Drugs Regulating Arterial Blood Pressure

PHC 721

Winter 2022

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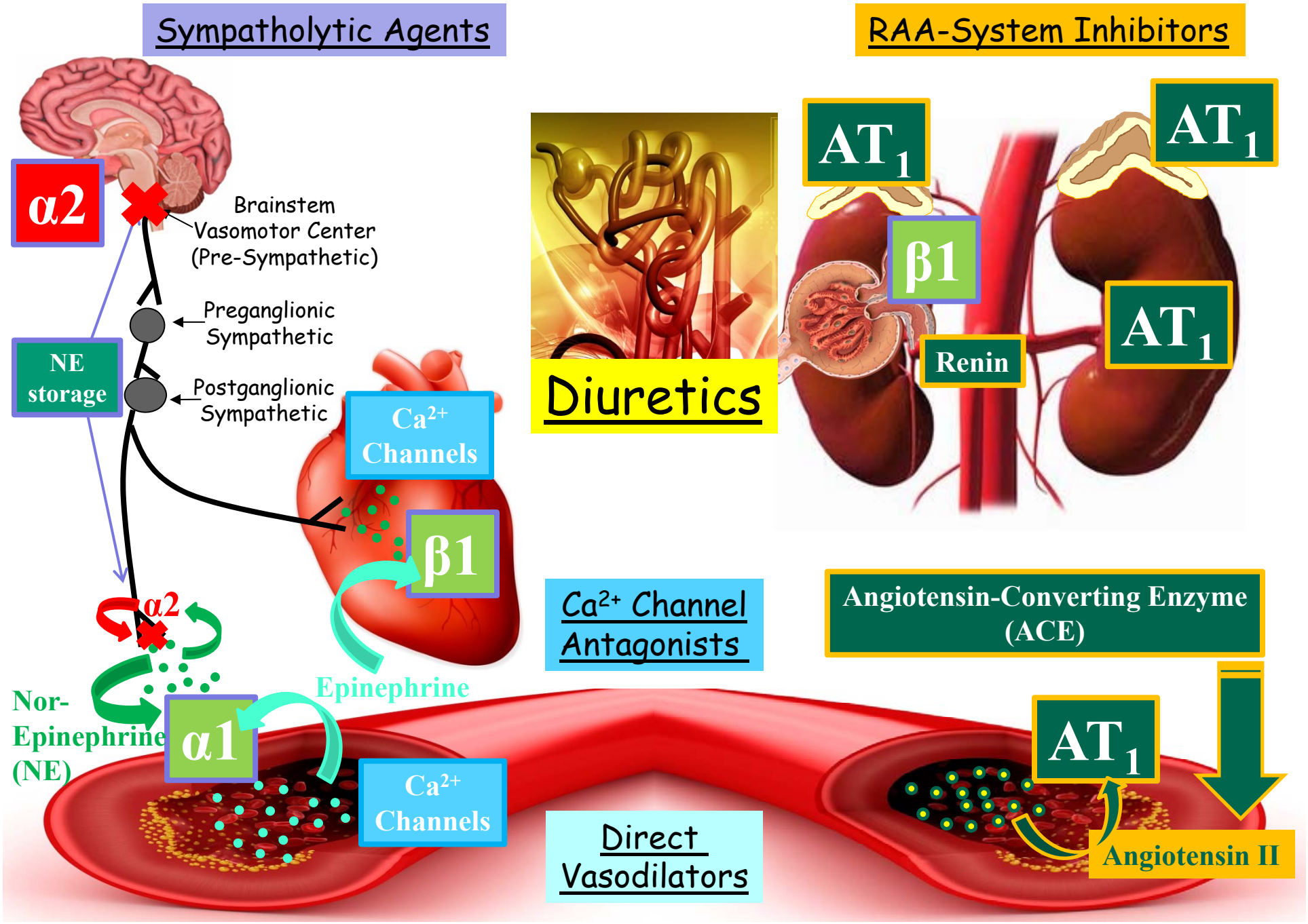
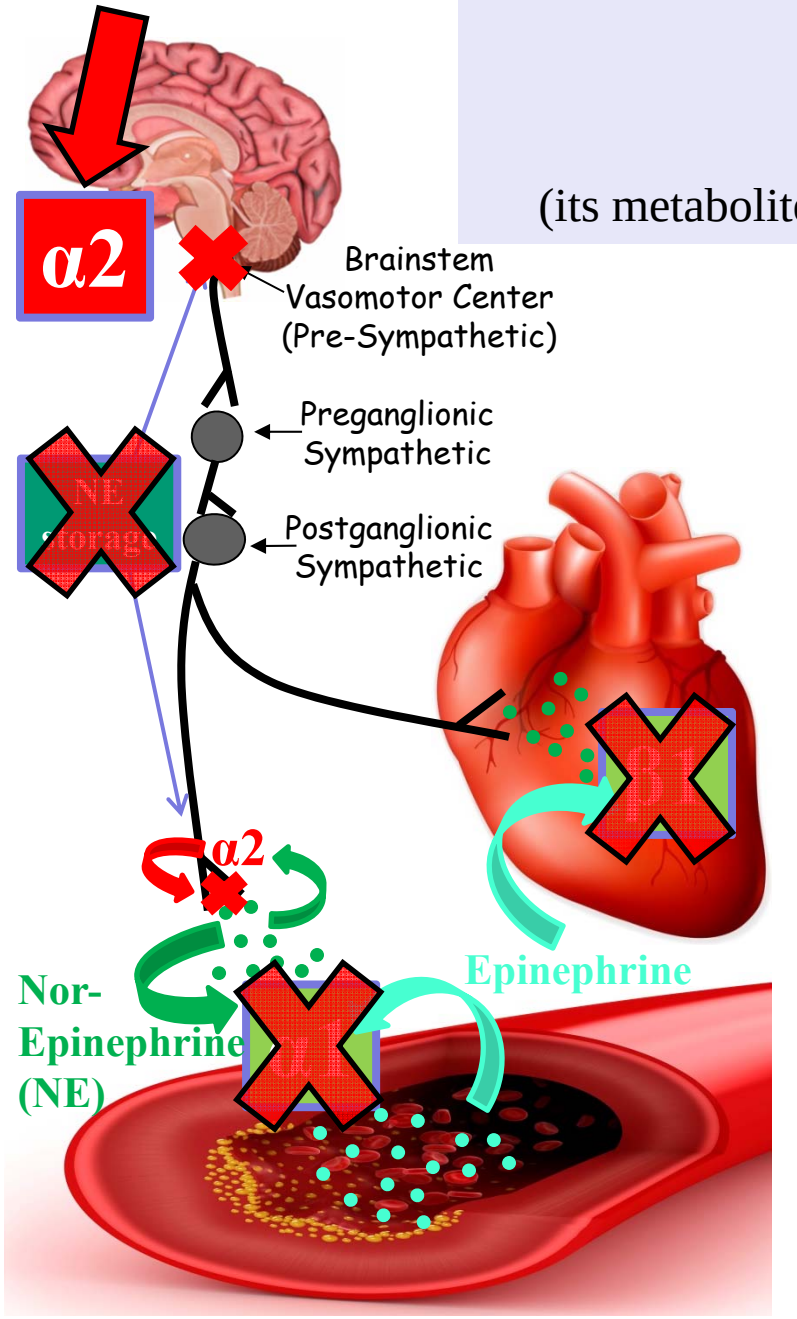
Antihypertensive Drug Targets: Overview



Sympatholytic Agents



Centrally Acting:
- Selective **α2**-adrenergic **agonist**: ***Clonidine***
- Adrenergic neuron inhibitor: ***Methyldopa***
(its metabolite replaces central NE and likely activates **α2** receptors)

Centrally and Peripherally Acting:
- NE-depleting agent: ***Reserpine***

- **α**-adrenergic **antagonists** (alpha-blockers): ***Phentolamine***

- Selective **α1**-adrenergic **antagonists**: ***Prazosin***

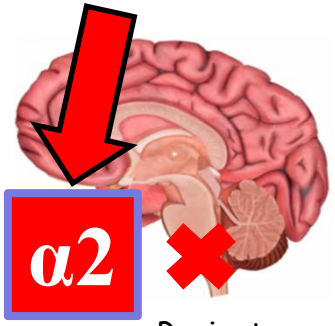
- **β**-adrenergic **antagonists** (beta-blockers): *Propranolol*, ***Bisoprolol***

- **β-antagonists** with **α1-antagonist** activity: ***Labetalol***

Sympatholytic Agents: Centrally Acting

Mechanism of Action:

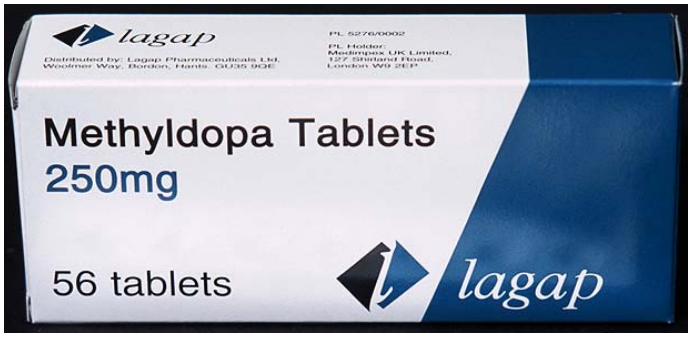
Activation of alpha-2-adrenergic receptors in the Brainstem Vasomotor Center ⇒ inhibition of pre-sympathetic, preganglionic and postganglionic sympathetic neurons ⇒ ↓ norepinephrine release from postganglionic neurons ⇒ vasodilation ⇒ ↓ vascular resistance



Brainstem Vasomotor Center (Pre-Sympathetic)

Indications:

Methyldopa is used for management of **Pregnancy-induced Hypertension**
(WHO Model List of Essential Medicines)

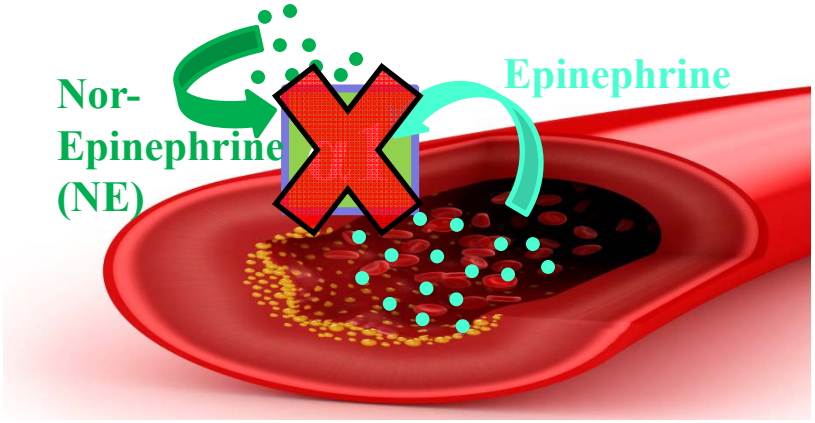


Dental Implications:

Centrally-acting sympatholytic agents cause Xerostomia (dry mouth).

Sympatholytic Agents: α-Adrenergic Receptor Antagonists

Mechanism of Action:
Blockade of alpha-adrenergic receptors
in smooth m. of arteriolar resistance vessels and veins
⇒ vasodilation ⇒ ↓ vascular resistance

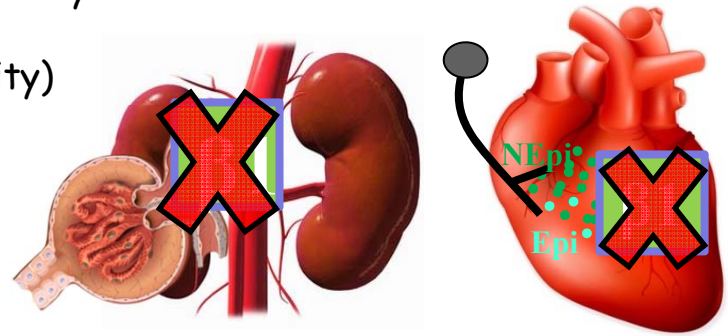


Indications:
In conjunction with other antihypertensive agents
(e.g., diuretics)

Dental Implications:
Phentolamine (OraVerse) to reverse or shorten the duration of soft-tissue anesthesia by antagonizing the vasoconstricting effect of sympathomimetics (alpha-agonists, e.g., Epinephrine) that are applied with local anesthetics.

Sympatholytic Agents: β-Adrenergic Receptor Antagonists

Mechanism of Action:
Blockade of β-adrenergic receptor signaling. The blood pressure-lowering effect of beta-blockers is not completely understood:
↓ Renin secretion,
↓ Cardiac Output (↓ HR/Contractility)



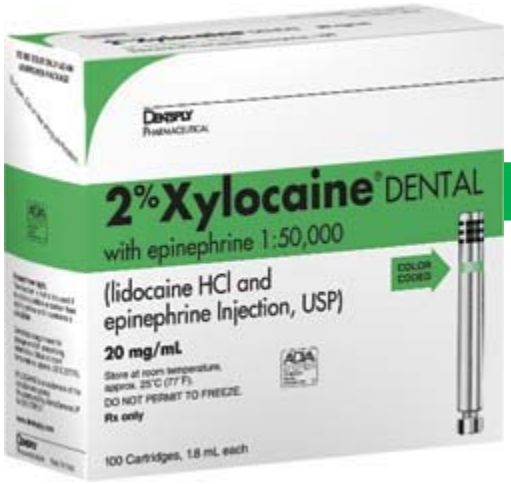
Indications:
- Hypertension, Exertional Angina, Congestive heart failure (↓ mortality)
- Arrhythmias (e.g., prevention of arrhythmias triggered by emotional stress)

Side effects / Contraindications:
- Life-threatening bronchoconstriction / Asthma
- Altered sensitivity to Insulin (↑risk of hypoglycemia) / Diabetes
- *Abrupt discontinuation may cause Sudden Death and exacerbate Angina*

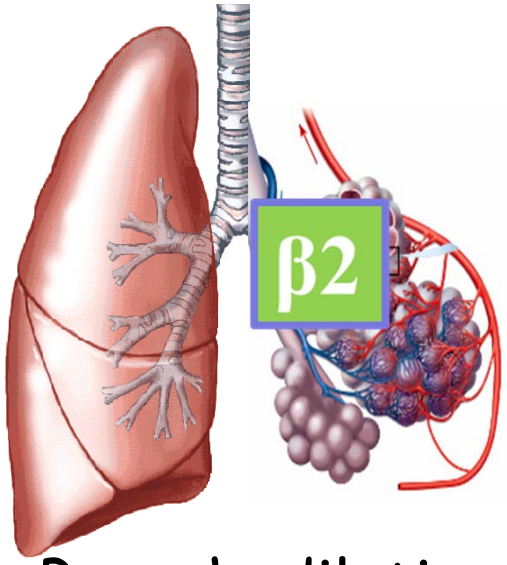
Dental Implications:
- **NSAIDs** can blunt antihypertensive effects of β-blockers

- **Epinephrine (in local anesthetics) can severely rise blood pressure (⇒ reflex bradycardia) in patients on non-selective β-antagonists:**
  Epi causes severe systemic vasoconstriction (*via* α-adrenoceptors), when applied intravascularly in the absence of functional β2 receptors (blocked by non-selective β-blockers) whose normal action is vasodilatory.

Dangerous Interactions of Epinephrine in Local Anesthetics with Non-Selective Beta-Blockers (β1/β2)

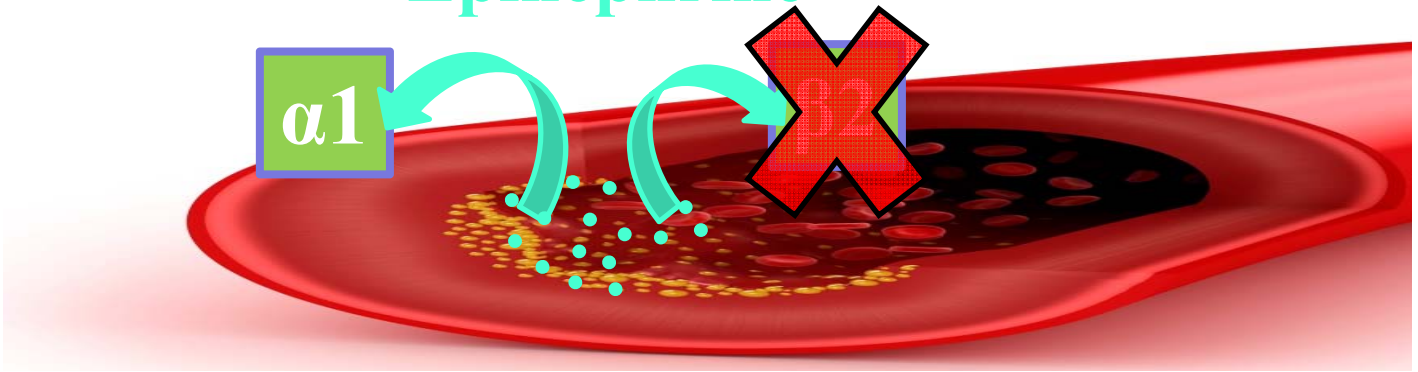


Non-selective β1/β2 antagonist



Bronchodilation

Epinephrine



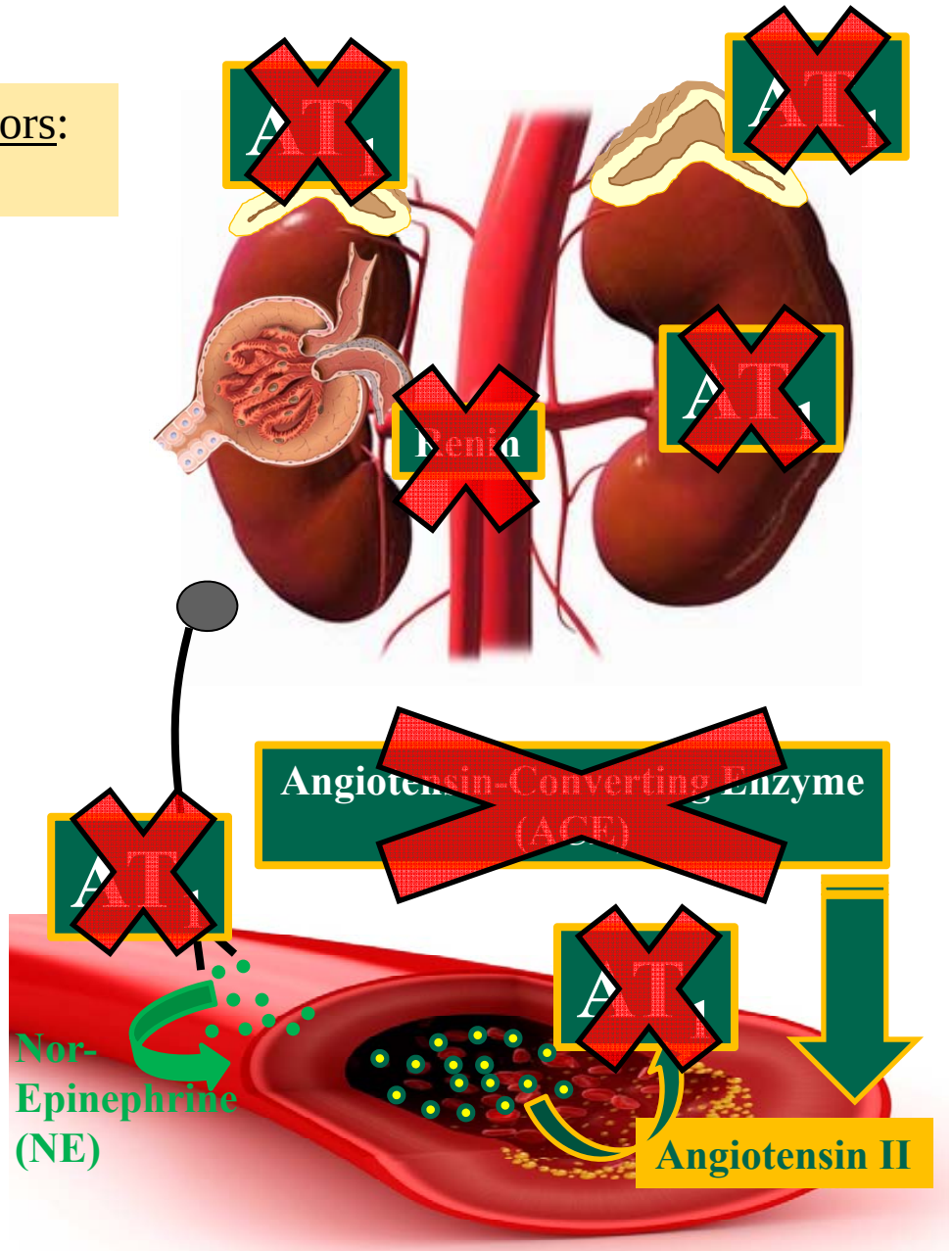
Vasoconstriction Vasodilation

Renin-Angiotensin-Aldosterone (RAA)-System Inhibitors

Angiotensin-Converting Enzyme (ACE) Inhibitors:
Captopril, ***Enalapril***, *Ramipril*

Angiotensin II Receptor (AT_1) Antagonists:
Losartan, *Valsartan*

Direct Renin Inhibitors:
Aliskiren



RAA-System Inhibitors: ACE Inhibitors

Mechanism of Action:

Blockade of Angiotensin-Converting Enzyme (ACE):

⇒ ↓ conversion of Angiotensin I to Angiotensin II ⇒
↓ Angiotensin II ⇒
↓ systemic vascular resistance & ↓ Aldosterone release
⇒ ↓ Blood Pressure & ↑ Natriuresis (⇒ ↑ Diuresis)

The blood pressure-lowering effect of ACE inhibitors is potentiated by ↓ Na^+ and by diuretics, which ↑ renin release.

Indications:

- Hypertension (except Primary Aldosteronism)
- Acute Myocardial Infarction, Coronary Artery Disease
- Diabetes Mellitus (renoprotective)

Side effects / Contraindications:

- Fetal pathology (fetal hypotension) / **Pregnancy**
- **Angioedema** (swelling in the nose, mouth, throat, **larynx, glottis**, lips)
- Acute renal failure

Dental Implications:

- NSAIDs blunt the hypotensive effect of ACE inhibitors
- Triple therapy with an NSAID, plus diuretic and an ACE inhibitor (e.g. Enalapril) may lead to acute renal failure (nephrotoxicity)

RAA-System Inhibitors: AT_1 Antagonists

Mechanism of Action:

Blockade of the Angiotensin II Receptor Type 1 (AT_1):

⇒ ↓ systemic vascular resistance, ↓ Aldosterone release,
↓ catecholamine release (adrenal medulla & sympathetic nn.)

⇒ ↓ Blood Pressure & ↑ Natriuresis (⇒ ↑ Diuresis)

AT_1 antagonists enhance the blood pressure-lowering effect of other antihypertensive drugs.

Indications:

- Hypertension (except resulting from Primary Aldosteronism)
- Heart Failure
- Acute Myocardial Infarction, Coronary Artery Disease

Side effects / Contraindications:

- Fetal pathology (potentially teratogenic) / **Pregnancy**
- Acute renal failure

Dental Implications:

- NSAIDs blunt the hypotensive effect of AT_1 receptor antagonists
- Triple therapy with an NSAID, plus diuretic and an AT_1 receptor blocker (e.g. Losartan) may lead to acute renal failure (nephrotoxicity)

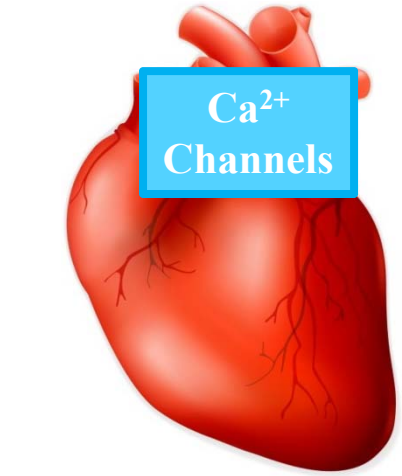
Ca^{2+} Channel Antagonists

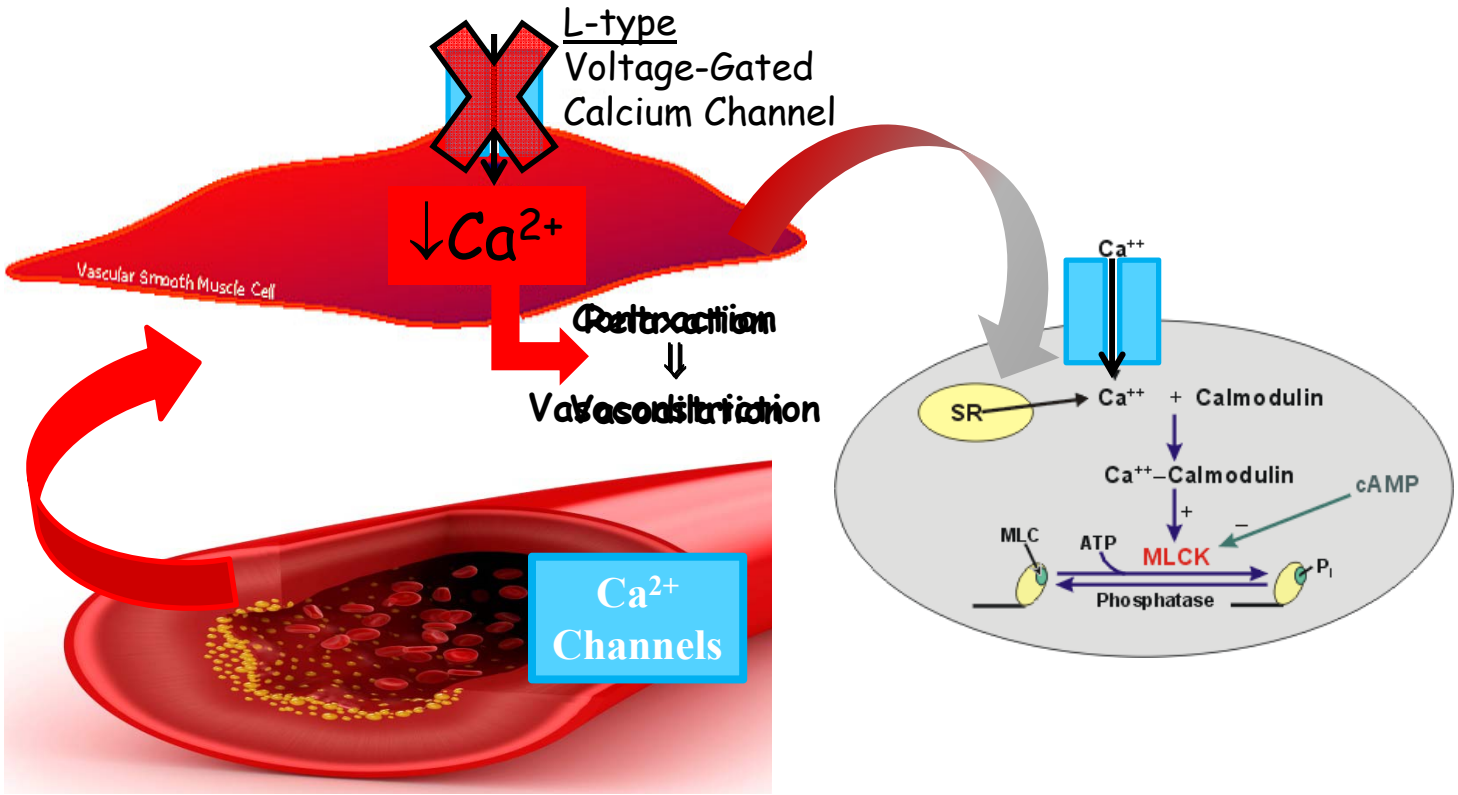
All Ca^{2+} channel antagonists approved for clinical use block <u>L-type voltage-gated calcium channels</u>

- Dihydropyridines: *Nifedipine*, ***Amlodipine***

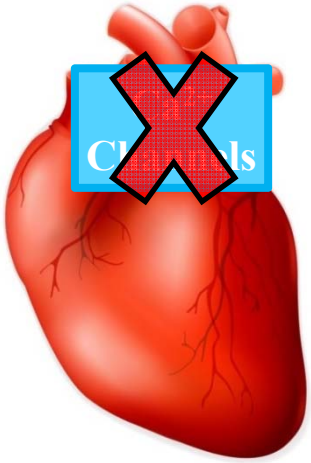
Verapamil

Diltiazem





Ca^{2+} Channel Antagonists

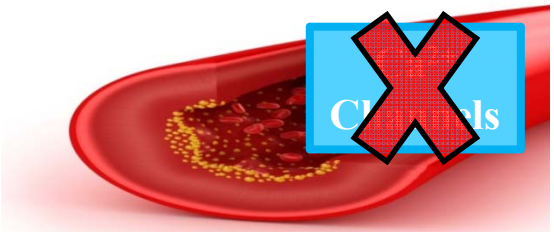


Mechanism of Action:

Blockade of L-type Ca^{2+} channels:

⇒ Arterial vasodilation ⇒ ↓ vascular resistance;

⇒ Coronary vasodilation (⇒ ↑ coronary blood flow)



Indications:

- Hypertension, Exertional and Variant (vasospastic) Angina
- Arrhythmias

Side effects:

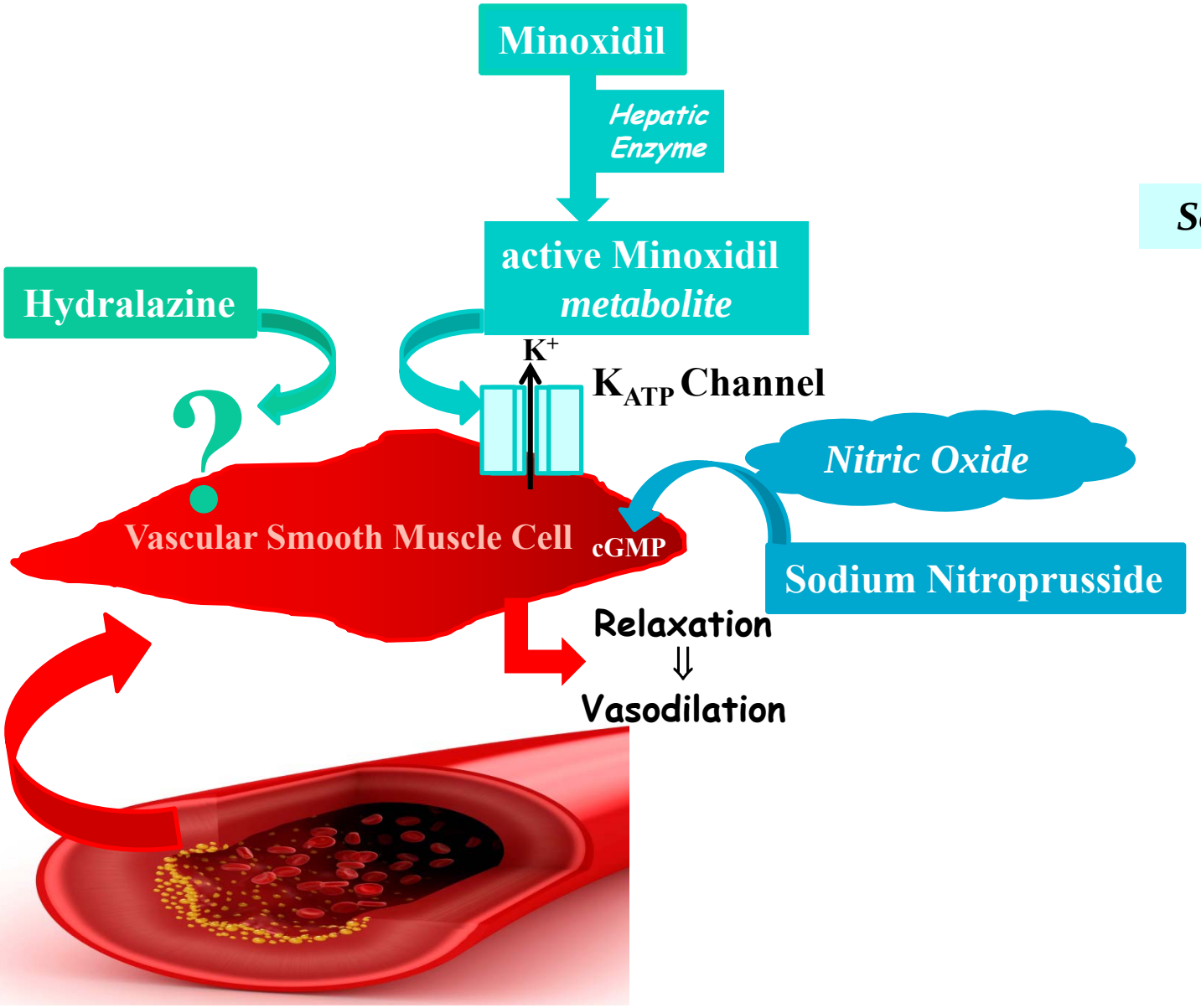
Inhibition of CYP3A4 drug-metabolizing enzyme by Verapamil.

Dental Implications:

Gingival Hyperplasia

Direct Vasodilators

"Direct" refers to: 1) direct action on vascular smooth m. leading to relaxation
2) *vasodilation* rather than *inhibition of vasoconstriction*



Hydralazine

Sodium Nitroprusside

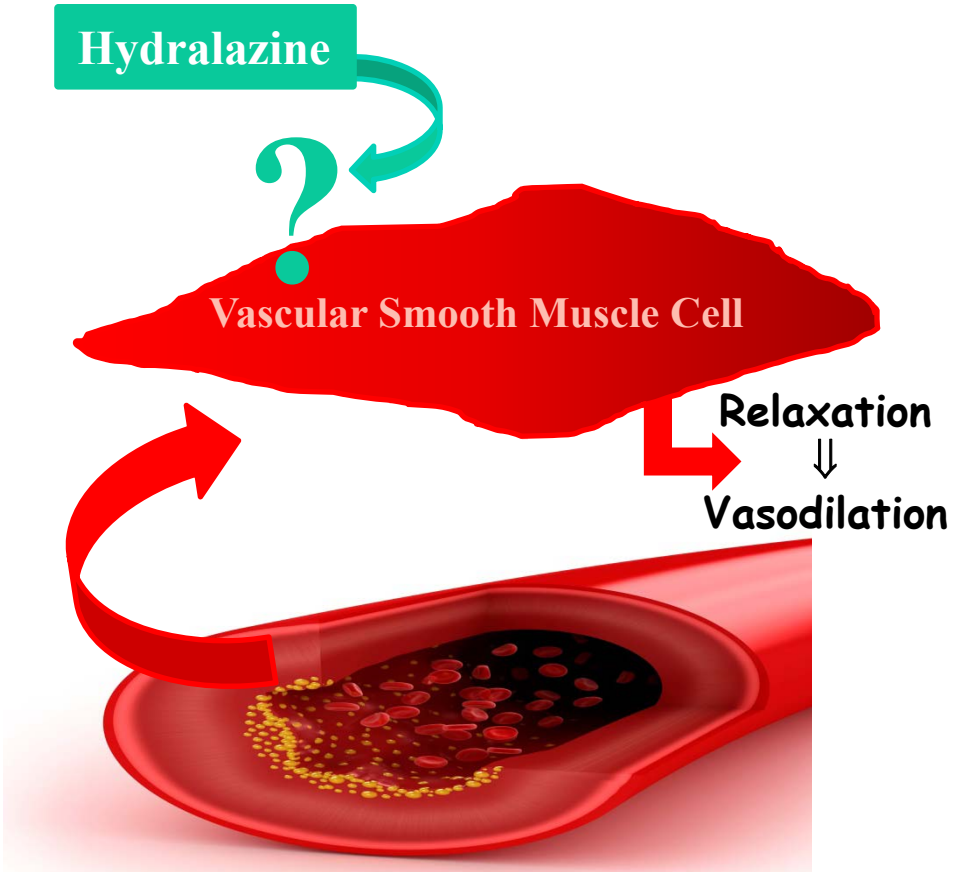
Minoxidil

Direct Vasodilators: Hydralazine

Mechanism of Action:

Unknown, leading to:

- *Arteriolar* smooth muscle relaxation ⇒ Vasodilation ⇒ ↓ Peripheral vascular resistance (coronary, cerebral, renal)
- Powerful secondary sympathetic activation (Baroreceptor unloading ⇒ ↑ HR)



Indications:

- Hypertension, severe
- Hypertensive emergencies of pregnancy (Preeclampsia)

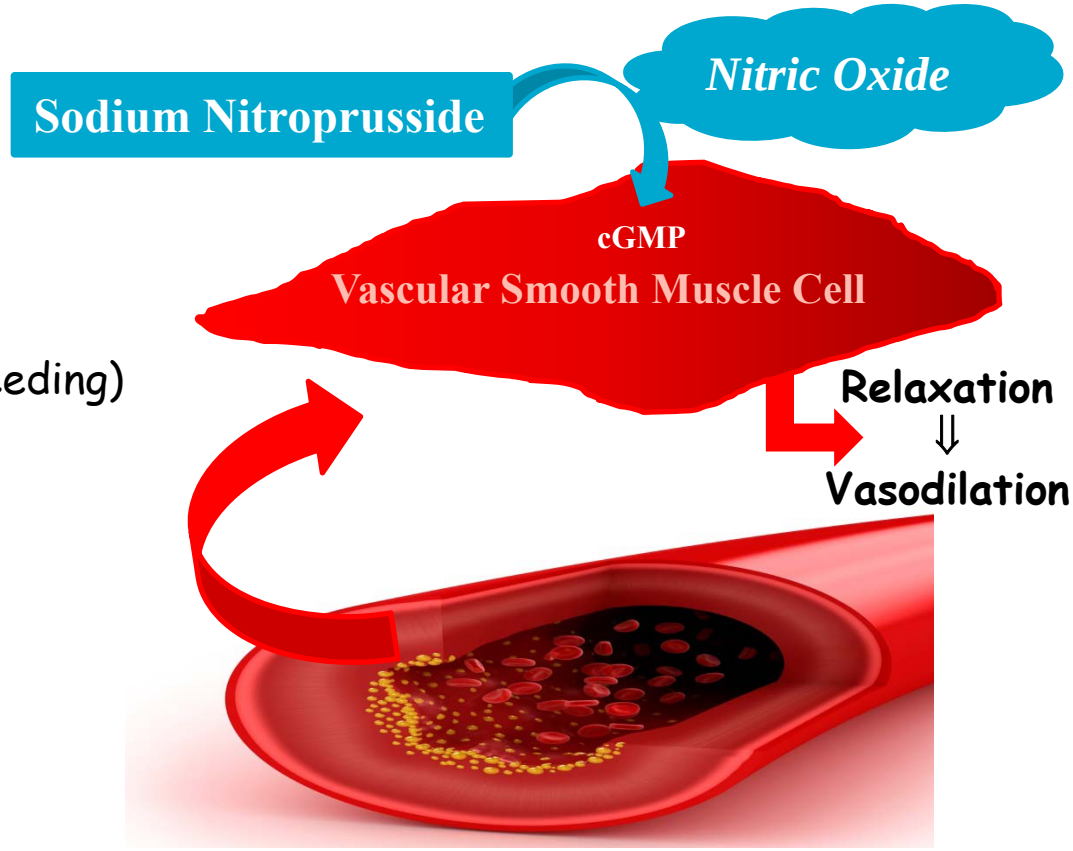
Direct Vasodilators: Sodium Nitroprusside (SNP)

Mechanism of Action:

Release of nitric oxide (NO) from Sodium Nitroprusside ⇒ Activation of Guanylyl Cyclase ⇒ Synthesis of cyclic GMP ⇒ Activation of Protein Kinase G and other kinases ⇒ Smooth muscle Relaxation *in Arterioles and Venules* ⇒ Vasodilation ⇒ ↓ Peripheral vascular resistance

Indications:

- Hypertensive emergencies
- Surgeries
  (short-term reduction in BP to ↓ bleeding)



Direct Vasodilators: Minoxidil

Mechanism of Action:

Minoxidil *is not active* (Prodrug) until metabolized (Liver)
Opening of the ATP-modulated potassium channel (K_{ATP}) ⇒ K^+ efflux ⇒
Hyperpolarization ⇒ *Arteriolar* smooth m. relaxation ⇒ Vasodilation ⇒
↓ Peripheral vascular resistance

Indications:

Hypertension, severe and poorly responding to other medication

Side effects:

Hypertrichosis (excessive hair growth)