Exploring the Pathophysiology of Migraine with Aura

June Choi

Abstract

A migraine is a common neurological disease that causes a headache with the symptoms of severe throbbing or pulsing pain, typically on one side of the head. Up to 30% of people with migraine experience auras or visual disturbances as a symptom that occurs before or during the headache. Through experiments using animal models, researchers have found many possible reasons for the cause of migraine. While the underlying mechanisms of this disease are not yet fully understood, current research theorizes that migraine with aura is likely due to Cortical Spreading Depression (CSD). CSD is a temporary wave of electrical activity that spreads in the outer layer of the brain, the cortex. CSD can also directly affect the visual cortex, which contributes to the development of auras associated with migraine. This wave is thought to be caused by the excessive buildup of glutamate, an excitatory neurotransmitter. CSD is also thought to trigger the release of Calcitonin Gene-Related Peptide (CGRP), a neuropeptide that causes blood vessels to dilate and widen. This leads to the inflammation and pain that occurs during a migraine attack. People with this disease usually take prescription drugs such as sumatriptan and rizatriptan to help reduce the pain. Another common method is using antibodies that target the CGRP receptors and CGRP itself. Further research is necessary to improve our understanding of aural migraines and develop more effective treatments.

1 Introduction

Migraines are essentially a type of headache, but there are some key differences between standard headaches and migraines. While headaches cause pain in the head and face, migraines produce more intense and debilitating symptoms in comparison to headaches (1). Also, headaches start in the nerves of muscles and blood vessels that surround one's facial areas, while migraines are thought to begin near the cortex. Migraines affect around 14% of the world's population (2). The frequency and duration of these migraines will vary, but they can be as frequent as 15 times a month, and last from 4 hours to 3 days. The disease is more common in women than men and is more frequent after puberty or when adults hit age 30 (3). This disease is divided into two main groups: migraine with aura (MwA) and migraine without aura. The common symptoms of MwA include visual disturbances, like flashing lights and hallucinations, pulsing head pain, nausea leading to vomiting, and sensitivity of the senses, especially sound and light (3). Based on observations, the visual aura can best be described as something that precedes migraine headache attacks. Migraines can also increase the chances of ischemic strokes and cardiovascular diseases such as heart attacks (4, 5).

There are many theories regarding the etiology of MwA that scientists have put forth based on their experiments in rodents and in patients experiencing migraine. The most common theory is that MwA is the result of Cortical Spreading Depression (CSD), a slowly propagating wave of neuronal and glial depolarization that moves across the cerebral cortex (6). Scientists have utilized Magnetic Resonance Imaging (MRI), Single-Photon Computed Tomography (SPECT), and Positron Emission Tomography (PET) to visualize this (7). Some possible causes of CSD include an excess of glutamate build-up in the body and changes in the blood flow in the brain. Changes in blood perfusion- the rate at which blood is flowing to an area, can also be a

consequence of CSD, along with the failure of brain homeostasis (8). The Trigeminovascular System, (TGVS) located in the Trigeminal Ganglion, also plays an important role in MwA. Activation of the TGVS can lead to the release of several neuropeptides, like substance P and CGRP.

Various medications and treatments, like CGRP inhibitors, nerve decompression surgery, and blood vessel relaxants, all aim to reduce migraine symptoms. However, these options often only offer short-term relief and do not fully address all the migrainous disturbances (9, 10). Those with chronic migraines must get some form of long-lasting treatment so that they can have a better quality of life.

2. The Trigeminovascular System (TGVS)

The trigeminovascular system (TGVS) is essentially a network of neurons that connects the blood vessels in the head to the brainstem and spinal cord. The TGVS is very crucial in regulating blood flow in the head and detecting and responding to pain and other sensations (11). Hence, the TGVS is involved in several neurological disorders, including migraines, cluster headaches, and trigeminal neuralgia.

In 1979, Moskowitz proposed the trigeminovascular hypothesis of the migraine which suggested that the trigeminal nerve, which supplies sensation to the face and head, plays a key role in migraine headaches (12). The trigeminal nerve has branches that innervate the blood vessels in the meninges, the thin membranes that surround the brain. When this nerve is activated, it often releases neuropeptides, such as substance P and CGRP. These neuropeptides can cause the dilation of blood vessels, which leads to increased inflammation and pain, which are prominent symptoms of migraine (13).

2.1. Neuropeptides

2.1.1. CGRP

CGRP is a type of protein that is widely distributed throughout the nervous system (14). Research has found that people with chronic migraines, especially women, tend to have much more CGRP in their blood. It is a key player in both physiological and pathological conditions. Around 50% of trigeminal neurons express CGRP. There are two major forms of CGRP- αCGRP and βCGRP. The CALCA gene encodes αCGRP, and the CALCB gene encodes βCGRP. These two peptides are very similar in their activities, but most of the CGRP expressed by the trigeminal neurons mentioned above are αCGRP (15).

CGRP injections or infusions can create migraine-like attacks in patients (16). During migraine attacks, salivary CGRP levels were found to be significantly increased. This supports the theory that an increase in CGRP leads to migraines (17). CGRP receptor antagonists have proven to be an effective way in reducing migrainous pain. Tests have also revealed that an increase in CGRP leads to vasodilation, the dilation of blood cells, neurogenic inflammation, and nociception, a type of pain caused by damage to tissues (18).

2.1.1.2 Substance P

Substance P is another neuropeptide that is thought to play a role in initiating migraines by inducing significant inflammation in the dura mater, the protective membrane surrounding the brain (19). The dura mater is a critical component of the meninges, the three-layered protective covering of the brain and spinal cord. When Substance P is activated, the dura mater amplifies pain signals and contributes to the perception of headaches and other migraine-related symptoms (20).

In a study published by Ramachandran et al., 2018, researchers induced inflammation in the dura mater of rats by injecting Complete Freund's Adjuvant (CFA). The study found that the CFA-induced inflammation led to the release of Substance P, which resulted in vasodilation and mast cell degranulation. Ultimately, this resulted in the release of inflammatory mediators such as histamine and leukotrienes (21). These mediators then have many effects on patients, like causing blood vessels to widen and increasing the permeability of blood vessels (22).

2.3 Cortical Spreading Depression (CSD)

Cortical Spreading Depression (CSD) is theorized to be the underlying cause of MwA. CSD is known to be a short disturbance of the cerebral cortex caused by a depolarization wave (6). This theory was created by Leao in 1944, who observed changes in blood vessel size as electrical brain activity decreased, with increased blood flow accompanying these electrical changes. In his paper from 1945, Leao along with Morrison showed a possible link between these events and MwA, especially given that the development of visual effects was slow (23).

2.3.1 Mechanisms of Cortical Spreading Depression

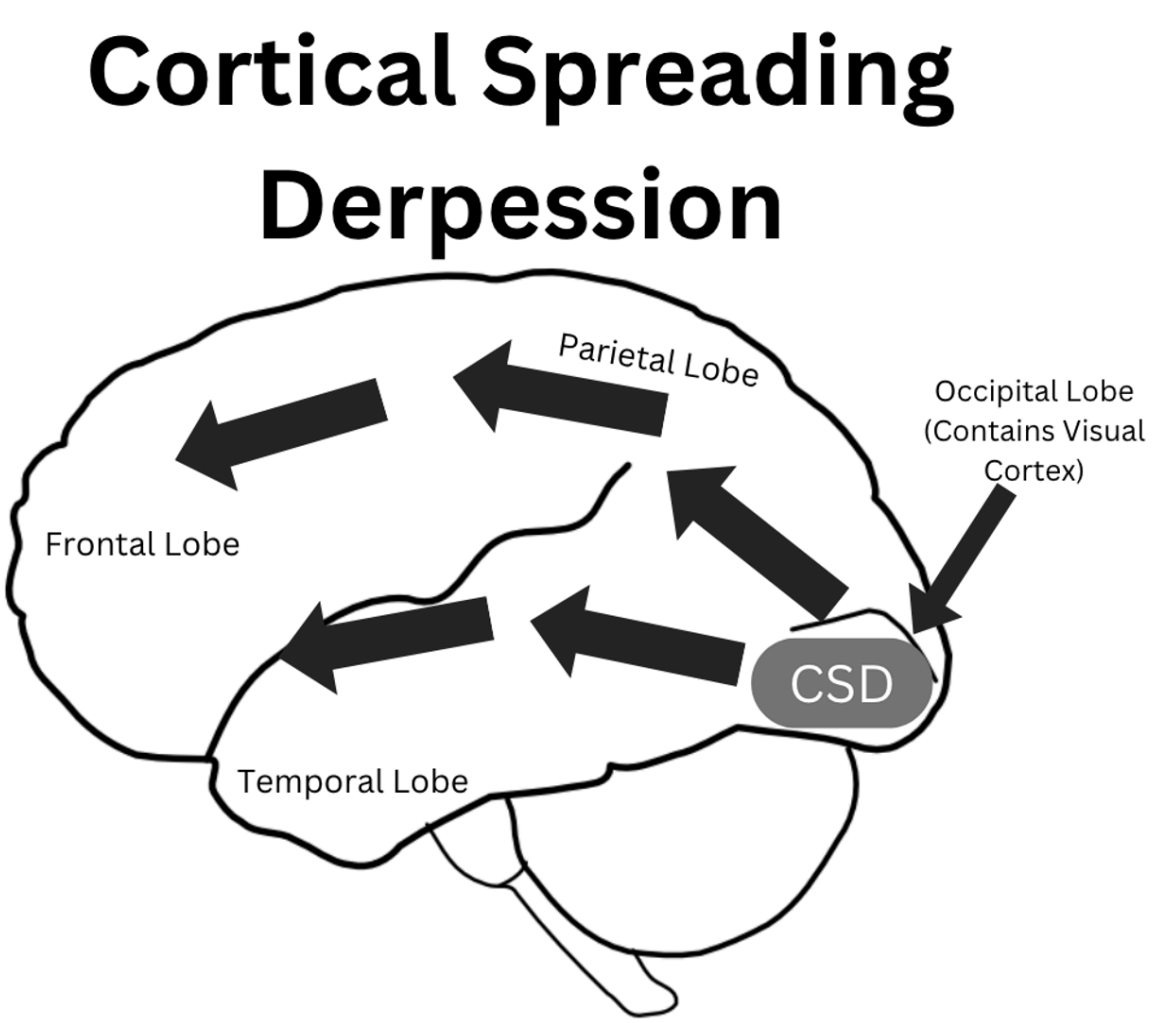

Figure 1: Schematic diagram of cortical spreading depression. Cortical spreading depression starts near the occipital lobe, where the visual cortex is, causing the development of auras. As the wave of depression spreads, there is a prolonged decrease in cerebral blood flow.

Currently, scientists believe that aural migraines are the result of the build-up of CSD. CSD is a slowly spreading wave of depolarization that represses parts of brain activity, which results in many changes between the vascular and neural systems. This activity lasts up to several minutes and spreads in all directions of the cortex at a rate of around 3-5 mm/min (6). Once this depression affects the primary sensory cortex, the common somatosensory symptoms such as numbness, prickling or tingling sensations, and burning will start to occur, along with neurovascular dysfunction (24). CSD can be measured through the use of an electroencephalogram (EEG), which measures the electrical activity of the brain. During the 30-60 seconds when the neurons of affected areas are silenced, the electrical activity is significantly reduced. This wave is also thought to directly affect the visual cortex, which is why the aural symptoms occur. After several minutes, this brain tissue will recover, with neuronal activities returning to normal. This is typically when aural symptoms are also thought to return back to normal with glial cells and neurons regaining homeostasis. Pi et al. induced CSD in the

visual cortex of mice using light inflammation and found that the somatosensory, primary sensory, olfactory, basal ganglia, and default-mode networks had been activated (25).

In addition to EEG, scientists have also used functional Magnetic Resonance Imaging (fMRI) in order to gain further insights into the effects of CSD during aural migraines. fMRI studies revealed blood oxygenation level-dependent (BOLD) signal changes during the visual aura, which demonstrated consistency with eight characteristics that are found in CSD: the initial cortical gray hyperemia, the characteristic duration, the characteristic velocity, hypoperfusion, the attenuated response to visual activation, the recovery to baseline mean level, the recovery of stimulus-driven activation, and the non-crossing of prominent sulci. (26)

2.3.3 Triggers and Effects of Cortical Spreading Depression

While the causes of CSD remain uncertain, there are some factors that scientists think might influence the likelihood of its occurrence and severity. For instance, one study conducted on rats has shown that high-fat diets could increase the susceptibility to CSD (8, 27).

Additionally, there is evidence suggesting a role for glutamate in CSD. Through studies conducted on human subjects, levels of glutamate have been confirmed to be much higher in the peripheral circulation, especially during migraine attacks. During CSD, glutamate transporters can operate in reverse, leading to the release of large amounts of glutamate in the occipital cortex. This prolonged release contributes to the extended duration of CSD and may result in longer-lasting effects of aural migraines. Alongside glutamate dysregulation, CSD also involves changes in cerebral blood flow, potassium levels, and cortical oxidation (28). Changes in the blood flow are a prominent feature of migraines. When CSD and migraines occur, the brain continues to regulate blood flow, but its responsiveness to changes in carbon dioxide becomes impaired, which leads to the changes in cerebral blood flow (CBF). CBF can also be decreased through vascular unresponsiveness or vasoconstriction (narrowing of blood vessels) after the initial depolarization-induced hyperemia (excess blood going to a part of the body) (29).

3 Treatment for Migraines

There are mainly two broad categories of medications designed to treat migraines: acute and preventive medications. The goal of acute medications is to stop a migraine as soon as it starts (30). When some warning signs of migraine occur, such as an aura, neck stiffness, mood changes, or food cravings, this type of medication is taken to relieve the pain, nausea, and other migrainous symptoms (3). On the other hand, preventive medications are types of drugs that are taken regularly to reduce the severity and frequency of migraines (31). This type of treatment is mainly used on chronic migraineurs since these migraineurs get migraines very frequently (32).

Some of the most common types of acute medications include ibuprofen, isometheptene-dichloralphenazone-acetaminophen, and CGRP antagonists like rimegepant and zavegepant (30). CGRP inhibitors have also been proven successful. When 2.5 mg of BIBN4096, a CGRP inhibitor, was given to patients intravenously, 66% of migraineurs were pain-free for around two hours. There was also a decrease in nausea and photophobia, along with an improvement in functional capacity among migraineurs (9). Frequently used preventive

medications include beta-blockers such as propranolol and metoprolol, calcium channel blockers like verapamil, and antidepressants such as amitriptyline. Beta-blockers work by blocking the effects of adrenaline, lowering the blood pressure. Calcium channel blockers, on the other hand, work by relaxing the blood vessels and reducing the amount of calcium that enters the heart and blood vessels, which can help constrict migraines (32, 33).

Aside from prescriptions and medication, there is also the option for migraine surgery, also known as nerve decompression surgery. This is a type of migraine surgery that involves removing tissues or blood vessels that are constricting nerves, thereby reducing the chances of migraines. Patients who have undergone this surgery have been shown to have a significant overall reduction in migraine intensity, frequency, and duration. Some have even been shown to have migraine elimination, showing the surgery's relative success in improving migraines (10). However, many people, afraid of side effects such as nerve injury, hair loss, and incomplete relief, don't take up this surgery (34). Moreover, many insurance companies are not willing to pay for this procedure, citing that there is too little evidence of its effectiveness. The American Headache Society has also urged patients not to pursue this surgery, since there isn't enough reliable research that shows its potential harms and long-term effects (35).

4 Conclusion

In conclusion, this review has provided an overview of the underlying mechanisms of migraines with aura. Looking forward, researchers should aim to prioritize the limitations and gaps in our understanding of migraines and their treatments especially due to the high incidence of migraine across the world. The low rates of success in many of the treatments underscore the need for a more consistent and universal cure for those who suffer migraines. Researchers should aim to develop therapies that target the fundamental causes of migraines to offer better relief to migraineurs.

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