Neuroplastic Changes in Chronic Musculoskeletal Pain: A Literature Review

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ABSTRACT

Objective: This article will review the peer-reviewed literature of the neuroplastic changes which cause an overly sensitized state in chronic pain syndromes. The transition from acute to chronic pain will be analyzed to determine the causes of the progression. A better understanding of this will allow for a more complete treatment of chronic pain. Emphasis will be placed on the nervous system's role in this process and how to apply an appropriate method of intervention. An increasing amount of evidence has shown the neural wiring of the body is of paramount importance when addressing chronic pain.
Data Collection: Internet databases such as PubMed and MANTIS were be used to locate peer-reviewed articles relevant to chronic pain, neuroplasticity, central sensitization, and the biopsychosocial model. Database searches generated over 58,000 articles on chronic pain, over 11,000 articles on neuroplasticity, over 3,300 articles on central sensitization, and over a 1,000 articles on the subject of the biopsychosocial model.
Data Synthesis: Selected information was compiled to provide a consensus on the mechanisms of chronic pain. Research articles were evaluated to formulate a cohesive model of the role of neuroplasticity and central sensitization in the chronic pain cycle.
Conclusion: Chronic pain is a complex syndrome resulting from dysfunction of the nervous system. The process is due to sensitization of the nervous system which allows the painful signal to be overly propagated to the brain. A multi-disciplinary approach must be utilized to help reverse chronic pain syndromes. Chiropractic adjustments, patient education, and rehabilitation programs used in conjunction have yielded the highest rates of decreasing chronic pain. This treatment must eclipse the older notion of primarily focusing on the area of complaint. Providing a more complete treatment will help reduce the burden on the American economy and will increase the quality of life of individuals dealing with chronic pain syndromes.

Key Indexing Terms: Chronic pain, neuroplasticity, central sensitization, biopsychosocial

INTRODUCTION

Chronic musculoskeletal pain is an epidemic in the American society. Billions of dollars are spent each year to alleviate the debilitating effects of persistent pain syndromes. The lack of efficacy in dealing with chronic pain has become a huge burden to the American health care system and economy.[1] Despite the amount of time and money spent on chronic pain there has been little advancement toward effective interventions. Many physicians focus specifically on the site of pain and try to mask symptoms. This treatment has shown to be of little value when dealing with chronic pain syndromes. The progression of acute musculoskeletal pain to chronic pain has been misunderstood and therefore mistreated. Relatively new research has investigated why a condition advances to a chronic status. The current focus is on the dysfunction of the nervous system which becomes overly sensitized to propagate a painful stimulus. The dysfunction results in a snow ball effect, creating a string of faulty neural input along the course of the nervous system. The afferent input to the brain and the descending inhibitory pathway no longer correctly respond to a relatively low level of tissue damage and create a state of persistent pain.[2,3] Further investigation must be directed at why this transition takes place and how to reverse it. Therapeutic interventions must harness the nervous system's capability to adapt and modulate pain. Addressing each level of dysfunction within the patient will provide a more comprehensive method to treat chronic musculoskeletal pain.

DISCUSSION

Nociception and Pain Perception

Nociception is the detection of a noxious stimulus which can be mechanical, thermal, or chemical in nature. The receptors consist of free nerve endings located throughout the tissues of the body.[4] The nerve endings react to a stimulus which creates an action potential that is transmitted along the axon. There are two types of fibers transmitting the signal, fast type A fibers, and slower type C fibers. These neurons enter the spinal cord through the dorsal root and are funneled into the dorsolateral fasciculus or tract of

Lissauer where they ascend and descend one to two levels. Once the impulse reaches the terminal buttons, neurotransmitters are released into the synapse.[5] The primary nociceptive nerve synapses on a dorsal horn cell in lamina I through VI within the grey matter.[6] The neurotransmitters land on the neuron's dendrites which changes the potential of the dorsal horn cell causing it to fire. These neurons immediately cross the ventral white commisure to the contralateral side of the cord where they ascend in a bundle called the lateral spinal thalamic tract. This tract then synapses on the cells located Ventral Posterior Lateral (VPL) nucleus in the thalamus.[4] Once this signal is transmitted to the thalamus pain has been perceived by the individual. Thalamocortical fibers ascend from the VPL of the thalamus to the somatosensory area in the post-central gyrus of the cortex. These cortical cell bodies allow the specific localization of pain. Type A fibers ascend all the way to the cortex and are well localized, where as type C fibers mostly terminate at the thalamus and have a more diffuse pain pattern.[5] Pain is an unpleasant experience but it serves a purpose. The biological purpose of pain is to inform the body that there is some level of tissue damage. This process becomes aberrant when the level of pain perception is out of proportion with the actual amount of tissue damage.

Pain Modulation

Pain sensation and nociceptive pathways are kept in balance through self-regulating positive and negative feedback loops just like the other systems of the body. There are three major components which make up this analgesic system. They are the periaqueductal gray and periventricular areas, the raphe magnus nucleus, and pain inhibitory complex located segmentally in the dorsal horn. The periaqueductal gray region is located in the midbrain around the cerebral aqueduct and the periventricular areas around part of the third and fourth ventricles.[2] These two regions have the ability to greatly reduce painful sensations and is known as the descending inhibitory pathway. Stimulation of the PAG and PV areas cause the stimulation of the raphe magnus nucleus located in the lower pons and upper medulla. Projections from the raphe magnus nucleus deposit enkephalins in the dorsal horn.[4] The enkaphalins block the propagation of the painful signal by inhibiting the dorsal horn cell from firing. The inhibitory complex in the dorsal horn consists of interneurons which can decrease the nociceptive pathway from

entering the cord. These interneurons have direct control over the threshold of the neurons located in the dorsal horn. Increasing the threshold suppresses the pain signal.

Another method the nervous system can inhibit pain is through the stimulation of mechanoreceptors. Melzack and Wall first proposed this notion and described it as a "gate theory." The idea is that mechanoreceptors laterally inhibit nociceptors at the level of the cord preventing afferent pain signals. This explains why an individual will rub their toe after stubbing it, the mechanoreceptor closes the gate.[7] Melzack and Wall's research has provided a strong foundation for the support of spinal manipulative therapy which will be discussed later in this paper. The nervous system's ability to modulate pain has been the main focus for current literature on chronic pain. Utilizing this inherent capacity through therapeutic and preventative means, has the potential to stop the propagation of the chronic pain cycle.

Neurotransmitters Involved in Pain

Neurotransmitters are chemicals that are released from neurons which bind to special receptors on a target cell. These substances are released from a pre-synaptic neuron which then crosses the synapse to bind with a post-synaptic cell. Neurotransmitters convey either an excitatory or inhibitory message. These messengers are especially important when dealing with pain's propagation and modulation. Glutamate is an amino acid based neurotransmitter which is excitatory.[4] Type Aδ fibers which terminate in the spinal cord release glutamate which excites secondary neurons to convey the painful stimulus. Glutamate is responsible for fast pain by acting on the AMPA receptor.[8] Prolonged depolarization of the dorsal horn cell by glutamate also acts on the NMDA channel receptor which adds to the painful stimulus. Substance P is a neuropeptide which is released much more slowly than glutamate and has a longer response. Substance P is the chemical which has been indicated in chronic pain.[9] The NMDA receptor is of particular interest in chronic pain because it allows for the continual propagation of C-fiber activity. Glycine is needed to remove the Mg^{+2} block of the NMDA receptor which then can be stimulated by glutamate and enhanced by substance P. Inflammatory substances such as bradykinin and prostaglandins further increase the

dorsal horn cell's receptivity and allow for increased propagation of pain. Nitric Oxide is not a true neurotransmitter but has important properties relating to pain. NMDA receptor activation triggers the synthesis of nitric oxide which allows a neuron to "wind-up."[10] This process triggers the pre-synaptic neuron to increase its release of excitatory neurotransmitters, enhancing the pain propagation. GABA is a neurotransmitter that has an inhibitory effect on neurons. This substance increases the threshold it takes for a neuron to fire which prevents the painful stimuli from depolarizing the dorsal horn cell.[11] Neurotransmitters are the mediators of pain at the cellular level. Understanding their role in the propagation and modulation of pain is necessary to develop appropriate therapeutic interventions in chronic pain syndromes.

LTP and LTD

Long term potentiation (LTP) and long term depression (LTD) are two important terms in dealing with the adaptive properties of neurons and their connections. Long term potentiation is a long lasting enhancement of signaling between two neurons. As these neurons continually utilize their connection they are able to more efficiently transmit a stimuli.[12] This is prominently due to the post-synaptic neurons receptivity to the pre-synaptic neuron's signal. There are two phases of long term potentiation which allow for the post-synaptic neurons increased sensitivity. The early phase is when the signal is overly propagated. This process is NMDA receptor dependant. The NMDA receptor no longer inhibits the influx of calcium into the cell and the neuron fires at a lower threshold. The late phase involves gene transcription and mRNA translation to increase the number of receptors on the post-synaptic neuron.[13] Long term potentiation explains how neuroplastic changes take place within the nervous system. Long term depression is the counter acting force of long term potentiation. LTD represents a decreased efficacy of neural transmission. Involution of receptors makes it harder for a neuron to reach threshold and fire. Long term depression may hold the answer to the problem of chronic pain syndromes. Utilizing the physiology involved in long term depression and long term potentiation will help to control the mal-adaptive nature of the nervous system in persistent pain.

Sensitization and Neural Plasticity

The understanding of chronic pain requires understanding the ideas of sensitization and neural plasticity. These processes allow for a relatively benign painful stimulus to develop into a chronic process. Increasing literature shows a similar pathogenesis shared among persistent pain syndromes. Sensitization is the process where afferent pain signals are facilitated and can therefore be transmitted with lower levels of stimulation. The nervous system allows for a normally self resolving condition to persist. The process is due to an increased efficiency in the afferent signal to reach the thalamus and cortex.[8] It is the same idea as repeating a phone number in your head to remember it. The more you say the number the easier it is for your brain to recall the information. Pain works in a similar fashion. As the nervous system continues to propagate the signal a feed forward system is created. Neurons can lower their own threshold by a process called "wind up." Nitrous oxide is released which lowers the threshold at which the neuron is activated. Vikman and Kristensson demonstrated this phenomenon in their experiment. They state, "whole-cell recordings of dorsal horn neurons showed that repetitive low-frequency stimulation of DRG axons induced a frequency-dependent cumulative depolarization of the membrane potential with a concomitant increase in action potential frequency in a subset of neurons (41%). The characteristics presented here for dissociated cells are in accordance with those ascribed to classical wind-up in the intact dorsal horn."[14] Pre-synaptic neurons increase their signal through the process of wind up which in turn sensitizes the post-synaptic cell. Central and peripheral sensitization cause a synergistic effect which makes it difficult for therapeutic intervention to counteract the changes which have taken place within the nervous system.

Neural plasticity allows for the neurons to undergo physiologic and anatomic changes. Arborization is when the amount of synaptic connections increases to make a neuron more able to receive input. Costigan, Scholz, and Woolf describe these processes in their paper titled "Neuropathic Pain." They state, "Peripheral axonal injury prompts sensory neurons into an actively growing state by increasing the expression of regeneration-associated genes."[15] Up-regulation of these genes allows for expression which results in the production of neurons devoted to the sensation and transmission of pain. These extra

neurons with increased sensitivity facilitate the pain process. Now the patient is disposed to experience intense pain, hyperalgesia, and even pain with innocuous stimuli, allodynia. Neural changes are not restricted to the peripheral nervous system but also occur in the spinal cord and brain. Balenzuela et. al. conducted a study using functional MRI (fMRI) to examine how pain shapes the brain. They showed that persistent pain increases the activity and size of the regions of the brain devoted to the sensation and processing of pain. The researchers focused on the areas of the brain termed the "pain matrix," consisting of the somatosensory, insular, anterior cingulate, and prefrontal cortices, as well as the thalamus. They showed that enduring pain results in a pronounced activation of the "pain matrix" which alters brain dynamics beyond the feeling of pain itself.[16] This explains why individuals may feel a myriad of symptoms such as sleep disturbances, depression, attention and cognitive deficits. Through these processes the body is now set up for chronic pain. Normally as the tissue heals and the nociceptive signaling decreases, the individual experiences less pain. In the chronic pain individual the tissue has started healing but the propagation of pain still persists.

Biopsychosocial Model

The biopsychosocial model is a relatively new approach to chronic pain. The model analyzes all the aspects which go into an individuals ability to process pain.[17] This is in contrast to the previous reductionist notion that all pain processes can be explained by disease, injury, or developmental abnormality. Although it may seem this concept is a somewhat metaphysical description of pain, recent neurologic research has proven this "mind-body" connection. The name accurately describes the model where the biology, psyche, and social aspects of the patient determine their response to certain conditions.[18] The main connection between these three concepts is the nervous system. The descending inhibitory pathway is monitored by various regions of the brain. An individual's emotional experience has shown to be an equal determinant of chronic pain as their physical condition. The limbic system is the emotional seat of the brain; there are connections from the pain pathway to this region of the brain. The amygdala located in the limbic system is a major part of an individual's emotions. It is involved in detecting motivationally significant stimuli such as those related to reward and fear in addition to

social function. Goncalves et. al. demonstrated changes in the amygdala in rats who had induced hyperalgesia and allodynia. "We demonstrate that neuropathic pain promotes generation of new neurons in the amygdala. Given the established role of the amygdala in emotional behaviour, we propose that these neuroplastic changes might contribute for the development of depressive-like symptoms that are usually present in prolonged pain syndromes in humans."[19] The study demonstrated the strong link between an individual's psychosocial factors and their predilection toward chronic pain syndromes. Finestone, Alfeeli, and Fisher's literature review revealed "that psychological stress is associated with slower or delayed wound healing in stressed older adults, restrained mice, socially isolated hamsters, adults with leg wounds, and surgical patients."[20] Their research showed how an individual's psychosocial aspect plays an equal or greater role than their actual physical status. The increasing support for the biopsychosocial model must urge physicians to change how they treat their patients.

Fear avoidance is when patients undergo changes in their behavior or lifestyle due to fear of exacerbating their pain. An example is the individual who lies in bed all day in order to decrease the chance they will make their low back pain worse. Fear avoidance behavior is a problem for musculoskeletal pain management. The lack of activity actually worsens their condition and causes further dysfunction in the nervous system. The patient's inactivity leads to deconditioning which leads to biomechanical changes resulting in more pain. This creates a cycle which prevents the individual from ever reaching resolution of their condition. Patient education has been shown to be the best way to reduce fear avoidance behavior.[21] Patients must be informed by their doctor which activities they should actually avoid and which will help alleviate their symptoms.

Catastrophizing is the patient's negative beliefs toward their treatment and outcome. This has been shown to correlate with patients transitioning from an acute to chronic condition. Having a negative attitude sets the individual up for failure and has been shown to be a strong indicator in chronic pain syndromes. Keefe et. al. conducted a study to analyze the effects of catstrophizing on patients with osteoarthritis of the knee. The study had patients complete a number of questionnaires relating to their disability,

attitude, pain intensity, and coping strategies. The study showed that participants with a negative attitude and poor coping strategies had the highest levels of pain and disability.[22] In a separate study conducted by Rodero et. al. the researchers set out to find the relationship between castrophizing and fibromyalgia. Three hundred and twenty eight subjects who were diagnosed with fibromyalgia were divided into three groups based on the level of chronicity. The subjects then answered questions to determine their pain castrophizing scale (PCS). The article concluded, "catastrophizing was a stronger predictor of fibromyalgia impact than pain itself…"[23] The researchers suggest the timing of treatment is equally important as the type of intervention. Early detection and treatment helps to prevent maladaptive patterns of coping strategies and pain behaviors. Health care practitioners must help to reduce the level of catastrophizing and increase the patient's expectations toward treatment.

Treatment

Chronic musculoskeletal pain is due to dysfunction of pain processing resulting from some initial level of tissue insult. Both the mechanical and neurologic aspects must be addressed by the practitioner to treat chronic pain. Current literature has confirmed the notion that a multi-dimensional approach is the most effective. Clinics have moved to an "integrated" model where they can apply a more holistic treatment of the patient. Maires et. al. conducted a research experiment examining the effectiveness of an integrated approach to treating low back pain. Two hundred individuals with back pain were included in the study; half were treated by a multi-disciplinary team and the other half only by a primary care physician. The multi-disciplinary team consisted of acupuncturists, chiropractors, cognitive behavioral therapists, exercise therapists, massage therapists, and primary care physicians. The subjects' response to the treatment was based on disability, functionality, and pain questionnaires. The patients treated with an integrative health care team scored much higher in all categories, and took less time to recover than those participants who were only treated by a solo physician.[24] A separate study in the European Journal of Pain conducted a similar study but used the amount of time it took the subjects to return to work and the amount of leave days to determine the outcome of treatment. The group treated with an integrative team took less time to get

back to work, and took less days off once they were back in the work place.[25] Numerous studies have shown that a team of physicians is the best approach to treat chronic pain syndromes. Due to the multi-faceted nature of chronic pain syndromes, a group of practitioners is necessary to address the many levels of dysfunction.

Spinal manipulative therapy has been shown to be an appropriate treatment of chronic musculoskeletal pain. The normalization of biomechanics helps to decrease the nociceptive response from the damaged tissue. A proprioceptive burst allows for the reordering of afferent neural signals. The increased proprioception dulls the transmission of pain which starts the reversal of the aberrant nociceptive affrentation. It has also been shown that spinal manipulation activates the descending inhibitory pathway. Vernon et al. reported an 8% increase in plasma endorphin levels 5 minutes after spinal manipulation but not after control interventions.[26] Bialosky et.al. demonstrated hypoalgesia in patients following spinal manipulative therapy. Sixty subjects were given verbal analog scales, pain disability questionnaires, and dynamometer pressure threshold readings of the forearm pre and post adjustment. The researchers found that after an adjustment subjects experienced a period of hypoalgesia. The effects were due to, "lessening of temporal summation due to spinal manipulative therapy."[27] In a related study by the same group of researchers they conducted a similar study using thermal sensation as a measure of hypoalgesia. Participants undergoing spinal manipulative therapy had a dramatic decrease in thermal sensitivity.[28] There has been extensive research conducted on the effects of spinal manipulative therapy. Although many studies state the effectiveness of manipulative therapy is inconclusive, an overwhelming majority declare the benefits of spinal manipulation. A spinal adjustment has an enormous effect on the nervous system and must be utilized to normalize neural function. Chronic pain treatment must evolve past the prescription of muscle relaxants and pain relievers to include therapies that alter the neurologic function of patients.

Acupuncture has been shown to be an effective conservative method to manage pain. The technique has been used for thousands of years but has not had the research

validation. Current imaging such as functional MRI has been able to prove the beneficial effects. Acupuncture activates the body's endogenous analgesic system. "Recent data suggest that acupuncture triggers a sequence of events involving the release of endogenous opioid-like substances, including enkephalin, β-endorphin, and endomorphin, that modulate pain signals processed along the pathway. Imaging studies demonstrate that the limbic system plays an important role in acupuncture-induced analgesia."[29] In a separate study conducted by Thomas et.al. the researchers set out to determine the effectives and economic benefits of acupuncture. The participants were divided into two groups, one treated by their general practitioner and the other by the general practitioner and an acupuncturist. The patients filled out disability and pain questionnaires at 3, 12, and 24 months. A cost-utility analysis was conducted at 24 months using the EuroQol 5 Dimensions (EQ-5D), which is a standardized tool to assess health care outcome and cost effectiveness. At each interval analyzed patients receiving acupuncture care reported lower disability scores ($p>0.05$), and at 24 months the EQ-5D analysis showed less overall health care costs in the group supplemented with acupuncture.[30] Acupuncture can be used to help facilitate analgesic pathways while dulling nociceptive pathways. This technique is cost effective and poses little to no detrimental effect on the patient. Although there is still much to be discovered regarding acupuncture, emerging evidence has confirmed its therapeutic value.

Diet and nutrition play a major role in chronic pain syndromes and have often been overlooked. Our diet provides our body the building blocks it needs to operate at a cellular and organic level. Certain substances have a positive effect on our body helping it revitalize and heal, while others have an adverse effect and promote inflammation and other detrimental processes. There has been a recent emphasis on the pro-inflammatory diet that has become common in industrialized nations. Saturated fats and omega-6 fatty acids promote the inflammatory cascade, while omega-3 fatty acids help to decrease inflammation.[31] By consuming more anti-inflammatory foods, and less pro-inflammatory foods our body will be less likely to undergo the process of inflammation. This helps to control the nervous systems reaction to noxious stimuli.

Willow bark is a natural substance which was the original inspiration for salicylic acid, commonly called aspirin. Willow bark has the same properties of aspirin which helps to control inflammation and decrease pain. Vlachojannis and Chrubasik conducted a systematic review on the literature pertaining to willow bark supplementation in patients with low back pain. They concluded that willow bark extract has an equal effect as salicylic acid in suppressing low back pain, and lacks the many adverse side effects.[32] Another substance which decreases pain and inflammation is bromelain. Bromelain is a proteolytic enzyme that is found in large amounts in pineapple. Onken, Greer, and Hale found that bromelain treatment decreased pro-inflammatory cytokines and chemeokines in colon biopsies in vitro. This is due to bromelian's suppression of the expression of mRNA translation of pro-inflammatory substrates.[33] Vitamin D has major implications in chronic non-specific musculoskeletal pain. Peter Lewis found that of 150 patients presenting to a major Minneapolis hospital for non-specific pain, 93% of them were deficient in Vitamin D.[34] Faraj and Mutairi conducted serum analysis on 360 patients with chronic spinal pain. They found that 83% of these patients had low levels of Vitamin D, and after undergoing supplementation all experienced improvement.[35] There is a vast amount of evidence available on nutritional therapies to help improve chronic pain syndromes. Nutrition and supplementation must be integrated into treatment of patients to help improve the quality of life of patients afflicted by persistent pain.

Cognitive behavioral strategies and exercise have been shown to be effective in treating chronic pain syndromes. Cognitive behavioral therapy is a form of psychotherapy which focuses on how the patient feels about their treatment and expectations. This form of therapy helps to control the psychosocial aspect of chronic pain. Improved coping strategies and a better outlook on the patient's condition have been correlated with better response to care.[36] The power of thought has been overlooked in dealing with chronic pain and must move to the forefront in order to manage patients. Exercise is the best advice for any individual, and for the pain patient it is of paramount importance. Physical activity not only promotes structural support of weak pain producing areas of the body, but also causes chemical changes of the body's physiology. Just fifteen minutes of exercise the body starts to release beta-endorphins which dull any painful

stimuli before on entering the spinal cord. Serotonin is released in the brain which controls mood and can alter one's perception and cortical processing of pain. Sculco et.al. published an article in the journal Spine, examining the effects of exercise on patients with low back pain. They took 68 patients aged 30-60 with low back pain, and divided them into two groups. One group of 35 individuals underwent a ten week exercise program where the other acted as a control of non-exercising individuals. Exercise consisted of light to moderate cycling or walking at four days per week and 45 minutes per day. The measure of mood states was accomplished through the Profile of Mode States, and the measure of pain was the Brief Pain Inventory. Patients in the exercise group scored significantly better on the mood profile and at 2.5 years follow up had, "received significantly few pain medication prescription (AE X=2.76; control X=13.35 $p<.02$) and were given fewer physical therapy referrals (AE X=0.17; control X=1.64; $p<.02$)." [37] Exercise, activity modification, proper diet, and education used in conjunction with spinal manipulative therapy provides a holistic approach to patients with chronic pain. Customized care to each patient will help reduce the burden on the economy and the American public.

CONCLUSION

The current method of treating chronic musculoskeletal conditions must be revised. A more holistic and less reductionistic approach will help treat the multiple dimensions of the patient's centrally sensitized persistent pain. Considerable good quality evidence demonstrates the process by which nervous system changes are shown to be the common denominator in persistent pain syndromes. Therapeutic interventions must be directed at modifying the neurologic changes responsible for centrally sensitized persistent pain. Emphasis should be placed on the prevention of centrally sensitized persistent pain through early interventions which interrupt the neuroplastic change processes responsible for persistent pain in the absence of nociception. Interdisciplinary teams of health care providers must work in conjunction to provide individualized treatment of patients dealing with chronic pain.

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