VASODILATORS

- Work directly on arterial blood vessels, or veins.
- Actions not antagonized by known blockers.
- Reduce peripheral resistance, which will elicit compensatory mechanisms leading to tolerance, resistance, or pseudo resistance.
- Usually, other drugs are combined with vasodilators to avoid or counteract this problem.

Compensatory responses to vasodilators

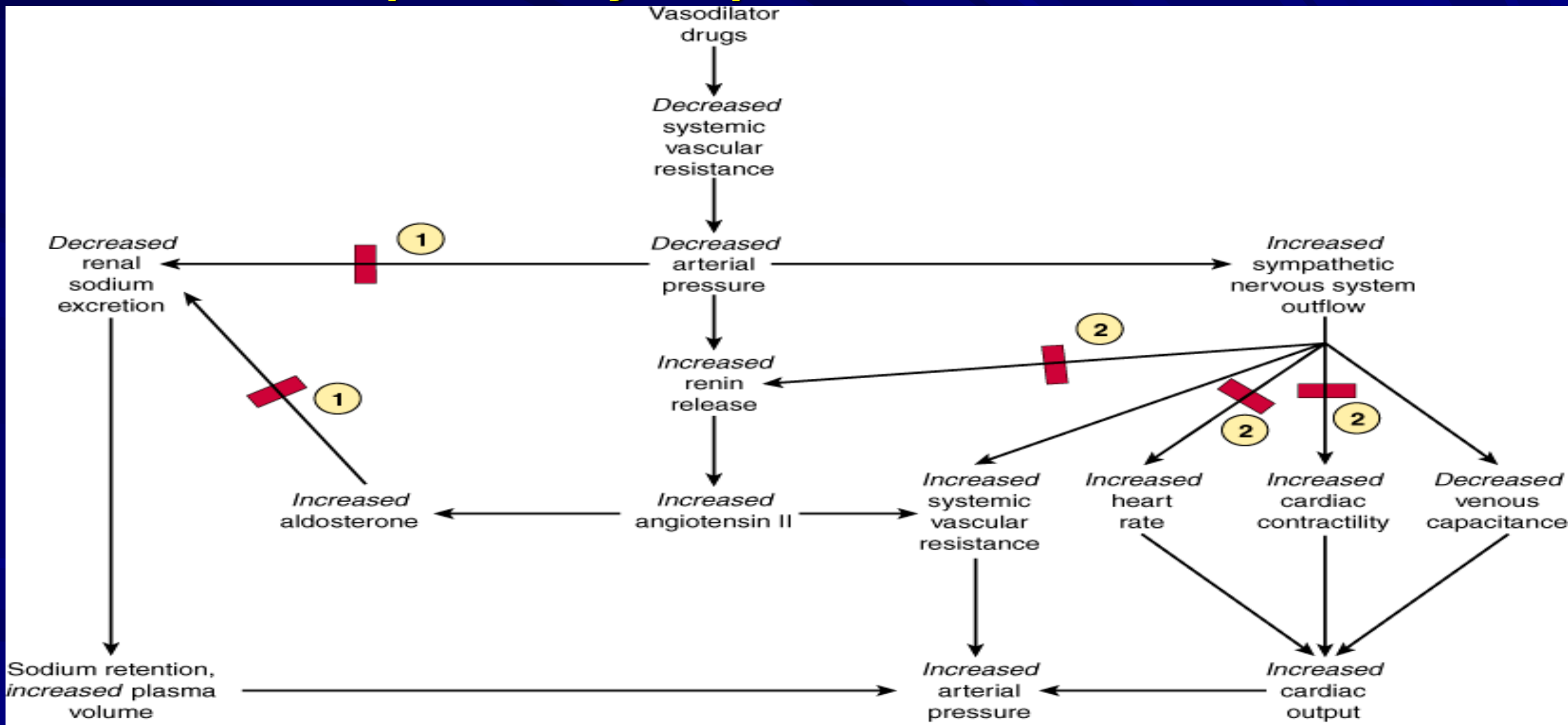


TABLE 11–3 Mechanisms of action of vasodilators.

Mechanism	Examples
Release of nitric oxide from drug or endothelium	Nitroprusside, hydralazine, nitrates,[1] histamine, acetylcholine
Reduction of calcium influx	Verapamil, diltiazem, nifedipine
Hyperpolarization of smooth muscle membrane through opening of potassium channels	Minoxidil, diazoxide
Activation of dopamine receptors	Fenoldopam

VASODILATORS

Hydralazine:

- Oldest vasodilator(1950s), was withdrawn and then came back.
- Arteriolar dilator, works by release of NO.
- Tachyphylaxis (**Tolerance or Pseudo resistance**).
- Activates baroreceptor reflex.
- Metabolized by acetylation.
- Drug-induced lupus syndrome.
- Other side effects.
- Replaced by CCBs(Ca channel blockers).
- Nowadays,used in heart failure, combined with isosorbide dinitrate.

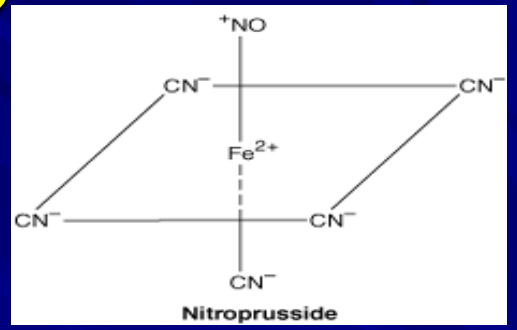
VASODILATORS

Diazoxide:

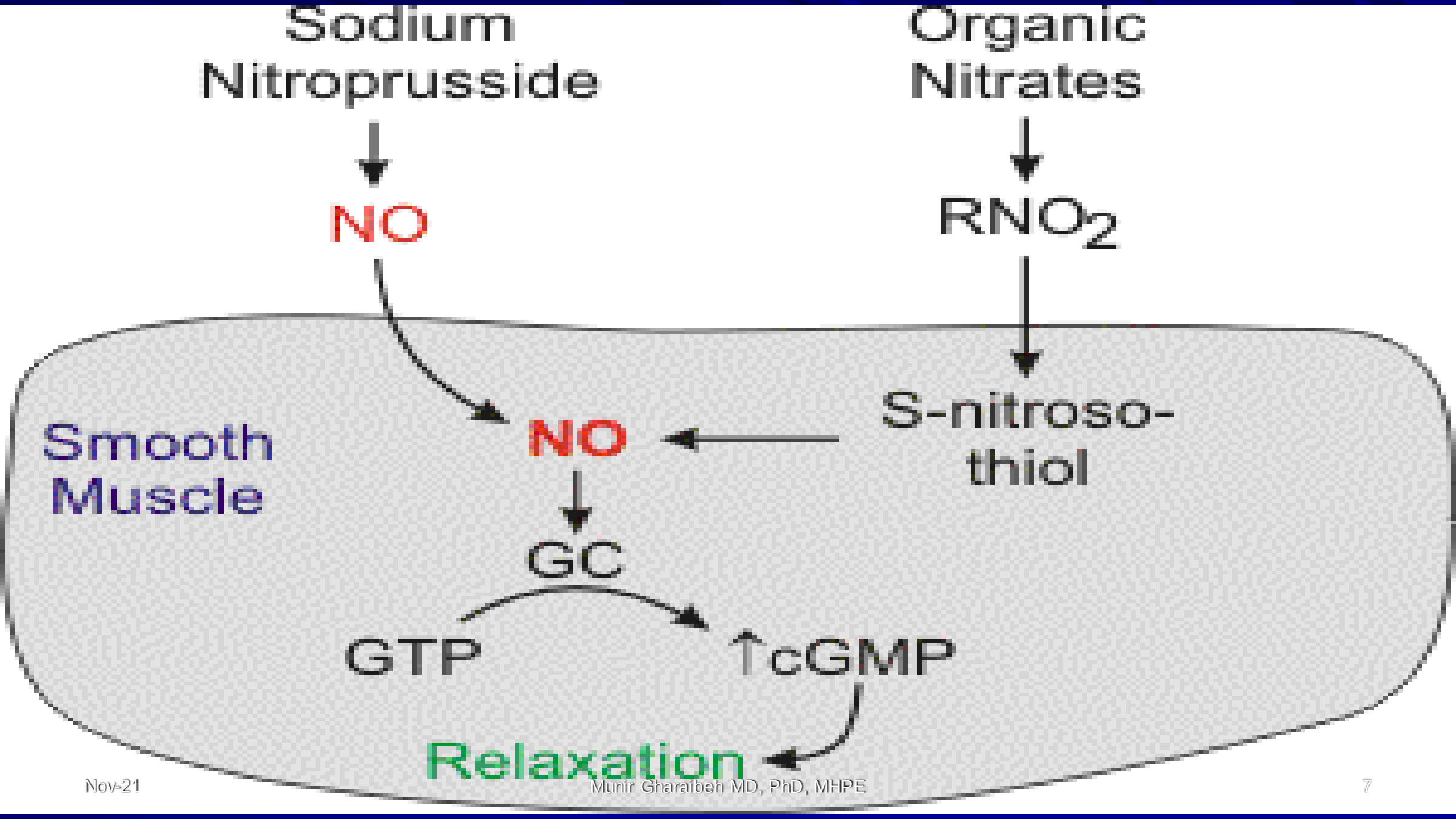
- Thiazide derivative, but not has no diuretic activity.
- Potent arterial dilator, works by opening potassium channels.
- Causes excessive hypotension.
- Used in emergencies by rapid I.V. bolus injection.
- Rapidly bound to albumin.
- Onset 10-30 seconds.
- Duration 2-4 hours.
- Does not require constant monitoring.

VASODILATORS

Sodium Nitroprusside:



- Cyanide-containing molecule.
- Useful in emergencies, during surgery, and in heart failure.
- Relaxes both arterial and venous smooth muscle, works by release of NO.
- No excessive reflex increase in cardiac output.
- Might increase C.O. if there is failure.


Sodium
Nitroprusside
Organic
Nitrates
NO
RNO2
Smooth
Muscle
NO
S-nitroso-
thiol
GC
GTP
↑cGMP
Relaxation

VASODILATORS

Sodium Nitroprusside:

- Short half life.
- Action is immediate, requires constant monitoring in ICU.
- Drug is light sensitive.
- Can elevate thiocyanate levels and disturb acid-base balance: weakness, nausea, tinnitus, flushing, lactic acidosis and anoxia.

VASODILATORS

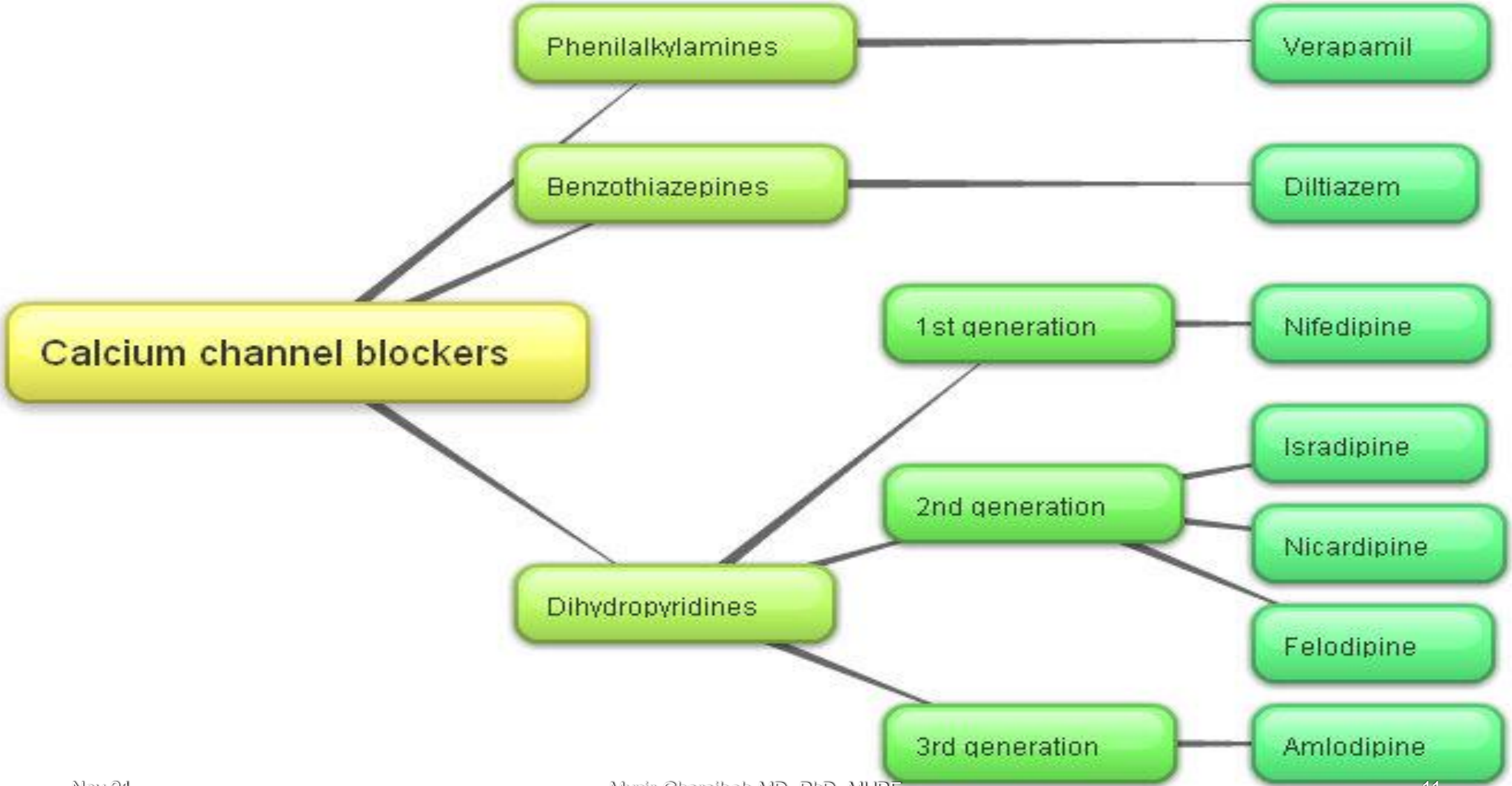
Minoxidil:

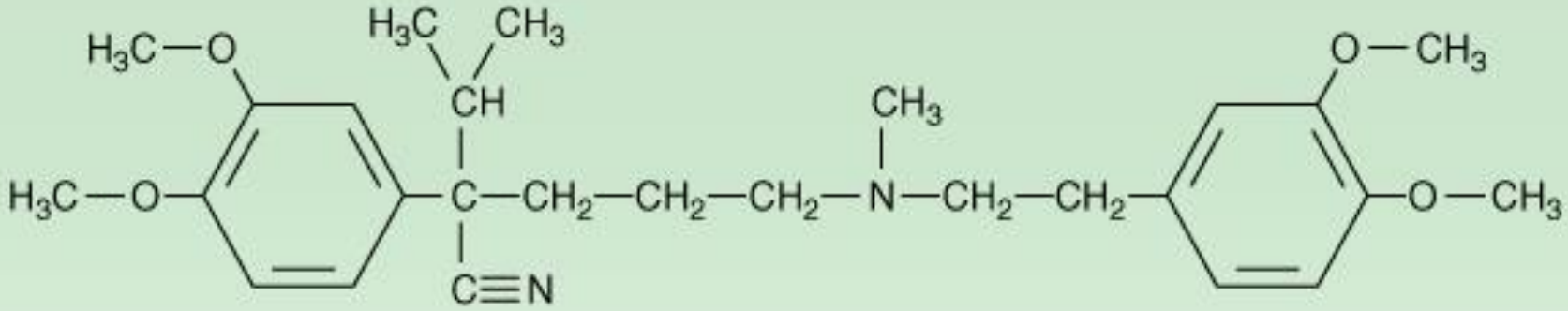
- K+ channel-opener: increases efflux leading to hyperpolarization.
- Prolonged arterial relaxation.
- Superior to hydralazine.
- For severe intractable hypertension, or renal insufficiency, usually in combination with a diuretic and β blocker.
- Hypertrichosis, so useful for baldness.
- Pericarditis.

VASODILATORS

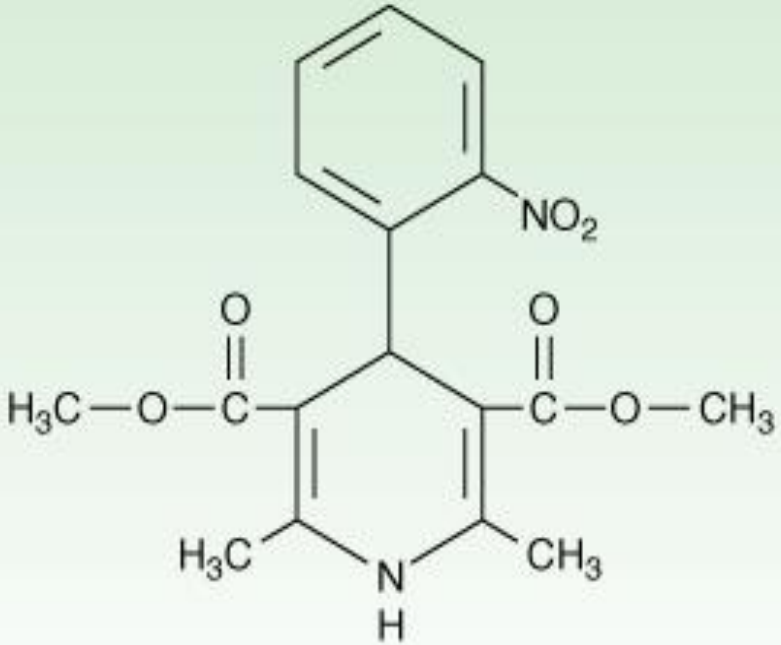
Fenoldopam:

- 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.

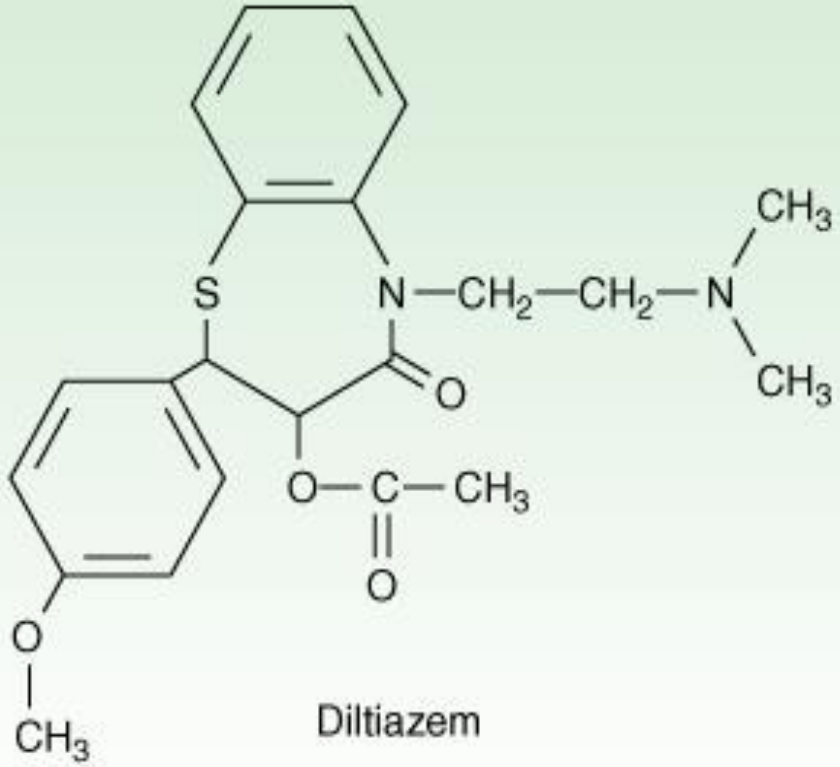

Calcium channel blockers
Phenilalkylamines
Verapamil
Benzothiazepines
Diltiazem
Dihydropyridines
1st generation
Nifedipine
2nd generation
Isradipine
Nicardipine
Felodipine
3rd generation
Amlodipine



Verapamil

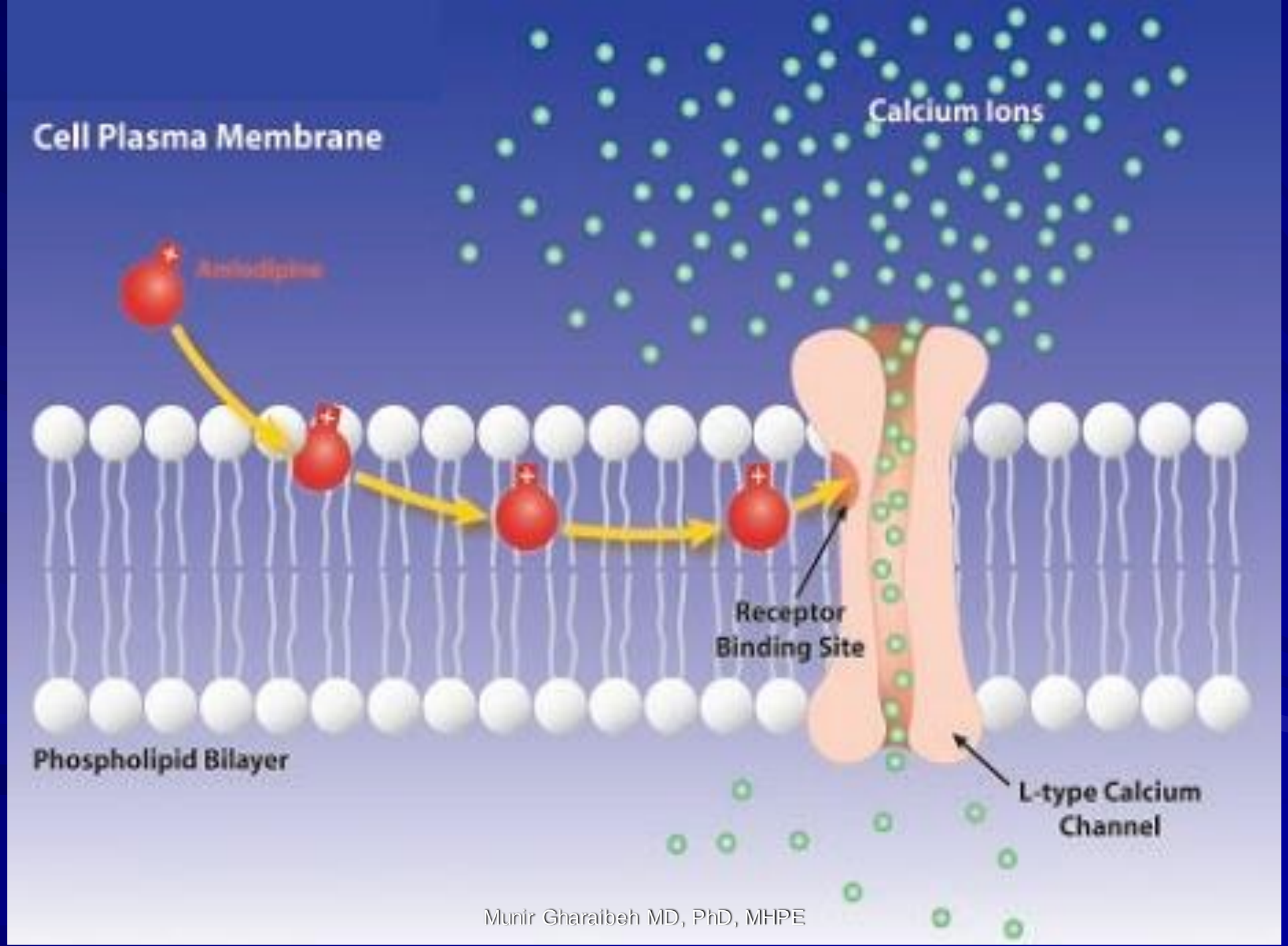


Nifedipine



Diltiazem

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com


Cell Plasma Membrane
Calcium Ions
Amlodipine
Receptor
Binding Site
Phospholipid Bilayer
L-type Calcium
Channel

Properties of Several Recognized Voltage-Activated Calcium Channels.

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, -aga-IIIA

Calcium Channel Blockers

- Primarily act to reduce PVR, aided by at least an initial diuretic effect, especially with the short-acting DHPs.
- Effective in the elderly.
- More effective than others, in protection against stroke.
- Equally effective in black and nonblack patients.

Calcium Channel Blockers

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

Calcium Channel Blockers

- **Side Effects:**
- Hypotension.
- Headache, dizziness.
  - Flushing, especially with short acting agents.
- Peripheral edema.
- Do not cause metabolic disturbances.

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

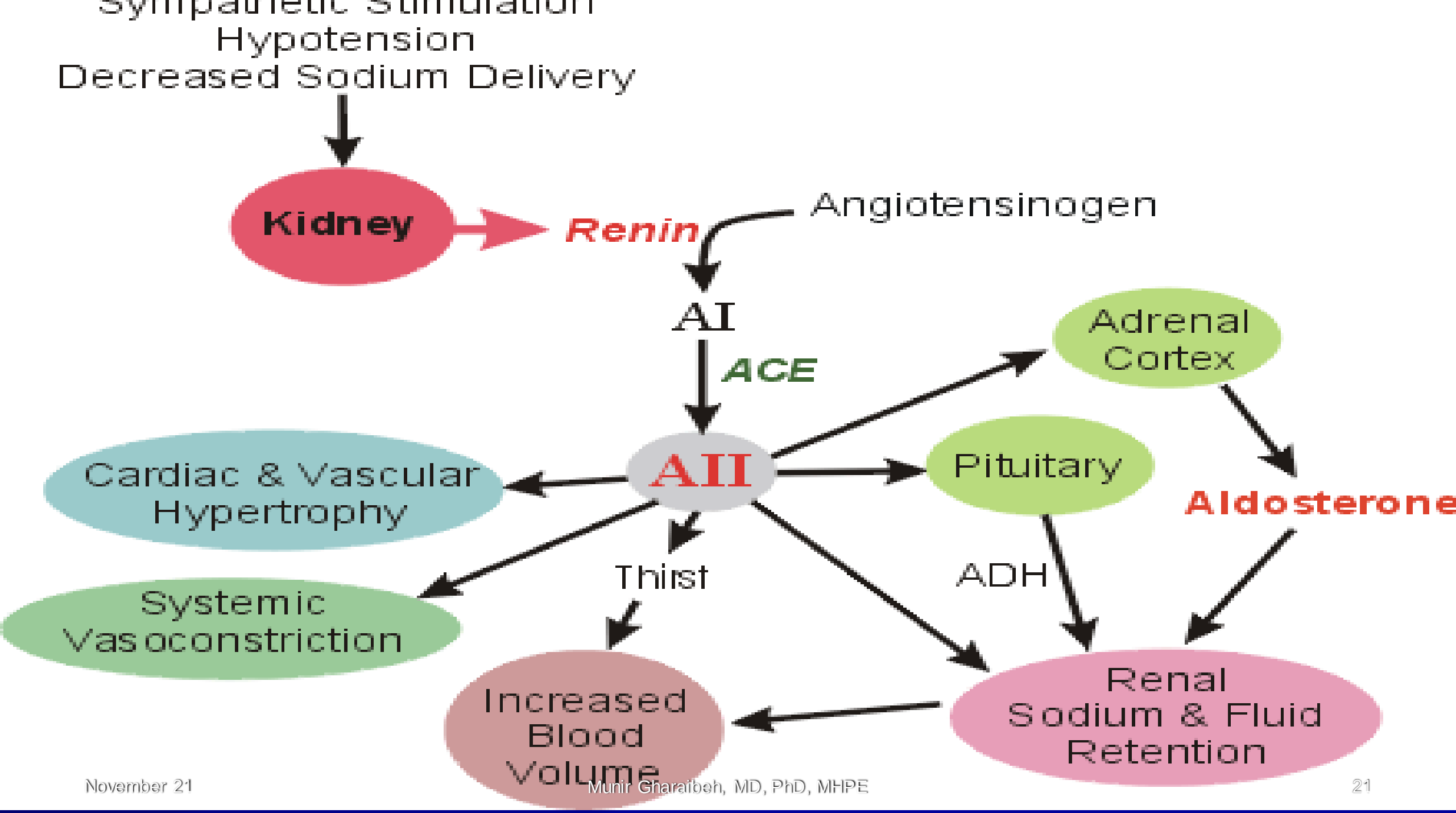
Angiotensin - Converting Enzyme Inhibitors (ACEI)

- Have many applications nowadays, for hypertension and other diseases.
- Inhibit ACE in the lungs.
- Also inhibit kinin metabolism.

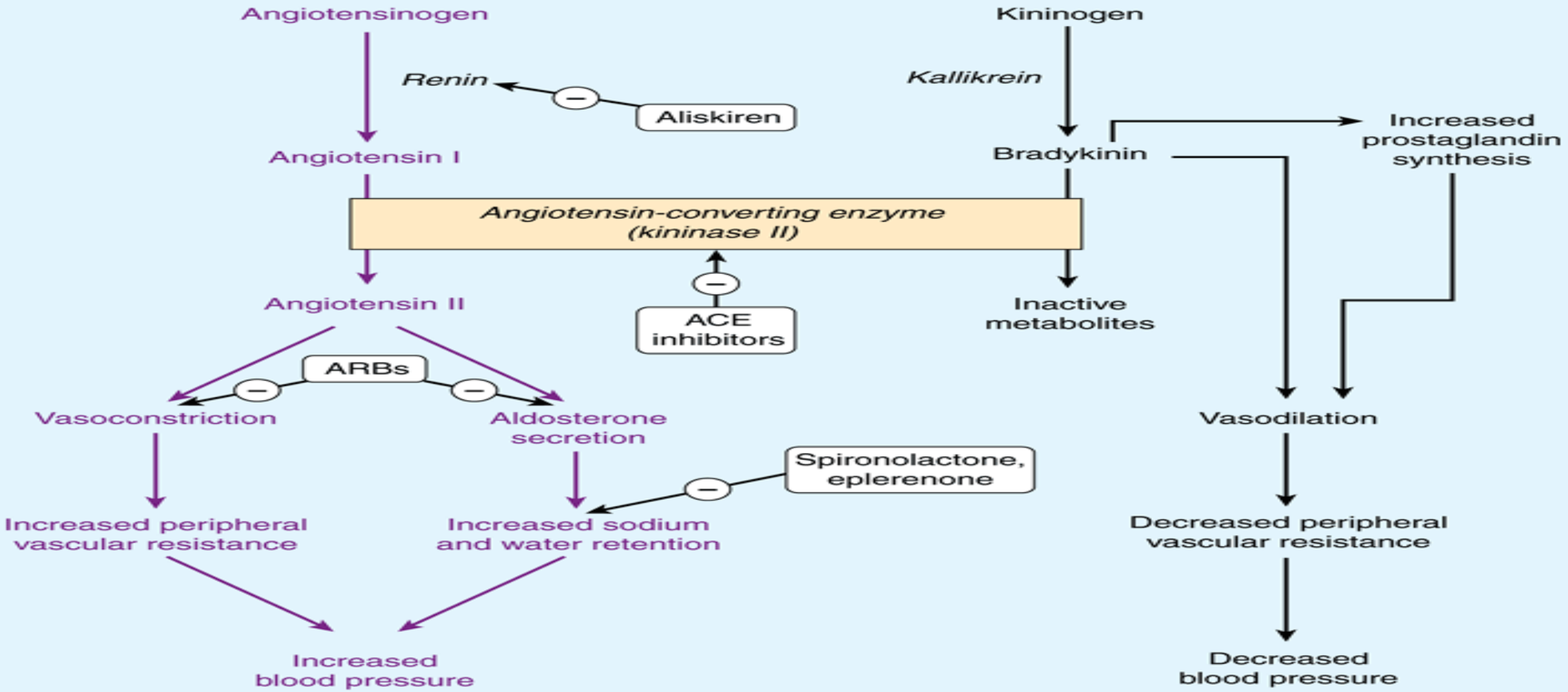
Angiotensin - Converting Enzyme Inhibitors (ACEI)

Angiotensin II:

- Potent vasoconstrictor by itself.
- Facilitates release of NE.
- Central actions to increase BP.
- Promotes release of aldosterone.
- Regulates tubular function.
- Regulates intra-renal blood flow.


Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery
Kidney
Renin
Angiotensinogen
AI
ACE
Adrenal Cortex
Cardiac & Vascular Hypertrophy
AII
Pituitary
Aldosterone
Thirst
ADH
Systemic Vasoconstriction
Increased Blood Volume
Renal Sodium & Fluid Retention

Sites of action of drugs that interfere with the renin-angiotensin-aldosterone system.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 11th edition: www.accessmedicine.com

Cardiorenal Effects of ACE Inhibitors

- Vasodilation (arterial & venous):
  - reduce arterial & venous pressure.
  - reduce ventricular afterload and preload.
- Decrease blood volume:
  - natriuretic.
  - diuretic.
- Depress sympathetic activity.
- Inhibit cardiac and vascular hypertrophy.

Angiotensin - Converting Enzyme Inhibitors (ACEI)

- Captopril ----------Prototype.
- Enalapril
- Quinapril
- Lisinopril.
- Benazepril
- Fosonopril

- *All are similarly effective*
- *Might differ in toxicity*

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Therapeutic Benefits:

- Effective in high-rennin hypertension (20%), HF and Ischemic Heart Disease.
- Do not increase HR.
- Useful in diabetic nephropathy by dilating efferent arterioles thus reducing intraglomerular pressure and consequently protect against progressive glomerulosclerosis.
- No need for a diuretic but a diuretic can be added.
- Can be combined with CCBs.
- Should not be combined with Beta blockers.
- No metabolic effects.
- * Contraindicated in established renal failure, pregnancy, and bilateral renal artery stenosis.

Angiotensin - Converting Enzyme Inhibitors (ACEI)

Side Effects:

Captopril is SH containing drug, so very toxic(bone marrow suppression, dysgeusia, proteinuria, allergic skin rash, fever)

- **Hypotension(*First Dose Phenomena*) especially with renovascular hypertension.**
- **K+ retention, especially in the presence of renal dysfunction or when combined with K+ sparing diuretics or ARBs.**
- **Cough(10% of patients).**
- **Angioedema.**

Angiotensin II Receptor Blockers (AT-1)

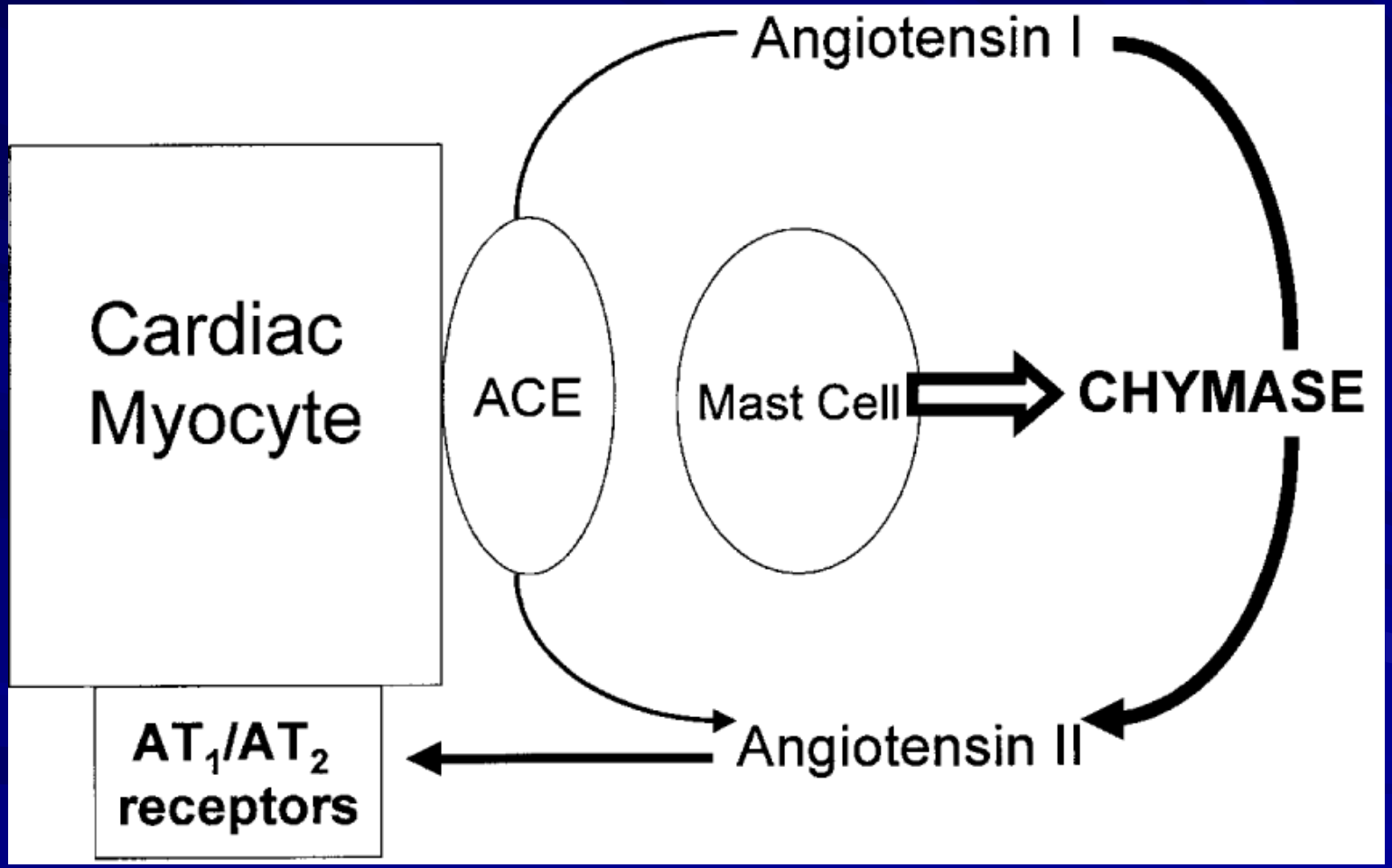
- Result in more complete inhibition of angiotensin actions, with no effects on bradykinins.
- May be only indicated when ACEI are intolerable.
- Most expensive, but fastest growing class of antihypertensive drugs.
- Free of side effects, especially cough.
- May be better than ACEI in protection against stroke (activation of AT-2 receptor facilitates collateral vessels and neuronal resistance).

Angiotensin II Receptor Blockers (AT-1)

- Losartan.
- Valsartan.
- Candesartan.
- Irbesartan.
- Telmisartan (***additional peroxisome proliferator-activated receptor "PPR "-γ agonist activity).***
- Eprosartan.

Chymase

- Long-term treatment with ACE inhibitors is often associated with so-called "***angiotensin escape,***" characterized by the return of plasma angiotensin II concentration to pretreatment levels (although the beneficial effects on blood pressure usually persist).
- This rebound generation of angiotensin II occurs through the action of the serine proteases such as chymase and cathepsin G.


Angiotensin I
Cardiac Myocyte
ACE
Mast Cell
CHYMASE
AT1/AT2 receptors
Angiotensin II

Chymase

- Vascular chymase has been implicated in the ACE-independent mechanism for local angiotensin II formation in human arteries.
- ACE-independent generation of angiotensin II plays a central role in the regulation of renal hemodynamics during the progression of diabetic nephropathy.

Chymase

The physiologic importance of chymase is uncertain, because of the presence of natural protease inhibitors in the interstitial fluid which inhibit chymase-induced angiotensin II production.

Renin Enzyme Inhibitors

- **Aliskiren:**
  - The first in the group.
  - Other better studied medications are typically recommended due to concerns of higher side effects and less evidence of benefit.

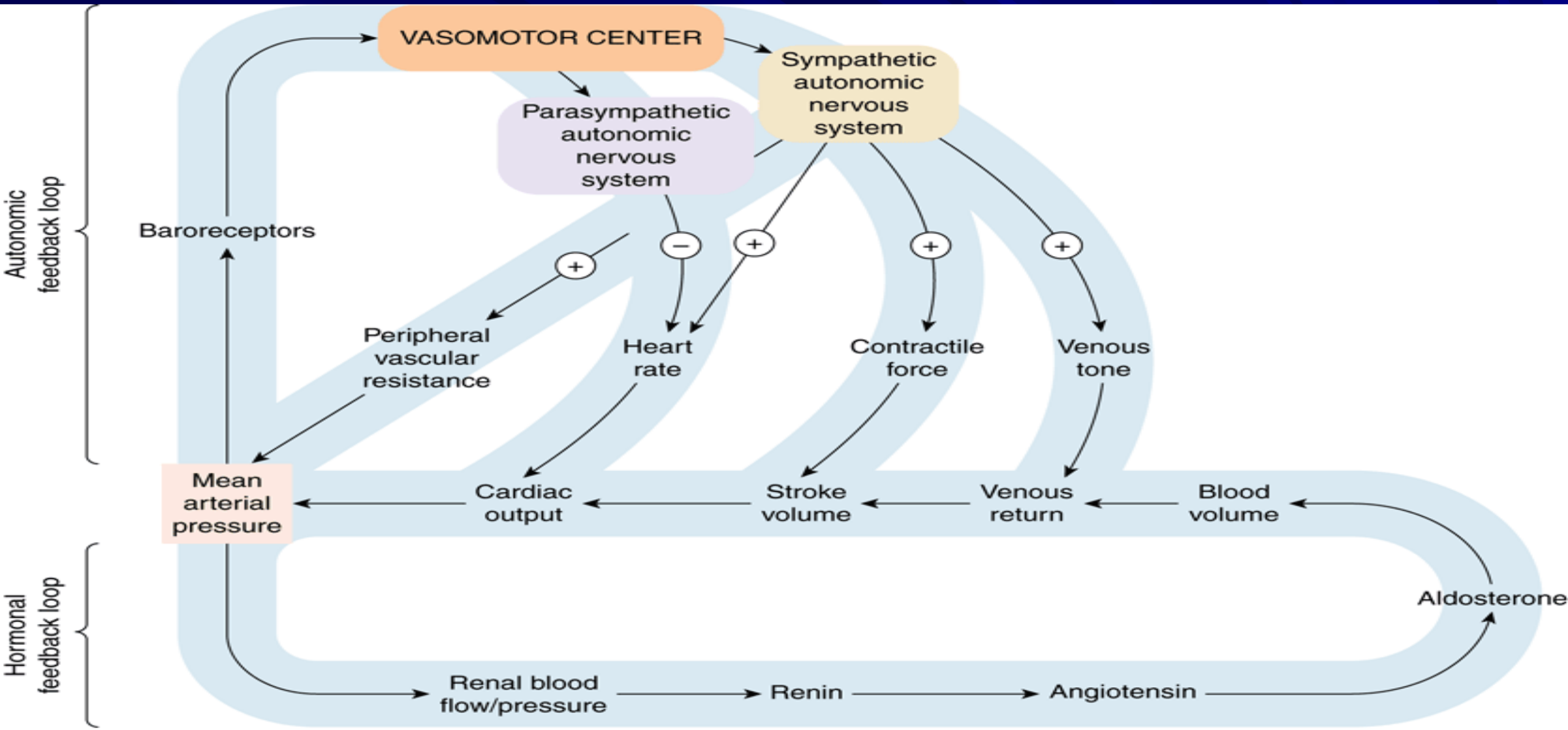
Centrally Acting Antihypertensive Drugs

Vasomotor Center:

- α Receptor activation decreases BP
- β Receptor activation increases BP

- Nucleus Tractus Solitarius
- Nucleus Ambiguus
- Rostral Ventral Medulla

Autonomic and hormonal control of cardiovascular function



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

Centrally Acting Antihypertensive Drugs

Common Properties:

- Cross BBB.
- Reduce preganglionic sympathetic activity.
- Orthostasis is unusual, due to preservation of peripheral sympathetic activity.
- CNS side effects.

Centrally Acting Antihypertensive Drugs

1. **Propranolol**
2. **Reserpine.**
3. **α- Methyl Dopa:**

Old drug, thought to work by forming a pseudo transmitter which works peripherally.

Central α agonist.

α MD-------- α MDA -------- α MNE.

Lowers BP but not CO or renal blood flow.

Can cause lactation and positive Coombs's test.

Safe in pregnancy.

Centrally Acting Antihypertensive Drugs

4. Clonidine:

- Imidazoline derivative, tried initially as a nasal decongestant.
- Central α agonist.
- I.V: Biphasic Effect: peripheral then central actions.
- Oral.
- Transdermal Patch(7 days).

Causes of Resistant Hypertension

- Improper BP measurement.
- "White Coat Hypertension".
- Noncompliance.
- Psychological stresses, secondary hypertension, sleep disorders
- Volume overload and pseudotolerance.
- Excess sodium intake
- Volume retention from kidney disease.
- Inadequate diuretic therapy.

Causes of Resistant Hypertension

- Inadequate doses.
- Inappropriate combinations .
- NSAID; cyclooxygenase 2 inhibitors.
- Cocaine, amphetamines, other illicit drugs.
- Sympathomimetics, e.g. decongestants, anorectics

Causes of Resistant Hypertension

- Oral contraceptives
- Corticosteroids
- Cyclosporine
- Erythropoietin
- Licorice (including some chewing tobacco).
- Excess alcohol intake.

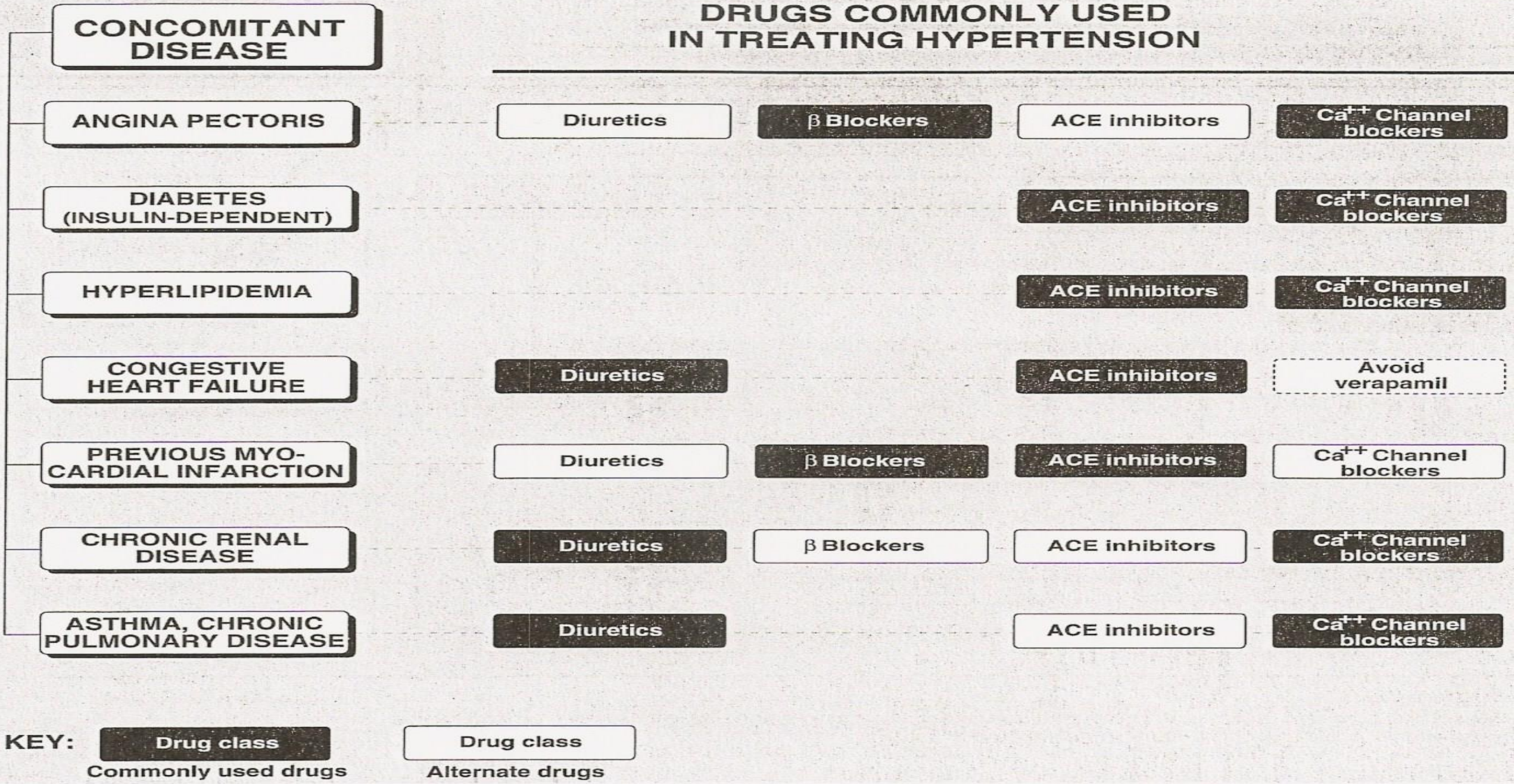


Figure 19.4
Treatment of hypertension in patients with concomitant diseases.