinidine, Disopyramide, and Propafenone produce open channel block.
- During the resting state dissipation of block occurs (drugs dissociate from the site).
- Drugs can produce Na channel block during the resting, open, or inactivated state. These are called state dependent blocks. The other type of channel block is voltage dependent.
- Two different sodium channel blocking drugs may act synergistically.
- Class IA drugs increase APD, thus increasing the time sodium channels spend in the inactivated state. This will enhance the effectiveness of the drugs that bind to the inactivated state (Class IB drug such as lidocaine).

- Drugs with different binding kinetics may interact. For example, drugs with fast kinetic may displace drugs with slower kinetic, thus reducing the overall block.
- Lidocaine may reverse the Quinidine, Propafenone Flecainide induced block.
- Ventricular tachycardia due to Flecaïnide, Yew needle toxin, dextropropoxylyene can be treated with Lidocaine.
- Class 1B drugs have dissociation constant of less than one second. These drugs have no effect on the conduction of normal tissue but decrease the conduction following closely coupled premature ventricular contractions (PVCs) and in diseased (ischemic) cells.
- Class 1C drugs have the slowest dissociation of 12 seconds. This results in slowing of conduction and widening of QRS.
- Class 1A drugs have intermediate kinetics of more than 1 second but less than 12 seconds, this may result in slowing of conduction and widening of QRS at the normal heart rate, which increases during tachycardia.
- Lidocaine blocks  $I_{Na}$  by shifting voltage for inactivation to more negative. It binds to the activated and inactivated states of the sodium channel.
- Lidocaine, Quinidine, and Flecaïnide exert use dependent block with fast, intermediate, and slow kinetics, respectively.

#### ***Drug kinetics and channel state***

- Membrane depressants such as increased extracellular potassium, hydrogen, and stretch reduce the resting membrane potential. This increases the fraction of inactivated channels and potentiates the effects of the drugs that act on the inactivated state. Fewer channels are available in the open state, thus decreasing the effectiveness of the drugs that are open state blockers.
- Decrease in extracellular pH slows the rate of dissociation of Lidocaine from the sodium channel. A combination of acidosis and membrane depolarization increases the block produced by Lidocaine.
- Class 1C drugs are slow to unbind from the channel site and cause slowing of conduction, which may produce incessant tachycardia.
- Marked sinus bradycardia may be proarrhythmic for drugs with fast half time of recovery from the block because the channels are left unprotected for the major part of APD.

#### **Slow sodium currents (inward)**

- Agents that increase the slow component of sodium current (Diphenylmethyl-Piperanzinyl-Indole derivatives) are likely to increase inotropy by increasing the entry of Na during the plateau phase. This leads to an increase in intracellular calcium through sodium/calcium exchange. Increase in intracellular Ca may lead to EAD and PVC.
- Methanesulfonamide Ibutilide prolongs APD by increasing the slow sodium channel current.

- Lidocaine and other class 1B agents block the slow component of sodium current and decrease QT in patients with LQT3<sup>5</sup>.
- Negative inotropy by sodium channel blockers may be due to blockage of the slow sodium channel current.
- Slowing of heart rate produced by class 1B agents is due to blocking of background sodium current that contributes to the phase 4 of pacemaker AP.
- $\beta$ -Adrenergic stimulation reverses the effects of class I drugs.
- Proarrhythmia from class IC drugs develops during increased heart rate when sympathetic activity is enhanced. Beta blockers may reverse this phenomenon<sup>5</sup>.
- Angiotensin II increases the frequency of reopening of the sodium channel and increases the Na current.

### 1.3 CALCIUM CHANNELS AND CURRENTS<sup>14–17</sup>

- The process of channel opening and closing is called gating.
- Open channels are active. Closed channels are inactive. Calcium and sodium channels open in response to depolarization and enter the nonconducting state during repolarization, a gating process known as inactivation.
- Alpha 1 subunit of the Ca channel contains the binding site for calcium channel blocking drugs.
- Calcium channels are very selective and allow Ca permeability 1000-fold faster.
- There are four types of calcium channels:
  - i L-type expressed on surface membrane.
  - ii T-type expressed on surface membrane.
  - iii Sarcoplasmic reticulum (SR) Ca release channel.
  - iv Inositol triphosphate (IP3) receptor channels are present on internal membrane.

#### **L-type calcium channel (L = Large and lasting)**

- It is a major source of Ca entry into the cell. It opens when depolarization reaches positive to  $-40$  mV.
- It is responsible for excitation in sino atrial node (SAN) and atrio-ventricular node (AVN). It produces inward current that contributes to depolarization in SAN and AVN.
- It produces inward current responsible for plateau of AP.
- Increased calcium current prolongs depolarization and increases the height of the AP plateau.
- Calcium channel dependent inward current is responsible for EAD.
- $I_{CaL}$  is responsible for excitation, contraction, and coupling. Blockade of these channels results in negative inotropic effects.
- In AF decrease activity of the  $I_{CaL}$  channel shortens APD and perpetuates arrhythmia (electrical remodeling).

## Regulation of pacemaker and Ca currents

### *$\beta$ -Adrenergic receptor stimulation*

- It increases L-type calcium channel activity.
- This results in increased contractility, heart rate, and conduction velocity.
- Stimulation of receptors activates guanosine triphosphate binding protein Gs, which in turn stimulates adenylyl cyclase activity, thus increasing the cAMP level.
- $\beta$ -Blockers have no direct effect on calcium channel.
- Sympathetic stimulation may also activate alpha1 receptors.

### *Parasympathetic stimulation*

- It decreases L-type calcium activity through muscarinic and cholinergic receptors.
- Acetylcholine, through G protein, activates inwardly rectifying  $I_{K_{Ach}}$ , which makes MDP more negative and decreases the slope of diastolic depolarization. This results in slowing of the heart rate.
- Magnesium acts as an L-type calcium channel blocker.

## T-type calcium channel

- These are found in cardiac and vascular smooth muscles, including coronary arteries.
  - i It opens at more negative potential.
  - ii It rapidly inactivates (Transient T).
  - iii It demonstrates slow deactivation.
  - iv Has low conductance (tiny T).
- It is found in high density in SAN and AVN.
- It does not contribute to AP upstroke which is dominated by sodium channel.
- It is implicated in cell growth.
- T-type Ca channel density is increased in the presence of the growth hormone, endothelin-1, and pressure overload.
- Failing myocytes also demonstrate increase density of T-type Ca channels.
- Drugs and compounds that block T-type Ca channels include the following:
  - i Amiloride
  - ii 3,4-Dichrobenzamil
  - iii Verapamil
  - iv Diltiazem
  - v Flunarizine
  - vi Tetradrine
  - vii Nickel
  - viii Cadmium
  - ix Mibefradil
- T-type Ca channel is up regulated by norepinephrine, alpha agonist (phenylephrine), extracellular ATP, and LVH.

### **Sarcoplasmic calcium release channels (also called Ryanodine receptors)**

- These are intracellular channels that are regulated by calcium.
- These channels mediate the influx of calcium from SR into cytosol.
- It provides calcium for cardiac contraction. SR controls the cytoplasmic Ca level by release or uptake during systole and diastole, respectively.
- Calcium release from SR is triggered by increase in intracellular calcium, produced by L-type Ca channel. It is called calcium-induced calcium release (CICR).
- When a cell is calcium overloaded SR releases calcium spontaneously and asynchronously causing DAD (delayed after depolarization) seen in digitalis toxicity.
- Caffeine releases calcium from SR.
- Doxorubicin decreases cardiac contractility by depleting SR calcium.
- Magnesium and ATP potentiates channel flux.
- In ischemia decreased intracellular ATP decreases calcium release and causes ischemic contractile failure.
- Verapamil has no effect on sarcoplasmic Ca release channel (SCRC).
- SR also has potassium, sodium, and hydrogen channels.

### **Inositol triphosphate receptors (IP3)**

- These receptors are found in smooth muscles and in specialized conduction tissue.
- These are up regulated by angiotensin II and  $\alpha$ -adrenergic stimulation.
- Stimulation of myocytes angiotensin II receptor by angiotensin increases intracellular IP3.
- The arrhythmogenic effect of angiotensin II in CHF may be due to elevated IP3.
- These receptors have been implicated in apoptosis.

### **Tetrodotoxin (TTX) sensitive calcium channel**

- It produces inward current. It is blocked by TTX.
- The channel that carries this current is permeable to both sodium and calcium.
- Elevated intracellular Na may activate reverse Na/Ca exchange, thus increasing the levels of intracellular Ca which may trigger SR calcium release.
- It may contribute to cardiac arrhythmias.

### **Sodium and calcium exchange**

- Opening of voltage operated calcium channel, during the plateau phase of APD, increases the flux of calcium into cytoplasm. This causes CICR from SR.
- During diastole calcium is removed from the cell by sodium/calcium exchange located in the cell membrane.
- Lowering of pH blocks sodium/calcium exchange.

- SR calcium ATPases, Sarcolemmal calcium ATPases and sodium/calcium exchange decrease cytoplasmic calcium from elevated systolic level to baseline diastolic level by pumping Ca back into SR or by extruding Ca out of the cell.
- During calcium removal inwardly directed current is observed, which may cause DAD.
- DAD occurs when there is pathologically high calcium load either due to digitalis toxicity or following reperfusion.
- Na/Ca exchange is able to transport calcium bi-directionally. Reverse mode will increase intracellular calcium, which may trigger SR calcium release.

### Effect of antiarrhythmic drugs on calcium channel

- Most Na and K channel blocking drugs also affect Ca channels.
- Quinidine, Disopyramide, Lidocaine, Mexiletine, Diphenylhydantoin, Flecainide, Propafenone, Moricizine, and Azimilide suppress L-type calcium current.
- Amiodarone blocks both L and T-type Ca currents.
- Sotalol has no effect on Ca channel.
- Digoxin inhibits sodium/potassium ATPases. This inhibition results in an increase in intracellular Na, which in turn leads to an increase in intracellular Ca through Na/Ca exchange.
- Verapamil blocks Ca current and decreases calcium activated chloride current.

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