Adrenergic Agonists

Pharmacology –Lecture 10

3rd Grade

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Adrenergic Agonists

norepinephrine (noradrenaline)

epinephrine (adrenaline)

→ Stimulate Adrenergic receptors

Adrenergic receptors activator are termed sympathomimetics:

- direct-acting agonists
- indirect-acting agonists

Blocker for adrenergic receptors activity are termed sympatholytics

Catecholamines

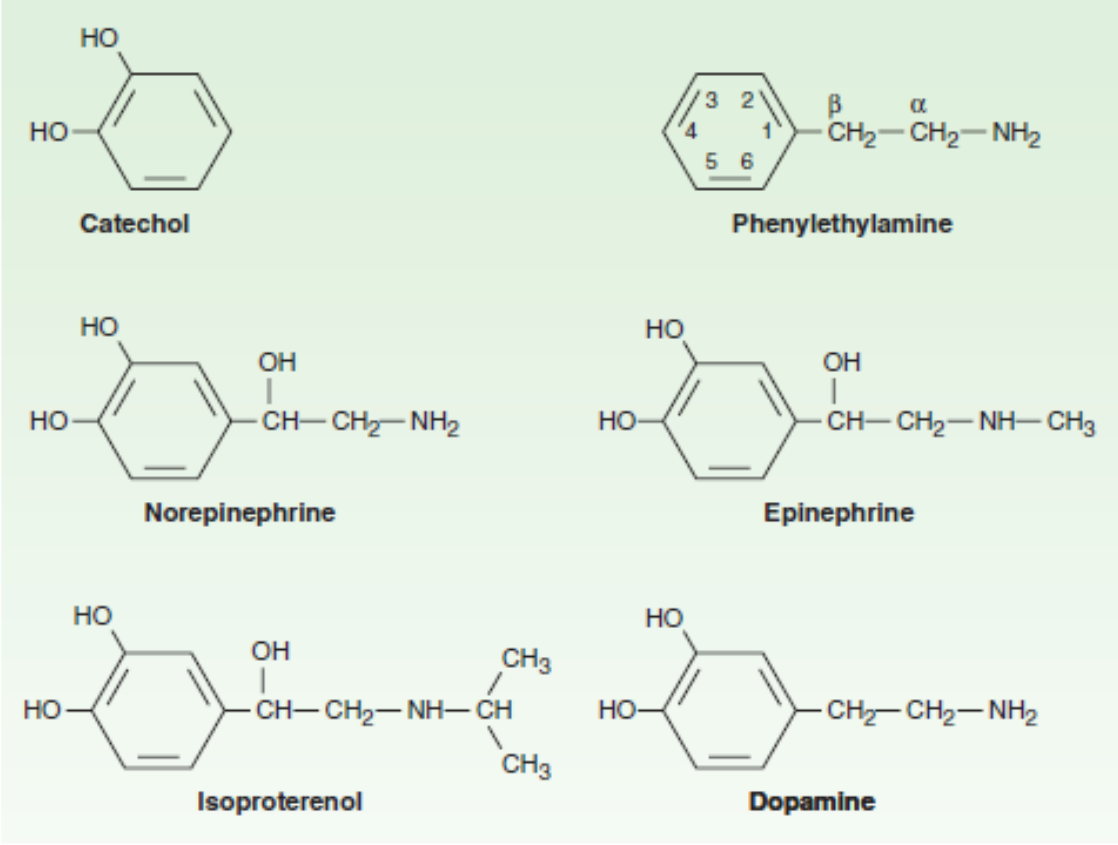
Catechol moiety (a benzene ring with two adjacent hydroxyl groups) and an amine side chain

Noradrenaline (**norepinephrine**)

Adrenaline (**epinephrine**)

Dopamine

Isoprenaline (**isoproterenol**)



Adrenergic Neuron

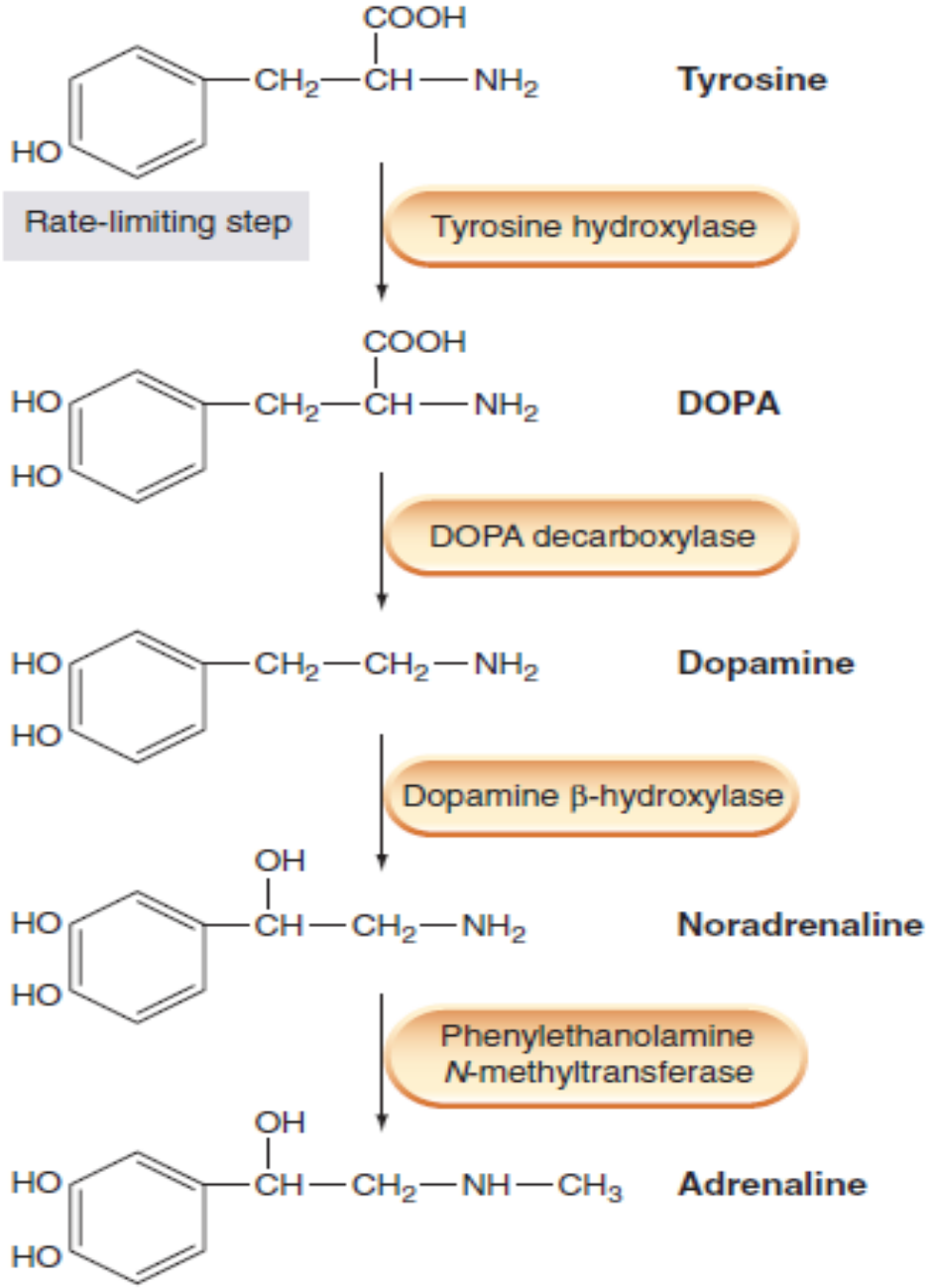
Adrenergic neurons release norepinephrine as the primary neurotransmitter.

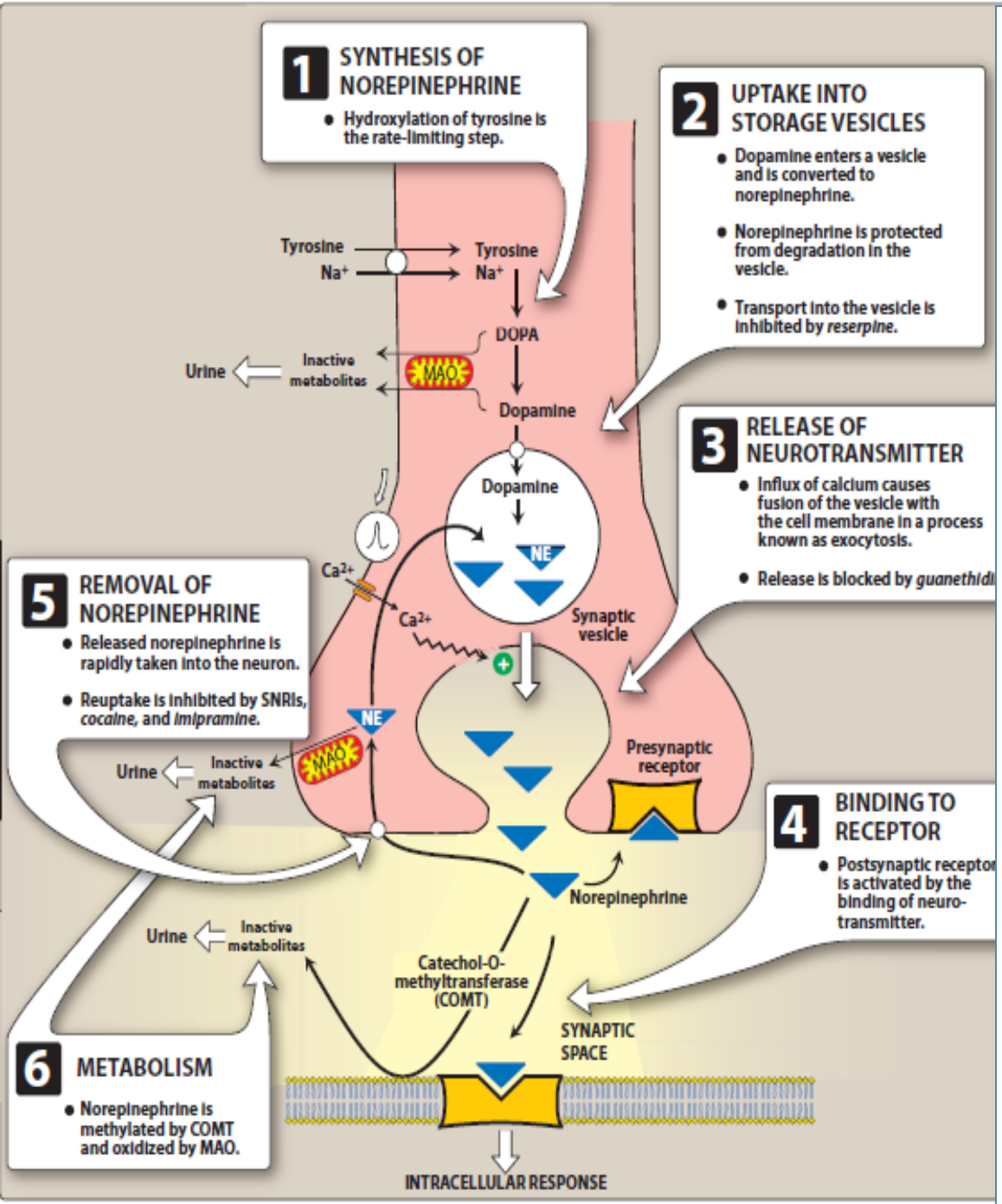
These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs.

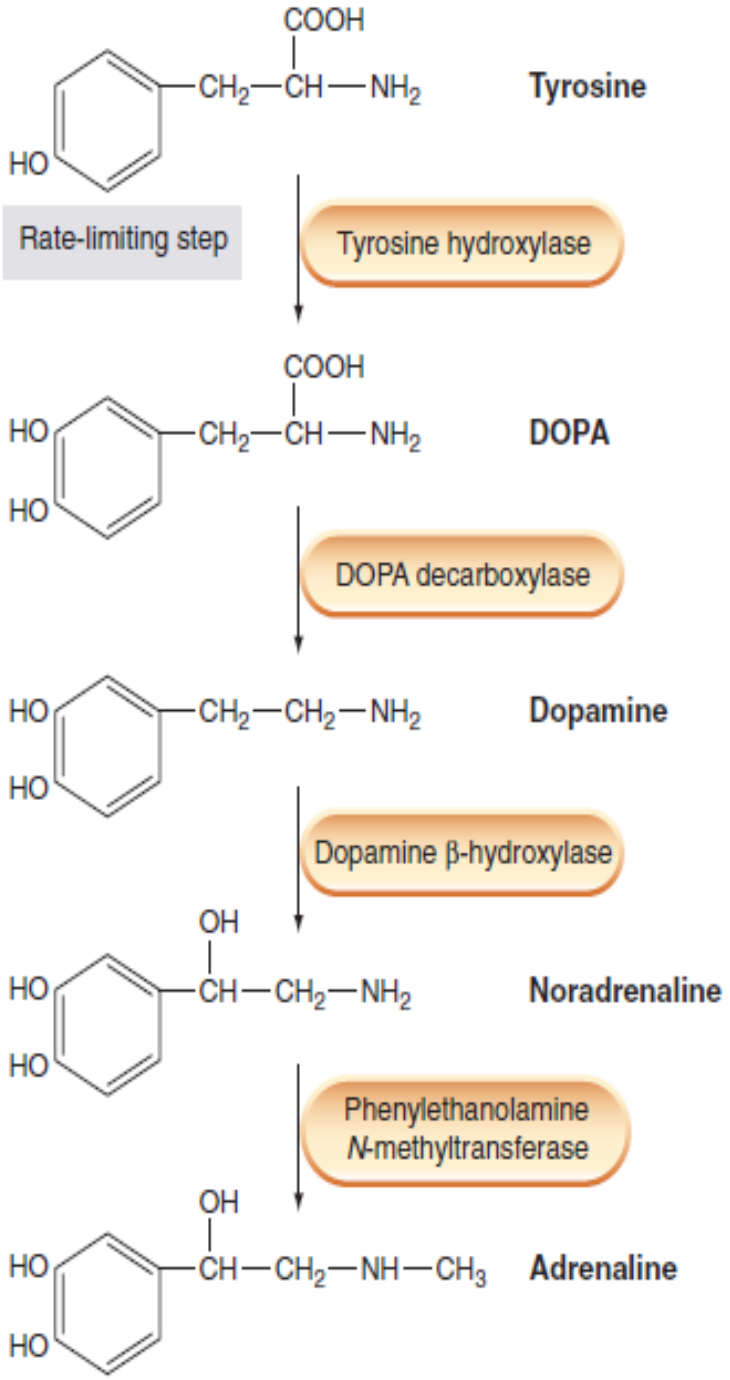
Neurotransmission at adrenergic neurons

Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap

Synthesis of norepinephrine



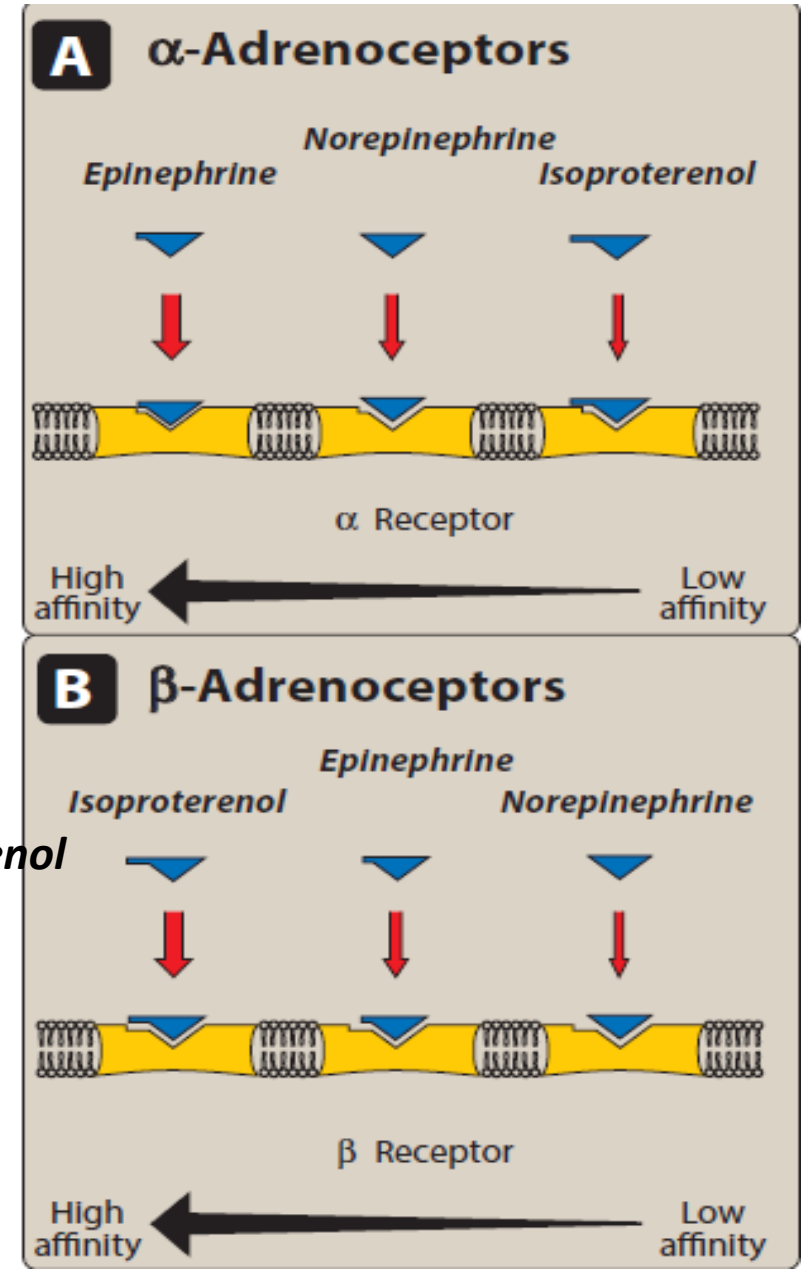

1 SYNTHESIS OF NOREPINEPHRINE
• Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
• Dopamine enters a vesicle and is converted to norepinephrine.
• Norepinephrine is protected from degradation in the vesicle.
• Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
• Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
• Release is blocked by guanethidi
4 BINDING TO RECEPTOR
• Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
• Released norepinephrine is rapidly taken into the neuron.
• Reuptake is inhibited by SNRIs, cocaine, and imipramine.
6 METABOLISM
• Norepinephrine is methylated by COMT and oxidized by MAO.
Tyrosine
Na+
Tyrosine
Na+
DOPA
Urine
Inactive metabolites
MAO
Dopamine
Dopamine
NE
Ca2+
Ca2+
Synaptic vesicle
NE
MAO
Urine
Inactive metabolites
Presynaptic receptor
Norepinephrine
Urine
Inactive metabolites
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE
INTRACELLULAR RESPONSE


COOH
CH2—CH—NH2
HO
Tyrosine
Rate-limiting step
Tyrosine hydroxylase
COOH
CH2—CH—NH2
HO
HO
DOPA
DOPA decarboxylase
CH2—CH2—NH2
HO
HO
Dopamine
Dopamine β-hydroxylase
OH
CH—CH2—NH2
HO
HO
Noradrenaline
Phenylethanolamine N-methyltransferase
OH
CH—CH2—NH—CH3
HO
HO
Adrenaline

Adrenergic receptors (adrenoceptors)

Two main families of receptors, designated α and β,

Each of these main receptor types has a number of specific receptor subtypes that have been identified



α-Adrenoceptors

epinephrine ≥ ***norepinephrine*** >> ***isoproterenol***

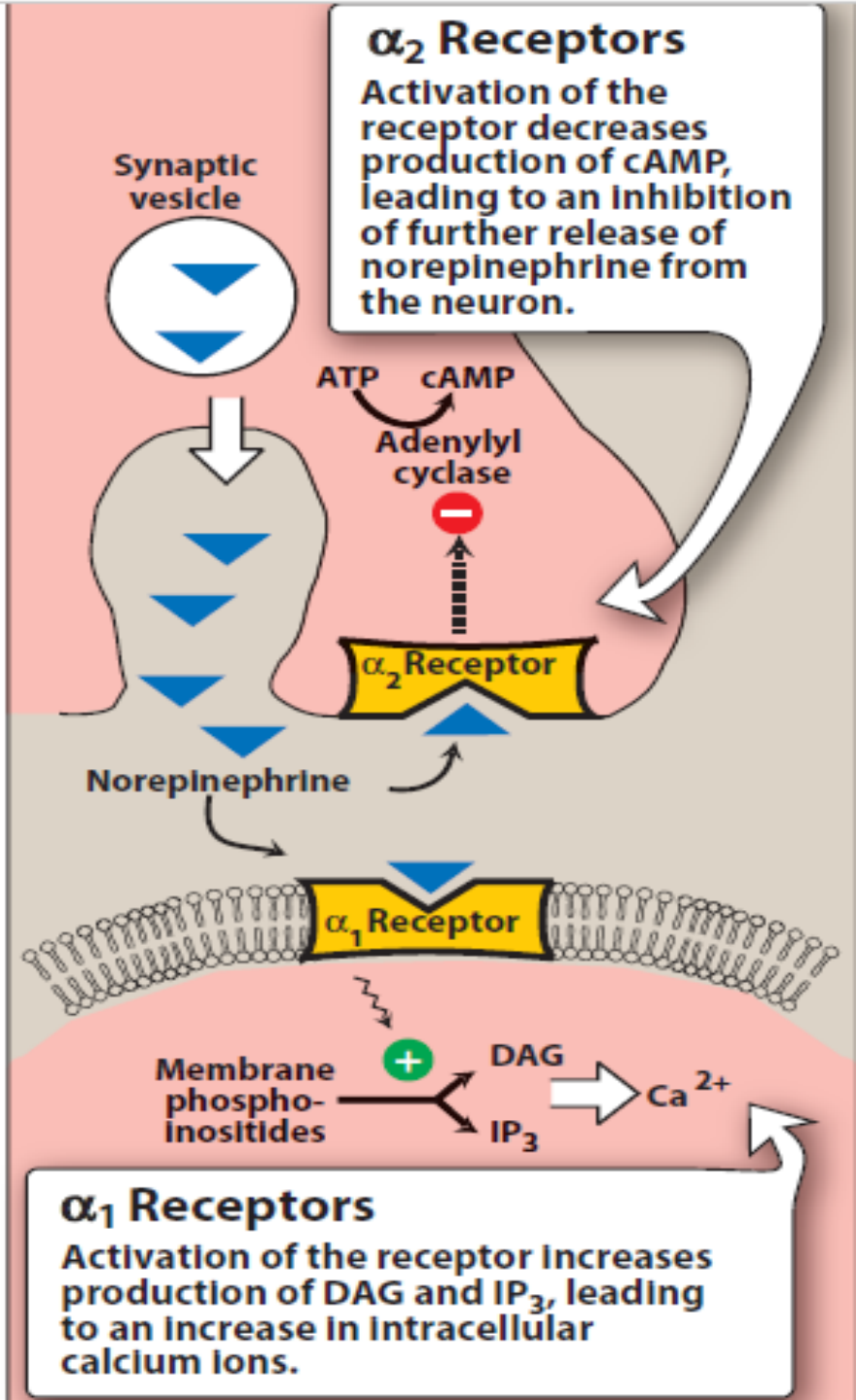
α-adrenoceptors have two subgroups α_1 and α_2

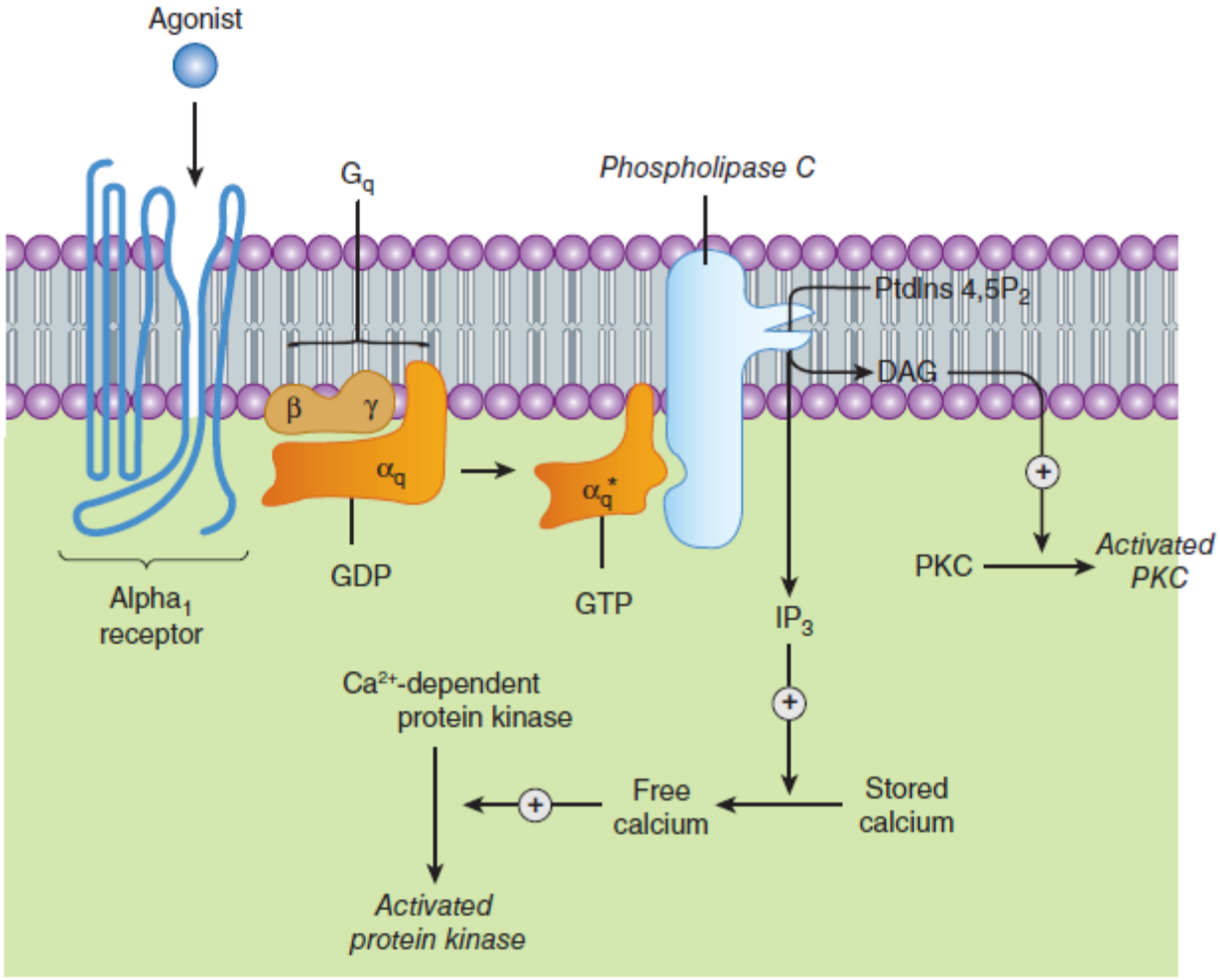
Phenylephrine agonist for α_1

Clonidine agonist for α_2

α1 Receptors

Activation of α_1 receptors initiates a series of reactions through the G protein activation of phospholipase C, ultimately resulting in the generation of second messengers inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).

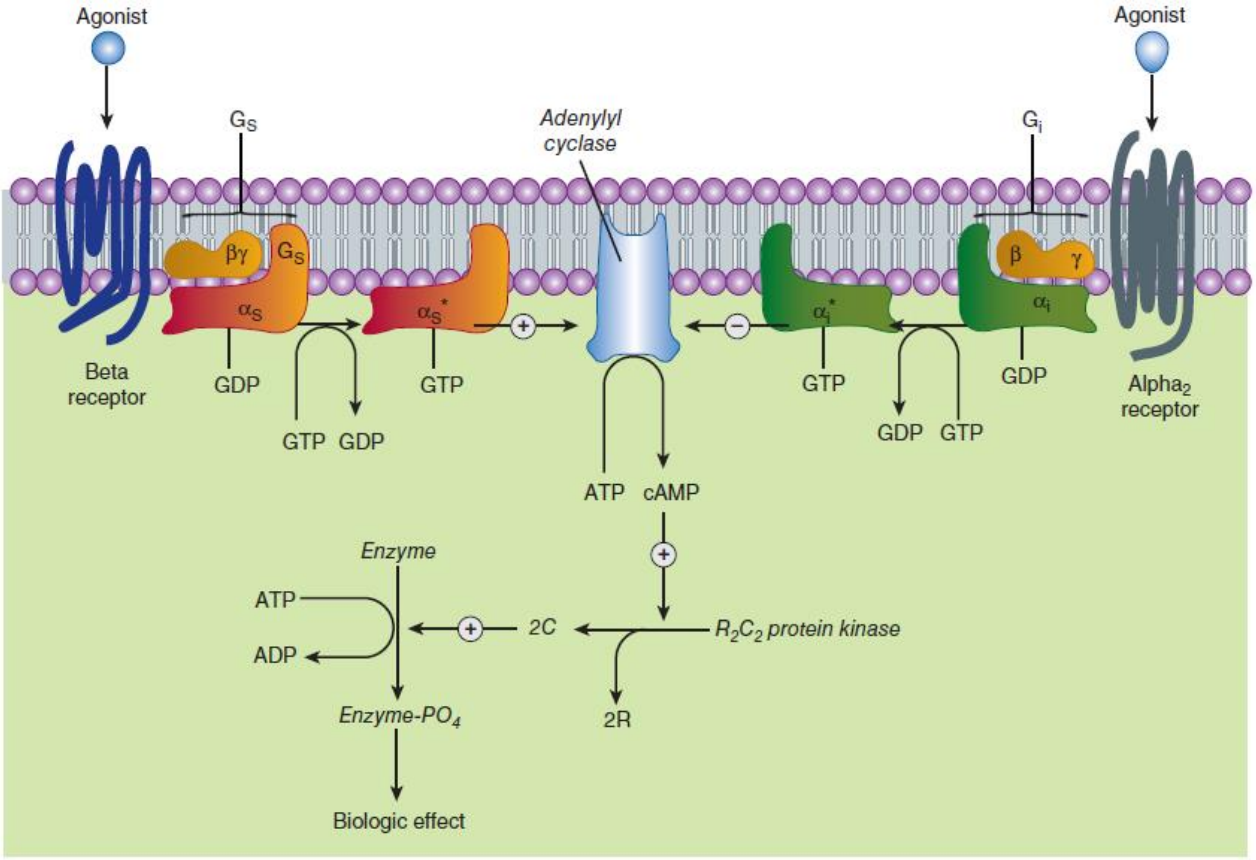



Agonist
G_q
Phospholipase C
PtdIns 4,5P_2
DAG
β
γ
α_q
α_q^*
GDP
GTP
Alpha$_1$ receptor
PKC
Activated PKC
IP_3
Ca^{2+}-dependent protein kinase
Free calcium
Stored calcium
Activated protein kinase

α_2 Receptors

located primarily on sympathetic presynaptic nerve endings

Effects of binding at α_2 receptors are mediated by inhibition of adenylyl cyclase and by a fall in the levels of intracellular cAMP.



Further subdivisions

α_{1A}, α_{1B}, α_{1C}, and α_{1D}

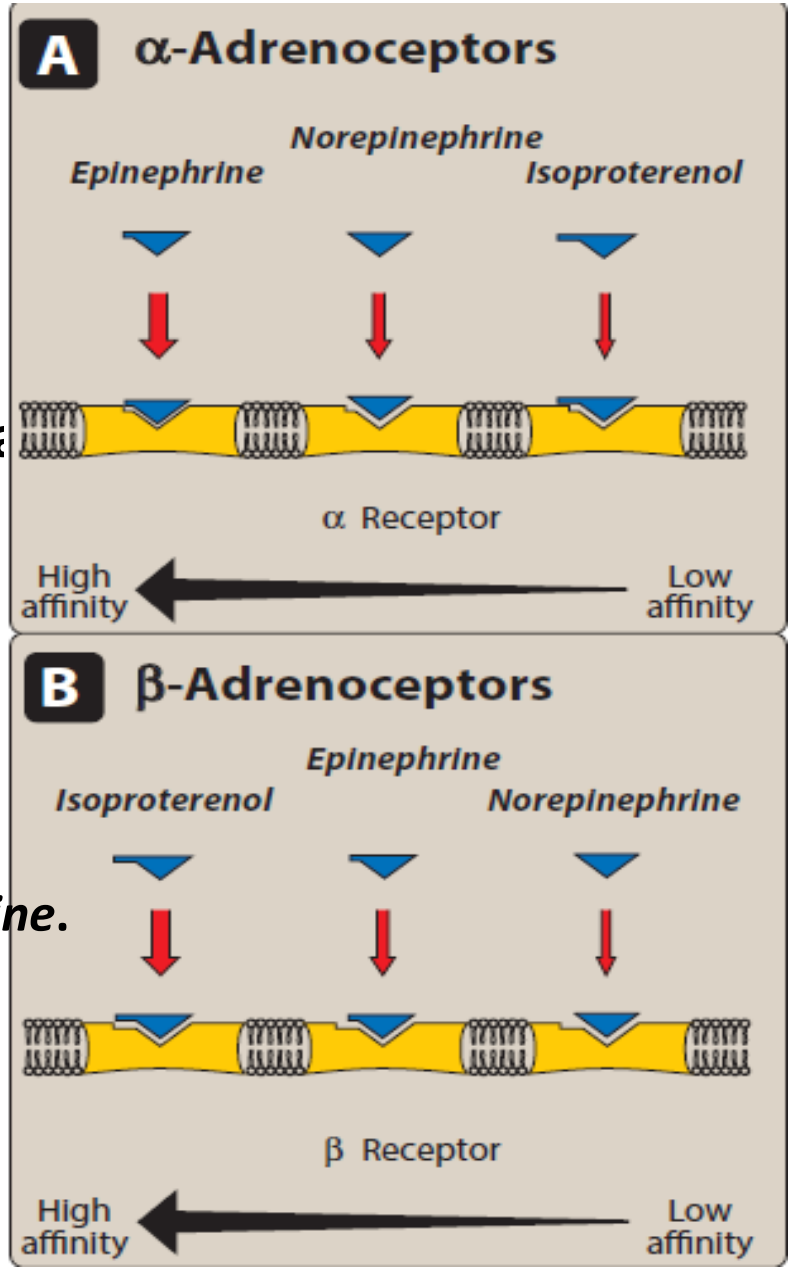
α_{2A}, α_{2B}, and α_{2C}

tamsulosin **is a selective α_{1A} antagonist tha**
prostatic hyperplasia.

β-Adrenoceptors

isoproterenol **>** ***epinephrine*** **>** ***norepinephrine*****.**

β_1, β_2, and β_3

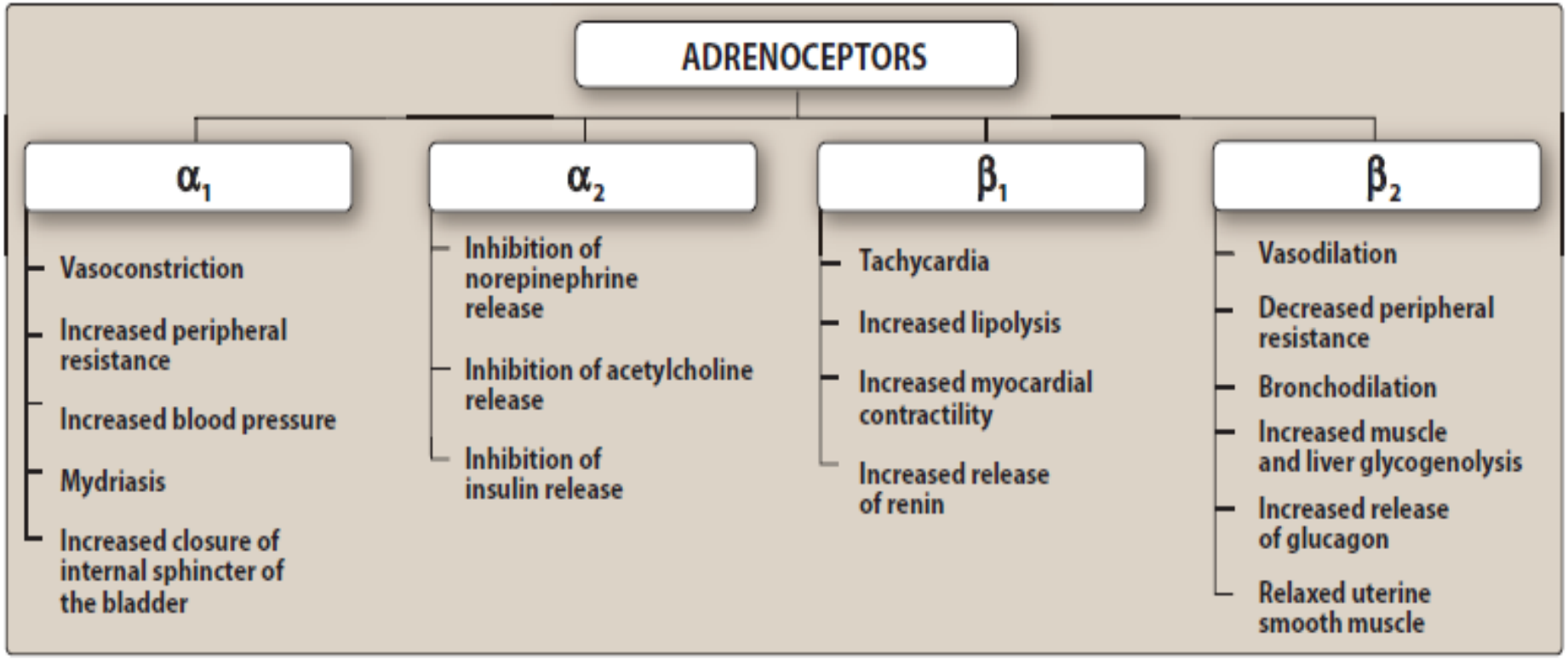


- β_1 receptors have approximately equal affinities for *epinephrine* and *norepinephrine.*

- whereas β_2 receptors have a higher affinity for *epinephrine* than for *norepinephrine*.

- β_3 receptors are involved in lipolysis

- Binding of a neurotransmitter at any of the three types of β receptors results in activation of adenylyl cyclase and increased concentrations of cAMP within the cell.


ADRENOCEPTORS
α1
Vasoconstriction
Increased peripheral resistance
Increased blood pressure
Mydriasis
Increased closure of internal sphincter of the bladder
α2
Inhibition of norepinephrine release
Inhibition of acetylcholine release
Inhibition of insulin release
β1
Tachycardia
Increased lipolysis
Increased myocardial contractility
Increased release of renin
β2
Vasodilation
Decreased peripheral resistance
Bronchodilation
Increased muscle and liver glycogenolysis
Increased release of glucagon
Relaxed uterine smooth muscle

	Relative Receptor Affinities
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine[1]	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$

Receptor	Agonist	Antagonist	G Protein	Effects
α_1 type	Phenylephrine	Prazosin	G_q	↑ IP3, DAG common to all
α_{1A}		Tamsulosin		
α_{1B}				
α_{1D}				
α_2 type	Clonidine	Yohimbine	G_i	↓ cAMP common to all
α_{2A}	Oxymetazoline			
α_{2B}		Prazosin		
α_{2C}		Prazosin		
β type	Isoproterenol	Propranolol	G_s	↑ cAMP common to all
β_1	Dobutamine	Betaxolol		
β_2	Albuterol	Butoxamine		
β_3	Mirabegron			

Desensitization of receptors: Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization.

Three mechanisms have been suggested to explain this phenomenon:

1) sequestration of the receptors so that they are unavailable for interaction with the ligand.

2) down-regulation, that is, a disappearance of the receptors either by destruction or by decreased synthesis

3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side.

CHARACTERISTICS OF ADRENERGIC AGONISTS

A. Catecholamines

(such as *epinephrine*, *norepinephrine*, *isoproterenol*, and *dopamine*)

1. **High potency:**
2. **Rapid inactivation:**
3. **Poor penetration into the CNS:**

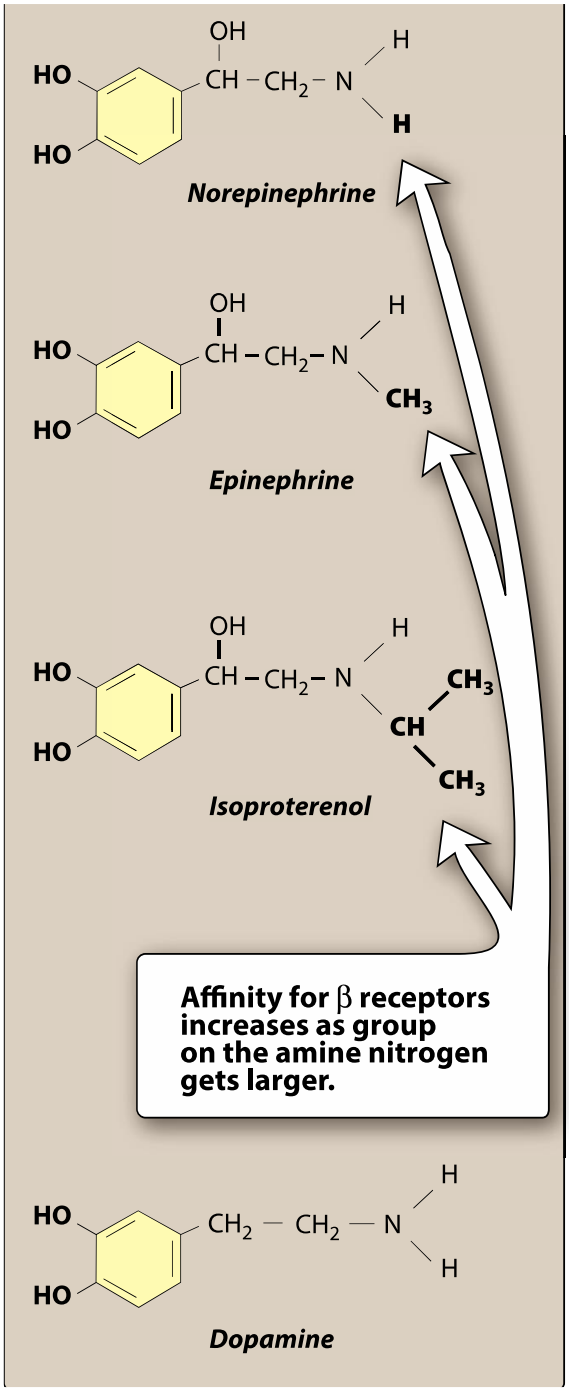
B. Noncatecholamines

Mechanism of action of adrenergic agonists

Direct-acting agonists:

Indirect-acting agonists:

Mixed-action agonists:



Thank you