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Indirect Regulation of Na^+, K^+-ATPase by Neurotransmitters: Participation of Neurotransmitters in the Sodium Theory for Migraine

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ABSTRACT

The European Migraine and Headache Alliance (https://www.emhalliance.org) estimates that migraine is one of the top ten leading causes of disability and affects 12-15% of the population. Migraine pathology is neurovascular. The neuroactivational aspect is strongly influenced by sodium ion concentration in the cerebrospinal fluid. Cerebrospinal fluid sodium levels' regulation primarily depends on the sodium pump Na^+, K^+-ATPase in the choroid plexus. The sodium theory for migraine suggests that the dysregulation of Na^+, K^+-ATPase in migraineurs results in elevated cerebrospinal fluid sodium, which is known to increase central sensitization, thereby predisposing these individuals to headaches.

The involvement of neurotransmitters in migraine pathology is well documented. Indirect regulation of Na^+, K^+-ATPase by neurotransmitters is well documented for many tissues including the brain. The focus of this review is to identify which neurotransmitters are involved in both migraine and Na^+, K^+-ATPase regulation in a manner consistent with the sodium theory for migraine. We believe that the identification of such neurotransmitters may lead to the development of new pharmaceuticals to address migraines.

1. Introduction

The European Migraine and Headache Alliance (https://www.emhalliance.org) estimates that migraine is one of the top ten leading causes of disability and affects 12-15% of the population. It is generally understood that migraine pathology is a neurovascular disorder. Vasodilation, vasoconstriction, and neuro-activation all play roles. However, more recent research has changed the emphasis from a primarily vascular cause[1,2] to one where the vascular component results from a neurological condition involving trigeminal nociceptive activation.[3-6] Further, central sensitization and increased responsiveness of nociceptors in the central nervous system also play a role in migraine pathology.[7,8] Here, an increasing intensity of peripheral sensitization leads to central sensitization and an amplification of pain.

Treatment of migraine generally involves either treating attacks once they have begun or prophylactic prevention, including lifestyle changes.[9,10] For many years, acute migraine has been treated with the triptan family of pharmaceuticals, alone or in combination with nonsteroidal anti-inflammatory drugs. However, triptans are not effective in all patients and new families of pharmaceuticals are currently being developed.[11] Further, there are numerous prophylactic pharmaceutical treatments in common use, but they must be individualized to the patient. Lifestyle modifications such as avoiding stress and fasting, as well as adequate aerobic exercise and sleep, effectively reduce migraine frequency. Avoiding dietary triggers is also an effective strategy to reduce frequency.[12] Further complicating treatment is that many factors have also been recognized as migraine triggers, including changes in barometric pressure, temperature, hydration, sleep disturbance, missing meals, stress, and hormonal fluctuations.[13-15]

A potential avenue for migraine treatment involves reducing the impact of triggering factors to reduce both the frequency and severity. One way to do this involves reducing the impact of central sensitization on migraines. It is well established that increased sodium ion concentration in the cerebrospinal fluid (CSF) serves to enhance central sensitization and thus predispose migraineurs to headaches.[16] Sodium ion concentration in the CSF is known to be regulated primarily by the Na^+, K^+-ATPase (NKA) pump located in the choroid plexus.[17,18] The sodium theory for migraine postulates that dysregulation of NKA in migraineurs predisposes them to headaches and exacerbates the pain associated with the headache.[19-22] We currently believe that addressing this dysregulation would provide a more generalized treatment for both prophylaxis and the reduction of intensity of acute migraine attacks. To this end, using pharmaceuticals that intervene in regulating choroid plexus NKA in a manner that reduces sodium output to the CSF should reduce central sensitization and migraine frequency and severity.

There are many known endogenous NKA regulators including cardiotonic steroids, endocrine hormones, neurotransmitters, endocannabinoids, and members of the eicosanoid families. Many of these regulators are also known to be involved in migraine pathology by enhancing or mitigating the frequency and severity of headaches. The focus of this review is to determine which neurotransmitters are involved in both migraine pathology and NKA regulation in a manner consistent with the sodium theory for migraine. We believe that the identification of such neurotransmitters may lead to the development of new pharmaceuticals to address migraines.

2. Neurotransmitter-based regulation and participation in migraine pathology

Over 100 neurotransmitters are currently known, of which a handful are associated with migraines in some fashion. Of these, four are involved in regulating NKA in some manner. Although these neurotransmitters have links to migraine pathology other than through NKA,[23] the following discussion intends to show whether NKA regulation by these neurotransmitters may contribute to migraine pathology.

As noted above, NKA is directly regulated by releasing cardiotonic steroid compounds such as

ouabain, which are transported into the cerebrospinal fluid (CSF) and act as noncompetitive NKA inhibitors. The overall concentrations of these inhibitors in the CSF regulate the rate at which sodium is pumped out of the CP into the CSF.[23-25] Indirect regulation of NKA, addressed here, is known to occur through signaling that activates kinases and phosphatases that modify the posttranslational phosphorylation state of NKA, resulting in changes in activity or expression.[23,26-28]

2.1 SEROTONIN

The publication of results supporting the involvement of serotonin in migraine pathology spans many decades.[29,30] Clinical studies have shown that plasma serotonin levels in migraineurs between attacks are lower than in controls and patients with tension headaches. At the same time, the main metabolic product, 5-hydroxyindolacetic acid, is higher than controls.[31,32] During a migraine attack, however, migraineur serotonin levels are higher, and 5-hydroxyindolacetic acid levels are lower than in controls and tension headache patients. In addition, the main platelet serotonin degradation enzymes are also lower, suggesting a change in the regulation of serotonin degradation is involved in the migraine trigger. Corresponding results for these metabolites in CSF of migraineurs and controls have also been found.[33] Such results suggest that low serotonin levels predispose migraineurs to headaches, and a rapid increase in serotonin serves as a trigger or a recovery response for headaches. These results suggest that maintaining a higher level of serotonin would be helpful for migraine prophylaxis. In contrast, the administration of 5-hydroxytryptophan, a serotonin precursor, is only slightly more effective than placebo in terms of preventing migraines or reducing their severity, and the difference is not statistically significant.[34] Further, selective serotonin reuptake inhibitors are not helpful for migraine prophylaxis.[35,36] However, triptans, serotonin receptor agonists for serotonin 5-HT1B and 5-HT1D receptors,[37-39] are very effective.[40] These conflicting results put into question how serotonin is involved in migraine. However, the data suggests that low serotonin may predispose migraineurs to headaches, and the action of specific serotonin receptors may also be key to migraine pathology.

Serotonin receptors are expressed throughout the central nervous system, where classes 5-HT1, 5-HT2, and 5-HT3 are involved in migraine.[41] For example, the 5-HT3, 5-HT1A, and 5-HT1F isoforms are involved in reducing nociception,[42,44] whereas 5-HT1B and 5-HT2A are known to cause vasoconstriction,[45] each known to reduce migraine symptoms. Notably, serotonin can also cause vasodilation through the 5-HT1B receptors expressed on endothelial cells by promoting the release of nitric oxide.[45] The fact that triptan analogs of serotonin are effective in reducing migraine pain for many migraineurs suggests that the vasodilatory effect of serotonin on 5-HT1B receptors is not involved in migraine pathology.[40,46] Of interest here is that the 5-HT2C receptor is highly expressed in the CP and is by far the primary serotonin receptor in the CP by orders of magnitude.[47] Data connecting the 5-HT2C receptors to sodium regulation in the CP remains to be discovered.

Data for regulating NKA by serotonin is less extensive than that for the involvement of serotonin in migraines. The activation of serotonin receptors results in the activation of protein kinase C in isolated rat CP, which in turn phosphorylates NKA, reducing NKA activity.[48] In contrast, serotonin was found to activate NKA in glial fractions of rat brains but not in other fractions.[49,50] Others have reported similar results.[51] Further, transfection of the rat wild-type α-subunit of NKA and the serine to alanine mutants S11A and S18A into cultured opossum kidney cells produced active NKA.[52] However, upon stimulation with serotonin, only the wild type exhibits increased NKA activity, suggesting phosphorylation of both serines is required for serotonin activation of NKA. If the data obtained for rat kidney and glial fractions represents what occurs in the human CP, the rise in serotonin levels observed for migraineurs during a migraine will activate NKA. The activation of NKA would increase CSF sodium, which is consistent with the sodium theory for migraines. If

the data obtained from the rat CP translates to the human CP, then the clinical data suggests that the reduced serotonin levels found in interictal migraineurs serve to increase the activity of NKA and thus potentially predispose them to migraine headaches. The substantial increase in serotonin levels during the attack could then be a protective response, serving to help reduce the severity of headaches. Although the latter is a considerably more convoluted explanation than the former, the full resolution of this conflict awaits further study.

2.2 DOPAMINE

Research into the involvement of dopamine in migraine pathology has been ongoing for over 46 years. Many publications note the root as the seminal paper by Sicuteri in 1977,[53] where the link between dopamine and symptoms involved in the prodrome (e.g., nausea and vomiting) and the ictal state is discussed. Early work is sometimes supportive and sometimes unconvincing.[54-58] Later work, particularly the successful use of dopamine D receptor antagonists in treating migraine,[59,60] and the use of dopamine D receptor agonists inducing headache,[61,62] confirms the involvement of dopamine in migraine pathology. The mechanism of action remains unclear but is clearly complex. What is known is that the D2 receptor is the primary dopamine receptor involved, and its activation can initiate migraine or exacerbate preexisting migraine.[55,58,63] In support of this, it has also been found that both plasma dopamine in chronic migraineurs and platelet dopamine levels in migraineurs without aura are significantly elevated compared to controls.[64,65] Further, stimulation with the dopamine agonist apomorphine enhances c-Fos expression, Calcitonin gene-related peptide release, and mast cell degranulation in brain regions central to migraine pain.[63] All three events are associated with the onset of migraine.

The action of dopamine on NKA is not well studied. It is known that mRNA for all five (D1-D5) human dopamine receptors are present in the CP.[47] All but the D3 isoform is present as protein in rat choroid plexus.[66] In either case, both D1 class (D1 and D5; $G_{\alpha s}$ signaling) and D2 class (D2, D3, and D4; $G_{\alpha i/o}$ signaling) receptors are represented in the rat and human choroid plexus. Only one study has reported regulation of NKA in the CP. In isolated guinea pig CP, high doses of dopamine reduce the ouabain-sensitive NKA activity.[67] Similar results are found in rat brains. Dopamine and its fencamfamine agonist analog inhibit NKA activity in rat striatum indirectly via stimulation of D1 or D2 class receptors.[68,69] Further analysis reveals that the inhibition of NKA can be blocked by selective inhibition of cAMP-dependent protein kinase A but not through the inhibition of cGMP-dependent protein kinase G, indicating that inhibition follows a protein kinase A pathway.[68] These results would explain the action of D1 class receptors as they signal through a $G_{\alpha s}$ pathway that enhances adenylate cyclase activity and hence enhances cAMP-dependent protein kinase A activity. Since D2 class receptors signal through a $G_{\alpha io}$ pathway, which serves to inactivate adenylate cyclase, the effect of D2 activation on the inhibition of NKA must proceed through another route. In another study, dopamine was also shown to activate protein kinase A through the D1 receptor in rat neostriatum, resulting in NKA inhibition. Further, it characterized the effect by showing that the α2- and α3-isoforms are inhibited more than the α1-isoform, the most prevalent isoform in the human choroid plexus.[70] Further, they showed that an alternative protein kinase C pathway ($G_{\alpha q}$ signaling) was not involved and that phosphorylation leading to inhibition of NKA by protein kinase A did not occur, indicating some other mechanism is involved in the reduction of NKA activity.

In contrast to these studies, a more recent investigation showed that D1 and D2 exist in a complex with the α-subunit of NKA in HEK293T cells and brain cells.[71] In the absence of dopamine, the presence of either D1 or D2 receptors inhibited NKA through protein-protein interactions. In addition, the binding efficiency of dopamine to either receptor in the NKA complex is diminished, resulting in a reduction in the dopamine receptor signaling. Inhibition of NKA with ouabain reverses NKA's

inhibition of the dopamine receptors. In the presence of dopamine, however, the D2-induced reduction of NKA activity was unaffected, and the stimulation of D1 receptors significantly increased NKA function. The authors could not discern whether the increase in NKA activity was due to enhancement of cAMP production or to changes in the protein-protein interactions between D1 and NKA. The one study that found only enhancement of NKA activity showed that in rat cerebrocortex synaptosomes, dopamine and dopamine receptor agonists stimulated ATPase activity.[72] However, no distinction was made between ouabain-sensitive and ouabain-insensitive ATPase activity. Thus, the results may represent the action of an ouabain-insensitive ATPase and thus are irrelevant to this discussion.

Of all the data presented above, clinically, dopamine and its analogs serve to initiate headaches, and their antagonists are effective in migraine mitigation. In terms of NKA regulation, dopamine, and its analogs inhibit NKA, thus reducing Na^+ efflux into the CSF, which should mitigate migraines and thus is in opposition to the clinical observations regarding the sodium theory for migraine. For this reason, it appears that dopamine regulation of NKA is unlikely to contribute to the pain phase of migraine. However, elevated dopamine levels would necessarily elevate K^+ levels in the CSF by inhibiting NKA, which would, in turn, facilitate cortical spreading depression, resulting in aura,[73] a phenomenon long associated with prodrome for some migraine sufferers.

2.3 NOREPINEPHRINE (NORADRENALINE)

Several independent clinical studies have shown that plasma norepinephrine levels in interictal migraineurs are 41% to 91% lower than controls.[74] This suggests that dysregulation of norepinephrine production of distribution, resulting in lower plasma levels, predisposes migraineurs to headaches. In support of this, several studies indicate that the use of serotonin and norepinephrine reuptake inhibitors reduces the number of headaches in migraineurs,[36,75] suggesting that maintenance of higher levels of norepinephrine is required to prevent migraine attacks. However, other reports question the efficacy of norepinephrine reuptake inhibitors in migraine prevention.[76] In contrast, several clinical studies implicating norepinephrine in migraine pathophysiology involve beta-adrenergic receptor blocking agents (beta blockers)[77] and alpha-adrenergic receptor blocking agents (alpha-blockers)[78] for migraine prophylaxis. Both α-receptors and β-receptors are expressed in the choroid plexus as well as other areas of the brain. These results suggest that norepinephrine signaling initiates rather than prevents migraine at these receptors. A potential explanation for the difference in these observations is the fact that migraineurs are known to have a chronic adrenergic deficiency that is compensated for by receptor hypersensitivity.[74,79,80] Whether the reduced norepinephrine causes a change in receptor sensitivity or whether both are congenital disorders associated with a predisposition to migraine is unknown. Thus, although norepinephrine levels are low, only a minor increase in norepinephrine levels at the onset of migraine could cause a substantial signal at these sensitive receptors that initiate further progression into the headache state.

A significant amount of literature indicates that NKA is activated indirectly through adrenergic receptors, suggesting that the clinical observations indicate that norepinephrine-induced migraines could act through an increase in NKA activity.[75-85] The data falls into two categories: 1) NKA activity that was directly measured, and 2) CSF production was measured. The latter indicates NKA activity, as CSF production is controlled primarily by the activity of NKA in the choroid plexus.[86-88] In early work utilizing homogenates from fresh rat brains, norepinephrine appeared to serve as a trigger to enhance the exchange of sodium and potassium ions across the synaptic membrane,[89] suggesting an increase in NKA activity. Later work with rat brain homogenates in the presence and absence of Na^+ and K^+ showed that norepinephrine enhanced the Na^+, K^+-dependent ATPase activity and that ouabain reversed this effect,[90] clarifying that norepinephrine acts in some fashion on the activity of ouabain-sensitive NKA.

Further, the effect of norepinephrine on both ouabain-sensitive and ouabain-insensitive ATPase activity in rat brain homogenates confirms that norepinephrine enhances ATPase activity and that 42% of the activity is ouabain-sensitive.[91] Utilizing yohimbine to stimulate the release of norepinephrine in rat brain,[92] Swann utilized both α_1-receptor and β-receptor antagonists to show that norepinephrine works through both receptors to enhance ATPase activity,[93] and does so by increasing the expression of NKA as measured by the increase in the number of ouabain binding sites.[94] Similarly, perfusion of the α-androgenic agonist phenylephrine increased CSF production by 97% in cats and was blocked by infusion of the α-androgenic antagonist phentolamine,[95] indicating that NKA is activated following activation of the receptor. The fact that infusion of forskolin into rats also increases ouabain binding through activation of the cAMP pathway supports the involvement of the β-receptor,[96] as the signaling is known to proceed through a cAMP pathway, which also activates cAMP-dependent protein kinase A. Protein kinase A is known to enhance NKA activity through phosphorylating Ser-955 of the a-subunit of NKA, and it is known to promote cell surface localization of the homologous hydrogen potassium ATPase.[97] Support for the α1-subunit signaling is found in the observation that protein kinase C, a kinase activated by α1-signaling via an inositol trisphosphate pathway, has also been shown to enhance the activity of the homologous hydrogen potassium ATPase through phosphorylation of the α-subunit increasing maximal pumping velocity.[84,98] It should also be noted that phosphorylation of the γ-subunit by either kinase can also enhance activity.[84] It is also noteworthy that signaling through α1-adrenergic receptors can also signal through a cAMP pathway that could produce the same results observed for β-receptor activation.

Not all reports indicate that norepinephrine always enhances NKA activity. For example, intraventricular and intravenous norepinephrine infusion reduces CSF production in rabbits.[100] In contrast, CSF production in mice is enhanced rather than reduced following administration of a norepinephrine antagonist cocktail.[101] An explanation for the differences between these studies and others remains to be found.

2.4 GLUTAMATE

Glutamate has been implicated in migraine pathology for over 30 years.[102,103] However, the results are somewhat inconsistent, except that migraineurs typically exhibit different levels of glutamate than controls. For example, three studies reveal that plasma glutamate levels are higher in interictal migraineurs than controls,[104-108] and two reveal the opposite.[109-110] One pediatric study is consistent with the latter.[111] Two studies looking at platelet levels of glutamate are consistent in that glutamate is elevated in migraineurs compared to controls.[112,113] An additional study supports these findings, but only in migraineurs with aura, whereas platelet glutamate levels in migraineurs without aura were lower than controls.[104] Three groups report that glutamate levels in the CSF are higher in migraineurs than in controls.[107,108,110] There is one report indicating that salivary glutamate levels for female chronic migraineurs are higher than either female episodic migraineurs or controls, with episodic migraineur levels slightly higher than controls.[114] Lastly, a clinical study examined the effect of four drugs commonly used for migraine prophylaxis (topiramate, amitriptyline, flunarizine, and propranolol) on migraine frequency and plasma glutamate levels.[115] After eight weeks of treatment, migraineurs experienced, on average, a 50% reduction in migraine days and a three-fold reduction in plasma glutamate levels. The final glutamate levels for these patients were still twice that measured for controls. Although there are inconsistencies, most data indicate that migraineurs maintain higher levels of glutamate than non-migraineurs, which makes them prone to headaches.

There is significant support for glutamate as a signaling molecule regulating NKA. However, the results are often contradictory, which may reflect differences in the signaling in different brain regions and reflect the activation of different receptors by

glutamate. There are two general categories of glutamate receptors: those that facilitate the influx of cations, Ca^{2+} in particular (iGluRs), and those that are G-proteins that initiate various signaling pathways (mGluRs).[116-118] There are three main types of iGluRs: N-methyl-D-aspartate receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, and kainite receptor, named for their highly specific agonist. There are three groups of mGluRs (group I, II, and III).[119] Type I typically signals through $G_{\alpha q}$, which activates phospholipase C, leading to inositol trisphosphate and diacylglycerol production and protein kinase C activation. However, mGluR type I receptors are also known to signal through $G_{\alpha s}$ and $G_{\alpha i/0}$, which are known to upregulate cAMP and downregulate cAMP, respectively. The mGLuR groups II and III typically signal through $G_{\alpha i/0}$, resulting in downregulation of cAMP, inhibition of Ca^{2+} channels, and activation of K^+ channels. Specific activation of N-methyl-D-aspartate receptors in cultures of rat cerebellar neurons was shown to activate calcineurin, a Ser/Thr phosphatase that facilitates dephosphorylation of NKA, leading to its activation.[120] In contrast, others have shown that the activation of NMDA receptors in a similar system results in the inhibition of NKA due to the activation of protein kinase C that phosphorylates NKA,[121-123] leading to inactivation,[123] or the generation of free radical species that modify NKA sulfhydryl's resulting in inactivation.[121] Interestingly, specific activation of the mGluR group I receptor with (S)-3-hydroxyphenylglycine results in activation of NKA,[122] whereas using agonists selective for both mGluR group I and mGluR group II receptors results in inhibition of NKA. These data suggest that activating mGluR group I receptors leads to activation of NKA, and activating mGluR group II receptors leads to inactivation of NKA.

These contradicting results and the complexity of signaling render the question of whether glutamate could be involved in enhancing sodium CSF unanswered. However, a straightforward explanation could be that the high CSF glutamate levels reflect a high plasma glutamate level and an active high-affinity glutamate transporter (e.g. SLC1 family of transporters) that transports $3Na^+$ and $1H^+$ with each glutamate, thus enhancing CSF sodium through a pathway not involving NKA.[124]

3. Conclusion

The data supports the involvement of neurotransmitters serotonin, dopamine, norepinephrine, and glutamate in migraine pathology. There is also ample evidence that these neurotransmitters indirectly affect the activity of NKA. However, the link between neurotransmitter regulation of NKA activity and migraine is unclear primarily due to conflicting results. For example, a rapid increase in serotonin from abnormally low values at the start of the ictal state appears to trigger migraine, but whether NKA is activated or inhibited by this change is unclear. Similarly, an increase in dopamine serves to initiate migraines. However, the effect on NKA is quite the opposite, indicating that dopamine does not have a link to the sodium theory for migraines unless it is involved in a protective response. Norepinephrine levels are lower in migraineurs than in controls, and norepinephrine activation of NKA has been observed in vitro, supporting its potential role in the sodium theory for migraines. However, a few preclinical studies indicate that norepinephrine reduces the production of CSF, indicating that in these models, norepinephrine inhibits NKA, the opposite of what is required for the sodium model. Lastly, glutamate levels in interictal migraineurs are higher than in controls, suggesting that glutamate predisposes migraineurs to headaches. Glutamate also affects sodium pumping, but data for activation and inhibition of NKA have been reported.

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