Clinical Implications of Neuroplasticity and Chronic Low Back Pain: A Literature Review

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A senior research project submitted in partial requirement for the degree Doctor of Chiropractic

June 19, 2009

ABSTRACT

Objective: This paper will review the physiological mechanisms associated with nociceptive processing. Special emphasis will be placed on the concept of central sensitization and its link to long-term potentiation and long-term depression. The author will also review the latest proposed mechanisms of spinal manipulative therapy and its beneficial effect on chronic low back pain.

Data Collection: A computer search using PubMed and Ovid generated articles relating to neuroplasticity, chronic low back pain, and spinal manipulation. Referenced sources were identified from the individual searches as well as throughout the neuroscience literature. Searches of PubMed and Ovid generated over 26,000 articles relating to neuroplasticity. Over 5,000 articles related to chronic low back pain were generated. More than 2,800 articles related to spinal manipulation were generated. Only one article contained a combination of all three search titles.

Data Synthesis: Chronic pain states are influenced by many factors including nociceptive and non-nociceptive pathways. An understanding of these factors and the processes involved with neuroplasticity is essential for physicians treating those with chronic pain.

Conclusion: Neuroplastic processes such as long-term potentiation and long-term depression have recently been identified as possible mechanisms maintaining or reducing chronic pain states. Spinal manipulation may induce long-term depression through stimulation of low-threshold mechanoreceptors, which could be an explanation for the long lasting analgesic effects of SMT.

Key Indexing Terms: Neuroplasticity, chronic low back pain, spinal manipulation

INTRODUCTION

Pain, as defined by the International Association for the Study of Pain, is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. [1] Low back pain (LBP) affects approximately one quarter of adults in any 1 month. [2] Chronic low back pain has been defined as pain lasting for more than 3 months in the area below the inferior border of the twelfth rib and above the gluteal folds. [3,4] Much of the emphasis in treating this condition has been focused on restoring normal function to the pain producing tissue. It is now apparent that chronic pain can persist even when injured tissues are healed, and that the central nervous system is a large contributor to the maintenance of this pain. An understanding of the central nervous system mechanisms involved in chronic low back pain is essential to the practitioner attempting to treat this condition. A review of these processes that occur at sites throughout the nervous system will be discussed along with considerations for treatment of chronic low back pain.

DISCUSSION

Gate Control Theory

Over the past half century the way we view the brain and the processes in which we perceive pain has changed drastically. This shift in thinking was largely brought about by Ronald Melzack and Patrick Wall's proposed Gate Control Theory in 1965. [9] This theory opened the door to thousands of studies and undoubtedly has changed our understanding of pain processes. The gate control theory's most important contribution to biological and medical science was its emphasis on central nervous system mechanisms. The theory forced the

medical and biological sciences to accept the brain as an active system that filters, selects, and modulates inputs. The dorsal horns were no longer viewed only as passive transmission stations but sites at which dynamic activities including inhibition, excitation, and modulation occurred. The theory highlighted the central nervous system as an essential component in pain processes.

Melzack and Wall's theory states that afferent nociceptive input could be modulated at the dorsal horn level by afferent input provided by larger non-nociceptive fibers. This functions as a regulator or "gating" mechanism for the nociceptive information before it is sent to cortical centers where the pain could be perceived. It is now apparent that this "gating mechanism" along with plastic change also takes place at peripheral receptor sites, the spinal cord, and at higher CNS centers. [10]

Chronic pain can be elicited and maintained through several mechanisms. This paper will focus on the nociceptive mechanisms of pain. The author acknowledges that non-nociceptive (cognitive-evaluative) factors play a large role in the perception and maintenance of chronic pain, but discussion of these mechanisms lies outside the scope of this paper.

Peripheral Sensitization

When injury occurs at peripheral tissues there is activation of local nociceptors. For relevance to injuries commonly encountered by chiropractors, these peripheral tissues may include many structures like muscles, intervertebral discs, or ligaments of the spine. These nociceptive signals are transmitted through Aδ-fiber and C-fiber neurons. Fast conducting Aδ-fibers transmit impulses from low-threshold nociceptors while the slower unmyelinated C-

fibers conduct impulses from high-threshold nociceptors. Tissue injury also leads to a local inflammatory response which releases substances like potassium ions, bradykinin, prostaglandins, and substance P which can induce changes in the response characteristics of peripheral receptors. [11] It has been demonstrated that these receptors become sensitized and require lower thresholds for firing along with increased rates of firing when stimulated at levels similar to before injury. [12] Prior injury may also reduce the threshold of these primary afferent fibers. [10] These inflammatory substances may work to activate nociceptors that are normally dormant or inactive. [13-15] Aβ-fibers, which are normally mechanosensitive in nature, may show a phenotype change and begin to adopt characteristics normally found in nociceptive C-fibers.[16] This allows normal mechanical or thermal stimuli to elicit nociceptive or painful signals (allodynia). [10,17,18] All of these changes that occur at peripheral sites act to increase the amount of afferent nociceptive information traveling to the cord.

Central Sensitization

If this increase in afferent nociceptive input is maintained for a prolonged period, it may induce a reversible increase in the excitability of central sensory neurons. [10] It has been demonstrated that this increased excitability is influenced by activation of N-methyl D-aspartate receptors. [19,20] Other changes are noted at the level of the dorsal horn. Receptive fields of single dorsal horn neurons have been shown to enlarge during this "sensitized" state. This may allow stimuli distant from the site of peripheral injury to elicit a response from the hyperexcitable neuron. [21]

Peterson and Curatolo state that "Central hypersensitivity is not just confined to the painful areas, but may involve the whole central nervous system." [18] In fact, patients with chronic low back pain have been shown to have generalized augmented pain sensitivity and cortical activation patterns which suggests abnormal central processing of pain. [22]

Neuroplasticity

"It is clear from the material present that the perception of pain does not simply involve a moment-to-moment analysis of afferent noxious input, but rather involves a dynamic process that is influenced by the effects of past experiences." [23] Neuronal plasticity refers to changes in neuron behavior influenced by previous events (activity dependent) and includes such processes as synaptic potentiation, synaptic depression, alterations in gene expression, and synaptic structural change. [24] The most simple forms of plasticity are when repeated stimuli lead to habituation (decreased response) or sensitization (increased response). [25] The aforementioned changes over an extended period of time are known as long-term potentiation and long-term depression which will be discussed in greater detail later in the paper.

Long Term Potentiation/Long Term Depression

As theories of pain processing have evolved, there is a growing body of evidence that suggests that noxious stimulus-induced plasticity can lead to changes in the central nervous system which contribute to pathological processes. A review of central neuronal plasticity by Coderre concluded that central neuronal plasticity not only contributes to the initial response to injury, but that it also contributes to the persistence of pain perception even when tissues

appear to be healed.[17] We also know that these plastic changes may take place at the level of peripheral receptors, at the spinal cord, or at higher cerebral centers.[10]

Long-Term Potentiation (LTP) can be defined as an increase in synaptic strength and an increase in discharge activity over an extended period of time (hours, days). It has been found that repeated high-frequency (10-200 Hz) synaptic activation can result in LTP. [26] Much of what we know about LTP has come from studies of the hippocampus. Although the exact physiological function of LTP is unknown, it has been suggested that it possibly plays a role in long-term memory since it appears in the hippocampus. It has also been suggested that LTP may play a role in chronic pain.[27] While LTP has been shown to increase neuronal activity, Long-Term Depression (LTD) can decrease neuronal activity for time periods that are clinically relevant.[28] This process may be produced de novo or it can reverse LTP.[26] It is stimulated by repeated low frequency (1-3 Hz) electrical input.

Sandkühler [29] has proposed that stimulation of Aδ-fibers can initiate LTD in the dorsal horn. He goes on to state that this is the main mechanism responsible for the pain-relieving affects of electroacupuncture and high-intensity, low-frequency TENS. Although descending modulatory pathways are likely a co-factor in this analgesia, the proposed LTD is argued to be a result of direct afferent glutamatergic synaptic action.

Manipulation and Chronic Low Back Pain

Spinal Manipulative Therapy (SMT) has been the main tool utilized in chiropractic treatment since the profession's development over 110 years ago. SMT has been known for its

analgesic effects for many years, but has just recently been shown to be a useful form of treatment for acute and chronic low back pain. [5-8]

Ongoing spinal "dysfunction/subluxation" is thought to cause the release of pain-producing agents.[30-34] Spinal manipulative therapy has been demonstrated to be an effective treatment for acute and chronic back conditions.[24] SMT has been proposed to restore normal biomechanics to dysfunctional areas and also stimulate the release of algesic agents that result in a reduction of pain. It has also been suggested that SMT activates ascending and descending pain modulating elements of the pain system.[32,33] These suggestions do much to explain the immediate analgesic effects of spinal manipulation, but fall short of explaining the long-lasting effects of spinal manipulation. As of late, more is being discovered about the plastic changes that occur in the nervous system, namely LTP and LTD. Knowledge about the mechanisms of LTP and LTD has sparked new theories on how and why spinal manipulation may produce lasting changes in patients with chronic low back pain.

As discussed earlier, Sandkühler has proposed that electroacupuncture and low-frequency TENS act by stimulating Aδ fibers which drive LTD in dorsal horn neurons. He suggests that this process, along with other ascending and descending modulatory pathways is responsible for the long term algesic affects of these modalities.[29]

In a recent review by Boal and Gillette, it was proposed that spinal manipulative therapy also produces sufficient Aδ stimulation to induce LTD and thus reverse LTP.[24]

> **"Specifically, we propose that SMT provides low and, most importantly, high threshold mechanosensory (Aδ/III fiber) input to spinal cord neurons, and thus the therapeutic effects of SMT might be linked to at least 1 of the known persistent mechanisms of plasticity, LTD."**

They state that force measurements during a typical chiropractic adjustment are sufficient to trigger activation of both Aδ and C-fiber mechanosensitive afferents.[28,35] They also state that the total applied adjustive force is significantly dissipated by soft tissues, and that the remaining forces are likely to be at a lower frequency, thus similar to those frequencies needed for LTD. They propose that SMT effectively activates Aδ-fibers initiating LTD, which is responsible for reversing ongoing LTP in dorsal horn neurons that are likely participating in the generation of low back pain. A study by Sung et al. [36] used an animal model to demonstrate that loads applied at typical speeds for spinal manipulation were capable of activating low-frequency receptors (Aδ) in lumbar spine musculature. Boal and Gillette concluded that this neural discharge could be the process responsible for SMT's favorable physiological effects. They offer this statement on the urgency with which therapeutic intervention should be initiated.

> **"A new appreciation of the significance of plasticity in the development of persistent pain has underscored the general recommendation that early therapeutic intervention should be utilized to interrupt (or even preempt) the start up of sensitized (hyperexcitability) states in patients, thus decreasing the likelihood of developing of persistent pain condition.[1]**

Several studies dealing with amputation and phantom limb pain underline the importance of timely intervention. Bach et al. demonstrated phantom limb pain following amputation could be reduced by using epidural anesthesia to block the limb pain prior to amputation.[37]

It has been demonstrated that chronic pain can detrimentally affect cognitive processes. Pain has been shown to reduce cortical processing capacity, slow decision making, and increase cognitive error rate.[38-40] Recent evidence has shown decreased pre-frontal and thalamic gray

matter density in subjects experiencing chronic pain.[41,42] A recent study by Buckalew et al. [43] showed that patients with chronic low back pain had significantly decreased gray matter volume in the posterior parietal cortex and middle cingulate white matter volume of the left hemisphere. The chronic low back pain group also showed impaired attention and mental flexibility.

The above data suggest that therapeutic interventions aimed at reducing or preventing nociceptive afferent activity and central sensitization in the nervous system should be initiated as early as possible to prevent these changes from occurring. This presents as a challenge to health care providers where patients often present only after pain has significantly impacted their lives and these processes may be long established.

Although outside the scope of therapeutic interventions used in chiropractic, several pharmacological agents have shown benefit for preventing or reversing cortical reorganization. Among these substances, GABA agonists, N-Methyl-D-aspartate (NMDA) receptor antagonists and anticholinergic substances seem to be the most promising.[18]

CONCLUSION

A substantial amount of research exists on the topics of neuroplasticity, chronic low back pain, and spinal manipulation. PubMed and Ovid searches generated over 26,000 articles related to neuroplasticity, over 5,000 articles on chronic low back pain, and over 2,800 articles on spinal manipulation. The review by Boal and Gillette was the only article found to address all three topics.

Evidence strongly supports that neuroplastic changes such as long-term potentiation and long-term depression can promote or enhance nociceptive processes via central sensitization. It is also apparent that early therapeutic intervention should be utilized to interrupt the start-up of sensitized states in patients in order to decrease the likelihood of developing a persistent pain condition.

Although the amount of research continues to grow, much work needs to be done to explore how therapeutic interventions like SMT address the central nervous system changes discussed above. Knowledge gained in this area would likely improve treatment strategies and outcomes for patients dealing with chronic low back pain.

REFERENCES

1. Merskey H, Bogduk N (1994) Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms, 2nd edn. IASP, Seattle.
2. Webb R, Bammah T, Lunt M, et al. Prevalence and predictors of intense, chronic, and disabling neck and back pain in the UK general population. Spine 2003;28:1195-202.
3. Spitzer WO, LeBlac FE, Dupuis M. Scientific approach to the assessment and management of activity-related spinal disorders. Report of the Quebec task force on spinal disorders. Spine 1987; 12 (suppl 7):1-59.
4. Croft PR, Papageorgiou AC, Ferry S, et al. Psychologic distress and low back pain. Evidence from a prospective study in the general population. Spine 1995;10:2731-7.
5. Anderson R, Meeker W, Wirick B, Mootz R, Kirk D, Adams A. A meta-analysis of clinical trials of spinal manipulation. J Manipulative Physiol Ther 1992; 15:181-94.
6. Shekelle P, Adams A, Chassin M, Hurwitz E Brook R. Spinal manipulation for low-back pain. Ann Inter Med 1992;117:590-8.
7. Koes BW, Assendelft WJJ, van der Heijden G, Bouter LM. Spinal manipulation for low back pain. An updated systematic review of randomized clinical trials. Spine 1996; 21:2860-73.
8. Van Tulder MW, Koes BW, Bouter LM. Conservative treatment of acture and chronic nonspecific low back pain. Spine 1997;22:2128-56.
9. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971-979.
10. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000;288:1765-9.
11. Rang HP, Bevan S, Dray A. Chemical activation of nociceptive peripheral neurons. Dr Med Bull 1991;47:534-8.
12. J.M. Cavanaugh, Neurophysiology and neuroanatomy of neck pain, in: F.A. Pintar, N. Yoganandan (Eds.), IOS Press, Amsterdam, 2000, pp 79-96.
13. Scmidt R, Schmelz M, Forster C, et al. Novel classes of responsice and unresponsive c nocicpeptors in human skin. J Neurosci 1995;15:333-41.
14. A. Dray, M. Perkins, Bradykinin and inflammatory pain, Trends in Neuroscience 16 (3) (1993) 99-104.
15. R. Dubner, K.M. Hargreaves, the neurobiology of pain and its modulation, Clinical Journal of Pain S2 (1989) S1-S6.
16. Neumann S, Doubell TP, Leslie T, et al. Inflammatory pain hypersensitivity mediated by phenotypic switch in myelinated primary sensory neurons. Nature 1996: 384:360-4.
17. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contributions of central neuroplasticity to pathological pain: review of clinical and experimental studies. Pain 1993;52:259-85.

18. Peterson-Felix S, Curatolo M. Neuroplasticity – an important factor in acute and chronic pain. Swiss Med Wkly 2002; 132:273-278.
19. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitation is dependent on n-methyl-d-aspartic acid receptor activation: implications for the treatment of post injury pain hypersensitivity states. Pain 1991; 44:293-9.
20. Dickenson AH, Sullivan AF. Evidence for a role of the NMDA receptor in the frequency dependent potentiation of deep rat dorsal horn nociceptive neurons following c fibre stimulation. Neuropharmacology 1987;26:1235-8.
21. Anderson OK, Finnerup NB, Spuioaich EG, et al. Expansion of nociceptive withdrawal reflex receptive fields in spinal cord injured humans. Clin Neurophysiol 2004:115:2798-810.
22. Giesecke T, Gracely RH, Grant MA, et al. Evidence of augmented central pain processing in chronic low back pain. Arthritis Rheum 2004;50 (2):613-23.
23. Melzack R., Coderre T.J., Katz J., Vaccarino A. Central Neuroplasticity and Pathological Pain. *Department of Psychology, McGill University, Montreal, Quebec H3A 1B1, Canada.*
24. Boal RW, Gillette RG. Central Neuronal Plasticity, Low Back Pain and Spinal Manipulative Therapy. JMPT 2003;27: 314-326.
25. Eriksen HR, Irsin H (2004) Subjective health complaints, sensitization, and sustained cognitive activation (stress). J Psychosom Res 56:445-448.
26. Abraham WC, Christie BR, Logan B, Lawlor P, Dragunow M. Immediate early gene expression associated with the persistence of heterosynaptic long-term depression in the hippocampus. Proc Natl Acad Sci U S A 1994;91:10049-53.
27. Pocket S. Spinal cord synaptic plasticity and chronic pain. Anesth Analg 1995;80:173-9.
28. Gilette RG, Spinal cord mechanisms of referred pain and related neuro-plasticity. In: Gatterman MI, editor. Foundations of chiropractic subluxation. St. Louis; Mosby;1995:279-301.
29. Sandkühler J. Learning and memory in pain pathways. Pain 2000;88:113-8.
30. Will TE. The biochemical basis of manipulative therapeutics: hypothetical considerations. J Manipulative Physiol Ther 1978;1:153-6.
31. Slosberg M. Effects of altered afferent articular input on sensation, proprioception, muscle tone and sympathetic reflex responses. J Manipulative Physiol Ther 1988;11:400-8.
32. Irving RE. Pain and the protective reflex generators: relevance to the chiropractic concept of spinal subluxation. J Manipulative Physiol Ther 1981;4:69-71.
33. Zusman M. A theoretical basis for short term relief of some types of spinal pain with manipulative therapy. Man Med 1987;3:54-6.

34. Henderson CNR. Three neurophysiological theories on chiropractic subluxation. In: Gatterman MI, editor. Foundations of chiropractic subluxation. St. Louis: Mosby; 1995.
35. Gillette RG. A speculative argument for the co-activation of diverse somatic receptor populations by forceful chiropractic adjustments. Man Med 1987;3:1-14.
36. Sung PS, Kang Y, Pickar JG. Effect of spinal manipulation duration on low threshold mechanoreceptors in lumbar paraspinal muscles: A preliminary report. Spine 2004;30(1):115-22.
37. Bach S, Noreng FM, Tjellden NU. Phantom limb pain in amputees during the first 12 months following limb amputation, after preoperative lumbar epidural blockade. Pain 1988;33:297-301.
38. Bucklew S, De Good D, Schwartz D, Kerler R. Cognitive and somatic item response patterns of pain patients, psychiatric patients and hospital employees. Journal of Clinical Psychology 1986;42: 852-60.
39. Crombez G, Eccleston C, Baeyens F, Eelen P. The disruptive nature of pain: An experiment investigation. Behavior Research and Therapy. 1996;34(11-12):911-18.
40. Derbyshire SW, Vogt BA, Jones AK. Pain and Stroop interference tasks activate separate processing modules in anterior cingulated cortex. Experimental Brain Research 1998;118(1):52-60.
41. Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 2004;24(46):10410-5.
42. Grachev ID, Fredrickson Be, Apkarian AV. Brain chemistry reflects dual states of pain and anxiety in chronic low back pain. J Neural Transm 2002;109(10):1309-34.
43. Buckalew N, Haut MW, Morrow L, Weiner D. Chronic pain is associated with brain volume loss in older adults: Preliminary Evidence. Pain 2008;9(2):240-6.