The Role of Neuroplasticity in Persistent Low Back Pain: A Literature Review

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ABSTRACT

Objective: This article provides an overview of literature of the relationship between neuroplasticity, central sensitization and persistent low back pain. Emphasis is given to the involvement of pain mechanisms and differences between nociceptive, neuropathic, and psychological factors in persistent low back pain. Experimental evidence of long-term potentiation and long-term depression are covered. Finally, treatment options for persistent pain are highlighted.

Data Collection: A computer search using Pubmed and MANTIS generated articles relevant to neuroplasticity, central sensitization, and chronic/persistent LBP. Referenced sources were identified from the individual searches and from accumulated review of neuroscience literature. Pubmed and MANTIS searches generated over 18,000 articles on neuroplasticity, over 2,500 article on central sensitization, and over 4,000 articles on chronic/persistent LBP. Only one review was found to address all three topics.

Data Synthesis: Persistent pain is a complex process which involves neuroplastic changes inducing central sensitization. An understanding of the mechanisms of pain generation is crucial to determining treatment.

Conclusions: A consensus of over two thousand articles consisting of selective reviews and controlled studies, in addition to several noteworthy texts, supports the concept of neuroplastic changes promoting nociceptive processes via central sensitization. Emerging evidence suggests that psychological factors such as depression, anxiety, catastrophizing, fear avoidance, self-efficacy and coping style are important aspects which should be considered in the treatment of pain, particularly persistent pain. More research is needed for treatment plans which address central sensitization in persistent low back pain conditions. Treatment options aimed at combining a variety of approaches which address the physiological and pathological processes involved with central sensitization should be considered.

Key Indexing Terms: neuroplasticity, central sensitization, chronic/persistent low back pain

INTRODUCTION

Low Back Pain (LBP) and painful musculoskeletal disorders are common problems that plague today's society. Indirect and direct costs associated with LBP have been estimated to be over $50 billion, and could be as high as over $100 billion annually [1,2,3]. Comorbidities such as diabetes, rheumatoid arthritis, anxiety, psychotic illness, and depression, as well as use of opiates and NSAIDs, have been associated with increased costs and disability for patients with LBP [3]. The challenge lies with identifying strategies for the effective prevention and management of LBP and related disorders. Pursuant to this, an adequate understanding of the neurophysiology and pathomechanisms of pain is paramount. Although clinical emphasis has focused on local injury site interventions, more and more research is pointing to central nervous system physiology as having a strong contribution to pain maintenance. Lidbeck added "the growing awareness of dysfunctional central pain modulation may be a conceptual breakthrough leading to a better understanding of common chronic pain disorders." [4] Therefore, improved understanding of spinal and supraspinal modulation of pain may provide valuable contributions to the development of effective treatment modalities [5]. This review examines relevant recent and historical research regarding the involvement of the central nervous system in LBP. A discussion outlines the nociceptive, neuropathic, and especially, psychological pain processes that can be involved with persistent pain and their mechanisms of chronicity. The role of neuroplasticity in these processes in the form of central sensitization is included in this discussion. In particular, long term potentiation and long term depression are discussed to offer published evidence of possible clinical treatment and prevention options for central sensitization.

DISCUSSION

Nociceptive Pathway: Pain is a complicated and intricate concept. It is important to make distinctions in the terminology necessary for an adequate description of this phenomenon. Pain has been defined as "an unpleasant sensory and emotional experience associated with actual or potential damage" [6, 7] by Merskey and Bogduk in 1994. However, as early as 1965, Melzack and Wall proposed their gate control theory of pain [7, 8, 9], explaining different types of pain and triggering an explosion of research.

Actual 'pain' occurs in the brain and not at the level of the tissue receptor [10], while 'nociception' refers to the neuronal signal carried along the so-called 'nociceptive pathway'. Impulses generated by free nerve endings of nociceptors are carried to the central nervous system by primary afferent A-delta and unmyelinated C-fibers whose cell body is in the dorsal root ganglion. The central processes of these cells constitute the dorsal root and terminate on neurons in the Tract of Lissauer, the Substantia Gelatinosa (lamina II), or the Basal Spinal Nuclei in the dorsal horn of the spinal cord. These dorsal horn neurons are called transmitter (T) cells because when excited by afferent nociceptive impulses, they relay or transmit the activity to other parts of the nervous system, primarily the reticular system and the thalamus. They decussate anterior to the spinal canal and ascend in the ventral lateral funiculus in the Anterolateral System ascending pathways.

The ascending spinal tracts are bundles of axons of T cells that terminate in the brain. The T cells can be divided into two types—nociceptive specific cells (NS) and wide dynamic range (WDR) neurons. The NS cells receive excitatory input exclusively from noxious stimuli while WDR neurons respond maximally to intense noxious stimuli but also respond to hair movement and weak mechanical stimuli. WDR neurons receive convergent input from primary afferents innervating skin, subcutaneous tissue, muscle, and viscera. This convergence of somatic and visceral nociceptive input in lamina V may be the neural basis for referred pain [9, 10, 11, 12, 13] and will be explained later in this review.

Pain Categories: Nociceptive pain is an essential early warning device that helps protect us from the dangerous environment in which we find ourselves. To accomplish this, the sensation of pain must be so unpleasant that we cannot ignore it. [14] This is the typical pain that we have all experienced—a signal of non-neural tissue irritation, impending injury, or actual injury. Nociceptors in the affected area are activated and then transmit signals via the peripheral nerves and the spinal cord to the brain. Complex spinal reflexes (e.g. withdrawal) may be activated, followed by perception, cognitive and affective responses, and possibly voluntary action. The pain is typically time-limited and perceived as related to the specific stimulus as hot, sharp, etc. or with an aching or throbbing quality. Visceral pain is a subtype of nociceptive pain and tends to be paroxysmal and

poorly localized, while pain that is more constant and well-localized is usually of somatic origin. [10, 11, 12]

Non-nociceptive or neuropathic pain, by contrast, occurs in response to noxious stimulus causing nervous tissue injury and inflammation, or nervous system structural or functional damage. It features both spontaneous pain that arises without any apparent peripheral stimulus and hypersensitivity to peripheral stimuli [14]. Neuropathic pain results from a malfunction somewhere in the nervous system, either in the peripheral or in the central nervous system. The pain frequently has burning, lancinating, or electric shock qualities. Allodynia—pain resulting from a nonpainful stimulus, such as light touch—is also a common characteristic of neuropathic pain. This probably involves mechanoreceptor stimulation and the subsequent activation of nociceptive projection neurons as a result of dorsal horn reorganization in response to nerve injury. [10] Often the pain is triggered by an injury, although this injury may not clearly involve the nervous system, and the pain may persist for months or years beyond the apparent healing of any damaged tissues.

When pain sensations are ongoing for periods of time that are beyond the reasonable healing duration of an injury or beyond the usual course of an acute illness, the pain is considered 'chronic' or 'persistent'. 'Persistent pain' will be the terminology utilized in this review because this term has been more consistently utilized in contemporary work dealing with psychological factors involving pain. These psychological factors, which will be discussed later, are intimately related to the nature of prolonged pain. In the persistent pain setting, pain signals no longer represent ongoing or impending injury. Neuropathic pain is frequently persistent, [13] but nociceptive pain may also play a role in persistent pain states. Mense [15] discusses a novel hypothesis for the development of persistent pain that introduces a contributory mechanism by death of inhibitory interneurons due to a strong nociceptive input to the spinal cord. When the number of inhibitory interneurons decreases, the nociceptive neurons are chronically disinhibited and elicit continuous pain also in the absence of a noxious stimulus. [15] A difficulty with studying the development of persistent LBP is that back pain is not simply acute or persistent but fluctuates over time with frequent recurrences or exacerbations.

According to Boersma and Linton, "this makes longitudinal studies on the developmental process from acute pain to a chronic pain problem difficult to carry out." [16]

Psychological pain is the least understood of the three mechanisms of pain induction, and an in-depth review of the status of all of the psychological factors that might be relevant to understanding persistent pain is beyond the scope of this review. According to Seaman, "Because pain is defined as a psychologic state, a psychologic component will always be associated with both nociceptive and neuropathic pain." [10] When assessing a complaint of pain, it is critical to remember that pain is an experience, rather than a bodily function. Therefore it is valuable to investigate the appropriate mental and environmental factors with the primary goal to educate the patient about the relationship between mental states and physical disorders, such as back pain. [10] In a review by Linton, he claimed a "clear link between psychological variables and neck and back pain" and implicated a significant role of these variables in the etiology of acute pain and in the transition to persistent pain problems. [17] Hasenbring et al reinforces this second point with the following:

> "20 years of research, several qualitative reviews and a recently published systematic review of 37 good-quality prospective studies regarding the role of psychological, biomedical, social, and objective occupational factors in the process of chronicity of back pain revealed that psychological factors are significantly related to the onset of back pain as well as to the development of chronic pain. Furthermore, the psychological factors displayed more predictive power than biomedical or biomechanical variables." [18]

These psychological factors include psychosocial variables such as chronic distress in daily life, depression, anxiety, and work dissatisfaction, as well as coping and pain-related cognitions, such as catastrophizing, fear-avoidance, and self-efficacy. [15, 16, 17, 18]

Depression and anxiety are specific emotional factors that can enhance the experience of pain, can predict the onset of new episodes of back pain, and their reduction can lead to a considerable reduction in pain. [10] As clinical co-morbidities, these factors are known to complicate numerous pathological conditions.

Depressive disorders are found in approximately 50% of chronic pain patients. [19] Depression can significantly intensify the experience of pain and the associated suffering

by reducing the activity of powerful descending inhibitory pathways that emanate from the brainstem. [10] In some cases, depression manifests primarily with somatic symptoms and complaints. Therefore, on occasion, depression may even be the primary etiology of the pain. [19]

In a study evaluating the effect of symptoms of depression or clinically diagnosed major depressive disorder on pain processing in patients with fibromyalgia, Giesecke et al found that symptoms of depression and the presence of major depressive disorder were associated with the magnitude of pain-evoked neuronal activations in the amygdala and contralateral anterior insula—regions of the brain associated with affective-motivational pain processing. [20]

Boersma and Linton investigated the role of cognitive and behavioral psychological factors in the development of a chronic musculoskeletal pain problem. They divided 184 participants into three stages of chronicity, defined by the duration of pain. Depression and function were strongly correlated at all three stages. [16]

More than 50% of chronic pain patients suffer with anxiety disorders which may alter the experience of pain and suffering. [21] Anxiety may influence the activity of the reticular activating system and enhance the supraspinal transmission of nociceptive impulses, possibly because anxiety results in increased catecholamine release which increases RAS activity. Anxiety can also be expressed as increased muscle tension, which may result in the development of myofascial trigger points. [10, 22]

Although clinically diagnosed depression and anxiety have been documented to influence the pain experience, Seaman commented that the textbook pathological form of depression or anxiety is not the form seen in the average patient with LBP. Instead, the combination of daily life stress with painful injury results in a 'functional form' of these conditions. [10]

A digression at this point is necessary to address a couple of other psychological factors which sometimes play a role in pain. Stress affects the bodily functions and sensations in all people. Emotional distress is often felt and expressed as physical distress. These processes, when predominant, lead to excessive somatic attention and communication in the forms of somatization and hypochondriasis. These can sometimes be primary psychiatric disorders or tendencies, but often they are part of depressive or

anxiety disorders. These patients are prone to misinterpreting normal bodily sensations and to exaggerating the symptoms of illness. They are therefore more likely to believe that they are suffering from a catastrophic illness or complication. [23]

In addition to specific emotional disorders such as depression and anxiety, research exists which underscores the importance of cognitive aspects on pain conditions. Empirical support for the pain-related cognitions is predominantly for catastrophizing and fear-avoidance beliefs. [18]

Pain catastrophizing is the tendency to focus on pain and engage in negativistic evaluation of one's ability to deal with pain. [16,24] Keefe et al calls catastrophizing, "a coping response designed to deal with the negative emotions caused by persistent pain by eliciting proximity to and support from others." [24] Their review highlights some important discoveries, such as higher levels of psychological distress, depression, nervousness, pain-related disability, more negative general health status, greater limitations in social activities, and lower energy levels in individuals who engage in higher levels of pain catastrophizing. Additionally, early treatment methods aimed at decreasing catastrophizing predict decreases in pain and pain-related outcomes later in treatment. [24]

Patients who have pain, especially persistent pain, can demonstrate anxiety about their pain which can result in fear avoidance behaviors. Typically, these behaviors manifest in some manner of immobility or self-restriction of movement to prevent (re)injury. Some evidence describes fear of pain as an obstacle to recovery in populations of patients with LBP and suggests that fear may play a role when pain becomes persistent. [25] Keefe et al determined from self-report measures and physical performance measures that fear of pain predicts severe LBP, persistent LBP, and back pain-related disability at follow-up. [24] Boersma and Linton found the strength of the relationship between function and fear of movement progressively increased across the subsequent stages of pain chronicity, indicating that the time point in the development of a musculoskeletal pain problem might be an essential aspect of the importance of this relationship. Interestingly, fear of movement does not emerge as a significant predictor of function until after one year of pain duration. [16]

While the aforementioned factors are associated with poor adjustment to pain, pain coping styles and self-efficacy are cognitive aspects associated with improved adjustment to pain. In a study by Jones, of 974 patients with LBP who took part in a baseline survey which requested information on coping styles, pain severity, disability, duration, and a brief history of other chronic pain symptoms, 922 (95%) completed a follow-up questionnaire. Of these, 363 individuals (39%) reported persistent disabling pain at follow-up. They concluded that patients who report passive coping strategies experience a significant increase in the risk of persistent symptoms and, identification of this LBP subgroup may help target those at greatest risk of a poor outcome. [26] Other evidence suggests that extreme suppressive coping behavior (i.e. ignoring the pain) without integrating phases of passive relaxation into the daily routine may increase risk of persistent pain. [18]

Self-efficacy refers to a person's confidence in their ability to engage in a course of action sufficient to accomplish a desired outcome, such as control of pain. Recent evidence provides strong support for the importance of self-efficacy in understanding pain. Keefe et al reported that patients with higher levels of self-efficacy have lower levels of pain, lower levels of psychological distress and negative medical outcomes, higher pain thresholds and pain tolerance. [24]

Given the evidence supporting the association of psychological variables with pain, the clinician should always assess the patient's psychological state, and the emotions surrounding the pain problem. Keefe et al do an excellent job summarizing the role of specific psychological factors in connection with pain with the following:

> "There is strong evidence from multiple studies to support the conclusion that pain catastrophizing and pain-related anxiety and fear are related to poor adjustment to pain and that higher self-efficacy and adaptive pain coping are related to improved adjustment to pain." [24]

Anatomy of Pain: Many areas of the brain are involved in the experience of pain. Nociception involves portions of the medulla oblongata, mesencephalon, diencephalon (thalamus, hypothalamus) and the cerebral cortex. The medulla and mesencephalon participate in nociceptive function through their contributions to the reticular system. The

thalamus serves as the relay for ascending sensory information entering the cerebral cortex. The cerebral cortex plays a major role in pain perception, and certain areas are thought to form a genetically determined neural network called the 'neuromatrix'. [7, 13, 27, 28, 29, 30]

The pain experience has three dimensions, each subserved by distinct neural systems. The *sensory-discriminative* dimension provides information on the onset, location, intensity, type, and duration of the pain-inducing stimulus. This aspect is mediated primarily by the lateral ascending nociceptive tracts, thalamus and somatosensory cortex. The *motivational-affective* dimension disturbs the feeling of well-being of the individual resulting in the unpleasant affect of pain and suffering, triggering the individual to action. It is subserved by the medial ascending nociceptive tracts, reticular formation and limbic system. This dimension is closely linked to the autonomic nervous system and the associated cardiovascular, respiratory and gastrointestinal responses. The *cognitive-evaluative* dimension encompasses the effects of prior experience, social and cultural values, anxiety, attention, and conditioning. These activities are largely due to neocortical activity and are dependent on reticular activity. The frontal cortex appears to play a significant role in mediating between cognitive activities and motivational-affective features of pain.

Different models have emerged in order to explain the neurophysiological mechanisms of pain. In one model, pain is a multidimensional experience produced by characteristic 'neurosignature' patterns of nerve impulses generated by the neuromatrix. [30] These patterns are an aspect of touch that may be triggered by sensory inputs or generated independently of them. They can become sensitized in pathological states and can affect our emotional responses. [27, 29] The frontal cortex appears to play a significant role in mediating between cognitive activities and motivational-affective features of pain because it receives input from virtually all sensory and associated cortical areas via intracortical fiber systems and projects to the reticular and limbic systems. The frontal cortex also appears to be necessary to the maintenance of the negative affective and aversive motivational aspects of pain. Neocortical processes subserve cognition and psychological factors, including prior experience, conditioning, anxiety, attention, background, and evaluation of the pain-producing situation. This convergence model is

thought to explain referred pain, allodynia, hyperalgesia, and hyperpathia in terms of sensitization, 'crossed wires' or aberrant central processing of multiple inputs. However, this model cannot explain all features of pain. [31]

Craig offered a newer view—suggesting that specific pain centers which have evolved from a primitive system of the brain exist. [31] The limbic system or paleocortex consists of phylogenetically old parts of the telencephalon and parts of the diencephalon and mesencephalon. These structures include: the amygdala, hippocampus, septal nuclei, the preoptic region, hypothalamus, parts of the thalamus and the epithalamus. Some authors suggest that the parieto-insular cortex and the caudal part of the anterior cingulate in the medial frontal cortex are crucial for pain processing in the brain. [10, 31] The limbic system is concerned with mood and incentives to action, i.e., motivational interactions and emotions. Perceptions of the unpleasantness of pain are related to activation at these sites as well as in the cerebellum and striatum. Pain can be thought of as consisting of a distinct 'physical' sensation represented in the parieto-insular cortex and an 'emotional' component represented in the anterior cingulate. [10, 31] The hypothalamus and limbic structures have an important role in motivated, emotional and affective behaviors which are integral parts of the pain experience.

In a study by Aziz et al, healthy subjects were examined for the effects of emotional context on the brain processing of esophageal sensation. Using fMRI, they demonstrated marked activation in bilateral insular and anterior cingulate cortices only when esophageal stimulation was delivered during a negative emotional context, and not when it was presented during a neutral emotional context. This suggests that the brain processing of esophageal sensation is modulated by the emotional context in which they are perceived, providing a potential mechanism for the influence of negative mood states on symptom severity in functional pain disorders. [32]

In a study by Diers et al, [14] chronic LBP patients were examined with EEG recordings and pain ratings during the presentation of 800 painful electrical stimuli. Their results indicated enhanced perceptual sensitization and enhanced processing of the sensory-discriminative aspect of pain in chronic LBP patients. [33]

Other evidence was demonstrated in the Giesecke et al study of depression in patients with fibromyalgia. As measured by fMRI and sensory testing, they found that an

association exists between depression and the magnitude of pain-evoked neuronal activations in brain regions associated with motivational-affective pain processing but found no such modulations of the sensory-discriminative aspects of pain processing, suggesting that there are parallel, somewhat independent, neural pain-processing networks for sensory and affective pain elements. [20]

Neural Plasticity: Pain perception does not simply involve a moment-to-moment interpretation afferent noxious input, but rather involves a dynamic process that is influenced by the effects of past experiences [14, 34] i.e. previous activity-dependent events and neural changes which include such processes as synaptic potentiation, synaptic depression, alterations in gene expression, and synaptic structural changes. [35] These changes form the basis of neural plasticity and can take place both following increased and decreased afferent input. [36] A definition of neural plasticity offered by Kumazawa is "the capacity of neurons to change their function, chemical profile, or structure" [30, 37]. While these neuronal changes can be beneficial as in the case of learning, they can also pose a problem with regard to pain pathogenesis as prolonged nociceptive inputs induce either functional or structural alterations in the nociceptive pathways. Nociceptors do not fatigue with repeated stimulation, but instead display enhanced sensitivity and prolonged and enhanced response to stimulation. Enhanced sensitivity is induced by endogenous pain-producing mediators released into the extracellular fluid by damaged, diseased or inflamed tissues. These substances include H+, K+, serotonin, histamine, prostaglandins, bradykinin, substance P and many others. Additionally, injured primary afferents become sensitized to norepinephrine that can be released from sympathetic postganglionic neurons. These plastic changes lead to crosstalk among the neural networks, including circuits related to motor, autonomic, or psychological functions, and once established, persist even after the original pain sources disappear, playing a critical role in the evolution of persistent pain states. [30, 38, 39]

Ramachandran, who authored interesting research on phantom limb pain, suggested from studies of amputees that instead of phantom limb sensation emerging as a consequence of a diffuse neural matrix, that it occurs do to "the remapping hypothesis". [40] According to this concept of neural plasticity, topographical changes following

deafferentation (e.g. amputation) unmask *preexisting* neurological connections rather than the sprouting of new connections. The author concluded that topography is extremely labile and massive reorganization can occur over extremely short periods. His description of the dynamic structure of the brain "in which there is a tremendous amount of back-and-forth interaction between different levels in the hierarchy and across different modules" is illustrated by the following:

> "The fact that the mere visual appearance of the moving phantom limb (mirror) feeds all the way back from the visual to the somatosensory areas of the brain to relieve a spasm in a nonexistent hand shows how extensive these interactions can be." [41]

On a very general level, neuronal plasticity offers a useful explanation for changes in clinical pain conditions as well as changes in symptomatology that result from treatment of those clinical conditions. [35]

Sensitization: There is growing evidence that many persistent pain syndromes share the same pathogenesis—sensitization of pain-modulating systems in the CNS at both spinal and supraspinal levels. [41] Massive nociceptive input has profound intrinsic effects on dorsal horn neurons, interneurons, and anterior motor neurons altering the strength of synaptic connections between the nociceptors and the neurons of the spinal cord. C fibers from muscles, joints and periosteum can trigger long-latency, long-duration facilitation and very prolonged increased excitability of dorsal horn cells ("wind-up") rather than a simple stimulus-response relationship. In response to peripheral noxious stimuli these neurons show an induction of immediate early genes (IEGr) that encode transcription factors such as c-fos. The C fibers synapse at wide dynamic range cells where they dump glutamate at NMDA receptors. This allows Ca++ influx only with increased levels of stimulation. [11] The neuronal plasticity that builds eventually may allow an increase in the magnitude and duration of the response to above-threshold stimuli with a reduction in threshold so that stimuli that are not normally noxious activate neurons that normally transmit nociceptive information making the neurons more sensitive to other input, such as light touch. Expansion of neuronal receptive fields of nociceptive cells occurs. Cells

with receptive fields distant from that of the stimulated nerve are also affected and may be a mechanism for the poor localization and referral of LBP. [42] Additionally, low threshold A-beta afferents, which normally do not serve to transmit pain signals, become recruited to transmit pain. [5, 38]

The typical outcome of nociceptive activity is pain. However, the facilitation of the nociceptive system can lead to exaggerated forms of local and referred pain such as allodynia and hyperalgesia, widespread prolonged tenderness, and bouts of intense skeletal muscle spasm associated with excruciating pain that may persist for years or decades after all possible tissue healing has occurred. [10], [43] Additionally, this facilitation may play a role in the transition from acute to chronic pain. [43], [44] Melzack has reviewed experimental evidence of these changes, illustrated by the development of sensitization, wind-up, or expansion of receptive fields of CNS neurons, as well as by the enhancement of flexion reflexes and the persistence of pain or hyperalgesia after inputs from injured tissues are blocked. [27, 28], [34] There is strong evidence that the release of excitatory amino acids and neuropeptides in the dorsal horn after noxious stimulation leads to sensitization. [42] Furthermore, studies that induced central hypersensitivity experimentally suggest that hypersensitivity might persist after resolution of tissue damage. [45] Evidence from animal studies and also from human studies of somatic pain suggest that hyperalgesia at the site of injury occurs due to peripheral sensitization of primary afferent neurons while hyperalgesia adjacent to the injury site occurs due to a manifestation of abnormal sensory processing within the central nervous system. [31] Allodynia related to innocuous palpation of spinal musculature may involve the stimulation of sensitized C-fibers within the spinal muscles, i.e., nociceptive pain. [10]

Peripheral sensitization is an increase in responsiveness and a decrease in threshold of the peripheral ends of nociceptors as a result of changes in transduction proteins that determine the excitability of the nociceptors terminal. *Central sensitization* is an increase in the excitability of neurons within the central nervous system, so that normal inputs begin to produce abnormal responses. The synaptic changes increase the 'gain' of the system. A general theme with neuronal plasticity and its proposed role in central sensitization is that dorsal horn neurons are specifically involved and dynamic cellular changes in these neurons contribute to persistent pain states. [35]

The original hypothesis of central sensitization was done by Denslow and Hasset [46] in a review of the literature on how the spinal cord could become facilitated where they concluded that dysfunction of somatic tissue was associated with central sensitization of the cord. This conclusion, although simplified, opened a new field of neurology. [47] The process of central sensitization is an aspect of neuroplasticity that contributes to up-regulation of the nociceptive system in response to injury. [47] This process may provide a link between the pain in the motor system and autonomic dysfunction in patients with musculoskeletal disorders.

Mechanisms of central sensitization have been explored using experimental models including the study of wind-up in animals and temporal summation of pain in humans. Both wind-up and temporal summation appear to be dependent on NMDA receptor activation. [48] Experimentally induced nociception is of short duration. Therefore, the pathophysiology of hypersensitivity states in chronic pain patients is likely to differ substantially from those evoked experimentally. [45]

Mense offered mechanisms for sensitization utilizing examples of chronic muscle lesions such as myositis. [48] The association of myositis with higher innervation density of the tissue with free nerve endings that contain substance P, according to this author, constitutes a peripheral mechanism for hyperalgesia. Furthermore, he suggests that increased substance P and glutamate release from the spinal terminals of muscle afferents, with ensuing activation of NMDA channels in dorsal horn neurons, along with a decrease of nitric oxide in the spinal cord, paves the way for central sensitization and induction of persistent spontaneous pain. [48]

Neurophysiological processes of sensitization will lead to the development of persistent pain. Additionally, psychological factors may further complicate the issue. Coping strategies such as extreme suppressive behavior may lead to an overuse of muscles and joints with a repetitive combination of muscular hyperactivity and pain. These repetitive pain experiences will also elicit neurophysiological processes of sensitization. [18]

Curatolo et al offered: "persistent pain is due to an ongoing nociceptive input arising from an unidentified peripheral lesion that maintains a state of constant and continuous central hyperexcitability." However, the authors conceded that the possibility

of plasticity changes of the CNS as the sole determinants of pain cannot be ruled out. [45] According to Boal and Gillette, "at the very least, neuronal plasticity provides mechanisms that contribute to amplification of synaptic transmission in nociceptive circuits (central sensitization) leading to central neuronal elements overreacting to normal input with persistent hyperexcitability." [35]

Pain Generation: The musculoskeletal system consists of the richly innervated bones, joints, ligaments, muscles, nerves and blood vessels that interconnect within spinal column. All of these tissues can be affected by degenerative process and can be a source of pain, e.g., injury to ligaments leads to muscle discoordination, disrupting the neural apparatus as well as the structural support. The major sources of back pain are the disc, facet joints, sacroiliac joints, and muscles. [42], [50] There are only two sites of clinically significant pain production in the lumbar spine: the outer disc that causes back pain; and the nerve root that causes leg pain. [50] With respect to LBP, Boal and Gillette offered "neuronal plasticity within the low back pain-signaling system would help explain dynamic spatial changes in low back pain referral, temporal changes in ongoing and provoked low back pain, and sensory changes in the area of referral." [35] Both neurogenic and nonneurogenic pain can result in sensitization to spine motions, which ultimately leads to central sensitization. [51]

In response to stimulation of the nociceptors in the disc, the somatosensory system may increase its sensitivity producing peripheral sensitization with the release of algogenic substances that lower the activation threshold of nociceptors. Structural nerve root changes increase the sensitivity of the spinal nociceptive neurons. When disc degeneration leads to a disc herniation, structural changes of the nerve root or the dorsal root ganglion can increase the sensitivity of the spinal nociceptive neurons causing neuropathic pain of mechanical or biochemical origin. Thus, disc degeneration may be responsible for the development of chronic LBP without being the actual pain focus and increased transmission of nociceptive signals in the spinal cord result in permanent excitation and sensitization of the spinal convergent neurons. [39],[52] In a study of patients with chronic LBP or fibromyalgia, Giesecke et al found those patients to experience significantly more pain and show more extensive, common patterns of neuronal

activation in pain-related cortical areas consistent with the occurrence of augmented central pain processing. [53]

In another study, O'Neill et al exposed [12] patients with MRI confirmed lumbar intervertebral disc herniation to quantitative nociceptive stimuli. These patients demonstrated significantly higher pain intensity, duration, and larger areas of pain referral compared to controls. They concluded that the generalized deep-tissue hyperalgesia suggested that central sensitization should be addressed in the pain management regimes. [54]

Because of the convergent structure of the nervous system, it is common for pain to be referred from a separate, possibly quite distant site. This is most commonly seen if the site of painful stimulation or irritation is visceral or muscular. [30] However, there are a number of possible mechanisms responsible for pain referral.

Sclerotogenous pain is perceived as a deep ache distal to the site of damage. The referring source is from connective tissue, i.e. ligaments, discs, bone, and joints. No review of LBP would be complete without a discussion of myofascial trigger points. Myofascial trigger points are seen with pain referral when a palpable nodule in the belly of the muscle refers pain distal to the site being compressed. Upon palpation they produce specific regional pain patterns, typically to either anterior or posterior compartments, rather than widespread pain or tenderness. Simons describes trigger points as spots of point tenderness in taut bands of muscle which come from the presence of contraction knots within the muscle fibers. [55] These knots cause a regional shortening of the sarcomeres of numerous involved muscle fibers resulting in an increase in overall tension. The maximally contracted sarcomeres become fixed in this shortened state, leading to ischemia and retention of metabolic waste products. Resultant hypoxia of local nociceptors leads to a depletion of oxygen based energy and a failure to maintain concentration gradients across the membrane, elevating the resting membrane potential of local nociceptors. This sensitized state results in impulses generated in these nociceptive fibers which cause referred pain patterns. Through a reflex feedback loop, the neurotransmitter acetylcholine is released back at the muscle, causing additional localized contraction. [22]

Trigger points are incredibly common in patients suffering from musculoskeletal disorders and have been associated with many conditions, including LBP. As early as the 1930's, investigators attempted to identify referred pain patterns by injecting hypertonic saline into a variety of skeletal muscles and observing the location of both primary and referred pain sites. [56]

Trigger points are typically classified based upon the stimulus required for pain production and, to a lesser extent, upon their location. Active trigger points can produce pain without manual compression. They are normally found in the belly of the muscle or at its insertion. These points present with a characteristic referral pattern for each muscle and can cause muscle weakness and reduced flexibility. A patient usually does not complain of pain at the area of an active trigger point, but is very painful with applied pressure. Latent trigger points are tender upon palpation and produce specific pain patterns but are typically silent when left alone. These points can also cause weakness and a decrease in flexibility within the muscle. In persistent cases, an active trigger point can become latent. Similarly, a latent trigger point can become active following injury or trauma. Satellite trigger points are those that develop in the same muscle as a preexisting primary trigger point, forming secondarily to tension within the muscle fibers resulting from active or latent trigger points. These can be further classified as central or attachment points based on their location. According to Travell and Simons, satellite trigger points typically resolve once the primary trigger point is treated. [22]
Although trigger points are extremely common, other mechanisms may be involved in patients with pain referral.

Another mechanism for referred pain is offered by Giamerardino. [57] This author noted that massive afferent barrage and a reflex arc activation leading to central sensitization of viscero-somatic convergent neurons may explain referred visceral pain. He further comments that these connections are "opened by nociceptive input from skeletal muscle," and that referral to myotomes "results from the spread of central sensitization to adjacent spinal segments." [57]

Seaman points out that although clinical thought has trended toward neuropathic lesions to explain referred pain, nociceptive processes are more commonly involved. He attributes joint complex dysfunction and the 'deconditioning syndrome' as the cause of

the majority of back pains. Furthermore, hyperconvergent receptive fields of central nociceptive projection neurons which receive input from multiple peripheral structures contribute to nociceptive referral patterns. This lack of precision in central neural connections explains referral from peripheral input. However, as seen in phantom limb pain, referred pain can be generated centrally. [10]

LTD and LTP: Long term depression (LTD) and long term potentiation (LTP) are two major forms of activity-dependent synaptic plasticity in the brain which have been intensively studied for over twenty-five years. [58], [59] Specifically, LTP has been suggested as an amplifying mechanism within the pain system. [35] LTP is the tendency for synapses to strengthen their interconnections over a relatively long period of time. Lomo first introduced in 1966 and then confirmed it in 1968. [60] LTP is a form of synaptic plasticity that is most prominent in the hippocampus. It follows repetitive, high frequency stimulation of excitatory presynaptic fibers producing a long-lasting enhancement of synaptic strength that is usually revealed as an increased size of excitatory postsynaptic potentials. [61]

In the brain LTP is associated with a structural remodeling of the postsynaptic density and a process of dendritic spine duplication in which synaptic activity and calcium modulate changes in spine shape and formation of new spines. These modulations contribute to an increase in synaptic transmission and to synaptogenesis. [62], [63]

The term Hebbian plasticity is used to describe any long-lasing form of synaptic modification (strengthening or weakening) that is synapse specific and depends on correlations between pre- and postsynaptic firing. Bienenstock, Cooper and Munro suggested a mechanism in which correlated pre- and postsynaptic activity evokes LTP when the postsynaptic firing rate is higher than a threshold value and LTD when it is lower. [64], [65] LTD and LTP observed in the spinal cord are produced from nearly similar stimulus conditions, and it is presently unclear what exact conditions are necessary to selectively turn on one or the other of these processes in spinal cord neurons. Current work suggests that this LTD is a reversal of LTP, and vice versa, and that the

mechanisms of LTP and LTD may converge at the level of specific phosphoproteins. [66], [67]

Stanton found that when levels of neuronal activity are high, indicating circumstances increasing the likelihood of inducing LTP, compensatory changes cause the suppression of LTP and an enhanced likelihood of LTD. [68] Both processes involve glutamate release, activation of NMDA receptors, and increases of intracellular calcium with modest increases favoring LTD and larger changes required to trigger LTP. [35], [67], [68], [69], [70]

Artola et al explored the visual cortices of rats to determine whether raising extracellular Ca++ also induces long-term modifications of excitatory synaptic transmission in the neocortex. Their results suggested that a transient increase of postsynaptic Ca++ is sufficient to elicit LTD. [71] Liang et al also demonstrated in rat studies the activation of specific glutamate receptors may contribute to the induction of LTP increasing primary afferent synaptic transmission in the superficial layer of the trigeminal caudal nucleus. [72]

The induction of LTP during low back pain has yet to be investigated; however, given the current climate of pain research, it would seem reasonable to suggest that LTP within dorsal horn neurons has a function in both acute and chronic low back conditions. Evidence linking dynamic pain processing mechanisms to clinically relevant back pain phenomenology such as referral, ongoing pain, and tissue tenderness has been reviewed by Boal and Gillette. [35]

Treatment: The concept of dysfunctional central pain processing necessitates a pain mechanism-based classification for selecting individual management and treatment programs. [4] Additionally, treatment and therapeutic measures for chronic low back pain would seem incomplete without addressing the central sensitization in pain management regimes. [54] A new appreciation of the significance of plasticity on 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 (hyperexciteability) states in patients, thus decreasing the likelihood of developing a persistent pain condition. Interventions aimed at minimizing nociceptive afferent activity

or preventing nociceptive impulses from reaching the spinal cord might effectively decrease the hyperexcitable state. [45], [73] Additionally, during the past 20 years, numerous studies have demonstrated that behavioral and psychosocial protocols can benefit patients with persistent pain. [24]

SMT has been demonstrated to be an effective treatment for acute and chronic back pain. In addition to biomechanical effects, there have also been suggestions that spinal manipulation may alter the pattern of afferent input to the central nervous system (CNS) and, as a result, alter reflex mechanisms as well as ascending and descending pain-modulating elements of the pain system. [10], [74] Adjustments to decrease nociceptive input to the spinal cord seem to be an effective way to decrease the hyperexcitable state. [75] Since activity-dependent neuronal plasticity such as LTP is known to be reversible, the idea is presented that SMT may act to reverse LTP within an already sensitized pain-signaling system. It is known from recent experiments that the temporal correlation of pre- and postsynaptic activity is important for strengthening or weakening of the excitatory synapse strength connecting the pre- and postsynaptic neurons. Furthermore, since NMDA-dependent activity determines Ca++ concentration in the postsynaptic cell, LTP and LTD are timing-dependent. [76]

It has been proposed that stimulation of Aδ-fibers can initiate LTD in dorsal horn neurons, and if dorsal horn nocireceptive neurons are first hyperpolarized the same afferent input results in LTD instead of LTP. [77], [78], [79] Boal and Gillette proposed that, "it seems reasonable that SMT may provide sufficient afferent stimulation to trigger LTD," and 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." [35] Zupancich offered that using treatment applications to slow down expansion of the somatosensory cortex as a result of injury or stimulation as another approach for treating chronic pain. [80], [81]

Nociception involves four physiologic processes that are subject to pharmacologic modulation. Transduction is the translation of noxious stimuli into electric activity at the peripheral nociceptor. Transmission is the propagation of nerve impulses through the nervous system. Modulation occurs through the descending endogenous analgesic systems, which modify nociceptive transmission. These endogenous systems (opioid,

serotonergic and noradrenergic) modulate nociception through inhibition of the spinal dorsal horn (T) cells. [9] Perception is the final process resulting from successful transduction, transmission and modulation and integration of thalamocortical, reticular and limbic function to produce the final conscious subjective and emotional experience of pain. A significant portion of central nervous system activity is concerned with selection, modulation and control of ascending sensory information by fibers descending from telencephalic structures. The descending inhibitory system has been described as being activated centrally by enkephalins and opioids and sending serotonergic and noradrenergic fibers to terminate in the spinal and medullary dorsal horn. In addition, noradrenergic neurons arising from the locus coeruleus and other brain stem nuclei contribute to the endogenous system. The ability of endogenous opioids to reduce pain-induced suffering, while preserving discriminative function, is attributed to effects of these opioids on reticular neurons. Additionally, they depress activity in the amygdala. [9], [11]

In addition to the aforementioned treatment ideas, it would seem beneficial to include in a management protocol potential methods to desensitize central mechanisms with pain gating at the spinal and suprasegmental levels, while promoting re-education and plasticity of non-nociceptive systems. Pain-producing methods such as trigger point therapy should be avoided as they may build plasticity in the nociceptive system. Use of mild strength and conditioning exercises of the proximal muscles, particularly those associated with the reticulospinal tract could be appropriate in order to increase endogenous opioids and because these muscles have the least cortical representation. Oxygen therapy and supplementation with lysine, ubiquinone, magnesium, choline, and B6 for creation of a chemical environment to promote plasticity of non-nociceptive systems is a recommended area of study. According to Keefe, "a hallmark of psychosocial treatment programs for persistent pain is their insistence that patients need to take an active role in learning to manage their pain." [24] Creating brain based suppression through the activation of the periaqueductal grey area (PAG) of the brainstem which controls the descending inhibitory pathways, increased cortical frequency of firing, induction of LTD, increased endogenous opioids, and psychological

interventions delivered during the first few months after pain onset might be an appropriate treatment package to be researched.

CONCLUSION

LBP is a complex problem which involves several mechanisms, some of which are not entirely understood. Nociceptive, neuropathic, and especially, psychological processes can be involved with persistent pain. For the clinician, it is extremely important to be familiar with these mechanisms so the appropriate treatment can be rendered.

A substantial amount of research exists on the topics of neuroplasticity, central sensitization, and persistent LBP. However, considerably less work exists which address these topics together. Pubmed and MANTIS searches generated over 18,000 articles on neuroplasticity, over 2,500 article on central sensitization, and over 4,000 articles on chronic/persistent LBP. Only the Boal and Gillette [35] review was found to address all three topics.

Conclusions that are strongly supported by evidence are the following: [1] Neuroplastic changes promote nociceptive processes via central sensitization. [2] Psychological factors such as depression, anxiety, catastrophizing, fear avoidance, self-efficacy and coping are important aspects which should be considered in the treatment of pain, particularly persistent pain. [3]. Treatment which encompasses the psychological factors involved with pain provides better outcomes. [4] Neural plasticity in spinal and supraspinal structures promote central sensitization in the form of LTP and LTD.

More research is definitely needed in the area of treatment options, e.g., SMT for the treatment of persistent pain. This author hopes that researchers will soon answer the calling to publish more work focusing on empirical evidence for treatment plans which address central sensitization in pain conditions. Additional studies which address central sensitization in persistent LBP might add to our understanding and provide more potential treatment ideas. Treatment options aimed at combining a variety of approaches which address the physiological and pathological processes involved with central sensitization should be considered.

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