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Evidence, Mechanisms, and Clinical Implications of Central Hypersensitivity in Chronic Pain After Whiplash Injury

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Objectives: To provide insights into the mechanisms underlying central hypersensitivity, review the evidence on central hypersensitivity in chronic pain after whiplash injury, highlight reflections on the clinical relevance of central hypersensitivity, and offer a perspective of treatment of central hypersensitivity.

Methods: A review of animal and human studies focusing on the mechanisms of postinjury central sensitization, an analysis of psychophysical investigations on central hypersensitivity in patients with chronic pain after whiplash injury, and a review of possible treatment modalities.

Results: Animal data show that tissue damage produces plasticity changes at different neuronal structures that are responsible for amplification of nociception and exaggerated pain responses. Some of these changes are potentially irreversible. There is consistent psychophysical evidence for hypersensitivity of the central nervous system to sensory stimulation in chronic pain after whiplash injury. Tissue damage, detected or not by the available diagnostic methods, is probably the main determinant of central hypersensitivity. Psychologic distress could contribute to central hypersensitivity via imbalance of supraspinal and descending modulatory mechanisms. Although specific treatment strategies are limited, they are largely unexplored.

Implications: Central hypersensitivity may explain exaggerated pain in the presence of minimal nociceptive input arising from minimally damaged tissues. This could account for pain and disability in the absence of objective signs of tissue damage in patients with whiplash. Central hypersensitivity may provide a common neurobiological framework for the integration of peripheral and supraspinal mechanisms in the pathophysiology of chronic pain after whiplash. Therapy studies are needed.

In the last years, pain research has enormously increased the current knowledge on the central mechanisms involved in pain modulation. Overwhelming evidence from animal studies has demonstrated the occurrence of profound changes in the central nervous system after peripheral injury that are responsible for enhanced neuronal excitability and enhanced pain perception. [1] Studies in healthy volunteers have shown that experimentally induced peripheral injury or inflammation determines exaggerated pain response, which results from increased excitability of the central nervous system. [2] The logical development of this basic research is its transposition into clinical setting, whereby the presence and clinical relevance of hypersensitivity states in patients with pain is investigated. The involvement of central hyperexcitability in pain after whiplash injury is appealing, given the limited knowledge on the causes of the pain complaints in this syndrome.

The purposes of the present paper are: 1) to provide insights into the mechanisms underlying central hypersensitivity; 2) to review the published evidence on the presence of central hypersensitivity in chronic pain after whiplash injury; 3) to highlight reflections on the possible clinical relevance of central hypersensitivity; 4) to offer a perspective of possible prevention and treatment of central hypersensitivity.

This review applies to patients with chronic pain after whiplash injury, independent of the presence of neurologic signs, fractures, or dislocations of the spine (grades I–IV of the Quebec Task Force Report). [3]

MECHANISMS OF POSTINJURY CENTRAL HYPERSENSITIVITY^

This section presents the preclinical evidence on the presence and mechanisms of central hyperexcitability after peripheral injury. It is divided into three parts, according to the sites at which changes in the excitability of the nociceptive system after peripheral injury are observed: the periphery, the spinal cord, and the brain.

Peripheral Sensitization^

Tissue injury due to trauma or surgery leads to an inflammatory response with release of potassium ions, substance P, bradykinin, prostaglandins, and other substances (often termed the “inflammatory or sensitizing soup”). [4] These substances may induce a sensitization of peripheral receptors with changes in the response characteristics of primary afferent fibers. [5] They may also activate normally inactive or “silent” nociceptors. [6] Furthermore, the inflammatory response induces a gene expression in the dorsal root ganglion resulting in an increased synthesis of peripheral receptors, which contributes to the increased sensitivity of the nociceptor. [7] Long lasting nociceptive stimulation may lead to a modification in the peripheral fibers: A[beta]-fibers may start synthesizing receptors that are normally found only in C-fibers, thereby simulating a phenotype shift, with the A[beta]-fiber adopting C-fiber characteristics. [8] These sensitizing events mediate primary hyperalgesia, [9] in which a reduced threshold for eliciting pain and enhanced pain to suprathreshold stimuli within the injured area can be recorded. Peripheral sensitization ultimately results in an increased nociceptive input to the spinal cord.

Spinal Cord Plasticity^

Prolonged afferent nociceptive input may induce a reversible increase in the excitability of central sensory neurons. [1] The important role of the N-methyl D-aspartate (NMDA) receptor in the development of spinal cord hyperexcitability has been shown in early animal experiments. [10,11] Activation of NMDA receptors seems to be linked to expression of cyclooxygenase-2 (COX-2) in the

spinal cord, and there is evidence for COX-2 inhibition of central sensitization in the animal. 12 Importantly, COX-2 expression is not confined to the neural structures connected to the site of inflammation, but involves the whole spinal cord and the supraspinal centers. 13 This phenomenon seems to be mediated by humoral factors, rather than by a neural transmission of the peripheral input into the spinal cord. 13 It may be responsible, at least in part, for a generalized hypersensitivity to peripheral stimulation, such the one evoked after stimulation of tissues that are at distance from the site of injury.

An expansion of the receptive fields (the cutaneous area which is innervated by a single spinal neuron) of individual dorsal horn neurons is also documented 14: afferent input from areas adjacent to the normal receptive field may be able to depolarize the hyperexcitable dorsal horn neuron. As a result, a peripheral stimulus activates a higher number of dorsal horn neurons and hyperalgesia may also be evoked in areas outside the injured region. The glial cells, which were earlier regarded as purely supportive, have become implicated in exaggerated pain states. 15 They may be activated by peripheral injury and can contribute to central hyperexcitability.

Additional profound structural changes include destruction of inhibitory interneurons and aberrant excitatory connections. 1 Destruction of inhibitory interneurons that has been observed after nerve injury contributes to hyperexcitability. 16 Interestingly, this phenomenon is prevented by NMDA-antagonists. 16 After nerve injury, A[beta]-fibers that normally terminate in the deep dorsal horn may sprout to establish functional synaptic contacts in superficial dorsal horn layers where nociceptive C-fibers terminate. 17 This is one of the possible explanations for the induction of pain sensations after stimulation of A[beta]-fibers by, for example, touch.

Both the peripheral sensitization and the hyperexcitability of dorsal horn neurons will reduce the threshold for eliciting A[delta]- and C-fiber pain. Although peripheral sensitization is responsible for primary hyperalgesia (ie, hyperalgesia recorded within the injured area), secondary hyperalgesia (ie, hyperalgesia recorded in the surrounding uninjured tissue) is the result of central hyperexcitability. 17 A[beta]-fiber-transmitted mechanical stimuli, which do not produce pain under normal conditions, may activate the hyperexcitable dorsal horn neurons, ultimately resulting in pain sensation (allodynia). 1,18

Supraspinal Modulation^

Spinal cord hyperexcitability elicited by trauma, inflammation, or surgery is influenced by descending facilitatory and inhibitory pathways. 19 Wall in 1967 demonstrated that stimulation of brainstem structures could inhibit spinal cord nociceptive neurons. 20 The periaqueductal gray and endogenous opioid peptides play a central role in the inhibition of spinal cord neuronal responses. 21 Release of encephalin at supraspinal and spinal levels is evoked by noxious stimulation. 22,23 Further inhibitory modulation is exerted by serotonergic 24 and noradrenergic systems. 25,26

The cortical representation of body areas can also undergo alteration. Reorganization of the cortical body map has been demonstrated in patients with phantom limb pain. 27 Treating phantom limb pain with opioids can reduce the cortical reorganization. 28 This fascinating phenomenon has still unclear clinical implications. Nevertheless, it suggests that profound plasticity changes can occur at high brain centers in chronic pain conditions. In a review, Sandkühler mentioned the striking similarities between central sensitization and the processes of learning and memory, which suggests that long lasting plastic changes with a “memory” of nociceptive experiences is possible. 29

Summary^

There is clear evidence that tissue trauma leads to a reversible increase in the excitability of the central nervous system. Potentially irreversible changes have been documented. These alterations may be responsible, at least in part, for persisting pain after injury.

CENTRAL HYPERSENSITIVITY IN PATIENTS WITH WHIPLASH^

Methods to Investigate Central Hypersensitivity in Patients^

In patients, direct measurements at spinal cord neurons cannot be made. Therefore, it is impossible to provide direct evidence for neuronal hyperexcitability. However, hypersensitivity can be investigated indirectly by quantitative sensory tests. Typically, a sensory stimulus is applied at a peripheral tissue. Then the stimulus intensity is increased gradually until the subject perceives the stimulus as painful. The intensity at which the stimulus perception turns to pain is defined as pain detection threshold. The intensity at which the pain is perceived as intolerable is defined as pain tolerance threshold. Alternatively, a standardized painful stimulus is applied and the intensity of the evoked pain is recorded. Using these methods, hypersensitivity is detected when sensory stimulation evokes pain at stimulus intensities that do not induce pain in normal subjects (lower pain threshold) or when a standardized painful stimulus evokes stronger pain in patients than in normal subjects. Other methods to explore the sensory system are available, but a detailed description is beyond the scope of this paper. The interested reader can find more information in a review. 30

In the above examples, however, the reader would probably wonder whether hypersensitivity to sensory stimulation is the result of peripheral or central mechanisms. In fact, enhanced pain response is also observed after peripheral sensitization, in which the sensitizing factor (typically, trauma or inflammation) decreases the threshold to activate the nociceptors. However, peripheral sensitization is limited to the site of injury or inflammation. At this level, quantitative sensory tests cannot distinguish peripheral from central hypersensitivity. Conversely, whenever pain hypersensitivity is observed after sensory stimulation of healthy areas, its cause must be a hyperexcitability of the central nervous system (central hypersensitivity). Indeed, there is no evidence that peripheral mechanisms could account for a higher pain sensitivity at healthy tissues. Therefore, it is generally accepted that sensory stimulation of healthy tissues explores the excitability state of the central nervous system.

Evidence for Central Hypersensitivity in Patients With Whiplash^

Sheather-Reid and Cohen examined pain detection and tolerance thresholds after cutaneous electrical stimulation of the neck in patients with whiplash and healthy volunteers. 31 They found lower pain thresholds in patients than in healthy subjects. The absence of tissue damage at the site of testing suggested a central sensitization of nociceptive pathways as the cause of the pain hypersensitivity. In particular, the findings were interpreted as secondary hyperalgesia. As mentioned in the section “Mechanisms of Postinjury Sensitization,” secondary hyperalgesia is defined as enhanced perception of painful stimuli at healthy areas that surround damaged tissues and has been shown to be determined by central sensitization. 32

Koelback Johansen et al 33 investigated muscle pain sensibility after intramuscular injection of hypertonic saline. This method typically induces pain lasting few minutes both at the area of injection (local pain) and at areas at distance from the site of injection (referred pain). Additionally, pressure pain thresholds were assessed. Patients with whiplash displayed higher pain scores, longer duration of pain, and larger areas of local and referred pain after intramuscular injection of hypertonic saline, compared with healthy controls. They also had lower pressure pain thresholds. These differences were found at both neck and leg. Interestingly, several patients reported pain spreading to the whole leg and on the contralateral side, which was not the case in healthy subjects. These data suggest that pain hypersensitivity is not limited to the injured and surrounding areas (primary and secondary hyperalgesia), but may be generalized to the whole central nervous system.

We measured pain thresholds to electrical and heat stimulation, applied at both skin and muscles of both neck and lower limb, in patients with whiplash and healthy controls. 34 Measurements were made before and after injection of a local anesthetic into the painful muscles. Patients displayed lower pain thresholds with both cutaneous and muscular electrical stimulation, applied at both the neck and the lower limb. This confirms the previous findings of generalized central hypersensitivity. Interestingly, the pain thresholds after heat stimulation were similar in the two groups. This is consistent with previous evidence from studies on animals and healthy volunteers, showing that tissue damage does not necessarily result in secondary hyperalgesia to heat stimulation. 2,35–37 This finding, however, was not confirmed by other studies on patients with whiplash 38 and fibromyalgia, 39 in which an

enhanced reactivity to thermal stimuli was observed. The reasons for this discrepancy are unclear. Differences in stimulation modality may play a role. For instance, in the aforementioned study on fibromyalgia, 39 a repeated heat stimulus evoking a short-lasting spinal cord hyperexcitability (temporal summation) was applied. The response may be different from the one obtained by measuring a pain threshold. An additional finding of our study 34 was that infiltration of the local anesthetic into the painful and tender muscles did not reduce either neck pain or pain thresholds. This indicates that the source of pain was not located in the infiltrated muscles, and central hypersensitivity was not maintained by a nociceptive input arising from these muscles, at least in the patient population investigated.

Kasch et al 40 compared acute whiplash-injured with patients with acute ankle injuries over a period of 6 months. Pain thresholds after pressure stimulation, applied at the neck and the hand, were measured. Pain thresholds at the neck were lower in whiplash than in ankle patients at days 0 and 90 after trauma, but were similar in the 2 groups after 6 months. However, 87% of patients with whiplash had returned to work within 6 months after trauma. Therefore, the sample analyzed does not represent the patients with chronic pain. Pain thresholds after pressure stimulation applied at the hand was similar in the two groups. Because no control group of healthy subjects was included, it cannot be ruled out that both whiplash and ankle patients had abnormally low pain threshold after stimulation at the hand.

Moog et al 38 analyzed responses to a variety of nonpainful stimuli in patients with whiplash and healthy controls. Sixty-five percent of patients, but no control subject, reported pain after vibration stimulus. Patients reacted with more pain to heat and cold stimulation than healthy subjects. Because sensory stimuli were applied to nondamaged tissues, the results of this study confirm the presence of central hypersensitivity in patients with whiplash.

All the above studies employed psychophysical methods, which rely on the subject's report of the perceived stimulus. We have recently completed a study that analyzed spinal hypersensitivity using an electrophysiological method, namely the nociceptive withdrawal reflex. 41 An electrical stimulus was applied to the innervation area of the sural nerve and the withdrawal reflex response was recorded by electromyography of the biceps femoris muscle. 42 A voluntary knee flexion could be excluded by measuring the reflex latency (ie, the interval between application of the stimulus and muscle contraction). The latency must lie below 150 milliseconds to define the muscle contraction as spinal reflex. Therefore, we used this method as an electrophysiological quantitative parameter for hypersensitivity of spinal nociceptive neurons. Patients after whiplash injury and patients with fibromyalgia displayed lower reflex thresholds than healthy subjects. These findings, therefore, provide objective electrophysiological evidence for generalized spinal cord hypersensitivity. Because of the nature of the recordings, the study allows conclusions on nociceptive processes without the influence of pain behavior, which is inevitably present in studies based on patient's report of the perceived stimulus.

Taken together, the evidence shows that patients with chronic pain after whiplash injury display pain hypersensitivity after sensory stimulation of healthy tissues, most likely resulting from an alteration of the central processing of sensory input. The central hypersensitivity is not confined to the areas of the central nervous system that are connected to the painful region, but is probably generalized.

It is important to recognize that central hypersensitivity is not specific for whiplash, but has been observed in other chronic pain syndromes, such as fibromyalgia, 43 osteoarthritis, 44 tension-type headache, 45 temporomandibular joint pain, 46 and postmastectomy pain. 47

Mechanisms of Central Hypersensitivity in Patients^

This section discusses the possible mechanisms involved in central hypersensitivity in patients with chronic pain. Because it is impossible to perform direct measurements at the central nervous system in patients, most of the explanations are based on animal data and surrogate assessments on healthy volunteers or patients. The limitations of transposing these experimental data to chronic pain are evident. First, in basic research, it is possible to perform assessments before and after the injury.

Therefore, changes of the assessed outcomes can be attributed to the induced trauma. Conversely, the cause-effect relationship between trauma and exaggerated pain responses cannot be established in patients with certainty, for there is no recording of the sensory function before the injury. The possibility that the low pain thresholds recorded in patients were also present in the same individuals before the trauma cannot be ruled out. Second, studies on experimentally induced central hypersensitivity, either in animals or in healthy volunteers, cannot reproduce the complexity of the pain experience in patients. Third, unlike chronic pain, experimentally induced nociception is of short duration. Therefore, the pathophysiology of hypersensitivity states in patients is likely to differ substantially from the one evoked experimentally. Despite these limitations, it is surprising that most data from basic research are consistent with phenomena observed in patients and reasonably explain many of the abnormal pain responses typical of chronic pain.

Tissue Damage^

Based on the evidence presented in the section “Mechanisms of Postinjury Sensitization,” trauma-induced tissue damage can determine the neuronal plasticity changes that underlie central hypersensitivity. Therefore, this phenomenon could be defined as “central sensitization,” whereby the central nervous system is “sensitized” by a peripheral event.

At this point, an important question arises. Can central sensitization persist after resolution of tissue damage and explain chronicity? Or rather, does central sensitization amplify nociception from a diseased tissue, but disappears after injury heals and no nociceptive input arrives at the spinal cord? It is very difficult to address this question in patients, mainly because it is impossible to rule out peripheral damage with certainty even using advanced diagnostic tools. The fact that radiofrequency lesion of the nerves that supply the zygapophysial joints produces complete pain relief in patients with zygapophysial joint pain [48] indicates that tissue damage is the most important determinant of the pain complaints in these patients. Thus, although central hypersensitivity probably contributes to the magnitude of pain, it likely disappears or looses clinical relevance when the nociceptive input from the diseased tissue is blocked distal to the spinal cord. In a study on painful osteoarthritis of the hip, [49] abnormally low pain thresholds normalized after surgery, indicating that central hypersensitivity was maintained by chronic nociceptive pain. By arbitrarily extrapolating these considerations to patients with whiplash with an unidentified source of pain, we can hypothesize that the persistent pain is due to an ongoing nociceptive input arising from an unidentified peripheral lesion that maintains a state of constant and continuous central hyperexcitability.

The above explanation may not apply to all patients with whiplash. The role of ongoing nociception in maintaining central hyperexcitability may vary from patient to patient. Furthermore, central hypersensitivity could be observed in the absence of a nociceptive focus. As mentioned in the section “Mechanisms of Postinjury Central Hypersensitivity,” there are animal data suggesting that central sensitization may be the result of irreversible structural changes in the spinal cord. This leads to the hypothesis that the peripheral lesion may heal after whiplash injury, but irreversible changes take place in the spinal cord that maintain a state of central hyperexcitability. To date, there is no evidence supporting this hypothesis, mainly because of the difficulty in investigating this issue in patients.

Supraspinal Modulation—Psychologic Factors^

In the two aforementioned studies on central hypersensitivity in patients with whiplash, altered pain thresholds were not associated with alterations in personality traits. [34,41] In one of those studies, [41] we provided objective evidence for central hypersensitivity, in that voluntary exaggerated responses could be ruled out by electrophysiological methods. Based on these data, the results of psychophysical studies showing exaggerated pain responses in patients with whiplash are very unlikely the result of personality disorders or malingering. However, patients with whiplash displayed psychologic distress in our [34,41] and other investigations. [38,50] One of these studies [38] failed to demonstrate a correlation between psychologic distress and vibration pain. Nevertheless, there is experimental support for the influence of cognitive and behavioral alterations on injury-induced central sensitization. [19] Furthermore, experimentally induced anxiety lowers pain thresholds. [51] Therefore, psychologic distress may have a role in the determination of central hypersensitivity in patients.

The possibility that central hypersensitivity has a pure psychogenic origin cannot be ruled out, but has almost no experimental support. Attributing central hypersensitivity solely to psychologic factors would ignore the overwhelming and consistent evidence that injury and tissue damage induces hypersensitivity of the central nervous system. The fact that tissue damage is frequently not detected by the available diagnostic tools does not necessarily imply that there has been no tissue damage, as diagnostic methods do not always detect tissue damage. This is the case of zygapophysial joint pain: although these joints represent the best documented anatomic origin of pain after whiplash, diagnosis is frequently missed by clinical examination and imaging techniques. [52,53] As mentioned in the section "Evidence for Central Hypersensitivity in Patients With Whiplash," hypersensitivity was not observed after heat stimulation in our investigation, [34] which is consistent with experimental data on postinjury central sensitization. It is unlikely that psychologic distress selectively spares heat pain, as confirmed by a psychophysical study. [51]

Integration of Peripheral and Supraspinal Mechanisms^

Perhaps a further step in the understanding of the mechanisms of central hypersensitivity in patients with whiplash may be offered by a recently completed study by our group (R. Herren et al, unpublished data, March 2003). To investigate the correlation between nociceptive input and central hypersensitivity, we analyzed the modulating effect of infiltration of painful and tender points with a local anesthetic on pressure pain thresholds measured at the neck and the foot. The assessments were made 15 minutes after injection. Infiltration produced a variable immediate response, ranging from relief to enhancement of neck pain. The latter effect can be explained by the transient trauma induced by puncture and injection. Therefore, we used infiltration as a means of modulating nociceptive input from the periphery. The correlation between changes in neck pain and changes in pressure pain thresholds 15 minutes after infiltration was analyzed. Statistically significant negative correlations were found for threshold measurements performed at areas of secondary hyperalgesia of the neck: increases in neck pain after infiltration were associated with decreases in pain threshold, and vice versa. These areas of secondary hyperalgesia were not infiltrated with the local anesthetic. No significant correlation between neck pain and thresholds were found for measurements performed at the foot.

The above results suggest that different mechanisms underlie hyperalgesia localized at areas surrounding the site of injury and hyperalgesia generalized to distant body areas. Central hypersensitivity responsible for hyperalgesia at the neck may be a dynamic condition, modulated by changes in nociceptive input from the periphery. Conversely, short-term changes in nociceptive input may not affect generalized central hypersensitivity that determines hyperalgesia at areas far distant from the neck. It can be hypothesized that regional spinal cord mechanisms, such as expansion of receptive fields [14] and activation of glial cells, [15] are mainly responsible for hyperalgesia at the neck. These central changes would respond rapidly to changes in nociceptive input from the injured areas. Conversely, expression of COX-2 in the whole central nervous system, [13] cortical mechanisms and imbalance of the descending modulatory system [19] may play an important role in the determination of generalized hypersensitivity and would not respond rapidly to changes in nociceptive input. Clearly, in the absence of specific measurements of neuronal activity in humans, these explanations remain speculative. Nevertheless, the findings show that the mechanisms underlying central hypersensitivity are multiple, and that there may be place for the coexistence of peripheral lesions and supraspinal mechanisms as determinants of central hypersensitivity states.

Patients with whiplash are a heterogeneous population, in which the relative importance of tissue damage and supraspinal factors is likely to display great interindividual variability. Central hypersensitivity may be the mechanism in which somatic and psychologic factors find their common neurobiological correlate. We propose that tissue damage, either detected or not by the available diagnostic methods, produces central hypersensitivity as a result of the plasticity of the central nervous system. The psychologic distress that results from the chronic pain condition contributes to central hypersensitivity, thereby producing further amplification of pain (Fig. 1).

FIGURE 1. Possible role of central hypersensitivity in the pathophysiology of chronic whiplash pain.

CLINICAL IMPLICATIONS

Role of Central Hypersensitivity in the Pain Complaints

Central hypersensitivity may have high clinical relevance. In patients with whiplash, there is frequently lack of signs of tissue damage. [54] It is possible that a nociceptive signal of low intensity, arising from minimally damaged tissues, is amplified by sensitized spinal cord neurons, ultimately producing an exaggerated pain response. Even in patients with evident tissue damage, such as fractures or dislocations of the spine, central hypersensitivity probably develops and affects the magnitude of pain and disability.

Studies that induced central hypersensitivity experimentally suggest that hypersensitivity might persist after resolution of tissue damage. [2,36] This is supported by the potentially irreversible changes in the central nervous system discussed in the section “Mechanisms of Postinjury Sensitization.” Whether central hypersensitivity persists and explains pain after resolution of peripheral damage in patients still remains hypothetical (see section “Mechanisms of Central Hypersensitivity in Patients”). The fact that hypersensitivity was observed at the neck and leg to the same extent [33,34] indicates a state of generalized hypersensitivity of the central nervous system. This suggests that central hypersensitivity alone is unlikely to explain the pain syndrome, because pain is not generalized, but regional. Thus, the role of central hypersensitivity seems to be the amplification of a nociceptive input arising from a focus in the neck. Nevertheless, because of the limited knowledge on this issue in patients, the possibility of plasticity changes of the central nervous system as the sole determinants of pain cannot be ruled out.

Therapeutic Options

Theoretically, central hypersensitivity can be prevented or treated by the following approaches: 1) block or reduction of the nociceptive input from the injured areas; 2) specific pharmacological intervention on the spinal cord mechanisms underlying central hypersensitivity; and 3) pharmacologic or psychologic interventions acting at a supraspinal level and the descending modulatory system.

Peripheral Modulation

If ongoing nociceptive input from a diseased tissue is the main determinant of central hypersensitivity, interventions aiming at treating tissue damage or preventing nociceptive impulses from arriving at the spinal cord could also produce resolution of central hypersensitivity. To date, the only scientifically validated treatment modality for chronic whiplash pain that is able to completely block pain transmission is radiofrequency lesion of the nerves that supply the zygapophysial joints. [48]

Strictly speaking, this consideration applies to patients with painful peripheral lesions, identified or not by the common diagnostic tools. Unfortunately, the anatomic source of pain remains unidentified in the majority of patients with whiplash. For many patients, neither a causal nor a palliative treatment that can produce resolution of symptoms and disability is available. Nevertheless, if nociceptive input is amplified by the state of central hypersensitivity, preventing or treating central hypersensitivity is expected to reduce symptoms. In this case, one way of attenuating hypersensitivity is to reduce nociceptive input to the spinal cord neurons by pharmacologic interventions. For instance, nonsteroidal anti-inflammatory drugs and opioids act partly by reducing prostaglandin synthesis at peripheral tissues and presynaptic inhibition of transmitter release in the spinal cord, respectively. These drugs may therefore provide unspecific attenuation of central hypersensitivity, in that the postsynaptic exposure of spinal neurons to excitatory transmitters is reduced. Unfortunately, there is a disconcerting paucity of high quality clinical trials investigating pharmacological interventions in chronic patients with whiplash. [3,55] Thus, the efficacy of this drugs, alone or in combination, remains unproven.

Spinal Cord Modulation

NMDA-antagonists may provide specific treatment of central hypersensitivity, given the aforementioned involvement of the NMDA receptor in the generation of neuronal hyperexcitability. 11 Although the use of the NMDA-antagonist ketamine is limited by its unfavorable side effect profile, low intravenous doses have proven well tolerated and effective in acute pain. 56,57 Oral ketamine has been used in few investigations on neuropathic pain syndromes, with inconsistent results. 58,59 There is some evidence in acute pain that ketamine and opioids are mostly effective when used in combination, rather than as single drugs. 57 This drug combination is potentially useful, given the effect of the two drugs on different spinal cord mechanisms: opioids act presynaptically on the initial neuronal response, whereas NMDA-antagonists inhibit the following neuronal hyperexcitability. 60 Because of the involvement of COX-2 in central sensitization (see section "Mechanisms of Postinjury Central Hypersensitivity"), 12 COX-2 inhibitors, either selective or not, may have a role in the treatment of hypersensitivity states. The above treatment modalities have not been formally evaluated in patients with whiplash.

Antagonists of the NMDA receptor acting on its glycine site inhibited central hypersensitivity in animal studies. 61,62 The same was observed with antagonists of G-protein coupled metabotropic glutamate receptors. 63 These drugs could therefore represent in the future new classes for the treatment of hypersensitivity states. Antagonism of spinal inhibitory mechanisms mediated by glycine and gamma-aminobutyric acid receptors induces central sensitization. 64,65 Therefore, imbalance of these mechanisms may be involved in the determination of central hypersensitivity and might be treated by drugs acting at inhibitory spinal receptor sites. The above investigations are still at a preclinical stage.

Supraspinal Modulation^

Because of a possible role of cognitive and behavioral factors in postinjury central sensitization, 19 psychologic treatments have a potential to attenuate central hypersensitivity. The authors are not aware of investigations that have addressed this issue.

Descending opioidergic, 66 serotoninergic, 67 and noradrenergic 67 pathways modulate nociceptive transmission in the spinal cord and could therefore attenuate central hypersensitivity. Thus, opioids, antidepressants, and [alpha]$_2$-adrenoreceptor antagonists could attenuate central hypersensitivity by enhancing descending inhibition. Again, clinical trials that address the effects of these drugs in patients with whiplash are lacking.

Conclusions^

The above data show that there are potentially useful modalities for the treatment of hypersensitivity states. Some of these therapies are currently used in clinical practice but have not been subjected to rigorous scientific scrutiny. Other ones are completely unexplored. Perhaps, the possibility that central hypersensitivity may play an important role in the pathophysiology of whiplash pain will prompt the analysis of new therapeutic strategies.

CONCLUSIONS^

The available literature consistently shows increased pain sensitivity after sensory stimulation of healthy tissues in patients with chronic pain after whiplash injury. This indicates a state of hypersensitivity of the central nervous system that can explain exaggerated pain response following minimal tissue damage, detected or not by the available diagnostic methods. Experimental data indicate that central hypersensitivity is probably induced primarily by nociceptive input arising from a diseased tissue. In patients, imbalance of descending modulatory system connected with psychologic distress may also play a role. The limited evidence available is against a role of personality disorders or malingering in the determination of exaggerated responses to sensory stimulation in patients with whiplash.

Although there is experimental support for the persistence of central hypersensitivity after complete resolution of tissue damage, evidence in patients is lacking. Therefore, despite the likely importance

of central hypersensitivity in whiplash pain, the search for a peripheral lesion as the cause of pain and disability should not be stopped. Central hypersensitivity should not be used to justify our lack of understanding on the anatomic origin of the pain complaints.

Treatment strategies for central hypersensitivity in patients are limited, but largely unexplored. They may offer a perspective of better treatment of chronic pain after whiplash injury.

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