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21 Pain and Analgesia

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INTRODUCTION

The mechanisms of pain and the ability to control pain may vary in different pain states. This is of particular importance in consideration of a rational basis for the treatment of both inflammatory and neuropathic pain where the damage to tissue and nerve leads to alterations in both the peripheral and central mechanisms of pain signalling. In respect of existing drug therapies, this plasticity, the ability of the system to change in the face of a particular pain syndrome, explains the effectiveness of NSAIDs in inflammatory conditions and yet is also responsible for some of the limitations in the effectiveness of opioids in neuropathic pain.

For many years, the neurobiological basis for understanding the causes and improving the treatment of pain states remained somewhat unclear. Fortunately, the development of a number of animal models of inflammation and nerve injury, produced by manipulation of either peripheral tissue or nerves, has greatly aided our understanding of the mechanisms of pain and realised many examples of this plasticity. Over the past two decades our knowledge of the pharmacology of pain and analgesia has made enormous strides so that whereas 25 years ago we had a rudimentary idea that morphine worked somewhere in the nervous system we can now recite the complete amino-acid sequence of the four opioid receptors. In parallel with advances in the opioid pharmacology a bewildering list of interacting mediators, transmitters and receptors, some peripheral, some central and some located at both sites, has been established as parts of the initiation and conception of pain.

In recent years, further progress has been made in our understanding of both acute and chronic pain mechanisms that can be largely attributed to advancements in molecular biology and genomic techniques, as well as the use of animals. This has fundamentally altered our understanding of the pathophysiology of pain mechanisms, allowed us to explore new targets for pain relief and has led to the hope of development of novel analgesics. Unfortunately, despite this progress, the management of pain remains a major clinical concern and is still inadequate in many cases and a significant problem even to this day. Not only does it bring undesirable sensations, it can often impair the quality of living for many if not effectively treated.

In broad terms, pain can be divided into two categories, acute and chronic, which differ in their aetiology, mechanisms and pathophysiology. Acute pain and its associated responses are provoked by noxious stimulation and/or disease, or by abnormal function of muscle or viscerae which does not involve actual tissue damage. Although acute pain conditions may last for a length of time if not treated effectively, many cases of acute

pain often resolve within days or weeks. In contrast, chronic pain can persist for a long period of time (3 months is usually considered as the transition point from acute to chronic) and results from damage and/or pathology in peripheral tissues or viscerae, or from dysfunction or lesions to the nervous system, either peripheral or central. Pain after tissue damage can be considered as inflammatory pain whereas nerve damage is termed neuropathic pain.

In fact, pain provides a model system for examining how the CNS deals with sensory inputs from both the external and internal areas of the body. Not surprisingly, the intensity, duration and origins of the pain will all have a bearing on the mechanisms underlying the final perception of the patient. Many clinicians, noting the advances made in the basic sciences and our understanding of the pathology and physiology of pain, appear a little disillusioned by the lack of new therapies, and indeed, any magic bullet. First, drug development rests in the hands of the pharmaceutical companies — yet more and more of them are becoming involved in analgesic research, a hopeful change. Second, animal studies really only shed light on efficacy — side-effects may confound the clinical utility of agents. Finally, given the plethora of mediators of pain and analgesia the chance of a single drug being effective in all pain states is unlikely. Combination therapy is possibly the best approach, in that targeting more than one mechanism or site may be fruitful.

PERIPHERAL EVENTS IN THE INITIATION OF PAIN

SENSORY RECEPTORS

Pain is initiated as activation of peripheral sensory fibres by injury or an insult to tissue but is perceived as a sensation through central responses. Thus, it may be relieved either by reducing its initiation by drugs acting peripherally or by drugs acting centrally to reduce the transmission and effects of nociceptive messages sent to the spinal cord and brain. Knowing the mediators involved in both the initiation and transmission of nociceptive impulses provides targets for drug therapy and pain control.

The first stage in the transmission of acute pain involves activation of specialised sensory receptors, the nociceptors, on peripheral C-fibres. These receptors include mechano-, chemo- and thermoreceptors. The terminology of 'receptor' for transmission of somatosensory information can incorporate the type of nerve fibre they are activating, the proposed transduction mechanisms, as well as the form of the adequate stimulus which activates them. Generally, the nerve fibres which respond to non-painful, low-threshold stimulation are the Aβ-fibres and their associated endings. By contrast, Aδ-fibres can be nociceptive or non-nociceptive while nociceptors associated with C-fibres are often termed polymodal since they can respond to a variety of adequate stimuli. The transduction mechanism associated with the free endings of these latter fibres has still to be ascertained. Some C-fibres can, however, also convey low-threshold information while some Aδ-fibres have also been shown to behave as polymodal receptors in their own right with Aδ-mechanoreceptors behaving like C-polymodal afferents after sensitisation.

Primary afferent fibres mediating painful inputs

The somatosensory primary afferent fibre, which conveys sensory information to the spinal cord, can be classified into several classes, according to the transduction

Table 21.1 Classification of somatosensory primary afferent fibres innervating the skin

Primary afferent fibre type	Mean diameter (μm)	Myelination	Mean conduction velocity (m/s)
Aβ	6–12	Myelinated	25–70
Aδ	6–5	Thin myelinated	10–30
C	0.2–1.5	None	<2.5

properties of the individual nerve fibre. The properties of each afferent fibre are summarised in Table 21.1 and their termination sites in the spinal cord are shown in Fig. 21.1.

The afferent fibres differ in their conduction velocity and degree of myelination, and can be distinguished by their diameter. The large diameter Aβ-fibres are myelinated by Schwann cells and hence have a fast conduction velocity. This group of nerve fibres innervates receptors in the dermis and is involved in the transmission of low-threshold, non-noxious information, such as touch. The Aδ-fibre is less densely myelinated and conveys both non-noxious and noxious sensory information. The unmyelinated C-fibre conveys high-threshold noxious inputs and has the slowest conduction velocity of all three fibre types.

Aβ-fibres

The large diameter Aβ-afferent fibre enters the dorsal horn of the spinal cord through the medial division of the dorsal root. It then descends through the medial region of lamina I or II, or alternatively, curves around the medial (central) edge of the dorsal horn down to the ventral horn. On reaching deeper laminae, laminae IV and V, the Aβ-fibres ascend back up into laminae III and IV where they repeatedly subdivide and form a characteristic termination pattern. The densest arborisation appears to occur in lamina III. Axons originating from specialised muscle stretch receptors have collaterals that pass ventrally to make monosynaptic connections with neurons of laminae V, VI and VII. Some also extend to laminae VIII and IX of the ventral horn where they synapse directly onto motor neurons and form the basis of monosynaptic reflexes.

Aδ-fibres

The termination pattern exhibited by Aδ-fibres is entirely different from that of large Aβ-fibres. Aδ-fibres travel extensively in Lissauer's tract, overlying the dorsal horn and their terminals form a plexus at the surface of the spinal cord Aδ-fibres from high-threshold mechanoreceptors distributed to laminae I, II outer and V. Projections also appear to terminate on the contralateral side, in lamina V. Aδ-fibre innervations from deep tissues (muscles and joint) have been shown to terminate exclusively in lamina I, or in laminae IV and V.

C-fibres

Extensive studies have investigated the organisation and termination patterns of C-fibres, employing various techniques including Golgi staining, degeneration techniques

and HRP transport. Unmyelinated C-fibres enter the spinal cord through the lateral part of the dorsal white matter, including Lissauer's tract. Studies have shown that unmyelinated primary afferents terminate in the superficial dorsal horn, although there is conflicting evidence as to whether the terminations are restricted to lamina II or whether it includes both laminae I and II. Current evidence suggests that lamina II is the main termination area for cutaneous primary afferent C-fibres while that for Aδ-fibres is in lamina I.

TISSUE DAMAGE AND CHEMICAL MEDIATORS

These polymodal receptors, on C-fibres, can be selectively activated by noxious thermal and mechanical stimuli. In the case of the former modality, we now suspect that a recently characterised receptor-channel (vanilloid receptor 1, VR1) that responds to capsaicin, the extract of hot peppers, may also be responsible for the generation of action potentials after application of heat. Although the endogenous ligand for this receptor is unclear, it may be anandamide, the cannabinoid. The peripheral terminals of small-diameter neurons, especially in conditions of tissue damage like inflammation, are excited by a number of endogenous chemical mediators. These can be released from local non-neuronal cells, the afferent fibres themselves, and from products triggered by activation of the body's defence mechanisms. These chemical mediators then interact to sensitise nociceptors so that afferent activity to a given stimulus is increased. This is known as primary hyperalgesia.

Some of the most important components in inflammation are the products of arachidonic acid metabolism. Arachidonic acid, a component of cell membranes, is liberated by phospholipase A2 and subsequently metabolised by two main pathways which are controlled by two different enzymes, cyclo-oxygenase (COX) and lipoxygenase. This metabolism gives rise to a large number of eicosanoids (leukotrienes, thromboxanes, prostacyclins and prostaglandins) (see Chapter 13). These chemicals do not normally activate nociceptors directly but, by contrast, reduce the C-fibre threshold and so sensitise them to other mediators and stimuli. Thus the value of both steroids and the non-steroidal anti-inflammatory (NSAIDs) drugs in pain after tissue damage is based on their ability to block the conversion of arachidonic acid to these mediators. It should be emphasised that these drugs can only prevent further conversion and will not change the effects of eicosanoids that have already been produced. The short half-life of these mediators makes this fact less important than it would be if the mediators had long-lasting effects. Importantly, a second inducible form of COX, COX-2, has been described. COX occurs in two isoforms, 1 and 2. The former is a constitutive enzyme, always present so that its inhibition affects not only inflammation but also other actions of the products leading to gastric and renal side-effects. By contrast, COX-2 is induced in the periphery by tissue damage and a new generation of selective COX-2 inhibitors have improved therapeutic profiles over existing non-selective drugs. Several novel agents with actions on this latter enzyme are effective in inflammatory pain. Interestingly, COX-2 is normally present in the brain and spinal cord and so may be responsible for some of the central analgesic effects of NSAIDs.

Bradykinin is another chemical with important peripheral actions but, as yet, cannot be manipulated in any direct way by drugs. It is a product of plasma kininogens that find their way to C-fibre endings following plasma extravasation in response to tissue

injury. Bradykinin receptors have been characterised and here again, there are two forms. The B_1-receptor is constitutively expressed less than the B_2-receptor, but in chronic inflammation, it is upregulated. Pain may arise via the activation of the B_2-receptor, which is abundant in most tissues and which can activate C-polymodal receptors. The response to bradykinin can be enhanced by prostaglandins, heat and serotonin, indicating the extent of interactions between these peripheral pain mediators.

Hydrogen ions accumulate in tissue damaged by inflammation and ischaemia and so pH is lowered. These protons may activate nociceptors directly via their own family of ion channels as well as sensitising them to mechanical stimulation. Acid-sensing ion channels (ASICS) are a family of sodium channels that are activated by protons — of special interest is one type found only in small dorsal root ganglion neurons that possibly are responsible for activation of nociceptors. Although the transduction of mechanical stimuli is poorly understood, ASICs are closely related to channels that respond to stretch.

VASCULAR DAMAGE, HEADACHE AND MIGRAINE

Serotonin, 5-hydroxytryptamine (5-HT), is released from a number of non-neuronal cells such as platelets and mast cells and can produce an excitation of nociceptive afferents via the activation of its large number of receptors, e.g. 5-HT_{1A}, 5-HT_2 and 5-HT_3 as well as sensitising nociceptors, especially to bradykinin. The key role, but not the mechanisms of action, of 5-HT in the pain associated with migraine and other headaches is well established but little is known about the actions of this mediator in other non-cranial pains. The aura of neurological symptoms and/or signs in migraine is thought to be caused by a vascular or a neuronal mechanism, or a combination of the two. One theory suggests that changes in the vasculature are responsible for causing migraine whereas a second theory proposes that the vascular changes only mediate the pain and symptoms of migraine. A third theory suggests the primary abnormality is neuronal and originates within the brain itself.

The original hypothesis was that vasoconstriction of intracranial vessels leads to a reduced blood flow, which results in cerebral hypoxia. If the arterioles are constricted sufficiently to cause a reduction in regional cerebral blood flow (rCBF), the brain tissue is hypoperfused, which can cause neurological deficits thought to be responsible for the 'aura'. Wolff, who proposed this idea, stated that following the vasoconstriction of the cranial vessels, vasodilatation of these vessels occurred which gave rise to the pain (via the stretching of nerve endings in the vascular walls), and which also resulted in a change in regional cerebral blood flow. There are some weaknesses in the theory that the primary problem is within the vasculature. As the progression of the symptoms does not respect vascular territories it is unlikely to be primarily due to spasm within the vasculature. The blood flow changes are more consistent with a primary neuronal event causing secondary vascular changes. Another factor that makes the theory of a primary vascular abnormality untenable is that the headache may begin while cortical blood flow is still reduced.

A related idea is that peripheral nerves are the source of the problem and then cause the associated vascular changes via release of 5-HT and other inflammatory mediators. The observation that the changes in the vasculature do not follow vascular anatomy has led to a new theory, that of 'spreading depression'. Here, the primary abnormality is

within the brain itself, a spreading decrease in electrical activity, that moves at a rate of 2–3 mm/min from the site of origin across the cortex. This transient wavefront suppresses both evoked and spontaneous neuronal activity. In spreading depression, the depolarisation is limited to one hemisphere, and there is a refractory period for further spreading depression of up to 3 min. Any decrease in neuronal firing leads to an increase in metabolism which would result in a decrease in rCBF, via autoregulation.

Sumatriptan is an agonist at 5-HT_{1B} and 5-HT_{1D} receptors. It has three distinct pharmacological actions.

Stimulation of the presynaptic inhibitory 5-HT_{1D} receptors on trigeminal Aδ-fibres inhibits the release of calcitonin gene related peptide (CGRP) which on release forms peripheral ends of sensory fibres via the antidromic axon reflex, causes vasodilatation. Sumatriptan therefore inhibits dural vasodilatation. 5-HT_{1D} receptors on trigeminal C-fibres are also activated by the drug, inhibiting the release of substance P (SP) and neurokinin A (NKA) and therefore blocking neurogenic inflammation and dural plasma extravasation.

Direct attenuation of the excitability of neurons in the trigeminal nuclei, as 5-HT_{1B}/5-HT_{1D} receptors on pain transmission neurons in the trigeminal nucleus caudalis and in the upper cervical cord, are activated. Stimulation of these receptors is caused by second-generation triptans that cross the blood–brain barrier such as zolmitriptan, naratriptan, rizatriptan and eletriptan.

Direct vasoconstriction is mediated by the stimulation of vascular 5-HT_{1B} receptors. These receptors are also found systemically, so coronary arteries also undergo vasoconstriction. Sumatriptan constricts cerebral arteries, but if the vasculature is normal, this does not affect rCBF.

Mast cells, as well as releasing 5-HT, can also release histamine which causes vasodilatation, oedema and itch and ATP and adenosine are also involved in inflammatory conditions. Substance P and CGRP released from the peripheral terminals of primary afferents (via axon reflex) can also cause the mast cells to degranulate and release 5-HT. The peptides cause a number of effects including vasodilatation, plasma extravasation and mast cell degranulation and ATP can result in a direct nociceptor activation via activation of P2X receptors. Other factors such as Nerve Growth Factor (NGF) and cytokines are also important at the peripheral level and resultant changes in the phenotype of the sensory neurons have been shown to be one of the resultant effects. Thus, NGF is upregulated in the area of tissue damage and then binds to its high-affinity receptor, the trkA receptor, one of the tyrosine kinase family. NGF and the receptor are then internalised and transported to the cell body in the dorsal root ganglion. Here, there is a resultant change in gene expression so that the gene for pre-pro tachykinins is turned on. Thus tissue damage causes complex changes in the transduction of painful stimuli. Figure 21.1 shows some of the mediators at the peripheral level with their receptors.

NERVE DAMAGE

Neuropathic pain states are thought to be generated in the peripheral sensory neurons by events within the nerve itself and so are independent of peripheral nociceptor activation. Damage to peripheral nerves can be caused by a number of pathological, metabolic and viral causes. According to the terminology guide of the International

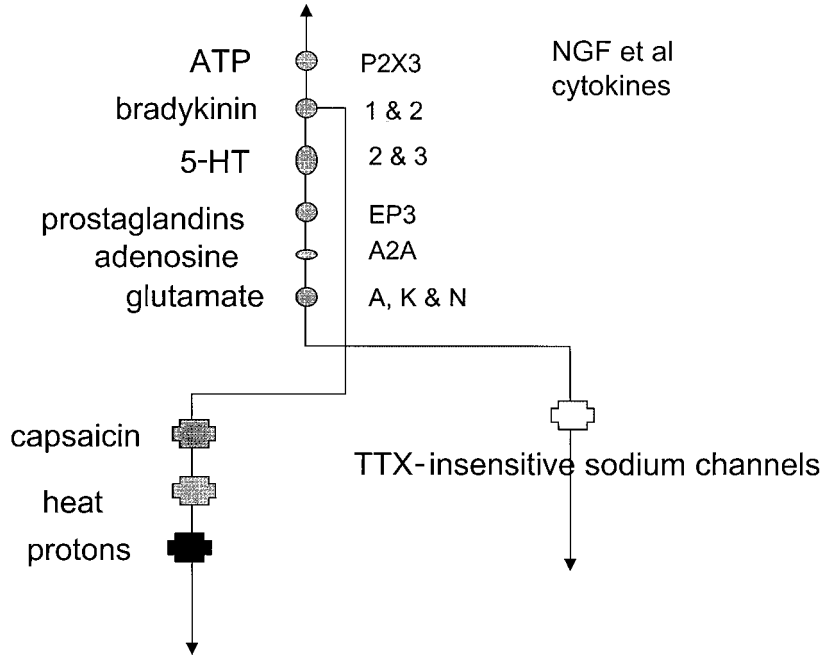

Figure 21.1 Some of the mediators of pain at the peripheral level with their receptors. Note that with regard to 5-HT, the cranial mechanisms have been omitted for clarity

Association of Pain, neuropathic pain is defined as '*pain initiated or caused by a primary lesion, dysfunction in the nervous system*'. Neuropathy can be divided broadly into peripheral and central neuropathic pain, depending on whether the primary lesion or dysfunction is situated in the peripheral or central nervous system. In the periphery, neuropathic pain can result from disease or inflammatory states that affect peripheral nerves (e.g. diabetes mellitus, herpes zoster, HIV) or alternatively due to neuroma formation (amputation, nerve transection), nerve compression (e.g. tumours, entrapment) or other injuries (e.g. nerve crush, trauma). Central pain syndromes, on the other hand, result from alterations in different regions of the brain or the spinal cord. Examples include tumour or trauma affecting particular CNS structures (e.g. brainstem and thalamus) or spinal cord injury. Both the symptoms and origins of neuropathic pain are extremely diverse. Due to this variability, neuropathic pain syndromes are often difficult to treat. Some of the clinical symptoms associated with this condition include spontaneous pain, tactile allodynia (touch-evoked pain), hyperalgesia (enhanced responses to a painful stimulus) and sensory deficits.

Neuropathy elicits a number of changes in nerves, in terms of activity, properties and transmitter content. The recent advent of a number of animal models of neuropathic pain states has facilitated understanding of the peripheral mechanisms involved. Damaged nerves may start to generate ongoing ectopic activity due to the accumulation and clustering of sodium channels around the damaged axons and there is also evidence that mechanoreceptors become highly sensitive to applied stimuli. This aberrant activity can then start to spread rapidly to the cell body in the dorsal root ganglia. Nerve fibres can start to cross-excite each other and the same occurs in the cell bodies.

In addition to changes within the nerve, sympathetic afferents become able to activate sensory afferents via as yet poorly characterised α-adrenoceptors. These interactions between adjacent sensory and autonomic nerve axons and between ganglion cells result in excitation spreading between different nerve fibres. These peripheral ectopic impulses can cause spontaneous pain and prime the spinal cord to exhibit enhanced evoked responses to stimuli, which themselves have greater effects due to increased sensitivity of the peripheral nerves.

This peripheral activity may be a rational basis for the use of systemic local anaesthetics in neuropathic states since ectopic activity in damaged nerves has been shown to be highly sensitive to systemic sodium channel blockers. This too is probably part of the basis for the analgesic effects of established effective anti-convulsants that block sodium channels such as carbamazepine, although central actions are important and may even predominate. The precise actions of excitability blockers therefore remains hazy as does any clear basis for the effectiveness of antidepressants and other adrenergic agents in the treatment of neuropathic pain as both central and peripheral actions, including sympathetic effects are possible.

It has been clearly shown recently that C-fibres can generate action potentials via unique sodium channels with very low TTX sensitivity that are different from those found in other tissues. These channels may become important targets for drugs in neuropathic and other pains since a systemic agent with selectivity for those channels would only block C-fibre activity. However, a complex regulation of these channels after nerve injury makes appraisal of their place in the control of this type of pain difficult — the TTX-resistant channels translocate from the cell bodies of the injured nerves to the site of injury and yet are upregulated in adjacent ganglia. Furthermore, TTX-sensitive channels also upregulate and a novel channel is induced.

CENTRAL EVENTS IN THE TRANSMISSION OF PAIN

SENSORY TRANSMISSION IN THE SPINAL CORD

Morphology of the spinal cord dorsal horn

The spinal cord is arranged in such a way that primary afferents originating from different regions of the body display specific somatotopic organisations upon entry into the cord. Hence in any given segment, there is a definite laterality (ipsilateral/contralateral) and a three-dimensional organisation (rostrocaudal, mediolateral, dorsoventral) of the afferent terminations.

The spinal cord is classically divided into white and grey matter (Fig. 21.2). The grey matter can be organised into ten different laminae, which run continuously along the entire length of the spinal cord. Within a given section of a spinal cord, each lamina can be seen as a layer of functionally distinct cells. Laminae I to VI comprise the dorsal horn, laminae VII to IX the ventral horn, and lamina X is the substantia grisea centralis which surrounds the central canal.

Lamina I

Lamina I forms the outer layer of the dorsal horn and contains the large marginal cells of Waldeyer and plays an important role in nociception since it is the layer in which

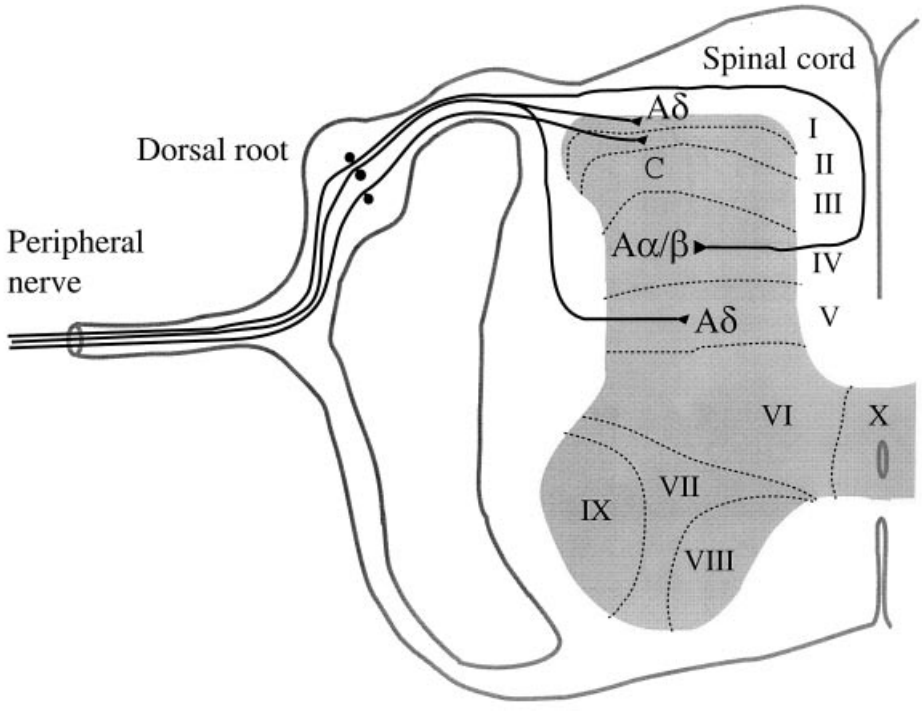

Figure 21.2 The anatomical organisation of the spinal cord, showing the grey and white matter with the laminae terminal zones of the different afferent fibre types

some nociceptive afferents terminate. It contains a number of cell types, including nociceptive-specific neurons, which received Aδ- and C-fibre input, neurons which only respond to innocuous thermal stimuli and wide dynamic range (WDR) neurons. Many marginal cells appear to be projection neurons, which contribute to the lateral spinocervical (SCT), spinoreticular and spinothalamic tracts (STT). The projections also extend to the periaquaductal grey (PAG), parabrachial nucleus and the nucleus submedius.

Lamina II

Lamina II is also known as the substantia gelatinosa (SG) and can be divided into two layers, the outer layer (IIo) and the inner layer (IIi). This layer is densely packed with small neurons and lacks myelinated axons. Neurons with cell bodies in IIi receive inputs from low-threshold mechanoreceptive primary afferents, while those in IIo respond to inputs from high-threshold and thermoreceptive afferents. The intrinsic cells which comprise the SG are predominantly stalk and islet cells. Stalk cells are found located in lamina IIo, particularly on the border of lamina I, and most of their axons have ramifications in lamina I although some also project to deeper layers. These cells are thought to predominantly relay excitatory transmission. Islet cells, on the other hand, are located in IIi and have been demonstrated to contain the inhibitory neurotransmitters, γ-aminobutyric acid (GABA), glycine and enkephalins in their dendrites. Hence these cells have been proposed to be inhibitory interneurons.

Lamina III

The cell bodies in lamina III are generally larger and less densely packed than those in the substantia gelatinosa. The main cell type of lamina III includes projection cells, which contribute to the SCT and postsynaptic dorsal column (PSDC). The dendrites of SCT cells are confined to lamina III and do not reach laminae I and IIo. However, those of PSDC are not flattened in the mediolateral plane and extend to laminae I and II, thus forming monosynaptic connections with small primary afferent fibres.

Laminae IV to VI

Lamina IV is composed of heterogeneous sized cells and is less densely packed than lamina III due to the number of nerve axons passing in this layer. At least three types of neurons have been identified in lamina IV, based on different dendritic projection patterns and these include SCT and PSDC cells. Another cell type has been described which has a dendritic pattern similar to SCT and PSDC, but with local axon terminations. Somas of STT cells are also found in lamina IV.

The cells comprising lamina V are more diverse than those of lamina IV and their dendrites extend vertically toward the superficial layers. Cell bodies in lamina V contribute to three projection pathways, the SCT, PSDC and STT. However, the STT cells appear to be predominant in this lamina. Lamina V plays an important role in nociception since it receives both Aδ- and C-fibre inputs. Some cells in lamina V also respond to cutaneous low- and high-threshold mechanical stimuli and receive nociceptive inputs from the viscerae. Many of these neurons also project onto mono-neurons and so act as interneurons in the polysynaptic withdrawal reflex to noxious stimuli.

Lamina VI forms the base of the dorsal horn and can be found only in certain levels of the spinal cord, the cervical and lumbar regions. Few data have been reported on the cell composition of lamina VI. Cells of lamina VI are small compared to those of lamina V and some axons appear to contribute to the STT and SCT pathways.

NEUROTRANSMITTERS AND DRUGS

Nociceptive sensory information arriving from primary afferent fibres enters via the dorsal horn and on entering the spinal cord undergoes considerable convergence and modulation. The spinal cord is an important site at which the various incoming nociceptive signalling systems undergo convergence and modulation and is under ongoing control by peripheral inputs, interneurons and descending controls. One consequence of this modulation is that the relationship between stimulus and response to pain is not always straightforward. The response of output cells could be greatly altered via the interaction of various neurotransmitter systems in the spinal cord, all of which are subject to plasticity and alterations during pathological conditions.

The arrival of action potentials in the dorsal horn of the spinal cord, carrying the sensory information either from nociceptors in inflammation or generated both from nociceptors and intrinsically after nerve damage, produces a complex response to pain. Densely packed neurons, containing most of the channels, transmitters and receptors found anywhere in the CNS, are present in the zones where the C-fibres terminate

and while excitatory mechanisms are of importance, the role of controlling inhibitory transmitter systems is perhaps paramount.

Since glutamate is the main excitatory neurotransmitter in the CNS it is not unexpected to find that the vast majority of primary afferents synapsing in the dorsal horn of the spinal cord, regardless of whether they are small or large diameter, utilise this transmitter. It has an excitatory effect on a number of receptors found on both postsynaptic spinal neurons, leading to a depolarisation via three distinct receptor subclasses, the α-amino-3-hydroxy 5-methyl-4-isoxazeloproprionic acid (AMPA) receptor, the N-methyl-D-aspartate (NMDA) receptors and the G-protein-linked metabotropic family of receptors. In addition, presynaptic kainate receptors for glutamate have been described in the spinal cord. Most is known about the first two receptors, the AMPA and NMDA receptors, named after chemical analogues of glutamate with selective actions on these sites (see Chapter 11).

Glutamate is released in response to both acute and more persistent noxious stimuli and it is fast AMPA-receptor activation that is responsible for setting the initial baseline level of activity in responses to both noxious inputs and tactile stimuli. However, if a repetitive and high-frequency stimulation of C-fibres occurs there is then an amplification and prolongation of the response of spinal dorsal horn neurons, so-called wind-up (Fig. 21.3). This enhanced activity results from the activation of the NMDA-receptor. If there are only acute or low-frequency noxious or tactile inputs to the spinal cord the activation of the NMDA-receptor is not possible. The reason is that under normal physiological conditions the ion channel of this receptor is blocked by the normal levels of Mg^{2+} found in nervous tissues. This unique Mg^{2+} plug of the channel requires a repeated depolarisation of the membrane to be removed and allows the NMDA receptor-channel to be activated. Here it is likely that the co-release of the peptides such as substance P and CGRP that are found in C-fibres with glutamate is responsible for a prolonged slow depolarisation of the neurons and subsequent removal of the block. Not only do AMPA receptor antagonists have no effect on wind-up but the brief depolarisation produced by this receptor would not be expected to produce any prolonged removal of the block, unlike the long-lasting slow (several seconds) activations caused by peptides. The lack of peptides in large Aβ afferent fibres explains the lack of wind-up after low-threshold stimuli. This NMDA receptor activation has been clearly shown to play a key role in the hyperalgesia and enhancement of pain signalling seen in more persistent pain states including inflammation and neuropathic conditions.

There are a number of antagonists at the multiple regulatory sites found on the NMDA receptor and its channel, including the licensed drugs, ketamine, a potent channel blocker, and the weaker agents, dextromethorphan and memantine. These drugs have been shown to be antinociceptive in a number of animal models of inflammation and nerve damage and there are also data from volunteer and clinical studies to support this. Overall, these studies indicate that it is likely that aberrant peripheral activity is amplified and enhanced by NMDA-receptor-mediated spinal mechanisms in tissue damage and neuropathic pain and that the receptor is critical for both the induction and maintenance of the pain. Thus, therapy after the initiating damage can still be effective. Although there is much good clinical evidence for the effectiveness of agents acting as antagonists at the NMDA-receptor complex, especially ketamine, and although some individual patients get good pain relief in nerve injury situations, the majority cannot achieve complete pain control. This is partly because adequate dosing is prevented by the narrow therapeutic window of the existing drugs.

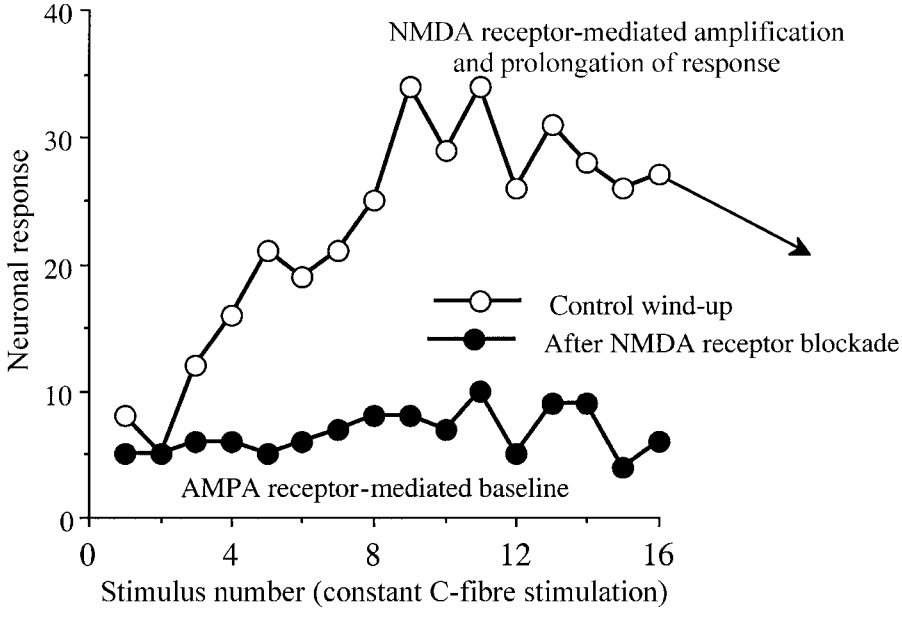

Figure 21.3 Wind-up in a dorsal horn neuron. Note the increased response to a constant peripheral stimulus as the NMDA receptor is activated. (Unpublished data)

Ultimately, the broad use of glutamate receptor/channel antagonists in the treatment of pain will therefore depend on strategies that increase their therapeutic window over existing drugs. These may include drugs acting on subtypes of the receptor (NR2B receptor antagonists are analgesic but side-effects have not been fully evaluated), drugs with different use-dependent block of the channel or more practically, use of low-dose NMDA blockers in combination with another agent.

As neurons become more active, then ion channels, other than sodium channels, open in their membranes. There are a number of voltage-operated calcium channels (see Chapter 3) that are critical for both transmitter release and neuronal excitability. Successful results in animals with agents that block neuronal voltage-sensitive calcium channels would also suggest that there is an increase in central neuronal excitability after both inflammation and nerve damage. N-type channels, blocked by ω-conotoxin, a marine snail toxin, have been shown to play a key role in behavioural allodynia and the neuronal responses to low- and high-threshold natural stimuli after nerve damage, and in the C-fibre-evoked central hyperexcitability that follows inflammation. Blockers of this channel (SNX-111 or ω-conotoxin) are considerably more effective after nerve injury (spinal nerve ligation) and since the channel is voltage operated then these results again suggest increased excitability of the spinal cord after injury. Less is known about P-type channels but ω-agatoxin GVIA, a selective blocker, is effective against persistent inflammatory inputs through central spinal actions. Unfortunately, since calcium channels are extensively distributed in all excitable tissue it is necessary to give blockers used for analgesia by the spinal route.

Gabepentin is an antiepileptic drug that has analgesic activity in neuropathic pain states from varying origins. Two recent randomised controlled trials of gabapentin in

patients, one group with postherpetic neuralgia and another with diabetic neuropathy, concluded that gabapentin was effective in the treatment of these pain states. It has also been reported that gabapentin is effective in pain due to peripheral nerve injury and central lesions, with particular effectiveness on paroxysmal pain and allodynia. How gabapentin works is not clearly established but it is thought the drug may interact with calcium channels in that it becomes attached to the so-called gabapentin-binding protein, itself associated with a subunit of the calcium channel. This action would fit with the evidence that N-type calcium channel blockers are more effective in reducing behavioural and electrophysiological responses to sensory stimuli after both nerve injury and tissue damage, conditions where it appears that N-type calcium channels are upregulated.

The influx of calcium through activation of the NMDA channel and also voltage-operated calcium channels may be a mechanism through which further profound changes in nociceptive processing occur. Rises in internal calcium in neurons is a key means by which genes can be activated. The protooncogene markers *c-fos* and *c-jun* can be observed in dorsal horn neurons only minutes after the application of noxious stimulation, either mechanical or thermal or from tissue damage. The one functional piece of evidence at present for the consequences of gene induction is the increase in the mRNA and dynorphin production in some dorsal horn cells, although the physiological consequences of this are unknown.

A comparatively new putative nociceptive transmitter is the gas nitric oxide (NO), and many studies have provided much indirect evidence for a spinal role of this gas during prolonged nociceptive events. NO therefore appears to have a role during prolonged chronic pain states which have been associated with NMDA-receptor activation. It has been proposed that NMDA-receptor activation and the associated Ca^{2+} influx results in the generation of NO by activation of the enzyme, nitric oxide synthase (NOS). The NOS antagonist, L-NAME, abolishes hyperalgesia in neuropathic animals, reduces pain-related behaviour after inflammation and blockers of the production of NO prevent wind-up. One proposed action of NO is as a retrograde transmitter feeding back from spinal neurons onto presynaptic sites to further increase transmitter release from C-fibres. The synthesis of inhibitors of the neuronal version of NOS which lack hypertensive effects yet are antinociceptive suggests possible therapeutic uses of NOS inhibitors.

This positive feedback may also be due to the spinal generation of prostanoids, following both NMDA- and substance P-induced activation of neurons. It is now recognised that in addition to the well-documented production of prostaglandins in peripheral tissues there can be central neuronal synthesis, again with calcium being the trigger. It is not yet known how important this central action is to the analgesic effects of systemic NSAIDs but, as mentioned earlier, COX-2 is constitutive in the spinal cord and further upregulated by peripheral inflammation.

There are important inhibitory systems built into the control of events following C-fibre stimulation. Thus, during peripheral noxious stimulation, spinal mechanism, driven by NMDA-receptor-mediated activity, can become active to damp down further neuronal responses, the purine, adenosine (see Chapter 13), appears to be involved in this type of control and has been reported to be effective in humans with neuropathic pain. It is thought that the depolarisations caused by activation of the NMDA receptor increase the metabolic demand on neurons and so ATP utilisation increases. ATP then is metabolised to adenosene and the purine then acts on its inhibitory A_1 receptor in the

spinal cord to reduce further neuronal activity — a negative feedback. Thus there are potential indirect targets for the control of NMDA events. These transmitter systems are summarised in Fig. 21.4.

CENTRAL INHIBITORY SYSTEMS

GABA

γ-Amino butyric acid (GABA) has been firmly established as the major inhibitory neurotransmitter in the central nervous system. The extensive distribution and influence of GABAergic terminals suggests the nervous system operates under considerable restraint, with GABA acting as a tonic controller of excitation. This is also true for the spinal cord where GABA is concentrated in interneurons of the superficial dorsal horn. About one-third of neurons in the superficial spinal cord, the main site of termination of Aδ- and C-fibre afferents, contain GABA. In addition, there is evidence that GABA can co-exist with either glycine, galanin, enkephalin or neuropeptide Y in separate populations of neurons. GABAergic terminals contact more Aδ-fibre terminals than C-fibre terminals, and in support of this anatomical data, the benzodiazepine (Bz), midazolam, has weak depressive effects on C-fibre-evoked responses, but marked effects on Aδ-fibre-evoked responses. In addition, the $GABA_A$ antagonist bicuculline facilitates C-fibre-evoked activity less than the profound potentiation of Aδ-fibre-evoked responses. Both presynaptic and postsynaptic $GABA_A$ receptor-mediated mechanisms are documented in the spinal cord. Several studies have demonstrated Bzs to be analgesic, whereas others have found no antinociceptive properties. In addition, there are contradictory reports of Bzs both potentiating and antagonising morphine analgesia. This diversity of results, however, is the product of many different experimental protocols, models of nociception and routes of administration. In addition, the sedative and myorelaxant effects of these compounds must be considered and these will always limit the usefulness of GABAergic agonists.

In the spinal cord GABA can also activate the G-protein-linked $GABA_B$ receptor, also found pre- and postsynaptically. Baclofen modulation of nociceptive transmission is seen under inflammatory conditions in animals but in humans the drug appears to lack any analgesic effect.

OPIATES

Opiate receptors

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 due to nerve damage where some patients have inadequate control. 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 could be effective in a group of patients with neuropathy. Another study concluded that opioids were entirely ineffective and finally, opioid analgesia was less in

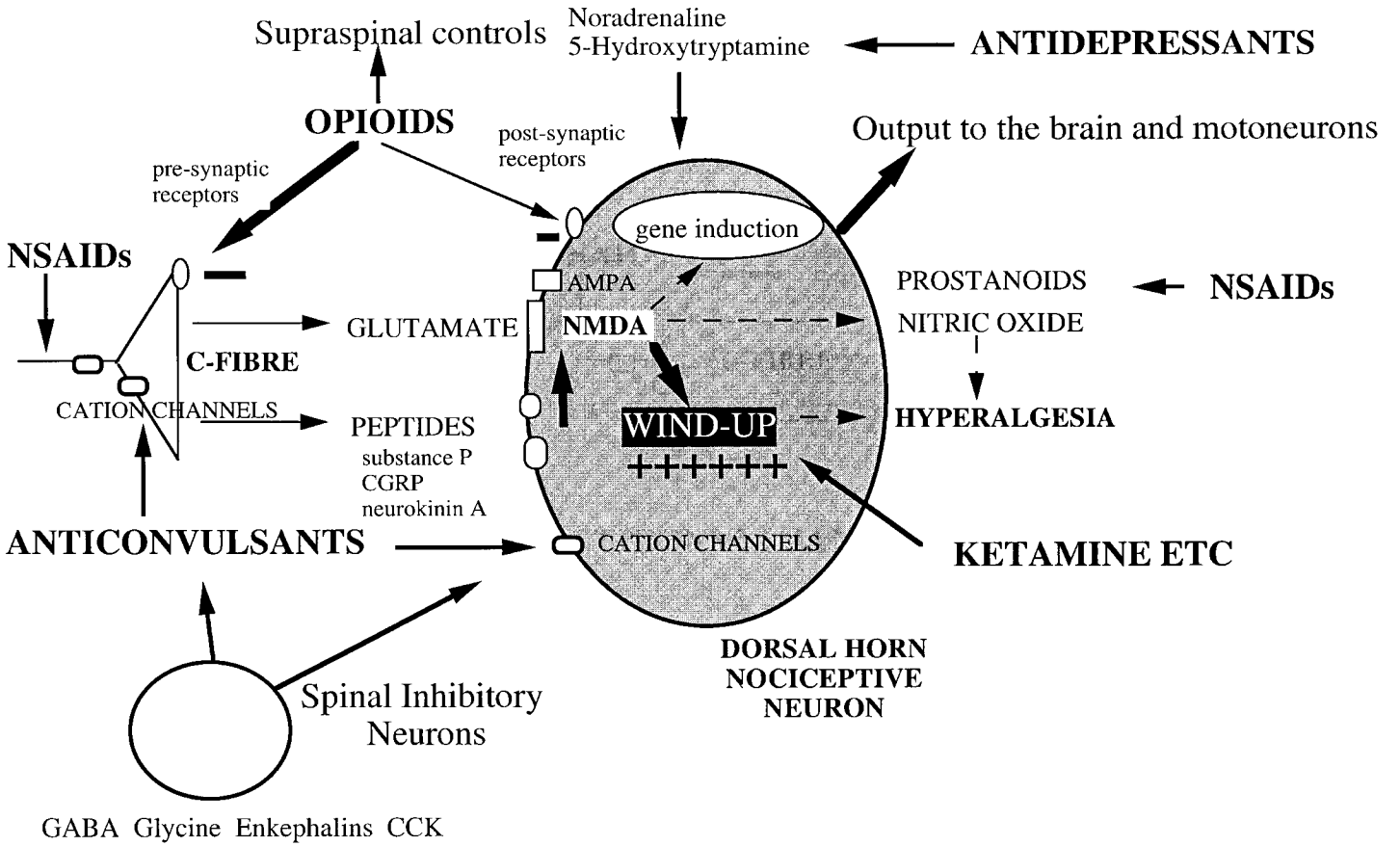

Figure 21.4 An overview of the pharmacological systems involved in the transmission and modulation of pain together with some drugs that act on these systems

neuropathic pain patients as compared to a group with nociceptive pain. Resolution of this problem has important implications yet a similar series of discrepant results can be found in the animal literature.

Following the description and then isolation of opioid receptors, there were three known receptors for the opioids, the mu, delta and kappa opioid receptors, but a novel fourth receptor, the orphan receptor, has been characterised very recently. 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 'anti-opioid' 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 provide 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.

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 (Table 21.2).

The opioid receptors are for the endogenous opioids, peptide transmitters, β-endorphin, endomorphins, enkephalins, dynorphins and nociceptin. Thus all the problems of drugs based on peptides need to be overcome in order for the roles of these

Table 21.2 The four opioid receptors with transmitters and drugs acting on the various receptors together with the effector mechanisms and the effects of receptor activation for each receptor

Receptor	Mu	Delta	Kappa	ORL-1
Endogenous opioid	β-endorphin Endomorphins	Enkephalins	Dynorphins	Nociceptin
Synthetic agonist	Morphine Codeine Fentanyl Pethidine	DSTBULET DPDPE	U50488H Pentazocine Oxycodone?	–
Antagonists	Naloxone Beta FNA	Naloxone Naltrindole	Naloxone Not 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	Hyperpolarisation of neurons, inhibition of neurotransmitter release			
	Analgesia Relief of anxiety Euphoria Nausea Constipation Cough suppression Dependence	Similar to mu but less marked	Analgesia Aversion Diuresis	Analgesia Hyperalgesia

receptors to be elucidated. The use of morphine and naloxone, non-peptides with mu selectivity has been responsible for the wealth of knowledge about the mu receptor but much less is known about the delta and ORL-1 receptors. Kappa opioids have weak actions in many animal studies and also cause aversive effects — clinical studies with these drugs have been discontinued. Side-effects are due to the peripheral and central receptors whereas the analgesic effects are due to the interaction of opioid with central receptors. The degree of analgesia can be limited by the side-effects.

These issues make appraisal of different opioid receptors as a target in the development of opioid analgesics lacking the side-effects of mu-receptor-selective agonists such as morphine rather difficult. Progress has been limited in terms of new synthetic opioids that act on the delta receptor, partly due to the peptide nature of the endogenous opioid transmitters but also poor selectivity of drugs between the mu, delta and kappa receptors. The kappa receptor, where synthetic drugs have been produced, does not appear to be a viable analgesic target at present due to central and peripheral side-effects but delta receptor-selective compounds appear to have limited analgesic effects in primate behavioural studies.

There is little new with regard to the mu receptor, the main target for opioid drugs. The receptor is remarkably similar in structure and function in all species studied so animal studies will be good predictors for clinical applications. Although there have been suggestions of subtypes of the receptor, the cloned mu receptors have all been identical.

SPINAL OPIATE ANALGESIA

Opioids act in the brain and within the dorsal horn of the spinal cord, where their actions are better understood. The actions of opioids important for analgesia and their side-effects involve pre- and postsynaptic effects: (1) reduced transmitter release from nerve terminals so that neurons are less excited by excitatory transmitters, and (2) direct inhibitions of neuronal firing so that the information flow from the neuron is reduced but also inhibitions of inhibitory neurons leading to disinhibition. This dual action of opioids can result in a total block of sensory inputs as they arrive in the spinal cord (Fig. 21.5). Thus any new drug would have to equal this dual action in controlling both transmitter release and neuronal firing.

C-fibre stimulation will release a number of transmitters in the spinal cord including substance P, CGRP, glutamate and aspartate. By actions on their receptors the peptides produce slow depolarising responses of dorsal horn neurons which in concert with the fast AMPA and delayed NMDA receptor-mediated depolarisations produced by the excitatory amino-acids activate ascending, local and motoneurons to cause both the sensation of pain and the withdrawal reflex to the stimulus (see Fig. 21.4). There is good reason to believe that the spinal processing of pain is highly plastic and can be altered in different pain states.

The opiate receptors in the spinal cord are predominantly of the mu and delta type and are found in the C-fibre terminal zone (the substantia gelatinosa) in the superficial dorsal horn. Considerable numbers of ORL-1 receptors are also found in this area. 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

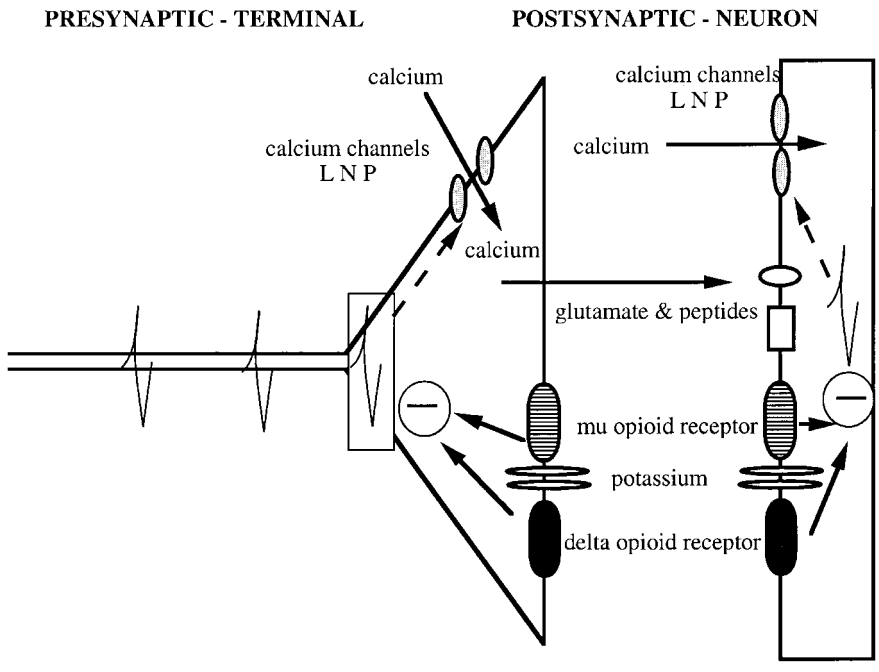

Figure 21.5 Mechanisms of opioid analgesia at the spinal level. Action potentials in nociceptive afferent fibres invade the terminal and by opening calcium channels (L, N and P-type) cause the release of glutamate and peptides that further transmit pain subsequent to activation of their postsynaptic receptors. Presynaptic opioid receptor activation (mu- and delta-mediated effects have been most clearly shown) opens potassium channels which hyperpolarise the terminal, so reducing transmitter release and inhibiting the postsynaptic neuron

release of all the transmitters in the C-fibres. The remaining postsynaptic receptors appear to hyperpolarise the dendrites of projection neurons and interneurons and disinhibit inhibitory interneurons; the net result is further inhibition of the C-fibre-induced activity. 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.

Complete C-fibre inhibitions can be produced under normal conditions but opiates do not always produce a complete analgesia in some clinical situations, especially when the pain arises from nerve damage. Reasons for this are suspected to be excessive NMDA-mediated activity which is hard to inhibit and the mobilisation of cholecystokinin in the spinal cord which can act as a physiological antagonist of opiate actions. The idea that pre-emptive analgesia aids post-operative pain relief by preventing the pain-induced activation of these systems is becoming popular.

SUPRASPINAL OPIATE ANALGESIA

There are other important sites of opiate actions located in the 5-HT and noradrenergic nuclei of the brainstem and midbrain including the raphé nuclei, the periaquaductal

grey matter and the locus coeruleus. Opiate receptors in these zones (mu, delta and kappa) 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 which simply inhibit spinal pain transmission. The relative roles of the 5-HT receptors in the spinal cord are yet unknown but the spinal target for the noradrenaline released from descending pathways is alpha-2 receptors which have similar actions and distribution to the opiate receptors. Sedation and hypotension with alpha-2 agonists presently limit their use as analgesics.

Opioid actions at a number of other supraspinal sites (thalamic levels, the amygdala and the sensory cortex) are likely to be of relevance to analgesia.

SIDE-EFFECTS OF OPIATES

CENTRAL

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. Opiates acting in the brainstem reduce the sensitivity of the respiratory centres to pCO_2 and this is the most common cause of death from overdose with street use of opiates.

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

Sites in the monoamine nuclei such as the well-demonstrated actions of opioids on noradrenergic transmission in the locus coeruleus and enhancing dopamine-release in the ventral tegmental area (again 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. Thus, 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 is rapid to develop and overwhelming. 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 the stimulus produces not only 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.

The relative extent of the unwanted effects caused by selective agonists at the different opioid receptors is of great importance in determining if non-mu opioids will have better spectra of actions as compared to morphine. However, there are good indications that the kappa and delta receptor agonists cause less respiratory depression than mu

opioids. A lack of dependence is also seen with kappa agonists but is accompanied by aversive or non-rewarding effects that limit the usefulness of these agents in humans. The endogenous enkephalins are rapidly degraded. Kelatorphan, an inhibitor of the peptidases which degrade the enkephalins, was thought be a novel route to analgesia by prolonging the duration of their actions. This protection of the enkephalins by the peptidase inhibitors has no dependence liability but as yet no peptidase inhibitor selective for the opioid peptides has been reported in humans.

PERIPHERAL

There are a number of side-effects of opiates that 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 activating a maintained contraction of the smooth muscle of the gut which reduces motility. This diminished propulsion coupled with opiates reducing secretion in the gut underlie the anti-diarrhoeal effect. Opiates contract sphincters throughout the gastrointestinal tract. Although these effects are predominantly peripheral in origin 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.

OPIATE AGONISTS

All clinically used opiates have the same pharmacology since they all act on the mu receptor with the exception of the kappa agonist, pentazocine. Opiates are used to relieve moderate to severe pain whatever the cause (accidents, post-operative pain, cancer, etc.) and are used pre-, intra- and post-operatively. The mu opiates differ only in potency and pharmacokinetics. Examples are:

- Codeine: a weak opiate which is orally effective and is used for mild pains.
- Methadone: long duration and orally effective, thereby useful in weaning off heroin.
- Fentanyl: highly potent but with a short duration of action, used for short analgesia in surgical settings.
- Heroin (diacetylmorphine): a highly lipophilic drug but has very weak or no affinity for opiate receptors. It penetrates the brain rapidly whereupon it is metabolised to morphine which then binds to the mu receptor.
- Tramadol: a weak opioid that also blocks the reuptake of NA and 5-HT — these combined actions synergise to give a good analgesia that lacks some of the typical opioid side-effects.

OPIATE ANTAGONISTS

There are now selective antagonists for all three opiate receptors (see Table 21.2) but with the exception of naloxone they are experimental tools for probing the functional roles of the opiate receptors. Naloxone is a potent competitive antagonist at all three receptors with highest affinity for the mu receptor. It will rapidly reverse all opiate

actions but has a short half-life compared to morphine itself. It is used in cases of overdose, usually to reverse the respiratory depression but with the cost of also reversing the analgesia.

INTERACTIONS WITH OTHER NEUROTRANSMITTERS

Some opioids, such as methadone and ketobemidone, have been reported to bind additionally to NMDA receptors and so may be different in their pharmacological profile. However, it is very unclear that this has any bearing on their effects in patients, especially in cases where morphine effectiveness is reduced, such as in neuropathic pain. In terms of changes in opioid systems relevant to the control of pain after nerve injury, nerve damage can lead to a loss of opioid receptors such as the marked reduction in spinal opioid receptor number seen after nerve section. Although this may be an explanation of the poor effectiveness of opioids in post-amputation pains, less severe nerve damage, where opioids can also lack effectiveness, only slightly alters opioid receptor number. However, the levels of the non-opioid peptide, cholecystokinin (CCK), can determine the potency of morphine and the peptide may, in turn, be upregulated after nerve damage. Activation of the CCK_B receptor mobilises internal calcium whereas opioid receptors hyperpolarise — these actions of CCK thereby physiologically antagonise those of opioids. Antagonists at the CCK_B receptor have been predicted to enhance or restore morphine analgesia after nerve injury but none have been tested in patients as yet.

As discussed earlier, the changes that occur in the periphery and spinal cord after nerve damage can result in overexcitability of spinal neurons so that a hypersensitive state is induced. The N-methyl-D-aspartate (NMDA) receptor is a major candidate in the generation of hyperalgesic states in neuropathic and tissue damage pain states. Quite simply, if neuronal excitability is dramatically increased then opioid controls may be insufficiently efficacious unless doses are increased sufficiently to increase the degree of inhibition required to balance the level of excitation. Here, the combination of a low dose of opioid, increasing inhibition, with a drug that blocks excitation such as ketamine may result in synergistic or additive effects that result in the desired degree of analgesia without adverse side-effects. Other combinations could include the use of anti-convulsants with opioids.

In common with neuropathy, NMDA receptor activation occurs after inflammation but here opioid actions are enhanced since CCK levels decrease. Thus, this augmented opioid actions may counter the increased excitability without the need for large increase in doses of opioid.

BEHAVIOUR AND PAIN

Finally, as outlined above, descending monoamine systems, originating in the midbrain and brainstem that act through the spinal release of noradrenaline and 5-HT, modulate the spinal transmission of pain. $Alpha_2$ adrenoceptors appear to be important in this role but it is unlikely that behavioural effects such as sedation can be separated from the analgesia. Since both noradrenaline and 5-HT are key transmitters in the control of mood and anxiety and yet also participate in the control of sensory events that lead to

pain we can start to see links between state of mind and the level of pain experienced. This may be just one early step in the understanding of some of the chemistry of the psychological aspects of pain. Independently of their effects on mood, antidepressants increase activity in these descending control systems and are used as analgesics in neuropathic pain states.

Individual differences in levels of pain, in the transition from acute to chronic pain, in susceptibility to neuropathic pain after nerve damage and in analgesic effectiveness may have a genetic basis. There is marked variability in animal genetic strains in terms of the sequelae of tissue and nerve damage and even in their responses to morphine. Given the huge range of human phenotypes, this may indicate important individual differences in susceptibility to pain and analgesia but we have no way of monitoring this possibility.

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