PHARMACOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 8

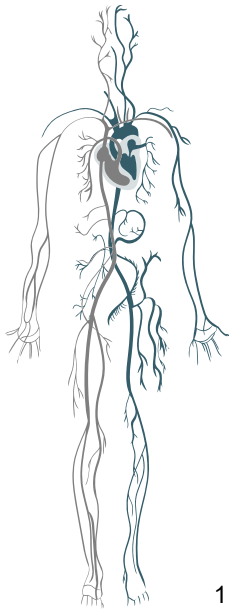
وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا

Anti-hypertensives (pt.5)

Written by: Ansam Othman, Raghad Hamdan

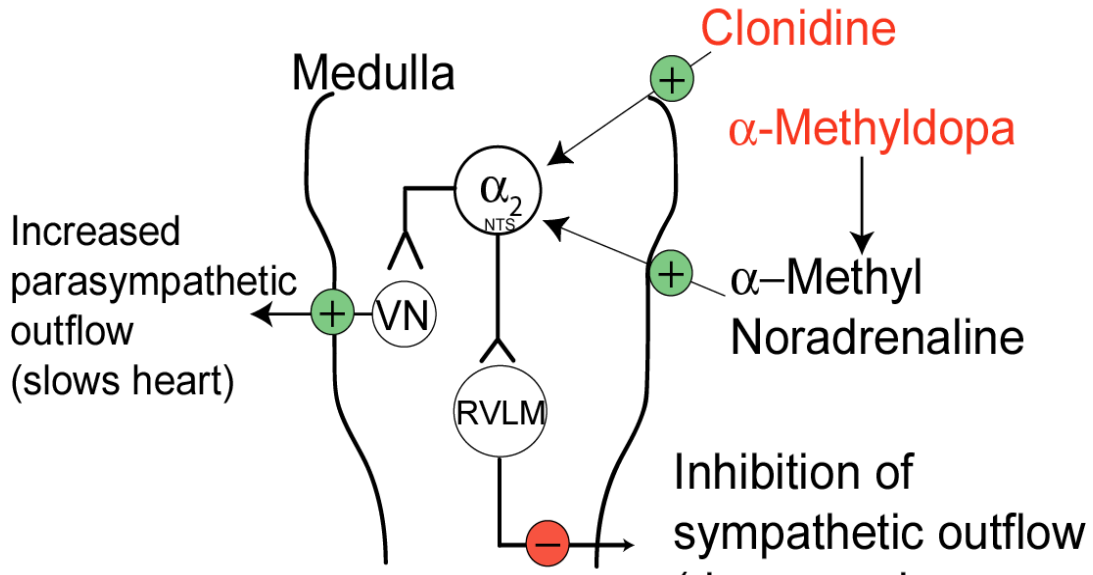
Reviewed by: Sarah Mahasneh



Centrally Acting Sympathoplegic Drugs
'Central α_2 Agonists'

Although α2-receptors are present in blood vessels, they are much fewer than α1-receptors. Their main location and function is in the **presynaptic nerve terminals** of the central nervous system, where they provide negative feedback to inhibit norepinephrine release. This action controls sympathetic outflow and helps maintain homeostasis by balancing sympathetic stimulation.

Central α_2-Adrenergic Agonists



Vasomotor center

VN=ventral nucleus

RVLM=rostral ventrolateral medulla

- Methyldopa and clonidine cross BBB to stimulate α_2 receptors in vasomotor center in brainstem
- Inhibit sympathetic and increase parasympathetic outflow to periphery
- Decrease BP
- At high concentrations, increase BP by stimulating peripheral α_2 receptors but the net effect is a decrease in peripheral resistance

Mechanism and Effects of Central α2-Agonists

- After activation of the sympathetic nervous system and the release of norepinephrine (NE), the NE binds to presynaptic α2-receptors to provide negative feedback, which reduces further NE release.
  - Drugs known as α2-agonists (such as clonidine and methyldopa) **mimic** this action.
- Clonidine's net effect is a decrease in blood pressure because it reduces sympathetic outflow and decreases vasoconstriction.
  - In general, α2-agonists inhibit sympathetic outflow, leading to ↓ cardiac output, ↓ NE binding to α1-receptors, ↓ peripheral resistance, ↓ heart rate, and ↑ parasympathetic activity.

- Although α2-receptors exist in blood vessels, they are much fewer than α1-receptors, **and when activated they can cause vasoconstriction**, **similar to α1-effects**.
- However, this effect is mainly seen in **laboratory settings**, or when **high IV doses** of α2-agonists are used.
  - At high concentrations, even selective drugs become less selective, producing α1-like **vasoconstriction**.

Central α_2-AR Agonists: Mechanism of Action

- Heart rate, cardiac output, total peripheral resistance, plasma renin activity, and baroreceptor function are reduced

- Reduced plasma renin activity means less angiotensin II and aldosterone. However, with α2-agonists, sodium and water retention can still happen. This is because these drugs lower sympathetic tone and blood pressure, so the kidneys sense reduced perfusion and retain more sodium and water, even though renin stays low.

- Vascular smooth muscle: α_2 adrenergic receptors located on vascular smooth muscle open Ca^{2+} channels and cause vasoconstriction. Not evident clinically unless given intravenously or at high doses.

Summary:

Normal therapeutic doses: ↓ BP and ↓ vascular resistance through ↓ cardiac output and ↓ heart rate.
High concentrations (**lab/IV**): cause vasoconstriction, similar to α1-receptor activation.

Central α_2-AR Agonists

They act more centrally than peripherally

- **Clonidine, (guanabenz and guanfacine):** Direct acting α_2 adrenergic receptor agonists.

- **α-methyldopa** Prodrug taken up by central adrenergic neurons and converted to the α_2 adrenergic receptor agonist α- methylnorepinephrine. Although its structure resembles dopa, its main role is that it replaces norepinephrine in storage vesicles, so it is considered a false neurotransmitter. Its final active form produces central α_2 activation, leading to reduced sympathetic outflow.

سبحان الله، الحمدلله

Clonidine (Catapres): Pharmacokinetics

- Oral plasma $t_{1/2}$ – 12-16 hrs
- Transdermal administration of clonidine by patch (replaced once per week) useful in patients unable to take oral medication

Clonidine patches provide steady, continuous delivery over a week, overcoming the drug's short half-life and improving adherence while maintaining stable blood pressure.

Clonidine: Side Effects

- Dry mouth (44%) – peripheral effect
- Drowsiness (50%)
- Dizziness (15%)

These are central effects.

- Clonidine can cause sodium retention, but may be used at low doses w/o addition of diuretic

Clonidine: Drug Interactions

- Tricyclic antidepressants can reverse the antihypertensive effects of clonidine

Methyldopa (Aldomet):
Side Effects

- Like Clonidine, causes **sedation**, dry mouth, sodium retention, and dizziness

These drugs depress central nervous system activity, which can cause sedation and reduce symptoms such as pain and over-alertness. By the central action of clonidine, it can indirectly reduce muscle tone, giving a muscle-relaxing effect in certain conditions.

- With prolonged use, hemolytic anemia is a rare side effect

Clonidine and Methyldopa: Drug interactions

Drugs that influence blood pressure—particularly those that affect CNS sympathetic activity—can diminish their effect or cause loss of blood-pressure control.

- Tricyclic antidepressants affect the uptake mechanism of catecholamines (epinephrine and norepinephrine) which will increase their concentration in the synaptic cleft and may prevent the antihypertensive effect.
- Barbiturates, a CNS inhibitor (used in anaesthesia, epilepsy), may reduce the efficacy through the induction of hepatic microsomal enzymes.

Clonidine and Methyldopa: Drug interactions

- Drugs are metabolized by the body mainly to make them easier to eliminate, and in some cases, metabolism can activate the drug

Drug metabolism occurs in two steps:

1. Oxidation-reduction reactions
2. Conjugation reactions

If a drug induces microsomal enzymes such as CYP450, it will increase metabolism and lower the drug's plasma concentration. For example, barbiturates induce CYP450, which can reduce the effect of antihypertensive drugs and therefore lessen their ability to lower blood pressure.

- Monoamine oxidase inhibitors when co-administered may produce hypertension and CNS stimulation because they increase the concentration of monoamines.

MAO is an enzyme that breaks down catecholamines.

لا اله الا الله وحده لا شريك له ، له الملك
وله الحمد وهو على كل شيء قدير

Indications

- Methyldopa is a first choice for hypertension during pregnancy

□ Other medications considered safe in pregnancy include certain β-blockers (such as labetalol) and calcium channel blockers like nifedipine (a dihydropyridine). Therefore, if a woman becomes pregnant and is already taking these drugs for chronic hypertension, they usually do not need to be changed.

□ However, if she is taking ACE inhibitors or ARBs, they must be stopped immediately and replaced, because they are unsafe in pregnancy.

- Clonidine is useful in the diagnosis of pheochromocytoma (adrenal tumor that secretes high amounts of NE and cause hypertensive crisis) in hypertensive patients; it will reduce NE to lower then 500 pg/mL in tumor-free patients, If the concentration of norepinephrine remains high after a course of clonidine, this indicates that there is another source of NE release.

Ganglionic Blockers

act on the autonomic ganglia.

Trimethaphan

Pentolinium

Mecamylamine

- **Block transmission in both sympathetic & parasympathetic systems.**
- **Act immediately and are very efficacious. Effect rapidly**
- **reversed, so used for short term control of BP, e.g. intraoperatively or emergency.**
- **Many side effects.**

The autonomic ganglia act as synapses between the preganglionic and postganglionic neurons, and they belong to both the sympathetic and parasympathetic systems. Nicotinic receptors are present in both systems, and they have two main types: **Nm** (muscle type) and **Nn** (neuron type).

The effect of blocking both sympathetic and parasympathetic systems depends on which division is dominant in each organ.

<u>Cardiovascular system (CVS):</u>

Blood vessels (arterioles and veins): Parasympathetic innervation is minimal, so the sympathetic system is dominant. Blocking sympathetic tone causes vasodilation.

Heart: The atria and SA node are predominantly parasympathetic, while the ventricles are predominantly sympathetic.

Blocking parasympathetic input → **tachycardia**.

Blocking sympathetic input to the ventricles → **decreased contractile force**.

Other tissues here are important to know as side effects of these drugs.

For example, mydriasis in iris, constipation in GIT, urinary retention in urinary bladder, dry mouth in salivary glands...

Organ	Predominate System	Results
Cardiovascular System Heart Arterioles Veins	 Parasympathetic Sympathetic Sympathetic	 Tachycardia Vasodilatation Dilation
Eye Iris Ciliary Muscle	 Parasympathetic Parasympathetic	 Mydriasis Cycloplegia
GI Tract	Parasympathetic	Relaxation (constipation)
Urinary Bladder	Parasympathetic	Urinary retention
Salivary Glands	Parasympathetic	Dry Mouth
Sweat Glands	Sympathetic	Anhidrosis

Sweat glands are controlled only by sympathetic cholinergic fibers, so blocking this sympathetic tone reduces sweat secretion.

TABLE 14.2 Predominant Autonomic Tone at Various Neuroeffector Junctions and the Effect Produced by Ganglionic Blockade

Site	Effect of Ganglionic Blockade
Tissues predominantly under parasympathetic (cholinergic) tone	
Myocardium	
Atrium; S-A node	Tachycardia
Eye	
Iris	Mydriasis
Ciliary muscle	Cycloplegia
GI tract	Decrease in tone and motility; constipation
Urinary bladder	Urinary retention
Salivary gland	Dry mouth
Tissues predominantly under sympathetic (adrenergic) tone	
Myocardium	
Ventricles	Decrease in contractile force
Blood vessels	
Arterioles	Vasodilation; increase in peripheral blood flow; hypotension
Veins	Vasodilation; pooling of blood; decrease in venous return; decrease in cardiac output
Sweat glands[a]	Decrease in secretion

[a]Anatomically sympathetic; transmitter is ACh.

Trimethaphan

Trimethaphan camsylate (Arfonad) is an extremely short-acting agent whose major therapeutic use is in the production of controlled hypotension in certain surgical procedures and in the emergency treatment of hypertensive crisis.

Side effects:

- Potentiate the effect of tubocurarine in surgery.
- Have histamine (which causes bronchoconstriction and increases secretions of respiratory system) releasing properties (Caution in allergies) so, anti-histamine must be given to counteract this effect.

· These drugs are rarely used because they have many side effects.They act very quickly and their effect wears off rapidly, making them useful in emergency situations or surgical procedures where precise and short-term control of blood pressure is needed.For example, if blood pressure needs to be controlled for only 15 minutes, these drugs can be given for that period and stopped whenever desired.

Drug interaction:

Tubocurarine is a non-depolarizing skeletal muscle relaxant that blocks Nm nicotinic receptors at the neuromuscular junction. It is used during surgery to relax laryngeal and pharyngeal skeletal muscles, which helps with easy intubation, and to relax other skeletal muscles when surgical access is needed.When tubocurarine or other non-depolarizing muscle relaxants are given together with Trimethaphan, Trimethaphan's weak Nm-blocking action can enhance the muscle-relaxant effect. **Patient monitoring is essential**.

Remember from pharma MSS:

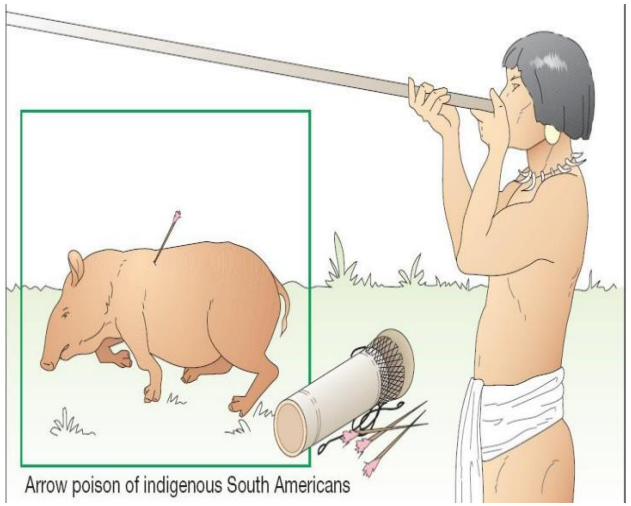

Arrow poison of indigenous South Americans

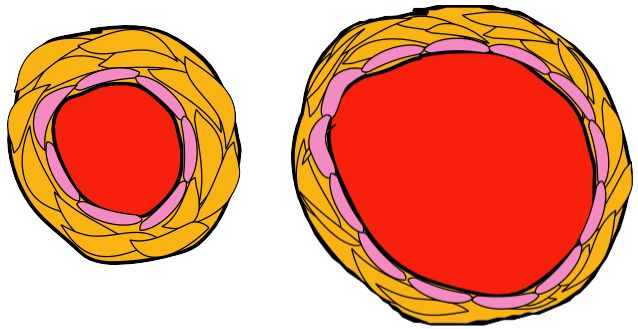
Image Interpretation

- One of the earliest uses of tubocurarine was for hunting animals.
- As mentioned earlier, this drug does not harm individuals when ingested because it cannot be absorbed in the gastrointestinal (GI) tract due to its polar nature.
- Tubocurarine has been used for centuries as a hunting poison, though the clinical use of these drugs started in the 1940's.

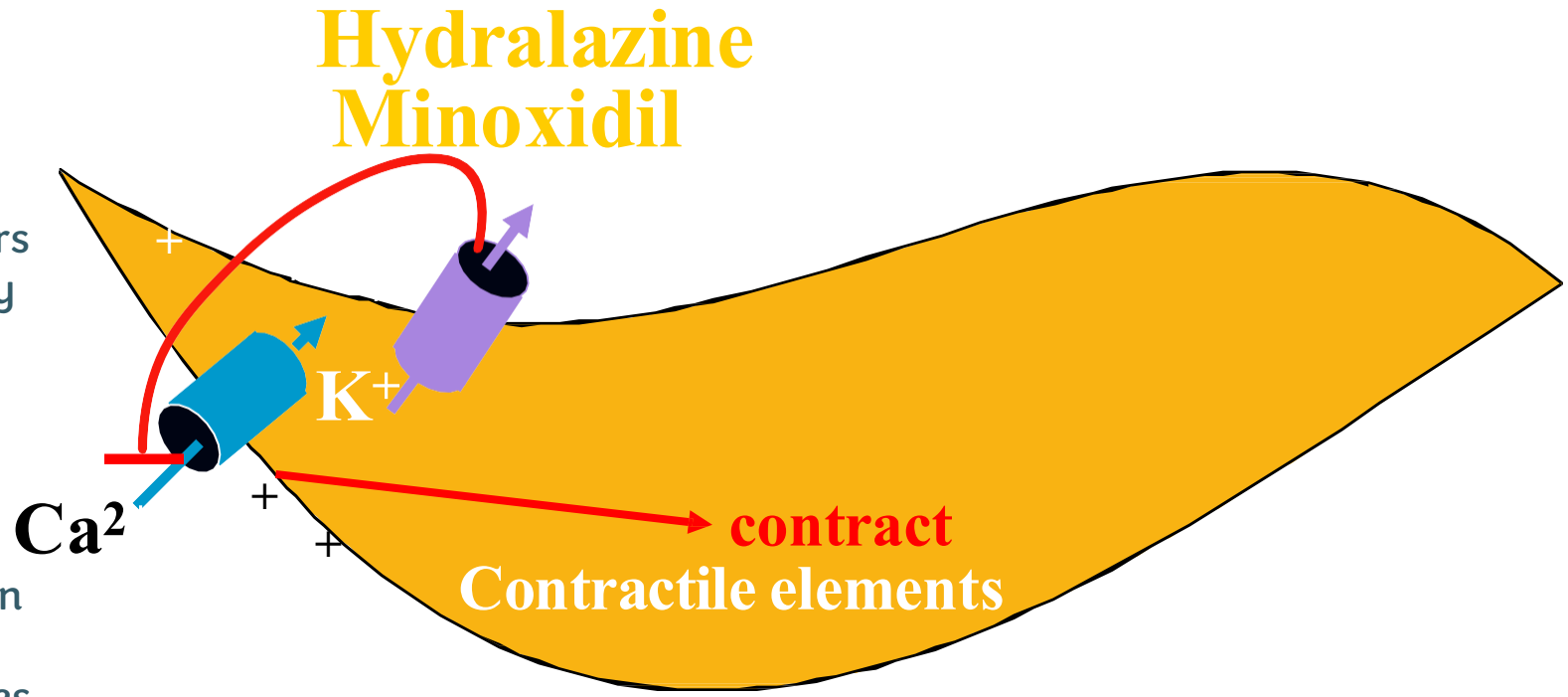
Quaternary nitrogen (not absorbed) so given IV in surgeries.

Vasodilators

Vasodilators: Mechanism of Action



- Relax Vascular smooth muscle cells
- Vasodilate Arterioles (mainly arterial vasodilation rather than the veins)
- Decrease PVR
- Decrease Blood Pressure



Remember:
· Calcium channel blockers also cause vasodilation by inhibiting calcium channels.
· Another way to inhibit calcium channels is through hyperpolarizing the cell. Hyperpolarization of the cell can occur by opening K+ channels (goes outside the cell).

Hydralazine (Apresoline):

Mechanism of Action

- Direct vasodilatory action on arterioles altering smooth muscle cell Ca^{2+} by hyperpolarizing cell (thought to do so by activating k+ channels).
- Decreases total peripheral resistance
- Sympathetic activity (Reflex responses)
  - Increased heart rate
  - Increased heart contractility
  - Increased plasma renin activity

- Very old drug.

- Mechanism of action is unknown.

- Given to the control group in animals because of it's know vasodilatory effect.

- Rarely used clinically today but may still be used in hypertensive emergencies—especially in pregnancy (preeclampsia).

- These drugs work only on BV (not heart), so hypotension caused by these drugs will result in reflex tachycardia.

Hydralazine: Pharmacokinetics

- Plasma $t_{1/2}$ – 1 hr, but antihypertensive action of 12 hrs possibly due to storage in arterial wall

Hydralazine: Side-effects

- Reflex tachycardia
  - Can precipitate MI in elderly patients or patients with coronary artery disease
  - **Reflex response can be blocked by addition of propranolol**
- Sodium and water retention (from the increased renin activity)– **can be prevented by addition of a diuretic**
- Headache, Nausea, Dizziness
- Lupus syndrome

Minoxidil (Loniten) : Mechanism of Action

- Activates ATP-sensitive K+ channels to cause hyperpolarization and smooth muscle cell relaxation
- Arteriolar vasodilation
- Decrease in total peripheral resistance

Minoxidil: Pharmacokinetics

- Plasma $t_{1/2}$ - 4 hrs, but hypotensive effect for 12-24 hrs
- A prodrug must be metabolized by the liver to form the active metabolite, minoxidil N-O sulfate

Minoxidil: Side effects

- Similar to hydralazine
- Hypertrichosis – accentuated hair growth
- Minoxidil is reserved for treatment of severe hypertension and must be given with a diuretic and a sympatholytic agent (usually a β-adrenergic receptor antagonist).

Remember:

Minoxidil is used for hair growth by dilating the BVs supplying the hair follicles which allows for more oxygen, blood, and nutrients to the follicles.

Minoxidil was first used as an anti-hypertensive agent, but it was noted that some patients had hypertrichosis as a side effect.

Indications

- Severe, resistant hypertension (rarely used as hypertensive drug)

VASODILATORS

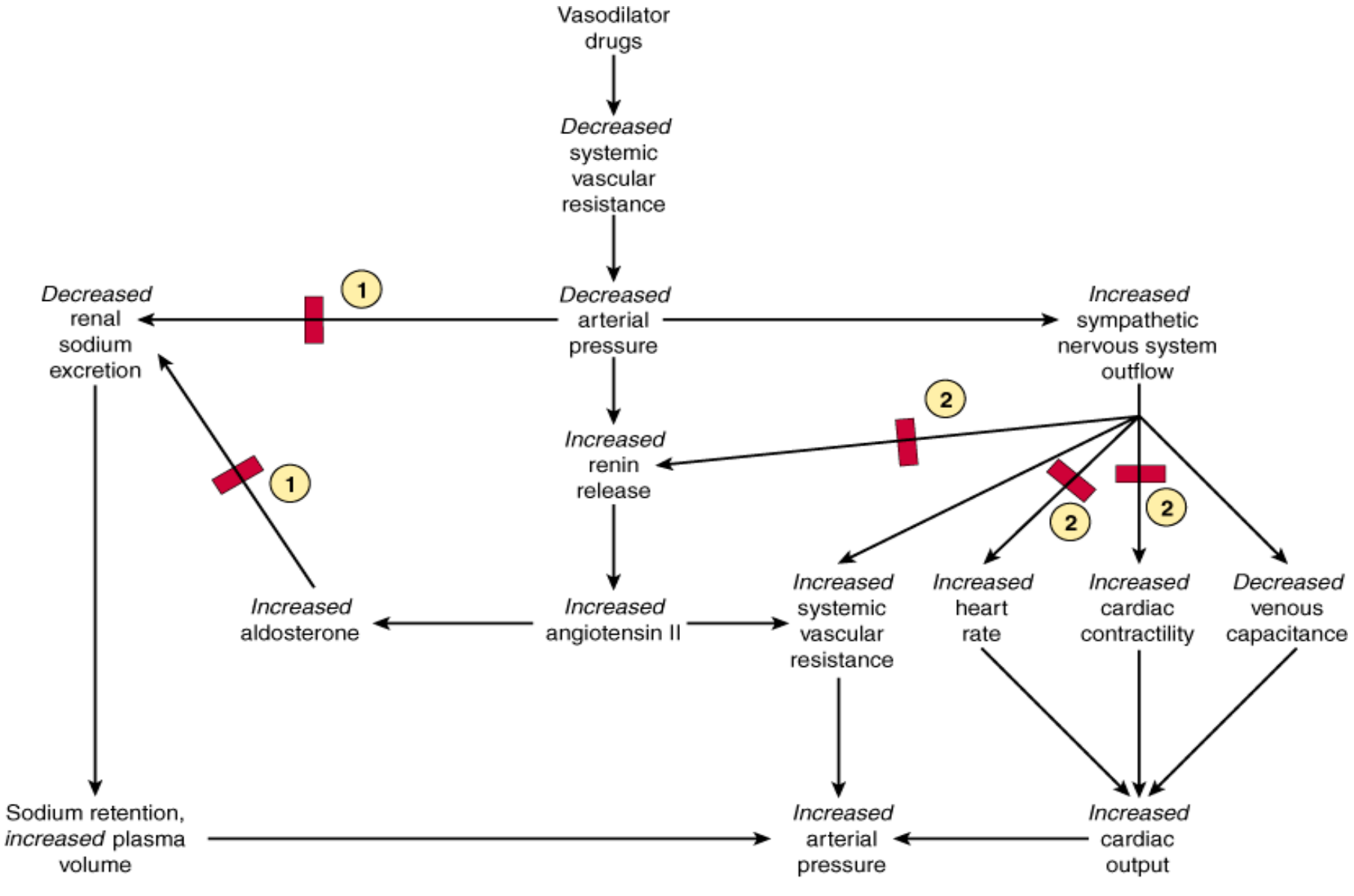
Fenoldopam:

- **Dopamine D_1 agonist, which results in vasodilation, renal vessel dilation, and natriuresis.**
- **Rapidly metabolized, short acting.**
- **Used by continuous infusion in emergencies or postoperatively.**

· Dopamine D1 receptors are located on the renal arterioles.

· In surgery, if blood pressure needs to be controlled while preserving renal perfusion (such as in a partial nephrectomy), Fenoldopam can be used because it increases renal blood flow. However, be cautious, as the increased perfusion may increase the risk of bleeding.

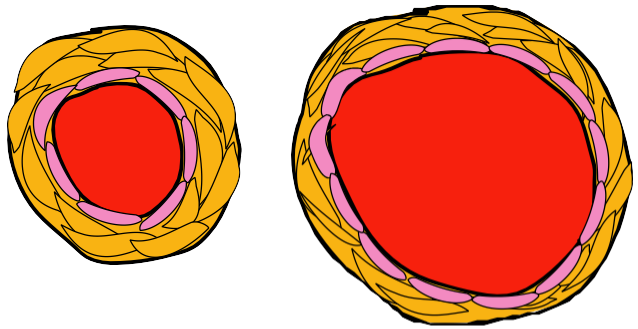
Compensatory responses to vasodilators



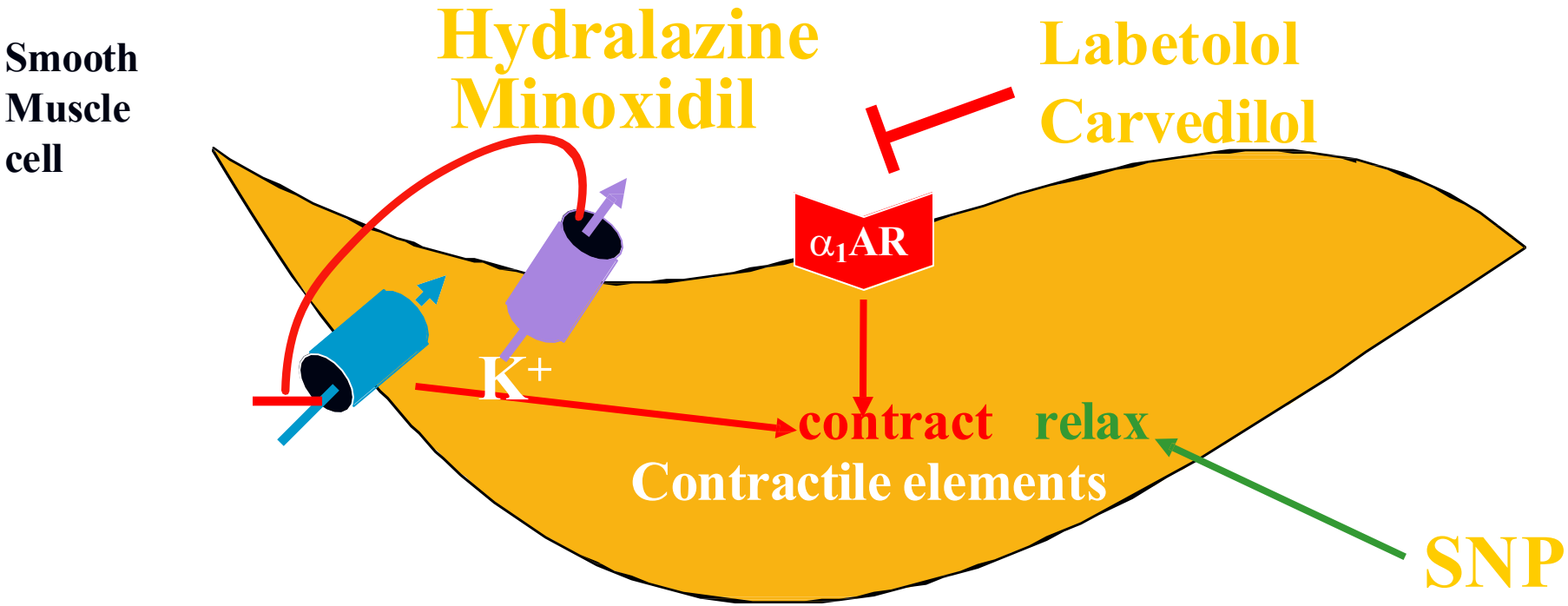
Vasodilators in Treatment of Hypertensive Crisis

A sudden rise in blood pressure is dangerous because it can lead to vascular rupture, hemorrhagic stroke, or other forms of intracranial bleeding. In hypertensive emergencies, blood pressure must be lowered promptly using fast-acting, potent IV medications. Commonly used agents include **labetalol**, **nicardipine**, **clevidipine**, and **hydralazine**.

Vasodilators: Mechanism of Action



- Relax Vascular smooth muscle cells
- Vasodilate Arterioles
- Decrease PVR
- Decrease Blood Pressure



Sodium Nitroprusside (SNP, Nipride): Mechanism of Action

□ Sodium nitroprusside (SNP, Nipride) releases nitric oxide (NO), which diffuses into vascular smooth muscle cells and activates guanylyl cyclase. This increases the production of cGMP, leading to vascular smooth muscle relaxation.

- Liberates nitric oxide (similar to nitroglycerin) which dilates vascular smooth muscle

- Thereby, decreases total peripheral resistance.

SNP:
Pharmacokinetics

Short lived because it releases NO which is a gas that diffuses quickly.

- Given by I.V. infusion
- Is light sensitive and unstable in aqueous solution, so it is administered using brown tubing.
- Antihypertensive effect ceases upon stopping infusion
- Metabolized to sodium thiocyanate – slowly cleared by kidneys
- Toxic accumulation (because of problems in the kidneys) of cyanide can lead to lactic acidosis.

SNP:
Side-effects

- Rebound hypertension
- Tolerance

Diazoxide (Hyperstat): Mechanism of Action

- Dilates arterial smooth muscle through activation of K_{ATP} channels.
- Little or no effect on venous smooth muscle.
- Decreases total peripheral resistance

□ Diazoxide causes arteriolar dilation, which reduces systemic vascular resistance and therefore decreases afterload. By lowering afterload, it can increase cardiac output indirectly, because the heart can eject blood more easily against a lower resistance

Diazoxide: Pharmacokinetics

- Administered I.V.
- Onset of action within 2 min.
- Duration of action – 6-24 hrs.

Longer duration of action so considered better than SNPs.

Diazoxide:
Side-effects

- Tachycardia
- Angina

Labetalol (Normodyne) and Carvedilol (Coreg) : Mechanism of Action

- Mixture of α_1 and non-selective β adrenergic receptor antagonist
  - Block adrenergic receptors in blood vessels and heart
  - Labetolol 1:3 selectivity α_1AR: βAR
  - Carvedilol 1:10 selectivity α_1AR: βAR
- Decrease total peripheral resistance w/o reflex tachycardia, because it blocks β_1 receptor in the heart.

Dual effect:

1) Decreased heart rate and contractility lead to a reduction in cardiac output.
2) Vasodilation.

Labetalol & Carvedilol: Pharmacokinetics

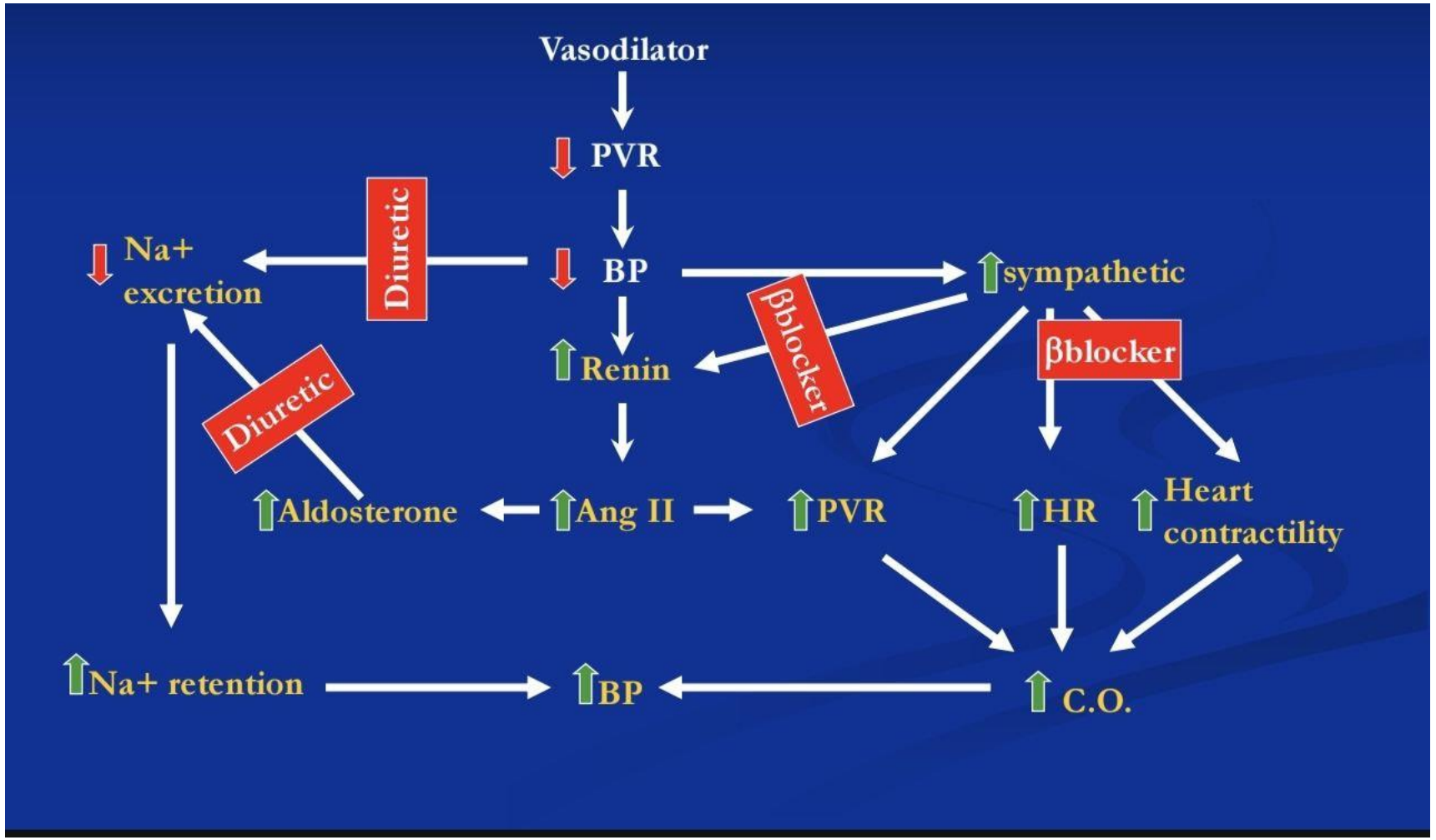
- Administered orally or i.v. (for hypertensive crisis)
- Useful in pheochromocytoma (Labetalol).

In pheochromocytoma, patients have excessive catecholamines—mainly norepinephrine, which causes α_1-mediated vasoconstriction, and epinephrine, which causes β_1-mediated tachycardia and β_2-mediated vasodilation.

Labetalol is useful because it blocks both α_1-receptors (causing vasodilation) and β-receptors (reducing heart rate and contractility), helping to control the severe hypertension and tachycardia.

- Plasma $t_{1/2}$ – 2 hrs (p.o.) and 5 hrs (i.v.)

Compensatory Responses to vasodilators can be managed with diuretics and β blockers



Generalized hierarchy of antihypertensive medication

Diuretic is given in case of mild to moderate hypertension.

Thiazide

- Least expensive and very effective first line therapy for mild to moderate hypertension
- Also useful in volume overload associated with congestive HF
- Under age 55, may consider giving ACE/ARB

If patient is not diabetic, start with beta blocker.

Low — **Risk of new-onset diabetes** — High

If diabetic, avoid beta blockers, instead start with ACE inhibitor and ARB.

B-blocker

ACE Inhibitor

Additional BP control

If all of the above did not work, then add CCB (calcium channel blocker).

CCB

If CCB is ineffective, add ACE or change.

ACE

ARB (if coughing)

Other (α blockers Central acting Agents)

If ALL of the above did not work, give patient alpha blocker.

PHARMACOLOGY QUIZ LECTURE 8

Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			