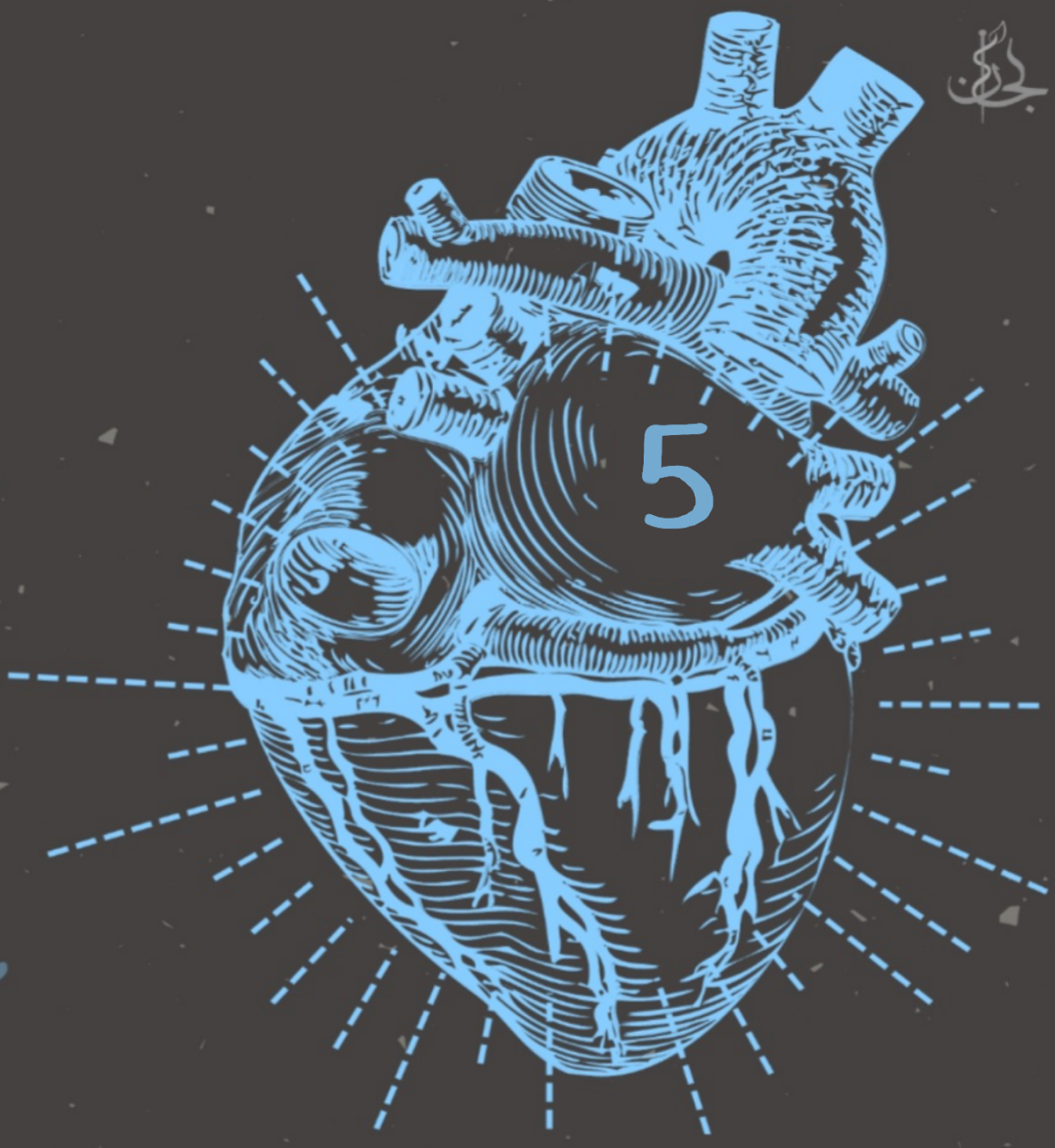
CVS



PHARMACOLOGY

WRITER: Doctor 018 ENTER

CORRECTOR: ENTER

DOCTOR: ENTER

Vasodilating Beta-Adrenergic Blockers

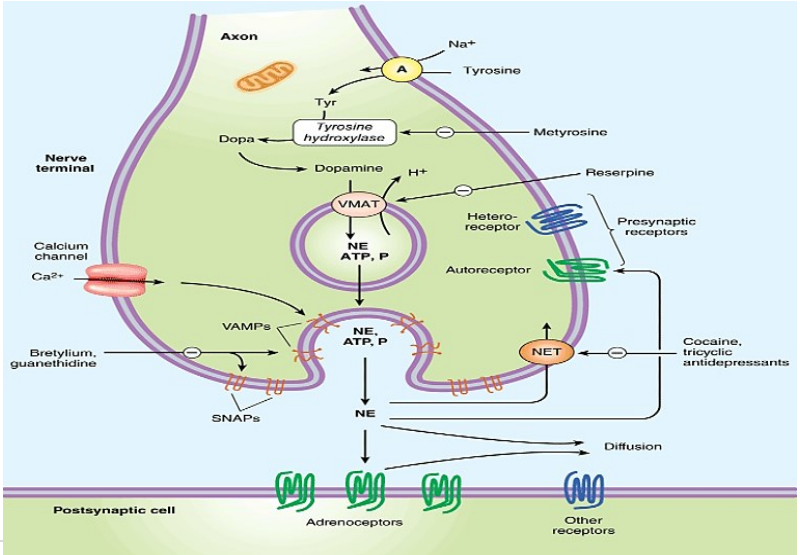
- Labetalol:
  - It's a beta antagonist, alpha1 antagonist (weak alpha1 blocking activity only 20% of those on beta receptors) & beta2 partial agonist - keep in mind that beta2 receptors cause vasodilation- .
  - Useful for pheochromocytoma and emergencies.
- Carvedilol: beta and alpha1 (10% of those on beta receptors) antagonist.
- Esmolol:
  - Beta1 selective, rapidly metabolized (short half-life)
  - Used by continuous IV infusion.

- Nebivolol:
  - Beta1 selective.
  - Nitric oxide potentiating vasodilatory effect.

Adrenergic Neuron Blockers

- Adrenergic neuron blocking agents act at the sympathetic nerve terminals to prevent the **release** of transmitter substance, rather than at the effector cell to inhibit the association of the transmitter with its receptors.
- They're generally hydrophilic.
- They are uptaken by **uptake 1**.
- Blocks NE release.

  These agents displace NE from intracellular vesicles, then, the free NE inside the cell will be metabolized by mono-amine oxidase (MAO).



Therefore, they cause the depletion of NE from peripheral nerve endings.

Examples:

- Guanethidine, Bethanedine, Debrisoquin, Guanadrel.

Reserpine:

- It's an adrenergic neuron blocking agents derived from the plant Rauwolfia alkaloid.
- *Lipophilic.*
- Binds to the sympathetic intracellular vesicles, and prevents DA (dopamine) uptake into these vesicles.
- Amines are metabolized by MAO.
- It depletes NE, 5HT (serotonin), ACTH, and DA.
- **Old** fashioned, **slow** onset and offset, and very **cheap**.
- It can cause depression and suicide (it can cross the BBB, since it's lipophilic), and has possible carcinogenic effect.

Ganglionic Blockers

- They work directly on the autonomic ganglions
- Blocks transmission in both sympathetic & parasympathetic systems.
- They act immediately and are very efficacious.
- The effect of ganglionic blockers can be rapidly reversed, thus, they're used for short term control of BP (e.g. intraoperatively and in emergencies). I.E. if you stop the drug, the effect terminates immediately due to their **short** duration of action.
- They have **many** side-effects.

Examples:

- Trimethaphan
- Pentolinium
- Mecamylamine

The table below shows the side effects of ganglionic blockers.

Notice the involvement of many organs that are controlled by ANS.

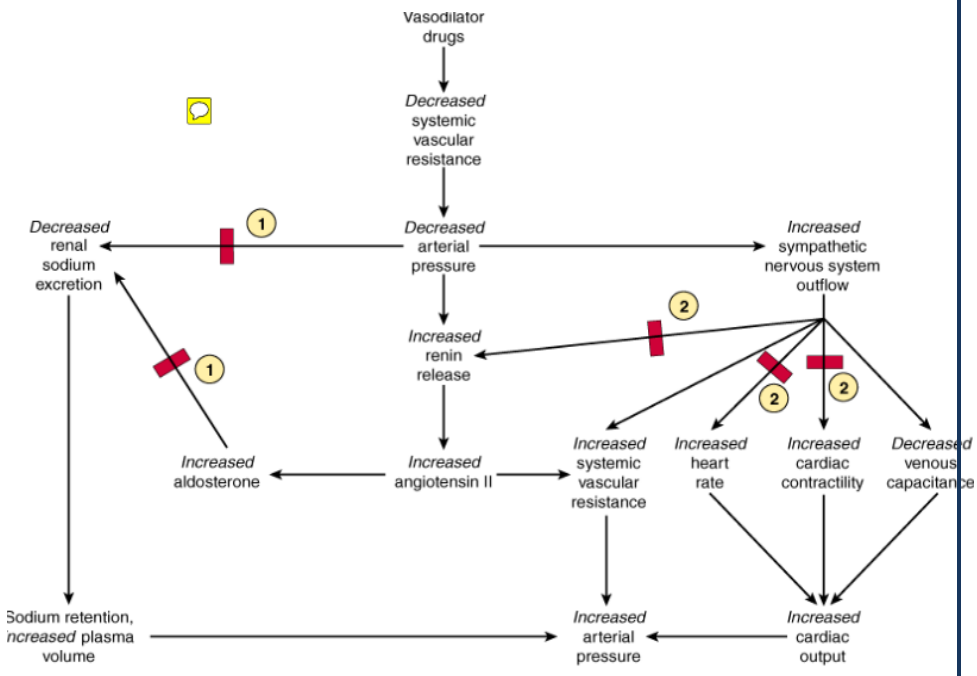
Organ	Predominate system	Results
Cardiovascular system heart veins arterioles	 Parasympathetic Sympathetic Sympathetic	 Tachycardia Vasodilation Dilation
Eye Iris, Ciliary muscles	 Parasympathetic Parasympathetic	 Mydriasis Cycloplegia

GI tract	Parasympathetic	Relaxation (constipation)
Urinary bladder	Parasympathetic	Urinary retention
Salivary glands	Parasympathetic	Dry mouth
Sweat glands	Sympathetic	Anhidrosis

VASODILATORS

- Vasodilators work directly on either the arterial blood vessels, veins or both, depending on the drug itself.
- Actions are not antagonized by known blockers.
- They work by reducing the peripheral vascular resistance, but this will elicit compensatory mechanisms through activation of baroreceptors, leading to tolerance, resistance or pseudo-resistance.
- Usually other drugs are combined with vasodilators to avoid this problem.

The figure to the right explains the compensatory mechanisms that occur following the administration of vasodilators, which eventually lead to increased arterial pressure, which we were aiming to reduce in first place. Therefore, resistance develops to this type of antihypertensive, and they will no longer be effective.



We can overcome this compensatory mechanism by using drugs that inhibit important pathways. Number one (in the figure) are diuretics, while number two are drugs which reduce the sympathetic nervous system activity, usually beta or alpha blockers.

Mechanisms of action of vasodilators:

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates, histamine, acetylcholine
Reduction of calcium influx (Ca channel blockers)	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

Hydralazine

- It is the oldest vasodilator (1950s) and it was withdrawn as it produced resistance due to reasons unknown at that time, but later came back (1970s).
- It is a pure arteriolar dilator and works by releasing NO.
- Tachyphylaxis (tolerance or pseudo-resistance).
- When hydralazine is used alone, there will be a drop in blood pressure the first few days. After that, the BP starts to increase, and may reach pre-treatment levels (tolerance). This tolerance (or resistance) is due to hydralazine's effect on stimulating the renin-angiotensin aldosterone system. The addition of a beta blocker can prevent this.
- Activates baroreceptor reflex (due to decreasing peripheral vascular resistance).
- Metabolized by acetylation, some people are rapid acetylators while others are slower, therefore responses to the drug differ from one population to another.
- Drug-induced lupus syndrome.
- Has other side effects such as hypotension and postural hypotension (orthostatic hypotension).
- It's no longer used alone it must be given in combination with diuretics or beta blockers.
- Can be replaced by calcium channel blockers (CCBs).
- Used in heart failure, combined with isosorbide dinitrate (a venodilator).

Diazoxide

- Thiazide derivative (structurally), but it's not a diuretic.
- Potent arterial dilator. It works by opening potassium channels, allowing k+ efflux.
- Causes excessive hypotension.
- Used in emergencies by rapid I.V. bolus injection.
- Rapidly bound to albumin.
- Onset 10-30 seconds.
- Duration 2-4 hours.
- Does not require constant monitoring, unlike other drugs such as sodium nitroprusside.

Sodium Nitroprusside

- Cyanide-containing molecule.
- Useful in emergencies, surgery, heart failure, malignant hypertension. This is because it's a short acting drug and has a fast onset of action.
- Relaxes both arterial and venous smooth muscle, works by release of NO.
- No excessive reflex increase in cardiac output.
- Might increase cardiac output if there is heart failure
- Short half-life.
- Action is immediate, requires constant monitoring in ICU.
- Drug is light sensitive, meaning that you have to protect it from light by covering the container.
- Can elevate thiocyanate levels (cyanide poisoning) and disturb acid-base balance causing weakness, nausea, tinnitus, flushing, lactic acidosis and anoxia

Minoxidil

- K+ channel-opener: Increases K+ efflux leading to hyperpolarization.
- Prolonged arterial relaxation (an arterial dilator).
- Superior to hydralazine.
- For severe intractable hypertension or renal insufficiency, it is usually given in combination with a diuretic and β blocker.

- One of the side effects is hypertrichosis (increased growth of hair) caused by vasodilation in hair follicles, leading to stimulation of hair growth, so it's very useful and now mainly used for baldness :(Available as topical solution applied locally to the scalp.
- Can cause pericarditis, one of the reasons why it's not used for treating hypertension.

Fenoldopam

- Dopamine D1 agonist, which results in vasodilation, especially renal vessel dilation (renal vessels have D1 receptors), and natriuresis.
- Rapidly metabolized, short acting.
- Used by continuous infusion in emergencies or postoperatively.
- After surgery or in patients with critical conditions it's not advisable to give a long acting antihypertensive because these patients need continuous monitoring. A long acting drug might interfere with the monitoring.

"And those who were seen dancing were thought to be insane by those who could not hear the music."
-Friedrich Nietzsche

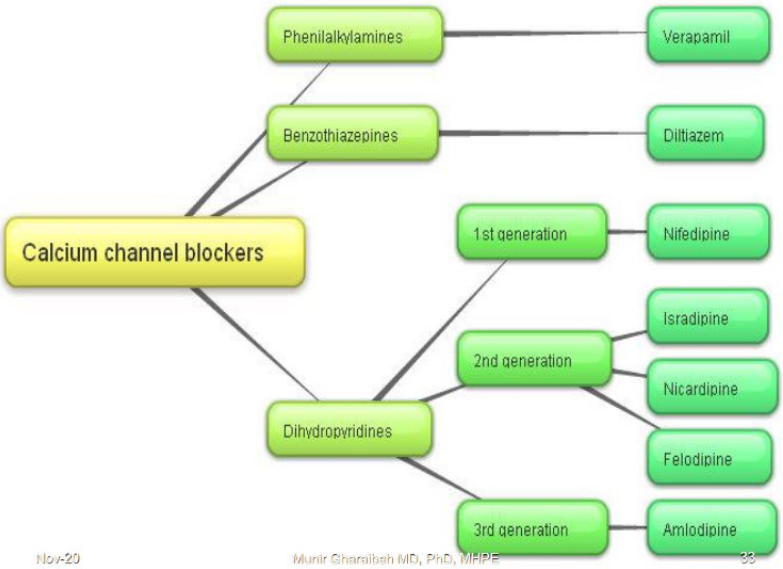
Good luck

Let's continue talking about antihypertensive drugs.

Calcium channel blockers (CCBs)

Calcium channels are essential part in most cells of the body, especially, calcium is important in cardiovascular function, its involved in cardiac muscle contraction, vascular smooth muscle contraction and other smooth muscles in the body, in the neural function of the CNS, nerve synapses, glandular secretion whether exocrine or endocrine, also in cell division.

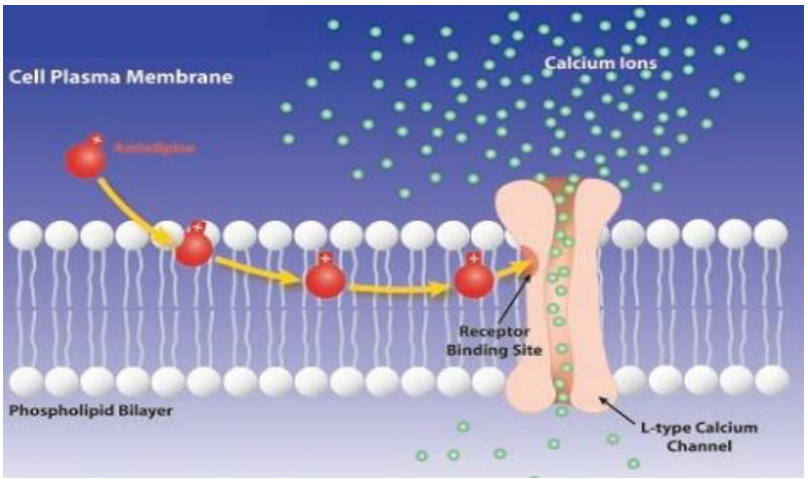
That's why calcium channel blockers are nowadays used for the treatment of many cardiovascular and non-cardiovascular diseases.



The first CCBs discovered were verapamil, diltiazem, nifedipine. Each belong to different chemical groups.

Newer drugs that belong to Dihydropyridines were manufactured, making 1st, 2nd and 3rd generation of this class.

As the name suggests, CCBs blocks calcium entry into the cell through the calcium channels, as you can see the drug passes through the plasma membrane and binds to the calcium channel from the inside rendering it inactive.



The table below shows the different types of calcium channels, their locations, calcium current properties, and what drugs block them.

- Calcium channel blockers have different affinities toward certain types, for example verapamil can block only the L type.
- The most common channel type is the L, its present almost everywhere.

- sFTX are drugs that were used on experimental animals and have proved to block the T type.
- DHP stands for dihydropyridines.

These are not for memorizing at all, just know we have different types, location, current properties, they blocked by different drugs.

Type	Channel Name	Where Found	Properties of the Calcium Current	Blocked By
L	$Ca_V1.1$–$Ca_V1.3$	Cardiac, skeletal, smooth muscle, neurons ($Ca_V1.4$ is found in retina), endocrine cells, bone	Long, large, high threshold	Verapamil, DHPs, Cd^{2+}, -aga-IIIA
T	$Ca_V3.1$–$Ca_V3.3$	Heart, neurons	Short, small, low threshold	sFTX, flunarizine, Ni^{2+}, mibefradil[1]
N	$Ca_V2.2$	Neurons, sperm[2]	Short, high threshold	Ziconotide,[3] gabapentin,[4] -CTX-GVIA, -aga-IIIA, Cd^{2+}
P/Q	$Ca_V2.1$	Neurons	Long, high threshold	-CTX-MVIIC, -aga-IVA
R	$Ca_V2.3$	Neurons, sperm[2]	Pacemaking	SNX-482, -

18-Nov-20 Munir Gharaibeh MD, PhD, MHPE 36

Mechanism of action:

- Calcium channel blockers are used to treat hypertension by primarily acting to reduce peripheral vascular resistance (PVR), by causing vasodilation through preventing vascular smooth muscles contraction.
- They have initial diuretic effect, the vasodilation of the renal arteries might cause some sort of diuresis, especially with the short-acting DHPs. For example, Nifedipine.
- More effective than others in protection against stroke, because they can affect the blood vessels in the brain.
- Effective in the elderly.
- Equally effective in black and nonblack patients. In contrast to diuretics, which were more effective in black patients.

They have different effects on PVR, heart rate HR and cardiac output CO.

	PVR	HR	CO
Nifedipine	---	+++ (Reflexly)	++
Diltiazem	--	-	-
Verapamil	--	--	--

CCBs they also work on the cardiac muscle itself, logically they must also suppress the cardiac muscles, which is true in case of Diltiazem and Verapamil (because they are not as potent as Nifedipine in reducing PVR), but Nifedipine is an exception.

Nifedipine is very potent in reducing PVR, so it acts as a rapid vasodilator, as a result of this rapid vasodilation, the baroreceptors gets activated initiating a reflex, consequently stimulating the sympathetic and inhibiting the parasympathetic systems, which as we know, will stimulate the heart rate and cardiac output.

Therefore, the direct effect of nifedipine on the heart is inhibitory, but as a result of the baroreceptor reflex, it indirectly stimulates the heart.

Side Effects:

- Relatively safe drugs, most of the side effects are due to vasodilation of blood vessels
- Risk of Hypotension. (in drugs like nifedipine)
- Headache, dizziness. (as a result of vasodilation in the brain vessels)
- Flushing, especially with short acting agents.
- Peripheral edema.
- Do NOT cause metabolic disturbances. In contrast with diuretics.

CCBs also differ in pharmacokinetic characteristics, they have different oral bioavailability, half-life, different indications. The doctor only read verapamil, nifedipine and diltiazem.

Drug	Oral Bioavailability (%)	Half-Life (hours)	Indication
Dihydropyridines			
Amlodipine	65–90	30–50	Angina, hypertension
Felodipine	15–20	11–16	Hypertension, Raynaud's phenomenon
Isradipine	15–25	8	Hypertension
Nicardipine	35	2–4	Angina, hypertension
Nifedipine	45–70	4	Angina, hypertension, Raynaud's phenomenon
Nimodipine	13	1–2	Subarachnoid hemorrhage
Nisoldipine	< 10	6–12	Hypertension
Nitrendipine	10–30	5–12	Investigational
Miscellaneous			
Diltiazem	40–65	3–4	Angina, hypertension, Raynaud's phenomenon
Verapamil	20–35	6	Angina, hypertension, arrhythmias, migraine