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Review

Glutamate and Migraine

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ABSTRACT

Migraine is a highly prevalent disease, with 4% of the population suffering from it. Although it was previously defined to be a vascular disease, current findings has shown that it is really such a complex neurological disorder. While the physiopathology of this condition, which is more common in women, is still unknown, the trigeminovascular system has supplied valuable data. Thus, migraine phases' clinical effects were correlated to their physiopathology, and the function of elements other than the trigeminovascular system (e.g., the hypothalamus) in migraine was revealed. Glutamate receptors, which are abundantly positioned in the nuclei of the trigeminovascular pathway in the medulla, contribute to the physiopathology of migraine. As a result, glutamate receptor modulators may be useful in the treatment of migraine.

Keywords: Cortical spreading depression, glutamate, migraine.

EPIDEMIOLOGY

Migraines are a widespread occurrence in society, with symptoms including headache, nausea, vomiting, reduced sensory tolerance, and a condition that affects 20% of people with temporary neurological symptoms.[1] According to the data, it is the sixth disease that causes the most damage to humanity.[2] More than 303 million people worldwide are struggling with this disease. The prevalence up to adolescents are the same in both sexes. Its incidence in preschool children is between 2-5%, while it is 10% in school age children. About 20% of the patients had their first migraine attack within their first five years of life. During the reproductive period, women are recorded three times more than men.[3,4] While migraine attacks are seen several times a year in children, they are seen several times a week in adulthood.[5-7] There may also be a genetic predisposition for migraine, because 65-90% of the patients have a positive family history.[5] It is a disorder with significant social and economic consequences. According to the reports, the United Kingdom has incurred a financial burden of 6 billion pounds due to the loss of workforce and the use of health services due to migraine.[1,3]

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CLINICAL SYMPTOMS

Migraine has 4 defined phases. These are prodromal, aura, headache and postdrome phases. There aren't any requirements for linear transitions between them. There may be overlap between phases in some patients. In both stages, fatigue and a loss of concentration are common.[3]

Prodromal phase

It is the process that takes days or hours before the migraine pain occurs. Irritability, fatigue, distraction, repetitive yawning, pallor, nausea, blurred vision, neck stiffness, euphoria, appetite, constipation, and sensitivity to light, sound, and scent are just some symptoms.[8,9]

Aura phase

It is observed in 20% of migraine patients.[10] It involves reversible neurological conditions that develop slowly over a duration of 5 to 60 minutes. Bright lighting, blind spots in the vision field (scotoma), tingling, numbness in the hand and face, tremor, bilateral muscle weakness, and speech

difficulties are all symptoms that can be seen.[7] In addition to cardiovascular risk factors (smoking, alcohol, oral contraceptive use, cholesterol level, etc.), it has been observed that the risk of ischemic stroke increases in women under 45 years of age who have migraine attacks involving aura phase.[11]

Headache phase

The pain is mostly throbbing and bilateral. It may worsen with physical activity and may last from a few hours to a few days. Nausea, vomiting, nasal discharge, increased tear secretion, yawning, ptosis, increased urinary frequency, diarrhea, depression, irritability, focus deficit, temporary memory loss, difficulties recognizing vocabulary, sound and light intolerance, and skin allodynia are all symptoms of pain.[7]

Postdrome phase

It's the time between the end of a migraine attack and the beginning of a new one. Symptoms such as fatigue, concentration problems and neck stiffness occur. Symptoms are similar to prodromal phase symptoms. Therefore, it is unclear whether these symptoms continue uninterrupted from the prodromal phase or reoccur after the headache phase.[9]

MIGRAINE PHYSIOPATHOLOGY

Migraine is one of the oldest diseases in history, tracked since ancient times. It was first described by Hippocrates 2400 years ago. Although migraine has long been thought to be a vascular disorder causing meningeal vasodilation, studies conducted in the last 20 years have shown that it is a complex neurological disease involving the cortical, subcortical, and brainstem regions of the brain, resulting in autonomic, motor, sensory, and cognitive dysfunctions.[12]

Findings such as fatigue, frequent yawning, appetite and temporary mood changes seen in the prodromal phase of migraine can be observed in everyone except the patients with migraine to human nature. Whereas these effects do not cause headaches in healthy people, it is crucial to understand the physiopathology of migraine to recognize why they cause attacks in migraine patients. In recent studies, attention has been drawn to the hypothalamus as the source of prodromal phase symptoms.

Hypothalamus is in responsible for maintaining homeostasis and regulating the circadian rhythm.[13] Hypothalamic neurons are thought to cause symptoms in the prodromal phase and associated migraine headaches, as the brain with migraine is extremely sensitive to internal and external conditions (hunger, lack of sleep, fatigue, stress, exposure to perfume with heavy odor) and other homeostasis changes. Hypothalamic and brainstem neurons trigger headache in two ways. One of them is that hypothalamic neurons shift the parasympathetic and sympathetic tone in the brain membranes towards parasympathetic dominance by meningeal nociceptors, thereby causing homeostasis changes. Another view is that hypothalamic neurons facilitate the transmission of nociceptive trigeminovascular signals from the thalamus to the cortex.[7] Let's search at these two theories more deeply.

HYPOTHALAMIC NEURONS STIMULATION OF MENINX NOCICEPTORS WITH PARASYMPATHETIC TONE INCREASE

Hypothalamic neurons control the stimulation of preganglionic parasympathetic neurons in the superior salivator nucleus projected by the spinal trigeminal nucleus in the trigeminovascular system. From the meningeal terminal branches of postganglionic parasympathetic neurons originating from the ganglion sphenopalatina, the superior salivator nucleus causes the release of acetylcholine, vasoactive intestinal peptide (VIP), and nitric oxide. These mediators cause vasodilation of the intracranial vessels, the passage of plasma proteins from the circulation to the tissue in the intracranial vessels, and finally the release of local inflammatory molecules that activate nociceptors in the pia and dura mater. As a consequence, a brain with increased excitability and followed by pain sensation occur. All this results with an increase in parasympathetic tone in the cranial vessels. Among migraine symptoms, nasal congestion and increased tear secretion can also be shown as evidence of increased parasympathetic tone. The blockade of the sphenopalatine ganglion causes partial or complete relief of migraine pain.[14-17]

FACILITATION OF THALAMOCORTICAL TRANSMISSION IN HYPOTHALAMIC AND BRAINSTEM NEURONS

The trigeminovascular pathway transmits the response produced by the nociceptive stimulus

that receives from the meninges to the brain. Meningeal vessels are heavily innervated by unmyelinated nociceptive C fibers and a few myelinated Aδ fibers.[12] Peripheral axons of these pseudounipolar neurons derived from the trigeminal ganglion receive the nociceptive stimulation from the pia mater, dura mater and large cerebral arteries and transmit them to the spinal trigeminal nucleus, which is located in the 1st and 5th laminae of the posterior horn of the medulla.[7,18,19] In addition to this nucleus, sensory signals also come from the cornea, facial skin and neck muscles.[18] The spinal trigeminal nucleus carries out projections to various parts of the brain. Some of these projections are in the brainstem nuclei (periaquaductal gray matter, reticular formation, superior salivator nucleus, parabrachial nucleus, cuneiform nucleus, tractus solitarius superior nucleus) some are in the hypothalamus nuclei (anterior, lateral, perifornical, dorsomedial, suprachiasmatic, supraoptic nuclei) and some others are in the basal ganglion nuclei. (caudate, putamen, globus pallidus, substantia innominata).[7,20] These projections are responsible for the emergence of symptoms such as headache, nausea, vomiting, yawning, anorexia, increased tear secretion, fatigue, anxiety, and irritation.[7,21] The ventral posteromedial, lateral, and parafasicular nuclei of the thalamus also receive stimulation from the spinal trigeminal nucleus. In this section of the trigeminovascular pathway, hypothalamic and brainstem neurons lower the threshold of action potentials of neurons to accelerate the data transmission from the thalamus to the cortex. This final step is critical in the progression of a headache.[22] While these nuclei of the thalamus receive stimulation from hypothalamic neurons via dopamine, histamine, orexin and melanin concentrating hormone (MCH), brainstem neurons receive stimulation via noradrenaline and serotonin.[7,22] Among these mediator molecules, those with excitatory character (dopamine, high concentration serotonin, noradrenaline, histamine, orexin) shift the activity of thalamus neurons from explosive mode to tonic mode, while those with inhibitory character (MCH, low concentration serotonin) shift from tonic mode to explosive mode. Control of the stimulus transmission of trigeminovascular thalamic neurons to the cortex by opposing factors increases the plasticity of the cortex in response to physiological and emotional changes in homeostasis (nutrition, sleep, stress, anxiety).[7]

Increased cortex excitability at the end of the prodromal phase is important in explaining the physiopathology of the aura phase. Although the pathology of aura has not been completely elucidated, it is hypothesized that cortical spreading depression (CSD) waves cause aura phase.[23]

CORTICAL SPREADING DEPRESSION WAVES AND AURA

Cortical spreading depression is intense depolarization waves that spread through the gray matter of the brain, causing to a decrease in cortical activity. These waves move in the cortex about 2-5 mm per minute and cause changes in synaptic activity, extracellular ion concentration, blood flow and metabolism. Synaptic activity decreases for 5-15 minutes and then returns to normal. When this process is examined with EEG, a short hyperexcitability period is observed, followed by a 30-60 second marked decrease in activity, and then a complete absence of neuronal function, which can require up to 1 minute.[24]

Cortical spreading depression waves cause an increase in extracellular potassium concentration; a decrease in sodium, chlorine and calcium concentrations. Afterwards, amino acids and various neurotransmitters are released. These mediator molecules also continue to produce waves of CSD depolarization. Depolarization waves cause vasodilation and an increase in local cerebral blood flow, and this increase is called diffuse hyperemia. This blood flow ends in 1-2 minutes, resulting in a condition of hypoperfusion that lasts 1-2 hours, known as diffuse oligemia. These changes in cerebral blood flow and oxygenation cause disintegration of cerebrovascular homeostasis. The release of CGRP (calcitonin gene-related peptide) from ipsilateral trigeminal nerve fibers increases as a result of hyperemia. Sensory trigeminal fibers and parasympathetic fibers are also stimulated in this process.[23] In an experiment on rats to explain how CSD causes visual disturbances in the aura phase (seeing bright lights, scotoma), CSD is triggered by stimulation of the visual cortex by electrical stimulus, potassium chloride (KCl) or pin prick method. The activity of meningeal nociceptors is determined before and after CSD. CSD induction resulted in 2-fold stronger stimulation of meningeal nociceptors and sustained activity in 31 of 64 rats. The aura phase of migraine is thought to be caused by CSD waves stimulating the trigeminovascular pathway, according to the research results.[25]

ACTIVATION OF NOCICEPTORS AND HEADACHE PHASE

Cortical spreading depression causes post-aura headache by activating peripheral and central trigeminovascular neurons. Although the vascular, cellular, and molecular bases of CSD-mediated meningeal nociceptor activation are not clearly understood, according to the studies, CSD-dependent peripheral calcitonin gene-related peptide release enhences repetitive vasoconstriction and vasodilation of the arteries feeding the pia mater, removes dural plasma proteins out of the vein, causing neurogenic inflammation, platelet aggregation and mast cell degranulation. As a result of all these, histamine, bradykinin, serotonin, prostaglandin E2 and hydrogen ion pass to the meninges. Changes in the molecular order of these regions where meningeal nociceptors are located causes activation of these nociceptors and headache.[25]

SENSITIZATION OF NOCICEPTORS

After a certain period of time of the meningeal nociceptors' activation, the threshold values for response to stimulation decrease and the severity of the response increases. They also start responding to alerts which they initially did not respond or respond very little. This is called sensitization. When the 1st and 5th laminae of the spinal trigeminal nucleus and central trigeminovascular neurons in the posterior, ventroposteromedial nuclei of the thalamus are sensitized, the area where they receive sensory stimuli expands. They perceive and transmit the harmless mechanical and thermal stimuli from extracephalic and cephalic skin areas as harmful. Peripheral sensitization develops in 10 minutes. It is felt as trembling pain or temporary aggravated pain when lying face down and coughing. Sensitization of central trigeminovascular neurons in the spinal trigeminal nucleus develops within 30-60 minutes and reaches its full effect at the 2nd hour. Cephalic allodynia findings occur. These are heart and muscle sensitivity, high sensitivity to touching the head and neck. Some patients cannot wear glasses, earrings, and hats due to allodynia, and they feel pain.

Thalamic sensitization occurs within 2-4 hours. Extracephalic allodynia findings are seen. Sensitivity to touch, massage, hugs, and the inability to wear tight clothes or jewelry are among them. The administration of triptans prior to central sensitization and allodynia is believed to disrupt signaling between peripheral and central trigeminovascular neurons, enabling meningeal nociceptors to return to the initial phase of headache. Likewise, dihydroergotamine (DHE), which occurs on central trigeminovascular neurons, is known to be effective in reversing central sensitization. DHE is used in patients who do not respond to tryptane.[24,26,27]

Glutamate is one of the mediators that play a role in the initiation and spread of CSD, and also in migraine physiopathology in general.[21]

GLUTAMATE

Glutamate is an important chemical intermediate in the nervous system for communication between cells. Brain tissue contains high concentrations of glutamate (5-15 mmol/kg). Most of this glutamate is found in neurons. The glutamate concentration in the cytoplasm of glutamatergic neurons is approximately 5-10mM. This value is several times higher than the glutamate value of other tissue types. Neuronal cytoplasmic glutamate concentration is 2-3 times higher at axon tips than soma and dendrites. As a result, glutamate is synthesized and used locally at the axon ends, and glutamate transport within the cell is limited. The presence of glutaminase enzymes involved in glutamate synthesis explains why glutamate is found more at the axon ends. Glutamate is encapsulated by vesicular glutamate transporters (VGluts) at the neuron's terminal ends, where its concentration can reach 100mM or higher. Synaptic vesicles merge with the plasma membrane in response to voltage-gated calcium channels opening as a result of plasma membrane voltage changes, increasing intracellular calcium and release glutamate molecules into the synaptic space. Glutamate, which released into the synaptic space, binds to glutamate receptor proteins found in the postsynaptic cell membrane and triggers the postsynaptic cell. There are two types of glutamate receptors, metabotrophic (mGluRs) and ionotrophic (iGluRs). Metabotrophic receptors are connected to intracellular G-proteins.

G-protein dependent cellular signal cascades are activated when glutamate binds to mGluRs.[28] Mammalian mGluRs have type I, type II and type III forms. Type I effects through phospholipase C, type II and type III with an increase in cAmp.On the other hand, Ionotrophic glutamate receptors are multimeric glutamate-gated ion channels.

As glutamate binds to the extracellular part of iGluR, the entire protein transforms shape, allowing ions to move through the plasma membrane. Postsynaptic membrane depolarization occurs as a result of this situation. There are three types of iGluRs in mammals. AMPA (α-amino-3-hidroksil-5-metil-4-isoksazol-propionat) receptors, NMDA (N-Metil-d-aspartik asit) receptors, and kainate receptors. AMPA receptors provide fast information flow in the nervous system. The NMDA receptors remain open for a long time, allowing a considerable amount of calcium to enter. Calcium-dependent signaling cascades are activated as a result, and gene expression increases. These changes strengthen synaptic connections, increasing memory and learning functions. Kainate receptors can be located in both the postsynaptic and presynaptic membranes, and they assist with glutamate secretion autoregulation. Though glutamate in the synaptic gap stops working, excitatory amino acid transporters (EAAT) move glutamate into the extracellular fluid.[29] Gamma aminobutyric acid (GABA) and glutamate are being used to maintain the balance between excitation and inhibition in the central nervous system. GABA is the major inhibitory neurotransmitter, while glutamate is the major excitatory neurotransmitter. The association between GABA and glutamate is important for regulating physiological functions and managing signals to and from the brain. Glutamatergic dysfunction effects diseases such as schizophrenia, drug addiction, depression and autism.[30]

THE ROLE OF GLUTAMATE IN MIGRAINE PHYSIOPATHOLOGY

Migraine occurs as a result of increased excitability of many regions in the central nervous system. Glutamate has an important role in the physiopathology of migraine, as it is the most common excitatory mediator molecule in the central nervous system.[31] Glutamate increases in blood, cerebrospinal fluid (CSF), saliva, occipital cortex and thalamus during a migraine attack and between attacks.[31,32] Monosodium glutamate administration caused headache in individuals was observed in a study. Monosodium glutamate administration caused headache in individuals was observed in a study.[33] In another study, GABA and glutamate concentrations in the occipital lobe and thalamus of a control group and patients with migraine attacks with aura were measured by proton magnetic resonance spectroscopy, and it was observed that the glutamate concentration in the occipital lobe and thalamus of migraine patients increased, but not in the control group. However, no relationship was found between glutamate concentration and pain intensity. GABA levels in the two groups were found to be equivalent.[34]

Kinurine, a metabolite of tryptophan, effects on synaptic glutamate release by iGluR and mGluR receptors. The increase in quinurine blocks trigeminal nociceptive neurons, regulates the activity of the spinal trigeminal nucleus in the brain stem and inhibits CSD. This anti-glutamatergic effect of quinurine has therapeutic value in the treatment of migraine.[35] Genetic studies have identified that there may be multiple polymorphisms in genes associated with migraine that modify glutamate signaling. Polymorphism was detected in LRP1, IGSF89, CARF, REST, JPH3, PHACTR1 and PRDM16 genes, which contains proteins that regulate glutamate receptor quantity and glutamate release.[30] There are also studies showing that the polymorphism seen in the gene encoding EAAT2 protein, which acts as a modulator in glutamatergic signal transmission, turns episodic migraine into chronic migraine.[24] Mutations also affect glutamate signaling in familial hemiplegic migraine disease (FHM). It is thought that mutations in genes encoding P/Q type calcium channels in FHM1 and voltage-gated sodium channels in FHM3 increase neuronal glutamate release.

Similarly, it has been observed that mutations in casein kinase 1, which is thought to be associated with migraine and delayed sleep phase syndrome, increase glutamate signaling by increasing the phosphorylation of glutamate receptors.[31]

GLUTAMATE AND CENTRAL SENSITIZATION

Glutamate ionotrophic and metabotrophic receptors are numerous in the spinal trigeminal nucleus, lamina 1 and 2 in the posterior horn of the medulla spinalis. This nucleus receives nociceptive afferents. Therefore, glutamate has a role in primary nociceptive signaling.[36]

The neuronal activity in this region has been facilitated with the application of glutamate to the caudal part of the spinal trigeminal nucleus in a microiontophoretic fashion. Stimulation of the meningeal artery and superior sagittal sinus, as well as the cornea and temporomandibular joint,

resulted in facilitation in the same zone. Thus, the function of glutamate in the transmission of nociceptive trigeminal signals to central parts was identified.[30]

The origin of central sensitization is synaptic plasticity. In this regard, the metabotrophic glutamate receptor-5 (mGluR5) is crucial. In an experiment in rats with chronic migraine showed the relationship between mGluR5 expression and allodynia, which is an indicator of sensitization; qRT-PCR and Western-blot to detect mGluR5 mRNA, mechanical and thermal threshold values to evaluate allodynia, CREB (cyclic amp-response element binding protein) amount to evaluate central sensitization, PSD (synaptic density protein) for synaptic plasticity measurement. 95), synaptophysin, synaptic structures and dendritic branches were observed. At the end of the experiment, it was observed that mGluR5 expression increased in rats with chronic migraine. Allodynia improves when mGluR5 expression is inhibited by 2-methyl-6-(phenylethynyl) pyridine, while CGRP, pCREB-S133, PSD, synaptophysin, and synaptic transmission are decreased. As a consequence, we can argue that glutamate leads to central sensitization in migraine patients by regulating synaptic plasticity.[32]

GLUTAMATE AND CSD

CSD is associated with glutamate release into the extracellular space. Glutamate release in CSD is a regenerative process in which glutamate binds to presynaptic NMDA receptors, causing more glutamate to be released.[31] Glutamate release and NMDA receptor activation help to maintain depolarization. The increase in glutamate leads to the CSD mechanism by increasing nitric oxide and arachidonic acid metabolites, which causes vasodilation.[23] Some NMDA receptor antagonists (MK801, APH, ifenprodil, memantine, ketamine) are known to inhibit the CSD spreading. Topiramate, which is a kainate receptor antagonist, also inhibits CSD. CSD is activated when the NMDA receptor blockage is removed by decreasing magnesium levels in the extracellular space. Unlike NMDA receptors, AMPA (α-amino-3-hydroxy-5 methyl-4-isoxazolepropionic acid receptor) activation suppresses CSD. CSD is also inhibited by systemic administration of kinurine, an endogenous glutamate receptor modulator.[30]

In a rat study, TFB-TBOA (2S, 3S) -3- [3- [4 (trifluoromethyl) benzoylamino] benzyloxy] aspartate blocked glutamate absorption of astrocytes, consisting in a fourfold increase in the period of CSD in the visual cortex. When the chemical effects of CSD are examined locally, we see the interaction of neurons, astrocytes and vascular system. When a neuron exposed to CSD is depolarized, significant amounts of glutamate and potassium are released into the extracellular space, while calcium, sodium, chlorine, and pH decrease. The decrease in glutamate intake also unable the neurons to recover the effects of CSD. Consequently, CSD is associated with the high potassium and glutamate levels in the extracellular space, as well as NMDA receptor activation and general ion imbalance.[37]

PHYSIOPATHOLOGY OF GLUTAMATE-RELATED MIGRAINE IN CHILDREN

In studies on migraine disease, which is believed to occur as a result of imbalances in cortical stimulation, GABA and glutamate levels in various brain areas were verified by magnetic resonance spectroscopy (MRS) and high glutamate levels were associated with migraine. These trials, which have been observed in adults, have yet to be confirmed in children with migraine. Low glutamate levels were observed in the visual cortex of children aged 7-13 years with migraine attacks with aura, compared to adults, in MRS tests. Furthermore, high GABA levels in these children were found to be significantly associated with the severity of migraine, despite the fact that there was no difference in GABA levels in adults with migraine compared to average people. Low GABA levels in the sensorimotor cortex indicate the beginning of the next migraine attack. When all of these factors are considered, we can conclude that the role of glutamate on the pathophysiology of migraine in adults and children is uncommon.[38]

GLUTAMATE RECEPTOR MODULATORS IN MIGRAINE TREATMENT

Magnesium causes blockade of NMDA receptors, which are involved in nociceptive transmission and CSD. During migraine attacks, the magnesium levels in the patients' CSF, serum, and saliva also increase. Oral magnesium is used in migraine prevention treatments. Magnesium has inhibitory effects on voltage-gated calcium channels and connex channels in addition to its effects on NMDA receptors in the nervous system. It is thought that the effects of magnesium on these ion channels may also be related to migraine. Topiramate has risen

to the fore with its anti-migraine effect in clinical trials. Animal experiments showed to inhibit CSD and nitroglycerin-induced hyperalgesia. One of the inhibition mechanisms is mediated by iGluR kainate receptors, while others are included inhibition of voltage-gated sodium and calcium channels, activation of GABA receptors, and carbonic anhydrase inhibition. Memantine is an NMDA receptor blocker that is also used in the treatment of Alzheimer's. It also blocks 5HT3 (5-hydroxytryptamine 3) and nicotinic acetylcholine receptors. It has been observed to inhibit CSD in animal experiments, but its use in anti-migraine treatment has not yet been approved. Nevertheless, it is thought that NMDA receptor blockade may inhibit cortex hyperexcitability without affecting the normal functions of the brain. Ketamine effects on extracellular glutamate, dopamine and opioid receptors. It has been reported to provide CSD inhibition. Although it is shown a temporary decrease in the headache severity with ketamine infusion, there is no significant statistical data on this subject.[31]

DISCUSSION AND CONCLUSION

As a result of the studies aimed to explain the physiopathology of migraine; Although the aura phase starting with CSD, activation and sensitization of nociceptors are clearly demonstrated and the function of glutamate in these pathways is clarified through its receptors, it is still uncertain what triggers migraine attacks. Moreover, studies conducted in adults to determine the function of glutamate and GABA in the physiopathology of migraine do not provide the same results in children. The detection of polymorphisms in some glutamate signaling genes also suggests that migraine may be hereditary. In view of this analysis, we can agree that what we know about migraine is remarkable, and that the concerns I discussed above that have yet to be clearly explained require additional studies.

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