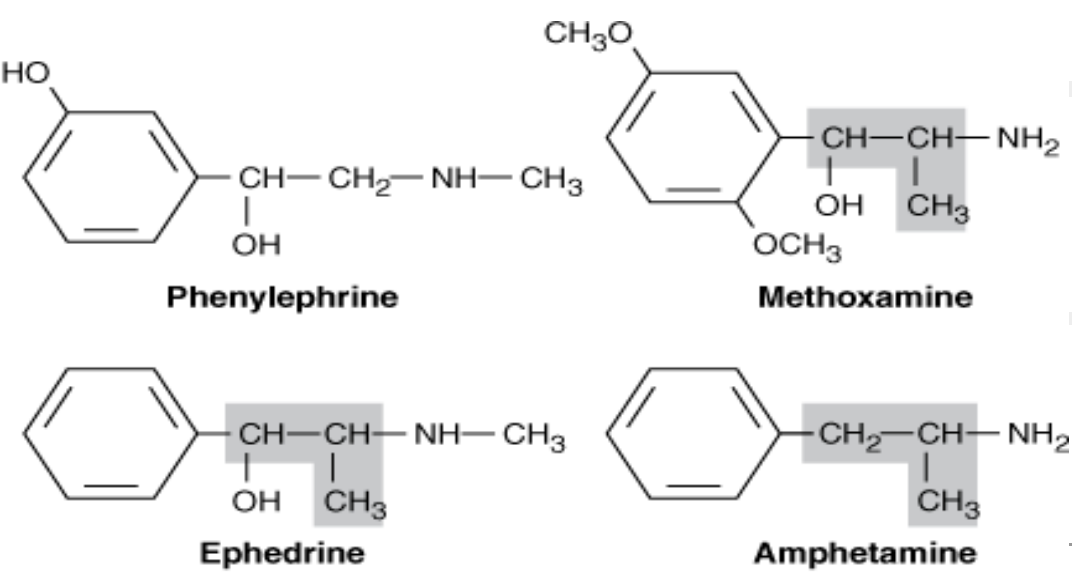
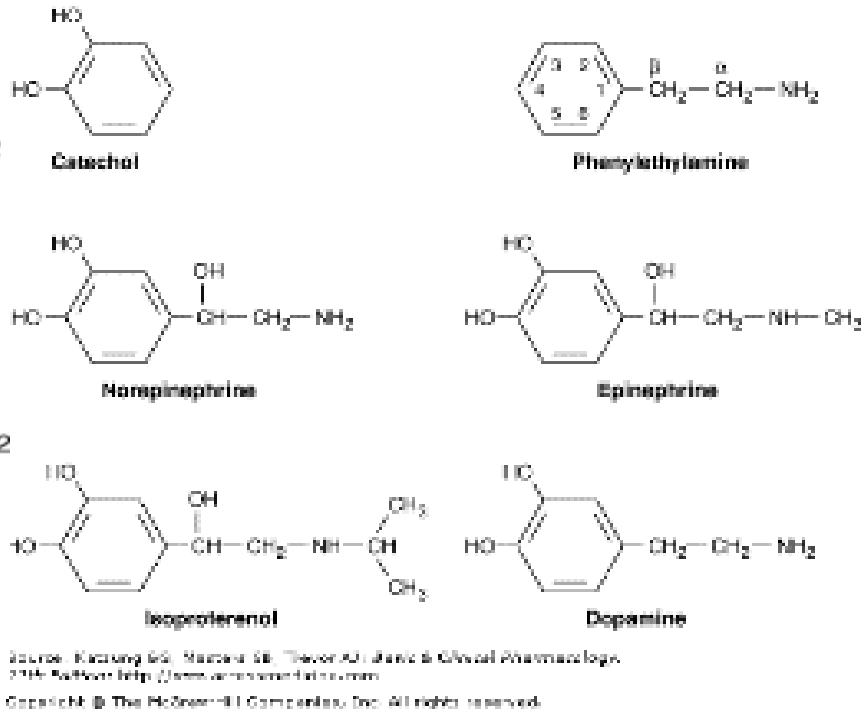
Sympathomimetic Drugs 1

	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	α 1 >α 2 >>>>> β
Clonidine, methylnorepinephrine	α 2 > α 1 >>>>> β
Mixed alpha and beta agonists	
Norepinephrine	α 1 = α 2; β1 >> β2
Epinephrine	α 1 = α 2; β1 = β 2
Beta agonists	
Dobutamine	β 1 > β 2 >>>> α
Isoproterenol	β1 = β 2 >>>> α
Albuterol (Salbutamol), terbutaline,, ritodrine	β 2 >> β 1 >>>> α

Medicinal Chemistry of Sympathomimetic Drugs



None catecholamines



catecholamines

Organ System Effects of Sympathomimetics.

Cardiovascular System.

The net effect **of a Sympathomimetic drug** depends on:

-its **relative selectivity for α or β** adrenoceptors

- the compensatory **baroreflex** mechanisms aimed at restoring homeostasis.

Effects of Alpha1-Receptor Activation

A pure **α** agonist e.g. **phenylephrine** causes:

arterial and venoconstriction ↑ peripheral arterial resistance ↓ venous capacitance.

↑ arterial resistance leads to

a rise in blood pressure (BP).

The rise in BP elicits a baroreceptor - mediated increase in vagal tone with slowing of the heart rate.

If baroreflex function is removed by pretreatment with the ganglionic blocker **trimethaphan**, the pressor effect of phenylephrine is increased approximately tenfold, and bradycardia is no longer observed.

The **skin vessels** & the **splanchnic vessels** have predominantly **α1** receptors and constrict in response to epinephrine and norepinephrine.

Vessels in **skeletal muscle** may constrict or dilate depending on whether alpha or **beta 2** receptors are activated.

The blood vessels of the **nasal mucosa** have **α** 1 receptors, and local vasoconstriction induced by sympathomimetics produces a **decongestant** action.

Effects of Alpha2-Receptor Activation

Alpha2 adrenoceptors are present in the vasculature, and their activation leads to **vasoconstriction**.

This effect is observed only when α 2 agonists are given by **rapid IV** injection or in **very high oral doses**.

When given systemically, these vascular effects are obscured by the **central effects of α 2 receptors**, which lead to **inhibition of sympathetic tone** and a decrease in BP.

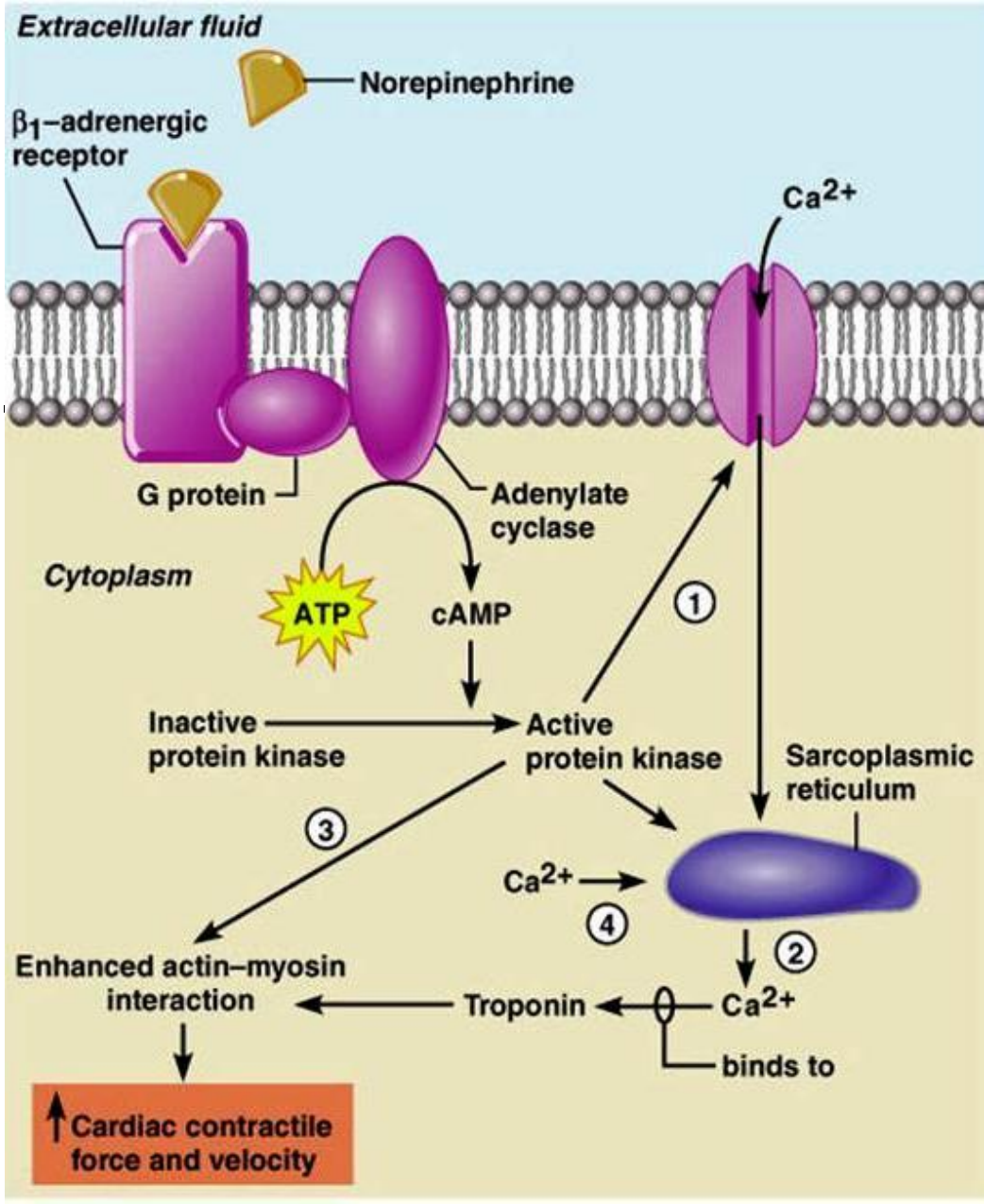
Hence, α 2 agonists are used in the treatment of hypertension .

Effects of Beta-Receptor Activation

Stimulation of β1 receptors in the **heart** increases **cardiac output** by:

- stimulating contractility
- increasing the heart rate

β agonists also **decrease peripheral resistance** by activating **β 2** receptors, causing vasodilation in vascular beds of sk. Muscles.



Isoproterenol activates both **β 1** and **β 2** receptors.

The net effect is to maintain or **slightly increase systolic pressure** and to **lower diastolic pressure**, so that mean blood pressure is decreased

Beta-receptor activation results in increased calcium influx in cardiac cells.

Pacemaker activity is increased **(positive chronotropic effect)**.

Conduction velocity in the AV node is increased (**positive dromotropic** effect), and the **refractory period is decreased**.

Intrinsic contractility is increased (**positive inotropic** effect).

The direct effects on heart rate (HR) may be dominated by a **reflex** response to BP changes.

Physiologic stimulation of the heart by catecholamines increases coronary blood flow.

Effects of Dopamine-Receptor Activation

Low IV infusion of dopamine promotes vasodilation of renal, splanchnic, coronary, and cerebral vessels, via activation of **D1** receptors.

Activation of the **D1** receptors in the renal vasculature induce **natriuresis (**↑Na+ excretion**).**

The renal effects of dopamine have been used clinically to improve perfusion to the kidney in situations of oliguria (abnormally low urinary output).

Moderate infusion rate of DA stimulate **β1 receptors** in the heart leading to increasing contractility & the HR increases slightely.

DA is used to treat congestive heart failure.

At low doses, peripheral resistance may decrease.

At higher rates of infusion, dopamine activates vascular α receptors, leading to vasoconstriction, including in the renal vascular bed (α receptor).

Consequently, high rates of infusion of dopamine may mimic the actions of epinephrine.

Noncardiac Effects of Sympathomimetics

Activation of **β 2** receptors in **bronchial smooth muscle** leads to **bronchodilation**, and β 2 agonists are important in the treatment of **asthma.**

In the **eye, α** receptors; activation by drugs such as phenylephrine causes **mydriasis** .

Alpha agonists also increase the outflow of aqueous humor from the eye and can be used clinically to **reduce intraocular pressure.**

In contrast, beta agonists have little effect, **but beta *antagonists* decrease the production of aqueous humor**.

These effects are important in the treatment of glaucoma

The bladder base, urethral sphincter, and prostate contain **alpha receptors** that mediate contraction and control urination. **α 1A** receptors play an important role.

Alpha-receptor activation in the ductus deferens, seminal vesicles, and prostate plays a role in normal ejaculation.

Hormone secretion

In pancreatic islets, **β receptors** increase and **α 2 receptors** decrease **insulin** secretion, but the major regulator of insulin release is the plasma concentration of glucose.

Renin secretion is stimulated by β 1 and inhibited by α 2 receptors.

CNS

The catecholamines are almost completely excluded by **blood-brain barrier.**

Peripheral effects of β- adrenoceptor agonists such as tachycardia and tremor are similar to the **somatic manifestations of anxiety.**

Noncatecholamines (**amphetamines**), which readily enter the CNS produce CNS effects.

These actions vary from mild alerting, with improved attention to boring tasks to full-blown psychotic behavior.

May also cause elevation of mood, insomnia, euphoria, & anorexia

Effects on Metabolism.

Increase lipolysis (**β 3**) with enhanced release of free fatty acids and glycerol into the blood.

Glycogenolysis in the liver, increasing glucose release into the blood **(β2)**.

Promotes uptake of **K** into cells, leading to a fall in extracellular **potassium (β 2)**

This may lead to a fall in the plasma potassium concentration during stress or protect against a rise in plasma potassium during exercise.