Sympathomimetic agents

Sympathomimetic agents produce effects resembling those produced by stimulation of the sympathetic nervous system. They may be classified as agents that produce effects by a direct, indirect, or mixed mechanism of action agents elicit a sympathomimetic response by interacting directly with adrenergic receptors. Indirect-acting agents produce effects primarily by causing the release of NE from adrenergic nerve terminals; the NE that is released by the indirect-acting agent activates the receptors to produce the response. Compounds with a mixed mechanism of action interact directly with adrenergic receptors and indirectly cause the release of NE. As described later, the mechanism by which an agent produces its sympathomimetic effect is related intimately to its chemical structure

Direct-Acting Sympathomimetic

The structure–activity relationships (SARs)

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.

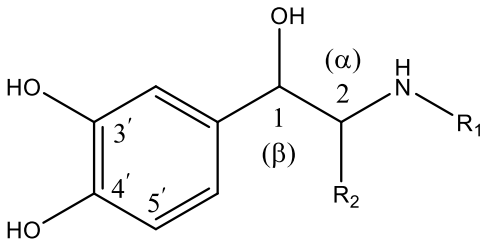
structure requirment for activity:
1)β-phenylethylamine
2)catechol ring
3)(1R)-OH

Aromatic substituents:
3′, 4′-di OH for both α and β activity
metabolism by COMT →
poor oral activity, short DOA
hydrophilic →poor CNS activity

3′, 5′ diOH (e.g. metaproterenol)
3′ CH_2OH, 4′ OH (e.g. albuterol)
↑β_2 activity
↓degredation by COMT→
↑absorbtion, oral activity, DOA

4′- OH important for β activity
3′- OH important for α activity
(e.g. phenylepherin α -agonist

No phenolic substitution
↓both α,β activity
direct, indirect activity



R_1 substitution on N:
↑ the size of R_1→
↑β activity
↓α activity
t.butyl: ↑β_2 activity
↓ degradation by MAO

R_2 substitution on C_2:
small alkyl group (Me, Et) tolerated
↓degredation by MAO
still substrate for COMT→little effect on DOA

Et. group:
↓α>>β (more β selective e.g. ethylnorepniphrine
↑CNS activity
↑oral activity, DOA
(2S) methyl group: ↑α_2 activity

Figure: Structure activity relationship of adrenergic phenylethylamine agonists.

Notes

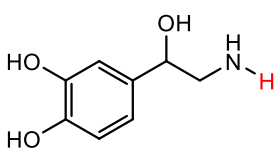
1. A critical factor in the interaction of adrenergic agonists with their receptors is stereoselectivity. Substitution on either carbon-1 or carbon-2 yields optical isomers. **(1R,2S)** isomers seem correct configuration for direct-acting activity.

Separation of Aromatic Ring and Amino Group

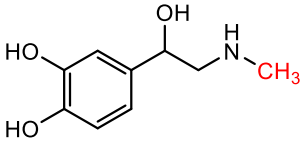
The greatest adrenergic activity occurs when **two carbon atoms** separate the aromatic ring from the amino group. This rule applies with few exceptions to all types of activities.

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

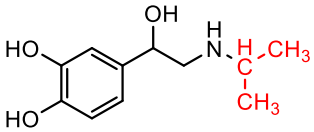
1. The amine is normally ionized at physiological pH. This is important for direct agonist activity, because replacing nitrogen with carbon results in a **large decline** in activity. The activity is also affected by the number of substituents on the nitrogen.
2. Primary and secondary amines have good adrenergic activity, whereas tertiary amines and quaternary ammonium salts do not.
3. The nature of the amino substituent also dramatically affects the receptor selectivity of the compound. As the size of the nitrogen substituent increases, α-receptor agonist activity generally decreases and β-receptor agonist activity increases. Thus, NE has more α -activity than β-activity and E is a potent agonist at α -, β_1-, and β_2-receptors. ISO, however, is a potent β1- and β2-agonist but has little affinity for α-receptors.
4. The nature of the substituents can also affect β1- and β2- receptor selectivity. In several instances, it has been shown that a β2-directing N-tert-butyl group enhances β2-selectivity. For example, N-tert-butylnorepinephrine (Colterol) is 9 to 10 times more potent as an agonist at tracheal β2-receptors than at cardiac β1-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 α-receptors.



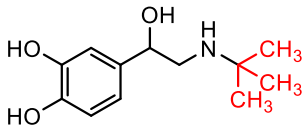
Norepinephrine NE
α>β agonist
α agonist



Epinephrine
α, β_1,β_2 agonist
nonselective α and β agonist



Iosproterenol
β_1, and β_2 agonist
non selective β agonist



N-t. butylnorepniphrine
selective β_2 agonist

5. 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, which can take part in H-bonding.
6. 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)

1. Substitution by small alkyl group (e.g., CH_3- or C_2H_5-) slows metabolism by MAO but has little overall effect on DOA of catechols because they remain substrates for COMT. the resistance to MAO activity is more important in noncatechol indirect-acting phenylethylamines. Because addition of small alkyl group increases the resistance to

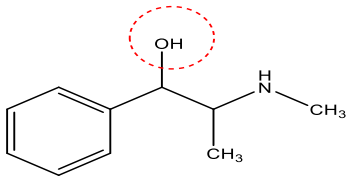
metabolism and lipophilicity, such compounds often exhibit enhanced oral effectiveness and greater CNS activity than their counterparts that do not contain an α-alkyl group. In addition, compounds with an α-methyl substituent persist in the nerve terminals and are more likely to release NE from storage sites. For example, metaraminol is an α-agonist and also exhibits a greater degree of **indirect sympathomimetic activity**.

2. Methyl or ethyl substitution on the α-carbon of the ethylamine side chain reduces direct agonist activity at both α- and β-receptors. α-Substitution also significantly affects receptor selectivity.
    - In the case of β-receptors, for example, -methyl or ethyl substitution results in compounds toward the β2-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.

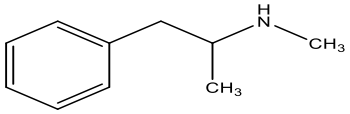
OH substitution on theβ-carbon (carbon-1)

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

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



ephedrine Log P=1.05
more α and β activity
less lipophilic→less CNS activity



methamphetamine LogP=1.97
less α and β activity
more lipophilic→more CNS activity

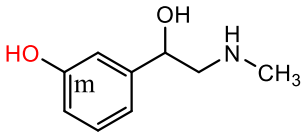
Substitution on the Aromatic Ring

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, indicating the importance of the OH groups.

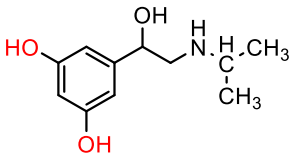
- ✓ Although the catechol moiety is an important structural feature in terms of yielding compounds with maximal agonist activity at adrenoceptors, it can be replaced with other substituted phenyl moieties to provide selective adrenergic agonists. This approach has been used in particular in the design of selective β2-agonists.

For example, replacement of the catechol function of ISO with the resorcinol structure gives a selective β_2-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.

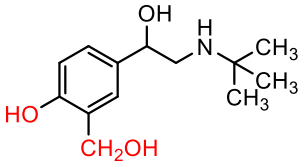
- ✓ In another approach, replacement of the meta-OH of the catechol structure with a hydroxymethyl group gives agents, such as albuterol, which show selectivity to the β_2-receptor. Because they are not catechols, these agents are not metabolized by COMT and thus show improved oral bioavailability and longer DOA.
- ✓ Modification of the catechol ring can also bring about selectivity at α-receptors as it appears that the catechol moiety is more important for α_2-activity than for α_1-activity. For example, removal of the p-OH group from E gives phenylephrine, which, in contrast to E, is selective for the α_1-receptor. Phenylephrine is less potent than E at both α- and β-receptors, with β_2-activity almost completely absent.



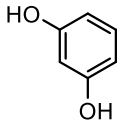
phenylephrin
less α and β activity than NE
selective $\alpha_1$agonsit
almost no β activity



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