Tryptophan Metabolic Pathways in Migraine-Related Mechanisms

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Migraine is a complex neurovascular disorder, which causes intense socioeconomic problems worldwide. The pathophysiology of disease is enigmatic; accordingly, therapy is not sufficient. Migraine research focused on tryptophan, which is metabolized via two main pathways, the serotonin and kynurenine pathways. Both produce neuroactive molecules that influence pain processing and stress response by disturbing neural and brain hypersensitivity and interacting with molecules that control vascular and inflammatory actions. Serotonin has a role in trigeminal pain processing, and melatonin, another product of this pathway, also has a role in these processes. One of the end products of the kynurenine pathway is kynurenic acid (KYNA), which can decrease the overexpression of migraine-related neuropeptides in experimental conditions. However, the ability of KYNA to cross the blood-brain barrier is minimal, necessitating the development of synthetic analogs with potentially better pharmacokinetic properties to exploit its therapeutic potential.

primary headaches migraine tryptophan serotonin pathway kynurenic acid melatonin kynurenine pathway

1. Migraine

Migraine is one of the most common neurological conditions with a high prevalence and morbidity [1] and is associated with a high economic burden [2]. The estimation of the Migraine Impact Model projected approximately 60,000–686,000 annual workdays as being affected by lost productive time due to migraine and estimated annual indirect costs as totaling 6.2–8.5 times the annual direct costs in USA [3]. Clinically, migraine is characterized by a unilateral throbbing, pulsing headache, associated with various symptoms, such as allodynia, photophobia, and phonophobia, which lasts for hours to days, and the pain has a negative impact on daily activities [4].

Despite extensive research, there are still questions that have not been fully answered about the pathomechanism of migraine; however, translational and clinical trials suggest that activation and sensitization of the trigeminal system (TS) are important during the attacks [5]. The theory of TS constitutes neurovascular incidence, peripheral and central sensitization, and neurogenic inflammation in the dural vessels. According to the literature, the major contributing pathophysiological event thought to initiate migraine is cerebral and meningeal arterial vasodilation. Nevertheless, the role of vasodilation in migraine is not fully understood, and recent findings challenge its necessity. During the attacks, several mediators are released from blood vessels, such as growth factors,

cytokines, adenosine triphosphate (ATP), and nitric oxide (NO), which induce local sterile meningeal inflammation [6][7].

2. Tryptophan and Its Role in Migraine

Tryptophan is an essential amino acid needed to produce and maintain proteins, muscles, enzymes, and neurotransmitters. Changes in tryptophan levels can cause an imbalance in the synthesis of 5-HT and melatonin in the brain and may play a role in the pathophysiology of numerous neuropsychiatric and neurodegenerative disorders [8].

Some research groups observed decreased serum and plasma tryptophan levels in migraine sufferers compared to healthy controls [9][10]. Furthermore, other clinical investigations showed increased tryptophan levels in migraine, especially during the aura phase [11][12]. Similarly, increased serum tryptophan was reported in cluster headaches [13].

Several studies have confirmed a reduction in tryptophan level in the interictal period and an increase in the ictal phase of migraine patients [14][15]. Tryptophan depletion does not trigger migraine attacks but causes lower levels of 5-HT in the brain, which enhance symptoms of migraine [16][17][18]. In a study, tryptophan depletion induced headache in migraineurs and increased nausea and dizziness. Moreover, ratings of glare and light-induced pain were greater in the tryptophan depletion condition [19]. Consistent with the results above, Jahromi et al. demonstrated that increased tryptophan intake reduces migraine attacks [20][21].

The fact that tryptophan is the precursor of several components that are possibly involved in migraine pathogenesis (e.g., 5-HT and kynurenines) can explain the relationship between tryptophan and migraine.

3. Role of the Tryptophan/Serotonin Pathway in Migraine

5-HT was first identified as a vasoconstrictor present in the blood [22], which constricts blood vessels, thereby potentially modulating nociceptive pain [23][24]. 5-HT receptors can be classified into seven families, which can be further divided into 14 subtypes, all of which are members of the G-protein-coupled receptor family, except the 5-HT_3 receptor, which is a ligand-gated ion channel [25]. 5-HT receptors are widely distributed in the CNS, including several areas involved in migraine, such as the striatum, cortex, hippocampus, thalamus, cerebellum, and raphe nuclei [26][27].

Sicuteri et al. were the first to suggest the importance of 5-HT in migraine when they found that, during a migraine attack, the amount of 5-hydroxyindoleacetic acid (5-HIAA), considered the main metabolite of 5-HT, increased in the urine, while the platelet 5-HT concentration decreased [28][29]; these results were confirmed by Curran et al. [30]. Other studies have reported that 5-HT infusion can interrupt spontaneous [31] or reserpine-induced [32] headache. Ren et al. reported low levels of serum serotonin in migraine patients, which was consistent with previous studies [33][34]. Moreover, they also found low levels of tryptophan in these patients [9].

3.1. Serotonin Pathway

The biochemical pathway for 5-HT synthesis initially involves the transformation of L-tryptophan into 5-hydroxytryptophan (5-HTP) by the rate-limiting enzyme L-tryptophan hydroxylase (TPH). 5-HTP is then decarboxylated to become 5-HT via the action of the cytosolic enzyme L-aromatic amino acid decarboxylase (AADC) [35][36]. Extracellular 5-HT enters the cells using the serotonin transporter (5-HTT), and excess 5-HT is metabolized. The metabolism of serotonin is primarily carried out by the outer mitochondrial membrane enzyme, monoamine oxidase (MAO) [37][38]. Finally, with the help of an aldehyde dehydrogenase enzyme, it is converted into 5-HIAA, which is excreted in the urine [35].

3.2. Serotonin Transporter

5-HTT retakes 5-HT from the synaptic gap to the presynaptic terminals, thereby reducing the effect of 5-HT. The transport process is controlled by the Na^+/Cl^- ion gradient [39]. 5-HTT occurs mainly in the area of the raphe nuclei and serotonergic projection areas (e.g., cortical areas, thalamus, hippocampus CA3 region, and amygdala) [40]. Imaging studies have established that the distribution of 5-HTT in the brain stem area is greater in migraine patients [41]. It has been observed that familial hemiplegic migraine (FHM) patients have a low level of 5-HT in platelets, and it has also been described that the 5-HT transport capacity is low. In addition, reduced metabolite levels in cerebrospinal fluid were observed in these patients [42].

3.3. Serotonin Receptors

5-HT receptors are important in the regulation of serotonergic neurotransmission, and they play a distinguished role in several behavioral and physiological functions [43]. In previous studies, it was observed that the neurons of the dorsal raphe and the trigeminal ganglia (TG) are mostly serotonergic [44][45].

In humans, it has been demonstrated that both receptor $5HT_{1B}$ and $5HT_{1D}$ subtypes are present in trigeminal neurons [46][47], and both receptors have been detected at mRNA and protein levels in the TG [48] and colocalize with calcitonin gene-related peptide (CGRP), substance P (SP), and nitric oxide synthases (NOS) [47].

Triptans are 5-$HT_{1B/1D}$ agonists with some affinity for the 5-HT_{1F} receptor subtype, and they are clinically effective anti-migraine drugs. They can have an inhibitory effect on the trigeminal sensory fibers, which is attributed to the inhibition of endogenous CGRP and SP release [49]. The efficacy of triptans also suggests that 5-HT may modulate the pathogenesis of migraine. Unfortunately, triptans are contraindicated in patients with high blood pressure and cardiovascular or cerebrovascular disease due to their vasoconstrictive effect. In addition, these drugs are not effective for everyone, often leading to excessive drug use, which eventually causes migraines to become chronic [50].

These facts led to the development of ditans, the new class of selective 5-HT_{1F} receptor agonists that do not have vasoconstrictive properties [51][52]. The 5-HT_{1F} receptor is expressed in several brain areas involved in migraine attacks, such as the cortex, the hypothalamus, the trigeminal ganglia, the trigeminal nucleus caudalis (TNC), the

locus coeruleus, the middle cerebral artery, and the upper cervical cord [53][54]. Several selective 5-HT_{1F} receptor agonists have been developed in the past years; in preclinical studies, they could successfully inhibit dural extravasation after TG stimulation and hinder neuronal activation in the TNC following trigeminovascular activation [55][56][57][58]. However, only lasmiditan can currently be used as anti-migraine therapy, but it has no therapeutic gain over triptans. Lasmiditan can cross the BBB and, thus, exert its effects centrally on the trigeminovascular system; however, at the same time, it also has a peripheral effect, via 5-HT_{1F} receptors expressed on trigeminal afferents or TG [59]. Lasmiditan can probably moderate the activation of Sp5C second-order trigeminal neurons, which has an important role in the pathomechanism of migraine [60][61].

5-HT_{2B} receptors can influence the release of 5-HT through the 5-HTT and are also involved in the normal physiological regulation of blood plasma 5-HT levels [62]. In rats, 5-HT_{2B} receptors are slightly expressed in neurons located in the cerebellum, the posterior hypothalamus, the lateral septum, the medial amygdala, the spinal cord, and the dorsal root ganglion (DRG). Unlike the 5-HT_1 receptor, it seems that the 5-HT_{2B} receptors do not inhibit/decrease the release of neuropeptides involved in migraine (CGRP, glutamate) from trigeminal neurons [63]. Indeed, the 5-HT_{2B} receptor can activate NOS, which promotes the synthesis of NO [64], a potentially key component in the development of a migraine attack. In guinea pigs, acute activation of 5-HT_{2B} receptors by m-chlorophenylpiperazine (mCPP) led to NO-dependent plasma protein extravasation (PPE) in the dura mater and neuronal activation in the TNC, which could be inhibited by selective 5-HT_{2B} receptor antagonists [65][66][67]. In humans, mCPP, with 5-$HT_{2B/2C}$ receptor affinity, leads to delayed migraine-like headaches in migraine sufferers and nonspecific headaches in healthy subjects [68]. Methysergide, a 5-HT_{2B} antagonist, can reduce the frequency of migraine, but it has to be used for a longer period to exert its therapeutic effect [69]. Johnson et al. reported that, after electrical stimulation of the TG, LY202146, a selective 5-HT_{2B} receptor antagonist, failed to inhibit protein extravasation [66], suggesting that the 5-HT_{2B} receptor may play a role in triggering the migraine attack, but is not related directly to the release of peptides from trigeminal neurons. These observations resemble the results obtained in clinical research where effective preventive agents, such as methysergide and pizotifen, could not inhibit the onset of a migraine attack.

3.4. Melatonin

Melatonin is a tryptophan metabolite that plays a role in regulating circadian rhythms, and numerous studies have demonstrated that melatonin can exert its anti-migraine effect in several ways. Melatonin can regulate neurotransmitters and neural pathways; it can inhibit the synthesis of NO, as well as the release of CGRP and dopamine, and it can antagonize glutamate-induced excitotoxicity [70][71][72][73]. Furthermore, it has an anti-free radical effect and inhibits the release of inflammatory factors [74]. It is supported by many studies that melatonin has a role in pain transmission and sensitization [73][75][76][77][78]. Membrane melatonin receptors (MT1 and MT2) have been identified in the thalamus, dorsal horn of the spinal cord, trigeminal tract, and trigeminal nucleus, which are involved in nociceptive transmission [79][80].

Melatonin can increase the release of β-endorphin from the pituitary gland and interacts with opioidergic, muscarinic, nicotinic, serotonergic, and α1 and α2-adrenergic receptors located in the CNS and the dorsal horn of

the spinal cord; thus, it may be able to exert an analgesic effect [81][82][83]. In fibromyalgia, inflammatory bowel syndrome, and migraine, melatonin was able to reduce pain [84][85][86]. In another study, melatonin treatment was able to modify the central level of brain-derived neurotrophic factor (BDNF) in rats submitted to acute and chronic inflammation [87].

Masruha and colleagues found low levels of 6-sulfatoxymelatonin—a urinary metabolite of melatonin—in migraine patients [88]. Previous studies found low levels of melatonin in episodic [89] and chronic [90] migraine patients. Murialdo et al. found that, during the luteal phase, migraineurs showed a less pronounced change in melatonin levels than controls. Melatonin secretion was further decreased during migraine attack [91]. In line with these observations, Brun et al. found significantly lower melatonin levels in women with migraine during the cycle, while healthy participants showed a significant increase in melatonin secretion from the follicular to the luteal phase [92].

According to these data, it is possible that melatonin may be beneficial in migraine prophylaxis.

4. Role of Tryptophan/Kynurenine Pathway in Migraine

The role of the tryptophan/kynurenine metabolic pathway is receiving more attention in various illnesses including migraine [36]. In parallel to 5-HT synthesis, the central route of the tryptophan metabolism is the KP [93].

4.1. Kynurenine Pathway

The transformation process of tryptophan into N-formyl-L-kynurenine is carried out by two rate-limiting enzymes: tryptophan-2,3-dioxygenase (TDO) and indoleamine-2,3-dioxygenase (IDO). N-formyl-L-kynurenine is degraded by formamidase to L-kynurenine (L-KYN). L-KYN can be metabolized into kynurenic acid (KYNA), 3-hydroxy-L-kynurenine (3-HK), or anthranilic acid (AA) under the action of kynurenine aminotransferase (KAT), kynurenine-3-monooxygenase (KMO), and kynureninase (KYNU) enzymes. 3-HK can be further converted to xanthurenic acid (XA) by KAT or to 3-hydroxyanthranilic acid (3-HANA) by KYNU. 3-Hydroxyanthranilic acid is then metabolized by 3-hydroxyanthranilate oxidase (3-HAO) to 2-amino-3-carboxymuconate-semialdehyde, which is transformed into picolinic acid (PIC) or quinolinic acid (QUIN). In the last step of the KP, QUIN is converted into the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) [94].

4.2. Kynurenines

KP produces neuroactive metabolites which have a role in the modification of the trigemino-vascular activation processes and can interact with glutamate receptors in the CNS [95]; therefore, they may be involved in the pathophysiology of migraine.

Among the kynurenines, KYNA should be mentioned, which can act through N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate receptors, and G-protein-coupled receptor 35 (GPR35), and these receptors have a major role in pain processing and neuroinflammation [94]. Experimental data suggest, that in the brain, an increased level of KYNA has neuroprotective effects [96][97]. Additionally, in an

animal model of migraine, KYNA was able to inhibit trigemino-vascular activation [98][99]. Furthermore, KYNA can modulate the activation of migraine generators and inhibits cortical spreading depression (CSD) [100]. Oláh and colleagues reported that, in rats, peripherally administered KYNA was able to reduce the number of CSD waves; moreover, it decreased the permeability of the blood–brain barrier (BBB) during CSD [101]. Knyihár-Csillik et al. reported reduced KAT expression after the electrical stimulation of the TG [102]. Moreover, Spekker et al. found that inflammatory soup was able to cause sterile neurogenic inflammation in the dura mater and increased the area covered by CGRP and transient receptor potential vanilloid 1 (TRPV1) immunoreactive fibers, as well as the number of neuronal nNOS-positive cells in the caudal trigeminal nucleus, and pretreatment with KYNA was able to modulate the changes caused by inflammatory soup. KYNA probably inhibited the glutamate system, thereby preventing the sensitization processes which are key actors in migraine [103].

It has been reported that KYNA has anti-nociceptive effects in both the first- and second-order trigeminal nociceptors. Zhang et al. found that KYNA dose-dependently suppressed carrageenan-induced thermal hyperalgesia and significantly reduced c-fos expression in both the superficial and the deep laminae of the dorsal horn in rats [104]. In another study, after carrageenan injection into the tibio-tarsal joint, locally administered KYNA was able to abolish allodynia and cause anti-nociception [105].

The therapeutic use of KYNA is hampered by the fact that it is difficult to cross the BBB [106]. The development of KYNA analogs with retained or modified activity can be a solution to this problem. These compounds are promising because they are capable of selectively inhibiting NMDA receptors containing the NR2B subunit, which play a role in the modulation of pain perception.

L-KYN is the source of all the other kynurenine metabolites, and it is readily transported across the BBB [106]. L-KYN in combination with probenecid can prevent nitroglycerin (NTG)-induced changes in c-fos expression in rat TNC [98]. Peripheral treatment with L-KYN can dose-dependently enhance the concentration of KYNA in the brain; thus, it may provide a possible therapeutic solution for the treatment of several neurological disorders, including primary headaches. However, the physiological effect and safety of L-KYN in vivo in humans are still awaiting clarification.

References

1. Steiner, T.J.; Stovner, L.J.; Vos, T. GBD 2015: Migraine is the third cause of disability in under 50s. J. Headache Pain 2016, 17, 104.
2. Cerbo, R.; Pesare, M.; Aurilia, C.; Rondelli, V.; Barbanti, P. Socio–economic costs of migraine. J. Headache Pain 2001, 2 (Suppl. S1), s15–s19.
3. Yucel, A.; Thach, A.; Kumar, S.; Loden, C.; Bensink, M.; Goldfarb, N. Estimating the Economic Burden of Migraine on US Employers. Am. J. Manag. Care 2020, 26, e403–e408.

4. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013, 33, 629–808.
5. Goadsby, P.; Holland, P.; Martins-Oliveira, M.; Hoffmann, J.; Schankin, C.; Akerman, S. Pathophysiology of Migraine: A Disorder of Sensory Processing. Physiol. Rev. 2017, 97, 553–622.
6. Edvinsson, L. Tracing neural connections to pain pathways with relevance to primary headaches. Cephalalgia 2011, 31, 737–747.
7. Spekker, E.; Tanaka, M.; Szabó, A.; Vécsei, L. Neurogenic Inflammation: The Participant in Migraine and Recent Advancements in Translational Research. Biomedicines 2021, 10, 76.
8. Comai, S.; Bertazzo, A.; Brughera, M.; Crotti, S. Tryptophan in health and disease. Adv. Clin. Chem. 2020, 95, 165–218.
9. Ren, C.; Liu, J.; Zhou, J.; Liang, H.; Wang, Y.; Sun, Y.; Ma, B.; Yin, Y. Low levels of serum serotonin and amino acids identified in migraine patients. Biochem. Biophys. Res. Commun. 2018, 496, 267–273.
10. D’Andrea, G.; D’Amico, D.; Bussone, G.; Bolner, A.; Aguggia, M.; Saracco, M.G.; Galloni, E.; De Riva, V.; D’Arrigo, A.; Colavito, D.; et al. Tryptamine levels are low in plasma of chronic migraine and chronic tension-type headache. Neurol. Sci. 2014, 35, 1941–1945.
11. Alam, Z.; Coombes, N.; Waring, R.H.; Williams, A.C.; Steventon, G.B. Plasma levels of neuroexcitatory amino acids in patients with migraine or tension headache. J. Neurol. Sci. 1998, 156, 102–106.
12. Curto, M.; Lionetto, L.; Negro, A.; Capi, M.; Fazio, F.; Giamberardino, M.A.; Simmaco, M.; Nicoletti, F.; Martelletti, P. Altered kynurenine pathway metabolites in serum of chronic migraine patients. J. Headache Pain 2015, 17, 47.
13. Curto, M.; Lionetto, L.; Negro, A.; Capi, M.; Perugino, F.; Fazio, F.; Giamberardino, M.A.; Simmaco, M.; Nicoletti, F.; Martelletti, P. Altered serum levels of kynurenine metabolites in patients affected by cluster headache. J. Headache Pain 2015, 17, 27.
14. Young, S. Acute tryptophan depletion in humans: A review of theoretical, practical and ethical aspects. J. Psychiatry Neurosci. 2013, 38, 294–305.
15. Deen, M.; Christensen, C.E.; Hougaard, A.; Hansen, H.D.; Knudsen, G.M.; Ashina, M. Serotonergic mechanisms in the migraine brain—A systematic review. Cephalalgia 2017, 37, 251–264.
16. Carpenter, L.L.; Anderson, G.M.; Pelton, G.H.; Gudin, J.A.; Kirwin, P.D.S.; Price, L.H.; Heninger, G.R.; McDougle, C.J. Tryptophan Depletion During Continuous CSF Sampling in Healthy Human Subjects. Neuropsychopharmacology 1998, 19, 26–35.

17. Williams, W.A.; Shoaf, S.E.; Hommer, D.; Rawlings, R.; Linnoila, M. Effects of acute tryptophan depletion on plasma and cerebrospinal fluid tryptophan and 5-hydroxyindoleacetic acid in normal volunteers. J. Neurochem. 1999, 72, 1641–1647.
18. Van Der Stelt, H.M.; Broersen, L.M.; Olivier, B.; Westenberg, H.G.M. Effects of dietary tryptophan variations on extracellular serotonin in the dorsal hippocampus of rats. Psychopharmacology 2004, 172, 137–144.
19. Drummond, P. Tryptophan Depletion Increases Nausea, Headache and Photophobia in Migraine Sufferers. Cephalalgia 2006, 26, 1225–1233.
20. Jahromi, S.R.; Togha, M.; Ghorbani, Z.; Hekmatdoost, A.; Khorsha, F.; Rafiee, P.; Shirani, P.; Nourmohammadi, M.; Ansari, H. The association between dietary tryptophan intake and migraine. Neurol. Sci. 2019, 40, 2349–2355.
21. Gecse, K.; Dobos, D.; Aranyi, C.S.; Galambos, A.; Baksa, D.; Kocsel, N.; Szabó, E.; Pap, D.; Virág, D.; Ludányi, K.; et al. Association of plasma tryptophan concentration with periaqueductal gray matter functional connectivity in migraine patients. Sci. Rep. 2022, 12, 739.
22. Villalón, C.M.; vanDenBrink, A.M. The Role of 5-Hydroxytryptamine in the Pathophysiology of Migraine and its Relevance to the Design of Novel Treatments. Med. Chem. 2017, 17, 928–938.
23. Taylor, B.K.; Basbaum, A.I. Neurochemical Characterization of Extracellular Serotonin in the Rostral Ventromedial Medulla and Its Modulation by Noxious Stimuli. J. Neurochem. 1995, 65, 578–589.
24. Comings, D.E. Serotonin: A Key to Migraine Disorders? Health Fit. Mag. 1994.
25. Nichols, D.E.; Nichols, C.D. Serotonin Receptors. Chem. Rev. 2008, 108, 1614–1641.
26. Varnäs, K.; Halldin, C.; Hall, H. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. Hum. Brain Mapp. 2004, 22, 246–260.
27. Barnes, N.M.; Sharp, T. A review of central 5-HT receptors and their function. Neuropharmacology 1999, 38, 1083–1152.
28. Sicuteri, F.; Testi, A.; Anselmi, B. Biochemical investigations in headache: Increase in hydroxytryindoleacetic acid excretion during migraine attacks. Int. Arch. Allergy 1961, 19, 55–58.
29. Anthony, M.; Hinterberger, H.; Lance, J.W. Plasma Serotonin in Migraine and Stress. Arch. Neurol. 1967, 16, 544–552.
30. Curran, D.A.; Hinterberger, H.; Lance, J.W. Total plasma serotonin, 5-hydroxyindoleacetic acid and p-hydroxy-m-methoxymandelic acid excretion in normal and migrainous subjects. Brain 1965, 88, 997–1010.

31. Lance, J.W.; Anthony, M.; Hinterberger, H. The control of cranial arteries by humoral mechanisms and its relation to the migraine syndrome. Headache 1967, 7, 93–102.
32. Kimball, R.W.; Friedman, A.P.; Vallejo, E. Effect of serotonin in migraine patients. Neurology 1960, 10, 107–111.
33. Ferrari, M.D.; Odink, J.; Tapparelli, C.; Van Kempen, G.; Pennings, E.J.; Bruyn, G.W. Serotonin metabolism in migraine. Neurology 1989, 39, 1239–1242.
34. Rossi, C.; Pini, L.A.; Cupini, M.L.; Calabresi, P.; Sarchielli, P. Endocannabinoids in platelets of chronic migraine patients and medication-overuse headache patients: Relation with serotonin levels. Eur. J. Clin. Pharmacol. 2008, 64, 1–8.
35. Best, J.; Nijhout, H.F.; Reed, M. Serotonin synthesis, release and reuptake in terminals: A mathematical model. Theor. Biol. Med. Model. 2010, 7, 34.
36. Höglund, E.; Øverli, Ø.; Winberg, S. Tryptophan Metabolic Pathways and Brain Serotonergic Activity: A Comparative Review. Front. Endocrinol. 2019, 10, 158.
37. Sandler, M. Changes in 5-hydroxytryptamine and its metabolites in neuropsychiatric disorders. Psychopharmacol. Bull. 1981, 17, 19–21.
38. Mohammad-Zadeh, L.F.; Moses, L.; Gwaltney-Brant, S.M. Serotonin: A review. J. Vet.-Pharmacol. Ther. 2008, 31, 187–199.
39. Lesch, K.; Aulakh, C.S.; Wolozin, B.L.; Tolliver, T.J.; Hill, J.L.; Murphy, D.L. Regional brain expression of serotonin transporter mRNA and its regulation by reuptake inhibiting antidepressants. Mol. Brain Res. 1993, 17, 31–35.
40. Murphy, D.L.; Mueller, E.A.; Aulakh, C.S.; Bagdy, G.; Garrick, N.A. Serotoninergic Function in Neuropsychiatric Disorders. In Serotonin; Mylechrane, E.J., Angus, J.A., de la Lande, I.S., Humphrey, P.P.A., Eds.; Macmillan Press: London, UK, 1989; pp. 257–264.
41. Schuh-Hofer, S.; Richter, M.; Geworski, L.; Villringer, A.; Israel, H.; Wenzel, R.; Munz, D.L.; Arnold, G. Increased serotonin transporter availability in the brainstem of migraineurs. J. Neurol. 2007, 254, 789–796.
42. Horvath, G.A.; Selby, K.; Poskitt, K.; Hyland, K.; Waters, P.J.; Coulter-Mackie, M.; Stockler-Ipsiroglu, S.G. Hemiplegic migraine, seizures, progressive spastic paraparesis, mood disorder, and coma in siblings with low systemic serotonin. Cephalalgia 2011, 31, 1580–1586.
43. Meneses, A. Physiological, pathophysiological and therapeutic roles of 5-HT systems in learning and memory. Rev. Neurosci. 1998, 9, 275–289.
44. Berman, N.E.; Puri, V.; Chandrala, S.; Puri, S.; MacGregor, R.; Liverman, C.S.; Klein, R.M. Serotonin in Trigeminal Ganglia of Female Rodents: Relevance to Menstrual Migraine. Headache 2006, 46, 1230–1245.

45. Lambert, G. The Lack of Peripheral Pathology in Migraine Headache. Headache 2010, 50, 895–908.
46. Longmore, J.; Shaw, D.; Smith, D.; Hopkins, R.; McAlliste, G.; Pickard, J.; Sirinathsinghji, D.; Butler, A.; Hill, R. Differential Distribution of 5Ht1D-and 5HT1B-Immunoreactivity within the Human Trigemino-Cerebrovascular System: Implications for the Discovery of New Antimigraine Drugs. Cephalalgia 1997, 17, 833–842.
47. Hou, M.; Kanje, M.; Longmore, J.; Tajti, J.; Uddman, R.; Edvinsson, L. 5-HT1B and 5-HT1D receptors in the human trigeminal ganglion: Co-localization with calcitonin gene-related peptide, substance P and nitric oxide synthase. Brain Res. 2001, 909, 112–120.
48. Bouchelet, I.; Cohen, Z.; Case, B.; Séguéla, P.; Hamel, E. Differential expression of sumatriptan-sensitive 5-hydroxytryptamine receptors in human trigeminal ganglia and cerebral blood vessels. Mol. Pharmacol. 1996, 50, 219–223.
49. Longmore, J.; Dowson, A.J.; Hill, R.G. Advances in migraine therapy—5-HT receptor subtype-specific agonist drugs. Curr. Opin. CPNS Investig. Drugs 1999, 1, 39–53.
50. Dodick, D.; Lipton, R.B.; Martin, V.; Papademetriou, V.; Rosamond, W.; MaassenVanDenBrink, A.; Loutfi, H.; Welch, K.M.; Goadsby, P.J.; Hahn, S.; et al. Consensus Statement: Cardiovascular Safety Profile of Triptans (5-HT1B/1D Agonists) in the Acute Treatment of Migraine. Headache 2004, 44, 414–425.
51. Cohen, M.L.; Schenck, K. Contractile responses to sumatriptan and ergotamine in the rabbit saphenous vein: Effect of selective 5-HT1F receptor agonists and PGF2α. J. Cereb. Blood Flow Metab. 2000, 131, 562–568.
52. Ramadan, N.; Skljarevski, V.; Phebus, L.; Johnson, K. 5-HT1F Receptor Agonists in Acute Migraine Treatment: A Hypothesis. Cephalalgia 2003, 23, 776–785.
53. Adham, N.; Kao, H.T.; Schecter, L.E.; Bard, J.; Olsen, M.; Urquhart, D.; Durkin, M.; Hartig, P.R.; Weinshank, R.L.; Branchek, T.A. Cloning of another human serotonin receptor (5-HT1F): A fifth 5-HT1 receptor subtype coupled to the inhibition of adenylate cyclase. Proc. Natl. Acad. Sci. USA 1993, 90, 408–412.
54. Vila-Pueyo, M. Targeted 5-HT1F Therapies for Migraine. Neurotherapeutics 2018, 15, 291–303.
55. Johnson, K.W.; Schaus, J.M.; Durkin, M.M.; Audia, J.E.; Kaldor, S.W.; Flaugh, M.E.; Adham, N.; Zgombick, J.M.; Cohen, M.L.; Branchek, T.A.; et al. 5-HT1F receptor agonists inhibit neurogenic dural inflammation in guinea pigs. NeuroReport 1997, 8, 2237–2239.
56. Mitsikostas, D.D.; del Rio, M.S.; Moskowitz, M.A.; Waeber, C. Both 5-HT1B and 5-HT1F receptors modulate c-fos expression within rat trigeminal nucleus caudalis. Eur. J. Pharmacol. 1999, 369, 271–277.

57. Mitsikostas, D.; del Rio, M.S.; Waeber, C. 5-Hydroxytryptamine1B/1D and 5-Hydroxytryptamine1FReceptors Inhibit Capsaicin-Induced C-Fos Immunoreactivity within Mouse Trigeminal Nucleus Caudalis. Cephalalgia 2002, 22, 384–394.
58. Nelson, D.L.; Phebus, L.A.; Johnson, K.W.; Wainscott, D.B.; Cohen, M.L.; Calligaro, D.O.; Xu, Y.-C. Preclinical pharmacological profile of the selective 5-HT1F receptor agonist lasmiditan. Cephalalgia 2010, 30, 1159–1169.
59. Kovalchin, J.; Ghiglieri, A.; Zanelli, E.; Ings, R.; Mathers, T. Lasmiditan acts specifically on the 5-HT1F receptors in the central nervous system. Cephalalgia 2016, 36, 103.
60. Akerman, S.; Romero-Reyes, M.; Holland, P.R. Current and novel insights into the neurophysiology of migraine and its implications for therapeutics. Pharmacol. Ther. 2017, 172, 151–170.
61. Huang, P.-C.; Yang, F.-C.; Chang, C.-M.; Yang, C.-P. Targeting the 5-HT1B/1D and 5-HT1F receptors for acute migraine treatment. Prog. Brain Res. 2020, 255, 99–121.
62. Callebert, J.; Esteve, J.M.; Hervé, P.; Peoc'H, K.; Tournois, C.; Drouet, L.; Launay, J.M.; Maroteaux, L. Evidence for a Control of Plasma Serotonin Levels by 5-Hydroxytryptamine2B Receptors in Mice. J. Pharmacol. Exp. Ther. 2006, 317, 724–731.
63. Xiao, Y.; Richter, J.A.; Hurley, J.H. Release of Glutamate and CGRP from Trigeminal Ganglion Neurons: Role of Calcium Channels and 5-HT1 Receptor Signaling. Mol. Pain 2008, 4, 12.
64. Florian, J.A.; Watts, S.W. Integration of mitogen-activated protein kinase kinase activation in vascular 5-hydroxytryptamine2A receptor signal transduction. J. Pharmacol. Exp. Ther. 1998, 284, 346–355.
65. Martin, R.S.; Martin, G.R. Investigations into migraine pathogenesis: Time course for effects of m-CPP, BW723C86 or glyceryl trinitrate on appearance of Fos-like immunoreactivity in rat trigeminal nucleus caudalis (TNC). Cephalalgia 2001, 21, 46–52.
66. Johnson, K.; Nelson, D.; Dieckman, D.; Wainscott, D.; Lucaites, V.; Audia, J.; Owton, W.; Phebus, L. Neurogenic Dural Protein Extravasation Induced by Meta-Chlorophenylpiperazine (mCPP) Involves Nitric Oxide and 5-HT2B Receptor Activation. Cephalalgia 2003, 23, 117–123.
67. Schmitz, B.; Ullmer, C.; Segelcke, D.; Gwarek, M.; Zhu, X.-R.; Lübbert, H. BF-1—A novel selective 5-HT2B receptor antagonist blocking neurogenic dural plasma protein extravasation in guinea pigs. Eur. J. Pharmacol. 2015, 751, 73–80.
68. Brewerton, T.D.; Murphy, D.L.; Mueller, E.A.; Jimerson, D.C. Induction of migrainelike headaches by the serotonin agonist m-chlorophenylpiperazine. Clin. Pharmacol. Ther. 1988, 43, 605–609.
69. Silberstein, S.D. Methysergide. Cephalalgia 1998, 18, 421–435.

70. Bettahi, I.; Pozo, D.; Osuna, C.; Reiter, R.J.; Acuña-Castroviejo, D.; Guerrero, J.M. Melatonin reduces nitric oxide synthase activity in rat hypothalamus. J. Pineal Res. 1996, 20, 205–210.
71. Lance, J.W.; Anthony, M.; Somerville, B. Comparative Trial of Serotonin Antagonists in the Management of Migraine. Br. Med. J. 1970, 2, 327–330.
72. Reiter, R.J.; Calvo, J.R.; Karbownik, M.; Qi, W.; Tan, D.X. Melatonin and Its Relation to the Immune System and Inflammation. Ann. N. Y. Acad. Sci. 2000, 917, 376–386.
73. Peres, M.F.P.; Masruha, M.R.; Zukerman, E.; Moreira-Filho, C.A.; Cavalheiro, E. Potential therapeutic use of melatonin in migraine and other headache disorders. Expert Opin. Investig. Drugs 2006, 15, 367–375.
74. Adnyana, I.M.O.; Tertia, C.; Widyadharma, I.P.E.; Mahadewi, N.P.A.P. Melatonin as a treatment for migraine sufferers: A systematic review. Egypt. J. Neurol. Psychiatry Neurosurg. 2022, 58, 94.
75. Scarabelot, V.L.; Medeiros, L.F.; de Oliveira, C.; Adachi, L.N.S.; de Macedo, I.C.; Cioato, S.G.; de Freitas, J.S.; de Souza, A.; Quevedo, A.; Caumo, W.; et al. Melatonin Alters the Mechanical and Thermal Hyperalgesia Induced by Orofacial Pain Model in Rats. Inflammation 2016, 39, 1649–1659.
76. Torres, I.L.; Laste, G.; de Macedo, I.C.; Rozisky, J.R.; da Silva, F.R.; Caumo, W. Melatonin administration reduces inflammatory pain in rats. J. Pain Res. 2012, 5, 359–362.
77. Noseda, R.; Hernández, A.; Valladares, L.; Mondaca, M.; Laurido, C.; Soto-Moyano, R. Melatonin-induced inhibition of spinal cord synaptic potentiation in rats is MT2 receptor-dependent. Neurosci. Lett. 2004, 360, 41–44.
78. Danilov, A.; Kurganova, J. Melatonin in Chronic Pain Syndromes. Pain Ther. 2016, 5, 1–17.
79. Weaver, D.; Rivkees, S.; Reppert, S. Localization and characterization of melatonin receptors in rodent brain by in vitro autoradiography. J. Neurosci. 1989, 9, 2581–2590.
80. Williams, L.M.; Hannah, L.T.; Hastings, M.H.; Maywood, E.S. Melatonin receptors in the rat brain and pituitary. J. Pineal Res. 1995, 19, 173–177.
81. Yu, C.-X.; Zhu, C.-B.; Xu, S.-F.; Cao, X.-D.; Wu, G.-C. The analgesic effects of peripheral and central administration of melatonin in rats. Eur. J. Pharmacol. 2000, 403, 49–53.
82. Shavali, S.; Ho, B.; Govitrapong, P.; Sawlom, S.; Ajjimaporn, A.; Klongpanichapak, S.; Ebadi, M. Melatonin exerts its analgesic actions not by binding to opioid receptor subtypes but by increasing the release of β-endorphin an endogenous opioid. Brain Res. Bull. 2005, 64, 471–479.
83. Srinivasan, V.; Lauterbach, E.C.; Ho, K.Y.; Acuña-Castroviejo, D.; Zakaria, R.; Brzezinski, A. Melatonin in Antinociception: Its Therapeutic Applications. Curr. Neuropharmacol. 2012, 10, 167–178.

84. Mease, P. Fibromyalgia syndrome: Review of clinical presentation, pathogenesis, outcome measures, and treatment. J. Rheumatol. 2005, 75, 6–21.
85. Reiter, R.J.; Acuna-Castroviejo, D.; Tan, D.-X. Melatonin therapy in fibromyalgia. Curr. Pain Headache Rep. 2007, 11, 339–342.
86. Song, G.H.; Leng, P.H.; Gwee, K.A.; Moochhala, S.M.; Ho, K.Y. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: A randomised, double blind, placebo controlled study. Gut 2005, 54, 1402–1407.
87. Laste, G.; Rozisky, J.R.; Caumo, W.; Torres, I.L.D.S. Short- but Not Long-Term Melatonin Administration Reduces Central Levels of Brain-Derived Neurotrophic Factor in Rats with Inflammatory Pain. Neuroimmunomodulation 2015, 22, 358–364.
88. Masruha, M.R.; Lin, J.; Vieira, D.S.D.S.; Minett, T.S.; Cipolla-Neto, J.; Zukerman, E.; Vilanova, L.C.; Peres, M.F. Urinary 6-Sulphatoxymelatonin Levels Are Depressed in Chronic Migraine and Several Comorbidities. Headache 2010, 50, 413–419.
89. Claustrat, B.; Loisy, C.; Brun, J.; Beorchia, S.; Arnaud, J.L.; Chazot, G. Nocturnal Plasma Melatonin Levels in Migraine: A Preliminary Report. Headache 1989, 29, 242–245.
90. Masruha, M.R.; Vieira, D.S.D.S.; Minett, T.S.C.; Cipolla-Neto, J.; Zukerman, E.; Vilanova, L.C.P.; Peres, M.F.P. Low urinary 6-sulphatoxymelatonin concentrations in acute migraine. J. Headache Pain 2008, 9, 221–224.
91. Murialdo, G.; Fonzi, S.; Costelli, P.; Solinas, G.P.; Parodi, C.; Marabini, S.; Fanciullacci, M.; Polleri, A. Urinary Melatonin Excretion Throughout the Ovarian Cycle in Menstrually Related Migraine. Cephalalgia 1994, 14, 205–209.
92. Brun, J.; Claustrat, B.; Saddier, P.; Chazot, G. Nocturnal Melatonin Excretion is Decreased in Patients with Migraine without Aura Attacks Associated with Menses. Cephalalgia 1995, 15, 136–139.
93. Wolf, H. The effect of hormones and vitamin B6 on urinary excretion of metabolites of the kynurenine pathway. Scand. J. Clin. Lab. Investig. 1974, 136, 1–186.
94. Vécsei, L.; Szalárdy, L.; Fülöp, F.; Toldi, J. Kynurenines in the CNS: Recent advances and new questions. Nat. Rev. Drug Discov. 2013, 12, 64–82.
95. Schwarcz, R.; Bruno, J.P.; Muchowski, P.J.; Wu, H.-Q. Kynurenines in the mammalian brain: When physiology meets pathology. Nat. Rev. Neurosci. 2012, 13, 465–477.
96. Miranda, A.; Boegman, R.; Beninger, R.; Jhamandas, K. Protection against quinolinic acid-mediated excitotoxicity in nigrostriatal dopaminergic neurons by endogenous kynurenic acid. Neuroscience 1997, 78, 967–975.

97. Silva-Adaya, D.; La Cruz, V.P.-D.; Villeda-Hernández, J.; Carrillo-Mora, P.; González-Herrera, I.G.; García, E.; Colín-Barenque, L.; Pedraza-Chaverrí, J.; Santamaría, A. Protective effect of l-kynurenine and probenecid on 6-hydroxydopamine-induced striatal toxicity in rats: Implications of modulating kynurenate as a protective strategy. Neurotoxicol. Teratol. 2011, 33, 303–312.
98. Knyihár-Csillik, E.; Toldi, J.; Krisztin-Péva, B.; Chadaide, Z.; Németh, H.; Fenyő, R.; Vécsei, L. Prevention of electrical stimulation-induced increase of c-fos immunoreaction in the caudal trigeminal nucleus by kynurenine combined with probenecid. Neurosci. Lett. 2007, 418, 122–126.
99. Vamos, E.; Párdutz, A.; Varga, H.; Bohár, Z.; Tajti, J.; Fülöp, F.; Toldi, J.; Vécsei, L. l-kynurenine combined with probenecid and the novel synthetic kynurenic acid derivative attenuate nitroglycerin-induced nNOS in the rat caudal trigeminal nucleus. Neuropharmacology 2009, 57, 425–429.
100. Párdutz, A.; Fejes, A.; Bohár, Z.; Tar, L.; Toldi, J.; Vécsei, L. Kynurenines and headache. J. Neural Transm. 2012, 119, 285–296.
101. Toldi, J.; Oláh, G.; Herédi, J.; Menyhárt, A.; Czinege, Z.; Nagy, D.; Fuzik, J.; Krucsó, E.; Kocsis, K.; Knapp, L.; et al. Unexpected effects of peripherally administered kynurenic acid on cortical spreading depression and related blood–brain barrier permeability. Drug Des. Dev. Ther. 2013, 7, 981–987.
102. Knyihár-Csillik, E.; Chadaide, Z.; Okuno, E.; Krisztin-Péva, B.; Toldi, J.; Varga, C.; Molnár, A.; Csillik, B.; Vécsei, L. Kynurenine aminotransferase in the supratentorial dura mater of the rat: Effect of stimulation of the trigeminal ganglion. Exp. Neurol. 2004, 186, 242–247.
103. Spekker, E.; Laborc, K.F.; Bohár, Z.; Nagy-Grócz, G.; Fejes-Szabó, A.; Szűcs, M.; Vécsei, L.; Párdutz, A. Effect of dural inflammatory soup application on activation and sensitization markers in the caudal trigeminal nucleus of the rat and the modulatory effects of sumatriptan and kynurenic acid. J. Headache Pain 2021, 22, 17.
104. Zhang, Y.-Q.; Ji, G.-C.; Wu, G.-C.; Zhao, Z.-Q. Kynurenic acid enhances electroacupuncture analgesia in normal and carrageenan-injected rats. Brain Res. 2003, 966, 300–307.
105. Mecs, L.; Tuboly, G.; Nagy, E.; Benedek, G.; Horvath, G. The Peripheral Antinociceptive Effects of Endomorphin-1 and Kynurenic Acid in the Rat Inflamed Joint Model. Anesthesia Analg. 2009, 109, 1297–1304.
106. Fukui, S.; Schwarcz, R.; Rapoport, S.I.; Takada, Y.; Smith, Q.R. Blood?Brain Barrier Transport of Kynurenines: Implications for Brain Synthesis and Metabolism. J. Neurochem. 1991, 56, 2007–2017.