Neuroplasticity and Headaches: A Review of the Literature

Bronson Baber

Logan College of Chiropractic

Faculty Advisor: Rodger Tepe, PhD

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Abstract

The neuroplastic effects of the central and peripheral nervous systems has been studied abundantly and more so in the last 20 years. The predominating thought has been that central sensitization takes place in times of prolonged headaches causing the headaches to become chronic in nature. Central sensitization is the decrease in the action potential of neurons involved in pain perception in the brain that causes hypersensitivity in the individual to pain stimuli. Previous research has shown a strong correlation between central sensitization (neuroplasticity) and headaches. More recently brain imaging such as voxel-based morphometry has been used to look at how chronic pain and headaches can affect the grey matter of areas of the brain. This use of MRI, VBM, and PET scans of the central nervous system in headache sufferers may begin to yield more and more treatments for patients suffering from a variety of different headaches. The use of VBM and PET scans has revealed that migraine headaches cause a decreased grey matter in the brain stem while cluster headaches cause a decreased grey matter in the hypothalamus. Research was performed mostly on migraines, cluster headaches, and chronic tension-type headaches. All three were shown to have grey matter effects in the areas of pain perception in the brain. The research summarized in this paper shows a strong case for neuroplastic changes in many different types of headaches. This neuroplasticity alters the way pain is perceived in the brain. Future research should look at the hereditary effects of neuroplasticity and headaches. This paper shows that neuroplasticity plays a large part in headache pathophysiology and should be a large focal point of headache research going forward.

Introduction

To begin to unravel how neuroplastic changes in the nervous system can influence chronic headaches we must begin with a working definition of pain. According to the International Association for the Study of Pain, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[1] This literature review, however, will deal more with the effects of chronic pain, and more particularly headaches, and the neuroplastic changes that take place with it. IASP defines chronic pain as "pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 months)."[2] According to the IASP approximately 10-55% of people in the US suffer from chronic pain[2]. The prevalence of chronic pain and headaches is rising in the US.[2] This paper is meant to understand some of the inter-workings of the brain following headaches that lead a patient down the road to chronic headaches and chronic pain.

Headaches are the result of disorders that affect the meninges, blood vessels, nerves, or muscles in the neck and head area.[4] All of these structures are very pain sensitive structures. Allopathic treatment of chronic headaches involves the use of NSAIDS to decrease the inflammation around the injured tissue, which in turn, decreases pain signals sent to the brain. As the pain persists more potent opioid drugs may be prescribed to these patients to alleviate pain which can possibly lead to dependency. Lastly, chronic headaches are often treated with 5-HT agonists, which are serotonin receptor agonists.[4] These are a few of the treatments used allopathically to treat chronic headaches. The focus of this paper is not on allopathic treatment, but there

is some discussion of how medication overuse can actually cause chronic headaches by neuroplastic changes.

To better understand what neuroplasticity is we must first define it. “Neuroplasticity can be defined as the ability of the nervous system to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections.”[3] Neuroplasticity has many aspects involved in it including central and peripheral sensitization of the nervous system. To understand central and peripheral sensitization we must first understand how a pain signal is sent from a pain stimulus to the brain to perceive it. When pain is encountered in the body it is sensed by nerves is in the periphery called nociceptors. These nerves must reach a threshold value in which a signal is sent to the spinal cord’s dorsal horn which sends a signal on C pain fibers or A Delta fibers to the brain. A delta fibers carry very sharp, strong pains to the brain very quickly so that the body can react quickly and get away from the cause of the stimulus to spare the body of harm. A delta fibers send their message to the thalamus and somatosensory cortex where it can be interpreted. Achy, dull, or cramping pain is sent to the brain via C fibers more slowly. These C fibers travel to the hypothalamus and also the limbic system. The connection with the limbic system explains why pain can elicit an emotional response[4].

Peripheral sensitization means that when nociceptors are constantly bombarded with stimuli eventually the nerves action potential to send a signal to the cord decreases so that it takes less of a pain stimulus to send a signal to the brain as pain. Central Sensitization is a change in the neurons function, structure, or connections in the brain in how the brain interprets pain signals. After many signals have bombarded the brain

over time the neurons adapt and can have many different reactions. This paper will discuss many of the neuroplastic changes that take place in the nervous system during chronic headaches.

Body

An important topic to consider when looking at headaches is the chronicity of the headaches. Research is showing that the very medications that patients are using to help relieve the symptoms of headaches can actually lead to neuroplastic changes in the brain that can cause headaches to become chronic in nature. Medication overuse headache (previously referred to as rebound headache, drug-induced head- ache or drug-misuse headache) is a secondary cause of chronic daily headache that occurs in patients with a primary headache disorder who overuse acute medications.[5] While the pathophysiology of migraine is unknown, it is widely acknowledged that activation of trigeminal primary afferent neurons that innervate the intracranial blood vessels and dura is likely to be responsible for producing the headache pain.[5] Prolonged exposure to drugs used to treat headaches turn up the neural regulators of vasodilation and neurogenic inflammation. Research has shown that daily intake of analgesics and triptans for the treatment of headaches increases the expression of CGRP and substance P in the trigeminal nuclei of the brain. Increase of these substances in the trigeminal nuclei have been shown to decrease the nociceptive threshold of neurons in the dura and blood vessels and also increase neurogenic inflammation. However, further demonstrating the neuroplastic changes capable of the brain, discontinuing the medications for several weeks causes a reversal of these trends.

Central sensitization plays a large role in the pathophysiology of headache sufferers. Central sensitization can be best described as an amplification of neural signaling in the brain and spinal cord that elicits pain hypersensitivity.[18] This happens by several different processes leading to temporal summation of pain signals causing hyperalgesia. Brain imaging of patients suffering from chronic tension type headache has shown a decrease in grey matter in many different areas of the brain. Subsequently, the decreased grey matter was mostly in areas associated with pain processing. This is most likely due to neuroplastic changes from central sensitization due to nociceptive inputs. Neuroplastic changes have been found with many different types of headaches. Migraines have been the most studied, but recent research also shows neuroplasticity in cluster headache sufferers. It has been shown that permanent abnormalities have been found in the trigeminal afferent pathways of the brain during cluster periods.[17]

A link has been shown between migraine sufferers and fibromyalgia patients. Both disorders have an increase in the activity of N-methyl-D-aspartate receptors in the brain.[6] These are serotonergic receptors. Inhibition of these receptors has been shown to be beneficial to both migraine patients and fibromyalgia patients.[6] This implies that redundant hyperalgesic neuroplastic changes play a huge role in both migraine and fibromyalgia patients. It also implies that the mechanism of both disorders are similar.[6] This demonstrates another way that neuroplastic changes can cause chronic headaches in patients and it also shows that the neuroplastic changes associated with chronic headaches sufferers can also cause other disorders to surface from the same mechanism.

In the article by Ashina et al, it was found that using suprathreshold stimulation on the muscles of the neck and also other areas of the body caused increased incidence of pain in patients suffering from chronic tension type headaches compared with controls.[7] This shows that chronic tension type headaches cause hyperalgesic changes in the pain sensitive portions of the brain. This happened in the hypertonic muscles usually involved with tension headaches and also in other muscles of the body that were tested.[7] This shows that the changes are taking place in the high processing centers of the body (ie. the brain). Bendtsen, in his study, found that the main problem in chronic tension-type headache is central sensitization at the level of the spinal dorsal horn/trigeminal nucleus due to prolonged nociceptive inputs from pericranial myofascial tissues.[8] The increased nociceptive input to structures outside of the central nervous system may in turn result in peripheral sensitization.[8] The central neuroplastic changes may affect the regulation of peripheral mechanisms and lead to increased pericranial muscle activity or release of neurotransmitters in the myofascial tissues.[8] By such mechanisms the central sensitization may be maintained even after the initial eliciting factors have been normalized, resulting in the conversion of episodic into chronic tension-type headache.[8] Nitric oxide has also been a possible player in central sensitization of chronic tension-type headaches sufferers. The use of nitric oxide synthase inhibitors has been shown to decrease nociception to the brain decreasing central sensitization during these headaches.[9] Nitric oxide is released at the beginning of headaches and causes vasoconstriction. The body then vasodilates these vessels causing nociceptive input to the brain which, over time, can cause neuroplastic changes through central sensitization causing chronic tension-type headaches. These

neuroplastic changes can cause chronic pain even after the peripheral noxious stimulus is gone.[10]

Peripheral Sensitization also plays a role in headaches. Peripheral sensitization is caused by neurons in the periphery being sensitized (decreased threshold to fire) by inflammatory chemicals being released around the neurons.[11] Central sensitization has been shown to play the largest role in chronic headaches, but peripheral sensitization aids in central sensitization. Increased firing of peripheral neurons from irritation sends an increased number of signals to the brain down the nociceptive pathway. This barrage of stimulus has a domino effect in that it causes neurons in the central nervous system to have a decreased threshold to fire. This sensitization can have a prolonged effect which can cause chronic sensitization and chronic headache.

A link has been shown between the neuroplastic changes involved in chronic headaches and motor learning. In one experiment the subjects were hooked up to an accelerometer on the thumb while their elbow is fixed to the table. The other four fingers were fixed in a cast while the thumb was left free to move. The subjects performed 2 sets of 225 thumb movements in which they were told to abduct the thumb and return it to neutral as fast as possible when they hear the beep. Headache sufferers were compared to normal control subjects. It was found that the control subjects showed a higher motor learning capability compared to the chronic tension-type headache sufferers. It was also found that the control group showed an increase in corticospinal excitability for at least 20 minutes after training whereas the headache group showed very little corticospinal excitability following motor learning. This shows that chronic tension-type headache not only causes central sensitization in the brain but also that it

causes impairments in the motor cortex of the brain possibly due to their close proximity in the brain.[12] A study by Cechinni et. al., also demonstrated a decreased habituation in the blink reflex in patients suffering from cluster headaches. This decreased blink reflex if also indicative of possible neuroplastic changes to the motor cortex from chronic nociception into the somatosensory cortex lying nearby. Also demonstrated was a decreased threshold for the corneal reflex during active period of cluster headaches which can be explained by the same logic as the blink reflex.[14] In another study comparing the blink reflex of people with headaches and controls it was found that there was no difference in the blink reflex of these two groups. Since there was no difference here they hypothesized that the problem must lie in the higher centers of the brain and not in the peripheral or pontine sturctures.[17]

A great summary of the morphogenic changes in the brain was done by using magnetic resonance imaging and segmenting the images into different tissue types. This technology is called voxel-based morphometry. This study found that in people suffering from cluster headaches there is a significant structural difference in grey matter density, a ‘lesion’ coinciding with the inferior posterior hypothalamus.[15] This showed that the area of decreased grey matter not only has morphometric alterations, but also functional alterations. Chronic tension-type headaches showed significant decrease in grey matter in the dorsal rostral and ventral pons, the perigenual cingulate cortex, the middle cingulate cortex and the right posterior cingulate cortex, the anterior and posterior insulae bilaterally, the right posterior temporal lobe, the orbito-frontal cortex and parahippocampus bilaterally and the right cerebellum. Interestingly, this decrease in grey matter correlated positively with increasing headache duration in

years.[15] This shows that there is a positive correlation between duration of chronic tension-type headache and decrease in grey matter in the brain. Due to what the other articles of this paper have shown us this is most likely due to neuroplastic changes due to chronic pain. Migraine sufferers were found to have a decrease in the grey matter in the anterior cingulate cortex and both insulae.[15] Earlier studies showed no difference in migraine sufferers and controls, however, recent studies have shown that using a 3T magnet compared to a 1.5T magnet on the MRI can show the changes.

The use of functional imaging has also shown us that changes in brain blood flow is associated with migraine with aura. Using PET scans it was found that the grey matter of the hypothalamus is targeted in cluster headaches. Whereas, migraines are more of an issue with the brain stem (trigeminal nuclei). Chronic tension-type headaches are associated with decreased grey matter in many different areas of the brain, but all areas that deal with transmission of nociception to perception. This agrees with the results of the VBM studies. [18]

Another aspect of neuroplasticity has been discovered by Sarchielli. In their research they found that patients suffering from chronic migraines and medication overuse headaches demonstrated increased levels of corticotrophin-releasing factor and Orexin-A in their coritospinal fluid. These increased levels in the CSF show that there is an abnormal pattern of hypothalamic hormonal control. These same headache sufferers also showed increased cortisol levels, a decreased nocturnal prolactin peak, and a delayed nocturnal prolactin peak. The aberrant hormonal control of the hypothalamus is hypothesized to be caused by the organs response to stress placed on the individual by the pain associated with headaches.

Woolf said it best when he said, “clinical pain is not simply the consequence of a “switching on” of the “pain system” in the periphery by a particular pathology, but instead reflects to a substantial extent, the state of excitability of central nociceptive circuits.”[18] This increased nociceptive activity causes the action potential to be decreased. This in turn causes normally innocuous inputs to be exaggerated, prolonged, and spread widely throughout the system.

Traditional Chinese medicine has an herb called Gastrodia elata Blume (tianma) that is believed to help promote neuro-regenerative processes. In the article by Manavalan, there was evidence of the effects of this herb on many of the signaling molecules of the brain.[20] Further research must be done on the ancient herb, but the evidence does help support the idea that the brain can have reversible changes. A possible treatment for cervicogenic and tension-type headaches is injection of botulinum toxin. Neuroplastic changes have been implicated in cervicogenic and tension-type headache. The idea behind the use of botulinum toxin is that is produces prolonged muscular relaxation around the area that is injected. Relaxing the muscles associated with tension-type headache causes decreased nociception to the brain decreasing the effects that neuroplasticity can have.[21]

Conclusion

In conclusion, the literature affirms previous thoughts that the brain is a moldable, ever-changing organ of the body. When outside stress is placed upon the body, ie. Headaches, over time the brain must adapt to the constant barrage of pain stimuli feeding into it. In the short term, it causes hyperalgesia due to temporal summation and

sensitization of neurons. Also reviewed, was the effects of chronicity of headaches due to medication overuse. Medication overuse has been shown to cause reversible changes in the gray matter of the brain, particularly the parts of the brain associated with pain reception. The failure of many pharmacological agents to relieve chronic pain, together with a complexity of regulation and side-effects of several current existing drugs, raises the question of whether alternative procedures for pain control can be brought into action clinically.[13]

This opens the door for alternative therapies such as chiropractic care and acupuncture to help alleviate chronic pain. Traditional Chinese medicine has a possible answer to neurological regeneration through the use of the herb tianma. Chiropractic care uses adjustments to access the neurological system to affect chronic pain. They also have the use of passive modalities as well as therapeutic exercise to give patients another option outside of medication that can cause medication overuse headaches over time. A recent advancement to help discover more about neuroplasticity in the brain is the use of voxel-based morphometry to see the increase or decrease of grey matter over time. The largest discovery using this technology has been by mapping out decreases in grey matter for different kinds of headache. Migraine sufferers show a decreased grey matter in the brain stem as compared to control subjects. In this area is the trigeminal nucleus and other pain conducting areas on their way to the thalamus for perception. Cluster headaches have shown to have a decreased grey matter in the hypothalamus and other areas of the brain that deal with nociception. Chronic tension-type headaches showed altered grey matter in many areas of the brain, all used in nociception transmission and perception. Also, the fact that the decrease in grey matter

is correlated to the duration of headaches shows that neuroplasticity has a temporal component involved. Further research involving the effect neuroplasticity can have on headaches can go in many different directions. Using VBM future research may unveil new and different ways of treatment for headaches. Another aspect to look into may be genetic predisposition and its effects on neuroplasticity. Neuroplasticity plays a huge role in the way headaches present and the chronicity of headaches. Future research should look more into how the role neuroplasticity plays in headaches because it may unveil secrets and treatments to treat other disorders as well.

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