Mechanisms of Migraine Pain Initiation

I. Pathology

Migraines are a common headache disorder that disables five percent of the general population with at least 18 days of migraines per year and one percent of the general population with at least one day of migraine per week. The WHO considers migraine headaches to be among the top 20 most disabling diseases. In Western countries, migraines are also two to three times more prevalent in women than men and the onset occurs most commonly between the ages of 20 and 40. The average, annual cost to employers is 13 billion dollars due to lost work and average, annual medical costs due to migraines reaches one billion dollars. Migraines can be triggered by a variety of things that may vary from person to person such as hormonal changes, certain food, stress, sensory stimuli, physical factors, changes in the environment, and some medications. Clinical manifestations of the disorder include moderate to severe head pain that can last anywhere from four to 72 hours. The pain can be felt in various locations on the head and can be felt as pulsate of throbs, can worsen with physical activity, and can eventually hinder regular daily activities due to nausea, photophobia, or phonophobia. Some headaches are preceded with attacks of focal neurological symptoms called auras, which include visual disturbances, tingling sensations in limbs, weakness, language and speech problems, or intense emotional feelings [1]. Although there are many widely accepted pathways of migraine pain initiation, the exact underlying mechanisms remain a mystery due to the lack of an identifiable cephalic pathology [2].

II. Mechanisms of pathology and methods of treatment

It has been generally accepted that the pain of migraines is due to referred pain to the forehead, neck, and occipital skin from activation of the trigeminovascular system. Although the brain itself is insensitive to pain, the pain and sensitivity in the head stems from the activation of nociceptive sensory afferent fibers that are a part of the ophthalamic branch of the trigeminal nerve. These fibers that are a part of the trigeminal ganglion heavily innervate the dura mater and meningeal blood vessels via neuropeptides. Also, trigeminal ganglion neurons simultaneously activate of the second-order dorsal horn neurons in the trigeminocervical complex. The trigeminocervical complex is comprised of the trigeminal nucleus caudalis (TNC) and the upper two divisions of the cervical spinal cord. When these second-order neurons of the trigeminocervical complex are innervated, they subsequently innervate the thalamus, the caudal
periaqueductal gray region (PAG), and the cortex, which are all involved in the processing and perception of pain information. The PAG not only contains ascending projections for pain perception, but it contains descending projections to the raphe nucleus, which can inhibit the nociceptive afferent information via interneurons. Additionally, innervation of the trigeminocervical complex via the trigeminovascular afferents activates a parasympathetic reflex that stimulates the superior salivatory nucleus (SSN) [1]. The SSN is also innervated by the hypothalamic and limbic areas of the brain [3]. The SSN then stimulates parasympathetic efferents of the superior sphenopalatine ganglion, which projects its axons to the meninges to release neuropeptides. Therefore, activation of the trigeminovascular afferents as well as these parasympathetic efferents leads to release of vasoactive neuropeptides from their peripheral nerve endings in the meninges. These neuropeptides include calcitonin gene-related peptide (CGRP), substance P, neuropeptide A, vasoactive intestinal peptide, nitric oxide, and acetylcholine. The release of these neuropeptides have been shown to produce vasodilation of the meningeal vessels, leakage of plasma from capillaries, and mast cell degranulation causing the secretion of proinflammatory substances in the dura mater. This entire process is depicted in Figure 1. The topic of debate and current study of migraines surrounds the mechanism of how the trigeminovascular system is initially activated in order to cause migraine pain. It is generally thought that the head pain is initiated by some primary brain dysfunction that leads to activation and sensitization of the trigeminovascular system [1]. However, due to the current lack of identifiable pathologies and lack of direct experimental data of specific pain pathways and mechanisms of pain initiation, there are currently many hypothesis and theories that remain unanswered and many hurdles must be overcome [2].

One proposed hypothesis that continues to be one of the leading theories on this matter with a large body of experimental evidence points to the involvement of inflammation in the
activation and sensitization of this pathway. For example, levels of inflammatory activity have been found to be proportional the intensity of the migraine pain. Increased levels of inflammatory mediators have also been detected during a migraine. Additionally, mast cells in meninges have been shown to cause inflammation and may play a role in causing migraines. Sensory neurons in meninges may act as inflammatory sensors to respond to inflammatory mediators and cause ongoing activation of pain pathways. Inflammatory activation causes sensitization of meningeal nociceptors and may explain the throbbing sensation and/or hypersensitivity experienced during migraines [2].

In addition, another hypothesis points to cortical spreading depression (CSD) as the cause of meningeal inflammation and activation of trigeminovascular afferents, which can lead to migraines with and without an aura. CSD is characterized by a slowly propagating wave of strong neuronal depolarization that travels slowly across the cortex and is followed by a long-lasting suppression of neuronal activity. This hypothesis proposes that the CSD activated trigeminovascular afferents could cause the release of noxious mediators such as K+ ions, H+ ions, NO, arachidonic acid, glutamate, and ATP. These noxious mediators may be released into the extracellular fluid near the pia, which then travel toward leptomeninges to activate the trigeminal ganglion terminals in the pia. This causes inflammatory neuropeptides (CGRP and substance P) to be released to meningeal vessels and the dura mater. Neuropeptides are also released by peripheral endings of the trigeminovascular afferents to the parasympathetic reflex pathway and to pain perceiving and processing structures. All of these events together cause localized sterile inflammation that can further amplify and sustain the initial CSD-related activation of meningeal nociceptors and cause sensitization. However, many doubts have been raised as to its validity due to the fact that CSD has not been directly demonstrated in humans [1, 2].

Another, alternative hypothesis as to what the ultimate generator of migraine pain activation entails is that migraine pain may be a consequence of a disturbance in the peripheral receptive fields of the afferent arms of trigeminovascular system via several transduction mechanisms. Migraine pain could arise via activation of mechanoreceptors in the dura mater or meninges by pressure or stretching from mechanical stimulation or changes caused by vasodilation or vasoconstriction. Also, pain could arise via activation of chemoreceptors in the dura. Many chemical agents applied to the dura cause the release of inflammatory mediating neuropeptides. Also, heat- or cold-sensitive receptors on trigeminovascular afferents may play a
role in transduction of pain [4]. Although just a small number of hypotheses have been mentioned here, there are many others, which have varying complexities and degrees of confliction when compared to these hypotheses.

Migraines are currently treated through a variety of anti-migraine drugs. One type are the serotonin 5-HT receptor agonists, which inhibit the release of vasoactive peptides from trigeminovascular afferents peripheral nerve endings and thus inhibit neurogenic inflammation and neurogenic vasodilation in the meninges. Triptans are another treatment that causes inhibition of neurotransmitter release from trigeminovascular afferents and neurotransmitter transmission to second-order neurons that lead to pain perception [1]. One recent study looked at holes and weaknesses of the current drug treatments for migraines such as rizatriptan and onabotulinumtoxinA, which lack the ability to block proton stimulated CGRP secretion that causes pain. They determined methods that block the gene expression of proton channels that lead to stimulation of CGRP and ways to implement this as a therapeutic method for migraine patients [5]. These are only a small number of the methods currently used and being studied. As the mechanism of migraine pain initiation is refined, even more new treatments will be discovered.

III. Vertebrate models

There have been an overwhelming amount of vertebrate studies conducted using vertebrate models, including humans, to study migraines. The nervous systems of other non-human vertebrates may not be identical to that of humans, but they are a very close model to be used for study. For example, the release of these neuropeptides can cause leakage of plasma from capillaries (dural extravasation) to cause secretion of proinflammatory substances in the dura mater, leading to migraine pain. In a recent study, rats were experimentally induced to experience dural extravasation by injection with infraorbital nerve constriction. Following this, the dural extravasation was able to be reversed for a long period of time via injection with botulinum toxin type A in this model. This experimental animal model demonstrated the fact that the botulinum toxin type A may have a lasting, beneficial effect on migraine patients suffering from pain that is initiated by dural extravasion [6].

Another vertebrate model used to study the inflammation involved in migraine initiation is the guinea pig. Specifically, the nasociliary nerve fibers, which are afferent axons from the trigeminovascular system, that innervate areas surrounding the dura were observed. Fibers from 38 individual guinea pigs were exposed to a variety of mechanical, chemical, and thermal
stimulations to better understand the stimuli that may activate these fibers and lead to migraine pain. This study showed that these fibers have properties similar to nociceptors of other tissues and they are likely to be involved in onset of persistent pain of migraines caused by inflammation in meninges [7].

Recently, the effectiveness of a new anti-migraine drug called St. John’s wort (SJW), which is a medicinal plant, was studied in a mouse model. First, a migraine was induced in the mouse via nitric oxide. The effectiveness of SJW was examined by looking at c-Fos and protein kinase C expression in the PAG via Western blots. When migraines are induced, the expression of these proteins in PAG is upregulated. However, SJW treatment prevented the expression of both proteins and caused no behavioral changes in the mice. Therefore, this experiment displayed that SJW is a safe remedy for migraine pain and showed that protein kinase C expression is an excellent target for future migraine therapeutics [8].

IV. Invertebrate models

Although invertebrate models that directly investigate migraine pain mechanisms are rare, invertebrates have been used to study concepts related to migraine initiation. The reason for the lack of invertebrate models is most likely due to the lack of similarity of the their nervous systems to that of humans and other mammals and vertebrates.

A recent study was done to look at CSD in locusts and how this could relate to the study of migraines and other neurological disorders in mammals. In response to environmental stress, locusts undergo spreading depression(SD)-like events within their nervous system in order to shut down many of their bodily functions so they can survive extreme environmental conditions. Many of the physiological events that lead to the induction of CSD in vertebrates also occur in locusts during this SD-like event. Locusts are an excellent model for studying CSD because their nervous systems remain intact and functioning during these SD events, locust preparation is convenient, and locusts allow for easy experimentation on glia, ion channels, and other pathways that are important in CSD such as the AMP-activated protein kinase pathway. Many studies of this type are currently underway [9].

Another invertebrate used to study the mechanisms involved in migraine pain initiation is the species Caenorhabditis elegans. C. elegans express a voltage-gated calcium channel, namely UNC-2, that has been shown experimentally to have an evolutionary and functional relationship with the CACNA1A channel expressed in humans. A mutation in the UNC-2 gene in C. elegans causes them to loose certain motor skills via the activation of an antagonistic pathway that
influences locomotion. This antagonistic pathway is responsible for the maintenance of serotonin levels in C. elegans neurons. The expression of CACNA1A by genetically altering the genome of C. elegans, restores normal motor function in the organism. This displayed the fact that the function of CACNA1A in humans may have an effect on serotonin levels, which could play a role in migraine initiation [10].

In a more broad, general study of mechanical nociception, Drosophila melanogaster have recently been used as a model organism. Unlike mammals, ion channels play a role in transduction of mechanical nerve signals for perception of pain in invertebrates and there are also a few similarities between the ions channels of mammals and invertebrates. However, the mechanically activated channels called Piezo1 and Piezo2 have recently been discovered to be expressed in both mammals and invertebrates. Piezo knockout D. melanogaster were exposed to a variety of noxious stimuli, which displayed the result that mechanical nociception was diminished with the absence of both Piezo channels via electrophysiological reading from other neurons. The results indicated that the Piezo channels play a role in the mechanotransduction of noxious stimuli and that D. melanogaster could be a useful organism in the study of the initiation of pain pathways [11].

V. Discussion

Due to the currently vast amount of data, hypotheses, and theories on migraine headaches, only a small amount is touched on here. And unfortunately, most of the research that has been done in order to pinpoint specific mechanisms is indirect and the underlying mechanism is still mysterious [4]. Ultimately, the current research and experimental models strive toward the identification of a unique, irrefutable pathology and pathway that causes migraine pain. According to Levy et al., if the pathology of a migraine and the unique pain pathway that causes it could be more accurately defined, the ability to identify sites and mechanisms underlying migraines could be more easily determined and studied [2]. Aftidi et al. states that the study of migraine initiation will lead to preventative treatments and imaging techniques [12]. All in all, addition of and development of new experimental models, new laboratory techniques, and new imaging techniques will lead to new discoveries and understanding of the initiation of migraine pain and the locations that mediate this pain. This will lead to the development of new and effective treatments for people who suffer from this debilitating disorder.

Through experimental laboratory studies and many rounds of trial and error, certain connections or mechanisms can be understood, ruled out, or added to existing theories or
hypothesis. Understanding these connections and mechanisms in the nervous system, no matter how complex, can lead to the discovery of unique and undisputable mechanisms in the nervous system that will allow for remedies and treatments for disturbances in these pathways in humans to improve quality of life and everyday functioning.

**Bibliography**