Calcium Channel Blockers:

Objectives:

At the end of the next hour the student:

1. be able to identify the calcium channel blocker drugs in use today for the treatment of angina and hypertension by their trade or generic names and if given a structural formula be able to recall the appropriate drug action (ie. agonist, antagonist, enzyme inhibitor, allosteric modulator, or channel blocker) and the receptor or enzyme system(s) involved.
2. be familiar with the hydropathy profile of the L-type calcium channels and the proposed mechanism of voltage-gating.
3.

Electronic References:


Review References:

2. Goodman and Gilman’s Pharmacological Basis of Therapeutics. pages 767-774

Class:

Ca⁺ Channel Blockers 377-379
β-adrenergic blocking drugs 359-362
α₁-Antagonists 358
Figure 1. Hydropathy Plot of Voltage Gated L-type Ca\(^+\) Channel.

The hydropathy plot shows four distinct domains of six transmembrane spanning regions. The helical wheel plot shows a 22 amino acid section from 906-928. This is one of the regions near TMD4 that is particularly rich in positively charged residues (R=Arginine and K=Lysine). This TMD is proposed to be the voltage sensor in Na\(^+\), Ca\(^+\), and K\(^+\) channels.

Figures 2 and 3.

Figures 2 and 3 on the previous page show a schematic diagram that illustrates a proposed two dimensional layout orientation pattern for the voltage-gated ion channels. Note that several large loops are located inside the cell.

Figure 4. Artists rendering of a voltage-gated ion channel with snake toxin binding sites labeled. (ScTX = Saxitoxin and TTX = Tetrodotoxin).
In addition to the topology of a voltage-gated ion channel, this figure shows two beta subunits whose function is currently unknown.

**Figure 5. Cartoon illustration of a proposed mechanism for voltage-gating.**

The closed channel exists when the membrane voltage is resting at ~-60 mv. When the action potential causes membrane depolarization, a positively charged voltage-gate undergoes a conformational change and causes the ion channel to open. As the inward current subsides, an inactivating particle is able to temporarily block the channel while outward conductance of K+ restores the membrane potential causing the normal gate to close.
L-Type Calcium Channel Blockers

These agents produce peripheral vasodilation leading to a decrease in vascular resistance. Coronary vascular resistance is decreased to a greater extent than systemic vascular resistance. These agents act by inhibiting the transmembrane flux of extracellular calcium ions into cardiac and vascular smooth muscle. Normally the movement of calcium through the "slow channel" triggers cardiac muscle contraction and constriction of coronary, peripheral, and cerebral arteries.

**Nifedipine (Procadia®)**

1,4-Dihydro-2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid dimethyl ester

logP = 3.14

Type II (dihydropyridine) calcium-channel blocker.

A neutral hydrophobic Ca\(^+\) channel blocker that “plugs” the Ca\(^+\) channel in its open or closed state.

**Nicardipine HCl (Cardene®) RN 55985-32-5.**

1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid methyl 2-methyl (phenylmethyl)amino)ethyl ester.

logP = 3.8

Type II (dihydropyridine) calcium-channel blocker.

**Isradipine (DynaCirc®) RN 75695-93-1.**

4-(4-Benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid methyl 1-methylethyl ester.

Long acting (t\(_{1/2}\)=8.8 hr) calcium channel blocker that is selective for vascular smooth muscle.
**Amlodipine (Norvasc®) RN 88150-42-9**

2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylic acid, 3-ethyl 5-methyl ester.

Long acting (t\(1/2\) = 35 - 45 hr) calcium-"slow"-channel blocker. Acts in peripheral and coronary vascular beds.

**Felodipine (Plendil®) RN 72509-76-3**

4-(2,3-Dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid ethyl methyl ester.

Vasodilatory calcium antagonist with vascular selectivity. ARMC 24:302

**Verapamil (Calan®)**

N-3,4-dimethoxyphenylethyl-N-methyl-N-3,4-dimethoxyphenyl-4-cyano-4-isopropylbutyl amine

logP (unionized) – 3.8

Ionized, water soluble Ca\(^+\) - entry blocker. Reaches its site of action via a hydrophilic pathway when the channel is open. Therefore, it is called a “use dependent” blocker. In the presence of Verapamil, an increase in contraction frequency causes a reduction of the force of contraction.

Due to its high logP when unionized, Verapamil can block the closed channel by crossing the cell membrane and approaching its binding site from the inside of the cell.
Bepridil (Vascor®)

N-phenyl-N-benzyl-N-2-pyrolidino-3-isobutoxypropyl amine
Bepridil is an effective calcium channel blocking agent by inhibiting the slow calcium channels. It also inhibits fast sodium channels, thus imparting a type I antiarrhythmic activity. Unlike many of the other calcium channel blockers, bepridil is not an effective antihypertensive agent.

Diltiazem (Cardizem®)

3-acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-p-methoxyphenyl-1,5-benzothiazepin-4-one
Ca\(^+\) channel blocker similar to Verapamil. Fb = 40%.
Metabolized by deacetylation, N and O-dealkylation.
The deacetylated drug has 40-50% of the activity of the parent.
Mibefradil is the first in a new class of "vascular-specific" calcium-channel antagonists and is the only drug that, at therapeutic concentrations, lowers both heart rate and blood pressure without producing a negative inotropic effect.

More than 25 drugs have been found to be potentially dangerous if used with Posicor®. Due to the complexity of the prescribing information, on June 8, 1998, Roche Laboratories, voluntarily withdrew the drug from the US market.

**Mibefradil (Posicor®)**

Mibefradil blocks both T-type (transient, low-voltage) calcium channels and L-type (long-lasting, high-voltage) calcium channels, with greater selectivity for T-type channels. Mibefradil is 50—100 times more selective for "T" channels than for "L" channels. T-type channels predominate on vascular muscle cells and on cardiac pacemaker cells, while L-type channels are the only type found on cardiac muscle cells. Since cardiac myocytes possess only L channels and mibefradil does not affect these, mibefradil is essentially free from negative inotropic effects.