23 Drugs acting on the adrenergic nervous system

23.1 The adrenergic nervous system

23.1.1 Peripheral nervous system

In Chapter 22, we studied the cholinergic system and the important role it plays in the peripheral nervous system (PNS). **Acetylcholine** is the crucial neurotransmitter in the cholinergic system and has specific actions at various synapses and tissues. The other important player in the PNS (sections 22.1 and 22.2) is the adrenergic system, which makes use of the chemical messengers **adrenaline** and **noradrenaline**. Noradrenaline (also called **norepinephrine**) is the neurotransmitter released by the sympathetic nerves which feed smooth muscle and cardiac muscle, whereas adrenaline (**epinephrine**) is a hormone released along with noradrenaline from the **adrenal medulla**.

The action of noradrenaline at various tissues is the opposite to that of acetylcholine, which means that tissues are under a dual control. For example, if noradrenaline has a stimulant activity at a specific tissue, acetylcholine has an inhibitory activity at that same tissue. Both the cholinergic and adrenergic systems have a 'background' activity, so the situation is analogous to driving a car with one foot on the brake and one foot on the accelerator. The overall effect on the tissue depends on which effect is predominant.

The adrenergic nervous system has a component that the cholinergic system does not have—the facility to release adrenaline during times of danger or stress. This is known as the **fight or flight** response. Adrenaline is carried by the blood supply round the body and activates adrenergic receptors in preparation for immediate physical action, whether that be to fight the perceived danger or to flee from it. This means that the organs required for physical activity are activated, while those that are not important are suppressed. For example, adrenaline stimulates the heart and dilates the blood vessels to muscles so that the muscles are supplied with sufficient blood for physical activity. At the same time, smooth muscle activity in the gastrointestinal tract is suppressed as digestion is not an immediate priority. This fight or flight response is clearly an evolutionary advantage and stood early humans in good stead when faced with an unexpected encounter with a grumpy old bear. Nowadays, it is unlikely that you will meet a grizzly bear on your way to the supermarket, but the fight or flight response is still functional when you are faced with modern dangers such as crazy drivers. It also functions in any situation of stress such as an imminent exam, important football game, or public performance. In general, the effects of noradrenaline are the same as those of adrenaline, although noradrenaline constricts blood vessels to skeletal muscle rather than dilates them.

23.1.2 Central nervous system

There are also adrenergic receptors in the central nervous system (CNS) and noradrenaline is important in many functions of the CNS, including sleep, emotion, temperature regulation, and appetite. However, the emphasis in this chapter is on the peripheral role of adrenergic agents.

23.2 Adrenergic receptors

23.2.1 Types of adrenergic receptor

In Chapter 22, we saw that there are two types of cholinergic receptor, with subtypes of each. The same holds true for adrenergic receptors. The two main types of adrenergic receptor are called the **α** and **β-adrenoceptors**. Both the α and the β-adrenoceptors are G-protein-coupled receptors (section 4.7), but differ in the type of G-protein with which they couple (G_o for α-adrenoceptors; G_s for β-adrenoceptors).

For each type of receptor, there are various receptor subtypes with slightly different structures. The α-adrenoceptor consists of α_1- and α_2-subtypes, which differ in the type of secondary message produced. The α_1 receptors activate **inositol triphosphate** (IP_3) and **diacylglycerol** (DG) as secondary messengers (section 5.3), whereas the α_2-receptors inhibit the production of the secondary messenger **cyclic-AMP** (section 5.2.3). The β-adrenoceptor consists of β_1-, β_2-, and β_3-subtypes, all of which activate the formation of cyclic-AMP. To complicate matters slightly further, both the α_1- and α_2-adrenoceptors have further subcategories (α_{1A}, α_{1B}, α_{1D} α_{2A}, α_{2B}, α_{2C}).

All of these adrenergic receptor types and subtypes are 'switched on' by adrenaline and noradrenaline, but the fact that they have slightly different structures means that it should be possible to design selective agonists that can distinguish between them. This is crucial in developing drugs that have minimal side effects and act at specific organs in the body, for, as we shall see, the various adrenoceptors are not evenly distributed in different tissues. By the same token, it should be possible to design selective antagonists with minimal side effects that switch off particular types and subtypes of adrenoceptor.

23.2.2 Distribution of receptors

The various adrenoceptor types and subtypes vary in their distribution, with certain tissues containing more of one type of adrenoceptor than another. Table 23.1 describes various tissues, the types of adrenoceptor which predominate in these tissues, and the effect of activating these receptors (see also Box 23.1).

A few points are worth highlighting here:

- activation of α-receptors generally contracts smooth muscle (except in the gut), whereas activation of β-receptors generally relaxes smooth muscle. This latter effect is mediated through the most common of the β-adrenoceptors—the β_2-receptor. In the heart, the β_1-adrenoceptors predominate and activation results in contraction of muscle;
- different types of adrenoceptor explain why adrenaline can have different effects at different parts of the body. For example, the blood vessels supplying skeletal muscle have mainly β_2-adrenoceptors and are dilated by adrenaline, whereas the blood vessels elsewhere have mainly α-adrenoceptors and are constricted by adrenaline. As more blood vessels are constricted than are dilated in the system, the overall effect of adrenaline is

TABLE 23.1 Distribution and effects of adrenoceptors in different parts of the body

Organ or tissue	Predominant adrenoceptors	Effect of activation	Physiological effect
Heart muscle	β_1	Muscle contraction	Increased heart rate and force
Bronchial smooth muscle	α_1	Smooth muscle contraction	Closes airways
	β_2	Smooth muscle relaxation	Dilates and opens airways
Arteriole smooth muscle (not supplying muscles)	α	Smooth muscle contraction	Constricts arterioles and increases blood pressure (hypertension)
Arteriole smooth muscle (supplying muscle)	β_2	Smooth muscle relaxation	Dilates arterioles and increases blood supply to muscles
Veins	α	Smooth muscle contraction	Constricts veins and increases blood pressure (hypertension)
	β_2	Smooth muscle relaxation	Dilates veins and decreases blood pressure (hypotension)
Liver	α_1 & β_2	Activates enzymes which metabolize glycogen and deactivates enzymes which synthesize glycogen	Breakdown of glycogen to produce glucose
Gastrointestinal tract smooth muscle	α_1, α_2, and β_2	Relaxation	'shuts down' digestion
Kidney	β_2	Increases renin secretion	Increases blood pressure
Fat cells	β_3	Activates enzymes	Fat breakdown

BOX 23.1 Clinical aspects of adrenergic agents

The main clinical use for adrenergic agonists is in the treatment of asthma. Activation of β_2-adrenoceptors causes the smooth muscles of the bronchi to relax, thus widening the airways. Agonists acting selectively on α_1-adrenoceptors cause vasoconstriction and can be used alongside local anaesthetics in dentistry to localize and prolong the effect of the anaesthetic at the site of injection. They are also used as nasal decongestants. Selective α_2-agonists are used in the treatment of glaucoma, hypertension, and pain.

The main uses for adrenergic antagonists are in treating angina and hypertension. Agents which act on the α-receptors of blood vessels cause relaxation of smooth muscle, dilatation of the blood vessels, and a drop in blood pressure. Selective α_1-antagonists are now preferred for the treatment of hypertension and are also being investigated as potential agents for the treatment of benign prostatic hyperplasia. Selective α_2-antagonists are being studied for the treatment of depression. Agents that block β_1-receptors in the heart (β-blockers) slow down the heart rate and reduce the force of contractions. β-blockers also have a range of effects in other parts of the body, which combine to lower blood pressure.

to increase the blood pressure, while at the same time providing sufficient blood for the muscles in the fight or flight response.

23.3 Endogenous agonists for the adrenergic receptors

The term **endogenous** refers to any chemical which is present naturally in the body. As far as the adrenergic system is concerned, the body's endogenous chemical messengers are the neurotransmitter noradrenaline and the hormone adrenaline. Both act as agonists and switch on adrenoceptors. They belong to a group of compounds called the **catecholamines**—so-called because they have an alkylamine chain linked to a **catechol** ring (the 1,2-benzenediol ring) (Fig. 23.1).

Test your understanding and practise your molecular modelling with Exercise 23.1.

23.4 Biosynthesis of catecholamines

The biosynthesis of noradrenaline and adrenaline starts from the amino acid **L-tyrosine** (Fig. 23.2). The enzyme

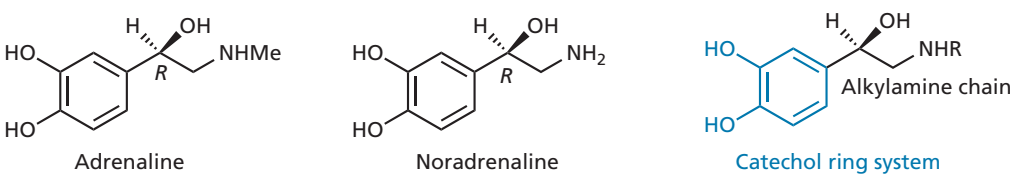


FIGURE 23.1 Adrenergic transmitters.

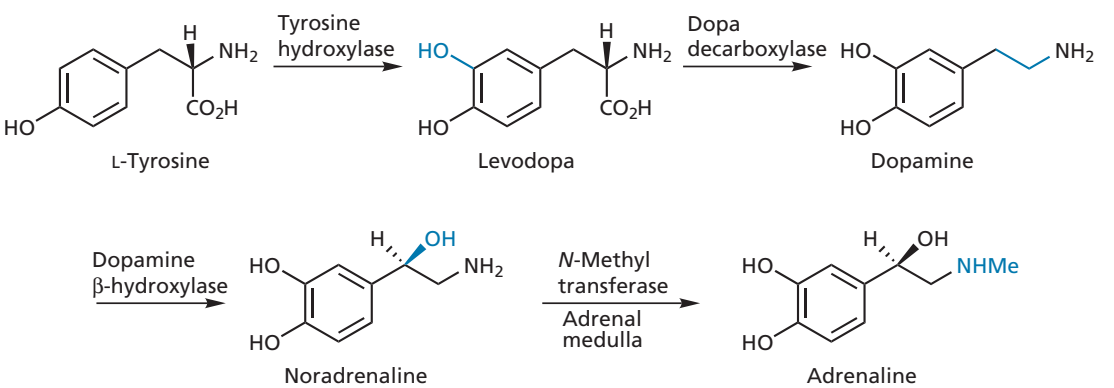


FIGURE 23.2 Biosynthesis of noradrenaline and adrenaline.

tyrosine hydroxylase catalyses the introduction of a second phenol group to form **levodopa** (L-dopa) which is then decarboxylated by **aromatic L-aminoacid decarboxylase** (**dopa decarboxylase**) to give **dopamine**—an important neurotransmitter in its own right. Dopamine is then hydroxylated to **noradrenaline**, which is the end product in adrenergic neurons. In the adrenal medulla, however, noradrenaline is *N*-methylated to form **adrenaline**. The biosynthesis of the catecholamines is controlled by regulation of **tyrosine hydroxylase**—the first enzyme in the pathway. This enzyme is inhibited by noradrenaline—the end product of biosynthesis, thus allowing self-regulation of catecholamine synthesis and control of catecholamine levels.

23.5 Metabolism of catecholamines

Metabolism of catecholamines in the periphery takes place within cells and involves two enzymes—**monoamine oxidase** (**MAO**) and **catechol *O*-methyltransferase** (**COMT**). MAO converts catecholamines to their corresponding aldehydes. These compounds are inactive as adrenergic agents and undergo further metabolism (as shown in Fig. 23.3 for noradrenaline). The final carboxylic acid is polar and excreted in the urine.

An alternative metabolic route is possible which results in the same product. This time the enzyme COMT catalyses the methylation of one of the phenolic groups of the catecholamine. The methylated product is oxidized by MAO then converted to the final carboxylic acid and excreted (Fig. 23.4).

Metabolism in the CNS is slightly different, but still involves MAO and COMT as the initial enzymes.

23.6 Neurotransmission

23.6.1 The neurotransmission process

The mechanism of neurotransmission is shown in Fig. 23.5 and applies to adrenergic neurons innervating smooth or cardiac muscle, as well as synaptic connections within the CNS.

Noradrenaline is biosynthesized in a presynaptic neuron then stored in membrane-bound vesicles. When a nerve impulse arrives at the terminus of a neuron, it stimulates the opening of calcium ion channels and promotes the fusion of the vesicles with the cell membrane to release noradrenaline. The neurotransmitter then diffuses to adrenergic receptors on the target cell where it binds and activates the receptor, leading to the signalling process which will eventually result in a cellular response. After the message has been received, noradrenaline departs the receptor and is taken back into the presynaptic neuron by a transport protein. Once in the cell, noradrenaline is repackaged into the vesicles. Some of the noradrenaline is metabolized before it is repackaged, but this is balanced out by noradrenaline biosynthesis.

23.6.2 Co-transmitters

The process of adrenergic neurotransmission is actually more complex than that illustrated in Fig. 23.5. For example, noradrenaline is not the only neurotransmitter released during the process. **Adenosine triphosphate** (**ATP**) and a protein called **chromogranin A** are released from the vesicles along with noradrenaline and

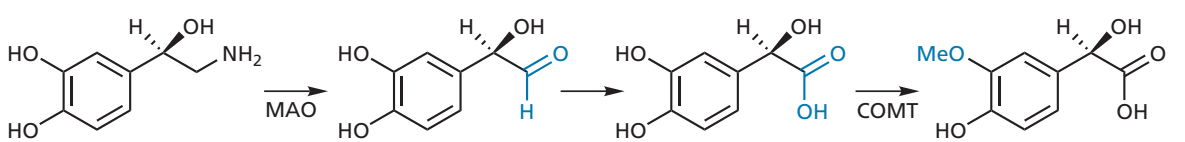


FIGURE 23.3 Metabolism of noradrenaline with monoamine oxidase (MAO) then catechol *O*-methyltransferase (COMT).

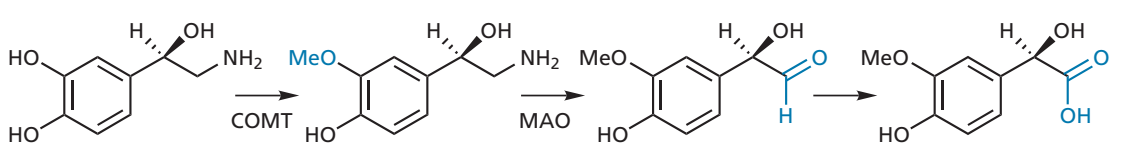


FIGURE 23.4 Metabolism of noradrenaline with catechol *O*-methyltransferase (COMT) then monoamine oxidase (MAO).

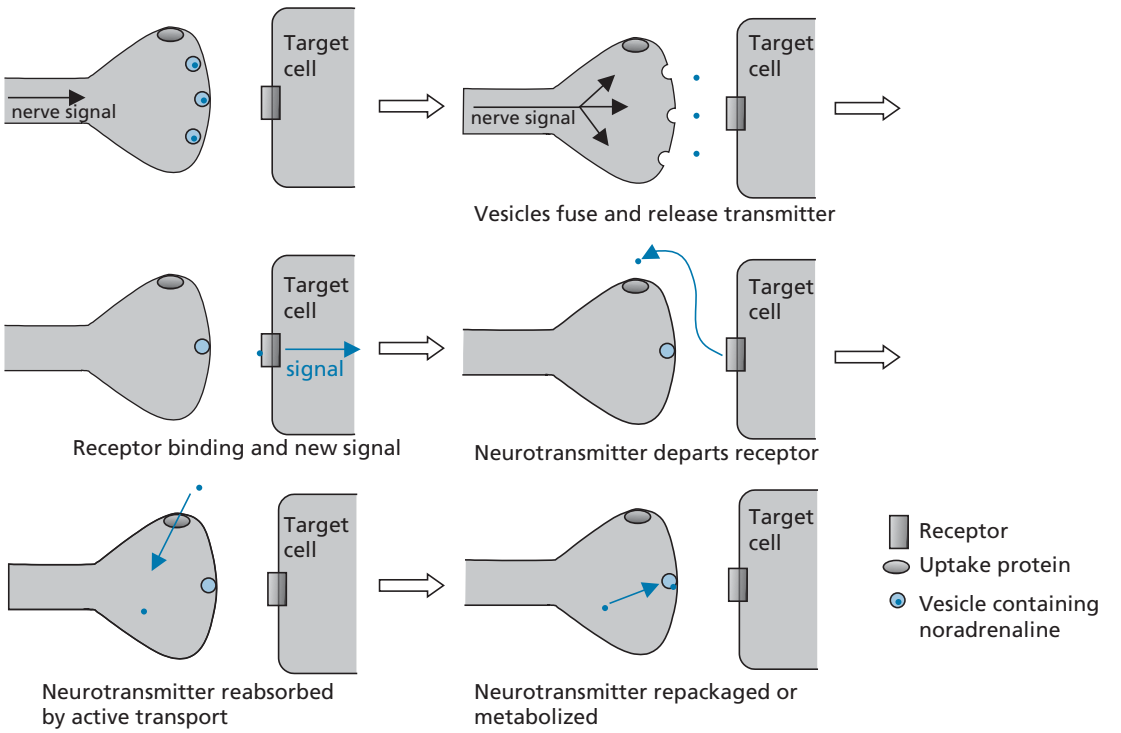


FIGURE 23.5 Transmission process for noradrenaline.

act as co-transmitters. They interact with their own specific receptors on the target cell and allow a certain variation in the speed and type of message which the target cell receives. For example, ATP leads to a fast response in smooth muscle contraction.

23.6.3 Presynaptic receptors and control

A further feature of the neurotransmission process not shown in Fig. 23.5 is the existence of presynaptic receptors which have a controlling effect on noradrenaline release (Fig. 23.6). There are a variety of these receptors, each of which responds to a specific chemical messenger. For example, there is an adrenergic receptor (the **α_2-adrenoceptor**) which interacts with released noradrenaline and has an inhibitory effect on further release of noradrenaline. Thus, noradrenaline acts to control its own release by a negative feedback system.

There are receptors specific for **prostaglandins** released from the target cell. For example, the prostaglandin **PGE_2** appears to inhibit transmission, whereas **$PGF_{2\alpha}$** appears to facilitate it. Thus, the target cell itself can have some influence on the adrenergic signals coming to it.

There are presynaptic muscarinic receptors that are specific for **acetylcholine** and serve to inhibit release of noradrenaline. These receptors respond to side branches of the cholinergic nervous system which synapse on to the adrenergic neuron. This means that when the cholinergic system is active, it sends signals along its side branches to inhibit adrenergic transmission. Therefore, as the cholinergic activity to a particular tissue increases, the adrenergic activity decreases, both of which enhance the overall cholinergic effect (cf. section 22.5.2).

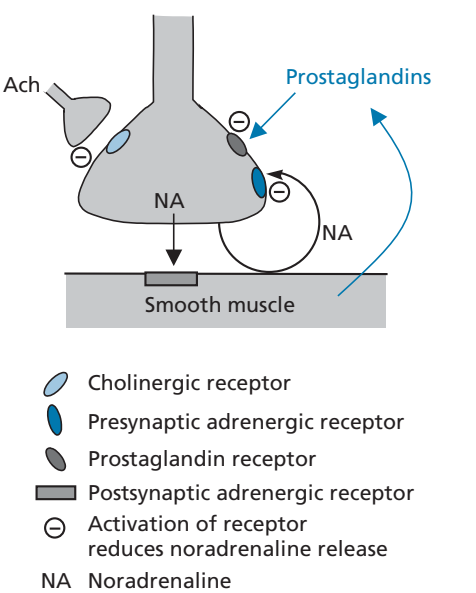


FIGURE 23.6 Presynaptic receptors on a neuron releasing noradrenaline as neurotransmitter.

23.7 Drug targets

Having studied the nerve transmission process, it is now possible to identify several potential drug targets which will affect the process (Fig. 23.7):

1. The biosynthetic enzymes involved in the synthesis of noradrenaline within presynaptic neurons (section 23.4)
2. The vesicle carriers which package noradrenaline within the presynaptic neuron prior to release
3. The process of exocytosis where vesicles fuse with the cell membrane and release noradrenaline into the synaptic gap when the neuron is active
4. Adrenergic receptors in the postsynaptic neuron which are activated by noradrenaline to generate a signal in that neuron
5. The transport proteins which are responsible for the reuptake of noradrenaline from the synaptic gap
6. The metabolic enzymes which metabolize noradrenaline (section 23.5)
7. The presynaptic adrenergic receptors which regulate noradrenaline release (section 23.6.3).

In the next section, we concentrate on the adrenergic receptors. In later sections, we will consider some of the other possible drug targets.

KEY POINTS

- The neurotransmitter involved in the adrenergic nervous system is noradrenaline. Adrenaline is a hormone which is released by the adrenal medulla at times of stress and activates adrenergic receptors.
- The sympathetic nerves innervating smooth muscle and cardiac muscle release noradrenaline.

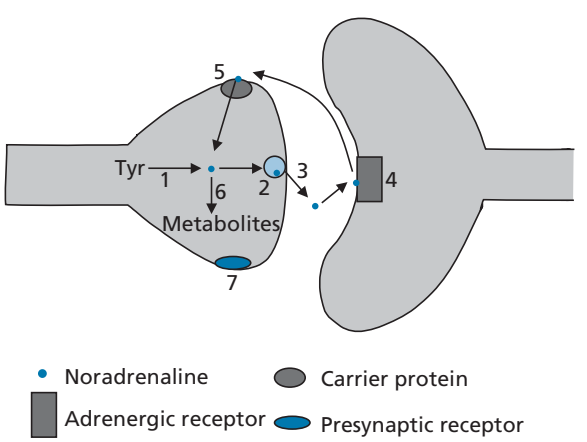


FIGURE 23.7 Drug targets affecting noradrenaline transmission.

- 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.
- Adrenaline, noradrenaline, and dopamine are catecholamines.
- The biosynthesis of catecholamines starts from tyrosine and involves levodopa as an intermediate.
- Catecholamines are metabolized by monoamine oxidase and catechol *O*-methyltransferase.
- Noradrenaline is synthesized in presynaptic neurons, and packaged in vesicles prior to release. Once released, it activates receptors on target cells. It is then is taken up into presynaptic neurons by a transport protein and repacked into vesicles. A certain percentage of noradrenaline is metabolized.
- Adrenergic receptors are the main targets for adrenergic drugs.

23.8 The adrenergic binding site

The adrenergic receptors are G-protein-linked receptors which consist of seven transmembrane (TM) helices (section 4.7). In order to study the binding site of a receptor, one would ideally crystallize it with a ligand bound to the binding site. X-ray crystallography would then be used to determine the crystal structure and identify how the ligand binds. Unfortunately, membrane-bound receptors are very difficult to crystallize, and it was only in 2007 that the β_2-adrenoceptor was crystallized (section 17.14.1). Unfortunately, the crystal structure obtained does not reveal how an agonist binds to the ligand binding site. Therefore, a knowledge of the binding site is based on mutagenesis studies and molecular modelling. Mutagenesis studies involve mutating amino acids to see which ones are crucial for ligand binding, while molecular modelling involves the construction of a model binding site based on the structures of similar proteins whose structures are known (section 17.14.1). From these studies, it has been proposed that three of the transmembrane helices (TM3, TM5, and TM6) are involved in the binding site, illustrated for the β-adrenoceptor in Fig. 23.8. Mutagenesis studies have indicated the importance of an aspartic acid residue (Asp-113), a phenylalanine residue (Phe-290), and two serine residues (Ser-207 and Ser-204). Modelling studies indicate that these groups can bind to adrenaline or noradrenaline as shown in

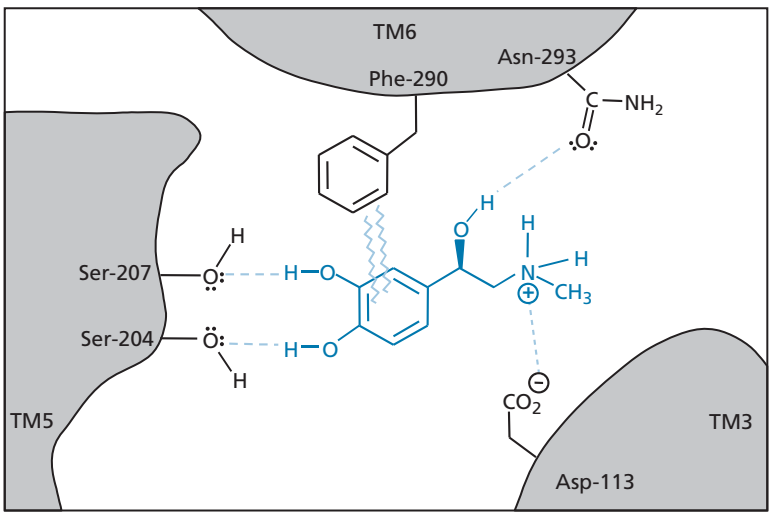


FIGURE 23.8 Adrenergic binding site.

the figure. The serine residues interact with the phenolic groups of the catecholamine via hydrogen bonding. The aromatic ring of Phe-290 interacts with the catechol ring by van der Waals interactions, while Asp-113 interacts with the protonated nitrogen of the catecholamine by ionic bonding. There is also a proposed hydrogen bonding interaction between Asn-293 and the alcohol function of the catecholamine.

23.9 Structure–activity relationships

23.9.1 Important binding groups on catecholamines

Support for the above binding site interactions is provided by studies of structure–activity relationships (SAR) on catecholamines. These emphasize the importance of having the alcohol group, the intact catechol ring system with both phenolic groups unsubstituted, and the ionized amine (Fig. 23.9).

Some of the evidence supporting these conclusions is as follows:

- **the alcohol group**—the *R*-enantiomer of noradrenaline is more active than the *S*-enantiomer, indicating that the secondary alcohol is involved in a hydrogen bonding interaction. Compounds lacking the hydroxyl group (e.g. dopamine) have a greatly reduced interaction. Some of the activity *is* retained, indicating that the alcohol group is important, but not essential;
- **the amine** is normally protonated and ionized at physiological pH. This is important as replacing nitrogen with carbon results in a large drop in activity. Activity is also affected by the number of substituents on the nitrogen. Primary and secondary amines have good adrenergic activity, whereas tertiary amines and quaternary ammonium salts do not;

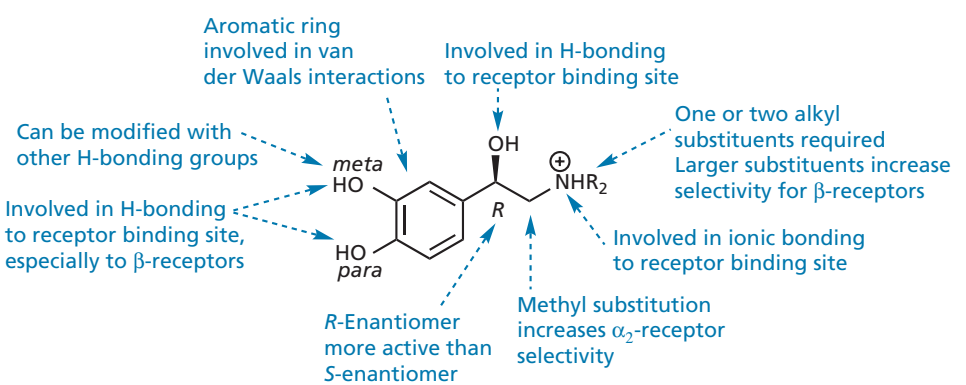


FIGURE 23.9 Important binding groups for adrenergic agents.

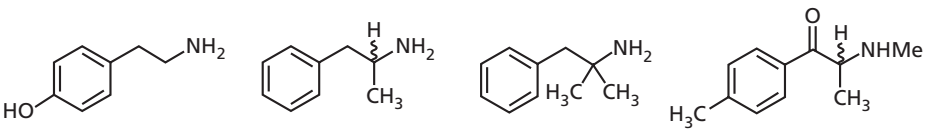


FIGURE 23.10 Agents that have no affinity for the adrenergic receptor.

- **both phenol substituents** are important. For example, **tyramine**, **amphetamine**, **phentermine**, and the banned substance **mephedrone** (Fig. 23.10) have little, or no, affinity for adrenoceptors, although they do have an effect on the adrenergic system through other mechanisms (section 23.12.4). Having said that, the phenol groups can be replaced by other groups capable of interacting with the binding site by hydrogen bonding. This is particularly true for the *meta* phenol group, which can be replaced by groups such as CH_2OH, CH_2CH_2OH, NH_2, NHMe, NHCOR, NMe_2, and $NHSO_2R$;
- **alkyl substitution** on the side chain linking the aromatic ring to the amine decreases activity at both α- and β-adrenergic receptors. This may be a steric effect which blocks hydrogen bonding to the alcohol or which prevents the molecule adopting the active conformation.

23.9.2 Selectivity for α- versus β-adrenoceptors

SAR studies demonstrate certain features which introduce a level of receptor selectivity between the α- and β-adrenoceptors.

- *N*-**Alkyl substitution**: it was discovered that adrenaline has the same potency for both types of adrenoceptor, whereas noradrenaline has a greater potency for α-adrenoceptors than for β-adrenoceptors. This indicates that an *N*-alkyl substituent has a role to play in receptor selectivity. Further work demonstrated that increasing the size of the *N*-alkyl substituent resulted in loss of potency at the α-receptor but an increase in potency at β-receptors. For example, the synthetic analogue **isoprenaline** (Fig. 23.11) is a powerful β-stimulant devoid of α-agonist activity. The presence of a bulky *N*-alkyl group, such as isopropyl or *tertiary*-butyl, is particularly good for β-adrenoceptor activity. These results indicate that the β-adrenoceptor has a hydrophobic pocket into which a bulky alkyl group can fit, whereas the α-adrenoceptor does not (Fig. 23.12).
- **Phenol groups** seem particularly important for β-receptors. If they are absent, activity drops more significantly for β-receptors than for α-receptors.
- **α-Methyl substitution**: addition of an α-methyl group (e.g. α-methylnoradrenaline; Fig. 23.13) increases α_2-receptor selectivity.
- **Extension**: as mentioned earlier, isopropyl or *t*-butyl substituents on the amine nitrogen are particularly good for β-selectivity. 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 C_2 alkyl chain results in a dramatic rise in activity, demonstrating that an extra polar binding region has been accessed which can take part in hydrogen bonding. For example, the activity of the extension analogue shown in Fig. 23.13 is increased by a factor of 800.

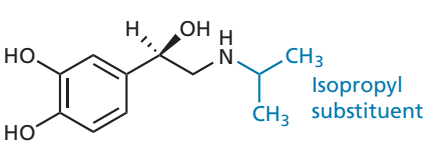


FIGURE 23.11 (*R*)-Isoprenaline.

23.10 Adrenergic agonists

23.10.1 General adrenergic agonists

Adrenaline is an obvious agonist for the overall adrenergic system and it is frequently used in emergency situations, such as cardiac arrest or anaphylactic reactions. The latter can be caused by hypersensitivity to certain foodstuffs (e.g. nuts) or foreign chemicals, such as a bee sting or penicillin. Individuals who have a high risk of suffering a severe anaphylactic reaction should carry a pre-assembled syringe carrying adrenaline which can be injected intramuscularly (**Anapen** or **Epipen**). Adrenaline is also administered with local anaesthetics in order to constrict blood vessels and prolong local anaesthetic activity at the site of injection.

Adrenaline is fast acting which makes it ideal for emergency situations, but it has a short duration of action and is rapidly cleared from the system. Moreover, it switches on all possible adrenergic receptors, leading

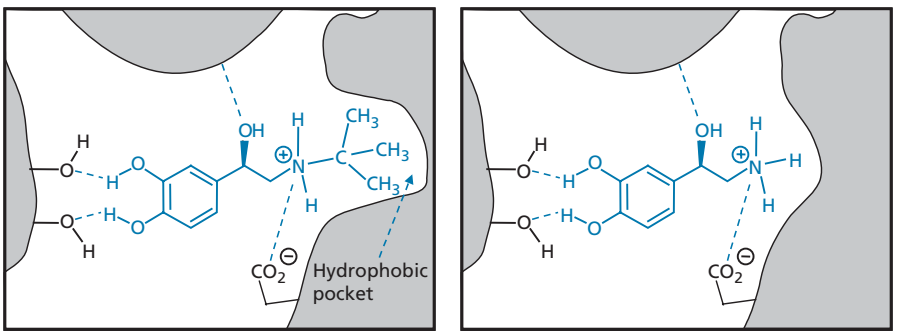


FIGURE 23.12 Comparison of β- and α-adrenoceptor binding sites.

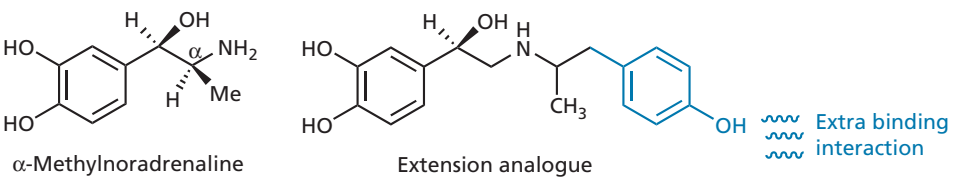


FIGURE 23.13 α-Methylnoradrenaline and extension analogue of noradrenaline.

to a whole range of side effects, including nausea, tachycardia, arrhythmias, hypertension, palpitations, anxiety, tremor, headache, restlessness, sweating, and dizziness. Therefore, if long-term medication is required, it is preferable to have agonists which are selective for specific adrenoceptors.

Ephedrine (Fig. 23.14) is a natural product present in various plants which have been used in folk medicine for many years. There are two asymmetric centres, and ephedrine exists as a racemate of the *R, S* and *S, R* stereoisomers. It activates both α– and β-adrenoceptors and has been used extensively in non-prescription preparations as a bronchodilator. It has also been used as a vasopressor and cardiac stimulant. As it lacks the phenolic groups of adrenaline, it is not susceptible to metabolism by catechol *O*-methyltransferase. It is also more lipophilic, and so it can cross the blood–brain barrier and act as a stimulant. Ephedrine is the active constituent of herbal remedies that contain the dried plant material ***ma-huang***.

Pseudoephedrine (Fig. 23.14) occurs naturally in certain plant species and is the *S,S* diastereomer of ephedrine. It is used as a nasal decongestant in preparations such as **Sudafed**, **Benylin**, and **Lemsip**. Unfortunately, it can be used in the illicit manufacture of amphetamines and so many pharmaceutical firms are starting to replace it with alternative decongestants.

23.10.2 α_1-, α_2-, β_1-, and β_3-Agonists

In general, there is limited scope for agonists at these receptors, although there is potential for anti-obesity drugs which act on the β_3-receptor. The β_1-agonist **dobutamine** (Fig. 23.15) is used to treat cardiogenic shock. Agonists acting on the α-adrenoceptors are less useful because these agents constrict blood vessels, raise blood pressure, and can cause cardiovascular problems. However, selective α_1 and α_2 agonists have found a number of uses as described in Box 23.1. **Clonidine** is a selective α_2-agonist which is used for the treatment of

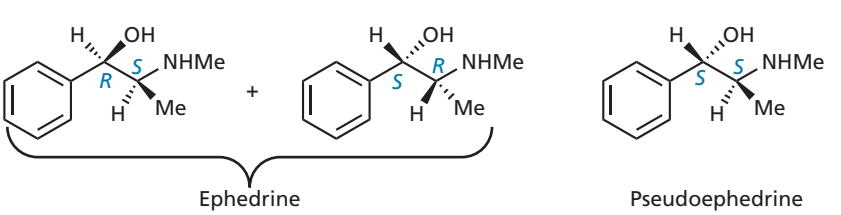
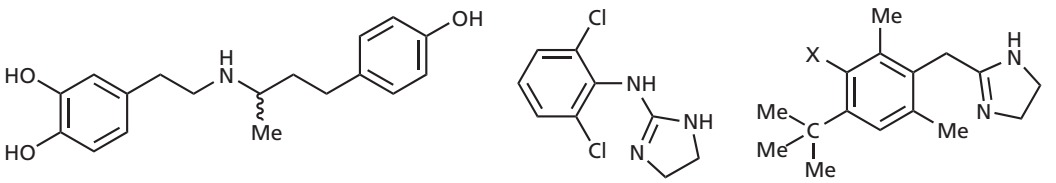


FIGURE 23.14 Ephedrine and pseudoephedrine.



Dobutamine | Clonidine | Oxymetazoline; X = OH, Xylometazoline; X = H

FIGURE 23.15 Adrenergic agonists.

hypertension. There is also strong evidence that it acts as an analgesic, especially if it is injected directly into the spinal cord. Selective α_1-agonists such as **oxymetazoline** and **xylometazoline** act as vasoconstrictors, and are used widely as topical medicines for the treatment of nasal congestion and bloodshot eyes.

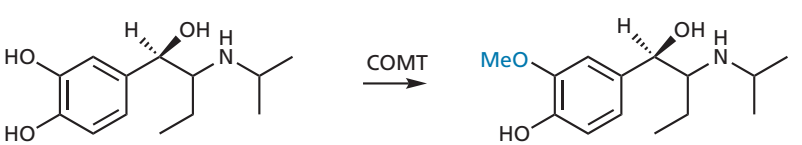
23.10.3 β_2-Agonists and the treatment of asthma

The most useful adrenergic agonists in medicine today are the β_2-agonists. These can be used to relax smooth muscle in the uterus to delay premature labour, but they are more commonly used for the treatment of asthma. Activation of the β_2-adrenoceptor results in smooth muscle relaxation and, as β_2-receptors predominate in bronchial smooth muscle, this leads to dilatation of the airways.

Adrenaline is often used to dilate the airways in emergency situations, but it is not suitable for long-term use because of its short duration of action and cardiovascular side effects (section 23.10.1). These side effects result from adrenaline interacting with all available adrenergic receptors and so a more selective agent for β_2-receptors is preferable.

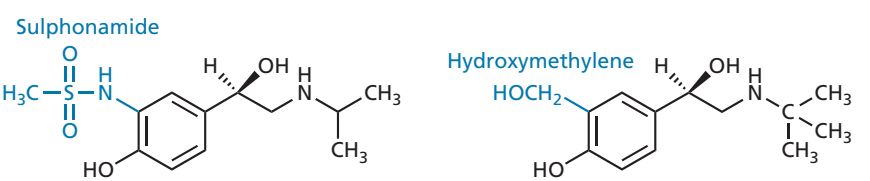
Isoprenaline (Fig. 23.11) shows some selectivity for β-receptors over α-receptors because of its bulky *N*-alkyl substituent. It was used for some time as an anti-asthmatic agent, but showed no selectivity between the different subtypes of β-receptors. Therefore, isoprenaline also activated the β_1-receptors of the heart, leading to unwanted cardiovascular effects. The search was then on to find a selective agonist for β_2-receptors which could be inhaled and have a long duration of action. Further research demonstrated that selectivity between different types of β-receptors could be obtained by introducing alkyl substituents to the side chain linking the aromatic ring and the amine, and/or varying the alkyl substituents on the nitrogen. For example, **isoetharine** (Fig. 23.16) was shown to be selective for β_2-receptors. Unfortunately, it was short lasting.

This short duration of action occurs because drugs such as isoetharine and adrenaline are taken up by tissues and methylated by the metabolic enzyme **catechol-*O*-methyltransferase** (COMT) to form an inactive ether. In order to prevent this, attempts were made to modify the *meta* phenol group and make it more resistant to metabolism (Fig. 23.17). This was no easy task as the



Isoetharine (active) | Inactive metabolite

FIGURE 23.16 Metabolism of (*R*)- isoetharine (COMT = catechol *O*-methyltransferase).



R-Soterenol | *R*-Salbutamol

FIGURE 23.17 Selective β_2 agonists.

phenolic group is important to activity, so it was necessary to replace it with a group which could still bind to the receptor and retain biological activity, but would not be recognized by the metabolic enzyme.

Various functional groups were tried at the *meta* position with a sulphonamide group ($MeSO_2NH$) proving successful. This resulted in a long-lasting selective β_2-agonist called **soterenol** (Fig. 23.17). However, this compound was never used clinically because a better compound was obtained in **salbutamol** (known as **albuterol** in the USA) (Box 23.2). Here, the *meta* phenol group of the catecholamine skeleton was replaced by a hydroxymethylene group—an example of a *group shift* strategy (section 14.2.6). Salbutamol has the same potency as isoprenaline, but is 2000 times less active on the heart. It has a duration of four hours and is not taken up by transport proteins or metabolized by COMT. Instead, it is more slowly metabolized to a phenolic sulphate. Salbutamol was marketed as a racemate and soon became a market leader in 26 countries for the treatment of asthma. The *R* enantiomer is 68 times more active than the *S* enantiomer. Furthermore, the *S* enantiomer accumulates to a greater extent in the body and produces side effects. Consequently, the pure *R* enantiomer (**levalbuterol**) was eventually marketed—an example of **chiral switching** (section 15.2.1).

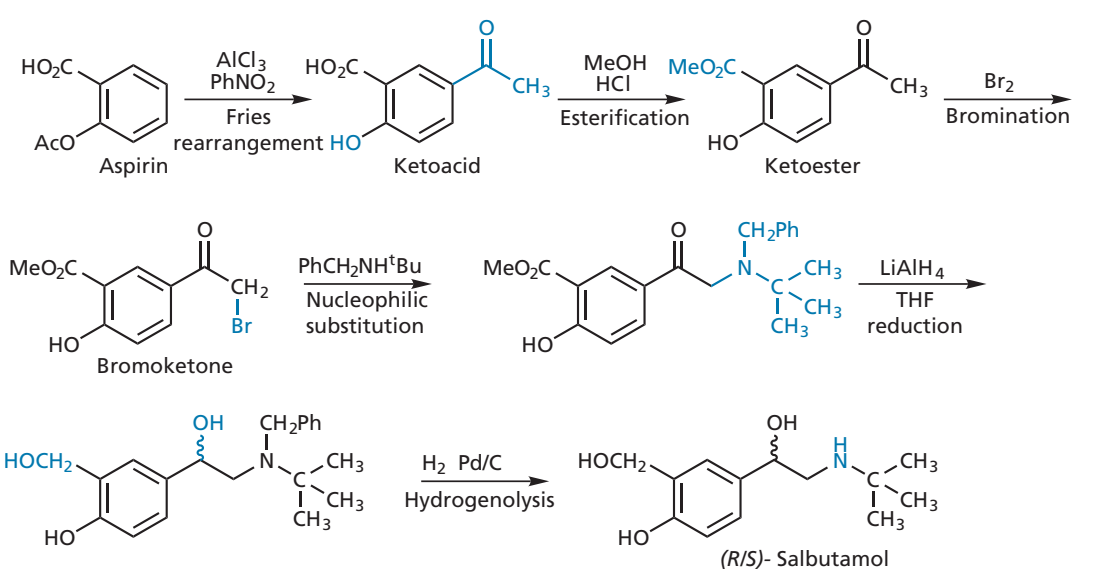
Several analogues of salbutamol have been synthesized to test whether the *meta* CH_2OH group could be modified further. These demonstrated the following requirements for the *meta* substituent:

- it has to be capable of taking part in hydrogen bonding—substituents such as $MeSO_2NHCH_2$, $HCONHCH_2$, and $H_2NCONHCH_2$ permitted this;
- substituents with an electron-withdrawing effect on the ring have poor activity (e.g. CO_2H);
- bulky *meta* substituents are bad for activity because they prevent the substituent adopting the necessary conformation for hydrogen bonding;
- the CH_2OH group can be extended to CH_2CH_2OH but no further.

Having identified the advantages of a hydroxymethyl group at the *meta* position, attention turned to the *N*-alkyl substituents. Salbutamol itself has a bulky t-butyl group. *N*-Arylalkyl substituents were added which would

BOX 23.2 Synthesis of salbutamol

Salbutamol is an important anti-asthmatic agent that can be synthesized from aspirin. **Fries rearrangement** of aspirin produces a ketoacid which is then esterified. A bromoketone is then prepared which allows the introduction of an amino group by nucleophilic substitution. The methyl ester and ketone are then reduced, and, finally, the *N*-benzyl protecting group is removed by hydrogenolysis.



Synthesis of salbutamol.

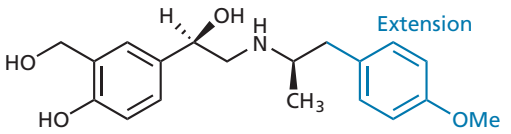


FIGURE 23.18 (*R*)- Salmefamol.

be capable of reaching the polar region of the binding site described earlier (*extension strategy*; section 23.9.2). For example, **salmefamol** (Fig. 23.18) is 1.5 times more active than salbutamol and has a longer duration of action (6 hours). The drug is given by inhalation, but in severe attacks it may be given intravenously.

Further developments were carried out to find a longer lasting agent in order to cope with nocturnal asthma—a condition which usually occurs at about 4 a.m. (commonly called the **morning dip**). It was decided to increase the lipophilicity of the drug because it was believed that a more lipophilic drug would bind more strongly to the tissue in the vicinity of the adrenoceptor and be 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. This led to **salmeterol** (Fig. 23.19), which has twice the potency of salbutamol and an extended action of 12 hours.

In 2009, **indacaterol** (Fig. 23.20) was approved in Europe for the treatment of chronic obstructive pulmonary disease and only needs to be taken once a day.

KEY POINTS

- The important binding groups in catecholamines are the two phenolic groups, the aromatic ring, the secondary alcohol, and the ionized amine.
- Placing a bulky alkyl group on the amine leads to selectivity for β-receptors over α-receptors.
- Extending the *N*-alkyl substituent to include a hydrogen-bonding group increases affinity for β-receptors.
- Agents which are selective for β_2-adrenoceptors are useful anti-asthmatic agents.
- Early β_2-agonists were metabolized by catechol-*O*-methyltransferase. Replacing the susceptible phenol group with a hydroxymethylene group prevented metabolism while retaining receptor interactions.
- Longer lasting anti-asthmatics have been obtained by increasing the lipophilic character of the compounds.

23.11 Adrenergic receptor antagonists

23.11.1 General α-/β-blockers

Carvedilol and **labetalol** are agents which act as antagonists at both the α– and β-adrenoceptors (Fig. 23.21). They have both been used as antihypertensives and carvedilol has been used to treat cardiac failure.

23.11.2 α-Blockers

Selective α_1-antagonists have been used to treat hypertension or to control urinary output. **Prazosin** (Fig. 23.22) was the first α_1-selective antagonist to be used for the treatment of hypertension, but it is short acting. Longer lasting drugs, such as **doxazosin** and **terazosin**, are better because they are given as once-daily doses. 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**. The enlarged prostate

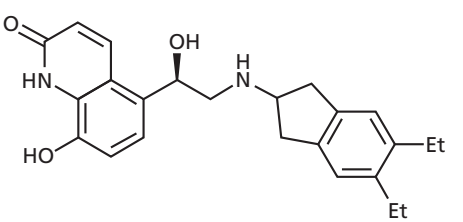


FIGURE 23.20 Indacaterol.

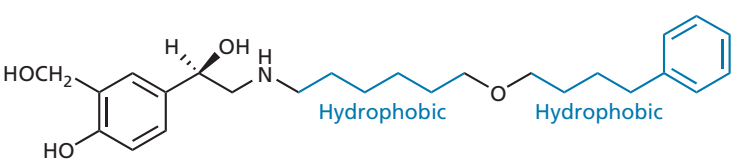


FIGURE 23.19 (*R*)- Salmeterol.

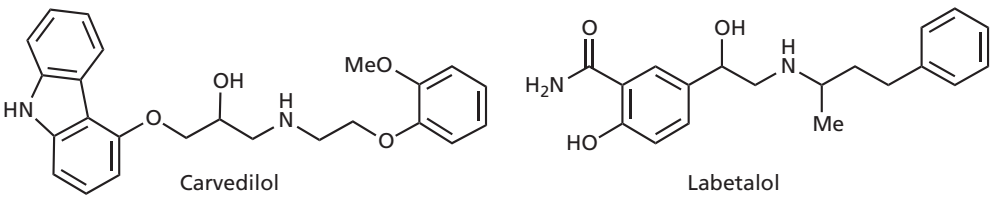


FIGURE 23.21 General α-/β-blockers.

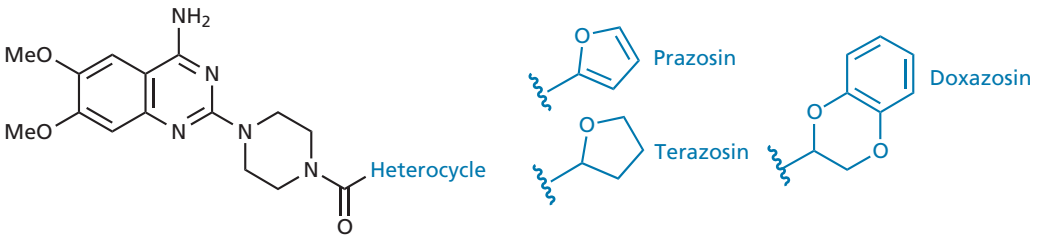


FIGURE 23.22 α_1-Selective antagonists.

puts pressure on the urinary tract and it becomes difficult to pass urine. The α_1-blockers prevent activation of the α_1-adrenoceptors that are responsible for smooth muscle contraction of the prostate gland, prostate urethra, and the neck of the bladder. This leads to smooth muscle relaxation at these areas, reducing the pressure on the urinary tract and helping the flow of urine. The agents are not a cure for the problem, but they relieve the symptoms.

α_2-Antagonists are being considered as antidepressants. Depression is associated with decreased release of noradrenaline and serotonin in the CNS, and antidepressants work by increasing the levels of one or both of these neurotransmitters. It may seem odd then, to consider an adrenergic antagonist as an antidepressant agent, but it makes sense when it is appreciated that the α_2-receptors are presynaptic adrenergic receptors or **autoreceptors** (section 23.6.3). Activation of these results in a decrease of noradrenaline released from the neuron, so blocking the autoreceptor will actually increase noradrenaline levels.

Mirtazepine (Fig. 23.23) is an antidepressant agent which blocks this receptor and increases the level of noradrenaline released. However, the α_2-receptor also controls the release of serotonin from serotonin nerve terminals, and so mirtazepine increases serotonin levels as well. It is not known for certain whether the antidepressant activity observed is due to increased noradrenaline levels or serotonin levels, or both. Current work is looking at the design of dual-action drugs which include the ability to block α_2-adrenoceptors (Case study 7).

Older antidepressants that are designed to increase noradrenaline and serotonin levels by different mechanisms can take 2–6 weeks before they have an effect. This delay in action is due to feedback control involving the α_2-receptors. When taken initially, the drugs certainly cause noradrenaline levels to increase, but feedback control counteracts this effect. It is only when the presynaptic receptors become desensitized that neurotransmitter levels increase sufficiently to have a clinical effect.

23.11.3 β-Blockers as cardiovascular drugs

23.11.3.1 First-generation β-blockers

The most useful adrenergic antagonists used in medicine today are the **β-blockers**, which were originally designed to act as antagonists at the β_1-receptors of the heart.

The first goal in the development of these agents was to achieve selectivity for β-receptors over α-receptors. **Isoprenaline** (Fig. 23.24) was chosen as the lead compound. Although this is an agonist, it is active at β-receptors and not α-receptors. Therefore, the goal

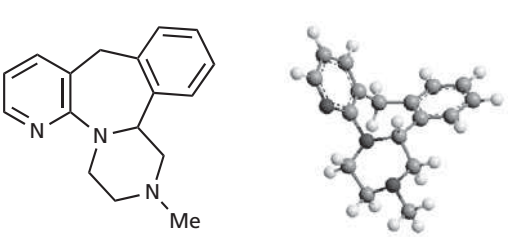


FIGURE 23.23 Mirtazepine.

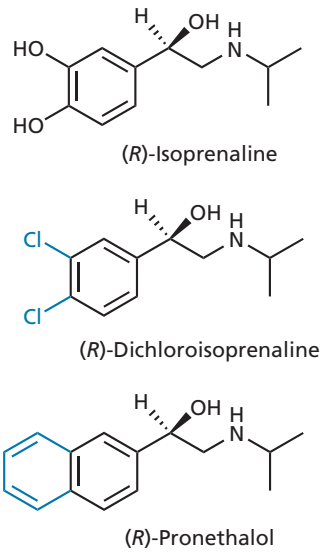


FIGURE 23.24 Partial β-agonists.

was to take advantage of this inherent specificity and modify the molecule to convert it from an agonist to an antagonist.

The phenolic groups are important for agonist activity, but this does not necessarily mean that they are essential for antagonist activity as antagonists can often block receptors by binding in a different way. Therefore, one of the early experiments was to replace the phenol groups with other substituents. Replacing the phenolic groups of isoprenaline with chloro substituents produced **dichloroisoprenaline** (Fig. 23.24). This compound was a partial agonist. In other words, it has some agonist activity, but it was weaker than a pure agonist. Nevertheless, dichloroisoprenaline blocks natural chemical messengers from binding and can therefore be viewed as an antagonist because it lowers adrenergic activity.

The next stage was to try to remove the partial agonist activity. A common method of converting an agonist into an antagonist is to add an extra aromatic ring. This can sometimes result in an extra hydrophobic interaction with the receptor which is not involved when the agonist binds. This, in turn, means a different induced fit between the ligand and the binding site, such that the ligand binds without activating the receptor. Therefore, the chloro groups of dichloroisoprenaline were replaced by an extra benzene ring to give a naphthalene ring system. The product obtained (**pronethalol**; Fig. 23.24) was still a partial agonist, but was the first β-blocker to be used clinically for angina, arrhythmia, and high blood pressure.

Research was carried out to see what effect extending the length of the chain between the aromatic ring and the amine would have. One of these projects involved the introduction of various linking groups between the naphthalene ring and the ethanolamine portion of the molecule (Fig. 23.25). At this stage, a chance event occurred. The researchers wanted to use β-naphthol as a starting material in order to introduce a linking group of X = O-CH_2 (Fig. 23.25). However, the stores had run out of the reagent and so α-naphthol was used instead to prepare the structure now known as **propranolol** (Fig. 23.25). In this structure, the chain was at the 1-position of the naphthalene ring rather than the 2-position, and nobody expected it to be active. To everyone's astonishment, propranolol was found to be a pure antagonist, having 10–20 times greater activity than pronethalol. It was introduced into the clinic for the treatment of angina and is now the benchmark against which all β-blockers are rated. Its contribution to medicine was so significant that its inventor, James Black, received the Nobel Prize in 1988. The *S*-enantiomer is the active form, although propranolol is used clinically as a racemate. When the original target structure from β-naphthol was eventually synthesized, it was similar in properties to pronethalol.

23.11.3.2 Structure–activity relationships of aryloxypropanolamines

Propranolol is an example of an aryloxypropanolamine structure (see Box 23.3). A large number of aryloxypropanolamines have been synthesized and tested, demonstrating the following SAR (Fig. 23.26):

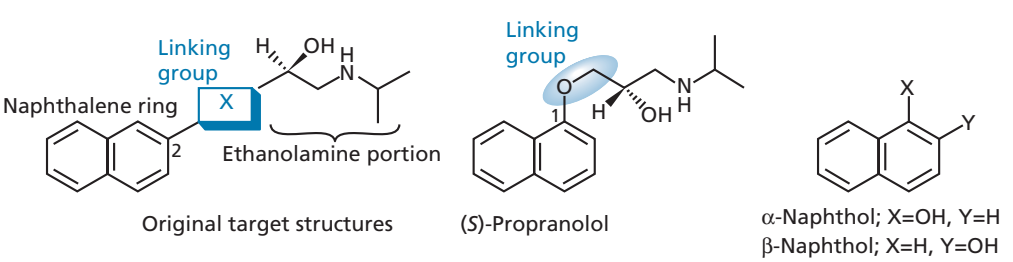


FIGURE 23.25 Chain extension tactics and the discovery of propranolol.

BOX 23.3 Synthesis of aryloxypropanolamines

Propranolol is a first-generation β-blocker and acts as an antagonist at β-adrenoceptors. The synthesis of propranolol is relatively simple and can be easily adapted to produce a large number of analogues. A phenol is reacted with 2-chloromethyloxirane such that nucleophilic substitution of the alkyl chloride takes place. The resulting product is then treated with an amine to ring-open the epoxide. This introduces the amine and generates the secondary alcohol at the same time. Because of the nature of the synthetic route, a huge variety of phenols and amines can be used to produce different analogues. There is an asymmetric centre in the final product, but it is only possible to synthesize the racemate using this route. A different, and more expensive, route would have to be used to synthesize the *R*- or the *S*-enantiomer.

Synthesis of aryloxypropanolamines.

- branched bulky *N*-alkyl substituents such as isopropyl and *t*-butyl groups are good for β-antagonist activity, suggesting an interaction with a hydrophobic pocket in the binding site (compare β-agonists);
- variation of the aromatic ring system is possible and heteroaromatic rings can be introduced, such as those in pindolol and timolol (Fig. 23.27);
- substitution on the side chain methylene group increases metabolic stability but lowers activity;
- the alcohol group on the side chain is essential for activity;
- replacing the ether oxygen on the side chain with S, CH_2, or NMe is detrimental, although a tissue-selective β-blocker has been obtained replacing O with NH;
- *N*-alkyl substituents longer than isopropyl or *t*-butyl are less effective (but see next point);
- adding an *N*-arylethyl group, such as -$CHMe_2$-CH_2Ph or CHMe-CH_2Ph, is beneficial (*extension*);
- the amine must be secondary.

23.11.3.3 Selective β_1-blockers (second-generation β-blockers)

Propranolol is a non-selective β-antagonist which acts as an antagonist at β_2-receptors, as well as β_1-receptors. Normally, this is not a problem, but it is serious if the patient is asthmatic as the propranolol could initiate an asthmatic attack by antagonizing the β_2-receptors in bronchial smooth muscle. This leads to contraction of bronchial smooth muscle and closure of the airways.

Practolol (Fig. 23.28) is not as potent as propranolol, but it is a selective cardiac β_1-antagonist which does not

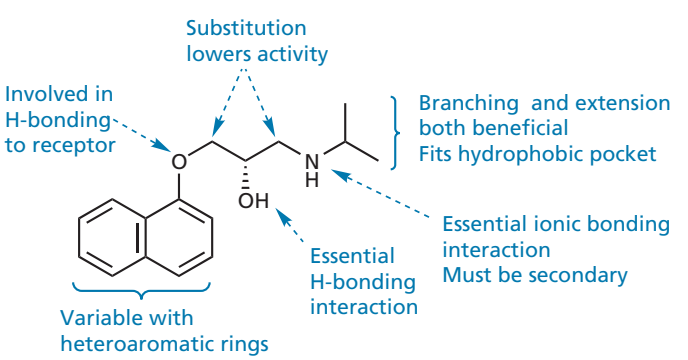


FIGURE 23.26 Structure–activity relationships of aryloxypropanolamines.

BOX 23.4 Clinical aspects of β-blockers

β-Blockers are used for the treatment of angina, myocardial infarction, arrhythmias, and hypertension. The effects of **propranolol** and other first-generation β-blockers depends on how active the patient is. At rest, propranolol causes little change in heart rate, output, or blood pressure. However, if the patient exercises or becomes excited, propranolol reduces the resulting effects of circulating adrenaline. The β-blockers were originally intended for use in angina, but they also had an unexpected antihypertensive activity (i.e. they lowered blood pressure). Indeed, the β-blockers are now more commonly used as antihypertensives rather than for the treatment of angina. The antihypertensive activity arises from the following effects:

- action at the heart to reduce cardiac output;
- action at the kidneys to reduce renin release; renin catalyses formation of angiotensin I, which is quickly converted to angiotensin II—a potent vasoconstrictor (Case study 2);
- action in the CNS to lower the overall activity of the sympathetic nervous system;

These effects override the fact that β-blockers block the β-receptors on blood vessels and would normally cause vasoconstriction.

First-generation β-blockers have various side effects, such as the following:

- bronchoconstriction in asthmatics—this is a dangerous side effect and the β-blockers are not recommended for patients with asthma;
- fatigue and tiredness of limbs due to reduced cardiac output;
- CNS effects (dizziness, nightmares, and sedation), especially with lipophilic β-blockers, such as **propranolol, pindolol**, and **oxprenolol**, all of which can cross the blood–brain barrier. More water-soluble agents, such as **nadolol**, are less likely to have such side effects (Fig. 1);
- coldness of the extremities;
- heart failure for patients on the verge of a heart attack—the β-blockers produce a fall in the resting heart rate and this may push some patients over the threshold;
- inhibition of noradrenaline release at synapses.

The second-generation β-blockers are more cardioselective and have fewer side effects. However, they still have some effect on bronchial smooth muscle and so they should only be used on asthmatic patients when there is no alternative treatment. Water-soluble β-blockers, such as **atenolol**, are less likely to enter the brain and so there is less risk of sleep disturbance or nightmares. β-Blockers which act as partial agonists (e.g. **acebutolol**) tend to cause less bradycardia and may also cause less coldness of the extremities. **Esmolol** is a short-acting β-blocker with a rapid onset of action. It is administered by slow intravenous injection during surgical procedures in order to treat any tachycardia (rapid heart rates) that might occur.

β-Blockers have a range of other clinical uses apart from cardiovascular medicine. They are used to counteract overproduction of catecholamines resulting from an enlarged thyroid gland or tumours of the adrenal gland. They can also be used to alleviate the trauma of alcohol and drug withdrawal, as well as relieving the stress associated with situations such as exams, public speaking, and public performances. There are some studies which suggest that propranolol might be a useful treatment for post-traumatic stress disorder and for the removal of traumatic memories. **Timolol** and **betaxolol** are used in the treatment of glaucoma (although their mechanism of action is not clear), while propranolol is used to treat anxiety and migraine.

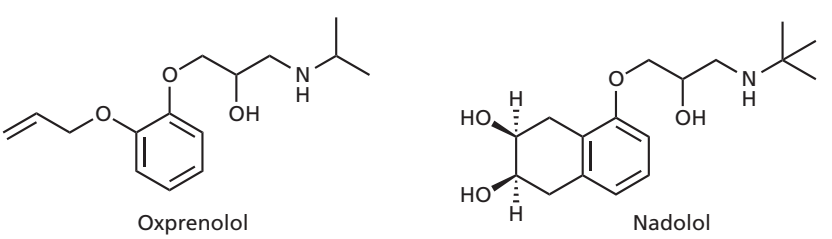


FIGURE 1 Oxprenolol and nadolol.

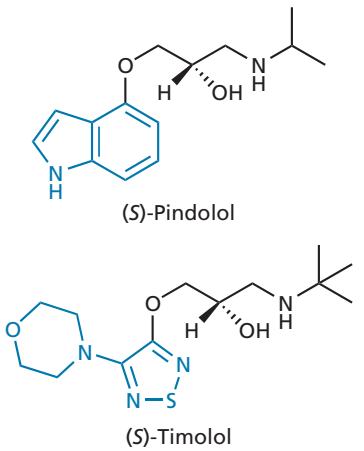


FIGURE 23.27 β_1-Antagonists containing heteroaromatic ring systems.

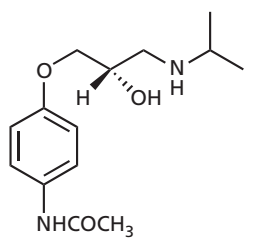


FIGURE 23.28 (*S*)-Practolol.

block vascular or bronchial β_2-receptors. It is much safer for asthmatic patients and, because it is more polar than propranolol, it has many fewer CNS effects.

Practolol was marketed as the first cardioselective β_1-blocker for the treatment of angina and hypertension, but after a few years it had to be withdrawn because of unexpected, but serious, side effects in a very small number of patients. These side effects included skin rashes, eye problems, and peritonitis.

Further investigations were carried out and it was demonstrated that the amido group had to be in the *para* position of the aromatic ring rather than the *ortho* or *meta* positions if the structure was to retain selectivity for the cardiac β_1-receptors. This implied that there was an extra hydrogen bonding interaction taking place with β_1-receptors (Fig. 23.29) which was not taking place with β_2-receptors.

Replacement of the acetamido group with other groups capable of hydrogen bonding led to a series of cardioselective β_1-blockers which included **acebutolol**, **atenolol**, **metoprolol**, and **betaxolol** (Fig. 23.30).

23.11.3.4 Short-acting β-blockers

Most clinically useful β-blockers should have a reasonably long duration of action such that they need only be taken once or twice a day. However, there is an advantage in having a very short-acting agent with a half-life measured in minutes rather than hours, because they can be administered during surgical procedures to treat any cardiac problems that may arise during the operation. **Esmolol** (Fig. 23.31) is one such agent. It has a rapid onset of action and is administered if the heart starts to beat too rapidly. Because it is a short-acting agent, its actions are quickly reversed once administration has been stopped.

Practolol was the lead compound used in the development of esmolol. The amide group was replaced with an ester, with the expectation that the ester would act as a bioisostere for the amide. Moreover, it was anticipated that the ester group would prove susceptible to esterase

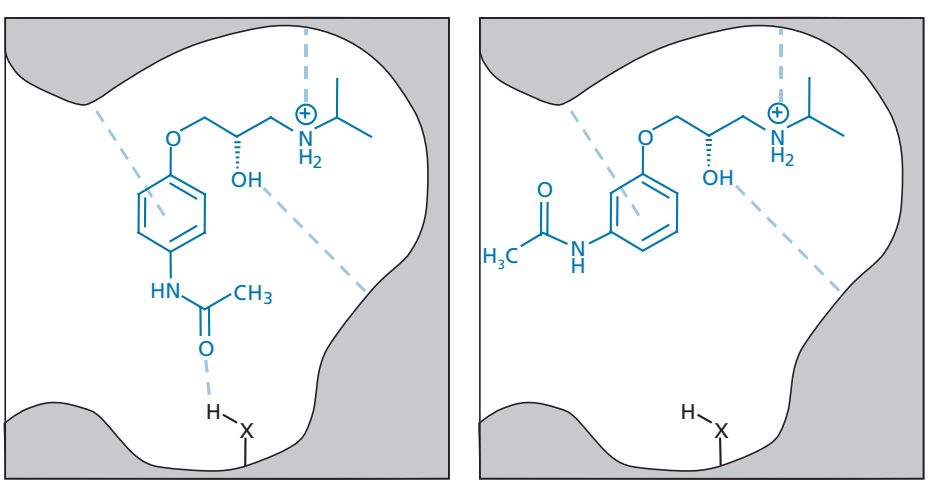


FIGURE 23.29 Binding interactions of antagonists with β_1-receptors.

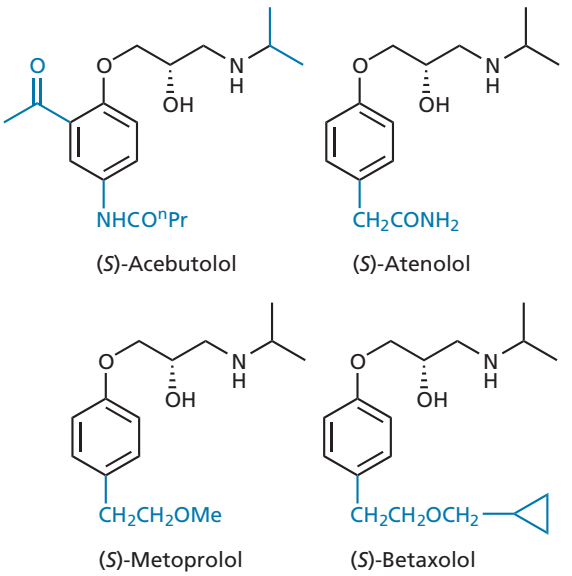


FIGURE 23.30 Second-generation β-blockers.

enzymes and be rapidly hydrolysed to an inactive metabolite. The aryl ester was indeed active as a β-blocker, but was not hydrolysed rapidly enough to be clinically useful. It was concluded that the aromatic ring was acting as a steric shield to the esterase enzymes, and so linker chains were inserted between the aromatic ring and the ester group to make the ester more 'exposed'. An ethylene linker proved ideal resulting in the discovery of esmolol. The structure is slightly more potent than practolol and is significantly more cardioselective. Once administration has been stopped, it takes 12 minutes to reach 80% recovery and 20 minutes to reach full recovery. The inactive carboxylic acid metabolite that is formed is rapidly conjugated and excreted.

KEY POINTS

- Antagonists of β-adrenoceptors are known as β-blockers.
- Replacing the catechol ring with a naphthalene ring changes an agonist into a partial agonist.
- Variation of the linking group between naphthalene and the ethanolamine moiety resulted in the first β-antagonists.
- SAR of aryloxypropanolamines reveal the importance of the ionized amine, the side chain alcohol, and the ether linkage. Substituents on the nitrogen can be varied. The naphthalene ring can be replaced by various heterocyclic rings.
- First-generation β-blockers inhibit all β-receptors and can induce asthma in susceptible patients.
- Second-generation β-blockers show selectivity for β_1-receptors over β_2-receptors. Aryloxypropanolamines bearing a hydrogen-bonding group at the *para* position of an aromatic ring show β_1-selectivity.
- Third-generation β-blockers bear an extended *N*-substituent, which includes a hydrogen-bonding group capable of an extra interaction with the β_1-adrenoceptor.

23.12 Other drugs affecting adrenergic transmission

In the previous sections, we discussed drugs which act as agonists or antagonists at adrenergic receptors. However, there are various other drug targets involved in the adrenergic transmission process which are important in controlling adrenergic activity. In this section, we briefly cover some of the most important aspects of these.

23.12.1 Drugs that affect the biosynthesis of adrenergics

In section 23.4, we identified **tyrosine hydroxylase** as the regulatory enzyme for catecholamine biosynthesis. This makes it a potential drug target. For example, **α-methyltyrosine** (Fig. 23.32) inhibits tyrosine hydroxylase and is sometimes used clinically to treat tumour cells which overproduce catecholamines.

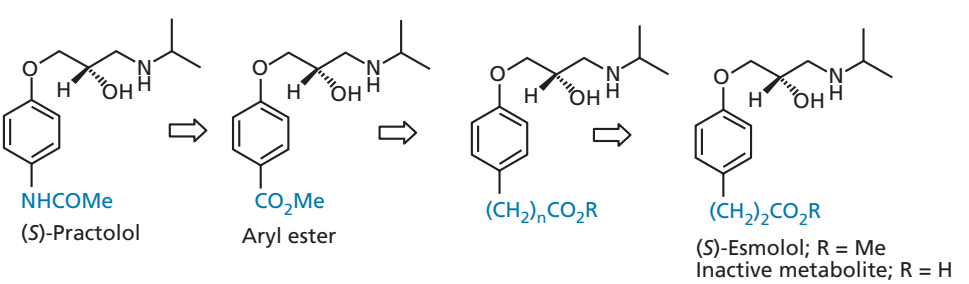


FIGURE 23.31 Development of short-acting β-blockers.

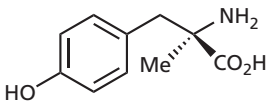


FIGURE 23.32 α-Methyltyrosine.

It is sometimes possible to 'fool' the enzymes of a biosynthetic process into accepting an unnatural substrate such that a false transmitter is produced and stored in the storage vesicles. For example, **α-methyldopa** is converted and stored in vesicles as **α-methylnoradrenaline** (Fig. 23.33) and displaces noradrenaline. Such false transmitters are less active than noradrenaline, so this is another way of down-regulating the adrenergic system. The drug has serious side effects, however, and is limited to the treatment of hypertension in late pregnancy.

A similar example is the use of **α-methyl-*m*-tyrosine** in the treatment of shock. This unnatural amino acid is accepted by the enzymes of the biosynthetic pathway and converted to **metaraminol** (Fig. 23.34).

23.12.2 Drugs inhibiting the uptake of noradrenaline into storage vesicles

The uptake of noradrenaline into storage vesicles can be inhibited by drugs. The natural product **reserpine** binds to the transport protein responsible for transporting noradrenaline into the vesicles and so noradrenaline accumulates in the cytoplasm where it is metabolized by monoamine oxidase (MAO). As noradrenaline levels drop, adrenergic activity drops. Reserpine was once prescribed as an antihypertensive agent, but it has serious side effects (e.g. depression). Therefore, it is no longer used.

23.12.3 Release of noradrenaline from storage vesicles

The storage vesicles are also the targets for the drugs **guanethidine** and **bretylium** (Fig. 23.35). Guanethidine is taken up into presynaptic neurons and storage vesicles by the same transport proteins as noradrenaline, and it displaces noradrenaline in the same way as reserpine. The drug also prevents exocytosis of the vesicle and so prevents release of the vesicle's contents into the synaptic gap. Guanethidine is an effective antihypertensive agent, but is no longer used in the clinic because of side effects resulting from non-specific inhibition of adrenergic nerve transmission. Bretylium works in the same way as guanethidine and is sometimes used to treat irregular heart rhythms.

23.12.4 Reuptake inhibitors of noradrenaline into presynaptic neurons

Once noradrenaline has interacted with its receptor, it is normally taken back into the presynaptic neuron by a transport protein. This transport protein is an important target for various drugs which inhibit noradrenaline uptake and thus prolong adrenergic activity. The tricyclic antidepressants, **desipramine**, **imipramine**, and **amitriptyline** (Fig. 23.36) work in this fashion in the CNS and were the principal treatment for depression from the 1960s to the 1980s.

It has been proposed that the tricyclic antidepressants (TCAs) are able to act as inhibitors because they are partly superimposable on noradrenaline. This can be seen in Fig. 23.37 where the aromatic ring and the nitrogen atoms of noradrenaline are overlaid with the nitrogen atom and one of the aromatic rings of desipramine.

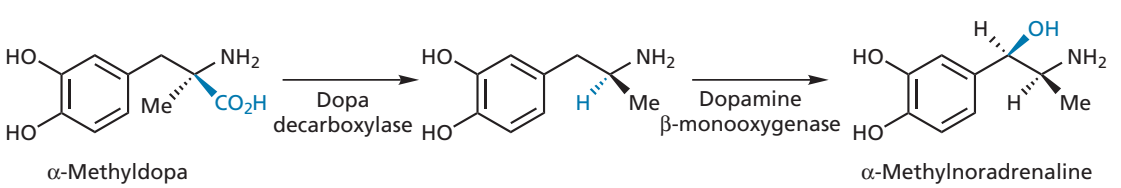


FIGURE 23.33 A false transmitter—α-methylnoradrenaline.

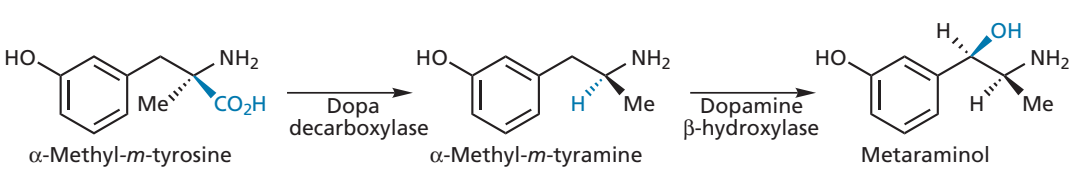


FIGURE 23.34 A false transmitter—metaraminol.

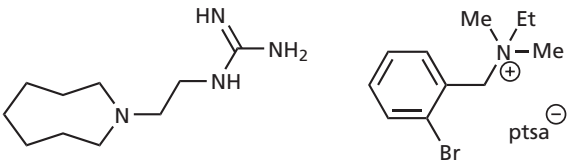


FIGURE 23.35 Agents that affect adrenergic activity (ptsa = *para*-toluenesulphonate).

Test your understanding and practise your molecular modelling with Exercise 23.2.

Note that the tricyclic system of desipramine is V-shaped, so that when the molecules are overlaid the second aromatic ring is held above the plane of the noradrenaline structure. Planar tricyclic structures would be expected to be less active as inhibitors, because the second aromatic ring would then occupy the space required for the amine nitrogen.

Unfortunately, the TCAs are not selective and interact with a variety of other targets, such as the reuptake protein for serotonin, the sodium and calcium ion channels in the heart, and the receptors for histamine, acetylcholine, and noradrenaline (mainly H_1, M_1 and α_1 respectively). Blockage of the transport protein for serotonin is beneficial to antidepressant activity, but interaction with ion channels and receptors results in various side effects including cardiotoxicity. Those agents containing tertiary amines (e.g. imipramine and amitriptyline) have the greatest side effects on the cholinergic system.

Newer antidepressant agents with better selectivity have now been developed and are termed **selective noradrenaline reuptake inhibitors** (SNRIs). **Reboxetine** (Fig. 23.38) is one such example and was marketed in 2003. It selectively inhibits noradrenaline uptake and has no appreciable action on cholinergic or α_1-adrenergic receptors. It also rapidly desensitizes presynaptic α_2-adrenergic receptors, which further enhances its activity and speeds up its onset of action. Dual noradrenaline and serotonin reuptake inhibitors such as **duloxetine** and **venlafaxine** (Fig. 23.38) are clinical agents which block the transport proteins for both noradrenaline and serotonin, but are more selective than the classical TCAs.

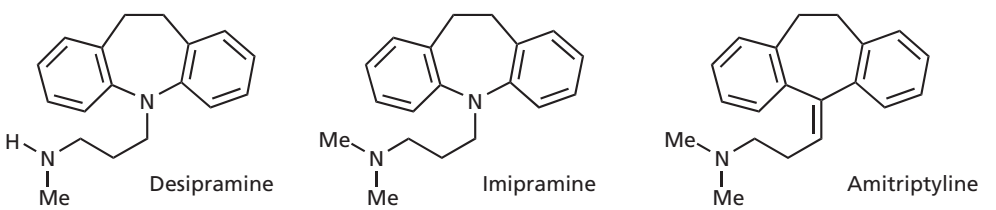


FIGURE 23.36 Tricyclic antidepressants.

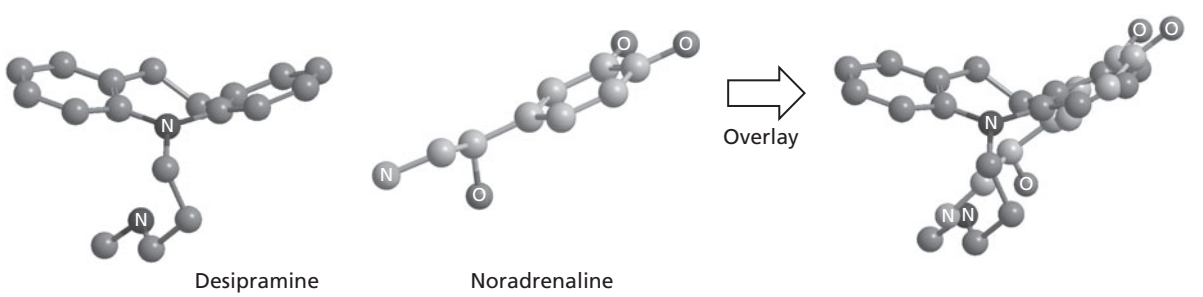


FIGURE 23.37 Overlay of desipramine and noradrenaline.

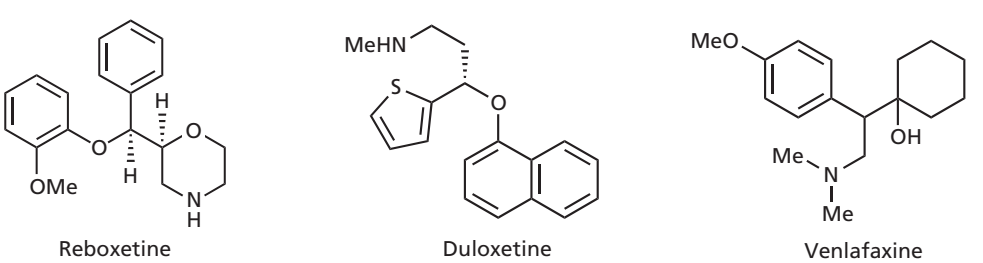


FIGURE 23.38 Reuptake inhibitors.

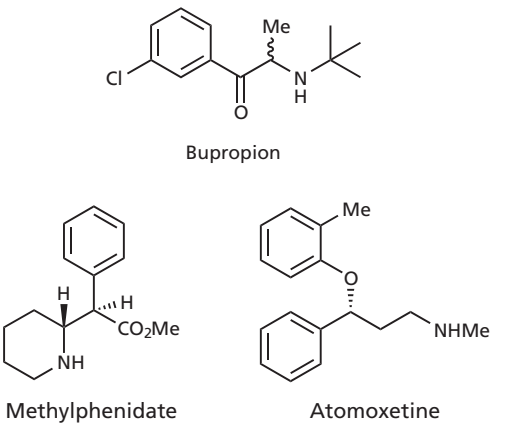


FIGURE 23.39 Adrenergic agents acting in the central nervous system.

Bupropion (**Zyban**; Fig. 23.39) inhibits the reuptake of both noradrenaline and dopamine. It has been used for the treatment of depression, and as an aid to giving up smoking (see also section 22.10.2.5). It is also being considered for the treatment of obesity in combination with the opioid antagonist naltrexone. This represents a massive market as it is predicted there will be 400 million obese people worldwide by 2015.

Stimulants acting as noradrenaline reuptake inhibitors have been used for the treatment of **attention deficit hyperactivity disorder**. This is the most commonly diagnosed childhood behavioural disorder and is associated with inattention, hyperactivity, and impulsivity. **Methylphenidate** (**Ritalin**; Fig. 23.39) is the most commonly prescribed medication for this disorder, while **atomoxetine** (Fig. 23.39) was approved in 2002. Both agents lead to increased levels of noradrenaline and dopamine in the brain.

Cocaine also inhibits noradrenaline uptake when it is chewed from coca leaves, but this time the inhibition is in the PNS rather than the CNS. Chewing coca leaves was well known to the Incas as a means of increasing endurance and suppressing hunger, and they would chew the leaves whenever they were faced with situations requiring long periods of physical effort or stamina. When the coca leaves are chewed, cocaine is absorbed into the systemic blood supply and acts predominantly on peripheral adrenergic receptors to increase adrenergic activity. Nowadays, cocaine abusers prefer to smoke or snort the drug, which allows it to enters the CNS more efficiently. There, it inhibits the uptake of dopamine rather than noradrenaline, resulting in its CNS effects.

Some amines such as **tyramine**, **amphetamine**, and **ephedrine** (Figs. 23.10 and 23.14) closely resemble noradrenaline in structure and are transported into the nerve cell by noradrenaline's transport proteins. Once in the cell, they are taken up into the vesicles. Because these amines are competing with noradrenaline for transport proteins, noradrenaline is more slowly reabsorbed into the nerve cells. Moreover, as the foreign amines are transported into the nerve cell, noradrenaline is transported out by those same transport proteins. Both of these facts mean that more noradrenaline is available to interact with its receptors. Therefore, amphetamines and similar amines have an indirect agonist effect on the adrenergic system.

Phentermine (Fig. 23.10) is very similar in structure to amphetamine, and causes increased levels of adrenaline and noradrenaline that result in hunger suppression. Consequently, it was approved in 1959 to suppress the appetite of obese patients. A combination of phentermine with the anticonvulsant and antimigraine drug **topiramate** is currently being considered as a treatment for obesity.

23.12.5 Inhibition of metabolic enzymes

Inhibition of the enzymes responsible for the metabolism of noradrenaline should prolong noradrenaline activity. We have seen how amines, such as tyramine, amphetamine, and ephedrine, inhibit the reuptake of noradrenaline into the presynaptic neuron. These amines also inhibit MAO, one of the important enzymes involved in the metabolism of noradrenaline. This, in turn, leads to a

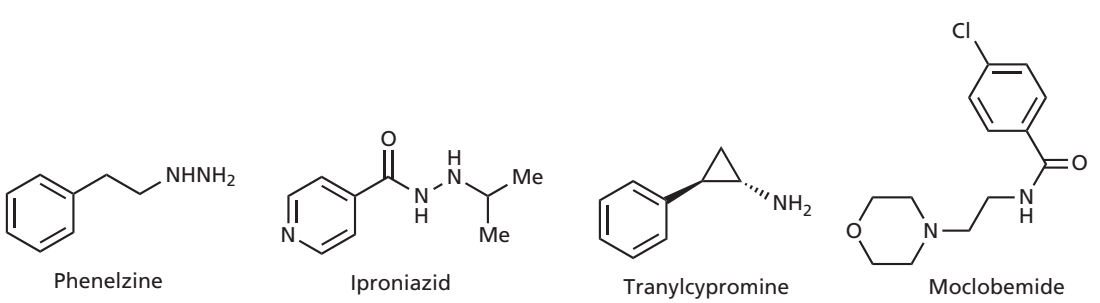


FIGURE 23.40 Monoamine oxidase inhibitors.

build-up in noradrenaline levels and an increase in adrenergic activity.

Monoamine oxidase inhibitors (**MAOIs**) such as **phenelzine**, **iproniazid**, and **tranylcypromine** (Fig. 23.40) have been used clinically as antidepressants, but other classes of compound such as the **tricyclic antidepressants** and **selective serotonin reuptake inhibitors** (SSRIs) are now favoured as they have fewer side effects. It is important to realize that the MAOIs affect the levels of all neurotransmitters that are normally metabolized by these enzymes, in particular, noradrenaline, dopamine, and serotonin. As a result of these widespread effects, it is difficult to be sure what mechanism is most involved in the antidepressant activity of these agents.

Another serious problem associated with MOAIs is their interaction with other drugs and food. A well-known example of this is the **cheese reaction**. Ripe cheese contains **tyramine** which is normally metabolized by MOAs in the gut wall and the liver, and so never enters the systemic circulation. If the MOAs are inhibited by MOAIs, tyramine is free to circulate round the body, enhancing the adrenergic system and leading to acute hypertension and severe headaches.

Better agents, such as **moclobemide** (Fig. 23.40), have been designed to act selectively on one of the isozymes of MAO (MAO-A; Box 7.4). They have also been designed to be reversible rather than irreversible in their action. This has the advantage that high levels of ingested tyramine will displace the inhibitor from MAO-A in the gut, allowing the enzyme to metabolize tyramine and prevent the high blood levels that would lead to toxic effects.

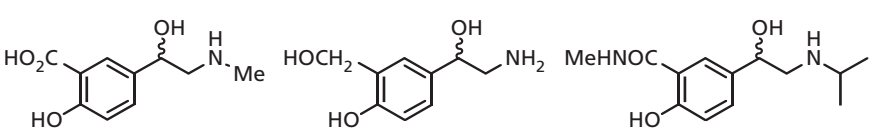
In recent years, there has been interest in using MAOIs as part of the treatment for Alzheimer's disease, as blocking MAO would lower the levels of free radical species present in the brain. A hybrid molecule with the ability to inhibit MAO and the cholinesterase enzymes has reached clinical trials (sections 13.3.14 and 22.15).

KEY POINTS

- Inhibitors of catecholamine biosynthesis affect adrenergic activity.
- Drugs that are similar to tyrosine may be converted by the catecholamine biosynthetic pathway to structures that act as false transmitters and lower adrenergic activity.
- The uptake and release of noradrenaline from storage vesicles can be inhibited by certain drugs.
- The tricyclic antidepressants inhibit the reuptake of noradrenaline into presynaptic neurons by blocking transport proteins. Adrenergic activity is increased in the CNS.
- Cocaine increases peripheral adrenergic activity by blocking noradrenaline reuptake. In the CNS it inhibits the reuptake of dopamine.
- Amphetamines compete with noradrenaline for the transport proteins responsible for transporting noradrenaline back into the presynaptic neuron. Adrenergic activity is increased in the CNS.
- Monoamine oxidase inhibitors (MAOIs) inhibit the metabolic enzyme monoamine oxidase (MAO) and result in increased levels of noradrenaline and other catecholamines.

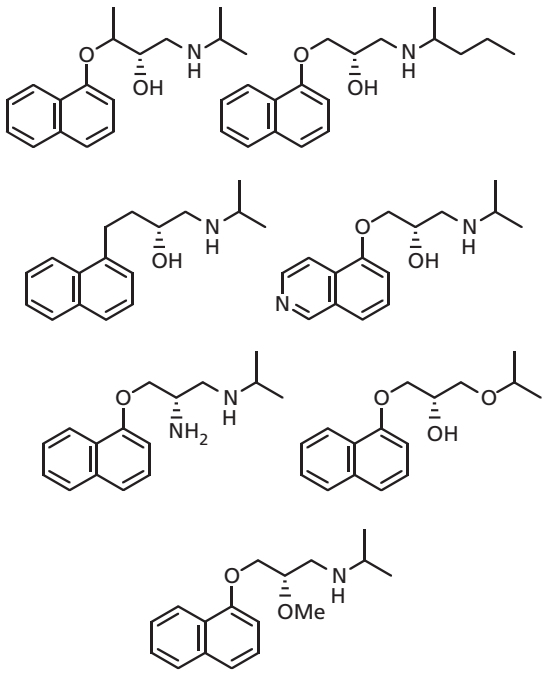
QUESTIONS

1. How would you synthesize the following structures to test their adrenergic agonist activity?



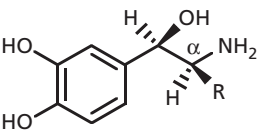
2. Suggest how you might synthesize the adrenergic antagonist, pindolol (Fig. 23.27).

3. Suggest whether the structures below are likely to have good or bad activity as β-blockers.



4. The catechol system is important for the binding of adrenergic agonists, yet is not required for adrenergic antagonists. Why should this be the case?

5. How would α-substitution affect the metabolism of adrenergic agents and why?



6. What synthetic complication arises from introducing an α-substituent as described in Question 5?

7. The active enantiomer of aryloxypropanolamines is the *S*-form, whereas the active enantiomer of arylethanolamines is the *R*-form. Does this imply that the two agents are binding differently to the binding site?

FURTHER READING

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Titles for general further reading are listed on p.763.