41 General anaesthetic agents

OVERVIEW

General anaesthesia aims to provide balanced anaesthesia meeting the requirements of amnesia, analgesia and relaxation tailored for the intended medical procedure. Different general anaesthetic agents provide varying amounts of the components of balanced anaesthesia but they are rarely used nowadays in isolation. Neuromuscular blocking drugs (Ch. 13), sedative and anxiolytic drugs (Ch. 44), and analgesic drugs (Ch. 42) are frequently co-administered. General anaesthetics are given systemically and exert their main effects on the central nervous system (CNS), in contrast to local anaesthetics (Ch. 43). Although we now take them for granted, general anaesthetics are the drugs that paved the way for modern surgery. Without them, much of modern medicine would be impossible.

In this chapter we first describe the pharmacology of the main agents in current use, which fall into two groups: intravenous agents and inhalation agents (gases and volatile liquids). The use of anaesthetics in combination with other drugs to produce balanced anaesthesia is discussed at the end of the chapter. Detailed information on the clinical pharmacology and use of anaesthetic agents can be found in specialised textbooks (e.g. Aitkenhead et al., 2013).

INTRODUCTION

It was only when inhalation anaesthetics were first discovered, in 1846, that most surgical operations became a practical possibility. Until that time, surgeons relied on being able to operate on struggling patients at lightning speed, and most operations were amputations.

▼ The use of **nitrous oxide** to relieve the pain of surgery was suggested by Humphrey Davy in 1800. He was the first person to make nitrous oxide, and he tested its effects on several people, including himself and the Prime Minister, noting that it caused euphoria, analgesia and loss of consciousness. The use of nitrous oxide, billed as 'laughing gas', became a popular fairground entertainment and came to the notice of an American dentist, Horace Wells, who had a tooth extracted under its influence, while he himself squeezed the inhalation bag. Ether also first gained publicity in a disreputable way, through the spread of 'ether frolics', at which it was used to produce euphoria among the guests. William Morton, also a dentist and a student at Harvard Medical School, used it successfully to extract a tooth in 1846 and then suggested to Warren, the illustrious chief surgeon at Massachusetts General Hospital, that he should administer it for one of Warren's operations. Warren grudgingly agreed, and on 16 October 1846 a large audience was gathered in the main operating theatre;[1] after some preliminary fumbling, Morton's demonstration was a spectacular success. 'Gentlemen, this is no humbug', was the most gracious comment that Warren could bring himself to make to the assembled audience.

In the same year, James Simpson, Professor of Midwifery at Edinburgh University, used chloroform to relieve the pain of childbirth, bringing on himself fierce denunciation from the clergy, one of whom wrote: 'Chloroform is a decoy of Satan, apparently offering itself to bless women; but in the end it will harden society and rob God of the deep, earnest cries which arise in time of trouble, for help.' Opposition was effectively silenced in 1853, when Queen Victoria gave birth to her seventh child under the influence of chloroform, and the procedure became known as *anaesthésie à la reine*.

MECHANISM OF ACTION OF ANAESTHETIC DRUGS

Unlike most drugs, anaesthetics, which include substances as diverse as simple gases (e.g. **nitrous oxide** and **xenon**), halogenated hydrocarbons (e.g. **isoflurane**), barbiturates (e.g. **thiopental**) and steroids (e.g. **alphaxalone**), belong to no recognisable chemical class. At one time it appeared that the shape and electronic configuration of the molecule were relatively unimportant, and the pharmacological action required only that the molecule had certain physicochemical properties. We now know much more about how different anaesthetics interact with neuronal membrane proteins and have come to realise that there are multiple mechanisms by which anaesthesia can be produced and that different anaesthetics work by different mechanisms.

As the concentration of an anaesthetic is increased, the switch from being conscious to unconscious occurs over a very narrow concentration range (approximately 0.2 of a log unit). This is a much steeper concentration–response curve than that seen with drugs that interact as agonists or antagonists at classical receptors (see Ch. 2).

LIPID SOLUBILITY

Overton and Meyer, at the turn of the 20th century, showed a close correlation between anaesthetic potency and lipid solubility in a diverse group of simple and unreactive organic compounds that were tested for their ability to immobilise tadpoles. This led to a bold theory, formulated by Meyer in 1937: 'Narcosis commences when any chemically indifferent substance has attained a certain molar concentration in the lipids of the cell.'

The relationship between anaesthetic activity and lipid solubility has been repeatedly confirmed for a diverse array of agents. Anaesthetic potency in humans is usually expressed as the minimal alveolar concentration (MAC) required to abolish the response to surgical incision in 50% of subjects. Figure 41.1 shows the correlation between MAC (inversely proportional to potency) and lipid solubility, expressed as oil : gas partition coefficient, for a wide range of inhalation anaesthetics. The Overton–Meyer studies did not suggest any particular mechanism, but revealed an impressive correlation, for which any theory of anaesthesia needs to account. Oil : gas partition was assumed to predict partition into membrane lipids,

[1]Now preserved as the Ether Dome, a museum piece at Massachusetts General Hospital.

consistent with the suggestion that anaesthesia results from an alteration of membrane function.

How the simple introduction of inert foreign molecules into the lipid bilayer could cause a functional disturbance was not explained. Two possible mechanisms, namely volume expansion and increased membrane fluidity, have been suggested and tested experimentally, but both are now largely discredited and attention has swung from lipids to proteins, the correlation of potency with lipid solubility being explained by molecules of anaesthetic binding to hydrophobic pockets within specific membrane protein targets.

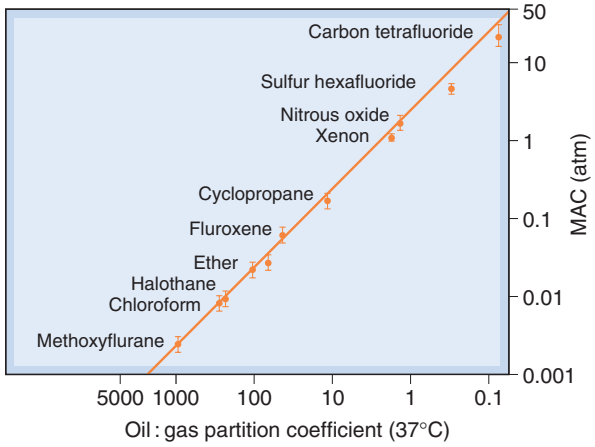

Fig. 41.1 Correlation of anaesthetic potency with oil : gas partition coefficient. Anaesthetic potency in humans is expressed as minimum alveolar partial pressure (MAC) required to produce surgical anaesthesia. There is a close correlation with lipid solubility, expressed as the oil : gas partition coefficient. *(From Halsey MJ 1989. Physicochemical properties of inhalation anaesthetics. In: Nunn JF, Utting JE, Brown BR (eds) General Anaesthesia. Butterworth, London.)*

EFFECTS ON ION CHANNELS

Following early studies that showed that anaesthetics can bind to various proteins as well as lipids, it was found that anaesthetics affect several different types of ion channels (see Rudolph & Antkowiak, 2004; Franks, 2008). For most anaesthetics, there are no known competitive antagonists, so this approach to identify sites of action is denied. Therefore the main criterion for identifying putative mechanisms of action of general anaesthetics is that, for an effect to be relevant to the anaesthetic or analgesic actions of these agents, it must occur at therapeutically relevant concentrations.

Cys-loop ligand-gated ion channels. Almost all anaesthetics (with the exceptions of **cyclopropane**, **ketamine** and **xenon**[2]) potentiate the action of GABA at $GABA_A$ receptors (Olsen & Li, 2011). As described in detail in Chapter 37, $GABA_A$ receptors are ligand-gated Cl^- channels made up of five subunits (generally comprising two α, two β and one γ or δ subunit). Anaesthetics can bind to hydrophobic pockets within different $GABA_A$ receptor subunits (see Fig. 41.2).

Specific mutations of the amino acid sequence of the α subunit inhibit the actions of volatile anaesthetics but not those of intravenous anaesthetics, whereas mutations of the β subunit inhibit both volatile and intravenous anaesthetics (see Franks, 2008). This suggest that volatile anaesthetics may bind at the interface between α and β subunits (analogous to benzodiazepines that bind at the interface between α and γ/δ subunits, see Ch. 38), whereas the

[2]There is some controversy about whether or not xenon potentiates $GABA_A$ responses but at present the weight of evidence suggests it does not.

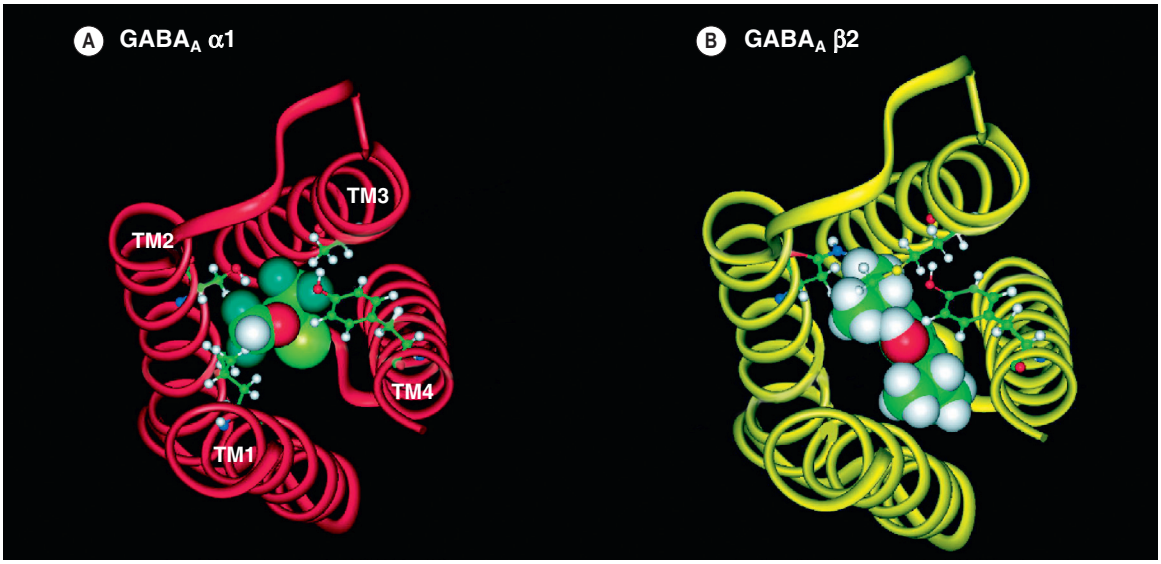

Fig. 41.2 Putative anaesthetic binding sites on $GABA_A$ receptor subunits. [**A**] A model of the α1 subunit of the $GABA_A$ receptor with a molecule of isoflurane shown sitting in a putative binding site. The transmembrane α-helices (TM) are numbered 1–4. [**B**] A model of the β2 subunit of the $GABA_A$ receptor with a molecule of propofol shown sitting in the putative binding site. *(Adapted from Hemmings HC et al. 2005 Trends Pharmacol Sci 26, 503–510.)*

intravenous anaesthetics may bind only on the β subunit. However, photoaffinity labelling experiments suggest that **etomidate** may bind to amino acid residues on both the α and β subunits. A further level of complexity arises because there are different subtypes of each subunit (see Ch. 38). Different subunit compositions give rise to subtly different subtypes of $GABA_A$ receptor and these may be involved in different aspects of anaesthetic action. $GABA_A$ receptors clustered at the synapse have different pharmacological and kinetic properties from those that are distributed elsewhere across the cell (extrasynaptic receptors; see Ch. 38). Extrasynaptic $GABA_A$ receptors contain α4 and α6 subunits as well as the δ subunit, and anaesthetics appear to have a greater potentiating effect on these extrasynaptic $GABA_A$ receptors.

General anaesthetics also affect other neuronal cys-loop ligand-gated channels such as those activated by glycine (Ch. 38), acetylcholine and 5-hydroxytryptamine (Ch. 39). Their actions on these channels are similar to those on $GABA_A$ receptors but the relative importance of such actions to general anaesthesia is still to be determined.

Two-pore domain K⁺ channels. These belong to a family of 'background' K^+ channels that modulate neuronal excitability. They are homomeric or heteromeric assemblies of a family of structurally related subunits (Bayliss & Barrett, 2008). Channels made up of TREK1, TREK2, TASK1, TASK3 or TRESK (see Ch 4, Table 4.2) subunits can be directly activated by low concentrations of volatile and gaseous anaesthetics, thus reducing membrane excitability (see Franks, 2008). This may contribute to the analgesic, hypnotic and immobilising effects of these agents. Two-pore domain K^+ channels do not appear to be affected by intravenous anaesthetics.

NMDA receptors. **Glutamate**, the major excitatory neurotransmitter in the CNS, activates three main classes of ionotropic receptor – AMPA, kainate and NMDA receptors (see Ch. 38). NMDA receptors are an important site of action for anaesthetics such as **nitrous oxide**, **xenon** and **ketamine** which act, in different ways, to reduce NMDA receptor-mediated responses. Xenon appears to inhibit NMDA receptors by competing with glycine for its regulatory site on this receptor whereas ketamine blocks the pore of the channel (see Ch. 38). Other inhalation anaesthetics may also exert effects on the NMDA receptor in addition to their effects on other proteins such as the $GABA_A$ receptor.

Other ion channels. Anaesthetics may also exert actions at cyclic nucleotide-gated K^+ channels and K_{ATP} channels. Some general anaesthetics inhibit certain subtypes of voltage-gated Na^+ channels. Inhibition of presynaptic Na^+ channels may give rise to the inhibition of transmitter release at excitatory synapses.

It may be overly simplistic to think of each anaesthetic as having only one mechanism of action: individual anaesthetics differ in their actions and affect cellular function in several different ways, so a single mechanism is unlikely to be sufficient.

Comprehensive reviews of the molecular and cellular actions of general anaesthetics can be found in Schüttler & Schwilden (2008).

EFFECTS ON THE NERVOUS SYSTEM

At the cellular level, the effects of anaesthetics are to enhance tonic inhibition (through enhancing the actions of GABA), reduce excitation (opening K^+ channels) and to inhibit excitatory synaptic transmission (by depressing transmitter release and inhibiting ligand-gated ion channels). Effects on axonal conduction are relatively unimportant.

Theories of anaesthesia

- Many simple, unreactive compounds produce general anaesthesia, the extreme example being the inert gas **xenon**.
- Anaesthetic potency is closely correlated with lipid solubility (Overton–Meyer correlation), not with chemical structure.
- Earlier theories of anaesthesia postulated interaction with the lipid membrane bilayer. Recent work favours interaction with membrane ion channels.
- Most anaesthetics enhance the activity of inhibitory $GABA_A$ receptors and other cys-loop ligand-gated ion channels. Other important effects are the activation of a subfamily of potassium channels (the two-pore domain K^+ channels) and inhibition of excitatory NMDA receptors.

The anaesthetised state comprises several components, including *unconsciousness*, loss of reflexes (*muscle relaxation*) and *analgesia*. Much effort has gone into identifying the brain regions on which anaesthetics act to produce these effects. The most sensitive regions appear to be the midbrain reticular formation, thalamic sensory relay nuclei and, to a lesser extent, parts of the cortex. Inhibition of these regions results in unconsciousness and analgesia. Some anaesthetics – particularly volatile anaesthetics – cause inhibition at the spinal level, producing a loss of reflex responses to painful stimuli, although, in practice, neuromuscular-blocking drugs (Ch. 13) are used as an adjunct to produce muscle relaxation rather than relying on the anaesthetic alone. Anaesthetics, even in low concentrations, cause short-term amnesia. It is likely that interference with hippocampal function produces this effect, because the hippocampus is involved in short-term memory, and certain hippocampal synapses are highly susceptible to inhibition by anaesthetics.

As the anaesthetic concentration is increased, all brain functions are progressively affected, including motor control and reflex activity, respiration and autonomic regulation. Therefore it is not possible to identify a critical 'target site' in the brain responsible for all the phenomena of anaesthesia.

High concentrations of any general anaesthetic affect all parts of the CNS, causing profound inhibition which, in the absence of artificial respiration, leads to death from respiratory failure. The margin between surgical anaesthesia and potentially fatal respiratory and circulatory depression is quite narrow, requiring careful monitoring by the anaesthetist and adjustment of the level of anaesthesia.

EFFECTS ON THE CARDIOVASCULAR AND RESPIRATORY SYSTEMS

Most anaesthetics decrease cardiac contractility, but their effects on cardiac output and blood pressure vary because of concomitant actions on the sympathetic nervous system

and vascular smooth muscle. **Isoflurane** and other halogenated anaesthetics inhibit sympathetic outflow, reduce arterial and venous tone and thus decrease arterial pressure and venous pressure. By contrast, **nitrous oxide** and **ketamine** increase sympathetic discharge and plasma noradrenaline concentration and, if used alone, increase heart rate and maintain blood pressure.

Many anaesthetics, especially **halothane**, cause ventricular extrasystoles. The mechanism involves sensitisation to adrenaline. Electrocardiogram monitoring shows that extrasystolic beats occur commonly in patients under anaesthesia, with no harm coming to the patient. If catecholamine secretion is excessive, however (*par excellence* in phaeochromocytoma, a neuroendocrine tumour that secretes catecholamines into the circulation; see Ch. 14), there is a risk of precipitating ventricular fibrillation.

With the exception of **nitrous oxide, ketamine** and **xenon**, all anaesthetics depress respiration markedly and increase arterial P_{CO_2}. Nitrous oxide has much less effect, in part because its low potency prevents very deep anaesthesia from being produced with this drug. Some inhalation anaesthetics are pungent, particularly **desflurane**, which is liable to cause coughing, laryngospasm and bronchospasm, so desflurane is not used for induction of anaesthesia but only for maintenance.

Pharmacological effects of anaesthetic agents

- Anaesthesia involves three main neurophysiological changes: unconsciousness, loss of response to painful stimulation and loss of reflexes (motor and autonomic).
- At supra-anaesthetic doses, all anaesthetic agents can cause death by loss of cardiovascular reflexes and respiratory paralysis.
- At the cellular level, anaesthetic agents affect synaptic transmission and neuronal excitability rather than axonal conduction. GABA-mediated inhibitory transmission is enhanced by most anaesthetics. The release of excitatory transmitters and the response of the postsynaptic receptors are also inhibited.
- Although all parts of the nervous system are affected by anaesthetic agents, the main targets appear to be the cortex, thalamus, hippocampus, midbrain reticular formation and spinal cord.
- Most anaesthetic agents (with the exception of **ketamine**, **nitrous oxide** and **xenon**) produce similar neurophysiological effects and differ mainly in respect of their pharmacokinetic properties and toxicity.
- Most anaesthetic agents cause cardiovascular depression by effects on the myocardium and blood vessels, as well as on the nervous system. Halogenated anaesthetic agents are likely to cause cardiac dysrhythmias, accentuated by circulating catecholamines.

INTRAVENOUS ANAESTHETIC AGENTS

Even the fastest-acting inhalation anaesthetics take a few minutes to act and cause a period of excitement before anaesthesia is induced. Intravenous anaesthetics act more rapidly, producing unconsciousness in about 20 s, as soon as the drug reaches the brain from its site of injection. These drugs (e.g. **propofol**, **thiopental** and **etomidate**) are normally used for induction of anaesthesia. They are preferred by many patients because injection generally lacks the menacing quality associated with a face mask in an apprehensive individual. With propofol, recovery is also fast due to rapid metabolism.

Although many intravenous anaesthetics are not suitable for maintaining anaesthesia because their elimination from the body is relatively slow compared with that of inhalation agents, propofol can be used as a continuous infusion, and the duration of action of ketamine is sufficient that it can be administered as a single bolus for short operations without the need for an inhalation agent. Under these circumstances a short-acting opioid such as **alfentanil** or **remifentanil** (Ch. 42) may be co-administered to provide analgesia.

The properties of the main intravenous anaesthetics are summarised in Table 41.1.[3]

PROPOFOL

Propofol, introduced in 1983, has now largely replaced thiopental as an induction agent. It has a rapid onset of action (approximately 30 s) and a rapid rate of redistribution ($t_{1/2}$ 2–4 min), which makes it short acting. Because of its low water solubility, it is administered as an oil-in-water emulsion, which can cause pain on injection, and supports microbial growth. **Fospropofol** is a recently developed water-soluble derivative that is less painful on injection and rapidly converted by alkaline phosphatases to propofol in the body. Propofol metabolism to inactive conjugates and quinols follows first-order kinetics, in contrast to thiopental (see below), resulting in more rapid recovery and less hangover effect than occurs with thiopental. It has a cardiovascular depressant effect that may lead to hypotension and bradycardia. Respiratory depression may also occur. It is particularly useful for day-case surgery, especially as it causes less nausea and vomiting than do inhalation anaesthetics.

There have been reports of a propofol infusion syndrome occurring in approximately 1 in 300 patients when it has been given for a prolonged period to maintain sedation, particularly to sick patients – especially children in whom it is contraindicated in this setting – in intensive care units. This is characterised by severe metabolic acidosis, skeletal muscle necrosis (rhabdomyolysis), hyperkalaemia, lipaemia, hepatomegaly, renal failure, arrhythmia and cardiovascular collapse.

THIOPENTAL

Thiopental is the only remaining barbiturate in common use. It has very high lipid solubility, and this accounts for the speed of onset and transience of its effect when it is injected intravenously. The free acid is insoluble in water, so thiopental is given as the sodium salt. On intravenous injection, thiopental causes unconsciousness within about

[3]**Propanidid** and **alphaxalone** were withdrawn because of allergic reactions including hypotension and bronchoconstriction – probably attributable to the solvent Cremophor – but a new formulation of alphaxalone has been reintroduced to veterinary medicine and is thought to be less allergenic.

Table 41.1 Properties of intravenous anaesthetic agents

Drug	Speed of induction and recovery	Main unwanted effect(s)	Notes
Propofol	Fast onset, very fast recovery	Cardiovascular and respiratory depression	Rapidly metabolised Possible to use as continuous infusion Causes pain at injection site
Thiopental	Fast (accumulation occurs, giving slow recovery) 'Hangover'	Cardiovascular and respiratory depression	Largely replaced by propofol Causes pain at injection site Risk of precipitating porphyria in susceptible patients
Etomidate	Fast onset, fairly fast recovery	Excitatory effects during induction and recovery Adrenocortical suppression	Less cardiovascular and respiratory depression than with thiopental Causes pain at injection site
Ketamine	Slow onset, after effects common during recovery	Psychotomimetic effects following recovery Postoperative nausea, vomiting and salivation Raised intracranial pressure	Produces good analgesia and amnesia with little respiratory depression
Midazolam	Slower than other agents	–	Little respiratory or cardiovascular depression

20 s, lasting for 5–10 min. The anaesthetic effect closely parallels the concentration of thiopental in the blood reaching the brain, because its high lipid solubility allows it to cross the blood–brain barrier without noticeable delay.

The blood concentration of thiopental declines rapidly, by about 80% within 1–2 min, following the initial peak after intravenous injection, because the drug is redistributed, first to tissues with a large blood flow (liver, kidneys, brain, etc.) and more slowly to muscle. Uptake into body fat, although favoured by the high lipid solubility of thiopental, occurs only slowly, because of the low blood flow to this tissue. After several hours, however, most of the thiopental present in the body will have accumulated in body fat, the rest having been metabolised. Recovery from the anaesthetic effect of a bolus dose occurs within about 5 min, governed entirely by redistribution of the drug to well-perfused tissues; very little is metabolised in this time. After the initial rapid decline, the blood concentration drops more slowly, over several hours, as the drug is taken up by body fat and metabolised. Consequently, thiopental produces a long-lasting hangover. Thiopental metabolism shows saturation kinetics (Ch. 10). Because of this, large doses or repeated intravenous doses cause progressively longer periods of anaesthesia, as the plateau in blood concentration becomes progressively more elevated as more drug accumulates in the body and metabolism saturates. For this reason, thiopental is not used to maintain surgical anaesthesia but only as an induction agent. It is also still used to terminate status epilepticus (see Ch. 45) or (in patients with a secured airway) to lower intracranial pressure.

Thiopental binds to plasma albumin (roughly 85% of the blood content normally being bound). The fraction bound is less in states of malnutrition, liver disease or renal disease, which affect the concentration and drug-binding properties of plasma albumin, and this can appreciably reduce the dose needed for induction of anaesthesia.

If thiopental – a strongly alkaline solution – is accidentally injected around rather than into a vein, or into an artery, this can cause pain, local tissue necrosis and ulceration or severe arterial spasm that can result in gangrene.

The actions of thiopental on the nervous system are very similar to those of inhalation anaesthetics, although it has little analgesic effect and can cause profound respiratory depression even in amounts that fail to abolish reflex responses to painful stimuli. Its long after-effect, associated with a slowly declining plasma concentration, means that drowsiness and some degree of respiratory depression persist for some hours.

ETOMIDATE

Etomidate has gained favour over thiopental on account of the larger margin between the anaesthetic dose and the dose needed to produce cardiovascular depression. It is more rapidly metabolised than thiopental, and thus less likely to cause a prolonged hangover. It causes less hypotension than propofol or thiopental. In other respects, etomidate is very similar to thiopental, although involuntary movements during induction, postoperative nausea and vomiting, and pain at the injection site are problems with its use. Etomidate suppresses the production of adrenal steroids, an effect that has been associated with an increase in mortality in severely ill patients. It should be avoided in patients at risk of having adrenal insufficiency, e.g. in sepsis. It is preferable to thiopental in patients at risk of circulatory failure.

OTHER INTRAVENOUS AGENTS

KETAMINE

▼ **Ketamine** closely resembles, both chemically and pharmacologically, **phencyclidine**. Both are used recreationally for their pronounced effects on sensory perception (see Ch. 48). Both drugs are believed to act by blocking activation of the NMDA receptor (see Ch. 38). They produce a similar anaesthesia-like state and profound analgesia, but ketamine produces less euphoria and sensory distortion than phencyclidine and is thus more useful in anaesthesia. Ketamine can be used in lower doses as an analgesic (Ch. 42) and as an acute treatment for depression (Ch. 47).

Intravenous anaesthetic agents

- Most commonly used for induction of anaesthesia, followed by inhalation agent. **Propofol** can also be used to maintain anaesthesia during surgery.
- **Propofol, thiopental** and **etomidate** are most commonly used; all act within 20–30 s if given intravenously.
- **Propofol**:
  - potent
  - rapid onset and distribution
  - rapidly metabolised
  - very rapid recovery; limited cumulative effect
  - useful for day-case surgery
  - low incidence of nausea and vomiting
  - risk of bradycardia
  - may induce an adverse 'propofol infusion syndrome' when administered at high doses for prolonged periods of time.
- **Thiopental**:
  - barbiturate with very high lipid solubility
  - rapid action due to rapid transfer across blood–brain barrier; short duration (about 5 min) due to redistribution, mainly to muscle
  - reduces intracranial pressure
  - slowly metabolised and liable to accumulate in body fat, therefore may cause prolonged effect if given repeatedly
  - narrow margin between anaesthetic dose and dose causing cardiovascular depression
  - risk of tissue damage if accidentally injected extravascularly or into an artery
  - can precipitate an attack of porphyria in susceptible individuals (see Ch. 11).
- **Etomidate**:
  - similar to thiopental but more quickly metabolised
  - less risk of cardiovascular depression
  - may cause involuntary movements during induction and high incidence of nausea
  - possible risk of adrenocortical suppression.
- **Ketamine**:
  - analogue of **phencyclidine**, with similar properties
  - action differs from other agents, probably related to inhibition of NMDA-type glutamate receptors
  - onset of effect is relatively slow (1–2 min)
  - powerful analgesic
  - produces 'dissociative' anaesthesia, in which the patient may remain conscious although amnesic and insensitive to pain
  - high incidence of dysphoria, hallucinations, etc. during recovery; used mainly for minor procedures in children
  - can raise intracranial pressure.

Given intravenously, ketamine takes effect more slowly (1–2 min) than thiopental, and produces a different effect, known as 'dissociative anaesthesia', in which there is a marked sensory loss and analgesia, as well as amnesia, without complete loss of consciousness. During induction and recovery, involuntary movements and peculiar sensory experiences often occur. Ketamine does not act simply as a CNS depressant, and it produces cardiovascular and respiratory effects quite different from those of most anaesthetics. Blood pressure and heart rate are usually increased, and respiration is unaffected by effective anaesthetic doses. This makes it relatively safe to use in low-technology healthcare situations or in accident and emergency situations where it can be administered intramuscularly if intravenous administration is not possible.[4] However, ketamine, unlike other intravenous anaesthetic drugs, can increase intracranial pressure, so it should not be given to patients with raised intracranial pressure or at risk of cerebral ischaemia. The other main drawback of ketamine is that hallucinations, and sometimes delirium and irrational behaviour, are common during recovery. These aftereffects limit the usefulness of ketamine but are said to be less marked in children,[5] and ketamine, often in conjunction with a benzodiazepine, is sometimes still used for minor procedures in paediatrics.

MIDAZOLAM

Midazolam, a benzodiazepine (Ch. 44), is slower in onset and offset than the drugs discussed above but, like ketamine, causes less respiratory or cardiovascular depression. Midazolam (or **diazepam**) is often used as a preoperative sedative and during procedures such as endoscopy, where full anaesthesia is not required. It can be administered in combination with an analgesic such as **alfentanil**. In the event of overdose it can be reversed by **flumazenil** (see Ch. 44).

INHALATION ANAESTHETICS

Many inhalation anaesthetics that were once widely used, such as ether, chloroform, trichloroethylene, cyclopropane, methoxyflurane and enflurane, have now been replaced in clinical practice, particularly by **isoflurane**, **sevoflurane** and **desflurane**, which have improved pharmacokinetic properties, fewer side effects and are nonflammable. Of the older agents, nitrous oxide is still used widely (especially in obstetric practice), and halothane now only occasionally.

PHARMACOKINETIC ASPECTS

An important characteristic of an inhalation anaesthetic is the speed at which the arterial blood concentration, which governs the pharmacological effect in the brain, follows changes in the partial pressure of the drug in the inspired gas mixture. Ideally, the blood concentration should follow as quickly as possible, so that the depth of anaesthesia can be controlled rapidly. In particular, the blood concentration should fall to a subanaesthetic level rapidly when administration is stopped, so that the patient recovers consciousness with minimal delay. A prolonged semicomatose state, in which respiratory reflexes are weak or absent, is particularly hazardous.

[4] An anaesthetist colleague tells of coming across a motorway accident where most of a victim was hidden under a mass of distorted metal but enough of a limb was available for an injection of ketamine to be given.
[5] A cautionary note: many adverse effects are claimed to be less marked in children, perhaps because they cannot verbalise their experiences. At one time, muscle relaxants alone were used without anaesthesia during cardiac surgery in neonates. The babies did not complain of pain, but their circulating catecholamines reached extreme levels.

The lungs are the only quantitatively important route by which inhalation anaesthetics enter and leave the body. For modern inhalation anaesthetics, metabolic degradation is generally insignificant in determining their duration of action. Inhalation anaesthetics are all small, lipid-soluble molecules that readily cross alveolar membranes. It is therefore the rates of delivery of drug to and from the lungs, via (respectively) the inspired air and bloodstream, which determine the overall kinetic behaviour of an anaesthetic. The reason that anaesthetics vary in their kinetic behaviour is that their relative solubilities in blood, and in body fat, vary between one drug and another.

The main factors that determine the speed of induction and recovery can be summarised as follows:

- Properties of the anaesthetic:
  - blood : gas partition coefficient (i.e. solubility in blood)
  - oil : gas partition coefficient (i.e. solubility in fat).
- Physiological factors:
  - alveolar ventilation rate
  - cardiac output.

SOLUBILITY OF INHALATION ANAESTHETICS

Inhalation anaesthetics can be regarded physicochemically as ideal gases: their solubility in different media is expressed as *partition coefficients*, defined as the ratio of the concentration of the agent in two phases at equilibrium.

The *blood:gas partition coefficient* is the main factor that determines the rate of induction and recovery of an inhalation anaesthetic, and the lower the blood:gas partition coefficient, the faster is induction and recovery (Table 41.2). This is because it is the partial pressure of the gas in the alveolar space that governs the concentration in the blood. The lower the blood:gas partition coefficient, the more rapidly the partial pressure of the gas in the alveolar space will equal that being administered in the inspired air (see below).

The *oil : gas partition coefficient*, a measure of fat solubility, determines the potency of an anaesthetic (as already discussed) and also influences the kinetics of its distribution in the body, the main effect being that high lipid solubility delays recovery from anaesthesia. Values of blood : gas and oil:gas partition coefficients for some anaesthetics are given in Table 41.2.

INDUCTION AND RECOVERY

Cerebral blood flow is a substantial fraction of cardiac output (~15%), and the blood–brain barrier is freely permeable to anaesthetics, so the concentration of anaesthetic in the brain closely tracks that in the arterial blood. The kinetics of transfer of anaesthetic between the inspired air and the arterial blood therefore determine the kinetics of the pharmacological effect.

When a volatile anaesthetic is first administered, the initial breaths are diluted into the residual gas volume in the lungs resulting in a reduction in the alveolar partial pressure of the anaesthetic as compared with the inspired gas mixture. With subsequent breaths, the alveolar partial pressure rises towards equilibrium. For an anaesthetic with a low blood:gas partition coefficient, the absorption into the blood will be slower, so with repeated breaths the partial pressure in the alveolar space will rise faster than with an agent of high blood:gas partition coefficient. Thus a smaller number of breaths (i.e. a shorter time) will be needed to reach equilibrium. Therefore, contrary to what one might intuitively suppose, the *lower* the solubility in blood, the *faster* is the process of equilibration. Figure 41.3 shows the much faster equilibration for **nitrous oxide**, a low-solubility agent, than for **ether**, a high-solubility agent.

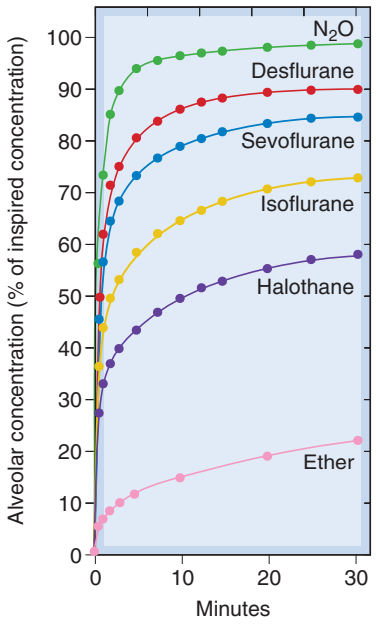

Fig. 41.3 Rate of equilibration of inhalation anaesthetics in humans. The curves show alveolar concentration (which closely reflects arterial blood concentration) as a function of time during induction. The initial rate of equilibration reflects solubility in blood. There is also a slow phase of equilibration, most marked with highly lipid-soluble drugs (ether and halothane), owing to the slow transfer between blood and fat (Fig. 41.4). *(Adapted from Yasuda N, Lockhart SH, Eger EI II, et al. 1991 Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 72, 316–324.)*

The rate of absorption into the blood can be enhanced by administering a volatile anaesthetic along with nitrous oxide. The rapid movement of nitrous oxide from the alveoli into the blood concentrates the volatile anaesthetic in the alveoli which will increase its movement into the blood – referred to as the *concentration effect*. Furthermore, replacement of the gas taken up into the blood by an increase in inspired ventilation augments the amount of volatile anaesthetic present in the alveoli – referred to as the *second gas effect*.

The transfer of anaesthetic between blood and tissues also affects the kinetics of equilibration. Figure 41.4 shows a very simple model of the circulation, in which two tissue compartments are included. Body fat has a low blood flow but has a high capacity to take up anaesthetics, and constitutes about 20% of the volume of a representative man. Therefore, for a drug such as **halothane**, which is about 100 times more soluble in fat than in water, the amount present in fat after complete equilibration would be roughly 95% of the total amount in the body. Because of the low blood flow to adipose tissue, it takes many hours for the drug to enter and leave the fat, which results in a pronounced slow phase of equilibration following the

Table 41.2 Characteristics of inhalation anaesthetics

Drug	Partition coefficient		Minimum alveolar concentration (% v/v)	Induction/ recovery	Main adverse effect(s) and disadvantage(s)	Notes
	Blood:gas	*Oil:gas*				
Nitrous oxide	0.5	1.4	100[a]	Fast	Few adverse effects Risk of anaemia (with prolonged or repeated use) Accumulation in gaseous cavities	Good analgesic effect Low potency precludes use as sole anaesthetic agent – normally combined with other inhalation agents
Isoflurane	1.4	91	1.2	Medium	Few adverse effects Possible risk of coronary ischemia in susceptible patients	Widely used Has replaced halothane
Desflurane	0.4	23	6.1	Fast	Respiratory tract irritation, cough, bronchospasm	Used for day-case surgery because of fast onset and recovery (comparable with nitrous oxide)
Sevoflurane	0.6	53	2.1	Fast	Few reported Theoretical risk of renal toxicity owing to fluoride	Similar to desflurane
Halothane	2.4	220	0.8	Medium	Hypotension Cardiac arrhythmias Hepatotoxicity (with repeated use) Malignant hyperthermia (rare)	Little used nowadays Significant metabolism to trifluoracetate
Enflurane	1.9	98	1.7	Medium	Risk of convulsions (slight) Malignant hyperthermia (rare)	Has declined in use May induce seizures
Ether	12.0	65	1.9	Slow	Respiratory irritation Nausea and vomiting Explosion risk	Now obsolete, except where modern facilities are lacking

[a]Theoretical value based on experiments under hyperbaric conditions.

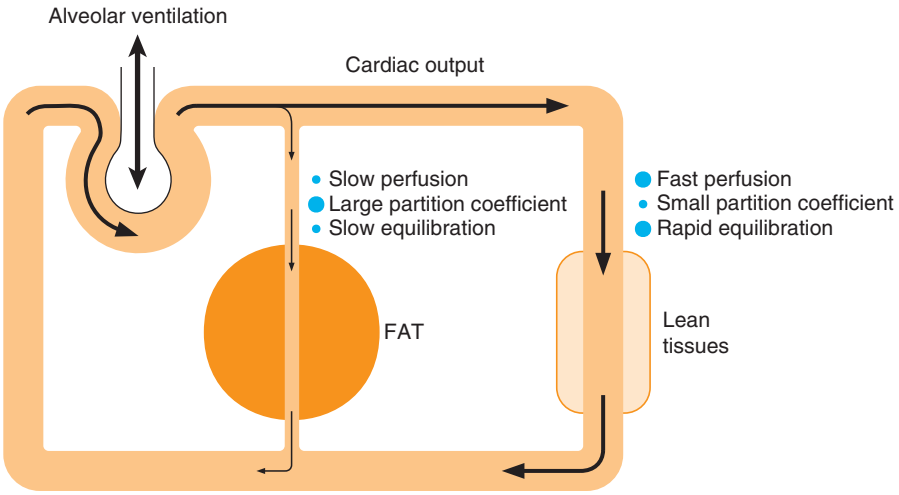

Fig. 41.4 Factors affecting the rate of equilibration of inhalation anaesthetics in the body. The body is represented as two compartments. Lean tissues, including the brain, have a large blood flow and low partition coefficient for anaesthetics, and therefore equilibrate rapidly with the blood. Fat tissues have a small blood flow and large partition coefficient, and therefore equilibrate slowly, acting as a reservoir of drug during the recovery phase.

rapid phase associated with the blood–gas exchanges (Fig. 41.3). The more fat-soluble the anaesthetic and the fatter the patient, the more pronounced this slow phase becomes and recovery will also be delayed.

Of the physiological factors affecting the rate of equilibration of inhalation anaesthetics, alveolar ventilation is the most important. The greater the minute volume (respiration rate × tidal volume), the faster is equilibration, particularly for drugs that have high blood:gas partition coefficients. Respiratory depressant drugs such as **morphine** (see Ch. 42) can thus retard recovery from anaesthesia. The effect of changes in cardiac output on the rate of equilibration is more complex. By reducing alveolar perfusion, a reduction of cardiac output reduces alveolar absorption of the anaesthetic, and thus speeds up induction, but this is partially offset by a reduction of cerebral blood flow slowing down delivery to the brain.

Recovery from anaesthesia involves the same processes as induction but in reverse, the rapid phase of recovery being followed by a slow 'hangover'. Because of these kinetic factors, the search for improved inhalation anaesthetics has focused on agents with low blood and tissue solubility. Newer drugs, which show kinetic properties similar to those of nitrous oxide but have higher potency, include **sevoflurane** and **desflurane** (Table 41.2 and Fig. 41.3).

METABOLISM AND TOXICITY

Metabolism, although not quantitatively important as a route of elimination of inhalation anaesthetics, can generate toxic metabolites (Ch. 57).[6] This is the main reason that agents that are now obsolete or obsolescent, such as chloroform, methoxyflurane and halothane, have been replaced by the less toxic alternatives described below.

Malignant hyperthermia is an important but rare *idiosyncratic reaction* (see Ch. 57), caused by heat production in skeletal muscle, due to excessive release of Ca^{2+} from the sarcoplasmic reticulum. The result is muscle contracture, acidosis, increased metabolism and an associated dramatic rise in body temperature that can be fatal unless treated promptly. Triggers include halogenated anaesthetics and depolarising neuromuscular-blocking drugs (see Ch. 13). Susceptibility has a genetic basis, being associated with mutations in the gene encoding the ryanodine receptor, which controls Ca^{2+} release from the sarcoplasmic reticulum (Ch. 4). Malignant hyperthermia is treated with **dantrolene**, a muscle relaxant drug that blocks these calcium-release channels.

INDIVIDUAL INHALATION ANAESTHETICS

The main inhalation anaesthetics currently used in developed countries are **isoflurane**, **desflurane** and **sevoflurane**, sometimes used in combination with **nitrous oxide**. Due to its relatively rapid onset of action and pleasant smell sevoflurane is used, under some circumstances, on its own to induce anaesthesia, e.g. in paediatrics or in adults frightened by the prospect of venous cannulation. **Xenon**, an inert gas shown many years ago to have anaesthetic properties, is making something of a comeback in the clinic because – not surprisingly for an inert gas – it lacks toxicity, but its relatively low potency and high cost are disadvantages. It may also be neuroprotective in neonatal hypoxia (see Ch. 40).

Pharmacokinetic properties of inhalation anaesthetics

- Rapid induction and recovery are important properties of an anaesthetic agent, allowing flexible control over the depth of anaesthesia.
- Speed of induction and recovery are determined by two properties of the anaesthetic: solubility in blood (blood:gas partition coefficient) and solubility in fat (lipid solubility).
- Agents with low blood:gas partition coefficients produce rapid induction and recovery (e.g. **nitrous oxide**, **desflurane**); agents with high blood:gas partition coefficients show slow induction and recovery.
- Agents with high lipid solubility accumulate gradually in body fat and may produce a prolonged 'hangover' if used for a long operation.
- Some halogenated anaesthetics (especially **halothane** and **methoxyflurane**) are metabolised. This is not very important in determining their duration of action, but contributes to toxicity (e.g. renal toxicity associated with fluoride production with **methoxyflurane** – no longer used).

ISOFLURANE, DESFLURANE, SEVOFLURANE, ENFLURANE AND HALOTHANE

Isoflurane is now the most widely used volatile anaesthetic. It is not appreciably metabolised and lacks the proconvulsive property of enflurane. It can cause hypotension and is a powerful coronary vasodilator. This can exacerbate cardiac ischaemia in patients with coronary disease, because of the 'steal' phenomenon (see Ch. 21).

Desflurane is chemically similar to isoflurane, but its lower solubility in blood and fat means that adjustment of anaesthetic depth and recovery are faster, so it is increasingly used as an anaesthetic in obese patients undergoing bariatric surgery and for day-case surgery. It is not appreciably metabolised. It is less potent than the drugs described above. At the concentrations used for induction of anaesthesia (about 10%), desflurane causes some respiratory tract irritation, which can lead to coughing and bronchospasm. Rapid increases in the depth of desflurane anaesthesia can be associated with a striking increase in sympathetic activity, which is undesirable in patients with ischaemic heart disease.

Sevoflurane resembles desflurane but is more potent and does not cause the same degree of respiratory irritation. It is partially (about 3%) metabolised, and detectable levels of fluoride are produced, although this does not appear to be sufficient to cause toxicity.

Enflurane has a moderate speed of induction but is little used nowadays. It was originally introduced as an alternative to methoxyflurane. It can cause seizures, either during induction or following recovery from anaesthesia, especially

[6]The problem of toxicity of low concentrations of anaesthetics inhaled over long periods by operating theatre staff has been a cause for concern. Strict measures are now used to minimise the escape of anaesthetics into the air of operating theatres.

in patients suffering from epilepsy. In this connection, it is interesting that a related substance, the fluorine-substituted diethyl-ether hexafluoroether, is a powerful convulsant agent, although the mechanism is not understood.

Halothane was an important drug in the development of volatile inhalation anaesthetics, but its use has declined in favour of isoflurane due to the potential for accumulation of toxic metabolites. Halothane has a marked relaxant effect on the uterus which can cause postpartum bleeding and limits its usefulness for obstetric purposes.

NITROUS OXIDE

Nitrous oxide (N_2O, not to be confused with nitric oxide, NO) is an odourless gas with many advantageous features for anaesthesia. It is rapid in onset of action because of its low blood:gas partition coefficient (Table 41.2), and is an effective analgesic in concentrations too low to cause unconsciousness. Its potency is low. It is used as a 50:50 mixture with O_2 to reduce pain during childbirth. It must never be given as 100% of the inspired gas as patients do need to breathe oxygen! Even at 80% in the inspired gas mixture, nitrous oxide does not produce surgical anaesthesia. It is not therefore used on its own as an anaesthetic, but is used (as 70% nitrous oxide in oxygen) as an adjunct to volatile anaesthetics to speed up induction – see description of the second gas effect (p. 504). During recovery from nitrous oxide anaesthesia, the transfer of the gas from the blood into the alveoli can be sufficient to reduce, by dilution, the alveolar partial pressure of oxygen, producing transient hypoxia (known as *diffusional hypoxia*). This is important for patients with respiratory disease.

Nitrous oxide tends to enter gaseous cavities in the body causing them to expand. This can be dangerous if a pneumothorax or vascular air embolus is present, or if the intestine is obstructed.

Given for brief periods, nitrous oxide is devoid of any serious toxic effects, but prolonged exposure (>6 h) causes inactivation of methionine synthase, an enzyme required for DNA and protein synthesis, resulting in bone marrow depression that may cause anaemia and leucopenia, so its use should be avoided in patients with anaemia related to vitamin B_{12} deficiency. Bone marrow depression does not occur with brief exposure to nitrous oxide, but prolonged or repeated use (for example, in intermittently painful conditions such as sickle cell anaemia) should be avoided. Nitrous oxide 'sniffers' are subject to this danger.

BALANCED ANAESTHESIA

Only in simple, short surgical procedures would a single anaesthetic be used on its own. In complex surgery, an array of drugs will be given at various times throughout the procedure. These may include a sedative or anxiolytic premedication (e.g. a benzodiazepine, see Ch. 44), an intravenous anaesthetic for rapid induction (e.g. **propofol**), a perioperative opioid analgesic (e.g. **alfentanil** or **remifentanil**, see Ch. 42), an inhalation anaesthetic to maintain anaesthesia during surgery (e.g. **nitrous oxide** and **isoflurane**), a neuromuscular blocking agent to produce adequate muscle relaxation (e.g. **vecuronium**, see Ch. 13) for access to the abdominal cavity for example, an antiemetic agent (e.g. **ondansetron**, see Ch. 30) and a muscarinic antagonist to prevent or treat bradycardia or to reduce bronchial and salivary secretions (e.g. **atropine** or **glycopyrrolate**, see Ch. 13) and, towards the end of the procedure, an anticholinesterase agent (e.g. **neostigmine**, see Ch. 13) to reverse the neuromuscular blockade and an analgesic for postoperative pain relief (e.g. an opioid such as **morphine** and/or a non-steroidal anti-inflammatory drug, see Ch. 42).

Individual inhalation anaesthetics

- The main agents in current use in developed countries are **isoflurane**, **desflurane** and **sevoflurane**, sometimes supplemented with **nitrous oxide**.
- As a rare but serious hazard, inhalation anaesthetics can cause malignant hyperthermia.
- **Nitrous oxide**:
  - low potency, therefore must be combined with other agents
  - rapid induction and recovery
  - good analgesic properties
  - risk of bone marrow depression with prolonged administration
  - accumulates in gaseous cavities.
- **Isoflurane**:
  - similar to **enflurane** but lacks epileptogenic property
  - may precipitate myocardial ischaemia in patients with coronary disease
  - irritant to respiratory tract.
- **Desflurane**:
  - similar to **isoflurane** but with faster onset and recovery
  - respiratory irritant, so liable to cause coughing and laryngospasm
  - useful for day-case surgery.
- **Sevoflurane**:
  - similar to **desflurane**, with lack of respiratory irritation.

Clinical uses of general anaesthetics

- *Intravenous anaesthetics* are used for:
  - induction of anaesthesia (e.g. **propofol** or **thiopental**)
  - maintenance of anaesthesia throughout surgery ('total intravenous anaesthesia', e.g. **propofol** sometimes in combination with muscle relaxants and analgesics).
- *Inhalational anaesthetics* (gases or volatile liquids) are used for maintenance of anaesthesia. Points to note are that:
  - volatile anaesthetics (e.g. **isoflurane**, **sevoflurane**) are delivered in air, oxygen or oxygen–nitrous oxide mixtures as the carrier gas
  - **nitrous oxide** must always be given with oxygen
  - because of its potential for inducing hepatotoxicity, **halothane** has largely been replaced by newer volatile anaesthetics such as **isoflurane**
  - all inhalational anaesthetics can trigger *malignant hyperthermia* in susceptible individuals.

Such combinations of drugs result in much faster induction and recovery, avoiding long (and potentially hazardous) periods of semiconsciousness, good analgesia and muscle relaxation and it enables surgery to be carried out with less undesirable cardiorespiratory depression.

Low doses of general anaesthetics may be used to provide sedation where a local anaesthetic (Ch. 43) administered intrathecally, is used to provide analgesia and relaxation needed to perform surgery to the lower parts of the body.

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42 Analgesic drugs

OVERVIEW

Pain is a disabling accompaniment of many medical conditions, and pain control is one of the most important therapeutic priorities.

In this chapter, we discuss the neural mechanisms responsible for different types of pain, and the various drugs that are used to reduce it. The 'classic' analgesic drugs, notably opioids and non-steroidal anti-inflammatory drugs (NSAIDs; described in Ch. 26), have their origins in natural products that have been used for centuries. The original compounds, typified by morphine and aspirin, are still in widespread use, but many synthetic compounds that act by the same mechanisms have been developed. Opioid analgesics are described in this chapter. Next, we consider various other drug classes, such as antidepressants and antiepileptic drugs, which clinical experience has shown to be effective in certain types of pain. Finally, looking into the future, many potential new drug targets have emerged as our knowledge of the neural mechanisms underlying pain has advanced. We describe briefly some of these new approaches at the end of the chapter.

NEURAL MECHANISMS OF PAIN

Pain is a subjective experience, hard to define exactly, even though we all know what we mean by it. Typically, it is a direct response to an untoward event associated with tissue damage, such as injury, inflammation or cancer, but severe pain can arise independently of any obvious predisposing cause (e.g. trigeminal neuralgia), or persist long after the precipitating injury has healed (e.g. phantom limb pain). It can also occur as a consequence of brain or nerve injury (e.g. following a stroke or herpes infection). Painful conditions of the latter kind, not directly linked to tissue injury, are often described as 'neuropathic pains'. They are very common and a major cause of disability and distress, and in general they respond less well to conventional analgesic drugs than do conditions where the immediate cause is clear. In these cases, we need to think of pain in terms of disordered neural function rather than simply as a 'normal' response to tissue injury.

The perception of noxious stimuli (termed *nociception* by Sherrington) is not the same thing as pain, which is a subjective experience and includes a strong emotional (affective) component. The amount of pain that a particular stimulus produces depends on many factors other than the stimulus itself. It is recognised clinically that many analgesics, particularly those of the morphine type, can greatly reduce the distress associated with pain. The affective component may be at least as significant as the antinociceptive component in the action of these drugs.

Good accounts of the neural basis of pain can be found in McMahon & Koltzenburg (2006).

NOCICEPTIVE AFFERENT NEURONS

Under normal conditions, pain is associated with impulse activity in small-diameter (C and Aδ) primary afferent fibres of peripheral nerves. These nerves have sensory endings in peripheral tissues and are activated by stimuli of various kinds (mechanical, thermal, chemical). The majority of umyelinated (C) fibres are associated with *polymodal nociceptive* endings and convey a dull, diffuse, burning pain, whereas myelinated (Aδ) fibres convey a sensation of sharp, well-localised pain. C and Aδ fibres convey nociceptive information from muscle and viscera as well as from the skin.

With many pathological conditions, tissue injury is the immediate cause of the pain and results in the local release of a variety of chemicals that act on the nerve terminals, either activating them directly or enhancing their sensitivity to other forms of stimulation (Fig. 42.1). The pharmacological properties of nociceptive nerve terminals are discussed in more detail below.

The cell bodies of spinal nociceptive afferent fibres lie in dorsal root ganglia; fibres enter the spinal cord via the dorsal roots, ending in the grey matter of the dorsal horn. Most of the nociceptive afferents terminate in the superficial region of the dorsal horn, the C fibres and some Aδ fibres innervating cell bodies in laminae I and II (also known as the *substantia gelatinosa*), while other A fibres penetrate deeper into the dorsal horn (lamina V). The substantia gelatinosa is rich in both endogenous opioid peptides and opioid receptors, and may be an important site of action for morphine-like drugs (see p. 513, Fig. 42.4).

Cells in laminae I and V give rise to the main projection pathways from the dorsal horn to the thalamus. For a more detailed account of dorsal horn circuitry, see Fields et al. (2006).

The nociceptive afferent neurons release glutamate and possibly ATP as the fast neurotransmitters at their central synapses in the dorsal horn. Glutamate acting on AMPA receptors is responsible for fast synaptic transmission at the first synapse in the dorsal horn. There is also a slower NMDA receptor-mediated response, which is important in relation to the phenomenon of 'wind-up' (see Fig. 42.2). The nociceptive afferent neurons also contain several neuropeptides (see Ch. 18), particularly substance P, calcitonin gene-related peptide (CGRP) and galanin. These are released as mediators at both the central and the peripheral terminals, and play an important role in the pathology of pain. In the periphery, substance P and CGRP produce some of the features of neurogenic inflammation whereas galanin is anti-inflammatory. CGRP antagonists have potential for the treatment of migraine (see Ch. 15) but have not proved effective for other pain states. In animal models, substance P acting on NK_1 receptors was shown to be involved in wind-up and central sensitisation in the dorsal horn (see Fig 42.2). Surprisingly, however, antagonists of substance P at NK_1 receptors turned out to be ineffective as analgesics in humans, although they do have antiemetic activity (Ch. 30).

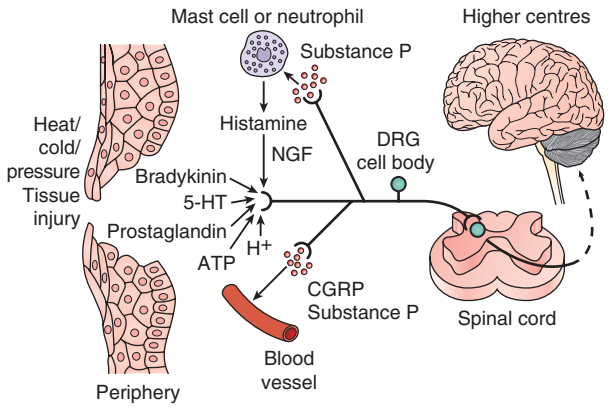

Fig. 42.1 Activation of nociceptive neurons. Various stimuli (physical and chemical) can initiate or enhance the rate of action potential firing in nociceptive primary afferent neurons (i.e. induce pain). These afferent fibres project to the dorsal horn of the spinal cord where they synapse on neurons projecting to higher centres. 5-HT, 5-hydroxytryptamine; ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; NGF, nerve growth factor. *(Adapted from Julius D, Basbaum A I 2001 Nature 413, 203–210.)*

MODULATION IN THE NOCICEPTIVE PATHWAY

Acute pain is generally well accounted for in terms of nociception – an excessive noxious stimulus giving rise to an intense and unpleasant sensation. In contrast, most chronic pain states[1] are associated with aberrations of the normal physiological pathway, giving rise to *hyperalgesia* (an increased amount of pain associated with a mild noxious stimulus), *allodynia* (pain evoked by a non-noxious stimulus) or spontaneous pain without any precipitating stimulus. Some of the main mechanisms are summarised in Figure 42.3.

HYPERALGESIA AND ALLODYNIA

▼ Anyone who has suffered a burn or sprained ankle has experienced hyperalgesia and allodynia. Hyperalgesia involves both sensitisation of peripheral nociceptive nerve terminals and central facilitation of transmission at the level of the dorsal horn and thalamus. The peripheral component is due to the action of mediators such as bradykinin and prostaglandins acting on the nerve terminals. The central component reflects facilitation of synaptic transmission in the dorsal horn of the spinal cord (see Yaksh, 1999). The synaptic responses of dorsal horn neurons to nociceptive inputs display the phenomenon of 'wind-up' – i.e. the synaptic potentials steadily increase in amplitude with each stimulus – when repeated stimuli are delivered at physiological frequencies. This activity-dependent facilitation of transmission has features in common with the phenomenon of long-term potentiation, described in Chapter 38, and the chemical mechanisms underlying it may also be similar. In the dorsal horn, the facilitation is blocked by NMDA-receptor antagonists and also in part by antagonists of substance P and by inhibitors of nitric oxide (NO) synthesis (see Figs 42.2 and 42.3).

[1]Defined as pain that outlasts the precipitating tissue injury. Many clinical pain states fall into this category. The dissociation of pain from noxious input is most evident in 'phantom limb' pain, which occurs after amputations and may be very severe. At the other extreme, noxious input with no pain, there are many well-documented reports of mystics and showmen who subject themselves to horrifying ordeals with knives, burning embers, nails and hooks (undoubtedly causing massive afferent input) without apparently suffering pain.

Substance P and CGRP released from primary afferent neurons (see Fig. 42.1) also act in the periphery, promoting inflammation by their effects on blood vessels and cells of the immune system (Ch. 18). This mechanism, known as neurogenic inflammation, amplifies and sustains the inflammatory reaction and the accompanying activation of nociceptive afferent fibres.

Central facilitation is an important component of pathological hyperalgesia (e.g. that associated with inflammatory responses). The mediators responsible for central facilitation include substance P, CGRP, brain-derived neurotrophic factor (BDNF) and NO as well as many others. For example, nerve growth factor (NGF), a cytokine-like mediator produced by peripheral tissues, particularly in inflammation, acts on a kinase-linked receptor (known as TrkA) on nociceptive afferent neurons, increasing their electrical excitability, chemosensitivity and peptide content, and also promoting the formation of synaptic contacts. Increased NGF production may be an important mechanism by which nociceptive transmission becomes facilitated by tissue damage, leading to hyperalgesia (see Mantyh et al., 2011). Increased gene expression in sensory neurons is induced by NGF and other inflammatory mediators; the upregulated genes include those for neuropeptides and neuromodulators (e.g. CGRP, substance P and BDNF) as well as for receptors (e.g. transient receptor potential TRPV1 and P2X) and sodium channels, and have the overall effect of facilitating transmission at the first synaptic relay in the dorsal horn. BDNF released from primary afferent nerve terminals activates the kinase-linked TrkB receptor on postsynaptic dorsal horn neurons leading to phosphorylation of the NMDA subunit GluN1 and thus sensitisation of these glutamate receptors, resulting in synaptic facilitation, in the dorsal horn.

Excitation of nociceptive sensory neurons depends, as in other neurons (see Ch. 4), on voltage-gated sodium channels. Individuals who express non-functional mutations of $Na_v1.7$ are unable to experience pain. The expression of certain sodium-channel subtypes (e.g. $Na_v1.3$, $Na_v1.7$ and Na_v 1.8 channels) is increased in sensory neurons in various pathological pain states and their enhanced activity underlies the sensitisation to external stimuli that occurs in inflammatory pain and hyperalgesia (see Ch. 4 for more detail on voltage-activated sodium channels). Consistent with this hypothesis is the fact that many antiepileptic and antidysrhythmic drugs, which act by blocking sodium channels (see Chs 21 and 45), also find clinical application as analgesics.

TRANSMISSION OF PAIN TO HIGHER CENTRES

From the dorsal horn, ascending nerve axons travel in the contralateral spinothalamic tracts, and synapse on neurons in the ventral and medial parts of the thalamus, from which there are further projections to the somatosensory cortex. In the medial thalamus in particular, many cells respond specifically to noxious stimuli in the periphery, and lesions in this area cause analgesia. Functional brain imaging studies in conscious subjects have been performed to localise regions involved in pain processing. These include sensory, discriminatory areas such as primary and secondary somatosensory cortex, thalamus and posterior parts of insula as well as affective, cognitive areas such as the anterior parts of insula, anterior cingulate cortex and prefrontal cortex (see Tracey, 2008).

DESCENDING INHIBITORY CONTROLS

Descending pathways (Fig. 42.4) control impulse transmission in the dorsal horn. A key part of this descending system is the *periaqueductal grey* (PAG) area of the midbrain, a small area of grey matter surrounding the central canal. In 1969, Reynolds found that electrical stimulation of this brain area in the rat caused analgesia sufficiently intense that abdominal surgery could be performed without anaesthesia and without eliciting any marked response. Non-painful sensations were unaffected. The

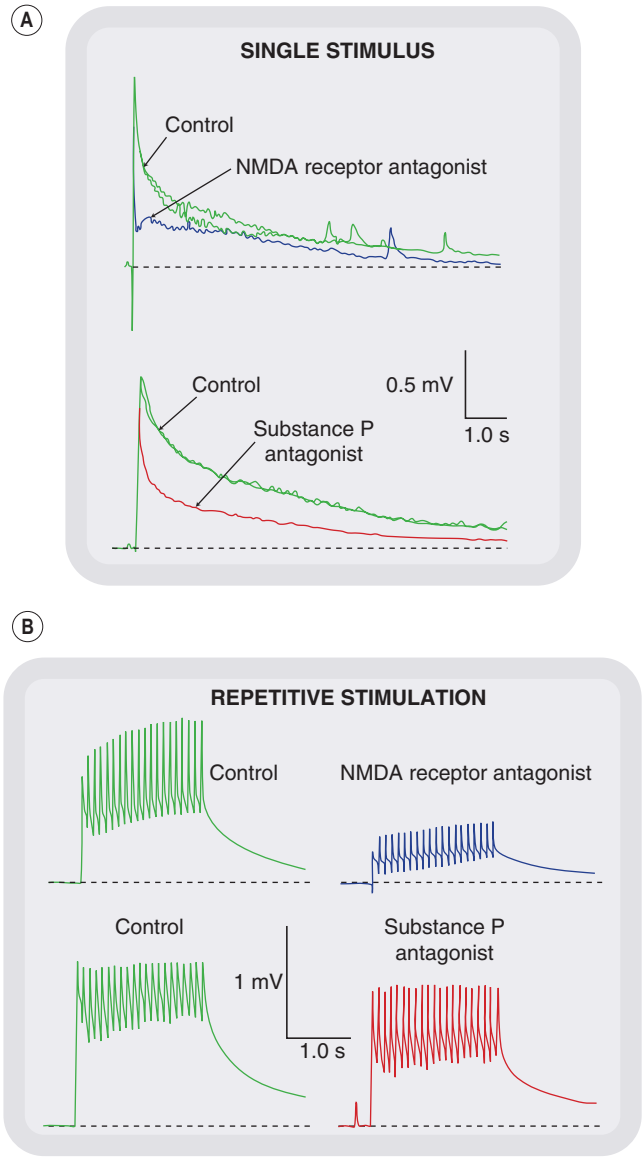

Fig. 42.2 Effect of glutamate and substance P antagonists on nociceptive transmission in the rat spinal cord. The rat paw was inflamed by ultraviolet irradiation 2 days before the experiment, a procedure that induces hyperalgesia and spinal cord facilitation. The synaptic response was recorded from the ventral root, in response to stimulation of C fibres in the dorsal root with [**A**] single stimuli or [**B**] repetitive stimuli. The effects of the NMDA receptor antagonist D-AP-5 (see Ch. 38) and the substance P antagonist RP 67580 (selective for neurokinin type 2, (NK_2) receptors) are shown. The slow component of the synaptic response is reduced by both antagonists [**A**], as in the 'wind-up' in response to repetitive stimulation [**B**]. These effects are much less pronounced in the normal animal. Thus both glutamate, acting on NMDA receptors, and substance P, acting on NK_2 receptors, are involved in nociceptive transmission, and their contribution increases as a result of inflammatory hyperalgesia. *(Records kindly provided by L Urban and SW Thompson.)*

PAG receives inputs from many other brain regions, including the hypothalamus, amygdala and cortex, and is the main pathway through which cortical and other inputs act to control the nociceptive 'gate' in the dorsal horn.

The PAG projects first to the rostroventral medulla (RVM) and thence via the dorsolateral funiculus of the spinal cord to the dorsal horn. Two important transmitters in this pathway are 5-hydroxytryptamine (5-HT; serotonin) and the enkephalins, which act directly or via interneurons to inhibit the discharge of spinothalamic neurons (Fig. 42.4).

The descending inhibitory pathway is probably an important site of action for opioid analgesics. Both PAG and substantia gelatinosa (SG) are particularly rich in enkephalin-containing neurons, and opioid antagonists such as naloxone (see p. 526) can prevent electrically induced analgesia, which would suggest that endogenous opioid peptides may function as transmitters in this system. The physiological role of opioid peptides in regulating pain transmission has been controversial, mainly because under normal conditions naloxone has relatively little effect on pain threshold. Under pathological conditions, however, when stress is present, naloxone causes hyperalgesia, implying that the opioid system is active.

GABA (see Ch. 38) is contained in interneurons in the dorsal horn. Activation of these interneurons releases GABA, which inhibits transmitter release from primary afferent terminals.

There is also a noradrenergic pathway from the *locus coeruleus* (LC; see Ch. 39), which has a similar inhibitory effect on transmission in the dorsal horn. Surprisingly, opioids inhibit rather than activate this pathway. The use of tricyclic antidepressants to control pain probably depends on potentiating this pathway.

It is thought that descending inhibitory purinergic pathways may release adenosine on to A_1 receptors on dorsal horn neurons to produce analgesia.

NEUROPATHIC PAIN

Neurological disease affecting the sensory pathway can produce severe chronic pain – termed *neuropathic pain*

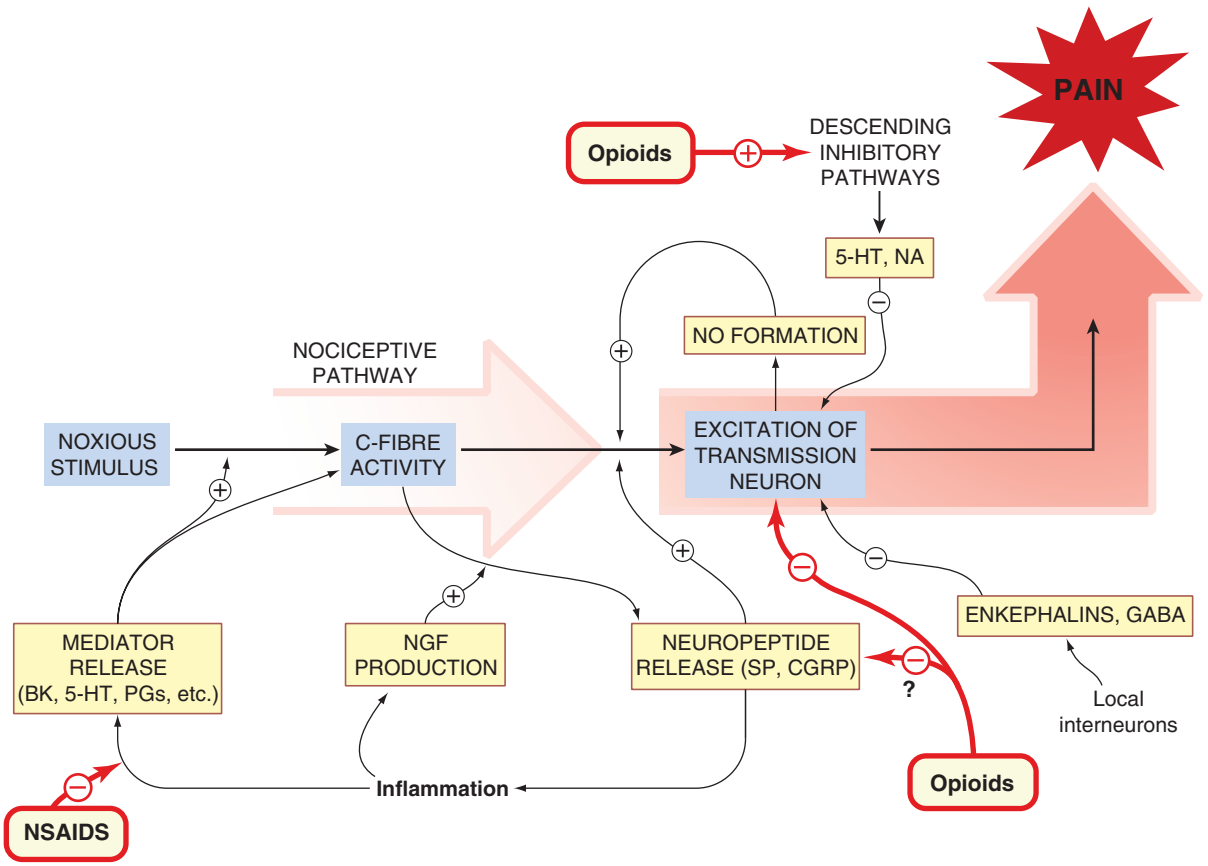

Fig. 42.3 Summary of modulatory mechanisms in the nociceptive pathway. 5-HT, 5-hydroxytryptamine; BK, bradykinin; CGRP, calcitonin gene-related peptide; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; SP, substance P.

Modulation of pain transmission

- Descending pathways from the midbrain and brain stem exert a strong inhibitory effect on dorsal horn transmission. Electrical stimulation of the midbrain periaqueductal grey area causes analgesia through this mechanism.
- The descending inhibition is mediated mainly by endogenous opioid peptides, 5-hydroxytryptamine (serotonin), noradrenaline and adenosine. Opioids cause analgesia partly by activating these descending pathways, partly by inhibiting transmission in the dorsal horn and partly by inhibiting excitation of sensory nerve terminals in the periphery.
- Repetitive C-fibre activity facilitates transmission through the dorsal horn ('wind-up') by mechanisms involving activation of NMDA and substance P receptors.

– unrelated to any peripheral tissue injury. This occurs with central nervous system (CNS) disorders such as stroke and multiple sclerosis, or with conditions associated with peripheral nerve damage, such as mechanical injury, diabetic neuropathy or herpes zoster infection (shingles). The pathophysiological mechanisms underlying this kind of pain are poorly understood, although spontaneous activity in damaged sensory neurons, due to overexpression or redistribution of voltage-gated sodium channels, is thought to be a factor. In addition, central sensitisation occurs. The sympathetic nervous system also plays a part, because damaged sensory neurons can express α adrenoceptors and develop a sensitivity to noradrenaline that they do not possess under normal conditions. Thus, physiological stimuli that evoke sympathetic responses can produce severe pain, a phenomenon described clinically as sympathetically mediated pain. Neuropathic pain, which appears to be a component of many types of clinical pain (including common conditions such as back pain and cancer pain, as well as amputation pain), responds poorly to conventional analgesic drugs but can be relieved by some antidepressant and antiepileptic agents (see p. 527). Potential new targets are discussed at the end of this chapter.

CHEMICAL SIGNALLING IN THE NOCICEPTIVE PATHWAY

CHEMOSENSITIVITY OF NOCICEPTIVE NERVE ENDINGS

In most cases, stimulation of nociceptive endings in the periphery is chemical in origin. Excessive mechanical or thermal stimuli can obviously cause acute pain, but the persistence of such pain after the stimulus has been removed, or the pain resulting from inflammatory or ischaemic changes in tissues, generally reflects an altered chemical environment of the pain afferents. The current state of knowledge is summarised in Figure 42.5.

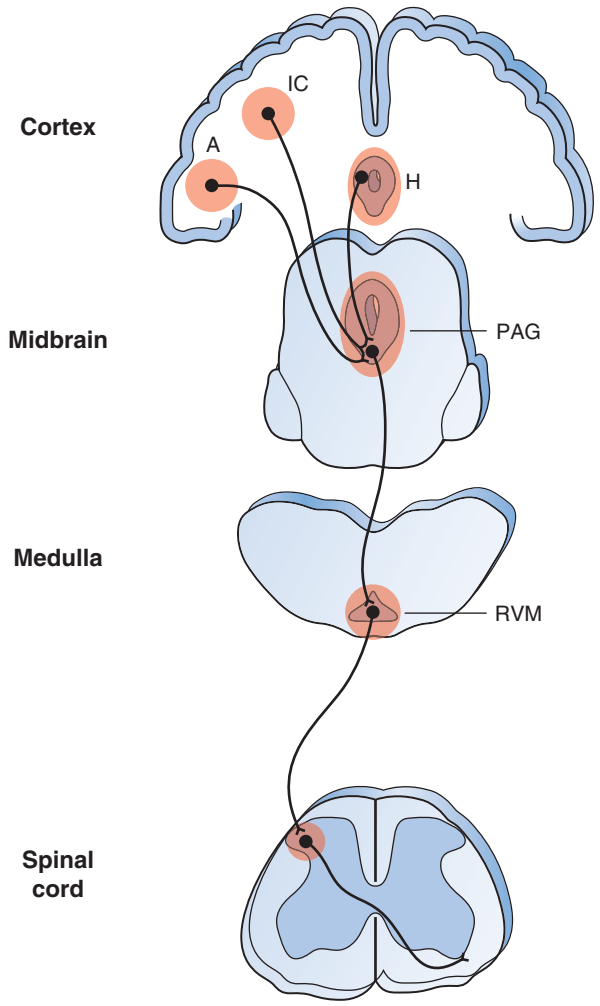

Fig. 42.4 The descending pain control system and sites of action of opioids to relieve pain. Opioids induce analgesia when microinjected into the insular cortex (IC), amygdala (A), hypothalamus (H), periaqueductal grey (PAG) region and rostroventral medulla (RVM) as well as into the dorsal horn of the spinal cord. The PAG receives input from higher centres and is the main output centre of the limbic system. It projects to the RVM. From the RVM, descending inhibitory fibres, some of which contain 5-hydroxytryptamine, project to the dorsal horn of the spinal cord. Pink shaded areas indicate regions expressing μ opioid receptors. The pathways shown in this diagram represent a considerable oversimplification. *(Adapted from Fields H 2001 Prog Brain Res 122, 245–253. For a fuller account of the descending pain modulating pathways, see Fields, 2004.)*

TRP channels – thermal sensation and pain

The *transient receptor potential* (TRP) channel family comprises some 27 or more structurally related ion channels that serve a wide variety of physiological functions (see Flockerzi & Nilius, 2007). Within this family are a group of channels present on sensory neurons that are activated both by thermal stimuli across a wide range of temperatures and by chemical agents (Table 42.1). With respect to pain, the most important channels are TRPV1, TRPM8 and TRPA1.

▼ **Capsaicin**, the substance in chilli peppers that gives them their pungency, selectively excites nociceptive nerve terminals, causing intense pain if injected into the skin or applied to sensitive structures such as the cornea.[2] It produces this effect by activating TRPV1.[3] Agonists such as capsaicin open the channel, which is permeable to Na^+, Ca^{2+} and other cations, causing depolarisation and initiation of action potentials. The large influx of Ca^{2+} into peripheral nerve terminals also results in peptide release (mainly substance P and CGRP), causing intense vascular and other physiological responses. The Ca^{2+} influx may be enough to cause nerve terminal degeneration, which takes days or weeks to recover. Attempts to use topically applied capsaicin to relieve painful skin conditions have had some success, but the initial strong irritant effect is a major disadvantage. Capsaicin applied to the bladder causes degeneration of primary afferent nerve terminals, and has been used to treat incontinence associated with bladder hyper-reactivity in stroke or spinal injury patients. C-fibre afferents in the bladder serve a local reflex function, which promotes emptying when the bladder is distended, the reflex being exaggerated when central control is lost.

TRPV1 responds not only to capsaicin-like agonists but also to other stimuli (see Table 42.1), including temperatures in excess of about 42°C (the threshold for pain) and proton concentrations in the micromolar range (pH 5.5 and below), which also cause pain. The receptor thus has unusual 'polymodal' characteristics and is believed to play a central role in nociception. TRPV1 is, like many other ionotropic receptors, modulated by phosphorylation, and several of the pain-producing substances that act through G protein-coupled receptors (e.g. bradykinin) work by sensitising TRPV1. A search for endogenous ligands for TRPV1 revealed, surprisingly, that **anandamide** (a lipid mediator previously identified as an agonist at cannabinoid receptors; see Ch. 19) is also a TRPV1 agonist, although less potent than capsaicin. TRPV1 knockout mice show reduced responsiveness to noxious heat and also fail to show thermal hyperalgesia in response to inflammation. The latter observation is interesting, because TRPV1 expression is known to be increased by inflammation and this may be a key mechanism by which hyperalgesia is produced. A number of pharmaceutical companies have been developing TRPV1 agonists – to act as desensitising agents – and antagonists as analgesic agents. However, TRPV1 agonists were found to induce hypothermia, associated with activation of hypothalamic thermosensitive neurons, and TRPV1 antagonists were found to induce hyperthermia, consistent with a role of TRPV1 in body temperature control as well as nociception.

TRPM8 and TRPA1 respond to cold rather than heat (Table 42.1). TRPM8 is important in cold hypersensitivity, which is often a feature of neuropathic pain. TRPA1 is activated in some experimental settings by noxious cold temperatures, calcium, pain-producing substances and inflammatory mediators; it can therefore also be considered to be a polymodal sensor. It may be important for the analgesic action of paracetamol (see p. 526).

Kinins

When applied to sensory nerve endings, *bradykinin* and *kallidin* (see Ch. 18) induce intense pain. These two closely related peptides are produced under conditions of tissue injury by the proteolytic cleavage of the active kinins from a precursor protein contained in the plasma. Bradykinin acts partly by release of prostaglandins, which strongly enhance the direct action of bradykinin on the nerve terminals (Fig. 42.6). Bradykinin acts on B_2 receptors (see Ch. 18) on nociceptive neurons. B_2 receptors are coupled to activation of a specific isoform of protein kinase C (PKCε), which phosphorylates TRPV1 and facilitates opening of the TRPV1 channel.

▼ Bradykinin is converted in tissues by removal of a terminal arginine residue to *des-Arg9 bradykinin*, which acts selectively on B_1 receptors. B_1 receptors are normally expressed at very low levels, but their expression is strongly upregulated in inflamed tissues.

[2]Anyone who has rubbed their eyes after cutting up chilli peppers will know this.

[3]The receptor was originally known as the vanilloid receptor because many capsaicin-like compounds are based on the structure of vanillic acid.

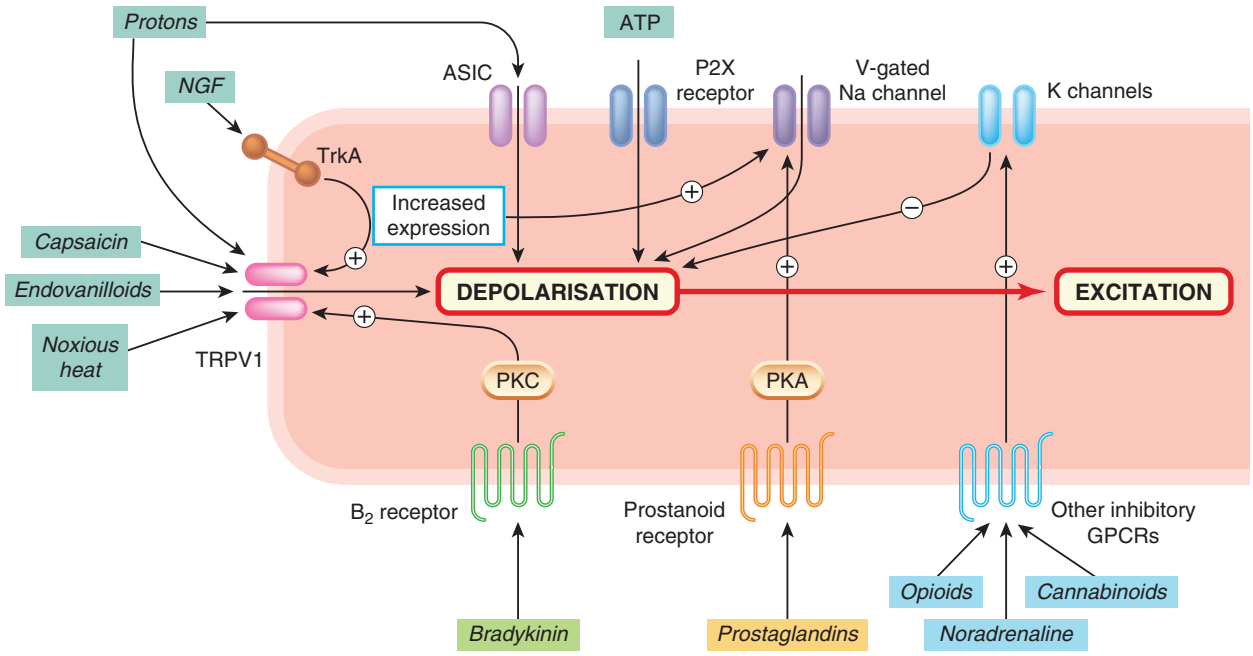

Fig. 42.5 Channels, receptors and transduction mechanisms of nociceptive afferent terminals. Only the main channels and receptors are shown. Ligand-gated channels include acid-sensitive ion channels (ASICs), ATP-sensitive channels (P2X receptors) and the capsaicin-sensitive channel (TRPV1), which is also sensitive to protons and to temperature. Various facilitatory and inhibitory G protein-coupled receptors (GPCRs) are shown, which regulate channel function through various second messenger systems. Growth factors such as nerve growth factor (NGF) act via kinase-linked receptors (TrkA) to control ion channel function and gene expression. B_2 receptor, bradykinin type 2 receptor; PKA, protein kinase A; PKC, protein kinase C.

Table 42.1 Thermosensitive TRP channels expressed on sensory neurons

Channel type	TRPA1	TRPM8	TRPV4	TRPV3	TRPV1	TRPV2
Activation temperature (°C)	<17	8–28	>27	>33	>42	>52
Chemical activators	Icilin Wintergreen oil Mustard oil	Menthol Icilin Eucalyptol Geraniol	4αPDD	Camphor Menthol Eugenol	Capsaicin Protons Anandamide Camphor Resiniferatoxin Eugenol	Δ^9-THC

4αPDD, 4 alpha-phorbol 12,13-didecanoate; Δ^9-THC, Δ^9-tetrahydrocannabinol.

Transgenic knockout animals lacking either type of receptor show reduced inflammatory hyperalgesia. Specific competitive antagonists for both B_1 and B_2 receptors are known, including peptides such as the B_2 antagonist **icatibant** (Ch. 18), as well as non-peptides. These show analgesic and anti-inflammatory properties, but are not yet developed for clinical use.

Prostaglandins

Prostaglandins do not themselves cause pain, but they strongly enhance the pain-producing effect of other agents such as 5-hydroxytryptamine or bradykinin (Fig. 42.6). Prostaglandins of the E and F series are released in inflammation (Ch. 17) and also during tissue ischaemia. Antagonists at EP_1 receptors decrease inflammatory hyperalgesia in animal models. Prostaglandins sensitise nerve terminals to other agents, partly by inhibiting potassium channels and partly by facilitating – through second messenger-mediated phosphorylation reactions (see Ch. 3) – the cation channels opened by noxious agents. It is of interest that bradykinin itself causes prostaglandin release, and thus has a powerful 'self-sensitising' effect on nociceptive afferents. Other eicosanoids, including prostacyclin, leukotrienes and the unstable hydroxyeicosatetraenoic acid (HETE) derivatives (Ch. 17), may also be important. The analgesic effects of NSAIDs (Ch. 26) result from inhibition of prostaglandin synthesis.

Other peripheral mediators

Various metabolites and substances are released from damaged or ischaemic cells, or inflamed tissues, including ATP, protons (produced by lactic acid), 5-HT, histamine and K^+, many of which affect nociceptive nerve terminals.

ATP excites nociceptive nerve terminals by acting on homomeric $P2X_3$ receptors or heteromeric $P2X_2/P2X_3$ receptors (see Ch. 16), ligand-gated ion channels that are selectively expressed by these neurons. Downregulation

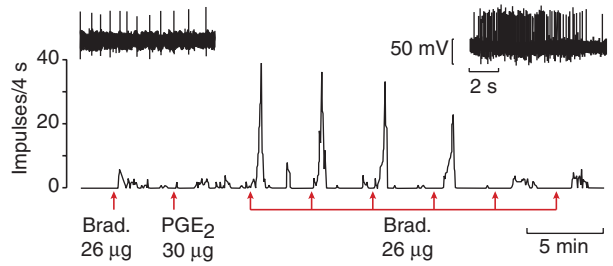

Fig. 42.6 Response of a nociceptive afferent neuron to bradykinin (Brad.) and prostaglandin. Recordings were made from a nociceptive afferent fibre supplying a muscle, and drugs were injected into the arterial supply. Upper records: single-fibre recordings showing discharge caused by bradykinin alone (left), and by bradykinin following injection of prostaglandin (right). Lower trace: ratemeter recording of single-fibre discharge, showing long-lasting enhancement of response to bradykinin after an injection of prostaglandin E_2 (PGE_2). Prostaglandin itself did not evoke a discharge. *(From Mense S 1981 Brain Res 225, 95.)*

of $P2X_3$ receptors, by antisense DNA, reduces inflammatory pain.[4] Antagonists at this receptor are analgesic in animal models and may be developed for clinical use. They may also be effective in treating cough. Other P2X receptors ($P2X_4$ and $P2X_7$) are expressed on microglia in the spinal cord; activation results in the release of cytokines and chemokines that then act on neighbouring neurons to promote hypersensitivity. ATP and other purine mediators, such as adenosine, also play a role in the dorsal horn, and other types of purinoceptor may also be targeted by analgesic drugs in the future. In the periphery adenosine exerts dual effects – acting on A_1 receptors it causes analgesia but on A_2 receptors it does the opposite.

Low pH excites nociceptive afferent neurons partly by opening proton-activated cation channels (acid-sensitive ion channels) and partly by facilitation of TRPV1 (see p. 513).

5-Hydroxytryptamine causes excitation, but studies with antagonists suggest that it plays at most a minor role. Histamine is also active but causes itching rather than pain. Both these substances are released locally in inflammation (see Chs 15 and 17).

In summary, pain endings can be activated or sensitised by a wide variety of endogenous mediators, the receptors for which are often up- or downregulated under pathophysiological conditions.

Mechanisms of pain and nociception

- Nociception is the mechanism whereby noxious peripheral stimuli are transmitted to the central nervous system. Pain is a subjective experience not always associated with nociception.
- Polymodal nociceptors (PMNs) are the main type of peripheral sensory neuron that responds to noxious stimuli. The majority are non-myelinated C fibres whose endings respond to thermal, mechanical and chemical stimuli.
- Chemical stimuli acting on PMNs to cause pain include bradykinin, protons, ATP and vanilloids (e.g. **capsaicin**). PMNs are sensitised by prostaglandins, which explains the analgesic effect of **aspirin**-like drugs, particularly in the presence of inflammation.
- The TRPV1 receptor responds to noxious heat as well as to **capsaicin**-like agonists. The lipid mediator **anandamide** is an agonist at TRPV1 receptors, as well as being an endogenous cannabinoid-receptor agonist.
- Nociceptive fibres terminate in the superficial layers of the dorsal horn, forming synaptic connections with transmission neurons running to the thalamus.
- PMN neurons release glutamate (fast transmitter) and various peptides that act as slow transmitters. Peptides are also released peripherally and contribute to neurogenic inflammation.
- Neuropathic pain, associated with damage to neurons of the nociceptive pathway rather than an excessive peripheral stimulus, is frequently a component of chronic pain states and may respond poorly to opioid analgesics.

ANALGESIC DRUGS

OPIOID DRUGS

Opium is an extract of the juice of the poppy *Papaver somniferum* that contains **morphine** and other related alkaloids. It has been used for social and medicinal purposes for thousands of years as an agent to produce euphoria, analgesia and sleep, and to prevent diarrhoea. It was introduced in Britain at the end of the 17th century, usually taken orally as 'tincture of laudanum', addiction to which acquired a certain social cachet during the next 200 years. The situation changed when the hypodermic syringe and needle were invented in the mid-19th century, and opioid dependence began to take on a more sinister significance (see Ch. 49).

The history of opioid research is reviewed by Corbett et al. (2006).

CHEMICAL ASPECTS

The structure of morphine (Fig. 42.7) was determined in 1902, and since then many semisynthetic compounds (produced by chemical modification of morphine) and fully synthetic opioids have been studied. Important members of each chemical class are shown in Figure 42.7, with chemical structures drawn in a style that highlights their similarity to morphine.

Morphine is a phenanthrene derivative with two planar rings and two aliphatic ring structures, which occupy a plane roughly at right-angles to the rest of the molecule (Fig. 42.7). The most important parts of the molecule for opioid activity are the free hydroxyl on the benzene ring that is linked by two carbon atoms to a nitrogen atom. Variants of the morphine molecule have been produced by substitution at one or both of the hydroxyls (e.g. **diamorphine**[5]

[4] $P2X_3$ knockout mice are, in contrast, fairly normal in this respect, presumably because other mechanisms take over.

[5] While 'diamorphine' is the recommended International Nonproprietary Name (rINN), this drug is widely known as heroin.

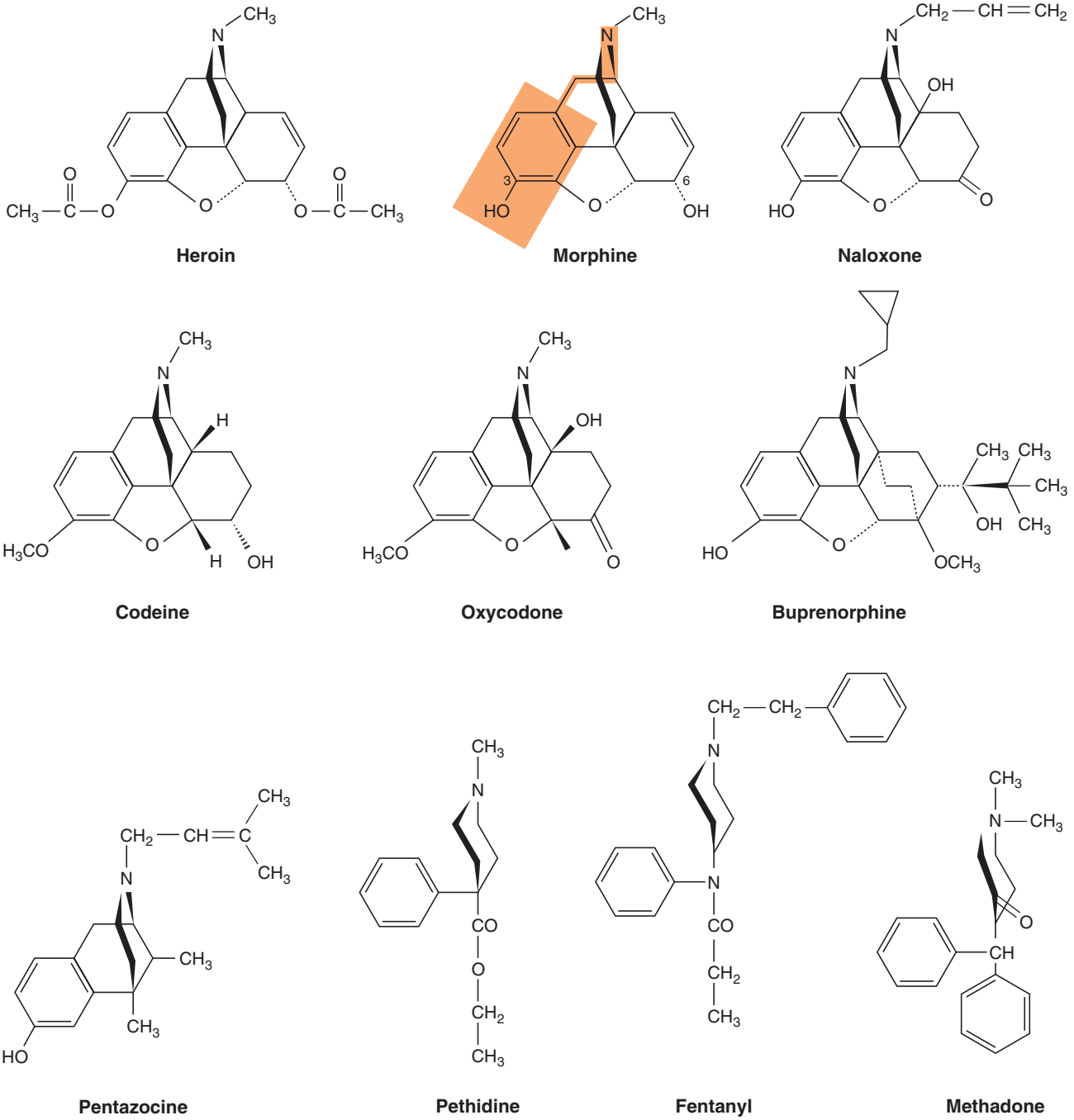

Fig. 42.7 Structures of some opioid analgesics. The red shaded area indicates the part of the morphine molecule that is structurally similar to tyrosine, the N-terminal amino acid in the endorphins. Carbon atoms 3 and 6 in the morphine structure are indicated. Diamorphine (heroin) is 3,6-diacetylmorphine and morphine is metabolised by addition of a glucuronide moiety at either position 3 or position 6.

3,6-diacetylmorphine, **codeine** 3-methoxymorphine and **oxycodone**). **Pethidine** and **fentanyl** represent more dramatic changes to the basic morphine structure. Pethidine was originally investigated as a new antimuscarinic agent but was found to have opioid analgesic activity. Although the structure of **methadone** bears no obvious chemical relationship to that of morphine, it is thought to assume a similar conformation in solution. Substitution of a bulky substituent on the nitrogen atom of morphine introduces antagonist activity to the molecule (e.g. **naloxone**).

OPIOID RECEPTORS

The proposal that opioids produce analgesia and their other effects by interacting with specific receptors first arose in the 1950s, based on the strict structural and stereochemical requirements essential for activity. It was, however, only with the development of molecules with antagonist activity (e.g. naloxone) that the notion of a specific receptor became accepted. Martin and co-workers then provided pharmacological evidence for multiple types of opioid receptors. They proposed three

Opioid analgesics

- Terminology:
  - *opioid*: any substance, whether endogenous or synthetic, that produces **morphine**-like effects that are blocked by antagonists such as **naloxone**
  - *opiate*: compounds such as **morphine** and **codeine** that are found in the opium poppy
  - *narcotic analgesic*: old term for opioids; *narcotic* refers to their ability to induce sleep. Unfortunately, the term narcotic has subsequently been hijacked and used inappropriately by some to refer generically to drugs of abuse (see Ch. 49).
- Important morphine-like agonists include **diamorphine**, **oxycodone** and **codeine**.
- The main groups of synthetic analogues are the piperidines (e.g. **pethidine** and **fentanyl**), the **methadone**-like drugs, the benzomorphans (e.g. **pentazocine**) and the thebaine derivatives (e.g. **buprenorphine**).
- Opioid analgesics may be given orally, by injection or intrathecally to produce analgesia.

different types of receptor, called μ, κ and σ.[6] Subsequently, in the early 1970s, radioligand binding (see Ch. 2) was used to demonstrate the presence of μ receptors in the brain.

Why are there specific receptors in the brain for morphine, a drug that is present in the opium poppy? Hughes and Kosterlitz argued that there must be an endogenous substance or substances in the brain that activated these receptors.[7] In 1975 they reported the isolation and characterisation of the first endogenous ligands, the *enkephalins*. We now know that the enkephalins are only two members of a larger family of endogenous opioid peptides known collectively as the *endorphins*, all of which possess a tyrosine residue at their N-terminus. The chemical structure of tyrosine includes an amine group separated from a phenol ring by two carbon atoms. This same structure (phenol-2 carbon atom chain-amine) is also contained within the morphine structure (Fig. 42.7). It is probably just chance (good or bad luck depending on one's viewpoint) that the opium poppy synthesises a semi-rigid alkaloid molecule, morphine, part of which structurally resembles the tyrosine residue in the endogenous opioid peptides.

Following on from the discovery of the enkephalins, pharmacological and ligand-binding studies revealed another receptor, δ, and the three recognised receptor types (μ, δ and κ) were cloned. Later, another opioid receptor (ORL_1) that had a high a degree of amino acid sequence homology (>60%) towards the μ, δ and κ opioid receptors was identified by cloning techniques, although the antagonist, naloxone, did not bind to this new receptor. The terminology used for opioid receptors has in recent years been through several revisions; in this chapter we shall use the classical terminology. The four opioid receptors, μ, δ, κ and ORL_1 are all G protein-coupled receptors (see Ch. 3).[8] The main behavioural effects resulting from their activation are summarised in Table 42.2. The interaction of various endogenous opioid peptides with the various receptor types is summarised in Table 42.3. Some agents that are used as experimental tools for distinguishing the different receptor types are also shown.

Table 42.2 Functional effects associated with the main types of opioid receptor

Receptor (classical terminology)	μ	δ	κ	ORL_1
Receptor (recommended new terminology)	**MOPr**	**DOPr**	**KOPr**	**NOPr**
Analgesia				
Supraspinal	+++	–?	–	Anti-opioid[a]
Spinal	++	++	+	++
Peripheral	++	–	++	–
Respiratory depression	+++	++	–	–
Pupil constriction	++	–	+	–
Reduced gastrointestinal motility	++	++	+	–
Euphoria	+++	–	–	–
Dysphoria and hallucinations	–	–	+++	–
Sedation	++	–	++	–
Catatonia	–	–	–	++
Physical dependence	+++	–	–	–

[a]ORL_1 agonists were originally thought to produce nociception or hyperalgesia but it was later shown that they reverse the supraspinal analgesic effects of endogenous and exogenous μ-opioid-receptor agonists.

[6]The σ 'receptor' is no longer considered to be an opioid receptor. It was postulated in order to account for the dysphoric effects (anxiety, hallucinations, bad dreams, etc.) produced by some opioids. It is now accepted that these effects result from drug-induced block of the NMDA receptor channel pore, an effect that is also produced by agents such as ketamine (see Ch. 41). Subsequently, the term σ receptor has also been used to describe other, non-NMDA receptor sites and a subdivision into σ_1 and σ_2 subtypes proposed. These proteins may be novel drug targets for psychiatric disorders.

[7]It may seem obvious today that if there is a receptor then there is likely also to be an endogenous ligand for that receptor but it was the search for, and subsequent discovery of, the enkephalins that gave credence to this idea. There are, however, exceptions to this rule. For example, although several endogenous ligands for the benzodiazepine 'receptor' or binding site on the $GABA_A$ receptor have been suggested, none so far has achieved universal acceptance (see Ch. 44).

[8]The opioid receptors are unusual among G protein-coupled receptors. First, in that there are many (20 or more) opioid peptides but only four receptors. In contrast, 5-hydroxytryptamine (5-HT), for example, is a single mediator interacting with many (about 14) receptors, which is the more common pattern. Second, all four receptors couple to the same types of G protein (G_i/G_o) and therefore activate the same spectrum of cellular effector mechanisms. In contrast, other receptor families (e.g. muscarinic receptors) couple to different types of G proteins and therefore give rise to different cellular responses (see Ch. 13).

Table 42.3 Endogenous opioid peptides and receptor-selective drugs

	μ	δ	κ	ORL_1
Endogenous peptides				
β-Endorphin	+++	+++	+	–
Leu-enkephalin	(++)	+++	+	–
Met-enkephalin	++	+++	+	–
Dynorphin	+	+	+++	–
Orphanin FQ/nociceptin[a]	–	–	–	+++
Research tools				
AGONISTS				
DAMGO[b]	+++	–	–	–
DPDPE[b]	–	++	–	–
Enadoline	–	–	+++	–
Ro64-6198	–	–	–	+++
ANTAGONISTS				
CTOP[b]	+++	–	–	–
Naltrindole	–	+++	+	–
Nor-binaltorphimine	+	+	+++	–
SB 612111	–	–	–	+++

Note: + symbols represent agonists activity; partial agonists in parentheses; – symbols represent weak or no activity.
[a]The endogenous ligand for the ORL_1 receptor is referred to in the literature both as orphanin FQ and as nociceptin.
[b]DAMGO, DPDPE and CTOP are synthetic peptides.

Opioid receptors

- μ Receptors are responsible for most of the analgesic effects of opioids, and for some major unwanted effects (e.g. respiratory depression, constipation, euphoria, sedation and dependence).
- δ Receptor activation results in analgesia but also can be proconvulsant.
- κ Receptors contribute to analgesia at the spinal level and may elicit sedation, dysphoria and hallucinations. Some analgesics are mixed κ agonists/μ antagonists.
- ORL_1 receptors are also members of the opioid receptor family. Activation results in an antiopioid effect (supraspinal), analgesia (spinal), immobility and impairment of learning.
- σ Receptors are not true opioid receptors but are the site of action of certain psychotomimetic drugs, with which some opioids also interact.
- All opioid receptors are linked through G_i/G_o proteins and thus open potassium channels (causing hyperpolarisation) and inhibit the opening of calcium channels (inhibiting transmitter release). In addition they inhibit adenylyl cyclase and activate the MAP kinase (ERK) pathway.
- Functional heteromers, formed by combination of different types of opioid receptor or with other types of G protein-coupled receptor, may occur and give rise to further pharmacological diversity.

The development of transgenic mouse strains lacking each of the three main opioid receptor types has revealed that the major pharmacological effects of morphine, including analgesia, are mediated by the μ receptor.

All four opioid receptors appear to form homomeric as well as heteromeric receptor complexes. Opioid receptors are, in fact, quite promiscuous and can form heteromers with non-opioid receptors. Heteromerisation between opioid receptors has been shown to result in pharmacological characteristics distinct from those observed with the monomeric receptors and may explain some of the subtypes of each receptor that have been proposed. Another level of complexity may reflect 'bias' (see Ch. 3), whereby different ligands acting on the same opioid receptor can elicit different cellular responses and differential receptor trafficking (see Kelly, 2013).

AGONISTS AND ANTAGONISTS

Opioids vary not only in their receptor specificity but also in their efficacy at the different types of receptor. Thus, some agents act as agonists or partial agonists on one type of receptor, and antagonists or partial agonists at another, producing a very complicated pharmacological picture.

Morphine is in fact a partial agonist at the μ opioid receptor. This may surprise some clinicians because it is a powerful analgesic that can, at high doses, induce death due to severe respiratory depression. However, when considering receptor activation, it has lower intrinsic efficacy than full agonists (see Ch. 2). Other opioid drugs, notably **codeine** and **dextropropoxyphene**, are sometimes referred to as weak agonists because their maximal effects, both analgesic and unwanted, are less than those of morphine. **Buprenorphine** is a partial agonist that dissociates slowly from opioid receptors. It induces less respiratory depression than other opioids. It is a very potent drug that can also antagonise the effect of other opioids by virtue of its high affinity and low efficacy. **Pentazocine** combines a degree of κ agonist and μ antagonist (or weak partial agonist) activity. Drugs with κ agonist tend to cause dysphoria rather than euphoria. Antagonists such as **naloxone** and **naltrexone** produce very little effect when given on their own to healthy subjects, while worsening chronic pain and blocking the effects of opioids.

MECHANISM OF ACTION OF OPIOIDS

The opioids have probably been studied more intensively than any other group of drugs in the effort to understand their powerful effects in molecular, cellular and physiological terms, and to use this understanding to develop new drugs as analgesics with significant advantages over morphine. Even so, morphine – described by Osler as 'God's own medicine' – remains the standard against which any new analgesic is assessed.

Cellular actions

All four types of opioid receptor belong to the family of G_i/G_o protein-coupled receptors. Opioids thus exert

powerful effects on ion channels on neuronal membranes through a direct G protein coupling to the channel. Opioids promote the opening of potassium channels (see Ch. 4) and inhibit the opening of voltage-gated calcium channels. These membrane effects decrease neuronal excitability (because the increased K^+ conductance causes hyperpolarisation of the membrane making the cell less likely to fire action potentials) and reduce transmitter release (due to inhibition of Ca^{2+} entry). The overall effect is therefore inhibitory at the cellular level. Nonetheless, opioids do increase activity in some neuronal pathways (see p. 513, Fig. 42.4). They do this by a process of *disinhibition* whereby they cause excitation of projection neurons by suppressing the activity of inhibitory interneurons that tonically inhibit the projection neurons (see Ch. 37, Fig. 37.2).

At the biochemical level, all four receptor types inhibit adenylyl cyclase and cause MAP kinase (ERK) activation (see Ch. 3). These cellular responses are likely to be important in mediating the long-term adaptive changes that occur in response to prolonged receptor activation and which, for μ-receptor agonists, may underlie the phenomenon of physical dependence (see Ch. 49).

At the cellular level, therefore, all four types of opioid receptor mediate very similar effects. It is their heterogeneous anatomical distributions across the CNS that give rise to the different behavioural responses seen with selective agonists for each type of receptor.

Sites of action of opioids to produce analgesia

Opioid receptors are widely distributed in the brain and spinal cord. Opioids are effective as analgesics when injected in minute doses into a number of specific brain nuclei (such as the insular cortex, amygdala, hypothalamus, PAG region and RVM) as well as into the dorsal horn of the spinal cord (see Fig. 42.4). There is evidence to suggest that supraspinal opioid analgesia involves endogenous opioid peptide release both at supraspinal and spinal sites and that at the spinal level there is also a component of the analgesia that results from the release of serotonin (5-HT) from descending inhibitory fibres. Surgical interruption of the descending pathway from the RVM to the spinal cord reduces analgesia induced by morphine that has been given systemically or microinjected into supraspinal sites, implying that a combination of effects at supraspinal and spinal sites contribute to the analgesic response.

At the spinal level, morphine inhibits transmission of nociceptive impulses through the dorsal horn and suppresses nociceptive spinal reflexes, even in patients with spinal cord transection. It can act presynaptically to inhibit release of various neurotransmitters from primary afferent terminals in the dorsal horn as well as acting postsynaptically to reduce the excitability of dorsal horn neurons.

There is also evidence (see Sawynok, 2003) that opioids inhibit the discharge of nociceptive afferent terminals in the periphery, particularly under conditions of inflammation, in which the expression of opioid receptors by sensory neurons is increased. Injection of morphine into the knee joint following surgery to the joint provides effective analgesia, undermining the age-old belief that opioid analgesia is exclusively a central phenomenon.

PHARMACOLOGICAL ACTIONS

Morphine is typical of many opioid analgesics and will be taken as the reference compound.

The most important effects of morphine are on the CNS and the gastrointestinal tract, although numerous effects of lesser significance on many other systems have been described.

Effects on the central nervous system

Analgesia

Morphine is effective in most kinds of acute and chronic pain, although opioids in general are less effective in neuropathic pain than in pain associated with tissue injury, inflammation or tumour growth.

As well as being antinociceptive, morphine also reduces the affective component of pain. This reflects its supraspinal action, possibly at the level of the limbic system, which is probably involved in the euphoria-producing effect. Drugs such as pentazocine share the antinociceptive actions of morphine but have much less effect on the psychological response to pain.

Hyperalgesia

In both animal studies and in patients receiving opioids for pain relief, prolonged exposure to opioids may paradoxically induce a state of hyperalgesia in which pain sensitisation or allodynia occurs (see Lee et al., 2011). This can appear as a reduced analgesic response to a given dose of opioid but should not be confused with tolerance, which is a reduced responsiveness due in large part to μ-receptor desensitisation (see p. 521) and occurs with other opioid-induced behaviours in addition to analgesia. Hyperalgesia appears to have peripheral, spinal and supraspinal components. At the neuronal level, the mechanisms underlying this phenomenon are still unclear but appear to involve PKC and NMDA receptor activation. In addition, $P2X_4$ receptor expression in microglia is upregulated resulting in BDNF release, TrkB signalling and downregulation of the K^+/Cl^- co-transporter KCC2. In mice in which BDNF has been deleted from microglia hyperalgesia to morphine does not occur, whereas antinociception and tolerance are unaffected. Opioid-induced hyperalgesia can be reduced by ketamine, an NMDA antagonist, propofol, α_2-adrenoceptor agonists and COX-2 inhibitors. Switching to another opioid can also reduce hyperalgesia; in this regard, methadone may be a good choice as it is a weak NMDA receptor antagonist.

Euphoria

Morphine causes a powerful sense of contentment and well-being (see also Ch. 49). This is an important component of its analgesic effect, because the agitation and anxiety associated with a painful illness or injury are thereby reduced. If morphine or diamorphine (heroin) is given intravenously, the result is a sudden 'rush' likened to an 'abdominal orgasm'. The euphoria produced by morphine depends considerably on the circumstances. In patients who are distressed, it is pronounced, but in patients who become accustomed to chronic pain, morphine causes analgesia with little or no euphoria. Some patients report restlessness rather than euphoria under these circumstances.

Euphoria is mediated through μ receptors, whereas κ-receptor activation produces dysphoria and hallucinations (see Table 42.2). Thus, different opioid drugs vary greatly in the amount of euphoria that they produce. It does not occur with codeine or with pentazocine to any marked extent. There is evidence that antagonists at the κ receptor have antidepressant properties which may

indicate that release of endogenous κ agonists may occur in depression.

Respiratory depression

Respiratory depression, resulting in increased arterial P_{CO_2}, occurs with a normal analgesic dose of morphine or related compounds, although in patients in severe pain the degree of respiratory depression produced may be less than anticipated. Respiratory depression is mediated by μ receptors. The depressant effect is associated with a decrease in the sensitivity of the respiratory centres to arterial P_{CO_2} and an inhibition of respiratory rhythm generation. Changes in P_{CO_2} are detected by chemosensitive neurons in a number of brain stem and medullary nuclei. Increased arterial CO_2 (hypercapnia) thus normally results in a compensatory increase in minute ventilation rate (V_E). In some of the chemosensitive regions, opioids exert a depressant effect on the hypercapnic response, making the increase in V_E insufficient to counteract the increased CO_2. Respiratory movements originate from activity of a rhythm generator (the *pre-Bötzinger complex*) within the ventral respiratory column of the medulla. μ Opioid receptors are located in this region, and local injection of opioid agonists decreases respiratory frequency.

Respiratory depression by opioids is not accompanied by depression of the medullary centres controlling cardiovascular function (in contrast to the action of general anaesthetics and other CNS depressants). This means that respiratory depression produced by opioids is much better tolerated than a similar degree of depression caused by, say, a barbiturate. Nonetheless, respiratory depression is a dangerous unwanted effect of these drugs and, unlike that due to general CNS depressant drugs, it occurs at therapeutic doses. It is the commonest cause of death in acute opioid poisoning.

Depression of cough reflex

Cough suppression (antitussive effect; see also Ch. 28), surprisingly, does not correlate closely with the analgesic and respiratory depressant actions of opioids, and its mechanism at the receptor level is unclear. In general, increasing substitution on the phenolic hydroxyl group of morphine increases antitussive relative to analgesic activity. **Codeine** and **pholcodine** suppress cough in subanalgesic doses but they cause constipation as an unwanted effect.

▼ **Dextromethorphan**, the dextro-isomer of the opioid analgesic **levorphanol**, has no affinity for opioid receptors and its cough suppression is not antagonised by naloxone. It is an uncompetitive NMDA receptor antagonist – this might explain why at high doses it evokes CNS effects similar to ketamine – and has putative actions at σ receptors. It is believed to work at various sites in the brain stem and medulla to suppress cough. In addition to its antitussive action, dextromethorphan is neuroprotective (see Ch. 40) and has an analgesic action in neuropathic pain (see p. 527-528).

Nausea and vomiting

Nausea and vomiting occur in up to 40% of patients to whom morphine is given, and do not seem to be separable from the analgesic effect among a range of opioid analgesics. The site of action is the *area postrema* (chemoreceptor trigger zone), a region of the medulla where chemical stimuli of many kinds may initiate vomiting (see Ch. 30).[9]

Nausea and vomiting following morphine injection are usually transient and disappear with repeated administration, although in some individuals they persist and can limit patient compliance.

Pupillary constriction

Pupillary constriction is caused by μ and κ receptor-mediated stimulation of the oculomotor nucleus. Pinpoint pupils are an important diagnostic feature in opioid poisoning,[10] because most other causes of coma and respiratory depression produce pupillary dilatation. Tolerance does not develop to the pupillary constriction induced by opioids and therefore can be observed in opioid-dependent drug users who may have been taking opioids for a considerable time.

Effects on the gastrointestinal tract

Opioids increase tone and reduce motility in many parts of the gastrointestinal system, resulting in constipation, which may be severe and very troublesome to the patient.[11] The resulting delay in gastric emptying can considerably retard the absorption of other drugs. Pressure in the biliary tract increases because of contraction of the gall bladder and constriction of the biliary sphincter. Opioids should be avoided in patients suffering from biliary colic due to gallstones, in whom pain may be increased rather than relieved. The rise in intrabiliary pressure can cause a transient increase in the concentration of amylase and lipase in the plasma.

The action of morphine on visceral smooth muscle is probably mediated mainly through the intramural nerve plexuses, because the increase in tone is reduced or abolished by atropine. It is also partly mediated by a central action, because intracerebroventricular injection of morphine inhibits propulsive gastrointestinal movements. **Methylnaltrexone bromide** (see also Ch. 8) and **alvimopan** are opioid antagonists that do not cross the blood–brain barrier. They have been developed to reduce unwanted peripheral side effects of opioids such as constipation without significantly reducing analgesia or precipitating withdrawal in dependent individuals.

Other actions of opioids

Morphine releases histamine from mast cells by an action unrelated to opioid receptors. Pethidine and fentanyl do not produce this effect. The release of histamine can cause local effects, such as urticaria and itching at the site of the injection, or systemic effects, namely bronchoconstriction and hypotension. The bronchoconstrictor effect can have serious consequences for asthmatic patients, to whom morphine should not be given.

Hypotension and bradycardia occur with large doses of most opioids, due to an action on the medulla. With morphine and similar drugs, histamine release may contribute to the hypotension.

Effects on smooth muscle other than that of the gastrointestinal tract and bronchi are slight, although spasms of the ureters, bladder and uterus sometimes occur. Opioids also exert complex immunosuppressant effects, which may be important as a link between the nervous

[9] The chemically related compound apomorphine is more strongly emetic than morphine, through its action as a dopamine agonist; despite its name, it is inactive on opioid receptors.

[10] The exception is pethidine, which causes pupillary dilatation because it blocks muscarinic receptors.

[11] In treating pain, constipation is considered as an undesirable side effect. However, opioids such as codeine and morphine can be used to treat diarrhoea.

system and immune function. The pharmacological significance of this is not yet clear, but there is evidence in humans that the immune system is depressed by long-term opioid use, and that in addicts suffering from AIDS the use of opioids may exacerbated the immune deficiency.

Actions of morphine

- The main pharmacological effects are:
  - analgesia
  - euphoria and sedation
  - respiratory depression
  - suppression of cough
  - nausea and vomiting
  - pupillary constriction
  - reduced gastrointestinal motility, causing constipation
  - histamine release, causing itch, bronchoconstriction and hypotension.
- The most troublesome unwanted effects are nausea and vomiting, constipation and respiratory depression.
- Acute overdosage with **morphine** produces coma and respiratory depression.
- **Diamorphine** is inactive at opioid receptors but is rapidly cleaved in the brain to 6-acetylmorphine and **morphine**.
- **Codeine** is also converted to **morphine** but more slowly by liver metabolism.

TOLERANCE AND DEPENDENCE

Tolerance to many of the actions of opioids (i.e. an increase in the dose needed to produce a given pharmacological effect) develops within a few days during repeated administration. There is some controversy over whether significant tolerance develops to the analgesic effects of morphine, especially in palliative care patients with severe cancer pain (see McQuay, 1999; Ballantyne & Mao, 2003). Drug rotation (changing from one opioid to another) is frequently used clinically to overcome loss of effectiveness. As tolerance is likely to depend upon the level of receptor occupancy, the degree of tolerance observed may reflect the response being assessed, the intrinsic efficacy of the drug and the dose being administered.

Physical dependence refers to a state in which withdrawal of the drug causes adverse physiological effects, i.e. the abstinence syndrome.

Different adaptive cellular mechanisms underlie tolerance and dependence (see Williams et al., 2013; see also Chs 2 and 49). These phenomena occur to some degree whenever opioids are administered for more than a few days. They must not be confused with addiction (see Ch. 49), in which physical dependence is much more pronounced and psychological dependence (or 'craving') is the main driving force.

Tolerance

In animal experiments, tolerance can be detected even with a single dose of morphine. Tolerance extends to most of the pharmacological effects of morphine, including analgesia, emesis, euphoria and respiratory depression, but affects the constipating and pupil-constricting actions much less. Therefore, addicts may take 50 times the normal analgesic dose of morphine with relatively little respiratory depression but marked constipation and pupillary constriction.

The cellular mechanisms responsible for tolerance are discussed in Chapter 2. Tolerance results in part from desensitisation of the μ opioid receptors (i.e. at the level of the drug target) as well as from long-term adaptive changes at the cellular, synaptic and network levels (see Williams et al., 2013). Tolerance is a general phenomenon of opioid-receptor ligands, irrespective of which type of receptor they act on. Cross-tolerance occurs between drugs acting at the same receptor, but not between opioids that act on different receptors. In clinical settings, the opioid dose required for effective pain relief may increase as a result of developing tolerance, but it does not constitute a major problem.

Physical dependence

Physical dependence is characterised by a clear-cut abstinence syndrome. In experimental animals (e.g. rats), abrupt withdrawal of morphine after repeated administration for a few days, or the administration of an antagonist such as naloxone, causes an increased irritability, diarrhoea, loss of weight and a variety of abnormal behaviour patterns, such as body shakes, writhing, jumping and signs of aggression. These reactions decrease after a few days, but abnormal irritability and aggression persist for many weeks. The signs of physical dependence are much less intense if the opioid is withdrawn gradually. Humans often experience an abstinence syndrome when opioids are withdrawn after being used for pain relief over days or weeks, with symptoms of restlessness, runny nose, diarrhoea, shivering and piloerection.[12]

Many physiological changes have been described in relation to the abstinence syndrome. For example, spinal reflex hyperexcitability occurs in morphine-dependent animals and can be produced by chronic intrathecal as well as systemic administration of morphine. The noradrenergic pathways emanating from the LC (see Ch. 39) may also play an important role in causing the abstinence syndrome and the α_2-adrenoceptor agonist clonidine (Ch. 14) can be used to alleviate it. The rate of firing of LC neurons is reduced by opioids and increased during the abstinence syndrome. In animal models, and also in humans, the abstinence syndrome is reduced by giving NMDA receptor antagonists (e.g. ketamine).

PHARMACOKINETIC ASPECTS

Table 42.4 summarises the pharmacokinetic properties of the main opioid analgesics. The absorption of morphine congeners by mouth is variable. Morphine itself is slowly and erratically absorbed, and is commonly given by intravenous injection to treat acute severe pain; oral morphine is, however, often used in treating chronic pain, and slow-release preparations are available to increase its duration of action. Oxycodone is also available as a slow-release oral preparation. Codeine is well absorbed and normally given by mouth. Most morphine-like drugs undergo considerable first-pass metabolism, and are therefore markedly less potent when taken orally than when injected.

The plasma half-life of most morphine analogues is 3–6 h. Hepatic metabolism is the main mode of inactivation, usually by conjugation with glucuronide. This occurs

[12]Causing goose pimples. This is the origin of the phrase 'cold turkey' used to describe the effect of morphine withdrawal.

Table 42.4 Characteristics of the main opioid analgesic drugs

Drug	Use(s)	Route(s) of administration	Pharmacokinetic aspects	Main adverse effects	Notes
Morphine	Widely used for acute and chronic pain	Oral, including sustained-release form Injection[a] Intrathecal	Half-life 3–4 h Converted to active metabolite (morphine-6-glucuronide)	Sedation Respiratory depression Constipation Nausea and vomiting Itching (histamine release) Tolerance and dependence Euphoria	Tolerance and withdrawal effects not common when used for analgesia
Diamorphine (heroin)	Acute and chronic pain	Oral Injection	Acts more rapidly than morphine because of rapid brain penetration.	As morphine	Not available in all countries Metabolised to morphine and other active metabolites
Hydromorphone	Acute and chronic pain	Oral Injection	Half-life 2–4 h No active metabolites	As morphine but allegedly less sedative	Levorphanol is similar, with longer duration of action
Oxycodone	Acute and chronic pain	Oral, including sustained-release form Injection	Half-life 3–4.5 h	As morphine	Claims for less abuse potential are unfounded
Methadone	Chronic pain Maintenance of addicts	Oral Injection	Long half-life (>24 h) Slow onset	As morphine but less euphoric effect Accumulation may occur	Slow recovery results in attenuated withdrawal syndrome because of long half-life
Pethidine	Acute pain	Oral Intramuscular injection	Half-life 2–4 h Active metabolite (norpethidine) may account for stimulant effects	As morphine Anticholinergic effects Risk of excitement and convulsions	Known as meperidine in USA Interacts with monoamine oxidase inhibitors (Ch. 47)
Buprenorphine	Acute and chronic pain Maintenance of addicts	Sublingual Injection Intrathecal	Half-life about 12 h Slow onset Inactive orally because of first-pass metabolism	As morphine but less pronounced Respiratory depression not reversed by naloxone (therefore not suitable for obstetric use) May precipitate opioid withdrawal (partial agonist)	Useful in chronic pain with patient-controlled injection systems

Pentazocine	Mainly acute pain	Oral Injection	Half-life 2–4 h	Psychotomimetic effects (dysphoria) Irritation at injection site May precipitate opioid withdrawal (μ antagonist effect)	Nalbuphine is similar
Dipipenone	Moderate to severe pain	Oral	Half life 3.5 h (although there are longer values quoted)	In addition to effects similar to morphine it produces psychosis	Marketed in combination with cyclazine (Diconal) and became a popular IV drug of abuse
Fentanyl	Acute pain Anaesthesia	Intravenous Epidermal Transdermal patch	Half-life 1–2 h	As morphine	High potency allows transdermal administration Sufentanil is similar
Remifentanil	Anaesthesia	Intravenous infusion	Half-life 5 min	Respiratory depression	Very rapid onset and recovery
Codeine	Mild pain	Oral	Acts as prodrug Metabolised to morphine and other active metabolites	Mainly constipation No dependence liability	Effective only in mild pain Also used to suppress cough Dihydrocodeine is similar
Dextropropoxyphene	Mild pain	Mainly oral	Half-life ~4 h Active metabolite (norpropoxyphene) with half-life ~24 h	Respiratory depression May cause convulsions (possibly by action of norpropoxyphene)	Similar to codeine No longer recommended
Tramadol	Acute (mainly postoperative) and chronic pain	Oral Intravenous	Well absorbed Half-life 4–6 h	Dizziness May cause convulsions No respiratory depression	Mechanism of action uncertain Weak agonist at opioid receptors Also inhibits monoamine uptake. Tapentadol is similar

[a]Injections may by given intravenously, intramuscularly or subcutaneously for most drugs.

Tolerance and dependence

- Tolerance develops rapidly.
- The mechanism of tolerance involves receptor desensitisation. It is not pharmacokinetic in origin.
- Dependence comprises two components:
  - physical dependence, associated with the withdrawal syndrome and lasting for a few days
  - psychological dependence, associated with craving and lasting for months or years; it rarely occurs in patients being given opioids as analgesics.
- Physical dependence, characterised by a withdrawal syndrome on cessation of drug administration, occurs with μ-receptor agonists.
- The withdrawal syndrome is precipitated by μ-receptor antagonists.
- Long-acting μ-receptor agonists such as **methadone** and **buprenorphine** may be used to relieve withdrawal symptoms.
- Certain opioid analgesics, such as **codeine**, **pentazocine**, **buprenorphine** and **tramadol**, are much less likely to cause physical or psychological dependence.

at the 3- and 6-OH groups (see Fig 42.7), and these glucuronides constitute a considerable fraction of the drug in the bloodstream. Morphine-6-glucuronide is more active as an analgesic than morphine itself, and contributes substantially to the pharmacological effect. Morphine-3-glucuronide has been claimed to antagonise the analgesic effect of morphine, but the significance of this experimental finding is uncertain as this metabolite has little or no affinity for opioid receptors. Morphine glucuronides are excreted in the urine, so the dose needs to be reduced in cases of renal failure. Glucuronides also reach the gut via biliary excretion, where they are hydrolysed, most of the morphine being reabsorbed (enterohepatic circulation). Because of low conjugating capacity in neonates, morphine-like drugs have a much longer duration of action; because even a small degree of respiratory depression can be hazardous, morphine congeners should not be used in the neonatal period, nor used as analgesics during childbirth. Pethidine (see p. 525) is a safer alternative for this purpose.

Analogues that have no free hydroxyl group in the 3 position (i.e. diamorphine, codeine) are converted to morphine, which accounts for all or part of their pharmacological activity. With heroin the conversion occurs rapidly in aqueous solution and in the brain but with codeine the effect is slower and occurs by metabolism in the liver. Morphine produces very effective analgesia when administered intrathecally, and is often used in this way by anaesthetists, the advantage being that the sedative and respiratory depressant effects are reduced, although not completely avoided. **Remifentanil** is rapidly hydrolysed and eliminated with a half life of 3–4 min. The advantage of this is that when given by intravenous infusion during general anaesthesia, the level of the drug can be manipulated rapidly when required (see Ch. 10 for a description of how, for intravenous infusion, both the rate of rise and the rate of decay of the plasma concentration are determined by the half-time of elimination).

For the treatment of chronic or postoperative pain, opioids are often given 'on demand' (patient-controlled analgesia). The patients are provided with an infusion pump that they control, the maximum possible rate of administration being limited to avoid acute toxicity. Patients show little tendency to use excessively large doses and become dependent; instead, the dose is adjusted to achieve analgesia without excessive sedation, and is reduced as the pain subsides. Being in control of their own analgesia, the patients' anxiety and distress are reduced, and analgesic consumption actually tends to decrease. In chronic pain, especially that associated with cancer, patients often experience sudden, sharp increases in the level of pain they are experiencing. This is referred to as breakthrough pain. To combat this, there is a therapeutic need to be able to increase rapidly the amount of opioid being administered. This has led to the development of touch-sensitive transdermal patches containing potent opioids such as fentanyl that rapidly release drug into the bloodstream.

The opioid antagonist, naloxone, has a shorter biological half-life than most opioid agonists. In the treatment of opioid overdose, it must be given repeatedly to avoid the respiratory depressant effect of the agonist reoccurring once the naloxone has been eliminated. Naltrexone has a longer biological half-life.

UNWANTED EFFECTS

The main unwanted effects of morphine and related drugs are listed in Table 42.4.

Acute overdosage with morphine results in coma and respiratory depression, with characteristically constricted pupils. It is treated by giving naloxone intravenously. This also serves as a diagnostic test, for failure to respond to naloxone suggests a cause other than opioid poisoning for the comatose state.[13] There is a danger of precipitating a severe withdrawal syndrome with naloxone, because opioid poisoning occurs mainly in addicts.

Individual variability

▼ Individuals vary by as much as 10-fold in their sensitivity to opioid analgesics. This can be due to altered metabolism or altered sensitivity of the receptors (for extensive review, see Rollason et al., 2008). For morphine, reduced responsiveness may result from mutations in a number of genes including that for the drug transporter, P-glycoprotein (see Chs 9 and 11), for glucuronyltransferase that metabolises morphine and for the μ receptor itself. Mutations of various cytochrome P450 (CYP) enzymes influence the metabolism of codeine, oxycodone, methadone, tramadol and dextromethorphan. Genotyping could in principle be used to identify opioid-resistant individuals, but first the contribution of genotype to clinical outcome must be confirmed in the population at large.

OTHER OPIOID ANALGESICS

Diamorphine (heroin) is 3,6-diacetylmorphine; it can be considered as a prodrug as its high analgesic potency is attributable to rapid conversion to 6-monoacetylmorphine and morphine. Its effects are indistinguishable from those of morphine following oral administration. However, because of its greater lipid solubility, it crosses the blood–brain barrier more rapidly than morphine and gives a

[13]Naloxone is less effective in reversing the effects of buprenorphine as this agonist dissociates very slowly from the receptors.

greater 'buzz' when injected intravenously. It is said to be less emetic than morphine, but the evidence for this is slight. It is still available in Britain for use as an analgesic, although it is banned in many countries. Its only advantage over morphine is its greater solubility, which allows smaller volumes to be given orally, subcutaneously or intrathecally. It exerts the same respiratory depressant effect as morphine and, if given intravenously, is more likely to cause dependence.

Codeine (3-methoxymorphine) is more reliably absorbed by mouth than morphine, but has only 20% or less of the analgesic potency. Its analgesic effect does not increase appreciably at higher dose levels. It is therefore used mainly as an oral analgesic for mild types of pain (headache, backache, etc.). It is metabolised to morphine as well as undergoing glucuronidation in the liver. About 10% of the population is resistant to the analgesic effect of codeine, because they lack the demethylating enzyme that converts it to morphine. Unlike morphine, it causes little or no euphoria and is rarely addictive. It is often combined with **paracetamol** in proprietary analgesic preparations (see later section on combined use of opioids and NSAIDs). In relation to its analgesic effect, codeine produces the same degree of respiratory depression as morphine, but the limited response even at high doses means that it is seldom a problem in practice. It does, however, cause constipation. Codeine has marked antitussive activity and is often used in cough mixtures (see Ch. 28). **Dihydrocodeine** is pharmacologically very similar, having no substantial advantages or disadvantages over codeine.

Oxycodone is used in the treatment of acute and chronic pain. The suggestion that it acts on a subtype of κ opioid receptor is not generally accepted. Claims that it has less euphoric effect and less abuse potential appear unfounded. It is available as a slow release oral preparation but diversion to the street where addicts grind up the tablets that contain large amounts of drug has resulted in it becoming a major drug of abuse (see Ch. 49), sometimes referred to as 'hillbilly heroin'.

Fentanyl, **alfentanil**, **sufentanil** and **remifentanil** are highly potent phenylpiperidine derivatives, with actions similar to those of morphine but with a more rapid onset and shorter duration of action, particularly remifentanil. They are used extensively in anaesthesia, and they may be given intrathecally. Fentanyl, alfentanil and sufentanil are also used in patient-controlled infusion systems and in severe chronic pain, when they are administered via patches applied to the skin. The rapid onset is advantageous in breakthrough pain.

Methadone is orally active and pharmacologically similar to morphine, the main difference being that its duration of action is considerably longer (plasma half-life >24 h). The increased duration seems to occur because the drug is bound in the extravascular compartment and slowly released. On withdrawal, the physical abstinence syndrome is less acute than with morphine, although the psychological dependence is no less pronounced. Methadone is widely used as a means of treating heroin addiction (see Ch. 49). It is possible to wean addicts from heroin by giving regular oral doses of methadone – an improvement if not a cure.[14] Methadone has actions at other sites in the CNS, including block of potassium channels, NMDA receptors and 5-HT receptors that may explain its CNS side effect profile. There is also interindividual variation in the response to methadone, probably due to genetic variability between individuals in its metabolism.

Pethidine (meperidine) is very similar to morphine in its pharmacological effects, except that it tends to cause restlessness rather than sedation, and it has an additional antimuscarinic action that may cause dry mouth and blurring of vision as side effects. It produces a very similar euphoric effect and is equally liable to cause dependence. Its duration of action is the same or slightly shorter than that of morphine, but the route of metabolic degradation is different. Pethidine is partly *N*-demethylated in the liver to norpethidine, which has hallucinogenic and convulsant effects. These become significant with large oral doses of pethidine, producing an overdose syndrome rather different from that of morphine. Pethidine is preferred to morphine for analgesia during labour, because it does not reduce the force of uterine contraction. Pethidine is only slowly eliminated in the neonate, and naloxone may be needed to reverse respiratory depression in the baby. (Morphine is even more problematic in this regard, because the conjugation reactions on which the excretion of morphine, but not of pethidine, depends are deficient in the newborn.) Severe reactions, consisting of excitement, hyperthermia and convulsions, have been reported when pethidine is given to patients receiving monoamine oxidase inhibitors. This seems to be due to inhibition of an alternative metabolic pathway, leading to increased norpethidine formation, but the details are not known.

Etorphine is a morphine analogue of remarkable potency, more than 1000 times that of morphine, but otherwise very similar in its actions. Its high potency confers no particular human clinical advantage, but it is used in veterinary practice, especially in large animals. It can be used in conjunction with sedative agents (neuroleptanalgesia) to immobilise wild animals for trapping.[15]

Buprenorphine is a partial agonist on μ receptors that produces strong analgesia but there is a ceiling to its respiratory depressant effect. Because of its antagonist actions, it can produce mild withdrawal symptoms in patients dependent on other opioids. It has a long duration of action and can be difficult to reverse with naloxone. It has abuse liability but, like methadone, it is also used in the treatment of heroin addiction. When heroin is injected 'on top' of buprenorphine, less euphoria is obtained because buprenorphine is a partial agonist. It is marketed as a sublingual preparation combined with naloxone for the management of opioid dependence; when administered as intended the naloxone is not absorbed and does not influence the effect of the buprenorphine, but if it is administered parenterally the effects of the buprenorphine are hopefully reduced by the naloxone, discouraging such abuse. How effective this is in practice has been questioned.

Meptazinol is an opioid of unusual chemical structure. It can be given orally or by injection and has a duration of action shorter than that of morphine. It seems to be relatively free of morphine-like side effects, causing neither euphoria nor dysphoria, nor severe respiratory depression. It does, however, produce nausea, sedation

[14]The benefits come mainly from removing the risks of self-injection and the need to finance the drug habit through crime.

[15]The required dose of etorphine, even for an elephant, is small enough to be incorporated into a dart or pellet.

and dizziness, and has atropine-like actions. Because of its short duration of action and lack of respiratory depression, it may have advantages for obstetric analgesia.

Tramadol is widely used as an analgesic for postoperative pain. It is a weak agonist at μ opioid receptors and also a weak inhibitor of monoamine reuptake. It is effective as an analgesic and appears to have a better side effect profile than most opioids, although psychiatric reactions have been reported. It is given by mouth or by intramuscular or intravenous injection for moderate to severe pain. **Tapentadol** acts similarly and is effective in acute and chronic pain, including the pain associated with diabetic neuropathy (see p. 527).

Pentazocine is a mixed κ agonist/μ antagonist with analgesic properties similar to those of morphine. However, it causes marked dysphoria, with nightmares and hallucinations, rather than euphoria, and is now rarely used.

Loperamide is an opioid that is effectively extruded from the brain by P-glycoprotein and therefore lacks analgesic activity. It inhibits peristalsis, and is used to control diarrhoea (see Ch. 30).

OPIOID ANTAGONISTS

Naloxone was the first pure opioid antagonist, with affinity for all three classic opioid receptors (μ > κ ≥ δ). It blocks the actions of endogenous opioid peptides as well as those of morphine-like drugs, and has been extensively used as an experimental tool to determine the physiological role of these peptides, particularly in pain transmission.

Given on its own, naloxone produces very little effect in normal subjects but produces a rapid reversal of the effects of morphine and other opioids. It has little effect on pain threshold under normal conditions but causes hyperalgesia under conditions of stress or inflammation, when endogenous opioids are produced. This occurs, for example, in patients undergoing dental surgery, or in animals subjected to physical stress. Naloxone also inhibits acupuncture analgesia, which is known to be associated with the release of endogenous opioid peptides. Analgesia produced by PAG stimulation is also prevented.

The main clinical uses of naloxone are to treat respiratory depression caused by opioid overdosage, and occasionally to reverse the effect of opioid analgesics, used during labour, on the respiration of the newborn baby. It is usually given intravenously, and its effects are produced immediately. It is rapidly metabolised by the liver, and its effect lasts only 2–4 h, which is considerably shorter than that of most morphine-like drugs and therefore it may have to be given repeatedly.

Naloxone has no important unwanted effects of its own but precipitates withdrawal symptoms in addicts. It can be used to detect opioid addiction.

Naltrexone is very similar to naloxone but with the advantage of a much longer duration of action (half-life about 10 h). It may be of value in addicts who have been 'detoxified', because it nullifies the effect of a dose of opioid should the patient's resolve fail. For this purpose, it is available in a slow-release subcutaneous implant formulation. It is also effective in reducing alcohol consumption in heavy drinkers (see Ch. 49), the rationale being that part of the high from alcohol comes from the release of endogenous opioid peptides. It may also have beneficial effects in septic shock. It is effective in treating chronic itching (pruritus), as occurs in chronic liver disease. Again, this may indicate the involvement of endogenous opioid peptides in the pathophysiology of such itch conditions.

Methylnaltrexone bromide and **alvimopan** are μ opioid-receptor antagonists that do not cross the blood–brain barrier. They can be used in combination with opioid agonists to block unwanted effects, most notably reduced gastrointestinal motility, nausea and vomiting.

Specific antagonists at μ, δ and κ receptors are available for experimental use (Table 42.3) but they are not used clinically.

Opioid antagonists

- Pure antagonists include **naloxone** (short acting) and **naltrexone** (longer acting). They block μ, δ and κ receptors. Selective antagonists are available as experimental tools.
- **Alvimopan** is a μ-receptor antagonist that does not cross the blood–brain barrier. It blocks opioid-induced constipation, nausea and vomiting.
- Some drugs, such as **pentazocine**, produce a mixture of κ agonist and μ antagonist effects.
- **Naloxone** does not affect pain threshold normally but blocks stress-induced analgesia and can exacerbate clinical pain.
- **Naloxone** rapidly reverses opioid-induced analgesia and respiratory depression, and is used mainly to treat opioid overdose or to improve breathing in newborn babies affected by opioids given to the mother.
- **Naloxone** precipitates withdrawal symptoms in **morphine**-dependent patients or animals. **Pentazocine** may also do this.

PARACETAMOL

Non-steroidal anti-inflammatory drugs (NSAIDs, covered in detail in Ch. 26) are widely used to treat painful inflammatory conditions and to reduce fever. **Paracetamol** (known as **acetaminophen** in the USA) deserves special mention. It was first synthesised more than a century ago, and since the 1950s has (alongside aspirin and ibuprofen) been the most widely used over-the-counter remedy for minor aches and pains. Paracetamol differs from other NSAIDs in producing analgesic and antipyretic effects while lacking anti-inflammatory effects. It also lacks the tendency of other NSAIDs to cause gastric ulceration and bleeding. The reason for the difference between paracetamol and other NSAIDs is unclear. Biochemical tests showed it to be only a weak cyclo-oxygenase (COX) inhibitor, with some selectivity for brain COX. It remains contentious whether paracetamol relieves pain centrally by inhibiting COX-3 (not a separate gene product but a splice variant of COX-1) or by inhibiting COX-2 at low rates of enzyme activity. Interestingly, the antinociceptive effects of paracetamol are absent in mice lacking the TRPA1 receptor (see p. 513). The antinociceptive effect appears to be mediated by metabolites (i.e. *N*-acetyl-*p*-benzoquinoneimine and *p*-benzoquinone), not by paracetamol itself. These activate TRPA1 and thus reduce voltage-gated calcium and sodium currents in primary sensory neurons.

Paracetamol is well absorbed by mouth, and its plasma half-life is about 3 h. It is metabolised by hydroxylation,

conjugated mainly as glucuronide, and excreted in the urine. In therapeutic doses, it has few adverse effects. However, in overdose, paracetamol causes severe liver damage, which is commonly fatal (see Chs 26 and 57), and the drug is often used in attempted suicide.

USE OF OPIOIDS AND NSAIDS IN COMBINATION

The rationale behind co-administration of two drugs that produce analgesia by different mechanisms is that, if the effects are additive, less of each drug can therefore be given but the same degree of analgesia produced. This has the effect of reducing the intensity of the unwanted side effects produced by each drug. In the case of opioids (e.g. codeine) in combination with paracetamol or aspirin, the combination appears to produce synergy rather than simple additivity. The combination of dextropropoxyphene and paracetamol has been withdrawn in the UK due to concerns about overdosing.

TREATMENT OF NEUROPATHIC PAIN

Neuropathic pain is the severe, debilitating, chronic pain that occurs in conditions such as trigeminal neuralgia, diabetic neuropathy, postherpetic neuralgia and phantom limb pain, affecting millions of people worldwide. It is often stated that neuropathic pain is opioid-resistant. However, clinical studies have shown opioids such as morphine, oxycodone, levorphanol, tramadol and tapentadol to be effective in the treatment of neuropathic pain, provided an adequate dose can be reached that provides analgesia without excessive side effects. The monamine uptake inhibiting properties of tramadol and tapentadol may contribute to their effectiveness.

Several non-opioid drugs that are also used clinically for effects other than analgesia have been found to be effective in neuropathic pain (see Dworkin et al., 2010), largely as a result of serendipitous observations rather than a rational programme of drug discovery.

Tricyclic antidepressants, particularly **amitriptyline**, **nortriptyline** and **desipramine** (Ch. 47) are widely used. These drugs act centrally by inhibiting noradrenaline reuptake and are highly effective in relieving neuropathic pain in some, but not all, cases. Their action is independent of their antidepressant effects. Drugs such as **duloxetine** and **venlafaxine**, which inhibit serotonin and noradrenaline uptake, are also effective and have a different side effect profile, but selective serotonin reuptake inhibitors show little or no benefit.

Gabapentin and its congener, **pregabalin**, are antiepileptic drugs (Ch. 45) that are also effective in the treatment of neuropathic pain. They reduce the expression of α2δ subunits of voltage-activated calcium channels on the nerve membrane (see Ch. 4) and reduce neurotransmitter release. The α2δ subunits are upregulated in damaged sensory neurons, thus explaining why these agents are more effective across a range of pain states associated with nerve damage than in other forms of pain.

Carbamazepine, another type of antiepileptic drug, is effective in trigeminal neuralgia but evidence for effectiveness against other neuropathic pains is lacking. Carbamazepine blocks voltage-gated sodium channels (see Ch. 4) being slightly more potent in blocking $Na_v1.8$ than $Na_v1.7$ and $Na_v1.3$ channels; all of these channel subtypes are thought to be upregulated by nerve damage and contribute to the sensation of pain. At higher concentrations, it inhibits voltage-activated calcium channels. **Phenytoin** administered intravenously is sometimes used in a crisis.

Other antiepileptic agents such as **valproic acid**, **lamotrogine**, **oxcarbazepine** and **topiramate**, may have efficacy in some neuropathic pain states.

Lidocaine (lignocaine), a local anaesthetic drug (Ch. 43), can be used topically to relieve neuropathic pain. It probably acts by blocking spontaneous discharges from damaged sensory nerve terminals. Some antidysrhythmic drugs (e.g. **mexiletine**, **tocainide**, **flecainide**; see Ch. 21) are effective orally.

Other analgesic drugs

- **Paracetamol** resembles non-steroidal anti-inflammatory drugs and is effective as an analgesic, but it lacks anti-inflammatory activity. It may act by inhibiting cyclo-oxygenase (COX)-3, a splice variant of COX-1, but probably has other effects as well. In overdose, it causes hepatotoxicity.
- **Nefopam** is an amine uptake inhibitor that can be used to treat opioid-resistant pain.
- Various antidepressants (e.g. **amitriptyline**), as well as antiepileptic drugs (e.g. **carbamazepine**, **gabapentin**), are used mainly to treat neuropathic pain.
- The NMDA-receptor antagonist **ketamine** is occasionally used.

Drugs used to treat neuropathic pain

- Opioids may be effective at higher doses if side effects can be tolerated.
- Various antidepressants (e.g. **amitriptyline**, **duloxetine**) provide therapeutic benefit.
- **Gabapentin** and **pregabalin** are now used more to relieve neuropathic pain than as antiepileptic agents.
- **Carbamazepine**, as well as some other antiepileptic agents that block sodium channels, can be effective in treating trigeminal neuralgia.
- **Lidocaine** may provide relief when applied topically.

TREATMENT OF FIBROMYALGIA

Fibromyalgia is a chronic disorder characterised by widespread musculoskeletal pain, fatigue and insomnia. Its cause is unknown, with no obvious characteristic pathology being apparent. It is associated with allodynia. As with neuropathic pain, classical analgesics (i.e NSAIDs and opioids), while bringing some relief, are not very effective in treating this disorder. Various antidepressant drugs (e.g. amitriptyline, **citalopram**, **milnacipram**, duloxetine, venlafaxine; see Ch. 47), antiepileptic agents (e.g. gabapentin, pregabalin; see Ch. 45), benzodiazepines (e.g. **clonazepam**, **zopiclone**; see Ch. 44) are currently used for this disorder – this long list reflecting their uncertain efficacy.

OTHER PAIN-RELIEVING DRUGS

Nefopam, an inhibitor of amine uptake with some sodium channel blocking properties is used in the treatment of persistent pain unresponsive to non-opioid drugs. It does not depress respiration but does produce sympathomimetic and antimuscarinic side effects.

Ketamine, a dissociative anaesthetic (Ch. 41), **memantine** and **dextromethorphan** work by blocking NMDA receptor channels, and probably reduce the wind-up phenomenon in the dorsal horn (Fig. 42.2). Given intrathecally, ketamine's effects on memory and cognitive function are largely avoided.

Ziconotide, a synthetic analogue of the N-type calcium-channel blocking peptide ω-conotoxin MVIIA, is effective when administered by the intrathecal route. It is used in patients whose pain does not respond to other analgesic agents. Blockers of low-voltage-activated T-type calcium channels may also be effective analgesics in some pain states.

Cannabinoids acting at CB_1 receptors are effective pain-relieving agents in animal pain models, including models of acute, antinociceptive, inflammatory and neuropathic pain. Although in clinical trials on neuropathic pain these drugs are able to reduce pain perception, the effect is generally weak and clinical relevance remains under evaluation (see Hosking & Zajicek, 2008). The strongest evidence of their benefit is for central neuropathic pain in multiple sclerosis. **Sativex** is an extract of the cannabis plant containing Δ9-tetrahydrocannabinol (THC) and cannabidiol that has been suggested to have improved therapeutic efficacy. CB_2-receptor agonists may also be potential analgesic agents.

In addition, cannabinoids and related drugs that lack agonist action at CB_1 receptors have been observed to induce analgesia by potentiating the actions of the inhibitory amino acid glycine at the ionotropic glycine receptor (see Ch. 38) in the spinal cord. This may lead to the development of new therapeutic agents lacking the unwanted effects of CB_1 agonism.

Botulinum toxin injections are effective in relieving back pain and the pain associated with spasticity. This effect is due mainly to a relief of muscle spasm (Ch. 13).

Ropinirole, **pramipexole** and **rotigotine**, dopamine-receptor agonists (see Ch. 39) are used to treat restless leg syndrome, which can be painful in some individuals.

Clinical uses of analgesic drugs (1)

- Analgesics are used to treat and prevent pain, for example:
  - pre- and postoperatively
  - common painful conditions including headache, dysmenorrhoea, labour, trauma and burns
  - many medical and surgical emergencies (e.g. myocardial infarction and renal colic)
  - terminal disease (especially metatastic cancer).
- Opioid analgesics are used in some non-painful conditions, for example acute heart failure (because of their haemodynamic effects) and terminal chronic heart failure (to relieve distress).
- The choice and route of administration of analgesic drugs depends on the nature and duration of the pain.
- A progressive approach is often used, starting with non-steroidal anti-inflammatory drugs (NSAIDs), supplemented first by weak opioid analgesics and then by strong opioids.
- In general, severe acute pain is treated with strong opioids (e.g. **morphine**, **fentanyl**) given by injection. Mild inflammatory pain (e.g. sprains, mild arthralgia) is treated with NSAIDs (e.g. **ibuprofen**) or by **paracetamol** supplemented by weak opioids (e.g. **codeine**). Severe pain (e.g. cancer pain) is treated with strong opioids given orally, intrathecally, epidurally or by subcutaneous injection. Patient-controlled infusion systems are useful postoperatively.
- Chronic neuropathic pain is less responsive to opioids and can be treated with tricyclic antidepressants (e.g. **amitriptyline**) or anticonvulsants (e.g. **carbamazepine**, **gabapentin**).

Clinical uses of analgesic drugs (2)

- Non-steroidal anti-inflammatory drugs (see clinical box 1), including **paracetamol**, are useful for musculoskeletal and dental pain and for dysmenorrhoea. They reduce opioid requirements in acute (e.g. postoperative) and chronic (e.g. bone metastasis) pain.
- Weak opioids (e.g. **codeine**) combined with **paracetamol** are useful in moderately severe pain if non-opioids are not sufficient. **Tramadol** (a weak opioid with additional action on 5-hydroxytryptamine and noradrenaline uptake) is an alternative.
- Strong opioids (e.g. **morphine**) are used for severe pain, particularly of visceral origin.
- Note that:
  - the intravenous route provides rapid relief from pain and distress
  - the intravenous dose is much lower than the oral dose because of presystemic metabolism
  - **morphine** is given orally as a solution or as 'immediate-release' tablets every 4 h
  - dose is titrated; when the daily requirement is apparent, the preparation is changed to a modified-release formulation to allow once- or twice-daily dosing
  - **morphine** and **oxycodone** can be given orally in slow-release tablet form
  - transdermal administration (e.g. patches of **fentanyl**) is an alternative, rapid means of pain relief
  - adverse effects (nausea, constipation) are anticipated and treated pre-emptively
  - addiction is not an issue in the setting of terminal care.
- Subanaesthetic doses of **nitrous oxide** (Ch. 41) are analgesic, and self-administration of a mixture of **nitrous oxide** with oxygen is widely used during labour or for painful dressing changes.

NEW APPROACHES

▼ As in other fields of neuropharmacology, increasing knowledge of the various chemical mediators and signalling pathways responsible for pain sensation suggests many new approaches to the control of pain. Pain treatment is currently far from perfect, and novel approaches are being explored.

- *Nerve growth factor* (NGF) is a major mediator of both inflammatory and neuropathic pain (Mantyh et al., 2011). It is therefore an important therapeutic target. It has proved difficult to design small-molecule, selective antagonists of NGF. Current alternative options being explored include the development of monoclonal antibodies to NGF or its receptor TrkA and the sequestration of NGF using a soluble decoy receptor protein that binds NGF with picomolar affinity.
- *TRP channel ligands*. It was hoped that TRPV1 antagonists would be effective analgesics but despite promising results in animal models, none has yet been developed for human use, mainly because they cause hyperthermia, and may suppress thermosensitivity and thus predispose to burn injury. TRPV1 agonists induce receptor desensitisation or a reversible sensory nerve terminal degeneration due to prolonged cation influx. Topical high-dose **capsaicin** is efficacious in a number of neuropathic pain conditions, but causes burning pain initially.
- *Other TRP channels* have been suggested to be involved in pain particularly when sensitised by some pathophysiological changes. Agonists and antagonists for TRPA1 and TRPM8 are in development. TRPM8 may also be a target for anticancer drugs.
- It had been hoped that *sodium channel blockers* especially those with selectivity at channels upregulated in chronic pain states would be effective pain relieving drugs. Clinical trails with **lacosamide** (antiepileptic) and **ralfinamide** in chronic pain have been disappointing.
- **Retigabine**, a K_v7 (M-current) *opener* (see Ch. 45) inhibits C-fibre- and Aδ-fibre-mediated nociceptive responses in dorsal horn neurons in both naive and neuropathic rats. It is chemically related to **flupirtine** which is used as an analgesic agent in some countries.
- Agonists at *nicotinic acetylcholine receptors*, based on **epibatidine** (an alkaloid from frog skin, which is a potent nicotinic agonist) show – unexpectedly – potent analgesic effects in animal models. Derivatives with fewer side effects are under investigation.
- Various *neuropeptides*, such as **somatostatin** (see Ch. 34) and **calcitonin** (see Ch. 36), produce powerful analgesia when applied intrathecally, and there are clinical reports suggesting that they may have similar effects when used systemically to treat endocrine disorders.
- *Glutamate antagonists* acting on NMDA or AMPA receptors show analgesic activity in animal models, but it has not yet been possible – with the exception of ketamine – to obtain this effect in humans without unacceptable side effects. To circumvent this, attempts are being made to develop antagonists selective for channels of different subunit compositions (see Ch. 38) or antagonists at the glycine site on the NMDA receptor. Paradoxically inhibitors of glycine reuptake may also be analgesic. Antagonists of metabotropic glutamate receptors, mGluR1 and mGluR5, are currently in development and may have fewer side effects.

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43 Local anaesthetics and other drugs affecting sodium channels

OVERVIEW

As described in Chapter 4, the property of electrical excitability is what enables the membranes of nerve and muscle cells to generate propagated action potentials, which are essential for communication in the nervous system and for the initiation of mechanical activity in striated muscle. Initiation of the action potential depends on voltage-gated sodium channels, which open transiently when the membrane is depolarised. Here we discuss local anaesthetics, which act mainly by blocking sodium channels, and mention briefly other drugs that affect sodium-channel function.

There are, broadly speaking, two ways in which channel function may be modified, namely block of the channels and modification of gating behaviour. Blocking sodium channels reduces excitability. On the other hand, different types of drugs can either facilitate channel opening and thus increase excitability, or inhibit channel opening and reduce excitability.

LOCAL ANAESTHETICS

Although many drugs can, at high concentrations, block voltage-sensitive sodium channels and inhibit the generation of the action potential, the only drugs used clinically for this effect are the local anaesthetics, various antiepileptic and analgesic drugs (see Chs 42 and 45) and class I antidysrhythmic drugs (see Ch. 21).

HISTORY

Coca leaves have been chewed for their psychotropic effects for thousands of years (see Ch. 48) by South American Indians, who knew about the numbing effect they produced on the mouth and tongue. **Cocaine** was isolated in 1860 and proposed as a local anaesthetic for surgical procedures. Sigmund Freud, who tried unsuccessfully to make use of its 'psychic energising' power, gave some cocaine to his ophthalmologist friend in Vienna, Carl Köller, who reported in 1884 that reversible corneal anaesthesia could be produced by dropping cocaine into the eye. The idea was rapidly taken up, and within a few years cocaine anaesthesia was introduced into dentistry and general surgery. A synthetic substitute, **procaine**, was discovered in 1905, and many other useful compounds were later developed.

CHEMICAL ASPECTS

Local anaesthetic molecules consist of an aromatic part linked by an ester or amide bond to a basic side-chain (Fig. 43.1). They are weak bases, with pK_a values mainly in the range 8–9, so that they are mainly, but not completely, ionised at physiological pH (see Ch. 8 for an explanation of how pH influences the ionisation of weak bases). This is important in relation to their ability to penetrate the nerve sheath and axon membrane; quaternary derivatives such as QX-314, which are fully ionised irrespective of pH, are ineffective as local anaesthetics but have important experimental uses. **Benzocaine**, an atypical local anaesthetic, has no basic group.

The presence of the ester or amide bond in local anaesthetic molecules is important because of its susceptibility to metabolic hydrolysis. The ester-containing compounds are fairly rapidly inactivated in the plasma and tissues (mainly liver) by non-specific esterases. Amides are more stable, and these anaesthetics generally have longer plasma half-lives.

MECHANISM OF ACTION

Local anaesthetics block the initiation and propagation of action potentials by preventing the voltage-dependent increase in Na^+ conductance (see Ch. 4) (see Strichartz & Ritchie, 1987; Hille, 2001). At low concentrations they decrease the rate of rise of the action potential, increasing its duration, and increase the refractory period thus reducing the firing rate. At higher concentrations they prevent action potential firing. Currently available local anaesthetic agents do not by and large distinguish between different sodium channel subtypes although their potencies vary (see Ch. 4). They block sodium channels, by physically plugging the transmembrane pore, interacting with various amino acid residues of the S6 transmembrane helical domain of the channel protein (see Ragsdale et al., 1994).

▼ Local anaesthetic activity is strongly pH-dependent, being increased at alkaline extracellular pH (i.e. when the proportion of ionised molecules is low) and reduced at acid pH. This is because the compound needs to penetrate the nerve sheath and the axon membrane to reach the inner end of the sodium channel (where the local anaesthetic-binding site resides). Because the ionised form is not membrane-permeant, penetration is very poor at acid pH. Once inside the axon, it is primarily the ionised form of the local anaesthetic molecule that binds to the channel and blocks it (Fig. 43.2), the unionised form having only weak channel-blocking activity. This pH dependence can be clinically important, because the extracellular fluid of inflamed tissues is often relatively acidic and such tissues are thus somewhat resistant to local anaesthetic agents.

Further analysis of local anaesthetic action (see Strichartz & Ritchie, 1987) has shown that many drugs exhibit the property of '*use-dependent' block* of sodium channels, as well as affecting, to some extent, the gating of the channels. Use-dependence means that the more the channels are opened, the greater the block becomes. It is a prominent feature of the action of many class I antidysrhythmic drugs (Ch. 21) and antiepileptic drugs (Ch. 45), and occurs because the blocking molecule enters the channel much more readily when the channel is open than when it is closed. Furthermore, for local anaesthetics that rapidly dissociate from the channel, block only occurs at high frequencies of action potential firing when the time between action potentials is too short for drug dissociation from the channel to occur. The channel can exist in three functional states: resting, open and inactivated (see Ch. 4). Many local anaesthetics

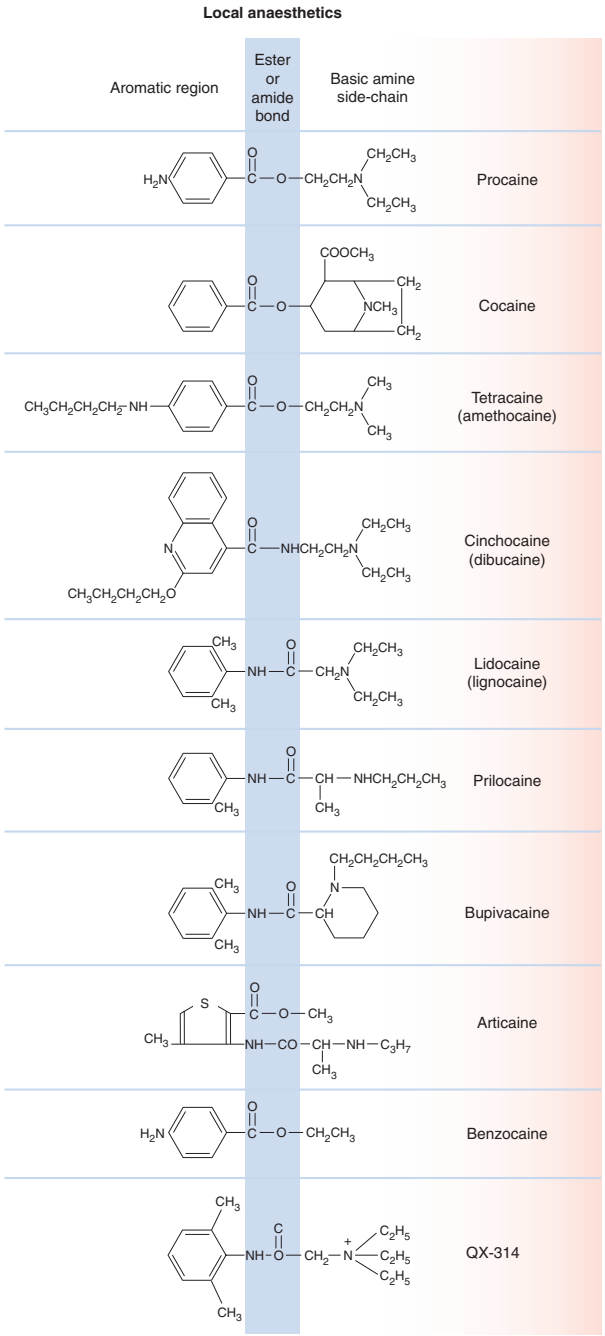

Fig. 43.1 Structures of local anaesthetics. The general structure of local anaesthetic molecules consists of an aromatic group (left), ester or amide group (shaded blue) and amine group (right).

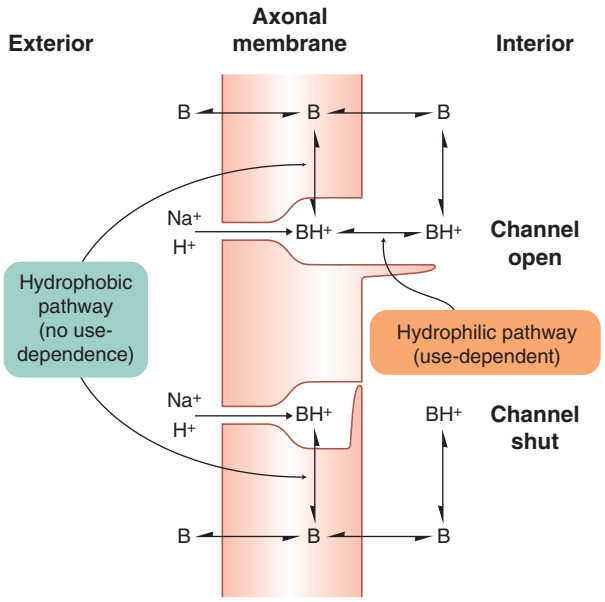

Fig. 43.2 Interaction of local anaesthetics with sodium channels. The blocking site within the channel can be reached via the open channel gate on the inner surface of the membrane by the charged species BH^+ (hydrophilic pathway), or directly from the membrane by the uncharged species B (hydrophilic pathway).

bind most strongly to the inactivated state of the channel. Therefore, at any given membrane potential, the equilibrium between resting and inactivated channels will, in the presence of a local anaesthetic, be shifted in favour of the inactivated state, and this factor contributes to the overall blocking effect by reducing the number of channels available for opening, and by prolonging the refractory period following an action potential. The passage of a train of action potentials, for example when a painful stimulus is applied to a sensory nerve, causes the channels to cycle through the open and inactivated states, both of which are more likely to bind local anaesthetic molecules than the resting state; thus both mechanisms contribute to use-dependence, which explains in part why pain transmission may be blocked more effectively than other sensory modalities.

Quaternary amine local anaesthetics only work when applied to the inside of the membrane and the channels must be cycled through their open state a few times before the blocking effect appears. With tertiary amine local anaesthetics, block can develop even if the channels are not open, and it is likely that the blocking molecule (uncharged) can reach the channel either directly from the membrane phase or via the open gate (Fig. 43.2). The relative importance of these two blocking pathways – the hydrophobic pathway via the membrane and the hydrophilic pathway via the inner mouth of the channel – varies according to the lipid solubility of the drug.

Local anaesthetics exert a number of effects on other ion channels as well as on membrane and intracellular signalling proteins. The importance of these actions to local anaesthetic action is as yet unclear (see Yanagidate & Stricharz, 2007).

In general, local anaesthetics block conduction in small-diameter nerve fibres more readily than in large fibres. Because nociceptive impulses are carried by Aδ and C fibres (Ch. 42), pain sensation is blocked more readily than other sensory modalities (touch, proprioception, etc.). Motor axons, being large in diameter, are also relatively resistant. The differences in sensitivity among different nerve fibres, although easily measured experimentally, are not of much practical importance, and it is not possible to block pain sensation without affecting other sensory modalities.

Local anaesthetics, as their name implies, are mainly used to produce local nerve block. At low concentrations, they are also able to suppress the spontaneous action potential discharge in sensory neurons that occurs in neuropathic pain. The properties of individual local anaesthetic drugs are summarised in Table 43.1.

Table 43.1 Properties of local anaesthetics

Drug	Onset	Duration	Tissue penetration	Plasma half-life (h)	Main unwanted effects	Notes
Cocaine	Medium	Medium	Good	~1	Cardiovascular and CNS effects owing to block of amine uptake	Rarely used, only as spray for upper respiratory tract
Procaine	Medium	Short	Poor	<1	CNS: restlessness, shivering, anxiety, occasionally convulsions followed by respiratory depression Cardiovascular system: bradycardia and decreased cardiac output; vasodilatation, which can cause cardiovascular collapse	The first synthetic agent No longer used
Lidocaine (lignocaine)	Rapid	Medium	Good	~2	As procaine but less tendency to cause CNS effects	Widely used for local anaesthesia Also used intravenously for treating ventricular dysrhythmias though no longer as first choice (Ch. 21)
Mepivacaine	Rapid	Medium	Good	~2	As procaine	Less vasodilatation (may be administered without a vasoconstrictor)
Tetracaine (amethocaine)	Very slow	Long	Moderate	~1	As lidocaine	Used mainly for spinal and corneal anaesthesia
Bupivacaine	Slow	Long	Moderate	~2	As lidocaine but greater cardiotoxicity	Widely used because of long duration of action Ropivacaine is similar, with less cardiotoxicity Levobupivacaine causes less cardiotoxicity and CNS depression than the racemate, bupivacaine
Prilocaine	Medium	Medium	Moderate	~2	No vasodilator activity Can cause methaemoglobinaemia	Widely used; not for obstetric analgesia because of risk of neonatal methaemoglobinaemia
Articaine	Rapid	Short	Good	0.5	As lidocaine	Used in dentistry While its chemical structure contains an amide linkage it also has an ester group on a side chain (Fig 43.1). Hydrolysis of the side chain inactivates the drug

CNS, central nervous system.

UNWANTED EFFECTS

When used clinically as local anaesthetics, the main unwanted effects involve the central nervous system (CNS) and the cardiovascular system (Table 43.1). Their action on the heart can also be of use in treating cardiac arrhythmias (see Ch. 21). Although local anaesthetics are usually administered in such a way as to minimise their spread to other parts of the body, they are ultimately absorbed into the systemic circulation. They may also be injected into veins or arterioles by accident.

Most local anaesthetics produce a mixture of depressant and stimulant effects on the CNS. Depressant effects predominate at low plasma concentrations, giving way to stimulation at higher concentrations, resulting in restlessness, tremor and sometimes convulsions, accompanied by subjective effects ranging from confusion to extreme

Actions of local anaesthetics

- Local anaesthetics block action potential generation by blocking sodium channels.
- Local anaesthetics are amphiphilic molecules with a hydrophobic aromatic group and a basic amine group.
- Local anaesthetics are weak bases that act in their cationic form but must reach their site of action by penetrating the nerve sheath and axonal membrane as un-ionised species.
- Many local anaesthetics show use-dependence (depth of block increases with action potential frequency). This arises:
  - because anaesthetic molecules gain access to the channel more readily when the channel is open
  - because anaesthetic molecules have higher affinity for inactivated than for resting channels.
- Use-dependence is mainly of importance in relation to antidysrhythmic and antiepileptic effects of sodium channel blockers.
- Local anaesthetics block conduction in peripheral nerves in the following order: small myelinated axons, non-myelinated axons, large myelinated axons. Nociceptive and sympathetic transmission is thus blocked first.
- Sodium-channel block in cardiac muscle and in CNS neurons is exploited in the therapy of cardiac dysrhythmias (Ch. 21) and epilepsy (Ch. 45).

agitation. Further increasing the dose produces profound CNS depression and death due to respiratory depression. The only local anaesthetic with markedly different CNS effects is **cocaine** (see Ch. 48), which produces euphoria at doses well below those that cause other CNS effects. This relates to its specific effect on monoamine uptake, an effect not shared by other local anaesthetics. **Procaine** is particularly liable to produce unwanted central effects, and has been superseded in clinical use by agents such as **lidocaine** and **prilocaine**. Studies with **bupivacaine**, a widely used long-acting local anaesthetic prepared as a racemic mixture of two optical isomers, suggested that its CNS and cardiac effects were mainly due to the *S*(+) isomer. The *R*(–) isomer (**levobupivacaine**) has a better margin of safety.

The adverse cardiovascular effects of local anaesthetics are due mainly to myocardial depression, conduction block and vasodilatation. Reduction of myocardial contractility probably results indirectly from an inhibition of the Na^+ current in cardiac muscle (see Ch. 21). The resulting decrease of $[Na^+]_i$ in turn reduces intracellular Ca^{2+} stores (see Ch. 4), and this reduces the force of contraction. Interference with atrioventricular conduction can result in partial or complete heart block, as well as other types of dysrhythmia. **Ropivacaine** has less cardiotoxicity than bupivacaine.

Vasodilatation, mainly affecting arterioles, is due partly to a direct effect on vascular smooth muscle, and partly to inhibition of the sympathetic nervous system. This leads to a fall in blood pressure, which may be sudden and life-threatening. Cocaine is an exception in respect of its cardiovascular effects, because of its ability to inhibit noradrenaline reuptake (see Chs 14 and 48). This enhances sympathetic activity, leading to tachycardia, increased cardiac output, vasoconstriction and increased arterial pressure.

Hypersensitivity reactions sometimes occur with local anaesthetics, usually in the form of allergic dermatitis but rarely as an acute anaphylactic reaction. Other unwanted effects that are specific to particular drugs include mucosal irritation (cocaine) and methaemoglobinaemia (which occurs after large doses of prilocaine, because of the production of a toxic metabolite).

PHARMACOKINETIC ASPECTS

Local anaesthetics vary a good deal in the rapidity with which they penetrate tissues, and this affects the rate at which they cause nerve block when injected into tissues, and the rate of onset of, and recovery from, anaesthesia (Table 43.1; see Becker & Reed, 2012). It also affects their usefulness as surface anaesthetics for application to mucous membranes.

Most of the ester-linked local anaesthetics (e.g. **tetracaine**) are rapidly hydrolysed by plasma cholinesterase, so their plasma half-life is short. Procaine – now rarely used – is hydrolysed to *p*-aminobenzoic acid, a folate precursor that interferes with the antibacterial effect of sulfonamides (see Ch. 51). The amide-linked drugs (e.g. lidocaine and prilocaine) are metabolised mainly in the liver, usually by *N*-dealkylation rather than cleavage of the amide bond, and the metabolites are often pharmacologically active.

Benzocaine is an unusual local anaesthetic of very low solubility, which is used as a dry powder to dress painful skin ulcers, or as throat lozenges. The drug is slowly released and produces long-lasting surface anaesthesia.[1]

The routes of administration, uses and main adverse effects of local anaesthetics are summarised in Table 43.2.

Most local anaesthetics have a direct vasodilator action, which increases the rate at which they are absorbed into the systemic circulation, thus increasing their potential toxicity and reducing their local anaesthetic action. **Adrenaline** (**epinephrine**) or **felypressin**, a short-acting vasopressin analogue (see Ch. 33), may be added to local anaesthetic solutions injected locally in order to cause vasoconstriction. Adrenaline absorbed into the circulation may induce unwanted cardiovascular effects such as tachycardia and vasoconstriction and felypressin may cause coronary artery constriction. Their use in patients with cardiovascular disease is contraindicated.

NEW APPROACHES

Blocking specific sodium-channel subtypes is seen as a promising therapeutic strategy for a variety of clinical conditions, including epilepsy (see Ch. 45), neurodegenerative diseases and stroke (see Ch. 40), neuropathic pain (see Ch. 42) and myopathies. As our understanding of the role of specific sodium-channel subtypes in different pathophysiological situations increases, so too will be the likelihood that selective blocking agents can be developed for use in different clinical situations.

[1]Benzocaine is also used in 'endurance' condoms to delay ejaculation.

Table 43.2 Methods of administration, uses and adverse effects of local anaesthetics

Method	Uses	Drug(s)	Notes and adverse effects
Surface anaesthesia	Nose, mouth, bronchial tree (usually in spray form), cornea, urinary tract, uterus (for hysteroscopy) Not very effective for skin[a]	Lidocaine, tetracaine, (amethocaine), dibucaine, benzocaine	Risk of systemic toxicity when high concentrations and large areas are involved
Infiltration anaesthesia	Direct injection into tissues to reach nerve branches and terminals Used in minor surgery	Most	Adrenaline (epinephrine) or felypressin often added as vasoconstrictors (not with fingers or toes, for fear of causing ischaemic tissue damage) Suitable for only small areas, otherwise serious risk of systemic toxicity
Intravenous regional anaesthesia	LA injected intravenously distal to a pressure cuff to arrest blood flow; remains effective until the circulation is restored Used for limb surgery	Mainly lidocaine, prilocaine	Risk of systemic toxicity when cuff is released prematurely; risk is small if cuff remains inflated for at least 20 min
Nerve block anaesthesia	LA is injected close to nerve trunks (e.g. brachial plexus, intercostal or dental nerves) to produce a loss of sensation peripherally Used for surgery, dentistry, analgesia	Most	Less LA needed than for infiltration anaesthesia Accurate placement of the needle is important Onset of anaesthesia may be slow Duration of anaesthesia may be increased by addition of vasoconstrictor
Spinal anaesthesia[b]	LA injected into the subarachnoid space (containing cerebrospinal fluid) to act on spinal roots and spinal cord Sometimes formulated with glucose ('hyperbaricity') so that spread of LA can be controlled by tilting patient Used for surgery to abdomen, pelvis or leg LA can be used alone or in conjunction with a general anaesthetic to reduce stress Provides good postoperative pain relief	Mainly lidocaine	Main risks are bradycardia and hypotension (owing to sympathetic block), respiratory depression (owing to effects on phrenic nerve or respiratory centre); avoided by minimising cranial spread Postoperative urinary retention (block of pelvic autonomic outflow) is common
Epidural anaesthesia[c]	LA injected into epidural space, blocking spinal roots Uses as for spinal anaesthesia; also for painless childbirth	Mainly lidocaine, bupivacaine	Unwanted effects similar to those of spinal anaesthesia but less probable, because longitudinal spread of LA is reduced Postoperative urinary retention common

LA, local anaesthetic.

[a]Surface anaesthesia does not work well on the skin, although a non-crystalline mixture of lidocaine and prilocaine (eutectic mixture of local anaesthetics or EMLA) has been developed for application to the skin, producing complete anaesthesia in about 1 h. Lidocaine is available in a patch preparation that can be applied to the skin to reduce pain in conditions such as post-herpetic neuralgia (shingles).

[b]Use of spinal anaesthesia is declining in favour of epidural administration.

[c]Intrathecal or epidural administration of LA in combination with an opioid (see Ch. 42) produces more effective analgesia than can be achieved with the opioid alone. Only a small concentration of LA is needed, insufficient to produce appreciable loss of sensation or other side effects. The mechanism of this synergism is unknown, but the procedure has proved useful in pain treatment.

▼ Charged local anaesthetics do not cross the plasma membrane and thus when applied to the outside of nerves do not inhibit action potential firing. They can, however, enter cells via the pore of TRP channels such as TRPV1 (see Ch. 42). As TRPV1 channels are primarily localised on sensory neurons carrying pain information this raises the possibility of applying a charged local anaesthetic such as QX-314 along with a TRPV1 activator thus allowing the local anaesthetic to enter and block sodium channels only on nociceptive neurons resulting in the block of pain sensation without affecting motor, autonomic or other sensory nerves.

OTHER DRUGS THAT AFFECT SODIUM CHANNELS

TETRODOTOXIN AND SAXITOXIN

▼ Tetrodotoxin (TTX) is produced by a marine bacterium and accumulates in the tissues of a poisonous Pacific fish, the puffer fish. The puffer fish is regarded in Japan as a special delicacy partly because of the mild tingling sensation that follows eating its flesh. To serve it in public restaurants, however, the chef must be registered as

Unwanted effects and pharmacokinetics of local anaesthetics

- Local anaesthetics are either esters or amides. Esters are rapidly hydrolysed by plasma and tissue esterases, and amides are metabolised in the liver. Plasma half-lives are generally short, about 1–2 h.
- Unwanted effects are due mainly to escape of local anaesthetics into the systemic circulation.
- Main unwanted effects are:
  - central nervous system effects, namely agitation, confusion, tremors progressing to convulsions and respiratory depression
  - cardiovascular effects, namely myocardial depression and vasodilatation, leading to fall in blood pressure
  - occasional hypersensitivity reactions.
- Local anaesthetics vary in the rapidity with which they penetrate tissues, and in their duration of action. **Lidocaine** (lignocaine) penetrates tissues readily and is suitable for surface application; **bupivacaine** has a particularly long duration of action.

sufficiently skilled in removing the toxic organs (especially liver and ovaries) so as to make the flesh safe to eat. Accidental TTX poisoning is quite common, nonetheless. Historical records of long sea voyages often contained reference to attacks of severe weakness, progressing to complete paralysis and death, caused by eating puffer fish. It was suggested that the powders used by voodoo practitioners to induce zombification may contain TTX but this is disputed.

Saxitoxin (STX) is produced by a marine microorganism that sometimes proliferates in very large numbers and even colours the sea, giving the 'red tide' phenomenon. At such times, marine shellfish can accumulate the toxin and become poisonous to humans.

These toxins, unlike conventional local anaesthetics, act exclusively from the outside of the membrane. Both are complex molecules, bearing a positively charged guanidinium moiety. The guanidinium ion is able to permeate voltage-sensitive sodium channels, and this part of the TTX or STX molecule lodges in the channel, while the rest of the molecule blocks its outer mouth. In the manner of its blockade of sodium channels, TTX can be likened to a champagne cork. In contrast to the local anaesthetics, there is no interaction between the gating and blocking reactions with TTX or STX—their association and dissociation are independent of whether the channel is open or closed. Some voltage-sensitive sodium channels expressed in cardiac muscle or upregulated in sensory neurons in neuropathic pain (i.e. $Na_V1.5$, $Na_V1.8$ and $Na_V1.9$) are relatively insensitive to TTX (see Ch. 42).

Both TTX and STX are unsuitable for clinical use as local anaesthetics, being expensive to obtain from their exotic sources and poor at penetrating tissues because of their very low lipid solubility. They have, however, been important as experimental tools for the isolation and cloning of sodium channels (see Ch. 4).

AGENTS THAT AFFECT SODIUM CHANNEL GATING

▼ Various substances modify sodium-channel gating in such a way as to *increase* the probability of opening of the channels (see Hille, 2001). They include various toxins, mainly from frog skin (e.g. batrachotoxin), scorpion or sea anemone venoms; plant alkaloids such as **veratridine**; and insecticides such as DDT and the pyrethrins. They facilitate sodium-channel activation so that sodium channels open at more negative potentials close to the normal resting potential; they also inhibit inactivation, so that the channels fail to close if the membrane remains depolarised. The membrane thus becomes hyperexcitable, and the action potential is prolonged. Spontaneous discharges occur at first, but the cells eventually become permanently depolarised and inexcitable. All these substances affect the heart, producing extrasystoles and other dysrhythmias, culminating in fibrillation; they also cause spontaneous discharges in nerve and muscle, leading to twitching and convulsions. The very high lipid solubility of substances like DDT makes them effective as insecticides, for they are readily absorbed through the integument. Drugs in this class are useful as experimental tools for studying sodium channels but have no clinical uses.

Clinical uses of local anaesthetics

- Local anaesthetics may be injected into soft tissue (e.g. of gums) or to block a nerve or nerve plexus.
- Co-administration of a vasoconstrictor (e.g. **adrenaline**) prolongs the local effect.
- Lipid-soluble drugs (e.g. **lidocaine**) are absorbed from mucous membranes and are used as surface anaesthetics.
- **Bupivacaine** has a slow onset but long duration. It is often used for epidural blockade (e.g. to provide continuous epidural blockade during labour) and spinal anaesthesia. Its isomer **levobupivacaine** is less cardiotoxic if it is inadvertently administered into a blood vessel.

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44 Anxiolytic and hypnotic drugs

OVERVIEW

In this chapter we discuss the nature of anxiety and the drugs used to treat it (anxiolytic drugs), as well as drugs used to treat insomnia (hypnotic drugs). Historically there was overlap between these two groups, reflecting the fact that older anxiolytic drugs commonly caused a degree of sedation and drowsiness. Newer anxiolytic drugs show much less sedative effect and other hypnotic drugs have been introduced that lack specific anxiolytic effects. Many of the drugs now used to treat anxiety were first developed, and are still used, to treat other disorders such as depression (Ch. 47), epilepsy (Ch. 45) and schizophrenia (Ch. 46). Here we will focus on their use as anxiolytics.

THE NATURE OF ANXIETY AND ITS TREATMENT

The normal fear response to threatening stimuli comprises several components, including defensive behaviours, autonomic reflexes, arousal and alertness, corticosteroid secretion and negative emotions. In anxiety states, these reactions occur in an anticipatory manner, independently of external events. The distinction between a 'pathological' and a 'normal' state of anxiety is not clear-cut but represents the point at which the symptoms interfere with normal productive activities. The term 'anxiety' is applied to several distinct disorders. A useful division of anxiety disorders that may help to explain why different types of anxiety respond differently to different drugs is into (i) disorders that involve *fear* (panic attacks and phobias) and (ii) those that involve a more general feeling of *anxiety* (often categorised as general anxiety disorder).

Anxiety disorders recognised clinically include the following:

- *generalised anxiety disorder* (an ongoing state of excessive anxiety lacking any clear reason or focus)
- *social anxiety disorder* (fear of being with and interacting with other people)
- *phobias* (strong fears of specific objects or situations, e.g. snakes, open spaces, flying)
- *panic disorder* (sudden attacks of overwhelming fear that occur in association with marked somatic symptoms, such as sweating, tachycardia, chest pains, trembling and choking). Such attacks can be induced even in normal individuals by infusion of sodium lactate, and the condition appears to have a genetic component
- *post-traumatic stress disorder* (anxiety triggered by recall of past stressful experiences)
- *obsessive–compulsive disorder* (compulsive ritualistic behaviour driven by irrational anxiety, e.g. fear of contamination).

Extensive descriptions of anxiety disorders can be found in DSM-5.[1]

It should be stressed that the treatment of such disorders generally involves psychological approaches as well as drug treatment. Over the last decade the drug treatment of anxiety has changed from using traditional anxiolytic/hypnotic agents (i.e. benzodiazepines and barbiturates) to using a range of drugs that are also used to treat other central nervous system (CNS) disorders (e.g. antidepressant, antiepileptic and antipsychotic drugs) or 5-hydroxytryptamine $(5\text{-HT})_{1A}$ receptor agonists (e.g. buspirone) that have no hypnotic effect. Furthermore, benzodiazepines, while being effective anxiolytic drugs, have the disadvantages of producing unwanted side effects such as amnesia, and of inducing tolerance and physical dependence, as well as being drugs of abuse. They are also ineffective in treating any depression that may occur along with anxiety. Antidepressants and **buspirone** do, however, require three or more weeks to show any therapeutic effect and must be taken continuously, whereas benzodiazepines can be useful for patients who need acute treatment, as they reduce anxiety within 30 min, and can be taken on an 'as needed' basis.

In recent years a number of over the counter 'relaxation' drinks containing CNS neurotransmitters, their precursors or other hormones and amino acids have been marketed, without any evidence of efficacy.[2]

MEASUREMENT OF ANXIOLYTIC ACTIVITY

ANIMAL MODELS OF ANXIETY

In addition to the subjective (emotional) component of human anxiety, there are measurable behavioural and physiological effects that also occur in experimental animals. In biological terms, anxiety induces a particular form of behavioural inhibition that occurs in response to novel environmental events that are threatening or painful. In animals, this behavioural inhibition may take the form of immobility or suppression of a behavioural response, such as bar pressing to obtain food (see p. 537). A rat placed in an unfamiliar environment normally responds by remaining immobile although alert (behavioural suppression) for a time, which may represent 'anxiety' produced by the strange environment. This immobility is reduced if anxiolytic drugs are administered. The 'elevated cross maze' is a widely used test model (see Fig 44.1). Two arms of the raised horizontal cross are closed in, and the others are open. Normally, rats spend most of their time in the closed arms and avoid the open arms (afraid, possibly, of falling off or being attacked). Administration of anxiolytic

[1]DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition 2013. American Psychiatric Association, Washington, DC.
[2]Because 'relaxation' drinks are classified as dietary supplements they are not subject to the same efficacy and safety tests as drugs (see Editorial in Nature Neuroscience, 2012, vol. 15, p. 497).

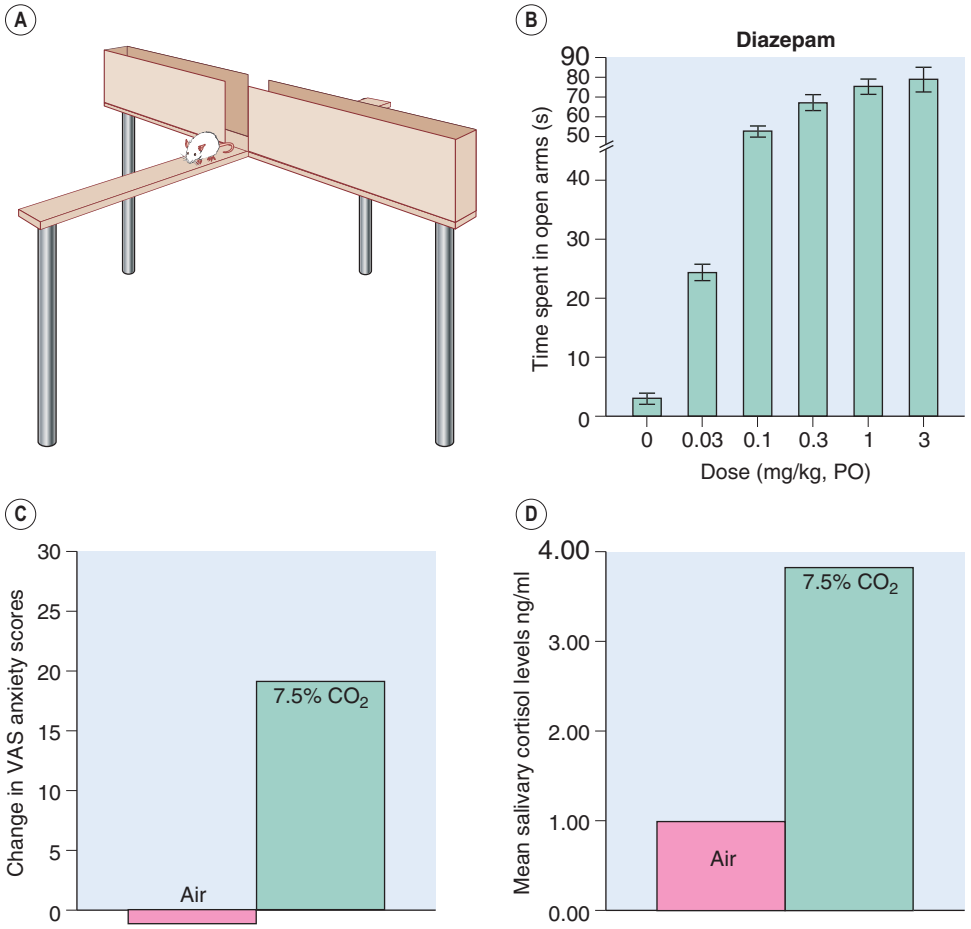

Fig. 44.1 Anxiety testing. [**A**] Illustration of the elevated plus maze with open and closed arms. [**B**] Effect of diazepam on time spent by rats in the open arms of the elevated plus maze. Each bar represents time spent with movement in the open arms during a 5 min test period. [**C**] and [**D**] Effect of a 7.5% CO_2 challenge for 20 min on anxiety, measured on a visual analogue scale (VAS), and salivary cortisol levels in human subjects. *(Panel [B], data taken from Kapus et al. 2008 Psychopharmacology 198, 2231–2241; panels [C] and [D], data taken from Seddon et al. 2011 J Psychopharmacol 25, 43–51.)*

drugs increases the time spent in the open arms and also increases the number of entries made into the open arm but without an increase in motor activity.

Conflict tests can also be used. For example, a rat trained to press a bar repeatedly to obtain a food pellet normally achieves a high and consistent response rate. A conflict element is then introduced: at intervals, indicated by an auditory signal, bar pressing results in an occasional 'punishment' in the form of an electric shock in addition to the reward of a food pellet. Normally, the rat ceases pressing the bar (behavioural inhibition), and thus avoids the shock, while the signal is sounding. The effect of an anxiolytic drug is to relieve this suppressive effect, so that the rats continue bar pressing for reward despite the 'punishment'. Other types of psychotropic drug are not effective, nor are analgesic drugs. Other evidence confirms that anxiolytic drugs affect the level of behavioural inhibition produced by the 'conflict situation', rather than simply raising the pain threshold.

Some of these 'anxiety' models may measure fear rather than general anxiety, which occurs in humans in the absence of specific stimuli. To develop new anxiolytic drugs, it is important to have animal tests that give a good guide to efficacy in humans, and much ingenuity has gone into developing and validating such tests (see Ramos, 2008).

TESTS ON HUMANS

Various subjective 'anxiety scale' tests have been devised based on standard patient questionnaires. Galvanic skin reactions – a measure of sweat secretion – are also used to monitor anxiety. Neuropsychological tests have been developed to investigate emotional and attentional biases associated with responses to emotive faces and words. An experience akin to a panic attack can be induced in many subjects by breathing an increased level of CO_2, usually prolonged breathing of 7.5% CO_2 or a single inhalation of 35% CO_2 (see Fig. 44.1). Such tests have confirmed the efficacy of many anxiolytic drugs, but placebo treatment often also produces highly significant responses.

A human version of the conflict test described above involves the substitution of money for food pellets, and the use of graded electric shocks as punishment. As with rats, administration of diazepam increases the rate of button pressing for money during the periods when the punishment was in operation, although the subjects reported no change in the painfulness of the electric shock.

Measurement of anxiolytic activity

- Behavioural tests in animals are based on measurements of the behavioural inhibition (considered to reflect 'anxiety') in response to conflict or novelty.
- Human tests for anxiolytic drugs employ psychiatric rating scales or measures of autonomic responses, such as the galvanic skin response.
- Tests such as these can distinguish between anxiolytic drugs (benzodiazepines, **buspirone**, etc.) and sedatives (e.g. barbiturates).

DRUGS USED TO TREAT ANXIETY

The main groups of drugs (see review by Hoffman & Mathew, 2008) are as follows:

- Antidepressants (see Ch. 47 for details). Selective serotonin (5-HT) reuptake inhibitors (SSRIs; e.g. **fluoxetine**, **paroxetine** and **sertraline**) and serotonin/noradrenaline reuptake inhibitors (SNRIs; e.g. **venlafaxine and duloxetine**) are effective in the treatment of generalised anxiety disorder, phobias, social anxiety disorder and post-traumatic stress disorder. Older antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) are also effective but a lower side effect profile favours the use of SSRIs. These agents have the additional advantage of reducing depression, which is not uncommonly associated with anxiety.
- **Benzodiazepines.** Used to treat acute anxiety. Those used to treat anxiety have a long biological half-life (see Table 44.1). They may be co-administered during stabilisation of a patient on an SSRI. There is some evidence that in panic disorders the combination of a benzodiazepine with an SSRI may be better than an SSRI alone.
- **Buspirone**. This 5-HT_{1A} receptor agonist is effective in generalised anxiety disorder but ineffective in the treatment of phobias or social anxiety disorder.
- **Gabapentin, pregabalin, tiagabine, valproate** and **levetiracetam**, antiepileptic drugs (see Ch. 45), are also effective in treating generalised anxiety disorder.
- Some atypical antipsychotic agents (see Ch. 46) such as **olanzapine**, **risperidone**, **quetiapine** and **ziprasidone** may be effective in some forms of anxiety, including generalised anxiety disorder and post-traumatic stress disorder.
- β-Adrenoceptor antagonists (e.g. **propranolol**; Ch. 14). These are used to treat some forms of anxiety, particularly where physical symptoms such as sweating, tremor and tachycardia are troublesome.[3] Their effectiveness depends on block of peripheral sympathetic responses rather than on any central effects.

Antidepressants (Ch. 47), antiepileptics (Ch. 45), antipsychotics Ch. 46), β-adrenoceptor antagonists (Ch. 14) and antihistamines (Ch. 26) are described in detail elsewhere in this book. Some discussion of how SSRIs exert their anxiolytic activity is included in the section on buspirone (see p. 543). Here we focus on drugs whose primary use is to treat anxiety.

[3]β-Blockers are sometimes used by actors and musicians to reduce the symptoms of stage fright, but their use by snooker players to minimise tremor is banned as unsportsmanlike.

Classes of anxiolytic drugs

- Antidepressant drugs (SSRIs, SNRIs, TCAs and MAOIs – see Ch. 47) are effective anxiolytic agents.
- Benzodiazepines are used for treating acute anxiety and insomnia.
- **Buspirone** is a 5-HT_{1A} receptor agonist with anxiolytic activity but little sedative effect.
- Some antiepileptic drugs (e.g. **gabapentin, pregabalin, tiagabine, valproate** and **levetiracetam**) have anxiolytic properties.
- Some atypical antipsychotic agents can be useful to treat some forms of anxiety, but have significant unwanted effects.
- β-Adrenoceptor antagonists are used mainly to reduce physical symptoms of anxiety (tremor, palpitations, etc.); no effect on affective component.

BENZODIAZEPINES AND RELATED DRUGS

▼ The first benzodiazepine, **chlordiazepoxide**, was synthesised by accident in 1961, the unusual seven-membered ring having been produced as a result of a reaction that went wrong in the laboratories of Hoffman–La Roche. Its unexpected pharmacological activity was recognised in a routine screening procedure, and benzodiazepines quite soon became the most widely prescribed drugs in the pharmacopoeia.

The basic chemical structure of benzodiazepines consists of a seven-membered ring fused to an aromatic ring, with four main substituent groups that can be modified without loss of activity. Thousands of compounds have been made and tested, and about 20 are available for clinical use, the most important ones being listed in Table 44.1. They are basically similar in their pharmacological actions, although some degree of selectivity has been reported. For example, some, such as **clonazepam**, show anticonvulsant activity with less marked sedative effects. From a clinical point of view, differences in pharmacokinetic behaviour among different benzodiazepines (see Table 44.1) are more important than differences in profile of activity. Drugs with a similar structure have been discovered that specifically antagonise the effects of the benzodiazepines, for example **flumazenil** (see p. 540).

The term 'benzodiazepine' refers to a distinct chemical structure. Drugs such as **zolpidem** and **zopiclone** as well as **abecarnil** – a β-carboline (not licensed for clinical use) – have different chemical structures and are therefore not benzodiazepines. However, since they bind to the same sites, often referred to as the 'benzodiazepine receptor', they are discussed along with the benzodiazepines.

MECHANISM OF ACTION

Benzodiazepines act selectively on $GABA_A$ receptors (Ch. 38), which mediate inhibitory synaptic transmission throughout the central nervous system. Benzodiazepines enhance the response to GABA by facilitating the opening of GABA-activated chloride channels (Ch. 38, Fig. 38.5). They bind specifically to a regulatory site on the receptor, distinct from the GABA-binding sites (see Fig. 44.3), and act allosterically to increase the affinity of GABA for the receptor. Single-channel recordings show an increase

Table 44.1 Characteristics of benzodiazepines in humans

Drug(s)	Half-life of parent compound (h)	Active metabolite	Half-life of metabolite (h)	Overall duration of action	Main use(s)
Midazolam[a]	2–4	Hydroxylated derivative	2	Ultrashort (<6 h)	Hypnotic Midazolam used as intravenous anaesthetic
Zolpidem[b]	2	No	–	Ultrashort (~4 h)	Hypnotic
Lorazepam, oxazepam, temazepam, lormetazepam	8–12	No	–	Short (12–18 h)	Anxiolytic, hypnotic
Alprazolam	6–12	Hydroxylated derivative	6	Medium (24 h)	Anxiolytic, antidepressant
Nitrazepam	16–40	No	–	Medium	Anxiolytic
Diazepam, chlordiazepoxide	20–40	Nordazepam	60	Long (24–48 h)	Anxiolytic, muscle relaxant Diazepam used as anticonvulsant
Flurazepam	1	Desmethyl-flurazepam	60	Long	Anxiolytic
Clonazepam	50	No	–	Long	Anticonvulsant, anxiolytic (especially mania)

[a]Another short-acting benzodiazepine, triazolam has been withdrawn from use in the UK on account of side effects.
[b]Zolpidem is not a benzodiazepine but acts in a similar manner. Zopiclone and zaleplon are similar.

in the frequency of channel opening by a given concentration of GABA, but no change in the conductance or mean open time, consistent with an effect on GABA binding rather than the channel-gating mechanism. Benzodiazepines do not affect receptors for other amino acids, such as glycine or glutamate (Fig. 44.2).

▼ The $GABA_A$ receptor is a ligand-gated ion channel (see Ch. 3) consisting of a pentameric assembly of different subunits, the main ones being α, β and γ (see Ch. 38). The $GABA_A$ receptor should actually be thought of as a family of receptors as there are six different subtypes of α subunit, three subtypes of β and three subtypes of γ. Although the potential number of combinations is therefore large, certain combinations predominate in the adult brain (see Ch. 38). The various combinations occur in different parts of the brain, have different physiological functions and have subtle differences in their pharmacological properties.

Benzodiazepines bind across the interface between the α and γ subunits but only to receptors that contain γ2 and α1, α2, α3 or α5 subunits. Genetic approaches have been used to study the roles of different subunits in the different behavioural effects of benzodiazepines. Behavioural analysis of mice with various mutations of the $GABA_A$ receptor subunit indicates that α1-containing receptors mediate the anticonvulsant, sedative/hypnotic and addictive effects but not the anxiolytic effect of benzodiazepines whereas α2-containing receptors mediate the anxiolytic effect, α2-, α3- and α5-containing receptors mediate muscle relaxation and α1- and α5-containing receptors mediate the amnesic effects (Tan et al., 2011).

The obvious next step was to try to develop subunit-selective drugs. Unfortunately, this has proved difficult, due to the structural similarity between the benzodiazepine binding site on different α subunits. The α-subunit selectivity of some benzodiazepines is given in Table 44.2. It was hoped that selective efficacy at α2-containing receptors would produce anxiolytic drugs lacking the unwanted effects of sedation and amnesia. However, such compounds have not yet translated into human therapeutic agents (Skolnick, 2012). **Pagoclone**, reported to be a full agonist at α3 with less efficacy at α1, α2 and α5, has little or no sedative/hypnotic or amnesic actions.

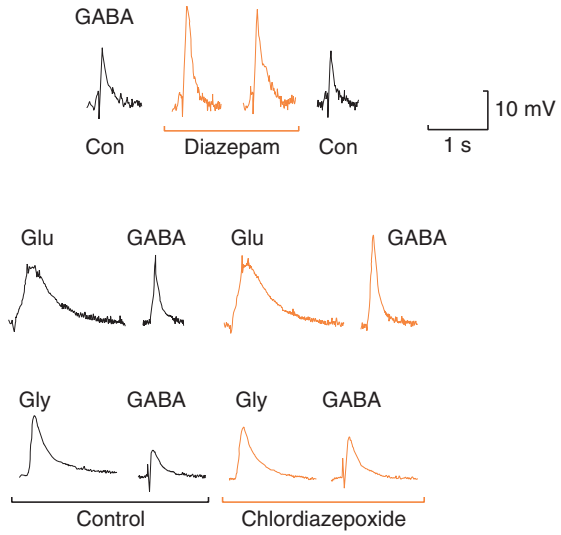

Fig. 44.2 Potentiating effect of benzodiazepines and chlordiazepoxide on the action of GABA. Drugs were applied by ionophoresis to mouse spinal cord neurons grown in tissue culture, from micropipettes placed close to the cells. The membrane was hyperpolarised to –90 mV, and the cells were loaded with Cl^- from the recording microelectrode, so inhibitory amino acids (GABA and glycine, Gly), as well as excitatory ones (glutamate, Glu), caused depolarising responses. The potentiating effect of diazepam is restricted to GABA responses, glutamate and glycine responses being unaffected. Con, control.

Table 44.2 $GABA_A$-receptor α-subunit selectivity of some therapeutically used benzodiazepines

Drug	Subunit selectivity
Diazepam	α1, α2, α3, α4, α5, α6
Flunitrazepam	α1, α2, α5
Midazolam	α1, α2, α3, α4, α5, α6
Zolpidem	α1
Flumazenil	Antagonist at α1, α2, α3, α4, α5, α6

(Adapted from Tan KR, Rudolph U, Lüscher C 2011 Hooked on benzodiazepines: $GABA_A$ receptor subtypes and addiction. Trends Neurosci 34, 188–197)

Peripheral benzodiazepine-binding sites, not associated with GABA receptors, are present in many tissues. The target is a protein known as *translocator protein* located primarily on mitochondrial membranes.

BENZODIAZEPINE ANTAGONISTS AND INVERSE AGONISTS

Competitive antagonists of benzodiazepines were first discovered in 1981. The best-known compound is flumazenil. This compound was originally reported to lack effects on behaviour or on drug-induced convulsions when given on its own, although it was later found to possess some 'anxiogenic' and proconvulsant activity. Flumazenil can be used to reverse the effect of benzodiazepine overdosage (normally used only if respiration is severely depressed), or to reverse the effect of benzodiazepines such as midazolam used for minor surgical procedures. Flumazenil acts quickly and effectively when given by injection, but its action lasts for only about 2 h, so drowsiness tends to return. Convulsions may occur in patients treated with flumazenil, and this is more common in patients receiving tricyclic antidepressants (Ch. 47). Reports that flumazenil improves the mental state of patients with severe liver disease (hepatic encephalopathy) and alcohol intoxication have not been confirmed in controlled trials, although partial inverse agonists do appear to be effective in animal models of hepatic encephalopathy (Ahboucha & Butterworth, 2005).

▼ The term *inverse agonist* (Ch. 2) is applied to drugs that bind to benzodiazepine receptors and exert the opposite effect to that of conventional benzodiazepines, producing signs of increased anxiety and convulsions. Ethyl-β-carboline-3-carboxylate (βCCE) and diazepam-binding inhibitor (see p. 541), as well as some benzodiazepine analogues, show inverse agonist activity. It is possible (see Fig. 44.3) to explain these complexities in terms of the two-state model discussed in Chapter 2, by postulating that the benzodiazepine receptor exists in two distinct conformations, only one of which [A] can bind GABA molecules and open the chloride channel. The other conformation [B] cannot bind GABA. Normally, with no benzodiazepine receptor ligand present, there is an equilibrium between these two conformations; sensitivity to GABA is present but submaximal. Benzodiazepine agonists (e.g. diazepam) are postulated to bind preferentially to conformation [A], thus shifting the equilibrium in favour of [A] and enhancing GABA sensitivity. Inverse agonists bind selectively to [B] and have the opposite effect. Competitive antagonists would bind equally to [A] and [B], and consequently would not disturb the conformational equilibrium but antagonise the effect of both agonists and inverse agonists

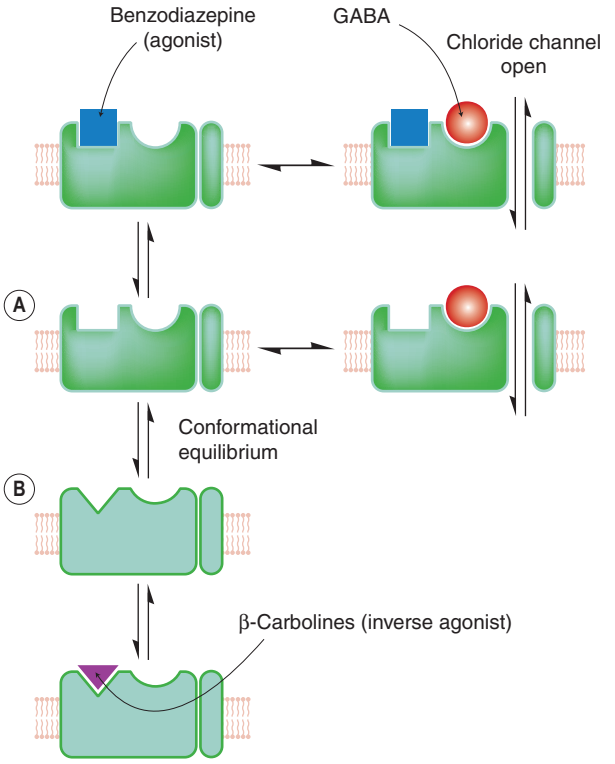

Fig. 44.3 Model of benzodiazepine/GABA receptor interaction. Benzodiazepine agonists, antagonists and inverse agonists are believed to bind to a site on the GABA receptor distinct from the GABA-binding site. A conformational equilibrium exists between states in which the benzodiazepine receptor exists in its agonist-binding conformation [**A**] and in its inverse agonist-binding conformation [**B**]. In the latter state, the GABA receptor has a much reduced affinity for GABA; consequently, the chloride channel remains closed.

PHARMACOLOGICAL EFFECTS AND USES

The main effects of benzodiazepines are:

- reduction of anxiety and aggression
- induction of sleep (see section on hypnotic drugs, p. 544)
- reduction of muscle tone
- anticonvulsant effect
- anterograde amnesia.

Reduction of anxiety and aggression

Benzodiazepines show anxiolytic effects in animal tests, as described above, and also exert a marked 'taming' effect, allowing animals to be handled more easily.[4] With the possible exception of alprazolam (Table 44.1), benzodiazepines do not have antidepressant effects. Benzodiazepines may paradoxically produce an increase in irritability and aggression in some individuals. This appears to be particularly pronounced with the ultrashort-acting drug triazolam (and led to its withdrawal in the UK and some other countries), and is generally more common with short-acting compounds. It is probably

[4]This depends on the species. Cats actually become more excitable, as a colleague of one of the authors discovered to his cost when attempting to sedate a tiger in the Baltimore zoo.

a manifestation of the benzodiazepine withdrawal syndrome, which occurs with all these drugs (see p. 542) but is more acute with drugs whose action wears off rapidly.

Benzodiazepines are now used mainly for treating acute anxiety states, behavioural emergencies and during procedures such as endoscopy. They are also used as premedication before surgery (both medical and dental). Under these circumstances their anxiolytic, sedative and amnesic properties may be beneficial. Intravenous midazolam can be used to induce anaesthesia (see Ch. 41).

Reduction of muscle tone

Benzodiazepines reduce muscle tone by a central action on $GABA_A$ receptors, primarily in the spinal cord.

Increased muscle tone is a common feature of anxiety states in humans and may contribute to the aches and pains, including headache, that often trouble anxious patients. The relaxant effect of benzodiazepines may therefore be clinically useful. A reduction of muscle tone appears to be possible without appreciable loss of coordination. However, with intravenous administration in anaesthesia and in overdose when these drugs are being abused, airway obstruction may occur. Other clinical uses of muscle relaxants are discussed in Chapter 13.

Anticonvulsant effects

All the benzodiazepines have anticonvulsant activity in experimental animal tests. They are highly effective against chemically induced convulsions caused by **pentylenetetrazol**, **bicuculline** and similar drugs that act by blocking $GABA_A$ receptors (see Chs 38 and 45) but less so against electrically induced convulsions.

Clonazepam (see Table 44.1), **diazepam** and **lorazepam** are used to treat epilepsy (Ch. 45). They can be given intravenously to control life-threatening seizures in status epilepticus. Diazepam can be administered rectally to children to control acute seizures. Tolerance develops to the anticonvulsant actions of benzodiazepines (see p. 542).

Anterograde amnesia

Benzodiazepines prevent memory of events experienced while under their influence, an effect not seen with other CNS depressants. Minor surgical or invasive procedures can thus be performed without leaving unpleasant memories. **Flunitrazepam** (better known to the general public by one of its trade names, Rohypnol) is infamous as a date rape drug and victims frequently have difficulty in recalling exactly what took place during the attack.

Amnesia is thought to be due to benzodiazepines binding to $GABA_A$ receptors containing the α5 subunit. α5-Knockout mice show an enhanced learning and memory phenotype. This raises the possibility that an α5 subunit-selective inverse agonist could be memory enhancing.

IS THERE AN ENDOGENOUS BENZODIAZEPINE-LIKE MEDIATOR?

▼ Despite considerable scientific effort, the question of whether or not there are endogenous ligands for the benzodiazepine receptors, whose function is to regulate the action of GABA, remains unanswered.

That the antagonist **flumazenil** produces responses both *in vivo* and *in vitro* in the absence of any exogenous benzodiazepines is frequently cited to support the view that there must be ongoing benzodiazepine receptor activation by endogenous ligand(s). Although flumazenil was originally described as a neutral antagonist, it is possible that it has agonist or inverse agonist activity at subtypes of $GABA_A$ receptor (depending on the α subunit present) or in some pathological conditions in which the $GABA_A$ receptors have become modified.

Several endogenous compounds that act on benzodiazepine receptors have been isolated, including *β-carbolines* (e.g. βCCE), structurally related to tryptophan, and *diazepam-binding inhibitor*, a 10-kDa peptide. Whether these molecules exist in the brain (i.e. are endogenous) or are generated during the processes involved in extracting them from the tissue is an open issue. Interestingly, both βCCE and diazepam-binding inhibitor have the opposite effect to benzodiazepines, i.e. they are inverse agonists and inhibit chloride channel opening by GABA and, in the whole animal, exert anxiogenic and proconvulsant effects. There was also a suggestion that benzodiazepines themselves may occur naturally in the brain but the origin of these compounds and how biosynthesis occurs is unclear. At present there is no general agreement on the identity and function of endogenous ligands for the benzodiazepine receptor. Other possible endogenous modulators of $GABA_A$ receptors include steroid metabolites but they bind to a different site from benzodiazepines (see Ch. 38).

PHARMACOKINETIC ASPECTS

Benzodiazepines are well absorbed when given orally, usually giving a peak plasma concentration in about 1 h. Some (e.g. oxazepam, lorazepam) are absorbed more slowly. They bind strongly to plasma protein, and their high lipid solubility causes many of them to accumulate gradually in body fat. They are normally given by mouth but can be given intravenously (e.g. diazepam in status epilepticus, midazolam in anaesthesia) or rectally. Intramuscular injection often results in slow absorption.

Benzodiazepines are all metabolised and eventually excreted as glucuronide conjugates in the urine. They vary greatly in duration of action and can be roughly divided into short-, medium- and long-acting compounds (Table 44.1). Duration of action influences their use, short-acting compounds being useful hypnotics with reduced hangover effect on wakening, long-acting compounds being more useful for use as anxiolytic and anticonvulsant drugs. Several are converted to active metabolites such as *N*-desmethyldiazepam (**nordiazepam**), which has a half-life of about 60 h, and which accounts for the tendency of many benzodiazepines to produce cumulative effects and long hangovers when they are given repeatedly. The short-acting compounds are those that are metabolised directly by conjugation with glucuronide. Figure 44.4 shows the gradual build up and slow disappearance of nordiazepam from the plasma of a human subject given diazepam daily for 15 days.

▼ Advancing age affects the rate of oxidative reactions more than that of conjugation reactions. Thus the effect of the long-acting benzodiazepines tends to increase with age, and it is common for drowsiness and confusion to develop insidiously for this reason.[5]

UNWANTED EFFECTS

These may be divided into:

- toxic effects resulting from acute overdosage
- unwanted effects occurring during normal therapeutic use
- tolerance and dependence.

[5]At the age of 91, the grandmother of one of the authors was growing increasingly forgetful and mildly dotty, having been taking nitrazepam for insomnia regularly for years. To the author's lasting shame, it took a canny general practitioner to diagnose the problem. Cancellation of the nitrazepam prescription produced a dramatic improvement.

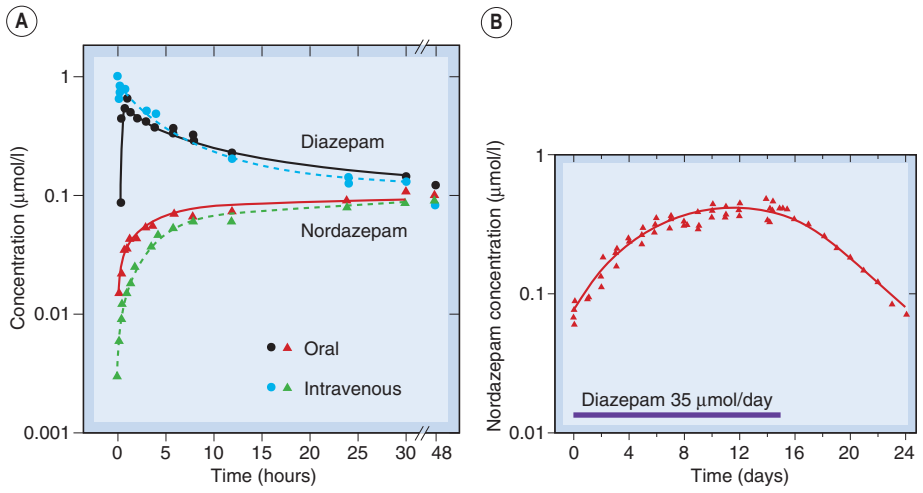

Fig. 44.4 Pharmacokinetics of diazepam in humans. [**A**] Concentrations of diazepam and nordazepam following a single oral or intravenous dose. Note the very slow disappearance of both substances after the first 20 h. [**B**] Accumulation of nordazepam during 2 weeks' daily administration of diazepam, and slow decline (half-life about 3 days) after cessation of diazepam administration. *(Data from Kaplan SA et al. 1973 J Pharmacol Sci 62, 1789.)*

Acute toxicity

Benzodiazepines in acute overdose are considerably less dangerous than other anxiolytic/hypnotic drugs. Because such agents are often used in attempted suicide, this is an important advantage. In overdose, benzodiazepines cause prolonged sleep, without serious depression of respiration or cardiovascular function. However, in the presence of other CNS depressants, particularly alcohol, benzodiazepines can cause severe, even life-threatening, respiratory depression. This is a frequent problem when benzodiazepines are abused (see Chs 49 and 58). The availability of an effective antagonist, flumazenil, means that the effects of an acute overdose can be counteracted,[6] which is not possible for most CNS depressants.

Side effects during therapeutic use

The main side effects of benzodiazepines are drowsiness, confusion, amnesia and impaired coordination, which considerably impairs manual skills such as driving performance. Benzodiazepines enhance the depressant effect of other drugs, including alcohol, in a more than additive way. The long and unpredictable duration of action of many benzodiazepines is important in relation to side effects. Long-acting drugs such as nitrazepam are no longer used as hypnotics, and even shorter-acting compounds such as lorazepam can produce a substantial day-after impairment of job performance and driving skill.

Tolerance and dependence

Tolerance (i.e. a gradual escalation of dose needed to produce the required effect) occurs with all benzodiazepines, as does dependence, which is their main drawback. They share these properties with other sedatives. Tolerance appears to represent a change at the receptor level, but the mechanism is not well understood. There may be selective loss of membrane $GABA_A$ receptors containing the α2 subunit (Jacob et al., 2012).

At the receptor level, the degree of tolerance will be governed both by the number of receptors occupied (i.e. the dose) and the duration of receptor occupancy (which may vary according to the therapeutic use). Therefore, marked tolerance develops when benzodiazepines are used continuously to treat epilepsy whereas less tolerance occurs to the sleep-inducing effect when the subject is relatively drug free during the day. It is not clear to what degree tolerance develops to the anxiolytic effect.

Benzodiazepines produce dependence, and this is a major problem. In human subjects and patients, abrupt cessation of benzodiazepine treatment after weeks or months causes a rebound heightened anxiety, together with tremor, dizziness, tinnitus, weight loss and disturbed sleep due to enhanced REM sleep (see p. 544). It is recommended that benzodiazepines be withdrawn gradually by stepwise lowering of the dose. Animals show only a weak tendency to self-administer benzodiazepines. Withdrawal after chronic administration causes physical symptoms, namely nervousness, tremor, loss of appetite and sometimes convulsions.[7] The withdrawal syndrome, in both animals and humans, is slower in onset than with opioids, probably because of the long plasma half-life of most benzodiazepines. With diazepam, the withdrawal symptoms may take up to 3 weeks to become apparent. Short-acting benzodiazepines cause more abrupt withdrawal effects.

The physical and psychological withdrawal symptoms make it difficult for patients to give up taking benzodiazepines, but craving (i.e. severe psychological dependence that outlasts the physical withdrawal syndrome), which occurs with many drugs of abuse (Ch. 49), is not a major problem.

Abuse potential

Benzodiazepines are widely abused drugs, often taken in combination with other drugs such as opioids or alcohol. Most illicit use comes from diversion of prescribed benzodiazepines. They induce a feeling of calm and reduced anxiety, with users describing a dream state where they are cushioned from reality. The risk of overdose is greatly increased when used in combination with alcohol. Tolerance and physical dependence occur as described above.

[6]In practice, patients are usually left to sleep it off, because there is a risk of seizures with flumazenil; however, flumazenil may be useful diagnostically to rule out coma of other causes.

[7]Withdrawal symptoms can be more severe. A relative of one of the authors, advised to stop taking benzodiazepines after 20 years, suffered hallucinations and one day tore down all the curtains, convinced that they were on fire.

Benzodiazepines

- Act by binding to a specific regulatory site on the $GABA_A$ receptor, thus enhancing the inhibitory effect of GABA. Subtypes of the $GABA_A$ receptor exist in different regions of the brain and differ in their functional effects.
- Anxiolytic benzodiazepines are agonists at this regulatory site. Other benzodiazepines (e.g. **flumazenil**) are antagonists or weak inverse agonists and prevent the actions of the anxiolytic benzodiazepines. Inverse agonists (not used clinically) are anxiogenic.
- Anxiolytic effects are mediated by $GABA_A$ receptors containing the $\alpha 2$ subunit, while sedation occurs through those with the $\alpha 1$ subunit.
- Benzodiazepines cause:
  - reduction of anxiety and aggression
  - sedation, leading to improvement of insomnia
  - muscle relaxation and loss of motor coordination
  - suppression of convulsions (antiepileptic effect)
  - anterograde amnesia.
- Differences in the pharmacological profile of different benzodiazepines are minor; **clonazepam** appears to have more anticonvulsant action in relation to its other effects.
- Benzodiazepines are active orally and differ mainly in respect of their duration of action. Short-acting agents (e.g. **lorazepam** and **temazepam**, half-lives 8–12 h) are metabolised to inactive compounds and are used mainly as sleeping pills. Some long-acting agents (e.g. **diazepam** and **chlordiazepoxide**) are converted to a long-lasting active metabolite (**nordazepam**).
- Some are used intravenously, for example **diazepam** in status epilepticus, **midazolam** in anaesthesia.
- **Zolpidem** is a short-acting drug that is not a benzodiazepine but acts similarly and is used as a hypnotic.
- Benzodiazepines are relatively safe in overdose. Their main disadvantages are interaction with alcohol, long-lasting 'hangover' effects and the development of tolerance and physical dependence – characteristic withdrawal syndrome on cessation of use.

BUSPIRONE

Buspirone is used to treat generalised anxiety disorders. It is less effective in controlling panic attacks or severe anxiety states.

Buspirone is a partial agonist at $5\text{-}HT_{1A}$ receptors (Ch. 15) and also binds to dopamine receptors, but it is likely that its 5-HT-related actions are important in relation to anxiety suppression, because related experimental compounds (e.g. ipsapirone and gepirone), which are highly specific for $5\text{-}HT_{1A}$ receptors, show similar anxiolytic activity in experimental animals. However, buspirone takes days or weeks to produce its effect in humans, suggesting a more complex mechanism of action than simply activation of $5\text{-}HT_{1A}$ receptors. SSRIs also have a delayed onset to their anxiolytic actions.

$5\text{-}HT_{1A}$ receptors are expressed on the soma and dendrites of 5-HT-containing neurons, where they function as inhibitory autoreceptors, as well as being expressed on other types of neuron (e.g. noradrenergic locus coeruleus neurons) where, along with other types of 5-HT receptor (see Ch. 39), they mediate the postsynaptic actions of 5-HT. Postsynaptic $5\text{-}HT_{1A}$ receptors are highly expressed within the cortico-limbic circuits implicated in emotional behaviour. One theory of how buspirone and SSRIs produce their delayed anxiolytic effect is that over time they induce desensitisation of somatodendritic $5\text{-}HT_{1A}$ autoreceptors, resulting in heightened excitation of serotonergic neurons and enhanced 5-HT release. This might also explain why early in treatment anxiety can be worsened by these drugs due to the initial activation of $5\text{-}HT_{1A}$ autoreceptors and inhibition of 5-HT release. This receptor desensitisation theory would predict that a $5\text{-}HT_{1A}$ antagonist that would rapidly block the action of 5-HT at $5\text{-}HT_{1A}$ autoreceptors and thus swiftly enhance 5-HT release, might be anxiolytic without delayed onset. Drugs with combined $5\text{-}HT_{1A}$ antagonism and SSRI properties have been developed but have not been found to be effective in man, perhaps because they block both $5HT_{1A}$ autoreceptors and postsynaptic receptors, the latter effect occluding the beneficial effect of the former. Elevated 5-HT levels may also induce other postsynaptic adaptations. $5\text{-}HT_2$ receptors have also been implicated, down-regulation of which may be important for anxiolytic action. Drugs with $5\text{-}HT_2$ and $5\text{-}HT_3$ receptor antagonist activity are in clinical trials for treating anxiety.

Buspirone inhibits the activity of noradrenergic locus coeruleus neurons (Ch. 39) and thus interferes with arousal reactions. It has side effects quite different from those of benzodiazepines. It does not cause sedation or motor incoordination, nor have tolerance or withdrawal effects been reported. Its main side effects are nausea, dizziness, headache and restlessness, which generally seem to be less troublesome than the side effects of benzodiazepines. Buspirone does not suppress the benzodiazepine withdrawal syndrome, presumably because it acts by a different mechanism. Hence, when switching from benzodiazepine treatment to buspirone treatment, the benzodiazepine dose still needs to be reduced gradually.

Antidepressants and $5\text{-}HT_{1A}$ agonists as anxiolytic drugs

- Anxiolytic effects take days or weeks to develop.
- Antidepressants (SSRIs, SNRIs, TCAs and MAOIs – see Ch. 47):
  - effective treatments for generalised anxiety disorder, phobias, social anxiety disorder and post-traumatic stress disorder
  - may also reduce depression associated with anxiety.
- **Buspirone** is a potent agonist at $5\text{-}HT_{1A}$ receptors:
  - it is an effective treatment for generalised anxiety disorder but not phobias
  - side effects appear less troublesome than with benzodiazepines; they include dizziness, nausea, headache, but not sedation or loss of coordination.

OTHER POTENTIAL ANXIOLYTIC DRUGS

Besides the GABA and 5-HT mechanisms discussed above, many other transmitters and hormones have been

implicated in anxiety and panic disorders, particularly noradrenaline, glutamate, corticotrophin-releasing factor, cholecystokinin (CCK), substance P, neuropeptide Y, galanin, orexins and neurosteroids. Anxiolytic drugs aimed at these targets are in development (see Mathew et al., 2009).

An exciting recent development is the realisation that the unpleasant, negative memories that underlie fear are not necessarily permanent. When such memories are reactivated (recalled) they return transiently to a labile state that can be disrupted. In humans, propranolol administered before memory reactivation may erase negative memories (see Lonergan et al., 2013). NMDA receptor antagonists may have a similar effect. Disrupting unpleasant memories in this way may provide a new treatment for post-traumatic stress disorder.

Clinical use of drugs as anxiolytics

- Antidepressants are now the main drugs used to treat anxiety, especially when this is associated with depression. Their effects are slow in onset (>2 weeks).
- Benzodiazepines are now usually limited to acute relief of severe and disabling anxiety.
- **Buspirone** (5-HT_{1A} agonist) has a different pattern of adverse effects from benzodiazepines and much lower abuse potential. Its effect is slow in onset (>2 weeks). It is licensed for short-term use, but specialists may use it for several months.

DRUGS USED TO TREAT INSOMNIA (HYPNOTIC DRUGS)

Insomnia can be *transient*, in people who normally sleep well but have to do shift work or have jet lag, *short-term*, usually due to illness or emotional upset, or *chronic*, where there is an underlying cause such as anxiety, depression, drug abuse, pain, pruritus or dyspnoea. While in anxiety and depression the underlying psychiatric condition should be treated, improvement of sleep patterns can improve the underlying condition. The drugs used to treat these conditions are:

- Benzodiazepines. Short-acting benzodiazepines (e.g. lorazepam and temazepam) are used for treating insomnia as they have little hangover effect. Diazepam, which is longer-acting, can be used to treat insomnia associated with daytime anxiety.
- **Zaleplon**, **zolpidem** and **zopiclone**. Although chemically distinct, these short-acting hypnotics act similarly to benzodiazepines. They lack appreciable anxiolytic activity (see p. 540).
- **Chlormethiazole.** It acts as a positive allosteric modulator of $GABA_A$ receptors acting at a site distinct from the benzodiazepines.
- Melatonin receptor agonists. **Melatonin** and **ramelteon** are agonists at MT_1 and MT_2 receptors (see Ch. 39). They are effective in treating insomnia in the elderly and autistic children.
- Orexin receptor antagonist. **Suvorexant** is in development as a hypnotic. It is an antagonist of OX_1 and OX_2 receptors which mediate the actions of the orexins, peptide transmitters in the CNS that are important in setting diurnal rhythm (see Ch. 39). Orexin levels are normally high in daylight and low at night, so the drug reduces wakefulness.
- Antihistamines[8] (see Ch. 26; e.g. **diphenhydramine** and **promethazine**) can be used to induce sleep. They are included in various over-the-counter preparations. **Doxepin** is an SNRI antidepressant (see Ch. 46) with histamine H_1- and H_2-receptor antagonist properties that can be used to treat insomnia.
- Miscellaneous other drugs (e.g. **chloral hydrate** and **meprobamate**). They are no longer recommended, but therapeutic habits die hard and they are occasionally used. **Methaqualone**, used as a hypnotic and once popular as a drug of abuse, has been discontinued.

Induction of sleep by benzodiazepines

Benzodiazepines decrease the time taken to get to sleep, and increase the total duration of sleep, although the latter effect occurs only in subjects who normally sleep for less than about 6 h each night. With agents that have a short duration of action (e.g. zolpidem or temazepam), a pronounced hangover effect on wakening can be avoided.

▼ On the basis of electroencephalography measurements, several levels of sleep can be recognised. Of particular psychological importance are rapid-eye-movement (REM) sleep, which is associated with dreaming, and slow-wave sleep, which corresponds to the deepest level of sleep when the metabolic rate and adrenal steroid secretion are at their lowest and the secretion of growth hormone is at its highest (see Ch. 33). Most hypnotic drugs reduce the proportion of REM sleep, although benzodiazepines affect it less than other hypnotics, and zolpidem least of all. Artificial interruption of REM

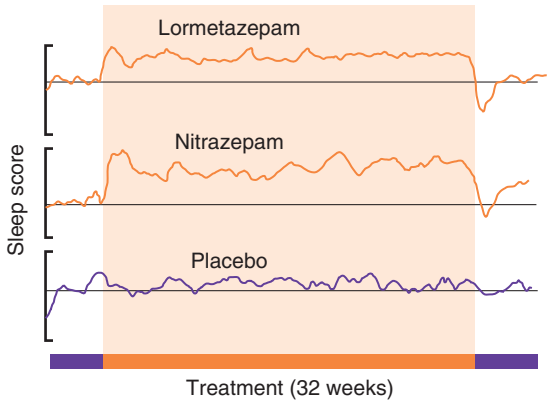

Fig. 44.5 Effects of long-term benzodiazepine treatment on sleep quality. A group of 100 poor sleepers were given, under double-blind conditions, lormetazepam 5 mg, nitrazepam 2 mg or placebo nightly for 24 weeks, the test period being preceded and followed by 4 weeks of placebo treatment. They were asked to assess, on a subjective rating scale, the quality of sleep during each night, and the results are expressed as a 5-day rolling average of these scores. The improvement in sleep quality was maintained during the 24-week test period, and was followed by a 'rebound' worsening of sleep when the test period ended. *(From Oswald I et al. 1982 Br Med J 284, 860–864.)*

[8]This is an interesting example of an initial unwanted side effect – sedation is undesired when treating hay fever – subsequently becoming a therapeutic use.

sleep causes irritability and anxiety, even if the total amount of sleep is not reduced, and the lost REM sleep is made up for at the end of such an experiment by a rebound increase. The same rebound in REM sleep is seen at the end of a period of administration of benzodiazepines or other hypnotics. The proportion of slow-wave sleep is significantly reduced by benzodiazepines, although growth hormone secretion is unaffected.

Figure 44.5 shows the improvement of subjective ratings of sleep quality produced by a benzodiazepine, and the rebound decrease at the end of a 32-week period of drug treatment. It is notable that, although tolerance to objective effects such as reduced sleep latency occurs within a few days, this is not obvious in the subjective ratings.

Benzodiazepines are now, however, only recommended for short courses of treatment of insomnia. Tolerance develops over 1–2 weeks with continuous use, and on cessation rebound insomnia and withdrawal occurs.

Hypnotic drugs

- Drugs that potentiate the action of GABA at $GABA_A$ receptors (e.g. benzodiazepines, **zolpidem**, **zopiclone**, **zaleplon** and **chlormethiazole**) are used to induce sleep.
- Drugs with shorter half-lives in the body reduce the incidence of hangover the next morning.
- H_1-receptor antagonists induce sedation and sleep.
- Drugs with novel mechanisms of action have been developed, e.g. melatonin receptor agonists and orexin receptor antagonists.

Clinical use of hypnotics ('sleeping tablets')

- The cause of insomnia should be established before administering hypnotic drugs. Common causes include alcohol or other drug misuse (see Ch. 49) and physical or psychiatric disorders (especially depression).
- Tricyclic antidepressants (Ch. 47) cause drowsiness, so can kill two birds with one stone if taken at night by depressed patients with sleep disturbance.
- Optimal treatment of chronic insomnia is often by changing behaviour (e.g. increasing exercise, staying awake during the day) rather than with drugs.
- Benzodiazepines should be used only for short periods (<4 weeks) and for severe insomnia. They can be useful for a few nights when transient factors such as admission to hospital, jet lag or an impending procedure cause insomnia.
- Drugs used to treat insomnia include:
  - benzodiazepines (e.g. **temazepam**) and related drugs (e.g. **zolpidem**, **zopiclone**, which also work on the benzodiazepine receptor)
  - **chloral hydrate** and **triclofos**, which were used formerly in children, but this is seldom justified
  - sedating antihistamines (e.g. **promethazine**), which cause drowsiness (see Ch. 26) are less suitable for treating insomnia. They can impair performance the next day.

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45 Antiepileptic drugs

OVERVIEW

In this chapter we describe the nature of epilepsy, the neurobiological mechanisms underlying it and the animal models that can be used to study it. We then proceed to describe the various classes of drugs that are used to treat it, the mechanisms by which they work and their pharmacological characteristics.

Centrally acting muscle relaxants are discussed briefly at the end of the chapter.

INTRODUCTION

Epilepsy is a very common disorder, characterised by *seizures*, which take various forms and result from episodic neuronal discharges, the form of the seizure depending on the part of the brain affected. Epilepsy affects 0.5–1% of the population i.e. ~50 million people worldwide. Often, there is no recognisable cause, although it may develop after brain damage, such as trauma, stroke, infection or tumour growth, or other kinds of neurological disease, including various inherited neurological syndromes. Epilepsy is treated mainly with drugs, although brain surgery may be used for suitable severe cases. Current antiepileptic drugs are effective in controlling seizures in about 70% of cases, but their use is often limited by side effects. In addition to their use in patients with epilepsy, antiepileptic drugs are used to treat or prevent convulsions caused by other brain disorders, for example trauma (including following neurosurgery), infection (as an adjunct to antibiotics), brain tumours and stroke. For this reason, they are sometimes termed anticonvulsants rather than antiepileptics. Increasingly, some antiepileptic drugs have been found to have beneficial effects in non-convulsive disorders such as neuropathic pain (Ch. 42), bipolar depression (Ch. 47) and anxiety (Ch. 44). Many new antiepileptic drugs have been developed over the past 20 or so years in attempts to improve their efficacy and side-effect profile, for example by modifying their pharmacokinetics. Improvements have been steady rather than spectacular, and epilepsy remains a difficult problem, despite the fact that controlling reverberative neuronal discharges would seem, on the face of it, to be a much simpler problem than controlling those aspects of brain function that determine emotions, mood and cognitive function.

THE NATURE OF EPILEPSY

The term 'epilepsy' is used to define a group of neurological disorders all of which exhibit periodic seizures. For information on the underlying causes of epilepsy and factors that precipitate periodic seizures see Browne & Holmes (2008). As explained later, not all seizures involve convulsions. Seizures are associated with episodic high-frequency discharge of impulses by a group of neurons (sometimes referred to as the *focus*) in the brain. What starts as a local abnormal discharge may then spread to other areas of the brain. The site of the primary discharge and the extent of its spread determine the symptoms that are produced, which range from a brief lapse of attention to a full convulsive fit lasting for several minutes, as well as odd sensations or behaviours. The particular symptoms produced depend on the function of the region of the brain that is affected. Thus, involvement of the motor cortex causes convulsions, involvement of the hypothalamus causes peripheral autonomic discharge, and involvement of the reticular formation in the upper brain stem leads to loss of consciousness.

Abnormal electrical activity during and following a seizure can be detected by electroencephalography (EEG) recording from electrodes distributed over the surface of the scalp. Various types of seizure can be recognised on the basis of the nature and distribution of the abnormal discharge (Fig. 45.1). Modern brain imaging techniques, such as magnetic resonance imaging and positron emission tomography, are now routinely used in the evaluation of patients with epilepsy (see Fig. 45.2) to identify structural abnormalities (e.g. ischaemic lesions, tumours; see Deblaere & Achten, 2008).

TYPES OF EPILEPSY

The clinical classification of epilepsy is done on the basis of the characteristics of the seizure rather than on the cause or underlying pathology. There are two major seizure categories, namely *partial* (localised to part of the brain) and *generalised* (involving the whole brain).

PARTIAL SEIZURES

Partial seizures are those in which the discharge begins locally and often remains localised. The symptoms depend on the brain region or regions involved, and include involuntary muscle contractions, abnormal sensory experiences or autonomic discharge, or effects on mood and behaviour, often termed *psychomotor epilepsy* – which may arise from a focus within a temporal lobe. The EEG discharge in this type of epilepsy is normally confined to one hemisphere (Fig. 45.1D). Partial seizures can often be attributed to local cerebral lesions, and their incidence increases with age. In complex partial seizures, loss of consciousness may occur at the outset of the attack, or somewhat later, when the discharge has spread from its site of origin to regions of the brain stem reticular formation. In some individuals, a partial seizure can, during the seizure, become generalised when the abnormal neuronal activity spreads across the whole brain.

[1]After Hughlings Jackson, a distinguished 19th-century Yorkshire neurologist who published his outstanding work in the *Annals of the West Riding Lunatic Asylum*.

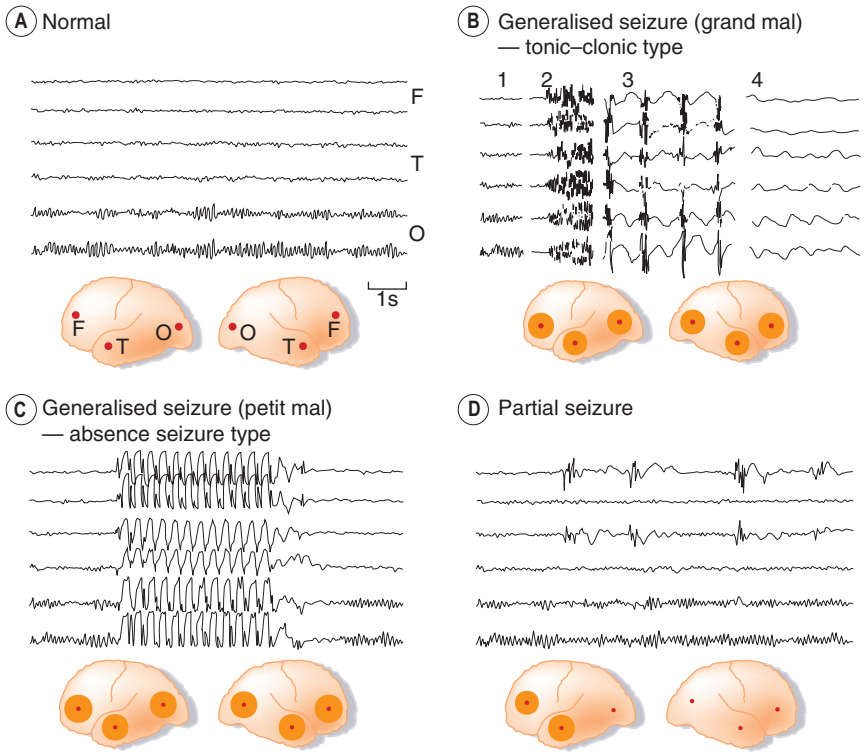

Fig. 45.1 Electroencephalography (EEG) records in epilepsy. [**A**] Normal EEG recorded from frontal (F), temporal (T) and occipital (O) sites on both sides, as shown in the inset diagram. The α rhythm (10/s) can be seen in the occipital region. [**B**] Sections of EEG recorded during a generalised tonic–clonic (grand mal) seizure: 1, normal record; 2, onset of tonic phase; 3, clonic phase; 4, postconvulsive coma. [**C**] Generalised absence seizure (petit mal) showing sudden brief episode of 3/s 'spike-and-wave' discharge. [**D**] Partial seizure with synchronous abnormal discharges in left frontal and temporal regions. *(From Eliasson SG et al. 1978 Neurological Pathophysiology, 2nd edn. Oxford University Press, New York.)*

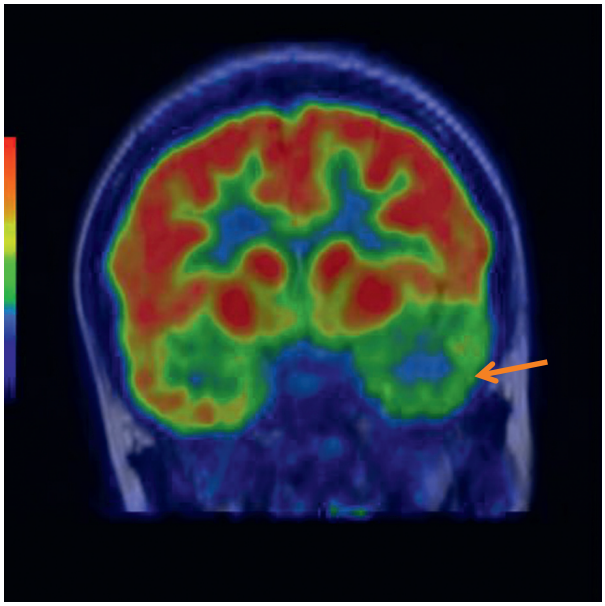

Fig. 45.2 Positron emission tomography (PET) image using [^{18}F]-fluoro-2-deoxyglucose (FDG) of the brain of a female patient suffering from temporal lobe epilepsy. The interictal area of hypometabolism in the left temporal lobe (indicated by the arrow) is suggestive of the site of the epileptic focus. *(Image kindly provided by Prof. John Duncan and Prof. Peter Ell, UCL Institute of Neurology, London.)*

An epileptic focus in the motor cortex results in attacks, sometimes called *Jacksonian epilepsy*,[1] consisting of repetitive jerking of a particular muscle group, beginning on one side of the body, often in the thumb, big toe or angle of the mouth, which spreads and may involve much of the body within about 2 min before dying out. The patient loses voluntary control of the affected parts of the body but does not necessarily lose consciousness. In *psychomotor epilepsy* the attack may consist of stereotyped purposive movements such as rubbing or patting movements, or much more complex behaviour such as dressing, walking or hair combing. The seizure usually lasts for a few minutes, after which the patient recovers with no recollection of the event. The behaviour during the seizure can be bizarre and accompanied by a strong emotional response.

GENERALISED SEIZURES

Generalised seizures involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres. Immediate loss of consciousness is characteristic of generalised seizures. There are a number of types of generalised seizure – two important categories are *tonic–clonic* seizures (formerly referred to as grand mal, Fig. 45.1B) and *absence seizures* (petit mal, Fig. 45.1C); others include myoclonic, tonic, atonic and clonic seizures.

A *tonic–clonic seizure* consists of an initial strong contraction of the whole musculature, causing a rigid extensor spasm and an involuntary cry. Respiration stops, and defecation, micturition and salivation often occur. This tonic phase lasts for about 1 min, during which the face is suffused and becomes blue (an important clinical

distinction from syncope, the main disorder from which fits must be distinguished, where the face is ashen pale), and is followed by a series of violent, synchronous jerks that gradually die out in 2–4 min. The patient stays unconscious for a few more minutes and then gradually recovers, feeling ill and confused. Injury may occur during the convulsive episode. The EEG shows generalised continuous high-frequency activity in the tonic phase and an intermittent discharge in the clonic phase (Fig. 45.1B).

Absence seizures occur in children; they are much less dramatic but may occur more frequently (many seizures each day) than tonic–clonic seizures. The patient abruptly ceases whatever he or she was doing, sometimes stopping speaking in mid-sentence, and stares vacantly for a few seconds, with little or no motor disturbance. Patients are unaware of their surroundings and recover abruptly with no after effects. The EEG pattern shows a characteristic rhythmic discharge during the period of the seizure (Fig. 45.1C). The rhythmicity appears to be due to oscillatory feedback between the cortex and the thalamus, the special properties of the thalamic neurons being dependent on the T-type calcium channels that they express (see Shin, 2006). The pattern differs from that of partial seizures, where a high-frequency asynchronous discharge spreads out from a local focus. Accordingly, the drugs used specifically to treat absence seizures act mainly by blocking T-type calcium channels, whereas drugs effective against other types of epilepsy act mainly by blocking sodium channels or enhancing GABA-mediated inhibition.

A particularly severe kind of epilepsy, *Lennox–Gastaut syndrome*, occurs in children and is associated with progressive mental retardation, possibly a reflection of excitotoxic neurodegeneration (see Ch. 40).

About one-third of cases of epilepsy are familial and involve genetic mutations. While some are due to a single mutation, most result from polygenetic mutations (see Pandolfo, 2011). Most genes associated with familial epilepsies encode neuronal ion channels closely involved in controlling action potential generation (see Ch. 4), such as voltage-gated sodium and potassium channels, GABA receptors and nicotinic acetylcholine receptors. Some other genes encode proteins that interact with ion channels.

Status epilepticus refers to continuous uninterrupted seizures, requiring emergency medical treatment.

NEURAL MECHANISMS AND ANIMAL MODELS OF EPILEPSY

▼ The underlying neuronal abnormality in epilepsy is poorly understood. In general, excitation will naturally tend to spread throughout a network of interconnected neurons but is normally prevented from doing so by inhibitory mechanisms. Thus, *epileptogenesis* can arise if excitatory transmission is facilitated or inhibitory transmission is reduced (exemplified by $GABA_A$ receptor antagonists causing convulsions; see Ch. 38). In certain respects, epileptogenesis resembles long-term potentiation (Ch. 38), and similar types of use-dependent synaptic plasticity may be involved. Neurons from which the epileptic discharge originates display an unusual type of electrical behaviour termed the paroxysmal depolarising shift (PDS), during which the membrane potential suddenly decreases by about 30 mV and remains depolarised for up to a few seconds before returning to normal. A burst of action potentials often accompanies this depolarisation (Fig. 45.3). This event probably results from the abnormally exaggerated and prolonged action of an excitatory transmitter. Activation of NMDA receptors (see Ch. 38) produces 'plateau-shaped' depolarising responses very similar to the PDS. It is known that repeated seizure activity can lead to neuronal degeneration, possibly due to excitotoxicity (Ch. 40).

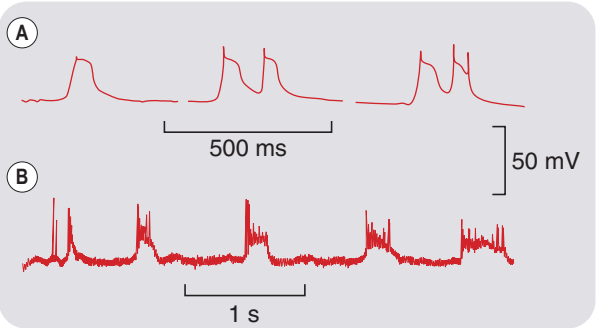

Fig. 45.3 'Paroxysmal depolarising shift' (PDS) compared with experimental activation of glutamate receptors of the NMDA type. [**A**] PDS recorded with an intracellular microelectrode from cortical neurons of anaesthetised cats. Seizure activity was induced by topical application of penicillin. [**B**] Intracellular recording from the caudate nucleus of an anaesthetised cat. The glutamate analogue NMDA was applied by ionophoresis from a nearby micropipette. *(Panel [A] from Matsumoto H, Marsan CA 1964 Exp Neurol 9, 286; panel [B] from Herrling PL et al. 1983 J Physiol 339, 207.)*

Because detailed studies are difficult to carry out on epileptic patients, many different animal models of epilepsy have been investigated (see Bialer & White, 2010). Several transgenic mouse strains have been reported that show spontaneous seizures. They include knockout mutations of various ion channels, receptors and other synaptic proteins. Local application of penicillin crystals results in focal seizures, probably by interfering with inhibitory synaptic transmission. Convulsant drugs (e.g. **pentylenetetrazol** [PTZ]) are often used as are seizures caused by electrical stimulation of the whole brain. Drugs that inhibit PTZ-induced convulsions and raise the threshold for production of electrically induced seizures are generally effective against absence seizures, whereas those that reduce the duration and spread of electrically induced convulsions are effective in focal types of epilepsy such as tonic–clonic seizures. In the *kainate model* a single injection of the glutamate receptor agonist kainic acid into the amygdaloid nucleus of a rat can produce spontaneous seizures 2–4 weeks later that continue indefinitely. This is believed to result from excitoxic damage to inhibitory neurons.

In the *kindling model* brief low-intensity electrical stimulation of certain regions of the limbic system, such as the amygdala, normally produces no seizure response but if repeated daily for several days the response gradually increases until very low levels of stimulation will evoke a full seizure, and eventually seizures occur spontaneously. This kindled state can persist indefinitely but is prevented by NMDA receptor antagonists or deletion of the neurotrophin receptor, TrkB.

In human focal epilepsies, surgical removal of a damaged region of cortex may fail to cure the condition, as though the abnormal discharge from the region of primary damage had somehow produced a secondary hyperexcitability elsewhere in the brain. Furthermore, following severe head injury prophylactic treatment with antiepileptic drugs reduces the incidence of post-traumatic epilepsy, which suggests that a phenomenon similar to kindling may underlie this form of epilepsy.

Nature of epilepsy

- Epilepsy affects about 0.5% of the population.
- The characteristic event is the seizure, which may be associated with convulsions but may take other forms.
- The seizure is caused by an asynchronous high-frequency discharge of a group of neurons, starting locally and spreading to a varying extent to affect other parts of the brain. In absence seizures, the discharge is regular and oscillatory.
- Partial seizures affect localised brain regions, and the attack may involve mainly motor, sensory or behavioural phenomena. Unconsciousness occurs when the reticular formation is involved.
- Generalised seizures affect the whole brain. Two common forms of generalised seizure are the tonic–clonic fit and the absence seizure. Status epilepticus is a life-threatening condition in which seizure activity is uninterrupted.
- Partial seizures can become secondarily generalised if the localised abnormal neuronal activity subsequently spreads across the whole brain.
- Many animal models have been devised, including electrically and chemically induced generalised seizures, production of local chemical damage and kindling. These provide good prediction of antiepileptic drug effects in humans.
- The neurochemical basis of the abnormal discharge is not well understood. It may be associated with enhanced excitatory amino acid transmission, impaired inhibitory transmission or abnormal electrical properties of the affected cells. Several susceptibility genes, mainly encoding neuronal ion channels, have been identified.
- Repeated epileptic discharge can cause neuronal death (excitotoxicity).
- Current drug therapy is effective in 70–80% of patients.

ANTIEPILEPTIC DRUGS

Antiepileptic (sometimes known as *anticonvulsant*) drugs are used to treat epilepsy as well as non-epileptic convulsive disorders.

With optimal drug therapy, epilepsy is controlled completely in about 75% of patients, but about 10% (50 000 in Britain) continue to have seizures at intervals of 1 month or less, which severely disrupts their life and work. There is therefore a need to improve the efficacy of therapy.

Patients with epilepsy usually need to take drugs continuously for many years, so avoidance of side effects is particularly important. Nevertheless, some drugs that have considerable adverse effects are still quite widely used even though they are not drugs of choice for newly diagnosed patients.[2] There is a need for more specific and effective drugs, and a number of new drugs have recently been introduced for clinical use or are in late stages of clinical trials. Long-established antiepileptic drugs are listed in Table 45.1. Newer drugs (see Table 45.2) with similar mechanisms of action to older drugs or novel mechanisms of action may offer advantages in terms of efficacy in drug-resistant epilepsies, better pharmacokinetic profile, improved tolerability, lower potential for interaction with other drugs (see Ch. 57) and fewer adverse effects. The appropriate use of drugs from this large available menu depends on many clinical factors (see Macleod & Appleton, 2007; Azar & Abou-Khalil, 2008).

MECHANISM OF ACTION

Antiepileptic drugs aim to inhibit the abnormal neuronal discharge rather than to correct the underlying cause. Three main mechanisms of action appear to be important:

1. Enhancement of GABA action.
2. Inhibition of sodium channel function.
3. Inhibition of calcium channel function.

More recently newer drugs with other, novel mechanisms of action have been developed.

Antiepileptic drugs may exert more than one beneficial action, prime examples being **valproate** and **topiramate** (see Table 45.1). The relative importance and contribution of each of these actions to the therapeutic effect is somewhat uncertain.

As with drugs used to treat cardiac dysrhythmias (Ch. 21), the aim is to prevent the paroxysmal discharge without affecting normal transmission. It is clear that properties such as use-dependence and voltage-dependence of channel-blocking drugs (see Ch. 4) are important in achieving this selectivity, but our understanding remains fragmentary.

Enhancement of GABA action

Several antiepileptic drugs (e.g. **phenobarbital** and **benzodiazepines**) enhance the activation of $GABA_A$ receptors, thus facilitating the GABA-mediated opening of chloride channels (see Chs 3 and 44).[3] **Vigabatrin** acts by irreversibly inhibiting the enzyme GABA transaminase that is responsible for inactivating GABA (see Ch. 38) in astrocytes and GABAergic nerve terminals. Tiagabine is an equipotent inhibitor of both the neuronal and glial GABA transporter GAT1, thus inhibiting the removal of GABA from the synapse. It enhances the extracellular GABA concentration, as measured in microdialysis experiments, and also potentiates and prolongs GABA-mediated synaptic responses in the brain.

[2]Bromide was the first antiepileptic agent. Its propensity to induce sedation and other unwanted side effects has resulted in it being largely withdrawn from human medicine, although it is still approved for human use in some countries (e.g. Germany) and may have uses in childhood epilepsies. It is still widely used in veterinary practice to treat epilepsy in dogs and cats.

[3]Absence seizures, paradoxically, are often exacerbated by drugs that enhance GABA activity and better treated by drugs acting by different mechanisms such as T-type calcium channel inhibition.

Table 45.1 Properties of long-established antiepileptic drugs

Drug	Site of action				Main uses	Main unwanted effect(s)	Pharmacokinetics
	Sodium channel	*$GABA_A$ receptor*	*Calcium channel*	*Other*			
Carbamazepine[a]	+				All types except absence seizures Especially temporal lobe epilepsy Also trigeminal neuralgia Most widely used antiepileptic drug	Sedation, ataxia, blurred vision, water retention, hypersensitivity reactions, leukopenia, liver failure (rare)	Half-life 12–18 h (longer initially) Strong induction of liver enzymes, so risk of drug interactions
Phenytoin	+				All types except absence seizures	Ataxia, vertigo, gum hypertrophy, hirsutism, megaloblastic anaemia, fetal malformation, hypersensitivity reactions	Half-life ~24 h Saturation kinetics, therefore unpredictable plasma levels Plasma monitoring often required
Valproate[b]	+	?+	+	GABA transaminase inhibition	Most types, including absence seizures	Generally less than with other drugs Nausea, hair loss, weight gain, fetal malformations	Half-life 12–15 h
Ethosuximide[c]			+		Absence seizures May exacerbate tonic–clonic seizures	Nausea, anorexia, mood changes, headache	Long plasma half-life (~60 h)
Phenobarbital[d]	?+	+			All types except absence seizures	Sedation, depression	Long plasma half-life (>60 h) Strong induction of liver enzymes, so risk of drug interactions (e.g. with phenytoin)
Benzodiazepines (e.g. clonazepam, clobazam, lorazepam, diazepam)		+			Lorazepam used intravenously to control status epilepticus	Sedation Withdrawal syndrome (see Ch. 44)	See Ch. 44

[a]Oxcarbazepine, recently introduced, is similar; claimed to have fewer side effects.

[b]Valproate is effective against both partial and generalised seizures, including absence seizures.

[c]Trimethadione is similar to ethosuximide in that it acts selectively against absence seizures but has greater toxicity (especially the risk of severe hypersensitivity reactions and teratogenicity).

[d]Primidone is pharmacologically similar to phenobarbital and is converted to phenobarbital in the body. It has no clear advantages and is more liable to produce hypersensitivity reactions, so is now rarely used.

Inhibition of sodium channel function

Many antiepileptic drugs (e.g. **carbamazepine, phenytoin** and **lamotrigine**; see Tables 45.1 & 45.2) affect membrane excitability by an action on voltage-dependent sodium channels (see Chs 4 and 43), which carry the inward membrane current necessary for the generation of an action potential. Their blocking action shows the property of use-dependence; in other words, they block preferentially the excitation of cells that are firing repetitively, and the higher the frequency of firing, the greater the block produced. This characteristic, which is relevant to the ability of drugs to block the high-frequency discharge that occurs in an epileptic fit without unduly interfering with the low-frequency firing of neurons in the normal state, arises

Table 45.2 Properties of newer antiepileptic drugs

Drug	Site of action				Main uses	Main unwanted effect(s)	Pharmacokinetics
	Sodium channel	*$GABA_A$ receptor*	*Calcium channel*	*Other*			
Vigabatrin				GABA transaminase inhibition	All types Appears to be effective in patients resistant to other drugs	Sedation, behavioural and mood changes (occasionally psychosis) Visual field defects	Short plasma half-life, but enzyme inhibition is long-lasting
Lamotrigine	+		?+	Inhibits glutamate release	All types	Dizziness, sedation, rashes	Plasma half-life 24–36 h
Gabapentin Pregabalin			+		Partial seizures	Few side effects, mainly sedation	Plasma half-life 6–9 h
Felbamate	+	+	?+	?NMDA receptor block	Used mainly for severe epilepsy (Lennox–Gastaut syndrome) because of risk of adverse reaction	Few acute side effects but can cause aplastic anaemia and liver damage (rare but serious)	Plasma half-life ~20 h Excreted unchanged
Tiagabine				Inhibits GABA uptake	Partial seizures	Sedation Dizziness, lightheadedness	Plasma half-life ~7 h Liver metabolism
Topiramate	+	?+	?+	AMPA receptor block	Partial and generalised tonic–clonic seizures. Lennox–Gastaut syndrome	Sedation Fewer pharmacokinetic interactions than phenytoin Fetal malformation	Plasma half-life ~20 h Excreted unchanged
Levetiracetam				Binds to SV2A protein	Partial and generalised tonic–clonic seizures	Sedation (slight)	Plasma half-life ~7 h Excreted unchanged
Zonisamide	+	?+	+		Partial seizures	Sedation (slight) Appetite suppression, weight loss	Plasma half-life ~70 h
Rufinamide	+			?+ Inhibits GABA reuptake	Partial seizures	Headache, dizziness, fatigue	Plasma half-life 6–10 h
Lacosamide	+				Partial seizures	Nausea, vomiting, dizziness, visual disturbances, impaired coordination, mood changes	Plasma half-life 13 h
Retigabine				Activates $K_v7.2$ (KCNQ2) potassium channels	Partial seizures	Prolongs QT interval, weight gain	Plasma half-life 6–11 h
Perampanel				Non-competitive AMPA antagonist	Partial seizures	Dizziness, weight gain, sedation, impaired coordination changes in mood and behaviour	Plasma half-life 70–100 h

SV2A, synaptic vesicle protein 2A.

from the ability of blocking drugs to discriminate between sodium channels in their resting, open and inactivated states (see Chs 4 and 43). Depolarisation of a neuron (such as occurs in the PDS described above) increases the proportion of the sodium channels in the inactivated state. Antiepileptic drugs bind preferentially to channels in this state, preventing them from returning to the resting state, and thus reducing the number of functional channels available to generate action potentials. **Lacosamide** enhances sodium channel inactivation, but unlike other antiepileptic drugs it appears to affect slow rather than rapid inactivation processes.

Inhibition of calcium channels

Drugs that are used to treat absence seizures (e.g. **ethosuximide** and **valproate**) all appear to share the ability to block T-type low-voltage-activated calcium channels. T-type channel activity is important in determining the rhythmic discharge of thalamic neurons associated with absence seizures (Khosravani et al., 2004).

Gabapentin, though designed as a simple analogue of GABA that would be sufficiently lipid soluble to penetrate the blood–brain barrier, owes its antiepileptic effect mainly to an action on P/Q-type calcium channels. By binding to a particular channel subunit (α2δ1), both gabapentin and **pregabalin** (a related analogue) reduce the trafficking to the plasma membrane of calcium channels containing this subunit, thereby reducing calcium entry into the nerve terminals and reducing the release of various neurotransmitters and modulators.

Other mechanisms

Many of the newer antiepileptic drugs were developed empirically on the basis of activity in animal models. Their mechanism of action at the cellular level is not fully understood.

Levetiracetam is believed to interfere with neurotransmitter release by binding to synaptic vesicle protein 2A (SV2A), which is involved in synaptic vesicle docking and fusion. **Brivaracetam**, a related potential antiepileptic agent, also binds to SV2A with ten-fold higher affinity: positive results have been noted in clinical trials.

While a drug may appear to work by one of the major mechanisms described above, close scrutiny often reveals other actions that may also be therapeutically relevant. For example, **phenytoin** not only causes use-dependent block of sodium channels (see p. 550) but also affects other aspects of membrane function, including calcium channels and post-tetanic potentiation, as well as intracellular protein phosphorylation by calmodulin-activated kinases, which could also interfere with membrane excitability and synaptic function.

Antagonism at ionotropic excitatory amino acid receptors has been a major focus in the search for new antiepileptic drugs. Despite showing efficacy in animal models, by and large they did not prove useful in the clinic, because the margin between the desired anticonvulsant effect and unacceptable side effects, such as loss of motor coordination, was too narrow. However, **perampanel**, a non-competitive AMPA-receptor antagonist, has recently been approved as adjunctive treatment for partial seizures.

Neuronal membrane excitability is controlled by potassium channel activity. Increasing potassium conductance hyperpolarises neurons making them less excitable. A new antiepileptic drug, **retigabine**, licensed for treatment of focal seizures, activates the 'M current' through channels containing $K_v7.2$ subunits and is used in refractory cases.

Mechanism of action of antiepileptic drugs

- The major antiepileptic drugs are thought to act by three main mechanisms:
  - reducing electrical excitability of cell membranes, mainly through use-dependent block of sodium channels
  - enhancing GABA-mediated synaptic inhibition; this may be achieved by an enhanced postsynaptic action of GABA, by inhibiting GABA transaminase or by inhibiting GABA uptake into neurons and glial cells
  - inhibiting T-type calcium channels (important in controlling absence seizures).
- Newer drugs act by other mechanisms, some yet to be elucidated.

CARBAMAZEPINE

Carbamazepine, one of the most widely used antiepileptic drugs, is chemically related to the tricyclic antidepressant drugs (see Ch. 47) and was found in a routine screening test to inhibit electrically evoked seizures in mice. Pharmacologically and clinically, its actions resemble those of phenytoin, although it appears to be particularly effective in treating certain partial seizures (e.g. psychomotor epilepsy). It is also used to treat other conditions, such as neuropathic pain (Ch. 42) and manic-depressive illness (Ch. 47).

Pharmacokinetic aspects

Carbamazepine is slowly but well absorbed after oral administration. Its plasma half-life is about 30 h when it is given as a single dose, but it is a strong inducer of hepatic enzymes, and the plasma half-life shortens to about 15 h when it is given repeatedly. Some of its metabolites have antiepileptic properties. A slow-release preparation is used for patients who experience transient side effects coinciding with plasma concentration peaks following oral dosing.

Unwanted effects

Carbamazepine produces a variety of unwanted effects ranging from drowsiness, dizziness and ataxia to more severe mental and motor disturbances.[4] It can also cause water retention (and hence hyponatraemia; Ch. 29) and a variety of gastrointestinal and cardiovascular side effects. The incidence and severity of these effects is relatively low, however, compared with other drugs. Treatment is usually started with a low dose, which is built up gradually to avoid dose-related toxicity. Severe bone marrow

[4]One of the authors who was a keen hockey player played in a team with a goalkeeper who sometimes made silly errors early in the match. It turned out that he suffered from epilepsy and had taken his dose of carbamazepine too close to the start of the match.

depression, causing neutropenia, and other severe forms of hypersensitivity reaction can occur, especially in people of Asian origin (see Ch. 11).

Carbamazepine is a powerful inducer of hepatic microsomal enzymes, and thus accelerates the metabolism of many other drugs, such as phenytoin, oral contraceptives, warfarin and corticosteroids, as well as of itself. When starting treatment, the opposite of a 'loading dose' strategy is employed: small initial doses are gradually increased since when dosing is initiated metabolising enzymes are not induced and so even low doses may give rise to adverse effects (notably ataxia); as enzyme induction occurs, increasing doses are needed to maintain therapeutic plasma concentrations. In general, it is inadvisable to combine it with other antiepileptic drugs, and interactions with other drugs (e.g. warfarin) metabolised by cytochrome P450 (CYP) enzymes are common and clinically important. **Oxcarbazepine** is a prodrug that is metabolised to a compound closely resembling carbamazepine, with similar actions but less tendency to induce drug-metabolising enzymes. Another related drug, **eslicarbazepine**, is in development and may also have less effect on metabolising enzymes.

PHENYTOIN

Phenytoin is the most important member of the hydantoin group of compounds, which are structurally related to the barbiturates. It is highly effective in reducing the intensity and duration of electrically induced convulsions in mice, although ineffective against PTZ-induced convulsions. Despite its many side effects and unpredictable pharmacokinetic behaviour, phenytoin is widely used, being effective against various forms of partial and generalised seizures, although not against absence seizures, which it may even worsen.

Pharmacokinetic aspects

Phenytoin has certain pharmacokinetic peculiarities that need to be taken into account when it is used clinically. It is well absorbed when given orally, and about 80–90% of the plasma content is bound to albumin. Other drugs, such as salicylates, phenylbutazone and valproate, inhibit this binding competitively (see Ch. 57). This increases the free phenytoin concentration but also increases hepatic clearance of phenytoin, so may enhance or reduce the effect of the phenytoin in an unpredictable way. Phenytoin is metabolised by the hepatic mixed function oxidase system and excreted mainly as glucuronide. It causes enzyme induction, and thus increases the rate of metabolism of other drugs (e.g. oral anticoagulants). The metabolism of phenytoin itself can be either enhanced or competitively inhibited by various other drugs that share the same hepatic enzymes. **Phenobarbital** produces both effects, and because competitive inhibition is immediate whereas induction takes time, it initially enhances and later reduces the pharmacological activity of phenytoin. **Ethanol** has a similar dual effect.

The metabolism of phenytoin shows the characteristic of saturation (see Ch. 10), which means that over the therapeutic plasma concentration range the rate of inactivation does not increase in proportion to the plasma concentration. The consequences of this are that:

- the plasma half-life (approximately 20 h) increases as the dose is increased
- the steady-state mean plasma concentration, achieved when a patient is given a constant daily dose, varies disproportionately with the dose. Figure 45.4 shows that, in one patient, increasing the dose by 50% caused the steady-state plasma concentration to increase more than four-fold.

The range of plasma concentration over which phenytoin is effective without causing excessive unwanted effects is quite narrow (approximately 40–100 µmol/l). The very steep relationship between dose and plasma concentration, and the many interacting factors, mean that there is considerable individual variation in the plasma concentration achieved with a given dose. Regular monitoring of plasma concentration has helped considerably in achieving an optimal therapeutic effect. The past tendency was to add further drugs in cases where a single drug failed to give adequate control. It is now recognised that much of the unpredictability can be ascribed to pharmacokinetic variability, and regular monitoring of plasma concentration has reduced the use of polypharmacy.

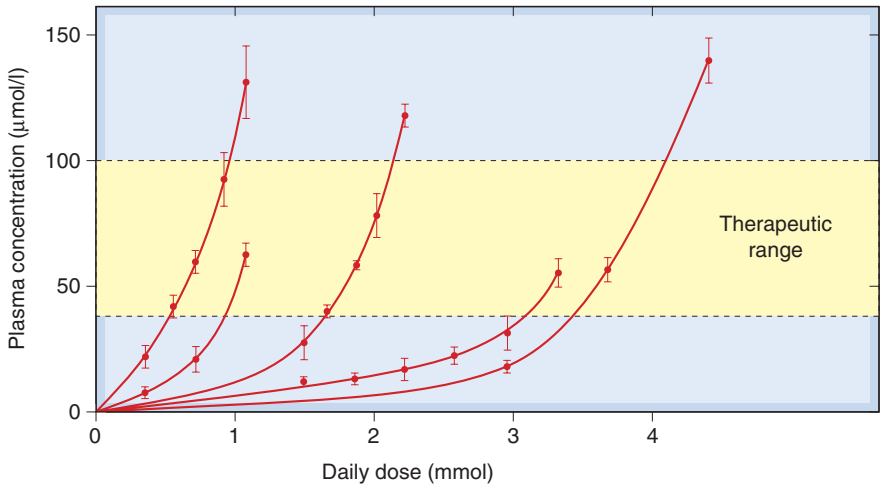

Fig. 45.4 Non-linear relationship between daily dose of phenytoin and steady-state plasma concentration in five individual human subjects. The daily dose required to achieve the therapeutic range of plasma concentrations (40–100 µmol/l) varies greatly between individuals, and for any one individual the dose has to be adjusted rather precisely to keep within the acceptable plasma concentration range. *(Redrawn from Richens A, Dunlop A 1975 Lancet 2, 247.)*

Unwanted effects

Side effects of phenytoin begin to appear at plasma concentrations exceeding 100 µmol/l and may be severe above about 150 µmol/l. The milder side effects include vertigo, ataxia, headache and nystagmus, but not sedation. At higher plasma concentrations, marked confusion with intellectual deterioration occurs; a paradoxical increase in seizure frequency is a particular trap for the unwary prescriber. These effects occur acutely and are quickly reversible. Hyperplasia of the gums often develops gradually, as does hirsutism and coarsening of the features, which probably result from increased androgen secretion. Megaloblastic anaemia, associated with a disorder of folate metabolism, sometimes occurs, and can be corrected by giving folic acid (Ch. 25). Hypersensitivity reactions, mainly rashes, are quite common. Phenytoin has also been implicated as a cause of the increased incidence of fetal malformations in children born to epileptic mothers, particularly the occurrence of cleft palate, associated with the formation of an epoxide metabolite. Severe idiosyncratic reactions, including hepatitis, skin reactions and neoplastic lymphocyte disorders, occur in a small proportion of patients.

VALPROATE

Valproate is a simple monocarboxylic acid, chemically unrelated to any other class of antiepileptic drug, and in 1963 it was discovered quite accidentally to have anticonvulsant properties in mice. It inhibits most kinds of experimentally induced convulsions and is effective in many kinds of epilepsy, being particularly useful in certain types of infantile epilepsy, where its low toxicity and lack of sedative action are important, and in adolescents who exhibit both tonic–clonic or myoclonic seizures as well as absence seizures, because valproate (unlike most antiepileptic drugs) is effective against each. Like carbamazepine, valproate is also used in psychiatric conditions such as bipolar depressive illness (Ch. 47).

Valproate works by several mechanisms (see Table 45.1), the relative importance of which remains to be clarified. It causes a significant increase in the GABA content of the brain and is a weak inhibitor of the enzyme system that inactivates GABA, namely GABA transaminase and succinic semialdehyde dehydrogenase (Ch. 38), but *in vitro* studies suggest that these effects would be very slight at clinical dosage. Other more potent inhibitors of these enzymes (e.g. **vigabatrin**; see p. 555) also increase GABA content and have an anticonvulsant effect in experimental animals. There is some evidence that it enhances the action of GABA by a postsynaptic action, but no clear evidence that it affects inhibitory synaptic responses. It inhibits sodium channels, but less so than phenytoin, and inhibits T-type calcium channels, which might explain why it is effective against absence seizures.

Valproate is well absorbed orally and excreted, mainly as the glucuronide, in the urine, the plasma half-life being about 15 h.

Unwanted effects

Valproate causes thinning and curling of the hair in about 10% of patients. The most serious side effect is hepatotoxicity. An increase in plasma glutamic oxaloacetic transaminase, which signals liver damage of some degree, commonly occurs, but proven cases of valproate-induced hepatitis are rare. The few cases of fatal hepatitis in valproate-treated patients may well have been caused by other factors. Valproate is a potent teratogen (even more so than other anticonvulsants that tend to share this secondary pharmacology) (see p. 557), causing spina bifida and other neural tube defects. Analogues of valproate with potentially reduced side effects are in development.

ETHOSUXIMIDE

Ethosuximide is another drug developed empirically by modifying the barbituric acid ring structure. Pharmacologically and clinically, however, it is different from the drugs so far discussed, in that it is active against PTZ-induced convulsions in animals and against absence seizures in humans, with little or no effect on other types of epilepsy. It supplanted **trimethadione**, the first drug found to be effective in absence seizures, which had major side effects. Ethosuximide is used clinically for its selective effect on absence seizures.

The mechanism of action of ethosuximide and trimethadione appears to differ from that of other antiepileptic drugs. The main effect is inhibition of T-type calcium channels, which may play a role in generating the firing rhythm in thalamic relay neurons that generates the 3/second spike-and-wave EEG pattern characteristic of absence seizures.

Ethosuximide is well absorbed, and metabolised and excreted much like phenobarbital, with a plasma half-life of about 60 h. Its main side effects are nausea and anorexia, sometimes lethargy and dizziness, and it is said to precipitate tonic–clonic seizures in susceptible patients. Very rarely, it can cause severe hypersensitivity reactions.

PHENOBARBITAL

▼ Phenobarbital was one of the first barbiturates to be developed. Its clinical effectiveness closely resembles that of phenytoin; it affects the duration and intensity of artificially induced seizures, rather than the seizure threshold, and is (like phenytoin) ineffective in treating absence seizures. **Primidone**, now rarely used, acts by being metabolised to phenobarbital. It often causes hypersensitivity reactions. The clinical uses of phenobarbital are virtually the same as those of phenytoin, but it is seldom used now because it causes sedation. Phenytoin does not produce this effect and is therefore the preferred option. For some years, phenobarbital was widely used in children, including as prophylaxis following febrile convulsions in infancy, but it can cause behavioural disturbances and hyperkinesias. It is, however, widely used in veterinary practice.

Pharmacokinetic aspects

▼ Phenobarbital is well absorbed, and about 50% of the drug in the blood is bound to plasma albumin. It is eliminated slowly from the plasma (half-life 50–140 h). About 25% is excreted unchanged in the urine. Because phenobarbital is a weak acid, its ionisation and hence renal elimination are increased if the urine is made alkaline (see Ch. 9). The remaining 75% is metabolised, mainly by oxidation and conjugation, by hepatic microsomal enzymes. Phenobarbital is a powerful inducer of liver CYP enzymes, and it lowers the plasma concentration of several other drugs (e.g. steroids, oral contraceptives, warfarin, tricyclic antidepressants) to an extent that is clinically important.

Unwanted effects

▼ The main unwanted effect of phenobarbital is sedation, which often occurs at plasma concentrations within the therapeutic range for seizure control. This is a serious drawback, because the drug may have to be used for years on end. Some degree of tolerance to the sedative effect seems to occur, but objective tests of cognition and motor performance show impairment even during long-term

treatment. Other unwanted effects that may occur with clinical dosage include megaloblastic anaemia (similar to that caused by phenytoin), mild hypersensitivity reactions and osteomalacia. Like other barbiturates, it must not be given to patients with porphyria (see Ch. 11). In overdose, phenobarbital depresses brain stem function, producing coma and respiratory and circulatory failure, as do all barbiturates.

BENZODIAZEPINES

Benzodiazepines can be used to treat both acute seizures, especially in children – **diazepam** often being administered rectally – and status epilepticus (a life-threatening condition in which epileptic seizures occur almost without a break) for which agents such as **lorazepam**, diazepam, or **clonazepam** are administered intravenously. The advantage in status epilepticus is that they act very rapidly compared with other antiepileptic drugs. With most benzodiazepines (see Ch. 44), the sedative effect is too pronounced for them to be used for maintenance therapy and tolerance develops over 1–6 months. **Clonazepam** is unique among the benzodiazepines in that in addition to acting at the $GABA_A$ receptor, it also inhibits T-type calcium channels. Both it and the related compound **clobazam** are claimed to be relatively selective as antiepileptic drugs. Sedation is the main side effect of these compounds, and an added problem may be the withdrawal syndrome, which results in an exacerbation of seizures if the drug is stopped abruptly.

NEWER ANTIEPILEPTIC DRUGS

VIGABATRIN

Vigabatrin, the first 'designer drug' in the epilepsy field, is a vinyl-substituted analogue of GABA that was designed as an irreversible inhibitor of the GABA-metabolising enzyme GABA transaminase. In animal studies, vigabatrin increases the GABA content of the brain and also increases the stimulation-evoked release of GABA, implying that GABA transaminase inhibition can increase the releasable pool of GABA and effectively enhance inhibitory transmission. In humans, vigabatrin increases the content of GABA in the cerebrospinal fluid. Although its plasma half-life is short, it produces a long-lasting effect because the enzyme is blocked irreversibly, and the drug can be given by mouth once daily.

Vigabatrin has been reported to be effective in a substantial proportion of patients resistant to the established drugs. However, a drawback of vigabatrin is the development of peripheral visual field defects in a proportion of patients on long-term therapy. Therefore the benefit of using this drug in refractory epilepsy must be weighed against the potential risk of developing visual problems. Vigabatrin may cause depression, and occasionally psychotic disturbances and hallucinations, in a minority of patients.

LAMOTRIGINE

Lamotrigine, although chemically unrelated, resembles phenytoin and carbamazepine in its pharmacological effects but it appears that, despite its similar mechanism of action, lamotrigine has a broader therapeutic profile than the earlier drugs, with significant efficacy against absence seizures (it is also used to treat unrelated psychiatric disorders). Its main side effects are nausea, dizziness and ataxia, and hypersensitivity reactions (mainly mild rashes, but occasionally more severe). Its plasma half-life is about 24 h, with no particular pharmacokinetic anomalies, and it is taken orally.

FELBAMATE

Felbamate is an analogue of an obsolete anxiolytic drug, **meprobamate**. It is active in many animal seizure models and has a broader clinical spectrum than earlier antiepileptic drugs, but its mechanism of action at the cellular level is uncertain. Its acute side effects are mild, mainly nausea, irritability and insomnia, but it occasionally causes severe reactions resulting in aplastic anaemia or hepatitis. For this reason, its recommended use is limited to intractable epilepsy (e.g. in children with Lennox–Gastaut syndrome) that is unresponsive to other drugs. Its plasma half-life is about 24 h, and it can enhance the plasma concentration of other antiepileptic drugs given concomitantly. **Carisbamate**, a sodium channel blocker, is a new drug currently in clinical trials that was originally designed with the intention of producing a drug similar to felbamate that does not cause aplastic anaemia.

GABAPENTIN AND PREGABALIN

Gabapentin is effective against partial seizures. Its side effects (sleepiness, headache, fatigue, dizziness and weight gain) are less severe than with many antiepileptic drugs. The absorption of gabapentin from the intestine depends on the L-amino acid carrier system and shows the property of saturability, which means that increasing the dose does not proportionately increase the amount absorbed. This makes gabapentin relatively safe and free of side effects associated with overdosing. Its plasma half-life is about 6 h, requiring dosing two to three times daily. It is free of interactions with other drugs. It is also used as an analgesic to treat neuropathic pain (Ch. 42). Pregabalin, an analogue of gabapentin, is more potent but otherwise very similar. As these drugs are excreted unchanged in the urine they must be used with care in patients whose renal function is impaired.

TIAGABINE

Tiagabine is an analogue of GABA that is able to penetrate the blood–brain barrier. It has a short plasma half-life and is mainly used as an add-on therapy for partial seizures. Its main side effects are drowsiness and confusion, dizziness, fatigue, agitation and tremor.

TOPIRAMATE

Topiramate is a drug that appears to do a little of everything, blocking sodium and calcium channels, enhancing the action of GABA, blocking AMPA receptors and, for good measure, weakly inhibiting carbonic anhydrase. Its clinical effectiveness resembles that of phenytoin, and it is claimed to produce less severe side effects, as well as being devoid of the pharmacokinetic properties that cause trouble with phenytoin. Currently, it is mainly used as add-on therapy in refractory cases of partial and generalised seizures.

LEVETIRACETAM

Levetiracetam was developed as an analogue of **piracetam**, a drug used to improve cognitive function, and discovered by accident to have antiepileptic activity in animal models. Unusually, it lacks activity in conventional models such as electroshock and PTZ tests, but is effective

in the audiogenic and kindling models (see p. 548). Levetiracetam is excreted unchanged in the urine. Common side effects include headaches, inflammation of the nose and throat, sleepiness, vomiting and irritability. Brivaracetam and **seletracetam** are similar to levetiracetam.

ZONISAMIDE

Zonisamide is a sulfonamide compound originally intended as an antibacterial drug and found accidentally to have antiepileptic properties. It is mainly free of major unwanted effects, although it causes drowsiness, and of serious interaction with other drugs. It tends to suppress appetite and cause weight loss, and is sometimes used for this purpose. Zonisamide has a long plasma half-life of 60–80 h, and is partly excreted unchanged and partly converted to a glucuronide metabolite. It is licensed for use as an adjunct treatment of partial and generalised seizures but may be effective as a monotherapy.

RUFINAMIDE

Rufinamide is a triazole derivative structurally unrelated to other antiepileptic drugs. It is licensed for treating Lennox–Gastaut syndrome and may also be effective in partial seizures. It has low plasma protein binding and is not metabolised by CYP enzymes.

RETIGABINE

Retigabine is used as an adjunct treatment for partial seizures. Side effects include weight gain, sedation and motor incoordination. It prolongs the QT interval so there is a theoretical possibility that it might provoke ventricular arrhythmia (see Ch. 21). As a precaution, the prescribing information recommends that an ECG is recorded before starting retigabine in patients who are taking other medication(s) that may prolong the QT interval.

PERAMPANEL

Perampanel is effective in refractory partial seizures. Side effects include dizziness, sedation, fatigue, irritability, weight gain, and loss of motor coordination. There is a risk of serious psychiatric problems (violent, even homicidal, thoughts and threatening behavior) in some individuals.

LACOSAMIDE

Lacosamide is used to treat partial seizures. Side effects include nausea, dizziness, sedation and fatigue. It produces relief of pain due to diabetic neuropathy.

STIRIPENTOL

Stiripentol has some efficacy as an adjunctive therapy in children. It enhances GABA release and prolongs GABA-mediated synaptic events in a manner similar to phenobarbital.

DEVELOPMENT OF NEW DRUGS

There are a number of new antiepileptic agents currently being evaluated in clinical trials (see Bialer & White, 2010). **Ganaxolone**, structurally resembling endogenous neurosteroids (see Ch. 38), is a positive allosteric modulator of $GABA_A$ receptors containing δ subunits. **Tonabersat** is a neuronal gap junction inhibitor.

The identification of epileptogenic mutations of genes encoding specific ion channels and other functional proteins (see Weber & Lerche, 2008) is expected to lead to new drugs aimed at these potential targets.

The major antiepileptic drugs

The main drugs in current use are carbamazepine, phenytoin, valproate, ethosuximide and benzodiazepines.

- **Carbamazepine**
  - acts mainly by use-dependent block of sodium channels
  - effective in most forms of epilepsy (except absence seizures); particularly effective in psychomotor epilepsy
  - also useful in neuropathic pain such as trigeminal neuralgia, and in bipolar disorder
  - strong liver-inducing agent, therefore many drug interactions
  - low incidence of unwanted effects, principally sedation, ataxia, mental disturbances, water retention
  - widely used in treatment of epilepsy.
- **Phenytoin**
  - acts mainly by use-dependent block of sodium channels
  - effective in many forms of epilepsy, but not absence seizures
  - metabolism shows saturation kinetics, so plasma concentration can vary widely; monitoring is therefore recommended
  - drug interactions are common
  - main unwanted effects are confusion, gum hyperplasia, skin rashes, anaemia, teratogenesis.
- **Valproate**
  - chemically unrelated to other antiepileptic drugs
  - effective in most forms of epilepsy including absence seizures
  - multiple possible mechanisms of action, including weak inhibition of GABA transaminase, some effect on sodium and T-type calcium channels
  - relatively few unwanted effects: baldness, teratogenicity, liver damage (rare, but serious).
- **Ethosuximide**
  - the main drug used to treat absence seizures; may exacerbate other forms
  - acts by blocking T-type calcium channels
  - relatively few unwanted effects, mainly nausea and anorexia.
- **Benzodiazepines** (mainly **clonazepam** and **diazepam**)
  - effective in the treatment of acute seizures
  - **lorazepam** used in treating status epilepticus.
- Other agents include **vigabatrin**, **lamotrigine**, **felbamate**, **gabapentin**, **pregabalin**, **tiagabine**, **topiramate**, **levetiracetam**, **zonisamide**, **rufinamide**, **retigabine**, **perampanel**, **lacosamide** and **stiripentol**.

OTHER USES OF ANTIEPILEPTIC DRUGS

Antiepileptic drugs have proved to have much wider clinical applications than was originally envisaged, and clinical trials have shown many of them to be effective in the following conditions:

- cardiac dysrhythmias (e.g. **phenytoin** – not used clinically, however; Ch. 21)
- bipolar disorder (**valproate**, **carbamazepine**, **oxcarbazepine**, **lamotrigine**, **topiramate**; Ch. 47)
- migraine prophylaxis (**valproate**, **gabapentin**, **topiramate**; Ch. 15)
- anxiety disorders (**gabapentin**; Ch. 44)
- neuropathic pain (**gabapentin**, **pregabalin**, **carbamazepine**, **lamotrigine**; Ch. 42).

This surprising multiplicity of clinical indications may reflect the fact that similar neurobiological mechanisms, involving synaptic plasticity and increased excitability of interconnected populations of neurons, underlie each of these disorders.

ANTIEPILEPTIC DRUGS AND PREGNANCY

There are several important implications for women taking antiepileptic drugs. By inducing hepatic CYP3A4 enzymes, some antiepileptic drugs may increase oral contraceptive metabolism, thus reducing their effectiveness. Taken during pregnancy, drugs such as phenytoin, carbamazepine, lamotrogine, topiramate and valproate are thought to produce teratogenic effects. It remains to be clarified if newer agents also have this problem. Induction of CYP enzymes may result in vitamin K deficiency in the newborn (Ch. 25).

Clinical uses of antiepileptic drugs

- Generalised tonic–clonic seizures:
  - **carbamazepine** (preferred because of a relatively favourable effectiveness : risk ratio), **phenytoin**, **valproate**
  - use of a single drug is preferred, when possible, to avoid pharmacokinetic interactions
  - newer agents include **vigabatrin**, **lamotrigine**, **topiramate**, **levetiracetam**.
- Partial (focal) seizures: **carbamazepine**, **valproate**; alternatives include **clonazepam**, **phenytoin**, **gabapentin**, **pregabalin**, **lamotrigine**, **topiramate**, **levetircetam**, **zonisamide**.
- Absence seizures: **ethosuximide**, **valproate**, **lamotrigine**:
  - **valproate** is useful when absence seizures coexist with tonic–clonic seizures, because most other drugs used for tonic–clonic seizures can worsen absence seizures.
- Myoclonic seizures and status epilepticus: **diazepam** intravenously or (in absence of accessible veins) rectally.
- Neuropathic pain: for example **carbamazepine**, **gabapentin** (see Ch. 42).
- To stabilise mood in mono- or bipolar affective disorder (as an alternative to **lithium**): for example **carbamazepine**, **valproate** (see Ch. 47).

MUSCLE SPASM AND MUSCLE RELAXANTS

Many diseases of the brain and spinal cord produce an increase in muscle tone, which can be painful and disabling. Spasticity resulting from birth injury or cerebral vascular disease, and the paralysis produced by spinal cord lesions, are examples. Multiple sclerosis is a neurodegenerative disease that is triggered by inflammatory attack on the CNS. When the disease has progressed for some years it can cause muscle stiffness and spasms as well as other symptoms such as pain, fatigue, difficulty passing urine and tremors. Local injury or inflammation, as in arthritis, can also cause muscle spasm, and chronic back pain is also often associated with local muscle spasm.

Certain centrally acting drugs are available that have the effect of reducing the background tone of the muscle without seriously affecting its ability to contract transiently under voluntary control. The distinction between voluntary movements and 'background tone' is not clear-cut, and the selectivity of those drugs is not complete. Postural control, for example, is usually jeopardised by centrally acting muscle relaxants. Furthermore, drugs that affect motor control generally produce rather widespread effects on the central nervous system, and drowsiness and confusion turn out to be very common side effects of these agents.

Baclofen (see Ch. 38) is a chlorophenyl derivative of GABA originally prepared as a lipophilic GABA-like agent in order to assist penetration of the blood–brain barrier, which is impermeable to GABA itself. Baclofen is a selective agonist at $GABA_B$ receptors (see Ch. 38). The antispastic action of baclofen is exerted mainly on the spinal cord, where it inhibits both monosynaptic and polysynaptic activation of motor neurons. It is effective when given by mouth, and is used in the treatment of spasticity associated with multiple sclerosis or spinal injury. However, it is ineffective in cerebral spasticity caused by birth injury.

Baclofen produces various unwanted effects, particularly drowsiness, motor incoordination and nausea, and it may also have behavioural effects. It is not useful in epilepsy.

Benzodiazepines are discussed in detail in Chapter 44. They produce muscle relaxation by an effect in the spinal cord. They are also anxiolytic.

Tizanidine is an α_2-adrenoceptor agonist that relieves spasticity associated with multiple sclerosis and spinal cord injury.

Sativex. For many years anecdotal evidence suggested that smoking **cannabis** (Ch. 19) relieves the painful muscle spasms associated with multiple sclerosis. **Sativex**, a cannabis extract containing Δ^9-tetrahydrocannabinol (also known as THC or **dronabinol**; see Ch. 19) and cannabidiol, is licensed in some countries as a treatment for spasticity in multiple sclerosis. It also has pain-relieving properties (see Chs 19 and 42).

Dantrolene acts peripherally rather than centrally to produce muscle relaxation (see Ch. 4).

Botulinum toxin (see Ch. 13) injected into a muscle, this neurotoxin causes long-lasting paralysis confined to the site of injection; its use to treat local muscle spasm is increasing. Its non-medicinal use as a 'beauty' treatment has become widespread.

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