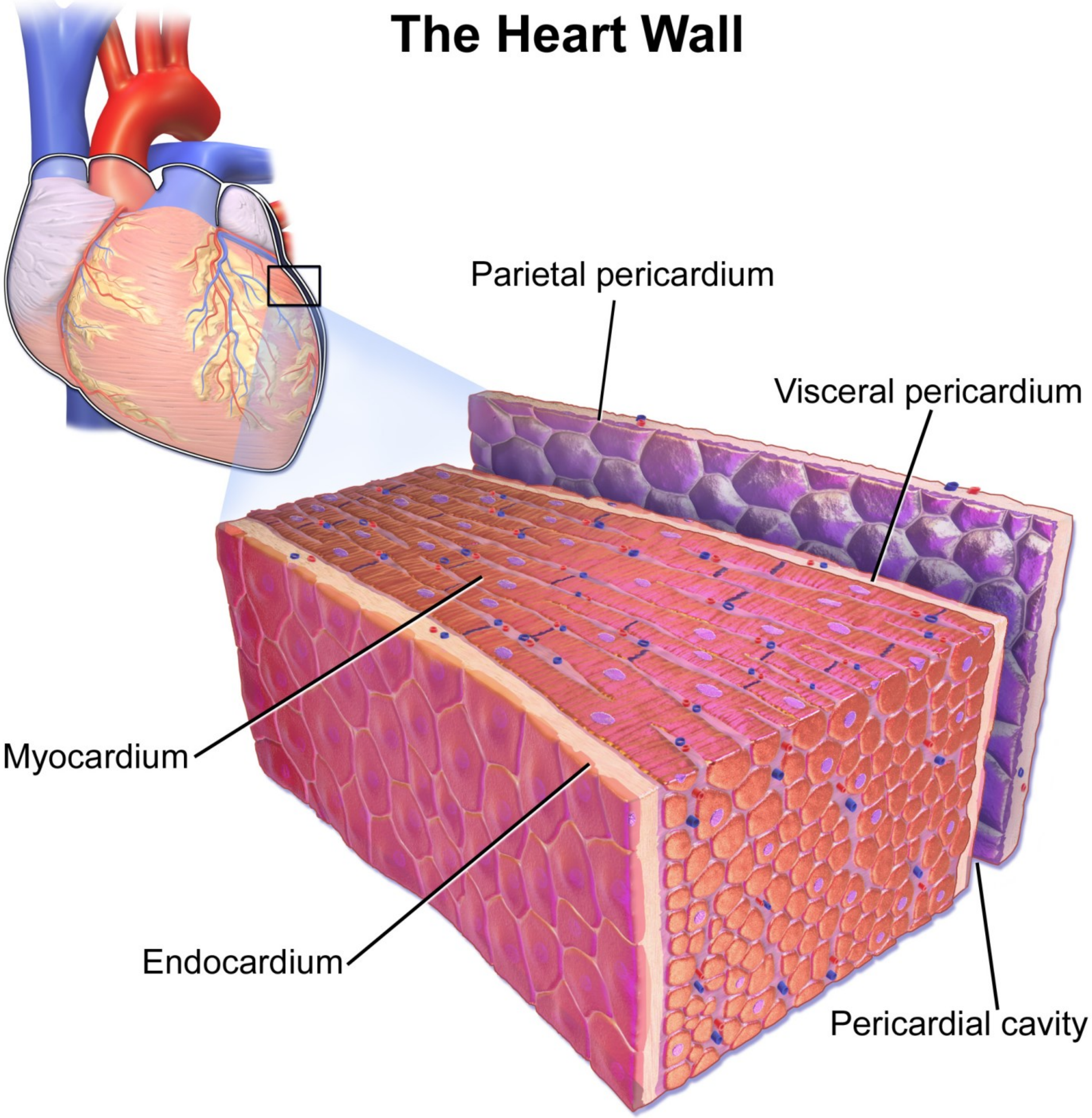
STIMULUS-CONDUCTION SYSTEM OF HEART
&
ACTION POTENTIALS IN HEART CELLS

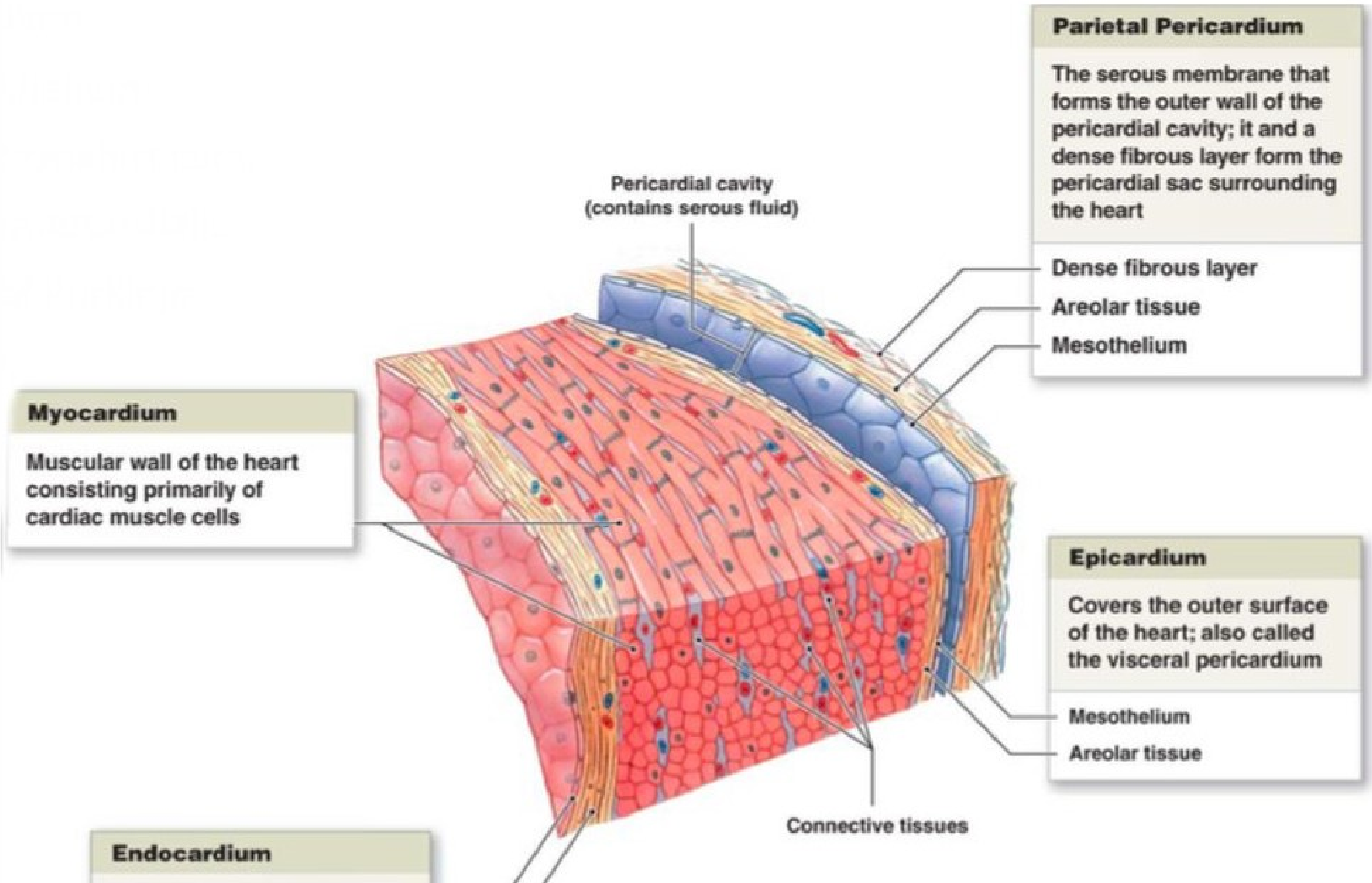
Serkan GÜRGÜL, Asst. Prof.

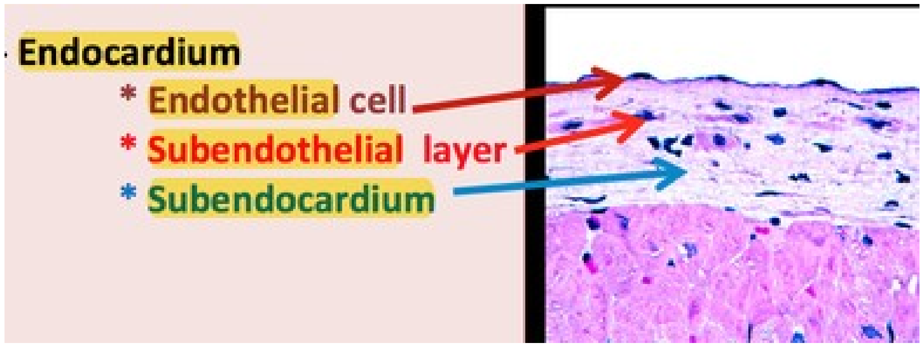
Department of Biophysics, Faculty of Medicine,

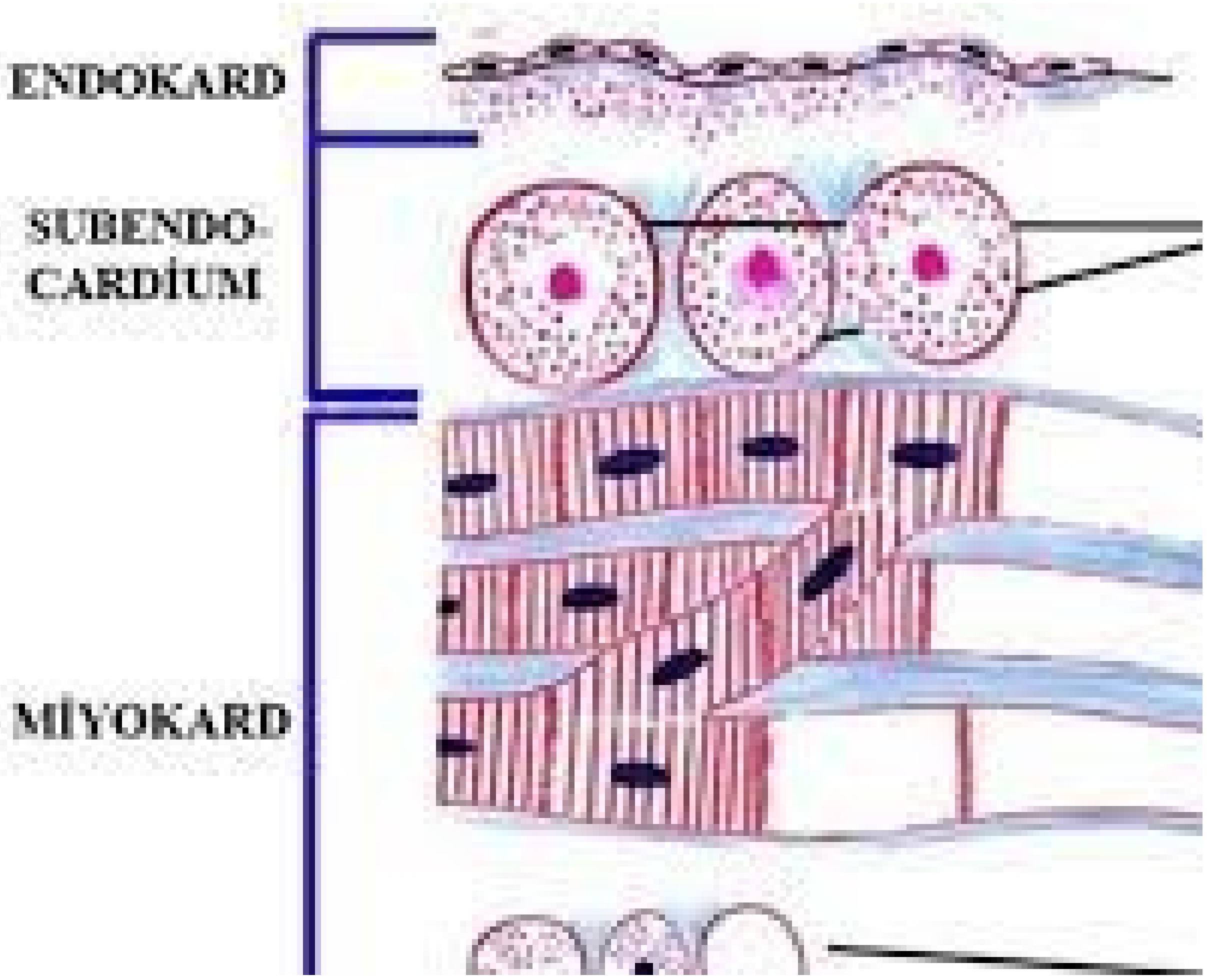
Gaziantep University

The Heart Wall

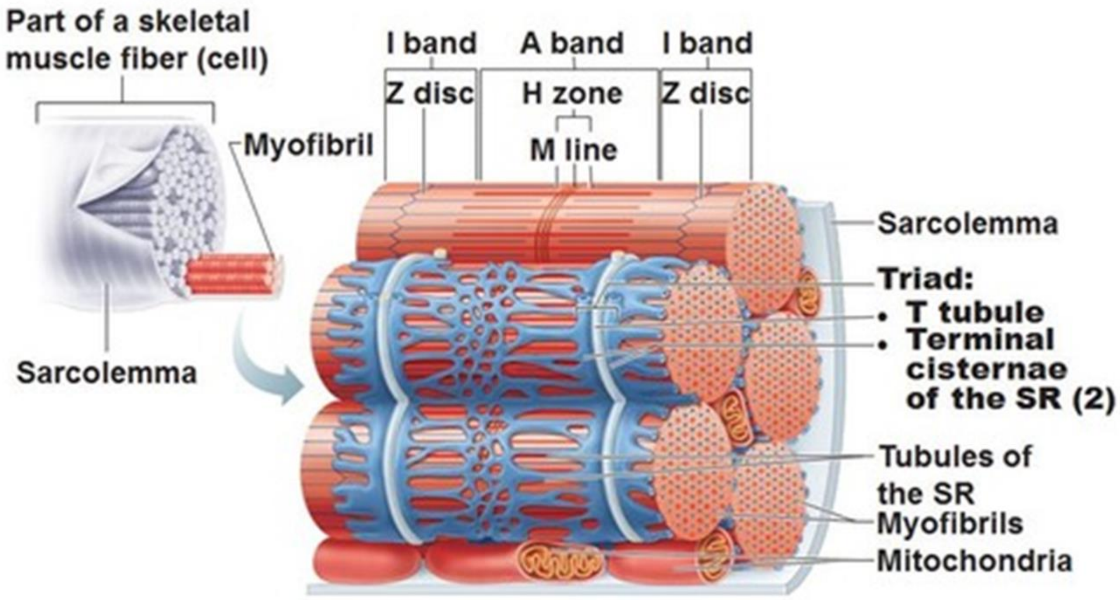



Parietal Pericardium
The serous membrane that forms the outer wall of the pericardial cavity; it and a dense fibrous layer form the pericardial sac surrounding the heart
Dense fibrous layer
Areolar tissue
Mesothelium
Pericardial cavity (contains serous fluid)
Myocardium
Muscular wall of the heart consisting primarily of cardiac muscle cells
Epicardium
Covers the outer surface of the heart; also called the visceral pericardium
Mesothelium
Areolar tissue
Connective tissues
Endocardium
Covers the inner surfaces of the heart
Endothelium
Areolar tissue


Endocardium
* Endothelial cell
* Subendothelial layer
* Subendocardium


ENDOKARD
SUBENDO-
CARDİUM
MİYOKARD

The Structure of Heart



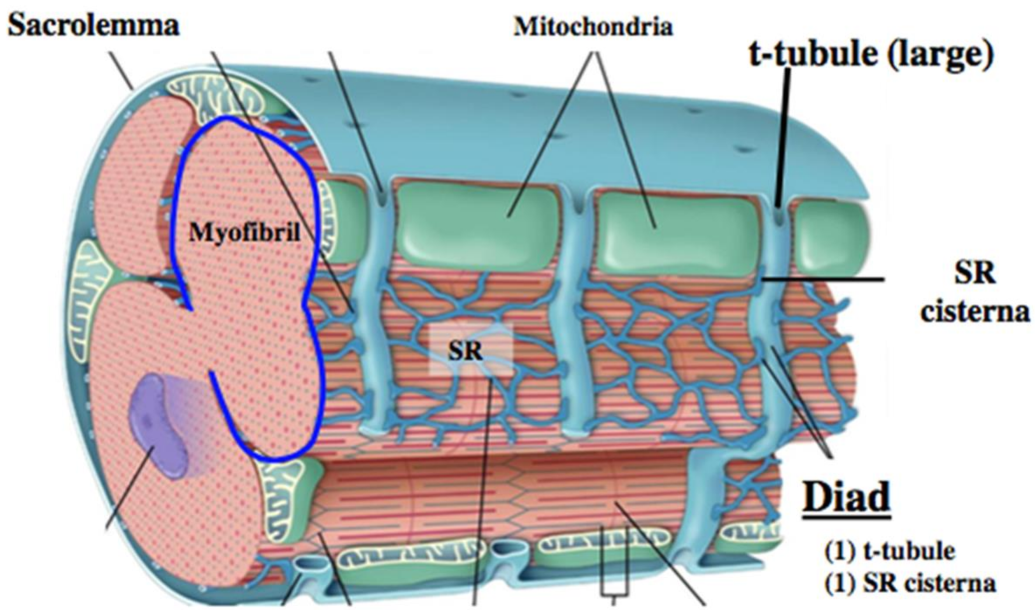
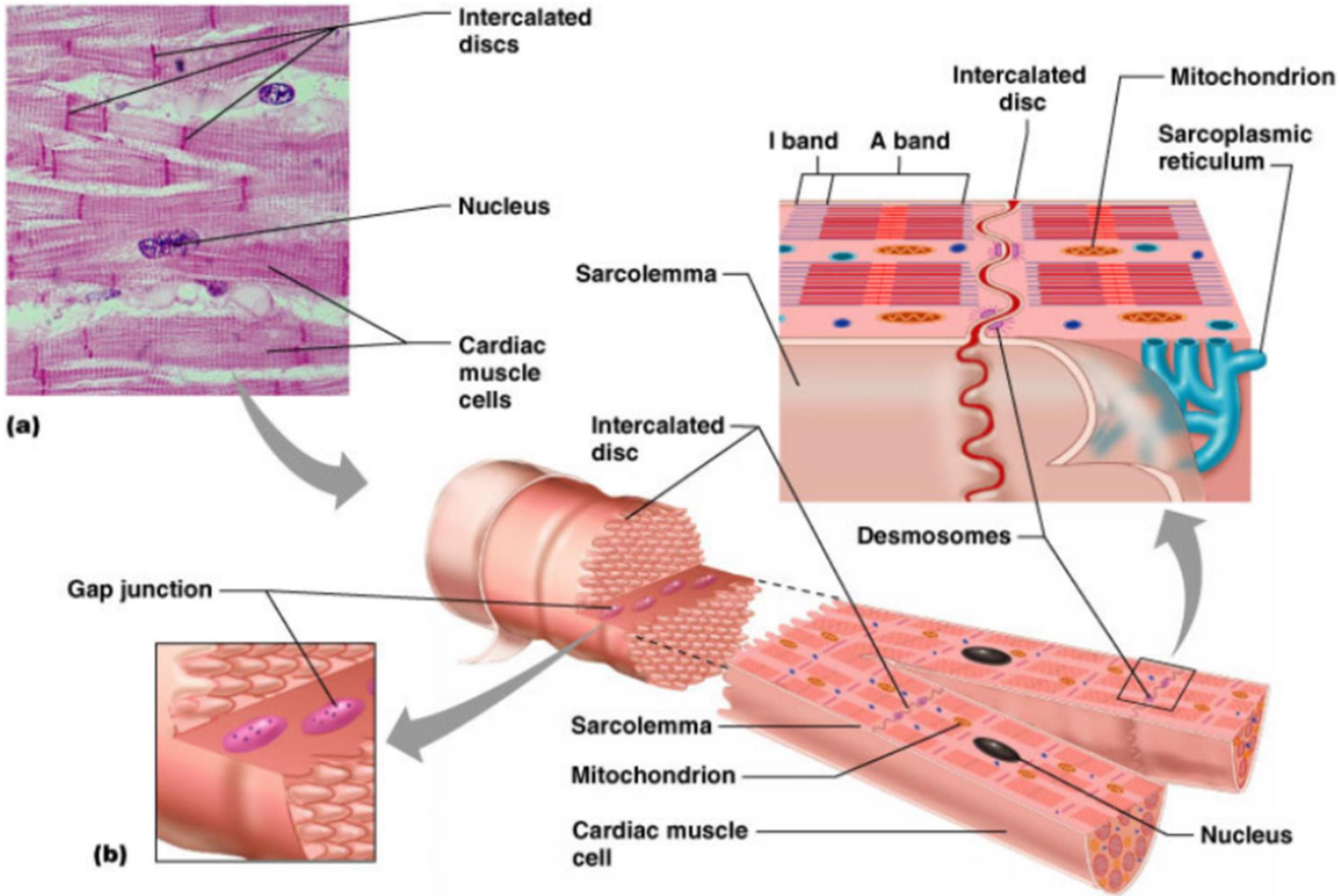
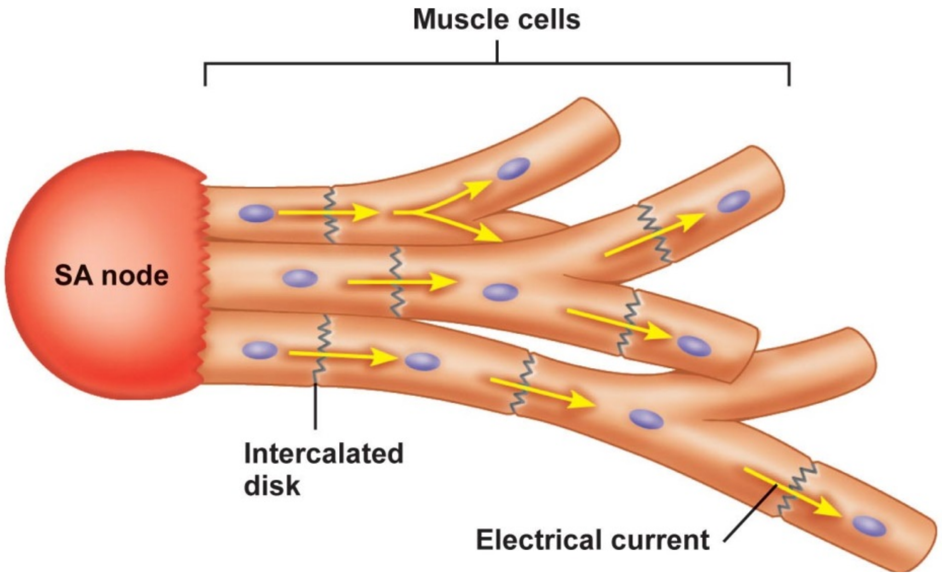


TABLE 28.1: Features of skeletal, cardiac and smooth muscle fibers

Features	Skeletal muscle	Cardiac muscle	
Location	In association with bones	In the heart	In the
Shape	Cylindrical and unbranched	Branched	Spind
Length	1 cm to 4 cm	80 µ to 100 µ	50 µ t
Diameter	10 µ to 100 µ	15 µ to 20 µ	2 µ to
Number of nucleus	More than one	One	One
Cross-striations	Present	Present	Abse
Myofibrils	Present	Present	Abse
Sarcomere	Present	*Present	Abse
Troponin	Present	Present	Abse
Sarcotubular system	Well developed	Well developed	Poorl
'T' tubules	Long and thin	Short and broad	Abse
Depolarization	Upon stimulation	Spontaneous	Spont
Fatigue	Possible	Not possible	Not p
Summation	Possible	Not possible	Possi
Tetanus	Possible	Not *possible	Possi
Resting membrane potential	Stable	Stable	Unsta
For trigger of contraction, calcium binds with	Troponin	Troponin	Calm
Source of calcium	Sarcoplasmic reticulum	Sarcoplasmic reticulum	Extra

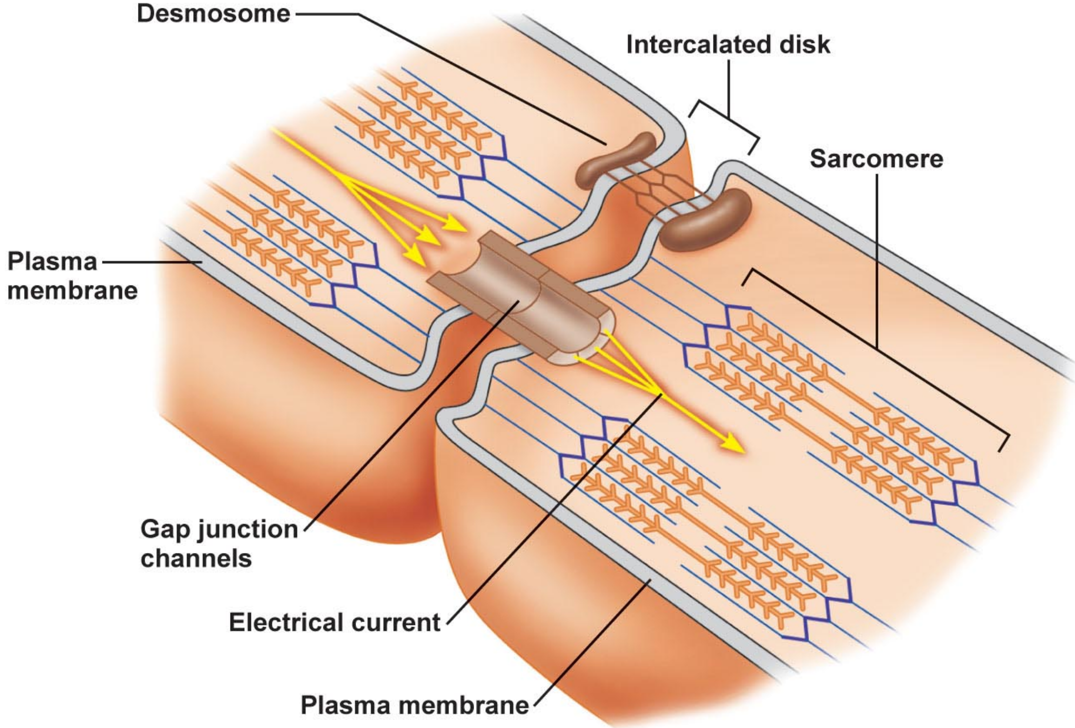


Intercalated discs
Nucleus
Cardiac muscle cells
(a)
Intercalated disc
Mitochondrion
I band
A band
Sarcoplasmic reticulum
Sarcolemma
Intercalated disc
Desmosomes
Gap junction
Sarcolemma
Mitochondrion
Cardiac muscle cell
Nucleus
(b)



Muscle cells
SA node
Intercalated disk
Electrical current

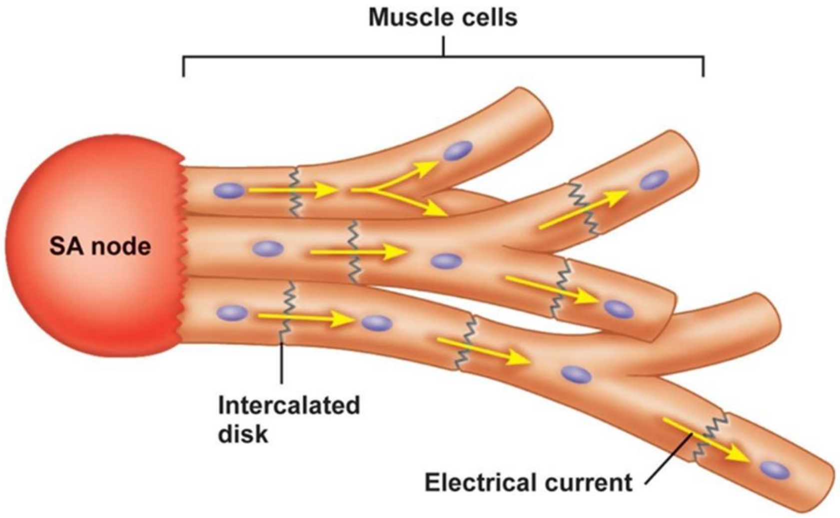
(a)



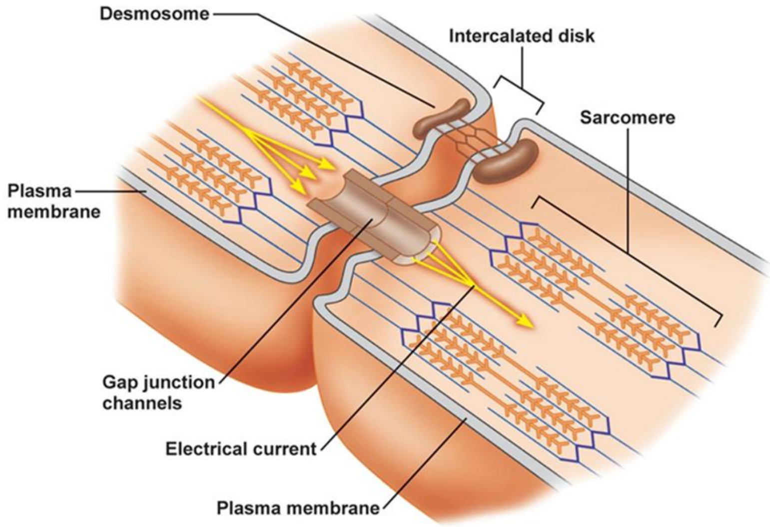
Desmosome
Intercalated disk
Sarcomere
Plasma membrane
Gap junction channels
Electrical current
Plasma membrane

(b)

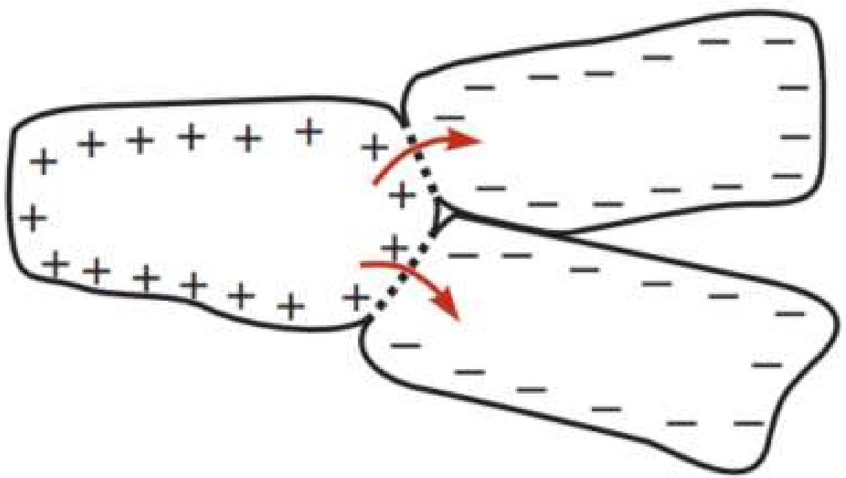
Electrical Conduction Within the Heart



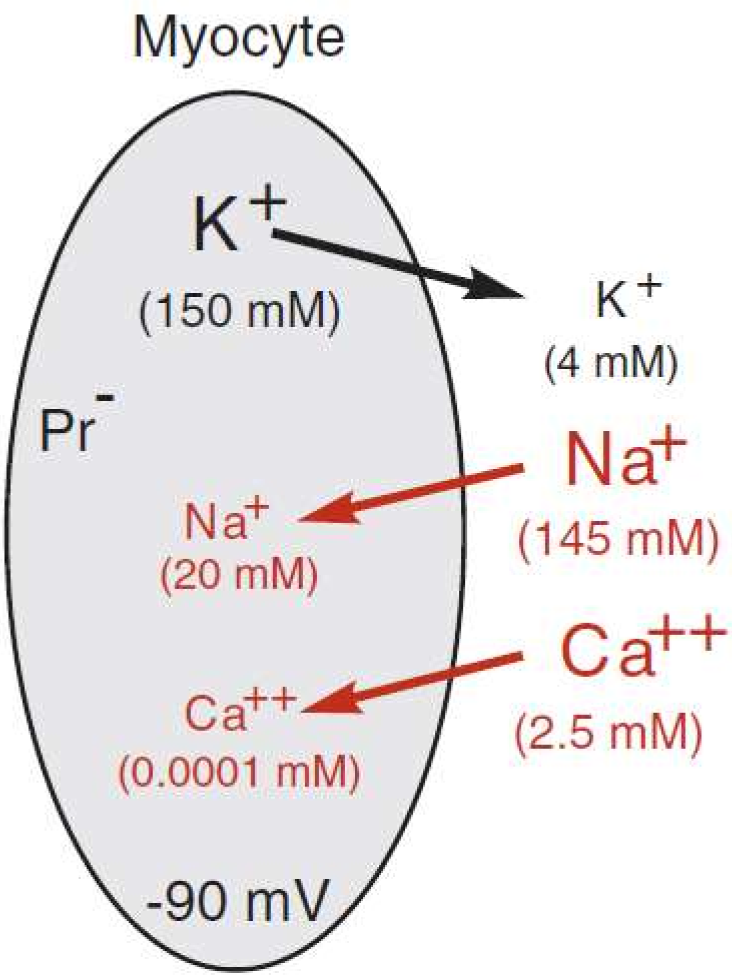
(a)



(b)



Ionic Gradients, Potentials & E_m



Concentrations of K^+, Na^+, and Ca^{++} inside and outside a cardiac myocyte at a resting membrane potential of −90 mV. *Pr*⁻, negatively charged proteins.

Ion	Equilibrium Potentials
Na^+	+ 52 mV
K^+	- 96 mV
Ca^{2+}	+ 134 mV
Cl^-	- 64 mV

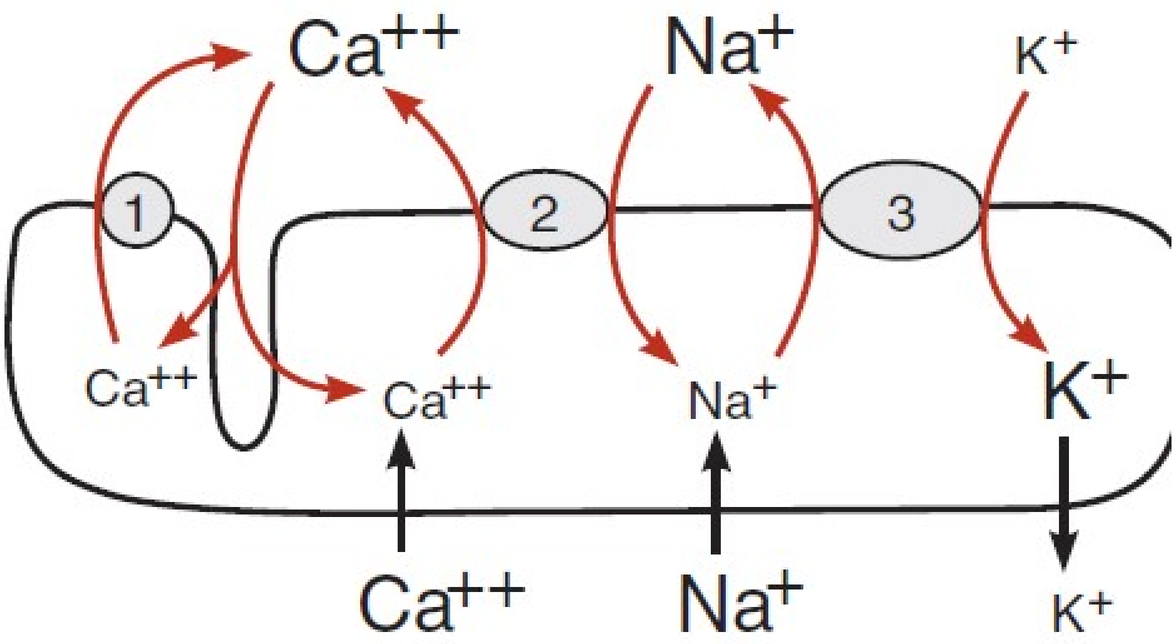
$$E_{ion} = -\frac{RT}{zF} \ln \frac{[ion]_i}{[ion]_o}$$

E_{ion}	=	equilibrium potential for that ion
	=	Nernst potential
R	=	universal gas constant
T	=	absolute temperature
z	=	the valence of the ion (e.g. +1 for K^+ and Na^+)
F	=	the faraday
		96,500 J / (volt·mole)

TABLE 1.3 Free Ion Concentrations and Equilibrium for Mammalian Skeletal Muscle

Ion	Extracellular concentration (mM)	Intracellular concentration (mM)	$\frac{[\text{Ion}]_o}{[\text{Ion}]_i}$	E
Na^+	145	12	12	
K^+	4	155	0.026	
Ca^{2+}	1.5	100 nM	15,000	
Cl^-	123	4.2[b]	29[b]	

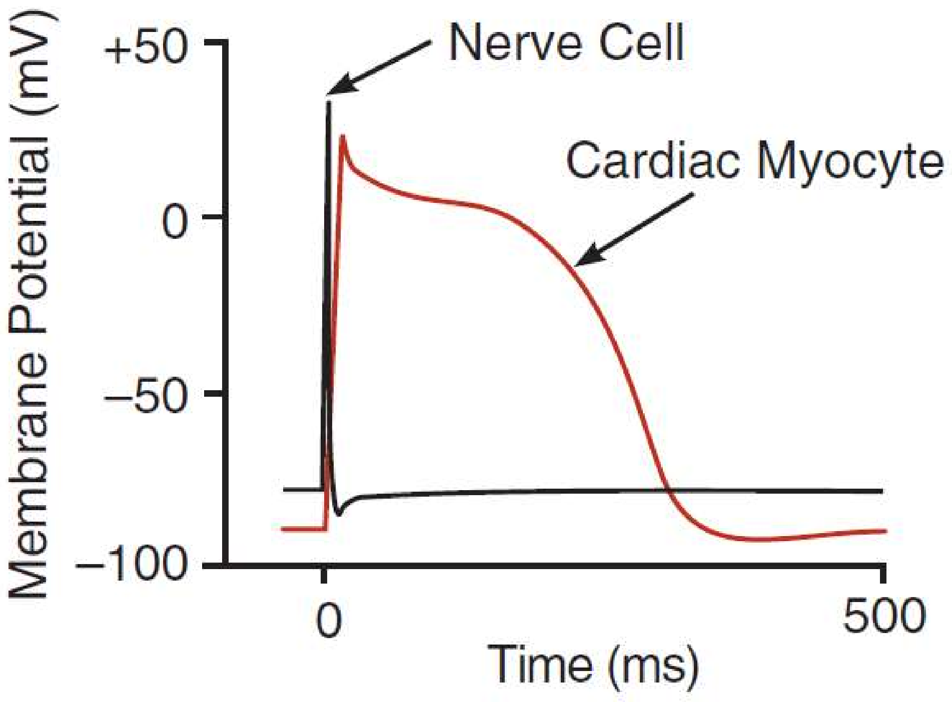
Maintenance of Ionic Gradients

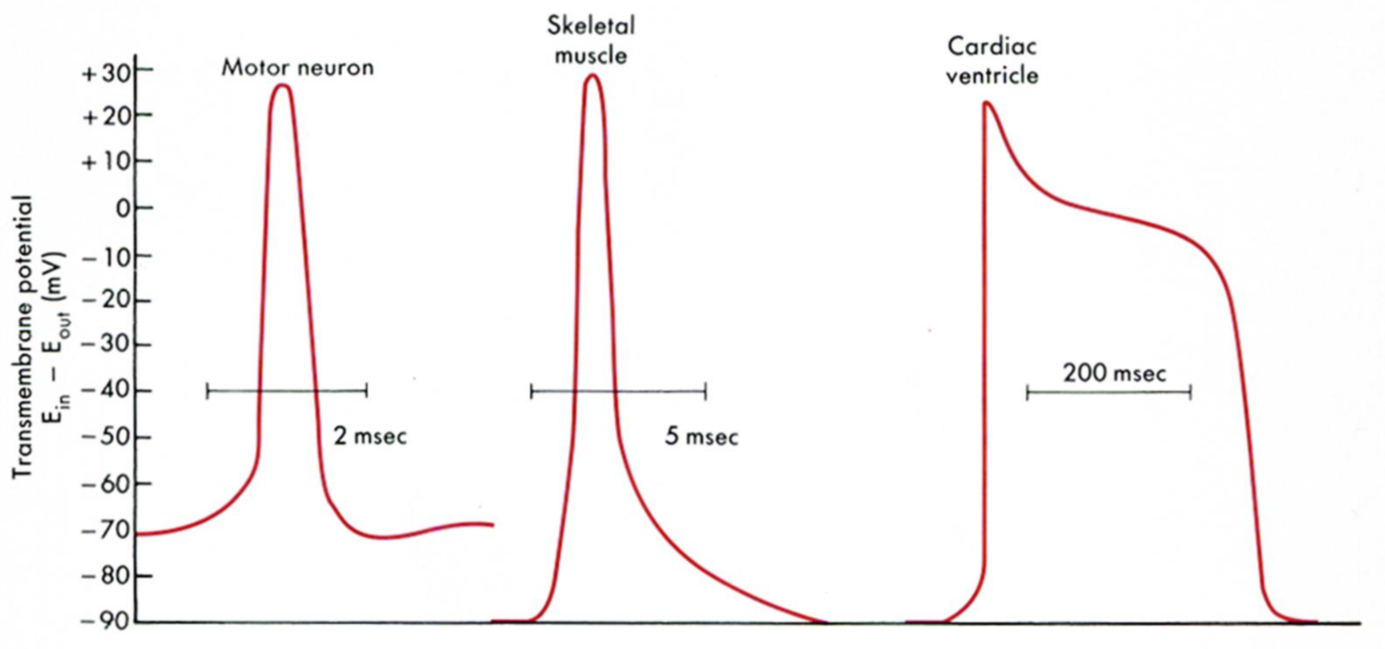


1 = ATP-dependent Ca^{++} pump
2 = Na^{+}/Ca^{++} exchanger (3:1)
3 = Na^{+}/K^{+}-ATPase pump (3:2)

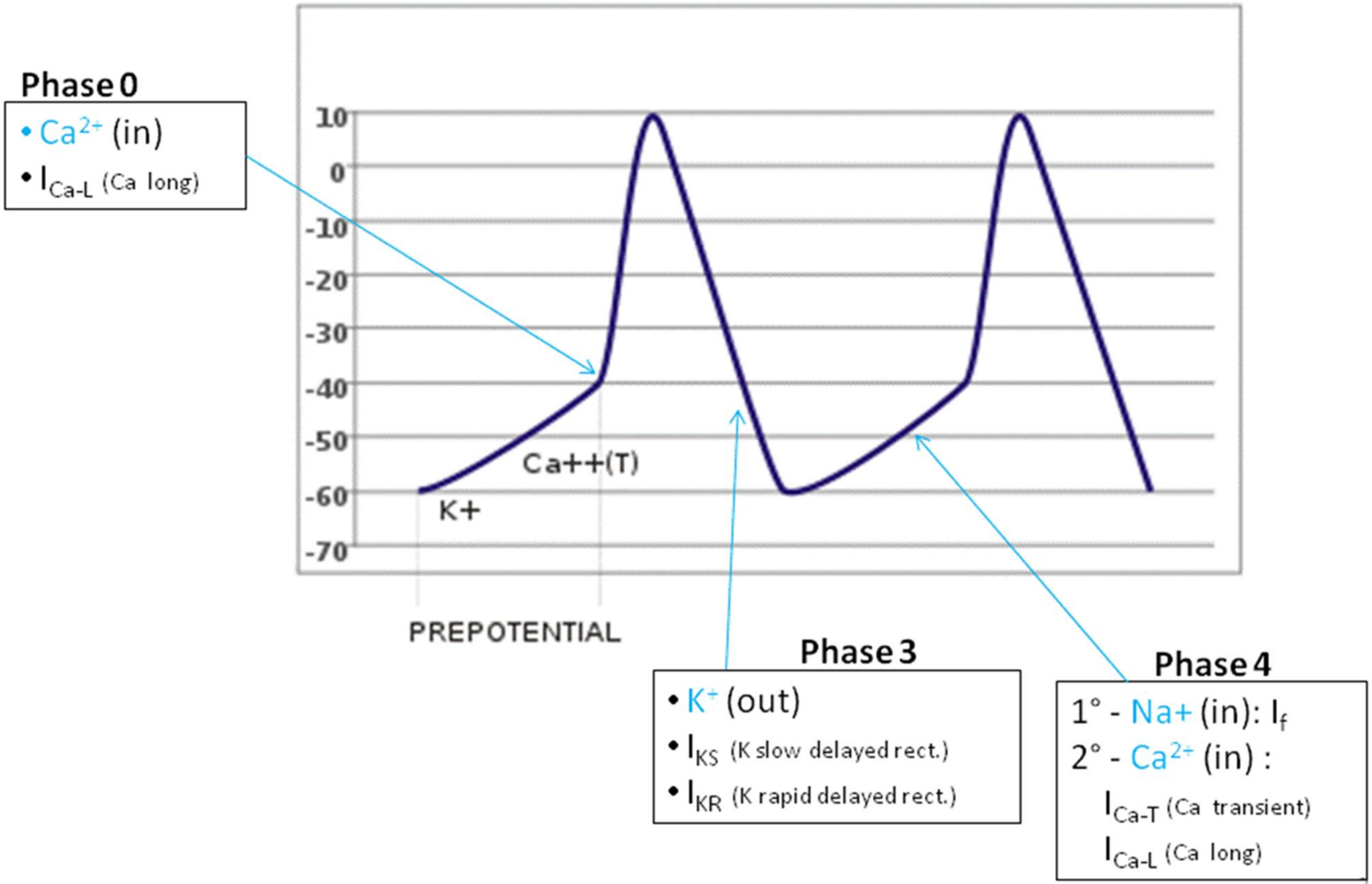
FIGURE 2.2 Sarcolemmal ion pumps and exchangers. These pumps maintain transm

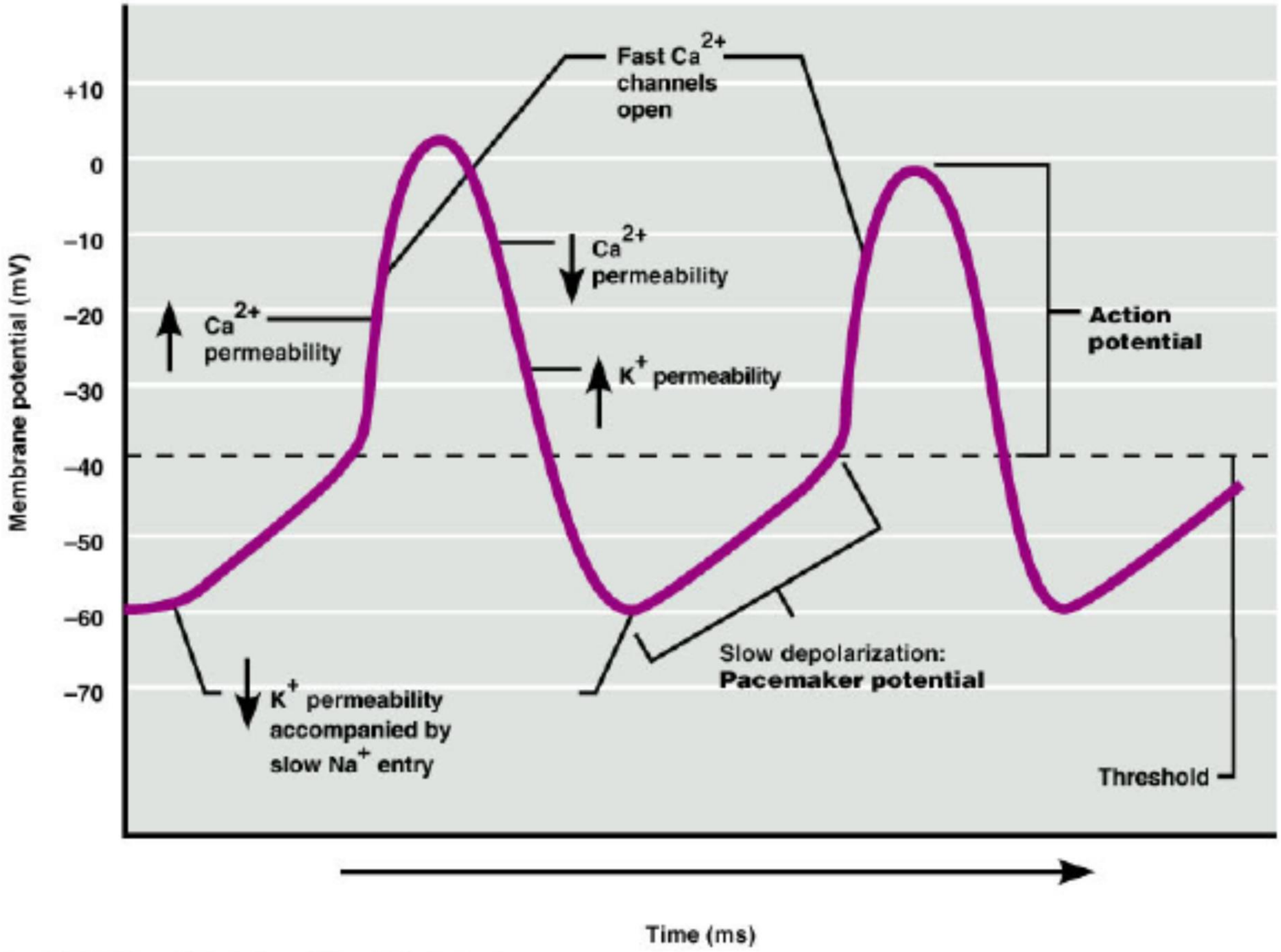
Cardiac APs


Nerve Cell
Cardiac Myocyte
Membrane Potential (mV)
+50
0
−50
−100
0
500
Time (ms)


Motor neuron
Skeletal muscle
Cardiac ventricle
Transmembrane potential $E_{in} - E_{out}$ (mV)
+30
+20
+10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
2 msec
5 msec
200 msec

Pacemaker APs
(SA & AV nodes)





Fast Ca2+ channels open
+10
0
−10
−20
−30
−40
−50
−60
−70
Membrane potential (mV)
Ca2+ permeability
Ca2+ permeability
K+ permeability
Action potential
K+ permeability accompanied by slow Na+ entry
Slow depolarization:
Pacemaker potential
Threshold
Time (ms)

Pacemaker AP

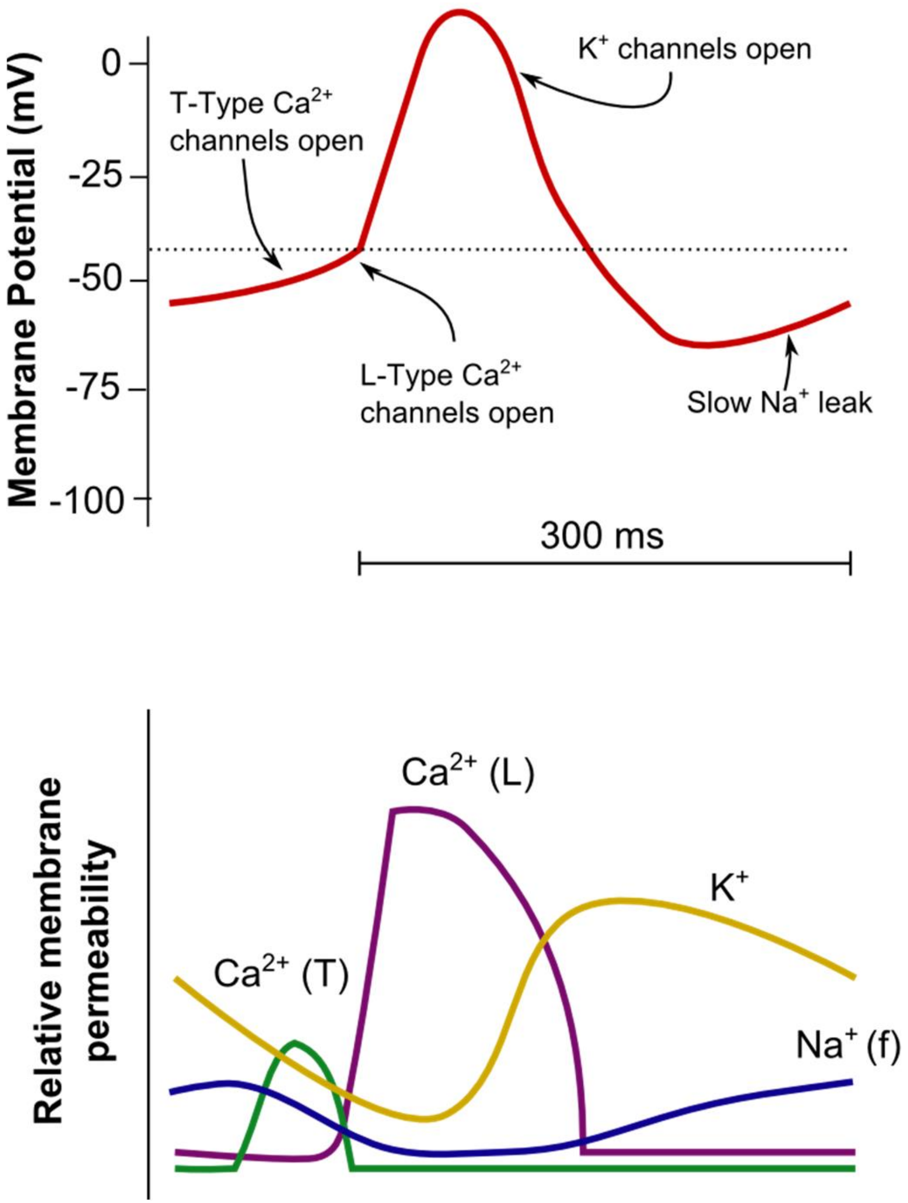
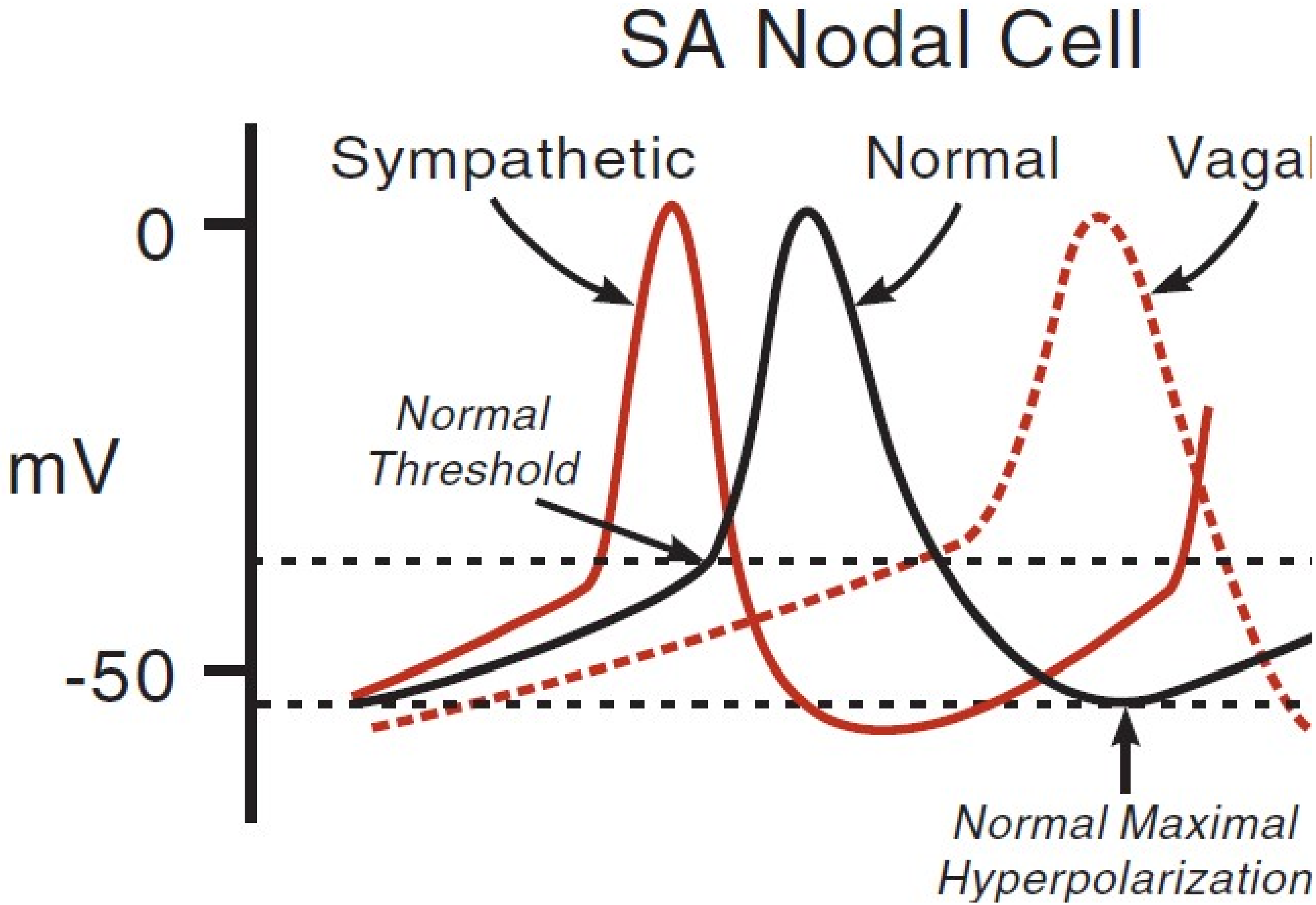


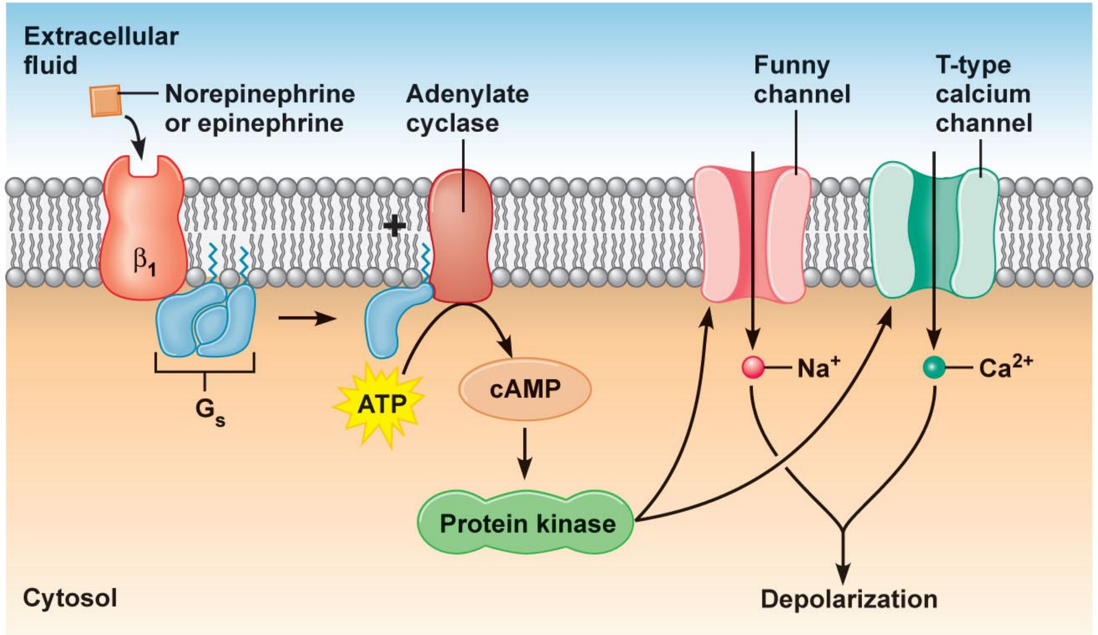
TABLE 2-1 CARDIAC ION CHANNELS AND CURRENTS

CHANNELS	GATING	CHARACTERISTICS
Sodium		
Fast Na^+ (I_{Na})	Voltage	Phase 0 of myocytes
Slow Na^+ (I_f)	Voltage and receptor	Contributes to phase 4 pacemaker current in SA and AV nodal cells
Calcium		
L-type (I_{Ca})	Voltage	Slow inward, long-lasting current; phase 2 of myocytes and phases 4 and 0 of SA and AV nodal cells
T-type (I_{Ca})	Voltage	Transient current; contributes to phase 4 pacemaker current in SA and AV nodal cells
Potassium		
Inward rectifier (I_{K1})	Voltage	Maintains negative potential in phase 4; closes with depolarization
Transient outward (I_{to})	Voltage	Contributes to phase 1 in myocytes
Delayed rectifier (I_{Kr})	Voltage	Phase 3 repolarization
ATP-sensitive ($I_{K, ATP}$)	Receptor	Inhibited by ATP; opens when ATP decreases during cellular hypoxia
Acetylcholine activated ($I_{K, ACh}$)	Receptor	Activated by acetylcholine and adenosine; Gi-protein coupled; slows SA nodal firing
Calcium activated ($I_{K,Ca}$)	Receptor	Activated by high cytosolic calcium; accelerates repolarization

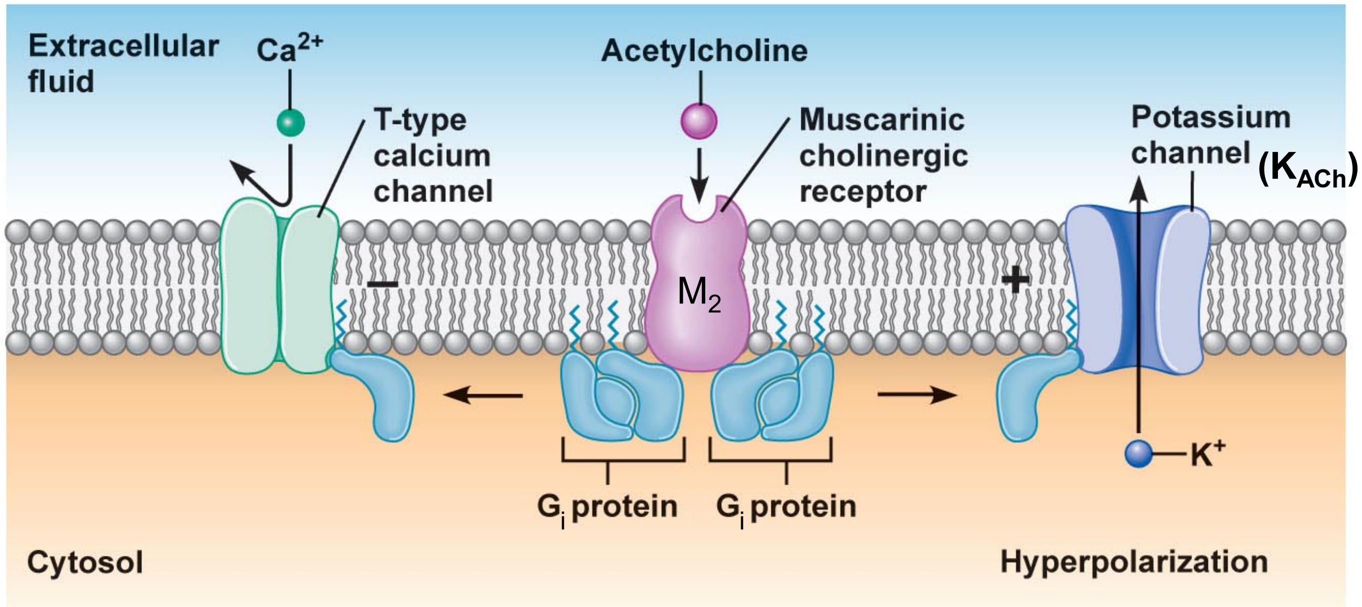
I_x, name of specific current.

Factors Affecting Changes in Heart Rate





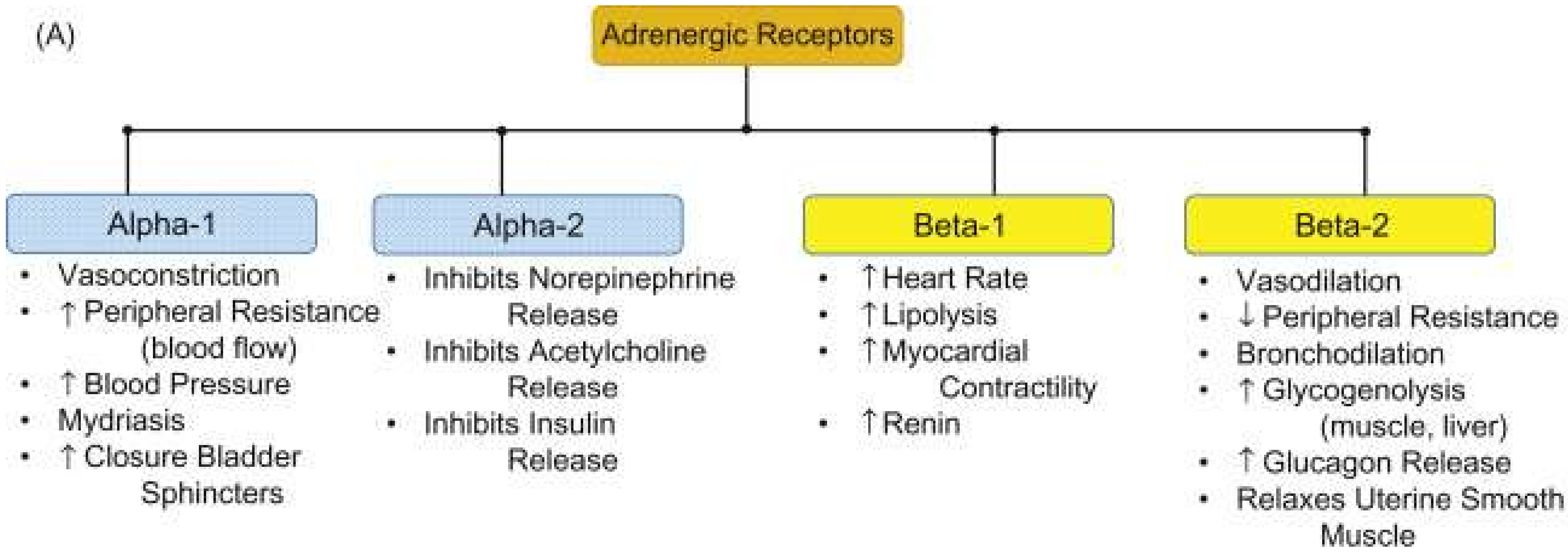
(a) Sympathetic



(b) Parasympathetic

Receptor type	Tissue location
$\alpha 1$	Arterioles (coronary, visceral, cutaneous), veins, internal sphincters, Iris dilator muscle.
$\alpha 2$	Presynaptic membrane, pancreas, veins, adipose tissue, GIT sphincters, salivary glands.
$\beta 1$	Heart (SA node, atrial muscle, AV node, ventricles), kidney(JG apparatus), Adipose tissue.
$\beta 2$	Arterioles(muscular), veins, bronchi (muscles), liver, pancreas, uterus , Iris constrictor muscle.
$\beta 3$	Adipose tissue, urinary bladder.

(A)



(B)

Alpha-1	Alpha-2	Beta-1	Beta-2
NE > E	E > NE	E = NE	E >> NE
NE = Norepinephrine; E = Epinephrine			

Receptor subtype	Second messenger	Organ/tissue	Response
M_1	IP_3/DAG↑	autonomic ganglion	depolarization, slow E
		including myenteric plexus	increased gastric acid vagus nerve
		vas deferens (rabbit)	reduced twitch height
		brain (cerebral cortex)	binding sites
		canine saphenous vein	contraction
M_2	cAMP↓ and direct coupling to K^+ channel	heart -	
		atrium	reduced contractile fo inotropy)
		sinu-atrial node	reduced rate (negative
		prejunctional at autonomic nerve endings	reduced NA or Ach re
		ileum smooth muscle	predominant binding s function
M_3	IP_3/DAG↑	smooth muscle -	
		gut	contraction
		urinary bladder	minor binding sites
		trachea	
		iris circular muscle	
		blood vessels-	
		endothelium	release of NO and vas
		smooth muscle	contraction
		glands -	
		oxyntic cells (gastric acid)	increased acid secreti
		salivary glands	salivation

Atropine,
Scopolamine,
Hyoscine butylbromide,
Ipratopium…

E,
NE,
Dopamine,
Dobutamine,
Isoprenaline,
Amphetamine
…

TABLE 2-2 FACTORS INCREASIN DECREASING THE SA FIRING RATE

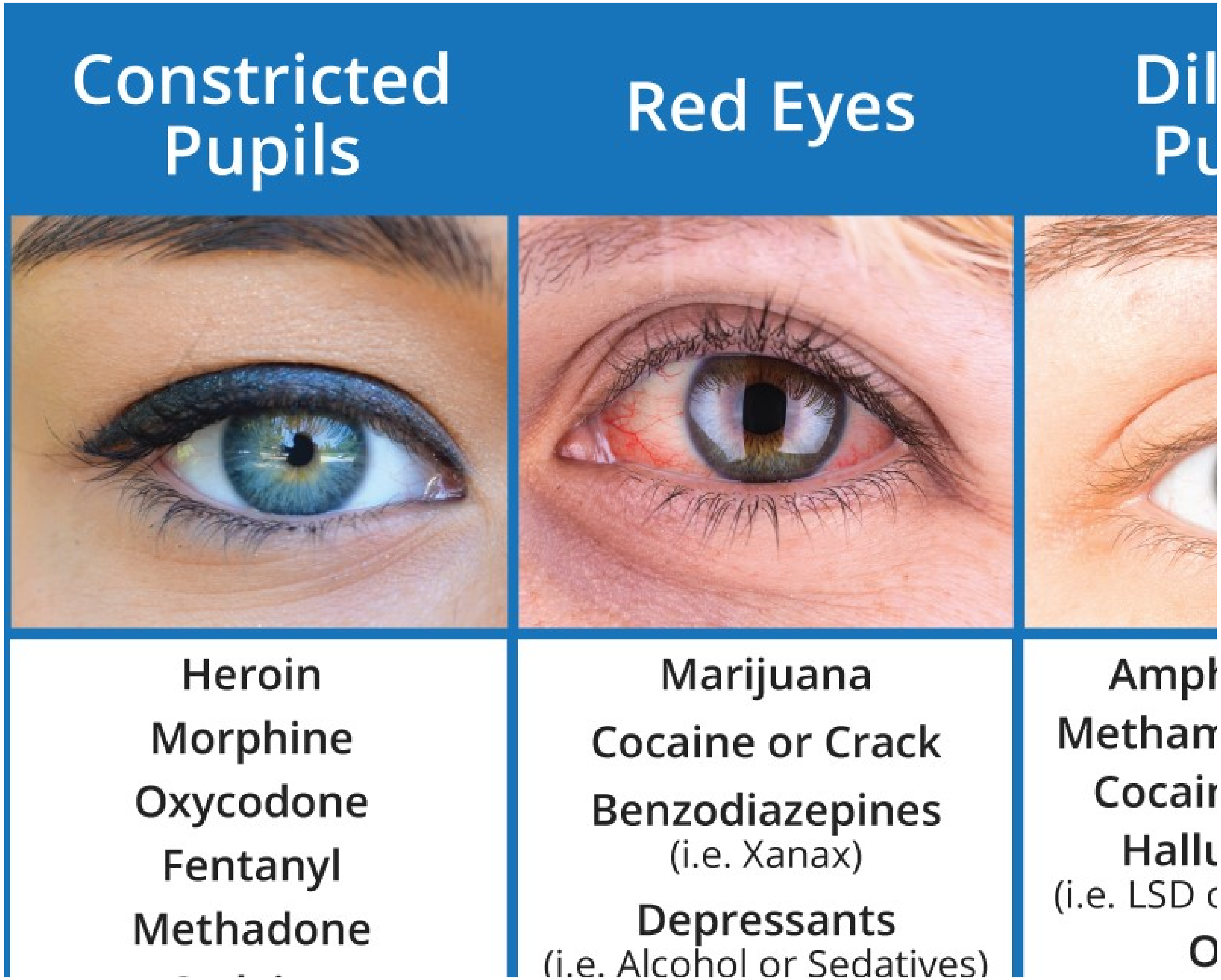
INCREASING	DECREASING
Sympathetic stimulation	Parasympath stimulation
Muscarinic receptor antagonist	Muscarinic re agonists
β-Adrenoceptor agonists	β-Blockers
Circulating cat-echolamines	Ischemia/hyp
Hypokalemia	Hyperkalemi

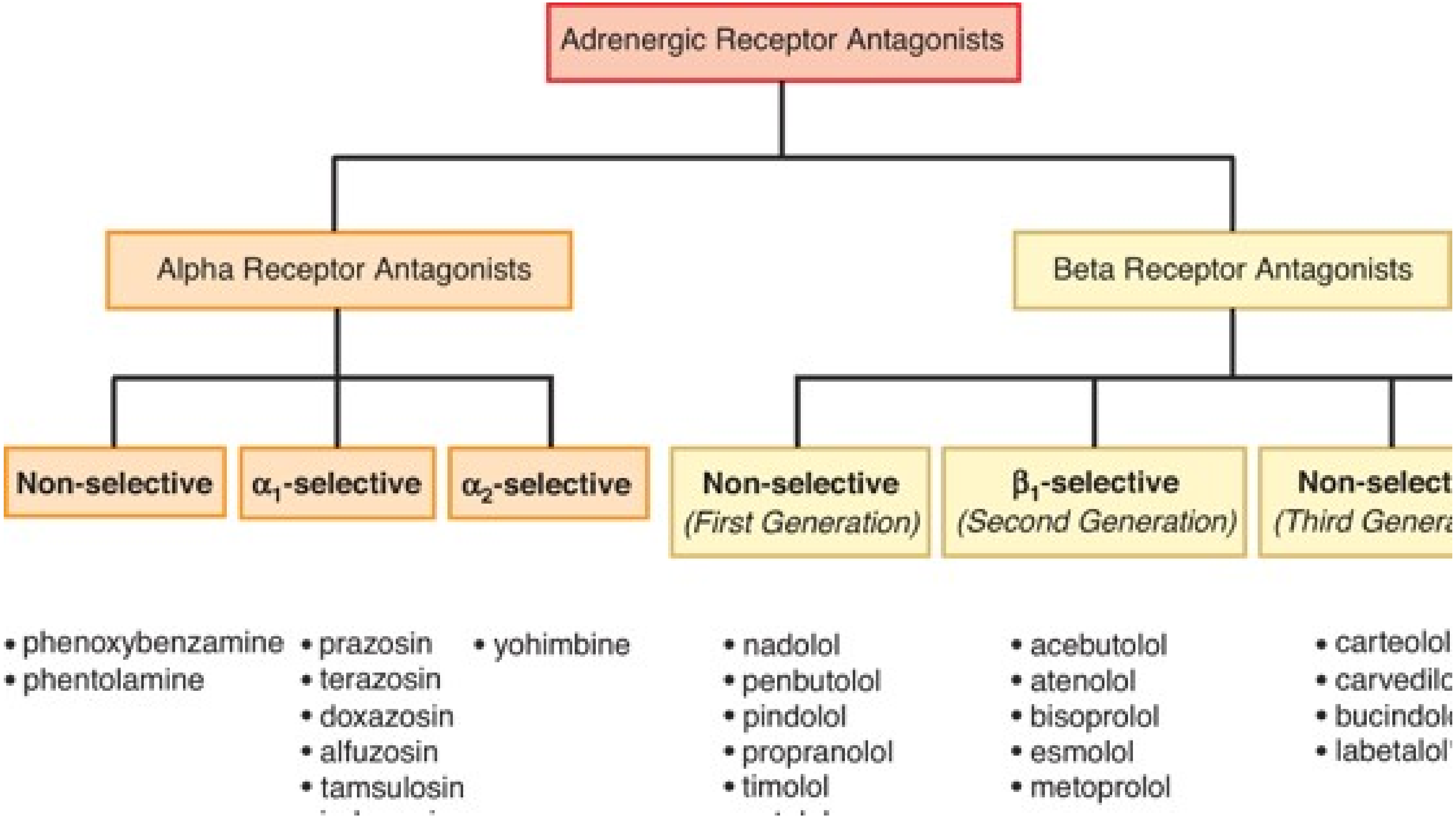
Methacholine,
Carbachol,
Bethaechol…

Acebutolol,
Atenolol,
Propranolol…

Na:
Quinidine,
Procainamide
Ca:
Verapamil,
Diltiazem,
Flunarizine…

Interesting Note!!!




Adrenergic Receptor Antagonists
Alpha Receptor Antagonists
Beta Receptor Antagonists
Non-selective
α1-selective
α2-selective
Non-selective (First Generation)
β1-selective (Second Generation)
Non-select
(Third Genera
• phenoxybenzamine
• phentolamine
• prazosin
• terazosin
• doxazosin
• alfuzosin
• tamsulosin
• yohimbine
• nadolol
• penbutolol
• pindolol
• propranolol
• timolol
• acebutolol
• atenolol
• bisoprolol
• esmolol
• metoprolol
• carteolol
• carvedilo
• bucindolo
• labetalol

Drug Facts for Your Personal Formulary: *Muscarinic Receptor Agonists and Antagonists*

Drugs	Therapeutic Uses	Clinical Pharmacology and Tips
Muscarinic Receptor Agonists		
Methacholine	• Diagnosis of bronchial airway hyperreactivity	• Muscarinic effects: GI cramps, diarrhea, nausea, vomiting; lacrimation, salivation, sweating; urinary urgency; vision problems; bronchospasm • Do not use in patients with GI obstruction, urinary retention, asthma/COPD
Carbachol	• Glaucoma (topical administration)	• Systemic muscarinic effects minimal with proper topical application, otherwise similar to methacholine
Bethanechol	• Ileus (postoperative, neurogenic) • Urinary retention	• Similar to methacholine • Take on empty stomach to minimize nausea/vomiting

Pilocarpine	• Glaucoma (topical administration)
	• Xerostomia due to
	  • Sjögren syndrome
	  • Head and neck irradiation
		• Systemic muscarinic effects minimal with proper topical application, otherwise similar to methacholine

Cevimeline	• Xerostomia due to • Sjögren syndrome	• Similar to methacholine
Muscarinic Receptor Antagonists		
Atropine	• Acute symptomatic bradycardia (e.g., AV block) • Cholinesterase inhibitor intoxication • Aspiration prophylaxis	• Antimuscarinic adverse effects: xerostomia, constipation, blurred vision, dyspepsia, and cognitive impairment • Contraindicated in patients with urinary tract obstruction (especially in benign prostatic hyperplasia), GI obstruction, and angle-closure glaucoma
Scopolamine	• Motion sickness	• CNS effects (drowsiness, amnesia, fatigue)
Homatropine, cyclopentolate, tropicamide	• Ophthalmological examination (cycloplegia and mydriasis induction)	• Antimuscarinic adverse effects are minimal with proper topical application
Ipratropium, tiotropium, aclidinium, umeclidinium	• COPD • Rhinorrhea (ipratropium)	• Minimal absorption as quaternary amine ⇒ fewer antimuscarinic adverse effects, otherwise similar to atropine
Pirenzepine, telenzepine	• Peptic ulcer disease (not in U.S.)	• Antimuscarinic adverse effects and contraindications similar to atropine
Oxybutynin, trospium, darifenacin, solifenacin, tolterodine, fesoterodine	• Overactive bladder, enuresis, neurogenic bladder	• Antimuscarinic adverse effects and contraindications similar to atropine • CNS-related antimuscarinic effects less likely with trospium (quaternary amine), darifenacin and solifenacin (some selectivity for M_3 receptors), fesoterodine (prodrug of tolterodine), and tolterodine (preference for muscarinic receptors in the bladder)
Glycopyrrolate	• Duodenal ulcer • Sialorrhea	• Antimuscarinic adverse effects and contraindications similar to atropine • Fewer CNS effects as glycopyrrolate is a quaternary amine and therefore unable to cross the blood-brain barrier
Dicyclomine, hyoscyamine	Diarrhea-predominant irritable bowel syndrome (IBS)	• Antimuscarinic adverse effects and contraindications similar to atropine (including constipation-dominant IBS) • Evidence for efficacy is limited
Trihexyphenidyl, benztropine	• Parkinson disease	• Antimuscarinic adverse effects and contraindications similar to atropine • Mainly used to treat the tremor in Parkinson disease • Not recommended for elderly or demented patients

Source : Goodman Gilman PHARMACOLOGICAL BASIS 13th edi

CLASSIFICATION OF {ADRENERGIC AGONIST } SYMPATHOMIMETIC agents according to mechanism of action. NO. I

DIRECTLY ACTING

CATECHOLAMINES

dihydroxybenzene agents having "OH" [HYDROXYL} GROUPS AT ADJACENT{ BOTH} 3RD & 4TH POSITIONS OF BENZENE RING .

ENDOGENEOUS

1. ADRENALINE
2. NOR-ADRENALINE
3. DOPAMINE

SYNTHETIC

1. DOBUTAMINE
2. ISOPRENALINE
3. ETHYLNORADRENALINE
4. PRENALTEROL
5. ISOETHARINE

NONCATECHOLAMINES

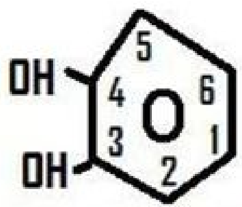
which do not posses "OH" GROUP AT BOTH ADJACENT POSITION OF BENZENE RING BUT ONLY AT ONE POSITION EITHER 3RD OR 4TH OR 5TH.

INDIRECTLY ACTING

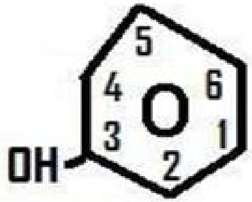
1. AMPHETAMINE
2. TYRAMINE

MIXED ACTING {DIRECT+ INDIRECT}

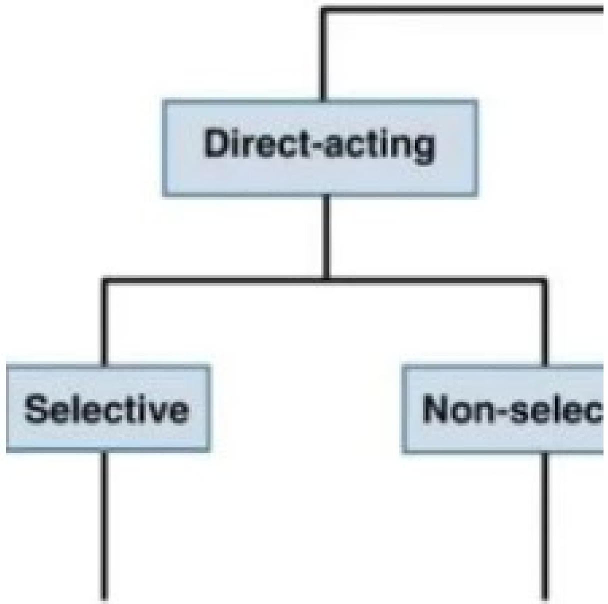
1. EPHEDRINE
2. METARAMINOL
3. DOPAMINE
4. MEPHENTERMINE



CATECHOL NUCLEUS

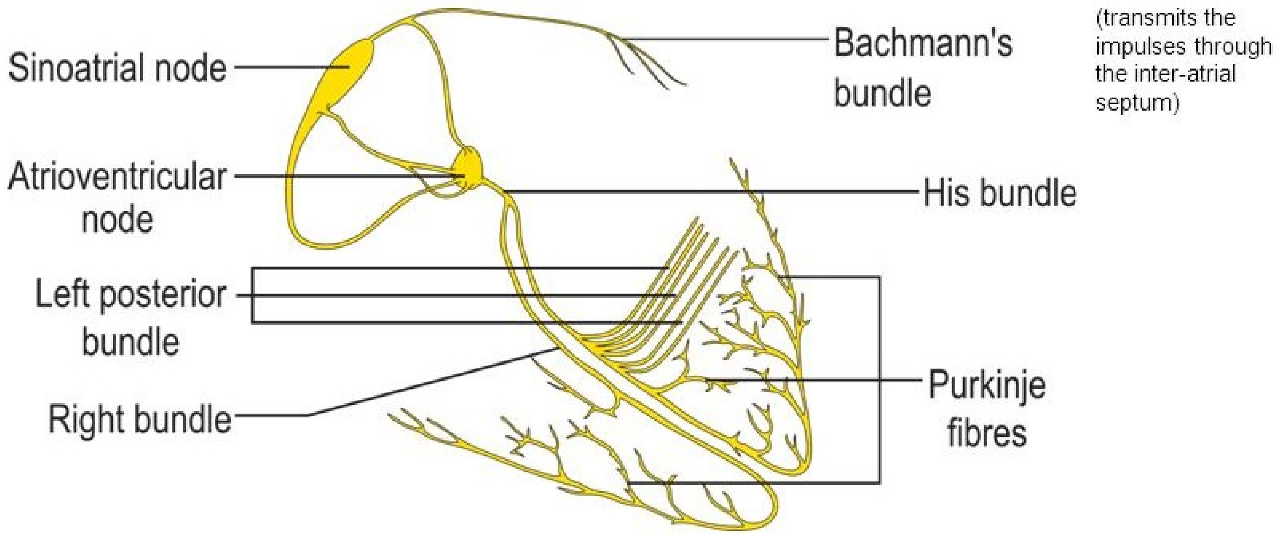


Phenylephrine


Direct-acting
Selective
Non-selec

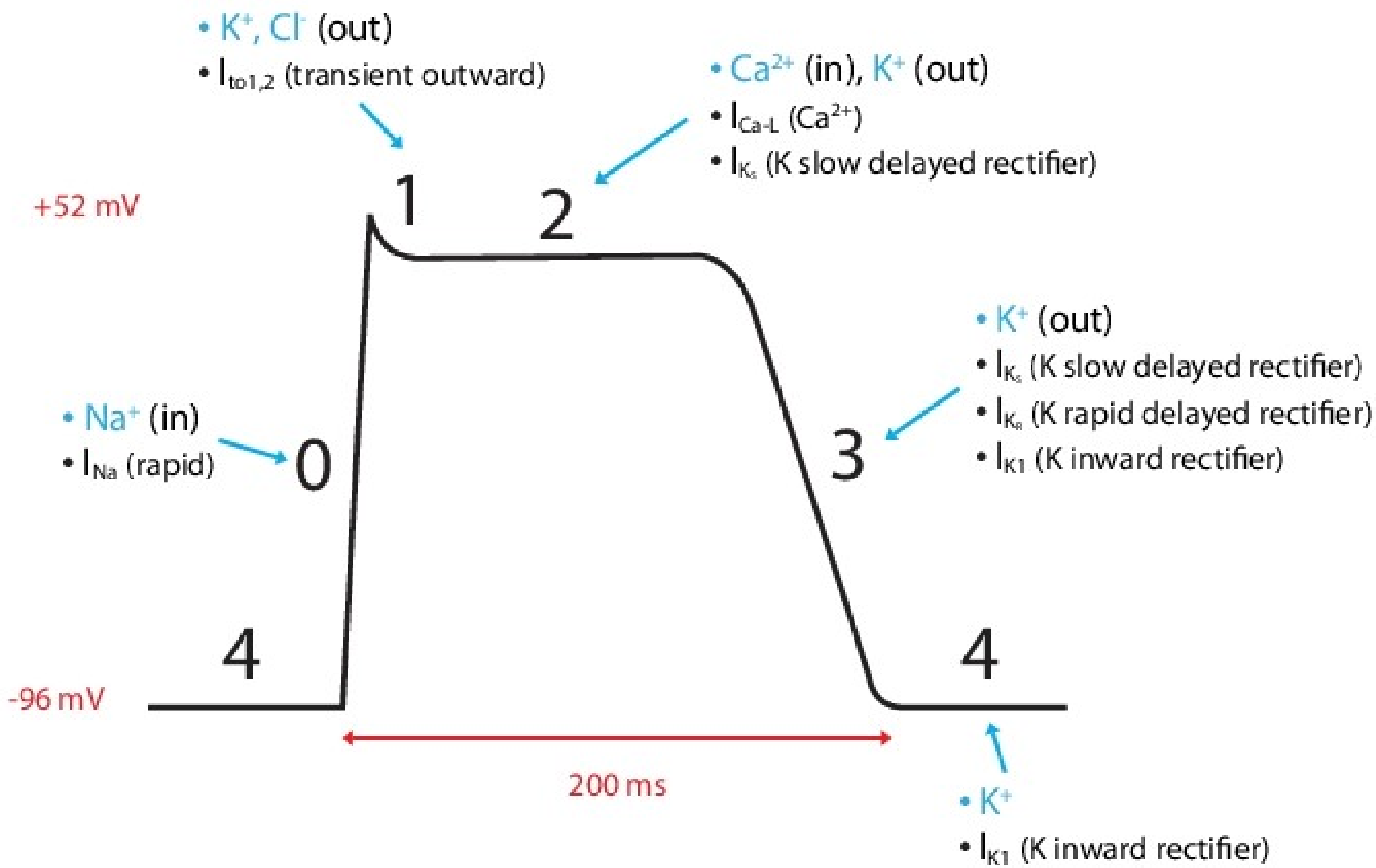
Voltage sensitive calcium channels			
	L-type (Long lasting current)	**T-type** (Transient current)	**N-** (Neu
1. Conductance	25 pS	8 pS	12–2
2. Activation threshold	High	Low	High
3. Inactivation rate	Slow	Fast	Med
4. Location and function	• Excitation-contraction coupling in cardiac and smooth muscle • SA, A-V node—conductivity • Endocrine cells—hormone release • Neurones—transmitter release	• SA node—pacemaker activity • 'T' current and repetitive spikes in thalamic and other neurones • Endocrine cells—hormone release • Certain arteries—	• Or in an —

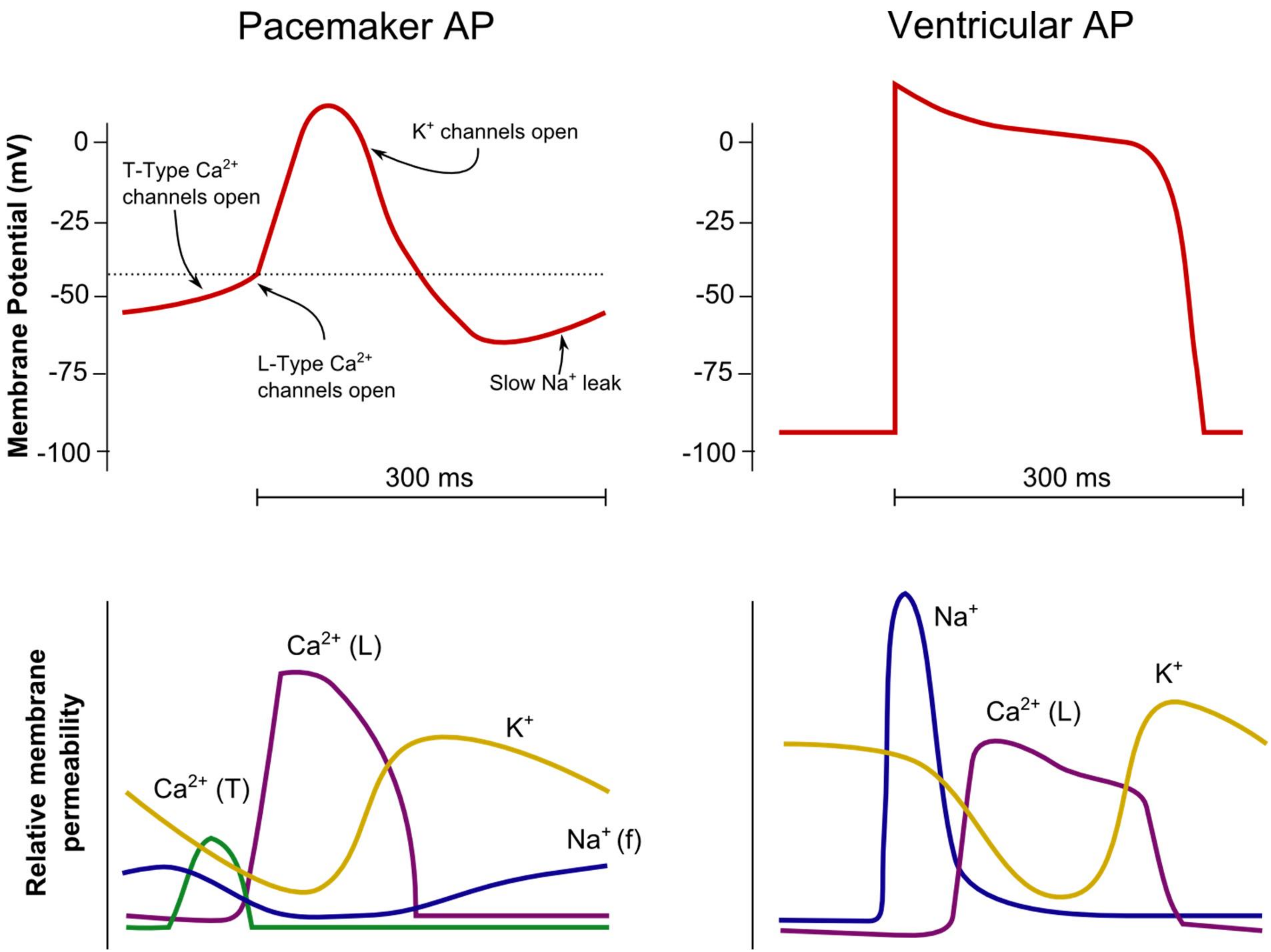
RATE: Intrinsic rates of pacing cells



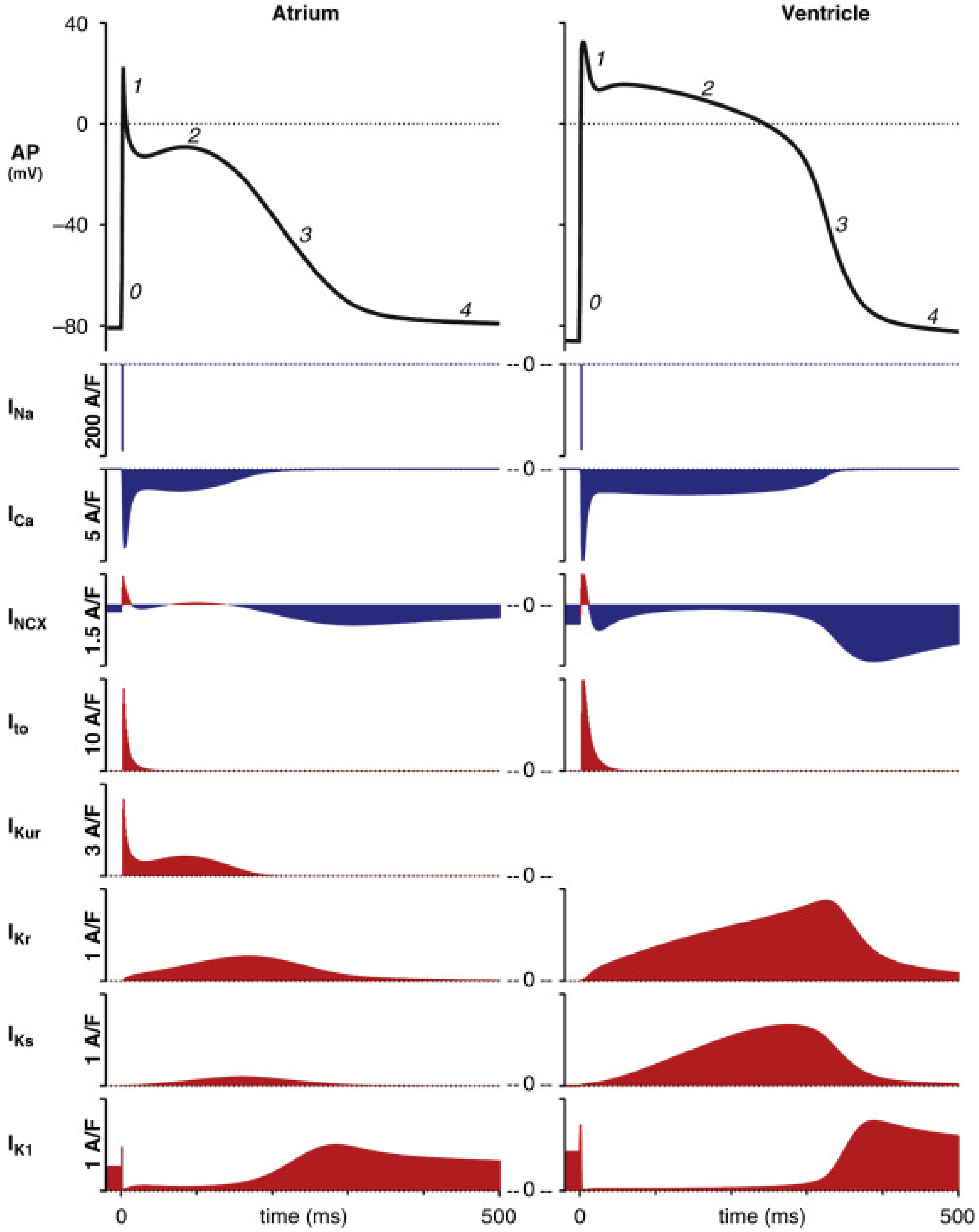
Structure	Pacemaker rate (beats/min; BPM)
SA node	60 – 100
Atrial myocardium	None
AV node	40 – 55
Bundle of His	25 – 40
Bundle branches	25 – 40
Purkinje fibers (network)	25 – 40
Ventricular myocardium	None

Non-Pacemaker APs
(Atrial, Ventricular & Purkinje Fiber APs)

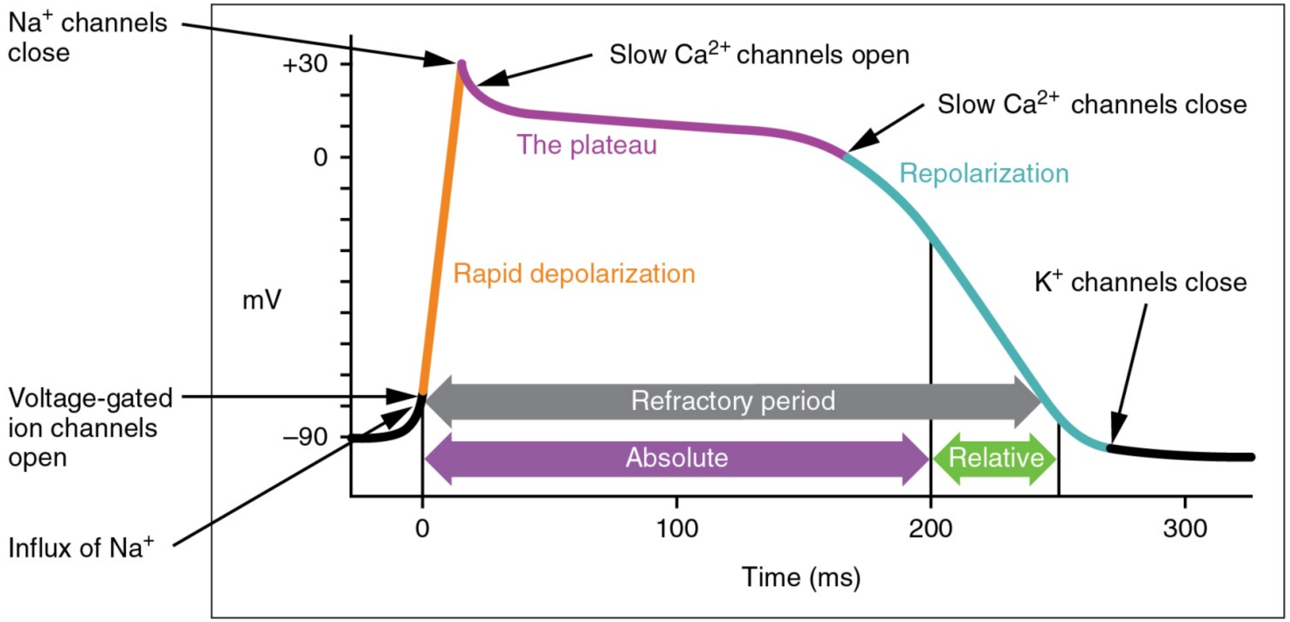




Pacemaker AP
Ventricular AP
Membrane Potential (mV)
0
-25
-50
-75
-100
T-Type Ca2+ channels open
K+ channels open
L-Type Ca2+ channels open
Slow Na+ leak
300 ms
300 ms
Relative membrane permeability
Ca2+ (L)
K+
Ca2+ (T)
Na+ (f)
Na+
K+
Ca2+ (L)

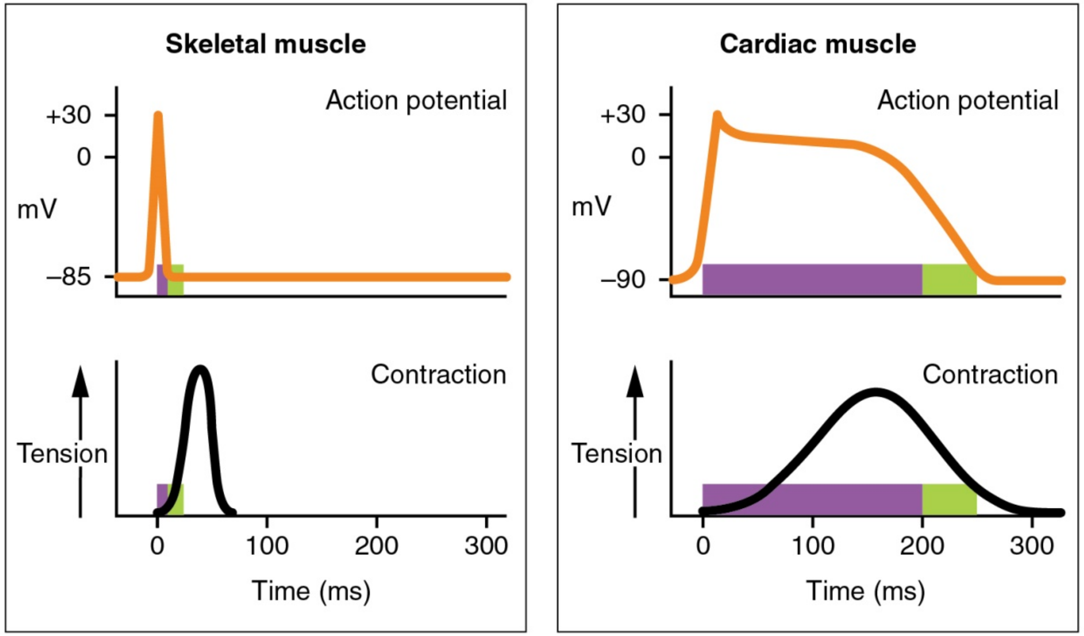


Atrium
Ventricle
AP
(mV)
40
0
−40
−80
1
2
3
4
0
I_{Na}
200 A/F
I_{Ca}
5 A/F
I_{NCX}
1.5 A/F
I_{to}
10 A/F
I_{Kur}
3 A/F
I_{Kr}
1 A/F
I_{Ks}
1 A/F
I_{K1}
1 A/F
0
time (ms)
500



Na+ channels close
Slow Ca2+ channels open
Slow Ca2+ channels close
+30
0
The plateau
Repolarization
Rapid depolarization
mV
K+ channels close
Voltage-gated ion channels open
Refractory period
–90
Absolute
Relative
Influx of Na+
0
100
200
300
Time (ms)

(a)



Skeletal muscle
Action potential
+30
0
mV
–85
Contraction
Tension
0
100
200
300
Time (ms)
Cardiac muscle
Action potential
+30
0
mV
–90
Contraction
Tension
0
100
200
300
Time (ms)

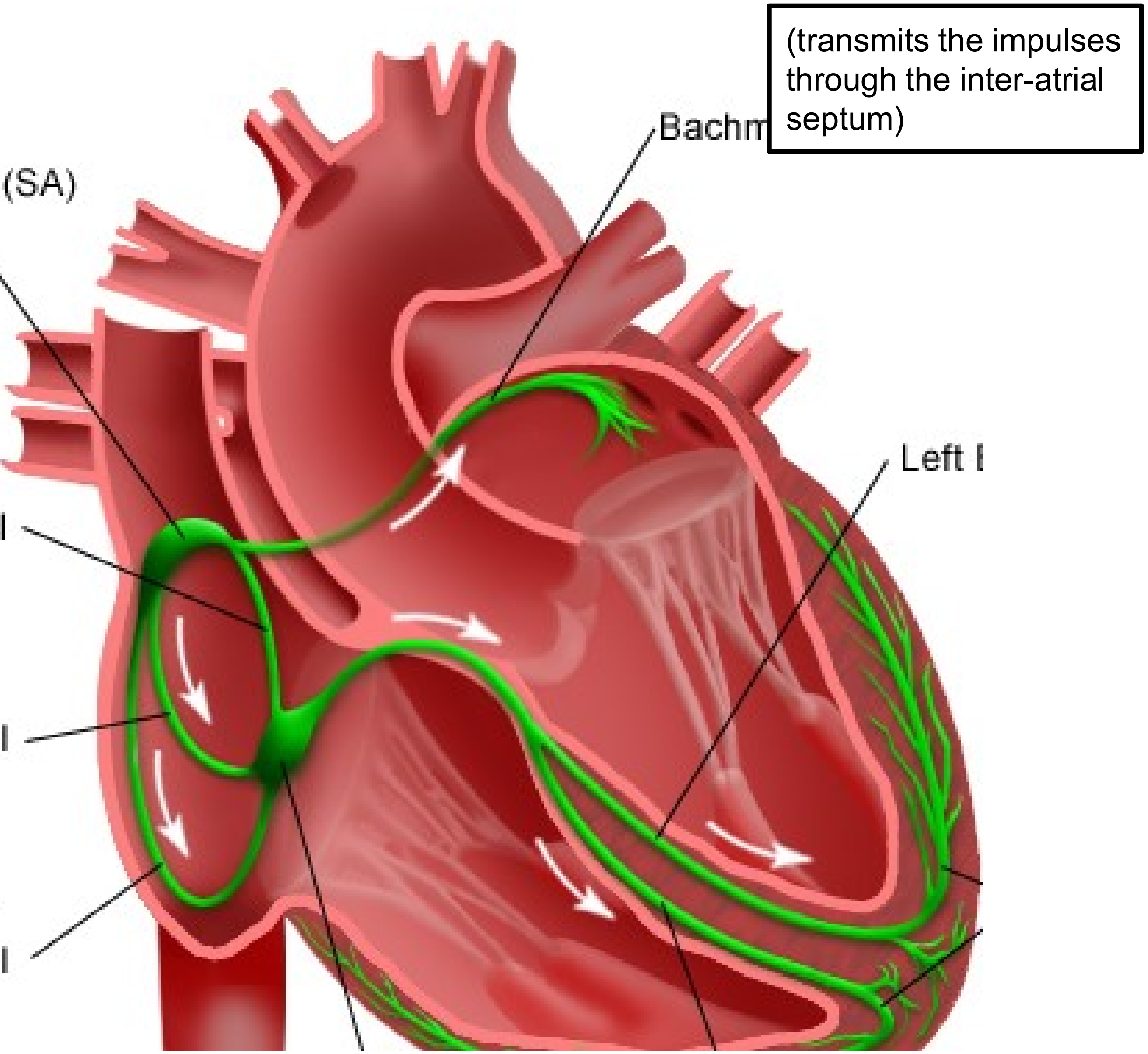
(b)

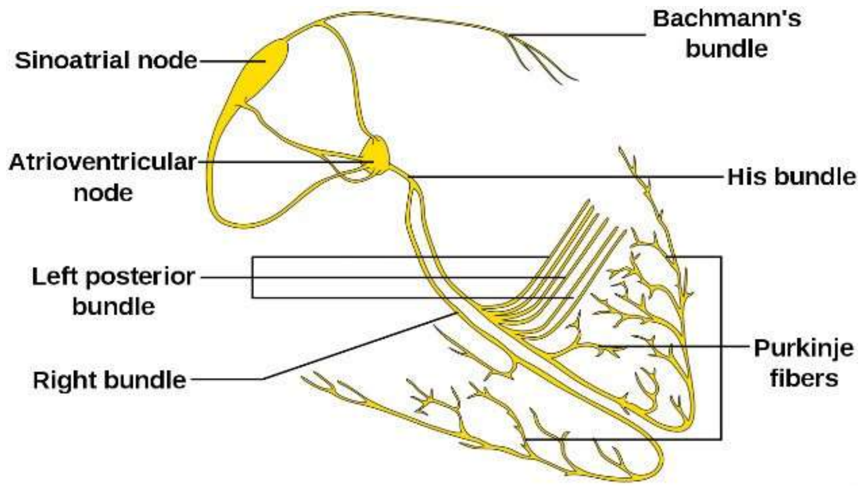
TABLE 2-1 CARDIAC ION CHANNELS AND CURRENTS

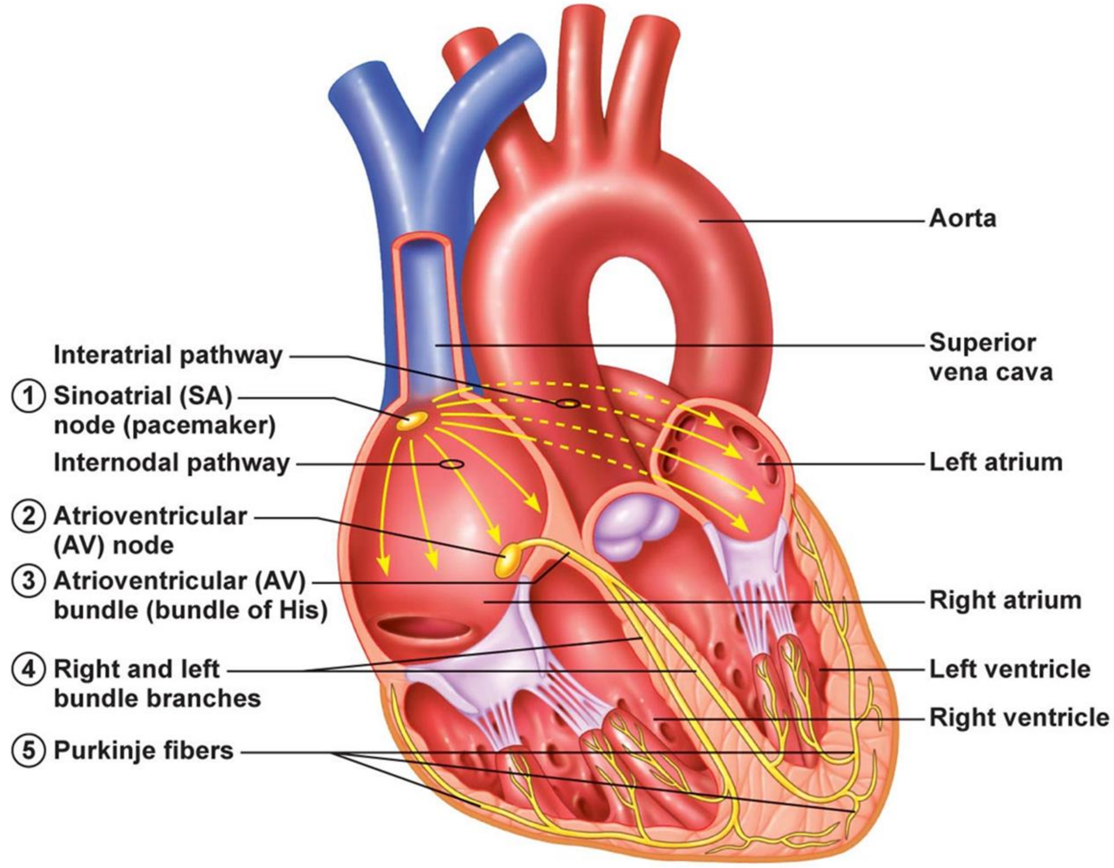
CHANNELS	GATING	CHARACTERISTICS
Sodium		
Fast Na^+ (I_{Na})	Voltage	Phase 0 of myocytes
Slow Na^+ (I_f)	Voltage and receptor	Contributes to phase 4 pacemaker current in SA and AV nodal cells
Calcium		
L-type (I_{Ca})	Voltage	Slow inward, long-lasting current; phase 2 of myocytes and phases 4 and 0 of SA and AV nodal cells
T-type (I_{Ca})	Voltage	Transient current; contributes to phase 4 pacemaker current in SA and AV nodal cells
Potassium		
Inward rectifier (I_{K1})	Voltage	Maintains negative potential in phase 4; closes with depolarization
Transient outward (I_{to})	Voltage	Contributes to phase 1 in myocytes
Delayed rectifier (I_{Kr})	Voltage	Phase 3 repolarization
ATP-sensitive ($I_{K,\ ATP}$)	Receptor	Inhibited by ATP; opens when ATP decreases during cellular hypoxia
Acetylcholine activated ($I_{K,\ ACh}$)	Receptor	Activated by acetylcholine and adenosine; Gi-protein coupled; slows SA nodal firing
Calcium activated ($I_{K,Ca}$)	Receptor	Activated by high cytosolic calcium; accelerates repolarization

I_x, name of specific current.

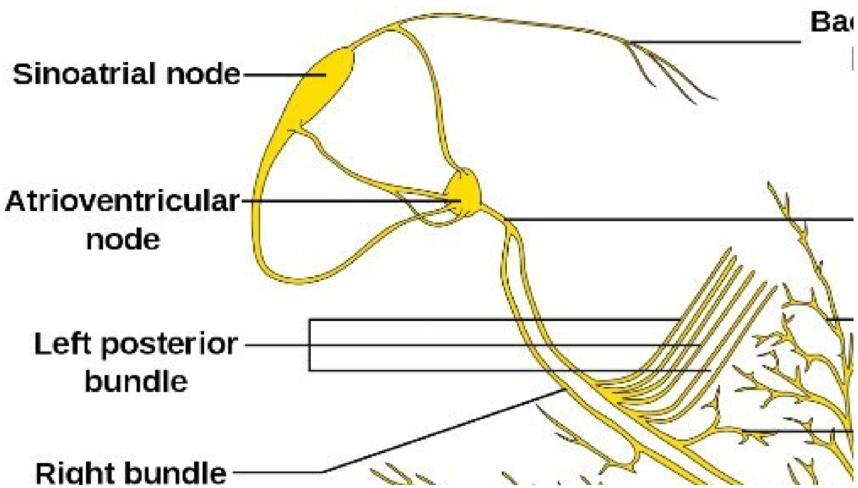
Electrical System of the Heart



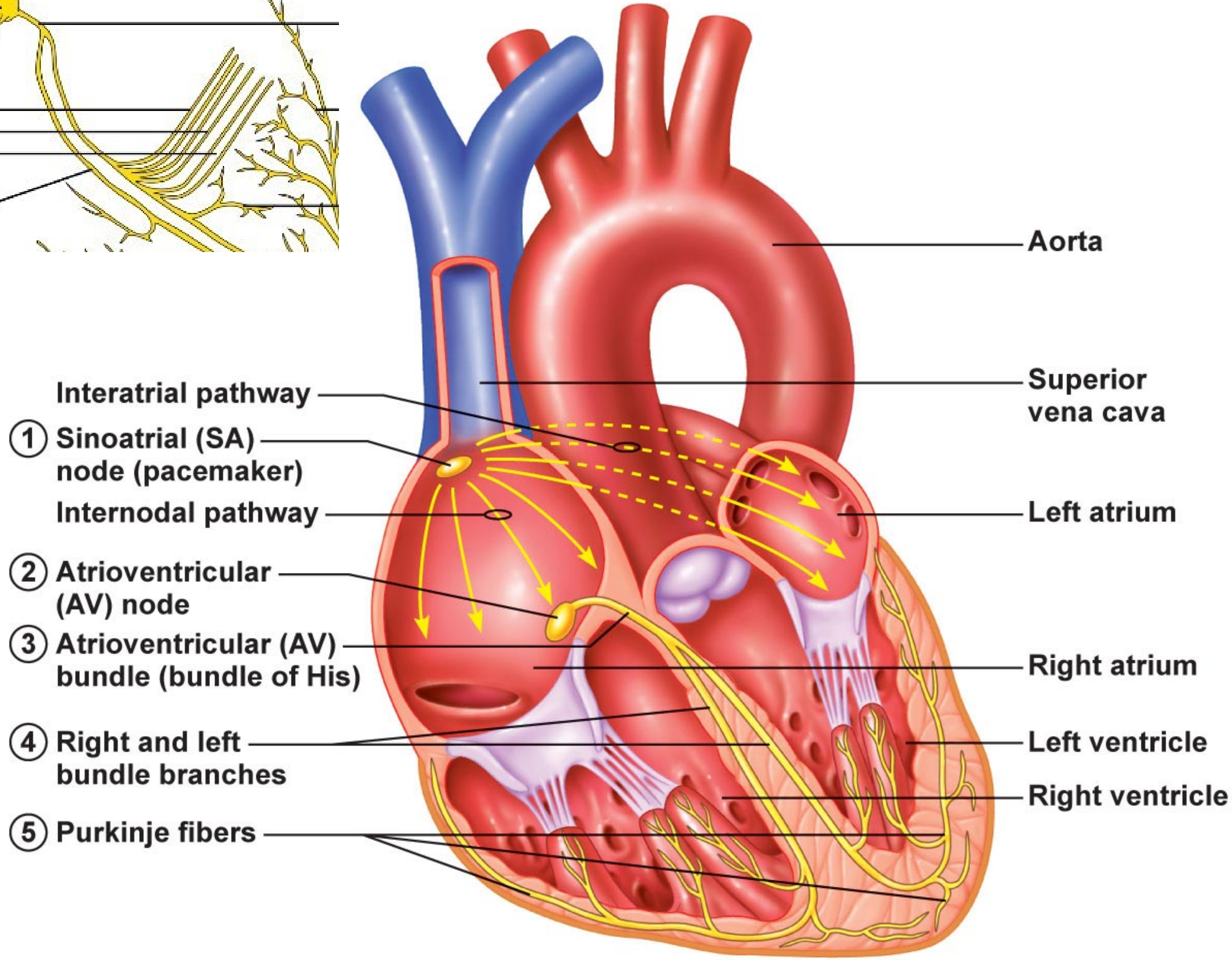




1. An action potential is initiated in the SA node and travels by way of conduction fibers to the AV node. Action potential spreads throughout the cells of the atria.
2. Impulse arrives at the AV node where there is a momentary delay because action potentials are transmitted more slowly in these cells than in other cells of the conduction system.
3. Impulse leaves the AV node and travels through the AV bundle (bundle of His) in the interventricular septum.
4. AV bundles only travels a short distance before splitting into right and left bundle branches.
5. Impulse travels to the myocardial cells of the ventricle by means of an extensive network of conduction fibers called Purkinje fibers.

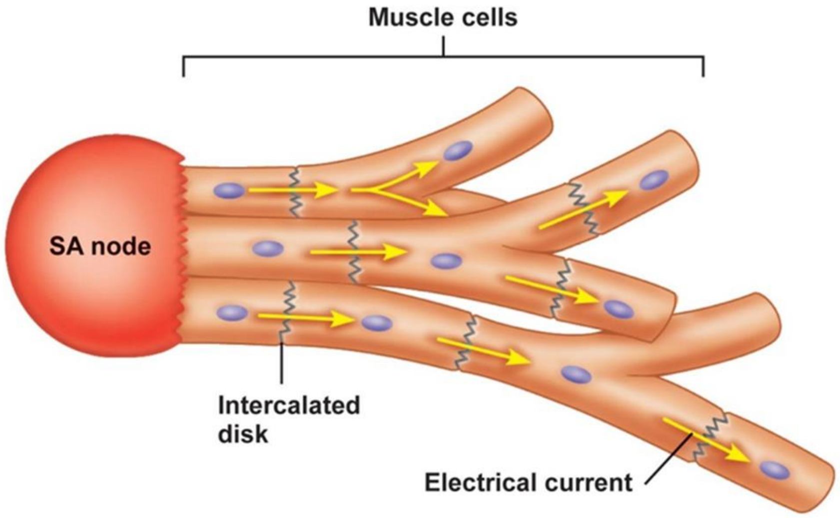


Sinoatrial node
Atrioventricular node
Left posterior bundle
Right bundle

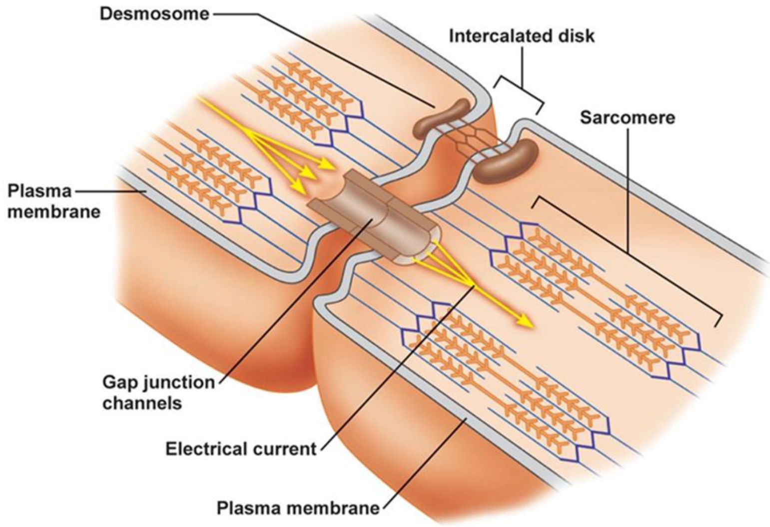


Interatrial pathway
1 Sinoatrial (SA) node (pacemaker)
Internodal pathway
2 Atrioventricular (AV) node
3 Atrioventricular (AV) bundle (bundle of His)
4 Right and left bundle branches
5 Purkinje fibers
Aorta
Superior vena cava
Left atrium
Right atrium
Left ventricle
Right ventricle

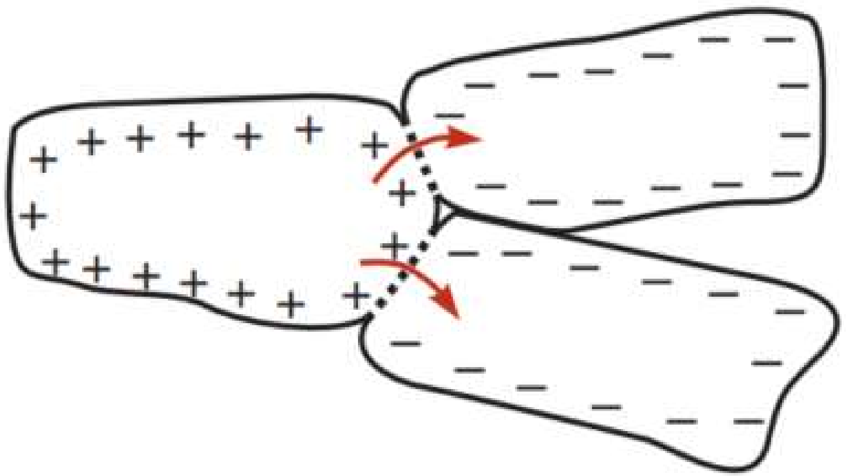
Electrical Conduction Within the Heart



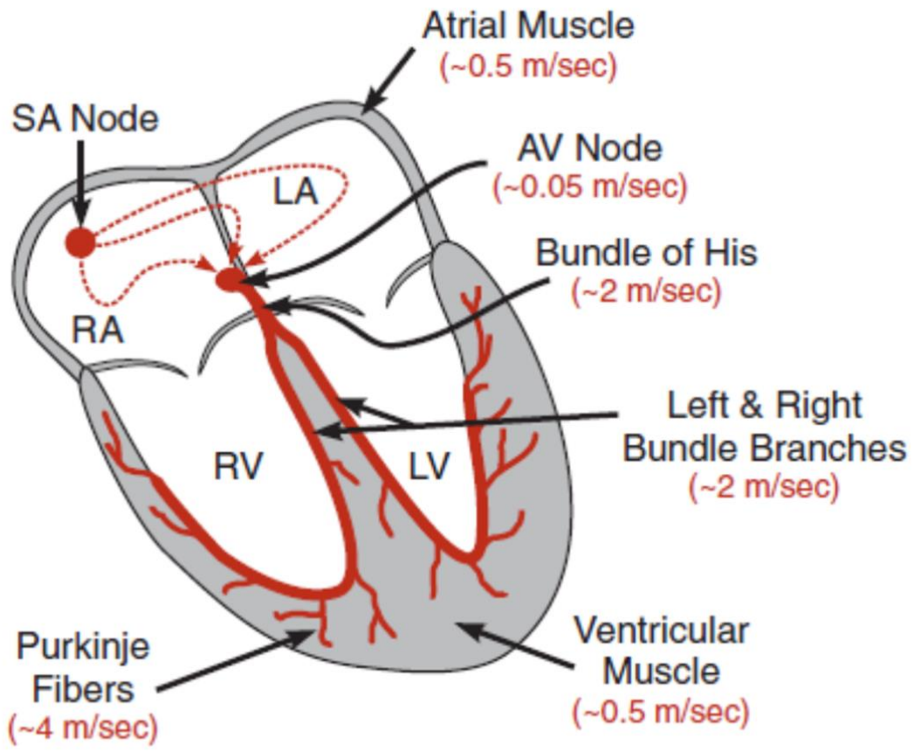
(a)

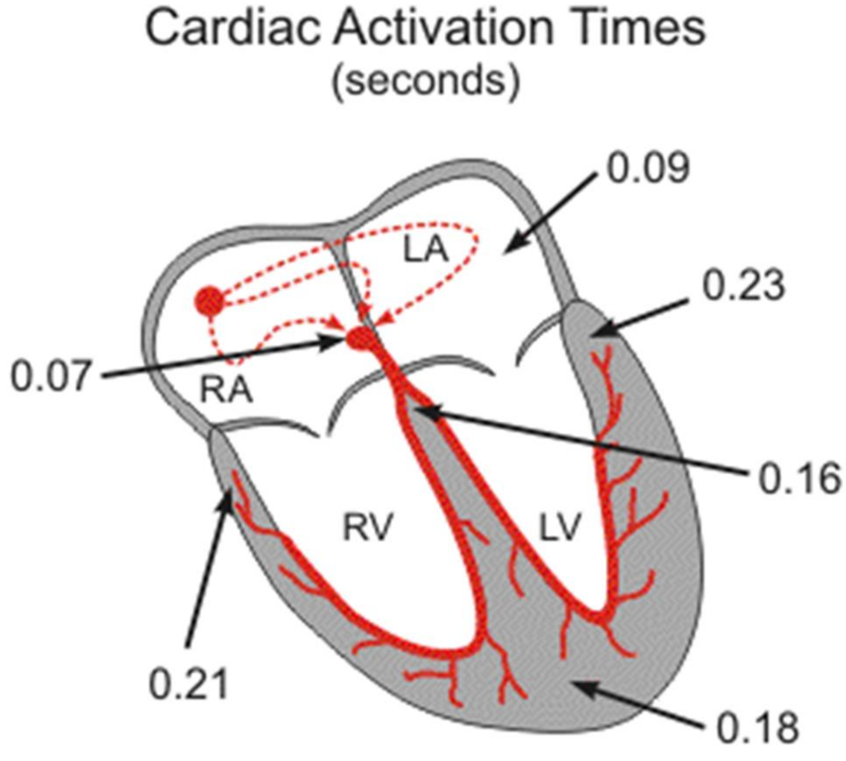


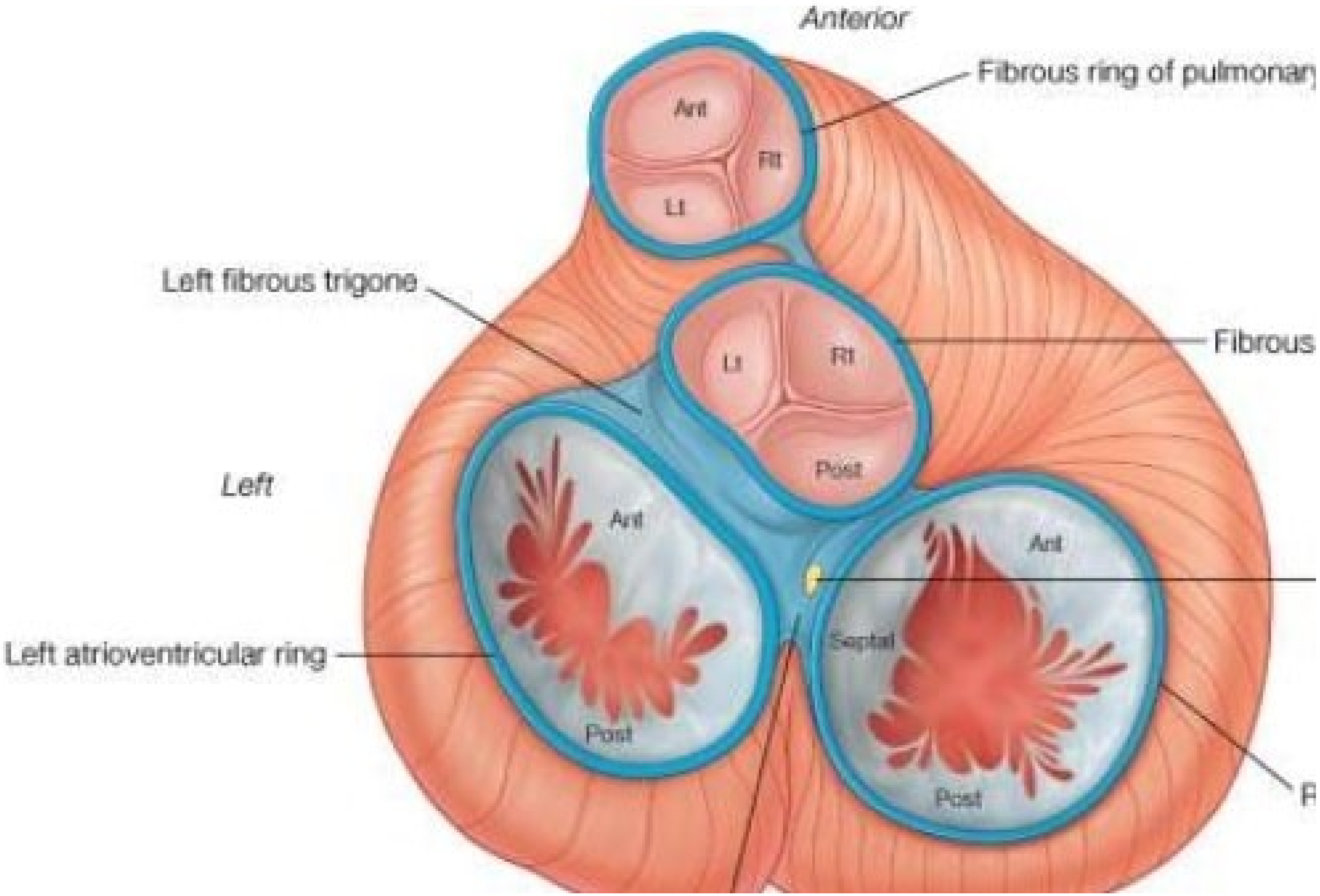
(b)

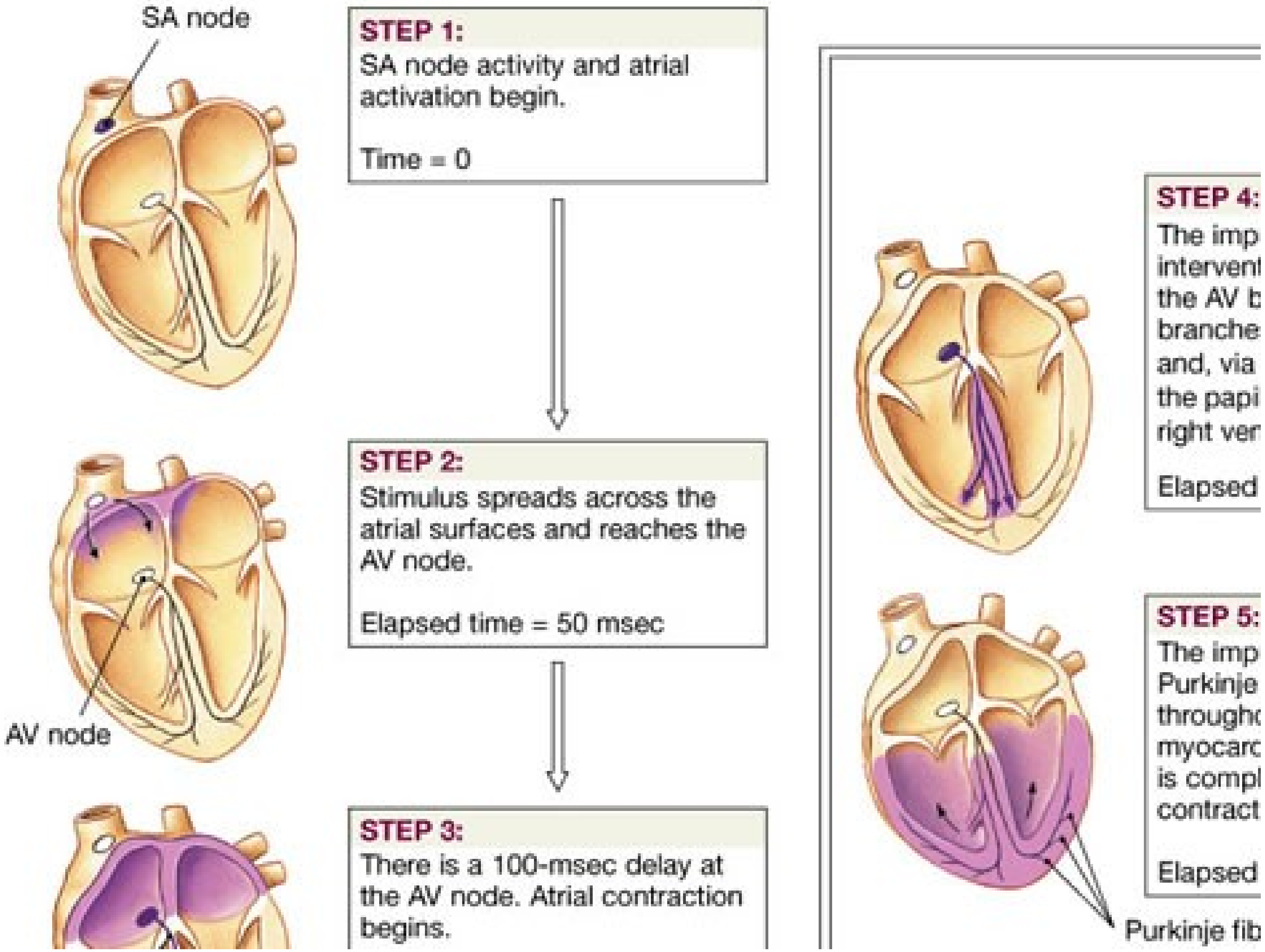


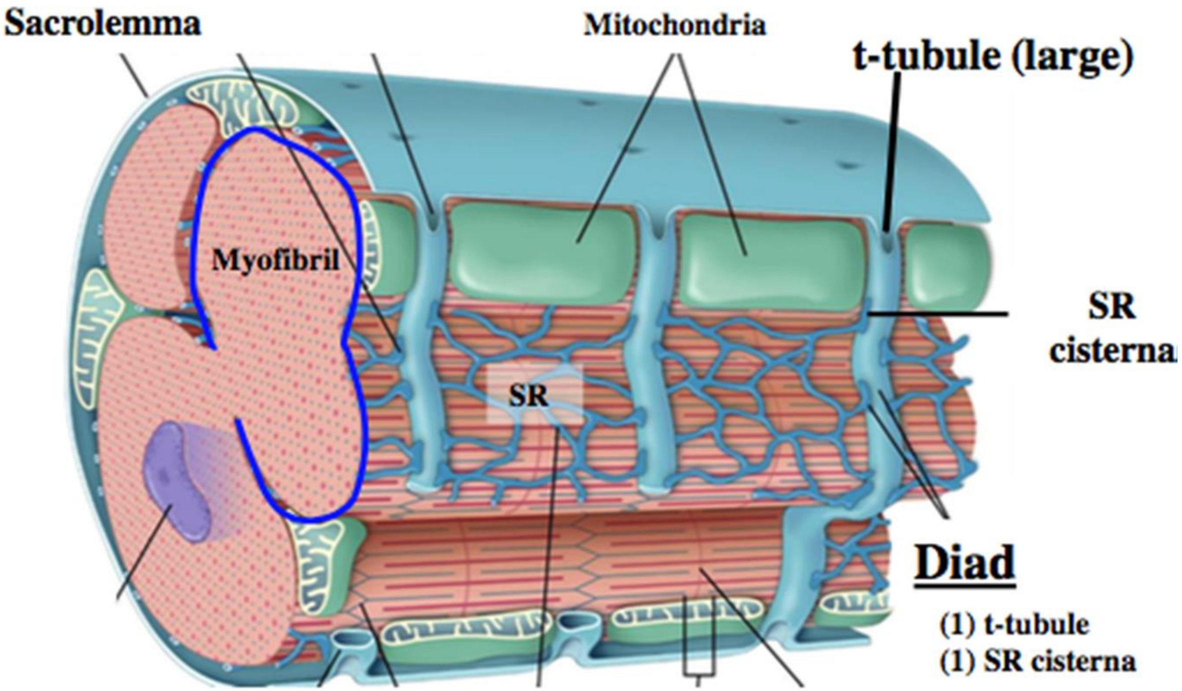
Conduction Velocities
&
Activation Times

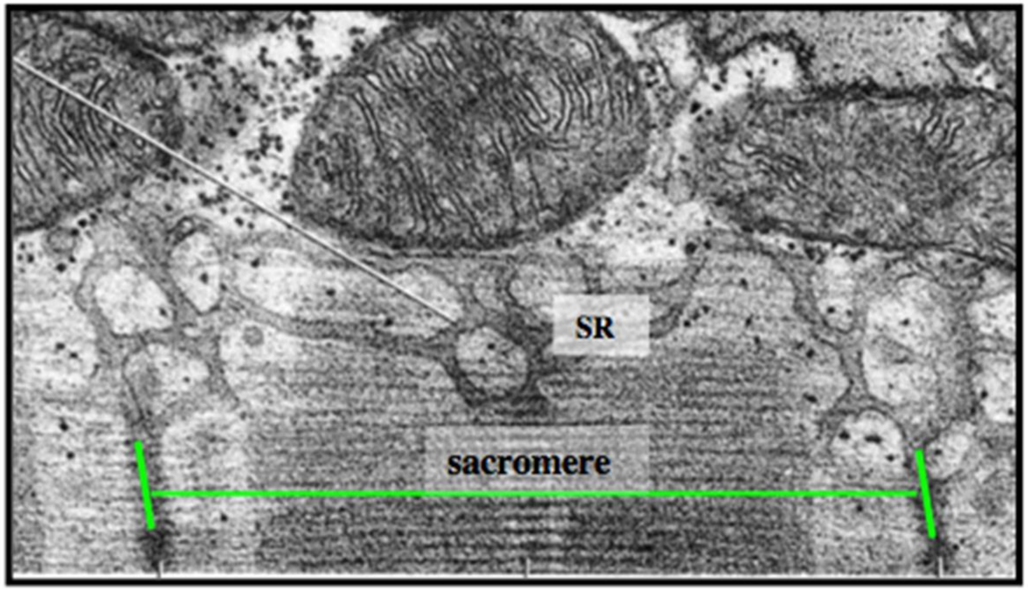




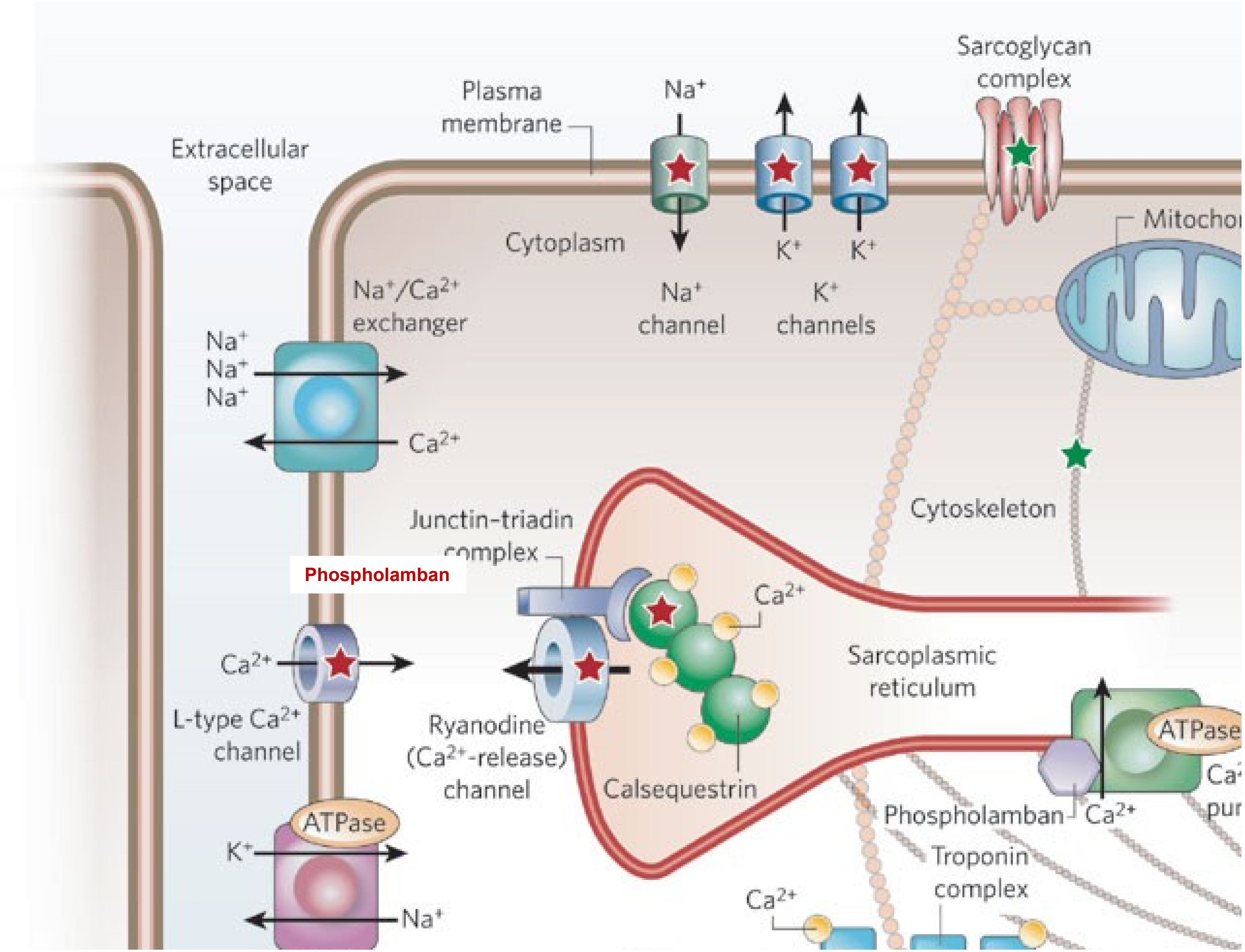

Anterior
Fibrous ring of pulmonar
Ant
Rt
Lt
Left fibrous trigone
Fibrous
Lt
Rt
Post
Left
Ant
Left atrioventricular ring
Post
Ant
Septal
Post

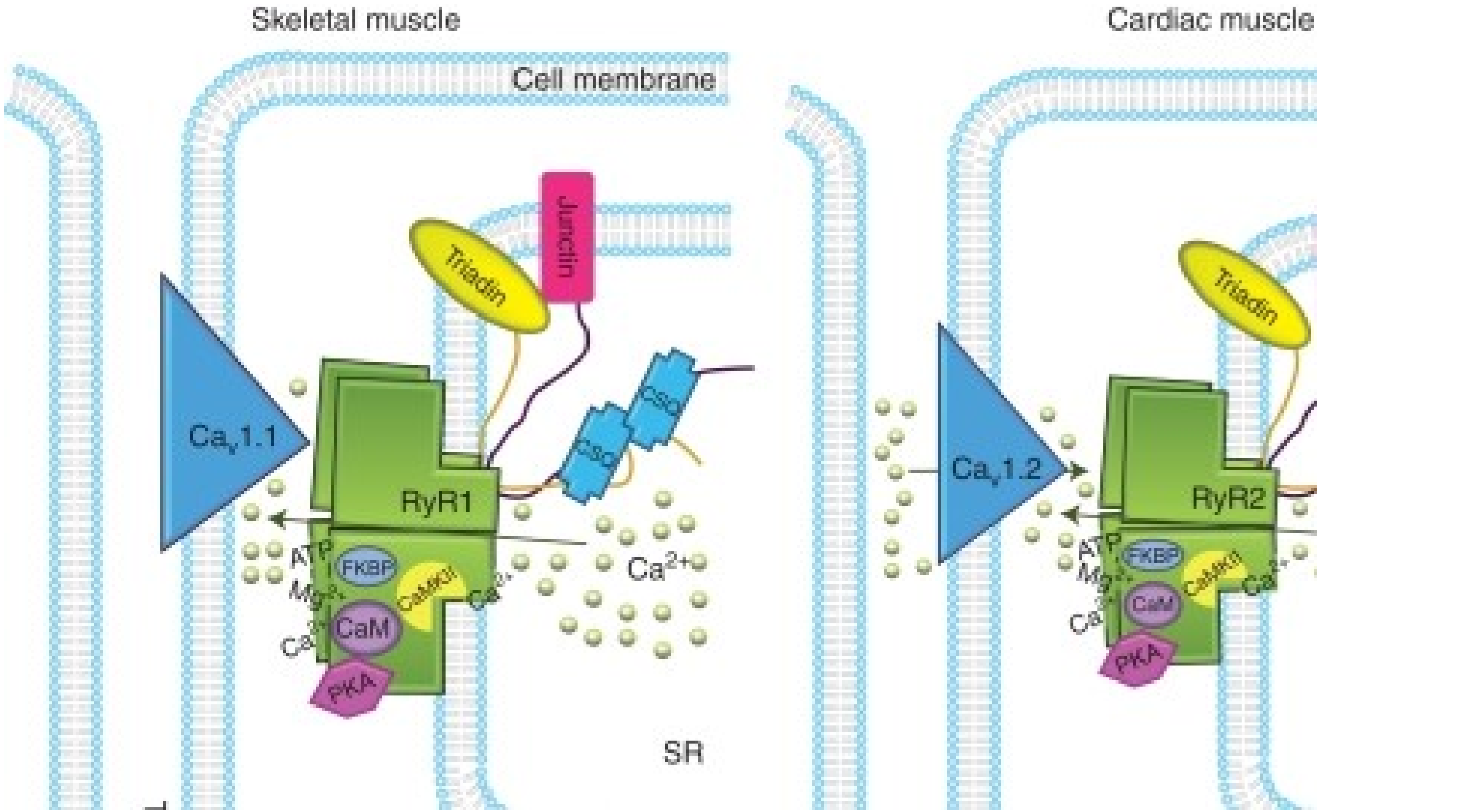

SA node
STEP 1:
SA node activity and atrial activation begin.
Time = 0
STEP 2:
Stimulus spreads across the atrial surfaces and reaches the AV node.
Elapsed time = 50 msec
AV node
STEP 3:
There is a 100-msec delay at the AV node. Atrial contraction begins.
STEP 4:
The imp
intervent
the AV b
branche
and, via
the papi
right ver
Elapsed
STEP 5:
The imp
Purkinje
through
myocard
is compl
contract
Elapsed
Purkinje fib


Sacrolemma
Mitochondria
t-tubule (large)
Myofibril
SR
SR
cisterna
Diad
(1) t-tubule
(1) SR cisterna


SR
sacromere

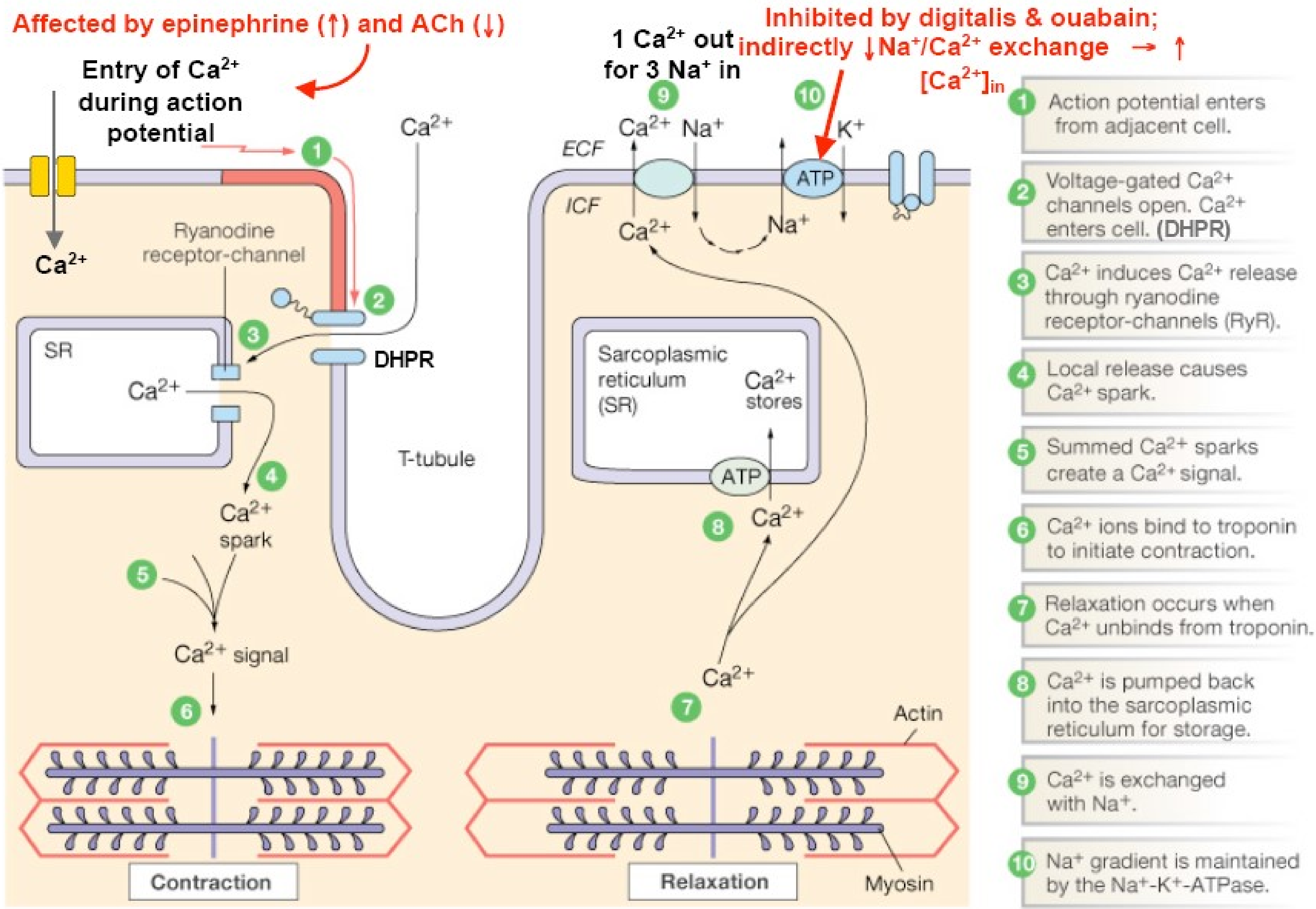
Excitation-Contraction Coupling

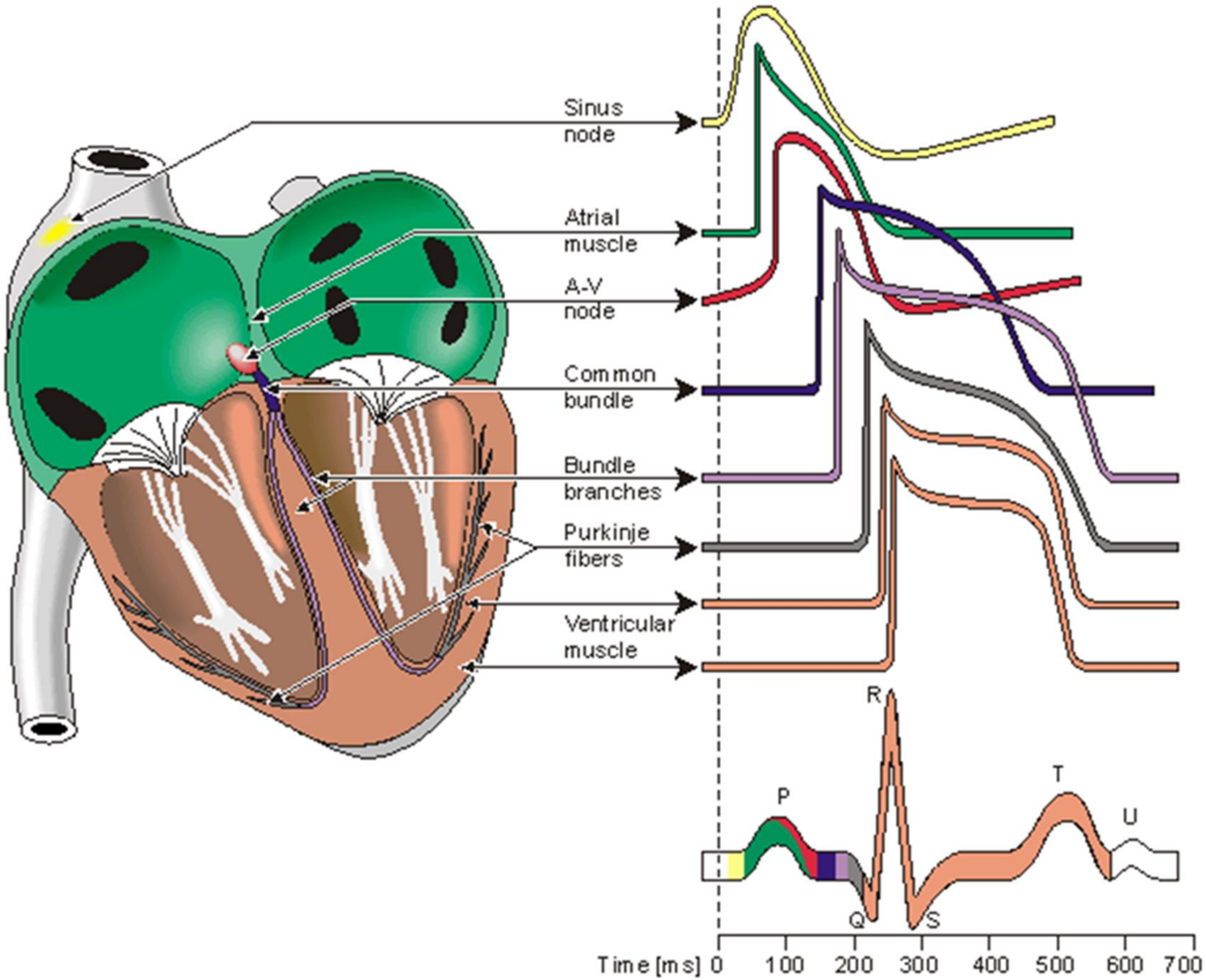


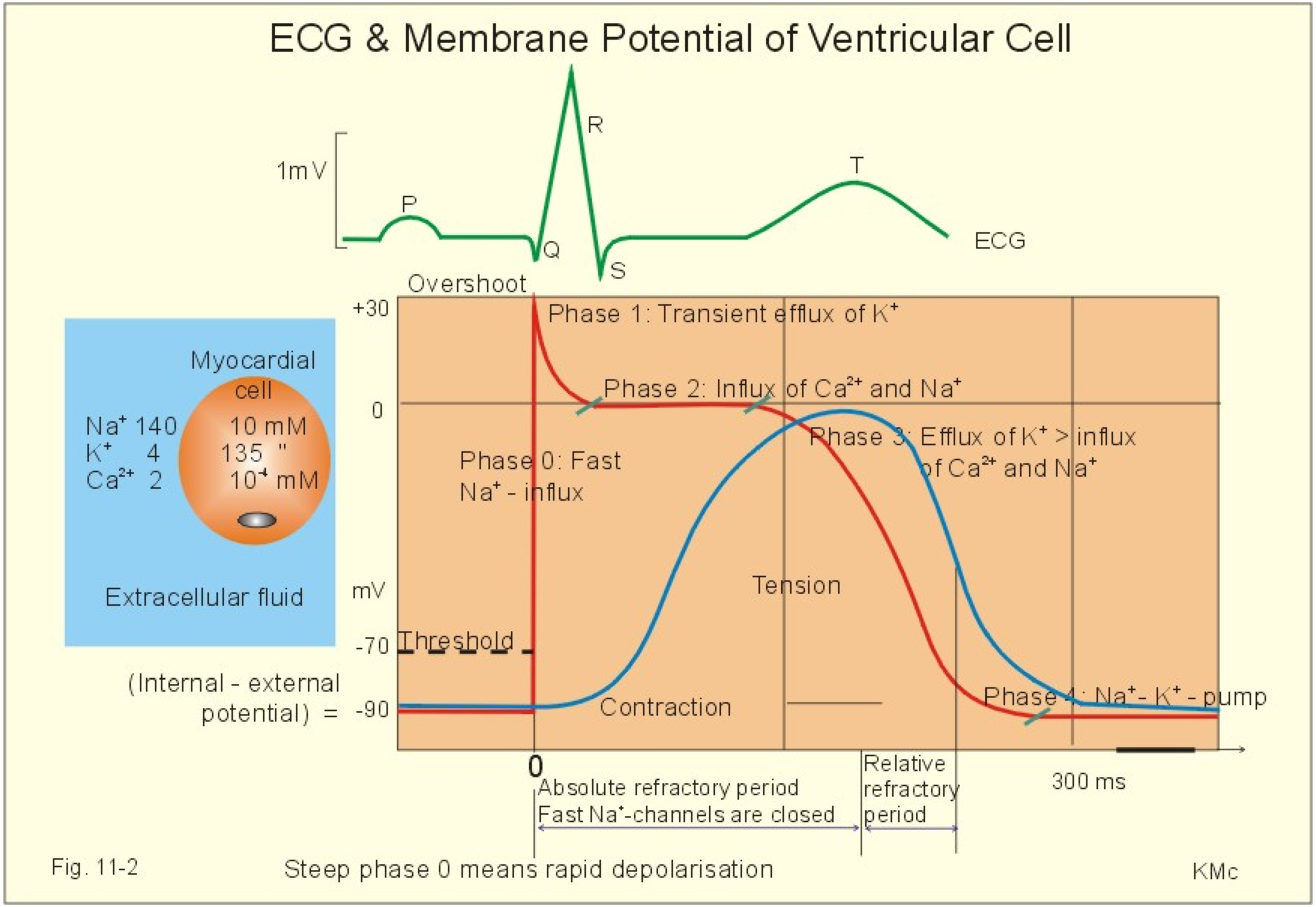


Skeletal muscle
Cardiac muscle
Cell membrane
Triadin
Junctin
CSQ
CSQ
$Ca_v1.1$
RyR1
ATP
Mg^{2+}
Ca^{2+}
FKBP
CaMKII
CaM
PKA
Ca^{2+}
SR
Triadin
$Ca_v1.2$
RyR2
ATP
Mg^{2+}
Ca^{2+}
FKBP
CaMKII
CaM
PKA

Ca^{2+} signaling in cardiac muscle



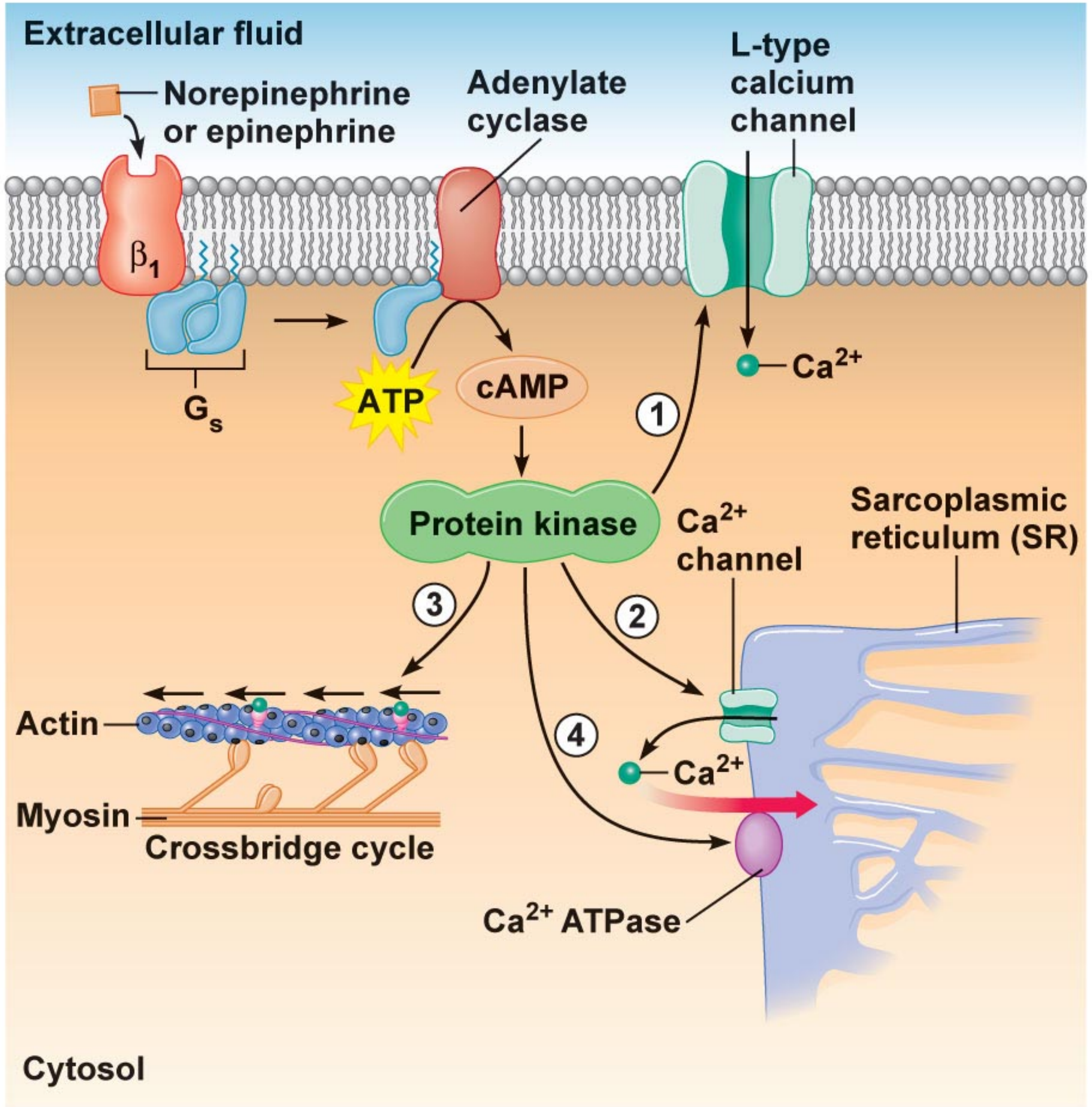

Sinus node
Atrial muscle
A-V node
Common bundle
Bundle branches
Purkinje fibers
Ventricular muscle
P
Q
R
S
T
U
Time [ms] 0 100 200 300 400 500 600 700



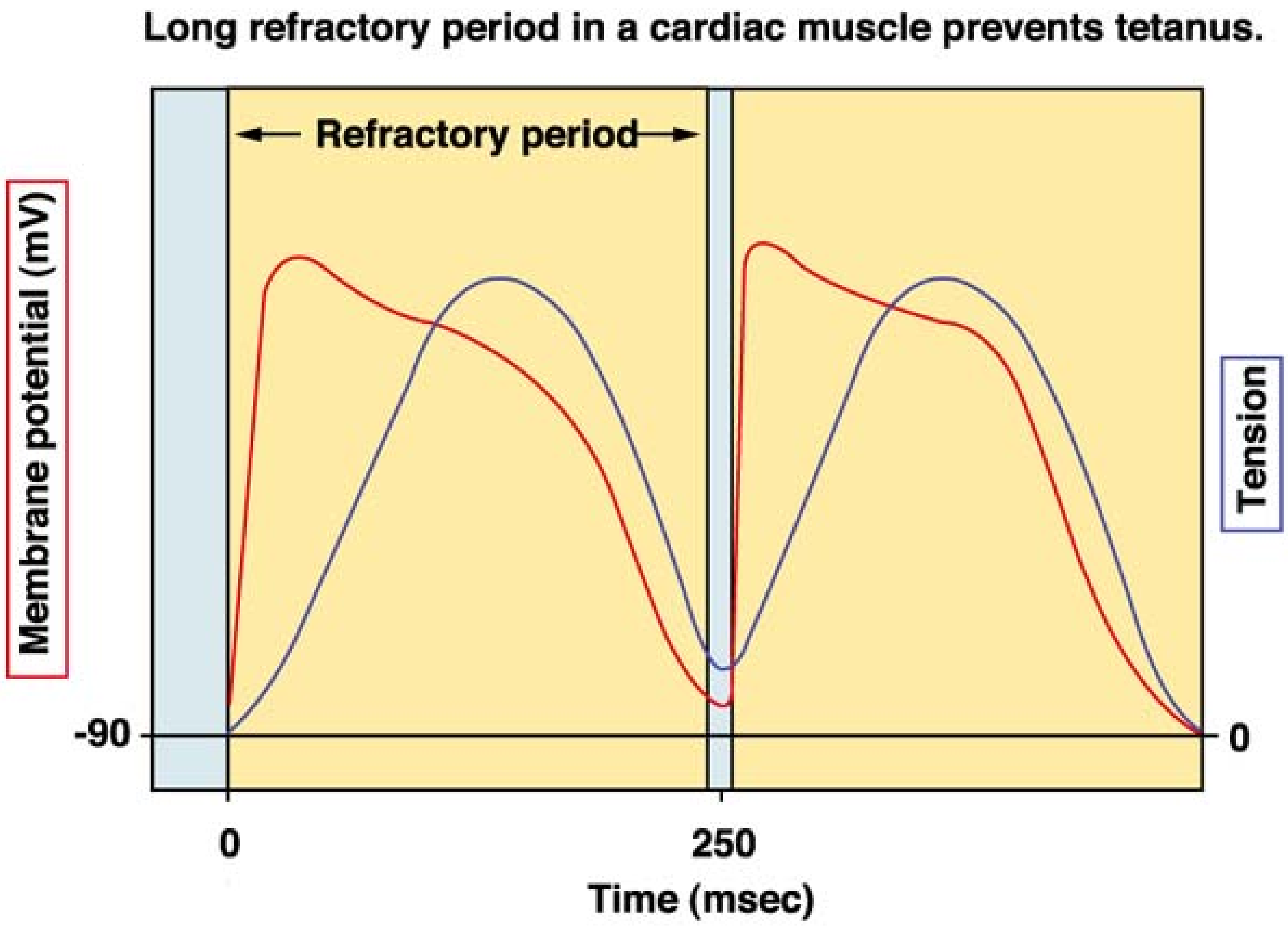
ECG & Membrane Potential of Ventricular Cell
1mV
P
Q
R
S
T
ECG
Overshoot
+30
0
mV
-70
-90
Phase 1: Transient efflux of K+
Phase 2: Influx of Ca2+ and Na+
Phase 3: Efflux of K+ > influx of Ca2+ and Na+
Phase 0: Fast Na+ - influx
Phase 4: Na+- K+ - pump
Tension
Contraction
Threshold
Myocardial cell
Na+ 140 10 mM
K+ 4 135 "
Ca2+ 2 10-4 mM
Extracellular fluid
(Internal - external potential) =
0
Absolute refractory period
Fast Na+-channels are closed
Relative refractory period
300 ms
Steep phase 0 means rapid depolarisation
KMc

Fig. 11-2

Ventricular contractility



Refracter Period in Cardiac Muscle



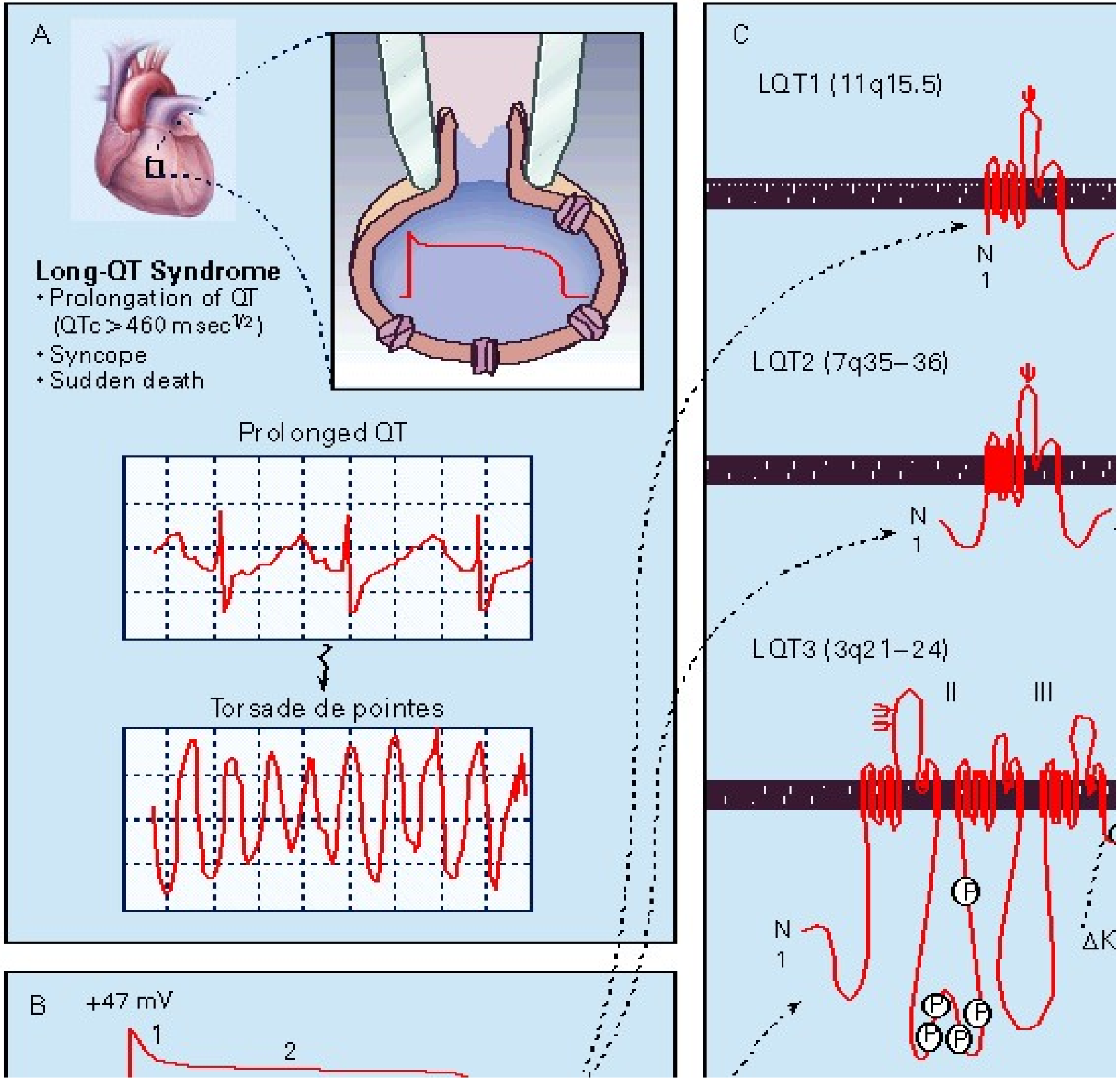
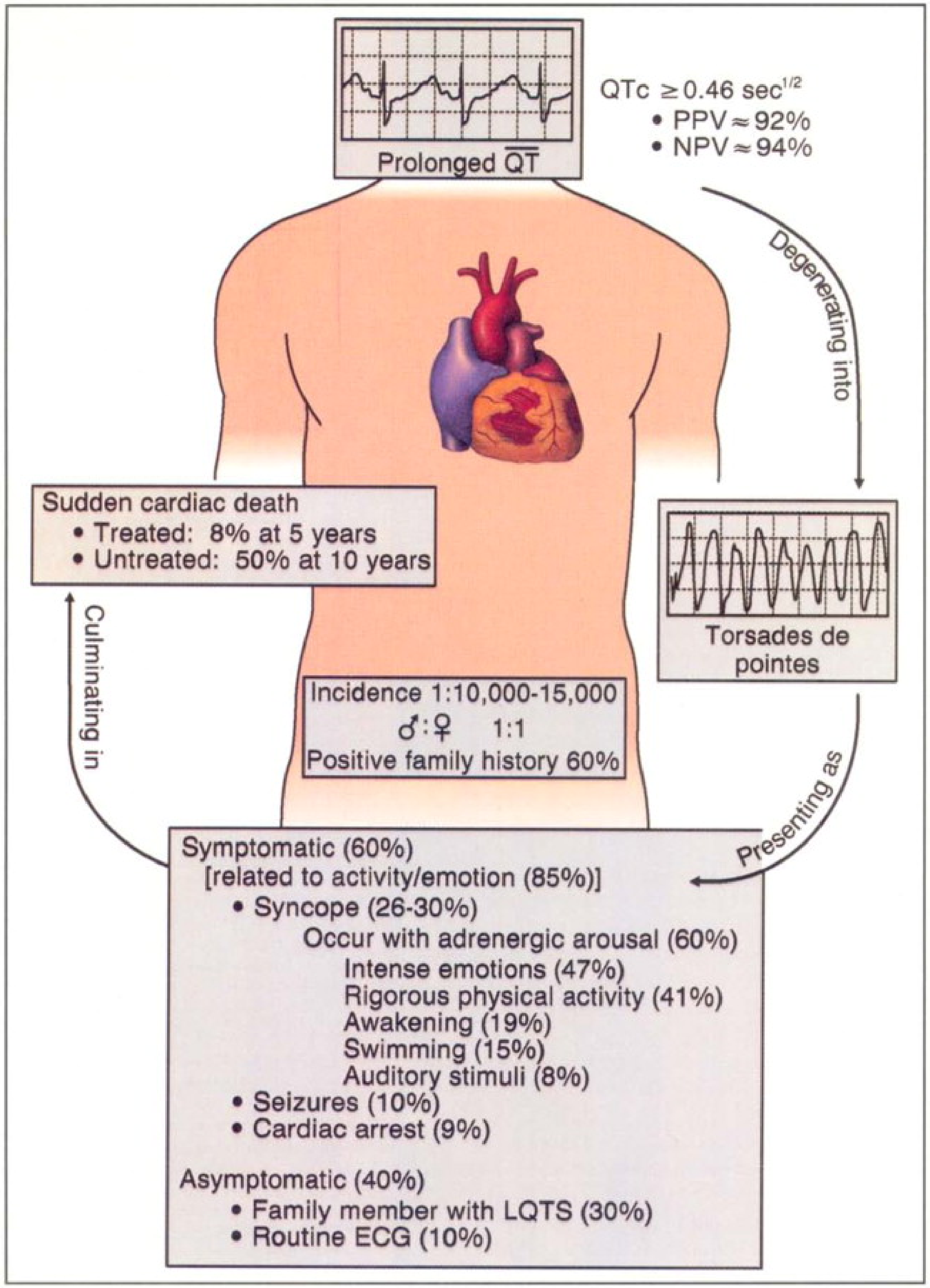

A
Long-QT Syndrome
• Prolongation of QT
(QTc > 460 msec1/2)
• Syncope
• Sudden death
Prolonged QT
Torsade de pointes
B
+47 mV
1
2
C
LQT1 (11q15.5)
N
1
LQT2 (7q35–36)
N
1
LQT3 (3q21–24)
II
III
N
1
P
ΔK

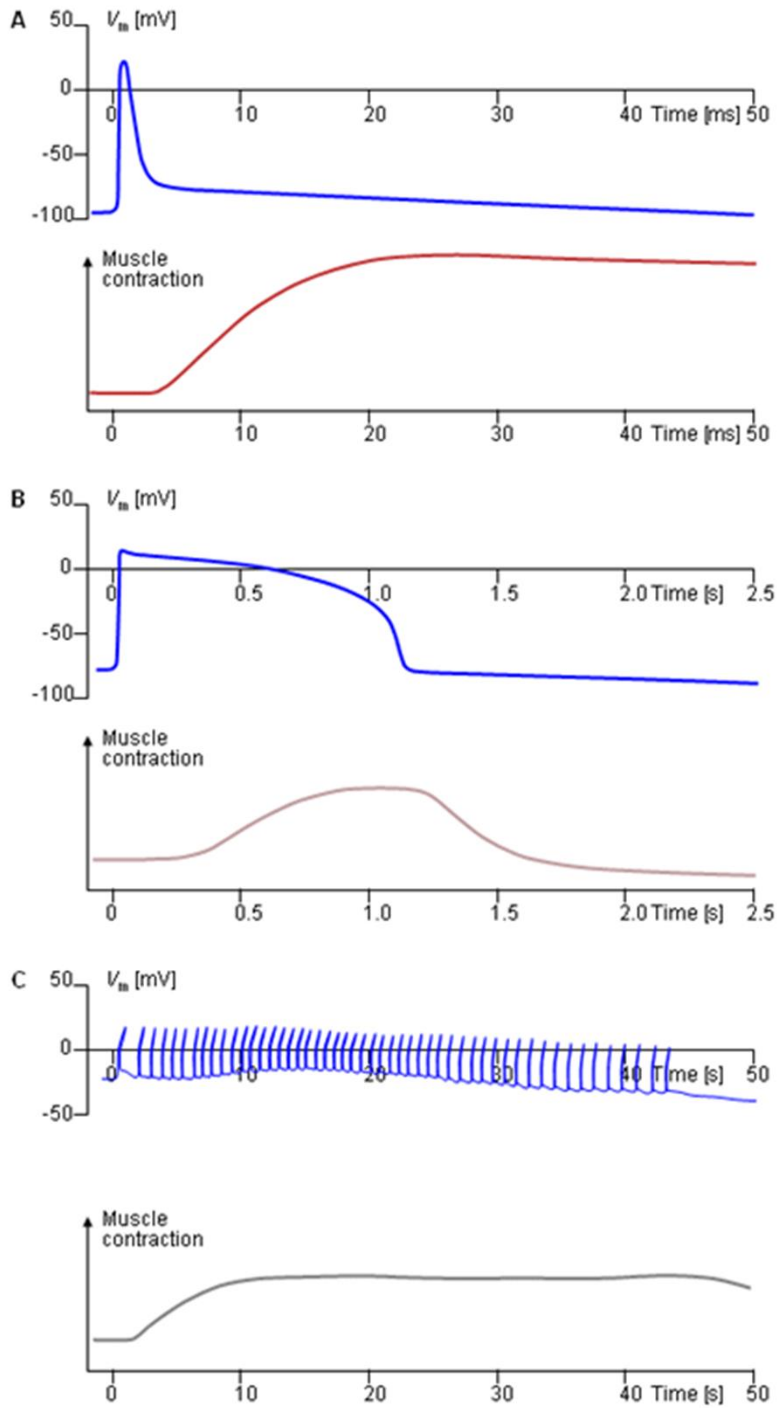
Table 1.—**Causes of the Long QT Syndro**

- *Inherited*
  - Romano-Ward (autosomal dominant, normal hea
    - LQT1—chromosome 11p15.5
      - KVLQT1—potassium channel (I_{Ks})
    - LQT2—chromosome 7q35-36
      - HERG—potassium channel (I_{Kr})
    - LQT3—chromosome 3p21-24
      - SCN5A—sodium channel (I_{Na})
    - LQT4—chromosome 4q25-27—gene?
    - LQT5—chromosome 21q22.1-22.2
      - KCNE1-β-subunit (minK) of potassium ch
    - LQT6—chromosome?
  - Jervell and Lange-Nielsen (JLN) (autosomal rece sensorineural hearing loss)
    - JLN1—chromosome 11p15.5—KVLQT1
    - JLN2—chromosome 21q22.1-22.2—KCNE1
  - LQTS with syndactyly (inheritance? gene?)
  - Sporadic (?)
- *Acquired*
  - Drugs
    - Antiarrhythmics
      - Class IA—quinidine (5%), procainamide, disopyramide
      - Class III—sotalol, dofetilide, bretylium, *N*-acetylprocainamide, amiodarone (rare)
    - Antidepressants (tricyclics like amitriptyline a desipramine, tetracyclics)
    - Antifungals (itraconazole and ketoconazole)
    - Antihistamines (astemizole and terfenadine)
    - Antimicrobials (erythromycin, trimethoprim-sulfamethoxazole, chloroquine)
    - Neuroleptics (phenothiazines like thioridazine haloperidol)
    - Oral hypoglycemics (glibenclamide)
    - Organophosphate insecticides
    - Promotility agents (cisapride)
  - Electrolyte derangements
    - Acute hypokalemia (associated with diuretics, hyperventilation)
    - Chronic hypocalcemia
    - Chronic hypokalemia
    - Chronic hypomagnesemia
  - Medical conditions

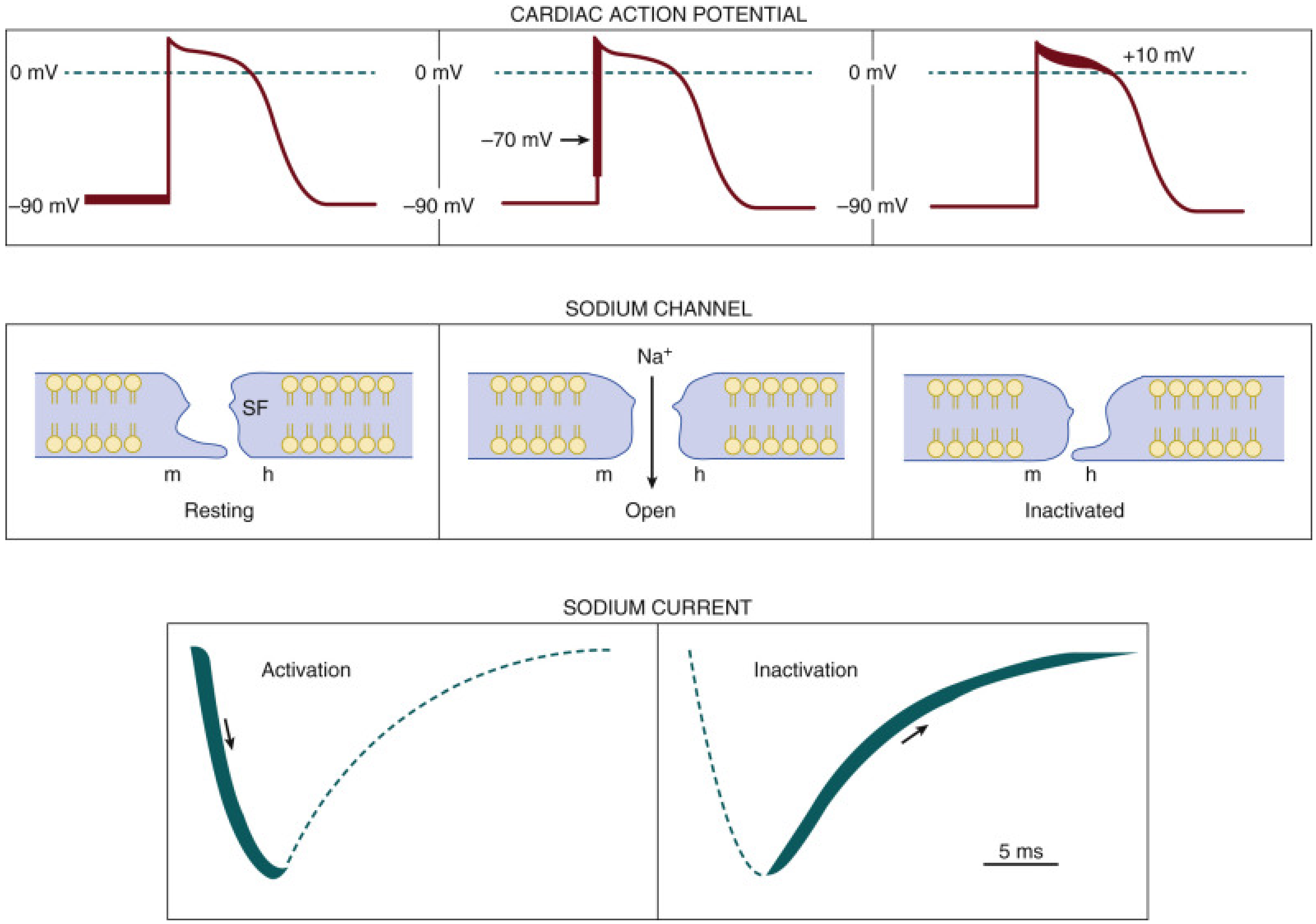


Prolonged $\overline{QT}$
QTc ≥ 0.46 sec^1/2
• PPV ≈ 92%
• NPV ≈ 94%
Degenerating into
Torsades de pointes
Presenting as
Symptomatic (60%)
[related to activity/emotion (85%)]
• Syncope (26-30%)
Occur with adrenergic arousal (60%)
Intense emotions (47%)
Rigorous physical activity (41%)
Awakening (19%)
Swimming (15%)
Auditory stimuli (8%)
• Seizures (10%)
• Cardiac arrest (9%)
Asymptomatic (40%)
• Family member with LQTS (30%)
• Routine ECG (10%)
Culminating in
Sudden cardiac death
• Treated: 8% at 5 years
• Untreated: 50% at 10 years
Incidence 1:10,000-15,000
♂:♀ 1:1
Positive family history 60%

Comparison of electrical and mechanical properties of heart muscle with other muscles



Lecture Notes


CARDIAC ACTION POTENTIAL
0 mV
–90 mV
0 mV
–70 mV
–90 mV
0 mV
+10 mV
–90 mV
SODIUM CHANNEL
SF
m
h
Resting
Na+
m
h
Open
m
h
Inactivated
SODIUM CURRENT
Activation
Inactivation
5 ms