



# Calcium Channel Blockers

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## CCBs

- Calcium antagonists, also known as calcium entry blockers or calcium channel blockers, have acquired and maintained an important position in the drug therapy of cardiovascular diseases, in particular hypertension, angina pectoris, and arrhythmias



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## Calcium Channels

- are members of a gene superfamily of transmembrane ion channel proteins that includes voltage-gated potassium and sodium channels

## Other Calcium Channels

- Other tissues which are calcium-dependent, e.g. skeletal muscle, secretory cells, nervous tissue, are not affected by the available calcium channel antagonists, either because they are dependent on intracellular calcium stores (skeletal muscle) or they have different types of calcium channels

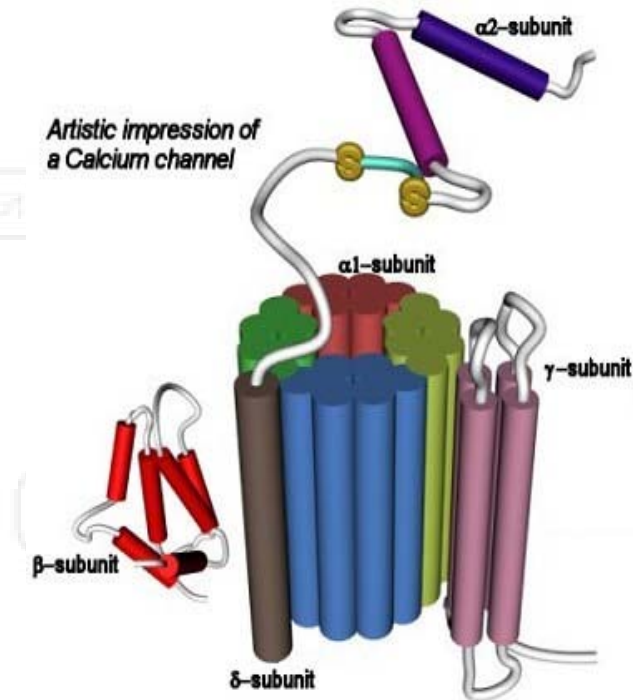
# Calcium Channels

- Voltage-gated calcium channels
  - mediate calcium influx in response to membrane depolarisation
  - regulate intracellular processes
    - contraction,
    - secretion,
    - neurotransmission
    - gene expression

# Calcium Channels

- Their activity is essential to couple electrical signals in the cell surface to physiological events in cells
- The calcium channels that have been characterized biochemically are complex proteins composed of four or five distinct subunits, which are encoded by multiple genes

# Calcium Channel



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# Calcium Currents

- Calcium currents recorded in different cell types have diverse physiological and pharmacological properties.
- Calcium channels are sub-typed according to the nature of the Calcium Current.
- Subtypes vary in:
  - Threshold for activation
  - Conductance
  - Kinetic behavior

# Calcium Channel-Sub types

- 5 sub types
  - L – long lasting
  - T- transient
  - N- neither long lasting nor transient
  - P/Q and
  - O
- L type in the heart and smooth muscles
- N type in NT and hormonal release
- T type in Neuronal function

## L Type Channels

- large sustained conductance
- inactivate slowly
- widespread in cardiovascular system and smooth muscle
- are responsible for plateau phase (slow inward current) of action potential
- sensitive to  $Ca^{++}$ -channel blockers,
- cardiac L-channels are regulated by cAMP-dependent protein kinase

# T Type Channels

- Structurally similar to L-type channels
- inactivate rapidly
- highest abundance in cardiac cells (SA nodal tissue)
- involved in cardiac pacemaker activity
  - growth regulation
  - contraction in vascular smooth muscle
- T-type channels are not very sensitive to most of the L-type  $\text{Ca}^{++}$ -channel blockers

# Calcium Channel Blockers

- Five major classes of  $\text{Ca}^{++}$  channel blockers with diverse chemical structures
- **Benzothiazepines:** diltiazem
- **Dihydropyridines:** nifedipine, amlodipine, nimodipine and others
- **Phenylalkylamines:** verapamil
- **Diarylaminopropylamine ethers:** bepridil
- **Benzimidazole-substituted tetralines:** mibefradil

# Effects on Vascular Smooth Muscle

- "Vascular selectivity" is seen with the Ca<sup>++</sup> channel blockers
- Decreased intracellular Ca<sup>++</sup> in arterial smooth muscle results in relaxation (vasodilatation) -> decreased cardiac afterload (aortic pressure)
- Little or no effect of Ca<sup>++</sup>-channel blockers on venous beds -> no effect on cardiac preload (ventricular filling pressure)
- Specific dihydropyridines may exhibit greater potencies in some vascular beds (e.g.- nimodipine more selective for cerebral blood vessels, nifedipine for coronary vessels)
- Little or no effect on nonvascular smooth muscle (e.g. - tracheal smooth muscle)

# Effects on Cardiac Cells

- Magnitude and pattern of cardiac effects depend on the class of Ca<sup>++</sup> channel blocker
- Negative inotropic effects are seen due to a direct effect on myocardial L-type channels.
  - The negative inotropic effect is due to reduced inward movement of Ca<sup>++</sup> during the action potential plateau phase (due to inhibition of slow (L-type) channel)
- Dihydropyridines have very little negative inotropic effects
- Mibefradil (a T-type channel blocker) has no negative inotropic effects because there appear to be few T-type channels in adult ventricular muscle

# Conducting Tissue

- Negative chronotropic/ dromotropic effects (pacemaker activity/conduction velocity)
- Verapamil (and to a lesser extent diltiazem) decrease the rate of recovery in AV conduction system and SA node, and therefore act directly to depress SA node pacemaker activity and slow conduction
- Ca<sup>++</sup>-channel block by verapamil and diltiazem is frequency and voltage-dependent, making them more effective in cells that are rapidly depolarizing

# Conducting tissue

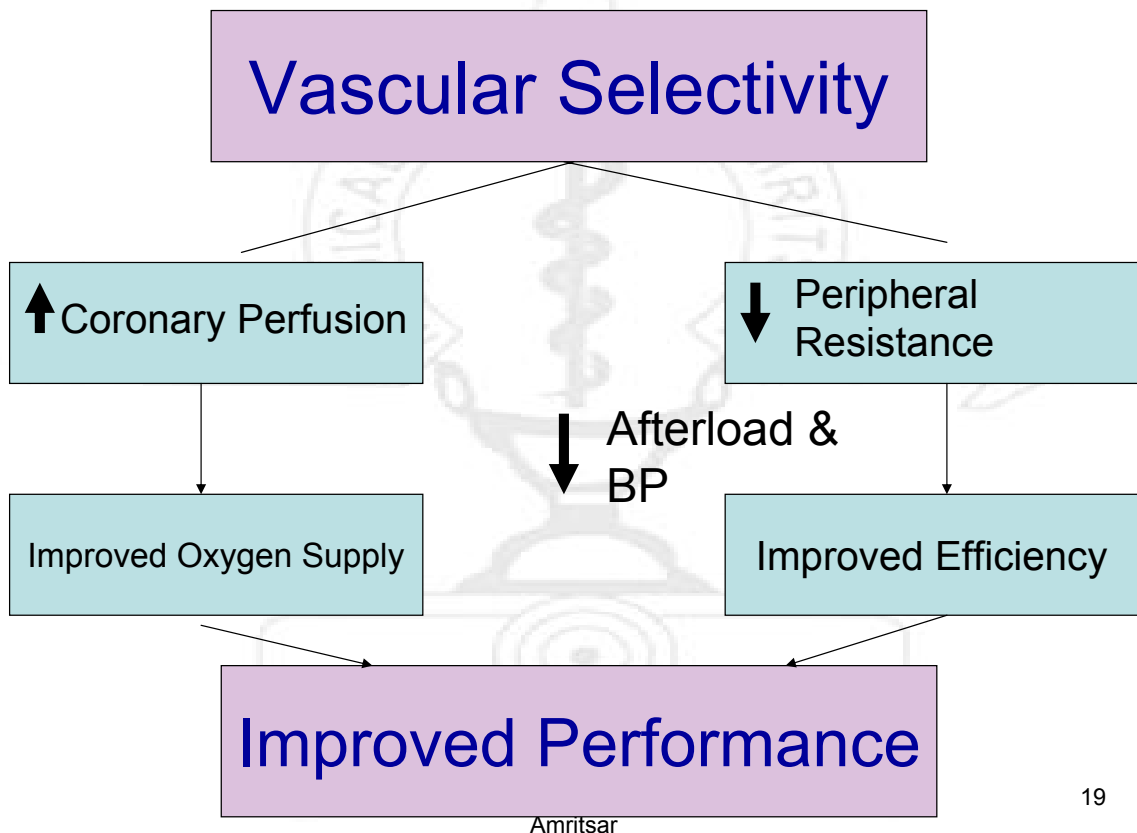
- Mibefradil has negative chronotropic and dromotropic effects
  - T-type channels are important for regulating Ca<sup>++</sup> influx in pacemaker cells and cells of the conduction system
- Nifedipine and related dihydropyridines do not have significant direct effects on the a-v conduction system or sinoatrial node at normal doses, and therefore do not have *direct* effects on conduction or automaticity
- The dihydropyridines can cause reflex tachycardia because of their potent vasodilating effects

# Hemodynamic Effects

- All of the clinically-approved  $\text{Ca}^{++}$ -channel blockers:
- Decrease coronary vascular resistance and increase coronary blood flow
- Decrease peripheral resistance via vasodilatation of arterioles
- Are without significant effect on venous tone at normal doses

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## Verapamil

- relaxes arteriolar smooth muscle resulting in
  - vasodilatation,
  - ↓ peripheral resistance
  - ↓ arterial pressure.
- depresses
  - myocardial contractility,
  - sinus node firing rate and
  - AV conduction.

- These cardiac effects may lead to:
  - cardiac failure,
  - heart block
  - sinus arrest, particularly when verapamil is combined with beta adrenergic blockers.

- The direct negative chronotropic and inotropic effects of verapamil
  - oppose any reflex-mediated sympathetic stimulation resulting from reducing the blood pressure,
  - there is no increase in heart rate and sometimes heart rate is slowed.

- Verapamil has
  - no significant effect on **venous tone**,
  - does not interfere with the **circulatory response**,
  - does not cause **postural hypotension**.
- has intrinsic **natriuretic effect** which balances any tendency for salt and water retention due to BP reduction.
- has a profound effect on GIT smooth muscle, reduces gut motility and causes **constipation**.

## Verapamil-Therapeutic use

- Verapamil is effective as monotherapy
  - **angina pectoris**
  - **Hypertension**
  - also in combination with either **diuretics or ACE inhibitors**.
  - *Combination with a beta blocker is not recommended because of additive myocardial depression.*

- Management of supraventricular arrhythmias.
  - Verapamil reduces calcium entry and thus slows AV conduction.
  - This action is beneficial in
    - terminating or preventing paroxysmal supraventricular tachycardia by interfering with AV nodal re-entry and also in controlling ventricular rate in the presence of atrial fibrillation.
- Verapamil and diltiazem are sometimes also used to enhance myocardial relaxation in hypertrophic obstructive cardiomyopathy.

## Diltiazem

- Diltiazem is an arteriolar dilator which reduces peripheral resistance and thus blood pressure, but it is less cardiodepressant.
- Reflex tachycardia is minimal.
- Diltiazem can be used safely in combination with a beta blocker for the treatment of hypertension without causing unacceptable cardiodepression.

- Diltiazem is used in
  - angina.
  - Its balance of both coronary and peripheral vasodilatation with mild cardiodepression is effective and well tolerated when used as monotherapy.
  - management of hypertension as a moderately effective arterial vasodilator.
  - It is used both as monotherapy and in combination with all of the other major classes of antihypertensive drugs.

## Dihydropyridines

- Nifedipine, felodipine, amlodipine and nimodipine are available.
- Nimodipine is marketed only for the treatment of cerebrovascular spasm following subarachnoid haemorrhage.
- The dihydropyridines are selective for blood vessels as they relax arteriolar smooth muscle without detectable cardiodepression.
- They cause a more profound reduction in peripheral resistance and blood pressure than verapamil or diltiazem.

- Heart reflex- mediated sympathetic stimulation of both heart rate and contractility.
  - This cardiac stimulation has been associated with the precipitation or worsening of angina or even the occurrence of myocardial infarction or sudden death.
  - Less likely with the longer-acting and slow-release preparations because their slower onset of effect allows baroreflex resetting. It is also effectively blocked by the concomitant administration of a beta blocker.

- Despite having an intrinsic diuretic effect, the dihydropyridines cause peripheral oedema.
  - The edema represents a redistribution of extracellular fluid rather than a net retention of salt and water and hence *does not respond to diuretics*.
- The dihydropyridines are more effective antihypertensive drugs than either verapamil or diltiazem

- not as well tolerated because of excessive vasodilator effects and reflex cardiac stimulation.
  - tolerability and effectiveness are enhanced if lower doses are used in combination with a beta blocker, ACE inhibitor or diuretic.
- Amlodipine and slow-release nifedipine have the least variability of plasma concentration and response within a 24-hour dosing interval.

- the major use of amlodipine is as an antihypertensive, it is approved for the management of angina as it is the least likely of all the dihydropyridines to cause reflex-mediated cardiac stimulation.
- Dihydropyridines can be used to treat peripheral vasospasm.
  - This is useful in patients treated with beta blockers who develop Raynaud's phenomenon.

# Pharmacokinetics

- The drugs are well absorbed from the gut, but their bioavailability varies depending on the extent of first-pass metabolism in the liver.
- The oral bioavailability is affected by factors or drugs which influence hepatic drug metabolism.
- Renal failure has no significant effect on clearance.

- Verapamil and diltiazem have short half-lives which require them to be given 3-4 times daily. However, slow-release formulations allow once-daily dosing.

# Pharmacokinetics

	Oral BA	Half life
• Verapamil	: 20%	4 h
• Diltiazem	: 40-50	4
• Nifedipine	: 50	2
• Felodipine	: 15-20	15-20
• Amlodipine	: 65	35-45

# Therapeutic Status

- Calcium channel antagonists are **useful in** individuals who have conditions such as
  - **diabetes, airways disease, peripheral vascular disease and depression** which limit treatment with some of the other classes of antihypertensives.
  - **contraindications** are the use as monotherapy in patients with ischemic heart disease and the use of verapamil and diltiazem in the presence of **impaired myocardial function, impulse generation or cardiac conduction.**

- No adverse metabolic effects on potassium or glucose homeostasis, renal function or lipid metabolism.
- **Potential benefits** include
  - reduction of cardiovascular hypertrophy in hypertension,
  - reduction of atherosclerotic lesions,
  - myocardial protection from ischemic damage.

## Adverse Effects

- The most prominent of these dose-dependent adverse effects **are due to arterial dilatation**.
- **flushing**, usually of the face but also of the legs, dull or throbbing headache and dependent edema.
- **lightheadedness and nausea** which may be associated with an excessive blood pressure reduction.
- these vasodilator adverse effects are more prominent with the dihydropyridines,

# Uses

- Subarachnoid hemorrhage (nimodipine)
- Treatment of migraine (nimodipine, nifedipine)
- Raynaud's phenomenon (nifedipine, diltiazem)
- Posthaemorrhagic cerebral vasospasm (nimodipine)
- Inhibition of platelet aggregation (unknown mechanism)
- To slow development of atherosclerosis
- Hypertrophic cardiomyopathy (nifedipine, verapamil)
- Postinfarct tissue preservation