41 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 over the past decade or so 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.

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; Julius & Basbaum, 2001; Julius & McCleskey, 2006). 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. 41.1). 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 below).

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. They also contain several neuropeptides (see Ch. 19), particularly substance P and calcitonin gene-related peptide (CGRP). These are released as mediators at both the central and the peripheral terminals, and play an important role in the pathology of pain. For a detailed description of synaptic transmission in the dorsal horn, see McMahon & Koltzenburg (2006).

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

[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.

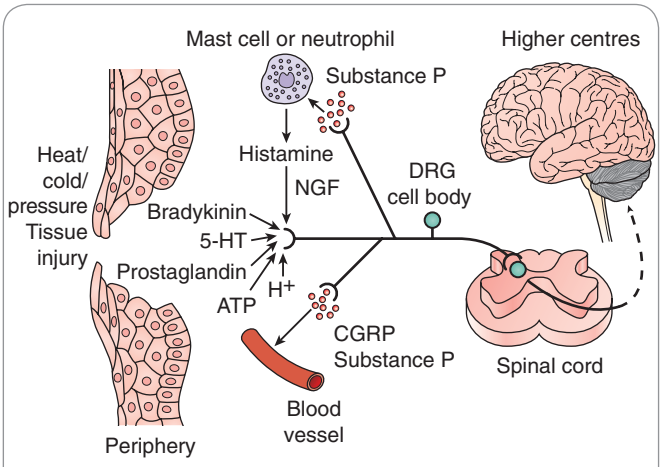


Fig. 41.1 Activation of nociceptive neurons. Various stimuli (physical and chemical) can initiate or enhance the rate of action potential firing in nociceptive primary afferent neurons (i.e. induce pain). These afferent fibres project to the dorsal horn of the spinal cord where they synapse on neurons 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.)

stimulus. Some of the main mechanisms are summarised in Figure 41.2.

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—changes defined by the term *neuroplasticity*. 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 in the hippocampus, described in Chapter 37, and the chemical mechanisms underlying it may also be similar (see Ji et al., 2003). 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 41.2 and 41.3).

Substance P and CGRP released from primary afferent neurons (see Fig. 41.1) also act in the periphery, promoting inflammation by their effects on blood vessels and cells of the immune system (Ch. 17). This mechanism, known as neurogenic inflammation, amplifies and

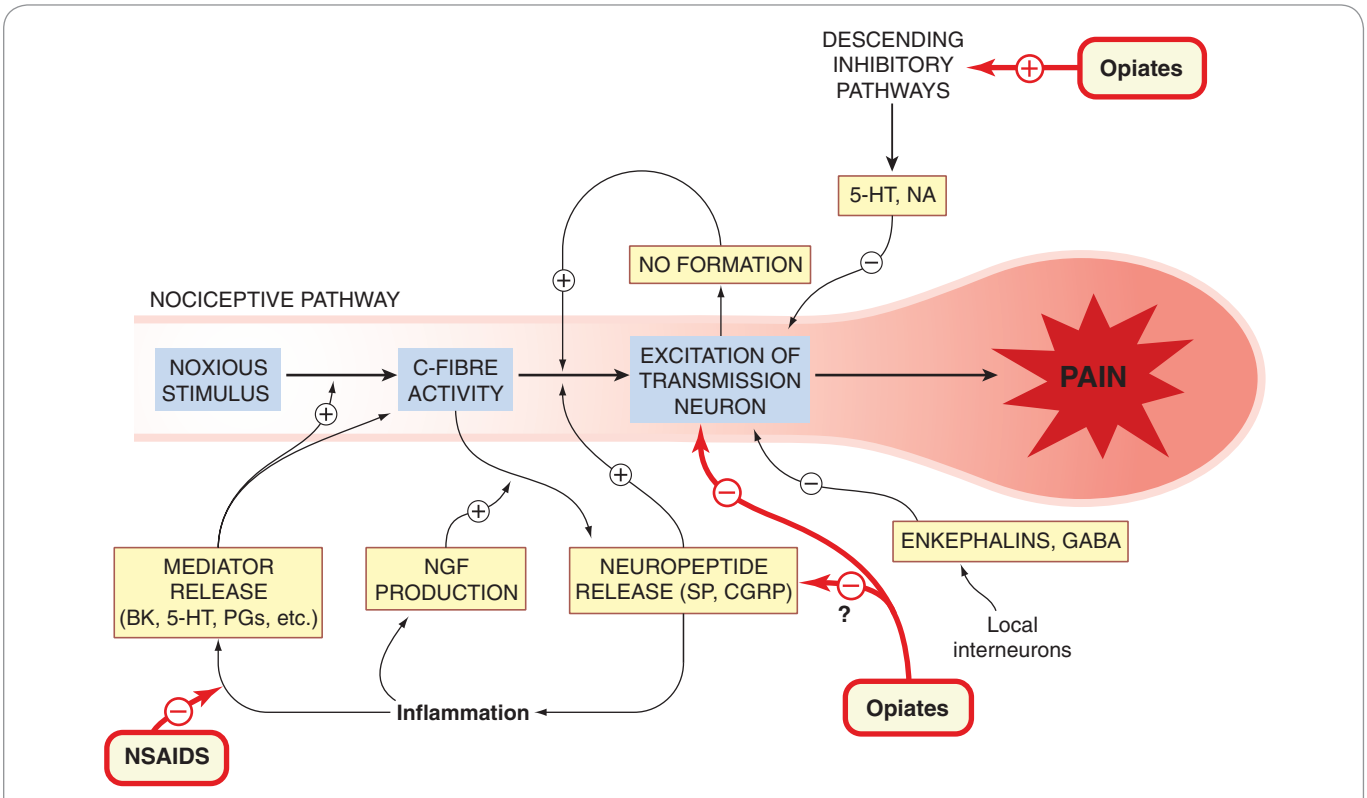
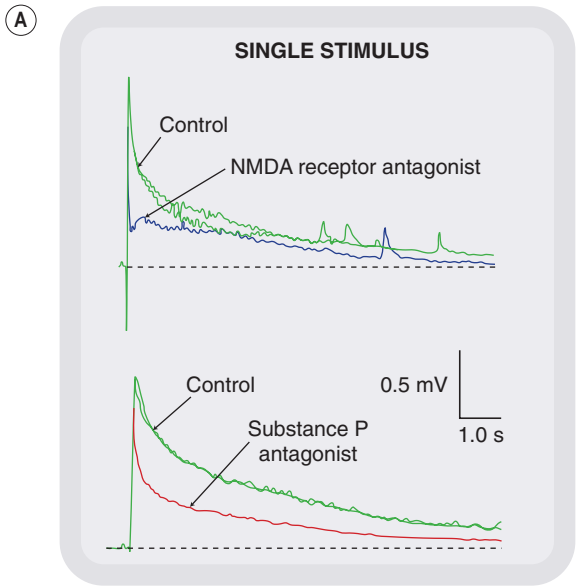


Fig. 41.2 Summary of modulatory mechanisms in the nociceptive pathway. 5-HT, 5-hydroxytryptamine; BK, bradykinin; CGRP, calcitonin gene-related peptide; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; SP, substance P.



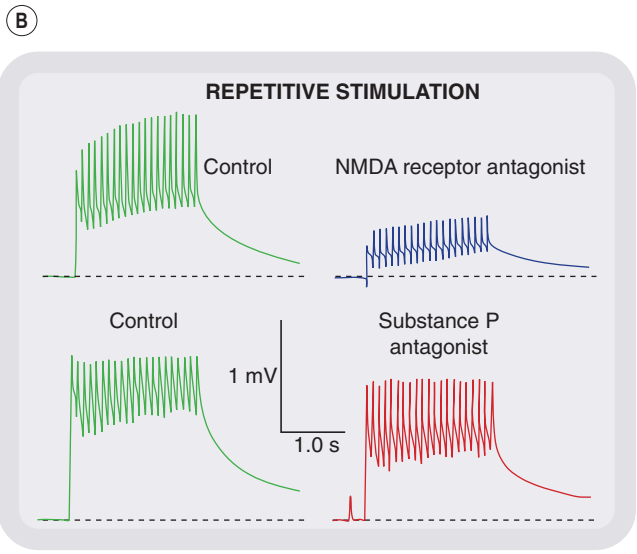


Fig. 41.3 Effect of glutamate and substance P antagonists on nociceptive transmission in the rat spinal cord. The rat paw was inflamed by ultraviolet irradiation 2 days before the experiment, a procedure that induces hyperalgesia and spinal cord facilitation. The synaptic response was recorded from the 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. 37) 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 is 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 S W Thompson.)

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, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and NO as well as many others (see Ji et al., 2003). For example, 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 Pezet & McMahon, 2006). 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 $P2X_3$) 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 (NR1) 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 (see Cox et al., 2006). The expression of certain sodium channel subtypes (e.g. $Na_v1.3$, $Na_v1.8$ and Na_v 1.7 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 a detailed description of 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 44) also find clinical application as analgesics (see below).

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. 41.4) control impulse transmission in the dorsal horn (see Millan, 2002). 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 PAG receives inputs from many other brain regions, including the hypothalamus, amygdala and cortex, and is

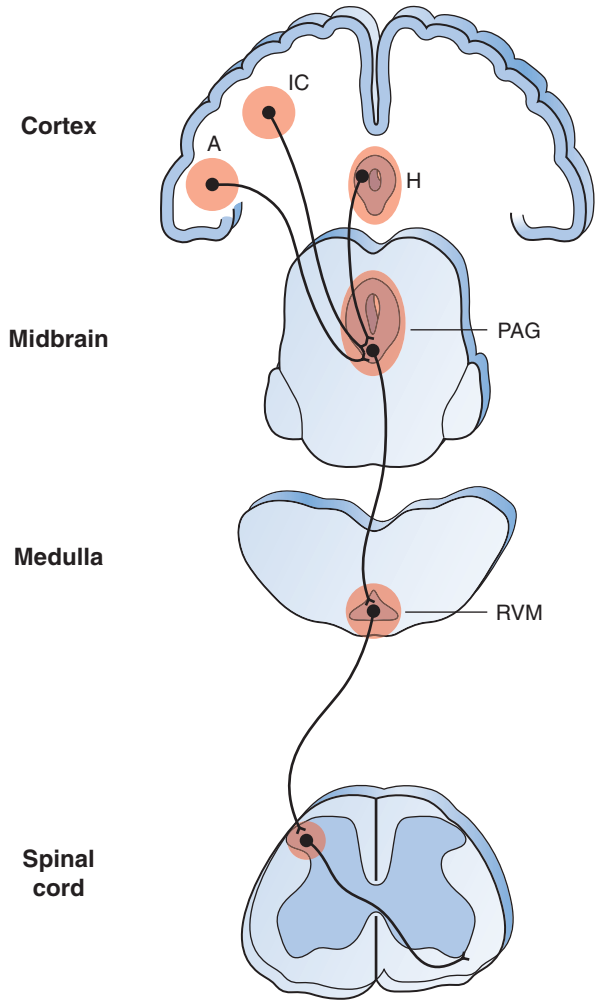


Fig. 41.4 The descending pain control system and sites of action of opioids to relieve pain. Opioids induce analgesia when microinjected into the insular cortex (IC), amygdala (A), hypothalamus (H), periaqueductal grey (PAG) region and rostroventral medulla (RVM) as well as into the dorsal horn of the spinal cord. The PAG receives input from higher centres and is the main output centre of the limbic system. It projects to the rostral ventromedial medulla (RVM). From the RVM, descending inhibitory fibres, some of which contain 5-hydroxytryptamine, project to the dorsal horn of the spinal cord. Shaded areas indicate regions expressing μ-opioid receptors. The pathways shown in this diagram represent a considerable oversimplification. (Adapted from Fields 2001 Prog Brain Res 122: 245–253. For a fuller account of the descending pain modulating pathways, see Fields, 2004.)

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 and the enkephalins, which act directly or via interneurons to inhibit the discharge of spinothalamic neurons (Fig. 41.4).

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 later section) 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.

There is also a noradrenergic pathway from the *locus coeruleus* (LC; see Ch. 38) 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.

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, 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.

NEUROPATHIC PAIN

Neurological disease affecting the sensory pathway can produce severe chronic pain—termed *neuropathic pain*—unrelated to any peripheral tissue injury. This occurs with central nervous system 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 (see Lai et al., 2004; Chahine et al., 2005). 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

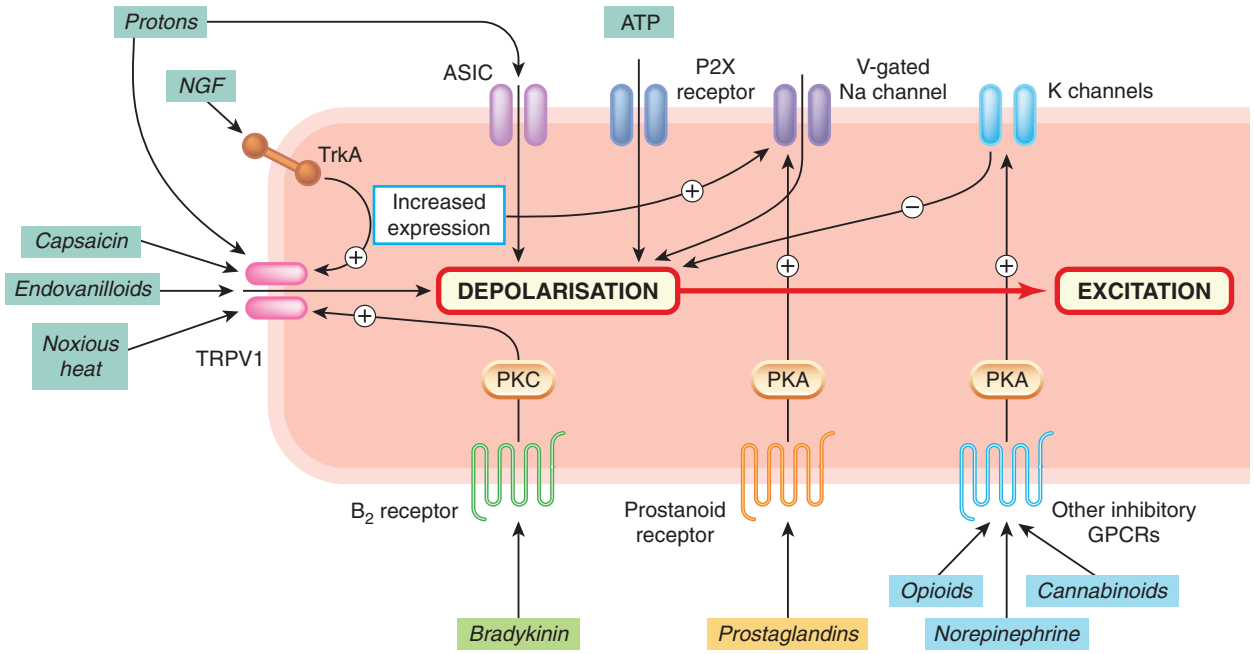


Fig. 41.5 Channels, receptors and transduction mechanisms of nociceptive afferent terminals. Only the main channels and receptors are shown. Ligand-gated channels include acid-sensitive ion channels (ASICs), ATP-sensitive channels (P2X receptors) and the capsaicin-sensitive channel (TRPV1), which is 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.

some antidepressant and antiepileptic agents (see later section). Potential new targets are discussed at the end of this chapter.

PAIN AND NOCICEPTION

▼ 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 even though the patient reports no great change in the intensity of the actual sensation. The affective component may be at least as significant as the antinociceptive component in the action of these drugs. There is thus often a poor correlation between the activity of analgesic drugs in animal tests (which mainly assess antinociceptive activity) and their clinical effectiveness.

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 reviewed by McMahon et al. (2006) and summarised in Figure 41.5.

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 (for review, 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 41.1). With respect to pain, the most important channels are TRPV1, TRPM8 and TRPA1 (see Patapoutian et al., 2009).

▼ **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

[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.

Table 41.1 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.

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 41.1), 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 that closely match those of nociceptive neurons, and it 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. 18) is also a TRPV1 agonist, although less potent than capsaicin. Confirming the role of TRPV1 in nociception, it has been found that 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 are actively developing TRPV1 antagonists as analgesic agents.

TRPM8 and TRPA1 respond to cold rather than heat (Table 41.1). TRPM8 is important in cold hypersensitivity in neuropathy. It may also be capable of eliciting a novel inhibitory, analgesic control over noxious inputs in chronic pain states (see Fleetwood-Walker et al., 2007). TRPA1 is activated in some experimental settings by noxious cold temperatures, calcium, pain-producing substances and inflammatory mediators (see Patapoutian et al., 2009); it can therefore also be considered to be a polymodal sensor.

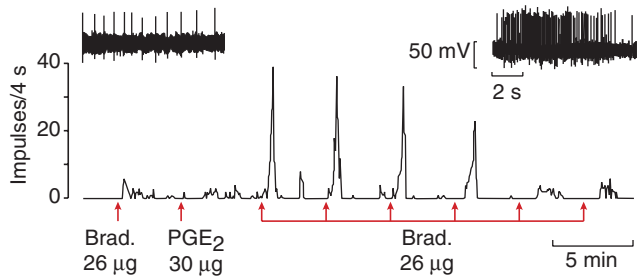


Fig. 41.6 Response of a nociceptive afferent neuron to bradykinin (Brad.) and prostaglandin. Recordings were made from a nociceptive afferent fibre supplying a muscle, and drugs were injected into the arterial supply. Upper records: single-fibre recordings showing discharge caused by bradykinin alone (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.)

Kinins

The most active pain-producing substances are *bradykinin* and *kallidin* (see Ch. 17), two closely related peptides produced under conditions of tissue injury by the proteolytic cleavage of the active kinins from a precursor protein contained in the plasma. Bradykinin is a potent pain-producing substance, acting partly by release of prostaglandins, which strongly enhance the direct action of bradykinin on the nerve terminals (Fig. 41.6). Bradykinin acts on B_2 receptors (see Ch. 17) 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 (see Calixto et al., 2004). 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. 17), as well as non-peptides. These show analgesic and anti-inflammatory properties, and may prove suitable for clinical use as analgesics (see Marceau & Regoli, 2004).

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. 41.6). 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 (Hall et al., 2007). 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 (see Samad et al., 2002). 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-hydroxytryptamine, 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 of $P2X_3$ receptors, by antisense DNA technology, reduces inflammatory pain.[4] Antagonists at this receptor are analgesic in animal models (see Jarvis, 2003) and may be developed for clinical use. 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 (see Sawynok, 2007).

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

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 actual pain. Both these substances are released locally in inflammation (see Ch. 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. Neuroplasticity plays an important role in persistent pain states, irrespective of their primary cause; not surprisingly, the signalling pathways have much in common with, and are at least as complex as, those involved in other neuroplasticity-based CNS pathologies discussed in later chapters. The strategies for developing the next wave of analgesic drugs therefore follow similar lines.[5]

TRANSMITTERS AND MODULATORS IN THE NOCICEPTIVE PATHWAY

The family of endogenous opioid peptides (see Ch. 19) plays a key role in modulating nociceptive transmission. Opioid analgesics act on the various receptors for these peptides.

Several neuropeptides are thought to play key roles in the transmission of nociceptive information in the dorsal horn of the spinal cord. These include substance P, CGRP and galanin, each of which is expressed by nociceptive afferent neurons and, it should be noted, can be released at their peripheral as well as their central terminals. 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 not as analgesics for other pain states. In the dorsal horn, substance P may be involved in wind-up and central sensitisation. In animal models, antagonists of substance P at the NK_1 receptor were shown to be effective analgesic drugs, but clinical trials have failed to confirm this in humans, so the high hopes for developing a new type of analgesic for clinical use have so far not come to fruition (see Hill & Oliver, 2007). The reason for this failure is not clear, but it may imply that substance P is less important as a pain mediator in humans than in rats.

Other mediators include the following:

- Glutamate (see Ch. 37) is released from primary afferent neurons and, acting on AMPA receptors, is responsible for fast synaptic transmission at the first

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 (transient receptor potential vanilloid receptor 1) responds to noxious heat as well as to **capsaicin**-like agonists. The lipid mediator **anandamide** is an agonist at vanilloid 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 (especially substance P) 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.

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

[5] And, sceptics may argue, face similar obstacles in relation to specificity and unwanted effects.

synapse in the dorsal horn. There is also a slower NMDA receptor-mediated response, which is important in relation to the wind-up phenomenon (see Fig. 41.3).
- GABA (see Ch. 37) is released by spinal cord interneurons and inhibits transmitter release by primary afferent terminals in the dorsal horn.
- ATP mediates a component of fast synaptic transmission at the first synapse in the dorsal horn as well as acting on primary afferent fibres to excite them (see above).
- 5-Hydroxytryptamine is the transmitter of inhibitory neurons running from the RVM to the dorsal horn.
- Noradrenaline is the transmitter of the inhibitory pathway from the LC to the dorsal horn, and possibly also in other antinociceptive pathways.
- Adenosine plays a dual role in regulating nociceptive transmission, activation of A_1 receptors causing analgesia, by acting on both peripheral nerve terminals and dorsal horn neurons, while activation of A_2 receptors in the periphery does the opposite (see Liu & Salter, 2005). There is evidence for descending inhibitory purinergic pathways acting on pain transmission through A_1 receptors.

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. 48).

The opioid field is reviewed thoroughly by Corbett et al. (2006).

CHEMICAL ASPECTS

The structure of morphine (Fig. 41.7) was determined in 1902, and since then many semisynthetic compounds (produced by chemical modification of morphine) and fully synthetic opioids have been studied.

Morphine analogues

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. 41.7). 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**[6] 3,6-diacetylmorphine, **codeine** 3-methoxymorphine and **oxycodone**). Substitution of a bulky substituent on the nitrogen atom introduces antagonist activity to the molecule (e.g. **naloxone**).

Synthetic derivatives

Phenylpiperidine series. **Pethidine** (known as meperidine in the USA), the first fully synthetic morphine-like drug (Fig. 41.7), was discovered accidentally when new atropine-like drugs were being sought. It is chemically unlike morphine, although its pharmacological actions are very similar. **Fentanyl** and **alfentanyl** as well as **sufentanil** (not used in the UK) are more potent and shorter-acting derivatives. **Remifentanyl** was designed as a potent analogue of fentanyl that is rapidly broken down by esterases in both blood and tissues, resulting in rapid elimination.

Methadone series. **Methadone**, although its structural formula bears no obvious chemical relationship to that of morphine, assumes a similar conformation in solution and was designed by reference to the common three-dimensional structural features of morphine and pethidine (Fig. 41.7).

Benzomorphan series. Therapeutically the most important member of this class is **pentazocine** (Fig. 41.7). Benzomorphans differ from morphine in their receptor-binding profile (see below), and so have somewhat different actions and side effects. **Cyclazocine** was an important pharmacological tool in the original description of the putative σ receptor (see below); it is not used in the UK.

Thebaine derivatives. **Buprenorphine** resembles morphine but is a partial agonist that binds very tightly to opioid receptors. Because it is a partial agonist, it induces less respiratory depression than other opioids. It is a very potent drug that can also antagonise the effect of other opioids. **Etorphine** is a highly potent full agonist used in veterinary practice.

OPIOID RECEPTORS

The proposal that opioids produce analgesia and their other behavioural effects by interacting with specific recep-

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. 48).
- 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.

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

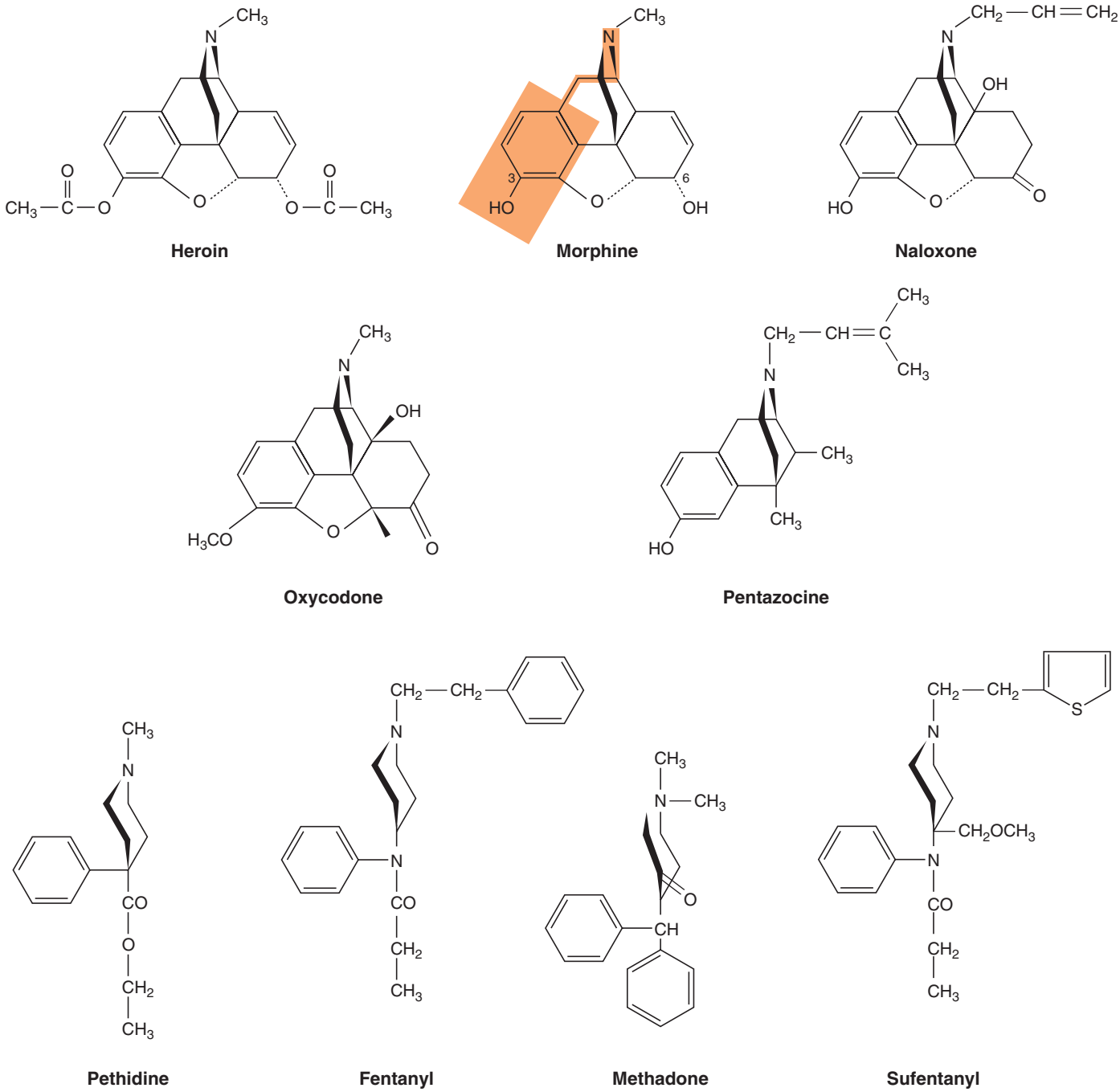


Fig. 41.7 Structures of some opioid analgesics. The red shaded area indicates the part of the morphine molecule that is structurally similar to tyrosine, the N-terminal amino acid in the endorphins. Carbon atoms 3 and 6 in the morphine structure are indicated. Diamorphine (heroin) is 3,6-diacetylmorphine and morphine is metabolised by addition of a glucuronide moiety at either position 3 or position 6.

tors 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 (first **nalorphine** and then **naloxone**) that the notion of a specific receptor became accepted. Martin and co-workers then provided evidence for multiple types of opioid receptors. They proposed three different types of receptor, called μ, κ and σ[7] for which the prototypical agonists were morphine, ketocyclazocine and

[7]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. 40). 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 (Hashimoto & Ishiwata, 2006). These proteins may be novel drug targets for psychiatric disorders.

Table 41.2 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	+++	–?	–	Antiopioid[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.

N-allylnormetazocine (SKF 10047), respectively. Subsequently, in the early 1970s three research groups led by Simon, Snyder and Terenius simultaneously described the use of radioligand binding 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 rationalised that there must be an endogenous substance or substances in the brain that activated these receptors.[8] 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. 41.7). It is probably just serendipity that the opium poppy synthesises a semirigid alkaloid molecule, morphine, part of which structurally resembles the tyrosine residue in the endogenous opioid peptides.

Following on from the discovery of the enkephalins, another receptor, δ, was discovered using a combination of classical pharmacological and radioligand binding approaches. 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 opioid 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).[9] The main behavioural effects resulting from their activation are summarised in Table 41.2. The interaction of various endogenous opioid peptides with the various receptor types is summarised in Table 41.3. Some agents that are used as experimental tools for distinguishing the different receptor types are also shown.

The development of transgenic mouse strains lacking each of the three main opioid receptor types (see Kieffer, 1999) has revealed that the major pharmacological effects of morphine, including analgesia, are mediated by the μ receptor.

All four opioid receptors apear to form homomeric as well as heteromeric receptor complexes (see Milligan, 2004). Opioid receptors are, in fact, quite promiscuous and can form heterodimers with non-opioid receptors. Heterodimerisation between opioid receptors has been shown to result in changes in the pharmacology of the receptors from that 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 'protean agonism' (see Ch. 3), whereby different ligands acting on the same opioid receptor can elicit different cellular responses and differential receptor trafficking (see Kelly et al., 2008).

[8] 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. 43).

[9] 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, 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 41.3 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, euphoria, sedation and dependence). Most of the analgesic opioids are μ-receptor agonists.
- 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 heterodimers, 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.

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.

Four main pharmacological categories are recognised:

1. *Pure agonists*. These can be either peptides (endogenous or synthetic) or non-peptides such as **etorphine** and **methadone**. They have high affinity for μ receptors and generally lower affinity for δ and κ sites. Methadone does, however, have activity at other, non-opioid receptors and this may explain its wide range of side effects.
2. *Partial agonists*. **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. 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.
3. *Mixed agonist–antagonists*. These drugs, typified by **nalorphine** and **pentazocine**, combine a degree of κ agonist and μ antagonist (or weak partial agonist) activity. Most of the drugs in this group tend to cause dysphoria rather than euphoria, probably by acting on the κ receptor.
4. *Antagonists*. These drugs produce very little effect when given on their own but block the effects of opioids. The most important examples are **naloxone** and **naltrexone**.

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 a specific type of potassium channel (the inwardly rectifying potassium channel) and inhibit the opening of voltage-gated calcium channels (mainly the N type of calcium channel). 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 below). They do this by a process of *disinhibition* whereby they cause excitation of projection neurons by suppressing the firing of inhibitory interneurons that tonically inhibit the projection neurons (see Ch. 36, Fig. 36.2).

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. 48).

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. 41.4 and (for a fuller description, see Fields, 2004). 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 in man 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 syndromes (such as phantom limb and other types of deafferentation pain, and trigeminal neuralgia) 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.

In both animal studies and in patients receiving opioids for pain relief, prolonged exposure to opioids may sometimes paradoxically induce a state of hyperalgesia in which pain sensitisation or allodynia occurs (see Chu et al., 2008). 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 below) and occurs with other opioid-induced behaviours in addition to analgesia. Hyperalgesia appears to have peripheral, spinal and supraspinal components. At the cellular level, the mechanisms underlying this phenomenon are still unclear but appear to involve PKC and NMDA receptor activation. 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. 48). 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 41.2). 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.

Respiratory depression

Respiratory depression, resulting in increased arterial PCO_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 PCO_2 and an inhibition of respiratory rhythm generation. Changes in PCO_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 anaesthetics and other general 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 the most troublesome 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. 27), 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 with putative actions at σ receptors and 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. 39) and has an analgesic action in neuropathic pain (see below).

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. 29).[10] 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. Acute administration of morphine-6-glucuronide, an active metabolite of morphine, may produce less nausea and vomiting, probably because it is more polar and does not penetrate the area postrema as well as morphine.

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,[11] 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.[12] 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 of morphine, because intraventricular injection of morphine inhibits propulsive gastrointestinal movements. **Methylnaltrexone bromide** (see also Ch. 8) and **alvimopan** (not yet approved in the UK) 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. Although histamine release by morphine does not appear to be opioid-receptor mediated, itching in individuals receiving opioids given systemically has been reported to be reduced by opioid antagonists indicating another potential therapeutic use of peripherally acting antagonists.

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. The *Straub tail reaction*, an improbable phenomenon beloved of opioid pharmacologists, consists of a raising and stiffening of the tail of rats or mice given opioid drugs, and is due to spasm of a muscle at the base of the tail. It was through this effect that the analgesic action of pethidine was discovered.

[10]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.

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

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

Actions of morphine

- The main pharmacological effects are:
  - analgesia
  - euphoria and sedation
  - respiratory depression and suppression of cough
  - nausea and vomiting
  - pupillary constriction
  - reduced gastrointestinal motility, causing constipation
  - histamine release, causing bronchoconstriction and hypotension.
- The most troublesome unwanted effects are constipation and respiratory depression.
- Acute overdosage with morphine produces coma and respiratory depression.
- The morphine metabolite, morphine-6-glucuronide, is more potent as an analgesic.
- Diamorphine is inactive at opioid receptors but is rapidly cleaved to 6-acetylmorphine and morphine.
- Codeine is also converted to morphine.

Opioids also exert complex immunosuppressant effects, which may be important as a link between the nervous system and immune function (see Vallejo et al., 2004). 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 abuse, leading to increased susceptibility to infections.

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., 2001; see also Chs. 2 and 48). 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. 48), in which physical dependence is much more pronounced and psychological dependence (or 'craving') is the main driving force. Addiction is rare in patients receiving opioids to control pain.

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 Christie, 2008). 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.[13] The intensity of the abstinence syndrome varies greatly, and dependence rarely progresses to addiction, in which psychological dependence (i.e. craving for the drug) is the predominant feature.

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. 38) may also play an important role in causing the abstinence syndrome (see Ivanov & Aston-Jones, 2001), 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 41.4 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 or intramuscular 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 now widely

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

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. Psychological dependence 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.

available as a slow-release oral preparation. Unfortunately, it has become popular among opioid addicts to grind up and inject such tablets as they contain large amounts of the drug. 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 at the 3- and 6-OH groups (see Fig 41.7), and these glucuronides constitute a considerable fraction of the drug in the bloodstream. Morphine-6-glucuronide is, surprisingly, 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 below) is a safer alternative for this purpose.

Analogues that have no free hydroxyl group in the 3 position (i.e. diamorphine, codeine) are metabolised to morphine, which accounts for all or part of their pharmacological activity. 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. **Remifentanyl** 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 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 41.4.

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.[14] 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.

[14]Naloxone is less effective in reversing the effects of buprenorphine as this agonist binds very tightly to the receptors.

Table 41.4 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 little 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. 46)
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
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

Table 41.4 (cont'd) Characteristics of the main opioid analgesic drugs

Drug	Use(s)	Route(s) of administration	Pharmacokinetic aspects	Main adverse effects	Notes
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 noradrenaline uptake

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

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 metabolism to 6-monoacetylmorphine and morphine (see Casy & Parfitt, 1986). 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 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. Furthermore, 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.). 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. 27). Dihydrocodeine is pharmacologically very similar, having no substantial advantages or disadvantages over codeine. About 10% of the population is resistant to the analgesic effect of codeine, because they lack the demethylating enzyme that converts it to morphine.

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. Diversion to the street market has resulted in it becoming a major drug of abuse (see Ch. 48), sometimes referred to as 'hillbilly heroin'.

Fentanyl, **alfentanyl**, **sufentanil** and **remifentanyl** are highly potent phenylpiperidine derivatives, with actions similar to those of morphine but with a more rapid onset and shorter duration of action, particularly remifentanyl. They are used extensively in anaesthesia, and they may be given intrathecally. Fentanyl, alfentanyl 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. 48). The lower intensity of the physical abstinence syndrome makes it possible to wean addicts from heroin by giving regular oral doses of methadone—an improvement if not a cure.[15] Methadone has actions at other sites in the CNS, including block of potassium channels, NMDA

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

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.[16]

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 that binds almost irreversibly to the receptors.

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 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 noradrenaline 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.

Pentazocine is a mixed agonist–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 does not enter the brain and therefore lacks analgesic activity. It inhibits peristalsis, and is used to control diarrhoea (see Ch. 29).

OPIOID ANTAGONISTS

Naloxone was the first pure opioid antagonist, with affinity for all three classical opioid receptors ($\mu > \kappa \geq \delta$). 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, 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 41.3) but they are not used clinically.

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

Opioid antagonists

- Pure antagonists include **naloxone** (short acting) and **naltrexone** (long 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) 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 (see Davies et al., 2004; Graham & Scott, 2005).

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 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, recent clinical studies have shown opioids such as morphine, oxycodone, levorphanol and tramadol to be effective in the treatment of neuropathic pain, provided an adequate dose can be reached that provides analgesia without excessive side effects.

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., 2007), largely as a result of serendipitous observations rather than a rational programme of drug discovery.

Tricyclic antidepressants, particularly **amitriptyline**, **nortriptyline** and **desipramine** (Ch. 46) 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 **venlafaxine**, which inhibit 5-HT 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. 44) that are also effective in the treatment of neuropathic pain. They bind to α2δ1 and α2δ2 subunits of voltage-activated calcium channels (see Ch. 4) and reduce neurotransmitter release. There has been considerable debate about how exactly these drugs inhibit calcium channel function: it may be by inhibiting channel opening or by interfering with the trafficking of the calcium channels to the plasma membrane. 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.

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. 42) with a short plasma half-life given either topically in a patch or intravenously, can give long-lasting relief in neuropathic pain states. It probably acts by blocking spontaneous discharges from damaged sensory nerve terminals, but the reason for its persistent analgesic effect is not clear. Some antidysrhythmic drugs (e.g. **mexiletine**, **tocainide**, **flecainide**; see Ch. 21) are effective orally (see Challapalli et al., 2005).

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.
- Various antidepressants (e.g. **amitriptyline**), as well as antiepileptic drugs (e.g. **carbamazepine**, **gabapentin**), are used mainly to treat neuropathic pain.
- Other drugs occasionally used include the NMDA receptor antagonist **ketamine** and the local anaesthetic drug lidocaine.

Drugs used to treat neuropathic pain

- Opioids may be effective at higher doses if side effects can be tolerated.
- Various antidepressants (e.g. **amitriptyline**) that block noradrenaline uptake 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 or administered intravenously.

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 (painful sensation in response to stimuli that normally would be innocuous). 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. 46), antiepileptic agents (e.g. **gabapentin**, **pregabalin**; see Ch. 44), benzodiazepines (e.g. **clonazepam**, **zopiclone**; see Ch. 43) and dopamine agonists (e.g. **ropinirole**; see Ch. 39) are currently used for this disorder—this long list reflecting their uncertain efficacy.

OTHER PAIN-RELIEVING DRUGS

Ketamine, a dissociative anaesthetic (Ch. 40), **memantine** and **dextromethorphan** work by blocking NMDA receptor channels, and probably reduce the wind-up phenomenon in the dorsal horn (Fig. 41.3). 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.

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).

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 many new approaches are being explored. For reviews of current areas of drug development, see Hill (2006) and Dray (2008).

- *Nerve growth factor* (NGF) is a major mediator of both inflammatory and neuropathic pain (Hefti et al., 2006). It is therefore an important new 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 TrkA domain 5 (TrkAd5), a soluble receptor protein that binds NGF with picomolar affinity.
- *TRP channel ligands*. Both TRPV1 agonist and antagonist drugs appear to have analgesic activity. 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. On the other hand, competitive and non-competitive antagonists aim to inhibit peripheral nerve fibre activity selectively by block of TRPV1 channels.
- *Other TRP channels* (TRPV3, TRPV4, TRPA1, and TRPM8) have been suggested to be involved in pain particularly when sensitised by some pathophysiological changes. Ligands for these channels are in early development.
- A number of *sodium channel blockers* are currently in development. These have varying selectivity at the channels whose expression may be altered in chronic pain states and include **lacosamide** (antiepileptic) and **ralfinamide** (undergoing clinical trials). Ralfinamide blocks sodium channels and also inhibits the enzyme monoamine oxidase, and has shown activity in a number of preclinical pain models.
- **Retigabine**, a *KCNQ channel* (K_v7, M-current) *opener*, inhibits C-fibre- and Aδ-fibre-mediated nociceptive responses in dorsal horn neurons in both naive and neuropathic rats.
- 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. 32) and **calcitonin** (see Ch. 35), 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.

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, 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 opioid 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) 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
  - **oxycodone** is given orally as a slow-release tablet
  - 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. 40) are analgesic, and self-administration of a mixture of nitrous oxide with oxygen is widely used during labour, for painful dressing changes.

- *Glutamate antagonists* acting on NMDA or AMPA receptors show analgesic activity in animal models, but it has not yet been possible 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. 37) or antagonists at the glycine site on the NMDA receptor. Antagonists of metabotropic glutamate receptors, mGluR1 and mGluR5, are currently in development and may have fewer side effects.

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Local anaesthetics and other drugs affecting sodium channels

42

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 and cardiac 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 41 and 44) and class I antidysrhythmic drugs (see Ch. 21).

History

Coca leaves have been chewed for their psychotropic effects for thousands of years (see Ch. 47) 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. 42.1). 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 (see below). **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 reducing the firing rate. At higher concentrations they prevent action potential firing. Currently available local anaesthetic agents do not distinguish between different sodium channel subtypes (see Ch. 4; Lai et al., 2004). 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. 42.2), the unionised form having only weak channel-blocking activity. This pH dependence can be clinically important, because inflamed tissues are often acidic and 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. 44), and occurs because the blocking molecule enters the channel much more readily when the channel is open than when it is closed. 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 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. The passage of a train of action potentials

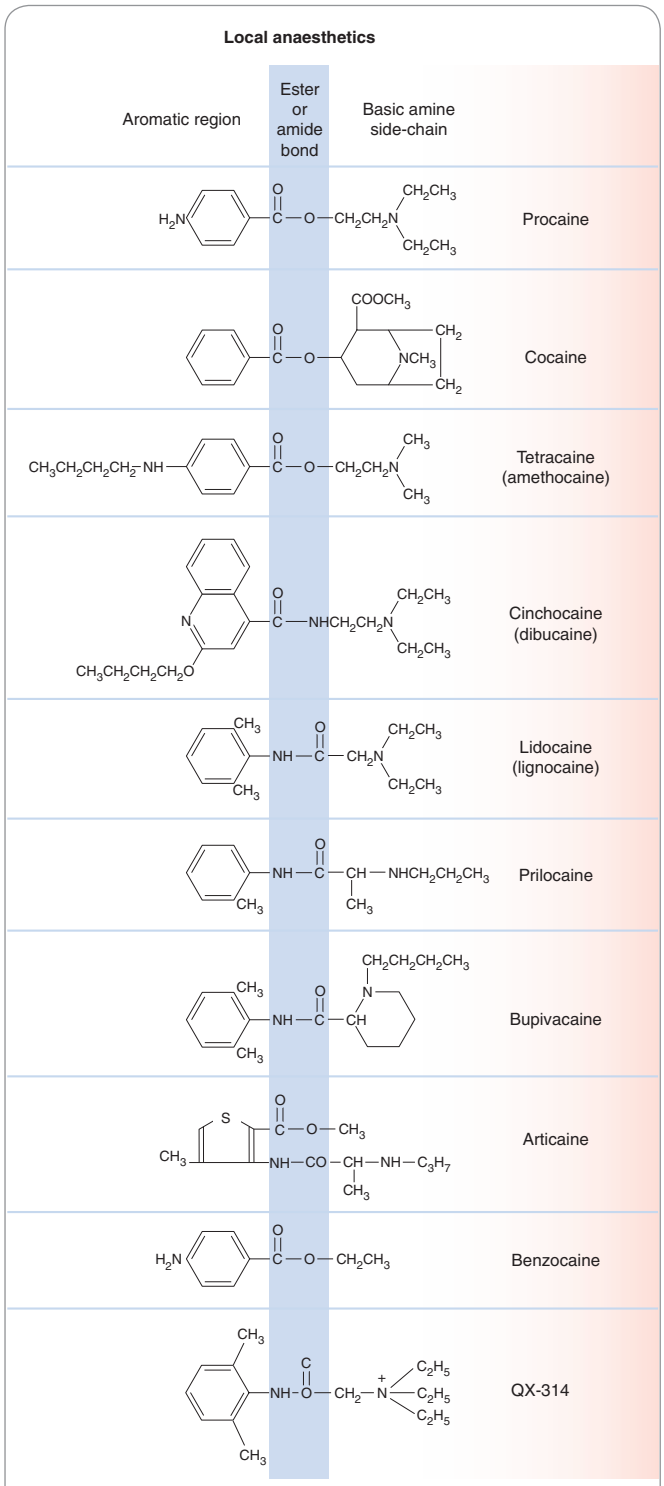

Fig. 42.1 Structures of local anaesthetics. The general structure of local anaesthetic molecules consists of an aromatic group (left), ester or amide group (shaded blue) and amine group (right).

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.

Quaternary amine local anaesthetics only work when applied to the inside of the membrane and the channels must be cycled through

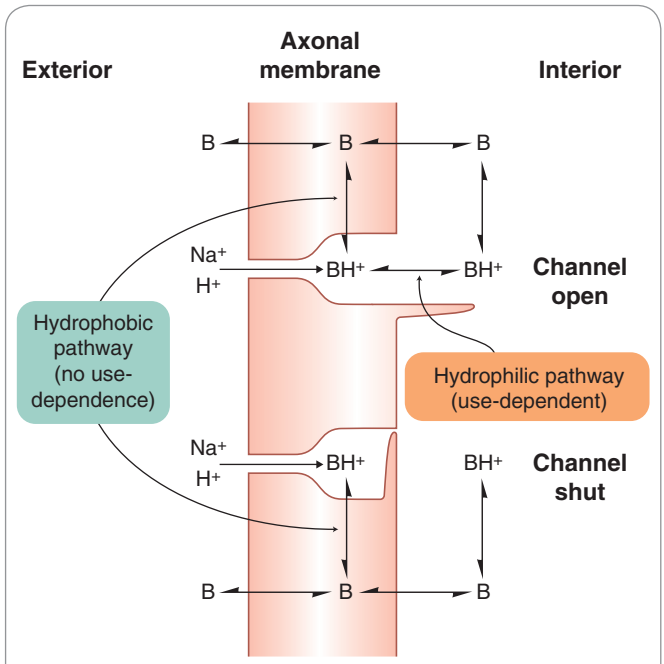

Fig. 42.2 Interaction of local anaesthetics with sodium channels. The blocking site within the channel can be reached via the open channel gate on the inner surface of the membrane by the charged species BH^+ (hydrophilic pathway), or directly from the membrane by the uncharged species B (hydrophilic pathway).

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. 42.2). 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. 41), 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. **Lidocaine** (lignocaine) can be used intravenously to control neuropathic pain (see Ch. 41).

The properties of individual local anaesthetic drugs are summarised in Table 42.1.

Table 42.1 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 (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 In a small proportion of patients it can induce paraesthesia (burning, tingling and sharp shooting pains) as well as numbness that outlasts the presence of the drug in the body	Used in dentistry

CNS, central nervous system.

Action 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 unionised 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. 44).

Unwanted effects

When used clinically as local anaesthetics, the main unwanted effects involve the central nervous system (CNS) and the cardiovascular system (Table 42.1). Their action on the heart can also be therapeutic in 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 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. 47), which produces euphoria at doses well below those that cause other CNS effects. This relates to its specific effect on monoamine uptake (see Ch. 47), 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 47). 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). **Articaine**, used in dentistry, can induce prolonged numbness (paraesthesia) that outlasts the presence of the drug in the body.

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 42.1). It also affects their usefulness as surface anaesthetics for application to mucous membranes.

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, 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.

Table 42.2 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 Not 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	LA injected into the subarachnoid space (containing cerebrospinal fluid) to act on spinal roots and spinal cord Glucose sometimes added so that spread of LA can be limited by tilting patient Used for surgery to abdomen, pelvis or leg, mainly when general anaesthesia cannot be used	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[b]	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

[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.
[b] Intrathecal or epidural administration of LA in combination with an opioid (see Ch. 41) 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.
LA, local anaesthetic.

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. 50). 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]

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

The routes of administration, uses and main adverse effects of local anaesthetics are summarised in Table 42.2.

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. 32), is often added to local anaesthetic solutions injected locally in order to cause vasoconstriction.

Other therapeutic uses

Blocking specific sodium channel subtypes is seen as a promising therapeutic strategy for a variety of clinical conditions, including epilepsy (see Ch. 44), neurodegenerative diseases and stroke (see Ch. 39), neuropathic pain (see Ch. 41) and myopathies. As our understanding of the role of

specific sodium channel subtypes in different pathophysiological situations has increased, it is likely that selective blocking agents will be developed for use in different clinical situations.

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 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 has subsequently been 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 are insensitive to TTX, notably those of cardiac muscle and those upregulated in sensory neurons in neuropathic pain (see Ch. 41).

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).

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.

AGENTS THAT AFFECT SODIUM CHANNEL GATING

Various substances are known that 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.

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43 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 and epilepsy. Here we will focus on their use as anxiolytics. Of the classical anxiolytic/hypnotic drugs, the benzodiazepines are the most important group. Possible new approaches are discussed briefly.

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 as recognised clinically include:

- *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)
- *panic disorder* (sudden attacks of overwhelming fear 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)
- *phobias* (strong fears of specific objects or situations, e.g. snakes, open spaces, flying)
- *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).

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 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.

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 below). 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. 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 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). 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.

DRUGS USED TO TREAT ANXIETY

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

- Antidepressants (see Ch. 46 for details). Selective serotonin (5-HT) reuptake inhibitors (SSRIs; e.g. **fluoxetine**, **paroxetine** and **sertraline**) and 5-HT/noradrenaline reuptake inhibitors (SNRIs; e.g. **venlafaxine**) 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 any depression that may be associated with anxiety.
- **Benzodiazepines**. Used to treat acute anxiety. Those used to treat anxiety have a long biological half-life (see Table 43.1). 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** and **valproate**, antiepileptic drugs (see Ch. 44), are also effective in treating generalised anxiety disorder.
- Some atypical antipsychotic agents (see Ch. 45) such as **olanzepine** and **risperidone** may be effective in generalised anxiety disorder and post-traumatic stress disorder but the incidence of side effects may be greater than with other anxiolytic drugs.
- 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.[1] Their effectiveness depends on block of peripheral sympathetic responses rather than on any central effects.

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 INSOMNIA (HYPNOTIC DRUGS)

- **Benzodiazepines**. Short-acting benzodiazepines (e.g. **lorazepam** and **temazepam**) are used for treating insomnia as they have little hangover effect.
- **Zolpidem** and **zopiclone**. Although chemically distinct, these short-acting sedatives act similarly to benzodiazepines. They lack appreciable anxiolytic activity (see below).
- **Antihistamines**[2] (see Ch. 26; e.g. **diphenhydramine** and **promethazine**) can be used to induce sleep. They are included in various over-the-counter preparations.
- Miscellaneous other drugs (e.g. **chloral hydrate**, **meprobamate** and **methaqualone**). They are no longer recommended, but therapeutic habits die hard and they are occasionally used.

Antidepressants (Ch. 46), antiepileptics (Ch. 44), antipsychotics Ch. 45), β-adrenoceptor antagonists (Ch. 14) and antihistamines (Ch. 26) are described in detail elsewhere in

[1]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.

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

Table 43.1 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)
Triazolam,[a] midazolam	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	Hypnotic, 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] 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 is similar.

this book. Some discussion of how SSRIs exert their anxiolytic activity is included in the section on buspirone (see below). In this chapter we focus on drugs whose primary use is as anxiolytic and hypnotic agents.

Classes of anxiolytic and hypnotic drugs

- Antidepressant drugs (SSRIs, SNRIs, TCAs and MAOIs–see Ch. 46) 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** and **valproate**) 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.
- Histamine H_1 receptor antagonists have sedative effects.
- Miscellaneous other agents (e.g. **methaqualone**, **chloral hydrate**) are still used occasionally to treat insomnia (benzodiazepines are preferable in most cases).

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 43.1. 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 below) 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 below).

The term 'benzodiazepine' refers to a distinct chemical structure. Drugs such as zolpidem and zopiclone have a different chemical structure 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. 37), 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 (Fig. 37.4). They bind specifically to a regulatory site on the receptor, distinct from the GABA-binding sites (see below), and act allosterically to increase the affinity of GABA for the receptor. Single-channel recordings show an increase 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. 43.1).

▼ 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. 37). 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. 37). The various combinations occur in different parts of the brain, have different physiological functions and have subtle differences in their pharmacological properties (see below).

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. Two genetic approaches have been used to study the roles of different subunits in the different behavioural effects of benzodiazepines—genetic knockout and loss of function mutants (see Whiting, 2003; Reynolds, 2008). The loss of function mutant approach has the advantage over subunit knockout that it reduces the likelihood of compensatory changes in the expression of other subunits. Mutation of a single amino acid (histidine 101 or its equivalent) in the α subunit eliminates benzodiazepine binding. Behavioural analysis of various mutant mice indicates that α1-containing receptors mediate the sedative but not the anxiolytic effect of benzodiazepines whereas α2- and α3-containing receptors mediate the anxiolytic effect.

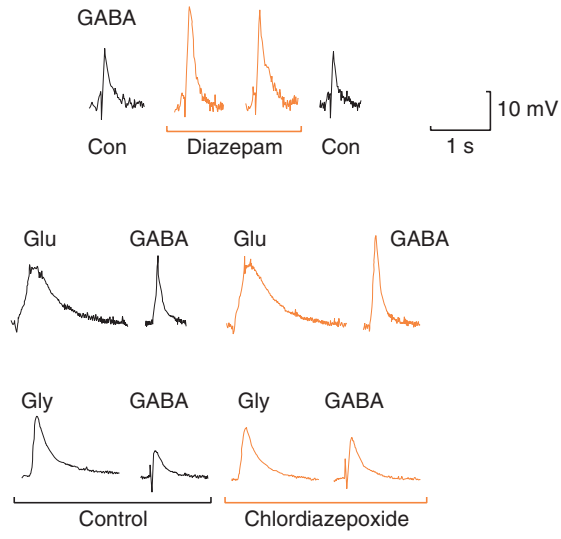

Fig. 43.1 Potentiating effect of benzodiazepines and chlordiazepoxide on the action of GABA. Drugs were applied by ionophoresis to mouse spinal cord neurons grown in tissue culture, from micropipettes placed close to the cells. The membrane was hyperpolarised to –90 mV, and the cells were loaded with 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.

The obvious next step has been to try and develop subunit-selective drugs (Reynolds, 2008; Christmas et al., 2008). Unfortunately, this has proved difficult, due to the structural similarity between the benzodiazepine binding site on different α subunits. What has been possible is the development of drugs that, while having little subunit-selectivity of binding, have different levels of agonist efficacy at receptors containing different subunits. Selective efficacy at α2- and α3-containing receptors may produce drugs that have an anxiolytic effect without the unwanted effects of sedation and amnesia. Such compounds have been developed (e.g. MK-0343, TPA023) but only limited data on their effectiveness in humans are currently available. **Pagoclone**, which is reported to be an α3 agonist and α1, α2 and α5 partial agonist, has little or no sedative or amnesic actions and is in development for the treatment of panic disorders and stuttering.

Peripheral benzodiazepine-binding sites, not associated with GABA receptors, are known to exist in many tissues. They are located primarily on mitochondrial membranes. For information on their structure and functions, see Veenman & Gavish (2006).

PHARMACOLOGICAL EFFECTS AND USES

The main effects of benzodiazepines are:

- reduction of anxiety and aggression
- induction of sleep and sedation
- reduction of muscle tone and coordination
- 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.[3] If given to the dominant member of a pair of animals (e.g. mice or monkeys) housed in the same cage, benzodiazepines reduce the number of attacks by the dominant individual and increase the number of attacks made on him. With the possible exception of **alprazolam** (Table 43.1), 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 a manifestation of the benzodiazepine withdrawal syndrome, which occurs with all these drugs (see below) but is more acute with drugs whose action wears off rapidly.

Benzodiazepines are now used mainly for treating acute anxiety states.

Induction of sleep and sedation

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

[3]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.

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. 32). Most hypnotic drugs reduce the proportion of REM sleep, although benzodiazepines affect it less than other hypnotics, and zolpidem (see below) least of all. Artificial interruption of REM 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 43.2 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 a withdrawal syndrome may occur (see below).

Benzodiazepines 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. 40).

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, which 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.

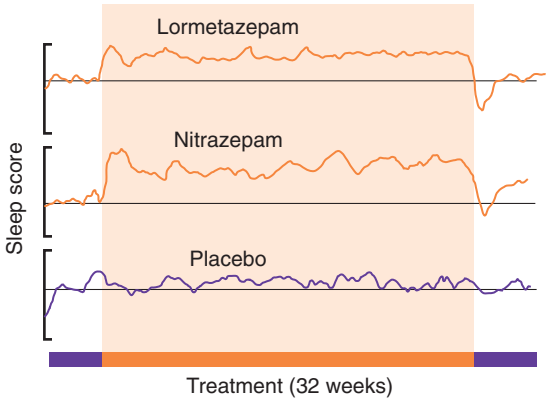

Fig. 43.2 Effects of long-term benzodiazepine treatment on sleep quality. A group of 100 poor sleepers were given, under double-blind conditions, lormetazepam 5 mg, nitrazepam 2 mg or placebo nightly for 24 weeks, the test period being preceded and followed by 4 weeks of placebo treatment. They were 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.)

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 37 and 44) but less so against electrically induced convulsions.

Clonazepam (see above) is used to treat epilepsy (Ch. 44), as is **diazepam**, which is administered rectally to children in acute seizures and intravenously to control life-threatening seizures in status epilepticus. Tolerance develops to the anticonvulsant actions of benzodiazepines (see below).

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 (see below for a general description of benzodiazepine inverse agonism) 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 (see below), it is possible, however, 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 molecules that act on benzodiazepine receptors have been isolated, including *β-carbolines* (e.g. ethyl-β-carboline-3-carboxylate, βCCE), structurally related to tryptophan, and *diazepam-binding inhibitor*, a 10-kDa peptide. Whether these molecules exist in the brain 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. 40).

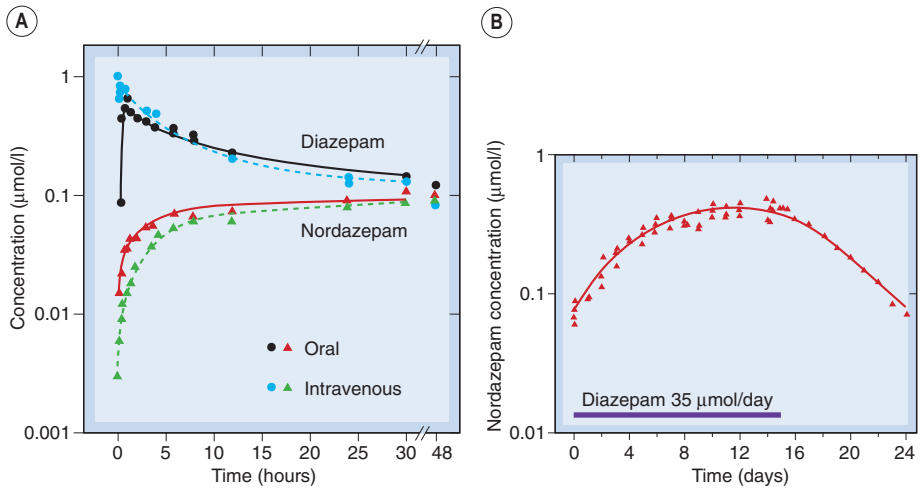

Fig. 43.3 Pharmacokinetics of diazepam in humans. [**A**] Concentrations of diazepam and nordazepam following a single oral or intravenous dose. Note the very slow disappearance of both substances after the first 20 h. [**B**] Accumulation of nordazepam during 2 weeks' daily administration of diazepam, and slow decline (half-life about 3 days) after cessation of diazepam administration. (Data from Kaplan S A et al. 1973 J Pharmacol Sci 62: 1789.)

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). 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 43.1). 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 (**nordazepam**), 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 43.3 shows the gradual build up and slow disappearance of nordazepam 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.[4]

UNWANTED EFFECTS

These may be divided into:

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

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 used as recreational drugs (see Chs 48 and 58). The availability of an effective antagonist, **flumazenil**, means that the effects of an acute overdose can be counteracted,[5] 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 affects 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

[4]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.

[5]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.

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 (Wafford, 2005).

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. It is recommended that benzodiazepines be withdrawn gradually by stepwise lowering of the dose. Although 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.[6] 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. With triazolam, a very short-acting drug and no longer in use, the withdrawal effect occurred within a few hours, even after a single dose, producing early-morning insomnia and daytime anxiety when the drug was used as a hypnotic.

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. 48), is not a major problem.

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. It can be used to treat comatose patients suspected of having overdosed with benzodiazepines. Convulsions may rarely occur in patients treated with flumazenil, and this is more common in patients receiving tricyclic antidepressants (Ch. 46). 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. βCCE, diazepam-binding inhibitor (see above) and some benzodiazepine analogues show inverse agonist activity. It is possible (see Fig. 43.4) 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,

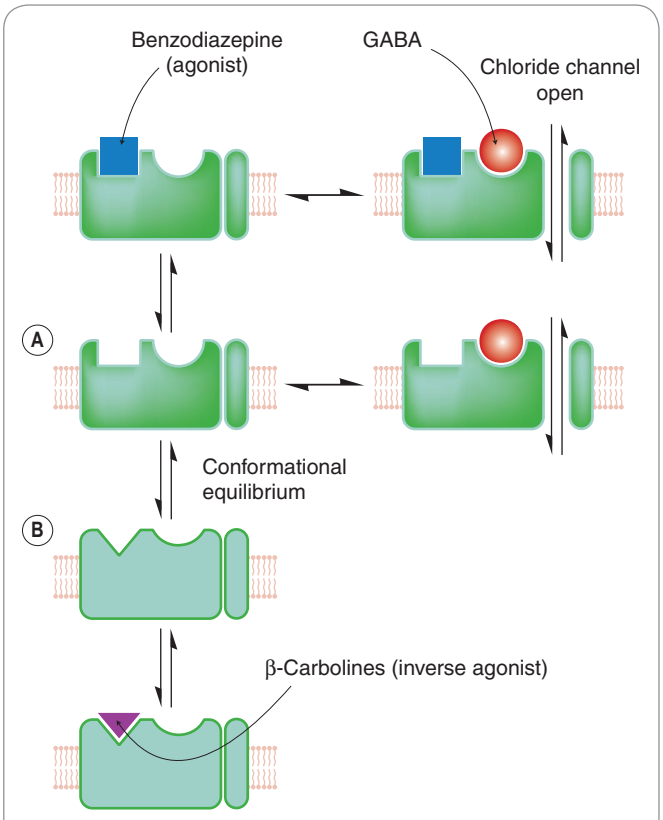

Fig. 43.4 Model of benzodiazepine/GABA receptor interaction. Benzodiazepine agonists, antagonists and inverse agonists are believed to bind to a site on the GABA receptor distinct from the GABA-binding site. A conformational equilibrium exists between states in which the benzodiazepine receptor exists 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.

[6]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 weak inverse agonists or antagonists and prevent the actions of the anxiolytic benzodiazepines. Other inverse agonists (not used clinically) are anxiogenic.
- Anxiolytic effects are mediated by $GABA_A$ receptors containing the α_2 or α_3 subunits, while sedation occurs through those with the α_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 dependence—characteristic withdrawal syndrome on cessation of use.

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

BUSPIRONE

Buspirone is used to treat generalised anxiety disorders. It is ineffective 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 (see Traber & Glaser, 1987). 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. 38), 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. Receptors that have received particular interest are the $5\text{-}HT_2$ receptors and downregulation of these 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. 38) and thus interferes with arousal

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. 46):
  - 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.

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 (see above).

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, but none is so far available for clinical use (see Christmas et al., 2008; Mathew et al., 2009).

Clinical use of drugs as anxiolytics

- Antidepressants are now the main drugs used to treat anxiety. Their effects are slow in onset (> 2 weeks). Effective against most forms of anxiety.
- Benzodiazepines are now largely used for acute relief of severe and disabling anxiety or in the early stages of treatment with antidepressants before they become effective.
- 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).

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. 48) and physical or psychiatric disorder (especially depression).
- Tricyclic antidepressants (Ch. 46) 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**, **nitrazepam**) 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**, **diphenhydramine**), which cause drowsiness (see Ch. 26) and are on general sale for occasional insomnia. They can impair performance the day after they are used.

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44 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. More information on the topics covered can be obtained from specialist textbooks (e.g. Engel & Pedley, 2007; Browne & Holmes, 2008; Hart & Sander, 2008).

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. 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 diseases, 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. 41) and bipolar depression (Ch. 46). Many new antiepileptic drugs have been developed over the past 20 or so years in attempts to improve their efficacy and side-effect profile. 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 which precipitate periodic seizures see Browne & Holmes (2008) and Hart & Sander (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. 44.1). Modern brain imaging techniques, such as magnetic resonance imaging and positron emission tomography, are now routinely used in the diagnosis of epilepsy (see Fig. 44.2) to identify structural abnormalities (e.g. lesions, tumours) that cause certain epilepsies (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 categories, namely *partial* and *generalised* seizures, although there is some overlap and many varieties of each. Either form is classified as *simple* (if consciousness is not lost) or *complex* (if consciousness is lost).

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*. The EEG discharge in this type of epilepsy is normally confined to one hemisphere (Fig. 44.1D). 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, develop into a generalised seizure (see below)—referred to as partial seizures with secondary generalisation—when the abnormal neuronal activity spreads across the whole brain.

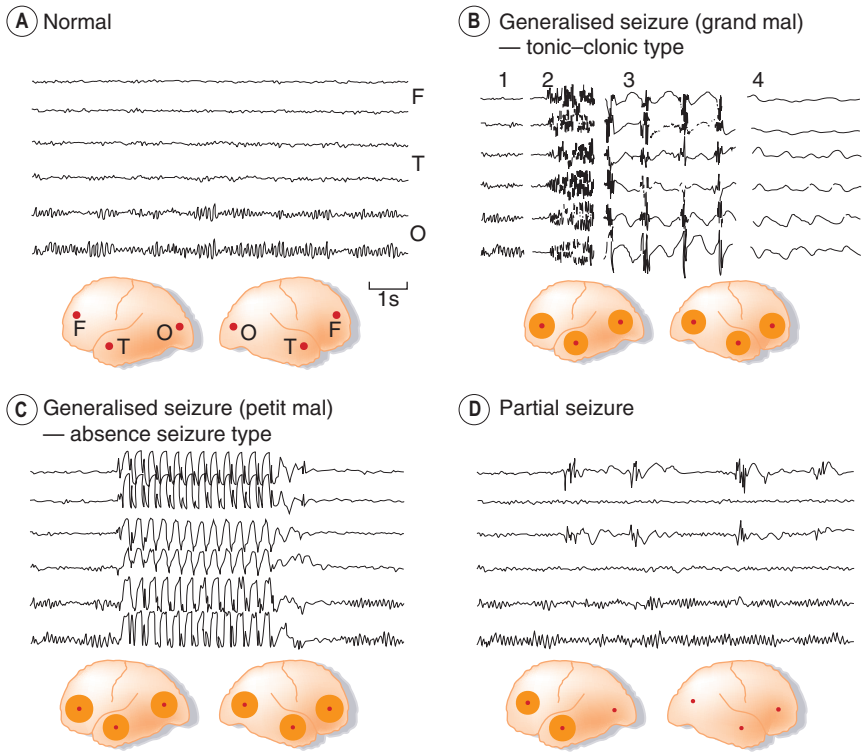

Fig. 44.1 Electroencephalography (EEG) records in epilepsy. [**A**] Normal EEG recorded from frontal (F), temporal (T) and occipital (O) sites on both sides, as shown in the inset diagram. The α rhythm (10/s) can be seen in the occipital region. [**B**] Sections of EEG recorded during a generalised tonic–clonic (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 S G et al. 1978 Neurological pathophysiology, 2nd edn. Oxford University Press, New York.)

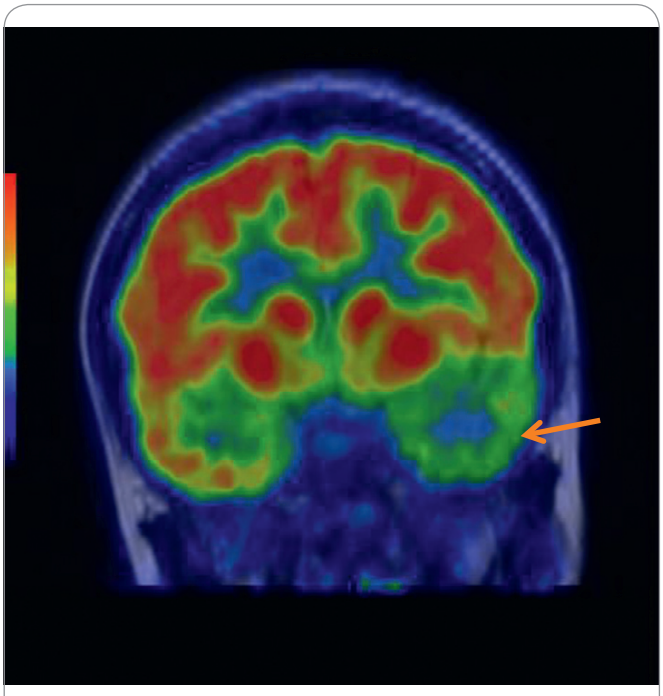

Fig. 44.2 Positron emission tomography (PET) image using [^{18}F]-fluoro-2-deoxyglucose (FDG) of the brain of a female patient suffering from temporal lobe epilepsy. The interictal area of hypometabolism in the left temporal lobe (indicated by the arrow) is suggestive of the site of the epileptic focus. (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*, which is often associated with a focus in the temporal lobe, 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. 44.1B) and *absence seizures* (petit mal, Fig. 44.1C); 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

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

spasm and an involuntary cry. Respiration stops, and defaecation, 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. 44.1B).

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. 44.1C). 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 (see below), 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. 39).

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 Weber & Lerche, 2008). 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, $GABA_A$ 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 e*pileptogenesis* can arise if excitatory transmission is facilitated or inhibitory transmission is reduced (exemplified by $GABA_A$ receptor antagonists causing convulsions; see Ch. 37). In certain respects, epileptogenesis resembles long-term potentiation (Ch. 37), and similar types of use-dependent synaptic plasticity may be involved (see Kulmann et al., 2000). Because detailed studies are difficult to carry out on epileptic patients, many different animal models of epilepsy have been investigated (see Sarkisian, 2001). These include a variety of genetic strains that show epilepsy-like characteristics (e.g. mice that convulse briefly in response to certain sounds, baboons that show photically induced seizures and beagles with an inherited abnormality that closely resembles human epilepsy). Recently, 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 cortical damage (e.g. by applying aluminium oxide paste or crystals of a cobalt salt) results in focal epilepsy. Local application of penicillin crystals has a similar effect, probably by interfering with inhibitory synaptic transmission. Convulsant drugs such as **pentylenetetrazol** (PTZ) are often used, particularly in the testing of antiepileptic agents, and seizures caused by electrical stimulation of the whole brain are used for the same purpose. It has been found empirically that 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.

The *kindling model* may approximate the human condition more closely than directly evoked seizure models. Low-intensity electrical stimulation of certain regions of the limbic system, such as the amygdala, with implanted electrodes normally produces no seizure response. If a brief period of stimulation is repeated daily for several days, however, the response gradually increases until very low levels of stimulation will evoke a full seizure, and eventually seizures begin to occur spontaneously. Once produced, the kindled state persists indefinitely. This change is prevented by NMDA receptor antagonists, and may involve processes similar to those that cause long-term potentiation of synaptic transmission in the hippocampus (see Ch. 37). 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, prophylactic treatment with antiepileptic drugs for 2 years following severe head injury reduces the subsequent incidence of post-traumatic epilepsy, which suggests that a phenomenon similar to kindling may underlie this form of epilepsy.

The *kainate model* entails a single injection of the glutamate receptor agonist kainic acid into the amygdaloid nucleus of a rat. After transient intense stimulation, spontaneous seizures begin to occur 2–4 weeks later, and then continue indefinitely. It is believed that excitotoxic damage to inhibitory neurons is responsible, associated with structural remodelling of excitatory synaptic connections, changes that may also be a factor in human epilepsies.

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. 44.3). This event probably results from the abnormally exaggerated and prolonged action of an excitatory transmitter. Activation of NMDA receptors (see Ch. 37) produces 'plateau-shaped' depolarising responses very similar to the PDS, as well as initiating seizure activity. This membrane response occurs because of the voltage-dependent blocking action of Mg^{2+} on channels operated by NMDA receptors (see Ch. 37). Glutamate must undoubtedly participate in the epileptic discharge, but efforts to develop glutamate antagonists as antiepileptic drugs have met with little success. It is known that repeated seizure activity can lead to neuronal degeneration, possibly due to excitotoxicity (Ch. 39).

Studies on experimental epilepsy in the kindling or kainate models have revealed a deficit in various biochemical markers of GABA-mediated inhibitory transmission, and an increase of markers associated with glutamate-mediated excitation (see Jarrott, 1999). Human studies have shown less consistent changes, although studies on brain samples removed at operation suggest that the epileptic focus contains more glutamate than normal; the GABA content is not affected. Potassium-stimulated glutamate release is also increased in the epileptic focus compared with in normal tissue.

Neurotrophins, particularly brain-derived neurotrophic factor (BDNF), may play a role in epileptogenesis. BDNF, which acts on a membrane

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.

receptor tyrosine kinase (TrkB; Ch. 3), enhances membrane excitability and also stimulates synapse formation. Deletion of the neurotrophin receptor, TrkB, in mice prevents seizures from developing in the kindling model. Production and release of BDNF is increased in the kindling models, and there is also evidence for its involvement in human epilepsy. Specific blocking agents represent a possible future strategy for treating epilepsy but remain to be identified.

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 clearly 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 (see Table 44.1) include **phenytoin**, **carbamazepine**, **valproate**, **ethosuximide** and **phenobarbital**, together with various benzodiazepines, such as **diazepam**, **clonazepam** and **clobazam**. Newer drugs in current use include **vigabatrin**, **gabapentin**, **pregabalin**, **lamotrigine**, **felbamate**, **tiagabine**, **topiramate**, **levetiracetam**, **oxcarbazepine**, **zonisamide** and **rufinamide**. Those new drugs in late stages of development that have novel mechanisms of action are described briefly towards the end of this section. The number of new antiepileptic drugs reflects the efforts being made to improve on the far from ideal properties of the earlier drugs. In general, the newer drugs are less likely to interact pharmacokinetically with other drugs (see Ch. 56) and have fewer adverse effects. The appropriate use of drugs from this large available menu depends on many clinical factors (for recent clinical use updates, see Macleod & Appleton, 2007; Azar & Abou-Khalil, 2008).

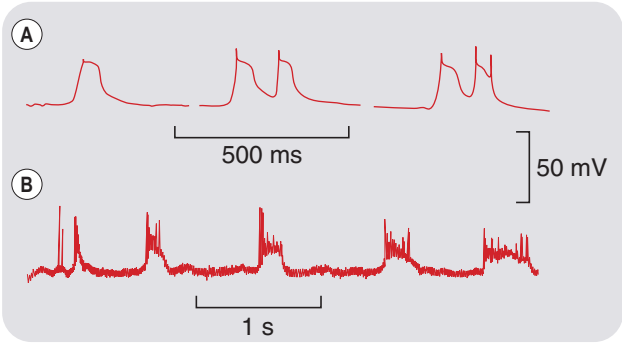

Fig. 44.3 'Paroxysmal depolarising shift' (PDS) compared with experimental activation of glutamate receptors of the NMDA type. [**A**] PDS recorded with an intracellular microelectrode from cortical neurons of anaesthetised cats. Seizure activity was induced by topical application of penicillin. [**B**] Intracellular recording from the caudate nucleus of an anaesthetised cat. The glutamate analogue NMDA was applied by ionophoresis from a nearby micropipette. Note the periodic waves of depolarisation, associated with a burst of action potentials, which closely resemble the PDS. (From: [**A**] Matsumoto H, Marsan C A 1964 Exp Neurol 9: 286; [**B**] Herrling P L et al. 1983 J Physiol 339: 207.)

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 (see Rogawski & Löscher, 2004a):

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

[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.

Table 44.1 Properties of the main 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)		++			All types Lorazepam used intravenously to control *status epilepticus*	Sedation Withdrawal syndrome (see Ch. 43)	See Ch. 43
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

Antiepileptic drugs may exert more than one beneficial action, prime examples being **valproate** and **topiramate** (see Table 44.1). 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

Table 44.1 (cont'd) Properties of the main antiepileptic drugs

Drug	Site of action				Main uses	Main unwanted effect(s)	Pharmacokinetics
	Sodium channel	$GABA_A$ receptor	Calcium channel	Other			
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	?+	?+	?+	Mechanism unknown	As phenytoin	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

[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.
SV2A, synaptic vesicle protein 2A.

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 43).[3] **Vigabatrin** acts by irreversibly inhibiting the enzyme GABA transaminase located within astrocytes, which is responsible for inactivating GABA (see Ch. 37), and **tiagabine** inhibits GABA uptake into neurons and glial cells, producing an increase in the extracellular concentration of GABA, and enhancing its action as an inhibitory transmitter. **Gabapentin** was designed as a brain penetrating agonist at $GABA_A$ receptors, but ironically was found to be an effective antiepileptic drug, not by affecting GABA receptors or the transporter, but by acting on calcium channels (see below).

Inhibition of sodium channel function

A large number of antiepileptic drugs (see Table 44.1) affect membrane excitability by an action on voltage-dependent sodium channels (see Chs 4 and 42), 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 from the ability of blocking drugs to discriminate between sodium channels in their resting, open and inactivated states (see Chs 4 and 42). 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,

[3] Absence seizures, paradoxically, are often exacerbated by drugs that enhance GABA activity (see Manning et al., 2003) and better treated by drugs acting by different mechanisms such as T-type calcium channel inhibition.

preventing them from returning to the resting state, and thus reducing the number of functional channels available to generate action potentials.

Inhibition of calcium channels

Drugs that are effective against absence seizures (**ethosuximide**, **valproate**, **clonazepam**) 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 ($\alpha 2\delta 1$), it reduces 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.[4]

Levetiracetam appears to act in a manner different from all other antiepileptic drugs, its target being a synaptic vesicle protein involved in neurotransmitter release (see below).

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 above) 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.

One theme, which has become familiar in earlier chapters in the central nervous system section of this book, is that antagonists at ionotropic excitatory amino acid receptors have not, despite showing efficacy in animal models, proved useful in the clinic, because the margin between the desired anticonvulsant effect and unacceptable side effects, such as loss of motor coordination, is too narrow.

CARBAMAZEPINE

Carbamazepine, one of the most widely used antiepileptic drugs, is chemically derived from the tricyclic antidepressant drugs (see Ch. 46) 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. 41) and manic-depressive illness (Ch. 46).

Mechanism of action of antiepileptic drugs

- Current 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, largely yet to be elucidated.
- Drugs that block ionotropic glutamate receptors are effective in animal models but are unsuitable for clinical use.

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 (see below).

Unwanted effects

Carbamazepine produces a variety of unwanted effects ranging from drowsiness, dizziness and ataxia to more severe mental and motor disturbances. It can also cause water retention (and hence hyponatraemia; Ch. 28) 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 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. In general, it is inadvisable to combine it with other antiepileptic drugs. **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,

[4]The highly complex actions of current antiepileptic drugs are apt to make discouraging reading for those engaged in trying to develop new drugs on simple rational principles. Serendipity, not science, appears to be the path to therapeutic success.

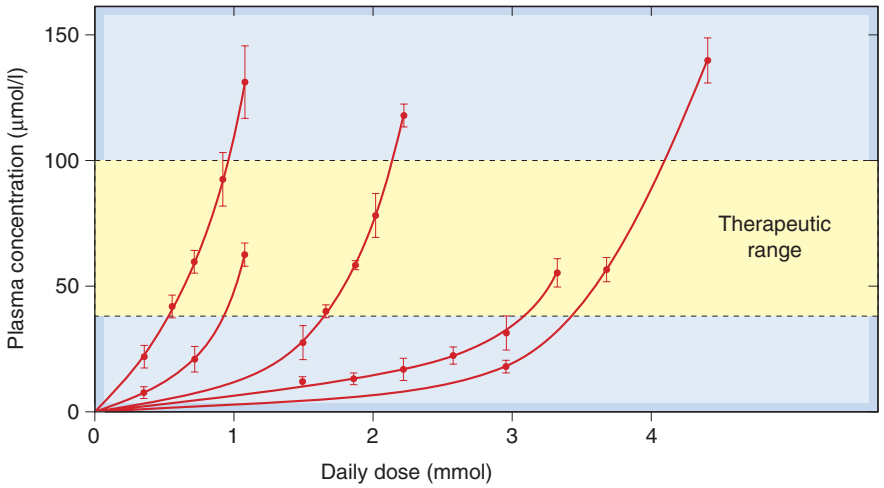

Fig. 44.4 Non-linear relationship between daily dose of phenytoin and steady-state plasma concentration in five individual human subjects. The daily dose required to achieve the therapeutic range of plasma concentrations (40–100 µmol/l) varies greatly between individuals, and for any one individual the 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.)

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 may even get worse.

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. 56). 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 44.4 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. A radioimmunoassay for phenytoin in plasma is available, and 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.

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. 46).

Valproate works by several mechanisms, 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 two enzyme systems that inactivate GABA, namely GABA transaminase and succinic semialdehyde dehydrogenase, 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 below) 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 teratogenic, causing spina bifida and other neural tube defects.

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 3/second firing rhythm in thalamic relay neurons that is 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, and its antiepileptic properties were recognised in 1912. In its action against experimentally induced convulsions and clinical forms of epilepsy, it closely resembles 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, although phenytoin is preferred because of the absence of sedation. It is now seldom used clinically because of sedation. For some years, it 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 after 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. 56). In overdose, phenobarbital produces 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 diazepam, lorazepam 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. 43), 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 inhibitor of the GABA-metabolising enzyme GABA transaminase. Vigabatrin is extremely specific for this enzyme and works by forming an irreversible covalent bond. 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 defect 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, acting on sodium channels as well as possibly calcium channels and inhibiting the release of excitatory amino acids. 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. It has only a weak effect on sodium channels and some effect on GABA, but causes some block of the NMDA receptor channel (Ch. 37). 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 new drug currently in clinical trials, was 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 (mainly sedation and ataxia) 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. 41). 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 is an equipotent inhibitor of both 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. It has a short plasma half-life, and its main side effects are drowsiness and confusion. Tiagabine is mainly used as an add-on therapy for partial seizures.

TOPIRAMATE

Topiramate is a recently introduced drug that, mechanistically, 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 spectrum of action 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. Its main drawback is that (like many antiepileptic drugs) it is teratogenic in animals, so it should not be used in women of child-bearing age (see below). Currently, it is mainly used as add-on therapy in refractory cases of epilepsy.

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. It is believed to interfere with neurotransmitter release by binding to synaptic vesicle protein 2A (SV2A), a protein thought to be involved in synaptic vesicle docking and fusion. **Brivaracetam**, a related antiepileptic agent, also binds to SV2A with tenfold higher affinity. Levetiracetam is excreted unchanged in the urine.

ZONISAMIDE

Zonisamide is a sulfonamide compound originally intended as an antibacterial drug and found accidentally to have antiepileptic properties. It is believed to act by blocking sodium channels and T-type calcium channels but

may well have other effects such as enhancing GABA function. It is 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 appears to act by enhancing sodium channel inactivation and may also inhibit GABA reuptake. 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.

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 et al., 2009). Several of these appear to act by novel mechanisms. **Retigabine** is an activator of neuronal KCNQ (K_v7) potassium channels that underlie the M current which controls membrane excitability. It also appears to be effective in treating some pain states. **Lacosamide** may enhance sodium channel inactivation, but unlike other antiepileptic drugs it appears to affect slow rather than rapid inactivation processes. **Ganaxolone**, structurally resembling endogenous neurosteroids (see Ch. 37), is a positive allosteric modulator of $GABA_A$ receptors containing δ subunits (see Ch. 37). **Tonabersat** is a neuronal gap junction inhibitor.

Novel targets for new antiepileptic agents are discussed by Meldrum & Rogawski (2007). 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—a field to watch.

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. 46)
- migraine prophylaxis (**valproate**, **gabapentin**, **topiramate**; Ch. 15)
- anxiety disorders (gabapentin; Ch. 43)
- neuropathic pain (gabapentin, carbamazepine, lamotrigine; Ch. 41).

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 (see Rogawski & Löscher, 2004b).

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
  - diazepam used in treating *status epilepticus*.
- Other agents include **vigabatrin**, **lamotrigine**, **felbamate**, **gabapentin**, **pregabalin**, **tiagabine**, **topiramate**, **levetiracetam**, **zonisamide**, **rufinamide** and **stiripentol**.

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. 41).
- To stabilise mood in mono- or bipolar affective disorder (as an alternative to **lithium**): for example **carbamazepine**, **valproate** (see Ch. 46).

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. 24). Phenytoin, valproate and topiramate may also induce fetal abnormalities if taken during pregnancy.

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 of 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. The main groups of drugs that have been used to control muscle tone are:

- **baclofen**
- **benzodiazepines** (see Ch. 43)
- **tizanidine**
- **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
- **dantrolene**: acts peripherally rather than centrally to produce muscle relaxation (see Ch. 4).

Baclofen (see Ch. 37) 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. 37). 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.

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

Anecdotal evidence suggests that smoking **cannabis** (Ch. 18) relieves the painful muscle spasms associated with multiple sclerosis. A full-scale controlled trial of Δ^9-tetrahydrocannabinol (also known as THC or **dronabinol**; see Ch. 18), however, showed no significant effect on muscle spasm, tremor, bladder control or disability, although the patients reported subjective improvements (Zajicek et al., 2003). More recently a number of different cannabinoids have been tested, including a 1:1 mixture of THC and cannabidiol (**sativex**), and **nabilone**. Such studies suggest that cannabinoids may be of limited use in some individuals suffering from multiple sclerosis.

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45 Antipsychotic drugs

OVERVIEW

In this chapter, we focus on schizophrenia and the drugs used to treat it. We start by describing the illness and what is known of its pathogenesis, including the various neurochemical hypotheses and their relation to the actions of the main types of antipsychotic drugs that are in use or in development.

INTRODUCTION

Psychotic illnesses include various disorders, but the term antipsychotic drugs—previously known as *neuroleptic drugs*, *antischizophrenic drugs* or *major tranquillisers*—conventionally refers to those used to treat schizophrenia, one of the most common and debilitating forms of mental illness. These same drugs are also used to treat mania (Ch. 46) and other acute behavioural disturbances (see clinical box on p. 562). Pharmacologically, most are dopamine receptor antagonists, although many of them also act on other targets, particularly 5-hydroxytryptamine (5-HT) receptors, which may contribute to their clinical efficacy. Existing drugs have many drawbacks in terms of their efficacy and side effects. Gradual improvements have been achieved with the newer drugs, but radical new approaches will probably have to wait until we have a better understanding of the causes and underlying pathology of the disease, which are still poorly understood.[1]

THE NATURE OF SCHIZOPHRENIA

Schizophrenia[2] (see Stahl, 2008) affects about 1% of the population. It is one of the most important forms of psychiatric illness, because it affects young people, is often chronic and is usually highly disabling. There is a strong hereditary factor in its aetiology, and evidence suggestive of a fundamental biological disorder (see below). The main clinical features of the disease are as follow.

Positive symptoms
- Delusions (often paranoid in nature).
- Hallucinations (often in the form of voices which may be exhortatory in their message).
- Thought disorder (comprising wild trains of thought, delusions of grandeur, garbled sentences and irrational conclusions).
- Abnormal, disorganised behaviour (such as stereotyped movements, disorientation and occasionally aggressive behaviours).
- Catatonia (can be apparent as immobility or purposeless motor activity).

Negative symptoms
- Withdrawal from social contacts.
- Flattening of emotional responses.
- Anhedonia (an inability to experience pleasure).
- Reluctance to perform everyday tasks.

In addition, deficits in cognitive function (e.g. attention, memory) are often present,[3] together with anxiety, guilt, depression and self punishment, leading to suicide attempts in up to 50% of cases, about 10% of which are successful. The clinical phenotype varies greatly, particularly with respect to the balance between positive and negative symptoms, and this may have a bearing on the efficacy of antipsychotic drugs in individual cases. Schizophrenia can present dramatically, usually in young people, with predominantly positive features such as hallucinations, delusions and uncontrollable behaviour, or more insidiously in older patients with negative features such as flat mood and social withdrawal. The latter may be more debilitated than those with a florid presentation, and the prognosis is generally worse. Schizophrenia can follow a relapsing and remitting course, or be chronic and progressive, particularly in cases with a later onset. Chronic schizophrenia used to account for most of the patients in long-stay psychiatric hospitals; following the closure of many of these in the UK, it now accounts for many of society's outcasts.

A characteristic feature of schizophrenia is a defect in 'selective attention'. Whereas a normal individual quickly accommodates to stimuli of a familiar or inconsequential nature, and responds only to stimuli that are unexpected or significant, the ability of schizophrenic patients to discriminate between significant and insignificant stimuli seems to be impaired. Thus, the ticking of a clock may command as much attention as the words of a companion; a chance thought, which a normal person would dismiss as inconsequential, may become an irresistible imperative.

[1] In this respect, the study of schizophrenia lags some years behind that of Alzheimer's disease (Ch. 39), where understanding of the pathogenesis has progressed rapidly to the point where promising new drug targets can be identified. On the other hand, pragmatists can argue that drugs against Alzheimer's disease are so far only marginally effective, whereas current antipsychotic drugs deliver great benefits, even though we do not quite know how they work.

[2] Schizophrenia is a condition where the patient exhibits symptoms of psychosis (e.g. delusions, hallucinations and disorganised behaviour). Psychotic episodes may also occur as a result of taking certain recreational drugs (see Ch. 47); as an adverse effect of drug treatment, for example steroid-induced psychoses; or in disorders such as mania, depression (see Ch. 46) and Alzheimer's disease (see Ch. 39).

[3] Kraepelin, who first described the condition, used the term *dementia praecox* (premature dementia) to describe the cognitive impairment associated with schizophrenia.

AETIOLOGY AND PATHOGENESIS OF SCHIZOPHRENIA

GENETIC AND ENVIRONMENTAL FACTORS

The cause of schizophrenia remains unclear but involves a combination of genetic and environmental factors (see Stahl, 2008). Thus a person may have a genetic makeup, probably an abnormality in more than just a single gene, that predisposes them to schizophrenia, but exposure to environmental factors may be required for schizophrenia to develop.

The disease shows a strong, but incomplete, hereditary tendency. In first-degree relatives, the risk is about 10%, but even in monozygotic (identical) twins, one of whom has schizophrenia, the probability of the other being affected is only about 50%, pointing towards the importance of environmental factors. Genetic linkage studies have identified more than 20 potential susceptibility genes (see Craddock et al., 2005; Harrison & Weinberger, 2005), but it is clear that no single gene is responsible. There are significant associations between polymorphisms in individual genes and the likelihood of an individual developing schizophrenia, but many are quite weak, and there appears to be no single gene that has an overriding influence.

▼ The most robust associations are with genes that control neuronal development, synaptic connectivity and glutamatergic neurotransmission. These include *neuregulin*, *dysbindin* and *DISC-1*. Transgenic mice that underexpress neuregulin-1, a protein involved in synaptic development and plasticity and which controls NMDA receptor expression, show a phenotype resembling human schizophrenia in certain respects. Malfunction of NMDA receptors is further implicated by genetic association with the genes for D-amino acid oxidase (DAAO), the enzyme responsible for making D-serine, an allosteric modulator of NMDA receptors (see Ch. 37), and for DAAO activator (G72). Dysbindin is located in postsynaptic density domains and may be involved in tethering receptors including NMDA receptors. DISC-1—which stands for **d**isrupted **i**n **sc**hizophrenia-**1**—is a protein that associates with cytoskeletal proteins and is involved with cell migration, neurite outgrowth and receptor trafficking. Among the other suggested susceptibility genes, some (such as the genes for monoamine oxidase A [MAO-A], tyrosine hydroxylase and the D_2 dopamine receptor) are involved in monoamine transmission in the CNS. However, the weight of current evidence seems to suggest that schizophrenia may result from abnormal glutamatergic transmission involving a decrease in NMDA receptor function (see below).

Some environmental influences early in development have been identified as possible predisposing factors, particularly maternal virus infections. This and other evidence suggests that schizophrenia is associated with a neurodevelopmental disorder affecting mainly the cerebral cortex and occurring in the first few months of prenatal development (see Harrison, 1997). This view is supported by brain-imaging studies showing cortical atrophy apparent in the early course of the disease which may increase with time and correlate with the progression of the disorder (van Haren et al., 2007). Studies of postmortem schizophrenic brains show evidence of misplaced cortical neurons with abnormal morphology. Other environmental factors such as cannabis consumption in adolescence and early adulthood (see Ch. 18) may also reveal schizophrenia.

THE NEUROANATOMICAL AND NEUROCHEMICAL BASIS OF SCHIZOPHRENIA

Different symptoms of schizophrenia appear to result from malfunctions in different neuronal circuits. Changes in the mesolimbic pathway (the neuronal projection from the ventral tegmental area (VTA) to the nucleus accumbens, amygdala and hippocampus) being associated with positive symptoms, whereas negative and cognitive impairment symptoms are associated with changes in the mesocortical pathway (the projection from the VTA to areas of the prefrontal cortex).

The main neurotransmitters involved in the pathogenesis of schizophrenia are dopamine and glutamate.

Dopamine

The original dopamine theory of schizophrenia was proposed by Carlson—awarded a Nobel Prize in 2000—on the basis of indirect pharmacological evidence in humans and experimental animals. **Amphetamine** releases dopamine in the brain and can produce in humans a behavioural syndrome indistinguishable from an acute schizophrenic episode—very familiar to doctors who treat drug users. Also, hallucinations are a side effect of L-dopa therapy for Parkinson's disease (see Ch. 39). In animals, dopamine release causes a specific pattern of stereotyped behaviour that resembles the repetitive behaviours sometimes seen in schizophrenic patients. Potent D_2 receptor agonists, such as **bromocriptine**, produce similar effects in animals, and these drugs, like amphetamine, exacerbate the symptoms of schizophrenic patients. Furthermore, dopamine antagonists and drugs that block neuronal dopamine storage (e.g. **reserpine**) are effective in controlling the positive symptoms of schizophrenia, and in preventing amphetamine-induced behavioural changes.

▼ It is now realised that the role of dopamine in schizophrenia is quite complex in that positive symptoms are thought to result from *overactivity* in the mesolimbic dopaminergic pathway activating D_2 receptors (for a more detailed description of the dopamine pathways in the brain, see Ch. 38) whereas negative symptoms may result from a *decreased activity* in the mesocortical dopaminergic pathway where D_1 receptors predominate (see Toda & Abi-Dargham, 2007). Other dopaminergic pathways in the brain (i.e. nigrostriatal and tuberoinfundibular; see Ch. 38) appear to function normally in schizophrenics.

There is a strong correlation between antipsychotic potency in reducing positive symptoms and activity in blocking D_2 receptors (Fig. 45.1) and receptor-imaging studies have shown that clinical efficacy of antipsychotic drugs is consistently achieved when D_2 receptor occupancy reaches about 80%.[4] Furthermore, brain imaging studies have revealed an increased dopamine release in the striatum of schizophrenic patients (Laruelle et al., 1999).[5] Injection of amphetamine caused dopamine release that was greater by a factor of two or more in schizophrenic subjects compared with control subjects, implying a greater amphetamine-induced release of dopamine. The effect was greatest in schizophrenic individuals during acute attacks, and absent during spontaneous remissions—clear evidence linking dopamine release to the symptomatology.

Thus, therapeutically it might be desirable to *inhibit* dopaminergic transmission in the limbic system yet *enhance* dopaminergic transmission in the prefrontal cortex (see below how this might be achieved).

Glutamate

In humans, NMDA receptor antagonists such as **phencyclidine**, **ketamine** and **dizocilpine** (Ch. 37) can produce

[4]There are, however, exceptions to this simple rule. Up to one-third of schizophrenic patients fail to respond even when D_2 receptor blockade exceeds 90%, and **clozapine** (see Table 45.1) can be effective at much lower levels of block.

[5]An increase in dopamine receptor density in schizophrenia has been reported in some studies, but not consistently, and the interpretation is complicated by the fact that chronic antipsychotic drug treatment is known to increase dopamine receptor expression.

both positive and negative psychotic symptoms—in contrast to amphetamine which produces only positive symptoms. It has therefore been postulated that schizophrenia may result from disruption of glutamatergic neurotransmission (Moghaddam, 2003), evident as a reduction in the function of NMDA receptors (the NMDA hypofunction hypothesis; see Coyle, 2006). Although schizophrenia is difficult to diagnose in a mouse, transgenic mice in which NMDA receptor expression is reduced (not abolished, because this is fatal) show stereotypic behaviours and reduced social interaction that are suggestive of schizophrenia and that respond to antipsychotic drugs.

▼ Glutamatergic neurons and GABAergic neurons play complex roles in controlling the level of neuronal activity in both the mesocortical and the mesolimbic dopaminergic pathways. NMDA receptor hypofunction is thought to *reduce* the level of activity in mesocortical dopaminergic neurons. This would result in a decrease in dopamine release in the prefrontal cortex and thus give rise to negative symptoms of schizophrenia. On the other hand, NMDA receptor hypofunction is thought to *enhance* activity in the mesolimbic dopaminergic pathway, perhaps because in this pathway the important NMDA receptors are those located on GABAergic interneurons. Thus NMDA receptor hypofunction would result in reduced GABAergic inhibition (disinhibition) of mesolimbic dopaminergic neurons and thus give rise to enhanced dopamine release in limbic areas such as the nucleus accumbens, resulting in the production of positive symptoms

Given the evidence that schizophrenic symptoms may be due to a reduction in NMDA receptor function, efforts have been made to develop new drugs to enhance NMDA receptor function but not to a level where it becomes neurotoxic (see Ch. 39). This could be achieved by activating the facilitatory glycine site on the NMDA receptor (see Ch. 37) with an agonist (Shim et al., 2008) or by raising extracellular glycine levels by inhibiting the GlyT1 transporter (Bridges et al., 2008). *AMPAkines*, agents that allosterically enhance the action of glutamate at the AMPA receptor, by enhancing glutamate-induced neuronal depolarisation, can potentiate NMDA responses. Paradoxically, reducing glutamate release by activating presynaptic mGluR2/3 autoreceptors may result in a compensatory upregulation of NMDA receptors which also might be beneficial. This provides a novel target for the development of new antipsychotic drugs (see below).

Other glutamate pathways thought to be involved in schizophrenia are the corticostriatal, thalamocortical, corticothalamic and corticobrain stem pathways. The thalamus normally functions as a sensory filter to limit unnecessary sensory input to the cortex. Disruption of the normal inputs to the thalamus, for example from a reduction in glutamatergic or GABAergic transmission, disables this 'sensory gate' function, allowing uninhibited input to reach the cortex. The role of the thalamus in schizophrenia is reviewed by Sim et al. (2006).

Neurodegeneration

Factors such as structural abnormalities in the brains of schizophrenics and progression of the disease—absence of symptoms in early childhood, the likelihood of positive symptoms becoming apparent before negative symptoms, progressive worsening, reduced responsiveness to drugs with time and the development of dementia—all indicate the involvement of ongoing neurodegeneration in the disease. The causes of such neurodegeneration are unclear at present but may involve glutamate-induced excitotoxicity (see Ch. 39).

The hope is that a fuller understanding of the altered function of glutamate transmission in schizophrenia will lead to the next generation of antipsychotic drugs (see Javitt, 2004).

The nature of schizophrenia

- Psychotic illness characterised by delusions, hallucinations and thought disorder (positive symptoms), together with social withdrawal and flattening of emotional responses (negative symptoms), and cognitive impairment.
- Acute episodes (mainly positive symptoms) frequently recur and may develop into chronic schizophrenia, with predominantly negative symptoms.
- Incidence is about 1% of the population, with a significant hereditary component. Genetic linkage studies suggest involvement of various genes associated with dopaminergic and glutamatergic transmission, but no single 'schizophrenia gene'.
- Pharmacological evidence is generally consistent with dopamine dysregulation and glutamate underactivity hypotheses, supported by biochemical findings, clinical efficacy and imaging studies.

ANTIPSYCHOTIC DRUGS

CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

More than 30 different antipsychotic drugs are available for clinical use. These can be divided into two groups—those drugs that were originally developed (e.g. **chlorpromazine**, **haloperidol** and many similar compounds), often referred to as *first-generation*, *typical* or *conventional* antipsychotic drugs, and more recently developed agents (e.g. **clozapine**, **risperidone**), which are termed *atypical antipsychotic drugs*. The term 'atypical' is widely used but not clearly defined (see Remington, 2003). In effect, it refers to the diminished tendency of the newer compounds to cause unwanted motor side effects (see below), but it is also used to describe compounds with a different pharmacological profile from first-generation compounds; several of these newer compounds improve the negative as well as the positive symptoms. In practice, however, it often serves—not very usefully—to distinguish the large group of similar first-generation dopamine antagonists from the more diverse group of newer compounds described below.

Table 45.1 summarises the main drugs that are in clinical use.

▼ The therapeutic activity of the prototype drug, **chlorpromazine**, in schizophrenic patients was discovered through the acute observations of a French surgeon, Laborit, in 1947. He tested various substances, including **promethazine**, for their ability to alleviate signs of stress in patients undergoing surgery, and concluded that promethazine had a calming effect that was different from mere sedation. Elaboration of the phenothiazine structure led to chlorpromazine, the antipsychotic effect of which was demonstrated, at Laborit's instigation, by Delay and Deniker in 1953. This drug was unique in controlling the symptoms of psychotic patients without excessively sedating them. The clinical efficacy of phenothiazines was discovered long before their mechanism was guessed at (let alone understood).

Pharmacological investigation showed that phenothiazines, the first-generation antipsychotic agents, block many different mediators, including histamine, catecholamines, acetylcholine and 5-HT, and this multiplicity of actions led to the trade name Largactil for chlorpromazine. It is now clear (see Fig. 45.1) that antagonism of dopamine is the main determinant of antipsychotic action.

Table 45.1 Characteristics of antipsychotic drugs

Drug	Receptor affinity						Main side effects				Notes
	D_1	D_2	α_1	H_1	mACh	5-HT_{2A}	EPS	Sed	Hypo	Other	
Chlorpromazine	+	+++	+++	++	+	++	++	+++	++	Increased prolactin (gynaecomastia) Hypothermia Anticholinergic effects Hypersensitivity reactions Obstructive jaundice	Phenothiazine class Fluphenazine, trifluperazine are similar but: • do not cause jaundice • cause less hypotension • cause more EPS Fluphenazine available as depot preparation Pericyazine, pipotiazine cause less EPS probably due to their greater muscarinic antagonist actions
Haloperidol	+	+++	++	–	–	+	+++	–	+	As chlorpromazine but does not cause jaundice Fewer anticholinergic side effects	Butyrophenone class Widely used antipsychotic drug Strong EPS tendency Available as depot preparation
Flupentixol	++	+++		+++	–	+	++	+	+	Increased prolactin (gynaecomastia) Restlessness	Thioxanthine class Clopentixol is similar Available as depot preparation
Sulpiride	–	++	–	–	–	–	+	+	–	Increased prolactin (gynaecomastia)	Benzamide class Selective D_2/D_3 antagonist Less EPS than haloperidol (reason for this unclear, but could result from action at D_3 or very weak partial agonism at D_2) Increases alertness in apathetic patients Poorly absorbed Amisulpride and pimozide (long acting) are similar
Clozapine	+	+	++	++	++	++	–	++	++	Risk of agranulocytosis (~1%): regular blood counts required Seizures Salivation Anticholinergic side effects Weight gain	Dibenzodiazepine class No EPS (first atypical antipsychotic) Shows efficacy in 'treatment-resistant' patients and reduces incidence of suicide Effective against negative and positive symptoms Olanzapine is somewhat less sedative, without risk of agranulocytosis, but questionable efficacy in treatment-resistant patients

Risperidone	+	++	++	++	–	+++	+	++	++	Weight gain EPS at high doses Hypotension	Significant risk of EPS ?Effective against negative symptoms Potent on D_4 receptors Available as depot preparation Paliperidone is a metabolite of risperidone
Sertindole	+	++	++	+	–	+++	+	+	++	Ventricular arrhythmias (ECG checks advisable) Weight gain Nasal congestion	Long plasma half-life (~3 days) ?Effective against negative symptoms
Quetiapine	–	+	++	+	+	+	–	++	++	Tachycardia Drowsiness Dry mouth Constipation Weight gain	No EPS No increase in prolactin secretion 5-HT_{1A} partial agonist Short acting (plasma half-life ~6 h)
Aripiprazole	–	+++ (PA)	+	+	–	++	–	+	–	–	Long acting (plasma half-life ~3 days) Unusual D_2 PA profile may account for paucity of side effects Also a $5HT_{1A}$ partial agonist No effect on prolactin secretion No weight gain Available as a depot preparation
Zotepine	+	++	++	++	–	++	–	+	–	Weight gain Hypotension Cardiac dysrhythmias	–
Ziprasidone	+	++	++	+	–	+++	+	–	+	Tiredness Nausea	Low incidence of EPS No weight gain ?Effective against negative symptoms Short acting (plasma half-life ~8 h) but a depot preparation is available

Table based on data contained at NIMH Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu/). Where available, data obtained on human receptors are given. 5-HT_{1A}, 5-HT_{2A}, 5-hydroxytryptamine types 1A and 2A receptors; α_1, α_1-adrenoceptor; D_1, D_2, D_3, D_4, dopamine types 1, 2, 3 and 4 receptor, respectively; ECG, electrocardiograph; EPS, extrapyramidal side effects; H_1, histamine type 1 receptor; Hypo, hypotension; mACh, muscarinic acetylcholine receptor; PA, partial agonist; Sed, sedation.

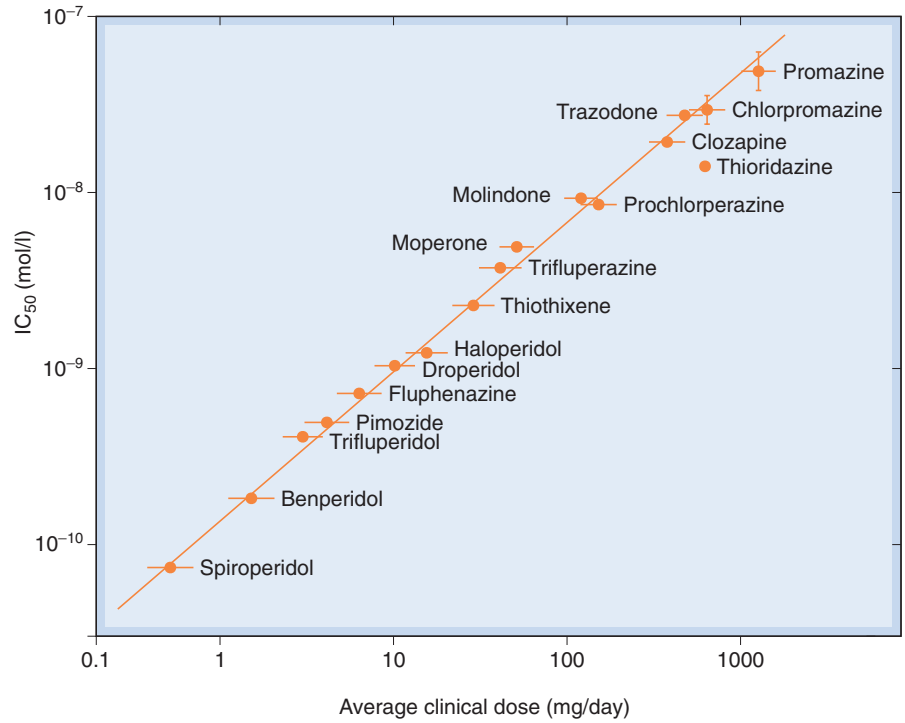

Fig. 45.1 Correlation between the clinical potency and affinity for dopamine D_2 receptors among antipsychotic drugs. Clinical potency is expressed as the daily dose used in treating schizophrenia, and binding activity is expressed as the concentration needed to produce 50% inhibition of haloperidol binding. (From Seeman P et al. 1976 Nature 361: 717.)

Classification of antipsychotic drugs

- Main categories are:
  - first-generation ('typical', 'classical' or 'conventional') antipsychotics (e.g. **chlorpromazine**, **haloperidol**, **fluphenazine**, **flupentixol**, **clopentixol**)
  - second-generation ('atypical') antipsychotics (e.g. **clozapine**, **risperidone**, **sertindole**, **quetiapine**, **amisulpride**, **aripiprazole**, **zotepine**, **ziprasidone**).
- Distinction between typical and atypical groups is not clearly defined but rests on:
  - receptor profile
  - incidence of extrapyramidal side effects (less in atypical group)
  - efficacy (specifically of clozapine) in 'treatment-resistant' group of patients
  - efficacy against negative symptoms.

PHARMACOLOGICAL PROPERTIES

DOPAMINE RECEPTORS

The classification of dopamine receptors in the central nervous system is discussed in Chapter 38 (see Table 38.1). There are five subtypes, which fall into two functional classes: the D_1 type, comprising D_1 and D_5, and the D_2 type, comprising D_2, D_3 and D_4. Antipsychotic drugs owe their therapeutic effects mainly to blockade of D_2 receptors.[6] As stated above, antipsychotic effects require about 80% block of D_2 receptors. The first-generation compounds show some preference for D_2 over D_1 receptors, whereas some of the newer agents (e.g. **sulpiride**, **amisulpride**, **remoxipride**) are highly selective for D_2 receptors. More recently, D_2 antagonists that dissociate rapidly from the receptor and D_2 partial agonists have been introduced in an attempt to reduce extrapyramidal motor side effects (see below).

It is the antagonism of D_2 receptors in the mesolimbic pathway that is believed to relieve the positive symptoms of schizophrenia. Unfortunately, systemically administered antipsychotic drugs do not discriminate between D_2 receptors in distinct brain regions and D_2 receptors in other brain pathways will also be blocked. Thus, antipsychotic drugs produce unwanted motor effects (block of D_2 receptors in the nigrostriatal pathway), enhance prolactin secretion (block of D_2 receptors in the tuberoinfundibular pathway), reduce pleasure (block of D_2 receptors in the reward component of the mesolimbic pathway) and perhaps even worsen the negative symptoms of schizophrenia (block of D_2 receptors in the prefrontal cortex, although these are only expressed at a low density—D_1 receptors being in greater abundance). While all antipsychotic drugs block D_2 receptors and should therefore in theory induce all of these unwanted effects, some have

[6]The D_4 receptor attracted attention on account of the high degree of genetic polymorphism that it shows in human subjects, and because some of the newer antipsychotic drugs (e.g. clozapine) have a high affinity for this receptor subtype. However, a specific D_4-receptor antagonist proved ineffective in clinical trials.

Mechanism of action of antipsychotic drugs

- Antipsychotic drugs are antagonists or partial agonists at D_2 dopamine receptors, but most also block a variety of other receptors.
- Antipsychotic potency generally runs parallel to activity on D_2 receptors, but activities at other receptors (e.g. 5-HT_{2A} and muscarinic) may reduce extrapyramidal side effects.
- Activity at muscarininc, H_1 and α receptors may determine unwanted side effect profile.
- Imaging studies suggest that therapeutic effect requires about 80% occupancy of D_2 receptors.

additional pharmacological activity (e.g. mACh receptor antagonism and 5-HT_{2A} receptor antagonism) that, to varying degrees, ameliorate unwanted effects (see below). 5-HT_{2A} antagonism may help to alleviate the negative and cognitive impairments of schizophrenia.

Antipsychotic drugs have classically been thought to have a delayed onset to their therapeutic actions, even though their dopamine receptor-blocking action is immediate. This view has, however, been called into question (Kapur et al., 2005; Leucht et al., 2005). In animal studies, chronic antipsychotic drug administration does produce compensatory changes in the brain, for example a reduction in the activity of dopaminergic neurons and proliferation of dopamine receptors, detectable as an increase in haloperidol binding (see Seeman, 1987), with a pharmacological supersensitivity to dopamine reminiscent of the phenomenon of denervation supersensitivity (Ch. 12). The mechanism(s) of these delayed effects are poorly understood. They are likely to contribute to the development of unwanted *tardive dyskinesias* (see below). The sedating effect of antipsychotic drugs occurs extremely rapidly, allowing them to be used in acute behavioural emergencies.

5-HYDROXYTRYPTAMINE RECEPTORS

The idea that 5-HT dysfunction could be involved in schizophrenia has drifted in and out of favour many times (see Busatto & Kerwin, 1997). It was originally based on the fact that LSD, a partial agonist at 5-HT_{2A} receptors (see Chs 15 & 47) produces hallucinations. Nowadays, conventional wisdom is that 5-HT may not be directly involved in the pathogenesis of schizophrenia. Nevertheless, pharmacological manipulation of 5-HT receptor activity, combined with D_2 receptor antagonism, has resulted in new drugs with improved therapeutic profiles.[7] There is a plethora of 5-HT receptors (see Chs 15 & 38) with disparate functions in the body (see also Chs 46 and 47). It is the 5-HT_{2A} receptor and, to a lesser extent, the 5-HT_{1A} receptor that are important in the treatment of schizophrenia.

5-HT_{2A} receptors are G_i/G_o-coupled receptors and their activation produces neuronal inhibition (through decreased neuronal excitability at the soma and decreased transmitter release at the nerve terminals; see Ch. 38). In this way, in the nigrostriatal pathway, 5-HT_{2A} receptors control the release of dopamine. Drugs with 5-HT_{2A} antagonist properties (e.g. **olanzapine** and **risperidone**) enhance dopamine release in the striatum by reducing the inhibitory effect of 5-HT. This will reduce extrapyramidal side effects (see below). In contrast, in the mesolimbic pathway, the combined effects of D_2 and 5-HT_{2A} antagonism are thought to counteract the increased dopamine function that gives rise to positive symptoms of schizophrenia. Further, enhancing both dopamine and glutamate release in the mesocortical circuit, 5-HT_{2A} receptor antagonism may improve the negative symptoms of schizophrenia (Stahl, 2008).

5-HT_{1A} receptors are somatodendritic autoreceptors that inhibit 5-HT release (see Ch. 38). Antipsychotic drugs that are agonists or partial agonists at 5-HT_{1A} receptors (e.g. **quetiapine**; see Table 45.1) may work by decreasing 5-HT release thus enhancing dopamine release in the striatum and prefrontal cortex.

MUSCARINIC ACETYLCHOLINE RECEPTORS

Some phenothiazine antipsychotic drugs (e.g. **pericyazine**) induce fewer extrapyramidal side effects than others, and this correlates with their affinity as muscarinic antagonists. Also, some newer, atypical drugs possess muscarinic antagonist properties (e.g. **olanzepine**). In the striatum, dopaminergic nerve terminals are thought to innervate cholinergic interneurons that express inhibitory D_2 receptors (Pisani et al., 2007). It is suggested that there is normally a balance between D_2 receptor activation and muscarinic receptor activation. Blocking D_2 receptors in the striatum with an antipsychotic agent will result in enhanced acetylcholine release on to muscarinic receptors, thus producing extrapyramidal side effects, which are counteracted if the D_2 antagonist also has muscarinic antagonist activity. Maintaining the dopamine/acetylcholine balance was also the rationale for the use of **benztropine** to reduce extrapyramidal effects of antipsychotic drugs (see Ch. 39). Muscarinic antagonist activity does, however, induce side effects such as constipation, dry mouth and blurred vision.

BEHAVIOURAL EFFECTS

Antipsychotic drugs produce many behavioural effects in experimental animals (see Ögren, 1996), but no single test distinguishes them clearly from other types of psychotropic drug. There are no good animal models of schizophrenia. For this reason, some pharmaceutical companies have even considered bypassing animal models, taking novel compounds directly from in vitro receptor assays to toxicology and preliminary clinical trials.

Antipsychotic drugs reduce spontaneous motor activity and in larger doses cause *catalepsy*, a state in which the animal remains immobile even when placed in an unnatural position. Inhibition of the hyperactivity induced by **amphetamine** parallels antipsychotic actions of these drugs, whereas their tendency to induce catalepsy parallels extrapyramidal symptoms (see below). Other tests reveal effects distinct from motor inhibition. For example, animals respond to an unexpected acoustic stimulus with a jump. This 'startle'

[7]Early antipsychotic drugs (e.g. chlorpromazine) had actions at various receptors but also had unwanted side effects that resulted from activity at other receptors. Towards the end of the 20th century, drug development, not just of antipsychotic drugs, was focused largely on developing agents with a single action with the intention of reducing unwanted side effects. This philosophy drove the search for selective D_4 receptor antagonists, which proved ineffective. What is now apparent is that drugs with selected multiple actions (e.g. a combination of D_2 antagonism and 5-HT_{2A} antagonism) may have a better therapeutic profile.

reflex can be reduced by a weak pre-stimulus (pre-pulse inhibition) such as a low-intensity tone or light. Schizophrenic patients exhibit less pre-pulse inhibition than control subjects. Drugs that mimic or release dopamine (e.g. apomorphine or amphetamine) as well as other drugs that induce schizophrenia-like behaviours (e.g. **cannabinoids** or **phencyclidine**) reduce pre-pulse inhibition in animals and antipsychotic drugs reverse this effect. Also, in a conditioned avoidance model, a rat may be trained to respond to a conditioned stimulus, such as a buzzer, by remaining immobile and thereby avoiding a painful shock; chlorpromazine impairs performance in this test, as well as in tests that demand active motor responses. In doses too small to reduce spontaneous motor activity, chlorpromazine reduces social interactions (grooming, mating, fighting, etc.) and also impairs performance in discriminant tests (e.g. requiring the animal to respond differently to red and green lights).

All first-generation antipsychotic drugs inhibit amphetamine-induced behavioural changes, reflecting their action on D_2 receptors. Some atypical drugs have less activity on D_2 receptors and are less active in such models, and also in the catalepsy model. They are, however, as efficacious as the older drugs in pre-pulse inhibition and conditioned avoidance tests. Both classic and atypical drugs, moreover, reduce the hyperactivity caused by **phencyclidine** (a glutamate antagonist; Ch. 37) in rodents. In humans, phencyclidine causes a schizophrenia-like syndrome. Conditioned avoidance and phencyclidine tests in animals may therefore be more appropriate guides to antipsychotic activity in humans.

In humans, antipsychotic drugs produce a state of apathy and reduced initiative. The recipient displays few emotions, is slow to respond to external stimuli and tends to drowse off. The subject is, however, easily aroused and can respond to questions accurately, with no marked loss of intellectual function. Aggressive tendencies are strongly inhibited. Effects differ from those of sedative anxiolytic drugs, which also cause drowsiness and confusion but with euphoria rather than apathy.

Many antipsychotic drugs are antiemetic (see Ch. 29), reflecting antagonism at dopamine, muscarinic, histamine and possibly 5-HT receptors.

UNWANTED EFFECTS

EXTRAPYRAMIDAL MOTOR DISTURBANCES

Antipsychotic drugs produce two main kinds of motor disturbance in humans: *acute dystonias* and *tardive dyskinesias*, collectively termed *extrapyramidal side effects*. These all result directly or indirectly from D_2 receptor blockade in the nigrostriatal pathway. Extrapyramidal side effects constitute one of the main disadvantages of first-generation antipsychotic drugs. The term *atypical* was originally applied to some of the newer compounds that show much less tendency to produce extrapyramidal side effects.

Acute dystonias are involuntary movements (restlessness, muscle spasms, protruding tongue, fixed upward gaze, torticollis [involuntary spasm of neck muscles]), often accompanied by symptoms of Parkinson's disease (Ch. 39). They occur commonly in the first few weeks, often declining with time, and are reversible on stopping drug treatment. The timing is consistent with block of the dopaminergic nigrostriatal pathway. Concomitant block of muscarinic receptors and 5-HT_{2A} receptors mitigates the motor effects of dopamine receptor antagonists (see above).

Tardive dyskinesia (see Klawans et al., 1988) develops after months or years (hence 'tardive') in 20–40% of patients treated with first-generation antipsychotic drugs, and is one of the main problems of antipsychotic therapy. Its seriousness lies in the fact that it is a disabling and often irreversible condition, which often gets worse when antipsychotic therapy is stopped and is resistant to treatment. The syndrome consists of involuntary movements, often of the face and tongue, but also of the trunk and limbs, which can be severely disabling. It resembles that seen after prolonged treatment of Parkinson's disease with **levodopa** (see Ch. 39). The incidence depends greatly on drug, dose and age (being commonest in patients over 50).

▼ There are several theories about the mechanism of tardive dyskinesia (see Casey, 1995). One is that it is associated with a gradual increase in the number of D_2 receptors in the striatum, which is less marked during treatment with the atypical than with the first generation of antipsychotic drugs. Another possibility is that chronic block of inhibitory dopamine receptors enhances catecholamine and/or glutamate release in the striatum, leading to excitotoxic neurodegeneration (Ch. 39).

Drugs that rapidly dissociate from D_2 receptors (e.g. **clozapine**, **olanzapine**, **sertindole**) induce less severe extrapyramidal side effects. A possible explanation for this (see Kapur & Seeman, 2001) is that with a rapidly dissociating compound, a brief surge of dopamine can effectively overcome the block by competition (see Ch. 2), whereas with a slowly dissociating compound, the level of block takes a long time to respond to the presence of endogenous dopamine, and is in practice non-competitive. Adverse motor effects may be avoided if fractional receptor occupation falls during physiological surges of dopamine. An extension of this idea is that perhaps a little D_2 receptor activation may be beneficial. This could be produced, for example, by drugs that are D_2 partial agonists (e.g. **aripiprazole**) in contrast to simple antagonists. It is thought that partial agonists reduce D_2 hyperactivation in the mesolimbic pathway, thus alleviating positive symptoms of schizophrenia, but provide enough D_2 receptor stimulation in the mesocortical pathway to prevent negative symptoms, and in the nigrostriatal pathway to prevent the development of extrapyramidal side effects. Newer D_2 partial agonists such as **bifeprunox** are being developed, although questions about their efficacy and safety have arisen.

ENDOCRINE EFFECTS

Dopamine, released in the median eminence by neurons of the tuberohypophyseal pathway (see Chs 32 and 38), acts physiologically via D_2 receptors to inhibit prolactin secretion. Blocking D_2 receptors by antipsychotic drugs can therefore increase the plasma prolactin concentration (Fig. 45.2), resulting in breast swelling, pain and lactation, which can occur in men as well as in women. As can be seen from Figure 45.2, the effect is maintained during chronic antipsychotic administration, without any habituation. Other less pronounced endocrine changes have also been reported, including a decrease of growth hormone secretion, but these, unlike the prolactin response, are believed to be relatively unimportant clinically.

OTHER UNWANTED EFFECTS

Drowsiness and sedation, which tend to decrease with continued use, occur with many antipsychotic drugs. Antihistamine (H_1) activity is a property of some phenothiazine antipsychotics (e.g. **chlorpromazine** and **methotrimeprazine**) and contributes to their sedative and antiemetic properties (Ch. 38), but not to their antipsychotic action.

All antipsychotic drugs block a variety of receptors, particularly acetylcholine (muscarinic), histamine (H_1), noradrenaline (α) and 5-HT (Table 45.1).

Antipsychotic-induced motor disturbances

- Major problem of antipsychotic drug treatment.
- Two main types of disturbance occur:
  - acute, reversible dystonias and Parkinson-like symptoms (indeed, antipsychotic drugs generally worsen Parkinson's disease and block the actions of drugs used to treat the disorder)
  - slowly developing tardive dyskinesia, often irreversible.
- Acute symptoms comprise involuntary movements, tremor and rigidity, and are probably the direct consequence of block of nigrostriatal dopamine receptors.
- Tardive dyskinesia comprises mainly involuntary movements of the face and limbs, appearing after months or years of antipsychotic treatment. It may be associated with proliferation of dopamine receptors in the corpus striatum. Treatment is generally unsuccessful.
- Incidence of acute dystonias and tardive dyskinesia is less with newer 'atypical' antipsychotics, and particularly low with clozapine, aripiprazole and zotepine.

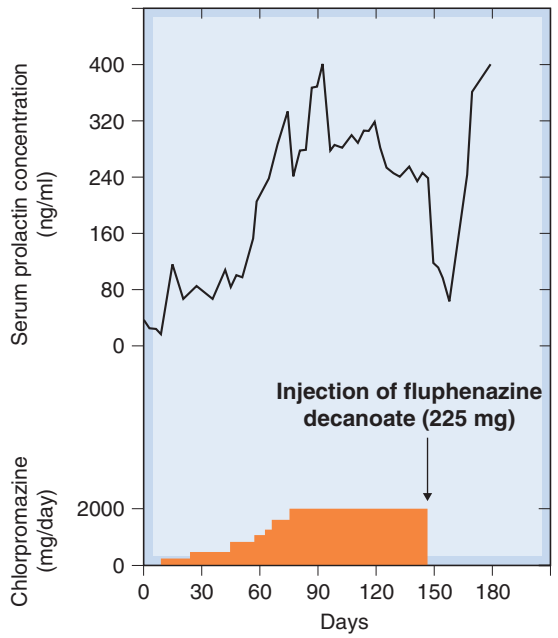

Fig. 45.2 Effects of antipsychotic drugs on prolactin secretion in a schizophrenic patient. When daily dosage with chlorpromazine was replaced with a depot injection of fluphenazine, the plasma prolactin initally dropped, because of the delay in absorption, and then returned to a high level. (From Meltzer H Y et al. 1978 In: Lipton et al. (eds) Psychopharmacology. A generation in progress. Raven Press, New York.)

While block of muscarinic receptors produces a variety of peripheral effects, including blurring of vision and increased intraocular pressure, dry mouth and eyes, constipation and urinary retention (see Ch. 13), it may, however, also be beneficial in relation to extrapyramidal side effects (see above).

Blocking α-adrenoceptors causes *orthostatic hypotension* (see Ch. 14) but does not seem to be important for their antipsychotic action.

Weight gain is a common and troublesome side effect. Increased risk of diabetes and cardiovascular disease occurs with several atypical antipsychotic drugs. These effects are probably related to their antagonist actions at H_1, 5-HT and muscarinic receptors.

Various idiosyncratic and hypersensitivity reactions can occur, the most important being the following:

- *Jaundice*, which occurs with older phenothiazines such as **chlorpromazine**. The jaundice is usually mild, associated with elevated serum alkaline phosphatase activity (an 'obstructive' pattern), and disappears quickly when the drug is stopped or substituted by a chemically unrelated antipsychotic.
- *Leukopenia* and *agranulocytosis* are rare but potentially fatal, and occur in the first few weeks of treatment. The incidence of leukopenia (usually reversible) is less than 1 in 10 000 for most antipsychotic drugs, but much higher (1–2%) with **clozapine**, whose use therefore requires regular monitoring of blood cell counts. Provided the drug is stopped at the first sign of leukopenia or anaemia, the effect is reversible. **Olanzapine** appears to be free of this disadvantage.
- *Urticarial skin reactions* are common but usually mild. Excessive sensitivity to ultraviolet light may also occur.
- *Antipsychotic malignant syndrome* is a rare but serious complication similar to the malignant hyperthermia syndrome seen with certain anaesthetics (see Ch. 40). Muscle rigidity is accompanied by a rapid rise in body temperature and mental confusion. It is usually reversible, but death from renal or cardiovascular failure occurs in 10–20% of cases.

Unwanted effects of antipsychotic drugs

- Important side effects common to many drugs are:
  - motor disturbances (see *Antipsychotic-induced motor disturbances* box)
  - endocrine disturbances (increased prolactin release)
  - these are secondary to dopamine receptor block.
- Sedation, hypotension and weight gain are common.
- Obstructive jaundice sometimes occurs with phenothiazines.
- Other side effects (dry mouth, blurred vision, hypotension, etc.) are due to block of other receptors, particularly muscarinic receptors and α-adrenoceptors.
- Some antipsychotic drugs cause agranulocytosis as a rare and serious idiosyncratic reaction. With clozapine, leukopenia is common and requires routine monitoring.
- Antipsychotic malignant syndrome is a rare but potentially dangerous idiosyncratic reaction.

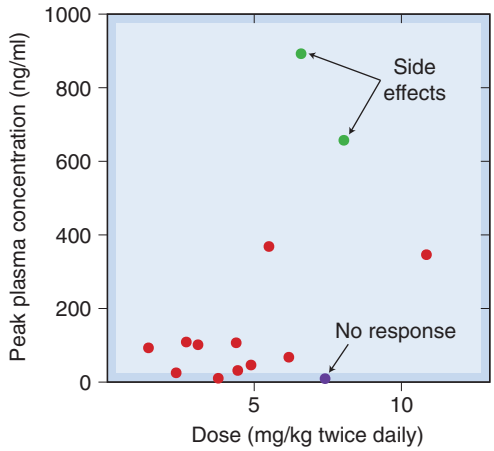

Fig. 45.3 Individual variation in the relation between dose and plasma concentration of chlorpromazine in a group of schizophrenic patients. (Data from Curry S H et al. 1970 Arch Gen Psychiatry 22: 289.)

PHARMACOKINETIC ASPECTS

Chlorpromazine, in common with other phenothiazines, is erratically absorbed after oral administration. Figure 45.3 shows the wide range of variation of the peak plasma concentration as a function of dosage in 14 patients. Among four patients treated at the high dosage level of 6–8 mg/kg, the variation in peak plasma concentration was nearly 90-fold; two showed marked side effects, one was well controlled and one showed no clinical response.

The relationship between the plasma concentration and the clinical effect of antipsychotic drugs is highly variable, and the dosage has to be adjusted on a trial-and-error basis. This is made even more difficult by the fact that at least 40% of schizophrenic patients fail to take drugs as prescribed. It is remarkably fortunate that the acute toxicity of antipsychotic drugs is slight, given the unpredictability of the clinical response.

The plasma half-life of most antipsychotic drugs is 15–30 h, clearance depending entirely on hepatic transformation by a combination of oxidative and conjugative reactions.

Most antipsychotic drugs can be given orally or in urgent situations by intramuscular injection. Slow-release (depot) preparations of many are available, in which the active drug is esterified with heptanoic or decanoic acid and dissolved in oil. Given as an intramuscular injection, the drug acts for 2–4 weeks, but initially may produce acute side effects. These preparations are widely used to minimise compliance problems.

CLINICAL USE AND CLINICAL EFFICACY

The major use of antipsychotic drugs is in the treatment of schizophrenia and acute behavioural emergencies, but they are also used to treat other conditions, such as deviant antisocial behaviour, motor tics and intractable hiccup. Their use to treat restlessness and agitation in the elderly is highly questionable. In addition, they are used as adjunct therapy in psychotic depression, bipolar disorder and mania. Some of the newer antipsychotic drugs (e.g. **sulpiride**) have been claimed to have specific antidepressant actions. Phenothiazines and related drugs are also useful as antiemetics (see Ch. 29). Minor uses include the treatment of Huntington's chorea (mainly **haloperidol**; see Ch. 39).

The clinical efficacy of antipsychotic drugs in enabling schizophrenic patients to lead more normal lives has been demonstrated in many controlled trials. The inpatient population (mainly chronic schizophrenics) of mental hospitals declined sharply in the 1950s and 1960s. The efficacy of the newly introduced antipsychotic drugs was a significant enabling factor, as well as the changing public and professional attitudes towards hospitalisation of the mentally ill.

Antipsychotic drugs, apart from their side effects, have two main shortcomings:

1. Not all schizophrenic patients respond to drug therapy. It is recommended to try **clozapine** in patients who are resistant to other antipsychotic drugs. The 30% of patients who do not respond are classed as 'treatment resistant' and present a major therapeutic problem. The reason for the difference between responsive and unresponsive patients is unknown at present, although there is some evidence (not conclusive) that polymorphisms within the family of dopamine and 5-HT receptors may be involved (see Basile et al., 2002).
2. While they control the positive symptoms (thought disorder, hallucinations, delusions, etc.) effectively,

Clinical uses of antipsychotic drugs

- *Behavioural emergencies* (e.g. violent patients with a range of psychopathologies including *mania*, *toxic delirium*, *schizophrenia* and others):
  - antipsychotic drugs (e.g. **chlorpromazine**, **haloperidol**, **olanzepine**, **risperidone**) can rapidly control hyperactive psychotic states
  - note that the intramuscular dose is lower than the oral dose of the same drug because of presystemic metabolism.
- *Schizophrenia*:
  - many chronic schizophrenic patients are treated with first-generation antipsychotic drugs. Depot injections (e.g. **flupentixol decanoate**) may be useful for maintenance treatment when compliance with oral treatment is a problem
  - **flupentixol** has antidepressant properties distinct from its antipsychotic action
  - newer antipsychotic drugs (e.g. **amisulpride**, olanzapine, risperidone) are used if extrapyramidal symptoms are troublesome or if symptom control is inadequate
  - **clozapine** can cause *agranocytosis* but is distinctively effective against 'negative' features of schizophrenia. It is reserved for patients whose condition remains inadequately controlled despite previous use of two or more antipsychotic drugs, of which at least one is atypical. Blood count is monitored weekly for the first 18 weeks, and less frequently thereafter.

most are ineffective in relieving the negative symptoms (cognitive impairment, emotional flattening, social isolation).

The newer atypical antipsychotic drugs may overcome these shortcomings to some degree. However, a recent meta-analysis (Leucht et al., 2009) concluded that, of the atypical antipsychotic drugs examined, only **amisulpride**, **clozapine**, **olanzapine** and **risperidone** were better than first-generation antipsychotic drugs for overall efficacy. The other atypical drugs were not more efficacious than the first-generation drugs, even for negative symptoms.

FUTURE DEVELOPMENTS

Preclinical and clinical studies have provided encouraging evidence that agonists of group II metabotropic glutamate receptors ($mGluR_2$ and $mGluR_3$; see Ch. 37) are effective in the treatment of the positive symptoms of schizophrenia (Patil et al., 2007). Furthermore, agonists at mGluR5 receptors may improve positive and negative symptoms as well as cognitive function. It may also be possible to enhance the action of endogenous glutamate at these receptors with positive allosteric modulator drugs. For more detailed information, see Conn et al. (2009).

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