Pharmaceutical chemistry lec 2

Adrenergic Agents

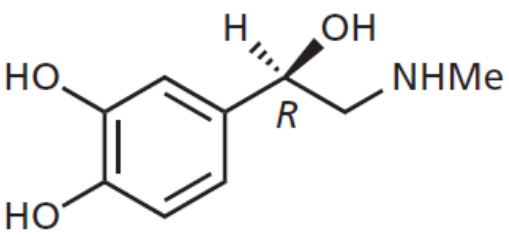
Dr. yahya saad yaseen

Adrenergic drugs

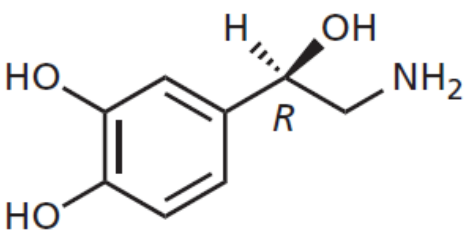
- exert their effects by either enhancing or reducing the activity of the various components of the sympathetic division of the autonomic nervous system.
- Sympathomimetic: produce effects similar to stimulation of sympathetic nervous activity
- Sympatholytic, antiadrenergic: decrease sympathetic activity.
- Adrenergic agents act on adrenergic receptors (adrenoceptors, ARs) or affect the life cycle of adrenergic neurotransmitters (NTs), including norepinephrine (NE, noradrenaline), epinephrine (E, adrenaline), and dopamine (DA).
- These NTs modulate many vital functions.

Structure and Physicochemical Properties

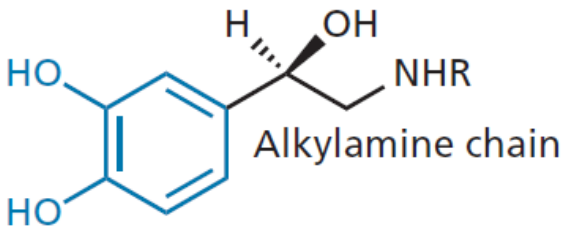
- NE, E, and DA are chemically catecholamines (CAs) ,[contain a catechol and an ethylamine group].
- E and NE each possess a chiral carbon atom;
- The enantiomer with the (R) configuration is biosynthesized by the body and possesses the biological activity.
- This (R) configuration contributes to the high affinity to the corresponding adrenoceptors.



Adrenaline



Noradrenaline



Catechol ring system

FIGURE 23.1 Adrenergic transmitters.

Biosynthesis

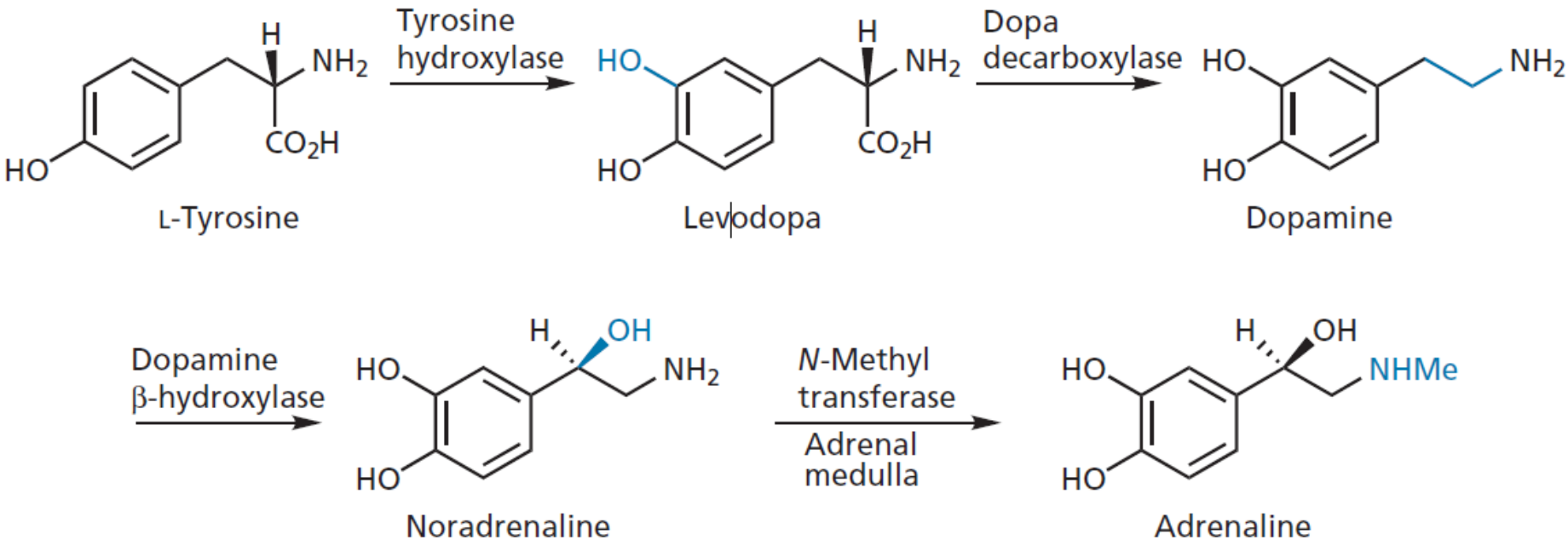


FIGURE 23.2 Biosynthesis of noradrenaline and adrenaline.

Storage, Release, Uptake, and Metabolism

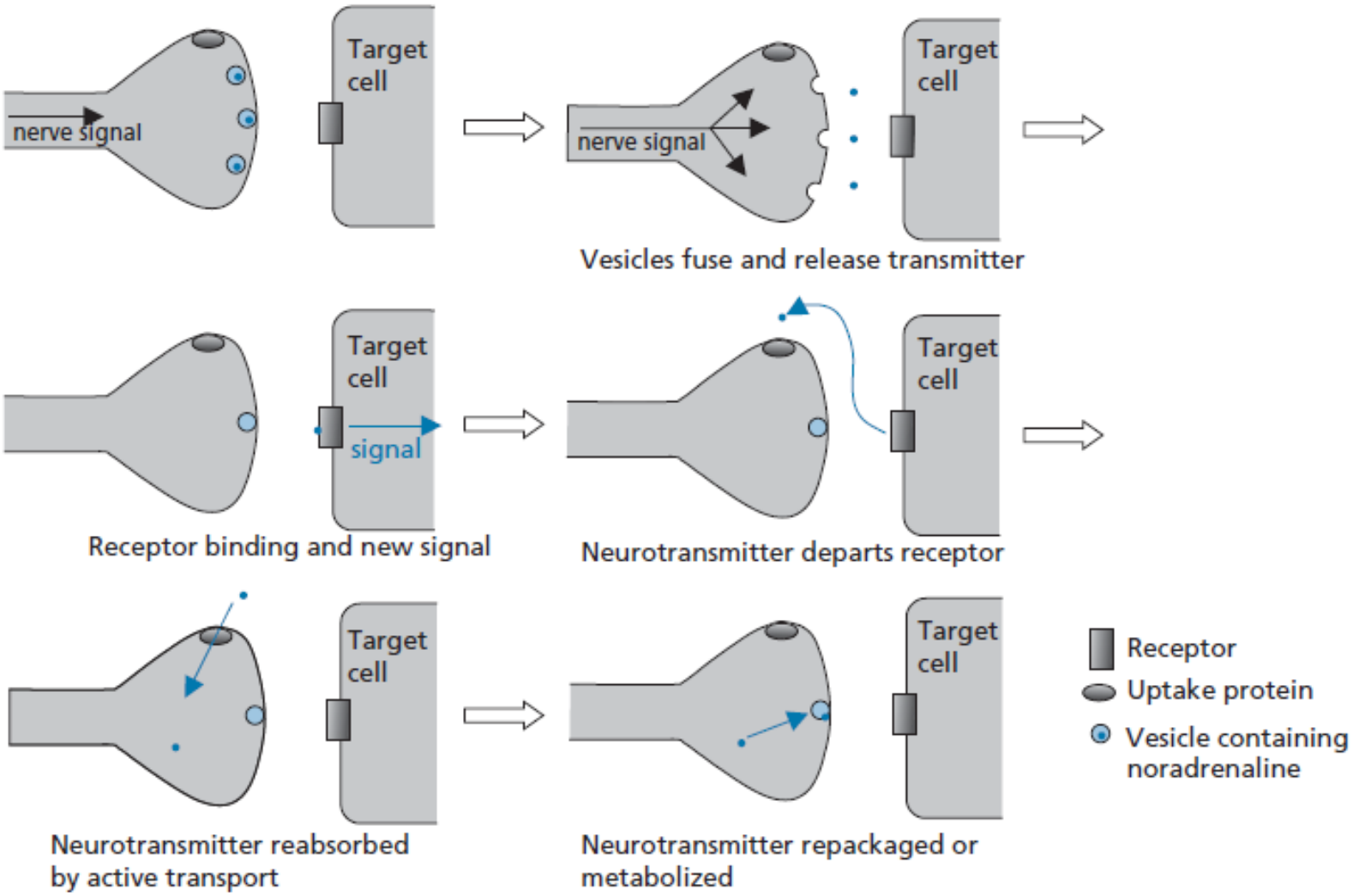


FIGURE 23.5 Transmission process for noradrenaline.

Metabolism

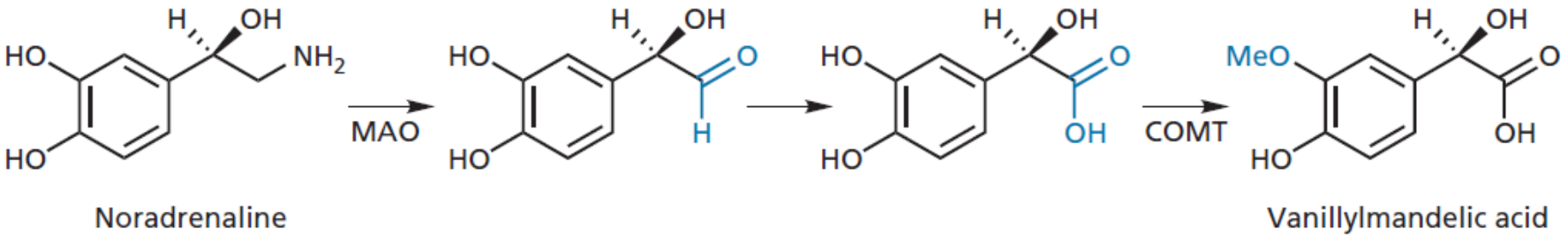


FIGURE 23.3 Metabolism of noradrenaline with monoamine oxidase (MAO) then catechol *O*-methyltransferase (COMT).

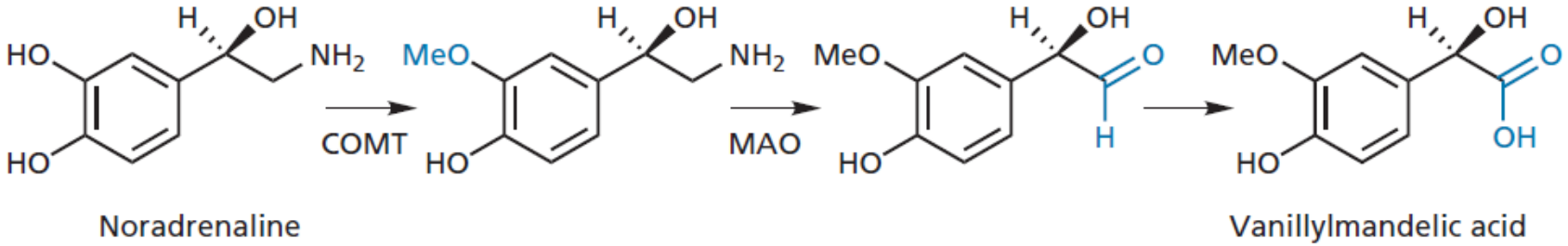


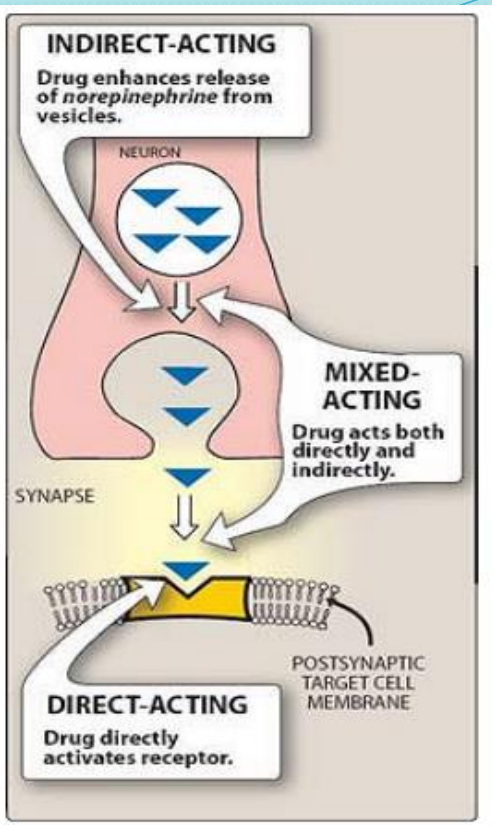
FIGURE 23.4 Metabolism of noradrenaline with catechol *O*-methyltransferase (COMT) then monoamine oxidase (MAO).

Adrenergic Receptor Subtypes

- Adrenergic receptors are G-protein-coupled receptors.
- There are two main types: the α- and the β-adrenoceptors. There are various subtypes of each.
- The different types and subtypes of adrenoceptor predominate in different tissues.
- Drugs which show receptor selectivity also show tissue selectivity.
- The major use of adrenergic agonists is in the treatment of asthma.
- The major use of adrenergic antagonists is in cardiovascular medicine.
- The α-adrenoceptor consists of α1 and α2 subtypes.

- α1 receptors activate inositol triphosphate (IP3) and diacylglycerol (DG) as secondary messengers (mediate excitatory responses).
- the α 2 -receptors inhibit the production of the secondary messenger cyclic-AMP. (mediate inhibitory responses).
- The β-adrenoceptor consists of β1 -, β2 -, and β3 -subtypes, all of which activate the formation of cyclic-AMP.
- The clinical use of receptors-selective drugs becomes obvious when one considers the adrenoceptor subtypes and their locations.
  - α1-Agonists as Vasoconstrictors and Nasal Decongestants.
  - α1-Antagonists for Treatment of Hypertension.
  - α2-Agonists for Treatment of Hypertension.
  - β1-Blockers for Treatment of Hypertension, Angina, and Certain Cardiac Arrhythmias.
  - β 2-Agonists for Treatment of Asthma and Premature Labor.

Sympathomimetic agents



classified as direct, indirect, or mixed action.

- Direct-acting agents:
  - Non-selective:

    Adrenaline, Noradrenaline, Isoprenaline, Dopamine
  - Selective:

    α1 selective: Phenylephrine, Oxymetazoline.

    α2 selective: α-Methyl dopa, clonidine

    β1 selective: Dobutamine.

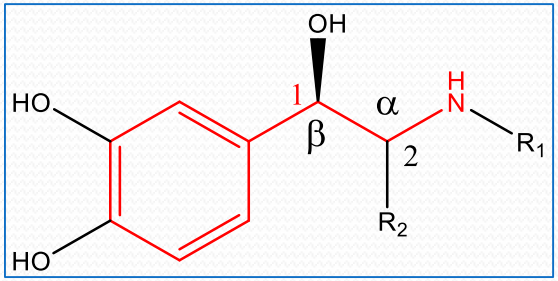
    β2 selective: Salbutamol/Albuterol, Terbutaline, Salmeterol.
- Indirect-acting agents

  Amphetamines, Tyramine, Nicotine, Caffeine,
- Mixed action

  Ephedrine, Pseudoephedrine

Direct Acting Sympathomimetics

- The parent structure is: β-phenyl ethyl-amine.
- The substitution on the meta-,and Para-positions of the aromatic ring, on the amino, and on α - (R2) and β-positions (R1) of the ethylamine side chain influences
  - their mechanism of action,
  - the receptor selectivity,
  - their absorption, oral activity, metabolism, degradation, → duration 0f 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

** For CAs, the more potent enantiomer has the (1R) configuration. (100-fold more potent than 1S enantiomer.

- This explanation of stereo selectivity is based on the presumed interaction of these three critical pharmacophoric groups with three complementary binding areas on the receptor.

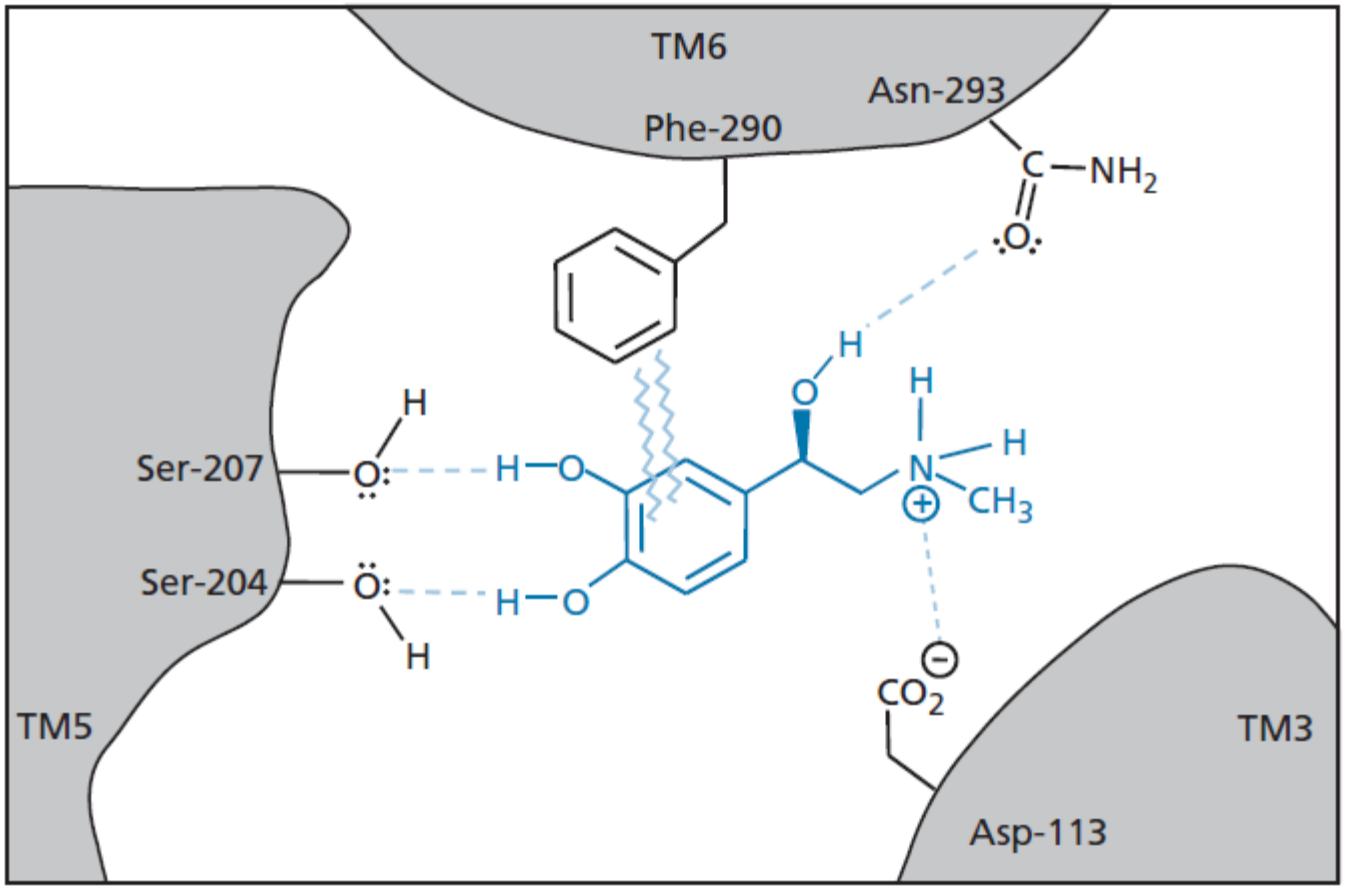
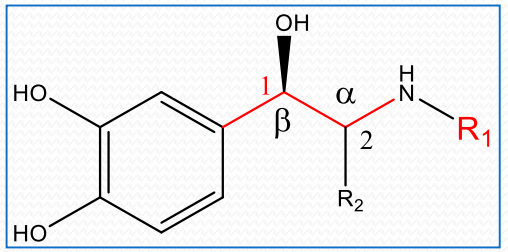


FIGURE 23.8 Adrenergic binding site.

Structure–activity relationships

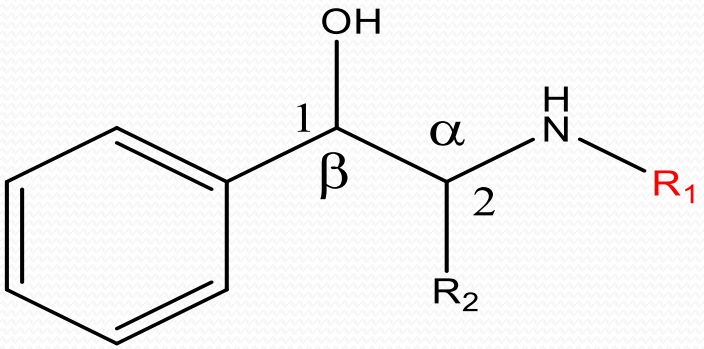
1. Separation of Aromatic Ring and Amino Group.
   - The greatest adrenergic activity occurs when two carbon atoms separate the aromatic ring from the amino group. This rule applies with few exceptions to all types of activities



Structure–activity relationships

2. R1, Substitution on the Amino Nitrogen Determines α – or β -Receptor Selectivity

- Replacing nitrogen with carbon results in a large decline in activity.
- Primary and secondary amines have good adrenergic activity.
- Tertiary amines are poor agonists, but may show norepinephrine releasing activity.



Primary amines show α and β agonist activity

R1-substitution on N

↑ the size of R1 →

- ↑β activity
- ↓α activity
- t-butyl: ↑ β2 activity
- ↓ degradation by MAO

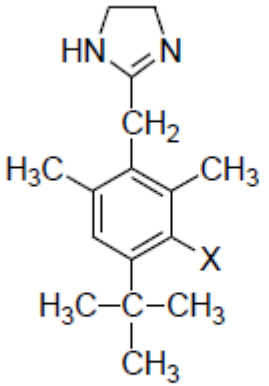
Structure–activity relationships

2. R1, Substitution on the Amino Nitrogen Determines α – or β -Receptor Selectivity

- Replacing nitrogen with carbon results in a large decline in activity.
- Primary and secondary amines have good adrenergic activity.
- Tertiary amines are poor agonists, but may show norepinephrine releasing activity.
- Imidazoline bioisosters of phenethylamine.

may act as α agonists or α antagonists. (Because imidazoline has a pKb = 3, with a pKa = 11, it is extensively protonated at physiological pH and there is generally poor penetration thru the blood brain barrier)

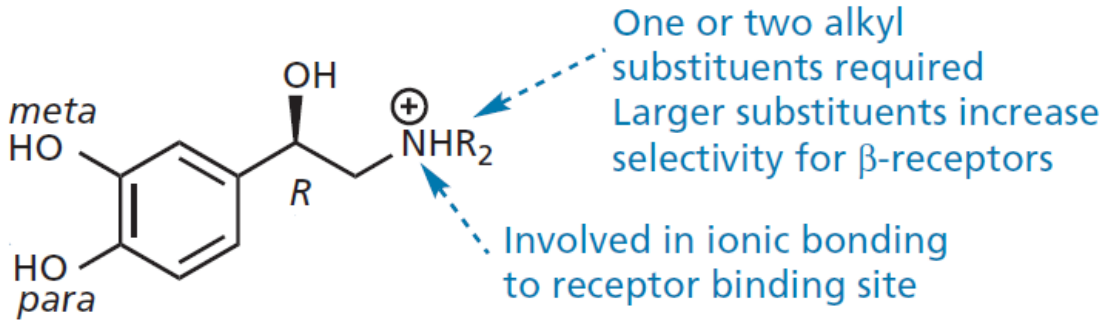
α_1-Agonists



X = H; Xylometazoline, Otrivin®
X = OH; Oxymetazoline, Afrin®

Structure–activity relationships

1. Separation of Aromatic Ring and Amino Group.
2. R1, Substitution on the Amino Nitrogen Determines α – or β -Receptor Selectivity

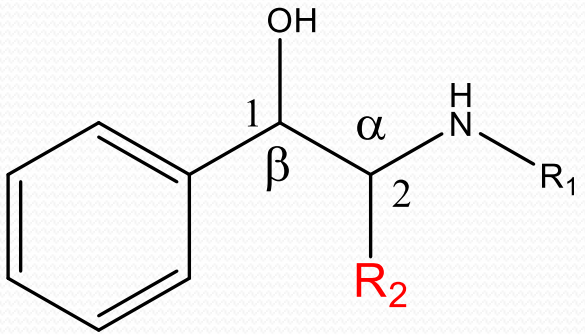


Important binding groups for adrenergic agents.

3. R2, Substitution on the alpha -Carbon (Carbon-2).

Substitution by small alkyl group (e.g., CH3- or C2H5-)

- slows metabolism by MAO
- has little overall effect on DOA of catechols because they remain substrates for COMT.



R2- substitution on C2

Small alkyl groups (Me, Et) tolerated

↓ Degradation by MAO

Still substrate for COMT → little effect on DOA

enhance GI (oral activity) & blood brain penetration (CNS activity).

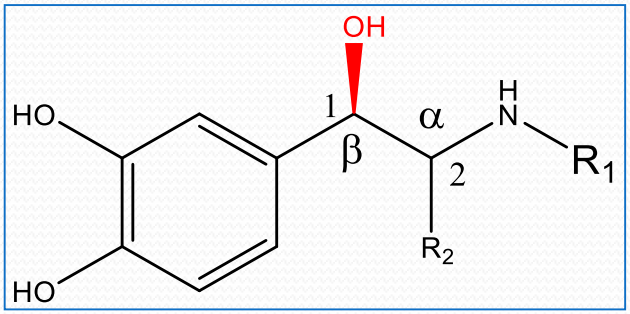
CNS activity: α (S) > α (R)

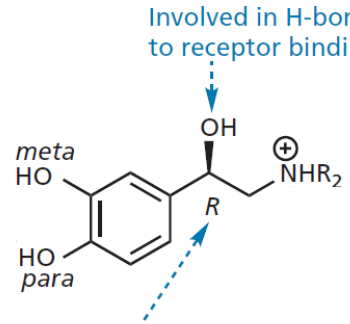
Et group: ↑β selectivity

(2S) methyl group : ↑α2 activity

4. OH substitution on the beta-carbon (carbon-1).

- generally decreases CNS activity largely because it lowers lipid solubility
- such substitution greatly enhances agonist activity at both α – and β - receptors.

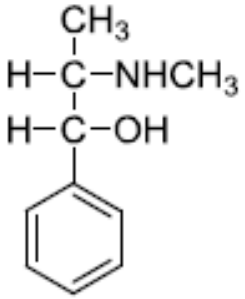




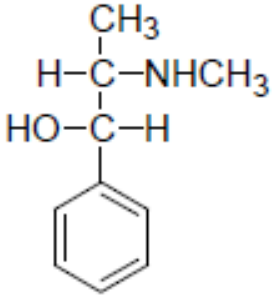
Important binding groups for adrenergic agents.

4) β-Hydroxy group (-π) Effects:

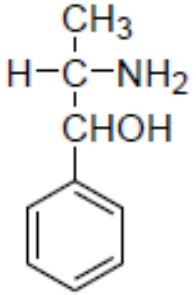
β-Phenylethylamines with OH in β-position are direct agonists and at the least can produce "mixed effects", acting as both direct agonists and norepinephrine releasers.



Ephedrine®
D-(-)erythro-[R-(R*,S*)]

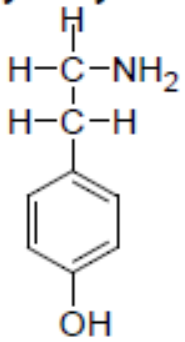


Pseudoephedrine, Sudafed®
L-(+)-theo-[S-R*, R*)]

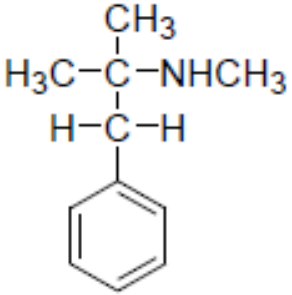


Phenylpropanolamine
Propadrine® (R*,S*)

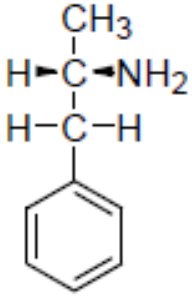
β-Phenylethylamines without a OH in the β-position are norepinephrine releasers.



Tyramime



Mephentermine, Wyamine®



Dextroamphetamine, Dexedrine®

5. Substitution on the Aromatic Ring.

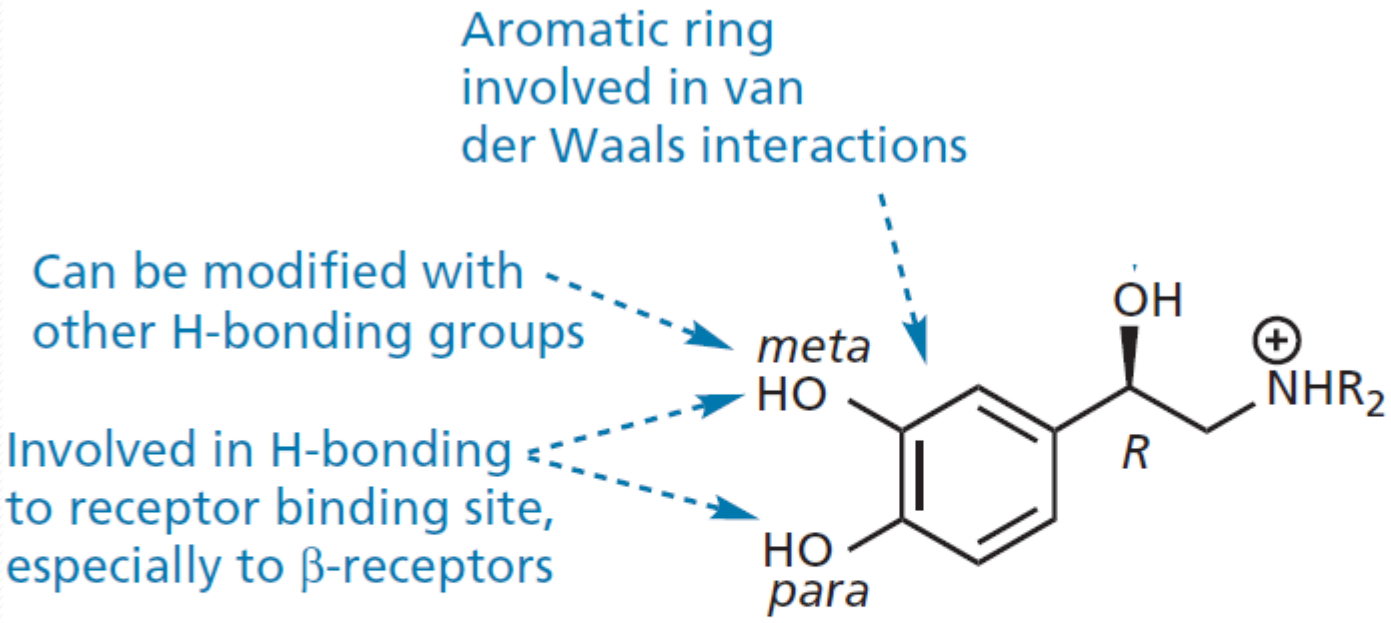
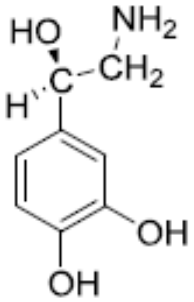


FIGURE 23.9 Important binding groups for adrenergic agents.

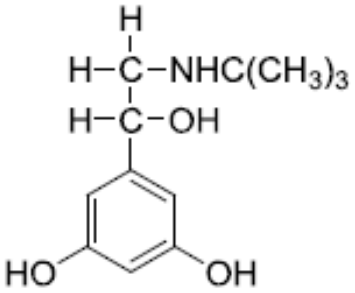
5. Substitution on the Aromatic Ring.

1. Phenyl or Acyclic Structure

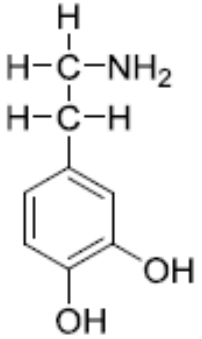
a) Diphenol derivatives with or without β-hydroxyl group are agonists. In general, they are poorly absorbed across the blood brain barrier. Dopamine and norepinephrine are very poorly absorbed from the GI tract, and have almost no blood brain barrier penetration.



Norepinephrine



Terbutaline, Brethine®,



Dopamine

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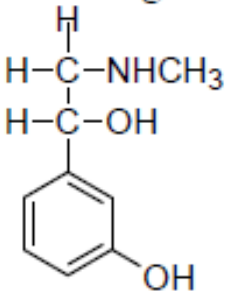
b) Monophenols with β-hydroxyl groups are agonists. Monophenols with a β-hydroxyl group can get across the GI barrier and can produce a systemic effect. However, they do not penetrate and cross the blood brain barrier to a significant degree.



Phenylephrine, Neosynephrine®

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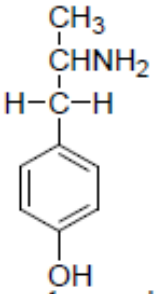
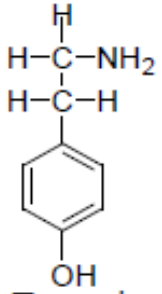
c) Monophenols without β-hydroxyl groups are norepinephrine releasers. Monophenols without a β-hydroxylgroup can get across the GI barrier and can cross, to a limited extent, the blood brain barrier.



Hydroxyamphetamine, Paredrine®



Tyramine

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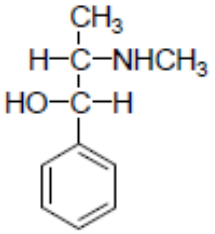
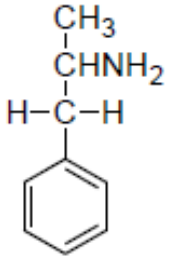
d) Nonphenolic derivatives act as norepinephrine releasers or as neuronal uptake inhibitors. These derivatives tend to exhibit good GI and blood brain barrier penetration, particularly in the absence of a β-hydroxyl group.



Pseudoephedrine, Sudafed®



Amphetamine, Benzedrine®

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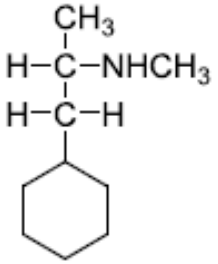
e) Aliphatics and Alicyclics: These agents are norepinephrine releasers with limited CNS activity.



Propylhexedrine, Benzedrex, ®

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5. Substitution on the Aromatic Ring.

Maximal α – and β -activity also depends on the presence of 3′ and 4′ OH groups.

- Tyramine, which lacks two OH groups, has no affinity for adrenoceptors.
- Replacement of the catechol function of ISO with the resorcinol structure gives a selective β2- agonist , (metaproterenol).
- 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.
- replacement of the meta-OH of the catechol structure with a hydroxymethyl group gives agents, such as albuterol, which show selectivity to the β2-receptor.

Aromatic substituents:

3`, 4`-di-OH for both α and β agonist activity

- Metabolized by COMT → Poor oral activity & short DOA
- Hydrophilic → poor CNS activity

3`-CH2OH, 4`OH(e.g. albuterol)

- ↑β activity
- ↓ degradation by COMT→ ↑oral activity & short DOA

4`-OH is more important for β activity

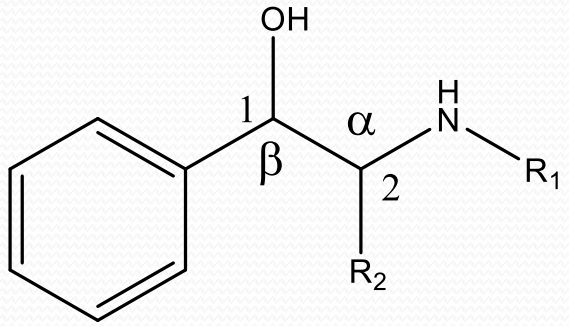
3`-OH is more important for α activity (phenylephrine α Agonist)

No phenolic substitution →

- ↓ Both α and β activity

Structural requirements:

1. β-phenylethylamine
2. Catechol ring
3. (1R)-OH (β)



R1-substitution on N

↑ the size of R1 →

- ↑β activity
- ↓α activity
- t-butyl: ↑ β2 activity
- ↓ degradation by MAO

R2- substitution on C2

Small alkyl groups (Me, Et) tolerated

↓ Degradation by MAO

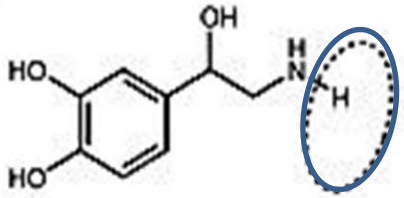
Still substrate for COMT → little effect on DOA

Et group:

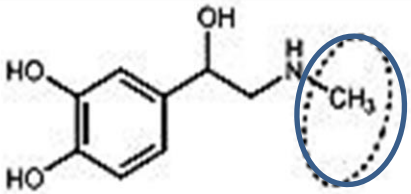
↓α >> β (more b selective e.g. ethyl-norepinephrine)

↑CNS activity, ↑oral activity & DOA

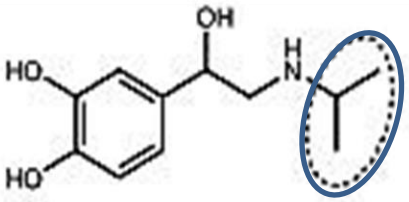
(2S) methyl group : ↑α2 activity



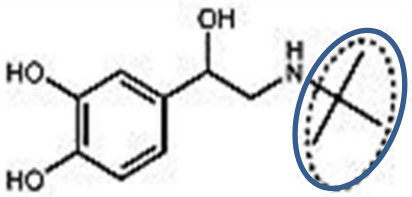
Norepinephrine (NE)
α > β agonist
α agonist



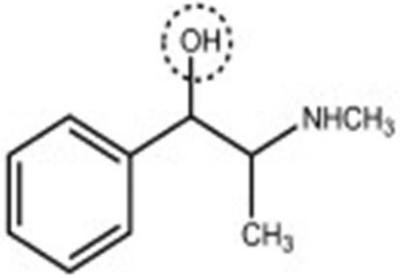
Epinephrine (E)
α, β_1 and β_2 agonist
nonselective α and β agonist



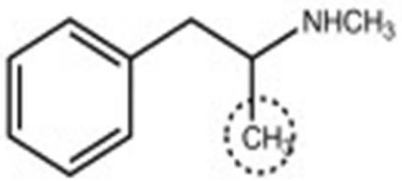
Isoproterenol (ISO)
β_1 and β_2 agonists
nonselective β agonist



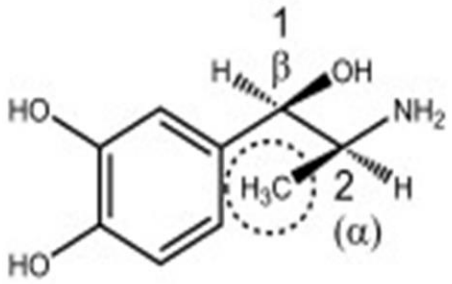
N-*t*-Butylnorepinephrine (Colterol)
selective β_2 agonist



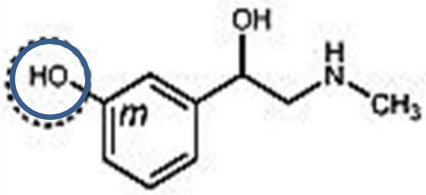
Ephedrine (Log P = 1.05)
more α and β activity
less lipophilic → less CNS activity



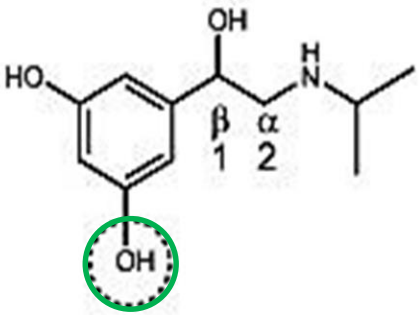
Methamphetamine (Log P = 1.97)
less α and β activity
more lipophilic → more CNS activity



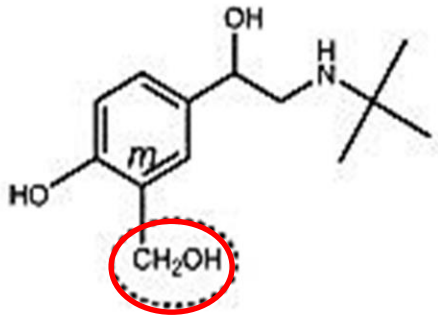
(1R, 2S)-α-Methylnorepinephrine
active isomer
selective α_2 agonist



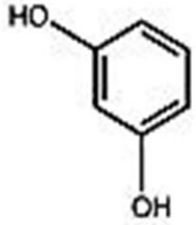
Phenylephrine
less α and β activity than NE
selective α_1 agonist
almost no β activity



Metaproterenol
selective β_2 agonist
not metabolized by COMT →
better absorption & longer DOA



Albuterol
selective β_2 agonist
not metabolized by COMT →
better oral bioavailability



Resorcinal

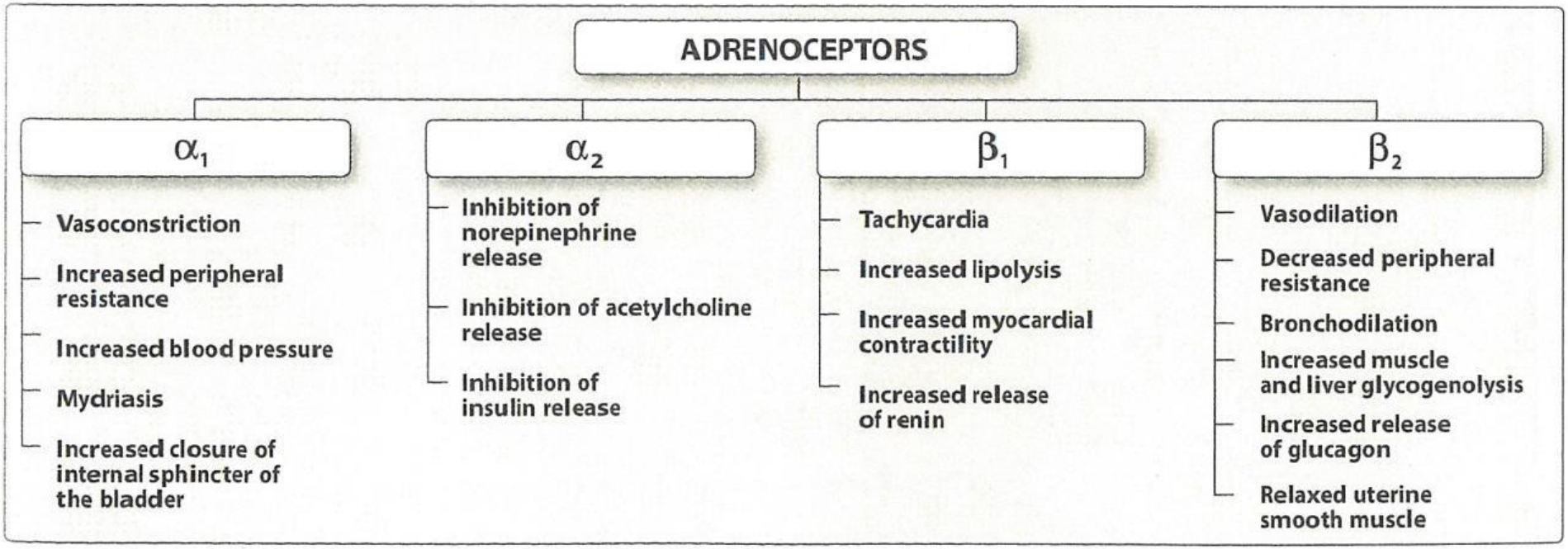


Figure 6.6
Major effects mediated by α- and β-adrenoceptors.

❑ β 2 -Agonists and the treatment of asthma

- Activation of the β 2 -receptor results in **smooth muscle relaxation** and, as β 2 -receptors **predominate in bronchial smooth** muscle, this leads to **dilatation** of the airways.
- relax smooth muscle in the uterus to delay premature labour.
- Adrenaline is used to dilate the airways in emergency situations, but it is not suitable for long-term use (short DOA& cardiovas cular side effects)
- Isoprenaline

selective for β-receptors over α-receptors _(bulky N –alkyl substituent).

no selectivity between the different subtypes of β-receptors → activated the β 1 -receptors of the heart, leading to unwanted cardiovascular effects.

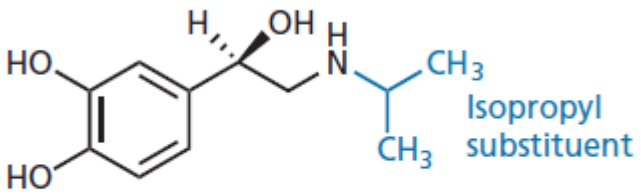
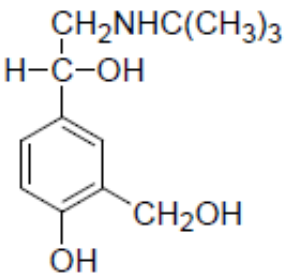


FIGURE 23.11 (*R*)-Isoprenaline.

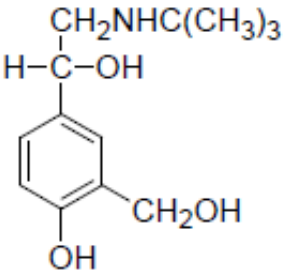
- β 2 -Agonists and the treatment of asthma
  - Salbutamol has the same potency as isoprenaline, but is 2000 times less active on the heart.
  - It has a duration of four hours and not metabolized by COMT.



Albuterol, (Salbutamol),
Ventolin®, Proventil®

❑β 2 -Agonists

- Several analogues of **Salbutamol** (test whether the *meta* CH2OH group could be modified further) These demonstrated the following requirements for the *meta* substituent:
  - it has to be capable of taking part in hydrogen bonding—substituents such as Me**SO2NH**CH 2 , H**CONH**CH 2 , and H2**NCONH**CH2 permitted
  - substituents with an electron-withdrawing effect on the ring have poor activity (CO2H);
  - bulky *meta* substituents are bad for activity because they prevent the substituent adopting the necessary conformation for hydrogen bonding;
  - the CH2OH group can be extended to CH2CH2OH but no further.



Albuterol, (Salbutamol), Ventolin®, Proventil®

- longer lasting agent (nocturnal asthma—a condition which usually occurs at about 4 a.m.)
  - increase the lipophilicity → more lipophilic drug would **bind more strongly to the tissue in the vicinity** of the adrenoceptor → available to act for a longer period.
  - increased lipophilicity was achieved by increasing the length of the N -substituent with a further hydrocarbon chain and aromatic ring. → **Salmeterol** (twice the potency of salbutamol and an extended action of 12 hours).
    - Extending the N -alkyl substituent to include a hydrogen bonding group increases affinity for β-receptors.

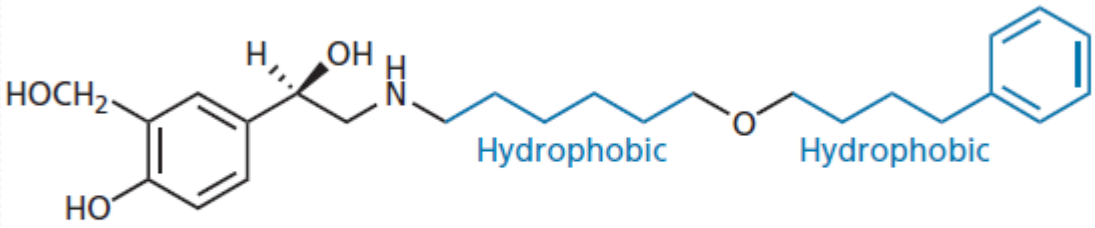


FIGURE 23.19 (*R*)- Salmeterol.

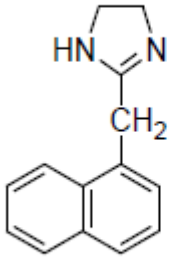
β3-Adrenergic Receptor Agonists

- The β3-receptor has been shown to mediate various pharmacological effects such as lipolysis, thermogenesis, and relaxation of the urinary bladder.
- Activation of the β3-receptor is thought to be a possible approach for the treatment of obesity, type 2 diabetes mellitus, and frequent urination.

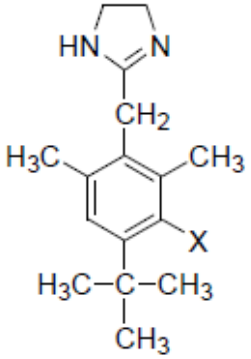
❑ Selective α 1 –agonists:

- such as **oxymetazoline, xylometazoline** and
- act as vasoconstrictors, and are used widely as topical medicines for the treatment of **nasal congestion**
- **Naphazoline** used for bloodshot eyes (ophthalmic) and nasal congestion .
- They have limited access to the CNS, (ionized form at physiological pH)

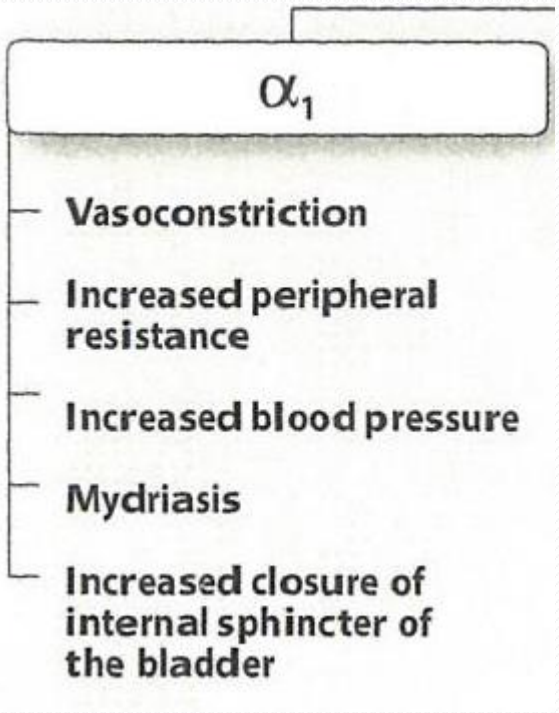
D. Imidazole Derivatives



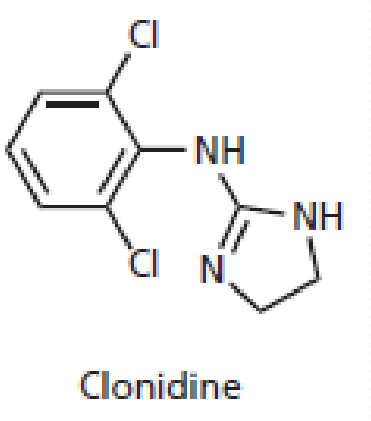
Naphazoline, Privine®



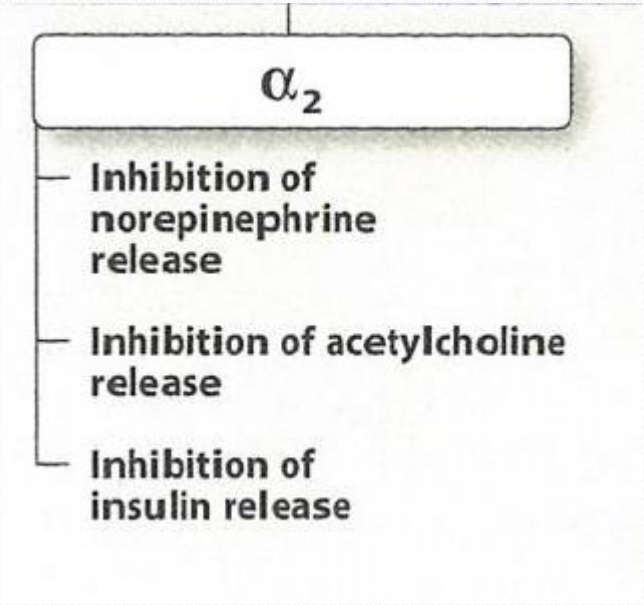
X = H; Xylometazoline, Otrivin®
X = OH; Oxymetazoline, Afrin®



- selective α 2 -agonist
  - **Clonidine** used for the treatment of **hypertension**.



Clonidine



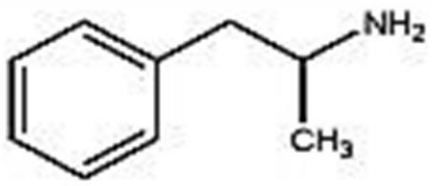
Indirect-Acting Sympathomimetics

- Indirect-acting sympathomimetics act by **releasing endogenous NE**. They also enter the nerve ending by way of the active-uptake process and displace NE from its storage granules.
- As with the direct-acting agents, the presence of the catechol OH groups enhances the potency of indirect-acting phenylethylamines. However, the indirect-acting drugs that are used therapeutically are not catechol derivatives and, in most cases, do not even contain an OH moiety.
- In contrast with the direct-acting agents, the presence of a β –hydroxyl group decreases, and an α-methyl group increases, the effectiveness of indirect-acting agents.

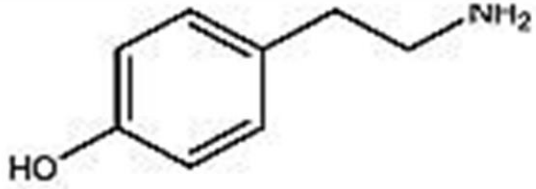
.

Indirect-Acting Sympathomimetics

- The presence of nitrogen substituents decreases indirect activity, with substituents larger than methyl groups rendering the compound virtually inactive.
- Phenylethylamines that contain a tertiary amino group are also ineffective as NE-releasing agents.
- Amphetamine and p-tyramine .



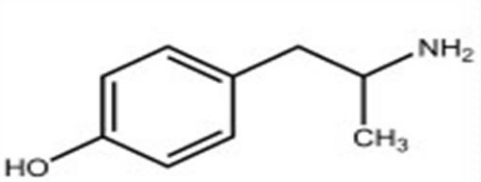
Amphetamine
Log P = 2.81



p-Tyramine

Indirect-Acting Sympathomimetics

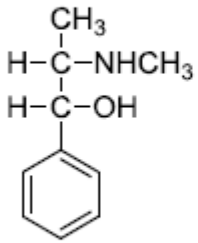
- Hydroxyamphetamine
  - Is an effective, indirect-acting sympathomimetic drug.
  - It differs from amphetamine in the presence of p-OH group and so it has **little or no CNS-stimulating action**.
  - It is used to dilate the pupil for **diagnostic eye examinations** and for surgical procedures on the eye.



Hydroxyamphetamine
Log P = 1.07
pKa = 10.71

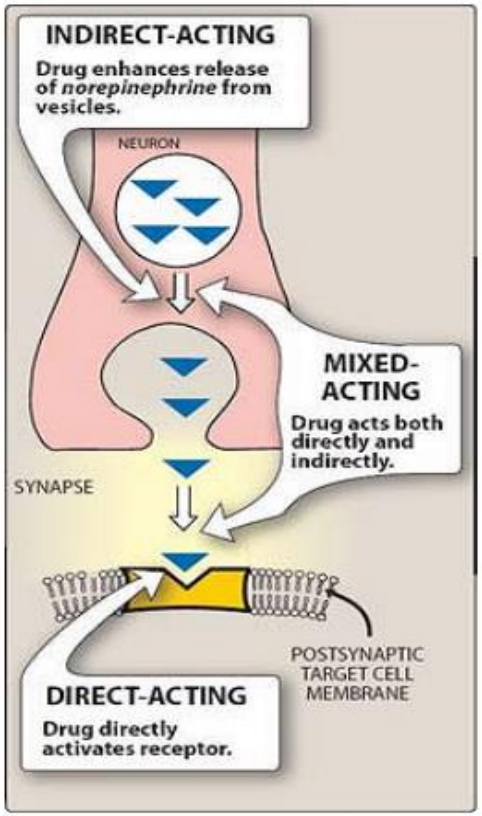
C. MIXED EFFECTS

1. Phenethylamines



Ephedrine®
D-(-)erythro-[R-(R*,S*)]

- is a natural product present
- in various plants which have been used in folk medicine
- two asymmetric centres, (racemic mixture)
- It activates both α– and β-adrenoceptors
- used extensively in non-prescription preparations as a bronchodilator.ephedrine
- used as a CNS stimulant (phenolic)
- not metabolized by either MAO or COMT and therefore has more oral activity and longer DOA than E.



Adrenergic antagonists (adrenergic blockers, antiadrenergic agents)

Drug	Receptor Specificity	Therapeutic uses
Phenoxy-benzamine	α_1, α_2	Incomplete urinary voiding ~~Autonomic hyperreflexia~~ Benign prostatic hypertrophy ~~Treatment of pheochromocytoma-~~ induced hypertension
Phentolamine	α_1, α_2	Diagnosis of pheochromocytoma Treatment of frostbite
Prazosin	α_1	Hypertension
Terazosin	α_1	Hypertension

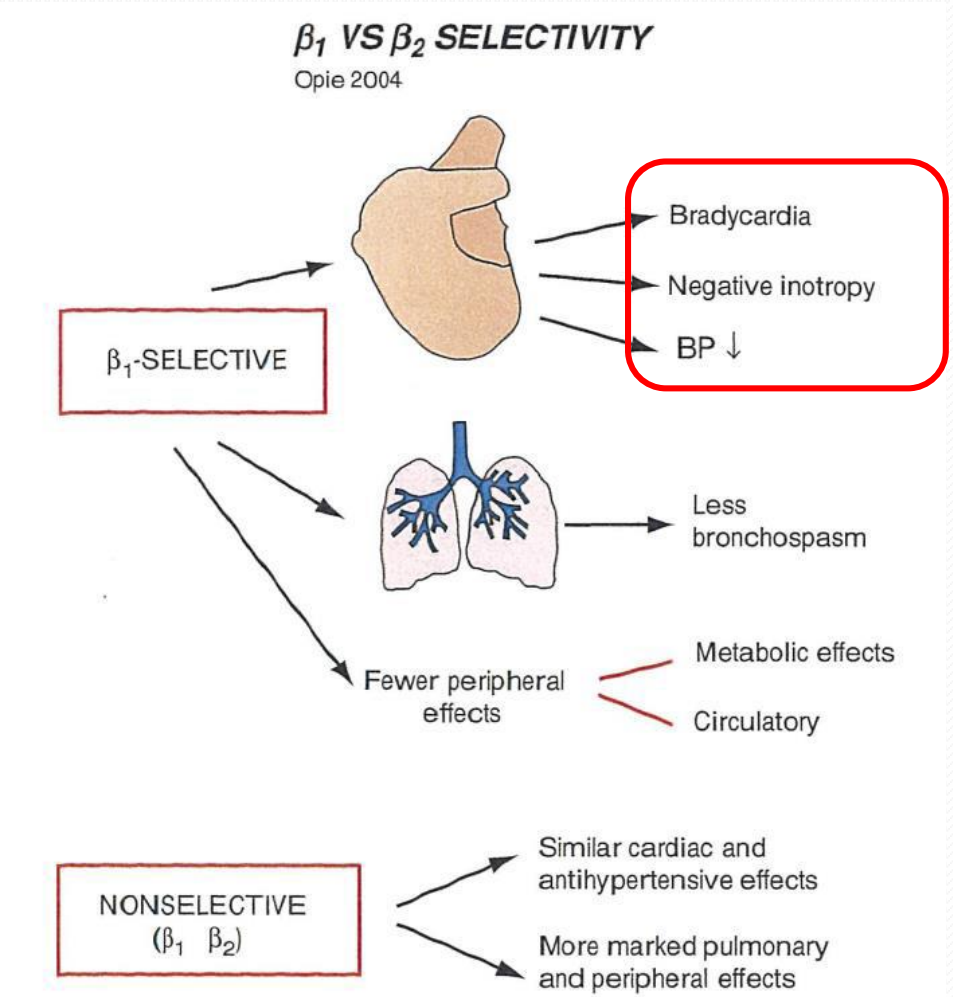


Figure 1-9 **β_1- versus β_2-cardioselectivity.** In general, note the several advantages of cardioselective β-blockers (exception: heart failure). Cardioselectivity is greatest at low drug doses. (BP, blood pressure.) (Figure © L.H. Opie, 2004.)

Selective α1-blockers

- Antagonist of α1-adrenoreceptors can affect smooth muscle which are abundant in the prostate, and bladder neck → reduction in **BPH** symptoms.
- These agents relieve hypertension by blocking the actions of noradrenaline or adrenaline at the α 1 - receptors of smooth muscle in blood vessels. This results in **relaxation of the smooth muscle and dilatation of the blood vessels**, leading to a lowering in blood pressure.
- These drugs have also been used for the treatment of patients with an enlarged prostate—a condition known as **benign prostatic hyperplasia (BPH)** .
- Praz**osin** was the first α 1 -selective antagonist but it is short acting.
- Longer lasting drugs, such as doxaz**osin** and teraz**osin**, are better because they are given as once-daily doses.

Selective α1-blockers

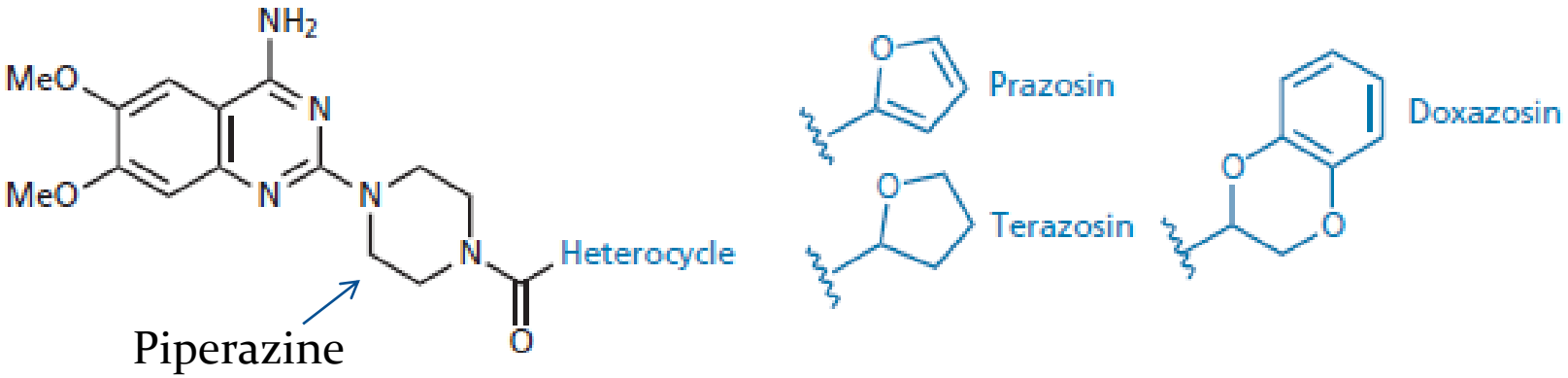


FIGURE 23.22 α_1-Selective antagonists.

β-Blockers as cardiovascular drugs

b) Aryloxypropanolamines: GENERAL STRUCTURE

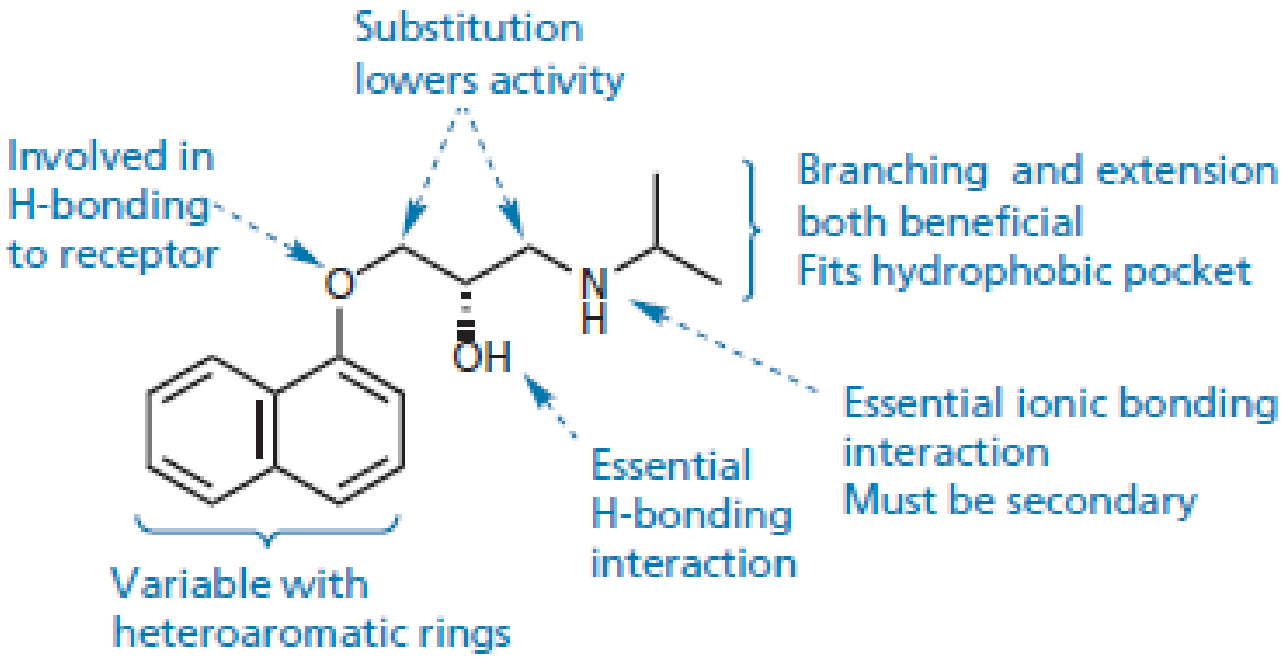
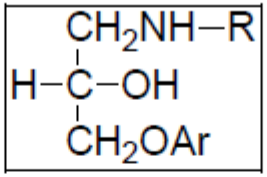
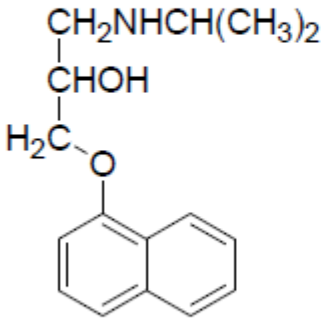


FIGURE 23.26 Structure–activity relationships of aryloxypropanolamines.

β-Blockers as cardiovascular drugs

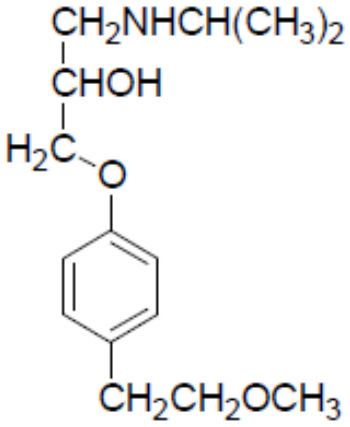
b) Aryloxypropanolamines: GENERAL STRUCTURE





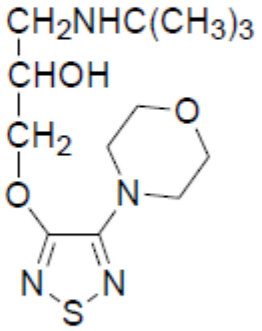
Propranolol, Inderal®
(β_1 and β_2 antagonist)

Bronchoconstriction
patient is asthmatic
CNS effects → anxiety
and migraine



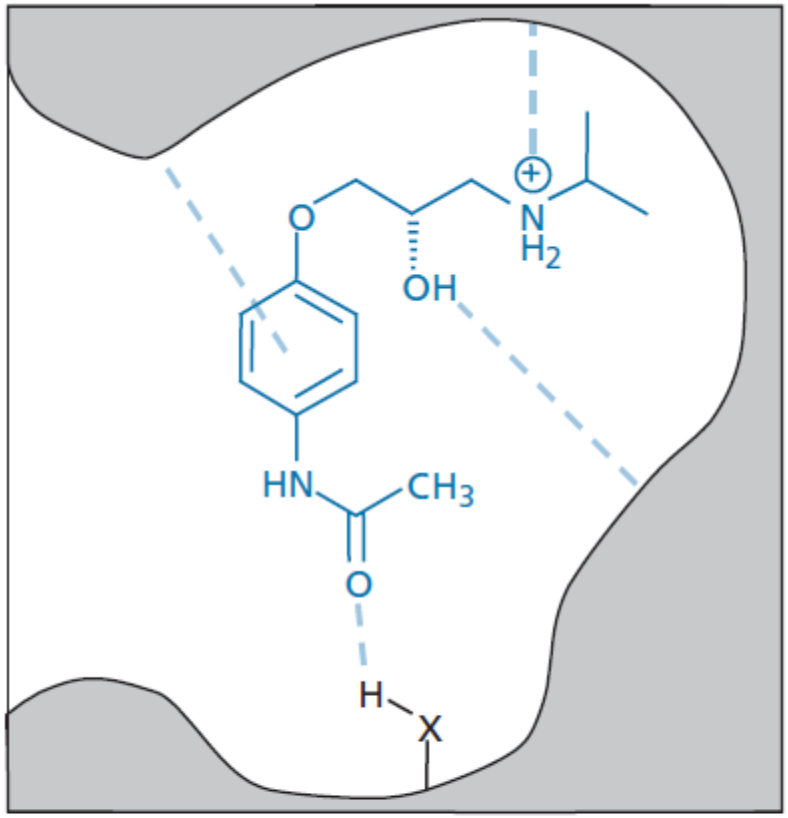
Metoprolol
Lopressor®
(β_1 antagonist)

Hydrogen bonding→ β 1 -selectivity.

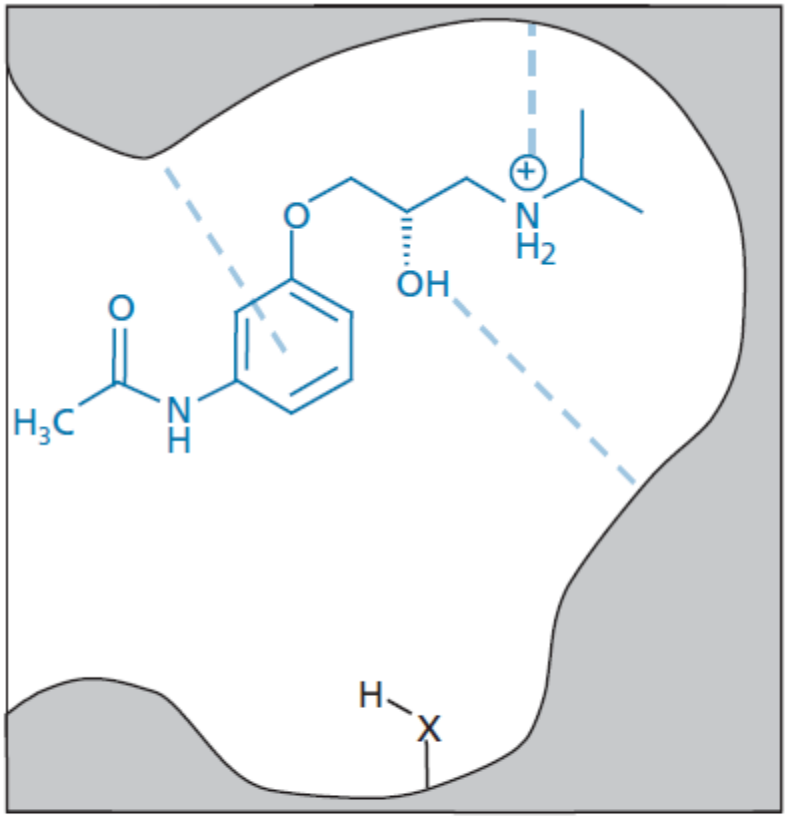


Timolol, Timoptic®
(β_1 and β_2 antagonist)

glaucoma



para Substitution
Extra H-bonding interaction



meta Substitution

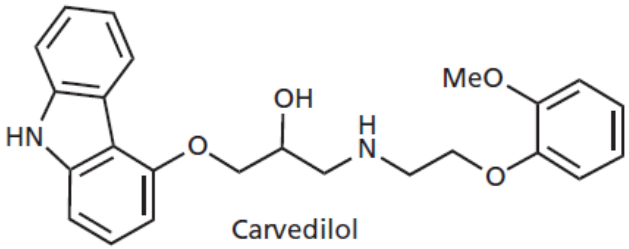
FIGURE 23.29 Binding interactions of antagonists with β_1-receptors.

- **β1-blockers** are drugs that have a greater affinity for the β1-receptors of the heart than for β2-receptors in other tissues.
- Such cardio selective agents should provide two important therapeutic advantages. The first advantage should be the lack of a blocking effect on the β2-receptors in the bronchi.
- Theoretically, this would make β1-blockers safe for use in patients who have bronchitis or bronchial asthma. The second advantage should be the absence of blockade of the vascular β2-receptors, which mediate vasodilation.

General α-/β-blockers

Carvedilol

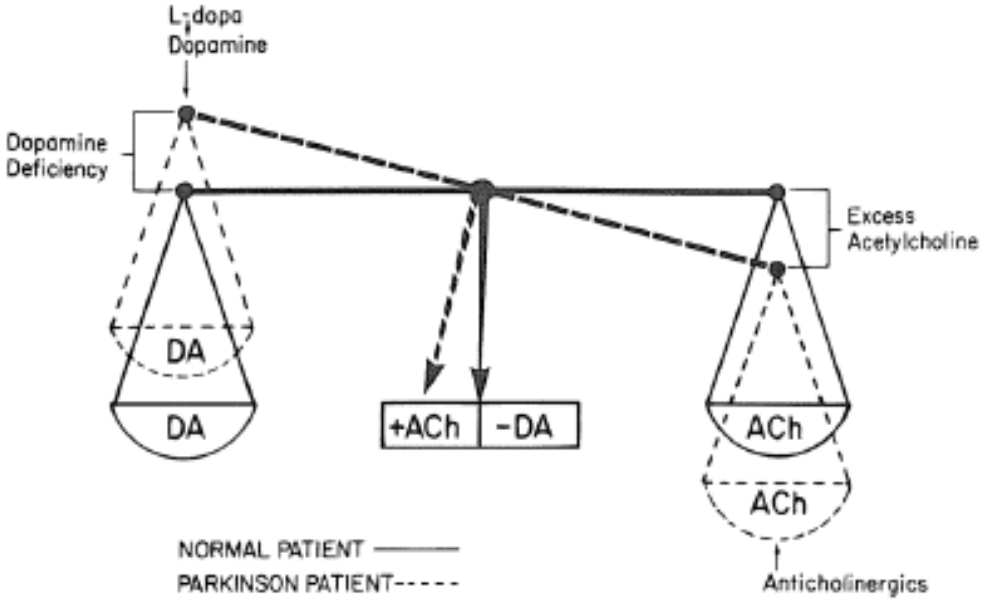
- Third-generation β1-blockers bear an extended N -substituent,
- act as antagonist at both the α1− and β1-adrenoceptors
- used as antihypertensives and to treat cardiac failure.(with vasodilating properties)
- β -blocking activity is 10- to 100-fold of its α- blocking activity.
- extended N –substituent which includes a hydrogen-bonding group capable of an extra interaction with the β1 -adrenoceptor.

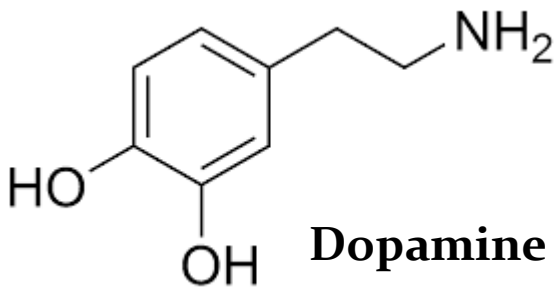


Carvedilol

Dopamine

Introduction to Receptor Types and Drugs Affecting Dopaminergic Neurotransmission



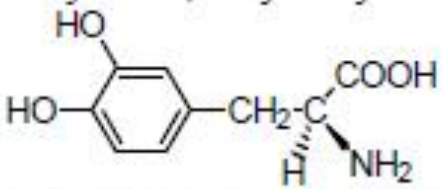


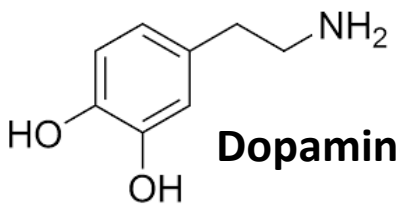
Dopamine

Agents used in the treatment of parkinson's disease

Levodopa

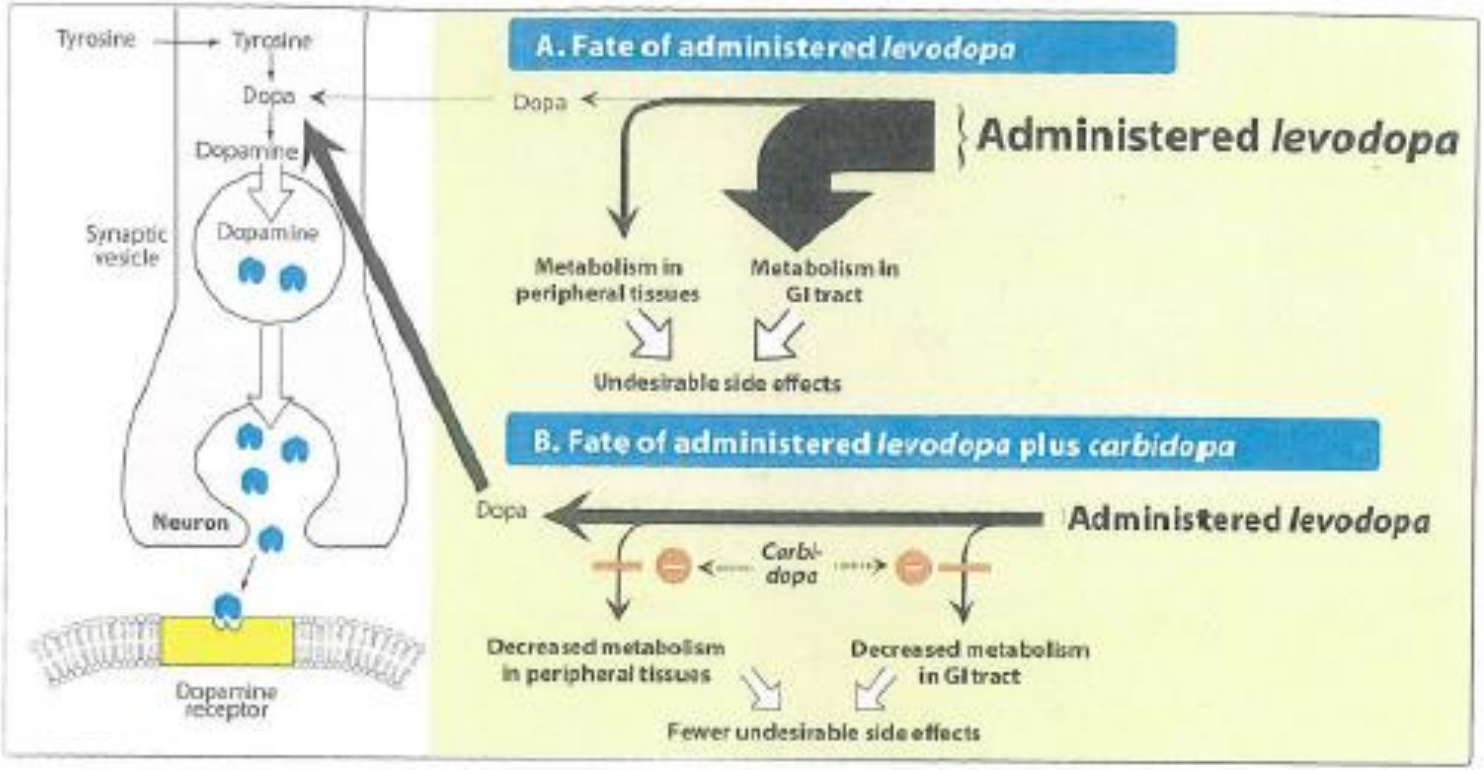
L-Tyrosine, 3-hydroxy-





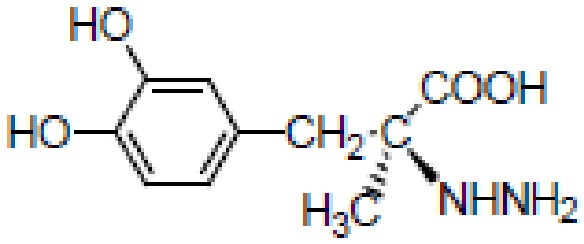
Dopamine

Levodopa can cross into the CNS. Dopamine cannot cross the blood brain barrier. However, significant amounts of L-dopa can be decarboxylated prior to cross the BBB. This can be prevennted by co-adminstration of a decarboxylase inhibitor, such as carbidopa.

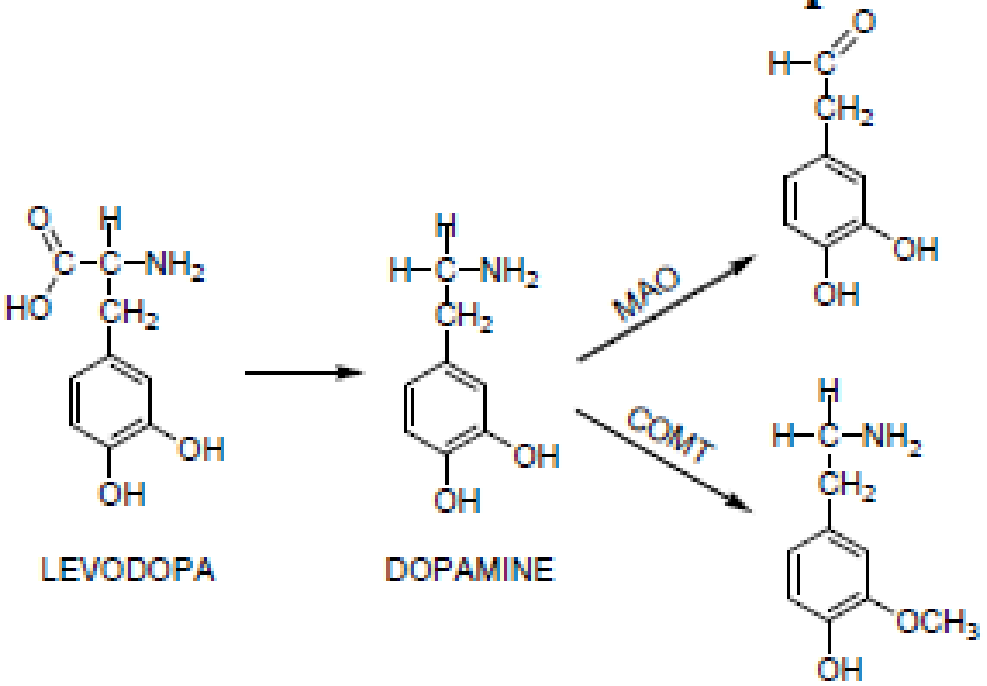


Inhibitors of Dopamine Decarboxylase

Carbidopa



Metabolic Fate of Levodopa




Thank
you!