

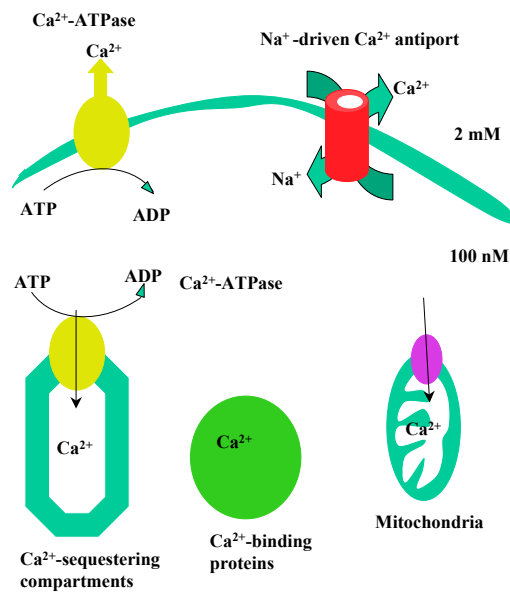
Calcium Antagonists

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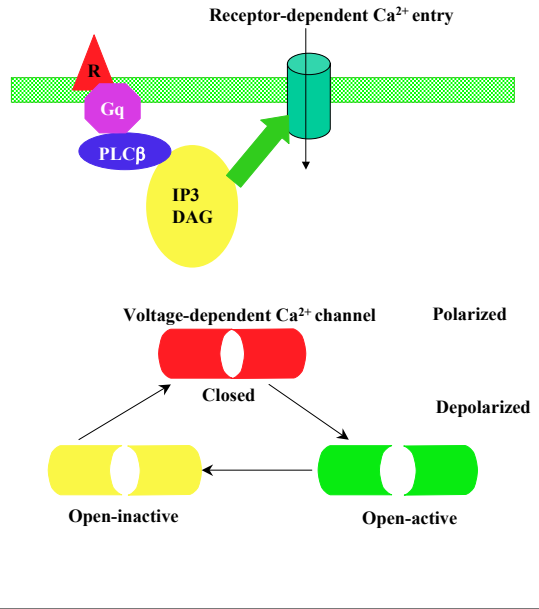
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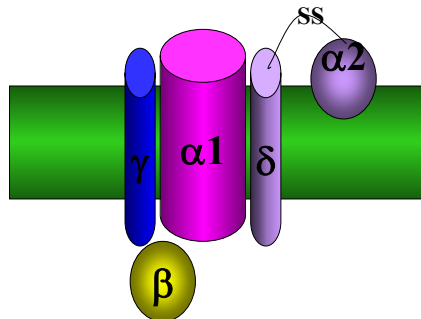
Regulation of Ca^{2+} extrusion



Regulation of Ca²⁺ entry

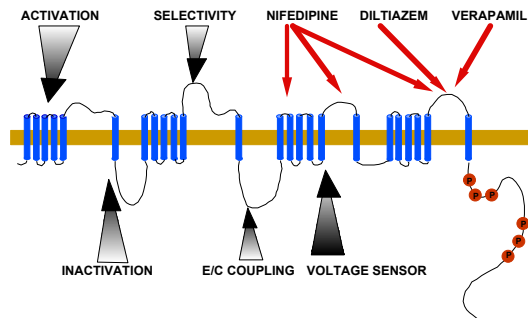


Subunit composition of L-type Ca²⁺ channel



- L-type (long-lasting)-excitation/contraction coupling of cardiac myocytes
- T-type (transient) - participate in pace making, highly expressed in sinusal cells
- N-, P-type - expressed in neurons, are not affected by Ca²⁺ antagonists

STRUCTURE OF THE L-TYPE CHANNEL⁴ ALPHA SUBUNIT



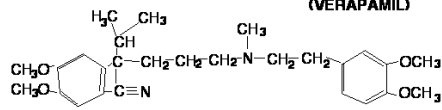
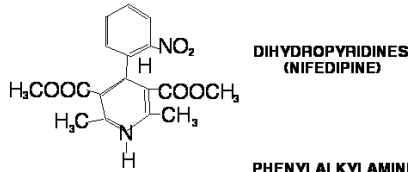
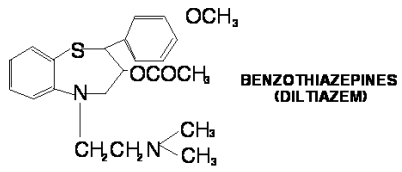
- CALCIUM ANTAGONISTS BIND TO THE SPECIFIC SITES ON THE ALPHA1 SUBUNIT OF THE L-TYPE CALCIUM CHANNEL

- CALCIUM ANTAGONISTS REDUCE THE PROBABILITY OF CHANNEL OPENING RATHER THAN REDUCE CALCIUM CURRENT FLOW THROUGH AN OPEN CHANNEL

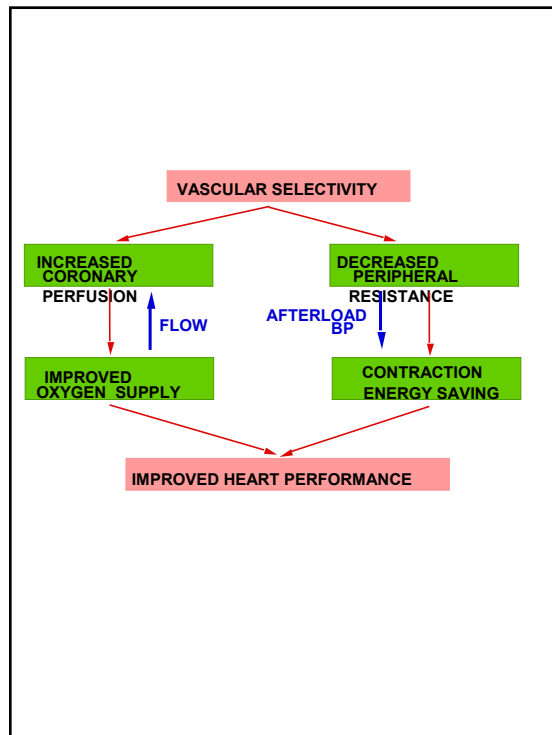
- TISSUE SELECTIVITY IS ONE OF THE MOST BENEFICIAL PROPERTIES OF CALCIUM ANTAGONISTS.

IN GENERAL, THE SKELETAL MUSCLE, THE BRONCHIAL, TRACHEAL, AND INTESTINAL SMOOTH MUSCLE AND NEURONAL TISSUE ARE RELATIVELY INSENSITIVE TO CALCIUM ANTAGONISTS.

CLASSES OF CALCIUM ANTAGONISTS 6



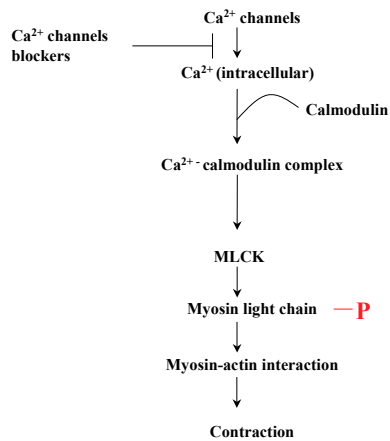
Hypertension Angina Arrhythmia



Degree of tissue selectivity of calcium antagonist in clinical use

	myocardium	vessels	sino-atrial node
verapamil	+	+	+
diltiazem	+	+	+
nifedipine	+	++	-
nimodipine	+	+++	-
felodipine	+	++++	-
nisoldipine	+	++++	-
amlodipine	+	++++	-

Control of smooth muscle contraction and the site of action of calcium channel-blocking drugs



Angina and Calcium Blockers

Angina is the chest pain that occurs when coronary blood flow is inadequate to supply the oxygen required by heart.

- Classic angina is caused by atherosclerosis
- Angiospastic or variant angina is caused by vasospasm

1. VASODILATION

- can be used in Prinzmetal's angina Ca antagonists are highly effective
- effective in coronary vasospasm
- not recommended in unstable angina/ acute MI

2. INCREASED OXYGEN SUPPLY

* Myocardial oxygen extraction is almost maximal, thus there is no reserve to meet increased demand

3. DECREASE OXYGEN DEMAND

three major determinants of the myocardial oxygen uptake are heart rate, blood pressure, and the contractile state of the myocardium

Ca²⁺ antagonists

- a) reduce the blood pressure because of peripheral vasodilation
- b) reduce heart rate (especially diltiazem and verapamil)
- c) decrease contractility thereby reduce the oxygen demand

1. ANGINA (Diltiazem, Nifedipine, Verapamil)

- mechanism of action is combination reduction of heart rate and vasodilation
- improve myocardial oxygen delivery because diltiazem is a vasodilator
- can be used in Prinzmetal's angina
- effective in coronary vasospasm
- effective in exercise-induced myocardial ischaemia

2. HYPERTENSION (Diltiazem, Nifedipine, Verapamil)

- mechanism of action is a vasodilation

Nifedipine

used commonly because nifedipine is at least 10 times more selective to vascular smooth muscle than to myocardial cells
often used in patients with contraindications to beta-antagonists

3. SUPRAVENTRICULAR DYSRHYTHMIA (Diltiazem, Verapamil)

- mechanism of action is the selectivity for pacemaker and nodal cells, blocks Ca²⁺-dependent conduction in the AV node, thereby reducing atrioventricular conduction
- restores synapse rhythm in 75% cases
- Atrial fibrillation – slows the ventricular response
- Atrial flutter – increases the block

Other Uses

- Migraine
- Subarachnoid hemorrhage
- Atherosclerosis

SIDE EFFECTS

Diltiazem

1. Edema
2. Headache
3. Depresses sinoatrial nodal function, causes high degree atrioventricular nodal block

Nifedipine

1. Dizziness is the result of acute vasodilation and rapid blood pressure fall
2. Headaches is the result of vasodilation
3. Ankle edema is caused by precapillary vasodilation

Verapamil

1. May increase digoxin levels when used in combination
Absolutely contraindicated in digoxin toxicity - high grade AV block
2. Tachycardia, flushing, headache, and edema
3. High rate of constipation up to 30%, presumably due to a specific interaction of verapamil with the calcium channels in smooth muscle cells of the gut.
4. Depresses sinoatrial nodal function, causes high degree atrioventricular nodal block

DRUG INTERACTION

DRUG AFFECTED	MECHANISM	PHARMACOKINETIC EFFECT	POTENTIAL CLINICAL EFFECT
Digoxin	Decreased clearance	Increased serum digoxin concentration	Digoxin toxicity
Carbamazepine	Decreased clearance	Increased serum carbamazepine concentration	Neurotoxicity (dizziness, headache, ataxia)
Antihistamines	Decreased clearance	Increased exposure to active drug	Ventricular arrhythmia
HMG-CoA reductase inhibitors	Decreased clearance	Increased exposure to active drug	Myopathy
Immunosuppressive drugs	Decreased clearance	Increased exposure to active drug	Nephrotoxicity
Beta-blockers	Decreased clearance	Increased exposure to active drug	Bradycardia, asystole