Subject | Pharmacology
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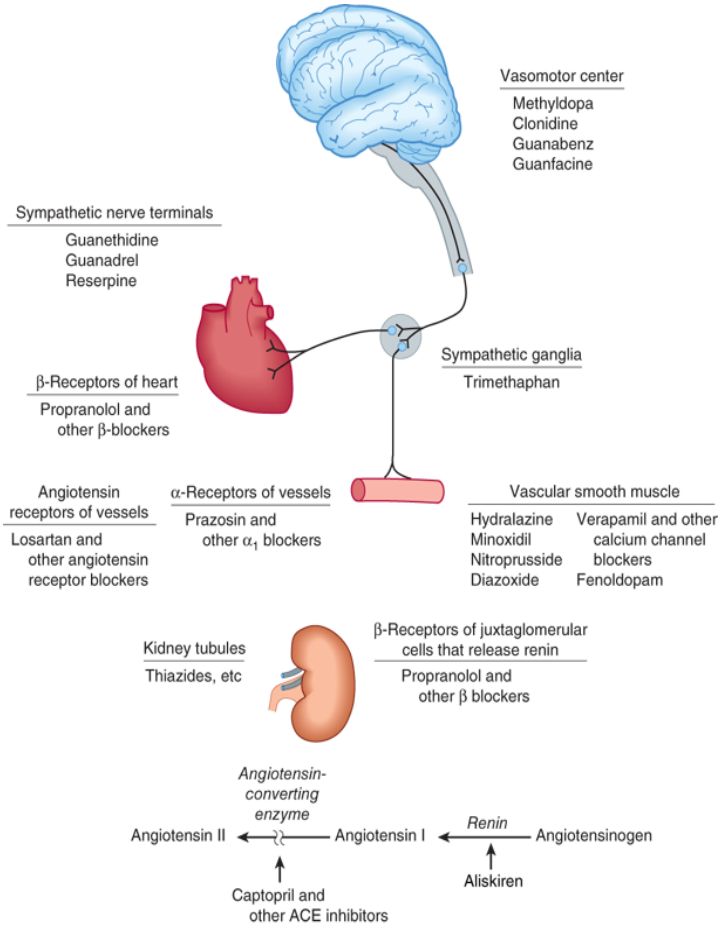
Different classes of antihypertensives have different sites of action:

1- **Can work on CNS :**
   On a vasomotor center, sympathetic ganglia, sympathetic nerve terminals

2- **Can work peripherally:**
   a- **Work on vascular smooth muscles**
   b- **Work on Beta (in heart) and Alpha (in vessels) adrenergic receptors**
   c- **Work on Angiotensin receptors of vessels**
   d- **Work on kidney, affecting the Angiotensin Convertase Enzyme (ACE)**



They are generally divided into the following classes:

- Diuretics
- Calcium channel blockers (CCBs)
- Beta-1 blockers
- Angiotensin converting enzyme (ACE) inhibitors (ACEIs)
- Angiotensin II Receptor Blockers (ARBs)
- Central alpha-2 adrenergic receptor agonists
- Adrenergic neuron blocking agents
- Peripheral alpha-1 adrenergic antagonists
- Vasodilators

Blood pressure = cardiac output (CO) * peripheral vascular resistance (PVR)

***So, if we want to control the BP, we either by control the cardiac output or the peripheral resistance**

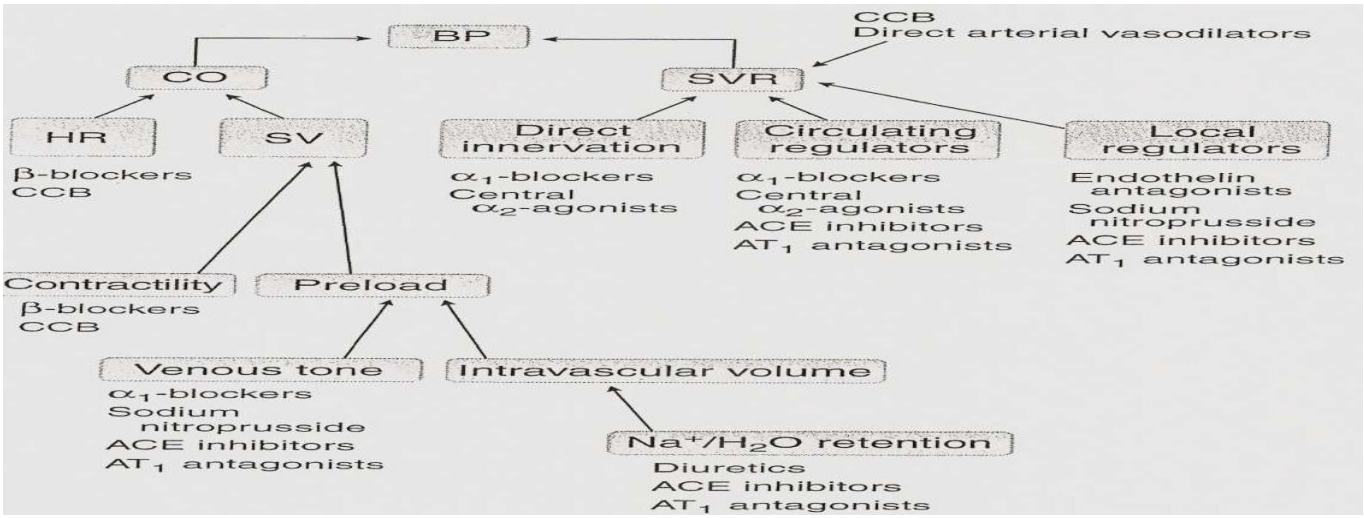
For example:

***If we want to control the heart rate we can use either beta blockers or calcium channel blockers (CCBs)**

***Systemic vascular resistance can be controlled by alpha blockers, Angiotensin 1 antagonists, ACEIs or by a new class of drugs still under clinical trials called Endothelin antagonists**

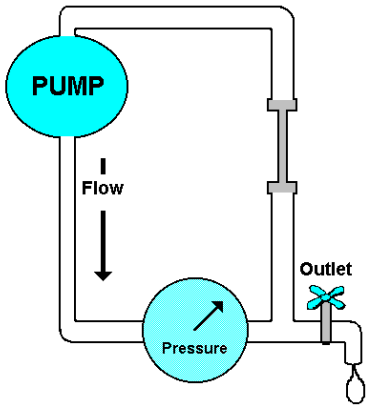
***Preload is controlled by controlling venous capacitance/tone or intravascular volume**

The dr. read the figure below and said all these drugs will be discussed:



- **Ways of lowering blood pressure:**

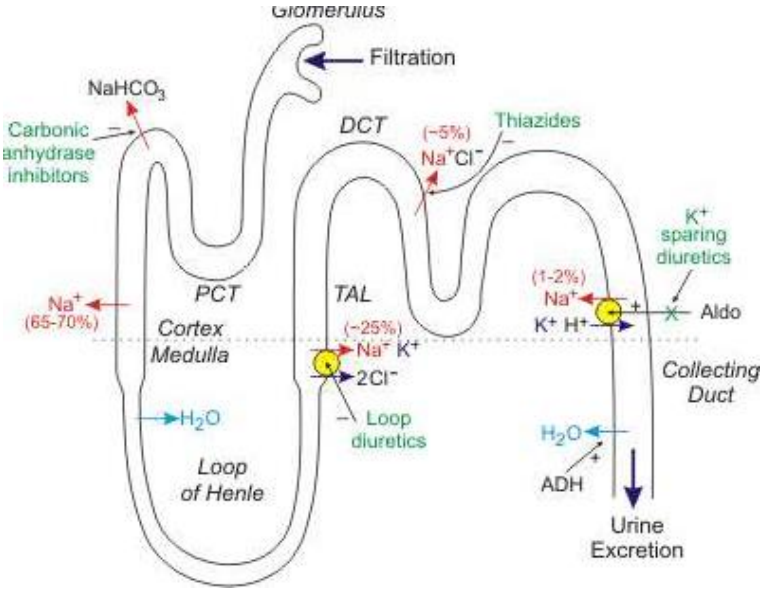
1- **Reduce the plasma volume (e.g. diuretics)**
2- **Reduce cardiac output (e.g. beta blockers, calcium channel blockers)**
3- **Reduce peripheral vascular resistance (vasodilation)**



Diuretic drugs (Water pills)

****The site and mechanism of actions of diuretic drugs aren't included and will be discussed in the urogenital system.**

Diuretics work on different ion transporters (that reabsorb essential ions) present in different parts of kidney tubules.



-We have drugs called Carbonic Anhydrase inhibitors that work on proximal convoluted tubules.

-Also, we have drugs that can work on the Loop of Henle

-Na^+/Cl^- ion exchanger → Thiazides; we will talk about them in details. They're used to treat mild-moderate cases of hypertension and may be the only drugs used in these cases.

-K^+ sparing diuretics such as→ Aldosterone antagonists

-If we interfere with one of these Na^+ reabsorption transporters and prevent their action → increased excretion of Na+ in urine → increased water excretion → decreased blood volume → decreased cardiac output → decreased blood pressure

Diuretics are highly recommended as first-line therapy, especially in the elderly, obese and African American patients.

ADVANTAGES of diuretics:

- **Inexpensive**
- **Combine well with other antihypertensive drug classes, such as vasodilators → because they will help in counteracting the Na+ retentive side effect of vasodilators**
- **Also, they combine well with beta blockers**
- **If we have a patient who has increased blood volume (e.g. a patient with heart failure) we can give them diuretic drugs to lower blood volume**
- **At lower doses → they cause fewer metabolic side effects but still retain their antihypertensive activity → we will later mention some of their side effects such as glucose tolerance and increasing lipid levels in the serum**
- **By controlling the doses we give to the patient → we can control these side effects , but at higher doses → there will be more side effects**
- **All diuretic drugs have the same efficacy in lowering blood pressure although not the same diuretic activity. This means their ability to help the body get rid of water is different among different classes, but the ability to lower blood pressure is similar at the dose given to patients; however, the ability to lower blood pressure becomes different between the classes at higher doses, but we don't use these higher doses clinically in treating hypertensive patients.**
- **Their early effect is diuresis which decreases blood volume → decreased cardiac output → decreased systolic pressure**
- **By using diuretic drugs for long time (long-term effect) → blood pressure will be reduced → through decreasing Na+ content in the body therefore→ decreased contraction activity of the blood vessels; why? → because Ca^{2+} is needed for contraction of blood vessels through the ion exchanger Na^+/ Ca^{2+}, less Na^+ in the body means less Ca^{2+} entering the cells and therefore less vessel contraction (less vasoconstriction) which lowers blood pressure. This effect is seen even at low doses.**
- **They also can stimulate an increase in plasma renin activity (true reflex mechanism of activation of the sympathetic nervous system)**

History of diuretics:

***Diuretics were discovered in the 1930s and were initially used to treat bacterial infections (use as antibiotics). Patients noticed that the drugs made them urinate frequently.**

***In 1950s, William Schwartz and Karl Beyer implemented this side effect and refined their usage to treat patients with hypertension.**

***Are very old antihypertensive drugs.**

***How effective are they and why do we use them? What are their general properties?**

***Reduce morbidity and mortality in patients with hypertension**

***Often first-line antihypertensive therapy either alone (in mild-moderate cases) or in combination, so they provide adequate BP control in patients with mild to moderate primary hypertension**

***Most efficacious in low-renin or volume-expanded (increased blood volume results in hypertension) forms of hypertension → since they work on the kidney increasing water and some electrolytes excretion .**

***They are very effective for treatment of hypertension in African Americans (since they have a great tendency to develop low-renin and volume expanded forms of hypertension)**

***Drawbacks (adverse effects):**

***Can adversely affect serum lipids and can reduce insulin sensitivity (only seen in continuous use and higher doses) → be careful in diabetic patients and those with abnormal lipid profiles → monitor their glucose and lipid levels**

-The effect in diabetics may occur in the long-term use of diuretics (i.e. years of treatment) and is dose-dependent. Doses used clinically aren't high enough to cause these side effects.

***Requires 2 weeks to become fully effective (initially decrease in blood volume and cardiac output) but at later stages (6-8 weeks of treatment), decreases vessel constriction (decreases PVR)**

***PVR may increase at first (first 2 weeks). Why?**

Decreased cardiac output will decrease venous return to the heart → this stimulates the sympathetic system activity which induces an increase in Renin level →Renin increases Angiotensin II which will increase peripheral vascular resistance. But later, we will lose this normal homeostasis, leading us to see the effects of the loss of Na^+ i.e. decreased PVR

**** General side effects of diuretics:**

1-K+ depletion therefore avoided in patients with arrhythmias or acute MI (take K+ supplements to prevent arrhythmias)

3-Impaired glucose tolerance

4-Increased serum lipid levels

5-Increased uric acid (gout) → most diuretic drugs cause increased absorption of uric acid

***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 functions within a damaged kidney will likely be diminished and hypertension may not effectively be resolved under these conditions**

-The three classes of diuretics we will discuss are: Thiazides, Loop/High Ceiling diuretics and K^+-sparing diuretics.

1-Thiazides

-Effective in mild and moderate hypertension with normal renal and heart function. But if the patient has abnormal renal function (if Glomerular Filtration Rate is below 40), we can't give him Thiazide diuretics → because Thiazides are not very effective in their diuresis action and therefore require preserved kidney function

Examples of thiazides :

- **Hydrochlorothiazide (prototype)**
- **Chlorthalidone (thiazide like): long acting.**
- **Bendrofluazide**
- **Indapamide (new drug): has extra action as a vasodilator and is lipid-neutral (so it doesn't have the side effect of altering the lipid profile)**

***Cause Na+ and water excretion (and are therefore used to relieve sodium retention caused by vasodilators or sympathoplegic (sympathetic antagonists) antihypertensives)**

***Reduce blood volume and Cardiac output; PVR may increase at first but chronically, PVR decreases (due to decrease in Na^+ in vascular smooth muscle)**

2-Loop diuretics/ High Ceiling diuretics

Are called high ceiling diuretics because of their high efficiency as diuretic agents; we can use them even in low renal function, as well as in severe heart failure, severe hypertension, nephrotic syndrome and heart cirrhosis

Examples: Furosemide, Torsemide

-Furosemide has metabolic side effects, but newer generations like Torsemide is free of these metabolic side effects

3-Potassium sparing diuretics

-Depending on their site of action, some of the diuretics will affect the reabsorption of K^+ in the body leading to hypokalemia.

***K+ is especially important in heart failure patients who take Digoxin; in these patients, we need ensure tight control of the level of K^+ and Na^+ equilibrium in the heart, because if hypokalemia occurs, it will cause serious problems. In heart failure patients who develop hypokalemia due to the use of diuretics, but still need to use diuretics, we can give them Potassium-sparing diuretics. These drugs reserve the reabsorption of K^+ and therefore will not cause hypokalemia.**

Examples:

- **Spironolactone**
- **Amiloride**
- **Eplerenone**
- **Triamterene**

Spironolactone has a special side effect called → gynecomastia (breast enlargement in males) because it has a structure similar to glucocorticoid sex hormones, therefore stimulates release of oestrogen. Eplerenone has less potential to develop gynecomastia

Ca^{2+} channel blockers (CCBs)

Why do think Ca^{2+} channels are a good target to treat hypertension?

1)Because blocking of calcium channels in the heart will decrease contractility → decreased CO (cardiac output). For the contraction of the muscle we need intracellular Ca^{2+} so when we block calcium channel → decreased intracellular calcium and therefore decreased contraction of the heart

2)Also, calcium has a role inside the vascular smooth muscle: it causes vasoconstriction in the vessels, increasing PVR. Using CCBs will reduce vascular contraction, thus lowering PVR

- **Classes of CCBs:**
  1) Dihydropyridine class:
  Examples : Amlodipine and Nifedipine
  ****Block Calcium in vascular smooth muscle (vasodilators)→ because they will decrease the contractility of the blood vessels, decreasing PVR**

**No effect on the heart therefore no effect on AV node conduction, so they are useful in angina (a form of ischemic heart disease) → this drug will cause vasodilation of coronary arteries so they can supply enough blood to the heart

2)Nondihyropyridines class

A)Verapamil

Inotropic effect→ affects the heart contractility

Chronotropic effect→ affects the heart rate

-Has a direct negative chronotropic and negative inotropic effect on the heart (cardiodepressive)

-It reduces the heart rate timing which is why it can have some side effects in patients with arrhythmias: can cause heart failure in patients with borderline cardiac reserve (cardiac reserve means not enough contractility in the heart to supply the whole body with blood; using this drug lowers cardiac output even further)

-Not used in patients with left ventricular dysfunction

B) Diltiazem

-Decreases AV conduction and heart rate

-Weaker negative inotropic effect than Verapamil

***Calcium Channel Blockers Side Effects**

1-Hypotension

2- Cardiac depression

3-Reflex Tachycardia (Nifedipine mainly); because of baroreceptor reflex (in response to low blood pressure sensed by the baroreceptors there will be activation of sympathetic and inhibition of parasympathetic on the heart, resulting in tachycardia). Reflex tachycardia is also a side effect in most vasodilators.

4-Headache

5- Flushing

6-Edema

7-Constipation

8-Gingival hyperplasia (gum enlargement) → Nifedipine

Drug Interactions

***Use of Verapamil or Diltiazem (non-dihydropyridines) in combination with beta-blockers could cause marked bradycardia and cardiac conduction blockade**

***Verapamil and Diltiazem may add to the inhibitory effects of Digoxin (a drug used in heart failure) on AV conduction causing cardiac arrhythmias**

***The above drug-drug interactions produce bad effects. However, use of Amlodipine in combination with ACEIs (Angiotensin converting enzyme inhibitors) reduces cardiovascular events in hypertensive patients (a good effect of drug-drug interaction!)**

CCB Indications

-Useful in low-renin hypertension (low-renin hypertension is usually more common in African American and elderly patients)

-Useful in controlling BP and cardiovascular events in patients with isolated systolic hypertension, particularly the elderly.

Beta 1 blockers(Beta-Adrenergic Receptor Blockers)

Prevent the binding of epinephrine and norepinephrine to beta adrenergic receptors

What happens when beta-1 receptors found in the heart are blocked?

- ***Decreased heart contractility and heart rate → decreased cardiac output (main effect used to treat hypertension)**
- ***Decreased Renin release (blocks beta 1 kidney receptors)**
- ***Central inhibition of sympathetic activity by inhibiting norepinephrine release**

-Propranolol

Non-selective beta blocker that can affect beta 1 and 2 receptors

It causes bronchoconstriction (by blocking beta 2 receptors in lungs) which is why Propranolol is not used in patients suffering asthma or coronary heart disease.

Other newer beta blockers (more selective to beta 1):

Atenolol, Metaprolol, Nadolol, Timolol, Esmolol, Atelolol, Acebutalol

- **Non-immediate therapeutic effectiveness**
- **Used in high-renin hypertension (alone or in combination)**
- **Used in hyperkinetic hearts as they decrease heart rate**
- **Used in other cardiovascular conditions such as cardiac arrhythmias and in heart failure (only if borderline cardiac reserve isn't reached)**
- **Not very effective in African Americans because beta blockers are effective in high-renin hypertension, but Africans usually have low-renin hypertension**
- **They don't cause postural/orthostatic hypotension (orthostatic hypotension is mostly caused by vasodilators since they affect constriction in the vasculature)**
- **Even when using selective beta blockers, we must worry about bronchoconstriction/bronchospasms because at high doses we always lose the selectivity of the drug**

***Side effects of Propranolol**

- **Hypotension, AV block, severe bradycardia (negative chronotropy), possibly heart failure therefore careful consideration in patients with conduction problems/bradycardia**
- **Bronchial constriction/spasm, do not use in asthmatic patients**
- **Acute withdrawal syndrome (due to receptor upregulation in response to these blockers) therefore must not be stopped abruptly**
- **Predisposition to MI or cardiac arrhythmia**
- **Impaired lipid and glucose metabolism: increase triglyceride levels and decrease HDL levels; induce glucose intolerance. Therefore use carefully in diabetic and obese patients**
- **Nightmares and hallucinations (since it crosses BBB)**
- **Fatigue, depression, impotence**
- **Claudication**