

REVIEW OF THE LITERATURE



Chronic Pain/Dysfunction in Whiplash-associated Disorders

Charles Davis, DC¹

ABSTRACT

Objective: The purposes of this article are (1) to review current knowledge of and recent concepts pertaining to the causes of chronic pain and/or dysfunction following whiplash-type injuries and (2) to acquaint those who treat these types of injuries with possible mechanisms of continued pain and or dysfunction following whiplash.

Data Collection: A review of the literature on mechanisms of injury and neurologic considerations was undertaken. A hand search of relevant medical, neuroscience, chiropractic, and online *Index Medicus* sources and other sources involving mechanisms of nociception, neurotransmitters, and receptors that might evolve from whiplash-type soft tissue injuries was conducted.

Results: Pain is a complex phenomenon that has great variability. Chronic pain appears to involve a deficient descending



inhibitory process and/or ongoing excitatory input.

Conclusions: There is a wide variety of reactions by individuals to any given type of stimulus. Injury may lead to increases in neuronal activity and prolonged changes in the nervous system. Chronic pain may be seen as part of a central disturbance accompanied by disinhibition or sensitization of central pain modulation, mirrored in the immune and endocrine systems. Patients with chronic whiplash syndrome may have a generalized central hyperexcitability from a loss of central inhibitory input (disinhibition) and/or

ongoing excitatory input contributing to dorsal horn hyperexcitability. Dysfunction of the motor system may also occur, with or without pain. The purpose of treatment should be not only to relieve pain but also to allow for proper proprioception. (*J Manipulative Physiol Ther* 2001;24:44-51) **Key Indexing Terms:** **Inhibition;** Whiplash Injury; Chronic Pain

INTRODUCTION

The types of injury produced in most low-speed motor vehicle collisions are soft tissue injuries involving the spine and nervous system. These injuries are inertial injuries and not crush injuries, which cause a variety of symptoms and syndromes. A human spinal column that is devoid of muscle function is incapable of carrying the loads imposed on it.¹ Without muscles, the spine buckles under very low loads. The average critical buckling load for the osteoligamentous human cervical spine is 10.5 N (SD 3.8). This is approximately one fifth to one fourth of the weight of the average human head.² In a low-velocity impact with whiplash, there is complex buckling of the cervical spine. Concomitant flexion and extension occur simultaneously in different regions of the cervical spine, resulting in an S-shaped curvature; motions in the lower cervical levels exceed their physiological motion limits in whiplash-type injuries.^{3,4} The soft tissue is seldom torn completely; instead, it is most likely stretched beyond its elastic limit, the result being an incomplete injury.⁵ This subfailure injury can significantly alter the tis-

sue's mechanical properties⁶; many subfailure injuries have potential injury consequence.⁷ Microscopic collagen fiber failure begins at 3% to 5% strain. Strain greater than 7% to 8% may result in the ligament's undergoing plastic deformation and may cause the load carrying capacity to be lost, even when the ligaments appear macroscopically intact.⁸ There is a wide range of variability in (1) ligament strength between individuals, (2) the body positions of occupants in the vehicle, (3) the amount of muscle activation and inhibition, (4) the size of the spinal canals, and (5) the excitability of the nervous system.⁹ A whiplash-type injury occurs in deep tissue that may involve the facets, disk, ligaments, or muscles.¹⁰ Deep tissue pain is different from superficial pain: the former lasts longer than the latter¹¹ and does not follow dermatomal patterns.^{12,13} Muscular or deep pain may be driven from both A-f and C fibers.¹⁴ A significantly lower pain threshold has been found in whiplash chronic pain subjects than in normal control subjects.¹⁵

DISCUSSION

Nociception

The perception of pain involves activation of nociceptors in the periphery, which then activate second-order neurons in the spinal cord. At the cord level, pain signals can be transmitted and modulated. Areas of the brain, thalamus, and

¹Private practice of chiropractic, Azusa, Calif. Submit reprint requests to: Charles G. Davis, DC, 474 S. Citrus, Azusa, CA 91702.

Paper submitted February 28, 2000; in revised form May 9, 2000.
doi:10.1067/jmpt.2001.112012

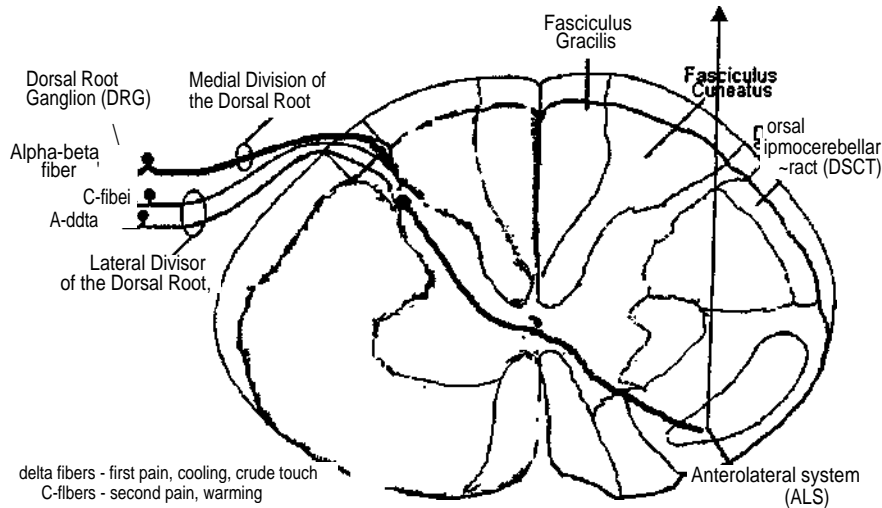


Fig 1. C- and A-5 fibers cross over to ascend in anterolateral system. Information is carried from spinal cord to thalamus through ascending pathways (ALS), including monosynaptic spinothalamic tract and poly synaptic spinoreticulothalamic tract.

brainstem receive the nociceptive information and can originate descending inhibition. Nociceptors are primary afferent neurons that respond to noxious or potentially tissue-damaging stimuli and can be sensitized. Acute pain can induce long-term neuronal remodeling and sensitization.¹⁶ After joint or muscle injury, the spinal cord processes nociceptive information and controls peripheral inflammation. The dorsal horn neurons can be sensitized by peripheral injury with activation of N-methyl-D-aspartate (NMDA), non-NMDA excitatory amino acid, and neurokinin 1 (NK1) receptors.¹⁷ A non-NMDA receptor, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), appears to set the baseline level of nociception and faithfully transmits the intensity and duration of the stimulus. NMDA receptors enhance noxious information.¹⁸

After tissue damage, the substances released include potassium (from damaged cells), serotonin (platelets), bradykinin (plasma), histamine (mast cells), prostaglandins (PGE₂; damaged cells), leukotrienes (damaged cells), and substance P (SP; primary afferent fibers).¹⁹

Tetrodotoxin sodium current receptors,²⁰ nerve growth factor (NGF), NK1 receptors (for SP), 5-p-K-opioid receptors, glutamate, NMDA and AMPA receptors, nitric oxide (NO), cyclooxygenase, and other neurotrophic factors and neurotransmitters can also affect nociception.²¹ Glutamate is the main excitatory neurotransmitter in the central nervous system and has been implicated in neurodevelopment and synaptogenesis,²² neurodegenerative disorders, neurotoxicity^{23,24} and synaptic plasticity, as in long-term potentiation (LTP) and long-term depression.²⁵ Adenosine 5'-triphosphate, which may also evoke nociceptor activation, is known to depolarize sensory neurons and may play a role in nociceptor activation when released from damaged tissue through primary afferent neurotransmission.²⁶⁻²⁷

Presynaptic NMDA receptors found in the afferent terminals in the dorsal horn may control the release of SP and other neuropeptides. Glutamate and SP coexist in primary afferent

terminals and are coexpressed and act synergistically in the dorsal horn. The release of SP in the dorsal horn is frequency dependent and appears to be controlled by NMDA receptors in laminae I and II of the spinal cord. Glutamate, an excitatory neurotransmitter in the dorsal horn, has its effects enhanced by SP acting on NK1 receptors.²⁸ SP is under the control of at least 2 functionally antagonistic glutamate receptors: inhibitory metabotropic receptors (groups I and III) and facilitatory ionotropic receptors (NMDA receptors). The predominance of the mechanisms depends on the pain condition, inasmuch as the pro-nociceptive function of mGluRs (a type of glutamate receptor) has been found to be mainly associated with inflammation.^{29,30} Various intracellular messengers linked to excitatory amino acid receptors (such as NO, arachidonic acid, and protein kinase C) may also play a critical role in the development of persistent nociception after tissue injury.^{31,34}

Inflammation

Inflammation increases the sensitivity of the receptors in the periphery and in the central nervous system by altering membrane properties of nociceptors, permitting a higher discharge frequency and contributing to hyperalgesia,³⁵ and by activating synapses that are usually inactive.³⁶ Inflammatory pain and the sensitization of peripheral nociceptors can be very rapid and involve non-neuronal cells such as mast cells, neutrophils, fibroblasts, and macrophages.³⁷ Inflammation increases the sensitivity in the peripheral terminals of A-5 and C fibers (Fig 1). Inflammation causes A- β fibers, which normally inhibit nociception, to sprout into lamina II in the dorsal horn³⁸ and express SP as C fibers.³⁹ Inflammation elevates the neurotrophin NGF,⁴⁰ increases levels of PGE₂,⁴¹ activates cholecystokinin-B receptors,⁴² alters the sensory processing in the substantia gelatinosa,⁴³ increases nociceptin (also known as *orphanin FQ*),⁴⁴ sensitizes tetrodotoxin sodium current receptors⁴⁵ that are present in peripheral terminals of primary afferent nociceptors,⁴⁶

increases NO that is involved in the maintenance of mechanical allodynia,⁴⁷ induces central sensitization in the spinal cord,⁴⁸ and increases the number of sensory axons containing ionotropic glutamate receptors that contribute to peripheral sensitization.⁴⁹ The medullary dorsal reticular nucleus plays a pronociceptive role in both acute and tonic inflammatory pain, leading to amplification of the nociceptive signal,⁵⁰ and it may also underlie the noxious response to the temporomandibular joint.⁵¹

Cytokines released from an injury may be proinflammatory or anti-inflammatory.⁵² Cytokines are small proteins that are essential for healing of connective tissue after injury and play roles in cell-to-cell signaling. The interaction between a cytokine and its receptor is highly specific. The response of a cell to its own cytokine is known as an *autocrine response*; the response of a cell to cytokines produced by adjacent cells is known as *apocrine response*.⁵³ Cytokines can also act as endocrine signals. Evidence points to tumor necrosis factor- α (a proinflammatory cytokine) having a role in inducing the hyperalgesic response to inflammation; this is likely to be the consequence of its induction of later-acting intermediaries, particularly interleukin-1 β and NGF.⁵⁴ Cytokines may act as a link between the nervous and immune systems.

Mechanisms of Chronic Pain

Chronic pain can be due to tissue injury, nervous system injury, or both. Pain may be stimulus-dependent or stimulus-independent.⁵⁵ In the development of chronic pain, wind-up-type mechanisms and LTP play roles in neuroplasticity to cause hyperalgesia and allodynia. Abnormal processing allows transmission of signals along the central nervous system pathways independent of the degree of nociception that is occurring in the periphery. The term *central sensitization* refers to an increase in spinal cord neuronal excitability and a decrease in threshold. Wind-up, a progressive increase in the magnitude of the C-fiber evoked response, may also produce some characteristics of central sensitization, including expansion of the receptive fields and enhanced responses to C-fiber stimulation.⁵⁶ Wind-up differs from LTP in that wind-up requires a very low frequency input and is manifest only during repetitive inputs. LTP requires a brief high-frequency input and is manifest only as a potentiated response to subsequent inputs for very prolonged periods⁵⁷; an ongoing afferent stimulation is not required. LTP can be suppressed by tonically active supraspinal descending systems.⁵⁸ Wind-up is not equivalent to central sensitization, but the stimulation that caused wind-up in the dorsal horn may give rise to central sensitization. Both are dependent on NMDA receptors and/or SP acting on neurokinin receptors. The NMDA receptor system in wind-up is changed after inflammation and central sensitization.^{59,60}

The NMDA receptor appears to be important for synaptic plasticity, and its function seems to be related to some characteristics of the receptor complex. The NMDA receptor is gated by both ligand binding to the receptor and by the membrane voltage. Activation of the channel can take place only when the membrane of the cell is partially depolarized by activation of other (non-NMDA) receptors. At normal resting membrane

potential, the NMDA channel is blocked by magnesium (Mg²⁺). Excitatory amino acids acting at non-NMDA receptors may produce a fast excitatory postsynaptic potential, whereas various neuropeptides may induce a slow synaptic potential, generating enough depolarization to remove Mg²⁺ from the NMDA receptor channel. Because the NMDA receptor is a high-capacity calcium (Ca²⁺) channel, the Ca²⁺ ions flow into the cell during NMDA receptor activation. Calcium triggers a number of intracellular biochemical processes that are important for LTP of the particular synapse. These processes include phosphorylation of membrane (receptor) proteins, activation of NO synthase, and activation of immediate early genes coding for factors regulating protein synthesis. The outcome of these biochemical alterations is a potentiation and consolidation of the particular synapse, and this may lead to persistent changes in neuronal excitability. It is assumed that the changes in cellular excitability caused by NMDA receptor-mediated Ca²⁺ influx may underlie wind-up.⁶¹

Chronic pain is characterized by an abnormal sensitivity that may be due to generation of pain in response of low-threshold mechanoreceptive A- β fibers that normally generate innocuous sensations.⁶² A decrease in non-nociceptive input may lead to pain by a deafferentation mechanism. The pain in deafferentation is described as "burning, raw, or searing" or as a "tingling, numb sensation."⁶³ A- β axons may exhibit spontaneous discharges as early as 1 day after injury. A- β fiber modification may cause allodynia by altering the processing of afferent input into the dorsal horn.⁶⁴ Because the pathophysiology of chronic pain indicates increased sensitivity to low threshold A- β fiber inputs, low levels of afferent activity are sufficient to maintain a state of central sensitization responsible for sensory changes. Pain and changed somatosensory thresholds may occur after relatively minor axonal damage and nerve sheath inflammation when no axonal damage is present.⁶⁵ Repeated low-intensity, non-painful stimulation can result in integration of neural responses and cause severe pain. Sparse nociceptive activity from minor pathologic conditions (minor nerve trauma or tissue inflammation) can become excruciatingly painful as a result of central integration of the neural responses.⁶⁶ Generated by tissue injury, persistent small afferent input results in a hyperalgesia at the site of injury and allodynia in areas adjacent to the injury site. Hyperalgesia reflects a sensitization of the peripheral terminal and a central facilitation evoked by the small afferent input, and allodynia reflects a central sensitization.⁶⁷ The changes in spinal sensory processing may occur without changes in blood flow⁶⁸ or inflammation.⁶⁹ Mediated by low-threshold mechanosensitive afferents projecting to sensitized dorsal horn neurons, the nociceptive processes are qualitatively altered in patients with chronic myofascial pain.⁷⁰ Patients suffering from chronic whiplash syndrome⁷¹ and patients with fibromyalgia⁷² have a generalized central hyperexcitability of the nervous system.

There is also evidence that chronic pain may be seen as part of a central disturbance accompanied by disinhibition or sensitization of central pain modulation, these being mirrored in the immune and endocrine systems.⁷³ Recent research indi-

cates that pain and immune function mechanisms have mutual features, immunocerebral communication playing an important role in hyperalgesia. Immune parameters have been shown to be related to activity in brain areas involved in pain perception, emotion, and attention.⁷⁴ This reflection does not need specific pathways or specific cerebral centers.^{75,76}

Dysfunction

Pain is not the only sequela to whiplash. Because the cervical spine is richly supplied with mechanoreceptors and muscle spindles, chronic pain can play a role in locomotor system dysfunction and in its perpetuation^{77,78} associated with whiplash trauma.⁷⁹ Patterns of normal proprioceptive input are distorted when articular nociception is incurred. This interferes with the precise continuous input necessary for coordinated normal patterns of motion, balance, coordination, and equilibrium.⁸⁰ Muscle spindle output from neck muscles is significantly altered when the bradykinin concentration is elevated. This may also induce pain through supraspinal projections and at the same time cause disturbances in motor coordination and proprioception by altering the activity of the γ -muscle spindle system.⁸¹ Hypertonicity of the muscles, autonomic reflexes, and overexcitation of proprioceptors affecting the central nervous system play a preeminent role in the genesis of disequilibrium and chronic postural instability from whiplash-induced injury.⁸²⁻⁸³ As a result of disorganized proprioceptive activity, a whiplash injury can cause distortion of the posture control system,⁸⁴⁻⁸⁵ including oculomotor dysfunction.^{86,87}

Some patients who claimed no symptoms after trauma showed oculomotor dysfunction and repositioning dysfunction. Neck pain measured with a cervicobrachial visual analog pain scale did not correlate significantly with oculomotor performance and kinesthetic sensibility. A proprioceptive dysfunction might be one of the most important factors for understanding the morbidity after a noncontact whiplash injury to the neck.⁸⁶ Dysfunction related to whiplash trauma may be seen with dysfunction of the smallest muscles (muscles of the eye),⁸⁷ which may reveal what otherwise might be overlooked.

Inhibition

Peripheral injury that produces inflammation can result in central sensitization and hyperalgesia. SP and glutamate, acting at the NK-1 and NMDA receptors, are involved in sensitizing spinal neurons inducing hyperalgesia. It is also evident that this is not the only mechanism. A decrease in the effectiveness of inhibitory synaptic transmission leads to increased responsiveness of spinal reflex pathways and pain sensations. In animals, damage to the descending inhibitory systems enhanced wind-up, indicating that wind-up is influenced by supraspinal, descending inhibitory pathways.⁸⁸ The inhibition of wind-up-like pain is associated with reduction in the intensity of continuous ongoing pain and with increased pressure-pain thresholds.⁶¹

Decreases in inhibitory processes—ie, disinhibition and/or an increase in excitatory input—are also involved in central sensitization and hyperalgesia. A disturbed inhibitory mechanism may result in widespread deep hyperalgesia.⁸⁹

Attenuated responses of deep dorsal horn neurons are dependent on the previous state of the neuron.⁹⁰ Descending inhibitory cortical control is effected by the opioidergic, noradrenergic, and serotonergic systems.⁹¹ Some patients may be genetically predisposed to decreased amounts of opioid receptors,⁹² and ischemia can reduce the expression of μ -opioid receptors in the dorsal horn.⁹³ The greater the quantity of opioid receptors one has, the more likely it is that the result will be less perception of pain.

The midbrain periaqueductal gray (PAG), rostral ventromedial medulla, and spinal cord are components of the endogenous pain modulating pathway^{94,96} (Fig 2). These brain stem-descending pathways are involved in modulation of spinal nociceptive neurons in response to transient stimuli and in modulation of spinal nociceptive processes in developing persistent pain. The fine-tuning by descending pathway modulating systems may underlie the variability of perceived pain and hyperalgesia. The imbalance can be a mechanism in acute and chronic pain conditions.⁹⁷ The endogenous descending antinociceptive system, including the serotonergic and noradrenergic descending pathways from the medulla and pons into the spinal cord, may be influenced by environmental stimuli. Functions of the PAG include pain, analgesia, anxiety, and cardiovascular control.⁹⁸ The descending pathways differentially modulate spinoparabrachial neurons in the superficial and deep dorsal horn in inhibiting nociceptive neurons in the superficial dorsal horn. The descending serotonergic pathway is more effective in suppressing neuronal hyperexcitability in the deep dorsal horn.⁹⁹ PAG μ -opioids activate a descending antinociceptive circuit with a δ -opioid receptor-mediated endogenous opioid link to the rostral ventromedial medulla.¹⁰⁰ The principal action of serotonin in this process is to limit neuronal excitability. Serotonergic transmission is largely mediated by nonjunctional contacts, which suggests that the actions of serotonin are mediated predominantly by volume rather than by wiring transmission.¹⁰¹ This release of serotonin may modulate nociceptive transmission in a tonic state-dependent manner.¹⁰² γ -aminobutyric acid (GABA) also reduces nociceptive reflexes, hyperalgesia, and allodynia.⁹⁰ In the spinal cord, GABA is concentrated in interneurons of the dorsal horn. Between 24% and 33% of the neurons in laminae I-III are reported to contain GABA.¹⁸ Normal tonic inhibition is partly by means of a GABA-dependent mechanism and, if it is not functioning properly, may play a role in prolonged pathologic states of increased spinal cord excitability.¹⁰³ Nociceptive transmission in the dorsal horn is subject to tonic-descending inhibition, and tonic-descending inhibition may prevent plastic changes in nociceptive transmission in the spinal cord.¹⁰⁴

Activation of NO signal transduction contributes to the sensitization of wide dynamic range spinothalamic tract neurons in the deep dorsal horn, causing simultaneous attenuation in inhibition produced in the PAG.¹⁰⁵ Sensitization of the spinothalamic tract cells is produced in part by disinhibition.^{90,105} Tinnitus (an auditory perception not caused by external stimulation) after head injury¹⁰⁶ or whiplash¹⁰⁷ may be due to a type of disinhibition.

Structures	Neurotransmitters
Brain Thalamus Hypothalamus	
Midbrain: Periaqueductal gray Locus	Enkephalin, GABA, Serotonin
Rons: Coeruleus	Noradrenaline
Medulla: Nucleus raphe magnus N. reticularis paragigantocellularis	Serotonin, non 5-HT Enkephalin, Serotonin
Spinal Cord	GABA, SP, 5-HT, Enkephalin, Glutamate and others

Fig 2. Simplified descending pain modulating pathway.

Modulation Stimulation

Impulses in primary afferent nerve fibers may produce short- or long-lasting modifications in spinal nociception. Afferent stimulation may facilitate or inhibit transmission of nociception information in the spinal dorsal horn. A-fiber stimulation selectively inhibits C-fiber-evoked and noxious stimulus-evoked excitation of dorsal horn neurons. Inhibition may considerably outlast the duration of the stimulus, presynaptic and postsynaptic mechanisms contributing to the inhibition. Somatosensory thalamic stimulation may activate pain modulation circuits. The effective thalamic output from the ventrocaudal nucleus of the thalamus to the cortex is affected by somatosensory input. Stimulation of the ventralposterior lateral nucleus has reduced mechanical allodynia in experiments.¹⁰⁸ A loss of non-nociceptive input into the thalamus may unmask or strengthen nociception and allow nociceptive neuronal input to be prominent.¹⁰⁹

Experimental studies suggest that myelinated afferents mediate electrically induced muscle pain and that unmyelinated afferents (C fibers) mainly mediate saline-induced muscle pain.¹¹⁰ Electric nerve stimulation is more effective for immediate relief of myofascial pain, and electric muscle stimulation has a better effect on the immediate release of muscle tightness.¹¹¹ The same transcutaneous electric nerve stimulation (TENS) has different degrees of antinociceptive influence on chronic and acute pain.¹¹² Stimulation frequencies have produced varied results. In one study, low-stimulation frequencies were found to be more effective than high-stimulation frequencies¹¹³; another study indicated that a high-frequency burst stimulation of A-8 fiber strength produced long-term depression of C-fiber-evoked potentials. TENS at high intensities (painful but tolerable) was found to be more effective than stimulation at low intensities. C-fiber synaptic transmission inhibition has been achieved by means

of high-frequency stimulation of A-8 fibers.¹¹⁴ This deep-tissue stimulation on the contralateral side activates inhibitory descending projections from higher centers.¹¹⁵ The resultant descending inhibition reduces the expression of LTP in dorsal horn cells, and that longterm descending inhibition may override a segmental facilitation.¹¹⁶ Physical activity can also significantly increase the threshold nociceptive reflex.¹¹⁷

Manipulation therapy can also improve pain tolerance. Spinal manipulative treatments show a consistent reflex response of multireceptor origin and may cause clinically observed benefits, including a reduction of pain and a decrease in hypertonicity of muscles.^{118,120}

The PAG-mediated descending pain inhibitory system is not the only mechanism associated with manipulative therapy-induced hypoalgesia.¹²¹ The cerebral cortex is involved in pain activity,^{122,124} pain facilitation,¹²⁵ and pain inhibition.¹²⁶ Afferent input evokes changes in the central nervous system and causes changes in the brain, depending on the side being treated (ipsilateral or contralateral).¹²⁷ In addition to antinociception, manipulation therapy produces changes in sudomotor, cutaneous vasomotor, respiratory, and cardiac activity. This suggests that activation is through a central control mechanism at a high level of the neuroaxis.¹²⁸ p-endorphin levels have also been shown to increase¹²⁹ after manipulation.

CONCLUSION

There is ample evidence that indicates diminished endogenous systems with chronic pain.¹³⁰ Injury may lead to increases in neuronal activity that are reflected in gene expression and prolonged changes in the nervous system. The functional result is hyperalgesia and spontaneous pain associated with tissue injury.¹³¹ Pain can be biochemical, with apparently normal structure.¹³² Patients suffering from chronic

whiplash syndrome may have a generalized central hyper-

excitability from a loss of tonic inhibitory input (disinhibition) and/or an increase in excitatory input contributing to dorsal horn hyperexcitability. This may lead to dysfunction of the motor system. The aim of treatment should be not only to relieve pain but also to allow for proper proprioception.^{86,133}

REFERENCES

- Panjabi MM, Abumi K, Duranceau J, Oxland T. Spinal stability and intersegmental muscle forces: a biomechanical model. *Spine* 1989; 14:194-200.
- Panjabi MM, Cholewicki J, Nibu K, Grauer J, Babat L, Dvorak J. Critical load of the human cervical spine: an in vitro experimental study. *Clin Biomech* 1998;13:11-7.
- Kaneoka K, Ono K, Inami S, Hayashi K. Motion analysis of cervical vertebrae during whiplash loading. *Spine* 1999;24:763-70.
- Grauer JN, Panjabi MM, Cholewicki J, Nibu K, Dvorak J. Whiplash produces S-shaped curvatures of the neck with hyperextension at lower levels. *Spine* 1997;22:2489-94.
- Panjabi MM, Cholewicki J, Nibu K, Babat LB, Dvorak J. Simulation of whiplash trauma using whole cervical spine specimens. *Spine* 1998;23:17-24.
- Panjabi MM, Yoldas E, Oxland TR, Crisco JJ. Subfailure injury of the rabbit ACL. *J Orthop Res* 1996;14:216-22.
- Herkowitz HN, Rothman RH. Subacute instability of the cervical spine. *Spine* 1984;9:348-57.
- Noyes FR, Keller CS, Grood ES, Butler DL. Advances in the understanding of knee ligament injury, repair, and rehabilitation. *Med Sci Sports Exerc* 1984;16:427-43.
- Davis CG. Injury threshold: whiplash associated disorders. *J Manipulative Physiol Ther* 2000;23:420-7.
- Malanga GA, editor. Cervical flexion-extension/whiplash injuries. Spine: state of the art reviews. Philadelphia: Hanley & Belfus; 1998.
- Woolf CJ, Wall PD. Relative effectiveness of C primary afferent fibers of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *J Neurosci* 1986;6:1433-42.
- Kellgren JH. On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. *Clin Sci* 1939;4:35-46.
- Feinstein B, Langton JNK, Jameson RM, Schiller F. Experiments on pain referred from deep somatic tissues. *J Bone Joint Surg Aml* 1954;36:981-97.
- Svendsen F, Tjolsen A, Hole K. AMPA and NMDA receptor-dependent spinal LTP after nociceptive tetanic stimulation. *Neuroreport* 1998;9:1185-90.
- Olivegren H, Jerkvall N, Hagstrom Y, Carlsson J. The long-term prognosis of whiplash-associated disorders. *Eur Spine J* 1999;8:366-70.
- CarrDB, Goudas LC. Acute pain. *Lancet* 1999;353:2051-8.
- Sluka KA. Pain mechanisms involved in musculoskeletal disorders. *J Orthop Sports Phys Ther* 1996;24:240-54.
- Dickenson AH, Chapman V, Green GM. The pharmacology of excitatory and inhibitory amino acid-mediated events in the transmission and modulation of pain in the spinal cord. *Gen Pharmacol* 1997;28:633-8.
- Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia AS, McNamara JO. Neuroscience. Sunderland (MA): Sinauer Associates; 1996. p. 165-77.
- Cummins TR, Waxman SG. Downregulation of tetrodotoxin-resistant sodium channels and up regulation of a rapidly repriming tetrodotoxin-sensitive sodium current in small spinal sensory neurons after nerve injury. *J Neurosci* 1997;17:3503-14.
- Svendsen F, Tjolsen A, Hole K, Doland S, Noland AM. N-methyl D-aspartate induced mechanical allodynia is blocked by nitric oxide synthase and cyclooxygenase-2 inhibitors. *Neuroreport* 1999; 10:449-52.
- McDonald JW, Johnston MV. Physiological and pathophysiological role of excitatory amino acids during central nervous system development. *Brain Res Rev* 1990; 15:41-70.
- Meldrum B, Garthwaite J. Excitatory amino acid neurotoxicity and neurodegenerative disease. *Trends Pharmacol Sci* 1990; 11:378-87.
- Beal MF. Role of excitotoxicity in human neurological disease. *Curr Opin Neurobiol* 1992;2:657-62.
- Baudry M, Massicotte G. Physiological and pharmacological relationships between long-term potentiation and mammalian memory. *Concepts in Neuroscience* 1992;3:79-98.
- Chen CC, Akopian AN, Sivlotti L, Colquhoun D, Burnstock G, Wood JN. A P2X purinoceptor expressed by a subset of sensory neurons. *Nature* 1995;377:428-31.
- Lewis C, Neidhart S, Holy C, North RA, Buell G, Surprenant A. Coexpression of P2X2 and P2X3 receptor subunits can account for ATP-gated currents in sensory neurons. *Nature* 1995;377:432-5.
- Marvizon JC, Martinez V, Grady EF, Bunnett NW, Mayer EA. Neurokinin 1 receptor internalization in spinal cord slices induced by dorsal root stimulation is mediated by NMDA receptors. *J Neurosci* 1997;17:8219-36.
- Cuesta MC, Arcya JL, Cano G, Sanchez L, Maixner W, Suarez-Roca H. Opposite modulation of capsaicin-evoked substance P release by glutamate receptors. *Neurochem Int* 1999;35:471-8.
- Marvizon JCG, Martinez V, Grady EF, Bunnett KW, Mayer EA. Neurokinin 1 receptor internalization in spinal cord slices induced by dorsal root stimulation is mediated by NMDA receptors. *J Neurosci* 1997; 12:8129-36.
- Malmberg AB, Yaksh TL. Antinociceptive actions of spinal nonsteroidal anti-inflammatory agents on the formalin test in the rat. *J Pharmacol Exp Ther* 1992;263:136-46.
- Yamamoto T, Shimoyama N, Mizuguchi T. Nitric oxide synthase inhibitor blocks spinal sensitization induced by formalin injection into rat paw. *Anesth Analg* 1993;77:886-90.
- Coderre TJ, Yashpal K. Intracellular messengers contributing to persistent nociception and hyperalgesia induced by L-glutamate and substance P in the rat formalin pain model. *Eur J Neurosci* 1994;6:1328-34.
- Callsen-Cencic P, Hoheisel U, Kaske A, Mense S, Tenschert S. The controversy about spinal neuronal nitric oxide synthase: under which conditions is it up- or downregulated? *Cell Tissue Res* 1999;295:183-94.
- Djouhri L, Lawson SN. Changes in somatic action potential shape in guinea-pig nociceptive afferent neurons during inflammation in vivo. *J Physiol* 1999;520:565-76.
- Li P, Zhou M. Silent glutamatergic synapses and nociception in the mammalian spinal cord. *Nature* 1998;393:695.
- Mendell LM, Albers KM, Davis BM. Neurotrophins, nociceptors, and pain. *Microsc Res Tech* 1999;45:252-61.
- Neumann S, Doubell TP, Leslie T, Woolf CJ. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. *Nature* 1996;384:360-4.
- Ma AP, Woolf CJ. The progressive tactile hyperalgesia induced by peripheral inflammation is nerve growth factor dependent. *Neuroreport* 1997;8:807-10.
- Woolf CJ, Shortland P, Coggeshall RE. Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 1992; 355:75-7.
- Izumi H, Mori H, Uchiyama T, et al. Sensitization of nociceptive C-fibers in zinc-deficient rats. *Am J Physiol* 1995;268:1423-8.
- Schafer M, Zhou L, Stein C. Cholecystokinin inhibits peripheral opioid analgesia in inflamed tissue. *Neuroscience* 1998; 82:603-11.
- Baba H, Doubel TP, Woolf CJ. Peripheral inflammation facilitates A-beta fiber-mediated synaptic input to the substantia gelatinosa of the adult rat spinal cord. *J Neurosci* 1999; 19:859-67.
- Andoh T, Itoh M, Kuraishi Y. Nociceptin gene expression in rat

- dorsal root ganglia induced by peripheral inflammation. *Neuroreport* 1997;8:2793-6.
45. Gold MS, Reichling DB, Shuster MJ, Levine JD. Hyperalgesia agents increase a tetrodotoxin-resistant Na⁺ current in nociceptors. *Proc Natl Acad Sci* 1996;93:1108-12.
 46. Khasar SG, Gold MS, Levine JD. A tetrodotoxin-resistant sodium current mediates inflammatory pain in the rat. *Neurosci Lett* 1998;256:17-20.
 47. Yoon YW, Sung B, Chung JM. Nitric oxide mediates behavior signs of neuropathic pain in an experimental rat model. *Neuroreport* 1998;9:367-72.
 48. Wu J, Lin Q, McAdoo DJ, Willis WD. Nitric oxide contributes to central sensitization following intradermal injection of capsaicin. *Neuroreport* 1998;9:589-92.
 49. Carlton SM, Coggeshall RE. Inflammation-induced changes in peripheral glutamate receptor populations. *Brain Res* 1999; 820:63-70.
 50. Almeida A, Storkson R, Lima D, Hole K, Tjolsen A. The medullary dorsal reticular nucleus facilitates pain behaviour induced by formalin in the rat. *Eur J Neurosci* 1999; 11:110-22.
 51. Tsai C. The caudal subnucleus caudalis (medullary dorsal horn) acts as interneuronal relay site in craniofacial nociceptive reflex activity. *Brain Res* 1999;826:293-7.
 52. Cunha FQ, Poole S, Lorenzetti BB, Veiga FH, Ferreira SH. Cytokine-mediated inflammatory hyperalgesia limited by interleukin-4. *Br J Pharmacol* 1999;126:45-50.
 53. Evans CH. Cytokines and the role they play in healing of ligaments and tendons. *Sports Med* 1999;28:71-6.
 54. Woolf CJ, Allchorne A, Safieh-Garabedian B, Poole S. Cytokines, nerve growth factor and inflammatory hyperalgesia: the contribution of tumour necrosis factor. *Br J Pharmacol* 1997;121:417-24.
 55. Woolf CJ, Bennett GJ, Doherty M, et al. Towards a mechanism-based classification of pain? *Pain* 1998;77:227-9.
 56. Li J, Simone DA, Larson AA. Windup leads to characteristics of central sensitization. *Pain* 1999;79:75-82.
 57. Woolf CJ. Windup and central sensitization are not equivalent. *Pain* 1996;66:91-8.
 58. Sandkuhler J, Liu X. Induction of long-term potentiation at spinal synapses by noxious stimulation or nerve injury. *Eur J Neurosci* 1998; 10:2476-80.
 59. Svendsen F, Rygh LJ, Hole K, Tjolsen A. Dorsal horn NMDA receptor function is changed after peripheral inflammation. *Pain* 1999;83:517-23.
 60. Carlton CSM, Coggeshall RE. Inflammation-induced changes in peripheral glutamate receptor populations. *Brain Res* 1999; 820:63-70.
 61. Hide PK. Wind-up and the NMDA receptor complex from a clinical perspective. *Eur J Pain* 2000;4:5-17.
 62. Woolf CJ, Doubel TP. The pathophysiology of chronic pain: increased sensitivity to low threshold Ab-fibre inputs. *Curr Opin Neurobiol* 1994;4:525-34.
 63. Tasker RR, Dostrovsky JO. Deafferentation and central pain. In: Wall PD, Melzack R, editors. *Textbook of pain*. Edinburgh: Churchill Livingstone; 1989. p. 154-80.
 64. Shin HC, Oh SJ, Jung SC, Choi YR, Won CK, Leem JW. Activity-dependent conduction latency changes in Ab-fibers in neuropathic rats. *Neuroreport* 1997;8:2813-6.
 65. Greening J, Lynn B. Minor peripheral nerve injuries: an underestimated source of pain? *Man Ther* 1998;3:187-94.
 66. Arendt-Nielsen L, Sonnenborg FA, Andersen OK. Facilitation of the withdrawal reflex by repeated transcutaneous electrical stimulation: an experimental study on central integration in humans. *Eur J Appl Physiol* 2000;81:165-73.
 67. Yaksh TL, Hua XY, Kalcheva I, Nozaki-Taguchi N, Marsala M. The spinal biology in human and animals of pain states generated by persistent small afferent input. *Proc Natl Acad Sci* 1999;96:7680-6.
 68. Andrews K, Baranowski A, Kinnman E. Subthreshold changes without initial pain or alterations in cutaneous blood flow, the area of secondary hyperalgesia caused by topical application of capsaicin in humans. *Neurosci Lett* 1999; 266:45-8.
 69. Alfredson H, Thorsen K, Lorentzon R. In situ microdialysis in tendon tissue: high levels of glutamate, but not prostaglandin E2 in chronic Achilles tendon pain. *Knee Surg Sports Traumatol Arthrosc* 1999;7:378-81.
 70. Bendtsen L, Jensen R, Olesen J. Qualitatively altered nociception in chronic myofascial pain. *Pain* 1996;65:259-54.
 71. Johansen MK, Graven-Nielsen T, Olesen AS, Arendt-Nielsen L. Generalized muscular hyperalgesia in chronic whiplash syndrome. *Pain* 1999;83:229-34.
 72. Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. *J Rheumatol* 1998;25:152-5.
 73. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines inflammation, illness responses and pathological pain states. *Pain* 1995;63:289-302.
 74. Lekander M, Fredrikson M, Wik G. Neuroimmune relations in patients with fibromyalgia: a positron emission tomography study. *Neurosci Lett* 2000;23:193-6.
 75. Jabbur SJ, Saade ME. From electrical wiring to plastic neurons: evolving approaches to the study of pain. *Pain* 1999;S6:S87-S92.
 76. Turrin NP, Plata-Salaman CR. Cytokine-cytokine interactions and the brain. *Brain Res Bull* 2000;51:3-9.
 77. Matre DA, Sinkaer T, Svensson P, Arendt-Nielsen L. Experimental muscle pain increases the human stretch reflex. *Pain* 1998;75:331-9.
 78. Sheather-Reid RB, Cohen ML. Psychophysical evidence for a neuropathic component of chronic neck pain. *Pain* 1998;75:341-7.
 79. Ellis SJ. Tremor and other movement disorders after whiplash-type injuries. *J Neurol Neurosurg Psychiatry* 1997;53:110-2.
 80. Wyke BD. Articular neurology and manipulative therapy. In: Glasgow EF, Twomey LT, Sell ER, Idezak RM, editors. *Aspects of manipulative therapy*. Melbourne: Churchill Livingstone; 1985. p. 72-7.
 81. Wenngren BI, Pedersen J, Sjolander P, Bergenheim M, Johannson H. Bradykinin and muscle stretch alter contralateral cat neck muscle spindle output. *Neurosci Res* 1998;32:119-29.
 82. Giacomini P, Magrini A, Sorace F. Changes in posture in whiplash evaluated by static posturography. *Acta Otorhinolaryngol* 1997;17:409-13.
 83. Hinoki M. Vertigo due to whiplash injury: a neurotological approach. *Acta Otolaryngol Suppl* 1985;419:9-29.
 84. Gimse R, Tjell C, Bjorgen IA, Saunte C. Disturbed eye movement after whiplash due to injuries the posture control system. *J Clin Exp Neuropsychol* 1996;18:178-86.
 85. Hinoki M, Hine S, Ushio N, Ishida Y, Koike S. Studies on ataxia of lumbar origin in cases of vertigo due to whiplash injury. *Equilibrium Res* 1973;3:141-52.
 86. Heikkila HV, Wenngren BI. Cervicocephalic kinesthetic sensibility, active range of cervical motion, and oculomotor function in patients with whiplash injury. *Arch Phys Med Rehabil* 1998;79:1089-94.
 87. Mosimann UP, Muri RM, Felblinger J, Radanov BP. Saccadic eye movement disturbances in whiplash patients with persistent complaints. *Brain* 2000;123:328-50.
 88. Gozariu M, Bragard D, Wilier JC, Lebars D. Temporal summation of C-fiber afferent input inputs: competition between facilitatory and inhibitory effects on c-fiber reflex in the rat. *J Neurophysiol* 1997;78:3165-79.
 89. Graven-Nielsen T, Babenko V, Svensson P, Arendt-Nielsen L. Experimentally induced muscle pain induces hypoalgesia in heterotopic deep tissues, but not in homotopic deep tissues. *Brain Res* 1998;787:203-10.
 90. Traub RJ. Spinal modulation of the induction of central sensitization. *Brain Res* 1997;778:34-42.
 91. Kharkevich DA, Churukanov VV. Pharmacological regulation

- of descending cortical control of the nociceptive processing. *Eur J Pharmacol* 1999;375:121-31.
92. Uhl GR, Sora I, Wang Z. The mu opioid receptor as a candidate gene for pain: polymorphisms, variations in expression, nociception, and opiate responses. *Proc Natl Acad Sci* 1999;24:7752-5.
 93. Yu W, Hao JX, Xu XJ, Hokfelt T, Hide R, Wiesenfeld-Hallin Z. Spinal cord ischemia reduces μ -opioid receptors in rats: correlation with morphine insensitivity. *Neuroreport* 1999;10:87-91.
 94. Gutstein HB, Mansour A, Watson SJ, Akil H, Fields H. Mu and kappa opioid receptors in periaqueductal gray and rostral ventromedial medulla. *Neuroreport* 1998;9:1777-81.
 95. Hammond DL, Wang H, Nakashima N, Basbaum AI. Differential effects of intrathecally administered delta and mu opioid receptor agonists on formalin-evoked nociception and on the expression of Fos-like immunoreactivity in the spinal cord of the rat. *J Pharmacol Exp Ther* 1998;284:378-87.
 96. Bellgowan PSF, Helmstetter FJ. The role of mu and kappa opioid receptors within the periaqueductal gray in the expression of conditional hypoalgesia. *Brain Res* 1998;791:83-9.
 97. Wei F, Dubner R, Ren K. Nucleus reticularis gigantocellularis and nucleus raphe magnus in the brain stem exert opposite effects on behavioral hyperalgesia and spinal Fos protein expression after peripheral inflammation. *Pain* 1999;80:127-41.
 98. Behbehani NM. Functional characteristics of the midbrain periaqueductal gray. *Prog Neurobiol* 1995;46:575-605.
 99. Wei F, Dubner R, Ren K. Laminar-selective noradrenergic and serotonergic modulation includes spinoparabrachial cells after inflammation. *Neuroreport* 1999;10:757-61.
 100. Hirakawa N, Tershner SA, Fields HL. Highly & selective antagonists in the RVM attenuate the antinociceptive effect of PAGDAMGO. *Neuroreport* 1999;10:3125-9.
 101. Lovick TA, Pary DM, Stezhka VV, Lumb BM. Serotonergic transmission in the periaqueductal gray matter in relation to aversive behavior: morphological evidence for direct modulatory effects on identified output neurons. *Neuroscience* 2000;95:763-72.
 102. Mason P. Central mechanism of pain modulation. *Curr Opin Neurobiol* 1999;9:436-41.
 103. Wall PD, Lidierth M, Hillman P. Brief and prolonged effects Lissauer tract stimulation on dorsal horn cells. *Pain* 1999;83:579-89.
 104. Gjerstad J, Tjolsen A, Svendsen F, Hole K. Inhibition of C-fibre responses in the dorsal horn after contralateral intramuscular injection of capsaicin activation of descending pathways. *Pain* 1999;80:413-8.
 105. Lin Q, Peng YB, Wu J, Willis WD. Involvement of cGMP in nociceptive processing by and sensitization by spinothalamic neurons in primates. *J Neurosci* 1997;17:3293-302.
 106. Ceranic BJ, Prasher DK, Raglan E, Luxon LM. Tinnitus after head injury: evidence from otoacoustic emissions. *J Neurol Neurosurg Psychiatry* 1998;65:523-9.
 107. Levine RA. Somatic (cranio-cervical) tinnitus and dorsal cochlear nucleus hypothesis. *Am J Otolaryngol* 1999;20:351-62.
 108. Duncan GH, Kupers RC, Marchand S, Villemure JG, Gybels JM, Bushnell C. Stimulation of human thalamus for pain relief: possible modulatory circuits revealed by positron emission tomography. *J Neurophysiol* 1998;80:3326-30.
 109. Davis KD, Kiss ZHT, Tasker RR, Dostrovsky JO. Thalamic stimulation-evoked sensations in chronic pain patients and nonpain (movement disorders) patients. *J Neurophysiol* 1996;75:1026-37.
 110. Laursen RJ, Graven-Nielsen T, Jensen TS, Arendt-Nielsen L. The effect of differential and complete nerve block on experimental muscle pain in humans. *Muscle Nerve* 1999;22:1564-70.
 111. Hsueh TC, Cheng PT, Kuan TS, Hong CZ. The immediate effectiveness of electrical nerve stimulation and electrical muscle stimulation on myofascial trigger points. *Am J Phys Med Rehabil* 1997;76:471-6.
 112. Cheing GLY, Hui-Chan CWY. Transcutaneous electrical nerve stimulation: nonparallel antinociceptive effects on chronic clinical pain and acute experimental pain. *Arch Phys Med Rehabil* 1999;80:305-12.
 113. Sandkuhler J, Chen JG, Chen G, Randic M. Low-frequency stimulation of afferent A δ -fibers induces long-term depression at primary afferent synapses with substantia nigra neuron in the rat. *J Neurosci* 1997;17:6483-91.
 114. Liu XG, Morton CR, Azuke JJ, Zimmerman M, Sandkuhler J. Long-term depression of C-fiber-evoked spinal field potentials by stimulation of primary afferent A δ -fibers in the adult rat. *Eur J Neurosci* 1998;10:3069-75.
 115. Gjerstad J, Tjolsen A, Svendsen F, Hole K. Inhibition of evoked C-fiber responses in the dorsal horn after contralateral injection of capsaicin involves activation of descending pathways. *Pain* 1999;80:413-8.
 116. Svendsen F, Tjolsen A, Rykkja F, Hole K. Behavioral effects of LTP-inducing sciatic nerve stimulation in the rat. *Eur J Pain* 1999;3:355-63.
 117. Guieu R, Blin O, Pouget J, Serratrice G. Nociceptive threshold and physical activity. *Can J Neurol Sci* 1992;19:69-71.
 118. Herzog W, Scheele D, Conway PJ. Electromyographic responses of back and limb muscles associated with spinal manipulative therapy. *Spine* 1999;24:146-53.
 119. Gillette RG, Kramis RC, Roberts WJ. Suppression of activity in spinal nociceptive "low back" neurons by paravertebral somatic stimuli in the cat. *Neurosci Lett* 1998;241:45-8.
 120. Terrett ACJ, Vernon H. Activity in nociceptive neurons can be suppressed by somatic stimulation. *Am J Phys Med* 1984;63:217-25.
 121. Vicenzino B, Cartwright T, Collins D, Wright A. An investigation of stress and pain perception during manual therapy in asymptomatic subjects. *Eur J Pain* 1999;3:13-8.
 122. Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JL, Carrier B. Pain perception: is there a role for primary somatosensory cortex? *Proc Natl Acad Sci* 1999;96:7705-9.
 123. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, et al. Dissociating pain from its anticipation in the human brain. *Science* 1999;284:1979-81.
 124. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol* 1999;82:1934-43.
 125. Calejesan AA, Kim SJ, Min Zhuo M. Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. *Eur J Pain* 2000;4:83-96.
 126. Kharkevich DA, Churukanov VV. Pharmacological regulation of descending cortical control of the nociceptive processing. *Eur J Pharmacol* 1999;375:121-31.
 127. Carrick R. Changes in brain function after manipulation of the cervical spine. *J Manipulative Physiol Ther* 1997;20:529-45.
 128. Vicenzino B, Collins D, Benson H, Wright A. An investigation of the interrelationship between manipulative therapy-induced hypoalgesia and sympathoexcitation. *J Manipulative Physiol Ther* 1998;21:448-53.
 129. Vernon HT, Dhami MSI, Howley TP, Annett R. Spinal manipulation and beta-endorphin: a controlled study of the effect of a spinal manipulation on plasma beta-endorphin levels in normal males. *J Manipulative Physiol Ther* 1986;9:115-23.
 130. Bruehl S, McCubbin JA, Harden RN. Theoretical review: altered pain regulatory systems in chronic pain. *Neurosci Biobehav Rev* 1999;23:877-90.
 131. Dubner R, Ruda MA. Activity-dependent neuronal plasticity following tissue injury and inflammation. *Trends Neurosci* 1992;15:96-103.
 132. Khan KM, Cook JL, Maffulli N, Kannus P. Where is the pain coming from in tendinopathy? It may be biomechanical, not only structural, in origin. *Br J Sports Med* 2000;34:81-3.
 133. Parkhurst TM, Burnett CN. Injury and proprioception in the lower back. *J Orthop Sports Phys Ther* 1994;19:282-95.