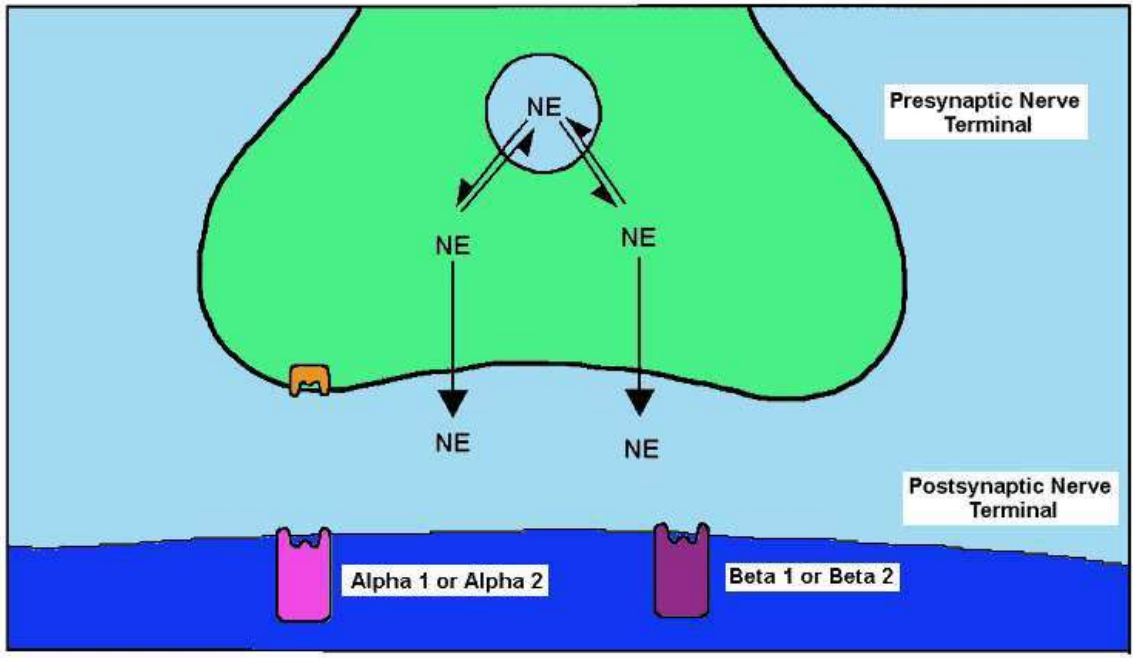
Case 1

- A patient with pheochromocytoma(嗜铬细胞瘤) had a BP of 250/150 mmHg and was i.v. injected phentolamine rapidly, resulted in BP decreasing to 65/40 mmHg.
- Why this happened, how to deal with the condition?

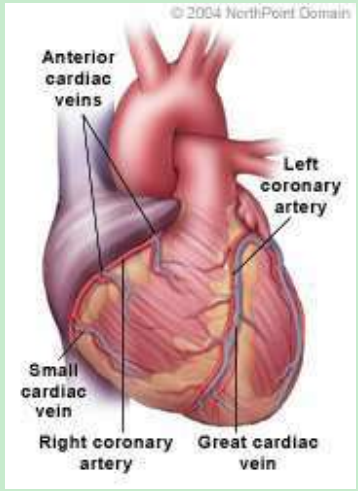
Classification:

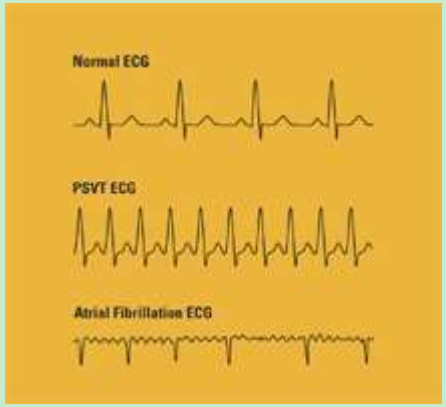
- α-R antagonists
- β-R antagonists
- α,β antagonists.

Their major effect is to occupy eitherα, or β receptors and prevent their activation by catecholamines and related agonists.



Beta-receptor antagonist drugs are firmly established in the treatment of hypertension, ischemic heart disease, arrhythmias, endocrinologic and neurologic disorders, and other conditions.





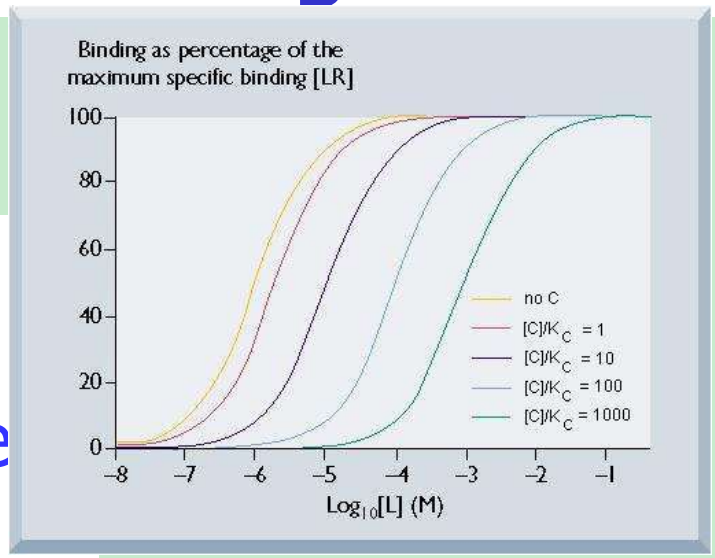
§ 1 α- Adrenoceptor Antagonists

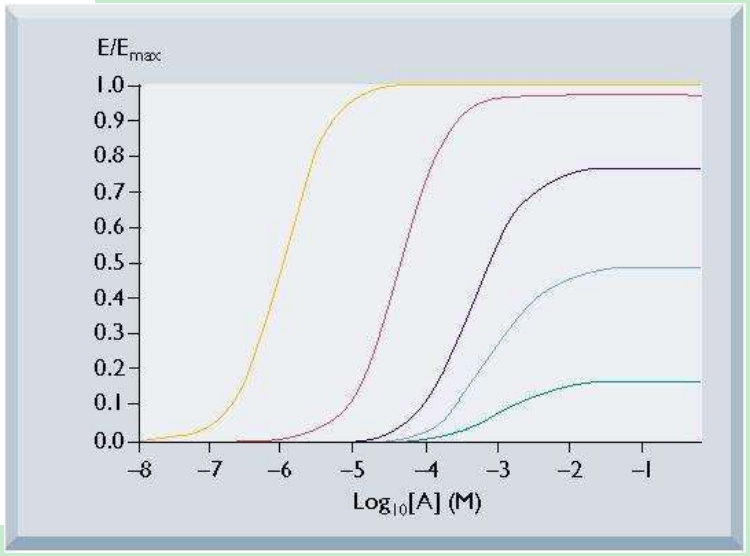
Classification

- α-receptor antagonists may be
  - reversible or irreversible.
  - Selective or non-selective

Reversible antagonists can dissociate from receptors. Phentolamine, tolazoline, prazosin and labetalol are reversible.

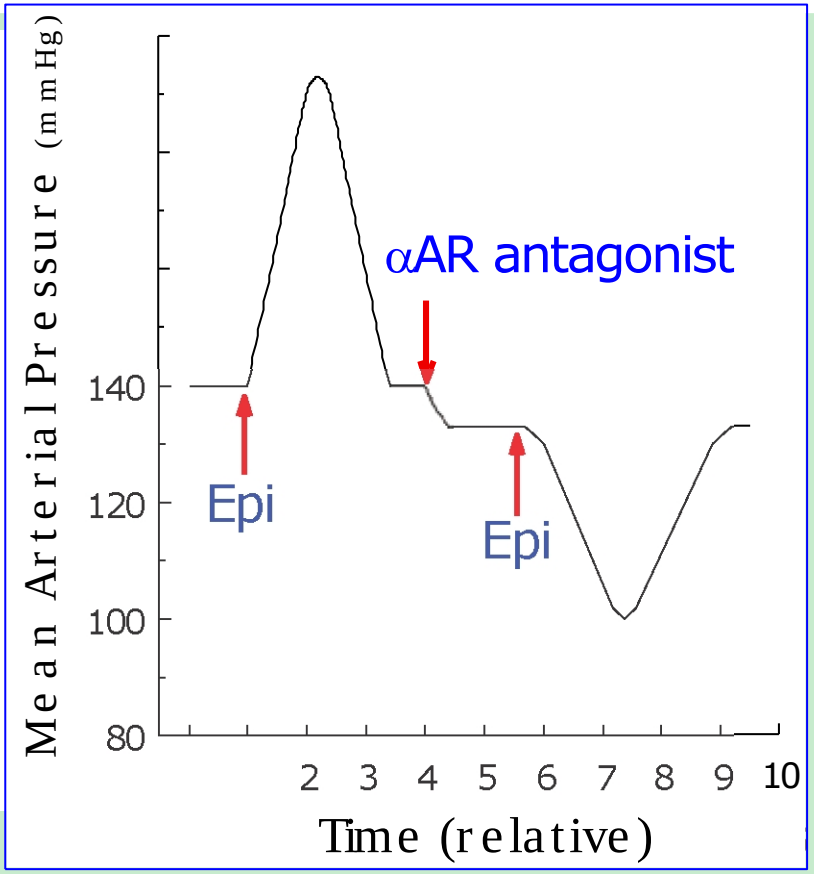
Phenoxybenzamine is irreversible.



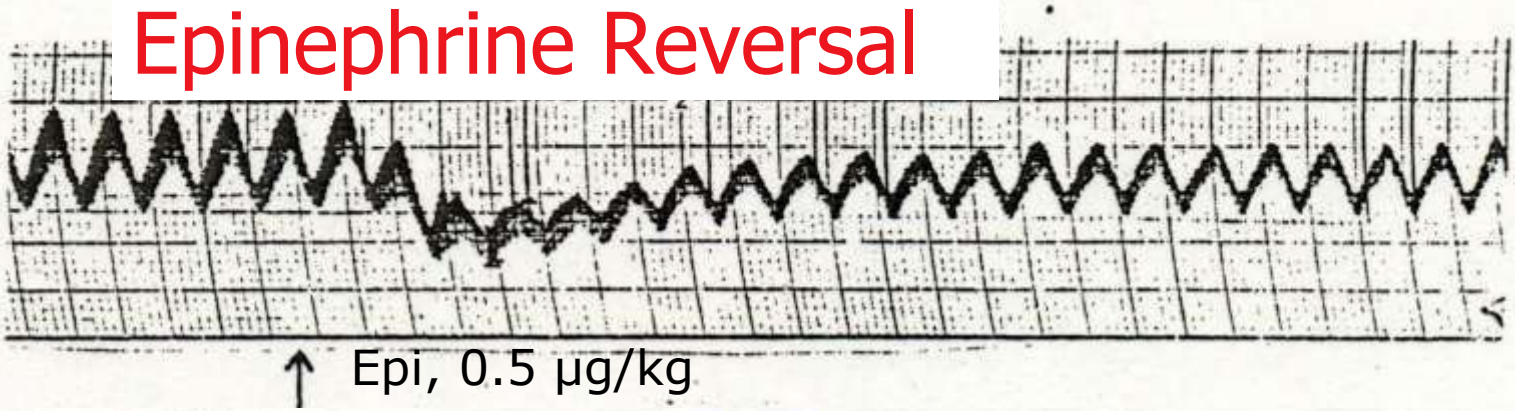


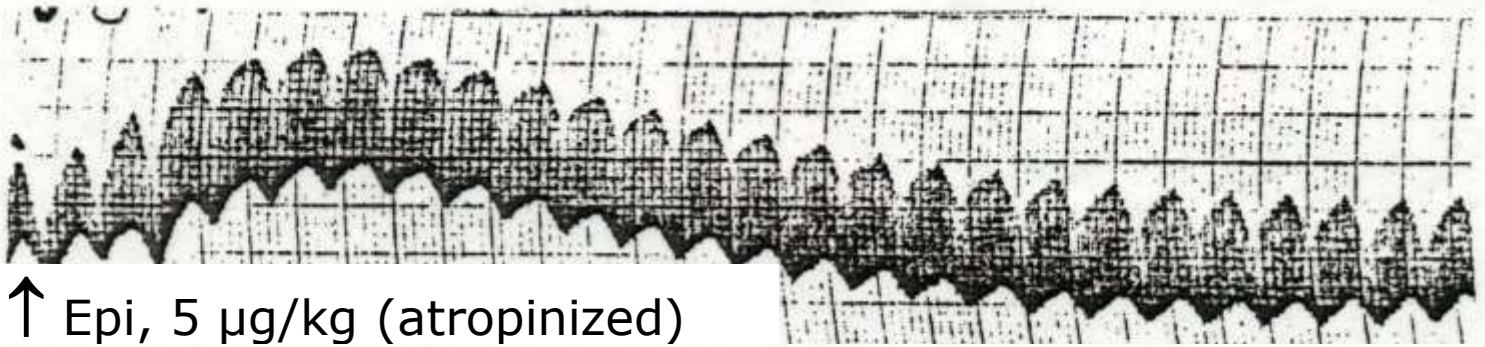
α- antagonist drugs block α receptors, dilate vascular smooth muscle, lower peripheral resistance and BP; can prevent the pressor effects of αagonists.

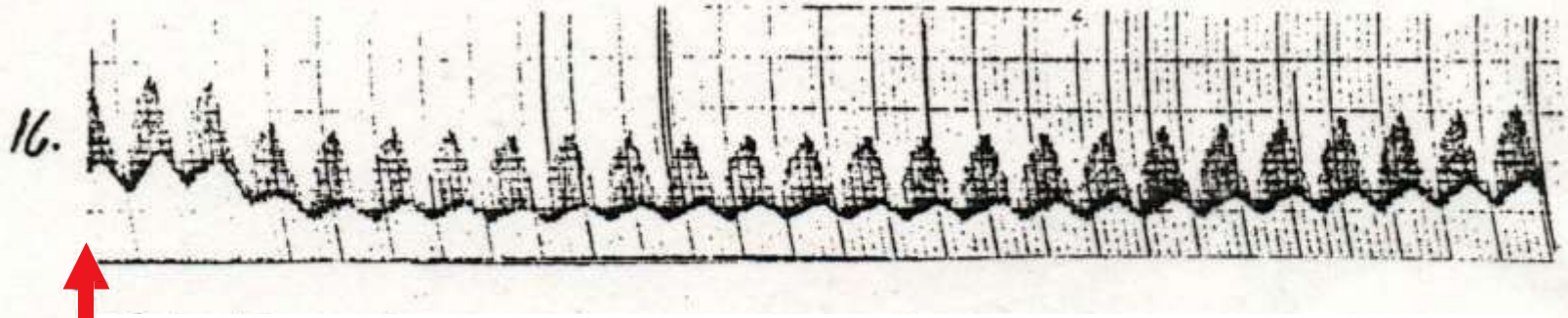
In the case of epinephrine with both αand β_2 effects, αreceptor antagonism may convert a pressor to a depressor response which is called adrenaline reversal.



Epinephrine Reversal







Inject Epi, 5 µg/kg. Pretreatment: atropine and 5 mg/kg phentolamine

Non-selective αantagonists(P67)

Phentolamine (regitin)

- a potent competitive antagonist at bothα_1 and α_2 receptors.

1. Blood vessel: reduces peripheral resistance

2. Heart: can stimulate the heart due to

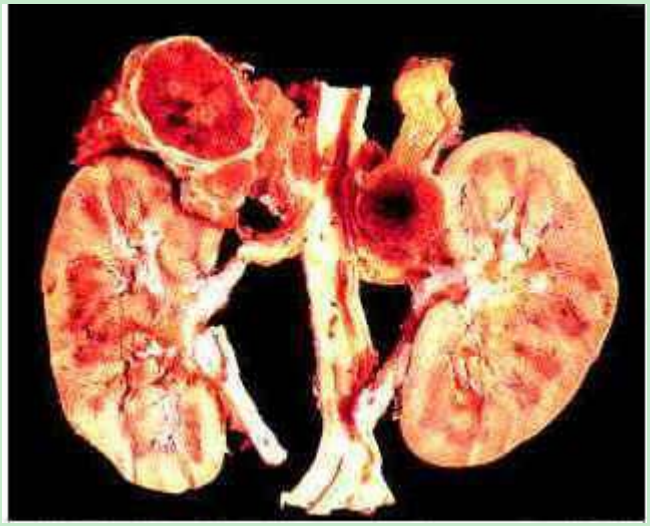
   - baroreflex mechanisms resulting in sympathetic stimulation.

   - blocks α_2 receptors, enhance release of NE from sympathetic nerves, contributing to cardiac stimulation via β receptors.

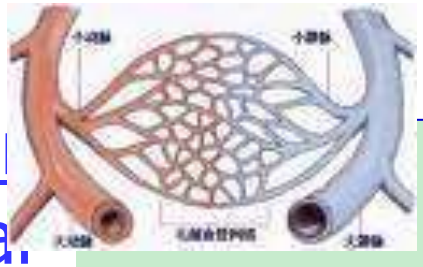
3. also activate M and histamine (H) receptors, has multiple potential actions,

Clinical uses

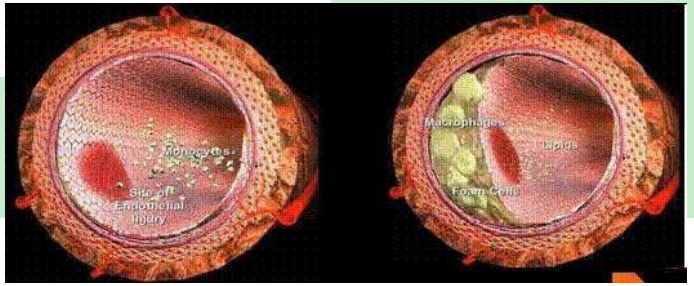
- Peripheral vascular occlusive diseases
- Local use to reverse the intense local vasoconstriction caused by NA leak
- pheochromocytoma (secrete catecholamines).
- Shock
- Infarction and CHF
- Other uses



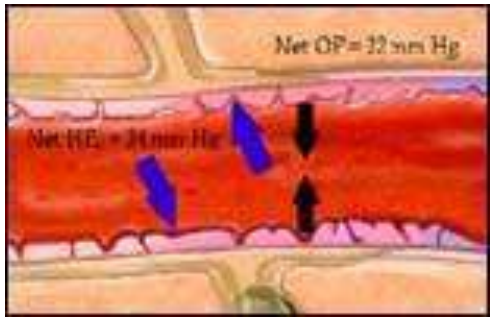
Peripheral Vascular Disease



Theα-receptor-blocking drugs have beeı used in the treatment of peripheral vascula. occlusive disease.



Local Vasoconstrictor



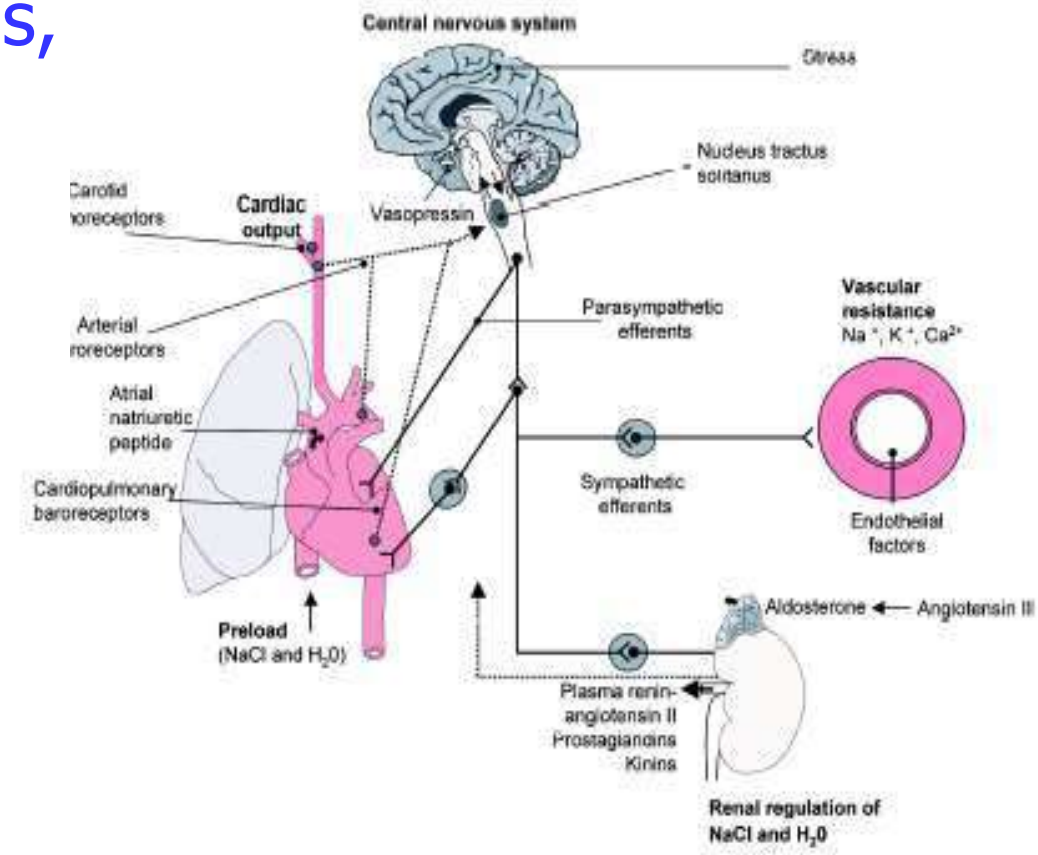
Phentolamine has been used to reverse the vasoconstriction caused by infiltration of αagonists (NE) into subcutis during intravenous administration.

The αantagonist is administered by local infiltration into the ischemic tissue.

Adverse effects

1.postural hypotension and reflex tachycardia. due to antagonism of sympathetic nervous system stimulation of α1 receptors in venous smooth muscle.

2.tachycardia, arrhythmias, myocardial ischemia and nasal congestion as well as headache.



Tolazoline is similar to phentolamine.

It has limited clinical application in the treatment of pulmonary hypertension in newborn infants with respiratory distress syndrome.

Phenoxybenzamine(酚卞明)

binds covalently to αreceptors, causing irreversible blockade of long duration (2 d).

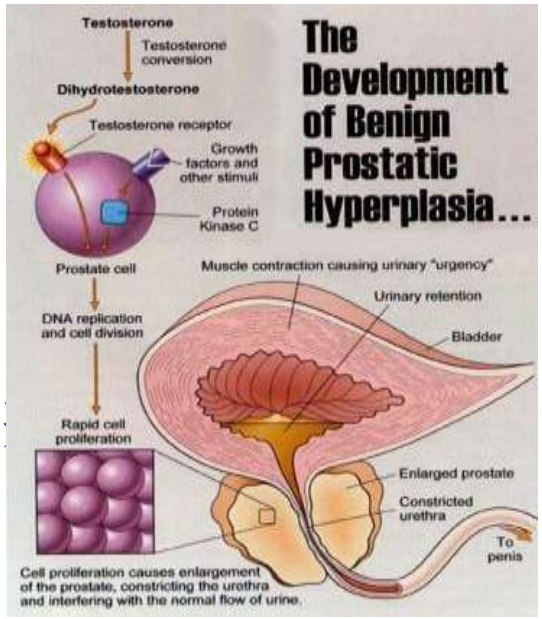
reduces BP when sympathetic tone is high and little fall in BP in normal supine(仰卧) individuals. It inhibits reuptake of NE by blocking α_2 on presynaptic terminals and increase cardiac output. It also blocks histamine (H_1), ACh, and serotonin receptors ,αreceptors.

Clinical uses:

Peripheral vascular occlusive diseases;

Shock treatment; pheochromocytoma,

benign prostatic hyperplasia(良性前列腺增生



Adverse effects

The most important are postural hypotension, tachycardia and nasal stuffiness.

Since phenoxybenzamine enters the CNS, it may cause less specific effects, including fatigue, sedation, and nausea.

selective α-receptor antagonists

Alpha1 selective drugs

Prazosin（哌唑嗪） is highly selective for α_1 receptors, leads to vasodilation. It is effective in the management of hypertension. It has relatively low affinity for α_2 receptors (1/ 1000). This may explain the relative absence of tachycardia.

Terazosin（特拉唑啉） is another reversible α_1-selective antagonist that is effective in hypertension, has high bioavailability but is extensively metabolized in the liver. Its half-life is 9-12 h.

Tamsulosin（坦洛新） high bioavailability, half-life is 9-15 h.

Alpha2 selective drugs: yohimbin（育亨宾）

Hypertension

Prazosin family of α_1-selective antagonists are efficacious in the treatment of hypertension.

The adverse effect is postural hypotension(体位性低血压), which may be severe after the first dose.

Nonselective α antagonists are not used in primary hypertension.

§ 2 β-Receptor Antagonists

Beta-blocking drugs occupy βreceptors and reduce receptor occupy by catecholamines and other βagonists.

Most β-blocking drugs are pure antagonists;

Some are partial agonists; ie, they cause partial activation of the receptor, less than that caused by the full agonist.

Partial agonists inhibit the activation of receptors in the presence of high catecholamine concentrations but moderately activate the receptors in the absence of endogenous agonists.

Case 2

- 26 yrs male, got insomnia, palpitation and e thin but with good appetite for half a year. PE: slight exophthalmos (突眼)，BP 150/80 mmHg, pulse &HR 124/min, hand tremor, II degree thyroid enlargement. Lab test found increased level of plasma T3 & T4, decreased TSH level.
- Treated with propranolol 10 mg, tid

Classification of the β-receptor blocking drugs

Some of these antagonists have a higher affinity for β_1 than forβ_2 receptors

The selectivity is dose-related, it tends to diminish at higher concentrations.

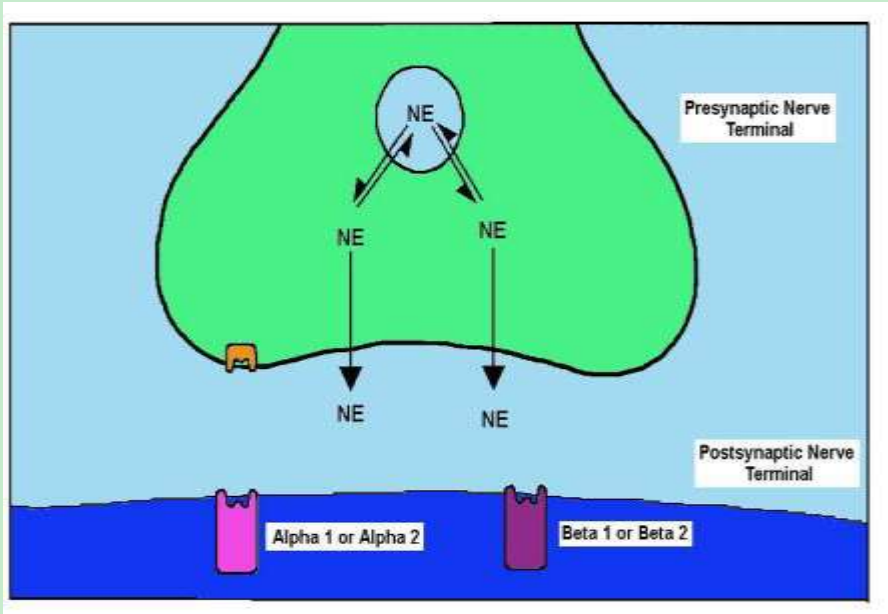
Other major differences among β antagonists relate to their pharmacokinetics.

Pharmacokinetics of β antagonists

- Oral administration
- Variation in bioavailability
- Propranolol blood concentration variated between 4~25 times for the same dose

Pharmacodynamics of theβ Antagonists

Most of the effects of these drugs are due to occupancy and blockade of βreceptors.

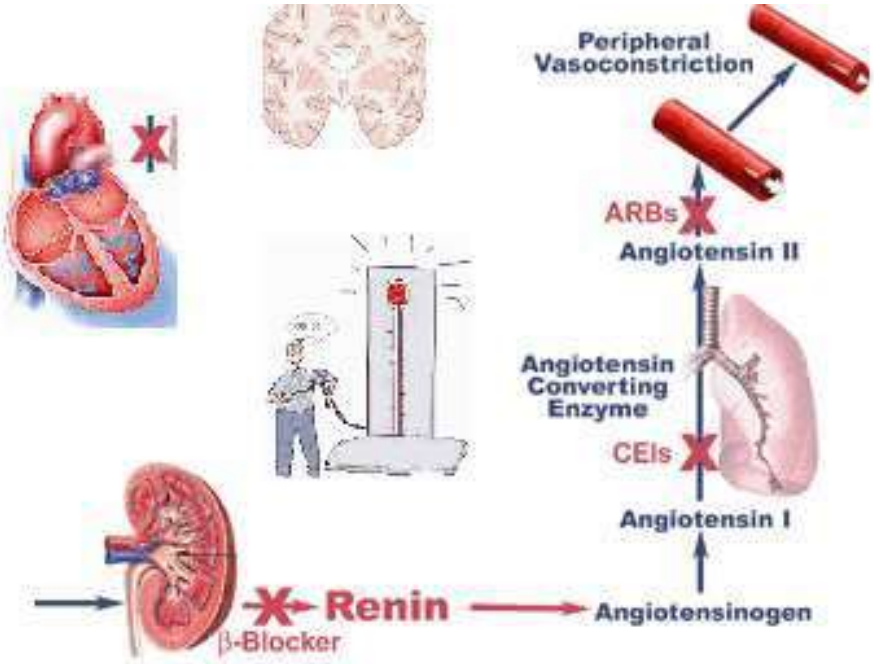


However, some actions may be due to partial agonist activity at βreceptors (intrinsic sympathomimetic activity, ISA) and local anesthetic action, which differ among the β-blockers.

Effects on the Cardiovascular System

Beta-adrenoceptor-blocking drugs are of major clinical importance in the treatment of hypertension.

The mechanisms include effects on the heart and blood vessels, the rennin-angiotensin system, and the CNS



Conventional doses do not cause hypotension in healthy individuals with normal BP.