



Calcium channel blockers/antagonists

History

- The term “calcium antagonists” was 1st coined by Fleckenstein & Colleagues in 1969.
- Investigating vasodilator effects of prenylamine and verapamil
- Observed that they have a negative inotropic effect on the heart
- Showed that the -ve inotropic effect can be antagonized by calcium

Classification

Phenylalkylamines:

- Verapamil, desmethoxyverapamil, tiapamil, anipamil, gallopamil, ronipamil, devapamil, terodilin

Benzothiazepines:

- Diltiazem, fostedil



Dihydropiridines:


- Nifedipine, nitrendipine, nimodipine, niludipine, niguldipine, nicardipine, nisoldipine, amlodipine, felodipine, isradipine, ryosidine, lacidipine

Piperazines:

- Cinnarizine, lidoflazine, flunarizine


Membrane effects of Ca^{+2} antagonists

- Free Ca^{+2} in the cytosol regulates a number of cellular functions
- The intracellular pools of Ca^{+2} are replenished by Ca^{+2} from the ECF
- The transport of Ca^{+2} takes place via the Ca^{+2} channels
- Interfere with Ca^{+2} transport over excitable membranes in different tissues

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- The channels have to be open for Ca^{+2} to enter the cells
 - opened by changes in membrane potential (Voltage-operated Ca^{+2} – channels)

AND

- Through hormone/neurotransmitter mediated changes (receptor-operated channels)




Calcium antagonists act on voltage operated channels which are differentiated into:


- **T-channels (transient):**


- have small conductance and transient opening times

- activated by small depolarisations from very negative potentials

- Involved in the initiation of action potentials

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- Occur in neuronal, smooth muscle, cardiac, skeletal muscle cells
 - Do not take part in intracellular Ca^{+2} homeostasis
 - Inhibited by neurotransmitters e.g. NA & dopamine
 - Not affected by calcium antagonists


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- N-type: neuronal channels
 - L-type: have a high conductance and a prolonged opening time
 - Play a central role in the regulation of intracellular calcium concentration
 - Activated by changes in membrane potential

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- Also modulated by hormones and neurotransmitters
 - Very sensitive to calcium antagonists
 - Considered to be their primary receptor
 - Have a wide distribution
 - High concs in atria, blood vessels & skeletal muscle T-tubules



Vascular effects

- All of them dilate blood vessels
- Vasodilator effect is most pronounced with dihydropyridines
- Within the dihydropyridines there are marked differences of the vasodilator effect
- Vasodilator effect occurs on arteries and resistance vessels

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- Have negligible effect on veins
 - Strongly reduce coronary and skeletal vascular resistance
 - Insignificant effect on skin
 - Small effect on renal vascular resistance
 - Vasodilator effect is maintained during chronic therapy in hypertensive patients



Other effects on blood vessels

- Inhibit arterial smooth muscle proliferation due to a decrease in vascular DNA synthesis
- Inhibit platelet activation (platelets are a rich source of vascular growth factors)

Effect on renal function

- ~~Calcium antagonists are vasodilators~~ that reduce BP without triggering renal compensatory mechanisms that lead to fluid and electrolyte retention with classical vasodilators
- Renal blood flow & GFR are maintained during acute and long-term treatment with Ca^{+2} antagonists



Effect on renal function

- Have a diuretic & natriuretic effect in spite of their relative lack of effect on GFR or RBF which may suggest a tubular site of action

Effects on the heart

- Block slow Ca^{+2} channels
- Block myocardial cellular Ca^{+2} uptake
- Reduce the amount of Ca^{+2} available for interaction with troponin
- Negative inotropic effect
- Phenylalkylamines & benzothiazepines > dihydropyridines


Effect on the heart


- The relatively strong vasodilator effects of dihydropyridines trigger a baroreflex-mediated rise in sympathetic nerve activity
- Leads to a +ve rather than -ve inotropic effect
- Verapamil & diltiazem: direct -ve and indirect reflexogenic inotropic effects usually cancel each other



Effect on AV conduction

- Limited to phenylalkylamines & benzothiazepines
- Slow AV node conduction & sinus pacemaker activity
- Dihydropyridines & piperazines are less effective and may increase the heart rate due to baroreflex-mediated alteration of sympathetic nerve activity


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- Verapamil & diltiazem: good for treatment of supraventricular tachyarrhythmias
 - The coronary vasodilator effect of dihydropyridines is useful for preventing coronary spasms that are responsible for causing angina

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- Whereas as nitroglycerine acts predominantly on large coronary arteries calcium antagonists dilate large and small coronary arteries

Effects on cardiac metabolism

- Cardiac ischaemia is followed by:
 - a decrease in tissue ATP levels
 - increase in free-radical production via xanthine oxidase pathway
 - alteration in ionic homeostatis

Leading to cardiac arrhythmias and structural disorganization of the heart

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- Upon reperfusion, cells injured by the above mechanisms accumulate large amounts of Ca^{+2} (Ca^{+2} -overload)
 - This leads to further damage of the heart
 - Ca^{+2} enters the myocardial cells via routes that can be blocked by calcium antagonists



They also protect the heart from post ischaemic injury by:

- Coronary vasodilatation
- Cardiac unloading
- Effect on adenosine metabolism
- Reduce cardiac hypertrophy due to chronic hypertension



Hemodynamic effects

- Verapamil & diltiazem cause a modest lowering of BP and TPR with little or no depressive effect on cardiac function
- Dihydropyridines (nifedipine) reduce BP via a strong fall in TPR with an early rise in CO and HR
- Piperazines have insignificant short-term BP-lowering activity



Clinical uses

- Angina pectoris
- Supraventricular tachyarrhythmias
- Hypertension
- migraine



Unwanted effects

- Headache, constipation (verapamil), ankle oedema(dihydropyridines)
- There is a risk of causing cardiac failure or heart block, especially with verapamil and diltiazem