Kynurenines and PACAP in migraine: medicinal chemistry and pathogenetic aspects

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Kynurenines and PACAP in migraine: medicinal chemistry and pathogenetic aspects

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Abstract

Background: Migraine is a highly disabling neurovascular primary headache disorder, with its exact pathomechanism being still unrevealed. The current leading hypotheses are based on the sensitization and activation of the trigeminovascular system.

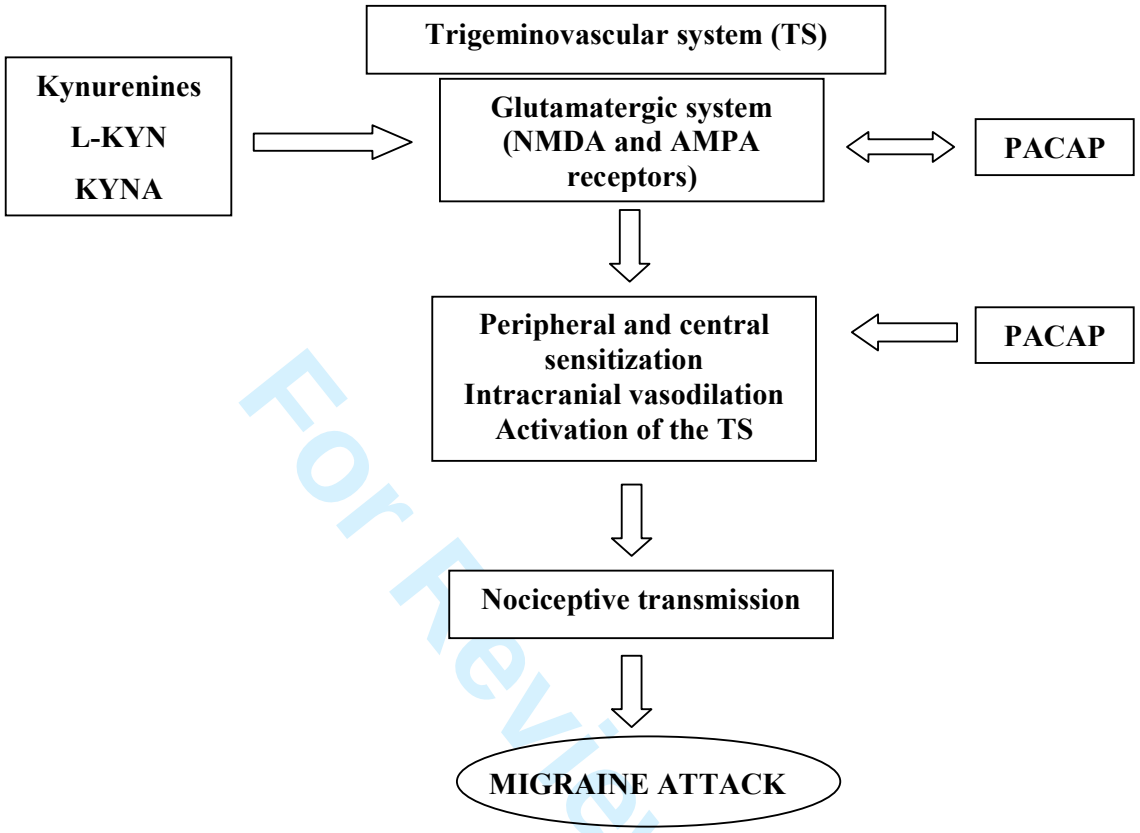
Objective: To review the literature with focus on the effects of kynurenines (L-kynurenine and kynurenic acid) and pituitary adenylate cyclase-activating polypeptide on the regulation of the trigeminovascular system.

Method: A literature search was conducted to identify preclinical and clinical publications **(198 references) by using the keywords '**kynurenines', 'pituitary adenylate cyclase-activating polypeptide', and 'migraine' in the database of MEDLINE/PubMed up to 10 September 2016**for topical review**. **Additional filters used included 'review', 'systematic review', 'original article', and 'English language'.**

Results: L-kynurenine and kynurenic acid act on the glutamatergic system at the level of the second-order nociceptive neurons in the trigeminal nucleus caudalis. Pituitary adenylate cyclase-activating polypeptide is released from the peripheral nerve endings of the trigeminal pseudounipolar neurons and causes vasodilation and mast cell degranulation, leading to consequent peripheral sensitization of the dural nociceptors. Centrally released pituitary adenylate cyclase-activating polypeptide in the trigeminal nucleus caudalis results in the central sensitization of the second-order neurons. The sensitization process leads to the characteristic features of migraine.

Conclusion: L-kynurenine, kynurenic acid, and pituitary adenylate cyclase-activating polypeptide may have fundamental roles in the initiation of migraine headache attacks.

Graphical abstract



Abbreviations: AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, KYNA: kynurenic acid, L-KYN: L-kynurenine, **NMDA: *N*-methyl-D-aspartate**, PACAP: pituitary adenylate cyclase-activating polypeptide, **TS: trigeminovascular system**

Keywords: glutamate, kynurenine, migraine, mode of action, pathomechanism, pituitary adenylate cyclase-activating polypeptide.

Introduction

Migraine as a neurovascular primary headache disorder is ranked the third most common disease worldwide [1]. On the basis of the latest classification of the International Headache Society, migraine can be divided into episodic (with and without aura) and chronic forms [2]. The typical features of a migraine attack include the unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia [2]. Migraine is a disabling disease, having high socio-economic and personal impacts [3-9].

The exact pathomechanism of migraine is still unrevealed. The proposed pathogeneses of the initiation and maintenance of a migraine attack include neuro-vascular alterations, neuropeptide release, neurogenic inflammation, plasma protein extravasation, peripheral and central sensitization, cortical spreading depression (CSD), brain energy deficit, and lesions in the cerebral white matter [10-14]. The trigeminovascular system (TS) provides an important pain transmission link between the vascular andneuronal elements [15, 16].

The TS includes the primary sensory pseudounipolar neurons, the cell bodies of which are located in the trigeminal ganglion (TRIG). Their peripheral branches innervate the cranial vessels and meningeal tissues, whereas their central fibers project to the area of the second-order neurons within the trigeminal nucleus caudalis (TNC) in the brainstem. The information is conveyed to the somatosensory cortex *via* the third-order neurons located in the thalamus [13, 14].

The coupling mechanism in the TNC is controlled by descending pathways from distinct brainstem nuclei, *e.g.,* the periaqueductal grey matter (PAG), the nucleus raphe magnus (NRM), the dorsal raphe nucleus (DRN), and the locus coeruleus (LC), collectively referred to as the migraine generators [14, 17].

It has recently been suggested that glutamate, kynurenines, and pituitary adenylate cyclase-activating polypeptide (PACAP) may play fundamental roles in the initiation and chronification of migraine headache attacks [18, 19].

Glutamate plays a pivotal role in neurotransmission, and emerging human and animal data suggest that it is crucial in the pathomechanism of migraine. Indeed, elevated levels of glutamate were detected in the plasma, platelets, and cerebrospinal fluid in migraine patients long after the attacks, supporting the hypothesis of a sustained hyperexcitability in the disease [20-22]. It is worthy of note that several genetic polymorphisms that affect glutamatergic neurotransmission have been described in migraineurs [23, 24]. It is also important to note

that glutamate receptor antagonists can terminate the aura in patients with familial hemiplegic migraine [25]. Monosodium glutamate is a naturally appearing form of glutamic acid and is able to mimic headache in healthy young volunteers and in rats, an effect mediated by the activation of peripheral *N*-methyl-D-aspartate (NMDA) receptors and dural vasodilation. Data from the literature demonstrate that glutamate has a prominent role in processes important in migraine generation, such as CSD and the activation and sensitization of the trigeminal system, and it is also present in the migraine generators [26-28]. Taken together, it seems clear that the role of glutamate is relevant in the pathomechanism of migraine, and its antagonists may have a therapeutic potential.

Kynurenines are less widely known but highly important products of tryptophan (**Trp**) metabolism [29]. L-kynurenine (L-KYN) and kynurenic acid (KYNA) have neuroprotective effects, whereas 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HA), and quinolinic acid (QIUN) have neurotoxic properties [18, 29]. KYNA is one of the endogenous glutamate receptor antagonists. Preclinical data revealed that L-KYN or synthetic analogues of KYNA can dramatically inhibit the activation of second-order neurons in the TNC in animal models of migraine with electrically or chemically stimulated TS [30-33]. Furthermore, L-KYN and KYNA can block the process of CSD in experimental conditions [34, 35]. In recent years, clinical studies have demonstrated multiple alterations in the levels of different kynurenine pathway metabolites (*e.g.,* a reduction in the level of L-KYN and an increased level of anthranilic acid (ANA)) in the serum of chronic migraine patients [36].

PACAP is a member of the vasoactive intestinal peptide (VIP)/secretin/glucagon neuropeptide family and exists in two biologically active forms: **PACAP1-27** and **PACAP1-38**[37]. The presence of PACAP in human TRIG and TNC has been demonstrated [38, 39]. The importance of PACAP in migraine has first been pointed out by clinical studies [40]. Intravenous administration of **PACAP1-38** provoked migraine-like attacks accompanied by vasodilation in migraine patients [40, 41]. Experimental data revealed the effect of PACAP on the TS in migraine animal models as well [42, 43]. In line with these, alterations in plasma **PACAP1-38** concentration have been demonstrated in migraineurs both ictally and interictally [44].

This paper gives an overview of the currently available data as regards the contribution of the kynurenine pathway and PACAP in the pathogenesis of migraine, with special focus on potential therapeutic implications.

Kynurenines

Chemistry of the kynurenine pathway

Trp is an essential amino acid, playing a crucial role in the synthesis of serotonin, melatonin, tryptamine, and L-KYN ((S)-2-amino-4-(2-aminophenyl)-4-oxobutonic acid). The major branch of **Trp** metabolism is the kynurenine pathway, producing neuroactive compounds and nicotinamide adenine dinucleotide (NAD^+) **(Figure 1)**.

The initial and rate-limiting step in the kynurenine pathway is linked to three iron-dependent enzymes, indolamine 2,3-dioxygenase 1 and 2 (IDO1 and IDO2), and tryptophan 2,3-dioxygenase (TDO). IDO was recognized in 1957 as a heme protein. The enzyme can be activated by interferon-γ (IFN-γ) and is present in the central nervous system (CNS), whereas TDO occurs primarily in peripheral tissues, especially in the liver. IDO and TDO convert **Trp** to *N*-formyl-L-kynurenine by opening the **Trp** ring in a reaction which produces peroxides and highly reactive oxygen and hydroxyl radicals [45-48]. *N*-formyl-L-kynurenine is then further degraded by formamidase to form L-KYN. Limited data are available about the biological activity of *N*-formyl-L-kynurenine, owing to its rapid degradation.

L-KYN has antioxidant properties and can cross the blood-brain barrier. Some 60% of L-KYN present in the CNS is taken up from the blood. L-KYN was demonstrated to be an endogenous ligand of the aryl-hydrocarbon receptor, which has important roles in the immune response and tumor genesis [48-52]. L-KYN can be metabolized *via* three different pathways.

The first branch of the kynurenine pathway transforms L-KYN to ANA by kynureninase (L-kynurenine hydrolase). ANA is supposed to have an anti-inflammatory effect *via* forming a complex with copper and inactivating hydroxyl radicals [53]. ANA is further metabolized to 3-HA by 3-hydroxy-anthranilic acid 3,4-dioxygenase (3-HAO), an iron-dependent enzyme. 3-HAO requires oxygen and sulfhydryl groups for its activation and it is predominantly present in astrocytes within the CNS [54, 55].

The second branch of the kynurenine pathway starts with the hydroxylation of L-KYN at the third position by the flavin-dependent kynurenine 3-monooxygenase (KMO) to yield 3-HK. 3-HK can be further converted to xanthurenic acid (XA) and 3-HA. 3-HK and 3-HA can increase the level of oxidative stress *via* the production of free radicals, leading to neuronal damage [56]. Moreover, these molecules can cause excitotoxicity and cell death in neuronal cell cultures [57, 58]. However, ANA is also able to transform into 3-HA, which further transforms into QUIN (pyridine-2,3-dicarboxylic acid). QUIN is an agonist of the NMDA

receptors and can cause neuronal death when administered intrastriatally [57]. It also provokes lipid peroxidation and generates reactive oxygen species [59]. QUIN is then converted to NAD^+ in the final step of this branch of the kynurenine pathway [60].

The last branch of the pathway starts with the modification of L-KYN to yield KYNA (4-hydroxi-1H-quinoline-2-carboxylic acid) by kynurenine aminotransferases (KAT)s, which have 4 subtypes with different biochemical profiles [61]. KATs belong to the group of pyridoxal 5-phosphate (PLP)-dependent enzyme family. PLP is connected covalently to the lysine residue of KATs by a Schiff base transaldimine link.

KAT I (glutamine transaminase K or cysteine conjugate beta-lyase) is present in neurons and asytrocytes [62, 63]. KAT II (alpha-aminoadipate aminotransferase) was isolated from rat kidney [64]. Under physiological conditions, KATI and KAT II are proposed to be responsible for the majority of KYNA production in mammalians [61, 63].

The more recently discovered KATs include KAT III (cysteine conjugate beta-lyase 2), which is present in the kidney, the heart, the liver, and the neuroendocrine tissues, and KAT IV (glutamic-oxaloacetic transaminase 2 or mitochondrial aspartate aminotransferase).

In contrast with QUIN, KYNA has a neuroprotective effect and can mitigate neuronal damage in excitotoxicity and ischemia [65, 66].

KYNA was discovered by Justus von Liebig in 1853 in urine, and half a century later, the substance was recognized as a bioproduct of **Trp** metabolism. KYNA is an endogenous metabolite of the kynurenine pathway and behaves as an antagonist at the strychnine-insensitive glycine-binding site and, at higher doses, at the NMDA recognition site [67]. In addition, KYNA exerts mild antagonistic effects on kainate- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-sensitive glutamate receptors. Furthermore, it is of note that the effect of KYNA on AMPA receptor-mediated action is facilitatory at low concentrations (nanomolar-micromolar) and inhibitory at high concentrations (micromolar-millimolar) [68, 69]. A line of evidence suggested that KYNA is an antagonist at the α7 nicotinic acetylcholine receptor, thereby decreasing the presynaptic release of glutamate; however, this theory has recently been questioned [70, 71]. In addition, KYNA influences the G protein-coupled receptor 35 (GPR35) and may provoke the generation of inositol trisphosphate, promoting Ca^{2+} mobilization. KYNA is present both in the central and peripheral tissues in low concentrations (10-150 nM), and is generated in the CNS predominantly by glial cells [54, 72].

Furthermore, it is worthy of note that KYNA is not the only kynurenine metabolite to have positive neuromodulatory effects: L-KYN, ANA, and XA can induce analgesia in the different types of experimental pain models [73].

Therapeutic limitations of KYNA and possible chemical solutions

The main limitation of the widespread use of KYNA is its poor ability to cross the blood-brain barrier. To overcome this problem, one possibility is to use the precursor of KYNA, L-KYN, or its halogenated derivatives. Data from animal studies showed that L-KYN has neuroprotective and antinociceptive effects, and its halogenated derivatives, 4,6-dicholorokynurenine and 4-chlorokynurenine are able to transform into halogenated KYNA derivatives (5,7-dichlorokynurenic acid and 7-chlorokynurenic acid, respectively), which have increased affinity to the glycine-binding site of NMDA receptors [33, 74, 75]. Another possibility is to develop KYNA analogues with improved ability to cross the blood-brain barrier. New KYNA analogues have a promising therapeutic potential in the treatment of headache as well neurodegenerative disorders [76]. Recently, our research group have created KYNA analogues, including(*N*-(2-*N,N*-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride (KA1) and *N*-(2-*N*-pyrrolidinylethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride (KA2), which successfully inhibited the trigeminal activation and sensitization in animal models of migraine [77, 78]. A third option is shifting the kynurenine pathway towards the production of KYNA by the use of specific enzyme inhibitors of kynureninase and KMO, the latter being the most comprehensively examined enzyme inhibitor of the pathway, since their inhibition prevents the production of neurotoxic kynurenines, such has 3-HK and QUIN. Supporting this concept, a wealth of animal data confirms that the inhibition of KMO is able to increase the level of KYNA and decrease that of 3-HK and QUIN [79, 80]. The administration of the KMO inhibitor, (R,S)-3,4-dichlorobenzoylalanine (FCE28833A), was effective in increasing KYNA and L-KYN concentrations in the rat brain[81]. Representatives from another group of KMO inhibitors, N-(4-phenylthiazol-2-yl)benzenesulfonamides, were likewise able to raise the level of KYNA in the extracellular hippocampal fluid [82].

Experimental data with KYNA and its analogues: preclinical and clinical implications

Numerous studies indicate that KYNA and its analogues have antinociceptive effects at the level of both the first- and the second-order sensory neurons [83]. KYNA is capable of

attenuating the activation of migraine generators and decreasing mechanical allodynia and pain sensitivity in the tail-flick and the hot-plate tests [84-86].

Systemic administration of nitroglycerin (NTG) is one of the human and animal models of migraine, resulting in the activation and sensitization of the trigeminal system. Pretreatment with L-KYN together with probenecid (PROB; an inhibitor of KYNA excretion) or that with KYNA analogues, KA1 or KA2, attenuated the NTG-induced behavioral changes in the rat as well as morphological alterations in the TNC, probably by the inhibition of NMDA receptors [32, 33, 78]. In a recent study, it has been shown that NTG decreased the expression of KAT II, an enzyme converting L-KYN to KYNA, probably implicating decreased KYNA levels as well[87].

Another experimental setting takes advantage of the electrical stimulation of the TRIG, which also results in decreased KAT immunoreactivity in mast cells, Schwann cells, and dural macrophages [88].

Several studies have shown that there is a connection between the kynurenines and the CSD. CSD is a self-propagating process, the electrophysiological correlate of migraine aura, and is able to activate the trigeminal system in experimental animals [89, 90]. L-KYN and KYNA suppressed CSD in a KCl-induced model [34, 35].

Another model of the trigeminal activation and sensitization takes advantage of the Complete Freund's Adjuvant (CFA)-induced dural inflammation. In this model, a KYNA analogue was able to abolish the CFA-generated inflammatory response [91].

To examine trigeminal inflammation and nociception, the orofacial formalin test can also be used, as a stable model for the investigation of somatic pain involving the activation and sensitization of the trigeminal system [92]. In this model, PROB exerted an antinociceptive effect in rats [93]. Notably, PROB is able to increase the concentration of KYNA by inhibiting its excretion in the nervous system, which may contribute to the observed antinociceptive effect [94]. In a most recent study, the effects of two KYNA analogues, KA1 and KA2, were tested in the orofacial formalin model, revealing that the two analogues were able to inhibit the formalin-induced behavioral and morphological changes and increased the concentration of KYNA [95].

Although the exact mechanism of action of KYNA and its analogues remains unknown, some pieces of the puzzle are starting to fall into place. KYNA can exert its effect both in the periphery and in the CNS. In the periphery, KYNA acts on the glutamate receptors, especially NMDA receptors, localized on certain components of the peripheral nervous system,

including the trigeminal and dorsal root ganglion, Schwann cells, and the primary sensory afferents [96-99]. As mentioned above, KYNA also has an effect on the GPR35 receptor, which is present in the nociceptive pathway, for example in the dorsal root ganglion; therefore, KYNA may exert its peripheral effect in part on this receptor [100].

In addition to a peripheral action, KYNA and its analogues have a modulatory potential on second-order neurons as well. KYNA was effective in providing analgesia in the tail-flick, hot-plate, and orofacial formalin tests in mice and rats, as mentioned above. These results are in line with animal studies reporting that kynurenine metabolites can influence pain sensation at the level of the spinal cord [84]. When administered into the spinal cord of cats, KYNA was effective in decreasing the muscular and cutaneous nociceptive reaction of wide dynamic range neurons [101]. In rats, KYNA and its analogues were able to prevent the NTG- or CFA-induced activation and sensitization of the trigeminal system in the TNC, where the trigeminal second-order nociceptive neurons are located [32, 33, 78, 91]. Therefore, KYNA and its derivatives can influence the second-order neurons in the trigeminal system.

There is a number of experimental data suggesting that kynurenines influence the activity of migraine generators, including the NRM, the DRN, the LC, and the PAG. Indeed, KYNA can decrease serotonergic responses of the DRN induced by phasic auditory stimulation or the electrical stimulation of the lateral habenula [102, 103]. KYNA can also diminish the activation of the NRM neurons induced by glutamate, and is able to prevent the activation of noradrenergic neurons in the LC provoked by electrical stimulation of the hindpaw of rats [104, 105]. In addition, the co-administration of KYNA with morphine into the PAG increased the nociceptive effect of morphine [106].

To date, only few clinical data are available as regards kynurenine pathway alterations in migraine. Recent studies by Curto and her colleagues showed altered serum levels of kynurenine metabolites (L-KYN, KYNA) in patients with chronic migraine and cluster headache [36, 107]. This group was the first to conclude that these two types of primary headaches are both associated with decreased levels of kynurenine metabolites in the peripheral blood.

Summarizing the preclinical and clinical data from the literature, we can conclude that the metabolites of the kynurenine pathway appear to play relevant roles in the pathomechanism of migraine, and they might represent a new potential therapeutic option in the treatment of the disease **(Figure 2)**.

Link between the kynurenines and the other endogenous systems

Several lines of evidence have been put forth to support the hypothesis that the kynurenine pathway has a strong interaction with other endogenous systems, including the endocannabinoid system. Recently, numerous studies have indicated that changes in the levels of endocannabinoids within the nervous system are associated with nociception and the pathomechanism of migraine [108]. An increased level of KYNA achieved by the use of the KMO inhibitor 3,4-dimethoxy-[-N-4-(nitrophenyl)thiazol-2-yl]-benzenesulfonamide (also known as Ro 61-8048) was capable of reducing the self-administration of Δ^9-tetrahydrocannabinol (THC) in squirrel monkeys [109]. In addition, the first discovered endocannabinoid, anandamide, was able to attenuate the NTG-induced decrease in KAT II expression [87].

Another endogenous system influenced by KYNA is the opioid system. The co-administration of KYNA with morphine raised the acute effect of morphine in rats [106]. Furthermore, KYNA and KA1 reduced the opioid and nociceptin receptor-mediated G-protein activity without demonstrating any affinity towards of opioid receptors [106, 110], an indirect effect which can be attributed to a decreased G-protein activity or a diminished expression of opioid receptors [110].

On the other hand, KYNA plays an important role in the regulation of dopaminergic neurotransmission. An increase in the level of KYNA results in the inhibition of dopamine release; therefore, KYNA is able to influence the levels of dopamine [111]. The decreased level of brain KYNA as a result of the inhibition of KAT II was able to cause an elevation in the extracellular levels of dopamine [112]. In addition, alterations in brain KYNA concentration can be associated with cognitive effects. Indeed, administration of KYNA or L-KYN to rats caused impairments in visuospatial working memory, sensory gating, and contextual learning, phenomena linked to glutamatergic and dopaminergic neurotransmission [113-115].

It is also important to note that TDO activity is under the control of blood corticosterone levels and the activity of IDO is regulated by steroids [116, 117].

The immune system represents another endogenous system which has a strong connection with kynurenines. IDO has essential roles in immune modulation in relation to processes such as infection, transplantation, autoimmunity, and pregnancy. IDO is an immunosuppressive enzyme, with a number of its products being able to inhibit T cell proliferation and activate regulatory T cells; therefore, IDO might have an effect on the negative feedback suppression

of T cell response [118]. Importantly, a chronic CNS inflammation might cause an increased activity of IDO by an IFN-γ-mediated process, a phenomenon which might contribute to the pathomechanism of migraine [18]. Notably, not only kynurenines can influence the immune system, but immune molecules such as cytokines can in turn modulate the activity of the kynurenine pathway as well: in particular, tumor necrosis factor-α (TNF- α) and interleukins (IL)s, IL-1, -2, -4, -13, and -23 have a strong modulatory effect on the activation of IDO [118].

Influencing the kynurenine pathway – chemical and nutritional aspects

Several enzymes of the kynurenine pathway are vitamin-dependent, including KMO, kynureninase, and the KATs [119]. A number of vitamins from the B family can either directly or indirectly upregulate and/or downregulate the activity of the above mentioned enzymes. In particular, vitamin B6 (pyridoxal) has a crucial role in **Trp** metabolism, being implicated in the physiological function of both the serotonin and kynurenine pathways, and it also functions as a coenzyme of the KATs and kynureninase [120]. These data are in accordance with a recent study demonstrating that the combined application of vitamin B6 and B12 was effective in the reduction of migraine-associated symptoms [121].

On the other hand, it is well-known that pyridoxal can form chelates with monovalent cations, such as K^+, Li^+, and Na^+, and divalent cations, including Mg^{2+} and Ca^{2+} [120]. Metal ions can also catalyze non-enzymatic reactions of amino acids with pyridoxal, influencing the function of PLP enzymes [122, 123]. As the polar side chain of proteins could interact with metal ions, these ions have an explicit effect on the enzyme function. Increased concentration of Pb^{2+} and Zn^{2+} are able to inhibit the activity of kynureninase; besides, Co^{2+} and Zn^{2+} can inhibit the activity of both the KATs and kynureninase by the blockage and inactivation of sulfhydryl groups of the enzymes [124, 125]. These results raise the interesting possibility that influencing the enzymes of the kynurenine pathway by vitamin B6 or cations might have a therapeutic potential.

Recently, a growing attention has been dedicated to the nutritional aspects of kynurenines. Resveratrol (3,5,4'-trihydroxystilbene) is a polyphenol, which can be found in several nutrients, including red wine, peanuts, and cocoa. It has immunomodulatory and anticancer effects [126, 127]. A recent study has shown that resveratrol intake enhanced the activity of IDO in human volunteers [128]. Though in this study, no significant change was observed in the levels of L-KYN, the possibility cannot be excluded that resveratrol can influence the levels of kynurenine metabolites. Furthermore, one should keep in mind that several types of

red wine are able to induce migraine attacks. The contribution of the non-flavonoid resveratrol in wine-triggered attacks is suggested to be unlikely, and tannins and phenolic flavonoid components of the wine are generally considered to be responsible for the induction of migraine attacks [129].

PITUITARY ADENYLATE CYCLASE-ACTIVATING POLYPEPTIDE

Basic biochemical features of PACAP and its receptors

PACAP is a member of the VIP/secretin/glucagon neuropeptide superfamily and is considered to be a 'brain-gut peptide', being widely expressed in the animal and human organisms [37, 130]. PACAP was discovered based on its ability to increase adenylate cyclase activity in rat pituitary cells, and was first isolated from the ovine hypothalamus in 1989 [131]. Genetic studies showed that the human gene of PACAP (ADCYAP1) is localized on the short arm of chromosome 18 (18p11) [132]. The chemical structure of the peptide exists in two biologically active amidated forms, referred to as **PACAP1-38** and **PACAP1-27**, containing 38 and 27 amino acids, respectively (**Figure 3**). **PACAP1-38**has been revealed to account for some 90% of the total PACAP content in mammalian tissues; however, it is rapidly metabolized and its plasma elimination half-life is very short, being less than 5 min [133]. PACAP can be found in the central and peripheral nervous systems, in the endocrine and exocrine glands, *e.g.,* pancreas and gonads, as well as in the urogenital and respiratory systems, thereby it functions as a pleiotropic peptide [134-142]. PACAP has many functions asa hypophysiotropic hormone; furthermore, it also works as a neuromodulator and neurotransmitter within the nervous system [143-147]

In addition, PACAP exerts antiapoptotic, neuroprotective, and differentiation-inducing effects in the developing nervous system [143-148]. In addition, it plays crucial modulatory and protective roles in the reproductive, cardiovascular, gastrointestinal, and respiratory systems [149-155].

The actions of PACAP are mediated via the following three receptors: $VPAC_1$ (formerly designated the VIP, VIP1 or PACAP type II receptor), $VPAC_2$ (known as the VIP2 or PACAP type III receptor), and PAC_1 (previously referred to as the PACAP type I receptor). The PAC_1 receptor has a 1000-fold higher affinity for **PACAP1-27** and **PACAP1-38** than for VIP [156-158]. The effect of PACAP on its different receptors induces two substantial signal transduction pathways. Through Gs- or Gq/11-protein activation, a number of kinases exert a

variety of physiological and pathophysiological effects [37, 156]. It has been demonstrated that **PACAP1-38**-induced meningeal vasodilation is realized by the activation of $VPAC_2$ receptors [159]. **The investigation of the TS as regards PACAP and the release of calcitonin gene-related peptide (CGRP), a molecule relevant in the pathogenesis of migraine[14], demonstrated that unlike PACAP1-38, maxadilan, a PAC_1 receptor agonist, had no effect on CGRP release in the TNC, whereasM65, a PAC_1 receptor antagonist, failed to inhibit the PACAP 1-38-induced release of CGRP. These together raised the possibility of the functional presence of a yet unidentified receptor of PACAP in the TS [160]. Another experimental study reported that only intracerebroventricular administration of a PAC1 receptor antagonist was able to diminish the activation of the second-order nociceptive neurons in the trigemino-cervical complex during dural stimulation [161].**

The functions of PACAP in nociceptive and vasodilation processes have been revealed by many studies [162-170]. Immunohistochemical studies demonstrated the presence of this peptide in the trigeminal system, e.g., TRIG, TNC, and different brainstem nuclei [38, 39, 134, 171, 172]. **Immunohistochemical data demonstrated the presence of PAC_1 and $VPAC_2$ receptors in small-diameter TRIG neurons [173]. Reverse transcription-polymerase chain reaction revealed the presence of $VPAC_2$ and several splice variants of the PAC_1 receptor in TRIG [173]. There is functional evidence that $VPAC_1$ receptors are lacking in the TRIG of rats [174] (Figure 4).** An early study showed that about 68% of nociceptin-immunopositive cells in the human TRIG contained PACAP [175]. A human tissue study examining the TNC and the cervical 1–cervical 2 (C_1–C_2) levels of the spinal cord concluded that the moderately dense CGRP- and PACAP-containing fibers can be detected in the vicinity of numerous substance P (SP)-immunoreactive fibers, but VIP-immunoreactive fibers were not observed [134]. Moreover, PACAP was detected in human parasympathetic otic and sphenopalatine ganglia [176-178]. **PACAP1-38** immunoreactivity was found in neurons and satellite glia cells in rat sphenopalatine ganglia [178]. A broad range of data suggests that PACAP functions as an integrator of nociceptive and sensitization processes, besides being involved in neurogenic inflammation [164, 166, 170, 179]. PACAP and glutamate were both detected in the TRIG of rhesus monkeys and rats [180].

Link between PACAP and migraine

The exact pathomechanism of migraine is unknown, but the activation and sensitization of the TS are among the leading hypotheses [13, 14]. There is a number of evidence highlighting the possible role of PACAP in the pathogenesis of migraine. The first human evidence that demonstrated the significance of PACAP in migraine was published by Schytz et al. in 2009 [40]. Intravenous infusion of **PACAP1-38** caused delayed migraine-like attacks, similarly to the effect of nitroglycerin infusion in migraineurs [40, 181, 182]. Moreover, the decrease of the mean blood flow velocity in the middle cerebral artery and the increase of the diameter of the superficial temporal artery were also observed in the PACAP study of migraineurs [40]. After these promising clinical data, preclinical animal studies were performed to explain the background of the effect of PACAP in the human body [42, 43]. After chemical (by nitroglycerin) and electrical (at the TRIG) stimulation of TS, **PACAP1-27** and **PACAP1-38**immunoreactivity were found significantly increased in TNC in rats. Even more, **PACAP1-38** elevation was found in the plasma after the electrical stimulation of the TRIG in rats [42]. PACAP-deficient mice displayed reduced light-aversive behavior (photophobia), and decreased meningeal blood flow and c-fos expression were detected in the TRIG and TNC relative to wild-type mice after nitroglycerin-induced TS activation [43]. Neurogenic inflammation and mast cell degranulation also take part in the process of migraine [183, 184]. After mast cell degranulation, the released histamine may induce a long-lasting activation of the TS. It has been demonstrated that vasodilation induced by systemically administered **PACAP1-38** was diminished in mastocyte-depleted and antihistamine-pretreated rats [185]. PACAP has the capability to release histamine from rat peritoneal or human skin mast cells [186, 187]. VPAC1 receptor is expressed on mast cells [188]. The importance of mast cell degranulation within the dura is given by its possible association with the activation of peripheral trigeminal fibers, which leads to peripheral sensitization [184, 189, 190]. Electrophysiological studies proved that **PACAP1-38** could cause delayed activation and sensitization of second-order neurons in the trigemino-cervical complex, in a process mediated by neuronal PAC_1 receptor in rats [161]. Magnetic resonance angiography of selective extra- and intracranial arteries in humans revealed marked and long-lasting dilation of extracranial arteries after **PACAP1-38** infusion [41]. Elevated plasma **PACAP1-38** immunoreactivity was detected in the spontaneous ictal period compared to the interictal phase of migraineurs [44]. Interestingly, similar data were found in episodic cluster headache patients [191]. However, in tension-type headache patients, interictal plasma PACAP level was unchanged, whereas in the same phase, it was found decreased in migraineurs [192]. A recent clinical study revealed that PACAP mRNA expression in the peripheral blood

mononuclear cells in migraine patients was significantly reduced compared to tension-type headache, cluster headache, or medication overuse headache patient groups [193]. During the ictal period, PACAP plasma level in the external jugular vein was found elevated, which alteration was reduced 1 hour after treatment with sumatriptan, a potent acute anti migraine drug [194]. In a clinical study, previously genotyped patients with migraine without aura were infused by **PACAP1-38**, which resulted in delayed migraine-like attacks and elevated plasma levels of VIP, prolactin, S100 calcium binding protein B, and thyroid-stimulating hormone [195]. This finding pointed out that PACAP may activate parasympathetic nerve endings, causing VIP release [195]. However, the presence of the MEF2D gene variant (rs2274316) was not associated with pre-ictal alterations in neuropeptide levels in the plasma, and neither a high family load nor the presence of this risk allele influenced the migraine response to PACAP1-38 infusion [195, 196]. A resting-state functional MRI study demonstrated that intravenously administered **PACAP1-38**-induced migraine attacks are associated with altered brain network connectivity (in terms of salience, sensorimotor, and default mode networks) [197].

Summary

Theoretically, PACAP may be released from the peripheral and central terminals of the trigeminal nerve endings. Peripherally released PACAP may cause vasodilation and mast cell degranulation, resulting in peripheral sensitization. On the other hand, centrally released PACAP may lead to the activation of second-order sensory neurons in the TNC in a process mediated by the PAC1 receptor, which leads to central sensitization. Both the peripheral and the central sensitization processes take part in the initiation of migraine attacks [19, 184, 198-201].

A possible link between PACAP and kynurenines in pathogenesis of migraine

The glutamatergic system represents a possible link between PACAP and kynurenine pathway as regards the pathomechanism of migraine. Electrophysiological and biochemical clinical studies revealed the presence of cortical hyperexcitability in migraine patients, which pointed to the role of the glutamatergic system in pathomechanism of migraine [20, 202-205]. Experimental data exist suggesting the role of PACAP on the glutamatergic system via its receptors. It has been proposed that

PACAP may promote the functional coupling between neuronal nitric oxide synthase and NMDA receptors in inflammatory pain processes [179]. Furthermore, a study using the contextual fear conditioning animal model demonstrated that PACAP modulated the consolidation and extinction through NMDA receptors [206]. In the ventromedial nuclei of the hypothalamus, PACAP modulated the NMDA receptor activity via tyrosine phosphorylation by the Src kinase family [207]. In addition to actions on NMDA receptors, PACAP1-38 was shown to regulate the phosphorylation of AMPA receptor in hippocampal cultures [208]. On the basis of the distribution of PACAP and glutamate in the TRIG, immunohistochemical data suggests a possible interaction between the glutamatergic and the CGRP systems [180].

Migraine-related peripheral and central sensitization of the TS is guided by the glutamatergic system, which can be influenced by kynurenines and PACAP. Recent clinical trials in migraine have investigated ionotropic NMDA receptor antagonists (e.g., ketamine and memantine) [209, 210], an ionotropic AMPA receptor antagonists (e.g., BGG492, a.k.a. selurampanel) [211], an ionotropic AMPA/kainate receptor antagonists (LY293558, a.k.a. tezampanel) [212], and a metabotropic glutamate receptor 5 modulator (ADX-10059, a.k.a. raseglurant) [213]. Glutamatergic receptors may serve as novel therapeutic targets in the treatment of migraine.

Conclusion

Migraine is a neurovascular disorder with an unknown etiopathogenetic background. One of the leading hypotheses is based on the activation and sensitization of the TS. Distinct members of kynurenine system, such as L-KYN and KYNA, as well as the recent hypothetical migraine-related neuropeptide, PACAP, may be connected by their influence on the glutamatergic elements of TS. The activation of excitatory glutamatergic receptors leads to the sensitization of TS. KYNA and its analogues are antagonists of the glutamatergic receptors. PACAP modulates the NMDA and AMPA receptors. Moreover, PACAP exerts its effects on the TS through its receptors ($VPAC_1$, $VPAC_2$, and PAC_1).

As regards future perspectives, KYNA analogues, PAC1 receptor antagonists, and glutamatergic receptor antagonists may provide innovative therapeutic options in migraine headache.

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Tables and figures

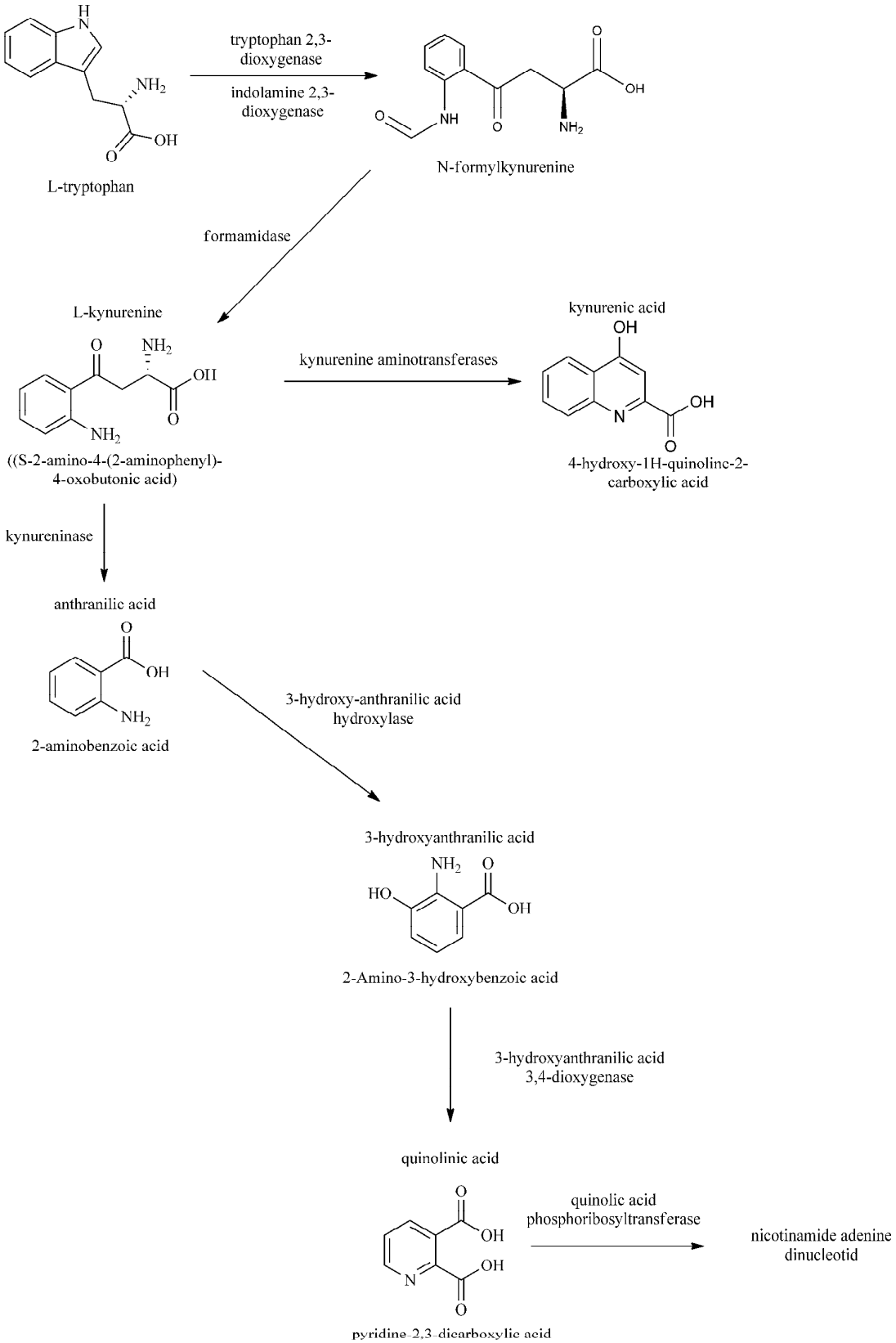

Figure 1. **A part of the kynurenine pathway**

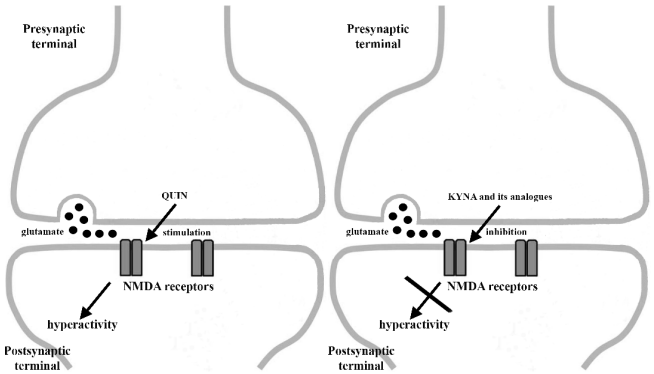

Figure 2. The main action of kynurenic acid and quinolinic acid.

Abbreviations: QUIN: quinolinic acid, KYNA: kynurenic acid, NMDA receptors: N-methyl-D-aspartate receptors

PACAP-27

His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-NH_2

PACAP-38

His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-**Gly-Lys-Arg-Tyr-Lys-Gln-Arg-Val-Lys-Asn-Lys**-NH_2

Figure 3. Amino acid sequences of PACAP-27 and PACAP-38 [131]

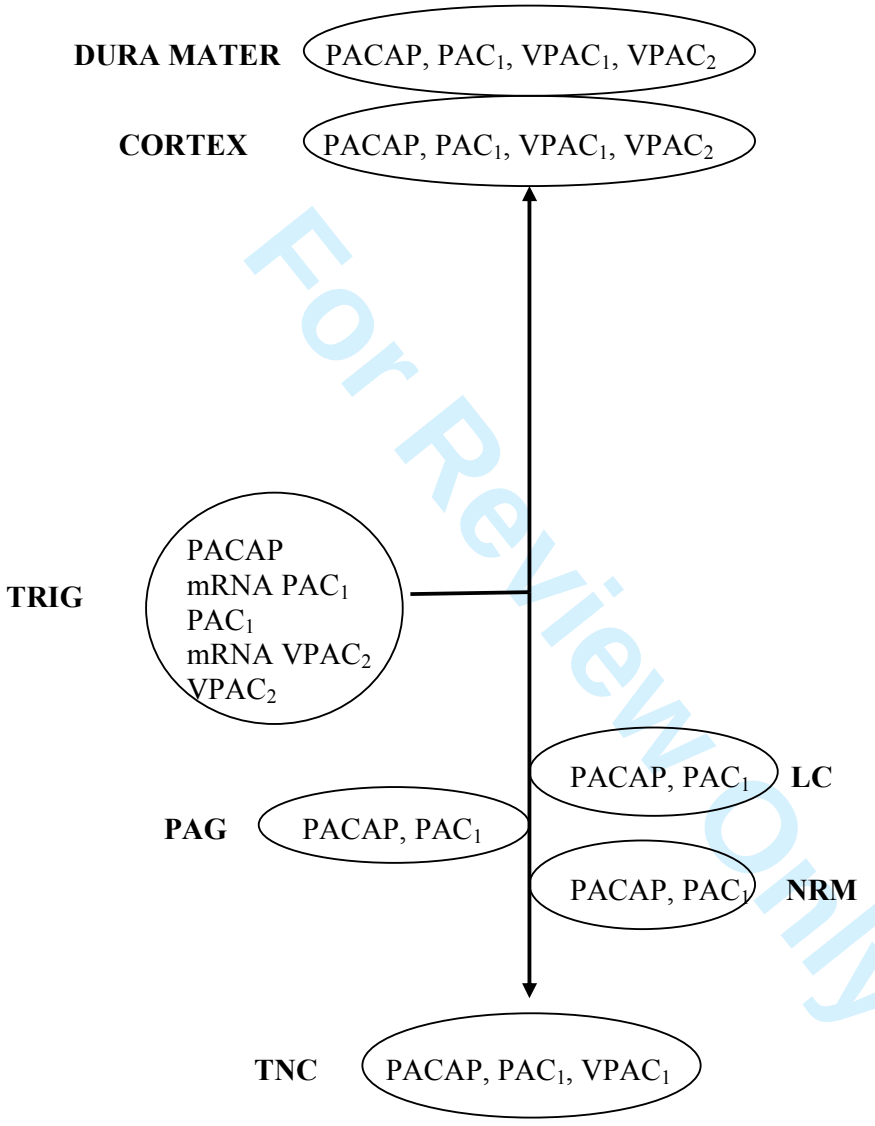

Figure 4. Localization of PACAP and its receptors in the trigeminovascular system

Abbreviations: NRM: nucleus raphe magnus; LC: locus coeruleus; $VPAC_1$: previously designated as the VIP, VIP1 or PACAP type II receptor, $VPAC_2$: known as the VIP2 or PACAP type III receptor; PAC_1: formerly known as the PACAP type I receptor; PACAP: pituitary adenylate cyclase-activating polypeptide; PAG: periaqueductal grey matter; TNC: trigeminal nucleus caudalis; TRIG: trigeminal ganglion [173, 174, 184]

Figure legends:

Figure 1. A part of the kynurenine pathway.

Figure 2. KYNA and its analogues are able to inhibit the glutamate-induced hyperexcitability, which has a relevant role in the pathomechanism of migraine.

Figure 3. Amino acid sequences of PACAP-27 and PACAP-38.

Figure 4. PACAP and its receptors are expressed in various parts of the trigeminovascular system.

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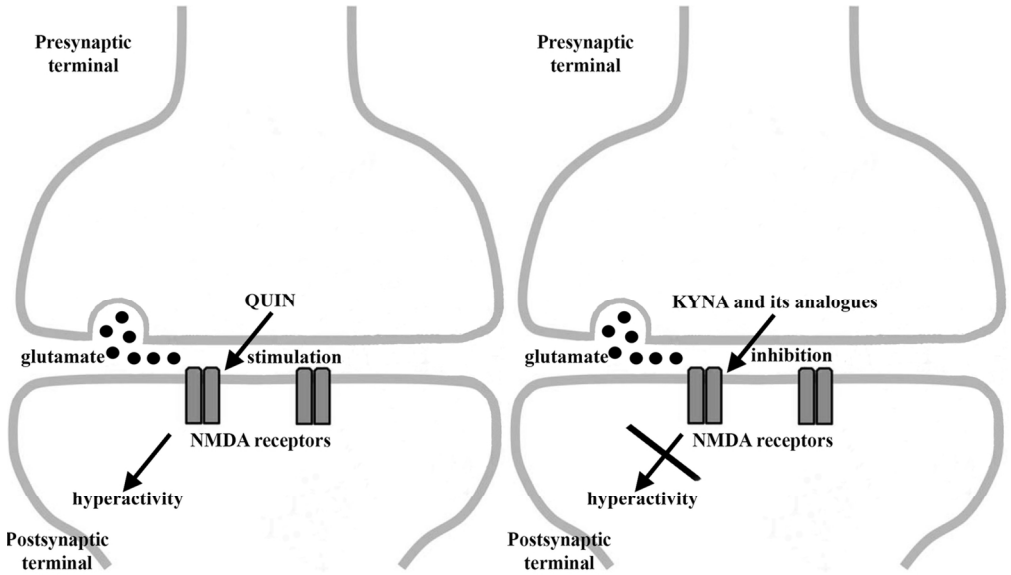


KYNA and its analogues are able to inhibit the glutamate-induced hyperexcitability, which has a relevant role in the pathomechanism of migraine.

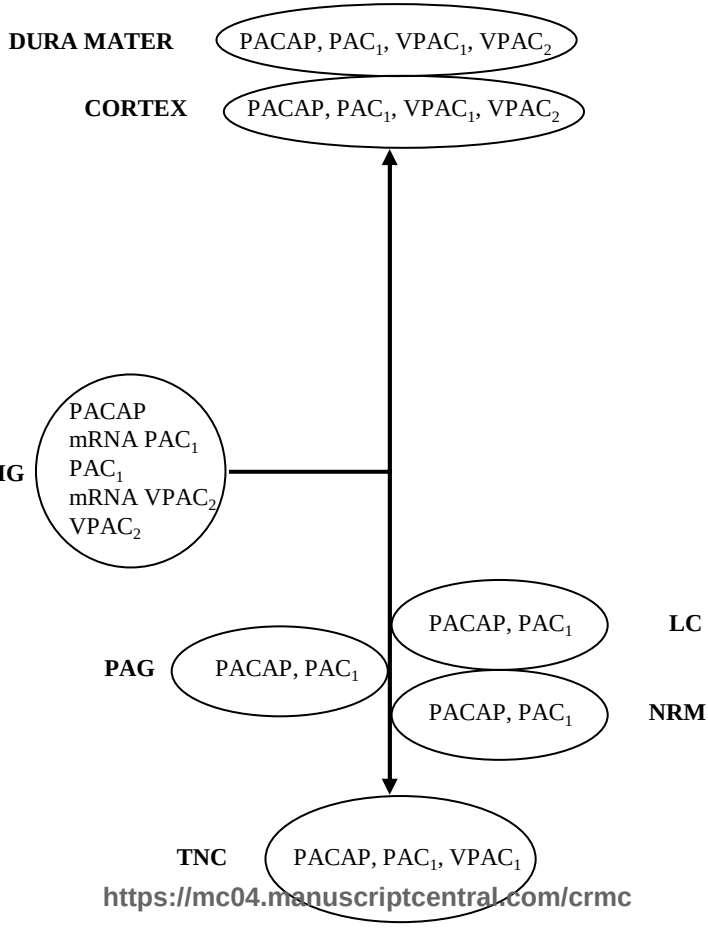
127x75mm (300 x 300 DPI)

PACAP-27

His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-NH_2

PACAP-38

His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-**Gly-Lys-Arg-Tyr-Lys-Gln-Arg-Val-Lys-Asn-Lys-**NH_2



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