Tryptophan Catabolites and Migraine

Zsuzsanna Bohár, Árpád Párdutz and László Vécsei

*MTA-SZTE Neuroscience Research Group, University of Szeged, Szeged, Hungary; bDepartment of Neurology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

Abstract: Migraine is a highly disabling neurological condition affecting around 15% of the population worldwide. Decades of intensive research shed some light on diseases pathomechanism, but information is still missing about the initiation of the attack. In the past century, serotonin emerged as the main target of both basic and therapeutic research. As a result, the triptans, the only approved migraine specific drugs were developed. The involvement of glutamatergic mechanism in migraine headache development such as cortical hyperexcitability, and cortical spreading depression as the pathological correlate of migraine aura called the attention to the kynurenine pathway in migraine pathomechanism. The serotonin and kynurenine pathways are closely connected, as they both are the metabolic routes of the amino acid tryptophan. Kynurenine catabolites are important participants in glutamatergic neurotransmission, regulation also nociceptive processing of the trigeminal system. The current work attempts to collect recent data on both serotonin and kynurenine research related to migraine and emphasizes the importance of further research on this topic.

Keywords: Migraine, kynurenine pathway, cortical spreading depression, serotonin, hyperexcitability, glutamate.

1. INTRODUCTION

Migraine is a common neurological disorder with a one-year prevalence of 14.7% [1]. Despite intensive research the exact pathomechanism of the disease is still not completely understood. The importance of migraine research is clearly shown by the fact that migraine is the sixth highest cause of disability worldwide, and together the headache disorders are the third on the list of causes of disability [2].

Based on data so far, migraine can be considered as a painful multifactorial disorder [3], involving autonomic, affective, cognitive and sensory functions. Glutamate and serotonin mediated neurotransmission both play an important role in the evolution of migraine headaches [4]. The kynurenine pathway (KP), the main route of tryptophan metabolism, is closely involved with both glutamatergic and serotonergic mechanisms placing the catabolites of this pathway under spotlight in migraine research [5]. The scope of our review is to highlight the possible connections of the KP with processes involved in migraine pathomechanism.

2. METABOLISM OF TRYPTOPHAN

In mammals, the excess of tryptophan not necessary for protein synthesis is utilized either for the synthesis of the important neurotransmitters serotonin (5-hydroxytryptamine, 5HT) and melatonin (N-acetyl-5-methoxytryptamine) or is oxidized via the KP. In humans more than 90% of dietary tryptophan is metabolized via the KP at the periphery [6]. Both metabolic routes include important neuroactive catabolites with a possible role in the pathomechanism of migraine headache.

2.1. The Kynurenine Pathway

The first, rate-limiting step of the kynurenine pathway (KP) is the irreversible cleavage of the indole ring of L-tryptophan (TRP) either by indoleamine 2,3-dioxygenase 1 and 2 (IDO 1 and 2), or by tryptophan 2,3-dioxygenase (TDO) (Fig. 1).

IDO1 can be found throughout the body, and functions as a monomeric protein. Besides TDP, it can also utilize D-tryptophan, 5-hydroxy-L-kynurenine, 5-hydroxy-D-kynurenine, melatonin [7] and serotonin [8].

Less is known about IDO2, since it was isolated less than 10 years ago [9]. Data gathered so far indicate that the expression of IDO2 is not as widespread as that of IDO1, and that this enzyme may influences immune regulation differently than IDO1 [10]. TDO functions as a homotetramer and contains a heme B group. It is expressed predominantly in the liver, but can also be found in the brain and placenta [11, 12]. TDO is more substrate specific than IDO 1, claiming only L-tryptophan for metabolism [13].

Reactions catalyzed by either enzymes result in the formation of N-formyl-L-kynurenine, which is further degraded by kynurenine formamidase to L-kynurenine (L-KYN), the central metabolite of the KP. From L-KYN the kynurenine aminotransferases (KATs) form kynurenic acid (KYNA), kynureninase forms anthranilic acid (AA), while kynurenine-3-monoxygenase (KMO) activity results in the formation of 3-hydroxykynurenine (3HK). In mammals four type of KATs are present, KAT I also known as glutamine transaminase K/cysteine conjugate beta-lyase I [14, 15], KAT II/aminoadipate aminotransferase [16, 17], KAT III/cysteine conjugate beta-lyase II [18] and KAT IV/glutamicoxaloacetic transaminase 2/mitochondrial aspartate aminotransferase [19, 20]. All of the KATs are able to metabolize L-KYN to KYNA, however their substrate specificity, metabolic rate and expression are different [21].

Kynureninase is a pyridoxal-5'-phosphate dependent enzyme, it is able to catalyze two reactions along the KP it converts L-KYN to AA and it promotes the conversion of 3HK to 3-hydroxyanthranilic acid (3HA). The first mechanism is common in prokaryotes while in eukaryotes the latter pathway is preferred, therefore in mammals the conversion of L-KYN proceeds either to the KYNA or to the 3HK route [22].

AA is further metabolized by anthranilae-3-monoxygenase to 3HA, while from 3HK kynureninase forms the same compound. 3HK can be also converted by KATs to xanthurenic acid. 3HA is either subjected to auto oxidation resulting in cinnabaracid, or it is converted to 2-amino-3-carboxymuconate semialdehyde (ACMS) by 3-hydroxyanthranilic acid oxygenase. ACMS can be
further processed by aminocarboxymuconate-semialdehyde decarboxylase to 2-aminomuconate semialdehyde, followed by a non-enzymatic transformation to picolinic acid. ACMS can also undergo spontaneous pyridine ring closure to form quinolinic acid (QUIN), which can be further processed to form nicotinamide adenine dinucleotide.

2.2. Serotonin Pathway

The first rate-limiting step in the synthesis of 5HT is the hydroxylation of L-tryptophan by the enzyme tryptophan hydroxylase (TPH) and results in the formation of 5-hydroxytryptophan. This metabolite is transformed by aromatic amino acid decarboxylase (AADA) to 5HT. Metabolism of 5HT by monoamine oxidase (MAO) to 5-hydroxyindole acetaldehyde and further by aldehyde dehydrogenase, results in the end product 5-hydroxyindoleacetic acid (5HIAA), which is generally used to indirectly detect changes in serotonin levels. In the pineal gland and in the retina 5HT is metabolized by serotonin N-acetyltransferase to N-acetylserotonin, which is further converted by hydroxyindole-O-methyltransferase to melatonin.

2.3. Receptorial and Non-Receptorial Actions of Tryptophan Catabolites

Several kynurenine catabolites were shown to have direct receptorial actions. L-KYN, KYNA and cinnabarinic acid are ligands of aryl hydrocarbon receptors (AHRs) [23-25]. AHR is a nuclear transcription factor regulating the expression of genes of xenobiotic metabolizing enzymes, such as cytochrome P450 protein and glutathione transferase. This receptor possesses important functions in immune regulation, and T-cell development [26].

KYNA is an endogenous ionotropic glutamate receptor antagonist, acting on N-methyl-D-aspartate (NMDA) receptors at both the strychnine-insensitive glycine site and on the glutamate recognition site [27, 28]. In addition it is also an antagonist of kainate glutamate receptors [29], while it has a Janus-face effect on α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, in nanomolar concentration it has a facilitatory, while in micromolar concentration an inhibitory effect on these receptors [30-32]. KYNA’s broad receptorial action indicates that it has a very important role in the regulation of glutamatergic neurotransmission. This regulatory role is further supported by the fact that KYNA is an antagonist of α7-nicotinic acetylcholine (α7nACh) receptors, thus is able to modulate presynaptic glutamate release [33]. KYNA also has weak agonistic effects on the G protein coupled receptor 35 (GPRC 35) [34].

QUIN is a weak endogenous agonist of NMDA receptors [35], while cinnabarinic acid acts on type 4 metabotropic glutamate receptors [36].

Besides the direct receptorial actions of tryptophan catabolites, they also participate on oxidative processes, and thus are important factors in mitochondrial energy metabolism [37].
The effects of 5HT are transmitted by 7 receptor subtypes, 5HT1-7 receptors. Throughout their 5HT exerts myriad of functions, modulating mood, memory, appetite and circadian rhythms. With one exception, 5HT3, which is a ligand gated cation channel, 5HT receptors are G protein coupled receptors (GPCRs) [38].

In humans melatonin exerts its effect via two GPCRs, MT1 and MT2 [39-41], regulating circadian rhythms, and participating in the pathomechanism of depression, autism spectrum disorders and neurodegenerative disorders [42-44]. Melatonin is also a potent antioxidant [45].

3. MIGRAINE

Migraine attacks present with an unilateral throbbing headache accompanied by nausea or vomiting, and photo- or phonophobia. Attacks can be divided into four phases (prodrome, aura, headache and postdrome), however not every phase is present in every patient [46].

3.1. Prodrome

The first phase is the prodrome/ premonitory symptom phase occurring hours or even days before the headache attack [47]. Premonitory phase can be present with diverse symptoms including fatigue, mood changes, food cravings, concentration problems, sleep disturbances, gastrointestinal disturbances and yawning [48, 49]. The prevalence of premonitory symptoms shows great variance among different studies ranging from 33 to 80% [46, 50, 51]. Griffen and colleagues have revealed that about two-third of migraine patients are able to predict the occurrence of the headache based on premonitory symptoms [52], suggesting that these symptoms are an integral part of the migraine attack, not just accompaniments. Two hypotheses emerged attempting to explain the mechanisms behind the symptoms, one involving the neurotransmitter dopamine, the other involving the hypothalamus.

The dopamine hypothesis is based on the observation that dopamine agonists produce the same symptoms which are present during the premonitory phase, while antagonists, such as domperidone and metoclopramide may reverse some of these symptoms and even prevent or moderate the headache [53-55].

Hypothalamus is the most important nucleus in the human brain involved in the maintenance of homeostasis; it regulates endocrine functions, circadian rhythms and harmonizes the function of the parasympathetic and sympathetic nervous systems. The diverse functions imply that the impaired operation of the hypothalamus may result in very different and at first glance not related symptoms, resembling migraine premonitory symptoms. Furthermore, the clear connection between migraine and the sleep-wake cycle supports the involvement of the hypothalamus in the pathomechanism of migraine, however the exact routes of action need to be clarified [56, 57].

3.2. Aura

According to the classification of the International Headache Society the two most common forms of migraine are migraine without aura and migraine with aura (MA) [58]. About one-third of the patients suffering from migraine can be classified to the MA group [59], where aura indicates the presence of preceding or accompanying transient focal neurological symptoms related to the headache. The aura symptoms are in the most cases visual, however sensory, language and motor symptoms can also manifest [60]. A typical aura develops within 5 minutes and lasts for 5-60 minutes [58].

Cortical spreading depression (CSD) is considered as the pathophysiological equivalent of migraine aura [61, 62]. During CSD, a wave of transient depolarization spreads along the cortex accompanied by hyper- and hypoperfusion. The spreading velocity of the depolarization wave, 2-5 mm/s, correlates with the spread of the visual aura [61, 63]. Zhang and colleagues showed that after focal induction of CSD in rats a long lasting activation of meningeal nociceptors occurs with a delay, suggesting that CSD is able to directly activate these neurons [64]. However, another study on awake animals did not show pain behaviour after the induction of CSD, challenging the theory of CSD being the primary trigger of migraine headache [65]. Knock in models of familial hemiplegic migraine (FHM), an autosomal dominantly inherited form of migraine, are more susceptible to CSD, suggesting common mechanisms in CSD and FHM development [66]. In the formation of CSD, glutamate neurotransmission and NMDA receptors play a crucial role. Agonist of glutamate receptors can trigger CSD [67], while the non-competitive NMDA antagonist MK 801 is able to suppress the formation of cortical CSD waves [68]. Recent data suggest that different subtypes of NMDA receptors may play diverse roles in the formation of CSD, thus subtype specific antagonist may provide a therapeutic approach against CSD [69].

3.3. Headache Phase and Postdrome

For the great part of patients the most debilitating part of the migraine attack is the headache phase. Headache can last for 4-72 hours without treatment, with mild or severe strength [58]. The headache is thought to be caused by the activation and sensitization of the trigeminovascular system, consisting of the trigeminal nerve and innervated areas [70]. The trigeminal nerve is the largest cranial nerves in humans; it is divided into three main divisions, the ophthalmic, maxillary and mandibular branch, of which the ophthalmic gives the sensory innervations of the meninges.

For decades the vascular changes during the migraine attack were thought to be the cause of the headache, later a neuronal basic mechanism was suggested, and more recently the neurovascular origin of the headache was proposed, however, the primary triggering step in migraine generation is still debated [70].

The activation of the primary nociceptive trigeminal afferents leads to peripheral neuropeptide release, calcitonin gene-related peptide (CGRP), neurokinin A and substance P are liberated to the perineural space [71, 72], leading to vasodilatation and plasma protein extravasation and to the activation of mast cells and leukocytes collectively termed as neurogenic inflammation [73]. These phenomena are well characterized in animals, however in humans only little direct evidence supports the actual presence of neurogenic inflammation during the attack [74]. Despite the lack of human data, the importance of neuropeptides, is supported by current drug research data focusing on CGRP receptor antagonist and anti-CGRP antibodies [75, 76].

The continuous activation of the peripheral trigeminal nociceptors leads to peripheral sensitization which presents with the worsening of headache during activities increasing intracranial pressure e.g. coughing and in the throbbing nature of the headache [77].

The next important structure during the process of migraine headache is the caudal part of the spinal trigeminal nucleus (TNC), where most of the primary nociceptive afferents project. Activation at the periphery proceeds to the TNC, mostly by the aid of glutamate, as its level increases in the TNC after stimulation of the first-order trigeminal neurons [78]. Both glutamate [79] and its receptors [80] are present in the trigeminal system providing an important modulatory aspect of trigeminal noiception. Activation of the second-order neurons in the TNC can lead to central sensitization at this site [81], which presents in migraineurs during the attack as the symptom of allodynia [82].

Activation of the trigeminal system spreads forward to thalamic and cortical sites, resulting in the pain experienced by migraine patients.

Imaging studies revealed, that specific brain regions (periaqueductal grey matter, nucleus raphe magnus, dorsal raphe nucleus, locus coeruleus) are active during the headache phase, raising the possibility of the existence of a migraine generator region [83, 84].
These nuclei are the part of the descending pain modulatory system, their activation suggest that the processing and transmission of nociceptive information can be dysfunctional in migraine, however these theory needs to be confirmed.

After the cessation of the migraine pain patients often experience tiredness, difficulties in concentration, weakness, dizziness, which can be regarded as the postdrome phase, the least well-defined phase of the migraine attack [85, 86].

### 3.4. Cortical Hyperexcitability in Migraine

Cortical hyperexcitability is thought to contribute to the formation of CSD in migraine. The first evidence for this hypothesis is that the mutations of the three FHM genes can lead to hyperexcitability. FHM 1 is caused by the mutation in the CACNA1A gene located on the chromosome 19p13 coding the α2 subunit of the voltage-gated P/Q type Cav2.1 calcium channel [87]. In knock in animals this mutation results in increased glutamate release in the brain [88]. The second type of FHM, FHM II is caused by the mutation in the ATP1A2 gene [89] encoding the α2 subunit of Na/K pumps. Mutations of this gene can cause decreased uptake of glutamate and K+ from the synaptic cleft. Mutations in the SCN1A gene are responsible for the third type of FHM, FHM III. This gene encodes the α1 subunit of the neuronal Nav1.1 voltage-gated sodium channels [90], and leads to accelerated recovery of the channel from fast inactivation, leading to a higher firing rate [91]. These data indicate that FHM mutations can result in cortical hyperexcitability, suggesting that this phenomenon may also be involved in the formation of simple migraine.

Migraine patients show increased response to various sensory stimuli, further implicating the presence of a hyperexcitable state even between migraine attacks [92]. The lack of habituation to repeated sensory stimuli also confirms the presence of a hyper-responsive state even between migraine attacks [93-95]. With positron emission tomography (PET) Bouloache and colleagues found that an altered activation of the visual cortex is present in the interictal phase in migraineurs compared to controls, confirming the possibility of hyperexcitability with functional imaging [96].

Increased glutamate levels can be the basis of the hyperexcitable state; however, measurements of glutamate content in migraineurs provided conflicting results. Platelet and plasma measurements of glutamate indicated lower or similar levels in migraineurs and controls [97, 98], while in other studies increased basal glutamate levels were found [99]. During the attack increased levels of glutamate were found in the cerebrospinal fluid of migraine patients [97]. Proton magnetic resonance spectroscopy revealed that a higher glutamate/glutamine ratio is present in migraine women during the interictal phase compared to controls in the occipital cortex [100], supporting the presence of altered GLU metabolism in migraine.

### 4. INVOLVEMENT OF TRYPTOPHAN CATABOLITES IN MIGRAINE

#### 4.1. Serotonin in Migraine

The involvement of 5HT in migraine pathomechanism was first proposed by Sicuiteri and colleagues in 1961 after detecting increased urinary 5HIAA levels during migraine attacks [101]. Based on these findings numerous studies examined peripheral 5HT and 5HIAA levels in plasma and platelets, and their results suggest that no alteration is present during the migraine attack in 5HT levels compared to controls [102]. These findings are not surprising if we consider that the main source of 5HT and 5HIAA is the gut, where enterochromaffin cells synthesize 5HT to fulfill its role in the modulation of peristalsis [103].

Serotonin is a vasoconstrictor [104], and it was revealed that the peripheral veins of migraineurs show higher reactivity to 5HT than controls, furthermore veins of women suffering from migraine react even more to 5HT than veins of migrainous men [102] supporting the involvement of 5HT in migraine.

The measurements of brain 5HT levels and synthetic rates also yielded conflicting results. PET scans with the aid of α-[11C] methyl-L tryptophan, a 5HT precursor, revealed an increased 5HT synthesis capacity and also a higher brain uptake rate in women with migraine [105]. Using the same method, another study found no differences in 5HT synthetic rates between migraineurs and controls during the attack, but interictally a lower synthetic rate was found in migraineurs [106]. The same group examined interictal 5HT synthesis in non-menopausal women, and found no alteration in synthetic rates, however after administration of a 5HT receptor agonist, eletriptan a decreased rate was found in migraineurs but not in controls, suggesting an altered regulation of 5HT synthesis between attacks [107].

Genetic research also attempted to link 5HT to migraine. Studies examining the genetic association between migraine and the serotonin synthesizing and metabolizing enzymes TPH, AADA, MAO detected no connection [108-111]. Genetic research on 5HT receptors revealed no obvious relation with migraine in the case of 5HT1A [112], 5HT2A [113-115] and 5HT2C [116, 117] receptors; however in a small number of affected families association was found with 5HT1D receptors [118]. A more promising subject is the 5HT transporter, as its gene polymorphisms were found to be associated with migraine in independent meta-analyses [119, 120].

In spite of the conflicting result regarding the levels of 5HT in migraineurs, the effectiveness of its agonist, triptans in migraine therapy confirms the importance of this compound in disease pathogenesis. Triptans activate 5HT1B/1D and 5HT1F receptors but many questions are unanswered regarding their mechanism and site of action [121, 122].

#### 4.2. Melatonin in Migraine

Several studies have found decreased nocturnal melatonin levels in migraineurs, especially in women [123, 124]. In an other study, no difference was found between pain free periods of migraine patients and controls, while a decrease of melatonin level was detected in migraineurs during headache attacks [125]. Based on these and on other results connecting migraine seasonal variations with melatonin [126], assumption raised, that melatonin may play an important role in migraine pathogenesis. Subsequently trials were conducted to examine the efficacy of melatonin in migraine therapy, but controversial results were obtained. In an open-label study of Peres an colleagues melatonin was effective in migraine prevention [127], while in a randomized, double-blind, placebo-controlled crossover study of Alstadhaug and co-workers no beneficial effect of melatonin was detected [56]. Considering the importance of melatonin in the regulation of circadian rhythms and its close relation with hypothalamic functions, participation in migraine pathomechanism is highly possible, however the exact molecular mechanism and thus possible therapeutic efficacy need to be further confirmed.

#### 4.3. Kynurenines in Migraine

Since Sicuiteri’s observations about the involvement of 5HT in migraine pathomechanism [101] research focused on the 5HT pathway of TRP metabolism, although in the past years the KP’s involvement was also confirmed [4, 128].

TRP was used as an analgesic agent [129], and later on it was revealed that its KP catabolites L-KYN, KYNA, AA, XA, PIC and QUIN also possess analgesic properties in the tail-flick and hot-plate tests when administered intraperitoneally to rats [130] further supporting their involvement in modulation of nociceptive processing and thus in migraine pathomechanism.

KP catabolites are present both peripherally and centrally in the trigeminal system [21], providing the opportunity to modulate tri-
Tryptophan Catabolites and Migraine

In studies conducted so far with KYNA derivatives the site of application was peripheral. Although the purpose of both the combinatory treatment and the application of derivatives are to increase KYNA content in the brain, the possible peripheral involvement of KYNA in migraine processes can not be excluded. On the periphery both KYNA and other KP catabolites can participate in the formation and modulation of neurogenic inflammation (Fig. 2). At the level of the secondary trigeminal neurons KYNA and QUIN could modulate glutamatergic neurotransmission of nociceptive signals, while at higher levels, at the thalamus and in the cortex they may also influence trigeminal pain pathways. In a recent work, Kageneck and colleagues showed that KYNA was able to inhibit capsaicin induced CGRP release in the TNC, but had no effect on dorsal CGRP release, supporting the idea, that KYNA may exert altering effects at different sites of the trigeminal system [147]. Further knowledge about the KP’s involvement in trigeminal nociceptive processing could lead to a better understanding of migraine pathomechanism.

5. CONCLUSION

The aim of the present work was to draw some attention on the role of different tryptophan catabolites, especially kynurenic catabolites, in migraine pathomechanism. 5HT have been shown to be involved in the nociceptive processing of trigeminal signals, and various aspects of migraine generation, and the other important transmitter of the same metabolic pathway, melatonin was also proposed to play a part in these processes. The close relationship of the 5HT pathway and the KP of tryptophan degradation suggest, that alterations in one arm of the pathway, may influence the other, thus refer to a highly probable involvement of the KP in migraine. Research conducted so far in relation with the KP and migraine were focused on KYNA, and results confirm the involvement of this compound in migraine related processes. However, further studies are needed to detail the possible sites and receptors of effect of KYNA and also the influence of other KP catabolites.

CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by EUROHEADPAIN FP7, Project Number: 602633 and the Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/9.

REFERENCES


Bohór et al.


Cephalalgia 2007; 14: 249-51.

Cephalalgia 2001; 16: 69-76.


