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Indirect Regulation of Na^+, K^+-ATPase by Endocrine Hormones: Participation of Endocrine Hormones 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 (NKA) in the choroid plexus. The sodium theory for migraine suggests that the dysregulation of NKA in migraineurs results in elevated CSF sodium, which is known to increase central sensitization, thereby predisposing these individuals to headaches.

The involvement of endocrine hormones in migraine pathology is well documented. Indirect regulation of NKA by endocrine hormones is well documented for many tissues including the brain. The focus of this review is to identify which endocrine hormones are involved in both migraine and NKA regulation in a manner consistent with the sodium theory for migraine. We believe that the identification of such endocrine hormones may lead to the development of new pharmaceuticals to address migraine.

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, affects 12-15% of the population, and is responsible for €27 billion annual economic loss in terms of reduced productivity and work days lost. It is generally understood that migraine pathology is neurovascular. Vasodilation, vasoconstriction, and neuro-activation all play roles. However, more recent research has changed the emphasis from a primarily vascular cause[1,2] where the vascular component results from the 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[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].

One 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 from cardiotonic steroids, endocrine hormones, neurotransmitters, endocannabinoids, and 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 endocrine hormones 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 endocrine hormones may lead to the development of new pharmaceuticals to address migraine.

2. Na^+, K^+-ATPase (NKA) Isoforms

NKA represents a subfamily of the membrane-bound P-type ATPase isozymes involved in the transport of Na^+ and K^+, where three Na^+ ions are pumped from the interior of the cell to the exterior in exchange for two K^+ ions at the expense of ATP hydrolysis. In most cells, this transport is required to establish and maintain the electrical polarization of the plasma membrane. In the choroid plexus, the transport of sodium ions into CSF is used primarily to drive water across the blood-CSF-barrier into the CSF to maintain the CSF volume that is continuously reabsorbed into venous circulation.

Human NKA is a dimer of heterotrimers consisting of α, β and γ subunits of which there are four known isoforms for both the α and β subunits and 10 known isoforms of the γ -subunit (http://proteinatlas.org). Human tissues typically have a mixture of various combinations of the subunit isoforms and the relative amounts of each are tissue dependent. Pumping rates depend on K^+ and Na^+ concentrations that, in turn, are specific for combinations of α and β isoforms and in some cases, auxiliary γ subunits where the α -subunit is responsible for pumping and ATPase activity, and the other subunits modulate the pumping rate and the α -subunit's stability[23]. Regulation of the pumping rate is two-fold: direct inhibition by endogenous cardiotonic steroids and activation, inhibition, or changes in expression through phosphorylation of the α -subunit in an indirect manner. Endogenous cardiotonic steroids, including ouabain-like compounds, inhibit the pump by binding to the α-subunits with an efficiency determined by the identity of the endogenous cardiotonic steroids and the α-subunit isoform to which it binds. In addition to reducing the rate of ion transport, endogenous cardiotonic steroid binding also stimulates a tyrosine phosphorylation cascade in which the Src family of kinases is intimately involved[24]. The phosphorylation of NKA is known to modulate its interaction with kinases, pumping rate, and plasma membrane expression, depending on the phosphorylation site. Phosphorylation of the α -subunit is also modulated through endocrine, neurotransmitter, and eicosanoid signal pathways. The focus of this review centers on the involvement of endocrine hormones in migraine pathology and the exploration of modulation of NKA by these hormones in a manner consistent with the sodium theory for migraine.

3. Indirect regulation of NKA by endocrine hormones and their involvement in migraine

Direct regulation of NKA is facilitated by the release of endogenous ouabain-like, bufadienolide -like, or digoxin-like compounds that are transported into the cerebrospinal fluid (CSF), where they act as noncompetitive inhibitors of NKA. Their overall concentrations in the CSF, and possibly high concentrations via localized secretion, regulate the rate at which sodium is pumped out of the choroid plexus cells into the CSF through the inhibition of NKA[25,26]. Indirect regulation of NKA, addressed here, occurs through posttranslational phosphorylation, resulting in changes in activity or expression[27-30]. This signaling activates specific kinases or phosphatases that regulate the phosphorylation state of NKA with the net result of either activation, inhibition, or alteration in plasma membrane expression levels depending on the tissue and species[23,31]. For example, cAMP-dependent phosphokinase A enhances NKA activity in rat brain and tail arteries in rats and pigs. In contrast, cAMP-dependent phosphokinase A inhibits NKA activity in rat kidney cortex and shark rectal gland[31]. Similar diversity in regulation for protein kinase C and protein kinase G is also observed. Hormonal-induced phosphorylation pathways for modification of the NKA α-subunit, the subunit involved in sodium pumping and ATPase activity, are well documented in tissues other than in the central nervous system[31-33], but may apply to the central nervous system, as receptors for these hormones are known to be present in the brain.

3.1 INSULIN-BASED REGULATION

The relationship between diabetes and the associated lower incidence of migraine is well documented. In an early study, people with diabetes attending outpatient diabetes clinics (n = 541) and non-diabetic controls (n = 350) were compared in terms of experiencing migraine[34]. Overall, 17% of the people with diabetes experienced migraine at some time, whereas 29% of the controls experienced migraine, suggesting an inverse relationship between diabetes and migraine. The study did not differentiate between diabetes mellitus and type 2 diabetes. In an extensive study involving the entire population of Norway on January 1, 2004 (n = 4,286,201),

individuals with diabetes mellitus (n = 7,883) and individuals with type 2 diabetes (n = 93,600) were identified based on their type of treatment[35]. The incidence of migraine within these groups, as determined by their prescription use of ergotamine or triptans for treatment, revealed that treated diabetics, in general, had a lower incidence of migraine than non-diabetics, and individuals with diabetes mellitus had a lower incidence of migraine than those individuals with type 2 diabetes.

Further, the data shows a decrease in migraines with increasing age for all groups. An earlier study of the Norwegian population in 2006 revealed similar results, and the authors speculated that the decrease in migraine in people with diabetes with increasing age may be related to an increase in diabetic neuropathy with age[36]. Similarly, an analysis of 1995-1997 and 2006-2008 data from the Nord-Trøndelag Health Surveys (n = 39,584) also indicates an inverse relationship between migraine and diabetes mellitus but no clear association with type 2 diabetes[37]. A smaller study involving type 2 diabetes patients (n = 147) and controls (n = 150) also indicated no significant relationship between type 2 diabetes and the incidence of migraine[38]. In contrast, a study involving the relationship between migraine and type 2 diabetes in women (n = 74,247) indicates an inverse relationship between type 2 diabetes and migraine[39]. Since diabetes mellitus patients have lower average plasma insulin levels than type 2 diabetes patients at any age and both groups have lower average insulin levels than non-diabetics, again at any age, the unifying theme is consistent with a direct relationship between the average insulin levels and the incidence of migraine. Further, five single-nucleotide polymorphisms in the insulin receptor are known to have a significant association with migraine[40]. The insulin binding of these isoforms was not statistically different from the wild type, and the authors speculated that the difference may be in receptor function or that the isoforms have a lower translational efficiency. Two recent reviews confirm the role of impaired brain glucose metabolism in migraine[41,42].

Insulin has been shown to enhance NKA activity and translocation to the plasma membrane in humans through both Ser and Thr phosphorylation of the α -subunit via an ERK1/2 pathway and enhanced NKA activity through Tyr phosphorylation in rat kidneys through a yet-to-be-determined pathway[43,44]. Insulin receptors in the brain are present with an exceptionally high density in the choroid plexus, suggesting a possible role in insulin modulation of NKA activity[45,46]. Insulin-enhanced sodium transport across the choroid plexus to the CSF is known to occur in the rat choroid plexus, an event the authors attributed to stimulation of the NKA pump[47]. This fact supports the involvement of insulin in the sodium theory of migraine. Further, it is consistent with the observed direct relationship between plasma insulin and the incidence of migraine in humans.

There are two sources of insulin for interaction with insulin receptors in choroid plexus: 1) plasma insulin for receptors located on the basolateral side of the blood-brain barrier, and 2) choroid plexus-produced insulin exported to the CSF for receptors located in the apical side of the brain-CSF barrier. Plasma insulin is readily transported to the apical side of endothelial cells of the brain from the blood. However, it is transferred across to the CSF at a much lower rate[48], resulting in a CSF concentration that is only 10-25% of that found in plasma[45,49]. The transfer of insulin across the blood-brain barrier is 400-fold greater than across the brain-CSF barrier[48], suggesting that stimulation of the insulin receptors on the basolateral side of the cuboidal cells of the choroid plexus by plasma insulin is a more likely explanation for the relationship between plasma insulin levels and susceptibility to migraine. A second source of insulin in the CSF is the production of insulin in the choroid plexus itself and subsequent secretion at the apical membrane[50]. The production and subsequent insulin release at this site depends not on glucose concentrations but on serotonin (5-HT) signaling facilitated by 5HT2C receptors located on the apical membrane of the choroid plexus. Since 5-HT reduces NKA activity[51], insulin produced in the

choroid plexus through 5-HT signaling would then reduce NKA activity, a result that would decrease CSF sodium and mitigate migraine. This result is quite the opposite of that observed for insulin. Since triptans (5HT2C agonists) effectively mitigate migraine pain, this suggests collectively that 5-HT-mediated insulin production and release would not be involved in migraine through NKA pumping. However, in cell cultures of rat choroid plexus cells, insulin was found to reduce the activity of 5HT2C, the only 5-HT receptor found in the choroid plexus, through a MAP kinase pathway[52]. If this is the dominant effect in humans, then choroid plexus-produced insulin could very well contribute to the onset of migraine through this mechanism.

3.2 ANGIOTENSIN/ALDOSTERONE-BASED REGULATION

The relationship between elevated angiotensin and aldosterone levels and migraine is well documented. An early study shows a direct relationship between aldosterone and migraine through examination of the effect of salt on promoting migraine attacks[53]. In this study involving 24 migraineurs and 24 non-migraineurs as controls, 93% of migraineurs given oral sodium chloride developed migraine headaches. In contrast, only 27% of migraine controls developed mild headaches the following day. None of those receiving the placebo developed headaches. Both aldosterone and angiotensin levels were monitored every 20 minutes for two hours after ingestion of salt or placebo. Levels of both hormones were higher in migraineurs than non-migraineurs before and after the administration of salt, but the difference was not statistically significant. However, the difference in combined mean peak in angiotensin levels - peaking in 40-60 minutes following salt administration in migraineurs receiving salt was significantly higher than the controls given salt, clearly showing the relationship between migraine pathology and elevated angiotensin levels. The study does not prove if angiotensin is a direct effector of migraine induction or if it is involved in an unrelated side effect of elevated sodium. A more direct indication of the involvement of angiotensin in migraine is found in studies involving angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors on migraine prophylaxis and reduction in onset frequency. A recent review of clinical studies clearly shows that both angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors do reduce both the frequency and intensity of migraine headaches[54]. However, the results do not allow for a mechanism to be defined. Since these pharmaceuticals are frequently used to treat hypertension, one could ascribe their efficacy to a reduction in blood pressure. However, although there is good evidence that migraine sufferers are at risk for hypertension, data supporting hypertension-initiating migraine is somewhat mixed and requires further study[55].

Support for the direct involvement of aldosterone in migraine is also found in a single-patient clinical study where daily high doses of spironolactone, an aldosterone antagonist, were found to prevent migraine for a known migraineur and reduction of the dosage by 44% led to only mild headache and no classic migraine[56]. However, migraine returned within 72 hours after stopping the administration of spironolactone. In addition, in a controlled study of the effect of spironolactone on female fibromyalgia patients, 4 of the 15 patients with concomitant migraine did not experience migraine attacks during the study[57]. Although both studies support a role for aldosterone in migraine, studies involving significantly more migraine patients are needed to confirm these results.

Several reports implicate Angiotensin II (AngII) in the regulation of NKA in support of a path leading to sodium-induced migraine. AngII-induced phosphorylation of the NKA α -subunit stimulates NKA activity in rat proximal tubules with short-term exposures to AngII[58]. Others have shown that short-term exposure to AngII in cultured rat vascular smooth muscle cells enhances NKA activity through phosphatidylinositol-3 kinase and mitogen-activated protein kinase pathways, but

the target of phosphorylation-was not determined[59]. However, longer-term exposure to AngII enhances the expression of both α1 and β1 NKA subunits in both vascular smooth muscle cells in rats. The enhancement of α -subunit expression occurred through MAP kinase signaling pathways and the β -subunit through some other pathway[57,58]. Earlier work also provided evidence for enhanced expression of both subunits stimulated by AngII but through a pathway not involving protein kinase C[51]. These results are in keeping with the established role of AngII in promoting migraine through the sodium pathway[60-63].

Both AngII receptors (AT1 and AT2) are present in the brains of humans and other mammals, where expression in the choroid plexus is particularly pronounced[54,64-66]. The relative expression of these receptors is significant as each signal is through a different pathway, leading to opposing functional results. For example, AT1 promotes protein phosphorylation, leading to vasoconstriction, while AT2 promotes protein dephosphorylation, leading to vasodilation[65]. The high degree of expression in the choroid plexus and the efficacy of AT1 antagonists tested for migraine prophylaxis strongly support a role for AngII and the AT1 receptor in regulating NKA through phosphorylation and migraine pathophysiology[54,67].

It is well established that AngII signals the adrenal release of aldosterone resulting in salt retention and hypertension[68]. Hence, the association between elevated angiotensin and salt leads one to suspect a potential relationship between aldosterone and migraine via NKA and the sodium pathway.

Aldosterone is known to enhance the maximal velocity for NKA pumping by increasing the pump's plasma membrane expression. Studies have shown that the increase in surface expression in mammalian kidney epithelial cells involves the translocation of pre-synthesized NKA into the apical surface and increasing NKA biosynthesis[69-73]. Regulation of the expression of NKA by aldosterone requires its binding to a mineral corticoid receptor that is isoform-specific for the α_1-subunit sequences for NKA[74], the dominant isoform present in the choroid plexus. Translocation of NKA appears to involve the serum- and glucocorticoid-regulated kinase 1[75]. Although aldosterone has limited blood-brain barrier penetration, the brain-CSF barrier readily passes aldosterone, which is involved in regulating CSF production, a process that is driven by sodium export via NKA[76]. Furthermore, aldosterone, NKA, mineral corticoid receptor, and sodium channels are present in the central nervous system and are known to regulate CSF [Na^+] through the choroid plexus and thus, the modality of NKA activity enhancement in the central nervous system is likely to be similar to that found in the kidney[77].

3.3 ESTROGEN/PROGESTERONE-BASED REGULATION

The association of menstruation with episodic migraine without aura has been known since the 9th century. It has more recently been associated with the fall of estrogen levels during the late luteal phase following a significant rise during the follicular and early luteal phases[78,79]. Further, postmenopausal women with a history of menstrual migraine are predisposed to migraine when estrogen replacement therapy is stopped[80], supporting the concept that the rapid drop in estrogen is a migraine trigger[81]. Although progesterone also rises and falls during the luteal phase, administration of this hormone does not protect against migraine[82]. However, progesterone is known to exhibit an antinociceptive effect on the trigeminal pathway, and its fall during the late luteal phase could exacerbate the estrogen-linked migraine[78].

In vivo, administration of 17 β -estradiol to male rats increased both activity and expression of NKA, resulting from the concomitant increase in α -subunit phosphorylation[83]. The enhanced phosphorylation of the α -subunit coincided with increased phosphorylation/activation of Akt (PKB) and ERK1/2, likely leading to the NKA α -subunit phosphorylation and subsequent activation. Estrogen also enhances the expression of the NKA β_1-subunit at both the mRNA and protein levels in rat cardiomyocyte cell culture[84]. In addition,

estrogen increases the half-life of the β_1-subunit by upregulating the N-myc downstream-regulated gene 2, the protein product that binds to and stabilizes the β_1-subunit against degradation[85]. These preclinical results suggest that elevated estrogen levels should promote migraine, whereas what is known about menstrual migraine suggests the opposite. One possibility is that the elevated estrogen levels before the late luteal phase predispose menstrual migraineurs to migraine by increasing CSF sodium levels, and the drop in estrogen levels serves as a migraine trigger through an unknown mechanism. Further, the antinociceptive effect associated with progesterone would serve to exacerbate this predisposition[86].

Although a direct link to estrogen-mediated brain NKA activity enhancement has yet to be established, it is known that estrogen receptors are expressed in the choroid plexus[87,88]. There is also evidence for the presence of organic anion transporters and ATP-binding cassette transporters in the choroid plexus that are capable of transporting estrogen into the epithelial cells present in the choroid plexus[89-91].

3.4 THYROID HORMONE-BASED REGULATION

The association between thyroid dysfunction and migraine is well established; however, both hypothyroidism[92-95] and hyperthyroidism[92,96-100] are implicated in migraine. The causal factor for this co-morbidity of thyroid function and migraine appears to be bidirectional and only hyperthyroidism has links to NKA activity. Triiodothyronine (T3) is known to increase the activity of NKA in adult rat alveolar epithelial cells through a MAPK/ERK1/2-dependent pathway in a dose-dependent manner[101]. Like insulin-promoted and ANGII-promoted increases in NKA activity, T3 increases NKA activity through enhanced expression of the α -subunit in the plasma membrane. Transcription of the α1-, α2-, and α3-subunits of NKA in isolated nuclei developing hypothyroid rat brains was found to be significantly reduced compared to normal controls[102]. Pre-incubation of hypothyroid rat nuclei with T3 increased the transcription rates of all three subunit isoforms, clearly showing the control of α -subunit transcription by T3. Similar results from other tissues have also been reported[103]. Enhanced expression of the α1, α2, α3, and β1 isoforms by T3 in rat cardiocytes has also been reported[104].

To affect choroid plexus NKA transcription and membrane expression, T3 or T4 must travel from the blood into the endothelial cells of the choroid plexus. The currently accepted modality for this process is that T3/T4 dissociates from its distributor proteins and then enters the endothelial cells via specific thyroid hormone transporters (TH) located on the basolateral surface, where it can then interact with its receptors, TRa1 or TRb1[105,106]. These complexes can be rapidly transported to the nucleus to affect NKA transcription[96] or interact with vesicles in the cytosol containing pre-synthesized NKA to facilitate enhanced expression[101]. T3/T4 can also be transported through the apical side via TH transporters into the CSF[105]. Data supporting transport across the blood-brain barrier and the choroid plexus-CSF-barrier have been presented[107,108]. Here, radiolabeled T3 and T4 (tetraiodothyronine, the T3 precursor) were transported across both barriers in rat brains and in overlapping timeframes. Notably, both hormones readily pass from the highly fenestrated choroid plexus capillaries to the choroid plexus endothelial cells without partitioning across the capillary endothelial cells. Further, the biosynthesis of the T4 binding protein transthyretin occurs in the choroid plexus of rats, independent of synthesis in the liver. This may be the primary driving force for T4 crossing from the blood to the brain[109], leading to an approximate 75 pM concentration in the CSF compared to 30 pM in the blood[105]. Importantly, conversion of T4 to T3 is readily accomplished enzymatically by brain deiodinases[110-112]. Further, there is a high density of thyroid hormone receptors in the choroid plexus of adult rat brains[113], supporting a potentially significant role for thyroid hormone in the expression of NKA in the choroid plexus, the likely primary source of CSF sodium.

4. Conclusion

This review presents data supporting that elevated insulin levels are associated with both an increase in migraine frequency and increased NKA activity, thus supporting the possible involvement of insulin in the sodium theory of migraine. The source of insulin involved here remains to be confirmed, as both pancreatic-derived insulin and choroid plexus-derived insulin are both potential contributors. The data regarding elevated angiotensin and aldosterone levels and their association with migraines is somewhat mixed, however, migraine mitigation by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers strongly supports the involvement of at least angiotensin in migraine pathology. Since both hormones also enhance the cell surface expression of NKA which would result in an elevation of CSF sodium levels, there is at least some support that both hormones are potential participants in the sodium theory for migraine. The relationship between estrogen and progesterone in the sodium theory for migraine is less clear. Preclinical data supports a direct relationship between estrogen levels and the enhancement of NKA activity. However, clinical migraine data indicate that it is the fall rather than an increase in estrogen levels that is associated with migraine, and this is in direct contrast to what would be expected if it is involved in the sodium theory for migraine. The resolution of this discrepancy awaits further research. There is little evidence to suggest that progesterone is involved in migraine beyond an involvement as an antinociceptive agent. Both hypothyroidism and hyperthyroidism are associated with migraine pathology. However, only elevated thyroid hormone levels are associated with an enhancement of NKA activity, and thus, only hyperthyroidism might be linked to the sodium theory for migraine.

Overall, there is a significant body of evidence for the involvement of endocrine hormones in migraine pathology. Further, preclinical studies clearly show that these hormones also increase the activity of NKA, supporting a potential involvement in the sodium theory for migraine. These results suggest that an alteration in the homeostasis of the endocrine hormones may predispose migraineurs to headaches and exacerbation of headache pain.

Conflict of Interest:

The authors have no conflicts of interest to declare.

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