Adrenergic Receptor Subtypes:

Membrane receptors transfer information from the environment to the cell's interior. A few nonpolar signal molecules such as estrogens and other steroid hormones are able to diffuse through the cell membranes and, hence, enter the cell. However, most signaling molecules such as CAs are too polar to pass through the membrane, and no appropriate transport systems are available. Thus, the information that they present must be transmitted across the cell membrane without the molecules themselves entering the cell. A membrane-associated receptor protein such as adrenergic receptors often performs the function of information transfer across the membrane.

In 1948, Ahlquist proposed and designated α- and β adrenoceptors based on their apparent drug sensitivity. The diverse physiological responses of CAs are mediated via α -1, α -2, and - adrenoceptors, which are further divided into α 1A, α 1B, α 1D, α 2A, α 2B, α2C, β1, β 2, and β 3. They all belong to the superfamily of guanine nucleotide (G)-regulatory proteins (G-protein)–coupled receptors (GPCR), which have seven-transmembrane (7TM) helical regions. Elucidation of the characteristics of these receptors and the biochemical and physiological pathways they regulate has increased our understanding of the seemingly contradictory and variable effects of CAs on various organ systems.

Although structurally related, different receptors regulate distinct physiological process by controlling the synthesis or release of various second messengers. An important factor in the response of any cell or organ to adrenergic drugs is the density and proportion of α- and β-adrenoceptors.

For example, NE has relatively little capacity to increase bronchial airflow, because the receptors in bronchial smooth muscle are largely of the β2-subtype. In contrast, isoproterenol (ISO) and E are potent bronchodilators. The various adrenoceptor types and subtypes are not uniformly distributed with certain tissues containing more of one type than another.

TABLE 16.3 Distribution and Effects of Adrenoceptors and Main Uses of the Adrenergic Drugs

Organ or Tissue	Predominant Adrenoceptors	Effect of Activation	Physiological Effect	Drugs	Therapeutic Uses
Blood vessels and skin	α_1	Vasoconstriction	↑ Blood pressure	α_1-Agonists	Shock, hypotension
Mucous membranes	α_1	Vasoconstriction		α_1-Agonists α_1-Antagonists	Nasal congestion Hypertension
Prostatic gland muscle	α_{1A}	Contraction	Prostatic hyperplasia	α_{1A}-Antagonists	BPH
CNS	α_2	↓ NE release	↓ Blood pressure	α_2-Agonists	Hypertension
Heart muscle	β_1 (minor β_2, β_3)	Muscle contraction	↑ Heart rate & force	β_1-Antagonists	Hypertension Arrhythmias
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways		
	β_2 (Bronchodilation)	Smooth muscle relaxation	Dilates & opens airways	β_2-Agonists	Asthma and COPD
Uterus (pregnant)	α_1	Muscle contraction			
	β_2	Smooth muscle relaxation	(–) Uterine contractions	β_2-Antagonists	Premature labor
Kidney	β_1	Increases rennin secretion	↑ Blood pressure		

α1-Agonists as Vasoconstrictors and Nasal Decongestants.

In blood vessels, the principal effect is vasoconstriction. Blood vessels with α1-receptors are present in skin and during the fight-or-flight response, vasoconstriction results in the decreased blood flow to this organ. This accounts for an individual's skin appearing pale when frightened. Agonists acting selectively on α1-receptors cause vasoconstriction and thus can be used alongside local anesthetics in dentistry to localize and prolong the effect on the anesthetic at the site of injection. They are also used as nasal decongestants (vasoconstriction of mucous membranes) and for raising blood pressure (vasoconstriction of blood vessels) in shock.

α 1-Antagonists for Treatment of Hypertension. Because α 1-agonists are vasoconstrictor and hypertensive, α 1-antagonists would be expected to be vasodilators and hypotensive with clear implications of treating hypertension. Similarly, they should block α 1A-receptor in prostate smooth muscle and relax the muscle with implication of treating benign prostatic hyperplasia (BPH).

α2-Agonists for Treatment of Hypertension.

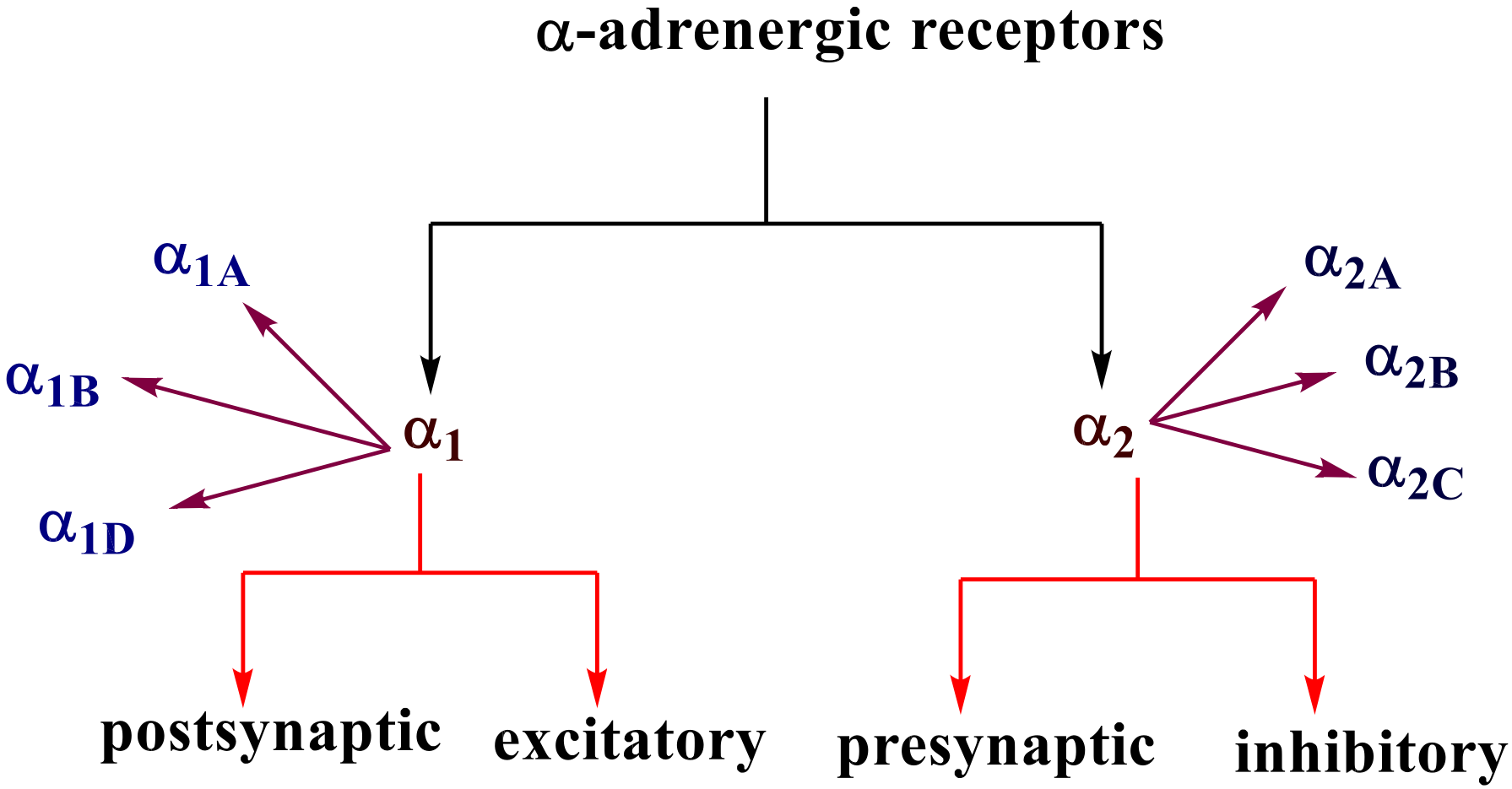
α2Agonists (e.g., clonidine) act at CNS sites to decrease sympathetic outflow to the periphery, resulting in decreased NE release at sympathetic nerve terminal and, therefore, relaxed vascular smooth muscle.

β1-Blockers for Treatment of Hypertension, Angina, and Certain Cardiac Arrhythmias.

Activation of the β 1receptors in heart causes an increase in rate and force of contraction and β 1-blockers should be expected to slow the heart rate and decrease the force of contraction. They are used in treating hypertension, angina, and certain cardiac arrhythmias.

β 2-Agonists for Treatment of Asthma and Premature Labor.

A major clinical use for adrenergic agonists is in treatment of asthma. Activation of β 2-receptors relaxes the smooth muscles in the bronchi, thus dilating and opening airways. Similarly, activation of β 2-receptors in the uterus relaxes the muscle, and some β 2-agonists are thus used to inhibit uterine contractions.



Both receptor subtypes belong to a superfamily of membrane receptors whose general structure consists of 7TM -helical segments. The interaction of adrenergic drugs and the receptors alters the tertiary or quaternary structure of the receptor, including the intracellular domain. These structural changes are not sufficient to yield an appropriate response, because they are restricted to a small number of receptor molecules in the cell membrane.

The information embodied by CAs or drugs, which act as primary messengers, must be transducer into downstream activity that can alter the biochemistry of the cell. The signal–transduction mechanisms involve coupling to G proteins. Each G protein is a heterotrimer consisting of δ-, β-, and γ-subunit and is classified based on their distinctive subunits. G proteins of particular importance for adrenoceptor function include Gs, the stimulatory G protein of adenylyl cyclase (AC); Gi, the inhibitory G protein of AC; and Gq, the protein coupling receptors to phospholipase C (PLC).

The δ - and β-receptors differ from each other in their structures, functions, and in the second-messenger system that is affected. Stimulation of δ 1-receptors results in the regulation of multiple effector systems. A primary mode of signal transduction involves

(a) activation of the Gq-PLCIP3-Ca2+ pathway and

(b) the activation of other Ca2+ and calmodulin-sensitive pathway such as CaM kinases.

The δ1-receptor subtype is coupled to the enzyme PLC via a Gq. When stimulated by activation of the δ 1-receptor, PLC hydrolyzes phosphatidylinositol-4,5-bisphosphate (PIP2) to give the second messengers inositol-1,4,5-triphosphate (IP3) and 1,2-diacylglycerol (DAG). In smooth muscle, IP3 stimulates the release of Ca2+ from the sarcoplasmic reticulum, resulting in an increase in free intracellular calcium levels. Increased free intracellular calcium is correlated with smooth muscle contraction, whereas DAG activates protein kinase C (PKC), which phosphorylates proteins, and may induce slowly developing contractions of vascular smooth muscle (Fig. 16.6).

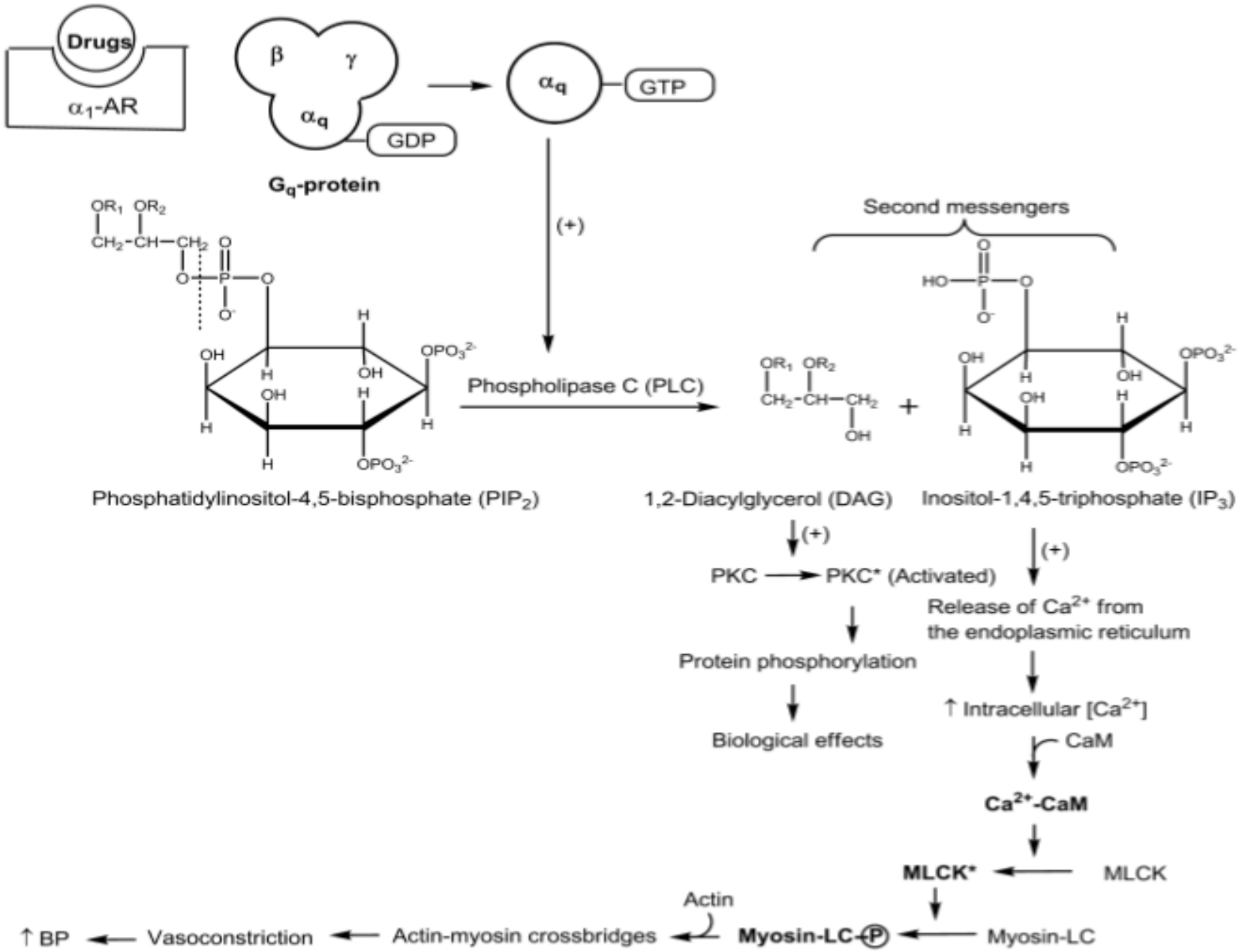
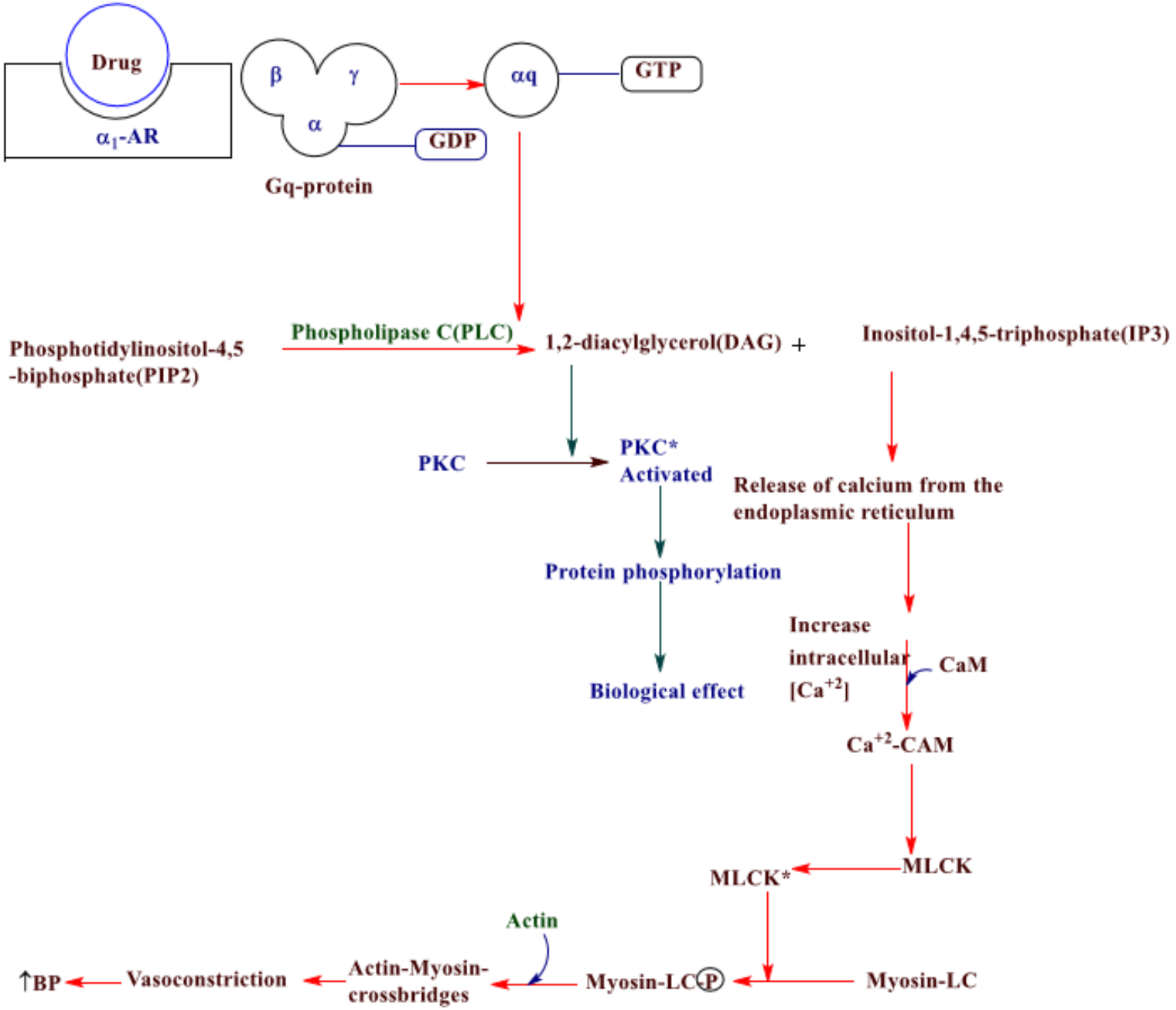


Figure 16.6 • Mechanism of α_1-receptor–mediated signal transduction.

Vasoconstriction is commonly initiated by the opening of voltage-gated L-type Ca+2 channels in the sarcolemma during plasma membrane depolarization, which mediates Ca+2 flux into the cytoplasm.

Ca+2 entry into the cell activates calmodulin (CaM). The Ca+2-CaM complex activates myosin light chain kinase (MLCK) to phosphorylate myosin light chain (myosin-LC). The phosphorylated myosin-LC interacts with actin to form actin-myosin crossbridges, a process that initiates vascular smooth muscle cell contraction.

The vascular constriction thus causes an increase in blood pressure. In contrast, relaxation is a coordinated series of steps that act to dephosphorylate and hence inactivate myosin-LC.


Drug
α_1-AR
β
γ
α
αq
GTP
GDP
Gq-protein
Phosphotidylinositol-4,5 -biphosphate(PIP2)
Phospholipase C(PLC)
1,2-diacylglycerol(DAG) +
Inositol-1,4,5-triphosphate(IP3)
PKC
PKC* Activated
Protein phosphorylation
Biological effect
Release of calcium from the endoplasmic reticulum
Increase intracellular [Ca^{+2}]
CaM
Ca^{+2}-CAM
MLCK
MLCK*
Actin
Myosin-LC
P
Myosin-LC
Actin-Myosin-crossbridges
Vasoconstriction
↑BP

Activation of α2-receptors leads to a reduction in the catalytic activity of AC (adenylyl cyclase), which in turn results in a lowering of intracellular levels of cyclic adenosine monophosphate (cAMP) (Fig. 16.7). The α 2-receptor–mediated inhibition of AC is regulated by the Gi.

α-Receptors of the CNS and in peripheral tissues perform a number of important physiological functions. In particular, α-receptors are involved in control of the cardiovascular system.

For example, constriction of vascular smooth muscle is mediated by both postjunctional α1- and α2-receptors, though the predominant receptor mediating this effect is α1.

In the heart, activation of α1-receptors results in a selective inotropic response with little or no change in heart rate. This is in contrast to the β1-receptor, which is the predominant postjunctional receptor in the heart, mediating both inotropic and chronotropic effects.

In the brain, activation of postjunctional α2-receptors reduces sympathetic outflow from the CNS, which in turn causes a lowering of blood pressure. The prototypical α2-receptor is the presynaptic α-receptor found on the terminal sympathetic neuron.

Interaction of this receptor with agonists such as NE and E results in inhibition of NE release from the neuron. The α2-receptors not only play a role in the regulation of NE release but also regulate the release of other NTs, such as acetylcholine and serotonin. Both α1and α2-receptors also play an important role in the regulation of several metabolic processes, such as insulin secretion and glycogenolysis.

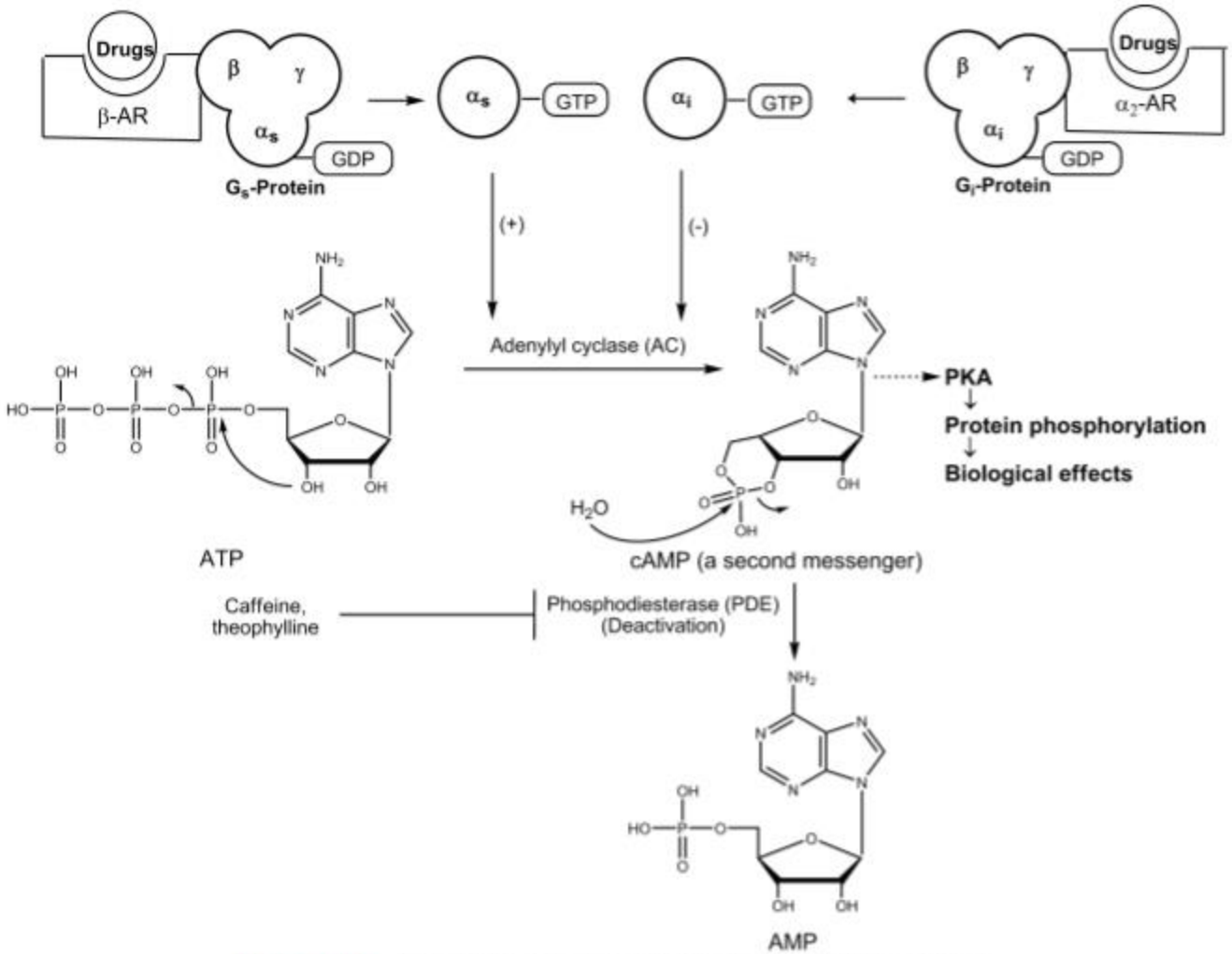
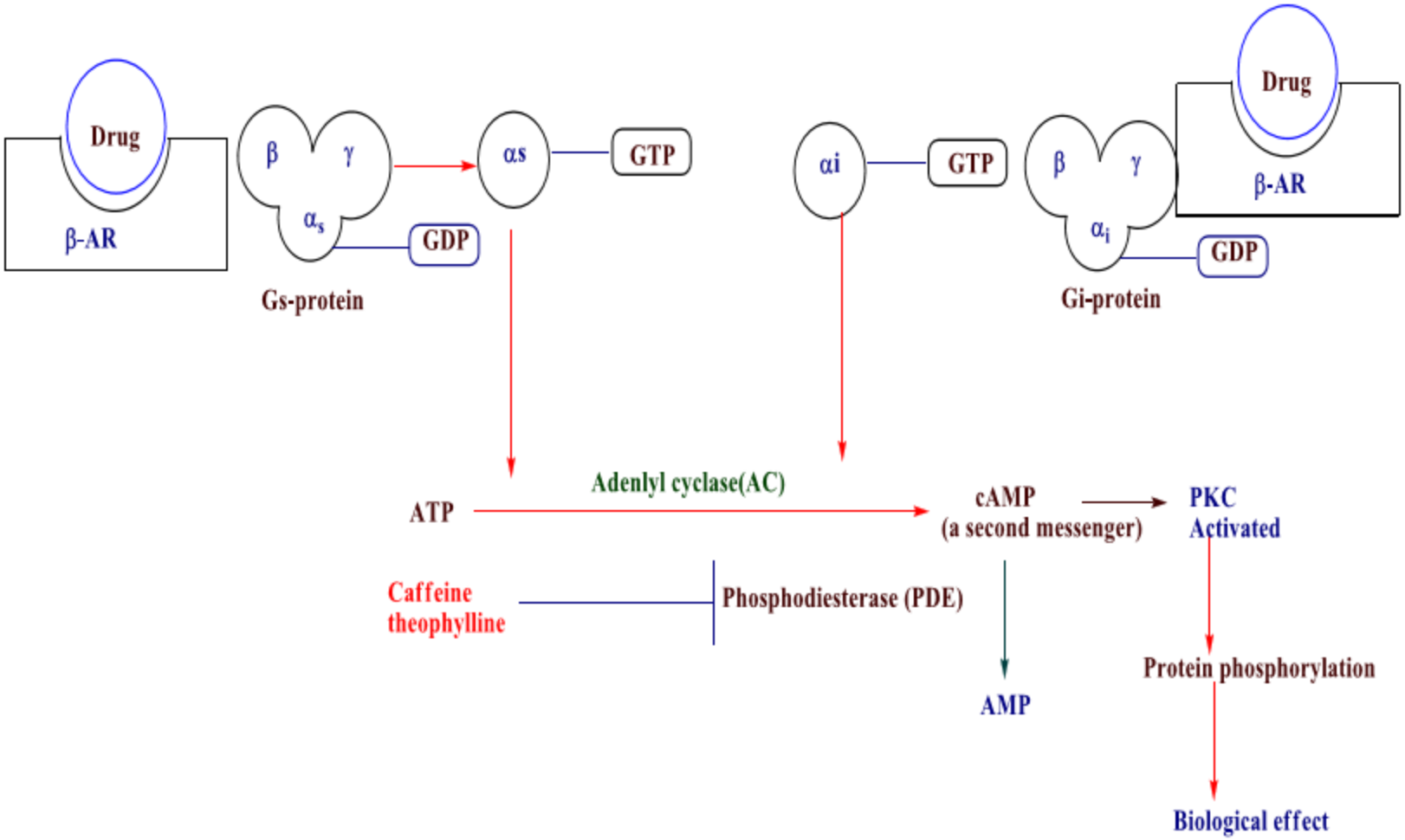


Figure 16.7 • Mechanism of β_2-receptor–mediated signal transduction.


Drug
β-AR
β
γ
αs
GTP
αs
GDP
Gs-protein
αi
GTP
β
γ
αi
GDP
Gi-protein
Drug
β-AR
ATP
Adenlyl cyclase(AC)
cAMP
(a second messenger)
PKC
Activated
Caffeine
theophylline
Phosphodiesterase (PDE)
AMP
Protein phosphorylation
Biological effect

β-Adrenergic Receptors

Arch et al. identified a third subtype of β-receptor in brown adipose tissue designated as the β3-subtype. All clinically relevant α1-, β1-, β2-, and β3-receptors are postsynaptic receptors that are linked to stimulation of biochemical processes in the postsynaptic cell. The function of presynaptic β-receptors is, however, unclear.

The use of β2-agonists as bronchodilators and β1- or β1/ β2-blockers as antihypertensives is well established. The β1-receptors are located mainly in the heart, where they mediate the positive inotropic and chronotropic effects of the CAs. They are also found on the juxtaglomerular cells of the kidney, where they are involved in increasing renin secretion.

The β2-receptors are located on smooth muscle throughout the body, where they are involved in relaxation of the smooth muscle, producing such effects as bronchodilation and vasodilation. They are also found in the liver, where they promote glycogenolysis.

The β3-receptor is located on brown adipose tissue and is involved in the stimulation of lipolysis. All three β-receptors are coupled to AC, which catalyzes the conversion of ATP to cAMP (Fig. 16.7).

This coupling is via the G-protein Gs. In the absence of an agonist, guanosine diphosphate (GDP) is bound reversibly to the Gs protein. Interaction of the agonist with the receptor causes a conformational change in the receptor, which decreases the affinity of the Gs protein for GDP and a concomitantly increases the affinity for guanosine triphosphate (GTP).

The αs-subunit of Gs-protein complex dissociates from the receptor–G protein tertiary complex and then binds to and activates AC. The intracellular function of the second-messenger cAMP is activation of protein kinases, which phosphorylate specific proteins, thereby altering their function. The action of cAMP is terminated by a class of enzymes known as phosphodiesterase (PDE) that catalyzes the hydrolysis of cAMP to AMP (Fig. 16.7) and is related to the mechanism of action of caffeine and theophylline.

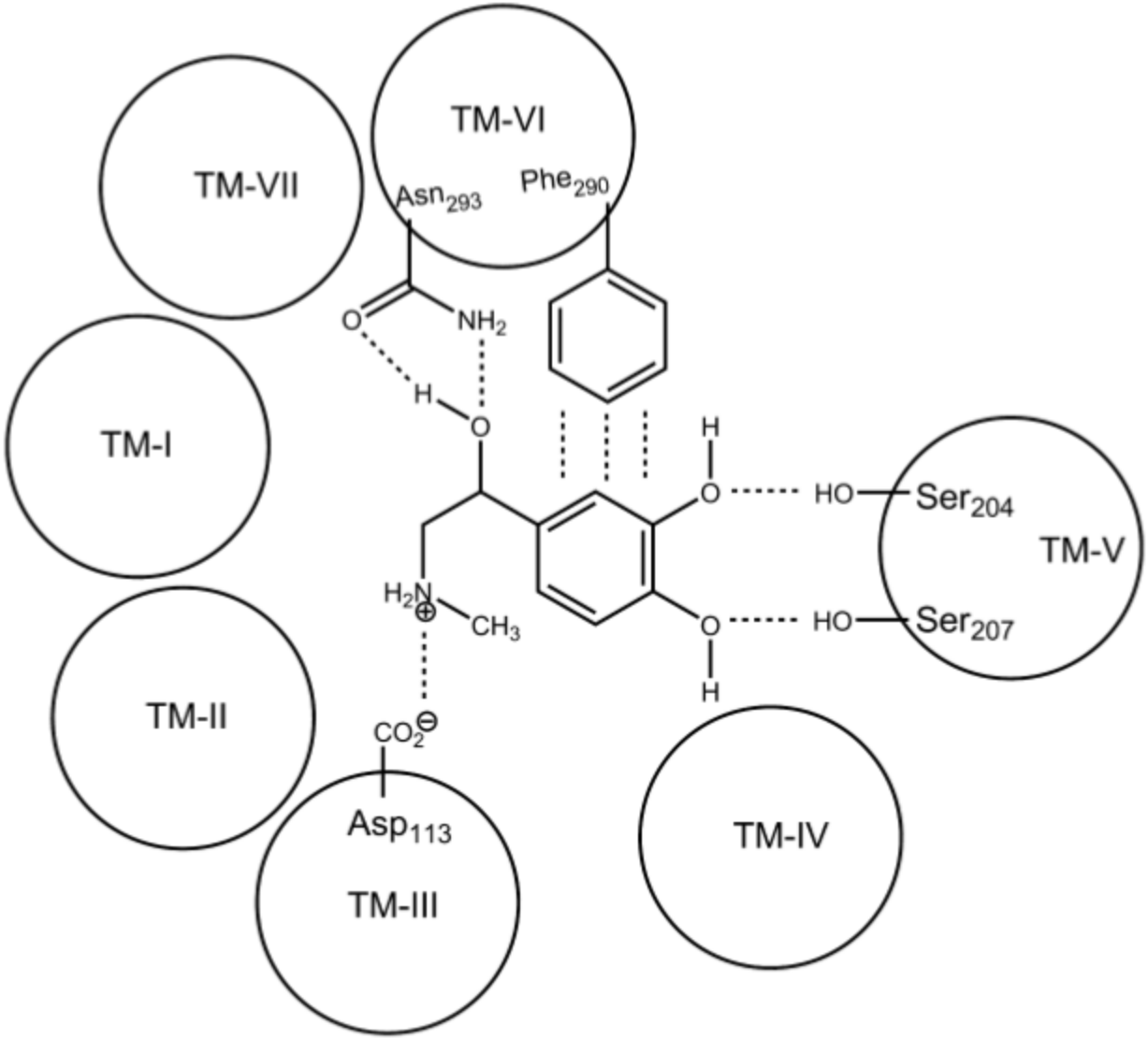
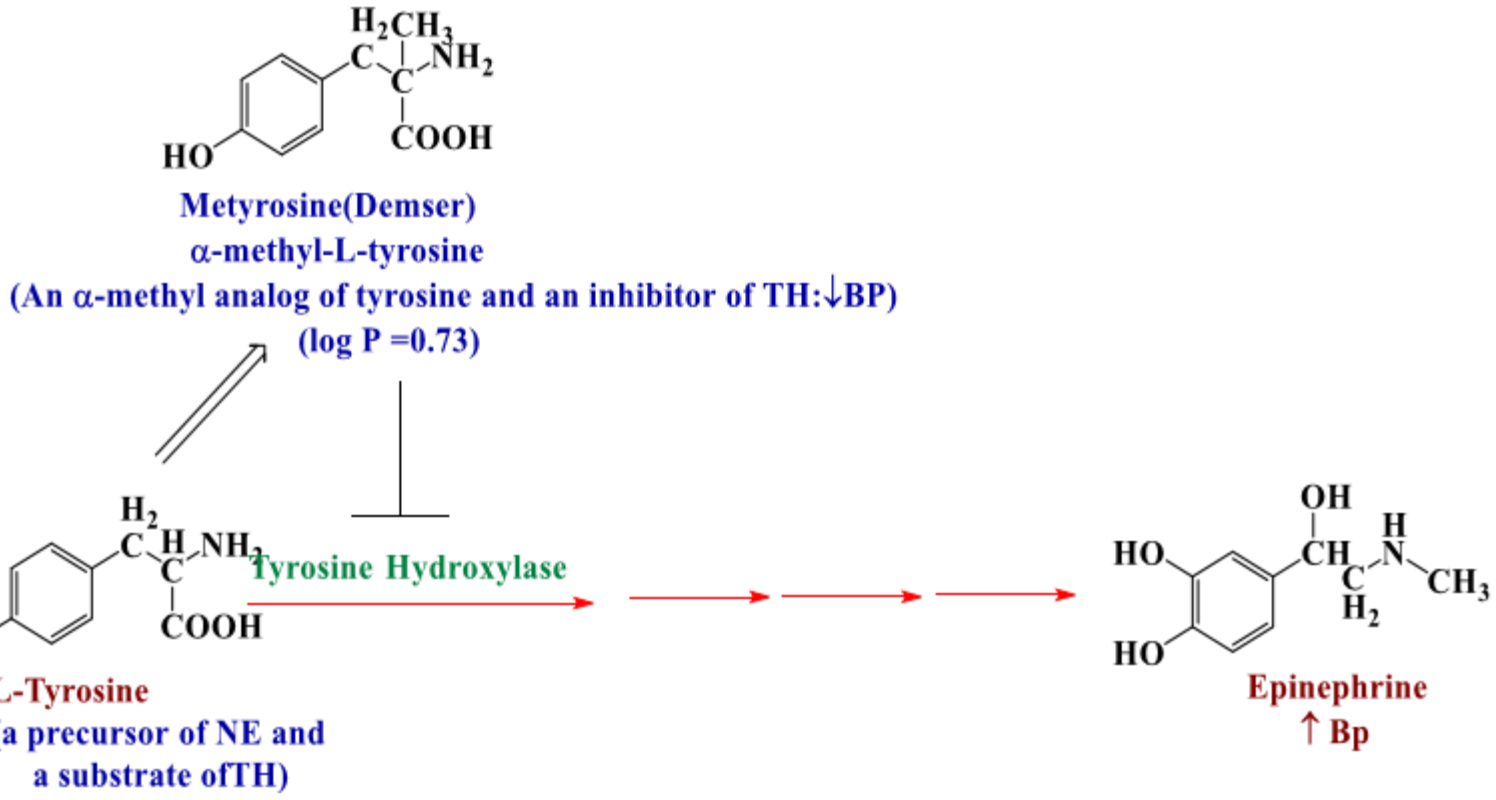


Figure 16.8 • Model of β_2-AR binding sites: Illustration of the Easson-Stedman hypothesis representing the interaction of three critical pharmacophoric groups of norepinephrine with the complementary binding areas on the adrenergic receptor as suggested by site-directed mutagenesis studies.

DRUGS AFFECTING ADRENERGIC NEUROTRANSMISSION

Drugs Affecting Catecholamine Biosynthesis

- **Metyrosine**



Uses

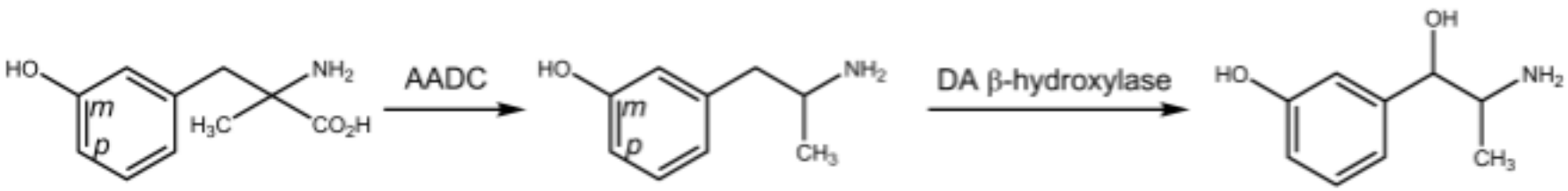
It is used for the preoperative management of pheochromocytoma, chromaffin cell tumors that produce large amounts of NE and E. Although these adrenal medullary tumors are often benign, patients frequently suffer hypertensive episodes. Metyrosine reduces the frequency and severity of these episodes by significantly lowering catecholamine production (35% to 80%).

S/E

The drug is polar (log p = 0.73) and excreted mainly unchanged in the urine. Because of its limited solubility in water caused by intramolecular bonding of the zwitterions, crystalluria is a potential serious side effect.

It can be minimized by maintaining a daily urine volume of more than 2 L. Inhibitors of CA synthesis have limited clinical utility because such agents nonspecifically inhibit the formation of all CAs and result in many side effects. Sedation is the most common side effect of this drug.

A similar example is the use of α-methyl-m-tyrosine in the treatment of shock. It differs structurally from metyrosine only in the presence of m-OH instead of p-OH in metyrosine. This unnatural amino acid is accepted by the enzymes of the biosynthetic pathway and converted to metaraminol (an α-agonist) as shown (Fig. 16.10).



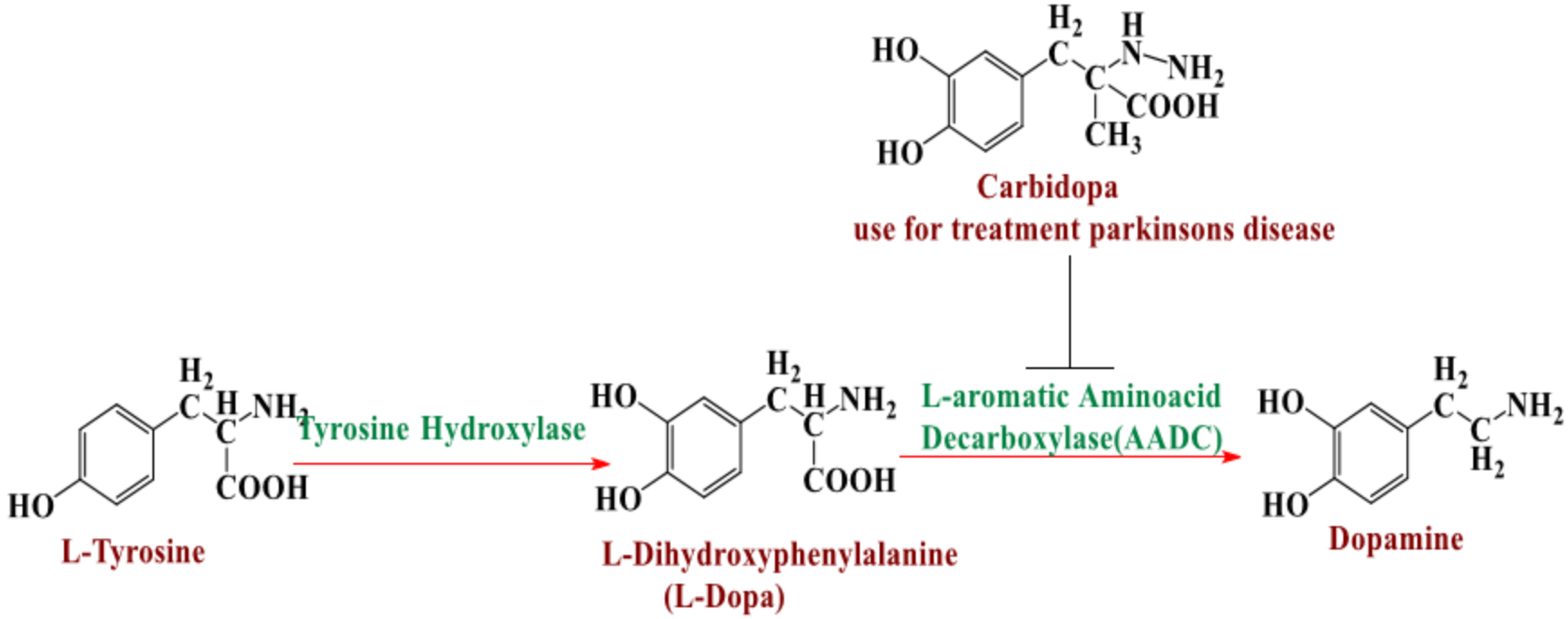
α-Methyl-*m*-tyrosine α-Methyl-*m*-tyramine Metaraminol (α_1-agonist)

Figure 16.10 • Metabolic activation of α-methyl-*m*-tyrosine to metaraminol.

Inhibitors of AADC

carbidopa

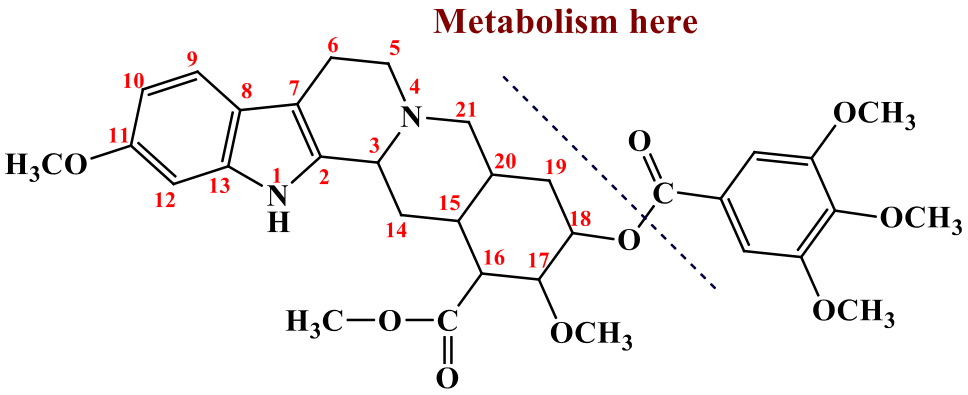
are used to inhibit the metabolism of drug L-DOPA administered in the treatment of Parkinson disease.



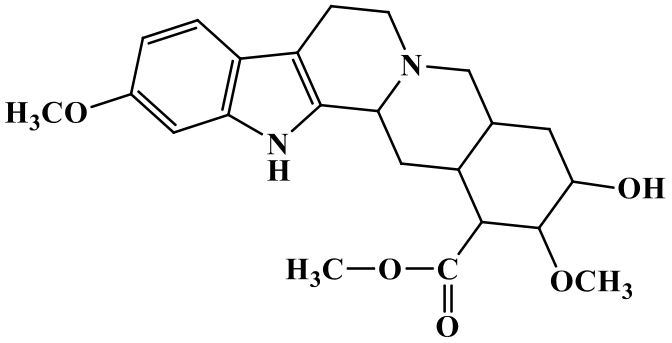
Inhibitors of AADC (e.g., carbidopa) have proven to be clinically useful, but not as modulators of peripheral adrenergic transmission. Rather these agents are used to inhibit the metabolism of drug L-DOPA administered in the treatment of Parkinson disease

2- Drugs Affecting Catecholamine Storage and Release

A- Reserpine (an NT deplete)

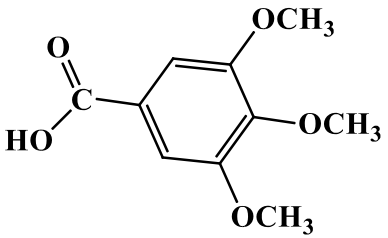


log P= 4.37, log D=3.93



Methyl reserpate

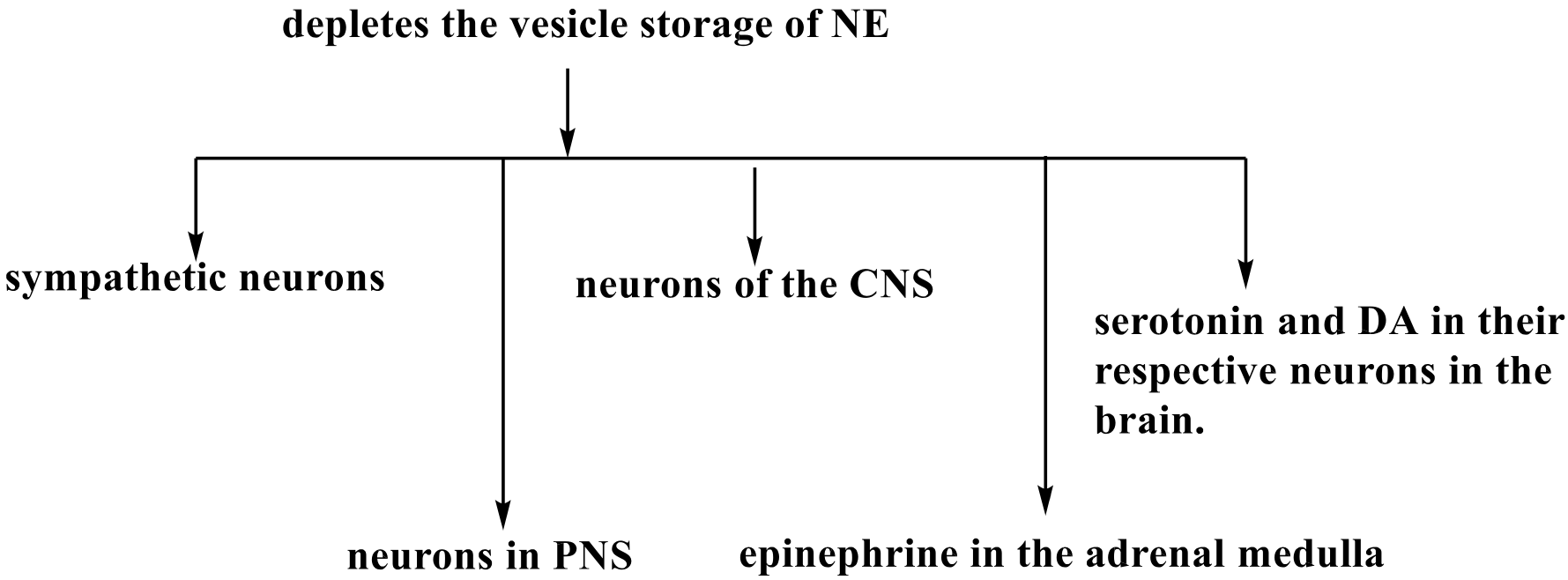
+



3,4,5-trimethoxybenzoic acid.

As is typical of many indole alkaloids, reserpine is susceptible to decomposition by light and oxidation. Reserpine is extensively metabolized through hydrolysis of the ester function at position 18 and yields methyl reserpate and 3,4,5-trimethoxybenzoic acid.

Mechanism of action



Reserpine → binds extremely tightly with and blocks VMAT → ~~BK~~ transports NE and other biogenic amines from the cytoplasm into the storage vesicles

instead ↓

metabolized by mitochondrial MAO in the cytoplasm

In addition, there is a gradual loss of vesicle-stored NE as it is used up by release resulting from sympathetic nerve activity so that the storage vesicles eventually become dysfunctional. The end result is a depletion of NE in the sympathetic neuron. Analogous effects are seen in the adrenal medulla with E and with 5-HT in serotonergic neurons.

When reserpine is given orally, its maximum effect is seen after a couple of weeks. A sustained effect up to several weeks is seen after the last dose has been given. This is because the tight binding of reserpine to storage vesicles continues for a prolonged time, and recovery of sympathetic function requires synthesis of new vesicles over a period of days to weeks after discontinuation of the drug.

Adverse effect:-Most adverse effects of reserpine (log P = 4.37) are caused by CNS

effects because it readily enters the CNS.

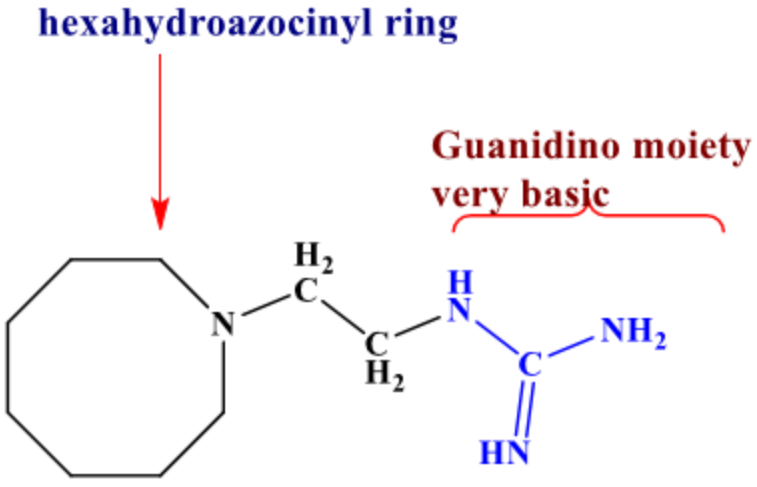
- Sedation.

- psychotic depression that can lead to Suicide which support monoamine theory of pathology of depression.

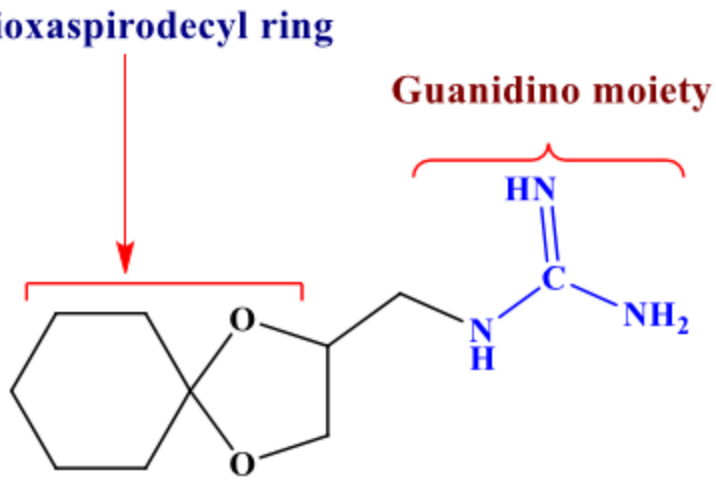
Uses:- reserpine are used in the treatment of hypertension. Preparations in which reserpine is combined with a diuretic also are available, as diuretics increase the efficacy of reserpine.

Guanethidine (Ismelin) and Guanadrel (Hylorel)

are seldom used orally active antihypertensives. neuronal blocking agent, block release of NE from sympathetic neuron

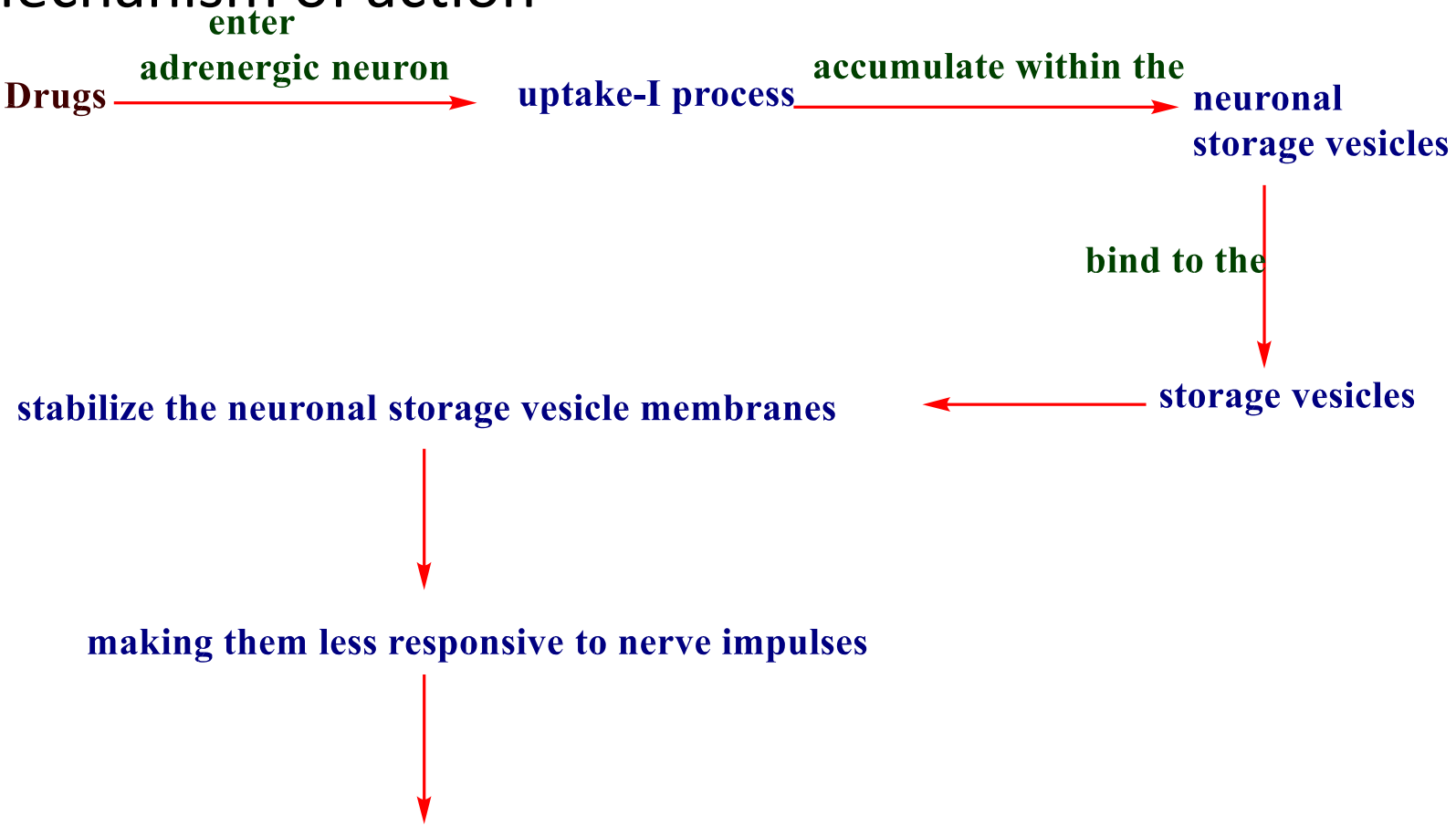


Guanethidine
PKa= 13.43
No CNS activity



Guanadrel
PKa= 12.76
No CNS activity

Mechanism of action

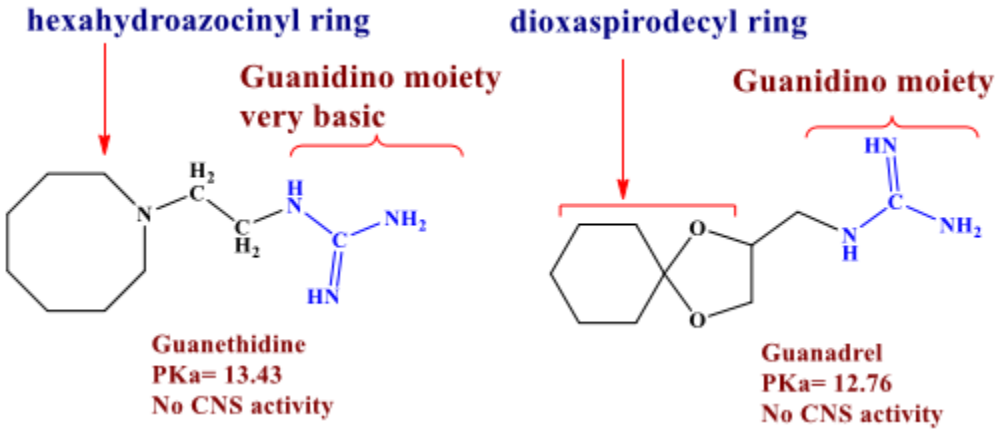


Long-term administration of some of these agents also can produce a depletion of NE stores in sympathetic neurons. Both neuronal blocking drugs possess a guanidino moiety [CNHC(=NH)NH2], which is attached to either a hexahydroazocinyl ring linked by an ethyl group as in guanethidine, or a dioxaspirodecyl ring linked by a methyl group as in guanadrel.

The presence of the more basic guanidino group (pKa >12) than the ordinary amino group in these drugs means that at physiological pH, they are essentially completely protonated. Thus, these agents do not get into the CNS. As a result, this drug has none of the central effects seen with many of the other antihypertensive agents

Guanethidine contains two basic nitrogen atoms with pKa values of 9.0 and 13.43, and can therefore form guanethidine monosulfate ($C_{10}H_{22}N_4 \cdot H_2SO_4$) or guanethidine sulfate [$(C_{10}H_{22}N_4)_2 \cdot H_2SO_4$].

Structurally



Although guanethidine and guanadrel have virtually the same mechanism of action on sympathetic neurons, they differ in their pharmacokinetic properties.

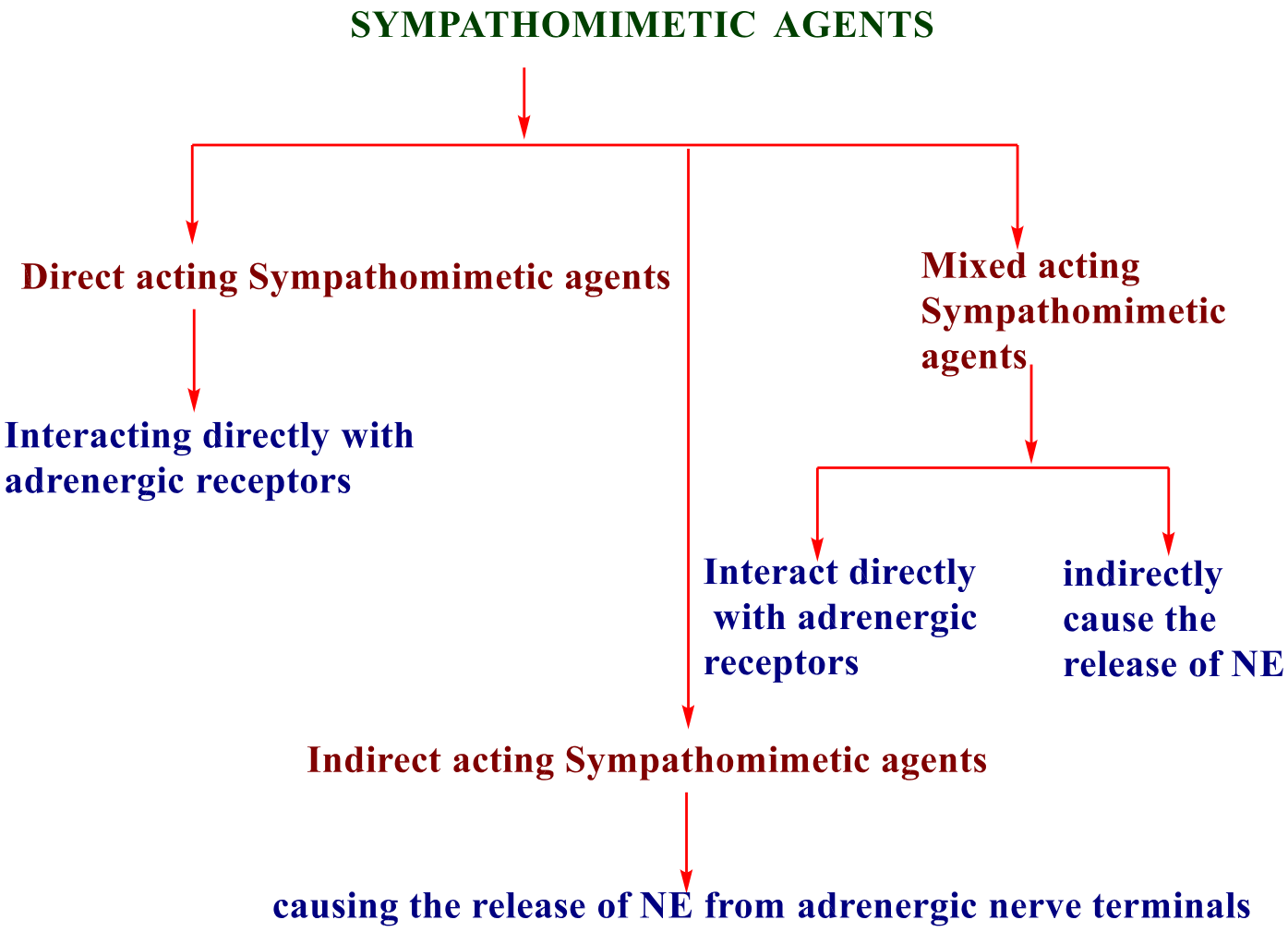
	guanethidine	guanadrel
1	It is absorbed incompletely after oral administration (3 to 50%)	It is well absorbed, with a bioavailability of 85%
2	It has a half-life of about 5 days	It has a half-life of 12 hours

Both agents are partially metabolized (50%) by the liver.

Uses:-Both are used to treat moderate-to-severe hypertension, either alone or in combination with another antihypertensive agent.

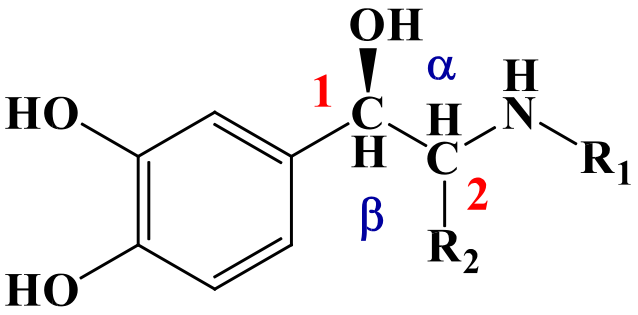
SYMPATHOMIMETIC AGENTS

Sympathomimetic agents produce effects resembling those produced by stimulation of the sympathetic nervous system. They may be classified as:-



Direct-Acting Sympathomimetics

STRUCTURE— ACTIVITY RELATIONSHIPS (SAR)



R_1=H, NE
R_1=CH_3, E
R_1=$CH(CH_3)_2$, Isoproterenol

1- Hydroxyl groups in the meta and para positions of the aromatic ring (a catechol)

2- (1R) -hydroxyl group on the ethylamine portion of the molecule.

3- β- Phenylethylamine.

The parent structure with the features in common for many of the adrenergic drugs is β-phenylethylamine. The manner in which β-phenylethylamine is substituted on the meta- and para-positions of the aromatic ring, on the amino (R1), and on α-, (R2)-, and β-positions of the ethylamine side chain influences not only their mechanism of action, the receptor selectivity, but also their absorption, oral activity, metabolism, degradation, and thus duration of action (DOA).

For the direct-acting sympathomimetic amines, maximal activity is seen in β-phenylethylamine derivatives containing (a) a catechol and (b) a (1R)-OH group on the ethylamine portion of the molecule. Such structural features are seen in the prototypical direct-acting compounds NE, E, and ISO.

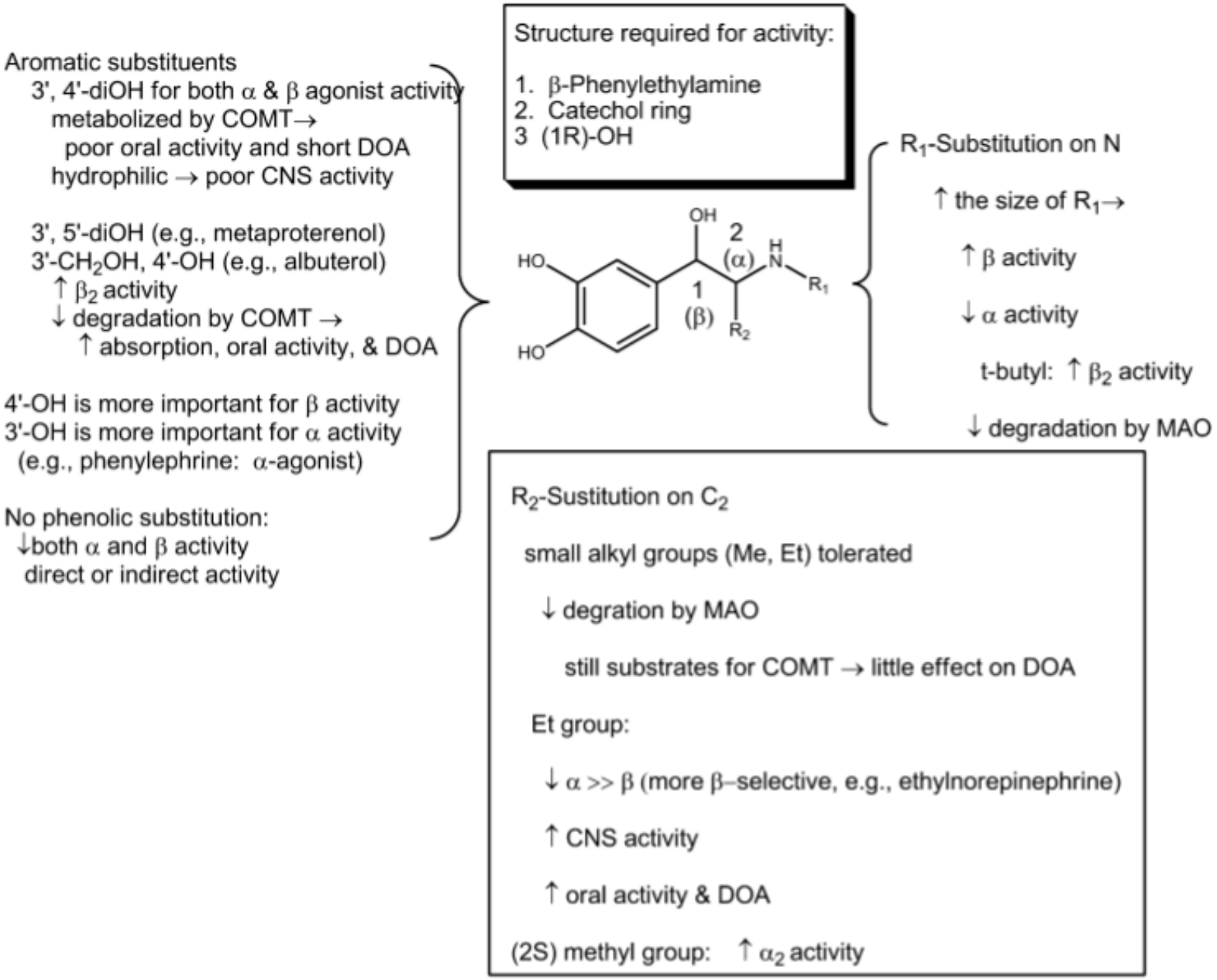


Figure 16.11 • Structure–activity relationship of adrenergic phenylethylamine agonists.

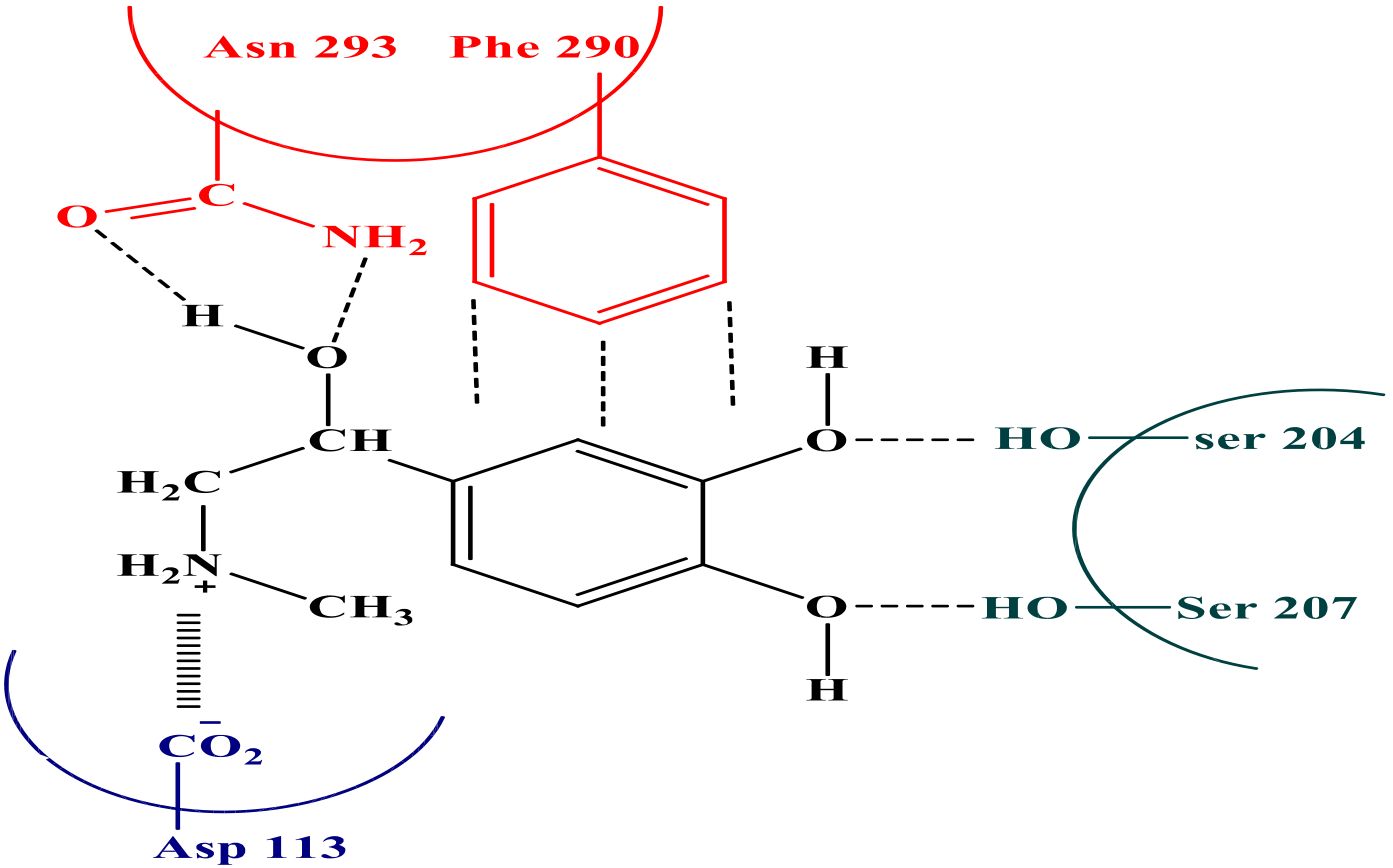
Optical Isomerism.

A critical factor in the interaction of adrenergic agonists with their receptors is stereoselectivity. Substitution on either carbon-1 or carbon-2 yields optical isomers. (1R,2S) isomers seem correct configuration for direct-acting activity. For CAs, the more potent enantiomer has the (1R) configuration. This enantiomer is typically several 100-fold more potent than the enantiomer with the (1S) configuration.

It appears that for all direct-acting, phenylethylamine-derived agonists that are structurally similar to NE, the more potent enantiomer is capable of assuming a conformation that results in the arrangement in space of the catechol group, the amino group, and the (1R)-OH group in a fashion resembling that of (1R)-NE.

This explanation of stereoselectivity is based on the presumed interaction of these three critical pharmacophoric groups with three complementary binding areas on the receptor and is known as the Easson-Stedman hypothesis.17,36 This three-point interaction is supported by site-directed mutagenesis studies28 on the adrenergic receptor and is illustrated in Figure 16.8.

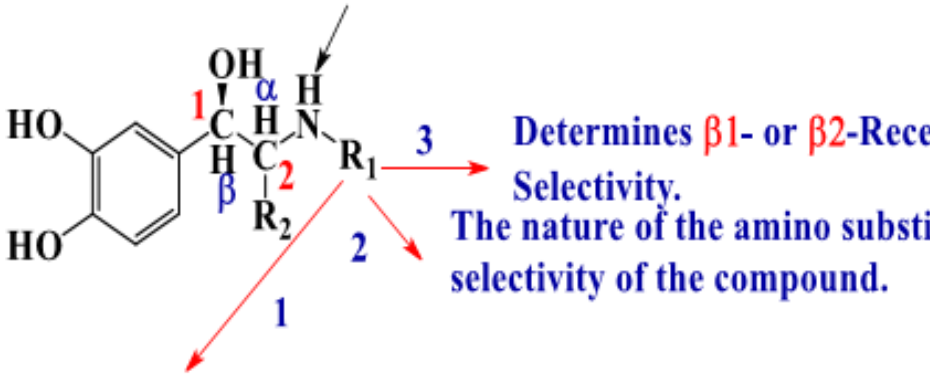
1-The interaction of adrenergic agonists with their receptors is stereoselectivity.



Easson-Stedman hypothesis.

R_1, Substitution on the Amino Nitrogen Determines α- or β-Receptor Selectivity

ionized at physiological pH. This is important for direct agonist activity, because replacing nitrogen with carbon results in a large decline in activity.



Determines β1- or β2-Receptor Selectivity.

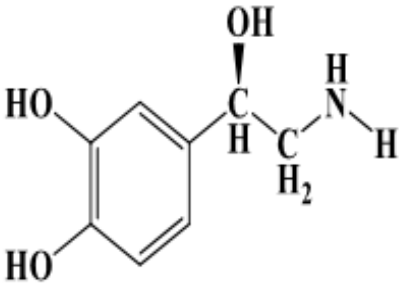
The nature of the amino substituent also dramatically affects the receptor selectivity of the compound.

The number of substitution on the nitrogen effect on the activity.

1°and 2° amines → good adrenergic activity

3°amines and 4° ammonium salts do not→ (poor adrenergic agonist)

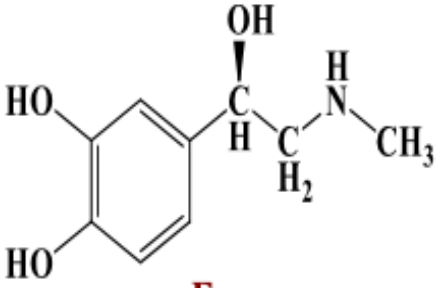
As the size of the nitrogen substituent ↑, α-receptor agonist activity generally ↓and ↑-receptor agonist activity increases.



NE

α⟩β agonist

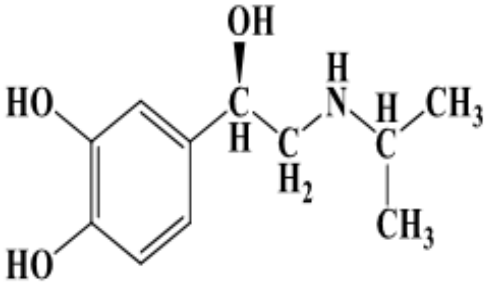
α agonist



E

α,β1 and β2-agonist

non selective α and β-agonist



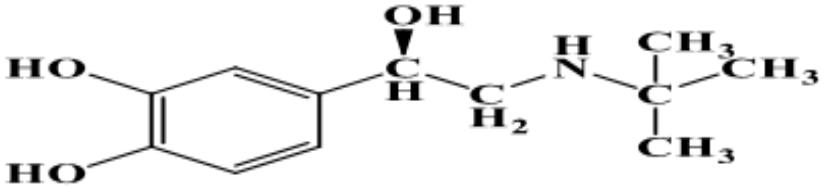
isoproterenol(ISO)

Selectiveβ1 and β2-agonist

non selective β-agonist

D- The nature of the substituents can also affect β_1- and β_2-receptor selectivity.

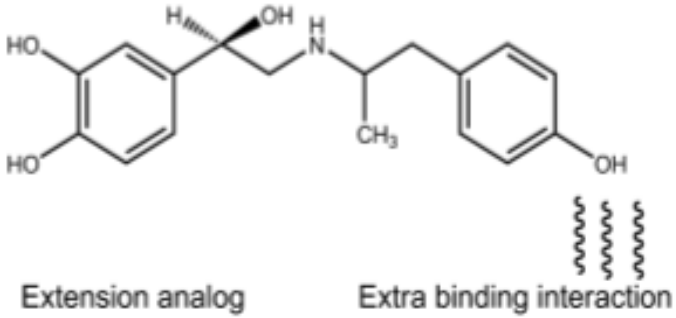
N-tert-butyl group enhances β_2-selectivity.



N-t-butylNE (Colterol)

9-10 times more piotent at β2 than β1

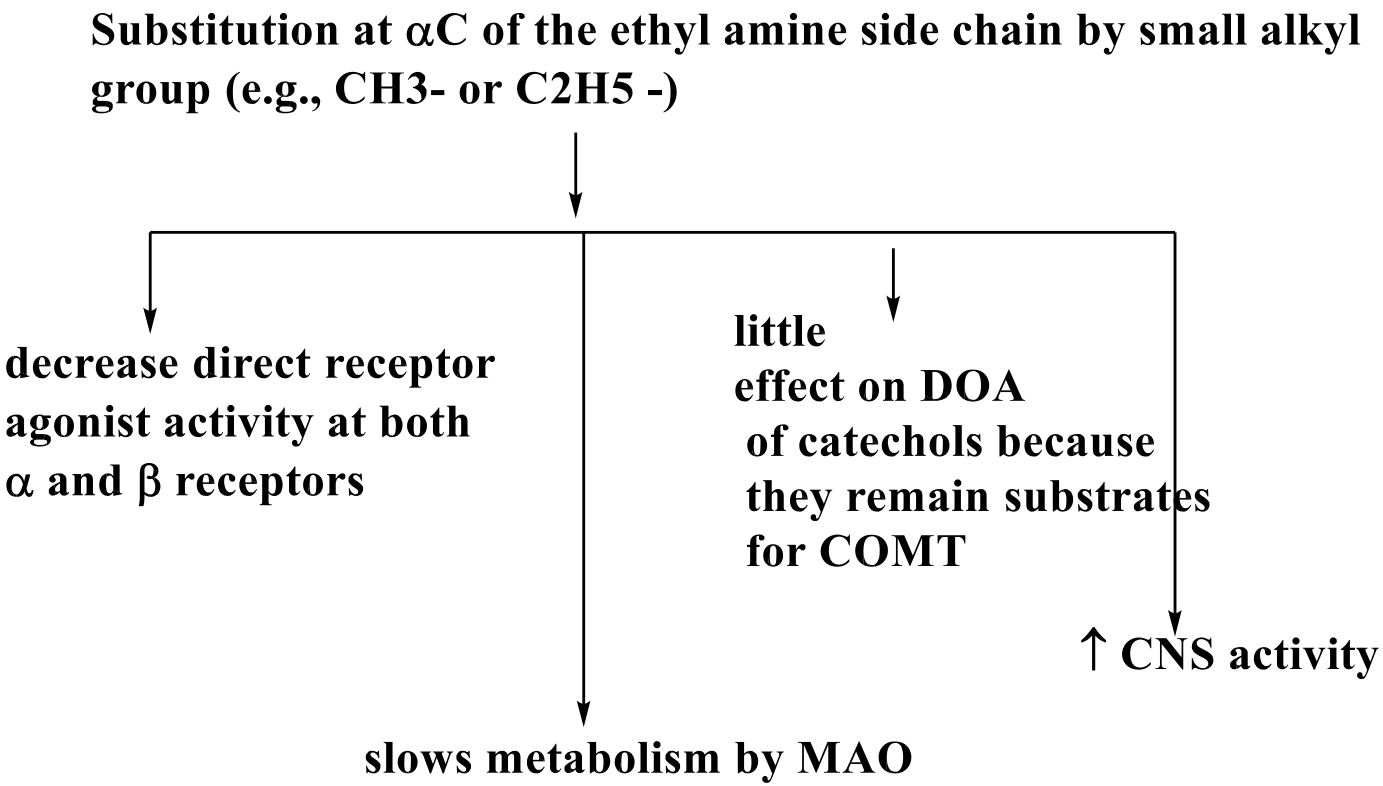
Selective β2-agonist



- Large substituents on the amino group also protect the amino group from undergoing oxidative deamination by MAO.

In several instances, it has been shown that a β2-directing N-tert-butyl group enhances β 2-selectivity. For example, N-tert-butylnorepinephrine (Colterol) is 9 to 10 times more potent as an agonist at tracheal β 2-receptors than at cardiac β 1-receptors. These results indicate that the β-receptor has a larger lipophilic binding pocket adjacent to the amine-binding aspartic acid residue than do the β -receptors. Increasing the length of the alkyl chain offers no advantage, but if a polar functional group is placed at the end of the alkyl group, the situation changes. In particular, adding a phenol group to the end of a C2 alkyl chain results in a dramatic rise in activity, indicating that an extra polar-binding region has been accessed, which can take part in H-bonding. Experiments have shown the activity of the extension analog is thereby increased by a factor of 800. As R1 becomes larger than butyl group, it can provide compounds with α1-blocking activity (e.g., tamsulosin and labetalol). Large substituents on the amino group also protect the amino group from undergoing oxidative deamination by MAO.

•R2, Substitution on the α-Carbon (Carbon-2)



The DOA of drugs such as ephedrine or amphetamine is thus measured in hours rather than in minutes. Because addition of small alkyl group increases the resistance to metabolism and lipophilicity, such compounds often exhibit enhanced oral effectiveness and greater CNS activity than their counterparts that do not contain an α-alkyl group. In addition, compounds with an α -methyl substituent persist in the nerve terminals and are more likely to release NE from storage sites. For example, metaraminol is an α -agonist and also exhibits a greater degree of indirect sympathomimetic activity.

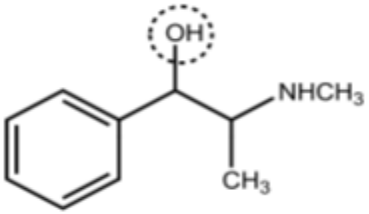
α- Substitution also significantly affects receptor selectivity

β

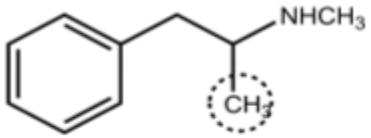
α

↑ β2

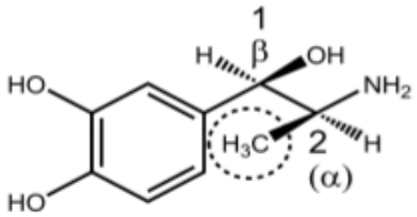
↑α2



Ephedrine (Log P = 1.05)
more α and β activity
less lipophilic → less CNS activity



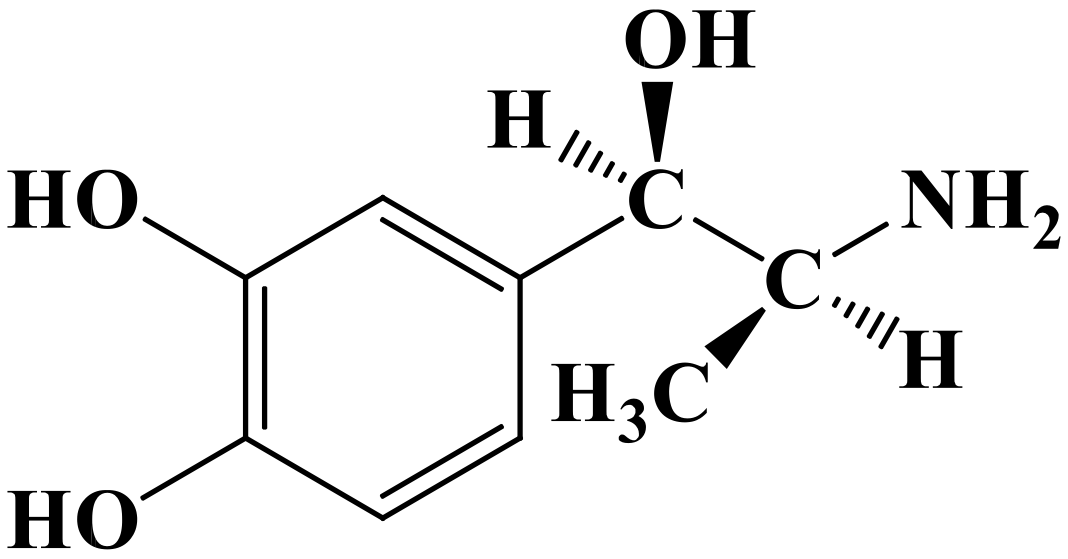
Methamphetamine (Log P = 1.97)
less α and β activity
more lipophilic → more CNS activity



(1R, 2S)-α-Methylnorepinephrine
active isomer
selective α_2 agonist

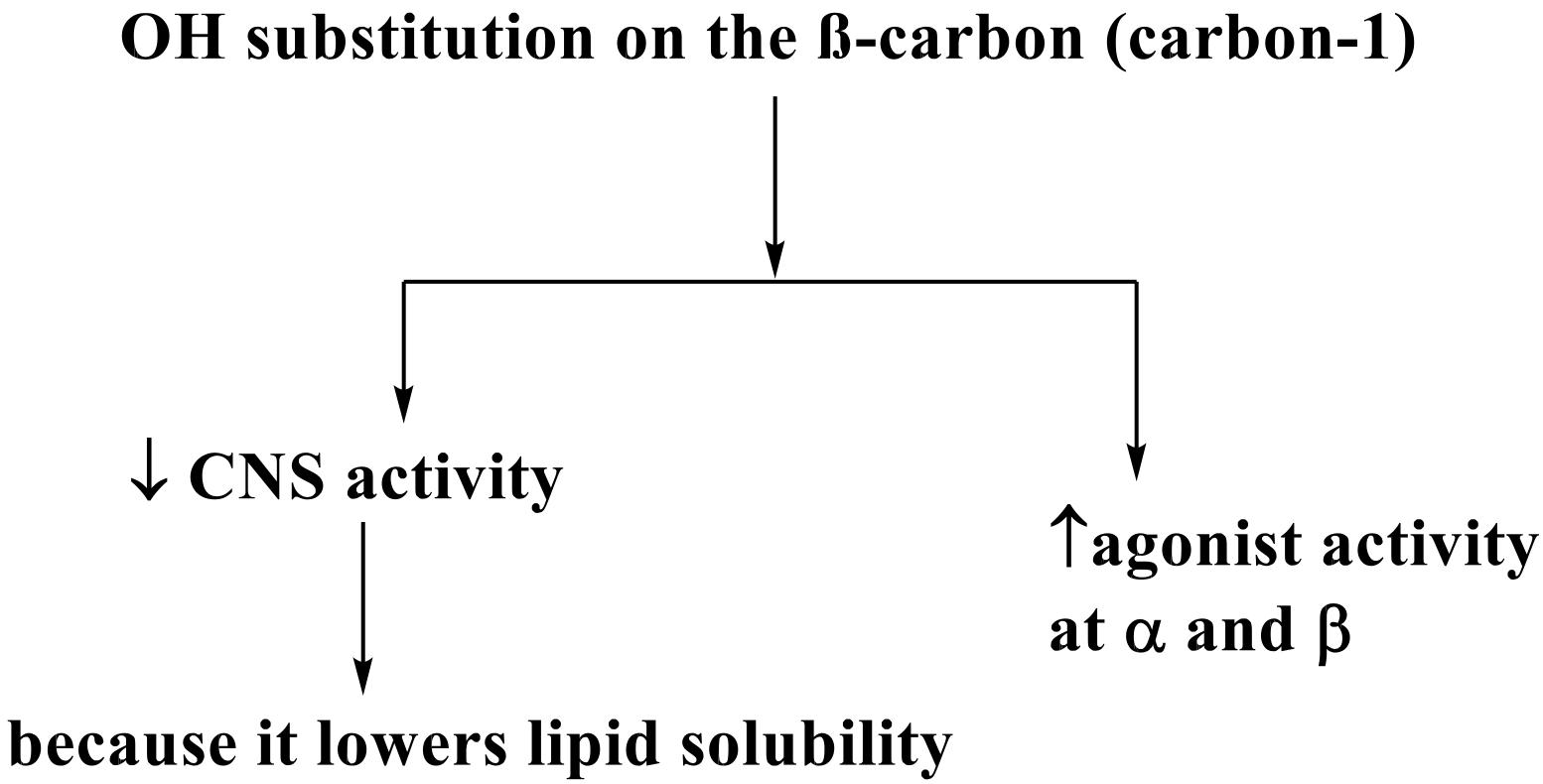
An ethyl group in this position diminishes α -activity far more than β-activity, affording compounds with β -selectivity (e.g., ethylnorepinephrine and isoetharine). In the case of β -receptors, for example, α-methyl or ethyl substitution results in compounds toward the β 2-selectivity, whereas in the case of α-receptors, α-methyl substitution gives compounds toward the α2-selectivity. Another effect of α-substitution is the introduction of a chiral center, which has pronounced effects on the stereochemical requirements for activity. For example, with α-methylnorepinephrine, it is the erythro (1R,2S) isomer that possesses significant activity at α2-receptors.

D- The introduction of a chiral center on the α-substitution, produce a pronounced effects on the stereochemical requirements for activity. For example, with α-methylnorepinephrine, it is the erythro(1R,2S) isomer that possesses significant activity at α2 -receptors.



(1R,2S) α–methylNE
selective α2 agonist

4- OH substitution on the β-carbon (carbon-1)



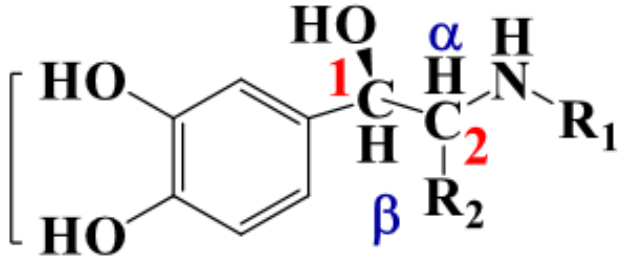
For example, ephedrine is less potent than methamphetamine as a central stimulant, but it is more powerful in dilating bronchioles and increasing blood pressure and heart rate.

Compounds lacking the β-OH group (e.g. DA) have a greatly reduced adrenergic receptor activity. Some of the activity is retained, indicating that the OH group is important but not essential.

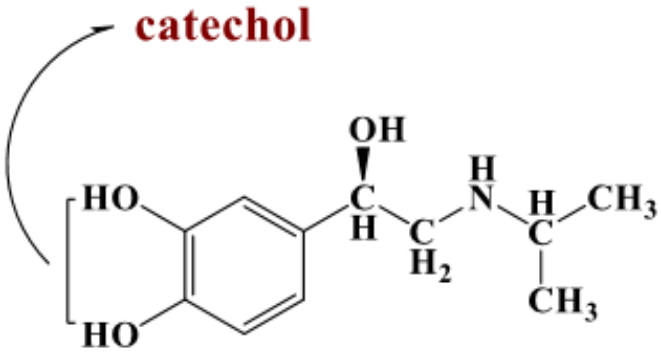
The R-enantiomer of NE is more active than the S enantiomer, indicating that the secondary alcohol is involved in an H-bonding interaction

5- Substitution on the Aromatic Ring.

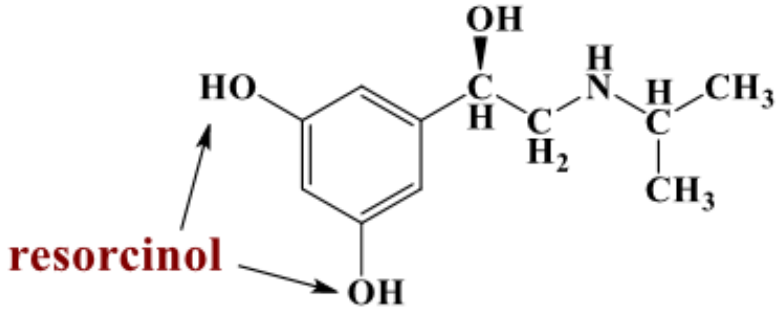
A- Catechol moiety (3,4-dihydroxybenzene) is an important for maximal activity.



B



isoproterenol(ISO)
Selectiveβ1 and β2-agonist
non selective β-agonist

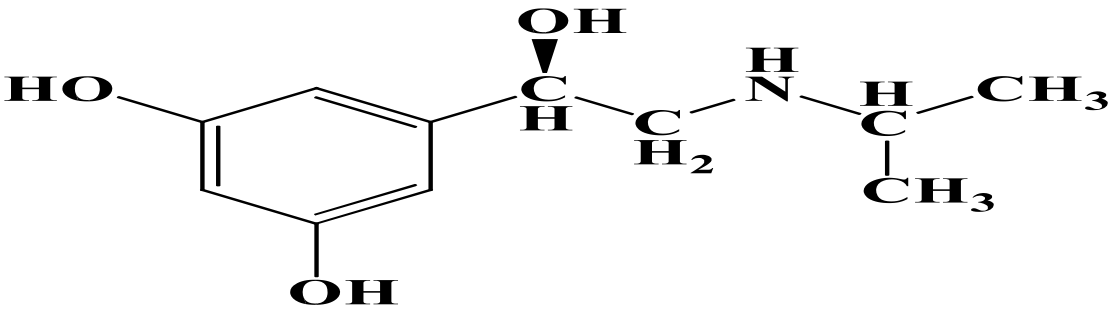


Metaproterenol
Selective β2-agonist
not metabolize by COMT→
better absorption and longer DOA

5- Substitution on the Aromatic Ring.

A- Catechol moiety (3,4-dihydroxybenzene) is an important for maximal activity.

B- Replacement of the catechol function of ISO with the resorcinol structure gives a selective β2 -agonist, metaproterenol. Furthermore, because the resorcinol ring is not a substrate for COMT, β-agonists that contain this ring structure tend to have better absorption characteristics and a longer DOA than their catechol-containing counterparts.

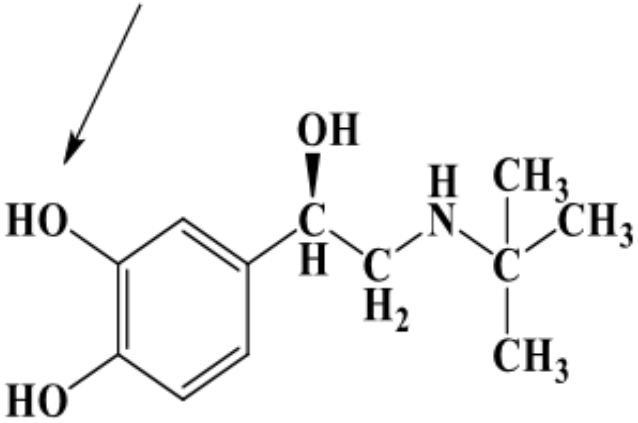


Metaproterenol
Selective β2-agonist
not metabolize by COMT→
better absorption and longer DOA

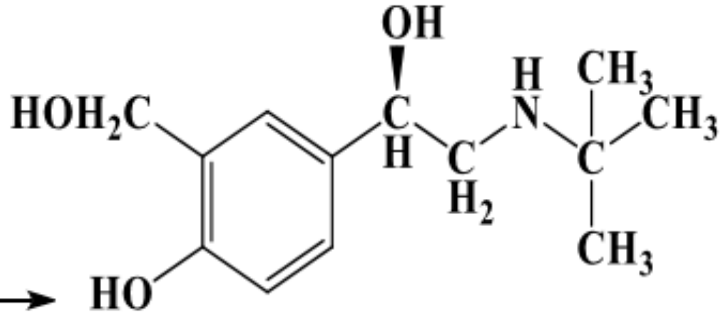
Tyramine, which lacks two OH groups, has no affinity for adrenoceptors, indicating the importance of the OH groups. Studies of β-adrenoceptor structure suggest that the OH groups on serine residues 204 and 207 probably form H bonds with the catechol OH groups at positions 3 and 4, respectively.

Although the catechol moiety is an important structural feature in terms of yielding compounds with maximal agonist activity at adrenoceptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonists.

c- Replacement of the meta- OH of the catechol structure **with** **hydroxymethyl group**



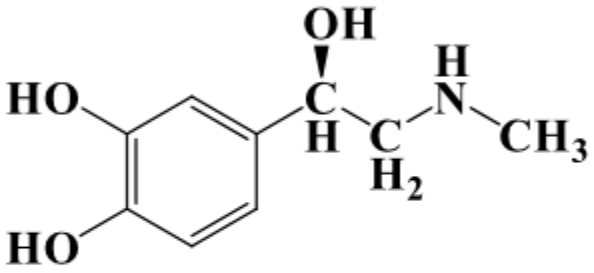
N-t-butylNE (Colterol)
Selective β2-agonist



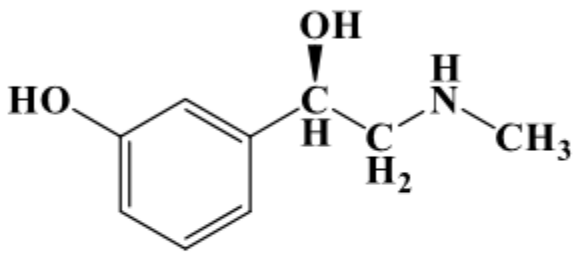
Albuterol
Selective β2-agonist
not metabolize by COMT→better absorption (bioavailability) and longer DOA

removal of the p-OH group from E

gives



E



Phenylephrine

less α and β-agonist activity than E

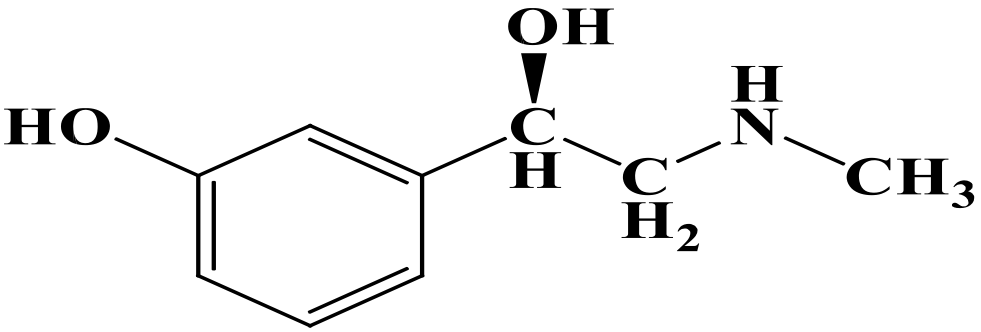
selective α1 agonist

no β activity

Modification of the catechol ring → **selectivity at α-receptors**

↓

more important for α2 -activity than for α1 -activity.



Phenylephrine

less α and β-agonist activity than E

selective α1 agonist

no β activity

CAs without OH Groups. Phenylethylamines that lack OH groups on the ring and the β-OH group on the side chain act almost exclusively by causing the release of NE from sympathetic nerve terminals and thus results in a loss of direct sympathomimetic activity. Because substitution of OH groups on the phenylethylamine structure makes the resultant compounds less lipophilic, unsubstituted or alkylsubstituted compounds cross the BBB more readily and have more central activity. Thus, amphetamine and methamphetamine exhibit considerable CNS activity. CAs per oral have only a brief DOA and are almost inactive, because they are rapidly inactivated in the intestinal mucosa and in the liver before reaching the systemic circulation. In contrast, compounds without one or both phenolic OH substituents are, however, not metabolized by COMT, and they are orally active and have longer DOA.

Imidazolines and α-Adrenergic Agonists.

Although nearly all β -agonists are β-phenylethanolamine derivatives, it is α-adrenoceptors that exhibit a far more diverse assortment of structures. A second chemical class of α -agonists, the

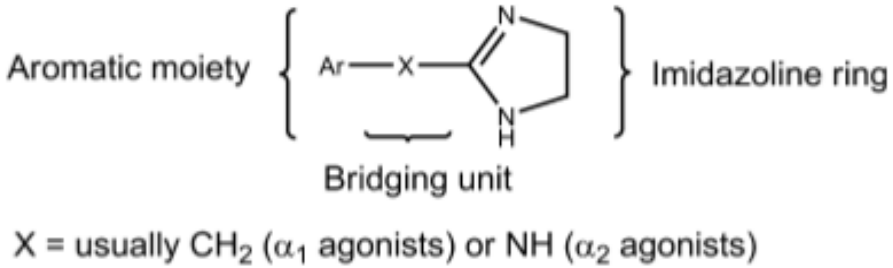


Figure 16.12 • General structural features of the imidazoline α-adrenergic receptor agonists.

imidazolines, which give rise to α-agonists and are thus vasoconstrictors. These imidazolines can be nonselective, or they can be selective for either α1- or α2-receptors. Structurally, most imidazolines have their heterocyclic imidazoline nucleus linked to a substituted aromatic moiety via some type of bridging unit (Fig. 16.12). The optimum bridging unit (X) is usually a single methylene group or amino group. Although modification of the imidazoline ring generally results in compounds with significantly reduced agonist activity, there are examples of so-called open-ring imidazolines that are highly active. The nature of the aromatic moiety, as well as how it is substituted, is quite flexible. However, agonist activity is enhanced when the aromatic ring is substituted with halogen substituents like chlorine (Cl) or small alkyl groups like methyl group, particularly when they are placed in the two ortho positions. Because the SARs of the imidazolines are quite different from those of the β -phenylethylamines, it has been postulated that the imidazolines interact with α -receptors differently from the way the β -phenylethylamines do, particularly with regard to the aromatic moiety

Q/ Explain the followings (support your answer with chemical structure, example, and drawing when needed otherwise answer will be neglected)

1- ambenonium chloride possesses a relatively prolonged duration of action and causes fewer side effects in the GI tract than the other anticholinesterase agents.

2- Reversible AChEI, are not useful as antidote for Succinyicholine chloride.