Anti-hypertensives

Dr. Alia Shatanawi

Blood Pressure

- Blood pressure is the force that circulating blood exerts on walls of arteries.
- Two blood pressures are measured, systolic blood pressure and diastolic blood pressure.
- Systole occurs while the heart contracts. Diastole occurs while the heart rests between beats.
- Blood pressure=Cardiac output x Peripheral vascular resistance(CO x PVR)

Definition: Hypertension

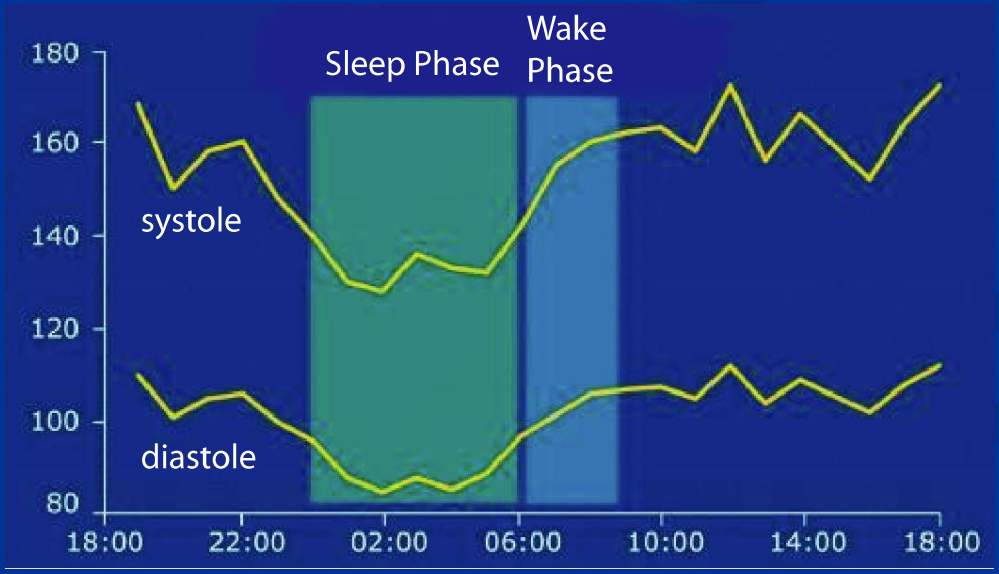
Elevation of arterial blood pressure above (130/80\) mm Hg

Primary (Essential) Hypertension

- 90% of cases have no specific cause
- High blood pressure associated with increased peripheral vascular resistance
- Multifactorial abnormalities
  - Genetics
  - Stress
  - Environment and diet (Smoking/High salt diet)

Clinical Presentation

- Most times asymptomatic (a 'silent' disease)
- Headache
  - Coincides with morning surge in BP
  - Circadian variation of blood pressure



Classification of Hypertension

Blood Pressure Categories

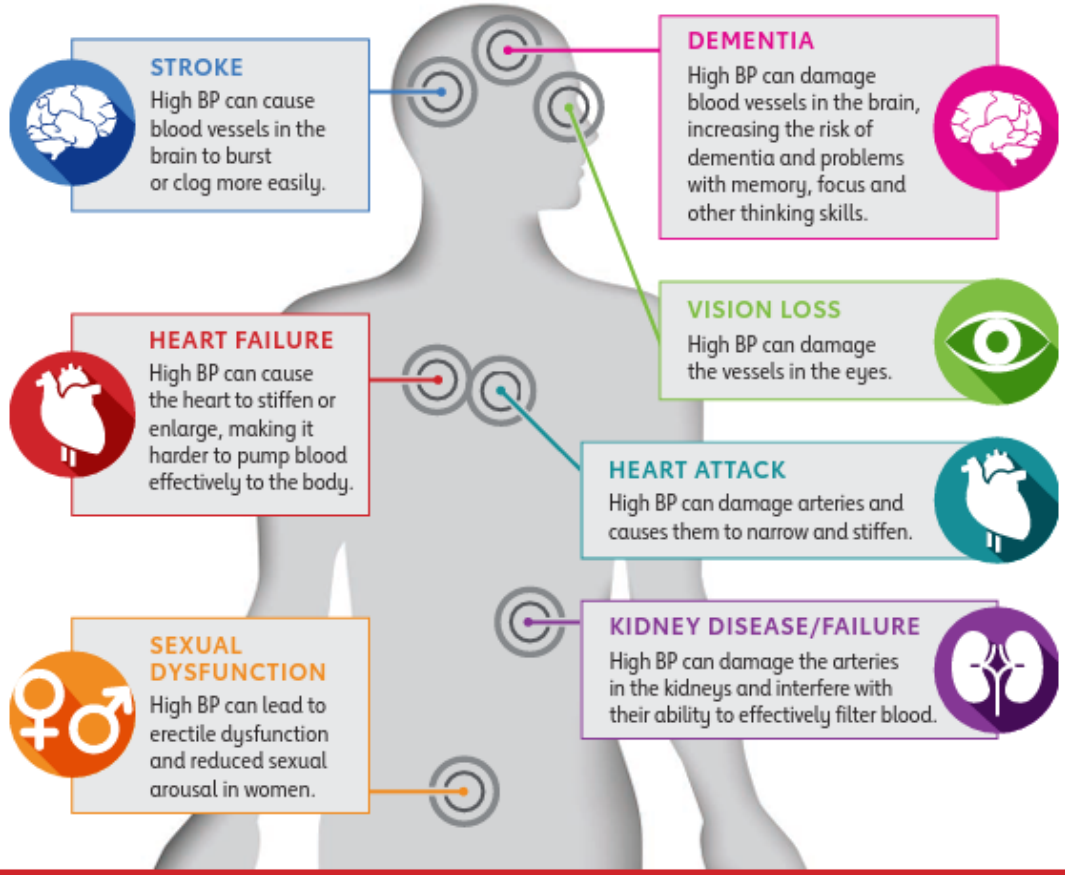
American Heart Association | American Stroke Association

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

American Heart Association.

Consequences of High Blood Pressure

High blood pressure (BP) can cause other health problems, like:

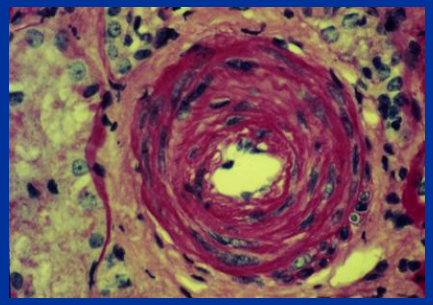


A healthy blood pressure helps protect your kidneys, heart and your body's ability to use energy (metabolic health). Check your blood pressure today. Learn more at **heart.org/BP**.

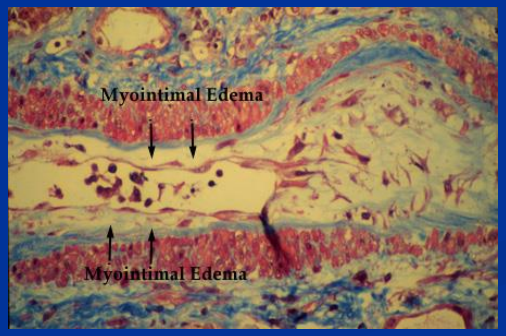
Uncomplicated to Complicated/Malignant Hypertension': End-Organ Damage

- Chronic hypertension alters blood vessel/cardiac muscle structure
  - Decreases blood vessel diameter
  - Diminishes distribution of oxygenated blood to tissue targets
  - Cardiac hypertrophy
  - High blood pressure ultimately leads to major end-organ damage i.e., heart attack, stroke, renal failure
- Need to diagnose and treat hypertension early

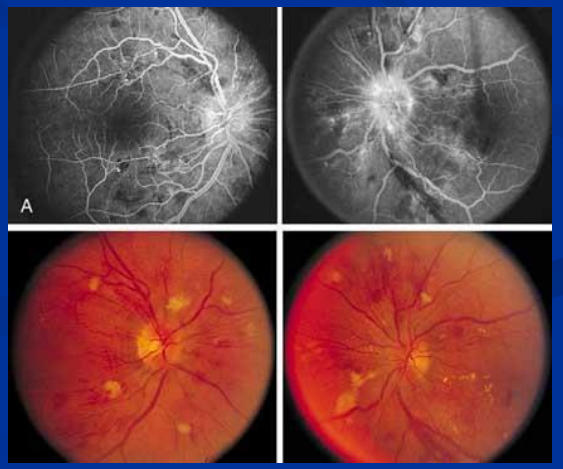
vascular hyperplasia



edema



papilledema



Treating Hypertension

Lifestyle Modification: Alterations in diet and exercise may reduce blood pressure in some patients.

Drug Treatments: There are many antihypertensive drugs, commonly used in combination therapy.

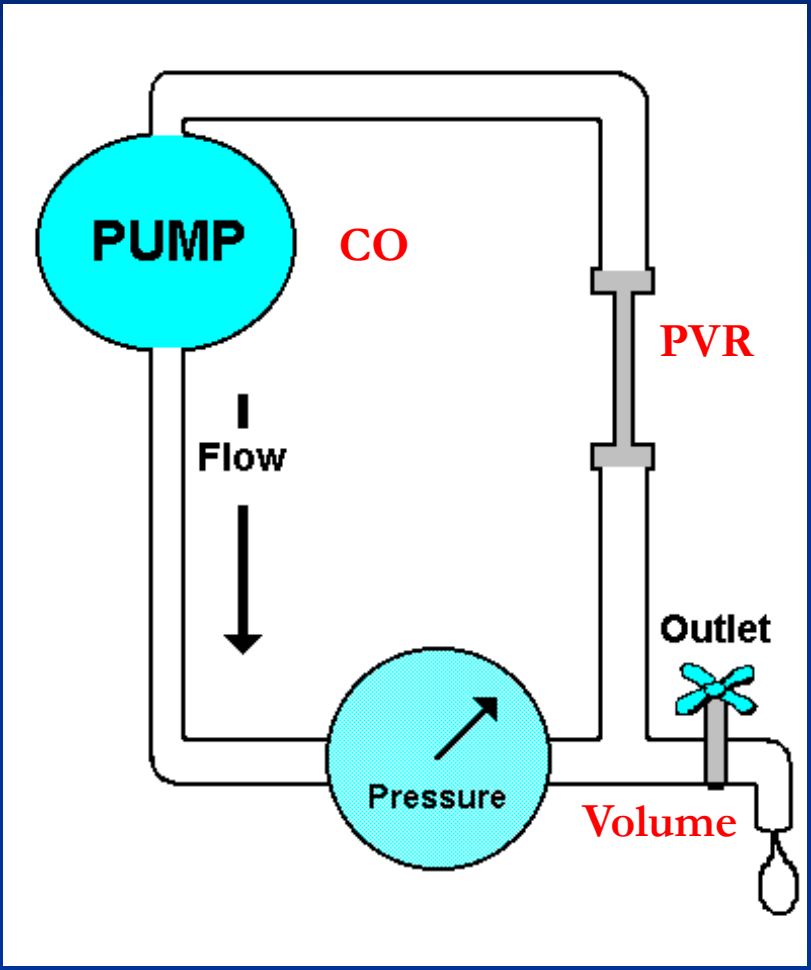
Tailor treatment according diagnostic exam

- Uncomplicated vs complicated disease
- Ethnicity
- Severity of hypertension
- Pregnancy
- Drug Interactions
- Patient compliance

Antihypertensive drugs may be divided into the following classes:

- Diuretics
- Calcium channel blockers
- Beta blockers
- Angiotensin converting enzyme (ACE) inhibitors (ACEI)
- Angiotensin Receptor Blockers (ARBs)
- Central α2-adrenergic receptor agonists
- Adrenergic neuron blocking agents
- Peripheral α-adrenergic antagonists
- Vasodilators

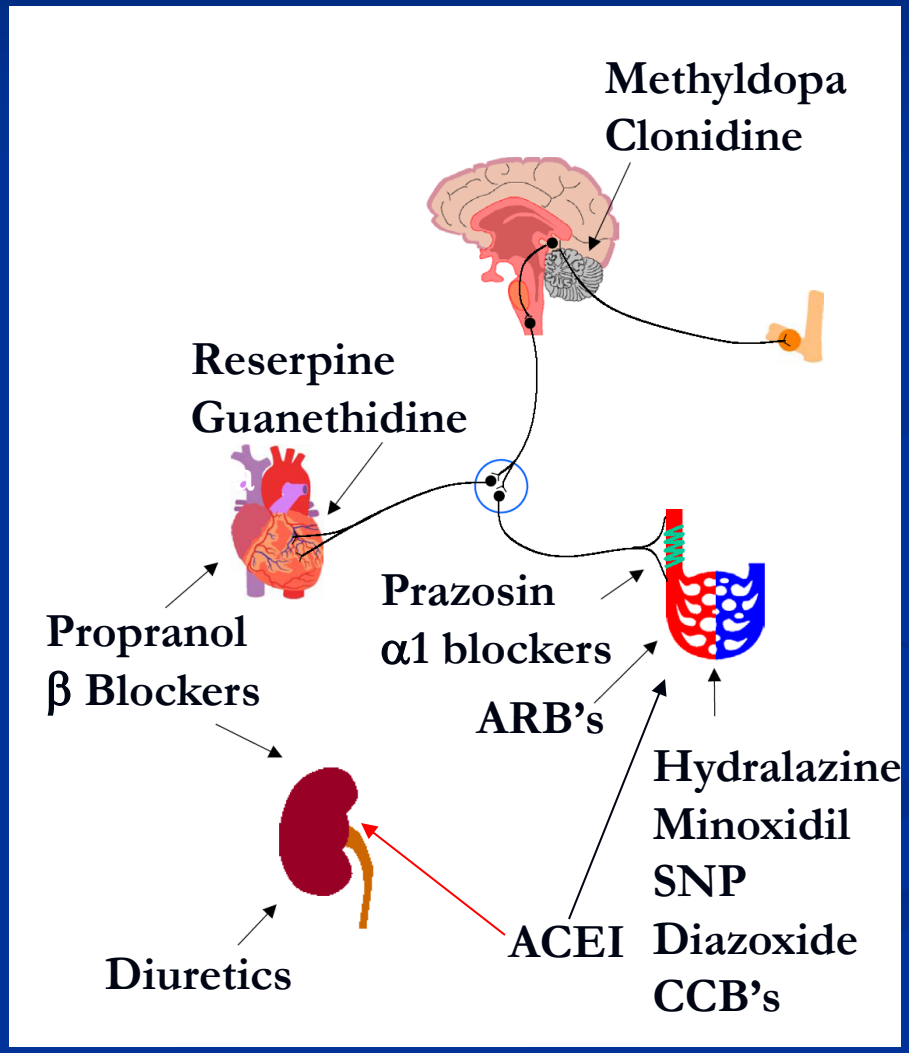
Ways of Lowering Blood Pressure



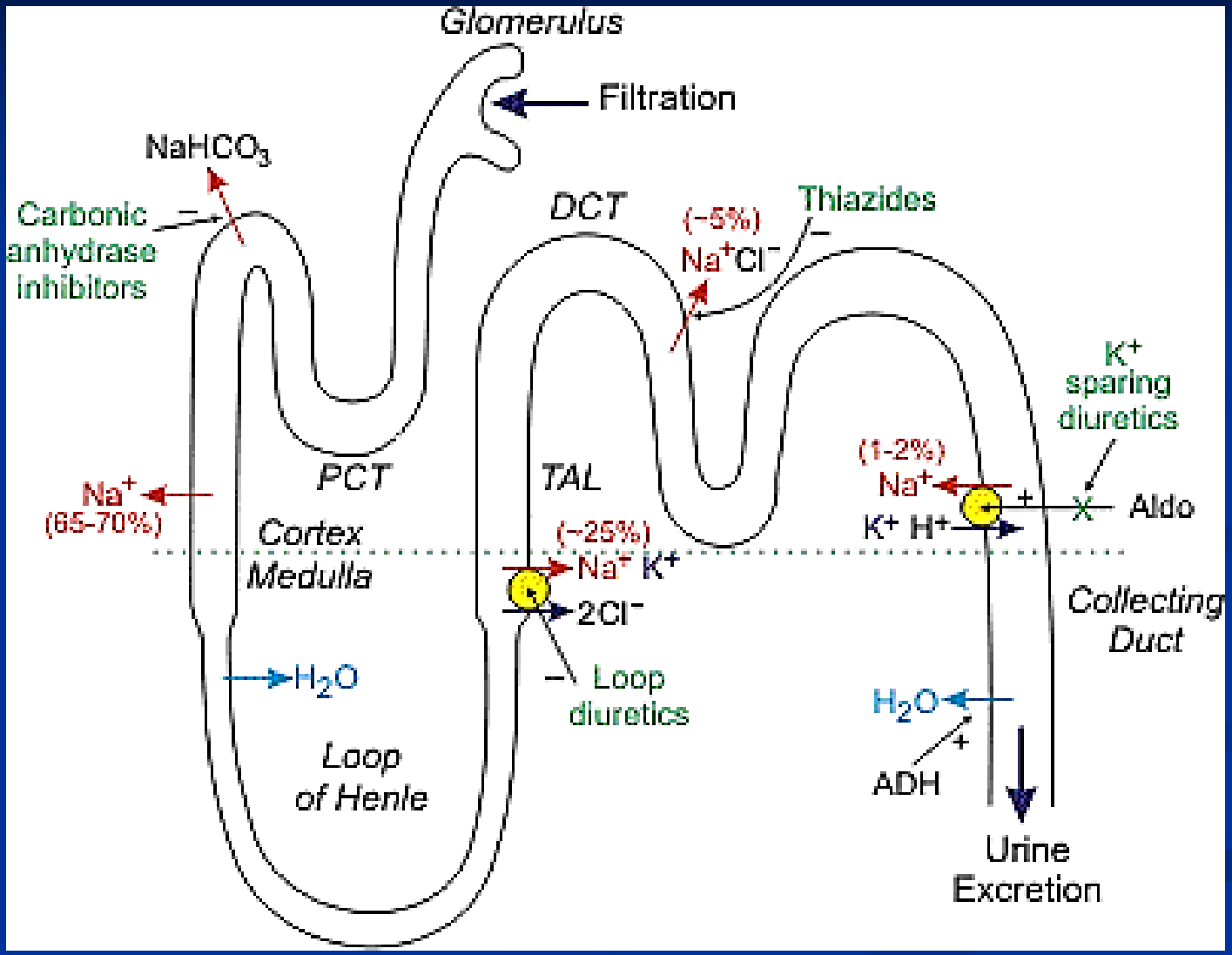
MAP = CO X TPR

- Reduce plasma volume (diuretics)
- Reduce cardiac output (ß-blockers, Ca^{2+} channel blockers)
- Reduce peripheral vascular resistance (vasodilators)

Overview: Antihypertensives and sites of action



Diuretics ('Water Pills')


Glomerulus
Filtration
NaHCO3
Carbonic anhydrase inhibitors
DCT
(~5%) Na+Cl−
Thiazides
K+ sparing diuretics
(1-2%) Na+
K+ H+
Aldo
Na+ (65-70%)
PCT
TAL
(~25%) Na+ K+ 2Cl−
Cortex
Medulla
Collecting Duct
H2O
Loop diuretics
Loop of Henle
H2O
ADH
Urine Excretion

History

- Diuretics discovered in the 1930s and used to treat antibacterial infections
- Patients noticed that the drugs made them urinate frequently
- In 1950s, William Schwartz and Karl Beyer implemented and refined their usage to treat patients with hypertension

Diuretics: General Properties

- Reduce morbidity and mortality in patients with hypertension
- Often first-line antihypertensive therapy either alone or in combination
- Provide adequate treatment of BP control in patients with mild or moderate primary hypertension
- Most efficacious in "low renin" or volume-expanded forms of hypertension
- Very effective for treatment of hypertension in African Americans

Diuretics: Drawbacks

- Can adversely affect serum lipids and can reduce insulin sensitivity (watch out for diabetic patients!)
  - The effect on diabetes may occur in the long-term use of diuretics (i.e. years of treatment)
- Requires 2 weeks to become fully effective
- PVR may increase at first

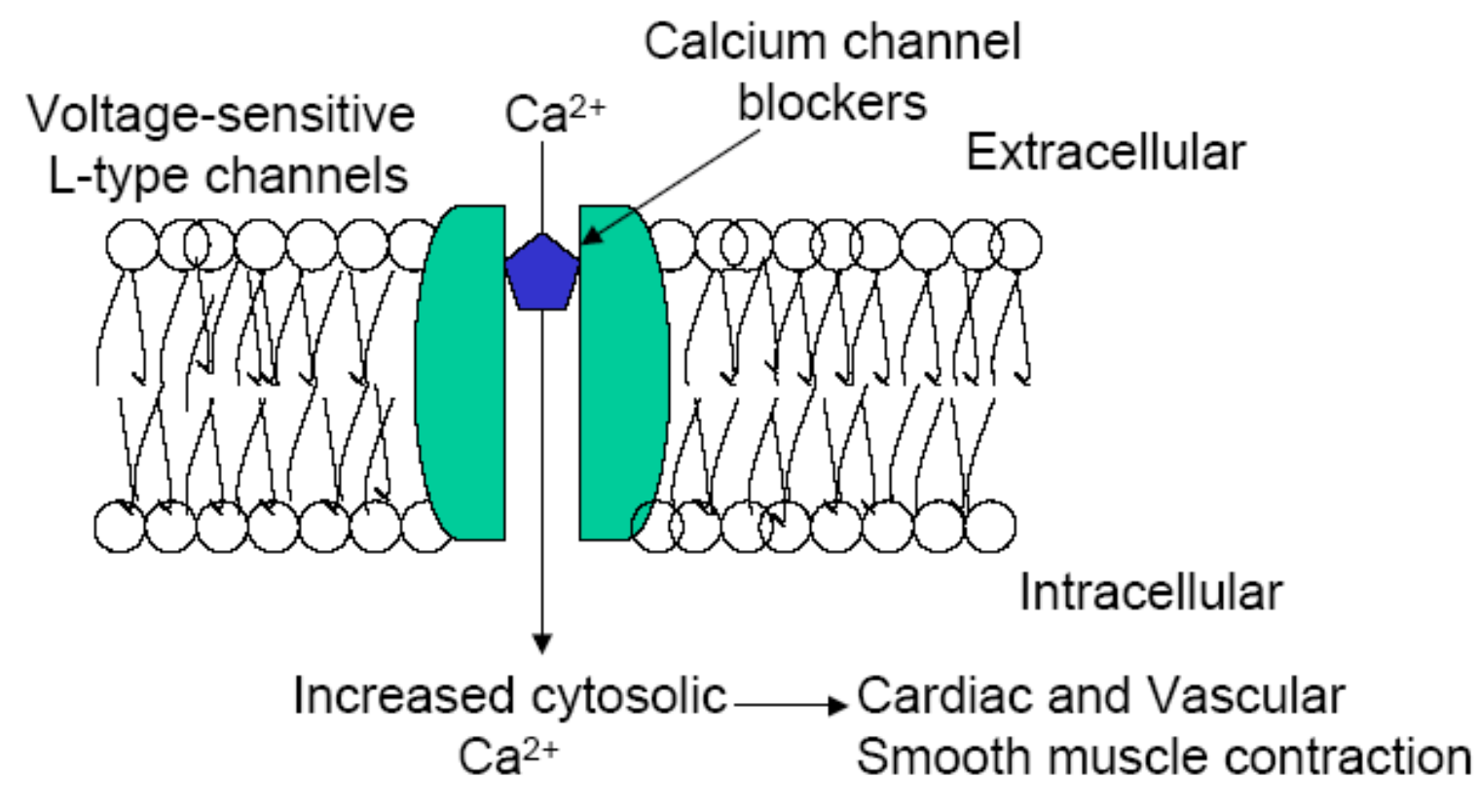
Diuretics and Kidney Disease

Efficacy of diuretics may be compromised during kidney failure

- Diuretics act to modulate electrolyte balance via effects on transporters/channels within the kidney
- Thus, the efficacy of diuretics to modulate transporter/channel function within a damaged kidney will likely be diminished
- May not effectively resolve hypertension under these conditions

Calcium Channel Blockers ‘CCBs’

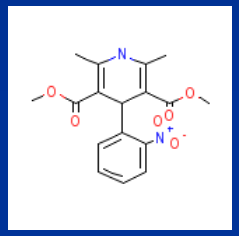
Calcium Channel Blockers



- Block Ca^{2+} in cardiac/smooth muscle
- Dilate peripheral arterioles
- Reduce peripheral vascular resistance

Calcium Channel Blockers (Dihydropyridine Class)

Amlodipine (Norvasc) and Nifedipine (Adalat)



- Block Calcium in vascular smooth muscle (vasodilate)
- Decrease PVR
- No effect on AV node conduction
- Useful in angina

Calcium Channel Blockers (Nondihyropyridines)

Verapamil (Isoptin)

- Direct negative inotropic and chronotropic action (cardiodepressive)
- May cause heart failure in patients with borderline cardiac reserve (Do not use in patients with LV dysfunction)

Diltiazem (Cardizem)

- Decreases AV conduction and heart rate
- Weaker negative inotrope then verapamil

Calcium Channel Blockers: Side Effects

- Hypotension
- Cardiac depression (Diltiazam, verapamil)
- Tachycardia (Nifedipine)
- Headache
- Flushing
- Edema (Nifedipine)
- Constipation

Calcium Channel Blockers: Drug Interactions

- Use of either verapamil or diltiazem (nondihydropyridines) in combination with β-blocker could cause marked bradycardia and cardiac conduction blockade
- Verapamil and diltiazem may add to the inhibitory effects of digoxin on AV conduction
- Amlodipine: combination with ACE inhibitor reduced CV events in hypertensive patients (ASCOT trial study)

CCB Indications

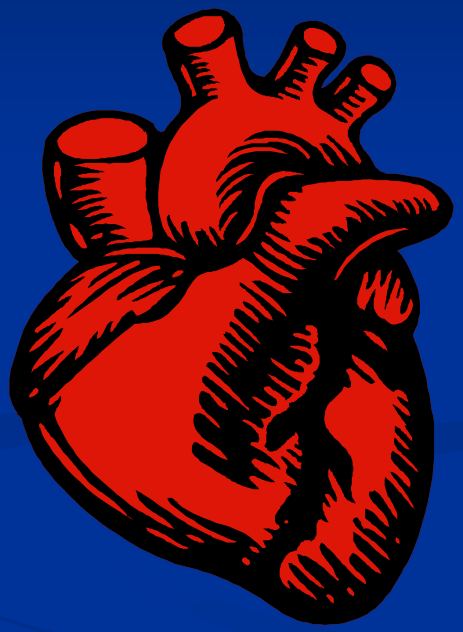
- Useful in low renin hypertension
  - Low renin hypertension is usually more common in certain ethnic groups (ex; African American) and also in elderly patients
- Useful in controlling BP and cardiovascular events in patients with isolated systolic hypertension, particularly the elderly

Beta-Adrenergic Receptor Blockers
β-Adrenoceptor Antagonists
'β Blockers'

β1 adrenergic receptor

Cardiac effects:

- **Increase cardiac output**
  - **Increase heart rate**
  - **Increase heart contractility**

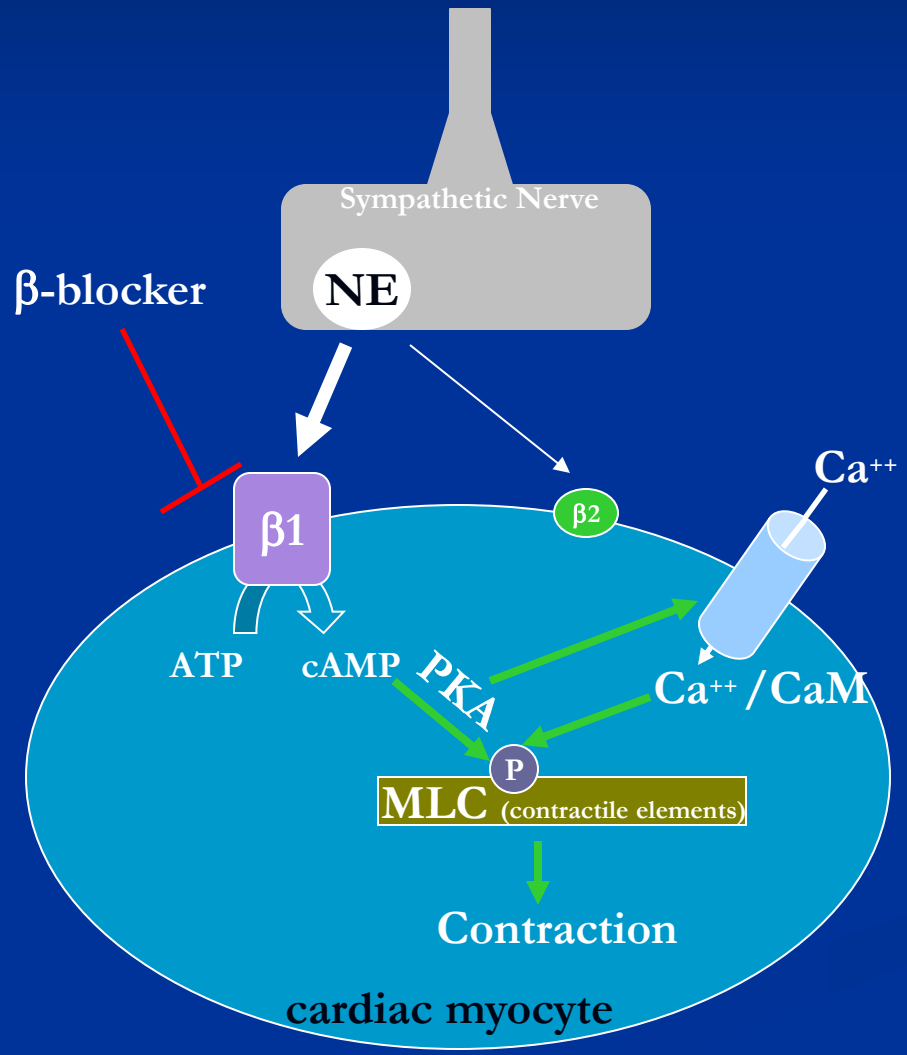


History

- Raymond Ahlquist (MCG) in 1948 was searching for a drug to relieve menstrual cramps and coincidently found epinephrine stimulated heart rate through a distinct set of receptors (β) in the heart

- By 1964, a research chemist, Sir James Black, having read these published observations developed β-blockers

Mechanism of Action: Effect on the cardiac myocyte



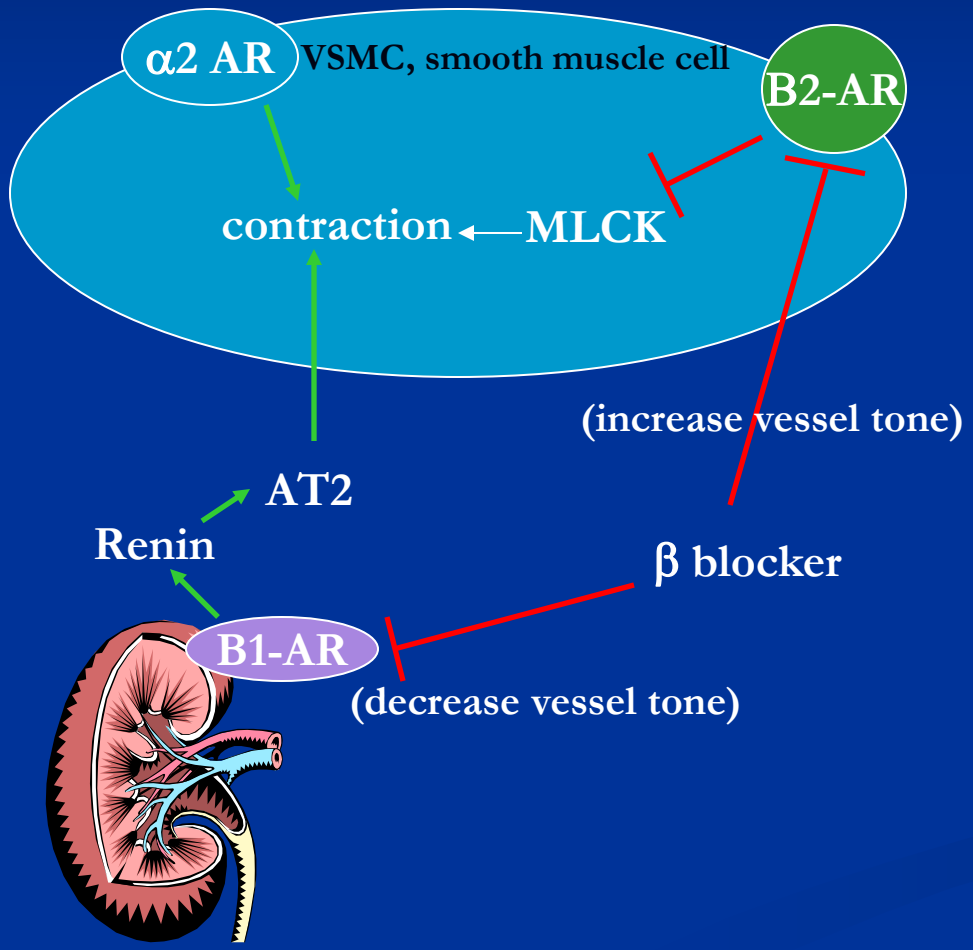
The endogenous pathway

- Beta-AR are coupled to Gs-proteins
- Gs-proteins activate adenylyl cyclase to form cAMP
- Increased cAMP activates PK-A
- PK-A phosphorylates L-type calcium channels and MLC-K,

1. Increase inotropy (contractility).
2. Gs-protein activation also increases heart rate (chronotropy)

A Beta blocker will block this pathway to decrease intropy and chronotropy

Mechanism of Action: Effect on the blood vessel



The endogenous pathway

- Beta-AR are again coupled to Gs-proteins
- However, in contrast to heart, increased cAMP inhibits MLC-K in VSMC

1. A modest effect (relative to other vasoactive autocoids) causing blood vessel relaxation

- *A Beta blocker will block this pathway to modestly increase vessel tone (contraction) and PVR in the short-term*

- *A Beta blocker will also block b1-AR in the kidney which will decrease renin production, and decrease vessel tone*

Propranolol (Inderal): Mechanisms of Action

- Nonselective, competitive antagonist of β1 and β*2* adrenergic receptors (block binding of NE)
- Cardioprotective
  - Decreases heart rate
  - Decreases contractile force
  - Decreases cardiac output
  - Delays AV node conduction
  - Neutralize reflex tachycardia induced by vasodilators
- Reduces central sympathetic nervous system output
- Small vasoconstrictive effect (Increase PVR)
- Reduces renin release (β1) (effective in patients with high renin activity as is common in younger patients having hypertension)

Propranolol: Side-effects

- Hypotension, AV block, severe bradycardia (negative chronotrope), possibly HF
  - Careful consideration in patients with conduction problems/bradycardia
- Bronchial constriction/spasm
  - Do not use in asthmathic patients
- Acute withdrawal syndrome (receptor supersensitivity) in patients, predisposing to myocardial ischemia
- Increase triglyceride levels and decrease HDL levels
- Induce glucose intolerance
  - Careful usage in diabetic and obese patients
- Lipid soluble, cross BBB-Nightmares/depression

Propranolol: Contraindications

- **Bronchial asthma**
- Peripheral vascular disease
- AV (heart) block

Other β blockers

Atenolol (Tenormin)

- β1 selective antagonist
- Administered once daily
- Less lipid soluble than other β antagonists

Metoprolol (Lopressor)

- Selective inhibitor to β1
- Useful in asthmatic patients

Nadolol (Corgard)

- Non-selective β antagonist
- Administered once daily

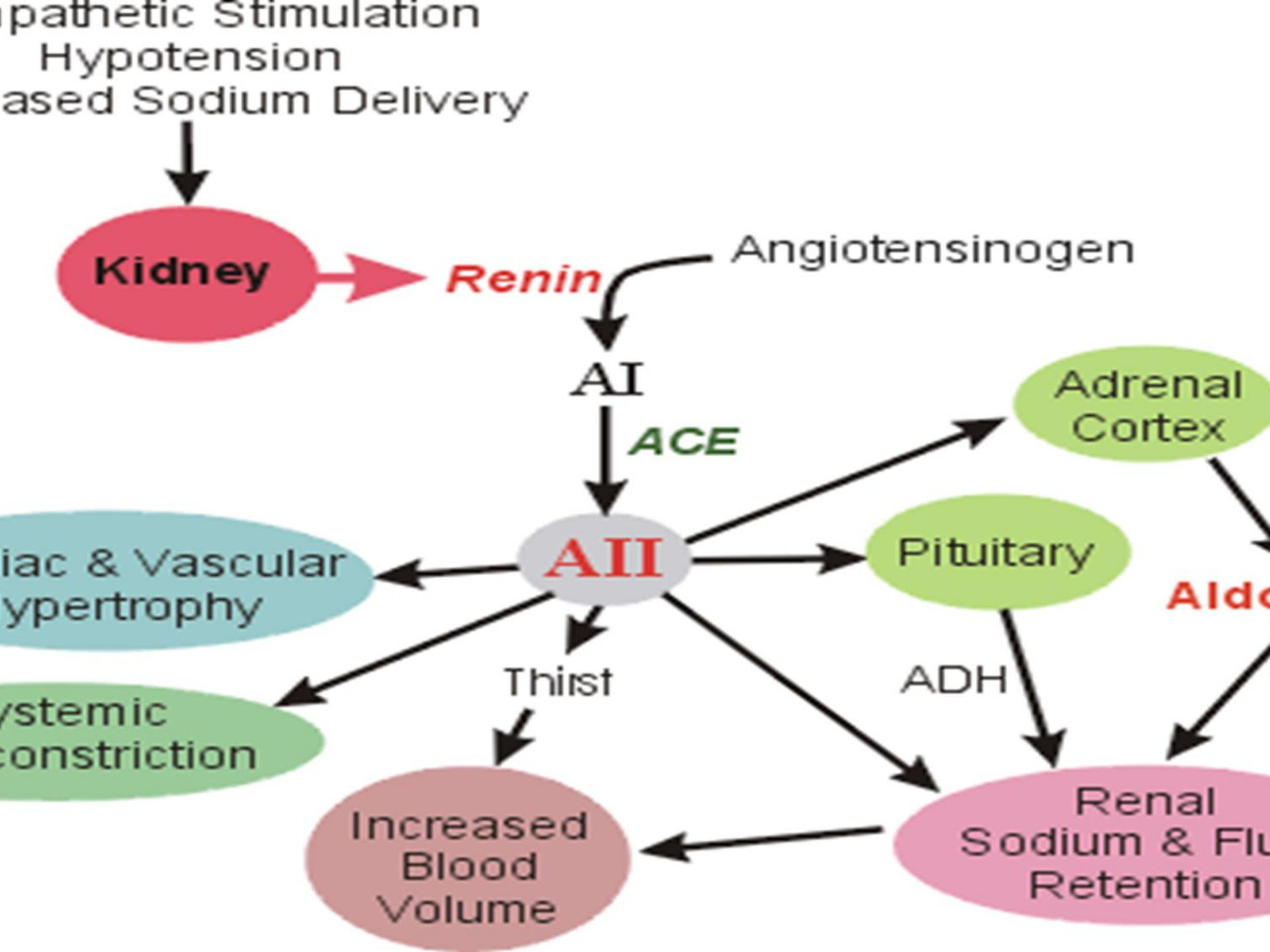
β Blockers: Indications

- Mild and moderate hypertensives
- Useful in patients receiving vasodilators to prevent sympathetic reflex tachycardia
- Also useful in controlling BP in patients with underlying heart disease (congestive HF, ischemia, MI)

Angiotensin Converting Enzyme Inhibitors
'ACE Inhibitors'

History

- Workers in the banana plantations of Brazil were known to collapse after being bitten by a specific viper
- A Brazilian biochemist Maricio Rocho e Silva purified the venom extracts and sent his post-doc with extracts to study their effects in the lab of Sir John Vane (London)
- By 1970, the lab of Sir John Vane found the effect was on ACE, ultimately leading to the development of ACE inhibitors

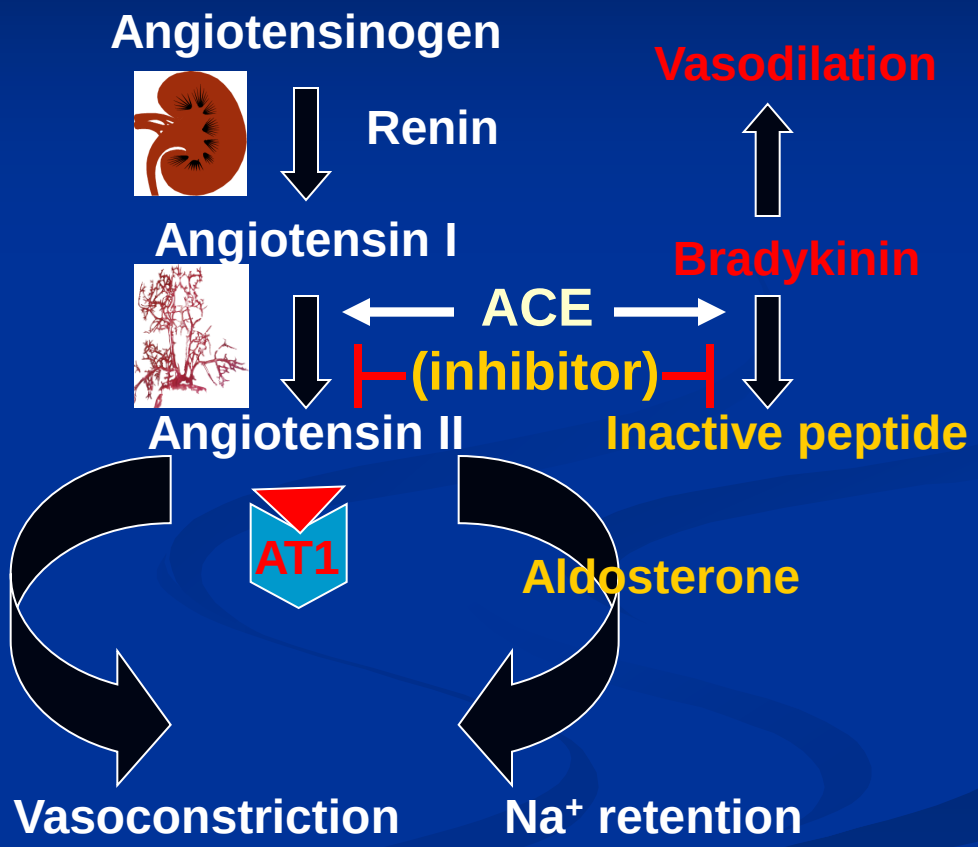

pathetic Stimulation
Hypotension
ased Sodium Delivery
Kidney
Renin
Angiotensinogen
AI
ACE
Adrenal Cortex
iac & Vascular ypertrophy
AII
Pituitary
Aldo
Thirst
ADH
ystemic onstriction
Increased Blood Volume
Renal Sodium & Flu Retention

Renin-Angiotensin-Aldosterone System (RAAS)

ACE Inhibitors

Inhibit conversion of inactive angiotensin I to angiotensin II which:

- reduces vessel tone
- reduces Na+ retention via aldosterone
- blocks degradation of bradykinin, a vasodilator
- **Very useful in diabetic patients**
  - **Slows progression of renal disease**



Thus RAAS pathway has multiple effects via discrete pathways which are important in blood pressure control, but which act to increase blood pressure

'pril' suffix=ACE-I

Enalapril

- Excretion is primarily renal – dose should be reduced in patients with renal insufficiency

Ramipril (Altace)

- Peak plasma concentration within 1 hour
- $t_{1/2}$ – 2-4 hrs

Lisinopril (Zestoretic)

- Slowly absorbed; plasma $t_{1/2}$ – 12 hrs; administered once daily

Captopril

- Sulfhydryl containing moiety causes some taste changes

ACEI: Side-effects

- Severe hypotension in hypovolemic patients
- Hyperkalemia
- Angioedema (0.1-0.5%)
  - rapid swelling of nose, throat, mouth, larynx, lips, or tongue
  - may relate to inhibitory effect bradykinin catalysis
  - Greater risk in African Americans
- Cough (10-20%)
- Skin rash (10%)
- Taste alterations (6%)

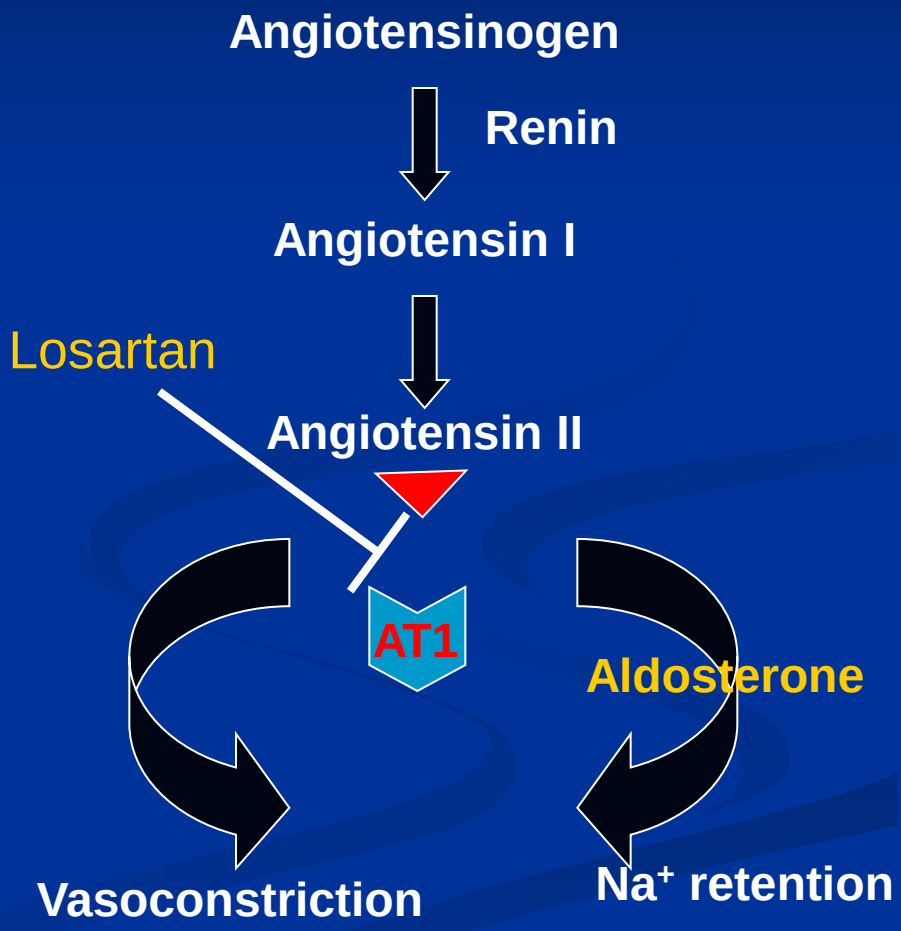
ACE inhibitors: Contraindications

- ACE Inhibitor
  - Can cause hyperkalemia
  - Hyperkalemia can be exacerbated with potassium sparing diuretic
- Some studies indicate that ACEI are not effective in lowering BP in the African American population
- Pregnancy – ACEI suppresses cell proliferation which will impair embryonic development; should not be administered in second or third trimester

Angiotensin I Receptor Blockers (ARB's)

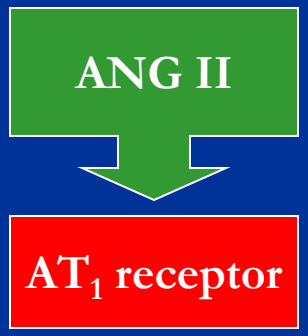
Losartan (Cozaar)

- Decreases TPR
- Inhibits Aldosterone release
- Block Na^+ reabsorption

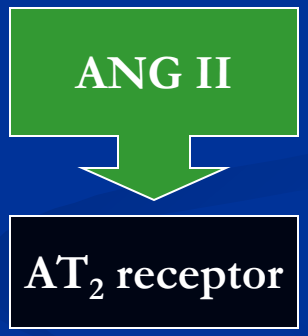


Blocking AT_1 receptor is antihypertensive

ATI Prototype antagonist=Losartan



- Vasoconstriction
- Cell Growth and Proliferation
- Aldosterone release
- Central Sympathetic activation
- Sodium and water retention



- Vasodilation
- Restrains cell growth and proliferation
- Mediates NO and PGI_2 release in kidney
- Renal sodium excretion
- Dilates afferent renal arteriole

Losartan:
Side Effects

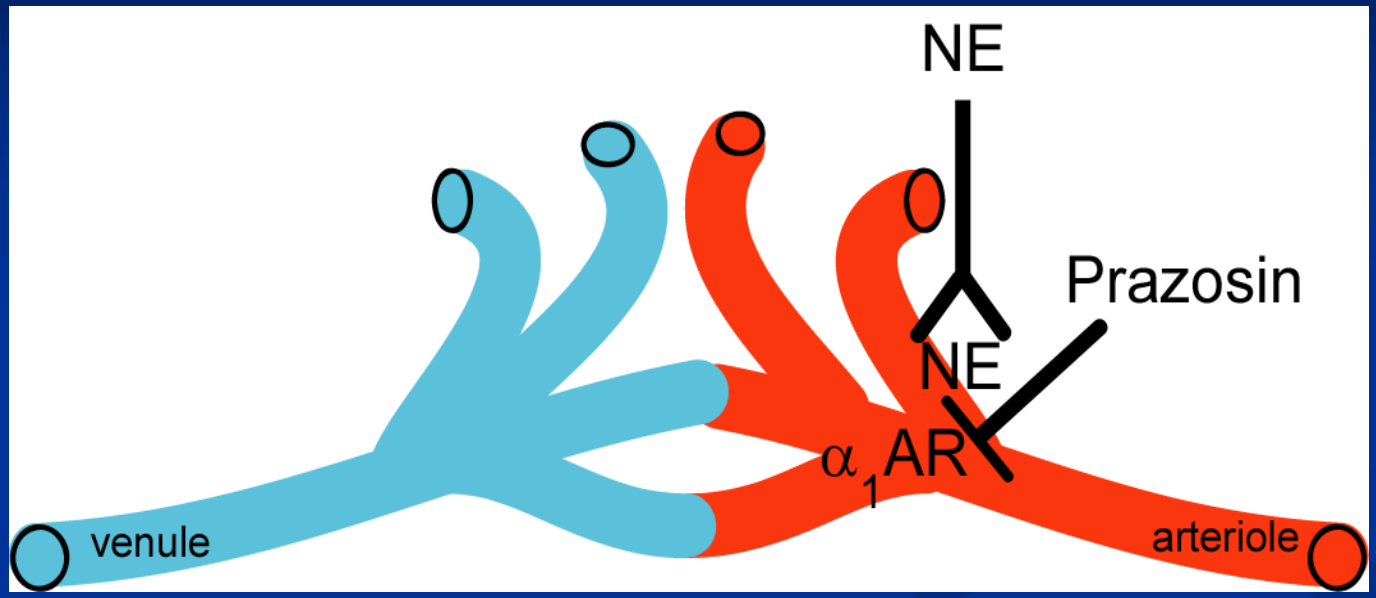
- Angioedema
  - Subcutaneous swelling of eyes and lips
- Not to be administered during pregnacy (first trimester)
  - AT receptors important in embryonic renal development
- Dizziness

ACEI versus ARB

- Use ACEI and ARB in hypertensive patients with heart failure, renal disease, and diabetes
- ACEI costs $0.11/cap vs. $0.48-0.90/cap for ARB
- Use ACEI as first choice vs. ARB, unless patients cannot tolerate ACEI (angioedema), then use ARB

Peripheral α_1 Adrenergic Receptor Blockers
'Peripheral α_1 Blockers'

Prazosin (Minipres): Mechanism of Action



- Blocks α_1-AR on resistance vessels from binding NE released from nerve terminals
- Decreases vascular tone (vasodilates)
- Thereby decreases PVR and BP

Prazosin:
Side effects

- Postural dizziness (14%)
- Headaches (8%)
- Drowsiness (8%)
- 'first dose phenomenon'
  - Syncopal reaction-orthostatic hypotension (upon standing)
  - After first dose, tolerance to this reaction

Other selective α1-adrenergic receptor blockers

Doxazosin and Terazosin

- longer $t_{1/2}$ than prazosin
- used for treatment of benign prostate hypertrophy

Recent Recommendations on α blockers

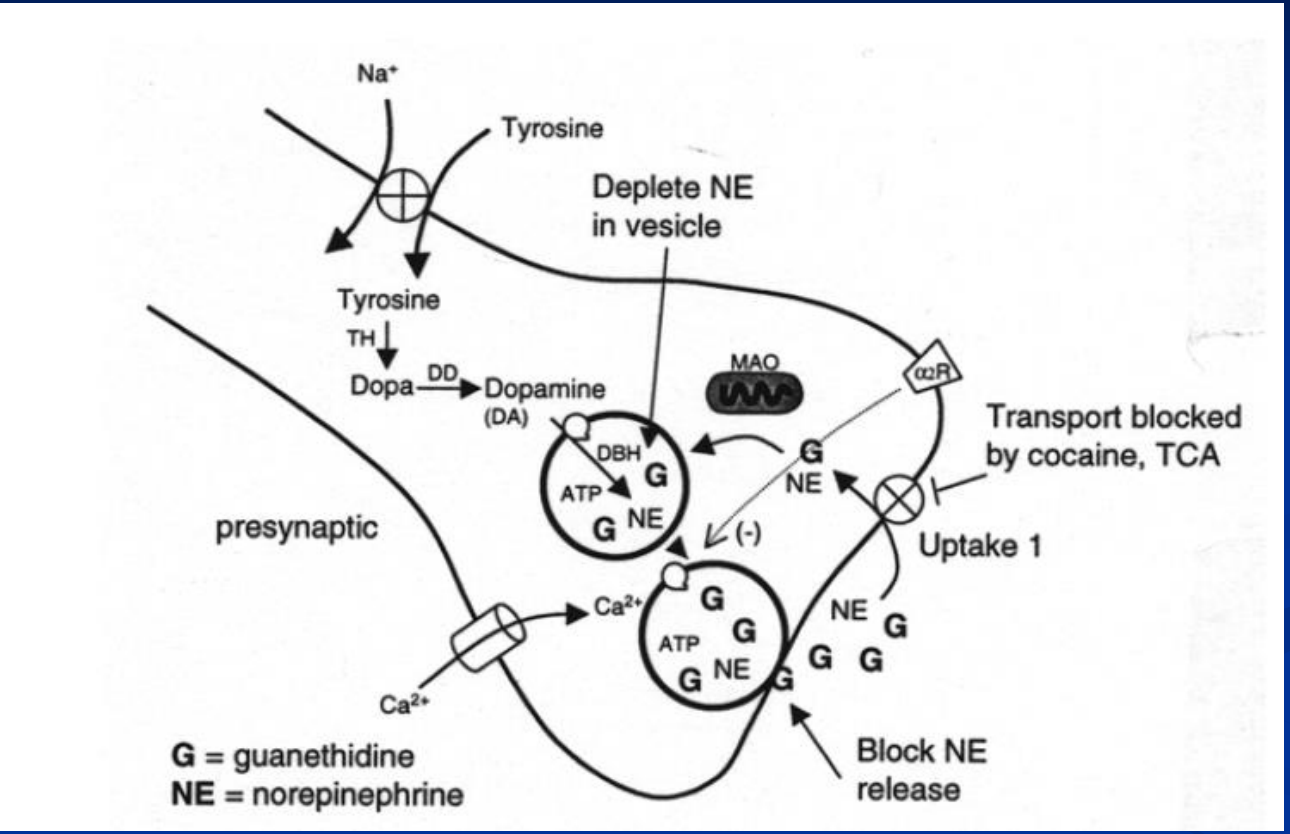
- *a*-blockers are less effective than diuretics in preventing cardiovascular events, mainly heart failure (ALLHAT clinical study)
- NIH recommends NOT to use α-blocker as the first drug of choice in hypertension (it is safe, just not effective in preventing heart failure)
- A reasonable addition, to facilitate blood pressure control

‘Adrenergic Neuron-Blocking Agents’
‘Sympatholytics’

Adrenergic Neuron-Blocking Agents

- Deplete norepinephrine from presynaptic, postganglionic sympathetic nerve terminals
- Inhibit release of norepinephrine in response to sympathetic nerve stimulation
- Reduce cardiac output and total peripheral resistance

Gaunethidine (Ismelin): Mechanism of action



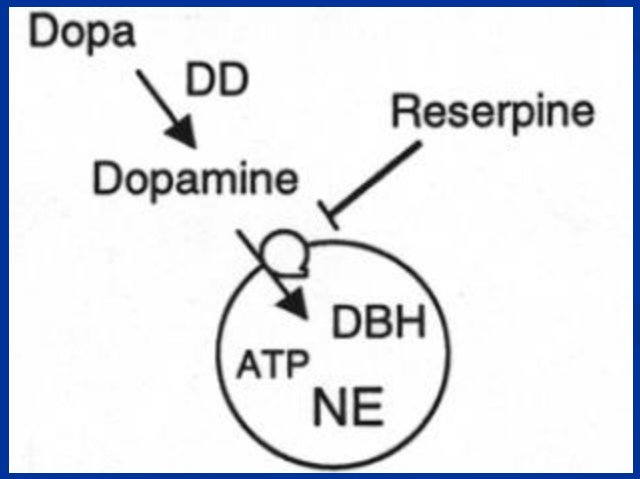
- Guanethidine enters peripheral nerve terminals via same transporter as NE
- Depletes NE stores in vesicles
- False neurotransmitter

Guanethidine: Pharmacokinetics

- Effective orally (takes 72 hrs to reach maximum effect)
- Plasma $t_{1/2}$ – approximately 5 days
- Guanethidine is indicated only for moderate to severe hypertension

Reserpine (Serpasil): Mechanism of Action

- Blocks transport of dopamine into storage granules in nerve terminals
- Depletes stores of catecholamines and serotonin in CNS and PNS
- Decreases sympathetic tone, total peripheral resistance and cardiac output



Reserpine: Pharmacokinetics

- Absorbed from GI tract (2-6 wks to achieve maximal effect)
- Plasma $t_{1/2}$ – 11.5-16 days
- Largely hepatic metabolism

Guanethidine and Reserpine: Side Effects

- Orthostatic hypotension (Guanethidine)
- Depression
- Nasal Congestion
- Bradycardia
- Impotence (Guanethidine)
- Diarrhea (Guanethidine)
- Salt and water retention

Guanethidine and Reserpine: Drug Interactions

- Drugs that alter function of the amine pump can block uptake to site of action: tricyclic antidepressants, monoamine oxidase inhibitors, ephedrine, amphetamines, phenothiazines

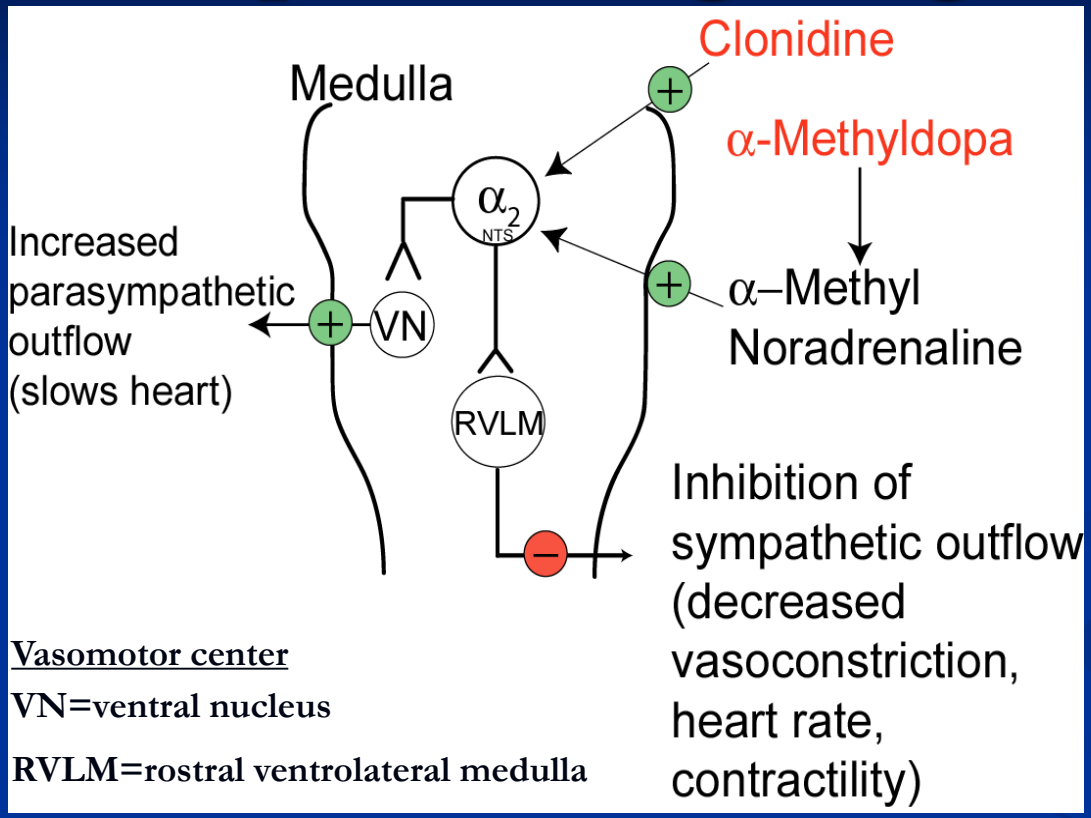
- After chronic use of guanethidine, the above agents could cause hypertension due to development of receptor supersensitivity

Rarely indicated

- The a adrenergic blocking agents are not frequently prescribed because of their adverse effects
- Can be a last resort in refractory (unmanageable) hypertension
- Reserpine is cost-effective

Central α_2-Adrenergic Receptor Agonists
Centrally Acting Sympathoplegic Drugs
'Central α_2 Agonists'

Central α_2-Adrenergic Agonists



- 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

Central α_2-AR Agonists: Mechanism of Action

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

- 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

Central α_2-AR Agonists

- **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.

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:
Side Effects

- Dry mouth (44%)
- Drowsiness (50%)
- Dizziness (15%)
- 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
- With prolonged use, hemolytic anemia is a rare side effect

Clonidine and Methyldopa: Drug interactions

- Tricyclic antidepressants may prevent the antihypertensive effect
- Barbiturates may reduce the efficacy of through induction of hepatic microsomal enzymes
- Monoamine oxidase inhibitors when coadministered may produce hypertension and CNS stimulation

Indications

- Methyldopa is a first choice for hypertension during pregnancy

- Clonidine is useful in the diagnosis of pheochromocytoma (adrenal tumor) in hypertensive patients; it will reduce NE to lower then 500 pg/mL in tumor-free patients

Ganglionic Blockers

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.**

Blockers

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

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:

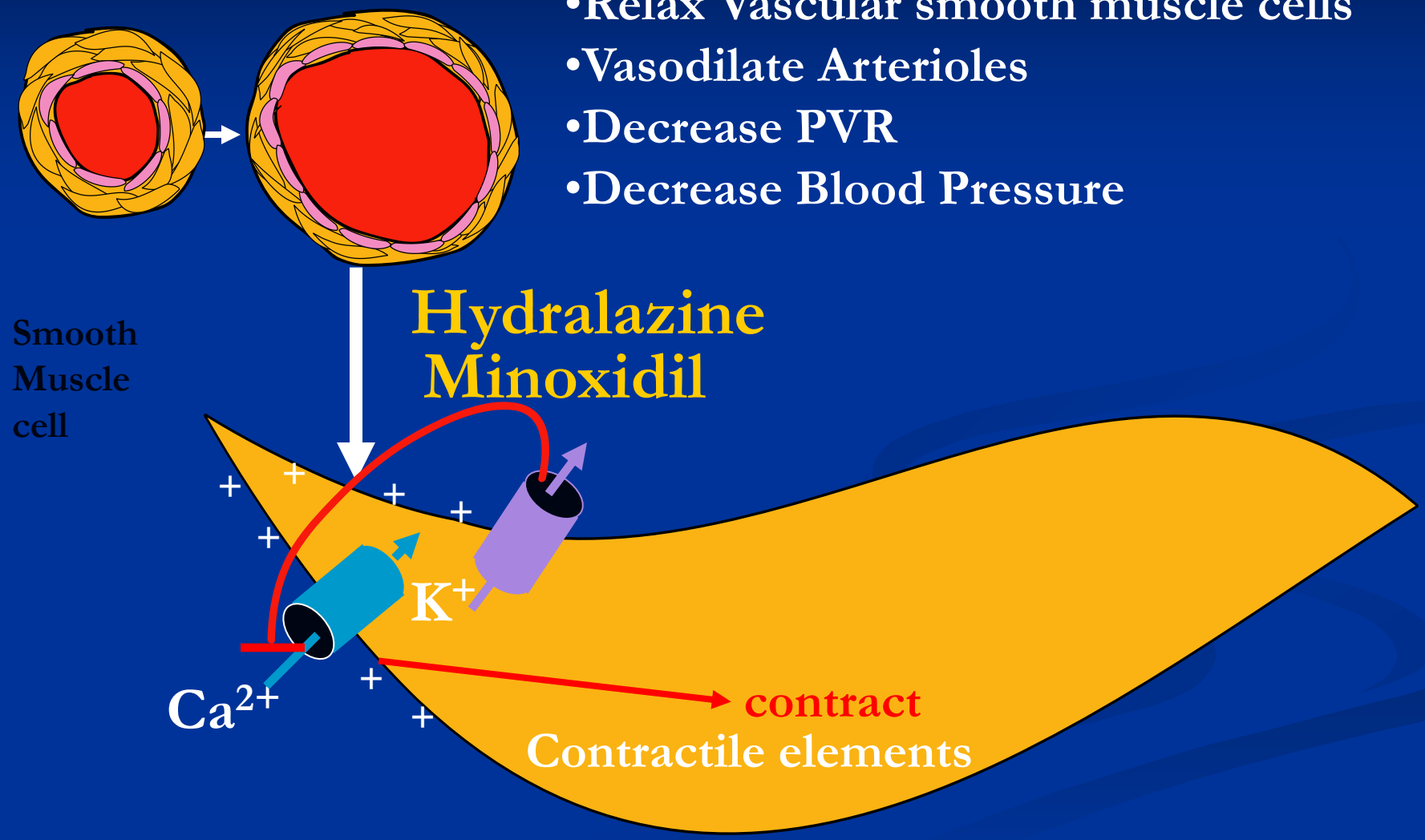
Potentiate the effect of tubocurarine in surgery.

Have histamine releasing properties (Caution in allergies)

Vasodilators

Vasodilators: Mechanism of Action

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



Hydralazine (Apresoline):
Mechanism of Action

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

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 – 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
- 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).

Indications

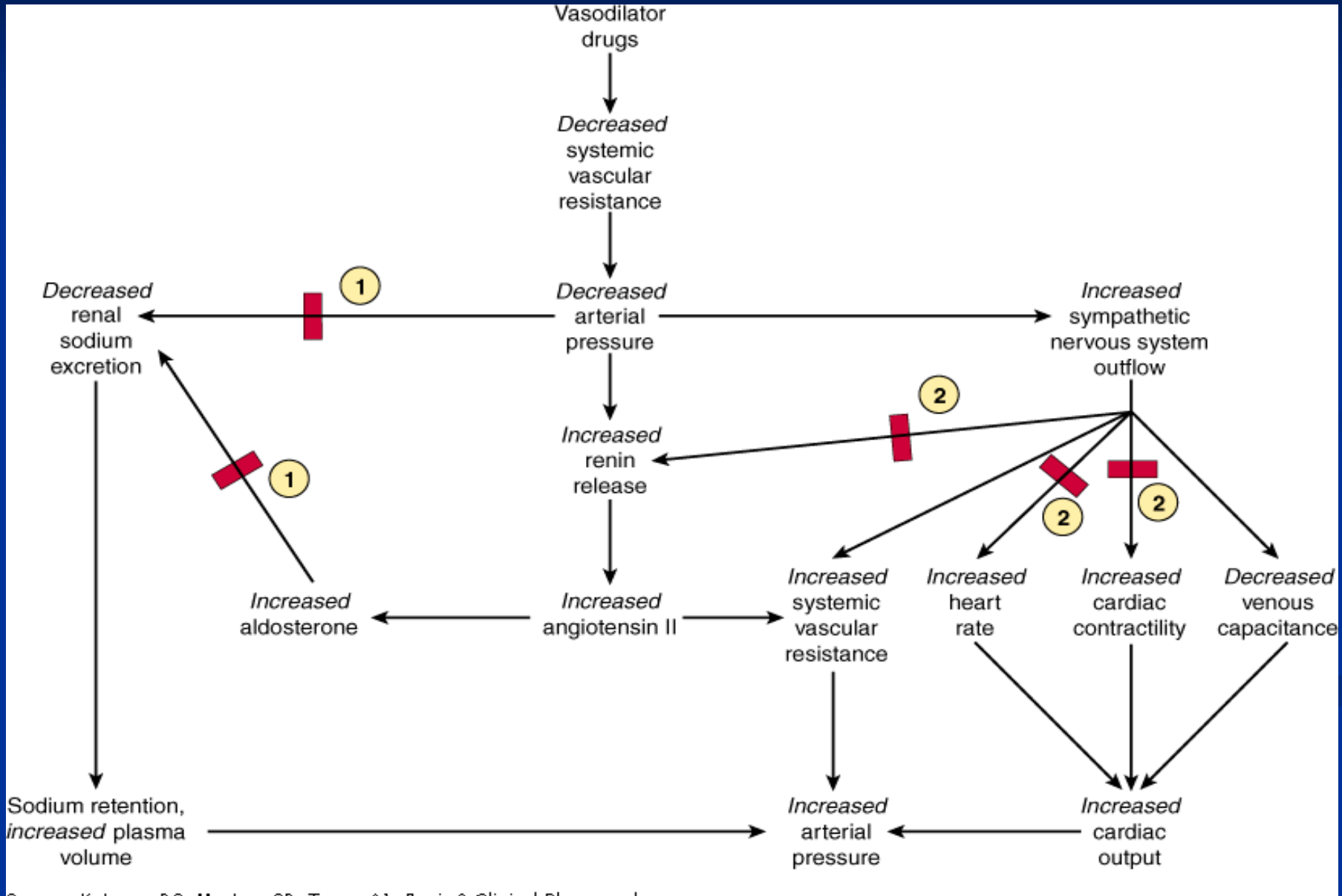
- Severe, resistant hypertension

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.

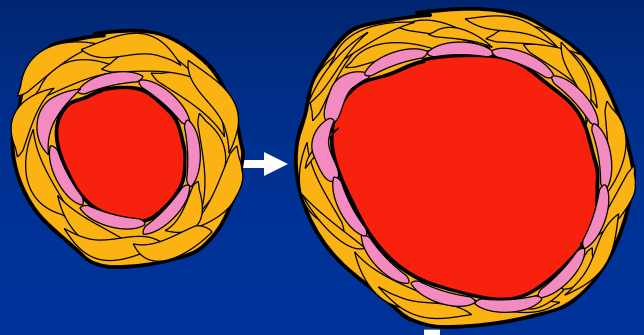
Compensatory responses to vasodilators

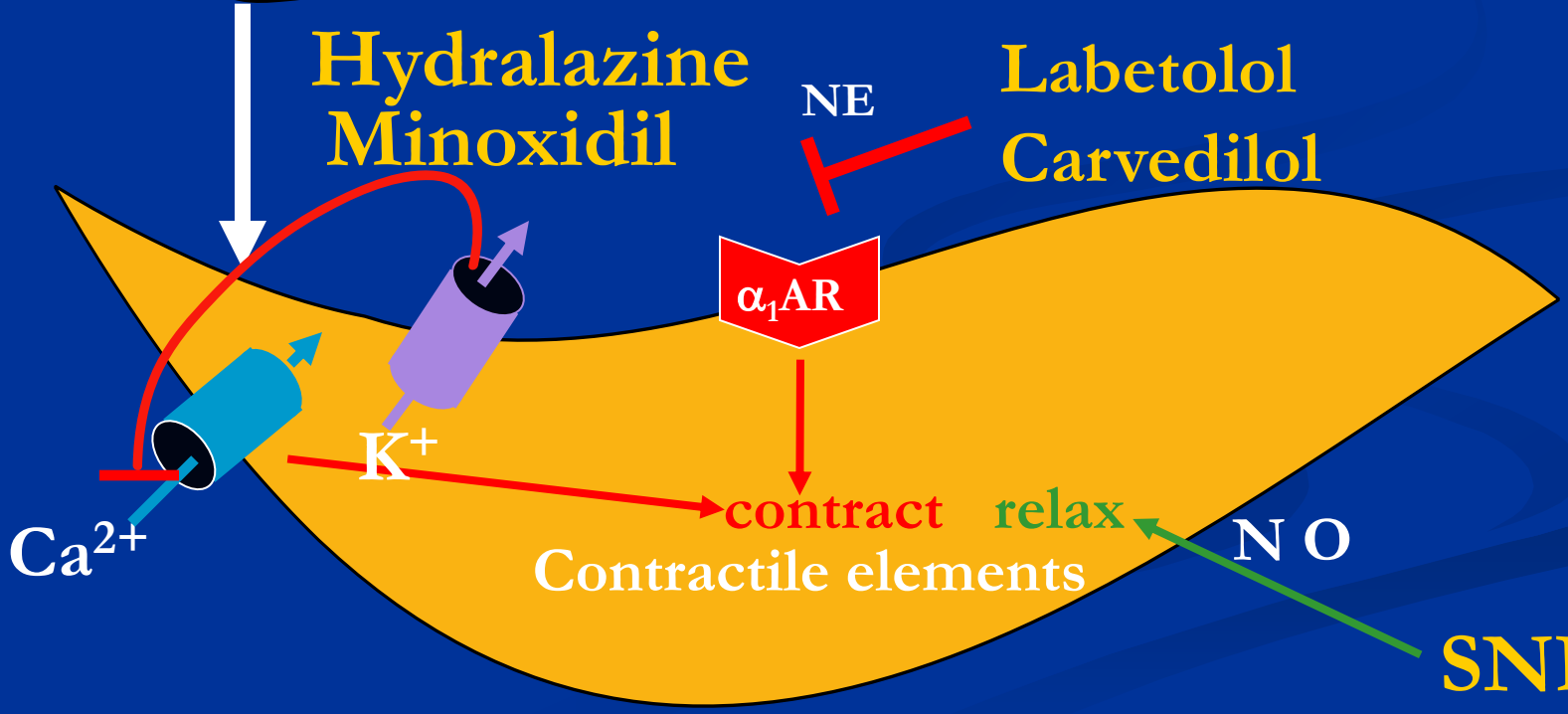


Vasodilators in Treatment of Hypertensive Crisis

Vasodilators: Mechanism of Action

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





Sodium Nitroprusside (SNP, Nipride): Mechanism of Action

- Liberates nitric oxide which dilates vascular smooth muscle
- Thereby, decreases total peripheral resistance

SNP:
Pharmacokinetics

- Given by I.V. infusion
- Is light sensitive and unstable in aqueous solution
- Antihypertensive effect ceases upon stopping infusion
- Metabolized to sodium thiocyanate – slowly cleared by kidneys
- Toxic accumulation 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: Pharmacokinetics

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

Diazoxide:
Side-effects

- Tachycardia
- Angina

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

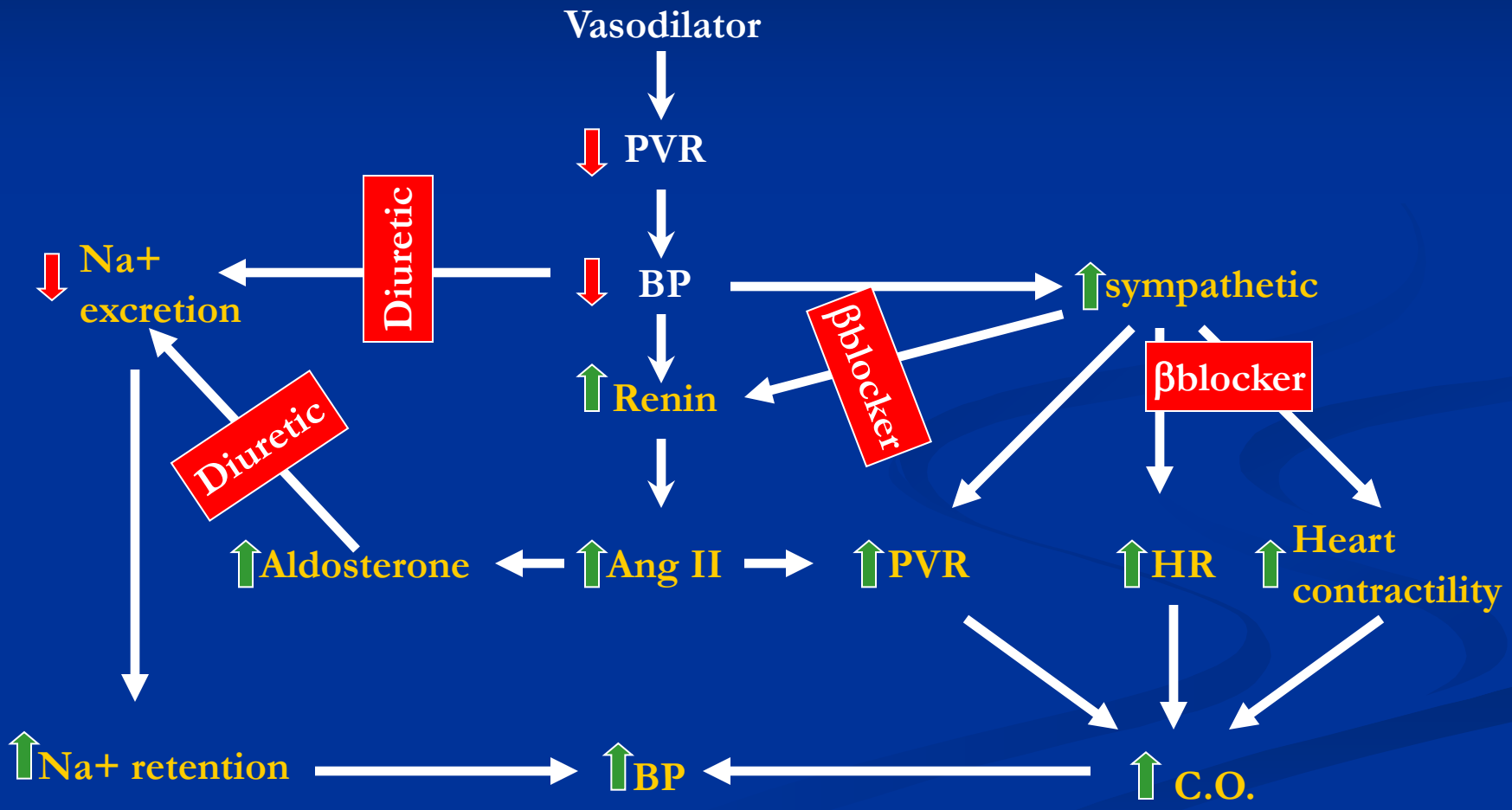
- Mixture of α_1 and non-selective β adrenergic receptor antagonist
  - Block adrenergic receptors in blood vessels and heart
  - Labetolol 1:3 selectivity α_1AR: βAR
  - Carvedilol 1:10 selectivity α_1AR: βAR
- Decrease total peripheral resistance w/o reflex tachycardia

Labetalol & Carvedilol: Pharmacokinetics

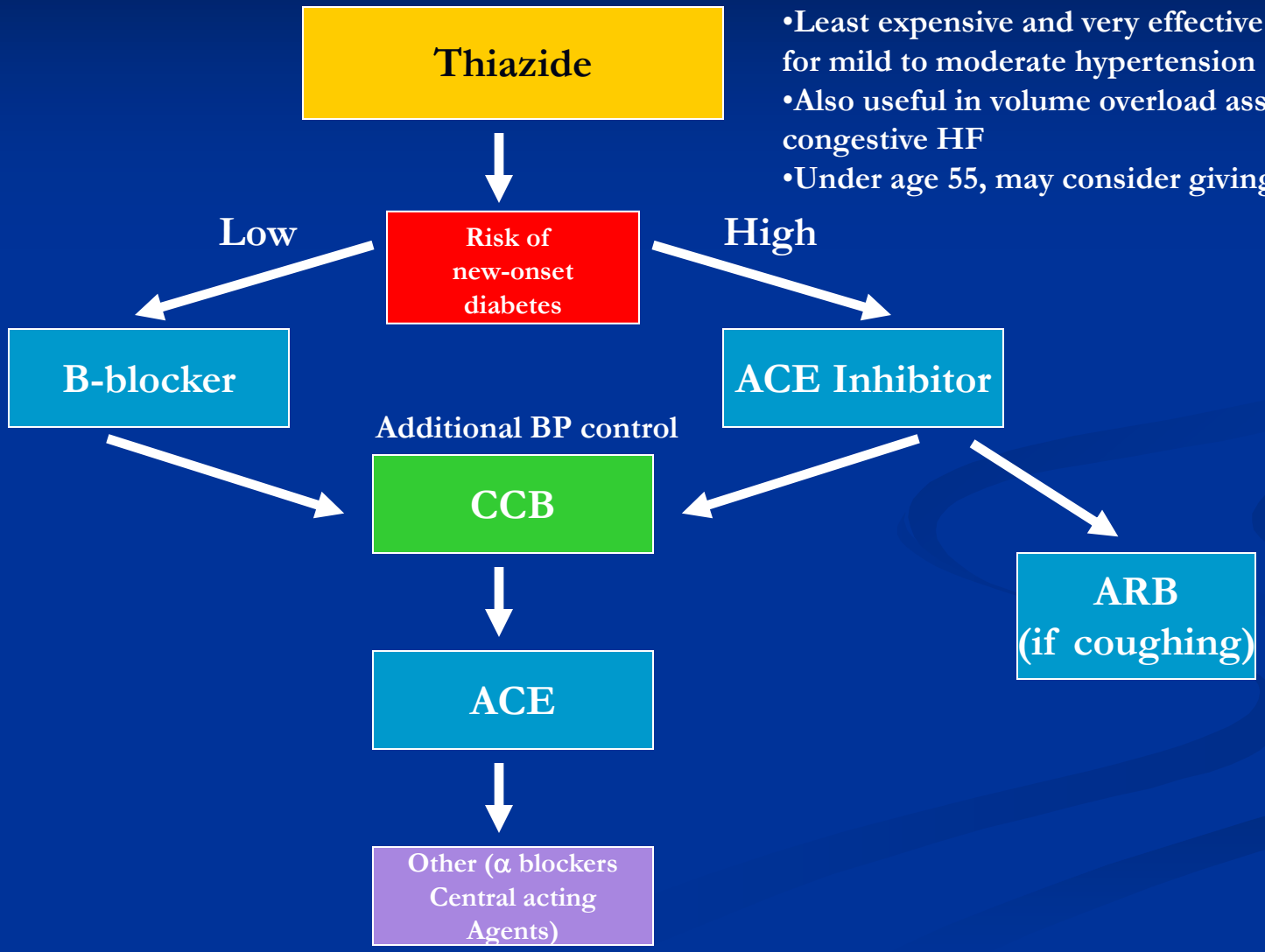
- Administered orally or i.v. (for hypertensive crisis)
- Useful in pheochromocytoma (Labetalol)

- 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



- 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