Scientific Review

Pathophysiological mechanisms of central neuropathic pain after spinal cord injury

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After spinal cord injury (SCI), between 10% and 20% of the patients may develop central neuropathic pain. This type of chronic pain usually is a very bothersome sequel and represents a major therapeutic challenge since conventional medical and surgical pain therapies generally are ineffective. This review focuses on recent advances in the understanding of the pathophysiology of this pain syndrome. Important clinical features of central neuropathic pain after SCI include loss of sensations mediated by spinothalamic pathways combined with development of abnormal pain perception (spontaneous continuous pain and abnormally evoked pain). Up-regulation of neuronal activity leading to spontaneous and evoked neuronal hyperactivity/hyperexcitability, may be the neurophysiological substrate for development of abnormal pain perception. This paper describes some neurochemical changes that may be important for the induction and maintenance of neuronal hyperactivity and abnormal pain perception: Increased excitatory glutamergic activity involving N-methyl-D-aspartate (NMDA) receptor activation, may trigger the intracellular cascade reaction leading to up-regulation of neuronal activity/excitability. Changes in voltage-sensitive Na⁺ channels may contribute to changes in nerve membrane excitability. Other important mechanisms may be loss of endogenous inhibition, including reduced γ -amino-butyric acid (GABA)ergic, opioid and monoaminergic inhibition. These various mechanisms may provide new targets for treatment of a pain syndrome that traditionally has been so difficult to handle.

Keywords: spinal cord injury; central neuropathic pain; pathophysiology, therapy

Pain following spinal cord injury

Pain represents a frequent and major sequel after spinal cord injury (SCI). Bonica¹ reviewed 10 studies published from 1947–1988 and found that about 69% had pain after SCI, with central dysaesthesia pain in about 30% of the patients. In a recent Scandinavian study² including 353 SCI patients, 64% reported significant pain, 30% neurogenic pain, 17% both neurogenic and non-neurogenic pain, and 17% non-neurogenic pain. Störmer *et al*³ examined 901 SCI patients, and found that 66% of the patients had pain/dysaesthesia, with pain alone in 50%, painful dysaesthesia in 11% and distressing dysaesthesia without pain in 5%.

The study of pain after SCI has been hampered by the lack of generally accepted definitions and diagnostic criteria for the various types of SCI pain. A number of different classifications and descriptions of the various types of pain associated with SCI have been used by the various authors.^{4–8} In this journal, Siddall *et al*⁹ recently reviewed the different classifications, and proposed that pain after SCI should be classified as musculoskeletal, visceral and neuropathic,

also including a group of non-classified pain. Neuropathic pain was divided into peripheral and central pain, depending on whether neuropathic pain was caused by damage of peripheral nerves/nerve roots or damage of the spinal cord itself.

A generally accepted taxonomy of SCI pain is required. Such a classification is not included in the Classification of chronic pain provided by the International Association for the Study of Pain (IASP).¹⁰ Therefore, the recent organisation of a task force comity on the taxonomy of pain after SCI initiated by IASP, represents important progress.

The various types of SCI pain differ with regard to clinic, pathophysiology and therapy. In particular, central neuropathic pain may be notoriously difficult to treat, and usually is resistant to medical and surgical pain treatment. An increased amount of data concerning the pathophysiology of this pain syndrome has accumulated from animal and human studies during the last few years. This paper highlights some of the new knowledge.

Both with regard to pain mechanisms in general and pain after SCI, an important consideration is to differentiate between nociceptive and neuropathic pain. These different types of pain have different clinical characteristics as well as different responses to pharmacological and surgical interventions.

Nociceptive pain

Nociceptive pain results from activation of peripheral nociceptors due to ongoing tissue damage. Peripheral nociceptors are high threshold free nerve endings stimulated by high intensity stimuli, including mechanical, thermal or chemical stimuli.¹¹

In SCI patients, peripheral nociceptor stimulation may be induced by damage of skeletal structures and ligaments in the spine, as well as overuse of muscles, and decubitus causing injury of skin and muscles. For instance, nociceptive pain mechanisms play an important role in musculoskeletal pain after SCI.

Ordinary analgesics including non-steroidal anti-inflammatory drugs (NSAIDs), and non-medical treatment including physical therapy, are far more effective for nociceptive pain than for neuropathic pain.

In the discussion of the pathophysiology of central neuropathic pain after SCI, the role of central sensitisation of pain is stressed. It should, however, be remembered that the mechanisms of central sensitisation also are involved in the pathophysiology of nociceptive pain. For instance, peripheral inflammation may produce central sensitisation of pain, involving comparable mechanisms as in neuropathic pain.¹²

Neuropathic pain

Neuropathic pain, according to IASP is 'Pain initiated or caused by a primary lesion or dysfunction in the nervous system'.¹⁰ Accordingly, neuropathic pain may not require peripheral nociceptor activation, but depends on an abnormal function of the nervous system. Peripheral neuropathic pain is caused by damage of peripheral nerves or nerve roots, and central neuropathic pain depends on damage within the central nervous system. With regard to central neuropathic pain after SCI, different terms have been used to describe this pain syndrome: Deafferentation pain, central dysaesthesia pain, neurogenic pain.

This type of pain often may be resistant to pharmacological agents used in the treatment of central pain such as antidepressants and antiepileptics.¹³ In a randomised, double-blind, placebo-controlled study, the antidepressant trazodone which is a selective 5-hydroxytryptamine (5-HT) uptake inhibitor, failed to relieve pain in 18 patients with central pain after SCI.¹⁴ Furthermore, the antiepileptic drug valproate in a double-blind, cross-over study did not reduce central pain in 20 patients with SCI.¹⁵

The results of conventional neurosurgical treatment may also be disappointing. In patients with central pain after SCI, destructive neurosurgery (cordotomy, cordectomy, dorsal root entry zone (DREZ) lesioning) reduced continuous pain in only 26% of the patients, though reduced intermittent pain in 89% and evoked pain in 84% of the cases.¹⁶ Young found that DREZ produced more than 50% pain relief in 11 of 20 patients with deafferentation pain after SCI.¹⁷ An important drawback is that destructive neurosurgical procedures lesioning spinothalamic pathways, may even aggravate central pain.¹⁸ Neither non-destructive neurosurgical techniques including spinal cord and deep brain stimulation, may be effective. Spinal cord or deep brain stimulation reduced continuous pain in 36%, intermittent pain in 0% and evoked pain in 16% in patients with central pain after SCI.¹⁶ Others reported that deep brain stimulation was non-effective in 3 patients with central pain after SCI.¹⁹

A more rational treatment of central neuropathic pain following SCI should be derived from an increased understanding of the pathophysiology underlying this pain syndrome.

Sensory loss and abnormal pain perception in central neuropathic pain

With regard to the pathophysiology of SCI pain, both peripheral and central neuropathic pain involve two important clinical characteristics: The presence of sensory loss and abnormal pain perception in the painful skin areas.

Sensory loss

The different sensory modalities are mediated to the brain via different sensory afferent neurones and central neuronal pathways.²⁰ Briefly, the sensations of temperature and pain are signalled via thin myelinated/unmyelinated A δ /C fibres, second order projecting neurones in the spinal cord dorsal horn ascending in the spinothalamic pathways, and third order thalamic neurones projecting to the cerebral cortex. The sensations of vibration, joint position as well as light pressure are signalled via thick, myelinated sensory neurones, second order neurones ascending in the dorsal column – medial lemniscal pathways, and third order thalamic neurones ascending to the cerebral cortex.

In patients with neuropathic pain, the relative affection of the various sensory modalities may be quantitatively assessed. Impaired sensation of temperature, determined by the quantitative thermotest,²¹ may suggest damage of thin myelinated/unmyelinated A δ /C fibres or central spinothalamic pathways. Impaired sensations of vibration and light pressure, on the other hand, may suggest damage of thick myelinated fibres or central dorsal column – medial lemniscal pathways. Neither of the tests may be used to assess the level of damage.

An influential hypothesis states that the pathogenesis of central pain, including central pain after SCI, depends on loss of balance between noxious and non-noxious sensory inputs at the thalamic level.^{6,13} Spinothalamic pathways appear to be consistently affected in patients with central pain, when comparing the occurrence of central pain with the anatomical location of the lesion.¹⁸ In patients with central pain of different causes, sensory modalities mediated by spinothalamic pathways are more frequently and severely affected than sensory modalities mediated by dorsal column – medial lemniscal pathways.^{6,13} The hypothesis is that central neurones misinterpret the peripheral signals caused by abnormal balance between input from dorsal column – medial lemniscal and spinothalamic pathways. In favour of this assumption, studies of the spinothalamic terminals in the thalamic ventrobasal complex of the rat have shown convergence of terminals of both column – medial lemniscal and spinothalamic fibres onto single postsynaptic thalamic neurones.²²

Based on the results of quantitative assessment of sensory perception, we questioned the hypothesis that central neuropathic pain after SCI results from imbalance of sensory input. In 16 patients with central neuropathic pain after traumatic SCI, we compared sensory loss in painful denervated skin areas with sensory loss in non-painful denervated skin areas.²³ An important observation was that sensory modalities mediated by spinothalamic pathways were not more significantly impaired than sensory modalities mediated by dorsal column – medial lemniscal pathways in the painful denervated skin areas compared to the non-painful denervated skin areas (Figure 1). Thus, in these patients deafferentation of spinothalamic pathways was not a sufficient condition for development of central neuropathic pain. Our data provided evidence that sensory loss must be coupled with abnormal pain responsiveness.²³

Abnormal pain perception

Abnormal pain perception in the affected regions of these patients include three different components: Spontaneous continuous pain (usually burning and aching in quality), spontaneous intermittent pain (usually stinging in quality) and abnormally evoked pain (usually produced by touch or movement). Stimulus-evoked pain may be abnormal leading to allodynia, hyperalgesia or hyperpathia. Allodynia is pain produced by normally non-painful stimulation. Verbal description of the characteristics of abnormal pain perception in 16 patients with central neuropathic pain after SCI are given in Table 1.

We compared abnormally evoked pain (abnormal temporal summation of pain) in painful denervated skin areas and non-painful denervated skin areas in 16 patients with central neuropathic pain after SCI. As shown in Figure 2, the intensity of abnormally evoked

pain was markedly and significantly more evident in the painful denervated skin area compared to the non-painful denervated skin area. Abnormal temporal summation of pain reflects one characteristic of allodynia, ie pain evoked by non-painful A β -fiber stimulation. This type of abnormally evoked pain was produced by repetitive stimulation of the skin with normally non-painful stimulation, and was characterised by progressively increasing pain that radiated outside the site of stimulation and lasted for a long time after the end of stimulation. Abnormal temporal summation of pain also is present in patients with other types of neuropathic pain.^{24,25}

Temporal summation of repetitive nociceptive stimulation is a physiological phenomenon, produced by repetitive stimulation of A δ and/or C nociceptors, but not by repetitive stimulation of low threshold A β fibers.²⁶ After induction of hyperexcitability in second order wide dynamic range neurones, these cells may respond to low-threshold mechanoreceptive A β fibers in a way that is normally produced by high threshold A δ /C nociceptor activation.^{26,27}

The working hypothesis is that abnormal temporal summation of pain represents a clinical correlate of the neuronal hyperexcitability recorded electrophysiologically. Therefore, the assessment of abnormally evoked pain, including allodynia and abnormal temporal summation of pain, may provide important information about functional changes in the neuronal pathways signalling pain sensation. Though clinical studies have not focused on abnormal pain perception after SCI, several animal models of central neuropathic pain include the assessment of mechanical allodynia, ie pain-like behaviour caused by tactile stimulation that normally does not induce such behaviour.

Figure 1 Comparison of changes in sensory thresholds in non-painful (open boxes) and painful (cross hatched boxes) denervated skin areas. The different sensory thresholds (warm thresholds, WT; cold thresholds, CT; heat pain thresholds, HPT; cold pain thresholds, CPT; tactile thresholds, TT) were not increased in painful compared to non-painful denervated skin areas ($P > 0.10$; Wilcoxon signed rank test). Data derived from Eide *et al*²³ with permission

Table 1 Abnormal pain perception in 16 patients with central neuropathic pain after SCI

Case	Description	Spontaneous continuous pain		Spontaneous intermittent pain		Evoked pain Provoking factors
		Intensity of pain		Description	Frequency	
1	<i>Aching</i> cutting cruel	59 mm		Stinging radiating	7–8/day	Touch
2	<i>Prickling/Tingling</i> burning aching	49 mm		Shooting radiating	0–1/week	Touch
3	<i>Burning</i> tightening piercing numbness	55 mm		Sharp stinging	1/week	Touch
4	<i>Tightening</i> pricking numbness	25 mm		Stinging	> 10/day	Touch
5	<i>Cutting</i> tingling	53 mm		Shooting sharp	7/day	Touch
6	<i>Tingling</i> tightening squeezing piercing	72 mm		Radiating	> 20/day	Touch
7	<i>Aching</i> burning cutting tingling pricking cruel piercing	76 mm		Shooting stinging throbbing	> 20/day	Touch Movement
8	<i>Burning</i> aching	81 mm		Shooting stabbing stinging	> 20/day	Touch Touch
9	<i>Piercing</i> cutting tingling	14 mm		Sharp radiating	2/week	Touch, Movement
10	<i>Tightening</i> squeezing	58 mm		Throbbing	1–2/day	Touch, Movement Cold
11	<i>Squeezing</i>	30 mm		Stinging	4/week	Touch, Movement Cold
12	<i>Burning</i> tingling tightening squeezing	46 mm		Stinging radiating	4–5/day	Touch, Movement Cold
13	<i>Burning</i> tingling pricking aching tightening squeezing piercing	73 mm		Shooting sharp stinging radiating	1–2/day	Touch, Movement Heat
14	<i>Burning</i>	32 mm		–	–	–
15	<i>Burning</i> cutting tingling pricking itching piercing	50 mm		Stabbing sharp stinging	4/week	Touch
16	<i>Burning</i> pricking aching cruel	87 mm		–	–	Touch

Intensity of continuous pain presented as mm change on a 100 mm VAS (no pain – unbearable pain). The word most exactly describing the continuous pain is italicised. Data from Eide *et al.*²³ with permission

Figure 2 Comparisons of temporal summation of pain either evoked by brush stimulation or repetitive von Frey stimulation in non-painful and painful denervated skin areas. Significant differences are indicated by * $P < 0.05$, ** $P < 0.001$ (Wilcoxon signed rank test). Data derived from Eide *et al.*²³ with permission

The role of neuronal hyperactivity in central pain

Abnormal up-regulation of neuronal activity after nerve injury may play a key role in the development of abnormal pain perception. Electrophysiological studies suggest that deafferentation may cause abnormal changes in the firing pattern of neurones signalling pain sensation, including increased spontaneous activity (a possible substrate for spontaneous

continuous pain), reduced thresholds and increased responsiveness to peripheral stimulation (a possible substrate for abnormally evoked pain including allodynia and hyperalgesia), prolonged after-discharges to repetitive stimulation (a possible substrate for pain that lasts after the end of peripheral stimulation), and the expansion of the peripheral receptive fields of central neurones (a possible substrate for radiation of pain outside the site of peripheral stimulation). Both animal and human studies provide evidence that comparable mechanisms are involved in both peripheral and central neuropathic pain. Therefore, in the discussion of central neuropathic pain, references to studies on peripheral neuropathic pain are relevant.

Animal studies

After peripheral nerve injury, behavioural changes indicative of mechanical allodynia in rats²⁸ and monkeys²⁹ were associated with electrophysiological changes in spinal cord spinothalamic projecting neurones including wide dynamic range (WDR) neurones. Neuronal hyperactivity was characterised by high background firing activity, reduced thresholds and increased responsiveness to peripheral stimulation.^{28,29} Similar up-regulation in the activity of WDR neurones has been found at different levels of the neuraxis (spinal cord, brainstem, thalamus, cerebral cortex) in various animal models of peripheral neuropathic pain.^{30–32}

Comparable changes in neuronal activity appear to take place after SCI. In early experiments, Loeser and Ward³³ showed that spinal cord hemisection in cats caused spontaneous hyperactivity and burst firing of dorsal horn neurones at the side of hemisection and also in some cells contralateral to the lesion. After transection of the spinothalamic tract in the cat, spontaneous and evoked neuronal hyperactivity was recorded in WDR neurones in the thalamic nucleus ventralis posterolateralis.³⁴ After spinal cord ischemic injury leading to mechanical allodynia, spinal cord WDR neurones became hyperresponsive with prolonged afterdischarges to mechanical stimulation.³⁵ Yeziarsky and Park³⁶ made intraspinal microinjections of the excitatory amino acid quisqualic acid in rats, and examined the electrophysiological abnormalities of dorsal horn neurones including WDR neurones several weeks after SCI. Extracellular recordings revealed increased level of background activity, increased sensitivity to mechanical stimulation and increased duration of afterdischarges that lasted several weeks after treatment, indicative of long-lasting neuronal hyperactivity produced by excitatory amino acids.³⁶

Abnormal ectopic impulse generation at the site of nerve injury and in axotomized dorsal root ganglion neurones represents an important pathophysiological mechanism in neuropathic pain.³⁷ The neuronal hyperactivity may be induced and maintained by increased afferent input that triggers wind-up mechanisms. In animals electrophysiological studies have demonstrated that repetitive stimulation of unmyelinated C fibres produces progressively increasing activity (wind-up) in spinal cord nociceptive neurones leading to neuronal hyperactivity that lasts after the end of stimulation.^{38–40} Such primary afferent hyperactivity may trigger wind-up of second order neurones. Analogue to this situation, the neuronal hyperactivity recorded in the thalamus after SCI might be produced by hyperactivity of damaged spinal cord spinothalamic tract neurones.

Human studies

Electrophysiological recordings of central neuronal activity in patients with central neuropathic pain after SCI, demonstrate similar changes in neuronal activity as shown in animal experiments. In a paraplegic patient with central pain, high frequency spontaneous hyperactivity with burst firing was recorded in dorsal horn neurones at the level of the injury.⁴¹ Another study demonstrated abnormal focal hyperactivity within the superficial laminae of the spinal cord in patients with central neuropathic pain after SCI.⁴² Microcoagulation of this area within the dorsal root entry zone (DREZ), produced pain relief that was associated with neurophysiological disappearance of neuronal hyperactivity.⁴²

Furthermore, in SCI patients with central pain, recordings in the denervated cells in the ventroposter-

ior thalamus have revealed abnormal spontaneous and evoked hyperactivity with abnormal somatotopic organisation and expansion of receptive fields.^{43,44} Electrical stimulation in the denervated region of the thalamus induced pain similar to the central pain. Other authors also demonstrated the presence of spontaneous high frequency discharge neurones (neuronal hyperactivity) in various thalamic nuclei in patients with either peripheral or central neuropathic pain, including central neuropathic pain after SCI.^{45–48} Accordingly, both peripheral and central lesions appear to cause comparable changes in the activity of central neurones. This is interesting because central neuropathic pain after SCI in some situations may also involve damage to spinal roots.

The neurochemical basis of central pain

Some putative mechanisms involved in the development of neuronal hyperactivity are summarised in Figure 3. In particular, the neurochemical mechanisms may become important targets for new treatments. Though the neurogenetic mechanisms are not described

Figure 3 A tentative hypothesis of the pathophysiological mechanisms leading to central neuropathic pain following spinal cord injury. Abbreviations: EAA (Excitatory amino acids), NMDA (N-methyl-D-aspartic acid), GABA (γ -aminobutyric acid), CCK (cholecystokinin), IEG (immediate early genes)

here, it should be noted that genetic changes as expression of immediate early genes (IEGs), probably play an important role in the development of pathological pain after nerve injury.^{12,49}

Nerve membrane hyperexcitability involving sodium (Na^+) channels

Abnormal impulse generation in injured nerves may depend on accumulation of sodium (Na^+) channels in the cell membrane. So-called 'membrane-stabilising' drugs have emerged as a new and exciting approach in the treatment of neuropathic pain.⁵⁰ Local anaesthetics (eg lidocaine (lignocaine) and mexiletine) block voltage-sensitive Na^+ channels, thereby producing membrane stabilisation by reducing the number of Na^+ channels available for the action potential. In animals, the generation of ectopic impulses at the site of nerve injury and in axotomized dorsal root ganglion cells was markedly inhibited by systemic administration of the Na^+ channel antagonists lidocaine⁵¹ or tetrodotoxin.⁵²

Sodium channel antagonists seem to be effective in both peripheral and central neuropathic pain. In a randomised, double-blind placebo-controlled study, systemic infusion of the Na^+ channel antagonist lidocaine reduced the intensity of pain as well as the size of mechanical allodynia in patients with peripheral neuropathic pain.⁵³ Oral treatment with mexiletine improved central neuropathic pain in eight of nine patients with vascular thalamic injury.⁵⁴ So far, only a few studies have focused on the role of Na^+ channel antagonists in the treatment of central neuropathic pain after SCI.

Studies in animals

In an animal model of central neuropathic pain reported by the group of Wiesenfeld–Hallin, vascular damage of the spinal cord is induced in rats, and an allodynia-like behaviour is assessed as a painful reaction to light tactile stimulation of the denervated skin area (mechanical allodynia).⁵⁵ The authors have described acute mechanical allodynia that appears in about 90% of the animals 24–48 h after ischaemic SCI. Chronic mechanical allodynia appears in about 50% of the animals with an onset 1–6 weeks after injury, and a duration of several months. The study of chronic mechanical allodynia-like behaviour probably is most relevant for the clinical situation. The Swedish group has presented a number of interesting neurochemical studies by using this animal model of central neuropathic pain.

Systemic administration of tocainide, an antiarrhythmic drug chemically related to lidocaine, relieved chronic mechanical allodynia-like behaviour in rats with ischaemic SCI.⁵⁶ In these animals, tocainide also inhibited the hypersensitivity of dorsal horn WDR neurones to mechanical stimuli, indicative of membrane stabilisation.⁵⁶ In another study, chronic

mechanical allodynia that occurred several weeks after ischaemic SCI, was relieved by systemic administration of the Na^+ channel antagonist mexiletine.⁵⁷

Studies in humans

In a single blind study, Glynn *et al*⁵⁸ showed that epidural buprenorphine reduced central pain in only two of five patients with SCI. In a randomised, double-blind, placebo-controlled study including 11 patients with dysaesthetic pain after SCI, oral mexiletine did not produce significant pain relief.⁵⁹ Furthermore, severe side-effects of mexiletine may occur.⁶⁰ Though these clinical studies appear to be disappointing, the modulation of central neuropathic pain after SCI by Na^+ channel antagonists should be examined in future studies.

Hyperfunction of glutaminergic excitatory mechanisms

The excitatory amino acids (EAAs) aspartate and glutamate play a significant role in the transmission of nociceptive information in the central nervous system. One of the EAA receptor subtypes, the N-methyl-D-aspartic acid (NMDA) receptor, has an important role in some forms of synaptic plasticity. NMDA receptor-mediated long-term potentiation in the rat hippocampus is a main experimental model for studying the neurobiological basis for learning and memory.⁶¹ The function of NMDA receptors is not confined to synaptic plasticity. Excitatory amino acids released in large amounts, for example during spinal cord injury, contribute to neuronal damage by excessive activation of NMDA receptors.⁶²

With regard to the pathophysiology of chronic pain, including neuropathic pain, the role of NMDA receptor mechanisms have received considerable interest. NMDA receptors appear to be critically involved in the synaptic processes leading to central neuronal hyperexcitability/hyperactivity, and so-called central sensitisation of pain.⁴⁹

Studies in animals

The induction of neuronal hyperactivity and hyperexcitability of spinothalamic tract WDR neurones probably involve the combined action of EAAs and peptides (eg substance P) released from hyperactive primary afferent neurones.⁶³ Data from animal models of neuropathic pain suggest that neuronal hyperactivity may be reversed by NMDA receptor antagonists.

In monkeys with peripheral nerve injury and a behavioural syndrome indicative of pain, the hyperexcitability recorded in WDR spinothalamic tract neurones in the spinal cord dorsal horn was reversed by iontophoretic application of the NMDA antagonist dextrorphan.⁶⁴ Furthermore, in an animal model of peripheral neuropathic pain, the neuronal hyperactiv-

ity recorded in thalamic neurones was markedly enhanced by iontophoretic application of glutamate, and markedly reduced by application of a NMDA receptor antagonist.³²

In the excitotoxic model of central neuropathic pain described by Yeziarsky,³⁶ the EAA quisqualic acid, a non-NMDA agonist, was injected intraspinally to mimic the neurotoxic effect of increased levels of excitatory amino acids. Recordings from WDR neurones caudal to the injection sites showed neuronal hyperactivity including lower response thresholds, increased responses to mechanical stimuli, abnormal temporal summation properties and long afterdischarges.³⁶ The up-regulation of neuronal activity was ascribed to NMDA receptor-mediated changes in neuronal excitability.

In another study, spontaneous and evoked neuronal hyperactivity was recorded in WDR neurones of the cat thalamus several weeks after transection of the spinothalamic tract.³⁴ Neuronal hyperactivity was significantly attenuated by a NMDA receptor antagonist, indicating that hyperactivity of thalamic WDR neurones was NMDA receptor-mediated.

A few behavioural studies concerning central neuropathic pain after SCI are available. Acute mechanical allodynia occurring 24–48 h after ischaemic SCI was inhibited by a non-NMDA excitatory amino acid receptor antagonist but not by an NMDA antagonist.⁶⁵ Chronic mechanical allodynia examined in the same model of central neuropathic pain several weeks after ischaemic SCI, was relieved by NMDA receptor blockade, though not by non-NMDA receptor blockade.⁶⁶ These results suggest a role of NMDA receptor activation in the maintenance of chronic mechanical allodynia after SCI.

Studies in humans

The only controlled clinical study of the effect of NMDA receptor blockade on central neuropathic pain after SCI was published by our group.⁶⁷ In nine patients with central neuropathic pain after traumatic SCI, the severity of continuous and evoked pain was examined before and after the intravenous infusion of either the NMDA receptor antagonist ketamine, the μ -opioid receptor agonist alfentanil or placebo. A randomised, double-blind, cross-over study design was used. The NMDA receptor antagonist used in this study, ketamine, has been shown to block NMDA receptors at different levels of the central nervous system, including the spinal cord,⁶⁸ thalamus,⁶⁹ and cortex.⁷⁰ As shown in Figure 4A, spontaneous continuous pain was markedly reduced by ketamine as well as by alfentanil. Ketamine-induced NMDA blockade also reduced abnormal temporal summation of pain in the painful skin areas (Figure 4B and C). The thresholds for the sensation of heat pain were not changed. The most severe side-effect of ketamine was bothersome dizziness in one patient and only modest side-effects were caused by alfentanil. The results

Figure 4 Changes in the intensity of (A) continuous pain, (B) brush-evoked temporal summation of pain and (C) von Frey evoked temporal summation of pain after intravenous infusion of ketamine (6 μ g/kg/min after a bolus dose of 60 μ g/kg), alfentanil (0.6 μ g/kg/min after a bolus dose of 7 μ g/kg) or placebo (9 mg/ml NaCl). Statistical differences: (A) Ketamine vs Placebo ($P=0.04$), Alfentanil vs Placebo ($P=0.01$); (B) Ketamine vs Placebo ($P=0.01$), Alfentanil vs Placebo ($P=0.03$); (C) Ketamine vs Placebo ($P=0.07$), Alfentanil vs Placebo ($P=0.01$) (Wilcoxon signed rank test). Data derived from Eide *et al*⁶⁷ with permission

provide clinical evidence that central neuropathic pain after SCI is dependent on NMDA receptor activation. Previously, we have shown that ketamine-induced NMDA receptor blockade reduced continuous and evoked pain in patients with post-herpetic neuralgia.²⁴

In the future, it should be examined whether the therapeutic efficacy of NMDA receptor antagonists might be enhanced by the co-administration of other neurochemicals. For instance, the co-administration of epidural ketamine and morphine significantly enhanced postoperative pain relief after orthopedic surgery.⁷¹

NMDA receptor blockade and pre-emptive analgesia

When considering the role of NMDA receptors in synaptic plasticity and induction of neuronal hyperactivity/hyperexcitability, it may be speculated whether NMDA receptor blockade might be used to reduce the incidence of neuropathic pain after SCI.

Pre- and per-operative NMDA receptor blockade may reduce post-operative pain, and perhaps the incidence of post-operative neuralgias.⁷² In a randomised, double blind study, the area of punctuate hyperalgesia surrounding the surgical incision was significantly reduced for several days after pre- and post-operative treatment with the NMDA receptor antagonist ketamine.⁷³ The results provide further evidence that NMDA receptor blockade prevents central sensitisation of pain. Others have demonstrated that a single i.th. injection of NMDA receptor antagonists prior to the lesioning of the sciatic and saphenous nerve, markedly inhibited the development of a behavioural syndrome indicative of nerve injury pain.⁷⁴ Pre-treatment with a NMDA receptor antagonist prevented the development of mechanical allodynia caused by ischaemic SCI.⁷⁵

On this background, an interesting issue is whether continuous low-dose infusion of a glutaminergic NMDA receptor antagonist the first day after SCI might reduce the incidence and severity of neuropathic pain in SCI patients.

Hypofunction of GABAergic inhibitory mechanisms

Loss of spinal inhibitory mechanisms including γ -amino-butyric acid (GABA)ergic inhibition, may be an important pathogenic mechanism in different types of neuropathic pain.

Studies in animals

Electrophysiological recordings suggest that neuronal hyperactivity may be down-regulated by GABAergic inhibition. In an animal model of peripheral neuropathic pain, neuronal hyperactivity recorded in thalamic neurones was markedly inhibited by iontophoretic application of GABA.³² In animals with acute mechanical allodynia after ischaemic SCI, the hypersensitivity of spinal cord WDR neurones to mechanical

stimulation was reversed by the GABA_B agonist baclofen, but not by the GABA_A agonist muscimol.⁷⁶ The number of GABA-like immunoreactive cells in the rat spinal cord dorsal horn was significantly reduced for 48–72 h after SCI, though normalised after 2 weeks.

Furthermore, acute mechanical allodynia that was present 24–48 h after ischaemic SCI, was reduced by systemic administration of baclofen, but not by muscimol.⁵⁵ However, baclofen failed to relieve chronic mechanical allodynia that was present several weeks after ischaemic SCI.⁷⁸ Thus, the animal studies leave sparse support to the hypothesis that loss of GABAergic inhibition has an important role in chronic mechanical allodynia after SCI.

Studies in humans

Clinical studies examining the effect of i.th. infusion of GABA receptor agonists on central neuropathic pain after SCI, have given variable results. The GABA_B agonist baclofen, given i.th., reduced central pain in one patient with SCI in a double-blind trial.⁷⁹ An i.th. bolus injection of baclofen reduced continuous central pain and allodynia/hyperalgesia, in three of six patients with central pain after SCI.⁸⁰ On the other hand, no effect of continuous i.th. baclofen infusion on neurogenic pain after SCI was demonstrated in one study, though the authors found beneficial effect on musculoskeletal pain associated with spasticity.⁸¹

Hypofunction of opioid inhibitory systems

Both animal and human studies suggest an important role of opioid mechanisms in the pathophysiology of neuropathic pain,⁸² though the role of opioids in the treatment of neuropathic pain has been disputed.⁸³

Some data suggest that in neuropathic pain, opioid-mediated analgesia may be reduced due to increased spinal level of the neuropeptide cholecystokinin (CCK).⁸² Cholecystokinin is an endogenous inhibitor of opioid-mediated analgesia, and antagonists of CCK receptors may both enhance morphine-induced analgesia and prevent opioid tolerance.

Studies in animals

The Swedish group reports that chronic mechanical allodynia develops in about 50% of the animals several weeks after ischaemic SCI. An interesting observation is that systemic naloxone induced marked allodynia in those animals that did not develop allodynia after SCI.⁸⁴ Naloxone-induced allodynia was transient and similar to that found in allodynic animals. The observations suggest that after SCI, opioid systems are tonically active and suppress the expression of allodynia. Allodynia may result from a dysfunction of this tonic opioid control. Chronic mechanical allodynia in animals with SCI was relieved by a CCK_B receptor

antagonist,⁸⁴ indicating that this type of allodynia involves impaired opioid function due to up-regulation of CCK function.

Some recent studies in animals suggest that the efficacy of morphine in relieving neuropathic pain depends on the route of drug administration. Chronic mechanical allodynia in rats with ischaemic SCI, was relieved by i.th. injection of morphine in non-sedative doses.⁸⁵ Systemic or intracerebroventricular injection of morphine, on the other hand, failed to relieve chronic mechanical allodynia, even at sedative doses.⁸⁵ This study also showed that the antinociceptive potency of morphine was reduced in allodynic versus normal rats.

Another exciting study suggests that relief of chronic allodynia after i.th. implantation of bovine adrenal chromaffin cells may be partly mediated by opioid mechanisms.⁸⁶ The implanted cells are known to secrete enkephalins, and the allodynia-like state was temporarily restored by the opioid antagonist naloxone.⁸⁶

With regard to opioid mechanisms, it should be noted that the endogenous opioid peptide, dynorphine A, may be involved in the development of pathological pain after SCI.¹² The level of this opioid is increased following SCI. Intrathecal injection of a single dose of dynorphine A has been shown to produce mechanical allodynia that lasts for several weeks, an effect that appears to be mediated by activation of NMDA receptors.⁸⁷

Studies in humans

Glynn *et al*⁵⁸ showed in a single blind study that epidural morphine reduced central pain in patients with SCI in only five of 14 patients. In a randomised, double-blind, cross-over study, we found that the μ -opioid receptor agonist alfentanil significantly reduced continuous pain as well as abnormal temporal summation of pain in nine patients with central neuropathic pain after SCI (Figure 4).

Hypofunction of monoaminergic inhibitory systems

In the spinal cord, descending neurones containing the monoamines noradrenaline (NA) or serotonin (5-hydroxytryptamine, 5-HT), are involved in the control of nociceptive transmission.^{88,89} Surgical transection of the spinal cord reduces the threshold for eliciting a spinal nociceptive reflex, indicating that descending inhibitory pathways tonically inhibit nociception at the spinal level.⁹⁰ Neuronal plasticity including development of supersensitivity to neurotransmitters, may contribute to restoration of normal function after SCI.^{89,91} In patients with central neuropathic pain after SCI, hypofunction of the inhibitory monoaminergic systems and dysfunction of the plasticity changes might be involved in the development of abnormal pain perception. In parti-

cular, the available studies suggest a role of α adrenergic mechanisms in the control of central neuropathic pain after SCI.

Studies in animals

Intrathecal treatment, but not systemic treatment, with the α_2 adrenoceptor agonist clonidine reduced chronic mechanical allodynia-like behaviour in animals with ischaemic SCI.⁹² In rats with ischaemic SCI, i.th. implantation of bovine adrenal chromaffin cells secreting catecholamines and enkephalins, abolished chronic mechanical allodynia and reduced cold allodynia for up to 8 weeks after implantation.⁸⁶ The allodynia-like state was temporarily restored by the α_2 adrenoceptor antagonist phentolamine, indicating that the effect of the implanted cells was partly mediated by α_2 adrenoceptors.

Studies in humans

Both NA and 5-HT uptake inhibitors that enhance the action of inhibitory monoamines, are used in the treatment of peripheral and central neuropathic pain.¹³ In a double-blind study, inhibition of uptake of 5-HT by trazodone failed to relieve central pain after SCI.¹⁴ Central pain after SCI was inhibited in 10 of 15 patients by epidural infusion of the α_2 receptor agonist clonidine.⁵⁸ Furthermore, in a case with neuropathic pain after SCI, i.th. clonidine produced pain relief both in combination and not in combination with morphine.⁹³

Conclusions

This paper summarises the current knowledge about the pathophysiological mechanisms of central neuropathic pain after SCI that may provide more efficient pain therapies. This pain syndrome is characterised by loss of sensory modalities mediated by spinothalamic tract neurones, and abnormal pain perception (spontaneous continuous pain and abnormally evoked pain). Evidence is given that abnormal pain perception results from neuronal hyperactivity and hyperexcitability induced by abnormal impulse generation in damaged spinothalamic tract neurones. The neurochemical mechanisms underlying abnormal neuronal activity may become important targets for various new treatment approaches: Membrane stabilisation by application of Na⁺ channel antagonists may inhibit abnormal impulse generation. Blockade of hyperactive glutaminergic mechanisms mediated by NMDA receptors may reverse wind-up mechanisms, thus reversing abnormal neuronal activity. Furthermore, enhancing endogenous inhibitory systems including GABAergic, opioid and monoaminergic inhibitory pathways may reverse abnormal neuronal hyperactivity, thereby reducing pathological pain.

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