

## Spinal cord pharmacology of pain

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The transmission of pain from peripheral tissues through the spinal cord to the higher centres of the brain is clearly not a passive simple process using exclusive pathways. Rather, circuitry within the spinal cord has the potential to alter, dramatically, the relation between the stimulus and the response to pain in an individual. Thus an interplay between spinal neuronal systems, both excitatory and inhibitory, will determine the messages delivered to higher levels of the central nervous system. The incoming messages may be attenuated or enhanced, changes which may be determined by the particular circumstances. The latter state, termed central hypersensitivity [61], whereby low levels of afferent activity are amplified by spinal pharmacological mechanisms has attracted much attention [13, 15]. However, additionally, inhibitory controls are subject to alteration so that opioid sensitivity in different pain states is not fixed [14]. This plasticity, the capacity for transmission in nociceptive systems to change, can be induced over very short time courses. Recent research on the pharmacology of nociception has started to shed some well-needed light on this rapid plasticity which could have profound consequences for the pharmacological treatment of pain [8, 13, 15, 23, 24, 35, 36, 41, 62].

The pharmacology of the sensory neurones in the dorsal horn of the spinal cord is complex, so much so that most of the candidate neurotransmitters and their receptors found in the CNS are also found here [4, 32]. The transmitters are derived from either the afferent fibres, intrinsic neurones or descending fibres. The majority of the transmitters and receptors are concentrated in the substantia gelatinosa, one of the densest neuronal areas in the CNS and crucial for the reception and modulation of nociceptive messages transmitted via the peripheral fibres [4]. Nociceptive C-fibres terminate in the outer lamina 1 and the underlying substantia gelatinosa, whereas the large tactile fibres terminate in deeper laminae. However, in addition to the lamina 1 cells which send long ascending axons to the brain, deep dorsal horn cells also give rise to ascending axons and respond to C-fibre stimulation. In the case of these deep cells the C-fibre input may be relayed via

interneurones or arrive on the dendrites of the cells which pass vertically into the gelatinosa. Low threshold inputs also arrive on these cells. Considerable convergence and modulation of the responses of these deep cells can therefore result from activation of different neuronal systems.

The first study to address central spinal hypersensitivity showed that brief activation of C-fibres could result in an marked and prolonged increase in the flexion withdrawal reflex in spinal-decerebrate rats [61]. It was also known that repeated constant C-fibre stimuli could induce the phenomenon of wind-up whereby the responses of the deep dorsal horn neurones increased dramatically despite a steady input into the spinal cord [12, 13, 16, 18]. Wind-up needs a certain frequency of stimulation to produce its effects but when produced can augment responses of dorsal horn neurones by up to 20-fold in amplitude and prolong responses even after the cessation of the peripheral input. It is therefore likely that wind-up-like events underlie central hypersensitivity.

At peripheral levels most of the nociceptive signalling of thermal and mechanical pain arises from the activation of polymodal nociceptors which are innervated by C-fibres. The acute application of these modalities of stimuli results in a good relation between the stimulus and the response since the stimulus directly activates nociceptors which in turn activate simple spinal systems. However, in the presence of tissue damage, these fibres now respond to locally generated chemical stimuli and become sensitized to chemical, thermal and mechanical stimuli. The effects of newly discovered peripheral mediators including the cytokines, nerve growth factors and catecholamines from the sympathetic nervous system, in addition to the longer established mediators such as bradykinin, 5-HT and prostanooids, means that the complexity of transmission at the peripheral level leading to hyperalgesia is greater than ever suspected [22, 23].

The existence of peripheral hyperalgesia has a bearing on the induction of central hypersensitivity in the spinal cord. The induction and the maintenance of these excitatory events will be enhanced in inflammatory states where the increased activity from the afferents will facilitate spinal excitation. By contrast, in neuropathic states the central hyper-

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Pain, pharmacology. Spinal cord. Hormones, somatostatin. Analgesic, substance P. Protein, amino acid. Analgesics opioid.

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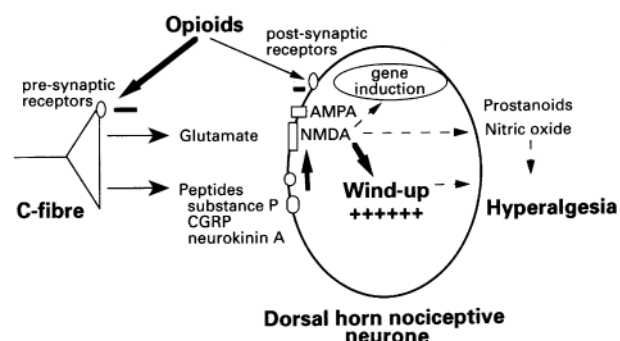
algnesia is likely also to result from the lifting of or loss of inhibitory controls [63]. The pharmacological bases for central alterations will be considered in the following sections.

### Spinal transmission of pain

There is considerable evidence for the involvement of the excitatory amino acids, glutamate and aspartate, and a number of peptides in nociceptive transmission in the dorsal horn of the spinal cord [2, 4, 23, 30]. The peptides implicated in nociception consist of the tachykinin family of peptides, calcitonin gene-related peptide (CGRP), somatostatin, vasoactive intestinal polypeptide, galanin, bombesin and neurotensin. All of these have been shown to be present in the afferent fibres and to be released after noxious stimulation (fig. 1); functional roles have been established only for the transmitters where antagonists for their receptors have been produced. These are discussed below.

#### NEUROKININS

Substance P (SP), one of a family of so-called neurokinins, has long been implicated as one of the neurotransmitters involved in nociceptive transmission [32, 43]. Dorsal horn SP has been shown to originate from primary afferent fibres and intrinsic neurones together with a contribution from descending fibres. Currently there are three subclasses of neurokinin or tachykinin receptors: neurokinin-1, neurokinin-2, neurokinin-3. SP has been shown to be the preferred tachykinin at the neurokinin-1 receptor. The neurokinin receptors have been shown to be postsynaptic to the afferent fibre terminals, located in laminae I, II and X of the dorsal horn of the spinal cord [43]. The release of SP into the dorsal horn by peripheral noxious stimuli has been shown in a number of studies [25]. Interestingly, the release of both substance P and the related peptide, neurokinin A, is increased after peripheral inflammation. Neurokinin A release into the cord can be substantial such that most of the dorsal horn can be reached by peptide. Antagonists at the tachykinin receptors are as yet not fully



**Figure 1** A schematic diagram illustrating the release of the excitatory transmitters from C-fibres and the subsequent effects on a dorsal horn nociceptive neurone. The predominant pre-synaptic action of opioids (reducing the release of these transmitters) and the post-synaptic action (reducing neuronal activity) are shown.

characterized but indications suggest that the NK1 and 2 receptors may have roles not in acute pain but in central states of hypersensitivity [6, 65, 69]. There is evidence that these receptors contribute to afferent-produced increases in excitability of the spinal cord, such as that produced by inflammation since the peripheral events will augment the spinal release of these peptides [32, 49].

#### CALCITONIN GENE-RELATED PEPTIDE

This primary afferent peptide is known to be released by noxious stimuli and to excite dorsal horn neurones but the lack of antagonists for the receptor(s) means that its role in pain processing is unknown. However, the presence of calcitonin gene-related peptide (CGRP) extends the release zone within the spinal cord for substance P which will contribute to increased excitability [45].

#### SOMATOSTATIN

Somatostatin is present in small diameter cells in the dorsal root ganglion and afferent terminals in the substantia gelatinosa of the spinal cord. Noxious thermal stimulation has been shown to increase the release of somatostatin within the dorsal horn of the spinal cord and application of somatostatin results in the hyperpolarization of dorsal horn neurones and a reduction in spontaneous firing. This suggests somatostatin has an inhibitory role in the dorsal horn, making the peptide the only potential primary afferent inhibitory transmitter. However, since there is behavioural evidence that the spinal application of the peptide can result in motor dysfunction and paralysis at doses just above those that produce antinociception, the potential of this peptide as an analgesic needs to be assessed with care [38].

#### GALANIN

Galanin is a putative inhibitory peptide which is co-localized with SP and CGRP in a large proportion of primary afferents. Studies of thermal nociception have indicated galanin has antinociceptive effects, but there is also evidence that galanin has pronociceptive effects [23]. Further studies of the role of galanin during nociceptive transmission and the development of selective antagonists are necessary for the further understanding of the role of this peptide during nociceptive transmission.

#### EXCITATORY AMINO ACIDS

There are considerable amounts of glutamate in the spinal cord, originating from myelinated and unmyelinated primary afferent fibres in addition to intrinsic interneurons and projection neurones [2, 4, 30]. The actions of the excitatory amino acids have been extensively shown to be mediated via the N-methyl-D-aspartate (NMDA) receptor and non-NMDA receptors. The latter group consists of three receptors, the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), the metabotropic and the kainate. Antagonists selective for all these

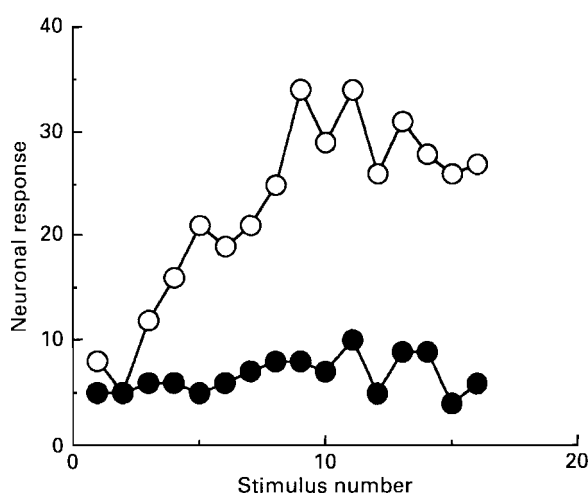


Figure 2 An example of wind-up in a dorsal horn nociceptive neurone from a rat under halothane anaesthesia. A number of repeated identical C-fibre stimuli are given and the response of the neurone is measured. In the control (○) the response starts to increase after the first few stimuli and ends up at a much higher level. Note how block of the NMDA receptor (●) prevents the neurone from exhibiting wind-up and so the response to the stimulus remains constant.

receptors are shedding light on their functional roles in pain processes although at present little is known about the latter two receptors.

The recent finding of considerable numbers of peripheral sensory fibres containing glutamate and subsequently aspartate and the observation that 90 % of substance P containing fibres also contained glutamate is of considerable interest [2]. This coexistence would make it highly likely that in addition to any glutamate released from intrinsic neurones a noxious stimulus would induce a release of both peptides and excitatory amino acids from the afferent fibres. Interest has centred on the involvement of excitatory amino acids especially their actions via the NMDA receptor complex in the post-synaptic events in the spinal cord [13, 16, 30]. There are large numbers of NMDA receptors in the spinal cord of a number of species including humans.

The NMDA receptor has been implicated in a number of long-term events in the CNS such as in long-term potentiation in the hippocampus, in synaptic plasticity in the visual cortex, epileptic activity and in sustained motor activity [9, 10, 30]. *In vitro* studies have shown that both A $\beta$  and C-fibre activation increase aspartate and glutamate outflow at the level of the spinal cord [31]. Activity in the former low threshold fibres appears to activate normally only the AMPA receptor which leads to a brief neuronal firing. Acute painful stimuli also release glutamate which acts on the AMPA receptor to produce short-lasting excitations [15, 21]. The conditions needed for NMDA-receptor activation are much more complex and only seem to be achieved by repeated C-fibre activity [16, 18]. Activation of the NMDA receptor requires not just the release of glutamate and its binding to the receptor but also the presence of glycine and the means to remove the physiological levels of Mg<sup>2+</sup> that normally block the channel. This channel block means that even though glutamate is binding to the NMDA receptor it

cannot activate the neurone since no ion flow can occur. The block can only be removed by sufficient depolarization of the membrane and it is very likely that this is produced by the tachykinins co-released with glutamate from the C-fibres. By acting on the neurokinin receptors, the peptides produce a slow summating depolarization which releases the NMDA channel block [16, 57]. Once the channel is open a massive depolarization of the neurone results from the fluxes of calcium into the cell. This causes a delayed sudden increase in activity, the wind-up, an example of which is shown in figure 2. So if a C-fibre stimulus is maintained and/or its frequency or intensity is sufficient the NMDA receptor will become activated and the resultant amplification and prolongation of the response seems to underlie many forms of central hyperalgesia [8, 18, 23, 24, 35, 37, 41, 62].

The first direct evidence for the involvement of the NMDA receptor and wind-up in the responses of cells to prolonged stimuli was the evidence that the responses of dorsal horn cells to the peripheral injection of formalin which induces a persistent inflammation, was reduced but not abolished by NMDA-receptor antagonists, glycine-site antagonism and channel blockers [29]. Both the behavioural responses and dorsal horn neuronal responses to formalin consist of an early acute response probably the result of a direct effect of the chemical on the peripheral nociceptive endings followed by a silent period and then a second phase which occurs 15 min later. This second prolonged phase is the result of peripheral inflammatory mediators such as prostaglandins and bradykinin activating C-fibres and subsequently dorsal horn nociceptive neurones. Only the second phase is sensitive to NMDA block, indicating that prolonged inflammatory pain can be distinguished from acute pain by sensitivity of the former to NMDA antagonism [29]. Similar events have subsequently been seen in other models of inflammation [46]. The hypersensitive withdrawal reflex produced by C-fibre stimulation, the original demonstration of central hypersensitivity, has now been shown to be NMDA mediated [64]. Furthermore both the induction and the maintenance of the neuronal responses are dependent on NMDA processes since both pretreatment and application of NMDA antagonists during the enhanced responses are equally effective. Augmented responses to pinch are produced by hindlimb ischaemia [48] and here again the potentiated responses but not the baseline responses are NMDA-receptor mediated. Bladder inflammation enhances nociception, again via NMDA-induced events [35]. Many of these sorts of experiments have been done in intact animals under full general anaesthesia, and it is clear that these events are likely to occur during surgical procedures in humans, even in the presence of general anaesthetic. It is therefore highly likely that post-operative pain, at least in part, results from NMDA and other events occurring during the operative procedures.

Recently, the role of the NMDA receptor in neuropathic pain models in animals has been investi-

gated. Again, the use of antagonists at the receptor has shown that the hyperalgesia to certain modalities of stimulation, the spontaneous pain and some forms of allodynia are mediated by the receptor. The NMDA receptor is responsible for the induction, the setting up of the enhanced response and its subsequent maintenance for prolonged periods of time [34, 41, 47, 55]. In many cases, not only is spinal NMDA-receptor antagonism, at any stage, effective against the central hypersensitivity but peripheral local anaesthetic block of the afferent barrage interrupts the spinal NMDA-mediated neuronal responses to inflammation [20]. A recent clinical study of disordered central processing in sympathetic dystrophy has also shown that interruption of the peripheral drive with local anaesthetic interrupts all symptoms [28]. Thus here is a system that requires a level of peripheral afferent input arriving in the spinal cord which is then amplified and prolonged by central processes with the NMDA receptor playing a key role.

Since the NMDA systems seem implicated in pathological pain states rather than in acute physiological pain their use may aid the treatment of difficult clinical pain. Ketamine and dextromethorphan are used clinically as an anaesthetic/analgesic and as an antitussive agent, respectively, and both have been shown to be effective NMDA channel blockers [44]. Ketamine blocks the NMDA channel at subanaesthetic doses. These two drugs have been used to treat opioid-insensitive neuropathic and cancer pains in humans and evidence is accumulating to support the ideas that have arisen from the animal studies. Thus wind-up in human psychophysical studies, painful symptoms of post-herpetic neuralgia and intractable cancer pain have been reported to be reduced or abolished by these drugs [26, 42]. NMDA antagonists have the potential not to abolish pain, but to prevent or block central hypersensitive states. Further studies will be needed before the potential of manipulation of the excitatory peptides is known.

NMDA activation may be a site through which further profound changes in nociceptive processing occur. The influx of calcium into neurones through the NMDA channel may be one means by which genes can be activated [24]. It is well established that noxious stimuli can produce gene induction in spinal neurones [60]; the physiological consequences are still poorly understood but are dealt with in more detail by Hunt [60].

#### NITRIC OXIDE AND PROSTANOIDS

A comparatively new putative nociceptive transmitter is nitric oxide (NO) and many studies have provided much indirect evidence for a spinal role of this gas during prolonged nociceptive transmission [36]. NO appears to have a role during prolonged chronic pain states which are associated with NMDA-receptor activation. It has been proposed that NMDA-receptor activation and the associated  $\text{Ca}^{2+}$  influx results in the generation of NO by activation of the enzyme, nitric oxide synthase (NOS). The NOS antagonist, L-NAME abolishes

facilitated reflexes, inhibits thermal hyperalgesia in neuropathic animals and the response of single dorsal horn neurones to a peripheral injection of formalin [36]. The synthesis of inhibitors of NOS which lack hypertensive effects yet are antinociceptive suggests possible therapeutic uses of NOS inhibitors [39]. One proposed action of NO is as a retrograde transmitter feeding back from spinal neurones onto pre-synaptic sites to further increase transmitter release [50].

This positive feedback may be also due to the spinal generation of prostanoids, following both NMDA and substance P-induced activation of neurones. It is now recognized that in addition to the well-documented production of prostaglanins in peripheral tissues there can be central neuronal synthesis. Correspondingly, the spinal application of non-steroidal anti-inflammatory drugs (NSAID) can be shown to reduce hyperalgesia. It is not yet known how important this central action is to the analgesic effects of systemic NSAID [33].

There will probably be marked increases in incoming nociceptive messages in the inflammatory models owing to effects of the peripheral mediators, growth factors, etc., acting to sensitize and activate afferents and upregulate the production of the peptides transmitters. This increased afferent barrage will elicit a greater than normal level and spread of release of peptides and excitatory amino acids in the spinal cord which will render the NMDA receptor more easily activated. However, in neuropathic states despite ectopic activity within the nerve [11] and sympathetic influences there is likely to be less afferent activity than in inflammation although NMDA-mediated hyperalgesia is apparent in both pain states. There may be reduced spinal inhibitions and rearrangement of connections resulting from the peripheral nerve damage; these alterations may facilitate NMDA-receptor activation [63].

#### Inhibitory controls

The role of spinal inhibitory systems in the control of central hypersensitivity is important and allodynia can be produced by pathological or pharmacological interference with spinal GABA or glycine. The resultant touch-evoked responses are NMDA-dependent showing that lifting of inhibitions controlling this receptor in otherwise normal animals causes allodynia [67]. This suggests that some of the consequences of neuropathic pain may be due to failure of spinal inhibitions. The converse is seen in inflammation where there is an upregulation of spinal GABA as a consequence of the peripheral inflammation. Whether GABA is a viable target remains to be determined but there have been several advances in the pharmacology of the major spinal inhibitory system, namely the opioids.

#### OPIOID SYSTEMS

Opioid receptors in the spinal cord are a key site in the production of analgesia, as demonstrated by opioid inhibition of nociceptive neurones in spinal animals, direct analgesia following epidural and intrathecal opioids in animals and then subsequently

in humans [17]. There have been considerable efforts 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.

Morphine acts on the mu receptor [40], one of the three opioid receptors—mu, delta and kappa. The highest concentrations of opioid receptors in the spinal cord are around the C-fibre terminal zones in lamina 1 and the substantia gelatinosa with lower concentrations found in deeper layers. Estimates suggest that the mu receptor forms 70 %, the delta receptor 24 % and the kappa receptor 6 % of the total opioid sites in the rat spinal cord [3]. It has been suggested that there are more kappa receptors in the mouse and guineapig spinal cord but these studies, in species other than the rat, have not been carried out with the most selective ligands for the receptors and so may not represent the true relative distribution of the receptors. We still lack systematic quantitative studies in a number of species on the relative distribution of the receptors at a variety of CNS sites. The recent cloning of the opioid receptors will provide unequivocal probes for the receptors and facilitate this task. Importantly, molecular biology has shown there are very close similarities between the opioid receptors in humans and laboratory animals [56].

Cutting the dorsal roots will lead to degeneration of the primary afferents and consequently a loss of opioid receptors located on the C-fibres. By this means, the relative numbers of pre- and post-synaptic receptors can be calculated. The proportions of presynaptic sites in the spinal cord varies for the three opioid receptors, but over 70 % of the total mu-receptor sites are on the afferent terminals, showing that the pre-synaptic sites on the peripheral nociceptive fibres predominate [3]. Presynaptic actions of mu and delta agonists, causing a reduced release of the primary afferent transmitters present in C-fibres, is produced by the receptors hyperpolarizing the terminals via the opening of potassium channels. Evidence for this pre-synaptic action of opioids comes from studies of opioid inhibition of C-fibre-evoked release of transmitters (substance P and glutamate) and from *in vitro* and *in vivo* electrophysiological studies [4, 17, 31]. The location of the pre-synaptic opioid receptors on C but not large A-fibre terminals allows for the observed selective effects of spinal opioids on noxious evoked activity [13]. The consequences of activation of the post-synaptic opioid receptors is more difficult to interpret since any direct hyperpolarization of a neurone could inhibit all responses of the cell, including that due to the innocuous inputs onto deep spinal cells. It is believed that many of the post-synaptic opioid receptors are located on nociceptive circuitry such as interneurons or on the dendrites of the deep cells penetrating into the C-fibre terminal zone; inhibitory effects here would also be selective. Whatever the case these different mechanisms will have overall

similar final effects in reducing activity in nociceptive pathways [17]. The pre- and post-synaptic target sites for opioids are shown in figure 1.

Nerve section will lead to a loss of all the pre-synaptic 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 post-synaptic actions require higher doses of morphine than the pre-synaptic effects based on comparative studies in animals with and without the pre-synaptic sites [3]. Consequently, if the loss of the pre-synaptic 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. There are now a number of clinical studies which have demonstrated this action.

Functional studies with antagonists and probes directed at the opioid receptors have demonstrated the independence of mu, delta and kappa receptors at the spinal level and elsewhere in the brain [17]. The analgesic effects following activation of non-mu receptors indicate that there is potential for opioid analgesics which are delta or kappa agonists [54]. Experience with kappa opioids, with dynorphin being the endogenous opioid, has been relatively disappointing but delta opioid receptor agonists may have good potential as analgesics with reduced side effect profiles when compared with morphine [5]. In general, no matter the modality of test of nociception in animals, mu opioids such as morphine have been shown to be effective. The exception is in models of neuropathic pain states, whether the pathology is central or peripheral, where reduced effects of mu opioids are observed in animals and humans [17]. By contrast, the same mu opioids have enhanced effectiveness in models of inflammation [15, 53]. The spinal pharmacological substrates for plasticity in opioid actions will now be discussed. These are factors which can be concurrent with the influence of receptor loss in nerve damage and the peripheral opioid actions seen in inflammation discussed previously.

### Plasticity in opioid controls

First, the ability of a given dose of opioid to inhibit pain will depend on the intensity of the stimulus and the level of activity in the excitatory systems. The level of neuronal activity produced by NMDA receptor activation is relevant to this point. Wind-up is less opioid sensitive than steady responses of cells which do not exhibit wind-up [13]. This can also be observed with the NMDA-mediated formalin response and in some measures of hyperalgesia in

neuropathic models [16, 17]. There is a marked difference between the effects of opioids and NMDA antagonists on wind-up. Since opioids reduce the release of primary afferent transmitters via inhibitory pre-synaptic opioid receptors on C-fibre terminals morphine will reduce or block the C-fibre inputs onto the dorsal horn nociceptive neurones. However, unless the dose is sufficient to completely block all transmitter release wind-up breaks through the inhibitions so that opioids delay the onset of wind-up [13]. By contrast, NMDA antagonists have no effect on the inputs onto the cells but abolish wind-up so converting the potentiated response to a steady response [12]. As a consequence of these different actions of the two agents, the combination of threshold doses of morphine combined with NMDA antagonists elicits marked inhibitions of nociceptive responses and can restore morphine effectiveness in some neuropathic models [7, 70]. Furthermore, spinal local anaesthetics will also synergize with morphine, partly as a result of the ability of local anaesthetics to reduce excitability and therefore, indirectly, NMDA-mediated activity [27].

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 [1, 52]. This peptide which is found in intrinsic spinal neurones in normal animals is upregulated in the afferent fibres after nerve damage [66]. 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 mu opioid analgesia. The upregulation of CCK in neuropathic models is responsible for the reduced opioid actions whereas in inflammation, decreased concentration of the peptide is a major factor in the enhanced opioid actions seen at the spinal level [53, 58]. There is further evidence that CCK also acts supraspinally to reduce mu 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 in other conditions [52, 71]. 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 [59].

The descending noradrenergic controls from the brainstem and midbrain is another pharmacological system which can act both to control nociception and be manipulated to change opioid analgesia. The spinal receptor target for the pathways is the  $\alpha_2$  adrenoceptor [19, 51]. Agonists at this receptor, such as clonidine, produce mild antinociception and potentiate the actions of morphine. More potent and selective agents such as dexmedetomidine are far more effective but have not been fully tested in humans. Increases in descending noradrenergic

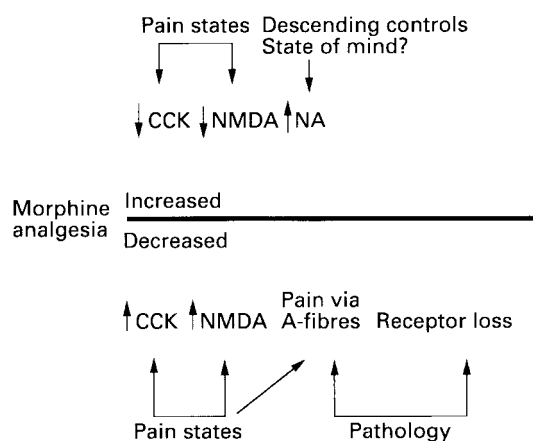


Figure 3 An overview of the influences on the level of morphine analgesia, showing how increases and decreases in analgesic effectiveness can be produced by pathology, transmitter systems, or both.

controls accompany inflammation and are likely to attenuate spinal nociception although CCK is far more important than noradrenaline in the accompanying increases in morphine analgesia seen in these models. The problems of sedation and hypotension seen with  $\alpha_2$  adrenoceptor agonists may be avoided by the production of drugs selective for the subtypes of the  $\alpha_2$  adrenoceptor. Very little is known regarding the roles of descending 5-HT pathways but the remarkable number of receptors for this transmitter may allow selective effects on nociception to be produced [4].

A summary of the factors that can influence opioid analgesia is given in figure 3.

## Conclusions

The past few years have seen remarkable increases in knowledge of the pharmacological systems operating in the spinal cord in different pain states. The concepts of central hypersensitivity and plasticity have had major implications. We now have a much better understanding of the events underlying neuropathic and inflammatory pain; in addition to excitatory processes leading to pain transmission, the induction of compensatory inhibitions in the latter case contrasts with the likely failure of spinal controls in neurogenic pains. Knowledge of pharmacological plasticity has produced leads for the pharmaceutical industry in the development of novel analgesics with actions as antagonists of the neurokinin and NMDA receptors, inhibitors of nitric oxide synthase, and the possibility of new delta opioids,  $\alpha_2$  adrenoceptor agonists and CCK receptor antagonists. In addition, the view of the pharmacology of spinal pain transmission and modulation not as a fixed system but as a plastic network has implications for the current clinical strategies for pain relief. This recent knowledge allows for the rational use of NMDA antagonists such as ketamine in particular pain states. The plasticity in opioid controls illustrates the advantages of the combination of opioids with local anaesthetics,  $\alpha_2$  agonists and NMDA antagonists where reducing excitability or enhancing inhibitions improves opioid efficacy [19, 68].

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## References

1. Baber NS, Dourish CT, Hill DR. The role of CCK, caerulein, and CCK antagonists in nociception. *Pain* 1989; **39**: 307–328.
2. Battaglia G, Rustioni A. Coexistence of glutamate and substance P in dorsal root ganglion cells of the rat and monkey. *Journal of Comparative Neurology* 1988; **277**: 302–312.
3. Besse D, Lombard MC, Zakac JM, Roques BP, Besson JM. Pre- and postsynaptic distribution of mu, delta and kappa opioid receptors in the superficial layers of the cervical dorsal horn of the rat spinal cord. *Brain Research* 1990; **521**: 15–22.
4. Besson J-M, Chaouch A. Peripheral and spinal mechanisms of nociception. *Physiology Reviews* 1987; **67**: 67–186.
5. Calderon SN, Rothman RB, Porreca F, Flippen-Anderson JL, McNutt RW, Xu H, Smith LE, Bilsky EJ, Davis P, Rice KC. Probes for narcotic receptor mediated phenomena. 19 1 synthesis of (+)-4-[aR]-a-((2S,5R)-4-allyl-2-5-dimethyl-1-piperazinyl-0-3-methoxy)-N,N-dibethylbenz amide (SNC80): a highly selective nonpeptide d opioid receptor agonist. *Journal of Medicinal Chemistry* 1994; **37**: 2125–2128.
6. Chapman V, Dickenson AH. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. *Brain Research* 1992; **573**: 321–323.
7. Chapman V, Dickenson AH. The effect of intrathecal administration of RP 67580, a potent neurokinin 1 antagonist on nociceptive transmission in the rat spinal cord. *Neuroscience Letters* 1993; **157**: 149–152.
- 8.Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central hypersensitivity to pathological pain: review of clinical and experimental evidence. *Pain* 1993; **52**: 259–285.
9. Collingridge G, Singer W. Excitatory amino acid receptors and synaptic plasticity. *Trends in Pharmacological Sciences* 1990; **11**: 290–296.
10. Daw NW, Stein PSG, Fox K. The role of NMDA receptors in information processing. *Annual Review of Neuroscience* 1993; **16**: 207–222.
11. Devor M, Wall PD, Catalan N. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction *Pain* 1992; **48**: 261–268.
12. Davies SN, Lodge D. Evidence for involvement of N-methyl-D-aspartate receptors in “Wind-up” of class 2 neurones in the dorsal horn of the rat. *Brain Research* 1987; **424**: 402–406.
13. Dickenson AH. A cure for wind-up: NMDA receptor antagonists as potential analgesics. *Trends in Pharmacological Sciences* 1990; **11**: 307–309.
14. Dickenson AH. Where and how opioids act. In: Gebhart GF, Hammond DL, Jensen T, eds. *Proceedings of the 7th World Congress on Pain, Progress in Pain Research and Management*. Vol. 2. Seattle: IASP Press, 1994; 525–552.
15. Dickenson AH. NMDA receptor antagonists as analgesics. In: Fields HL, Liebeskind JC, eds. *Progress in Pain Research and Management*. Seattle: IASP Press, 1994; 173–187.
16. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep dorsal horn neurones following C-fibre stimulation. *Neuropharmacology* 1978; **26**: 1235–1238.
17. Dickenson AH, Sullivan AF. Electrophysiological studies on the effects of intrathecal morphine on nociceptive neurones in the rat dorsal horn. *Pain* 1986; **24**: 211–222.
18. Dickenson AH, Sullivan AF. Differential effects of excitatory amino-acid antagonists on dorsal horn nociceptive neurones in the rat. *Brain Research* 1990; **506**: 31–39.
19. Dickenson AH, Sullivan AF. Combination therapy in analgesia; seeking synergy. *Current Opinion in Anaesthesiology* 1993; **6**: 861–865.
20. Dickenson AH, Sullivan AF. Peripheral and central modulation of subcutaneous formalin induced activity of rat dorsal horn neurones. *Neuroscience Letters* 1987; **83**: 207–211.
21. Dougherty PM, Palecek J, Paleckova V, Sorkin LS, Willis WD. The role of NMDA and non-NMDA excitatory amino-acid receptors in the excitation of primate spinothalamic tract neurons by mechanical, chemical, thermal and electrical stimuli. *Journal of Neuroscience* 1992; **12**: 3025–3041.
22. Dray A, Perkins MN. Bradykinin and inflammatory pain. *Trends in Neurological Sciences* 1993; **16**: 99–104.
23. Dray A, Urban L, Dickenson AH. Pharmacology of chronic pain. *Trends in Pharmacological Sciences* 1994; **15**: 190–197.
24. Dubner R, Ruda MA. Activity dependent neuronal plasticity following tissue injury and inflammation. *Trends in Neurological Sciences* 1992; **15**: 96–103.
25. Duggan AW, Hendrey IA, Morton CR, Hutchinson WD, Zhao ZO. Cutaneous stimuli releasing immunoreactive substance P in the dorsal horn of the cat. *Brain Research* 1988; **451**: 261–273.
26. Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartate receptor antagonist ketamine: a double blind, cross-over comparison with morphine and placebo. *Pain* 1994; **58**: 347–354.
27. Fraser H, Chapman V, Dickenson AH. Spinal local anaesthetic actions on afferent evoked responses and wind-up nociceptive neurones in the rat spinal cord: combination with morphine produces marked potentiation of antinociception. *Pain* 1992; **49**: 33–41.
28. Gracely R, Lynch SA, Bennett GJ. Painful neuropathy: altered central processing maintained dynamically by peripheral input. *Pain* 1993; **52**: 251–253.
29. Haley JE, Sullivan AF, Dickenson AH. Evidence for spinal N-methyl-D-aspartate receptor involvement in prolonged chemical nociception in the rat. *Brain Research* 1990; **518**: 218–222.
30. Headley PM, Grillner S. Excitatory amino-acids and synaptic transmission: the evidence for a physiological function. *Trends in Pharmacological Sciences* 1990; **11**: 205–211.
31. Kangra I, Randic M. Outflow of endogenous aspartate and glutamate from the rat spinal dorsal horn in vitro by activation of low- and high-threshold primary afferent fibres. Modulation by  $\mu$  opioids. *Brain Research* 1991; **553**: 347–352.
32. Levine JD, Fields HL, Basbaum AI. Peptides and the primary afferent nociceptor. *Journal of Neuroscience* 1993; **13**: 2273–2286.
33. Malmberg AB, Yaksh TL. Antinociceptive effects of spinal nonsteroidal antiinflammatory on the formalin test in the rat. *Journal of Pharmacology and Experimental Therapeutics* 1992; **263**: 136–146.
34. Mao J, Price DD, Hayes RL, Lu J, Mayer DJ, Frank H. Intrathecal treatment with dextrophan or ketamine potently reduces pain-related behaviours in a rat model of peripheral mononeuropathy. *Brain Research* 1993; **605**: 164–168.
35. McMahon SB, Lewin GR, Wall PD. Central excitability triggered by noxious inputs. *Current Opinion in Neurobiology* 1993; **3**: 602–610.
36. McQuay H, Dickenson AH. Implications of central nervous system plasticity for pain management. *Anesthesiology* 1990; **45**: 101–102.
37. Meller ST, Gebhart GF. Nitric oxide (NO) and nociceptive processing in the spinal cord. *Pain* 1993; **52**: 127–136.
38. Mollenholt P, Post C, Rawal N, Freedman J, Hokfelt T, Paulsson I. Antinociceptive and neurotoxic actions of somatostatin in rat spinal cord after intrathecal administration. *Pain* 1988; **32**: 95–105.
39. Moore PK, Wallace P, Gaffen ZA, Hart SL, Babbidge R. Characterisation of the novel nitric oxide synthase inhibitor and nitro imidazole and related indazoles: anti-nociceptive and cardiovascular effects. *British Journal of Pharmacology* 1993; **110**: 219–224.
40. Pasternak GW, Wood PJ. Multiple opioid receptors. *Life Sciences* 1986; **28**: 1889–1893.
41. Price DD, Mao J, Mayer DJ. Central neural mechanisms of normal and abnormal pain states. In: Fields HL, Lebeskind JC, eds. *Progress in Pain Research and Management*. Seattle: IASP Press, 1994; 61–84.
42. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate antagonist dextromethorphan selectively reduces temporal summation of second pain. *Pain* 1994; **59**: 165–174.
43. Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. *Physiological Reviews* 1993; **73**: 229–303.

44. Rogawski MA. Therapeutic potential of excitatory amino-acid antagonists; channel blocks and 2,3-benzodiazepines. *Trends in Pharmacological Sciences* 1993; **14**: 325–331.
45. Schaible HG, Hope PJ, Lang CW, Duggan AW. Calcitonin gene related peptide causes intraspinal spreading of substance P released by peripheral stimulation. *European Journal of Neuroscience* 1992; **4**: 750–757.
46. Schaible HG, Grubb BD, Neugebauer V, Oppmann M. The effects of NMDA antagonists on neuronal activity in cat spinal cord evoked by acute inflammation in the knee joint. *European Journal of Neuroscience* 1991; **3**: 981–991.
47. Seltzer Z, Cohn S, Ginzburg R, Beilin BZ. Modulation of neuropathic pain in rats by spinal disinhibition and NMDA receptor blockade of injury discharge. *Pain* 1991; **45**: 69–76.
48. Sher G, Mitchell D. N-Methyl-D-aspartate receptors mediate responses of rat dorsal horn neurones to hindlimb ischaemia. *Brain Research* 1990; **522**: 55–62.
49. Sluka KA, Dougherty PM, Sorkin LS, Willis WD, Westlund KN. Neural changes in acute arthritis in monkeys. III. Changes in substance P, calcitonin gene-related peptide and glutamate in the dorsal horn of the spinal cord. *Brain Research Reviews* 1992; **17**: 29–38.
50. Sorkin L. NMDA evokes an L-NAME sensitive spinal release of glutamate and citrulline. *NeuroReport* 1993; **4**: 479–482.
51. Stanfa LC, Dickenson AH. Enhanced alpha-2 adrenergic controls and spinal morphine potency in inflammation. *NeuroReport* 1994; **5**: 469–472.
52. Stanfa LC, Dickenson AH, Xu X-J, Wiesenfeld-Hallin Z. Cholecystokinin and morphine analgesia: variations on a theme. *Trends in Pharmacological Sciences* 1994; **15**: 65–66.
53. Stanfa LC, Sullivan AF, Dickenson AH. Alterations in neuronal excitability and the potency of spinal mu, delta and kappa opioids after carrageenan induced inflammation. *Pain* 1992; **50**: 345–354.
54. Sullivan AF, Dickenson AH, Roques BP.  $\delta$ -opioid mediated inhibitions of acute and prolonged noxious-evoked responses in rat dorsal horn neurones. *British Journal of Pharmacology* 1989; **98**: 1039–1049.
55. Tal M, Bennett GJ. Dextrophan relieves neuropathic heat-evoked hyperalgesia in the rat. *Neuroscience Letters* 1993; **151**: 107–110.
56. Uhl GR, Childers S, Pasternak G. An opiate receptor gene family reunion. *Trends in Neurological Sciences* 1994; **17**: 89–93.
57. Urban L, Thompson SWN, Dray A. Modulation of spinal excitability: co-operation between neurokinin and excitatory amino acid neurotransmitters. *Trends in Neurological Sciences* 1994; **17**: 432–438.
58. Wang J, Ren M, Han J. Mobilization of calcium from intracellular stores as one of the mechanisms underlying the antinociceptive effects of cholecystokinin octapeptide. *Peptides* 1992; **13**: 947–951.
59. Wiertelak EP, Maier SF, Watkins LR. Cholecystokinin antianalgesia: safety cues abolish morphine analgesia. *Science* 1992; **256**: 830–833.
60. Wisden W, Errington ML, Williams S, Dunnett SB, Waters C, Ditchcock D, Evan G, Bliss TVP, Hunt SP. Differential expression of immediate early genes in the hippocampus and spinal cord. *Neuron* 1990; **4**: 603–614.
61. Woolf CJ. Evidence for a central component of post-injury pain hypersensitivity. *Nature* 1983; **306**: 686–688.
62. Woolf CJ. A new strategy for the treatment of inflammatory pain. *Drugs* 1994; (Suppl. 5) 1–9.
63. Woolf CJ, Doubell TP. The pathophysiology of chronic pain – increased sensitivity to low threshold A $\beta$ -fibre inputs. *Current Opinion in Neurobiology* 1994; **4**: 525–534.
64. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury hypersensitivity states. *Pain* 1991; **44**: 293–299.
65. Xu XJ, Dalsgaard CJ, Wiesenfeld-Hallin Z. Intrathecal CP-96,345 blocks reflex facilitation induced in rats by substance P and C-fibre conditioning stimulation. *European Journal of Pharmacology* 1992; **216**: 337–344.
66. Xu XJ, Puke MJC, Verge VMK, Wiesenfeld-Hallin Z, Hughes J, Hokfelt T. Up-regulation of cholecystokinin in primary sensory neurons is associated with morphine insensitivity in experimental neuropathic pain in the rat. *Neuroscience Letters* 1993; **152**: 129–132.
67. Yaksh TL. Behavioural and autonomic correlates of the tactile evoked allodynia produced by spinal glycine inhibition: effects of modulatory receptor systems and excitatory amino acid antagonists. *Pain* 1989; **37**: 111–123.
68. Yaksh TL, Malmberg AB. Interaction of spinal modulatory systems. In: Fields HL, Liebeskind JC, eds. *Progress in Pain Research and Management*. Seattle: IASP Press, 1994; 151–171.
69. Yamamoto T, Yaksh TL. Stereospecific effects of a non-peptide NK1 selective antagonist, CP-96,345: antinociception in the absence of motor impairment. *Life Sciences* 1991; **49**: 1955–1963.
70. Yamamoto T, Yaksh TL. Studies on the spinal interaction of morphine and the NMDA antagonist MK-801 on the hyperesthesia observed in a rat model of sciatic mononeuropathy. *Neuroscience Letters* 1992; **135**: 67–70.
71. Zhou Y, Sun Y-H, Zhang Z-W, Han J-S. Increased release of immunoreactive cholecystokinin octapeptide by morphine and potential of  $\mu$ -opioid analgesia by CCK<sub>B</sub> receptor antagonist L-365,260 in rat spinal cord. *European Journal of Pharmacology* 1993; **234**: 147–154.