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Indirect Regulation of Na+, K+-ATPase by Arachidonic Acid-Derived Eicosanoids: Participation of Eicosanoids in the Sodium Theory for Migraine

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ABSTRACT

Migraines are a debilitating headache disorder affecting over a billion people worldwide. 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 eicosanoids in migraine pathology is well documented. Indirect regulation of Na^+, K^+-ATPase by eicosanoids is documented for many tissues including the brain. The focus of this review is to identify which eicosanoids 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 eicosanoids may lead to the development of new pharmaceuticals to address migraines.

1. Introduction

According to the World Health Organization (www.who.int), migraine headache disorder alone is one of the top ten leading causes of disability and affects 1 adult in every 7 in the world. Migraine most affects those aged between 35 and 45 years and usually starts at puberty. Migraine pathology is neurovascular, where the neurological component is considered the primary causal factor.[1-4] The vascular component is observed as a vasospasm, a small vasoconstriction followed by a much more significant vasodilation, that precedes the headache phase (ictal phase) of migraine. In addition, central sensitization, an increased responsiveness of nociceptors in the central nervous system, also plays a role in migraine pathology, where an increasing intensity of peripheral sensitization leads to central sensitization and amplification of pain.[5,6] The sodium theory for migraine states that an increase in sodium ion concentration in the cerebrospinal fluid (CSF) of migraineurs enhances central sensitization and thus predisposes them to migraine.[7] Sodium ion concentration in the CSF is known to be regulated primarily by the Na^+, K^+-ATPase (NKA) pump located in the choroid plexus.[8-9] The sodium theory postulates that dysregulation of NKA in the choroid plexus of migraineurs leads to elevated sodium in the CSF, predisposes them to headaches, and exacerbates the pain associated with the headache.[10-14]

NKA represents a subfamily of the membrane-bound P-type ATPase isozymes involved in transporting Na^+ out of the cell in exchange for K^+, at the expense of ATP hydrolysis. NKA is found in all organs of the human body where the ion pumping creates the required cell membrane electrical potential. In the choroid plexus, the pumping of sodium into the CSF is used to drive water across the brain-CSF-barrier to replenish the fluid lost to absorption into the veinous circulation. Mammalian NKA is a dimer of heterotrimers consisting of a, b, g subunits, of which there are multiple isoforms of each known and combinations of isoforms are tissue-dependent (http://proteinatlas.org). The rate of ion pumping is regulated both directly and indirectly. Direct regulation is accomplished through noncompetitive inhibition of NKA by endogenous cardiotonic steroids such as ouabain and ouabain-like compounds.[11] Indirect regulation of NKA activity is achieved through signaling that promotes posttranslational phosphorylation of NKA, resulting in changes in activity or expression of subunits.[15-18] Signaling that activates specific kinases or phosphatases regulates the phosphorylation state of NKA with the net result dependent on NKA isoforms present, which are tissue and species-specific.[18,19] Indirect regulation of NKA phosphorylation in tissues other than the central nervous system is well documented.[19-21] However, it may apply to the central nervous system, as receptors for these signaling molecules are known to be present in the brain.

As discussed below, many eicosanoids are known to affect migraine pathology by modifying susceptibility to or intensity of migraine headaches. Furthermore, some eicosanoids are known to regulate the activity of NKA. The focus of this manuscript is to investigate the potential involvement of lipid-based signaling in migraine pathology through mechanisms consistent with the sodium theory for migraine.

2. Prostaglandin-based regulation of Na^+, K^+-ATPase and migraine

Prostaglandins are bioactive metabolites derived from arachidonic acid through the action of arachidonate lipoxygenases. The relationship between the prostaglandin class of lipids and migraines is rich and well-documented.[22-25] As described above, the current view of migraine is that it is a neurovascular disorder where both vasoaction and enhanced nociception are standard features associated with the initiation of migraine headache. Eicosanoids and their receptors are well known for their effect on vasoaction and nociception and, hence, may participate in migraine by facilitating changes in either, the latter of greater import.[25] Infusion of Prostaglandin E2 (PGE2),[26] prostaglandin I2 (PGI2),[27] and prostaglandin D2 (PGD2)[28] induce vasodilation as noted by the decrease in the velocity of middle cerebral blood flow and increase in the diameter of the superficial temporal artery, into healthy volunteers produced headache. PGD2 produces milder headaches than the other prostaglandins. Infusion of proinflammatory Prostaglandin F2a into healthy volunteers is not involved in vasoaction, as there were no changes in velocity of middle cerebral blood flow and superficial temporal artery compared to controls and caused no headaches under experimental conditions.[29]

In migraineurs, infusion of either PGE2,[30] or PGI2[31] resulted in migraine-like headaches in all participants that were indistinguishable from spontaneous attacks. The stable PGI2 analog iloprost also induces headaches in non-migraineurs and migraineurs.[32-34] Similar studies involving migraineurs and PGD2 have not been reported. However, the infusion of healthy volunteers with PGD2 did result in headaches.[25,28] Infusions of PGI2 and PGE2 gave identical results.[25] In addition to the effects on vasoaction, prostanoids, namely PGE2 and PGI2 or its more stable analog carbaprostacyclin, enhance nociception through sensitization of the capsaicin receptor,[35] or suppression of the potassium current across the neuron membranes, increasing the number of action potentials.[36,37] These prostanoids are also well known for their involvement in inflammatory pain.[38,39] Although the studies involving inflammatory pain are not directly tied to migraine headaches, inflammatory pain is known to be associated with migraine pathology.[32]

In addition to the clear connection between certain eicosanoids and vasodilatory and pronociceptive induction of migraine, reports show the effect of eicosanoids on NKA activity and, thus, potentially on sodium levels in the CSF. Much of the data involves the action of PGE2 on NKA and the results are mixed. PGE2 upregulates the expression of the a1-subunit of NKA in human liver HepG2 cells by stimulating the EP4 receptor.[40] Similarly, PGE2 stimulates the expression of the b1-subunit of NKA in Madin Darby Canine Kidney cells by stimulating both EP1 and EP2 receptors.[42,43] Further, PGE2 activation of either EP2 or EP4 in rat distal colon cells enhances the activity of NKA through phosphorylation but not with enhanced expression .[41] All of these studies support a PGE2-initiated enhancement of NKA activity, potentially resulting in higher sodium concentrations in the CSF.

In contrast, low concentrations of PGE2 (1-10 nM), much lower than used in the studies noted above (> 100 nM), inhibit NKA activity and reduce the number of ouabain binding sites in Madin Darby Canine Kidney cells, suggesting a reduction in plasma membrane expression of NKA, with signaling through the EP3 receptor.[45,46] Human colon Caco-2 cell cultures showed similar results with signaling through the EP1 receptor.[47,48] These studies at low PGE2 concentrations are consistent with a reduction in NKA activity, the opposite of what is observed at higher PGE2 concentrations. Others have reported this dose dependency of contrasting PGE2 effects. This may be a function of the differential binding of PGE2 to the various EP receptors, which activate different G-protein coupled pathways. EP1 and EP3 stimulation with low concentrations of PGE2 results in the inhibition of NKA and EP2 and EP4 stimulation at high concentrations of PGE2 enhance NKA activity.[50]

Another possibility is that the expression levels of these receptors determine the results. The fact that the relative binding affinity of PGE2 to EP receptors is EP4>EP1>EP3>EP2[55-62], and the expression levels in the choroid plexus are EP3>>EP2>EP1EP4 (http://proteinatlas.org), suggests that a differential receptor expression might also explain the contrasting effects. The resolution of this dichotomy and association of PGE2 with the sodium theory of migraine awaits studies that examine the effect of PGE2 directly on human choroid plexus cells.

PGD2 does not affect the activity of either rat heart NKA[67] or human intestinal NKA.[68] For these reasons, it appears unlikely that PGD2 can be involved in NKA-related migraine pathology.

As noted above, PGI2 and the more stable analog, iloprost, have been shown to induce headaches. These prostaglandins and the additional PGI2 analogs 7-oxo-prostacyclin and beraprost also enhance the activity of NKA, through receptor-driven phosphorylation of NKA. PGI2 also enhances the activity of NKA in mouse macrophages[69] and iloprost enhances NKA activity in rat sciatic nerves.[70,71] PGI2, iloprost, and beraprost enhance NKA activity in canine airway smooth muscle.[72] 7-oxo-prostacyclin also increases the activity of NKA in rat heart sarcolemma membrane but apparently through enhanced transcription of an additional NKA isoform.[73] In contrast, one report indicates that PGI2 reduces NKA activity in rat heart sarcolemma membrane.[67] Although PGI2 and its analogs bind tightly to IP receptors, they are also known to bind to EP1 receptors. Although the K_i values for iloprost binding are in the low nM range for rat[74] and mouse,[75,76] binding to human EP1 receptors cloned into HEK-293 cells bind iloprost in the mM range,[77] suggesting that signaling through human IP receptors would dominate any EP1 activation.

There is significant support for PGI2 facilitating the induction of headache and NKA activation, supporting a role for PGI2 in the sodium pathway. If the high PGE2 concentration data is the dominant pathway, then PGE2 could very well induce migraine in a manner consistent with the sodium theory. However, no direct links implicating these prostanoids in CSF sodium homeostasis have been reported.

3.Hydroxy- and hydroperoxyeicosanoid-based regulation of Na^+, K^+-ATPase and migraine

Data supporting the involvement of peroxy eicosanoid and hydroxy eicosanoids in migraine pathology is highly suggestive, but no direct links have been reported. There is evidence that the 12-, 15-, and 20-hydroxylated derivatives and the 15-hydroperoxylated derivative of arachidonic may be involved in migraine pathology. The 15-hydroxylated derivative, 15-hydroxyeicosatreinoic acid (15-HETE), is not known to be involved in regulating NKA.

20-hydroeicosatetraenoic acid (20-HETE) is a potent vasoconstrictor in rat brain.[78] The resulting vasoconstriction decreases the cerebral blood flow and could initiate the initial phase of the vasospasm observed in migraineurs just before the ictal phase (11). It is also possible that 20-HETE acts as a migraine-resolving agent in response to the onset of migraine headaches, released to reduce the intensity of vasodilation associated with vasospasm. More direct links to migraine are not available.

Although there are no reports directly confirming a relationship between 15-HETE and migraine, there is one clinical study that shows that individuals with chronic daily headaches had elevated 15-HETE levels and that an increase in one standard deviation resulted in an 11% increase in the number of headaches per month.[84] In addition, two studies discuss the relationship between 15-HETE and vasoconstriction. One study examined the formation of 15-HETE in response to chronic hypoxia and found it is a potent vasoconstrictor, much like 20-HETE.[85] A second report examined the effect of 15-HETE on the activity of endothelial nitric oxide synthase.[86] Here, it was found that 15-HETE promotes the inhibition of endothelial nitric oxide synthase through a phosphorylation event, and the result is a reduction in plasma NO, also resulting in vasoconstriction. These results, taken together, suggest that 15-HETE could also be involved in the vasospasm phase of migraine or act as a migraine-resolving agent, a role like that suggested for 20-HETE. Only the involvement with vasospasm is consistent with the findings for chronic headache sufferers.

12-hydroxyeicosatetraenoic acid (12-HETE) increases the number of headaches per month in chronic headache sufferers by 15% for each concentration elevation of one standard deviation.[84] Further, a clinical study of women found that 12-HETE is the main product formed from arachidonic acid metabolism during menstruation, and the increased production of 12-HETE is associated with menstrual pain.[87] Although the pain observed is not headache pain, the rise in 12-HETE during menstruation corresponds to the timing associated with menstrual migraine[88,89] and thus may be involved in migraine onset. It also has been shown that 12-HETE dose-dependently enhances NO synthesis by upregulating inducible nitric oxide synthase transcription in rat-cultured vascular smooth muscle cells,[90] an event that would result in vasodilation, the second stage of the vasospasm that precedes headache. All data presented above points towards 12-HETE promoting migraine, but no direct link has been reported.

Lastly, 5-hydroxyeicosatetraenoic acid (5-HETE) is well-known as a proinflammatory mediator.[84,91] The fact that neuroinflammation is central to the pathophysiology of migraine,[92] suggests that 5-HETE could very well be involved. A direct link has yet to be established.

Numerous studies show that 20-HETE is an effective inhibitor of NKA. One study showed that 20-HETE reduces ouabain-sensitive NKA activity in rat kidneys.[93] This was confirmed by another study with neonatal piglets showing that infusion of 20-HETE into the putamen results in inhibition of NKA, and inhibition is reversible by administration of an inhibitor specific for the CYTP450 that converts arachidonic acid to 20-HETE.[94] Further detail involving sheep pulmonary artery segments indicates that the inhibition is mediated through a protein kinase C-modulated phosphorylation event.[95] In addition, 20-HETE has been shown to enhance protein kinase C phosphorylation of the a1-subunit at serine-23, which reduces NKA activity but does so indirectly through the 20-HETE-mediated activation of protein kinase C.[96] One other study reported that the phosphorylation enhances ubiquitination of the a1-subunit of NKA and thus downregulates its expression through degradation.[97] Lastly, 20-HETE has also been shown to enhance the dopamine-mediated inhibition of NKA through synergism with the D1 receptor in rat proximal tubules.[98] The reported data agree that 20-HETE inhibits NKA and would be consistent with 20-HETE acting as a migraine-resolving agent.

12(R)-HETE but not 12(S)-HETE inhibits ouabain sensitive NKA in vascular tissue,[99] corneal epithelium,[100-102] heart and kidney,[102] and ciliary epithelium from rabbit eye.[103] The fact that the NKA a1-subunit is highly expressed in all these tissues suggests that 12(R)-HETE acts similarly to 20-HETE in migraine pathology.

Data for 5-HETE is relatively sparse. One report indicates that 5-HETE in the GI tract does not affect ouabain-sensitive NKA activity, indicating that is not involved in the sodium theory for migraine. However, another report shows that the 5-HETE precursor 5-hydroperoxyeicosatetraenoic acid, not 5-HETE itself, is a potent inhibitor of rat cerebral cortex synaptosome NKA.[104] This suggests that 5-hydroperoxy eicosatetraenoic may be involved in migraines through the inhibition of NKA and thus act as a migraine-resolving agent like that suggested for 20-HETE and 12-HETE.

No reports indicate the effect of 19(S)-hydroxyeicosatetraenoic acid (19(S)-HETE) on migraine pathology. However, two reports indicate that 19(S)-HETE is a potent activator of NKA in rat vascular tissue[105] and rat kidney microsomes.[106] One might expect that if this holds for NKA in the choroid plexus, the activation will increase [Na^+] in the CSF and thus promote headache. The fact that the a-1 subunit of NKA is the most prevalent isoform in the kidney and choroid plexus suggests that this event may also occur in the choroid plexus. The involvement of 19(S)-HETE in migraine pathology is an area that should be explored in the future.

4.Lipoxin- and Leukotriene-based regulation of Na^+, K^+-ATPase and migraine

Lipoxin A4 (LXA4) and lipoxin B4 (LXB4) are bioactive metabolites of arachidonic acid, both well-known as pro-resolving mediators of inflammatory pain.[107] LXA4 also relieves neuropathic pain as well.[108] One connection of LXA4 to migraine comes from a study of 53 migraineurs (53 controls), where LXA4 levels were significantly lower than controls during both interictal and ictal states.[109] Further, the levels decrease more with migraine attack duration, suggesting that the reduction of LXA4 predisposes individuals to migraine and prolongs the migraine ictal state. One potential mode of action in migraine pathology is that LXA4 is an allosteric enhancer of the cannabinoid receptor 1.[110,111] The natural agonists for this receptor are the endocannabinoids for which lower than normal levels have been shown to predispose individuals to migraine attack.[112,113] It is reasonable then to assume that enhancement of cannabinoid receptor 1 binding to endocannabinoids would be compensatory, and the loss of enhancement would exacerbate the effect of the low levels of endocannabinoids.

Leukotrienes are also bioactive metabolites of arachidonic acid, well known as mediators of inflammatory and neuropathic pain.[114,115] However, only a few reports describe the involvement of leukotrienes in migraine pathology.

An early clinical study involving 17 migraineurs and 8 with cluster headaches revealed that plasma LTB4 levels spike at the beginning of a cluster headache attack and decline after that, but LTB4 levels in migraineurs did not differ significantly from controls during or between headaches.[116] The authors note, however, that they could not measure LTB4 early in the headache phase of migraine and thus may have missed a potential spike in concentration. Later clinical work with small numbers of patients confirms the LTB4 results but also indicates that LTC4 spikes at the onset of migraines and declines after that.[117,118] More recently, and in contrast to previous studies, LTB4 measured in both nasal lavage fluid and saliva was lower in migraineurs than controls.[119] The difference between the studies may merely reflect the difference in sample sources. Two clinical studies report the effect of montelukast, a specific LTD4 antagonist, on migraine prophylaxis. The earlier study involving 17 migraine patients given montelukast revealed that 53% showed a reduction in the frequency of migraine headaches greater than 50%.[120] However, the later study involving 76 treated with montelukast and 72 treated with placebo revealed no significant difference in the reduction of migraine between the two groups. A study involving children with migraine revealed that the urinary LTE4 for controls and interictal migraineurs were similar but rose significantly in migraineurs during the ictal phase,[121] suggesting that LTE4 might promote migraines.

Lipoxin A4 increases the activity of NKA in rat gastrocnemius muscle and heart muscle.[122,123] The increase is due to increased transcription of the a-1 and

b-1 subunit of NKA and their membrane expression.[124-126] In the sodium model of migraine, these results would indicate that LXA4 enhances migraine, quite contrary to that noted above. The low levels of LXA4 in migraineurs could also represent a compensatory action to reduce CSF [Na^+] levels. The resolution of these opposing observations requires further study.

The effects of leukotrienes on NKA activity are quite limited, and thus, leukotriene involvement in the sodium theory for migraines remains limited as well. Changes in NKA activity in the presence of LTC4 and LTE4 are unavailable. LTB4 and LTD4 do not affect NKA activity in isolated rat kidney cortical collecting ducts.[127] In contrast, LTD4 has been shown to increase the activity of NKA through recruitment of the a-1-subunit from intracellular compartments to the basolateral membranes in rat alveolar epithelial cell cultures.[128] Similarly, LTD4 has been shown to increase the transcription of and plasma membrane expression of the a-1 and b-1 subunits of NKA in plasma membrane fractions of rat intestinal epithelial cells.[129]

In summary, LXA4, LTD4, and LTE4 appear to have a connection to migraine headaches, but their effect on NKA activity is not consistent with what would be expected by the sodium theory for migraine. LTB4 and LTC4 may be involved in triggering the onset of migraine. However, neither has a known connection to regulating NKA.

5. Conclusions

Many eicosanoids are known to be involved in migraine pathology, and some are known to regulate the activity of NKA. Of the prostanoids discussed here, only the prostaglandins PGE2 and PGI2 have the potential to be a factor in the sodium theory of migraine, as both are known to initiate migraine and activate NKA. Of the hydroxy- and hydroperoxyeicosanoids, only 15-HETE and 12-HETE promote the onset of headache; the former only supported chronic headache sufferers. Currently, there is no data on the effect of 15-HETE on NKA, and thus, its involvement in the sodium theory for migraine is unknown. 12-HETE is a known NKA inhibitor, the opposite of what would be expected for a migraine promoter. It thus must promote migraines through a pathway other than that consistent with the sodium theory. Of the lipoxin and leukotrienes, only LTB4, LTC4, and LTE4 are involved in the onset of migraine headaches, but no data is available regarding their effect on NKA activity. LXA4 is pro-resolving for migraines but is also a potent activator of NKA activity and thus clearly addresses migraine through a pathway other than that consistent with the sodium theory.

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