From: **Ion Adventure in the Heartland**

exploring the heart's ionic-molecular microcosm

by Dale Dubin, M.D.

Useful information and data

Hey! Don't overlook this valuable reference section.

Please take a moment to familiarize yourself with this information,...

so when you need it, you know just where to find it.

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Common Parlance for Units of Measurement in Powers of 10 for every 3 Ciphers

("units" may be seconds, meters, volts etc.)

Milli- = 10^{-3} (one thousandth)
Micro- = 10^{-6} (one millionth)
Nano- = 10^{-9} (one billionth)
Pico- = 10^{-12} (one trillionth)

Conversion of Cycle Length in Milliseconds to Rate/minute

ms/cycle	rate	ms/cycle	rate	ms/cycle	rate	ms/cycle	rate	ms/cycle	rate
1000	60	779	77	638	94	387	155	250	240
984	61	769	78	632	95	375	160	245	245
968	62	760	79	625	96	364	165	240	250
952	63	750	80	619	97	353	170	235	255
937	64	741	81	612	98	343	175	231	260
923	65	732	82	606	99	333	180	226	265
909	66	723	83	600	100	324	185	222	270
895	67	714	84	571	105	316	190	218	275
882	68	706	85	545	110	308	195	214	280
870	69	698	86	522	115	300	200	211	285
857	70	690	87	500	120	293	205	207	290
845	71	682	88	480	125	286	210	203	295
833	72	674	89	462	130	279	215	200	300
822	73	667	90	444	135	273	220		
811	74	659	91	429	140	267	225		
800	75	652	92	414	145	261	230		
789	76	645	93	400	150	255	235		

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Diameter of hydrated ions in angstroms (Å)

Hydrated Ion Diameter (in angstroms)	Ion
5 Å	Rb^{+}, Tl^{+}, Cs^{+}, NH_4^{+}, Ag^{+}
6 Å	K^{+}, Cl^{-}, Br^{-}, I^{-}, NO_3^{-}
7 Å	OH^{-}, F^{-}
8 Å	Na^{+}, SO_4^{-}
9 Å	Pb^{++}, CO_3^{-}, SO_3^{-}, CH_3COO^{-}
10 Å	Sr^{++}, Ba^{++}, Cd^{++}
12 Å	Ca^{++}, Zn^{++}, Fe^{++}, Ni^{++}
16 Å	Mg^{++}
18 Å	H^{+}, Al^{+++}, Fe^{+++}, Cr^{+++}, La^{++}

From Dean, John A., Ed. *Lange's Handbook of Chemistry, 13th ed.* New York: McGraw-Hill Book Co., 1985.

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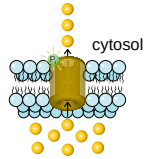
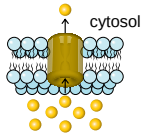
Sympathetic stimulation of the Na^+ channel



channel stimulated	effect on Na^+ channel	effect on current	ligand	receptor	G protein	target/effect	
Na^+ channel	increases open probability	↑ I_{Na}	N-epi, Epi	β_1	α-GTP	SA node: AV node: Myocardium: Automaticity foci:	• no significant Na^+ channels • no significant Na^+ channels • increases myocardial conduction velocity • shortens myocyte action potential to adjust to faster pacing rate • stimulates ventricular automaticity foci

Parasympathetic inhibition of the Na^+ channel



channel inhibited	effect on Na^+ channel	effect on current	ligand	receptor	G protein	target/effect	
Na^+ channel	decreases open probability	↓ I_{Na}	ACh (or Ado)	M_2 (or A_1)	βγ-AMP	SA node: AV node: Myocardium: Automaticity foci:	• no significant Na^+ channels • no significant Na^+ channels • decreases myocardial conduction velocity • lengthens myocyte action potential to adjust to slower pacing rate • reduces irritability of ventricular foci

The Na^+ channel is modulated by the autonomic nervous system [visualization of illustrations from previous chapters will be quite helpful.] Sympathetic stimulation of β receptors adjacent to the Na^+ channel involves N-epi release from stimulated sympathetic boutons. The activated β receptors initiate a biochemical pathway using α-GTP to deliver a P_i (energy-rich phosphate) to the Na^+ channel. The P_i phosphorylates the Na^+ channel, increasing its open probability when the channel is activated. This increases the Na^+ ion influx (i.e., the Na^+ current) through activated Na^+ channels. Sympathetic stimulation of the Na^+ channels increases the velocity of myocyte-to-myocyte conduction through the myocardium, to effectively adapt to sympathetic acceleration of sinus pacing. The AV node, SA node, and supraventricular automaticity foci have no Na^+ channels. The ventricular automaticity foci have Na^+ channels, and sympathetic stimulation makes these foci irritable. Parasympathetic inhibition of Na^+ channels employs the βγ-AMP phosphate steal (at the level of the Na^+ channel's autonomic receptors, at the bouton-bouton interface, or possibly within sympathetic ganglia), in order to inhibit sympathetic stimulation of the Na^+ channel. Adenosine can do the same with A_1 receptors.

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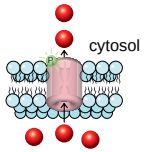
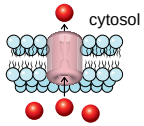
Sympathetic stimulation of Ca^{++} channels



Ca^{++} channel stimulated	effect on Ca^{++} channel	effect on current	ligand	receptor	G protein	target/effect
solitary L-type Ca^{++} channel L-type Ca^{++} channel assoc. with CICR	increases open probability	↑ I_{Ca}	N-epi, Epi	β_1	α-GTP	SA node: • accelerates sinus pacing AV node: • increases AV conduction velocity • reduces refractoriness Myocardium: • increases force of contraction Automaticity foci: • stimulates (increases irritability)
SR ryanodine Ca^{++} release channel	This special Ca^{++} channel functions in tandem with a proximal L-type Ca^{++} channel, so the activity of the SR ryanodine Ca^{++} release channel reflects the activity of its associated L-type Ca^{++} channel.					

Parasympathetic inhibition of Ca^{++} channels



Ca^{++} channel inhibited	effect on Ca^{++} channel	effect on current	ligand	receptor	G protein	target/effect
solitary L-type Ca^{++} channel L-type Ca^{++} channel assoc. with CICR	decreases open probability	↓ I_{Ca}	ACh (or Ado)	M_2 (or A_1)	βγ-AMP	SA node: • slows sinus pacing AV node: • slows AV conduction velocity • increases refractoriness (reduces the rate at which Wenckebach AV conduction occurs) Myocardium: • decreases force of contraction Automaticity foci: • reduces irritability
SR ryanodine Ca^{++} release channel	This special Ca^{++} channel functions in tandem with a proximal L-type Ca^{++} channel, so the activity of the SR ryanodine Ca^{++} release channel reflects the activity of its associated L-type Ca^{++} channel.					

Sympathetic stimulation of the *L-type* Ca^{++} channels increases their open probability when they are activated, taking the same type of biochemical pathway as Na^{+} channels [see previous page]. L-type Ca^{++} channels include both solitary Ca^{++} channels and those Ca^{++} channels associated with the SR ryanodine Ca^{++} release channels. Sympathetic stimulation of Ca^{++} channels: 1) accelerates SA node pacing, 2) accelerates conduction through the AV node, while reducing AV node refractoriness, 3) increases the irritability of automaticity foci, and 4) increases the force of myocardial contraction. Parasympathetic inhibition of sympathetic stimulation of Ca^{++} channels employs the βγ-AMP phosphate steal in proximity of the channel's receptors. Parasympathetic inhibition also may occur at the bouton-bouton junctions, or possibly in the sympathetic ganglia. Also, adenosine, released during cardiac distress, can inhibit Ca^{++} channels through A_1 receptors. T-type Ca^{++} channels are insensitive to autonomic modulation.

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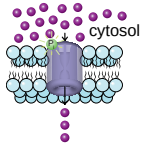
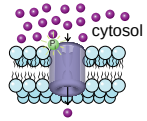
Sympathetic stimulation of certain K^+ channels



K^+ channel stimulated	effect on K^+ channel	effect on current	ligand	receptor	G protein	target/effect	
I_{to1} I_{Ks} I_{Kur}	increases open probability	↑ I_{to1} ↑ I_{Ks} ↑ I_{Kur}	N-epi, Epi	β_1	α-GTP	SA node: AV node: Myocardium: Automaticity foci:	• minimal effect • minimal effect • hastens repolarization to adjust to accelerated sinus pacing • hastens repolarization to adjust to passive depolarization during accelerated sinus pacing • no effect on automaticity

Parasympathetic inhibition of certain K^+ channels



K^+ channel inhibited	effect on K^+ channel	effect on current	ligand	receptor	G protein	target/effect	
I_{to1} I_{Ks} I_{Kur}	decreases open probability	↓ I_{to1} ↓ I_{Ks} ↓ I_{Kur}	ACh (or Ado)	M_2 (or A_1)	βγ-AMP	SA node: AV node: Myocardium: Automaticity foci:	• minimal effect • minimal effect • slows repolarization to adjust to slowed sinus pacing • slows repolarization to adjust to passive depolarization during slowed sinus pacing • no effect on automaticity

Three of the K^+ channels that take part in repolarization are sensitive to sympathetic stimulation. These K^+ channels are the I_{to1} channel, the I_{Ks} channel, and the I_{Kur} channel. Sympathetic stimulation of these K^+ channels takes the same biochemical pathway as sympathetic stimulation of the Na^+ and Ca^{++} channels. Norepinephrine is released from a stimulated sympathetic bouton, activating the β_1 receptor, which sends α-GTP to deliver an energy-rich phosphate, P_i to phosphorylate the K^+ channel. This increases the open probability of the activated K^+ channel. Following depolarization, the I_{to1} channel, the I_{Ks} channel, and the I_{Kur} channel are largely responsible for repolarizing the myocyte back to baseline potential. So sympathetic stimulation of these K^+ channels hastens repolarization of the depolarized cell back to baseline potential. Direct parasympathetic inhibition of sympathetically stimulated of K^+ channels employs the βγ-AMP phosphate steal, however, parasympathetic inhibition may occur at the bouton-bouton junction, or possibly in the ganglia. Also, adenosine released during cardiac distress can inhibit these K^+ channels through A_1 receptors.

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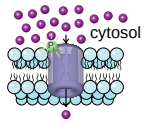
Parasympathetic activation of the (supraventricular) $I_{K(ACh)}$ K^+ channel



K^+ channel activated	effect on $I_{K(ACh)}$ channel	current activated	ligand	receptor	G protein	target/effect	
$I_{K(ACh)}$ channel	$I_{K(ACh)}$ channel activated by phosphorylation	$I_{K(ACh)}$	ACh (or Ado)	M_2 (or A_1)	$\beta\gamma$-PIP_2	SA node: AV node: Atrial myocytes: Automaticity foci:	• slows pacing • slows AV conduction • lengthens action potential reducing the rate at which AV Wenckebach conduction occur • lengthens action potential • slows conduction velocity • may slow active pacing by supraventricular foci.

$I_{K(ACh)}$ channels are primarily supraventricular, occurring in SA node and AV node cells, and also in atrial myocytes. Parasympathetic release of ACh activates the $I_{K(ACh)}$ channel.

The $I_{K(ACh)}$ channel is vital to the function the SA node, AV node and atrial myocytes. Its parasympathetic activation slows SA node pacing, and slows AV node conduction too.

The $I_{K(ACh)}$ channel can lengthen the action potential of AV node cells, so during rapid supraventricular rates…

the AV node can lower the rate at which it employs Wenckebach AV conduction to provide a more tolerable ventricular drive rate in the face of rapid supraventricular arrhythmias.

Unlike all other autonomically modulated ion channels (and other ion-kinetic structures) that are inhibited by parasympathetic reduction of sympathetic stimulation, the (mainly supraventricular) $I_{K(ACh)}$ potassium channels function only when *directly activated* by ACh that is released from the parasympathetic boutons and binds to the M_2 receptors. The resulting activation of the $I_{K(ACh)}$ channels causes a slow, steady release of K^+ ions that lowers the baseline potential to more negative levels. Therefore depolarization begins at a lower (more negative) level, so depolarization to the overshoot takes longer, slowing SA node pacing, and AV node conduction velocity. Repolarization down to the lowered baseline also takes longer, lengthening the action potential. During $I_{K(ACh)}$ activation, both depolarization and repolarization take longer, so the action potential is widened, extending refractoriness (including the RRP) of the AV node, therefore Wenckebach conduction occurs at less rapid supraventricular rates.

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The 20 basic Amino Acids

Green: "Essential" AA's that are not synthesized by the body so dietary intake is required.

Amino Acids Symbols		Amino Acid	Charge	Site of Phosphorylation
A	Al	Alanine	negative	
C	Cys	Cysteine		
D	Asp	Aspartic Acid	negative	yes
E	Glu	Glutamic Acid	negative	
F	Phe	Phenylalanine		
G	Gly	Glycine		
H	His	Histidine	positive	
I	Ile	Isoleucine		
K	Lys	Lysine	positive	
L	Leu	Leucine		
M	Met	Methionine		
N	Asn	Asparagine		
P	Pro	Proline		
Q	Gln	Glutamine		
R	Arg	Arginine	positive	
S	Ser	Serine		yes
T	Thr	Threonine		yes
V	Val	Valine		
W	Trp	Tryptophan		
Y	Tyr	Tyrosine		yes

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General List of Substances That Affect the Function of Cardiac Ion-kinetic structures

This a limited, general list and is intended merely as a guide; many other substances exist in all categories. Corrections and suggestions are welcomed. Most biologically active agents affect other ion-kinetic structures to some extent. Efficacy of these substances varies according to many factors, including genetic makeup of the patient, open/closed/inactivated state, concentration, potential, anatomical location, pH, solubility, state of oxygenation, hydrophyllic/hydrophobic qualities, etc.

Na^+ channel:

- function enhanced by adrenergic substances and inhibited by cholinergic substances and adenosine
- general, nonspecific Na^+ channel blockade by Cd^{++}, Zn^{++}

Na^+ channel antagonists:

- biological Na^+ channel blockers: TTX (tetrodotoxin), STX (saxitoxin)
- beta scorpion toxins: shift threshold in positive direction
- anesthetics/Na^+ channel blockers: lidocaine, procaine
- lipophilic blockers: quinidine, flecainide, propafenone, amiodarone, amiloride
- open-pore binder: N-methylstrychnine
- aconitine analog: N-desacetyllappaconitine

Na^+ channel agonists:

- veritridine, aconitine, batrachotoxin: negative shift of activation threshold, slows inactivation
- alpha scorpion toxins: negative shift of activation threshold, slows inactivation
- brevitoxin: negative shift of activation threshold, slows inactivation

Ca^{++} channels:

- general, nonspecific Ca^{++} channel blockade by divalent ions: La^{++}, Co^{++}, Mg^{++}
- nonspecific Ca^{++} channel blockers: flunarizine, bepridil, fendiline
- general, nonspecific Ca^{++} channel blockade by Na^+ channel blockers: quinidine, flecainide, propafenone, amiodarone, amiloride

L-type antagonists:

- inhibited by cholinergic substances and adenosine
- Dihydropyridines: nifedipine, nitrendipine, nimodipine
- Phenylalkylamines: verapamil, D-600
- Benzothiazepines: diltiazem
- Diphenylbutylpiperidines: fluspirilene
- snake venoms: taicatoxin, calciseptine

L-type agonists:

- function enhanced by adrenergic substances
- Dihydropyridines: Bay K 8644, CGP 28392
- benzoylpyrrole compound: FPL-64176
- biological toxins: gonioporotoxin, atrotoxin, maitotoxin

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Ca^{++} channels, cont:

T-type antagonists:

- Ni^{++}
- tetralol derivative: mibefradil
- U-92032, cycloheptatrien

T-type agonists:

- cytokine: endothelin-1

SR Ryanodine Ca^{++} release channel antagonists:

- cholinergic or adenosine inhibition of in-tandem L-type Ca^{++} channels
- ryanodine: binds foot receptor
- ruthenium red: binds foot receptor

SR Ryanodine Ca^{++} release channel agonists:

- adrenergic stimulation of in-tandem L-type Ca^{++} channels
- function enhanced by adrenergic substances
- Caffeine: enhances sensitivity to Ca^{++} ions

K^+ channels:

I_K delayed rectifier (includes I_{Ks}, I_{Kr}, and I_{Kur}) nonspecific antagonists:

- Ba^{++}, Cs^+, TEA, 4-AP, quinidine, phencyclidine

I_{Ks} antagonists:

- NE-10064, azimilide, A23187, peroxides

I_{Ks} agonists:

- niflumic acid, mefenamic acid, flufenamic acid

K^+ channels, cont:

I_{Kr} antagonists:

- ibutilide, E-4031, MK-499, terikalant, berberine
- Class III antiarrhythmics: quinidine, dofetilide, sotolol, sematilide, clofilium
- antihistamines: terfenadine, astemizole
- antibiotic: erythromycin

I_{Kr} agonist:

- increased intracellular K^+

I_{Kur} antagonists:

- nonspecific blockers: quinidine, propafenone, terfenadine, TEA, 4-AP, perhexiline

I_{K1} antagonists:

- terikalant

I_{to1} antagonists:

- nonspecific blockers: quinidine, flecainide, berberine, charybdotoxin, tedisamil
- specific blockers: ambasilide, phrixotoxin

$I_{K\,(ACh)}$ antagonists:

- anticholinergic: atropine
- specific blocker: methoctramine, tertiapin

$I_{K\,(ACh)}$ agonists:

- adenosine, adrenergic blockers

$I_{K\,(ATP)}$ antagonists:

- glibenclamide, tolbutamide

$I_{K\,(ATP)}$ agonists:

- adenosine, nicorandil, pinacidil

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Cl^- channel:

I_{to2} ($I_{Cl/Ca}$) antagonists:

- anthracene-9-carboxylic acid
- cyclic AMP

I_{to2} ($I_{Cl/Ca}$) agonist:

- increased intracellular Ca^{++}

Na-K ATPase pump:

Na-K ATPase pump antagonists:

- digoxin, acetylstrophanthidin and other digitalis preparations

Na-K ATPase pump agonists:

- alpha and beta adrenergic medications

Cell Membrane Ca ATPase pump:

Cell Membrane Ca ATPase pump antagonist:

- CH-103

Cell Membrane Ca ATPase pump agonist:

- increased intracellular Ca^{++}

Sarcoplasmic Reticulum Ca ATPase pump:

Sarcoplasmic Reticulum Ca ATPase pump antagonist:

- thapsigargin, caffeine

Sarcoplasmic Reticulum Ca ATPase pump agonist:

- increased intracellular Ca^{++}

Na/Ca exchanger:

Na/Ca exchanger antagonists:

- Ni^{++}, Cd^{++}, La^{+++}, intracellular H^+, amiloride

Na/Ca exchanger agonists:

- increased intracellular Ca^{++}, decreased intracellular K^+

Na/H exchanger:

Na/H exchanger antagonists:

- eniporide, amiloride, cariporide

Na/H exchanger agonist:

- increased intracellular H^+ ions

Connexons (gap junctions):

Connexon blockers:

- increased Ca^{++} ions, increased H^+ ions
- heptanol, glycyrrhetinic acid, halothane, ethrane

Calmodulin

Calmodulin inhibitors:

- Ophiobolin A, CaM-binding peptide, KN-62

W7 (N-(6-aminohexyl)-5-chloro-1-naphthalenesulfonamide)

Phospholamban (is an SR Ca ATPase inhibitor)

Phospholamban antagonists:

- cantharidin, C12E8, K3E/R14E

Troponin I (TnI) inhibits actin-myosin activation

Troponin I antagonists:

- 1D12, 5F4 (both of these products are anti-TnI monoclonal antibodies)

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Volume I

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Tampa, Florida 33601

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E-mail:
coverpub@gte.net

web site:
www.IonAdventure.com

Library of Congress Control Number: 2002093186

ISBN 0-912912-11-1