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REVIEW: PAIN

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Pathophysiology of joint pain

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The diversity of symptoms experienced by patients with musculoskeletal pain is in stark contrast to the relative paucity of effective treatment. The intensity and character of symptoms vary considerably and may be independent of the underlying disease. In some patients, pain may occur in the absence of demonstrable pathology, whereas in others obviously damaged joints may be relatively symptom free.

The past few decades have seen a move away from the concept of a 'fixed' pain pathway towards acceptance of a more flexible system capable of a wide range of responses to varied stimuli. It is now appreciated that tissue injury and inflammation produce prolonged changes in the function and activity of the nervous system. This review will focus first on peripheral events leading to sensitisation and abnormal excitation of sensory nerves, and second on central mechanisms resulting in enhanced transmission in the dorsal horn of the spinal cord and elsewhere. While many aspects of clinical pain remain unclear, the relevance of these mechanisms to symptoms arising as a consequence of musculoskeletal disease will be explored.

Peripheral sensitisation

Pain sensations arising from inflamed or damaged joints are mediated in the first instance by primary sensory (afferent) fibres linking peripheral receptors with second order neurones in the spinal cord. Traditionally, these fibres have been regarded as having relatively fixed or static properties, and the existence of specialised 'nociceptors' that detect tissue damage or potentially injurious stimuli was first postulated by Sherrington in 1900.[1] Single fibre recordings have since confirmed classes of afferent fibre with receptors that respond preferentially to high intensity stimuli and generate pain when stimulated.[2]

It is now reasonably clear that afferent fibres, far from being static as first assumed, are inherently dynamic structures with an ability to vary responses to a broad range of stimuli, including noxious stimuli.[3] There appears to be a critical interaction with the surrounding chemical environment whereby afferent fibres enhance or diminish their capacity to detect and respond to various stimuli. This is well illustrated in the joint, where inflammatory mediators elicit profound changes in the response properties of afferents to movement and other chemical mediators.[4]

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JOINT INNERVATION

Afferent fibres within peripheral nerves fall within three distinct groups: heavily myelinated Aβ (group II) fibres, thinly myelinated Aδ (group III) fibres and unmyelinated C (group IV) fibres.[5] Synovial joints are innervated with all three groups, in addition to unmyelinated sympathetic postganglionic fibres.[6] It is notable that the vast majority of articular fibres are unmyelinated, comprising sensory C fibres and sympathetic efferent fibres in nearly equal numbers.[7] Only 20% of the fibres in a typical articular nerve are myelinated, mainly comprising Aδ fibres, with relatively few of the larger diameter Aβ fibres.[8]

The articular capsule of the joint receives an extensive network of nerve fibres with free, complex, or encapsulated nerve endings. A similar innervation has been found in tendons, ligaments, deep fascia, and periosteum. More recent immunohistochemical studies have shown that normal human synovium is also richly supplied with nerves.[9 10] These include fibres containing substance P and calcitonin gene related peptide (CGRP), which are considered markers of small calibre sensory fibres, in addition to nerves containing neuropeptide Y and its C flanking peptide, found in the majority of sympathetic neurones.[10]

ARTICULAR NOCICEPTORS

Following a comprehensive series of studies performed largely in the cat knee,[4] Schaible and Schmidt have identified functional groups of articular afferent fibres on the basis of their response to mechanical stimuli.[11] The first group includes low threshold afferents activated by innocuous stimuli such as movement within the normal range, which presumably have a role in proprioception; the majority of rapidly conducting Aβ fibres fall into this category. The second group includes afferents activated mainly or purely by noxious stimuli such as movement exceeding the normal range; these are Aδ and C fibres and, in so far as they respond mainly to potentially damaging events within the joints, may be classed as nociceptors. Finally, some fibres do not react to any mechanical stimulus applied to the normal joint whatsoever; these have been termed mechanoinsensitive afferents or silent nociceptors,[12] and it is estimated that in the cat knee about one third of C fibres and a small percentage of Aδ fibres fall into this category.[4]

Several hours after induction of experimental arthritis, the response pattern of

articular sensory fibres changes dramatically.[13] The majority become 'sensitised' and show an increased responsiveness to stimuli applied to the joint. First, the high threshold sensory fibres become sensitised to movements in the normal range and may have resting activity in the absence of mechanical stimulation. Second, a proportion of the initially mechanoinsensitive sensory fibres develop responsiveness to mechanical stimuli. It is relevant that the time course of these changes in articular fibres mirrors the development of pain behaviour in awake animals.[4]

INFLAMMATORY MEDIATORS

Many, if not all, of the chemical mediators found in inflammatory joint fluid have potent and complex effects on afferent fibres, some acting to sensitise their receptors to mechanical and other stimuli, while others activate receptors directly. In either case, control of the receptor depends ultimately on the effects of these mediators on membrane ion channels, which may be directly coupled to membrane receptors (receptor gated ion channels) or controlled indirectly through intracellular second messengers.[14]

Prostaglandins—Prostanoids, particularly prostaglandins E_2, D_2, and I_2, may activate articular sensory fibres directly, but more usually they sensitise fibres to mechanical stimuli and chemicals such as bradykinin[4] (fig 1). Intra-articular injections of PGE_2 both sensitise and activate more than 50% of the Aδ and C fibres in the cat knee, but have relatively little effect in the rat knee, in which PGI_2 seems to be more important.[15]

Prostaglandin induced excitation of sensory membrane receptors leads to a sequence of intracellular events culminating in increased sensitivity which probably involves a stimulatory G protein and the cAMP second messenger system.[16] It has long been assumed that the principal site of analgesic activity of non-steroidal anti-inflammatory drugs (NSAIDs) is in the periphery, where they reduce the synthesis of prostaglandins by inhibiting cyclo-oxygenase activity. By reducing prostaglandins, it is reasoned, NSAIDs prevent sensitisation of articular sensory fibres and thereby inhibit or reduce activation by mechanical and chemical stimuli. While this serves to explain the all purpose analgesic properties of NSAIDs, other more central analgesic actions for these drugs have been proposed in recent years.[17]

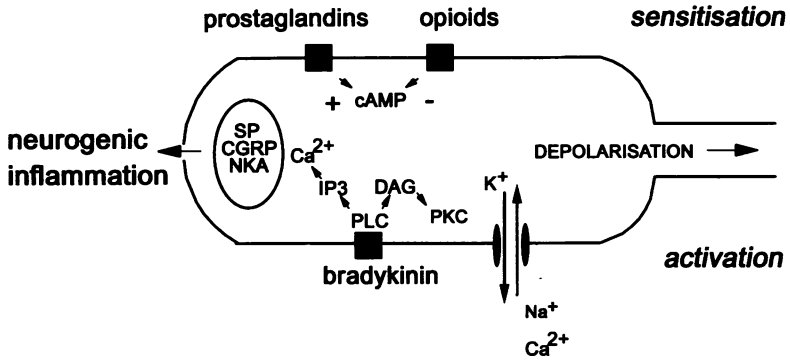

Figure 1 Sensitisation and activation of primary afferent C fibres. Prostaglandins sensitise C fibres, probably via a stimulatory G protein and the cAMP second messenger pathway. Opioids induce formation of inhibitory G proteins and act to inhibit this pathway. Bradykinin directly activates the C fibre by generation of pyruvate kinase C (PKC) activity and increasing sodium conductance. Heat and mechanical stimuli also increase ion conductance to produce activation, though exact mechanisms remain unclear. Release of neuropeptides secondary to changes in intracellular calcium concentration stimulates neurogenic inflammation. DAG = Diacylglycerol; PLC = phospholipase C; SP = substance P; CGRP = calcitonin gene related peptide; NKA = neurokinin A; IP3 = 1,4,5-inositol triphosphate.

Bradykinin—When injected into human skin, bradykinin causes an intense sensation of acute pain. Its intra-articular application to the cat knee directly activates a large proportion of group III and IV fibres, in addition to sensitising a population of fibres to movement.[18] Although the effects of bradykinin are mediated primarily by bradykinin B2 receptors during acute inflammation, B1 receptors are expressed during chronic disease and may become more important with time.[19 20] In either case, binding of the receptor is followed by G protein mediated activation of phospholipase C (PLC) which generates two intracellular second messengers—1,4,5-inositol-triphosphate (IP3) and diacylglycerol (DAG).[21] IP3 stimulates an increase in free calcium within the cell, whereas DAG activates protein kinase C, which plays a part in fibre activation by increasing membrane conductance, mainly to sodium ions. It should be stressed that other complex pathways have been described and the actions of bradykinin on afferent fibres remain to be fully determined.[22]

Protons—The acidic nature of inflammatory exudates has led to the proposal that protons may contribute to inflammatory pain.[23] Application of acidic fluid causes pain in experimental situations,[24] and protons have been shown to have an excitatory effect on many neurones, which may be of short or relatively prolonged duration.[25] The neuronal activation occurs by the opening of unique ion channels and is distinct from the non-specific effects of protons on membranes observed in many cell types.[23] The overall contribution of protons to pain would be particularly marked within inflamed joints, given the hypoxic environment and extreme acidosis of inflammatory synovial fluid.

Opioids—Although endogenous opioids traditionally have been thought to act principally at sites within the central nervous system, there is now compelling evidence to suggest additional sites of action in the periphery. Opioid receptors have been demonstrated on the terminals of peripheral nerves[26] and local applications of opioid agonists have been shown to reduce hyperalgesia in several experimental models.[27] Stein *et al* have demonstrated that hyperalgesia during adjuvant induced monarthritis can be reduced in a naloxone reversible manner after stress induced release of endogenous opioids.[26] Immunocytochemical studies by the same group have suggested that opioid peptides are produced by many of the cell types commonly found within inflammatory fluids.[27]

In clinical studies, intra-articular injections of morphine immediately before knee arthroscopy substantially reduced the postoperative analgesic requirement.[28] The doses used in these studies (1 mg) were small enough to preclude effective systemic spread and provide further evidence for a local opioid effect. In the periphery, opioids are believed to act via an inhibitory G protein to reduce cAMP, thus providing a theoretical basis for the analgesic synergy that is observed clinically between NSAIDs and opioids such as codeine or morphine[16 29] (fig 1).

OTHER INFLUENCES ON ARTICULAR NERVES

Sympathetic nervous system—Over recent years, a number of experimental studies have explored the contribution of the sympathetic nervous system to persistent activation of primary sensory fibres and hence chronic pain. The first experimental evidence for interactions between sympathetic and sensory fibres came from observations of neuronal activity in neuromas.[30] In this experimental model, damaged afferent fibres sprout within the neuroma and, unlike undamaged afferent fibres, develop sensitivity to noradrenaline mediated by α adrenergic receptors.[31] More recent models using subtotal resection or ligature constriction have shown the expression of adrenergic receptors on the peripheral terminals of those fibres that remain intact.[32] In the context of chronic arthritis it is relevant that primary sensory fibres activated by prolonged noxious stimulation become sensitised to noradrenaline and sympathetic discharge.[33] The overall conclusion from these and similar studies is that, whereas under normal conditions primary sensory nerves do not respond to sympathetic activity, the situation undoubtedly changes after any type of local injury, including nerve trauma and inflammation. Under these circumstances, sensory fibres may be stimulated by concurrent sympathetic activity.

Capsaicin—This compound is the active ingredient in hot red peppers, and has a direct action on a population of small sensory fibres within the joint and elsewhere. Low doses activate small sensory fibres to produce pain, neurogenic inflammation and, at least in skin, surrounding thermal and mechanical hyperalgesia. At these doses, capsaicin opens membrane ion channels to sodium and calcium ions to produce depolarisation.[34] The effect appears to be mediated through a specific receptor and there is some evidence linking this to the proton receptor.[23] Conversely, exposure to large concentrations of capsaicin blocks conduction in C fibres and produces selective sensory neurotoxicity which may be the result of osmotic lysis or enzyme mediated damage within the cell.[35] Repeated topical application of capsaicin to human skin causes desensitisation of C fibres to noxious stimuli and loss of neurogenic inflammation;[35] these effects are dependent on the concentration of capsaicin and time of exposure, though the underlying mechanisms remain unclear.

CLINICAL CONSEQUENCES

Different mediators released either by inflammatory cells or from the terminals of sympathetic nerves in response to inflammation or tissue damage produce varying effects on articular receptors and afferent fibres. The diverse nature of joint innervation ensures that, at least in the early stages of disease, the pattern of sensitisation and activation in the periphery is of pivotal importance in determining the character and magnitude of articular symptoms. Spontaneous activity in high threshold afferent fibres may well produce pain sensations at rest. Similarly, the development of mechanosensitivity in previously insensitive afferent fibres provides a convincing explanation of pain on joint movement—the so-called 'incident' pain.

Treatment regimens designed to reduce receptor sensitisation and abnormal afferent fibre activation undoubtedly represent a potent method for reducing joint pain. To date these have depended largely on inhibition of prostaglandin synthesis, but while this approach has proved successful, it is not without considerable morbidity. As Perkins and Dray will report later in this series of pain reviews, alternative approaches based on a knowledge of the pathophysiological changes that underlie joint pain have enabled the development of new analgesic treatments including bradykinin and cyclo-oxygenase II inhibitors, in addition to the use of capsaicin analogues to reduce small sensory fibre activity selectively.[36]

Neurogenic inflammation

Basic clinical observation indicates that sensory nerves not only signal potential or actual tissue damage, but also have an active role in inflammation. Stimulation of unmyelinated sensory fibres produces a local inflammatory response (neurogenic inflammation) characterised in the skin by the familiar weal and flare reaction.[37] An 'axon reflex' has been proposed whereby activation of sensory fibres after tissue injury results not only in impulse transmission to the central nervous system, but also in reverse transmission through the extensive network of peripheral nerve fibres known to terminate in close proximity to blood vessels and mast cells.[38]

Neurogenic inflammation is now understood to be mediated through biologically active peptides.[38] These are synthesised within small to medium sized dorsal root ganglion cell bodies and are transported via unmyelinated sensory fibres to peripheral tissues and to synaptic terminals within the superficial laminae (I and II) of the spinal dorsal horn.[39] One of the commonest peptides is substance P, but others including neurokinin A, CGRP, vasoactive intestinal polypeptide, and somatostatin have been reported.

Neurogenic vasodilatation—A number of clinical studies have provided evidence for altered neurogenic inflammatory responses in musculoskeletal disease. Capsaicin, as described earlier has a selective action on small diameter

unmyelinated afferent fibres to produce pain and axon reflex vasodilatation. Although used routinely for a number of years to investigate peripheral sensory function in neuropathic disorders, this property has only recently been used to study musculoskeletal disorders. Helme and colleagues have shown that capsaicin induced skin flares in patients with spinal pain secondary to degenerative disease are significantly smaller than those with pain of non-organic origin.[40] In contrast, a second study by the same group reported increased skin flares in patients with chronic pain syndromes characterised by muscle tender points.[41] A more recent study assessing sensory and autonomic axon reflex responses in rheumatoid arthritis has shown capsaicin induced axon reflex vasodilatation to be significantly greater over inflamed wrists (but not at control sites over the forearms) of patients with rheumatoid arthritis, compared with responses in age matched normal subjects.[42] The results suggest selective upregulation of sensory axon reflex activity in patients with rheumatoid arthritis, but whether this occurs as a result of local mediators or changes in central control remains unclear.

Substance P—This is an 11 amino acid peptide belonging to the tachykinin family that share a common sequence of six amino acids at the carboxyl terminal.[43] A number of studies have shown increased mRNA concentrations of preprotachykinin A, the precursor for substance P, in dorsal root ganglia after induction of arthritis.[44 45] Concomitant with this, substance P concentrations in the dorsal root ganglia and sciatic nerve have been shown to increase by 40 to 70% after induction of experimental adjuvant induced arthritis.[44 45] Somewhat paradoxically, concentrations of substance P in inflamed synovium have been reported to be reduced during the acute stages of short term inflammation models.[44] This has been taken to reflect rapid degradation of peptides by degradative enzymes known to be present in high concentrations within inflamed tissues. The same explanation may also serve to explain the wide variation in concentrations of substance P reported from synovial fluid removed from arthritic joints.[46]

Within the joint antidromic (reversed) stimulation of unmyelinated articular nerves causes plasma extravasation.[47] This effect appears to be mediated by substance P, as it is completely blocked by prior intra-articular administration of a substance P antagonist. Intra-articular injections of substance P produce vasodilatation and plasma extravasation,[48 49] while in vitro studies show mast cell degranulation, secretion of PGE_2 and collagenase from synoviocytes, and stimulation of interleukin-1 (IL-1)-like activity from macrophages.[29] A role in activation of the immune system has also been suggested. In studies of acute joint inflammation, substance P antagonists significantly inhibit the early articular responses to inflammatory agents such as carrageenin.[50]

Nerve growth factor—This is a major regulator of substance P gene expression in adult sensory nerves,[51] and may have an important role in the maintenance of inflammatory pain.[52] Nerve growth factor (NGF) is a member of the neurotrophin family of peptides and is produced by a range of cell types in response to a number of different cytokines, including IL-1B and tumour necrosis factor α.[53] Concentrations are increased during inflammation,[54] and NGF has been identified in synovial fluid of patients with chronic arthritis.[55] In the nervous system, NGF binds to a high affinity trkA receptor, where it is internalised and retrogradely transported to the cell body. Systemic administration of NGF neutralising antibodies in an experimental inflammatory model prevented the upregulation of neuropeptides, behavioural sensitivity, and development of long term changes within the spinal cord.[53 56]

Disease outcome—A number of experimental studies have examined the contribution of specific neural components to the expression and outcome of chronic arthritis. In 1983, Colpaert *et al* reported that capsaicin treatment of adult rats, using doses sufficient to deplete substance P stores, markedly reduced paw swelling and prevented weight loss during adjuvant arthritis.[57] This beneficial effect occurred irrespective of whether capsaicin was given before or after the onset of inflammation. More recent studies by Levine *et al* have confirmed and extended these observations by showing that disease outcome as measured by radiological score was also improved.[58 59] A neurogenic influence in the production of symmetrical joint disease has been suggested following the observation that inflammation or trauma in one joint can result in a neurogenically mediated response in the contralateral joint.[60 61]

Although neurogenic inflammation has long been thought to be a purely peripheral phenomenon, recent studies suggest that it may be under central control.[62 63] Spinally administered sensory receptor antagonists significantly reduce joint swelling in kaolin and carrageenan induced arthritis administered before[62] or after the onset of disease.[63] A similar effect has been demonstrated after dorsal rhizotomy.[64]

Central sensitisation

Sensitisation of primary afferent fibres allows neurogenic responses to be extensively modified according to the requirements of local tissues. A similar process also occurs in spinal neurones (central sensitisation), where it may have far reaching consequences for symptoms and signs arising not only from damaged or inflamed tissues, but also from tissues not directly involved in the primary pathology. The most obvious musculoskeletal examples are referred pain and the observation that apparently normal tissues around inflamed or damaged joints are often painful and tender despite having no apparent involvement in the underlying disease.

HYPERALGESIA AND REFERRED PAIN

Hyperalgesia is characterised by a reduction of the threshold for pain and an increased sensation of pain following a noxious stimulus. Damage to a joint, an area of skin, or other tissue produces tenderness and pain not only at the site of injury (primary hyperalgesia), but also in the surrounding area (secondary hyperalgesia).[65] Although Lewis first postulated in the 1940s that secondary hyperalgesia was produced by sensitisation of peripheral neurones,[65] later work by others argued strongly against this.[66-68] Studies performed primarily in human skin showed that, while an initial noxious stimulus from the periphery is required for induction of hyperalgesia and pain, continuing abnormal inputs from the periphery are not required for maintenance.[67-69] The observations suggested the existence of central mechanisms acting to enhance and modify the responsiveness of the spinal cord to both normal and abnormal input from the periphery.

The classical studies by Lewis and Kellgren,[70] and later by Hardy *et al*[66] showed that local injections of hypertonic saline into interspinous ligaments produced hyperalgesia and referred pain in the abdomen and elsewhere. These effects often occur in areas not sharing the same dermatome and may spread to sites of previous injury or disease;[66 71] knee pain referred from an osteoarthritic hip is an obvious example. The fact that hyperalgesia and pain spread to areas far removed from the injured region argues strongly against a local process and has provided further evidence for a central mechanism.[70 71]

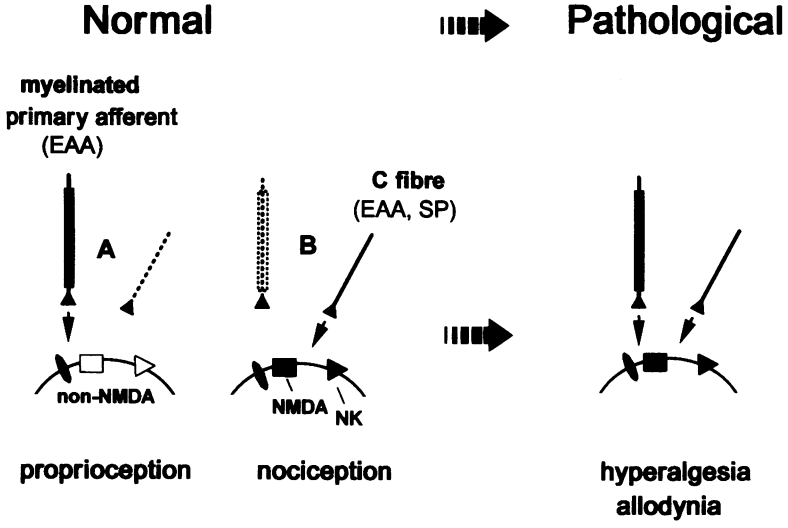

Figure 2 Activation of dorsal horn neurones by selective sensory input. NORMAL CONDITIONS: *Myelinated fibres are activated by innocuous stimuli (touch, light pressure etc) and release excitatory amino acids (EAA) in the spinal cord which excite non-NMDA receptors (A). In contrast, C fibres are activated by noxious stimuli (pinch, heavy pressure etc) and release EAAs and neurokinins (substance P (SP)) which excites neurokinin (NK), NMDA, and non-NMDA receptors (B), resulting in painful sensations.* PATHOLOGICAL CONDITIONS *(eg inflammation): C fibres are spontaneously active and maintain neurokinin and NMDA receptor activation to produce sustained hyperexcitability and consequent primary hyperalgesia. Because of the sustained background spinal hypersensitivity, inputs from other unmyelinated C fibres or large myelinated fibres may also produce depolarisation producing secondary hyperalgesia and allodynia, respectively. (Active fibres are represented by solid lines, inactive fibres by dotted lines, respectively. Filled shapes represent activated receptors on dorsal horn cells; empty ones are inactive.)*

WIND UP AND SPINAL HYPEREXCITABILITY

A major experimental breakthrough in the discovery of a central component to pain was the observation of C fibre dependent increases of excitability in dorsal horn neurones. The term 'wind up' was coined by Mendell and Wall to describe changes of activity in dorsal horn neurones whereby sustained or repetitive inputs from C fibres lead to a progressive increase in the discharge produced by further stimuli.[72] Subsequently, Woolf showed that acute peripheral injury produced prolonged changes in spinal cord excitability that outlasted the duration of the noxious stimulus.[73] Once wind up and central hyperexcitability are established, sensory processing within the spinal cord is substantially modified and may produce new sensory modalities such as allodynia, whereby normally innocuous stimuli are perceived as being painful (fig 2).

Neurokinins—The most important requirement for wind up is that it develops only after repetitive stimulation of C fibres terminating primarily in the superficial layer (lamina I) of the dorsal horn. Contrary to expectations, substantia gelatinosa (lamina II) neurones with C fibre input do not develop wind up.[74] Interestingly, these latter neurones do not express neurokinin receptors and it is now accepted that wind up occurs only in cells that express neurokinin receptors and are innervated by substance P containing afferent C fibres.[75]

The principal neurotransmitters within the spinal cord are the excitatory amino acids, which include glutamine and aspartate. Since the discovery that neurokinins (for example substance P, neurokinin A) and excitatory amino acids coexist in afferent C fibres,[76] it has been suggested that these transmitters may interact at postsynaptic neurones. There is much evidence that substance P has modulatory functions in the spinal dorsal horn,[75 77 78] and it is generally agreed that sustained activation of high threshold C fibres is required for these functions. Duggan *et al* have shown that substance P is released in increased quantitites during periods of C fibre activation,[79] and neurokinin-1 receptor antagonists have proved to be blockers of spinal hyperexcitability evoked by intradermal capsaicin or by acute arthritis in the primate.[80 81] Consistent with these observations, neurokinin-1 receptor antagonists proved to be analgesics in animal models of inflammatory pain.[82]

The NMDA receptor—At the heart of wind up and central sensitisation lies the *N*-methyl-D-aspartate (NMDA) receptor. This receptor belongs to the family of ionotropic glutamate receptors that are coupled to ion channels and are activated by endogenous excitatory amino acids (fig 3). Their activation evokes long lasting membrane depolarisation and enhanced membrane excitability. Blocking the NMDA receptor blocks the development of wind up after electrical stimulation[83] and hyperactivity of spinal neurones after injection of formalin[84] or acute inflammation of the knee joint.[85] In keeping with this, it has

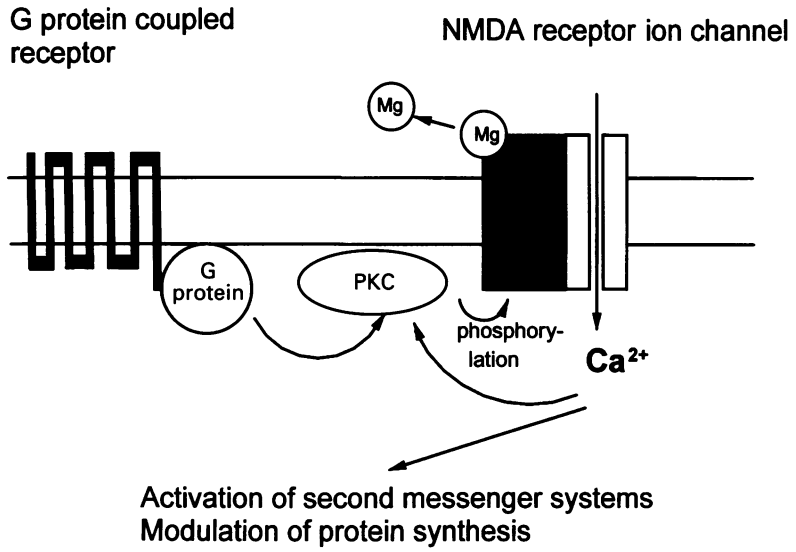

Figure 3 Interaction between neurokinin-1 (NK-1) and NMDA receptors. Activation of a G protein coupled receptor such as NK1 modulates magnesium ion binding of NMDA receptors through protein kinase C (PKC). Magnesium ions are released from the phosphorylated NMDA receptor and enable binding of excitatory amino acids. Activation of the NMDA receptor complex produces accumulation of intracellular calcium, with further consequences.

been shown that sensitisation of spinal neurones during acute arthritis is critically dependent on activation of NMDA receptors.[86 87]

Cellular mechanisms—NMDA receptors are activated by glutamate and aspartate, which are released in abundance within the spinal cord from both myelinated and unmyelinated primary afferent fibres and also from dorsal horn neurones. It is notable, however, that release of these neurotransmitters from non-neurokinin-containing A fibres does not evoke wind up in the dorsal horn.[88] The crucial role of neurokinins in modulation of NMDA receptor/ion channel properties has been studied by several groups.[75 80 89] It is established that neurokinin receptor activation by substance P and neurokinin A receptor enhances the activity of NMDA receptors both on single dorsal horn cells[89] and in isolated spinal cord.[78] The interaction takes place through the activation of protein kinase C[75 89] which can phosphorylate the NMDA receptor and change its Mg^{2+} binding kinetics. Under normal circumstances Mg^{2+} binding blocks the NMDA receptor, but the alteration of Mg^{2+} binding kinetics allows the release of Mg^{2+} from the receptor and permits glutamate induced activation and subsequent depolarisation of the cell membrane[75] (fig 3).

OTHER MEDIATORS

A number of endogenous mediators, including prostaglandins, nitric oxide, opioids, and adrenergic agonists, have been shown to influence the excitability of spinal neurones.[71]

It has been suggested that prostaglandins not only contribute to the peripheral component of hyperalgesia, but also have an important central role.[17 90 91] The basis of the argument is that, in rats, intrathecal NSAIDs reduce pain related behaviour evoked by the spinal action of substance P and NMDA[90] or injection of formalin into the hindpaw.[91] Glutamate release evoked by injection of formalin into the hindpaw is blocked by NSAIDs applied either intrathecally or systemically, with the potency of intrathecal application being two orders of magnitudes greater.[92] It is also suggested that spinal NSAIDs act primarily through blockade of cyclo-oxygenase as the inhibitory effect is stereospecific, such that S(+)-ibuprofen, which blocks cyclo-oxygenase, is active in the experimental model, while R(−)-ibuprofen (with no cyclo-oxygenase effect) is not. Taken together, the findings imply that NSAIDs have a direct antinociceptive effect in the spinal cord or at supraspinal level. It must be stressed, however, that the issue remains controversial.[93 94]

In addition, several classes of receptor selective agents act spinally to alter nociceptive processing. $Alpha_2$ adrenergic and μ opioid receptor agonists produce analgesia by presynaptic inhibition of C fibre neurotransmitter release and postsynaptic hyperpolarisation of second order neurones.[71] Coadministration of intrathecal morphine and selected α_2 agonists or NSAIDs results in substantial analgesic synergy[17] and highlights a role for combination treatments in clinical settings.

CLINICAL CONSEQUENCES

Understanding of the precise mechanism of receptor interaction in spinal neurones is far from complete; however, its importance in the development and maintenance of spinal hyperexcitability is now generally agreed.[75 95-98] The current model provides an explanation for altered sensations arising from peripheral injury or similar pathological stimuli. Once C fibre activity 'unmasks' receptors in spinal neurones, neurotransmitters released from both C and A fibres may produce increased NMDA receptor activation and maintain central hyperexcitability. Under these conditions, both C and A fibres become able to evoke pain (fig 3).

Dorsal horn neurones receive inputs from various afferent fibres with receptive fields that are not necessarily restricted to one area or even to the same tissue.[97] As an example of this, dorsal horn neurones with receptive fields in the knee also receive inputs from adjacent structures including skin and muscle, and from remotes sites near the ankle and even the contralateral limb.[99 100] Under normal circumstances these inputs remain suppressed. The development of central hyperexcitability, however, allows dorsal horn neurones to respond in an abnormal and exaggerated way.[96] The net effect is that responses to normal stimuli are increased, the size of the receptive fields is expanded, and the threshold for activation by novel inputs is reduced.[96] Clinically, this results in enhanced pain at the site of injury (primary hyperalgesia) and development of pain and tenderness in normal tissues both adjacent to (secondary hyperalgesia) and removed from (referred pain) the primary site.[98] Innocuous mechanical stimuli such as light pressure on the skin may produce

pain as a result of input from mechanoceptive A fibres (allodynia).

Increasing awareness of central mechanisms involved in pain has stimulated the search for and development of new analgesic treatment regimens. In particular, attention is being focused on neurokinin and NMDA receptor inhibitors, though other targets are also under investigation.[36] It is to be hoped that novel agents delivered alone or in combination with peripherally acting drugs will ultimately provide safer and more effective analgesia for use in that large group of long suffering patients with musculoskeletal disease.

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