

Opiates

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Morphine and the opiates are some of the most valuable drugs in medicine and their actions can now be explained in terms of their acting as agonists at one of the four opiate receptors found in the brain, spinal cord and peripheral nervous system. All four receptors are inhibitory.

Introduction

The main class of analgesic used in the clinical treatment of moderate to severe pain, whatever the cause, is that of the opiate drugs, namely drugs with actions similar to morphine, which is found in the juice of the opium poppy. The term opioid is synonymous. The synthetic drug naloxone is an opiate antagonist, and reversal of effects of a drug by naloxone is generally taken as the criterion for classification as an opiate or opioid. The opiates are used for the treatment of postoperative pain, pain of childbirth, trauma pain, cancer pain and many other pains and are generally highly effective except in some cases of neuropathic pains (arising after neuronal injury). Underprescribing of opiates because of the fear of side effects and dependence is dying out, as is the myth that these drugs are only used for terminal pain. (*see* Pain and analgesia.) (*see* Receptor binding in drug discovery.)

Opiates and Their Receptors

The actions of clinically used opiates can now be explained in terms of their acting as agonists at one of the four opiate receptors found in the brain, spinal cord and peripheral nervous system (**Table 1**). All four receptors are inhibitory. (*see* Opiate receptors.)

These receptors are for the endogenous opioids, peptide transmitters in the nervous system that, like all other peptides, are synthesized as large inactive precursors in the neuronal cell body and transported to the terminal with processing en route yielding the active fragment, which is then released into the synapse and activates the appropriate receptors. The cloned receptors fall into the family of seven-transmembrane spanning receptors; for unknown reasons, the binding sites for agonists and antagonists and peptides and nonpeptides appear to depend on different amino acids. Furthermore, the delta opioid receptor may be found on the membrane of vesicles in some nerve terminals. (*see* Protein synthesis in neurons.) (*see* Axonal transport and the neuronal cytoskeleton.) (*see* Synapses.) (*see* Neurotransmitters.)

The opiate receptors are found on postsynaptic sites, but presynaptic locations predominate, so that activation of the receptors can control the release of a number of

Introductory article

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neurotransmitters (e.g. glutamate, substance P, GABA (γ -aminobutyric acid) and acetylcholine). The endogenous opioids are rapidly degraded, so synthetic opioids are needed that penetrate the central nervous system (CNS). Side effects are due to the peripheral and central receptors, whereas the analgesic effects are due to the interaction of opioids with central receptors. The degree of analgesia can be limited by the side effects. (*see* Neurotransmitter release from presynaptic terminals.) (*see* Pain: control.)

Almost all clinically used opioid drugs act on the mu opioid receptor, the receptor for morphine, and they can be highly effective analgesics in many patients unless the pain is neuropathic pain, when some patients have inadequate control. Here, the assessment of the analgesic effectiveness of opioids in both animals and in patients is complicated by the fact that the type of neuropathy and the extent, duration and intensity of the symptoms will vary. There is no real consensus from clinical studies on the efficacy of morphine in neuropathic pain states. Dose escalation with morphine was shown to produce good analgesia in one study, and others have reported that, in general, morphine can be effective in a group of patients with neuropathy. Another study concluded that opioids were entirely ineffective and, finally, that opioid analgesia was less in some neuropathic pain patients compared to a group with pain from other causes. Resolution of this problem has important implications, yet a similar series of discrepant results can be found in the animal literature. (*see* Drugs and the synapse.)

Following the description and then isolation of the opioid receptors, for many years there were three known receptors for the opioids, the mu (μ), delta (δ) and kappa (κ) opioid receptors, but a novel fourth receptor, an orphan receptor, has subsequently been characterized. This newly discovered opioid receptor-like (ORL-1) receptor appears to be linked to an inhibitory receptor despite the endogenous agonist having been named nociceptin (orphanin FQ). The receptor system does not appear to be anything like the traditional opioids. Overall, this peptide produces spinal analgesia but may well function as an

Table 1 Opiate receptors and the endogenous opioids with examples of drugs acting on each receptor and the effects of receptor activation

Receptor	Mu (μ)	Delta (δ)	Kappa (κ)	ORL-1
Endogenous opioid	β -Endorphin Endomorphins	Enkephalins	Dynorphins	Nociceptin
Synthetic agonist	Morphine Codeine Fentanyl Pethidine	DSTBULET DPDPE	U50488H Pentazocine Oxycodone?	–
Antagonists	Naloxone β -FNA	Naloxone Naltrindole	Naloxone nor-BNI	Not naloxone
Effector mechanism	G protein opens K^+ channel	G protein opens K^+ channel	G protein closes Ca^{2+} channel	G protein opens K^+ Channel
Effects	Hyperpolarization of neurons, inhibition of neurotransmitter release			
	Analgesia Relief of anxiety Euphoria Nausea Constipation Cough suppression Dependence	Like μ but less marked	Analgesia Aversion Diuresis	Analgesia?

'antioioid' at supraspinal sites and cause excitation of C fibres in the periphery. The central effects of nociceptin include a low abuse potential compared to morphine, and so it provides an opportunity for the development of alternative analgesics to morphine. However, sufficiently selective tools for the receptor are lacking; the peptide itself is the only agonist available at present, and the putative antagonist appears to be at best a partial agonist. The apparently paradoxical site-dependent antinociceptive/hyperalgesic effects of this peptide are yet to be resolved. (see Sensory system organization.)

The μ , δ and κ opioid receptors are coupled to G_o and G_i proteins and the inhibitory actions of the opioids occur from the closing of calcium channels (in the case of the κ receptor) and the opening of potassium channels (for μ , δ and ORL-1 receptors). These actions result in either reductions in transmitter release or depression of neuronal excitability, depending on the pre- or postsynaptic location of the receptors. Excitatory effects can also occur via

indirect mechanisms – disinhibitions – which have been reported in various parts of the nervous system. (see G protein-coupled receptors.) (see Heterosynaptic modulation.)

The four opioid receptors, the μ , δ , κ and ORL-1 receptors, display *in vivo* binding preference for β -endorphin, enkephalins, dynorphin and nociceptin/orphanin FQ, respectively. These are not completely selective for each type of receptor since the opioid peptides show a degree of sequence homology, although modified synthetic agonists are more selective. Investigation of μ receptor-mediated controls has been hampered by the lack of an endogenous ligand for the receptor in many areas, in particular within the spinal cord. Two peptides (endomorphin-1 and -2), have now been isolated with high affinity and selectivity for μ opioid receptors making it likely that they are the natural endogenous ligands for the receptor for morphine itself (see Table 2). (see Peptides: biological activities of small peptides.)

Table 2 Amino acid sequences of the endogenous opioid peptides

Nociceptin	Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln
Dynorphin A (1-17)	Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Endomorphins 1 and 2	Tyr-Pro-Trp-Phe; Tyr-Pro-Phe-Phe
Leu- and Met-enkephalin	Tyr-Gly-Gly-Phe-Leu/Met

The actions of all clinically used opiates can now be explained in terms of their acting as agonists at one of the four opiate receptors found in the brain, spinal cord and peripheral nervous system. All four receptors are inhibitory.

Spinal Opiate Analgesia

The opiate receptors in the spinal cord are predominantly of the μ and δ types and are found in the C fibre terminal zone (the substantia gelatinosa) in the superficial dorsal horn. Up to 75% of the opiate receptors are found presynaptically on the C fibre terminals and, when activated, inhibit neurotransmitter release. The opening of potassium channels will reduce calcium flux in the terminal and so there will be a resultant decrease in release of all the transmitters in the C fibres (glutamate, substance P, etc.). The remaining postsynaptic receptors appear to hyperpolarize the dendrites of projection neurons and interneurons and disinhibit inhibitory interneurons; the net result is further inhibition of the C fibre-induced activity (see **Figure 1**). This spinal action of opiates can be targeted by using the intrathecal or epidural routes of administration which have an advantage over systemic application of avoiding the side effects mediated by opiate receptors in the brain and periphery. (see Spinal cord.) (see Somatosensory systems.)

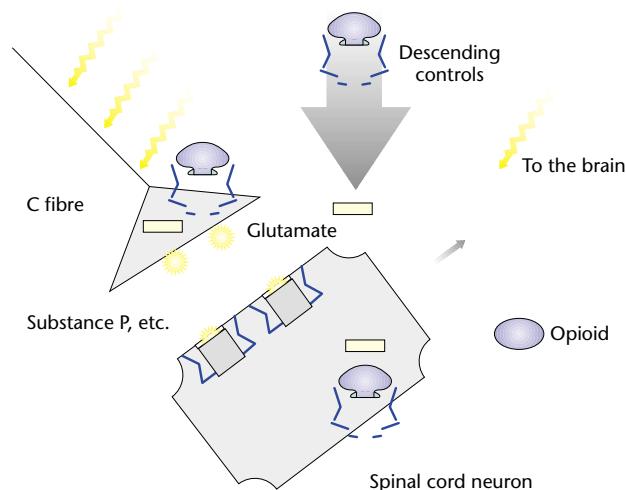


Figure 1 Spinal opiate analgesia. Action potentials in peripheral sensory neurons arrive in the central terminals of C fibres and produce the release of glutamate and substance P, among others. By activation of postsynaptic receptors on spinal neurons, 'pain messages' are sent to the brain. Opiates, by acting on inhibitory presynaptic receptors, reduce release of these transmitters. Furthermore, postsynaptic opioid receptors inhibit the excitability of the spinal neurons directly and actions of opiates in the brain trigger descending inhibitions. The ensemble of these actions leads to analgesia.

Complete C fibre inhibitions can be produced under normal conditions, but opiates do not always produce complete analgesia in some clinical situations, especially when the pain arises from neuronal damage. Reasons for this are suspected to be (1) excessive spinal hyperexcitability after repeated C fibre stimulation, which is hard to inhibit, (2) a loss of opioid receptors and (3) the mobilization of cholecystokinin in the spinal cord, which can interfere with opiate actions. The idea that pre-emptive analgesia aids postoperative pain relief by preventing the pain-induced activation of these systems is becoming popular. (see Pain and analgesia.)

Opioid receptors in the spinal cord are a key site in the production of analgesia, as demonstrated by opioid inhibition of spinal nociceptive neurons in animals and direct analgesia following epidural and intrathecal opioids in animals and then subsequently in man. Considerable efforts have been devoted to the study of opioid receptor subtypes in the spinal cord, using both electrophysiological and behavioural approaches. The recent studies on the spinal opioid systems have started to reveal plasticity in opioid spinal function, with indications that opioid activity and function are not immutable but can be enhanced or reduced depending on the circumstances. (see Anaesthesia: modern approaches.)

Morphine acts on one of the three opioid receptors, the μ receptor. The highest levels of opioid receptors in the spinal cord are around the C fibre terminal zones in lamina I and the substantia gelatinosa, with lower levels found in deeper layers. Estimates suggest that the μ receptor forms 70%, the δ 24% and the κ 6% of the total opioid sites in the rat spinal cord. The recent cloning of the opioid receptors will provide unequivocal probes for the receptors and facilitate the task of further understanding the operation of the receptors. Importantly, molecular biology has shown there are very close similarities between the opioid receptors in humans and laboratory animals so that species differences are likely to be minimal.

A major clinical problem is the treatment of neuropathic pain, as discussed earlier. Nerve section will lead to a loss of all the presynaptic opioid receptors and it is also possible that receptor dysfunction accompanies less severe nerve damage. Thus, in neuropathic pains there is a strong likelihood that the functional pool of opioid receptors will be reduced at the spinal level. Electrophysiological evidence indicates that the postsynaptic actions require higher doses of morphine than the presynaptic effects based on comparative studies in animals with and without the presynaptic sites. Consequently, if the loss of the presynaptic receptors contributes to any reduced opioid sensitivity of post-amputation pain, dose-escalation could overcome this. In addition, the supraspinal sites of action of opioids will not be perturbed by primary afferent damage or dysfunction. There are additional reasons for reduced morphine analgesia, which are described later. Interestingly, in inflammation, the presynaptic opioid

receptors, produced in the cell bodies of C fibres in the dorsal root ganglion, and transported both centrally and peripherally, become functional in the periphery. A number of clinical studies have demonstrated this action, but the efficacy of peripheral opioids after inflammation is much less than their central actions and so the contribution of this effect to the overall analgesia appears to be low. (see Sensory systems in vertebrates: general overview.)

Functional studies with antagonists and probes directed at the opioid receptors have demonstrated the independence of μ , δ and κ receptors at the spinal level and elsewhere in the brain. The analgesic effects following activation of non- μ receptors indicate that there is potential for opioid analgesics that are δ or κ agonists. Experience with κ opioids, with dynorphin being the endogenous opioid, has been relatively disappointing, but δ opioid receptor agonists may have good potential as analgesics with reduced side effect profiles as compared to morphine and the other clinically used drugs.

There is another transmitter, cholecystokinin (CCK), which is a major factor in the control of the level of opioid effectiveness, not only spinally but at supraspinal sites as well. This peptide, which is found in intrinsic spinal neurons in normal animals, is upregulated in the afferent fibres after nerve damage. The application of CCK can selectively reduce the analgesic actions of morphine, and antagonists of the CCK-B receptor enhance morphine analgesia. It is likely that activation of CCK-B receptors, located on the afferents, opposes the opioid reduction in nociceptive transmitter release. These studies demonstrate that the peptide acts as an endogenous control on the level of μ opioid analgesia. The upregulation of CCK in neuropathic models is responsible for the reduced opioid actions, whereas, in inflammation, decreased levels of the peptide are a major factor in the enhanced opioid actions seen at the spinal level. There is further evidence that CCK also acts supraspinally to reduce μ analgesia and it has also been implicated in events underlying tolerance. Antagonists of the CCK-B receptor may be useful in restoring morphine analgesia in neuropathic states and enhancing the actions of the opioid while reducing tolerance. At present we lack clinically useful agents. Interestingly, the role of cholecystokinin in the control of the level of morphine analgesia may extend to the impact of environmental factors on opioid sensitivity, so that the efficacy of opiates in producing their effects may depend on the context of their use and the behavioural state at that time. (see Peptide neurotransmitters and hormones.)

Supraspinal Opiate Analgesia

There are other important sites of opiate actions located in the 5-hydroxytryptamine (5-HT) and noradrenergic nuclei of the brainstem and midbrain including the raphe nuclei,

the periaqueductal grey matter and the locus coeruleus. Opiate receptors in these zones (μ , δ and κ), when activated, alter the level of activity in descending pathways from these zones to the spinal cord. The mechanisms of action of opioids at supraspinal levels are still poorly understood. One idea is that descending controls filter sensory messages at the spinal level, allowing a pain message to be extracted from the incoming barrage. Supraspinal morphine is thought to reduce these controls, so blurring the perception of pain. The second theory is that morphine turns on descending controls that simply inhibit spinal pain transmission. The relative roles of the 5HT receptors in the spinal cord are still unknown, but the spinal target for the noradrenaline released from descending pathways are α_2 receptors that have similar actions and distribution to the opiate receptors. Sedation and hypotension with α_2 agonists presently limit their use as analgesics. (see Serotonin.) (see Adrenaline and Noradrenaline: Introduction.) (see Brainstem.) (see Serotonin receptors.) (see Adrenergic receptors.)

Opioid mechanisms at a number of other supraspinal sites (thalamic levels, the amygdala and the sensory cortex) are likely to be of relevance to analgesia and also the changes in the psychological aspects of pain that these drugs produce.

Central Side Effects of Opiates

Complete analgesia may not be produced in some patients under certain conditions owing to insufficient doses being given: here, an increase in the dose may be prejudiced by the side effects of the opioids.

The large numbers of opioid receptors in areas of the brainstem such as the solitary tract and adjacent areas are probably related to respiratory effects of opiates, cough suppression and nausea and vomiting. (see Respiration: neural control.)

Opiates acting in the brain stem reduce the sensitivity of the respiratory centres to $p\text{CO}_2$ and this is the most common cause of death from overdose with street use of opiates. Here, opiates do not prevent breathing but reduce the automatic drive to respiration. Thus, if a person falls asleep he or she may die.

Opiates activate the chemoreceptor trigger zone in the medulla to cause nausea and vomiting; cough suppression also occurs because of the inhibitory effects of opiates on the brainstem nuclei in the cough reflex pathway. Dextromethorphan is the nonopiate isomer of the opiate, levorphanol and is an effective cough suppressant. (see Chemosensory systems.)

Sites in the monoamine nuclei, such as in the well-demonstrated actions of opioids on noradrenergic transmission in the locus coeruleus and enhancing dopamine release in the ventral tegmental area (via disinhibition), are likely to be associated with reward processes and so relate

to dependence. Psychological dependence does not appear to occur in the presence of pain. Although a patient prescribed morphine over a prolonged period of time will show signs of physical dependence, requiring slow reductions in dose at the end of treatment to avoid withdrawal, drug-seeking behaviour in these patients is very rare. However, with street use, psychological dependence on opioids develops rapidly and overwhelmingly. Thus, it would appear that pain prevents psychological dependence. The reason for this is unclear but it could result from the fact that pain is aversive, in that not only does the stimulus produce a sensation of pain but also an unpleasant psychological effect. Perhaps this latter characteristic of pain switches off the reward systems in the cortex. Thus, opioids in the presence of pain cannot trigger reinforcement. (*see* Dopamine.) (*see* Limbic system.)

Peripheral Side Effects of Opiates

A number of side effects of opiates are due to their actions on opiate receptors outside the central nervous system. Opiates constrict the pupils by acting on the oculomotor nucleus and cause constipation by causing a maintained contraction of the smooth muscle of the gut, which reduces motility. This diminished propulsion – coupled with opiates reducing secretion in the gut – underlies the antidiarrhoeal effect. Opiates contract sphincters throughout the gastrointestinal tract. Although these effects are predominantly peripheral actions, there are central contributions as well. Morphine can also release histamine from mast cells and this can produce irritation and bronchospasm in extreme cases. Opiates have minimal cardiovascular effects at therapeutic doses. (*see* Vertebrate peripheral nervous system.) (*see* Oculomotor system.) (*see* Histamine biosynthesis and function.)

Nonmedical Use of Opiates

Heroin (diamorphine) is one of the ‘opiates or opioids’ that are derived from the sap of the ripe opium poppy. Opium is the dried milk of the opium poppy. It contains morphine and codeine, both effective and widely used analgesics. Heroin can be made from morphine, and in its pure form is a white powder. Heroin is highly liposoluble because it has morphine with two additional acetyl groups that facilitate its ability to cross cell membranes. It therefore rapidly crosses into the brain after injection or smoking, whereas the effects of morphine are much slower. It is thought that the acetyl groups that allow heroin to access the brain so effectively also prevent the drug from binding to opiate receptors. However, as the heroin enters the brain, these groups are detached and morphine itself, now within the central nervous system, activates the opiate receptors.

Methadone, used for replacement therapy, is an orally active, long-lasting opiate. It is often prescribed as a substitute drug, as a syrup, in the treatment of heroin addiction. (*see* Blood–brain barrier.)

Most street heroin for the United Kingdom comes from southwest Asia, mainly Afghanistan, Iran and Pakistan, and is in the form of an off-white or brown powder.

Heroin can be smoked (‘chasing the dragon’), sniffed or injected and, whatever the route, its physical properties mean that it rapidly enters the brain. Some of the other opioids, prescribed for medical use, have been diverted onto the streets for use by heroin users who cannot otherwise get hold of heroin, but the amounts are very small. Thus, in the United States, despite dramatic increases in the number of prescriptions for medical opioids, the amount reaching the streets has hardly altered from tiny proportions.

The sudden influx of smokable heroin in the 1980s caused a dramatic increase in use, because it was no longer necessary to inject the drug in order to obtain its effects, and many young people used the drug believing that it was something other than heroin, which they associated with injections. Despite new initiatives, heroin use has continued to increase and at present there is concern about the wider availability and use of cheap heroin among young people, particularly in deprived areas.

There are many debates about the best way of tackling heroin use. The UK government participates with other countries in attempting to cut off the supply of heroin, although, given that the source of the drug can shift rapidly, it is not clear how effective this approach is. Likewise, removal of dealers from the street appears to simply allow others to move in to supply the constant demand. There is also a debate in the United Kingdom about the substitute drug methadone, which is similar to heroin except the user does not get the same ‘high’ as with heroin. The idea is to gradually reduce the dose of methadone until the person is able to come off drugs without suffering withdrawal symptoms. The problem is that many users seem to quickly go back to heroin, so that some doctors prescribe methadone on a maintenance basis, not reducing the dosage until the person feels ready to give up, a process that can be lengthy. One school of thought would claim that this approach simply keeps people dependent on a different drug. The opposite view is that methadone keeps people away from the dangerous street market in heroin, with the associated risks of crime and overdose. Unfortunately, many users obtain methadone legally and then sell it to buy street heroin.

Recent years have also seen the development of needle exchange schemes, whereby users of injectable heroin can receive clean equipment rather than sharing needles, to minimize the threat of hepatitis and HIV. These schemes seem to be very effective, although it has been claimed that they encourage injecting. Another issue is heroin-related crime, especially theft, burglary and forgery, since a

Table 3 Acute effects of opioids and the withdrawal symptoms

Acute effects	Symptoms of withdrawal
Analgesia	Spontaneous aches and pains
Depressed reflexes	Spontaneous twitches ('kick the habit')
Feeling of warmth	Feeling of cold ('cold turkey')
Anxiolysis	Anxiety and paranoia
Constipation	Diarrhoea
Drying up of secretions	Lacrimation, runny nose, salivation

dependent user will need considerable amounts of money to pay for the drug. The cost to the community is unknown, but some police forces have estimated that up to one-third of crime relates to drug use.

Effects

Heroin and other opiates are drugs that depress the nervous system via activation of the inhibitory opiate receptors. The desired effect on the street is not the analgesia that is the reason for their medical use, but the feeling of warmth, reduction in anxiety and detachment that they produce. The effects of both smoked and injected heroin are rapid and then last several hours, but this varies with how much is taken and the route of application. The feeling produced by the drug has been described as 'being wrapped in cottonwool'. Mental anguish is removed and hence the use of the drug as a means of escape from social and other pressures becomes clearer. Although initial use can result in a feeling of nausea and even actual vomiting, these unpleasant reactions are subject to tolerance. With high doses of heroin, a marked sedation takes over and people can fall asleep. Morphine was named after Morpheus, the Greek god of dreams. As discussed earlier, opioids can depress the respiratory centre, and with nonmedical use the most common form of death is from respiratory failure, which is compounded by the severe sedation and vomiting that can also occur. (*see* Addiction.)

Tolerance develops with regular use, as do psychological and physical dependence. Doses need to be increased to obtain the desirable effects and the person may end up simply having to take the drug to avoid withdrawal. The physical withdrawal syndrome leads to unpleasant flu-like symptoms that may include aches, tremor, sweating, chills and muscular spasms. Here, the idea that physical dependence results from opposing changes in the neuronal systems depressed by the drug of dependence is borne out by consideration of the acute effects of an opioid and the withdrawal symptoms. They are mirror images of each other (Table 3).

These effects fade after about a week but can be a major deterrent to giving up the drug. While many people do successfully give up long-term heroin use, coming off and staying off heroin can be very difficult. Fatal overdoses can

happen, especially when users take their initial dose after a break during which tolerance has faded, or when opiate use is combined with use of other drugs such as alcohol, depressants or other opiates. It is often difficult to know exactly what is being taken because the purity of street heroin varies and it is often mixed with adulterants. Injecting increases these risks and also puts users at risk of a range of infections including hepatitis and HIV if injecting equipment is shared. Regular injectors may suffer a wide range of health problems including chronic constipation, damaged veins, and heart and lung disorders. (*see* AIDS as a world health problem.)

Conclusions

Morphine and the opiates are probably some of the most valuable drugs in medicine. Their ability to alleviate pain and suffering led Thomas Sydenham, an English doctor in the nineteenth century to call them 'God's own medicine'. The use of opium to relieve pain dates back thousands of years, making opiates one of the oldest medical treatments known. Yet much of our understanding of how and why opiates work is derived from studies over the last few decades – there is clearly much more to be discovered. Despite their medical effectiveness, the use of these drugs on the street and the potential for addiction have led to an 'opiophobia' in some countries, so that patients are denied adequate pain relief. This is slowly changing, but clearly more work on why the context of drug use is so important for the effects of drugs will shed light on why patients simply do not show drug-seeking behaviour after clinical use of the same drugs as those used on the street. Social, psychological and other issues are of great relevance here. (*see* History of drug discovery.)

Further Reading

- Dickenson AH (1995) Spinal cord pharmacology of pain. *British Journal of Anaesthesia* **75**: 193–200.
- Dray A, Urban L and Dickenson AH (1994) Pharmacology of chronic pain. *Trends in Pharmacological Sciences* **15**: 190–197.
- The Pain Series (1999) *Lancet* **353**: 1607 ff.
- Tyler A (1988) *Street Drugs*. London: Hodder and Stoughton.
- Uhl GR, Childers S and Pasternak G (1994) An opiate receptor gene family reunion. *Trends in Neurosciences* **17**: 89–93.