Neurogenic Inflammation and its relationship to central sensitization, sympathetic nervous system, and somato-visceral mechanisms.

by
Bryan G. Dingsor B.S.

Submitted to:
Logan College of Chiropractic

Bryan Dingsor
132 Steamboat Ln Apt #3
Ballwin, MO 63011

ABSTRACT

Background: Pain continues to be the main symptom reported by patients. Frequently, clinicians may incorrectly diagnose pain states that may later lead to pain perpetuated by many different types of inflammatory perpetuating mechanisms (neurogenic inflammation and central sensitization); therefore, leading to a situation of chronic pain in those types of patients.

Objective: The purpose of this article are to review the current knowledge of and recent concepts pertaining to the causes of neurogenic inflammation, central sensitization, sympathetics and inflammation, and the somato-visceral link. The article will look at the latest research covering the above topics and will try to link together how these mechanisms work with one another.

Data Collection: A review of the literature on mechanisms of neurogenic inflammation, central sensitization, sympathetics and inflammation, and somato-visceral reflexes was undertaken. A computer search utilizing the online search by Medline was conducted to find articles relevant to the above topics

Data Synthesis: Chronic pain states are responsible for the majority of pain complaints in clinical practice. Some of these chronic pain states may manifest themselves in visceral diseases thus leading to syndromes in this set of patients. Care must be taken to avoid the common mistake of misdiagnosing patients that have entered into a peripheral and/or central sensitized state.

Conclusions: Although the research into the areas of neurogenic inflammation, central sensitization, sympathetic nervous system and inflammation, and the

somato-visceral link are in their infancy, it is exciting to note how all of the above are related to the central nervous system.

Key Indexing Terms: Pain; Neurogenic Inflammation; Central Sensitization; Sympatheticotonia; Somato-visceral Reflex

Introduction

Improvements in research methods have allowed researchers to correlate the relationship of the sympathetic nervous system with neurogenic inflammation. Neurogenic inflammation has been attributed to contributing to many of the inflammatory diseases of the airways, joints, bladder, eye, gut, and skin (1, 2). This literature review will discuss the latest studies covering the relationship of the sympathetic nervous system to neurogenic inflammation, and the correlation of the above two contributing to inflammatory diseases.

Background

Inflammation was first described by Celsus over 2000 years ago. He described the five cardinal signs of inflammation rubor (vasodialation), calor (heat), turgor (edema), dolor (pain), and loss of function (3). It wasn't until about 20 years ago that the term neurogenic inflammation was defined and found to be a contributing factor in many inflammatory diseases. Neurogenic inflammation refers to a process where peripheral nerve endings evoke local inflammatory responses through the releasing of certain neurotransmitters (substance P [SP], calcitonin gene related peptide [CGRP], neurokinin A [NKA], neurokinin B [NKB], and norepinephrine [NE]) (1). It has not been widely investigated up until the past few years due to the advances in available research methods used to track neuropeptides.

Increased sympathetic activation is defined as stimulation of the lateral horn (sympathetic area of the cord) via volume transmission of neurotransmitters in the interneuronal pool of the spinal cord leading to a state of increased release of NE and other prostaglandins at the sympathetic efferent terminals (4). Increased sympathetic tone contributing to diseases was first put forth by Dr. Irvin Korr. He was one of the first to postulate the effects of somato-visceral reflexes and disease models in the mid-1900's and described the reflex states to be caused by increased sympathetic tone or a term which he coined "sympatheticotonia" (5).

Research in the area of neurogenic inflammation and increased sympathetic tone is a relatively new area. As of yet, there has been some promising research correlating sympathetic tone with neurogenic inflammation in disease states, but current research still needs to be done to further uphold this theory.

The current problems within the literature have been with correlating visceral disease states with increased sympathetic tone. Nansel and Szlazak contend from their review of Korr's model based on increased afferent signals from dysfunctional somatic tissue leading to increased sympathetic tone resulting in disease to be faulty. Their reasoning for this was that increased sympathetic tone leading to a vasoconstrictor activity in the organs would not lead to any disease states such as cancer, colitis, diabetes mellitus, and other segmentally related diseases (5). The problem with the review was that neurogenic inflammation was not mentioned. Although increased sympathetic tone would

cause vasoconstrictive effects, the article did not discuss the latest findings in research discussing the role of neurogenic inflammation.

Other studies note the problems associated with the use of sympathetic nerve blocks to treat diseases such as Complex Regional Pain Syndrome or Herpes Zoster (both of which are associated with neurogenic inflammation) which has demonstrated only partial/lasting benefit in pain relief and other symptoms associated with the diseases (6). Other studies site a promising relief of symptoms with sympathetic blockade for relief of chronic pain in many conditions (7).

These conflicting studies make the subject of correlating the removal of sympathetic tone with decreased neurogenic inflammation difficult; therefore, the goals of this paper are to: 1. define neurogenic inflammation 2. define the role of the sympathetic nervous system in neurogenic inflammation 3. propose a mechanism as to how a subluxation complex could contribute to the perpetuation of neurogenic inflammation.

What is Neurogenic inflammation?

Neurogenic inflammation is defined as a process where peripheral nerve endings evoke local inflammatory responses through the releasing of certain neuropeptides like substance P [SP], calcitonin gene related peptide [CGRP], neurokinin A [NKA], neurokinin B [NKB], and norepinephrine [NE] (1, 2, 8) It has been referred to other processes such as antidromic vasodilation, axon reflex, and the triple response, but neurogenic inflammation has been the most utilized

term for the past twenty years to describe the above physiological process (9). Neurogenic inflammation plays a major role in the perpetuation of many pain states that patients present with in a typical chiropractic office. It has been proposed by some researchers that 'non-specific' back pain is biologically or 'ergonomically' caused by neurogenic inflammation (10). The tissue damage that occurs from an acute injury sets in motion mechanisms, neurogenic and non-neurogenic, which feed back upon each other's effects. These findings have much significance in the field of chiropractic. Understanding this concept could help many clinicians in understanding the mechanism behind many chronic pain states.

Neurogenic inflammation has only been found to be a relevant process within the past 20 years due to techonological advances in research which are able to measure the release of neuropeptides, vasodilation, and other inflammatory mediators. The first evidence showing this response was observed in experiments done by Bayliss in 1901. Bayliss stimulated the dorsal roots of the spine and found visible vasodilation on the skin surface. He termed this response as "antidromic" to indicate that there was a reverse response down the nerve caused by stimulating the affected afferent nerve (1). Bayliss was the first to advance the hypothesis that afferent nerve fibers could have efferent effects in experimental conditions.

Through the latest research it has been found that neurogenic inflammtion is related to two mechanisms which interact: 1. The activation of the sympathetic nervous system which leads to release of NE and other pro-inflammatory

substances at the axon terminal; 2. The antidromic release of neuropeptides from periepheral afferent nerves that are distributed throughout the whole body (1, 2, 8). Since both the sympathetic nervous system and afferent nerves are involved in the process, neither one can be separated from the other.

Nueropeptides have been studied extensively in different types of models involving neurogenic inflammation. The neuropeptides substance P (SP), neurokinen A (NA), and calcitonin gene-related peptide (CGRP) are now known to coexist in sensory neurons and to have potent vasodilatory, chemotactic, and other inflammatory properties (9, 10).

Of all the neuropeptides involved in neurogenic inflammation SP has been the most widely studied. SP is part of a group known as Tachykinins (2). SP and NKA both are a part of this group and have been extensively studied by a group of authors on their effects in asthma and the airway. For example, SP has been shown to constrict the smooth muscle of the human airways *in vitro*, to stimulate mucus secretion from the submucosal glands in the human airways *in vitro*, and cause mast cells and eosinophils to degranulate. (2). SP and NKA stimulate the chemotaxis and formation of lung fibroblasts explaining the effect of fibrotic formation that is commonly found in asthmatics. These factors have lead researchers to conclude that there are two causes (either separate or together) of asthma: immunogenic and neurogenic. The overlap of these two types of contributors of asthma has been summarized well in a table by William J. Meggs:

Immunogenic versus neurogenic asthma:

	Immunogenic	Neurogenic
Triggered by	Protein aeroallergens	Volatile chemicals
Interacting with	IgE antibody	Chemical irritant receptors
Located on	Mast cells	Sensory nerve C-fibers
Releasing	Histamines, leuktrienes	Neuropeptides: SP, NKA
Stimulating	Sensory nerve C-fibers	Mast cell degranulation
Producing	Bronchial inflammation	Bronchial inflammation
Manifesting as	Asthma	Asthma

The above table demonstrates how both neurogenic and immunogenic inflammation are intertwined. The effects of both types of inflammatory events are similar in their outcomes, but different in their triggers and locations. It is fascinating to note that a chronic inflammatory disease such as asthma can be affected by the sensitization of its nerve endings leading to a neurogenic inflammatory state.

It has been stated that 50% of nociceptors (afferent c-fibers) are normally turned off in any given area of the body when there has been no prior tissue damage. These nociceptors have been termed 'silent' or 'sleeping' because they do not have a role in nociception when the tissue has not been sensitized by some previous trauma (11). Once a significant inflammatory event occurs (from trauma or constant irritation), these turned off c-fibers become sensitized by the inflammatory mediators. "Sensitization is defined as the lowering of the nociceptor threshold (12). Once sensitized, the c-fibers in turn release SP and stimulate acrachidonic acid production, which perpetuates the inflammatory event. These findings indicate that once an inflammatory event has taken place

for a period of time to lower the threshold and sensitize 'silent' nociceptors, these sensitized afferent c-fibers will continue to perpetuate the neurogenic inflammatory event. A brief explanation by Jayson helps explain this concept more fully:

> Peripheral injury increases excitability of the central nervous system. Within the dorsal horn, stimulation of peripheral pain fibers causes increased activity with prolonged periods of discharge, so that patients continue to feel pain long after the physical cause of the pain has healed. The dorsal horn cells develop increased sensitivity to afferent impulses. As a result, the patient experiences pain and tenderness that is disproportionate to the evidence of peripheral tissue damage, giving rise to the phenomena of hyperpathia and allodynia. The dorsal horn receptor fields may expand so that pain is felt over a much wider area than the damage to pain fibers would predict(13).

Another mechanism in which the nocicpetors may become sensitized is by inhibition of the hyperpolarization that occurs after impulse generation. A slow after-hyperpolarization limits the number of impulses a nerve fiber can generate over a period of time. The prostaglandins and bradykinin act to inhibit the hyperpolarization which leads to the phenomena of the neuron firing repetitively (14, Dray 1996 from Neurophysiology of Pain. Man ther 1999).

There is increasing evidence of the role of nerve growth factor (NGF) as being a mediator of peripheral sensitization and hyperalgesia. Its actions include that of regulating proton ion channels and stimulate the release of neuropeptides. In states of neurogenic inflammation it has been found that administration of anti-NGF can relieve induced hyperalgesia (15).

Evidence supports the hypothesis that both the peripheral nerves and an inflammatory event in an injured tissue combine to create the phenomena of hyperinflammation and sensitization leading to a perpetual inflammatory state. The process of peripheral sensitization is one mechanism by which the nociceptive system becomes upregulated. It is apparent that peripheral sensitization is a complex process and does involve other processes which contribute to the upregulation of the nociceptive system. A good example of this is allodynia. Allodynia is manifested in many patients seen in the common chiropractic practice. Allodynia is defined as "pain produced by a stimulus that is normally not painful," such as that with normal palpation of muscles or joints (12). Patients with fibromylagia, chronic fatigue, or a myofascial pain syndrome all present with a degree of allodynia. Knowing that neurogenic inflammation can perpetuate these problems may help the clinician in identifying what may be leading to the chronic painful state.

The role of Central Sensitization

The process of central sensitization is another important aspect of neuroplasticity (a change in nerve signaling) that contributes to upregulation of the nociceptive system in response to injury This process may provide a link between the pain in the motor system and autonomic dysfunction in patients with musculoskeletal disorders. Central sensitization describes changes occurring at the cellular level to support the process of plasticity occurring in the neurons of the spinal cord and in the supraspinal centers, as a result of activation of the nociceptive system (15).

According to a review by Ke Ren, he states that "Peripheral tissue inflammation leads to prolonged central sensitization characterized by an enhanced neuronal activity in the spinal dorsal horn (17)." Central sensitization is defined as an increased excitability of nociceptive neurons in the central nervous system (CNS)(18). Thus, a facilitated/hyperstimulated central nervous system may lead to an overload or volume transmission in the interneuronal pool of the spinal cord. Too much overload in the interneuronal pool may lead to a spillover effect to the lateral horn. This increase of activity in the lateral horn leads to increased sympathetic activity and release of norepinephrine at its terminal endings (17,19).

The original hypothesis of central sensitization was done by Denslow and Hasset in a review of the literature on how the spinal cord could become facilitated. From the current research they concluded that dysfunction of somatic tissue (muscles and joints) was associated with central sensitization of the cord (20). Although this was a simplified explanation, it opened a new field of neurology.

Neurogenic inflammation is tightly interwoven with central sensitization in which any type of inflammatory reaction in the peripheral nociceptors leads to a sustained release of nociceptor input into the spinal cord. This sustained release of input leads to the release of excitatory neuropeptides such as substance P and neurokinin A from the presynaptic terminals of the nociceptive afferents. This increased excitability leads to neuronal plasiticity within the cord. The plasticity results in neurons which become more efficient and more easily

excitable. Making new synaptic connections allows them to excite other neuronal pools. The new synaptic connections account for why the autonomic system and motor system become affected in many pain conditions. This also explains how neurogenic inflammation can increase its effect—the spillover of excitable peptides into the sympathetic system leads to more release of NE and other neuropeptides that promote neurogenic inflammation at the site that has an over abundance of inflammation (21).

In a review done by Seaman and Winterstein they found in the latest research that C-fibers (the small unmyelinated pain carrying fibers) can produce extended excitation of the cord. It was also found that the C-fibers also cause a profound change in the receptive field properties of the dorsal horn. In later studies, they found researchers focusing on how input can change the plasticity of the cord in the development of central sensitization. This plasticity is now agreed upon as an increased spontaneous activity, reduced thresholds or increased responsiveness to afferent inputs which are prolonged after discharge from repeated stimulation of the afferent fibers. Seaman and Winterstein conclude their review on this topic with researchers currently hypothesizing that plastic changes in the cord are due to a an increase in excitatory inputs and/or a loss of inhibitory inputs, which result in a net excitation of the dorsal horn (22).

Central sensitization has been shown to be involved in many chronic pain states. In a review of the literature done by Charles Davis D.C. on chronic pain/dysfunction in whiplash disorder, he concluded that chronic pain indicates increased sensitivity to low threshold A-B fiber inputs and low levels of afferent

activity which are sufficient to maintain a state of central sensitization responsible for sensory changes. This repetition of low level stimulation can result in an integration of neural responses and cause severe pain in whiplash patients. He found from his literature search that patients suffering from chronic whiplash and patients fibromyalgia have a central hyperexcitability contributing to their chronic pain state. (24).

Although neurogenic inflammation plays a role in inducing a state of central sensitization, researchers have found that injury decreases the central inhibitory processes. The disinhibition leads to a state of hyperalgesia and central sensitization. Cortical disinhibition occurs through loss of the inhibitory control of the central nervous system by the opiodergic, noradernergic, and serotonergic receptors on the dorsal horn. It has been noted that some patients are predisposed to have fewer of these receptors in the dorsal horn, thus leading to a greater perception of pain in that patient (24).

The relationship of the afferent nerve fibers causing an overload of neurotransmitters within the interneuronal pool is an exciting area for research in the chiropractic profession and may need further studies to demonstrate the effectiveness of spinal manipulation to decrease central sensitization.

Sympathetic nervous system and its relationship to neurogenic inflammation

Increased sympathetic tone may be due to a number of causes, but it is usually separated into psychogenic and mechanical. This paper will focus on the mechanical causes of increased sympathetic tone. The reason for this is to

correlate somatic pain (back pain) causing increased sympathetic tone that may lead to increased neurogenic inflammation in peripheral tissues.

In an article by Bascom and Meggs on the physiology and integration of the sympathetic nervous system and periperhal nervous system, they describe the sympathetic nervous system/neurogenic inflammation interaction as:

> Neurogenic inflammation is initiated by stimulation of peripheral c-fiber neurons. A peripheral axon reflex results in the release of neuropeptides and in signs of inflammation at a peripheral sites distinct from the site of the original stimulus. The stimulus is also transmitted centrally and provides a central afferent signal and efferent reflexes (9).

The efferent reflex was the sympathetic system contributing to the perpetuation of the inflammatory event in the damaged tissue. The direct cause and effect relationship of neurogenic inflammation leading to increased sympathetic stimulation and vice versa has lead many authors to conclude that both have a direct role in influencing the amount of inflammation in any part of the body.

The presence of sympathetic/noradrenergic nerve fibers in lymphoid tissues, the release of NE from the nerve terminals in these organs, and the presence of sympathetic receptors in lymph cells all suggest that NE may meet the criteria as a neurotransmitter/neuromodulator of the immune system. Although the axon terminals of the sympathetic nerves may not make synaptic contact with immune cells, NE can still diffuse far away form the release site and affect and transmit to organs non-synaptically. Therefore, it has been concluded by some researchers that the CNS and the immune system are connected by the SNS (25).

A recent study performed by R.E. Coggeshall demonstrated that glutamate receptor sites found on sympathetic efferents increased in an induced inflammatory state. Coggeshall and colleagues took an inflammatory agent and injected it into one hindpaw of rats. Following the inflammatory event the authors measured and compared labeled axons in the control rats to those injected with the inflammatory agent. The authors concluded that:

> If numbers of sympathetic axons expressing glutamate receptors increase during inflammation, as shown in this study, then glutamate released into the extracellular fluid in the inflamed state could activate more postganglionic axons than in the normal state. This in turn might release more NE and prostaglandins as well as other substance from postganglionic sympathetic terminals (4).

A recent study perform by Gillette and colleagues on "Sympathetic activation of cat spinal neurons responsive to noxious stimulation of deep tissues in the low back" postulated that two plausible mechanisms for activation of spinal 'pain pathways' may occur via axons of the sympathetic chain. The first mechanism involves that of primary afferent fibers that go through the sympathetic trunk directly or polysynaptically onto somatosensory neurons. The second mechanism involves an indirect relationship of the sympathetic fibers indirectly exciting the afferent sensory fibers in somatic/visceral tissue. The results from his study suggest that both mechanisms are involved (25).

The Somatovisceral Relationship (a proposed mechanism)

A somato-visceral link has been supported and disputed by authors over the past century. The first to investigate the somato-visceral relationship was Dr.

Irwin Korr. Korr proposed his theory behind a framework of research that said that dysfunctional somatic tissue, once having entered the central nervous sytem, was responsible for generating segmentally specific or regionally specific increases in efferent activity (sympathetics) (5). His efforts were based on the proposal that a sympathetic response may cause ischemia in organs that were segementally innervated, but a review done by Nansel and Szlazak disputed his research. More recent research indicates that ischemic responses in the organs are of little consequence. Experiments done to test this hypothesis proved to be valid and disproved Korr's model of sympathetics causing ischemia which later would lead to visceral dysfunction (5).

Although Nansel and Szlazak disproved Korr's model through ischemia, it did not mention the latest research done to show that increased sympathetic firing (releasing of increased amounts of NE) at the nerve terminal results in an increased release of many neuropeptides that cause a cascade of inflammatory and other immunological responses (8,26).

Since it has been disproven that the somato-viscero reflex is due to increased sympathetic tone causing ischemia and later damage to organs, a new model was needed. Neurogenic inflammation has been studied and found as a means of increasing inflammation in local tissues through increased afferents and/or increased sympathetic stimulation (8). This model may help explain what Korr was trying to prove in his theory that a somato-visceral reflex does exist. But how does an increased sympathetic response lead to inflammation?

An inflammatory response is modulated mainly by immune organs and immune cells; therefore, it was necessary for research to find a connection between the sympathetic nervous system and the immune system. With current updates in technology, studies have been done to prove that the connection between the sympathetic nervous system (SNS) and the immune cells and organs does exist and is the basis for increased sympathetic tone and possible inflammation in visceral organs which later could lead to diseases such as asthma, migraines, or arthritis (8).

Some studies have demonstrated the direct effects of the above neuropeptides in visceral tissues. A study was done on a gastrointestinal apparatus with the release of CGRP from an afferent nerve ending (neurogenic inflammation). The release of CGRP caused the stomach to induce vasodilation, secretion and increase of permeability in post-capillary venules (1). This phenomena was also shown in a similar model of an enteric apparatus. This is of peculiar interest to those in the gastro-intestinal field.

Another study on the lower urinary tract demonstrated some interesting observations in animals carried out by Lecci and Maggi. A painful stimulus was shown to cause a direct efferent response (SNS) through the release of neuropeptides from terminal nerve endings provoking neurogenic inflammation in the site of the urinary tract, which caused symptoms varying from a urinary tract infection to cystitis. This mechanism has been studied extensively in both man and animals by researchers such as Giamberanrdino and colleagues (1).

Conclusion

The above evidence points to a highly organized process that is set in motion after damage to tissue. The purpose of inflammation is to heal and repair tissue, but violation of this process (lack of healing capabilities of the patient) may lead to a lingering painful state in the absence of tissue pathology.

The additional maladaptive change of the sympathetic system (peripheral pathology causing normal postganglionic sympathetic efferents to sprout to surrounding large diameter mechanoreceptor afferent neurons in the dorsal root ganglion) is an additional mechanism coupled with neurogenic inflammation that may lead to a long standing circuit in the pain pathway (27). The linking of the sympathetic nervous system with an inflammatory response within local tissue sites is an exciting area of research, but many areas have separate ideas and the research needs to be tied together in a review to find the latest findings of this exciting area.

Lastly, the contribution of neurogenic/sympathetic inflammatory states may cause a spillover effect into neighboring neuronal pools that lead to visceral organs. Although data in this area has been conflicting, it sounds quite plausible that many conditions such as migraine, inflammatory bowel disease, and asthma involve neurogenic inflammation mechanisms. This is an exciting area of research which needs clinical trials to determine if chiropractic care may be a means of decreasing the inflammatory states in the above conditions.

References

1. Procoacci, P., Maresca, M., Geppetti, P. Neurogenic Inflammation and Muscle Pain. *Journal of Musculoskeletal Pain.* 1999; 7 (1/2): 5-12.

2. Barnes PJ., Belvisi MG., Roger DF. Modulation of neurogenic inflammation: novel approaches to inflammatory disease. *Trends in Pharmocalogical Science.* 1990; 11(5): 185-9.

3. Chrousos, GP. The Hypothalamic-Pituitary-Adrenal Axis and Immune-Mediated Inflammation. *The New England Journal of Medicine.* 1995; 332: 1351-1363.

4. Coggershall. Evidence for an inflammation-induced change in the local glutamatergic regulation of postganglionic sympathetic efferents. *Pain.* 1999; 83(2): 163-8.

5. Nansel, D., Szlazak M. Somatic Dysfunction and the Phenomenon of Visceral Disease Simulation: A Probable Explanation for the Apparent Effectiveness of Somatic Therapy in Patients Presumed to be Suffering from True Visceral Disease. *Journal of Manipulative and Physiological Therapeutics.* 1995; 18 (6): 379-397.

6. Boas, RA. Sympathetic nerve blocks: in search of a role. *Regional Anesthesiology Pain Medicine.* 1998; 23(3): 292-305.

7. Chaturvedi A., Dash HH. Sympathetic blockade for relief in chronic pain. *Journal of Indian Medical Association.* 2001; 99(12): 698-703.

8. Apfel SC. Neurotrophic factors and pain. *Clinical Journal of Pain.* 2000; 16(2): S7-11.

9. Bascom, R., Meggs, W. Neurogenic inflammation: With additional discussion of central and perceptional integration of nonneurogenic inflammation. *Envrionmental Health Perspectives.* 1997; 105 (2): 1-7.

10. Wright A. Recent Concepts in the Neurophysiology of Pain. *Manual Therapy.* 1999; 4(4): 196-202.

11. McMahon S, Koltzenburg M. The changing role of primary afferent neurones in pain. *Pain.* 1990 Dec;43(3):269-72.

12. Seaman DR, Cleveland C 3rd. Spinal pain syndromes: nociceptive, neuropathic, and psychologic mechanisms. *Journal of Manipulative and Physiological Therapeutics.* 1999; 22 (7): 258-72.

13. Jayson M. Why does acute back pain become chronic?. *British Medical Journal.* 1997;314:1639 (7 June).

14. Dray 1996 from Neurophysiology of Pain. Man ther 1999

15. Woolf CJ. A new strategy for the treatment of inflammatory pain: prevention or elimination of central sensitization. *Drugs.* 1994; 47:1-9.

16. Ren K. Primary afferents and inflammatory hyperexcitability. *Pain.* 1996; 67(1): 1-2.

17. Coderre T., Katz J., Vaccarino A., Melzack R. constribution of central neuropalsticity to pathological pain: review of clinical and experimental evidence. *Pain.* 1993; 52: 259-85.

18. Caillet. Pain Mechanisms and Management. 1993; pg 36.

19. Denslow J, Hasset C. The central excitatory state associated with postural abnormalities. *Journal of Neurophysiology.* 1942; 5: 393-402.

20. Wright A. Recent Concepts in the Neurophysiology of Pain. *Manual Therapy.* 1999; 4(4): 196-202.

21. Niissalo S, Hukkanen M, Imai S, Tornwall J, Konttinen YT. Neuropeptides in experimental and degenerative arthritis. *Annals of New York Academy of Science.* 2002; 996;384-99.

22. Seaman DR., Winterstein JF., Dysafferentation: a Novel Term to describe neuropathophysiological effects of joint complex dysfunction. A Look at likely mechanisms of symptom generation. *Journal of Manipulative and Physiological Therapeutics.* 1998; 4; 267-280.

23. Davis C. Chronic pain/dysfunction in whiplash-associated disorders. *Journal of Manipulative and Physiological Therapeutics.* 2001; 24 (1): 44-51.

24. Elenkov IJ., Wilder RL., Chrousos GP., Vizi ES. The Sympathetic Nerve--An Integrative Interface between Two Supersystems: The Brain and the Immune System. *Pharmacological Reviews.* 2000; 52(4): 595-638.

25. Gillette RG., Kramis RC., Roberts WJ., Sympathetic activation of cat spinal neurons responsive to noxious stimulation of deep tissues in the low back. *Pain.* 1994; 56(1): 31-42.

26. Herbert MK., Holzer P. Neurogenic inflammation II. Pathophysiology and clinical implications. *Anasthesiol Intensivemed Notfallmed Schmerzther.* 2002; 37(7): 386-94.

27. Zusman M. Irritability. *Manual Therapy*. 1998; 3 (4): 195-202.