Review Article

Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence

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Summary Peripheral tissue damage or nerve injury often leads to pathological pain processes, such as spontaneous pain, hyperalgesia and allodynia, that persist for years or decades after all possible tissue healing has occurred. Although peripheral neural mechanisms, such as nociceptor sensitization and neuroma formation, contribute to these pathological pain processes, recent evidence indicates that changes in central neural function may also play a significant role. In this review, we examine the clinical and experimental evidence which points to a contribution of central neural plasticity to the development of pathological pain. We also assess the physiological, biochemical, cellular and molecular mechanisms that underlie plasticity induced in the central nervous system (CNS) in response to noxious peripheral stimulation. Finally, we examine theories which have been proposed to explain how injury or noxious stimulation lead to alterations in CNS function which influence subsequent pain experience.

Key words: Nociception; Plasticity; Hyperalgesia; Sensitization; Neuropathic pain; Pain; Pre-emptive analgesia

Introduction

The somatosensory system normally serves the valuable function of alerting the individual to actual or potential tissue damage. However, following peripheral tissue or nerve injury, a pathological state sometimes develops in which there is a reduction in pain threshold (allodynia), an increased response to noxious stimuli (hyperalgesia), an increase in the duration of response to brief stimulation (persistent pain) and a spread of pain and hyperalgesia to uninjured tissue (referred pain and secondary hyperalgesia). The most distressing feature of these pathological processes is that they persist long after healing of the damaged peripheral tissue. Peripheral neural mechanisms, such as nociceptor sensitization and neurogenic responses are likely to contribute to pathological pain at early stages following injury when tissue damage and inflammation are prevalent. However, the persistence of pathological pain after the healing of damaged tissue suggests that changes in CNS function may also play a significant role. In the present paper, we examine the clinical and experimental evidence which indicates that central neural plasticity contributes to the development of pathological pain. We also assess the physiological, biochemical, cellular and molecular changes that develop within the CNS in response to noxious peripheral stimulation. Finally, we provide a brief historical review of the development of the idea that pain processes are influenced by noxious stimulus-induced plas-

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Abbreviations: NMDA = *N*-methyl-D-aspartate; NSAID = non-steroidal anti-inflammatory drug; EAA = excitatory amino acid; SP = substance P; CGRP = calcitonin gene-related peptide; VIP = vasoactive intestinal polypeptide; CCK = cholecystokinin; AP-5 = 2-amino-5-phosphonopentanoic acid; CNQX = 6-cyano-7-nitroquinoxaline; AP-7 = 2-amino-7-phosphonoheptanoic acid; CPP = (±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid; MK-801 = diazocilpine maleate; AMPA = (±)-α-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; trans-ACPD = trans-(±)-1-amino-1,3-cyclopentanedicarboxylic acid; PLC = phospholipase C; IP_3 = inositol trisphosphate; DAG = diacylglycerol; PKC = protein kinase C; EGTA = ethylene glycol-bis(β-aminoethyl ether) *N,N,N',N'*-tetra-acetic acid.

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ticity, and examine recent theories that have been proposed to explain how peripheral injury or noxious stimulation leads to CNS alterations which contribute to pathological pain processes.

Clinical and experimental evidence that CNS plasticity contributes to pathological pain

Damage of peripheral tissue and injury to nerves typically produce persistent pain and hyperalgesia. However, there are significant differences in the underlying peripheral mechanisms of nociceptive and neuropathic pain. Damage of cutaneous or deep (muscle, joint and viscera) tissue is typically associated with peripheral inflammation, while injury of nerves often leads to pathological peripheral nerve processes, including neural degeneration, neuroma formation and the generation of spontaneous neural inputs. It is generally accepted that the nociceptive pain produced by tissue injury is significantly influenced by peripheral inflammatory changes, while neuropathic pain is influenced by pathological alterations in peripheral nerve function. Evidence suggests that although nociceptive and neuropathic pain depend on separate peripheral mechanisms, they are both significantly influenced by changes in CNS function.

A role of central plasticity in nociceptive pain

Secondary hyperalgesia

Hardy et al. (1950) proposed that there are two types of hyperalgesia: primary and secondary. Primary hyperalgesia involves increased sensitivity to noxious stimulation at the site of an injury, while secondary hyperalgesia involves increased sensitivity extending beyond the site of the injury, sometimes to remote sites distant from the site of injury. These investigators proposed that primary hyperalgesia was mediated by peripheral mechanisms (i.e., neurogenic inflammation), while secondary hyperalgesia was related to central hyperactivity or sensitization. This conclusion was based on their observation that hyperalgesia spread beyond the region of the flare response, which was known to be produced by neurogenic inflammation, and by the finding that the development of hyperalgesia after cutaneous injury was prevented by prior local anesthetic blocks of peripheral nerves proximal to the site of injury.

Recent evidence supports the view that hyperalgesia depends, in part, on central sensitization. Hyperalgesia to punctate mechanical stimuli, which develops after intradermal injection of capsaicin, is maintained even after anesthetizing the region where capsaicin was injected (LaMotte et al. 1991). However, if the skin region is anesthetized prior to capsaicin injection, cutaneous hyperalgesia does not develop. Furthermore, hyperalgesic responses to capsaicin can be prevented if the area of skin where the injection is made is rendered anesthetic by a proximal anesthetic block of the peripheral nerve which innervates it. Thus, for hyperalgesia to develop it is critical that initial inputs from the injury reach the CNS. However, once hyperalgesia is established, it does not need to be maintained by inputs from the injured peripheral tissue. In support of this, Torebjörk et al. (1992) have shown that pain thresholds to intraneural electrical stimulation of afferent fibers are dramatically reduced following intradermal capsaicin injection, even when the sensory projected field of the afferent nerve is anesthetized after the capsaicin injection.

Referred pain and hyperalgesia

Further evidence for a central mechanism of hyperalgesia is suggested by clinical and experimental cases of referred pain and hyperalgesia. Hardy et al. (1950) demonstrated that hyperalgesia is produced in the chest and abdomen following injections of hypertonic saline into intraspinous ligaments (also see Kellgren 1938). They also reported a case of spontaneous hyperalgesia which spread extensively over the skin of the back following a minor back injury, and another case of hyperalgesia in the face and scalp associated with an ear infection. In addition, Lewis (1942) showed that referred pain and hyperalgesia in the shoulder can be elicited by stimulation of the diaphragm. Indeed, referred pain and hyperalgesia are often reported in the muscle and skin within the same spinal cord dermatome as injured organs, and are commonly used for the diagnosis of conditions such as appendicitis and angina pectoris.

Referred pain appears to depend on neural mechanisms since local anesthesia of the injured region blocks its expression (Robertson et al. 1947). Furthermore, the role of central neural mechanisms is supported by the observation that phrenic nerve stimulation causes referred shoulder pain even after the sectioning of all cutaneous nerves from the painful region of the shoulder (Doran and Ratcliffe 1954), and by the finding that the injection of hypertonic saline into intraspinous ligaments resulted in pain referred to a phantom arm (Harman 1948). It is possible that referred pain depends on the misinterpretation of inputs from an injured region whose axons also branch to the uninjured referred area (Sinclair et al. 1948), or alternatively that axons from the injured and referred regions converge on the same cells in the sensory pathway (Ruch 1965). If referred pain could be explained exclusively by convergence, then such pains would not provide clear evidence of central sensitization. However, evidence that referred pain is also in part dependent on CNS changes is provided by findings that referred pain and hyperalgesia spread to areas which do not share the same dermatome (Lewis 1942; Livingston 1943). For

example, it has been shown that pain of cardiac origin is referred to sites as distant as the patient's ear (Brylin and Hindfelt 1984). The fact that pain and hyperalgesia can spread to areas far removed from the injured region implies that central changes, as opposed to convergence, are involved in the spread of hyperalgesia. Furthermore, referred pain has often been found to spread specifically to sites of a previous injury. Henry and Montuschi (1978) describe a case where the pain of an angina attack was referred to the site of an old vertebral fracture. Furthermore, Hutchins and Reynolds (1947) discovered that alterations in barometric pressure during high-altitude flights caused many of their patients to complain of pain localized to teeth which had been the site of previous painful stimulation (e.g., fillings, caries and extractions), in many cases years earlier. Reynolds and Hutchins (1948) were able to replicate this finding under controlled conditions. One week after damaged teeth were filled or extracted, pinprick of the nasal mucosa produced pain referred to the previously treated teeth. This phenomenon occurred among patients who had been treated under general anesthesia, but not under the influence of a local anesthetic block. Furthermore, in patients who had received bilateral dental treatment without a local anesthetic, subsequent blocks applied to one side permanently abolished the referred pain ipsilateral but not contralateral to the anesthetized side.

Behavioral and physiological studies in animals also demonstrate hyperalgesia or sensitization in response to stimulation of body regions which are at a distance from a cutaneous or deep tissue injury. Woolf (1984) found that localized thermal and chemical injuries cause reductions in flexion reflex thresholds to noxious mechanical and thermal stimulation in the limb contralateral as well as ipsilateral to the injury. Following inflammatory lesions of the rat knee joint, spinal dorsal horn (Neugebauer and Schaible 1990) and thalamic (Guildbaud et al. 1986) neurons exhibit an enhanced responsiveness not only to mechanical stimulation of the inflamed joint, but also to stimulation of the muscles in the thigh and lower regions of both the ipsilateral and contralateral legs. These finding are consistent with clinical observations that hyperalgesia develops in body regions which are distant from the area of a deep tissue injury (Hardy et al. 1950), and that flexion reflex thresholds are reduced in patients following gynecological surgery (Dahl et al. 1992a).

Cutaneous (Woolf 1983) and deep (Woolf and McMahon 1985) tissue injury, as well as noxious electrical stimulation of cutaneous and muscle afferent nerves (Wall and Woolf 1984) also produce an increase in the excitability of the ipsilateral and contralateral flexor efferent nerves in response to noxious mechanical stimulation of the hind paw. Since the increased excitability in the contralateral flexor efferent nerve is maintained even after inputs from the injured paw are blocked by local anesthesia, the results suggest that central, not peripheral, changes underlie this effect. In this way, cutaneous hyperalgesia after injury may depend on central hypersensitivity which is produced by inputs from a peripheral injury, but does not need to be maintained by them. Behavioral studies indicate that the spread of hyperalgesia to the hind paw contralateral to the paw that received a thermal injury is unaffected by either deafferentation or anesthetic blocks of the injured hind paw following the injury, but is prevented if deafferentation or anesthetic block precedes the injury (Coderre and Melzack 1985, 1987). These data provide further evidence that peripheral injury can produce central changes which are maintained even after the inputs from the injury are removed.

Central sensitization

Prolonged sensory disturbances associated with tissue injury (secondary hyperalgesia and referred pain, as well as allodynia and persistent spontaneous pain) are believed to result from either a reduction in the threshold of nociceptors or an increase in the excitability of CNS neurons involved in pain transmission. Since there is a large body of evidence documenting the sensitization of peripheral receptors following noxious stimulation (Beitel and Dubner 1976; Perl 1976; Campbell and Meyer 1983; Koltzenburg et al. 1992), a peripheral mechanism is usually held to be responsible for the hyperalgesia that develops after injury. However, recent experimental studies suggest that sensitization within the CNS also contributes significantly to this phenomenon. These studies indicate that following injury, noxious stimulation, or C-fiber afferent electrical stimulation, there is a sensitization of neurons in the dorsal horn of the spinal cord and other areas in the somatosensory pathway. This sensitization is reflected by increased spontaneous activity, reduced thresholds or increased responsivity to afferent inputs, prolonged afterdischarges to repeated stimulation, and the expansion of the peripheral receptive field of dorsal horn neurons.

Evidence of central sensitization was supported initially by reports that cutaneous hyperalgesia spreads well beyond the area of nociceptor sensitization. Thalhammer and LaMotte (1982) found that a heat injury in one half of a cutaneous nociceptor's receptive field did not produce heat sensitization in the other half, despite the fact that hyperalgesia spread into this area. Typically, nociceptor sensitization associated with injury is restricted to about 5–10 mm of the site of injury (Fitzgerald 1979) while, in contrast, cutaneous hyperalgesia spreads as far as 10–20 cm beyond the site of injury (Hardy et al. 1950). Furthermore, noxious me-

chanical and chemical stimuli produce extensive, spreading hyperalgesia (LaMotte et al. 1992) without producing the same degree of spreading sensitization of primary afferent nociceptors in monkeys (Campbell et al. 1988; Baumann et al. 1991) or humans (LaMotte et al. 1992).

Coincident with spreading hyperalgesia is the sensitization of spinal cord dorsal horn neurons. Dorsal horn neurons fire with increasing frequency in response to repeated applications of a noxious heat stimulus (Perl 1976; Kenshalo et al. 1979). This sensitization of dorsal horn neurons occurs after various types of tissue injury including thermal injury (Price et al. 1978; Kenshalo et al. 1982), chemical injury (Simone et al. 1991; Dougherty and Willis 1992), acute joint inflammation (Schaible et al. 1987; Dougherty et al. 1992c), polyarthritis (Menetrey and Besson 1982; Calvino et al. 1987) or stimulation of C-fiber afferents (Chung et al. 1979). Sensitization in response to tissue injury/inflammation or electrical nerve stimulation also occurs in spinal motoneurons (Woolf 1983), thalamus (Guilbaud et al. 1986), and somatosensory cortex (Lamour et al. 1983). Furthermore, repeated C-fiber afferent stimulation sequentially increases dorsal horn activity resulting in a prolonged discharge of the cell, lasting from seconds to minutes post-stimulation (Mendell 1966; Schouenbourg and Dickenson 1985). This phenomenon, which has been labelled as 'windup' (Mendell 1966), could potentially occur following intense noxious stimulation or injury.

In addition to the sensitization and prolonged excitation of dorsal horn cells, noxious stimulation associated with tissue injury also produces an expansion of the receptive fields of dorsal horn neurons. Neurons in the dorsal horn of the spinal cord with receptive fields adjacent to a cutaneous heat injury expand their receptive fields to incorporate the site of injury (McMahon and Wall 1984). Similar receptive field expansions have been observed in spinal cord following mechanical (Cervero et al. 1988), chemical (Hoheisel and Mense 1989; Woolf and King 1990), inflammatory (Hylden et al. 1989) and nerve (Devor and Wall 1978) injuries, as well as following the induction of polyarthritis (Menétry and Besson 1982; Calvino et al. 1987) and in response to electrical nerve stimulation (Cook et al. 1987). Receptive field expansions have also been observed in trigeminal brainstem neurons following chemical stimulation of deep craniofacial afferents (Hu et al. 1992). Inflammatory lesions also produce an expansion of receptive fields of cells in the ventrobasal thalamus (Guilbaud et al. 1986).

A role of central plasticity in neuropathic pain

Pain in phantom limbs and deafferented structures

A striking property of phantom limb pain is the persistence of a pain that existed in a limb prior to its amputation (Melzack 1971). This type of phantom limb pain, characterized by the persistence or recurrence of a previous pain, has the same qualities and is experienced in the same area of the limb as the pre-amputation pain. Case studies of amputees (see Katz and Melzack 1990) have demonstrated pain 'memories' of painful diabetic and decubitus ulcers, gangrene, corns, blisters, ingrown toe nails, cuts and deep tissue injury. In addition, the phantom limb may assume the same painful posture as that of the real limb prior to amputation, especially if the arm or leg had been immobilized for a prolonged period (Katz and Melzack 1990).

The literature indicates that the proportion of amputees who report that their phantom pains are similar to those felt in the limb before amputation may be as high as 79% (Katz and Melzack 1990). Reports of pain memories in phantom limbs appear to be less common when there has been a discontinuity, or a pain-free interval, between the experience of pain and the amputation. This is consistent with the observation that relief of pre-amputation pain by continuous epidural block for 3 days prior to amputation decreases the incidence of phantom limb pain 6 months later (Bach et al. 1988). Furthermore, if pain is experienced at or near the time of amputation, there is a higher probability that it will persist in the phantom limb (Jensen et al. 1985; Katz and Melzack 1990).

Pain also persists in patients with deafferentation that does not involve amputation. Patients with brachial plexus avulsions (Reisner 1981; Jensen and Rasmussen 1989) and spinal cord injuries often experience pain in the anesthetic, deafferented region (Conomy 1973; Berger and Gerstenbrand 1981). For example, Nathan (1962) described a patient who continued to feel the pain of an ingrown toe nail after a complete spinal cord break. In addition, patients undergoing spinal anesthesia (Van Bogaert 1934; Wallgren 1954) and those with injuries of the brachial plexus (Reisner 1981; Jensen and Rasmussen 1989) or spinal cord (Conomy 1973; Berger and Gerstenbrand 1981) sometimes report that a limb is in the same uncomfortable, often painful posture it was in prior to the injury or block. These postural phantom sensations do not usually persist beyond several days, and in most cases are at least temporarily reversed by competing visual inputs which reveal a dissociation between the real and perceived limb.

There is also a literature on the persistence of painful and non-painful sensations associated with removal or deafferentation of body structures other than the limbs, including breasts (Kroner et al. 1989), teeth (Hutchins and Reynolds 1947; Reynolds and Hutchins 1948), and internal and special sense organs. Ulcer pain has been reported to persist after vagotomy (Szasz 1949) or subtotal gastrectomy with removal of the ulcer (Gloyne 1954). Similarly, patients have reported labor

pain and menstrual cramps following total hysterectomy (Dorpat 1971), rectal and hemorrhoid pain following removal of the rectum (Ovesen et al. 1991), the burning pain of cystitis after complete removal of the bladder (Brena and Sammons 1979), and the pain of a severely ulcerated cornea after enucleation of an eye (Minski 1943).

When a missing or completely anesthetic limb continues to be the source of pain which resembles an old injury, it is reasonable to assume that the pain is centrally represented, but it is not clear whether deafferentation per se is necessary for pain memories to develop. The interruption of afferent input associated with deafferentation may facilitate the central neural changes that contribute to the formation of pain memories by removing normal inhibitory control mechanisms (see below). In addition, since amputation also results in the loss of visual and tactile information related to the limb, the central influences that normally inhibit the established pain 'traces' may be reduced further by the absence of information from external sources that could confirm or disconfirm the percept arising from the peripheral injury.

There is evidence that in some instances the reactivation of pain memories requires a peripheral trigger. Leriche (1947a,b) described a patient who did not experience phantom limb pain until 6 years after amputation, when an injection into the stump instantly, and permanently, revived the pain of a former painful ulceration of the Achilles tendon. Nathan (1962, 1985) reported a similar phenomenon when applying noxious stimulation to the stump of an amputee who later re-experienced the pain of an ice-skating injury he had sustained 5 years earlier when the leg was intact. Noordenbos and Wall (1981) also described 7 patients with partial peripheral nerve injury, and subsequent pain, who underwent complete nerve resection and graft or ligation. Following regeneration and a pain-free period, all re-developed pain of the same quality and in the same location as the pain they had experienced prior to nerve resection, although in some patients the recurrence of pain was restricted to a smaller area within the originally painful region. These studies and case reports indicate that past pains may be reactivated months or even years after the original injury, in some cases by a peripheral trigger which provides the input required to activate the central neural structures subserving the memory trace.

Deafferentation pain in animals

Deafferentation by peripheral neurectomy or dorsal rhizotomy in rodents is followed by self-mutilation (autotomy) in which the animals bite and scratch the insensate paw to the point of amputation (Wall et al. 1979). There is evidence that autotomy behavior is produced by ongoing pain or dysesthesia, associated with increased neuronal activity, which is referred to the anesthetic region (Coderre et al. 1986a; Blumenkopf and Lipman 1991; however, also see Sweet 1981; Rodin and Kruger 1984). Autotomy behavior is dramatically affected by alterations in the level of noxious input present at the time of, or prior to, nerve section. Thus, noxious chemical (Dennis and Melzack 1979; Coderre et al. 1986b), thermal (Coderre and Melzack 1985, 1987; Katz et al. 1991) and electrical (Katz et al. 1991; Selzter et al. 1991a) stimulation prior to nerve sections significantly increases the severity of autotomy following neurectomy or rhizotomy. These findings suggest that the prior injury produces central changes which influence nociceptive behavior, after nerve sections, at a time when inputs from the injured region are no longer capable of transmitting their message centrally.

The above findings are similar to clinical reports that phantom limb pain is more likely to occur in amputees who had pain in their limb prior to amputation (Melzack 1971), and strongly suggest that central neuroplasticity is crucial to the development of phantom limb pain. The clinical relevance of these findings is indicated by the observation that in human amputees the incidence of phantom limb pain at 7 days and 6 months after amputation is significantly greater in patients whose pain is not treated by epidural block with bupivacaine and morphine prior to amputation surgery (Bach et al. 1988). In contrast to the effect of increasing noxious inputs at the time of nerve injury, reducing or eliminating the afferent barrage induced by nerve section produces a dramatic reduction in autotomy. When the afferent barrage induced by nerve cuts in rats is blocked by treating the sciatic and saphenous nerves with local anesthetics prior to sectioning them, there is a significant reduction in the incidence and severity of autotomy (Gonzalez-Darder et al. 1986; Seltzer et al. 1991a).

An animal model has recently been developed (Katz et al. 1991) which parallels the observation that human amputees report similar pains in a limb before and after amputation. In this animal model, rats selectively initiated autotomy in either the lateral or medial half of a hind paw if that particular half had been given a thermal injury prior to sciatic and saphenous nerve sections. The selective attack on the previously injured region, despite the fact that the entire foot was deafferented, suggests that the rats were responding to pain referred to the injured area, which was produced by the prior injury and the central trace it created. Rats injured after neurectomy did not show a similar preference indicating that the rats were not responding simply to peripheral cues associated with the injury.

While the autotomy model has provided evidence for a contribution of central plasticity to pain associated with peripheral nerve injury, its usefulness as a

model of neuropathic pain has been questioned since it suffers from the weakness of lacking many of the signs of neuropathic pain found in humans. Recently, an animal model of peripheral neuropathy has been developed which produces behavioral signs of hyperalgesia, allodynia and spontaneous pain or dysesthesia, which are proposed to resemble the symptoms of nerve injury-related pain in humans. This model involves the placing of loosely constrictive ligatures around the sciatic nerve in rats and observing the behavioral symptoms associated with the nerve pathology that develops over the next several days (Bennett and Xie 1988). Recent evidence suggests that the nerve constriction injury produces profound changes in spinal cord physiology, including transynaptic degeneration (Sugimoto et al. 1990), increases in c-*fos* expression (Kajander et al. 1990) and the growth-associated protein GAP 43 (Cameron et al. 1991), as well as decreases in tachykinin immunoreactive staining (Bennett et al. 1989; Cameron et al. 1991) in the dorsal horn. The injury also produces increased spontaneous activity and increased excitability (lowered thresholds to mechanical stimulation, and afterdischarges to suprathreshold stimuli) of spinothalamic tract cells (Palecek et al. 1992), as well as the generation of spontaneous discharges in the dorsal root ganglion (Kajander et al. 1992). Furthermore, the constriction injury produces a dramatic increase in spinal cord metabolic (2-DG) activity in both the ipsilateral and contralateral spinal cord (Mao et al. 1992a). Since metabolic activity is increased in the absence of additional peripheral stimulation it has been argued that the behavioral symptoms are driven by sustained alterations in spinal cord function. This notion is supported by the finding that there is a reduction in the hyperalgesia that develops following constriction injury of the sciatic nerve if the nerve is locally anesthetized at the time of injury (Dougherty et al. 1992a). Furthermore, while hyperalgesia and spontaneous pain produced by nerve constriction injury are reduced by post-injury local anesthesia of the sciatic nerve (Mao et al. 1992b), suggesting a peripheral contribution to the pain pathology, hyperalgesia and spontaneous pain are also reduced by systemic or intrathecal treatment with *N*-methyl-D-aspartate (NMDA) antagonists (Davar et al. 1991; Mao et al. 1992b), suggesting a central contribution as well.

Denervation hypersensitivity and neuronal hyperactivity

Sensory disturbances associated with nerve injury have been closely linked to alterations in CNS function. Markus et al. (1984) have demonstrated that the development of hypersensitivity in a rat's hind paw following sciatic nerve section occurs concurrently with the expansion of the saphenous nerve's somatotopic projection in the spinal cord. Nerve injury may also lead to the development of increased neuronal activity at various levels of the somatosensory system. In addition to spontaneous activity generated from the neuroma (Wall and Gutnik 1974), peripheral neurectomy also leads to increased spontaneous activity in the dorsal root ganglion (Wall and Devor 1983; Burchiel 1984), dorsal spinal roots (Howe et al. 1977; Wiesenfeld and Lindblom 1980) and spinal cord (David and Aguayo 1980; Asada et al. 1990). Furthermore, after dorsal rhizotomy, there are increases in spontaneous neural activity in the dorsal horn (Loeser and Ward 1967; Basbaum and Wall 1976), the spinal trigeminal nucleus (Anderson et al. 1971; Macon 1979) and the thalamus (Lombard et al. 1979; Albe-Fessard and Lombard 1983).

Clinical neurosurgery studies reveal a similar relationship between denervation and CNS hyperactivity. Neurons in the somatosensory thalamus of patients with neuropathic pain display high spontaneous firing rates, abnormal bursting activity, and evoked responses to stimulation of body areas that normally do not activate these neurons (Gorecki et al. 1989; Hirayama et al. 1989; Lenz et al. 1989; Rinaldi et al. 1991). The site of abnormality in thalamic function appears to be somatotopically related to the painful region. In patients with complete spinal cord transection and dysesthesias referred below the level of the break, neuronal hyperactivity was observed in thalamic regions that had lost their normal sensory input, but not in regions with apparently normal afferent input (Lenz et al. 1987, 1988). Furthermore, in patients with neuropathic pain, electrical stimulation of subthalamic, thalamic and capsular regions may evoke pain and in some instances even reproduce the patient's pain (Nathan 1985; Gorecki et al. 1989; Hirayama et al. 1989; Tasker 1989). Direct electrical stimulation of spontaneously hyperactive cells evokes pain in some but not all pain patients, raising the possibility that in certain patients the observed changes in neuronal activity may contribute to the perception of pain (Lenz et al. 1988). Studies of patients undergoing electrical brain stimulation during brain surgery reveal that pain is rarely elicited by test stimuli unless the patient suffers from a chronic pain problem. However, brain stimulation can elicit pain responses in patients with chronic pain that does not involve extensive nerve injury or deafferentation. Nathan (1985) describes a patient who underwent thalamic stimulation for a movement disorder. The patient had been suffering from a toothache for 10 days prior to the operation. Electrical stimulation of the thalamus reproduced the toothache.

It is possible that receptive field expansions and spontaneous activity generated in the CNS following peripheral nerve injury are, in part, mediated by alterations in normal inhibitory processes in the dorsal horn. Within 4 days of a peripheral nerve section there is a reduction in the dorsal root potential, and there-

fore, in the presynaptic inhibition it is assumed to represent (Wall and Devor 1981). Nerve section also induces a reduction in the inhibitory effect of A-fiber stimulation on activity in dorsal horn neurons (Woolf and Wall 1982). Furthermore, nerve injury affects descending inhibitory controls from brain stem nuclei. In the intact nervous system, stimulation of the locus coeruleus (Segal and Sandberg 1977) or the nucleus raphe magnus (Oliveras et al. 1979) produces an inhibition of dorsal horn neurons. Following dorsal rhizotomy, however, stimulation of these areas produces excitation, rather than inhibition, in half the cells studied (Hodge et al. 1983).

Effects of anesthetic or analgesic pretreatment on post-injury pain

Persistent pain in animals

As noted above, deafferentation pain in rats is significantly reduced if the injured nerves are locally anesthetized prior to nerve injury. Thus, autotomy after nerve sections (Gonzalez-Darder et al. 1986; Seltzer et al. 1991a), or hyperalgesia following nerve ligation (Dougherty et al. 1992a), is significantly reduced if the sciatic and saphenous nerves are locally anesthetized prior to the nerve injury. Recent evidence indicates that persistent pain induced by tissue injury is also reduced by pretreatment with local anesthetics or opioids prior to the injury, suggesting a contribution of central plasticity to nociceptive pain. A subcutaneous injection of dilute formalin produces a biphasic nociceptive response with an early phase of intense pain that occurs in the first few minutes and a later tonic phase of moderate pain occurring about 20–60 min after formalin injection (Dubuisson and Dennis 1977). The nociceptive response to subcutaneous formalin is matched by a corresponding biphasic increase in the activity of dorsal horn neurons after formalin injection (Dickenson and Sullivan 1987b). Dickenson and Sullivan (1987b) have demonstrated that intrathecal administration of a mu-opiate agonist significantly inhibits the prolonged increase in dorsal horn activity produced by subcutaneous formalin injection. However, this inhibition occurs only if the drug is given before the formalin injection, and not if it is given 2 min after the injection. These results imply that the dorsal horn activity associated with the late phase of the formalin test depends upon spinal activation during the early phase immediately after formalin injection.

Behavioral studies support the electrophysiological finding that the late-phase response to formalin is, in part, dependent on spinal changes generated during the early phase. Tonic nociceptive responses in the late phase of the formalin test (30–60 min after formalin) are not eliminated by complete anesthetic blockade of the formalin injected area at the time of testing during the late phase, but are virtually abolished if the area was also blocked by local anesthetics at the time of formalin injection (Coderre et al. 1990). Furthermore, late-phase nociceptive responses are significantly reduced by spinal anesthesia induced immediately prior to formalin injection, but not by spinal anesthesia administered 5 min after formalin injection, that is, after the early phase had already occurred (Coderre et al. 1990). These results suggest that central neural changes, which occur during the early phase of the formalin test, are essential for the development of the later tonic phase of the formalin test.

Evidence suggests that peripheral tissue injury also induces plasticity in supraspinal structures, which affects persistent pain behavior. This evidence comes from assessing the effects of pre-injury treatment with local anesthetics (in this case injected into discrete brain regions) on post-injury pain responses. Nociceptive responses to subcutaneous formalin injection into the rat hind paw are suppressed after focal injection of lidocaine into specific limbic system sites such as the cingulum bundle and the fornix pathway. The lidocaine injection produces analgesia during the late phase of the formalin test (30–70 min after formalin injection) when injected into these areas 10 min before, but not 10 min after, the formalin injection (Vaccarino and Melzack 1992). These results suggest that activity in the cingulum bundle and fornix during the early-phase response to formalin is critical to the development of the late-phase response to formalin. The cingulum bundle and fornix are part of a neural loop that projects from the anterior thalamic nuclei to the cingulate cortex, hippocampus and mammillary bodies, and returns to the anterior thalamic nuclei (Papez 1937; Vinogradova 1975). It is proposed that activation of this 'closed' circuit during the early phase of the formalin response induces a sensitized state within the limbic system, enhancing responses to subsequent stimulation. Recent physiological evidence supports this concept. Brainstem stimulation has been found to enhance the responsiveness of the anterior thalamic nuclei to stimulation of the mammillary bodies and cingulate cortex (Pare et al. 1990). Furthermore, noxious peripheral stimulation produces bursting activity in CA1 neurons of the hippocampus (Sinclair and Lo 1986). The selective blocking of neural activity in the cingulum bundle or fornix during the early phase of formalin may reduce nociceptive responses by preventing the development of long-term changes in these structures.

Post-operative pain

The idea that CNS changes produced by tissue damage and noxious inputs associated with surgery could contribute to postoperative pain has existed for several decades (Crile 1913). However, it was only after the research by Woolf and Wall (1986a) provided a

sound justification for pre-emptive treatment that this idea began to receive the clinical attention it deserves. Woolf and Wall (1986a) demonstrated in experimental animals that opioids are much more effective at reducing stimulus-induced increases in the excitability of the dorsal horn if they are administered prior to, rather than following, C-fiber electrical nerve stimulation. Recent clinical evidence supports the hypothesis that the administration of analgesic agents prior to surgery may prevent the central sensitizing effects of the surgical procedure. In this manner it may be possible to reduce postoperative pain intensity or lower postoperative analgesic requirements for periods much longer than the duration of action of the pre-operatively administered agents.

In a recent issue of this journal, with a lead editorial on postoperative pain prevention by Wall (1988), McQuay et al. (1988) examined the possible prophylactic effect of opiate premedication and/or local anesthetic nerve blocks on postoperative pain. They provided data showing that the time to first request for postoperative analgesics was longest among patients who had received a pre-surgical treatment with opiates and nerve blocks, and shortest among patients who had received neither. Similar findings have recently been reported by Kiss and Kilian (1992) who showed that opiate pretreatment increased the length of time until request for first analgesic, reduced the percentage of patients requesting analgesics, and decreased analgesic consumption in the first 48 h for patients undergoing lumbar disc surgery. Over the past few years, additional evidence has accumulated to support the hypothesis that pre-emptive analgesia using a variety of agents (e.g., opiates, local anesthetics, NSAIDs) prolongs the time to first request for analgesics, reduces postoperative pain intensity, or decreases postoperative analgesic requirements among patients undergoing inguinal herniorraphy (Bugedo et al. 1990; Tverskoy et al. 1990), oral surgery (Tuffin et al. 1989; Hutchison et al. 1990; Campbell et al. 1991), tonsillectomy (Ågren et al. 1989; Jebeles et al. 1991), abdominal surgery (Mogensen et al. 1992), orthopedic surgery (Ringrose and Cross 1984; McGlew et al. 1991), lower limb amputation (Mann and Bisset 1983; Bach et al. 1988) and thoracotomy (Katz et al. 1992b).

Tverskoy et al. (1990) clearly demonstrated the benefits of pre-incisional blockade on postoperative pain. Patients who were undergoing inguinal herniorraphy received either general anesthesia alone, general anesthesia plus subcutaneous and intramuscular injections of bupivacaine prior to surgical incision, or spinal bupivacaine administered pre-operatively. All patients received the same regimen of postoperative analgesics. Twenty-four and 48 h after surgery, postoperative incisional pain, movement-associated pain, and pain induced by pressure applied to the surgical wound were all significantly lower in the two groups that had received bupivacaine prior to surgical incision compared to patients that received general anesthesia alone. Similar results were reported by Bugedo et al. (1990) who compared the effects of spinal lidocaine alone with spinal lidocaine plus ilioinguinal and iliohypogastric nerve blocks using bupivacaine prior to surgery in patients undergoing herniorraphy. The combination of spinal plus peripheral nerve blocks resulted in lower postoperative pain scores 24 and 48 h after surgery as well as reduced analgesic requirements during the first 48 postoperative hours.

Recently, a number of well-controlled, double-blind studies have also shown that pre-operative administration of NSAIDs by a variety of routes reduces postoperative pain long after the clinical duration of action of the NSAIDs. Campbell et al. (1990) found that intravenous diclofenac administered before tooth extraction resulted in less postoperative pain the day after surgery when compared with pretreatment using intravenous fentanyl or a placebo. Similarly, Hutchison et al. (1990) reported that compared to patients pre-treated with a placebo, significantly fewer patient who received orally administered prioxicam before tooth extraction required supplemental postoperative analgesics, and their time to first postoperative analgesic request was longer. McGlew et al. (1991) demonstrated that on days 1–3 after spinal surgery, postoperative pain scores and opiate consumption were significantly lower among patients who had received indomethacin suppositories compared with placebo suppositories 1 h before surgery.

Taken together, these studies demonstrate that opiate premedication, regional local anesthesia, spinal anesthesia, or systemic NSAIDs administered before incision are more effective than placebo or no treatment controls. The implication of these studies for clinical pathological pain is that changes in central neural function that are induced by surgery alter subsequent perception in such a way that nociceptive inputs from the surgical wound may be perceived as more painful (hyperalgesia) than they would otherwise have been, and innocuous inputs may give rise to frank pain (allodynia).

However, these early studies on the prevention of postoperative pain with pre-operative analgesics did not compare the pretreatment with the effects of the same treatments administered after surgery (McQuay 1992). Demonstrating that pretreatment with analgesics, but not a placebo, lessens pain and decreases postoperative analgesic requirements at a time when the agents are no longer clinically active indicates that the central component of postoperative pain can be prevented or pre-empted. In the absence of a postincisional or postoperative treatment condition, it is not possible to determine the separate contributions of

factors associated with the intra-operative versus the postoperative period to the enhanced postoperative pain experience. It may be that analgesic pretreatments reduce the development of local inflammation, a potential peripheral factor that could contribute to postoperative pain, rather than inhibiting central sensitization induced by noxious inputs during surgery. This may be particularly important in the case of NSAIDs (Campbell et al. 1990; Hutchison et al. 1990; McGlew et al. 1991) which act primarily to reduce peripheral inflammation, but may also be important in the case of infiltration with local anesthetics (Bugedo et al. 1990; Tverskoy et al. 1990) since local anesthesia would also reduce peripheral inflammation that is dependent on the efferent functions of peripheral nerves (i.e., neurogenic inflammation). Altering the timing of administration of analgesic agents (i.e., before or after incision vs. before or after surgery) may provide clues to the specific intra-operative (e.g., incision, wound retraction) or postoperative (e.g., inflammation) factors that contribute to the central neural changes underlying the enhanced pain.

Recently, studies have been directed at identifying specific intra- and postoperative factors that may contribute to surgically induced postoperative pain and hyperalgesia by comparing the effects on postoperative pain of opiates or local anesthetic agents administered either before or after surgery (Rice et al. 1990; Dahl et al. 1992b; Dierking et al. 1992; Ejlersen et al. 1992; Katz et al. 1992b). Rice et al. (1990) found that the timing of a caudal block with bupivacaine relative to the start of surgery had no effect on postoperative pain in a pediatric population undergoing brief (30 min) ambulatory surgical procedures. Dierking et al. (1992) evaluated the effects of a local-anesthetic inguinal field block administered before or after inguinal herniorraphy on postoperative pain and analgesic consumption. They also found that the timing of the block relative to surgical trauma did not produce differences in postoperative pain or analgesic use. Similarly, Dahl et al. (1992b) reported that postoperative pain and analgesic consumption did not depend on whether a 72-h continuous infusion of epidural bupivacaine and morphine was started before incision or immediately after surgery, approximately 2.5 h later.

In contrast, Ejlersen et al. (1992) reported that even though pre-incisional blockade was not associated with significantly less postoperative pain, fewer patients in the pre-incisional group, as opposed to a postincisional group, required supplemental postoperative analgesics, and their demand for analgesics was delayed. In addition, Katz et al. (1992b) recently demonstrated that pre-incisional treatment with epidural fentanyl in patients undergoing thoracotomy resulted in significantly lower visual analogue scale (VAS) pain scores 6 h after treatment when compared with a postincisional treatment. The significant difference in pain intensity could not be explained by lingering plasma concentrations of fentanyl, which at the time of pain assessment were equally sub-therapeutic in both groups, or by patient-controlled analgesia (PCA) morphine consumption, which until this point was virtually identical in both groups. Also, between 12 and 24 h after surgery, the control group self-administered more than twice the amount of PCA morphine than the experimental group, a finding that parallels the study by Woolf and Wall (1986a).

Although these latter studies comparing pre- and postincisional or surgical analgesic treatments have been somewhat inconclusive, several clinical, methodological and theoretical issues have arisen which significantly affect the conclusions drawn from these studies. One issue concerns the use of systemic opioids at the time of induction of the general anesthetic prior to surgery, or the use of these agents intra-operatively, as the surgery is underway. The pre-operative administration of opioids (alfentanyl, fentanyl) to all patients, as one component of the general anesthetic technique, may provide a sufficient block of nociceptive inputs to prevent or attenuate the development of CNS sensitization in all patients and may contribute to the lack of a clinically significant difference in outcome between the pre- and post-treatment groups in the studies of Dierking et al. (1992) and Dahl et al. (1992b). We do not as yet know the minimum effective doses of pre-operatively administered systemic opioids that significantly attenuate or prevent the central consequences of noxious peri-operative events that may contribute to postoperative pain. However, we do know from animal studies (Woolf and Wall 1986a) that the dose of systemic morphine required to abolish established noxious stimulus-induced central hyperexcitability is an order of magnitude greater than the pretreatment dose required to prevent these prolonged central changes. Until the effects of pre- and intra-operative narcotics on postoperative pain have been established, their administration as part of the general anesthetic procedure in clinical studies of pre-emptive analgesia will confound the main outcome measures that are assessed (Katz et al. 1992a).

A second issue concerns the trade off between achieving the clinical objective of abolishing postoperative pain and demonstrating specifically that the trauma associated with surgery may have a prolonged effect on postoperative pain. These two objectives run at cross purposes, since in order to demonstrate the latter the former may be compromised. In the study by Dahl et al. (1992b) described above, postoperative VAS pain scores at rest were near zero in both groups (i.e., the group treated before and after surgery as well as the group treated only after surgery), making it virtually impossible to demonstrate an advantage of pre- over

postoperative analgesic administration. The postoperative regimen of epidural bupivacaine and morphine may have been so effective as to block all nociceptive activity at the spinal level. Use of a lower dosage, or the use of epidural PCA instead of a fixed high dosage, may have provided the opportunity for lasting effects of the surgical trauma to become evident. This issue as it relates to pre-emptive analgesia is not whether postoperative pain can be abolished regardless of the timing of administration of analgesics relative to surgical incision, although abolishing postoperative pain is a clinical objective that we all should strive to achieve. When examining the efficacy of pre-emptive analgesia, patients must be able to demonstrate their level of pain either directly through verbal report (e.g., VAS pain scores) or indirectly, through their consumption of postoperative analgesics.

Neurochemical mediators of noxious stimulus-induced plasticity

The evidence presented above suggests that peripheral injuries are capable of producing changes in CNS function which in turn influence nociceptive processing. We will now examine the mechanisms that may underlie the central neuroplasticity generated by noxious stimulation or injury. Specifically, we will assess the contribution of C-fiber neuropeptides and excitatory amino acid (EAA) transmitters to noxious stimulus-induced changes in central neural function. We will also evaluate the role of these transmitters in animal models of secondary hyperalgesia and persistent pain.

C-fiber neuropeptides

Several lines of evidence suggest that C-fiber neuropeptides are involved in triggering CNS plasticity following injury or noxious stimulation. A role for C-fiber neuropeptides in nociception is suggested since noxious stimulation or peripheral inflammation causes the release of substance P (SP) (Go and Yaksh 1987; Oku et al. 1987; Duggan et al. 1988), neurokinin A (Hua et al. 1986; Duggan et al. 1990) somatostatin (Kuraishi et al. 1985; Morton et al. 1988), calcitonin gene-related peptide (CGRP) (Saria et al. 1986) and galanin (Morton and Hutchison 1990) in spinal cord dorsal horn. There is also a decrease in immunoreactive staining for the neuropeptides SP and CGRP in chronic pain models such as experimental arthritis (Sluka et al. 1992) and experimental peripheral neuropathy (Bennett et al. 1989; Cameron et al. 1992). Furthermore, the iontophoretic application of SP and other neurokinins produces an excitation of dorsal horn neurons (Henry 1976; Willcockson et al. 1984b), while intrathecal treatment produces behavioral hyperalgesia (Moochala and Sawynok 1984; Cridland and Henry 1986) or nociceptive behaviors (Hylden and Wilcox 1981; Seybold et al. 1982; Gamse and Saria 1986) in rodents.

A role of C-fiber neuropeptides in noxious stimulus-induced plasticity is suggested by several findings. Repetitive stimulation of dorsal roots elicits a slow depolarization in dorsal horn neurons which is mimicked by SP (Murase and Randic 1984), neurokinin A (Murase et al. 1989), CGRP (Ryu et al. 1988), vasoactive intestinal polypeptide (VIP) (Urban and Randic 1984) or cholecystokinin (CCK) (Murase et al. 1987), and is blocked by SP antagonists or capsaicin applied to the tissue bath (Urban and Randic 1984). Iontophoretic application of neuropeptides, such as SP, produces enhanced dorsal horn neuron responses to noxious thermal and mechanical stimulation (Henry 1976; Randic and Miletic 1977). The increased excitability in flexor efferents, induced either by C-fiber electrical stimulation or by the application of chemical irritants, is blocked by pretreatment of the sciatic and saphenous nerves with the C-fiber neurotoxin capsaicin (Woolf and Wall 1986b) or by the SP antagonist spantide II (Wiesenfeld-Hallin et al. 1990). Intrathecal application of the C-fiber neuropeptides SP (Woolf and Wiesenfeld-Hallin 1986), neurokinin A (Xu et al. 1991), CGRP (Woolf and Wiesenfeld-Hallin 1986), VIP (Wiesenfeld-Hallin 1987), somatostatin (Wiesenfeld-Hallin 1985) and galanin (Wiesenfeld-Hallin et al. 1989) produces prolonged enhancements in the excitability of the flexion reflex. In addition, the hyperalgesia that develops in the hind paw contralateral to a thermal injury is mimicked by intrathecal treatment with SP and neurokinin A, and reversed by pretreatment with the SP antagonist, D-Arg^1, Pro^2, D-Phe^2, -D-His^9-SP (Coderre and Melzack, 1991). Subcutaneous injection of formalin, which elicits a persistent nociceptive response associated with central changes (Coderre et al. 1990), evokes an immediate, intense barrage of C-fiber afferent activity (Heapy et al. 1990), and produces an increase in SP in the cerebrospinal fluid (Kuraishi et al. 1989). Furthermore, nociceptive responses to formalin are significantly suppressed in rats pretreated with peptide (Murray et al. 1991) and non-peptide (Yamamoto and Yaksh 1991; Yashpal et al. 1992) SP antagonists, as well as the C-fiber neurotoxin capsaicin and its non-pungent analogue olvanil (Dray and Dickenson 1991).

Excitatory amino acids

Additional evidence implicates a contribution of EAAs to injury-induced neuroplasticity. EAAs have widespread activity in the CNS including the spinal cord (Watkins and Evans 1981; Davies and Watkins 1983) and thalamus (Eaton and Salt 1990). The role of

EAAs in nociception is suggested since noxious stimulation or peripheral inflammation causes the release of glutamate and aspartate in spinal cord dorsal horn (Skilling et al. 1988; Sorkin et al. 1992). Furthermore, iontophoretic application of EAAs produces an excitation of dorsal horn neurons (Curtis and Watkins 1960; Willcoxson et al. 1984a; Schnieder and Perl 1988), while intrathecal treatment produces both behavioral hyperalgesia and spontaneous nociceptive behaviors (Aanonsen and Wilcox 1986, 1987).

A role of EAAs in noxious stimulus-induced plasticity is suggested by several findings. Repetitive C-fiber stimulation produces a 'wind-up' of dorsal horn neuron activity which is mimicked by the application of L-glutamate or NMDA (Gerber and Randic 1989; King et al. 1989), and blocked by application of either competitive (Dickenson and Sullivan 1987a; Thompson et al. 1990) or non-competitive (Davies and Lodge 1987; Thompson et al. 1990) NMDA antagonists. Iontophoretic application of EAAs produces receptive field changes in dorsal horn neurons (Zieglgansberger and Herz 1971), as well as enhanced dorsal horn neuron responses to non-noxious and noxious mechanical stimulation (Aanonsen et al. 1990; Dougherty and Willis 1991b). Dorsal horn neurons which are sensitized following peripheral tissue injury/inflammation show increased responsiveness to the iontophoretic application of EAAs (Dougherty and Willis 1992; Dougherty et al. 1992c), and exhibit a reduction in responsiveness or sensitization following intravenous administration of ketamine or iontophoretic application of ketamine or 2-amino-5-phosphonopentanoic acid (AP-5) (Schaible et al. 1991), or the administration of CNQX or 2-amino-7-phosphonoheptanoic acid (AP-7) to dorsal horn neurons by microdialysis (Dougherty et al. 1992b). Intrathecal administration of the EAAs L-glutamate or L-aspartate produces an increase in the excitability of flexor efferents (Woolf and Wiesenfeld-Hallin 1986), while competitive or non-competitve NMDA antagonists reduce the facilitation of flexion reflexes induced by electrical (C-fiber) stimulation or cutaneous application of the chemical irritant mustard oil (Woolf and Thompson 1991). Hyperalgesia that develops in the hind paw contralateral to a thermal injury is both mimicked following intrathecal treatment with NMDA, and reversed by the NMDA receptor antagonist (AP-5) (Coderre and Melzack 1991). In a recent study in humans (Gordh and Kristensen 1992), it has been shown that intrathecal treatment with the competitive NMDA receptor antagonist CPP abolished afterdischarges and spreading pain and hyperalgesia (symptoms proposed to be associated with windup) in a patient with neuropathic pain.

NMDA antagonists have been particularly effective at reducing persistent pain associated with central sensitization. The non-competitive NMDA antagonist MK-801 reduces the hyperalgesia which develops in rats with peripheral neuropathy (Davar et al. 1991; Mao et al. 1992b) or adjuvant-induced inflammation (Ren et al. 1992) and reduces autotomy behavior in rats with peripheral nerve sections (Seltzer et al. 1991b). MK-801 also reduces the adjuvant inflammation-induced expansion of the receptive fields of nociceptive neurons in spinal cord dorsal horn (Dubner and Ruda 1992). In humans, ischemic and postoperative pain is suppressed by subanesthetic doses of ketamine (Maurset et al. 1989), while in the rat, the increased activity in dorsal horn in response to ischemia associated with femoral artery occlusion is inhibited by intrathecal application of AP-5 (Sher and Mitchell 1990). Subcutaneous injection of formalin evokes an increased release of glutamate and aspartate in spinal cord dorsal horn (Skilling et al. 1988), while the sustained responses of spinal nociceptive cells to noxious peripheral stimulation produced by subcutaneous formalin injection are reduced by intrathecal administration of selective NMDA antagonists (Haley et al. 1990). Nociceptive responses to formalin are also both enhanced by pretreatment with the EAA agonists, L-glutamate and L-aspartate, as well as combinations of NMDA + AMPA or NMDA + trans-ACPD (Coderre and Melzack 1992a), and suppressed by pretreatment with the NMDA antagonists AP-5 or MK-801 (Murray et al. 1991; Coderre and Melzack 1992a).

Interaction of neuropeptides and excitatory amino acids

An interaction of neuropeptides and EAAs in central nociceptive processing is also suggested by several findings. Neuropeptides and EAAs are found to be co-localized in the central terminals of primary afferent neurons (DeBiasi and Rustioni 1988). SP produces a prolonged enhancement of the responses of dorsal horn neurons to ionotophoretically applied glutamate (Willcockson et al. 1984b) or NMDA (Dougherty and Willis 1991a). Combined treatment with SP and NMDA produces a profound enhancement of the responses of dorsal horn neurons to non-noxious and noxious mechanical stimulation (Dougherty and Willis 1991a), as well as the behavioral responses to noxious chemical stimulation (Mjellem-Joly et al. 1992). These effects likely depend on both pre-synaptic and postsynaptic actions of neuropeptides on EAA neurotransmission since SP, neurokinin A or CGRP have been found to enhance the release of glutamate and aspartate from spinal cord dorsal horn (Kangrga and Randic 1990; Smullin et al. 1990), while SP produces a potentiation of glutamate- and NMDA-induced currents in rat spinal dorsal horn neurons in vitro (Randic et al. 1990). Recent evidence also indicates that the amount of SP required to increase EAA release is reduced in rats with peripheral neuropathy following partial sciatic nerve ligation (Skilling et al. 1992a).

Cellular mechanisms of noxious stimulus-induced plasticity

The above data suggest that both neuropeptides and EAAs may contribute to CNS neuroplasticity affecting nociceptive behavior. However, the manner by which these substances produce these central changes is not clear. It is possible that neuropeptides and EAAs trigger alterations in membrane excitability through interactions with second messenger systems and protein kinases which phosphorylate membrane-bound proteins (Nestler and Greengard 1983). Evidence suggests that there is a contribution of intracellular calcium (Ca^{2+}), second messenger systems and protein kinases to the development of noxious stimulus-induced neuroplasticity.

Intracellular calcium

Recent evidence suggests that noxious stimulation may produce an increase of intracellular Ca^{2+} in nociceptive neurons which influences the excitability of the cell. Neurotransmitters released in response to noxious stimulation are known to affect the intracellular levels of Ca^{2+}. Glutamate and aspartate stimulate the influx of Ca^{2+} through NMDA receptor-operated channels (MacDermott et al. 1986). SP produces an elevation in intracellular Ca^{2+} by mobilizing its release from intracellular stores (Womack et al. 1988), while both SP (Womack et al. 1989) and CGRP (Oku et al. 1988) increase Ca^{2+} influx through voltage-gated Ca^{2+} channels.

Studies assessing the behavioral effects of agents affecting calcium availability suggest that Ca^{2+} influx is more critical in persistent pain models where central sensitization and plasticity are present. These studies indicate that brief, phasic nociceptive tests, such as the tail-flick and hot-plate tests, are unaffected by Ca^{2+} (Harris et al. 1975; Chapman and Way 1982), Ca^{2+} chelators (Harris et al. 1975; Ben-Sreti et al. 1983), or Ca^{2+} channel antagonists (Benedek and Sikszay 1984; Contreras et al. 1988), while tonic nociceptive tests, such as the formalin and acetic acid-induced writhing tests, are sensitive to Ca^{2+}, Ca^{2+} ionophores and Ca^{2+} channel agonists (Chapman and Way 1982; Coderre and Melzack 1992b) which increase nociceptive responses, or Ca^{2+} chelators and Ca^{2+} channel antagonists (Del Pozo et al. 1987; Coderre and Melzack 1992b; Miranda et al. 1992) which reduce nociceptive responses.

While the behavioral effects of agents affecting Ca^{2+} availability may depend, in part, on the effect of Ca^{2+} influx on presynaptic transmitter release (Rubin 1974), it is possible that their effects may also depend on Ca^{2+} influx in the postsynaptic cell. Although nociceptive responses to formalin are significantly suppressed by intrathecal administration of voltage-gated Ca^{2+} channel antagonists, they are more effectively suppressed by Ca^{2+} chelators which reduce all available extracellular Ca^{2+} (not just that which enters through voltage-gated Ca^{2+} channels), and by non-competitive NMDA antagonists which block Ca^{2+} influx through NMDA receptor-operated Ca^{2+} channels. Furthermore, the enhancement of nociceptive responses to formalin injury following intrathecal treatment with L-aspartate or L-glutamate is prevented by agents which block NMDA receptor-operated Ca^{2+} channels, but not by those which block voltage-gated calcium channels (Coderre and Melzack 1992b). These data suggest the development of persistent nociception after formalin injury is influenced by the influx of Ca^{2+} into postsynaptic cells, particularly through NMDA receptor-operated channels (MacDermott et al. 1986).

Intracellular second messengers

Recent evidence also implies that noxious stimulus-induced plasticity may depend, in part, on the phospholipase C (PLC) second messenger system. Activity at either NK-1 receptors by SP (Mantyh et al. 1984), or at metabotropic EAA receptors by glutamate and aspartate (Sugiyama et al. 1987), stimulates the hydrolysis of inositol phospholipids by activating a polyphosphoinositide-specific PLC. PLC is an enzyme which catalyzes the hydrolysis of polyphosphatidylinositol into the intracellular messengers inositol trisphosphate (IP_3) and diacylglycerol (DAG). It has recently been shown that neomycin (an agent which inhibits PLC activity) produces a substantial reduction in nociceptive responses during the formalin test (Coderre 1992). Since inhibition of PLC with neomycin produces a significant reduction in formalin nociceptive responses, it is assumed that IP_3 and DAG play a significant role in formalin-induced plasticity. Following its production, IP_3 stimulates the release of Ca^{2+} from internal stores; on the other hand DAG stimulates the translocation and activation of protein kinase C (PKC). When activated by DAG, PKC phosphorylates specific substrate proteins that contribute to various cellular processes, including neurotransmitter release and transduction (Nishizuka 1986). Stimulation of PKC with phorbol esters and synthetic DAG, or the intracellular microinjection of PKC, has been found to enhance Ca^{2+} currents (DeRiemer et al. 1985), which may increase neuronal excitability as well as presynaptic transmitter release, and to reduce both Ca^{2+}-dependent K^+ currents (Alkon et al. 1986) and Cl^- currents (Madison et al. 1986), which may result in the prolongation of depolarization and afterdischarges associated with an inhibition of spike accommodation.

Recently, Gerber et al. (1989) have shown that activators of PKC enhance the basal and evoked release of glutamate and aspartate in the spinal cord slice, as well as the depolarizing responses of dorsal horn neurons to exogenous glutamate and NMDA. Furthermore, Chen and Huang (1992) have demonstrated that PKC increases NMDA-activated currents in isolated trigeminal cells by increasing the probability of channel openings and by reducing the voltage-dependent Mg^{2+} block of NMDA-receptor channels. The resultant increased activity at the NMDA receptor would permit more Ca^{2+} ions to enter the cell, raising intracellular Ca^{2+}, and so further increasing PKC activity, and its effects on NMDA receptor channels. This positive feedback loop may be important for the induction or maintenance of sensitization in central neurons.

It has been shown recently that the activation of metabotropic EAA receptors with quisqualate or trans-ACPD produces an enhancement of NMDA currents in both hippocampal neurons (Anikstejn et al. 1991; Ben-Ari et al. 1992) and oocytes injected with rat brain RNA (Kelso et al. 1992). Furthermore, since in both these studies the effects of metabotropic EAA receptor activation were blocked by PKC inhibitors, it is likely that activity at the metabotropic receptor enhances NMDA currents by stimulating intracellular PKC.

Recent behavioral studies (Coderre 1992), indicate that nociceptive responses to formalin injury are suppressed following intrathecal treatment with H-7 which inhibits PKC, and enhanced after treatment with phorbol esters or SC-10 which stimulate PKC. These results are consistent with a contribution of PKC to the persistent nociceptive response elicited by subcutaneous injection of formalin. A contribution of PKC to noxious stimulus-induced plasticity is consistent with its established role in long-term potentiation (Malenka et al. 1986; Hu et al. 1987). Furthermore, a contribution of PKC to persistent pain is consistent with the findings of Hayes et al. (1992) who demonstrated that monosialoganglioside, which inhibits the translocation of PKC (Vaccarino et al. 1987), reduces behavioral hyperalgesia in rats with peripheral neuropathy.

Molecular mechanisms of noxious stimulus-induced plasticity

In addition to altering membrane permeability, increases in intracellular Ca^{2+} and the activation of PKC result in the increased expression of proto-oncogenes such as c-*fos*. The protein products of these proto-oncogenes act as third messengers which are believed to be involved in the transcriptional control of genes that encode a variety of neuropeptides, including enkephalins and tachykinins.

Expression of c-fos and other proto-oncogenes

Noxious stimulation leads to the expression of proto-oncogenes and their protein products. Hunt et al. (1987) first demonstrated that the c-*fos* protein product Fos is expressed in postsynaptic dorsal horn neurons following noxious thermal or chemical stimulation of the skin. The expression of Fos has also been demonstrated in rat spinal dorsal horn in response to noxious pinch of the hind paws (Bullitt 1989), the injection of formalin (Presley et al. 1990; Kehl et al. 1991) or carageenan (Draisci and Iadorola 1989) into a hind paw or sodium urate crystals into joints (Menétrey et al. 1989), the injection of acetic acid into viscera (Menétrey et al. 1989), the induction of poly-arthritis with Freund's adjuvant (Menétrey et al. 1989), and the development of a neuroma following nerve injury (Chi et al. 1990). Noxious stimulation also leads to the spinal cord expression of other proto-oncogenes products, including Fos B, Jun, Jun B, Jun D, NGF1-A, NGF1-B and SRF (Herdegen et al. 1990a,b; Wisden et al. 1990; Herdegen et al. 1991a–c). Furthermore, following noxious stimulation there is an increased expression of Fos in CNS structures involved in pain transmission, including the periaqueductal grey, thalamus, habenula and somatosensory cortex (Bullit 1989; Iadorola et al. 1990; Herdegen et al. 1991b). Importantly, there is a strong correlation between pain behavior and the number of cells expressing Fos (Presley et al. 1990). Moreover, morphine pretreatment produces a dose-dependent suppression of Fos expression which corresponds with its analgesic effects (Presley et al. 1990; Tolle et al. 1991).

Relationship between c-fos, central neuroplasticity and hyperalgesia

Although there is evidence that noxious stimulation leads to the expression of Fos, this does not necessarily mean that c-*fos* is involved in central plasticity associated with hyperalgesia. However, there is growing evidence of a relationship between noxious stimulus-induced Fos expression, central neuroplasticity and behavioral hyperalgesia. First, the noxious stimuli that produce Fos expression (heat injury, formalin injection and inflammatory agents) also produce behavioral hyperalgesia which is associated with central neuroplasticity (Coderre and Melzack 1985, 1987; Kayser and Guilbaud 1987; Coderre et al. 1990). Second, the time course of Fos expression coincides with the development of behavioral hyperalgesia. This co-occurrence is evident in cases where noxious inputs are driven by a specific peripheral lesion. For example, peripheral inflammation induced by carrageenan produces both an increase in c-*fos* mRNA and behavioral hyperalgesia that peak over a similar time course (Draisci and Iadorola 1989).

However, the co-occurrence of Fos expression and

behavioral hyperalgesia is also evident in cases where a peripheral stimulus initiates but does not apparently maintain the hyperalgesia. Thus, heat injury of a rat's hind paw produces an immediate hyperalgesia in the injured hind paw and hyperalgesia in the uninjured contralateral hind paw which develops between 4 and 24 h after injury (Coderre and Melzack 1985, 1991). Similarly, heat injury of a rat's hind paw, or C-fiber stimulation of the sciatic nerve, not only produces an immediate expression of Fos in the spinal cord dorsal horn ipsilateral to the injury, but also produces a 'second wave' of Fos (Williams et al. 1990) Jun (Herdegen et al. 1991a), Jun D (Herdegen et al. 1991c) and NGF1A (Herdegen et al. 1990b) activity in both ipsilateral and contralateral dorsal horns 4–24 h after the injury. An association of the behavioral hyperalgesia and Fos expression with neural plasticity after heat injury is suggested since both the contralateral hyperalgesia (Coderre and Melzack 1987) and the Fos expression in the contralateral dorsal horn (Williams et al. 1990) still develop when the injured hind limb is locally anesthetized shortly after the injury. Furthermore, Herdegen et al. (1990a) have shown that while 'low-level' noxious cutaneous stimulation of one hind paw induced Fos in only a few neurons, the same stimulus repeated 1 h later in the contralateral hind paw induced dense Fos labelling in many neurons. The 'second wave' expression of proto-oncogenes in the contralateral dorsal horn, and the enhanced expression of Fos if there has been prior noxious stimulation of the contralateral hind paw, are consistent with the idea that central sensitization results in the spread of hyperalgesia to a limb contralateral to a heat injury. Interestingly, while heat injury of a rat's hind paw leads to the development of both contralateral hyperalgesia and a 'second wave' of proto-oncogenes products in the contralateral dorsal horn, inflammatory lesions with formalin (Coderre et al. 1990) or carrageenan (Hargreaves et al. 1988) produce minimal contralateral behavioral responses and little or no proto-oncogene activity in the contralateral dorsal horn (Williams et al. 1990; Herdegen et al. 1991c, Noguchi et al. 1991, 1992).

Triggers of c-fos gene expression

Since an elevation of intracellular Ca^{2+} is crucial to the transcriptional activation of the c-*fos* proto-oncogene (Morgan and Curran 1986), it is possible that c-*fos* is induced in spinal cord dorsal horn following Ca^{2+} entry through NMDA receptor-operated Ca^{2+} channels, or through voltage-gated Ca^{2+} channels following the activation of other receptors, such as the NK-1 receptor by SP. Indeed, NMDA receptor activation with glutamate or NMDA leads to increases in c-*fos* mRNA or Fos protein in rat cerebellar granule cells (Szekely et al. 1989), dentate gyrus (Lerea et al. 1992) and cortical neurons (Hisanaga et al. 1992) in culture. Furthermore, the effect of glutamate is blocked by competitive or non-competitive NMDA receptor antagonists, or by Mg^{2+} which blocks NMDA-receptor-operated Ca^{2+} channels (Szekely et al. 1989; Hisanaga et al. 1992). Although c-*fos* activity can also be elevated by increasing Ca^{2+} availability with the Ca^{2+} ionophore ionomycin (Szekely et al. 1989) or reduced by the chelation of extracellular Ca^{2+} with EGTA (Lerea et al. 1992), the importance of NMDA-receptor operated Ca^{2+} channels is indicated by the finding that the glutamate or NMDA-induced increase in c-*fos* expression is unaffected by nifedipine or nitrendipine, selective blockers of voltage-gated Ca^{2+} channels (Szekely et al. 1989; Lerea et al. 1992).

While it has been demonstrated that noxious stimulation-induced expression of Fos in the spinal dorsal horn is substantially reduced by pretreatment with the NMDA receptor antagonist MK-801 (Kehl et al. 1991; Birder and de Groat 1992), others have found that NMDA antagonists do not affect the distribution of Fos-labelled neurons in spinal cord (Wisden et al. 1990; Tolle et al. 1991). This discrepancy may depend on differences in the nature of the noxious stimulus applied to the periphery (chemical vs. thermal stimulation), or specific differences in experimental methods, such as the type of anesthetic agent used.

Recently, Lerea et al. (1992) have demonstrated that c-*fos* mRNA is also induced in dentate gyrus neurons following the activation of kainate/AMPA receptors with kainic acid. While both NMDA- and kainic acid-induced c-*fos* expression was eliminated by chelation of extracellular Ca^{2+} with EGTA, only kainic acid-induced c-*fos* expression was reduced with the voltage-gated Ca^{2+} channel blocker nifedipine. These findings suggest that c-*fos* induction depends on increases in intracellular Ca^{2+} that results due to an influx of Ca^{2+} through either NMDA receptor-operated Ca^{2+} channels after NMDA receptor activation, or through voltage-gated Ca^{2+} channels after activation of non-NMDA EAA receptors.

There is also an increase in the expression of Fos protein in spinal cord neurons in response to SP (Bigot et al. 1991), and increase in c-*fos* mRNA in cerebellar granule cells in response to non-NMDA EAA receptor agonists (Szekely et al. 1987), such as quisqualate. Both SP and quisqualate act at metabotropic receptor sites to stimulate the second messengers IP_3 and DAG following the activation of PLC (Sugiyama et al. 1987). Furthermore, c-*fos* expression is also induced in cultures of neuronal cells (Naranjo et al. 1991) by stimulation of PKC with phorbol esters or DAG. Interestingly, the ability of quisqualate to induce the expression of c-*fos* in cerebral granule cells is lost when Mg^{2+} is added to block NMDA receptor-operated Ca^{2+} channels (Szekely et al. 1989). This suggests that the expression of c-*fos* depends on an interaction between Ca^{2+}

influx through NMDA receptor-operated Ca^{2+} channels and the stimulation of second messengers, such as DAG, which are linked to metabotropic receptors and activate PKC (Nishizuka, 1986). Perhaps this is not surprising, since the DAG-induced translocation and activation of PKC depends on an accompanying Ca^{2+} influx (see Rasmussen 1986). Thus, it is possible that the expression of early immediate genes, such as c-*fos*, is induced by Ca^{2+} influx and the translocation and stimulation of PKC, following the activation of both NMDA and non-NMDA EAA receptors or other metabotropic receptors, such as the NK-1 (SP) receptor, which by activating PLC stimulate the production of DAG.

Consequences of c-fos expression

We know that c-*fos* is expressed in response to noxious stimulation, and may be triggered by an EAA- and/or a neuropeptide-induced influx of Ca^{2+} and activation of PKC, but what is the significance of its expression to the development of noxious stimulus-induced plasticity or hyperalgesia? Early immediate genes are thought to code for transcription factors controlling the expression of downstream genes. The Fos protein forms a heterodimer with Jun which binds to AP-1-like elements to form a DNA binding site in the promoter region of its target gene (Morgan and Curran, 1989).

There is evidence to suggest that c-*fos* participates in the regulation of mRNA encoding various peptides in the rat spinal cord. Peripheral inflammation, trigeminal nerve stimulation or nerve lesions result in the increase in the expression of mRNA encoding dynorphin (Höllt et al. 1987; Ruda et al. 1988), enkephalin (Iadorola et al. 1988; Nishimori et al. 1989), SP (Noguchi et al. 1988; Minami et al. 1989) and CGRP (Piehl et al. 1991) in the dorsal root ganglion, dorsal horn or the nucleus caudalis. Furthermore, there is strong evidence suggesting that the preprodynorphin and preproenkephalin genes are targets for c-*fos*. Thus, the increase in Fos protein which peaks 2 h after peripheral inflammation is followed by a modest increase in preproenkephalin mRNA and a large increase in preprodynorphin mRNA, each peaking at 3 days (Iadorola et al. 1988). While the noxious stimulus-induced increase in preprodynorphin mRNA is followed by a subsequent increase in dynorphin peptide (Iadorola et al. 1988; Weihe et al. 1989), the increased preproenkephalin mRNA does not produce measurable increases in enkephalin peptide (Iadorola et al. 1988). In addition, following peripheral inflammation, Fos protein-like immunoreactive (Fos-IR) neurons are found to co-localize with neurons expressing either preprodynorphin or preproenkephalin mRNA (Noguchi et al. 1991; 1992). Over 80% of the neurons in the superficial laminae and the neck of the dorsal horn which express preprodynorphin or preproenkephalin co-localize Fos-IR. The high percentage of preprodynorphin and preproenkephalin mRNA co-localized with Fos-IR has been taken as evidence that Fos phosphoprotein signalling is coupled to dynorphin and enkephalin gene transcription (Dubner and Ruda 1992). It has also been shown that phorbol esters, which activate PKC, lead to an induction of c-*fos* mRNA (within 30 min) and a later increase in the level of preprodynorphin mRNA (between 1.5 and 6 h) in neuronal cells in culture (Naranjo et al. 1991). Furthermore, it has been recently shown that Fos and Jun proteins bind to form an AP-1-like site in the promoter regions of the rat preprodynorphin (Naranjo et al. 1991) and preproenkephalin (Sonnenberg et al. 1989) genes.

If c-*fos* is involved in the transcriptional control of the dynorphin and enkephalin genes, and its expression following noxious stimulation leads to an increased synthesis of dynorphin and perhaps enkephalin, what is the significance of dynorphin and enkephalin to noxious stimulus-induced plasticity and hyperalgesia? Enkephalin and other delta opioid agonists typically produce inhibitory or antinociceptive effects (Vaught et al. 1982), and may provide a mechanisms by which central plasticity and hyperalgesia is minimized (Dubner 1991). On the other hand, while dynorphin and other kappa opioids are typically found to produce moderate antinociceptive effects (Hayes et al. 1987; Millan and Colpaert 1991), they have dual effects in the spinal cord dorsal horn (Knox and Dickenson, 1987; Hylden et al. 1991). Dynorphin, in particular, has been found to produce expanded receptive fields and a facilitation of the responses of approximately one-third of superficial dorsal horn cells, while producing an inhibition of responses in another third of the cells (Hylden et al. 1991). It has been suggested that while dynorphin may produce direct excitatory effects on spinal projection neurons, it may also produce inhibition by a negative feedback mechanism on dynorphin-containing neurons (Dubner and Ruda 1992). In this way, dynorphin may have complex effects modulating the development of central plasticity and hyperalgesia in various ways.

Pain and neuroplasticity: a developing theory

The idea that injury or noxious stimulation can produce alterations in CNS function affecting pain sensitivity is not a new one. Sturge (1883) proposed that peripheral injury triggers a change in the excitability of the CNS so that normal inputs evoke exaggerated responses leading to pain hypersensitivity. MacKenzie (1893) suggested that increased pain sensitivity and referred pain could be the result of increased sensitiv-

ity of CNS structures. He proposed that sensory impulses arising from injured tissues create an 'irritable focus' in spinal cord segments onto which they impinge. In relation to peri-operative anesthesia, Crile (1913) wrote that patients given inhalational anesthesia still need to be protected by regional anesthesia; otherwise they might incur persistent CNS changes and enhanced postoperative pain. According to Hardy et al. (1950), secondary hyperalgesia and referred cutaneous hyperalgesia occur because an injury produces a state of hyperexcitability in the spinal cord. This hyperexcitability is sustained following the activation of a network of internuncial neurons, which produces a spreading facilitation of adjacent neurons in the spinal cord, allowing for the spread of hyperalgesia to uninjured regions of the body. In reference to deafferentation pain, Livingston (1943) suggested that the afferent activity generated by injured peripheral nerves elicits an abnormal firing pattern within the spinal cord. He proposed that a disturbance occurs in an internuncial pool of dorsal horn interneurons and results in reverberatory activity which eventually spreads to other parts of the spinal cord, including areas that affect the sympathetic chain. Increased activity in sympathetic efferents would disrupt vasoregulation and induce further hypersensitivity of peripheral tissue, leading to increased afferent input and a 'vicious-circle' of peripheral-central activity.

Aside from descriptive references to irritable foci, reverberatory activity and vicious circles, the above theories do not provide empiral evidence for, or details of, the nature of the CNS changes that occur following noxious stimulation. Only recently has there been specific empirical evidence indicating noxious stimulus-induced changes in CNS function. The studies of Perl (1976) and Kenshalo et al. (1979) were the first to demonstrate that noxious peripheral stimuli do produce changes in the sensitivity of dorsal horn neurons to further stimulation; while Woolf and Wall (Woolf 1983; Woolf and Wall 1986a) were the first to provide empirical evidence for a primary afferent input triggering *sustained* increases in central excitability. Woolf (1983) demonstrated that injury-induced increases in spinal cord excitability could be maintained even after local anesthesia of the injured site, providing empirical evidence that acute injury could produce lasting spinal changes. Woolf and Wall (1986a) showed that the amount of morphine required to prevent the development of this spinal hyperexcitability was 10-fold less than the amount required to reverse it after it was established, and provided the experimental basis for subsequent clinical investigations of the use of preemptive analgesia for the prevention or alleviation of postoperative pain.

The recent experimental literature of Woolf, Wall and others, described in earlier sections of this paper, indicates that noxious stimulation or injury can produce dramatic alterations in spinal cord function, including sensitization, wind-up or the expansion of the receptive fields of spinal neurons. Recently, several investigators have proposed detailed theories of how noxious stimuli produce these changes in CNS function. Woolf (1991) proposed that the release of EAAs and C-fiber neuropeptides produces slow depolarizations leading to both cellular and molecular changes which alter membrane properties. Thus, inputs arriving from small diameter primary afferents lead to the release of EAAs and neuropeptides within the spinal cord dorsal horn. EAAs acting at non-NMDA receptors produce a fast excitatory postsynaptic potential, but it is not until a slow synaptic potential stimulated by neuropeptides generates enough depolarization, to remove Mg^{2+} from the NMDA receptor ion channel, that the NMDA receptor is activated and Ca^{2+} ions enter the cell. It is proposed that the changes in intracellular Ca^{2+} and second messengers they affect which lead to persistent changes in the excitability of the dorsal horn cells. Dubner (1991) expands on this theory, suggesting that the neuropeptide-induced facilitation of activity at NMDA receptor sites results in excessive depolarization and EAA excitotoxicity leading to cell dysfunction and possibly a loss of normal inhibitory mechanisms. The effect of these changes include an expansion of dorsal horn receptive fields and hyperexcitability which, if allowed to persist, would presumably produce prolonged changes in excitability that could be maintained without further noxious peripheral input.

The most comprehensive model of how noxious input can produce prolonged changes in spinal cord dorsal horn function has been proposed by Wilcox (1991). According to this model, activity in small-diameter primary afferents produces a release of EAAs (such as glutamate) and neuropeptides (such as SP) into spinal cord dorsal horn. Glutamate produces a fast excitatory synaptic potential by acting at the AMPA receptor, and a long synaptic potential by acting at the NMDA receptor after activity at the AMPA site has helped to remove the voltage-gated block of the NMDA receptor by Mg^{2+} ions. While the AMPA effect would be brief, lasting only milliseconds to seconds, NMDA receptor activation would lead to persistent effects such as wind-up, lasting up to tens of seconds. Because of its high affinity for its receptor and its slow inactivation by enzymes, it is proposed that dissociation of SP from its receptors would take from several seconds up to minutes. In addition to producing a slow depolarization, SP may either stimulate glutamate release, or enhance activation of the NMDA receptor by relieving the Mg^{2+} dependent block. Activation of the SP receptor would also stimulate PLC activity, resulting in the production of IP_3 and DAG, second messengers which

would produce intracellular changes lasting many minutes to hours. From our own studies (Coderre 1992; Coderre and Melzack 1992a) described earlier, we would argue that nociception is also influenced by the stimulation of PLC activity by glutamate and aspartate acting at metabotropic EAA receptor sites.

According to Wilcox (1991), the noxious stimulus-induced release of excitatory neurotransmitters could also produce long-term changes (hours to days) in cellular processes by stimulating the induction of early immediate genes such as c-*fos* and c-*jun*. We would expand on this model by arguing that the induction of early immediate genes is triggered by a chain of events (see Fig. 1) involving both the influx of Ca^{2+} through NMDA receptor-operated Ca^{2+} channels, and the activation of PLC by both glutamate or aspartate acting at metabotropic EAA receptors and SP acting at NK-1 receptors. The activation of PLC would catalyze the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) producing IP_3 and DAG. DAG would stimulate the translocation of PKC, which is activated during high rates of Ca^{2+} influx through NMDA ion channels. The activated PKC would have two potential effects: first, the phosphorylation of substrate proteins, resulting in changes in membrane excitability; and second, the production of new gene products, such as Fos and Jun.

An important new development is the demonstration by Chen and Huang (1992) that PKC produces an enhancement of Ca^{2+} currents at NMDA receptor channels. Thus, PKC activation, initiated by glutamate- or aspartate-induced PLC activity and Ca^{2+} influx through NMDA channels, leads to further influx of Ca^{2+} through NMDA channels, creating a positive feedback loop for glutamate and aspartate neurotransmission. Furthermore, the induction of c-*fos* is triggered by DAG or activators of PKC, and is dependent on Ca^{2+} influx. As discussed above, it is expected that one consequence of c-*fos* induction is the transcriptional control encoding the preprodynorphin gene, leading to the increased synthesis of dynorphin peptide. Dubner and Ruda (1992) suggest that c-*fos*-induced increases in dynorphin gene expression and dynorphin peptide levels lead to enhanced excitability and the development of expanded receptive fields. According to their model, dynorphin produces excitatory effects on spinal projection neurons, but this excitatory effect is controlled, in part, by negative feedback on dynorphin-containing neurons by small inhibitory local circuit neurons. They propose that excessive depolarization may lead to a pathological state by promoting excitotoxicity and neuronal dysfunction, such as the release from inhibition of dynorphin-containing neurons following the destruction of the small local circuit neurons. It is possible that dynorphin may contribute to spinal hyperexcitability and excitotoxicity by producing a specific postsynaptic facilitation of NMDA receptor activity. Support for this mechanism comes from recent studies of Skilling et al. (1992b) which demonstrated that dynorphin augments nociceptive behaviors induced by intrathecal administration of

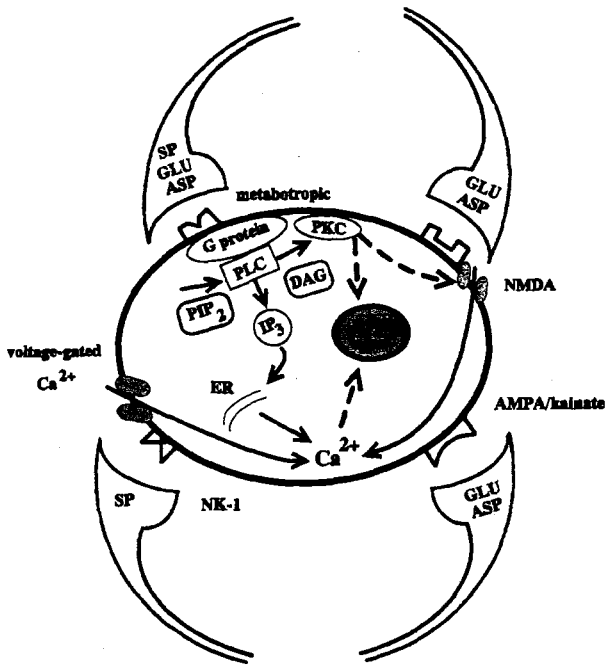

Fig. 1. Schematic diagram indicating a possible mechanism by which noxious stimulation or injury leads to central sensitization of spinal cord dorsal horn neurons. High levels of afferent input cause the release of aspartate, glutamate and substance P (SP) within the dorsal horn. Repetitive fast-transmitter activity of aspartate and glutamate at AMPA/kainate receptors produces a membrane depolarization which would counter a voltage-dependent blockade of the NMDA receptor by Mg^{2+}. Activation of neurokinin-1 (NK-1) receptors by SP produces a slow, prolonged depolarization and enhances influx of extracellular Ca^{2+} through voltage-gated Ca^{2+} channels. A further action of aspartate and glutamate at NMDA and metabotropic receptors, respectively, would produce an influx of Ca^{2+} (through NMDA receptor-operated Ca^{2+} channels), and the activation of phospholipase C (PLC). PLC catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) producing ionositol trisphosphate (IP_3) and diacyclglycerol (DAG), both of which act as intracellular second messengers. The production of IP_3 causes the release of Ca^{2+} from intracellular stores within the endoplasmic reticulum (ER). The increases in intracellular Ca^{2+} produced by the influx of Ca^{2+} through voltage-gated channels, NMDA receptor-operated channels, and by the release of Ca^{2+} from internal stores, results in increased expression of proto-oncogenes such as c-*fos* and c-*jun*. The production of DAG stimulates the translocation and activation of protein kinase C (PKC), which is activated during high rates of Ca^{2+} influx. The activated PKC induces sustained alterations in the cellular membrane affecting membrane permeability for prolonged periods. In particular, PKC produces an enhancement of ionic current at the NMDA receptor, allowing for additional extracellular Ca^{2+} to enter the cell. PKC also interacts with Ca^{2+} to stimulate further increases in the expression of the proto-oncogenes c-*fos* and c-*jun*. The protein products of these proto-oncogenes participate in the regulation of mRNA encoding dynorphin and enkephalin peptides in spinal cord, and can influence long-term changes in cellular function.

NMDA, and Bakshi et al. (1992) who found that NMDA antagonists block the motor deficits and neurotoxic histological changes induced by high dose dynorphin A.

Implications for treatment of acute and chronic pain

Recent advances in our understanding of the mechanisms that underlie pathological pain have important implications for the treatment of both acute and chronic pain. Since it has been established that intense noxious stimulation produces a sensitization of CNS neurons, it is possible to direct treatments not only at the site of peripheral tissue damage, but also at the site of central changes. Furthermore, it may be possible in some instances to prevent the development of central changes which contribute to pathological pain states. The fact that amputees are more likely to develop phantom limb pain if there is pain in the limb prior to amputation (Melzack 1971; Katz and Melzack 1990), combined with the finding that the incidence of phantom limb pain is reduced if patients are rendered pain-free by epidural blockade with bupivacaine and morphine prior to amputation (Bach et al. 1988), suggests that the development of neuropathic pain can be prevented by reducing the potential for central sensitization at the time of amputation. The evidence that postoperative pain is also reduced by premedication with regional and/or spinal anesthestic blocks and/or opiates (McQuay et al. 1988; Tverskoy et al. 1990; Katz et al. 1992) suggests that acute postoperative pain can also benefit from the blocking of the afferent barrage arriving within the CNS, and the central sensitization it may induce. Whether chronic postoperative problems such as painful scars, post-thoracotomy chest-wall pain, and phantom limb and stump pain can be reduced by blocking nociceptive inputs during surgery remains to be determined. Furthermore, additional research is required to determine whether multiple-treatment approaches (involving local and epidural anesthesia, as well as pretreatment with opiates and anti-inflammatory drugs) which produce an effective blockade of afferent input (Dahl et al. 1990), may also prevent or relieve other forms of severe chronic pain such as post-herpetic neuralgia and reflex sympathetic dystrophy.

Evidence indicating that neuropeptides and EAAs contribute to the development of noxious stimulus-induced central neuroplasticity outlines the potential for the use of selective receptor antagonists in pain treatment. The recent development of non-peptide neurokinin receptor antagonists (Snider et al. 1991), and of new agents that act at various sites within the NMDA receptor complex (see Lodge and Johnson 1991), may provide fruitful new tools for the treatment and prevention of pathological pain. Particularly exciting is the development of a new class of agents which block the binding of glycine to the NMDA receptor complex and prevent the allosteric potentiation by glycine of activity at the NMDA receptor binding site (Birch et al. 1988; Kemp et al. 1988). These agents cross the blood-brain barrier more easily than antagonists which act competitively at the NMDA receptor, and may not produce the psychomimetic side effects produced by dissociative anesthetics (such as ketamine). Also, since neuropeptide and EAA activity results in Ca^{2+} influx (MacDermott et al. 1986) and the activation of PLC-related second messenger systems (Sugiyama et al. 1987), it is possible that agents which inhibit second messenger cascades may be useful for the treatment of pathological pain. An intriguing possibility is the use of gangliosides, which block glutamate-stimulated translocation of PKC (Vaccarino et al. 1987), and have recently been found to reduce hyperalgesia in a rat model of peripheral neuropathy (Hayes et al. 1992). It is hoped that a combination of new pharmaceutic developments, careful clinical trials, and an increased understanding of the contribution and mechanisms of noxious stimulus-induced neuroplasticity, will lead to improved clinical treatment and prevention of pathological pain.

Conclusions

Clinical and experimental evidence suggests that noxious stimuli may sensitize central neural structures involved in pain perception. Salient clinical examples of these effects include amputees with pains in a phantom limb that are similar or identical to those felt in the limb before it was amputated, and patients after surgery who have benefited from pre-emptive analgesia which blocks the surgery-induced afferent barrage and/or its central consequences. Experimental evidence of these changes is illustrated by the development of sensitization, wind-up or expansion of receptive fields of CNS neurons, as well as by the enhancement of flexion reflexes and the persistence of pain or hyperalgesia after inputs from injured tissues are blocked. It is clear from the material presented that the perception of pain does not simply involve a moment-to-moment analysis of afferent noxious input, but rather, involves a dynamic process which is influenced by the effects of past experiences. Sensory stimuli act on neural systems which have been modified by past inputs, and the behavioral output is significantly influenced by the 'memory' of these prior events. Unlike previous theories of central sensitization, recent theories propose that in addition to a contribution of neuronal hyperactivity to pathological pain, there are specific cellular and molecular changes that affect membrane excitability and induce new gene expression, thereby allowing for enhanced responses to future stimulation. An increased understanding of the central

changes induced by peripheral injury or noxious stimulation should lead to new and improved clinical treatment for the relief and prevention of pathological pain.

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