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**Novel kynurenic acid analogues in the treatment of migraine and neurodegenerative disorders: preclinical studies and pharmaceutical design**

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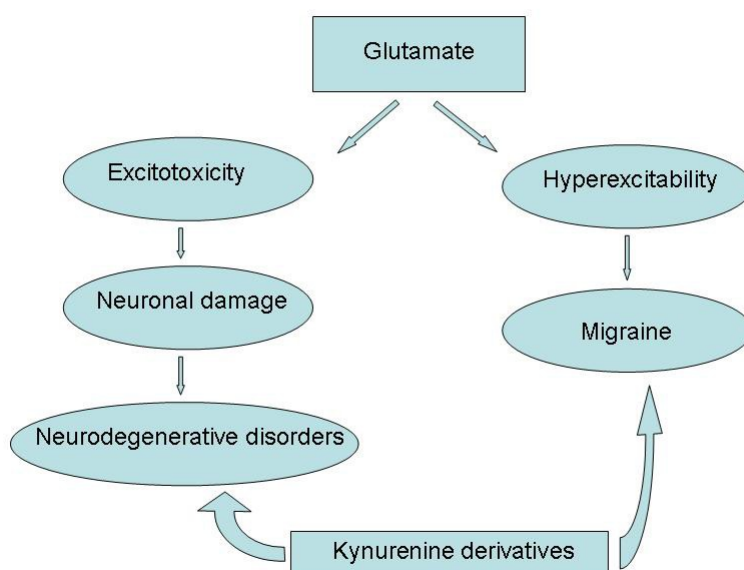
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## Abstract

Whereas migraine and neurodegenerative disorders have a high socioeconomic impact, their therapeutic management has not been fully solved. Their pathomechanisms are not completely understood, but glutamate-induced excitotoxicity, mitochondrial disturbances and oxidative stress all seem to play crucial roles. The overactivation of glutamate receptors contributes to the hyperexcitability observed in migraine and also to the neurodegenerative process. The kynurenine pathway of the tryptophan metabolism produces the only known endogenous *N*-methyl-D-aspartate receptor antagonist, kynurenic acid, which has been proven in different preclinical studies to exert a neuroprotective effect. Influencing the kynurenine pathway might be beneficial in migraine and neurodegenerative diseases, and in the normalization of glutamatergic neurotransmission and the prevention of excitotoxic neuronal damage. The synthesis of kynurenic acid analogues may offer a valuable tool for drug development.

## Graphical abstract



**Keywords:** migraine, hyperexcitability, neurodegeneration, neuroprotection, kynurenic acid, kynurenic acid analogues

## **Introduction**

Brain disorders account for around 35% of the total burden of all diseases in Europe . The WHO classifies all neurological, neurosurgical and psychiatric disorders in this category. Among the neurological diseases, stress must be placed on the impact of neurodegenerative disorders (i.e. Alzheimer's dementia (AD), Parkinson's disease (PD) and Huntington's disease (HD)) and migraine. Migraine, as a primary headache disorder was ranked by a WHO report as the 19th cause of disability worldwide, affecting 16% of the adult population . The prevalence of dementia in Western Europe is around 5.5%, and its incidence is almost 9/100,000 . The most common neurodegenerative disorder is AD , which affects around 70% of all dementia patients . PD has a lifetime risk of 2%, and overall prevalence of 1.5%, with no gender difference . HD is a less common, autosomal dominantly inheritable disorder, but the data indicate its rising prevalence, currently in the range 5.7-12.3/100,000 .

In spite of their high prevalence, the exact pathomechanisms of these neurodegenerative disorders and migraine are still not fully understood. However, there are several common features in their pathological background, including glutamate (Glu) hyperexcitability , mitochondrial impairment , oxidative stress and neuroinflammation . As a consequence of the lack of a precise understanding of their pathomechanisms, the therapeutic approaches are mainly symptomatic, and specific disease-modifying therapies are not available. The kynurenine pathway (KP) of the tryptophan (Trp) metabolism produces both neurotoxic and neuroprotective metabolites. Kynurenic acid (KYNA) is the only known endogenous Glu receptor antagonist, while quinolinic acid (QUIN) is an *N*-methyl-D-aspartate (NMDA) receptor agonist. The KP has additionally been implicated in the pathological process of neurodegeneration and migraine , and increasing evidence is emerging on both preclinical and clinical levels. Alterations in the balance of toxic and protective metabolites might lead to the dominance of neurotoxic compounds, which can contribute to the excitotoxic process and to

neuroinflammation. Influencing the KP metabolism might offer a valuable therapeutic target for the different neurological diseases. Kynurenine derivatives which are able to cross the blood-brain barrier (BBB) are promising candidates for future drug development. This review will focus on the role of Glu excitotoxicity and the KP in the pathomechanisms of migraine and neurodegenerative diseases, and on the possible therapeutic options.

### **The kynurenine pathway**

The metabolism of the essential amino acid Trp has two main routes: the well-known serotonin pathway and the lesser-known KP (Figure 1). This route is responsible for more than 90% of the peripheral Trp degradation in mammals. 40% of the brain L-kynurenine (L-KYN) is produced locally in the central nervous system (CNS), and 60% is taken up from the blood. The first, rate-limiting enzyme of the KP is indoleamine-2,3 dioxygenase (IDO), which forms the key intermediate, L-KYN. Here the pathway divides into two branches, and results either in the synthesis of KYNA or, through the action of kynurenine 3-monooxygenase (KMO), the formation of 3-hydroxy-kynurenine (3-OH-KYN). The neuroprotective KYNA (4-hydroxyquinoline-2-carboxylic acid) is mainly produced by astrocytes and neurones on the action of kynurenine aminotransferases (KATs), while the neurotoxic metabolites are synthesised in the microglia. KYNA is a wide-spectrum antagonist of ionotropic Glu receptors. In micromolar concentrations, it antagonizes the NMDA receptors by binding to the strychnine-insensitive glycine (Gly)-binding site, or with lower affinity to the Glu-binding site. Importantly, on  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, KYNA is a Janus-faced compound, displaying a concentration-dependent dual effect: in nanomolar concentrations it is capable of facilitating these receptors, while at higher concentrations it inhibits them. KYNA is also a non-competitive antagonist of the  $\alpha$ 7-nicotinic-acetylcholine receptors, which regulate Glu

release presynaptically . 3-OH-KYN is further metabolised to QUIN, and the cascade finally ends with the synthesis of nicotinamide adenine dinucleotide. 3-OH-KYN mainly causes toxicity by producing free radicals . The neurotoxic effect of QUIN is predominantly due to NMDA agonism, but it may also contribute to oxidative stress and a mitochondrial dysfunction . QUIN is a weak competitive agonist of NR2A and NR2B subunit-containing NMDA receptors . Trp, L-KYN and 3-OH-KYN are able to cross the BBB, whereas KYNA can do so only poorly .

## **Migraine**

Migraine is a highly disabling neurovascular disorder. The exact pathomechanism has not yet been fully elucidated, but Glu-induced hyperexcitability, peripheral and central sensitization and neurogenic inflammation have been reported to participate . The concept of cortical hyperexcitability in migraine patients was first suggested in the early 1980s, on the basis of the observation that migraineurs demonstrated an increased response to different sensory stimuli . This theory was confirmed by means of several electrophysiological methods, including the visual evoked potential, and transcranial magnetic stimulation . These early results were later supported by the use of various functional neuroimaging methods, such as positron emission tomography (PET) and proton magnetic resonance spectroscopy (MRS). PET disclosed elevated cortical activation in migraineurs after olfactory, visual or trigeminal stimulations . MRS revealed a significantly higher Glu/glutamine (Gln) ratio in the occipital cortex in women with migraine during the interictal state as compared to healthy controls . Glu and Gln in the CNS are highly compartmentalized (in the neurones for Glu and in the astrocytes for Gln) . Measurements of the excitatory amino acids yielded further evidence of neuronal hyperexcitability. Significantly higher concentrations of Glu, serine, Gly, arginine and tyrosine were found in saliva samples of migraine patients with or without aura as

compared with the controls in the interictal period . A decreased plasma level and an increased cerebrospinal fluid (CSF) level of Glu were detected ictally in migraine patients with or without aura relative to the controls. This suggests neuronal hyperexcitability of the CNS during migraine attacks . Experimental data indicated enhanced Glu release from the stimulated platelets in both migraine patients with or without aura, while the platelet Glu uptake was elevated only in migraine patients without aura. This is suggestive of a pronounced upregulation of the Glu-ergic metabolism in migraine patients without aura . The plasma levels of aspartic acid, Gly, cysteic acid and homocysteic acid were significantly higher in migraine patients than in the controls . All of the above data point to a cortical hyperexcitability state in migraineurs.

Clinical data have demonstrated lower plasma and salivary magnesium ion ( $Mg^{2+}$ ) levels in migraine sufferers with or without aura in the interictal period as compared with the controls . Another human investigation revealed that the  $Mg^{2+}$  level in the erythrocytes in migraine patients without aura was reduced in the period between attacks .

The predominance of excitatory amino acids and the lower  $Mg^{2+}$  levels may lead to a raised activation of Glu receptors and neuronal hyperexcitability.

Glu and its receptors, especially the NMDA receptor, have also been implicated also in the trigeminovascular activation and sensitization process .

One of the leading hypotheses is the activation of the trigeminovascular system (TS) . The TS includes the first-order neurones, such as the pseudounipolar neurones of the trigeminal ganglion (TRIG), the second-order neurones in the trigeminal nucleus caudalis (TNC) in the brainstem, and the third-order neurones in the thalamus and the somatosensory cortex .

In the activation of the TRIG, the calcitonin gene-related peptide (CGRP), which is a very potent vasodilatory neuropeptide and several pro-inflammatory cytokines have a special role. The neuronal CGRP acts on the satellite glial cells, which releases pro-inflammatory



cytokines like interleukin-1 beta, that further modulate the neuronal response . Neurogenic inflammation (vasodilatation and plasma protein extravasation) occurs in the vicinity of the dural vasculature due to the release of different neuropeptides, e.g. CGRP and pituitary adenylyl cyclase activating peptide .

Peripheral sensitization occurs when the meningeal nociceptors of the afferents of the trigeminal neurones are soaked with inflammatory mediators such as prostaglandin E2, bradykinin, histamine, serotonin, tumour necrosis factor-alpha, interleukins and other cytokines . Preclinical studies have shown that interleukin-6 enhances the excitability of dural trigeminal afferents, causing sensitization .

The central sensitization process involves the increased activity of the phosphorylated NMDA receptors in the second-order neurones in the TNC, which leads to enhanced Glu sensitivity and hence the hyperexcitability of the neurones . In the mid-1990s, the Weiller group elegantly demonstrated via high-resolution PET that the blood flow of specific brainstem nuclei, referred to as "migraine generators" (locus coeruleus – LC, nucleus raphe magnus – NRM, dorsal raphe nucleus – DRN and periaqueductal grey matter – PAG), was increased during spontaneous migraine attacks . These nuclei could influence the activation of the TNC . Overstimulation of the second-order neurones evoked the sensitization of the third-order neurones in the thalamus. A link is presumed between platelet activation and migraine pathogenesis involving pro-inflammatory cytokines (e.g. interleukins 1, 6 and 8) and tumour necrosis factor-alpha, which can contribute to the induction of sterile inflammation and hypersensitization of pain pathways in the brain . The highest neurone/astrocyte ratio is present in the human visual cortex. Elevations in extracellular Glu or potassium ion ( $K^+$ ) can be a trigger for cortical spreading depression (CSD). Astrocytes could play a role in the regulation of the amounts of the extracellular Glu and  $K^+$  . CSD is a slowly progressing wave of neurono-glia depolarisation, which is likely to lie in the background of the migraine aura

phase . Experimental findings demonstrated that an enhanced microglial production of pro-inflammatory cytokines could promote the initiation of CSD. It was observed experimentally that polarized microglia (M2a) reduced pro-inflammatory, but increased anti-inflammatory cytokine production .

Preclinical and clinical observations have strongly suggested that migraine is a cerebral neuronal hyperexcitability state.

### **Neurodegenerative disorders**

The pathomechanisms of AD, PD and HD, the most common neurodegenerative diseases, share several common characteristics. Glu excitotoxicity, mitochondrial impairments, neuroinflammation and oxidative stress have been reported to contribute to the development of these disorders .

Glu is the main excitatory neurotransmitter in the brain, but the overactivation of Glu receptors may cause the neuronal damage, known as excitotoxicity. Excitotoxicity is mainly mediated by an excessive calcium ion ( $\text{Ca}^{2+}$ ) influx into the cells, which induces a downstream metabolic cascade, finally leading to neuronal death . Neuronal nitric oxide synthase (nNOS) is one of the isoforms of nitric oxide synthase (NOS), which serves a crucial role in the neurotoxic process . NMDA receptors are linked to nNOS by a postsynaptic density protein of molecular weight 95 kDA, which preferentially binds to the NR2B subunit. This is the reason of Glu excitotoxicity is mediated principally by NR2B-subunit-containing receptors . Neuroinflammation involving astrocytic and microglial activation has been found to be present in several neurodegenerative disorders, such as HD, and this process may alter the release and uptake of Glu .

The KP involves both an NMDA agonist and an NMDA antagonist, and it may therefore be able to regulate Glu-ergic neurotransmission. The possible role of the KP in the

pathomechanisms of neurodegenerative diseases has been confirmed in a number of preclinical and clinical studies.

#### The KP and Alzheimer's disease

An increasing amount of evidence has emerged that indicates an altered KP metabolism in AD . In the serum, red blood cells and CSF of AD patients, lower KYNA concentrations have been measured . Several brain regions of AD patients have been reported to have reduced levels of L-KYN and 3-OH-KYN, whereas the levels of KYNA and KAT-I activity were significantly elevated in the striatum and caudate nucleus . Moreover, increased IDO activity was detected in the serum of AD patients, as reflected by a higher KYN/Trp ratio, which correlated inversely with the rate of cognitive decline . An immunohistochemical investigation revealed an increased IDO activity and QUIN production in the AD hippocampus, which was most pronounced in the perimeter of the senile plaques . A mitochondrial impairment in complex IV has been described in the AD cortex, with the activity reduced by 25-30% . This may contribute to increased amyloid production. Importantly, amyloid beta 1-42 has been shown to induce QUIN production in human macrophages and microglia . A recent study suggested that 3-HK might be a possible biomarker for AD, as increased serum 3-HK levels were found to be specific for AD patients as compared with controls. As concerns the possible background, it was suggested that an elevated 3-HK availability might promote enhanced QUIN synthesis in the brain .

#### The KP and Parkinson's disease

At the preclinical level, toxin models are widely used to assess the pathomechanism and potential therapeutic option in PD. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine have both been confirmed to influence the KP, and to result in a decrease

in KAT-I activity . MPTP treatment additionally gives rise to significant changes in aminoacid concentrations in the brain . Alterations in the KP metabolism have also been found in the blood of PD patients: a decrease in the plasma, and increased levels of KAT activity and KYNA production in the red blood cells . There is also evidence indicating an elevated immune activity, correlating with an increased Trp metabolism in PD patients. The neopterin concentrations and KYN/Trp ratios were elevated in the serum and CSF of PD patients, especially in advanced stages of the disease . Similarly, changes in the KP have been detected in the brain of PD patients. The contents of 3-OH-KYN were elevated, while those of KYNA and KYN were reduced in several brain regions . A recent metabolomic analysis study identified several novel biomarkers in the CSF of PD patients, one of them being 3-HK concentration elevation .

The described alterations in the KP suggest an increased formation of the neurotoxic metabolites, possibly associated with the neuroinflammatory process.

#### The KP and Huntington's disease

Intrastriatal administration of QUIN to rats induced a spatial learning deficit and characteristic histological changes, which closely mimicked HD symptoms, and this was therefore a widely-used experimental model of HD before transgenic animals became available . Human investigations revealed alterations in several brain regions of HD patients. The QUIN and 3-OH-KYN levels were elevated, while the KYNA concentration and KAT activity were reduced . Stoy et al. observed a higher KYN/Trp and a lower KYNA/KYN ratio in the blood of HD patients, reflecting increased IDO activity and decreased KAT activity . These alterations suggest a shift in the KP towards the synthesis of neurotoxic metabolites, which might contribute to excitotoxic neuronal damage. From a therapeutic aspect, the inhibition of KMO, a key enzyme in the KP, results in an enhancement of KYNA production and inhibits

the formation of neurotoxic metabolites. Accordingly, the application of KMO inhibitors reduced huntingtin-induced toxicity in animal models .

## **Future therapeutic strategies by kynurenine derivatives**

### **Migraine**

One of the experimental migraine models comprises the electrical stimulation of the TRIG. This demonstrated the decreased KAT expression of the Schwann cells, which ensheath the nerve trunks or single nerve fibres in the dura, the mast cells and the macrophages, while the content of the NOS- immunoreactive nerve fibres increased. This observation led to the release of the nitric oxide (NO) at the periphery . The main function of KAT is to synthesize KYNA, which has an anti-Glu-ergic effect. A migraine attack may be associated with a hyperexcitability condition, and KAT may play a role in the prevention of migraine attacks (Figure 2).

In a chemically (NTG) induced animal migraine model, the area covered by CGRP-immunoreactive fibres in the TNC is decreased. L-KYN in combination with PROB and a KYNA derivative, 2-(2-*N,N*-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride), inhibited the decrease in the region covered with CGRP-immunoreactive fibres . One possible mechanism behind this finding is that these substances might block the activation of the first-order neurones in the TRIG . However, a recent *in vitro* study indicated that KYNA has a central inhibitory effect on the capsaicin-induced CGRP release in mouse brainstem slices .

The main function of the second-order neurones in the TNC is to convey the pain transmission to the thalamus. The administration of NTG as an NO donor dramatically increases the number of c-fos-immunoreactive second-order neurones. In this model, L-KYN combined with PROB attenuated the number of c-fos-immunoreactive neurones in the TNC . Under the same experimental conditions, the L-KYN + PROB combination and a KYNA

derivative (2-(2-*N,N*-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride) diminished the nNOS and calmodulin-dependent protein kinase II alpha-immunoreactive cells . A recent study revealed that a newly synthesized KYNA-amide (*N*-(2-*N*-pyrrolidinyloethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride) prevented the nitroglycerol-induced neuronal activation and sensitization in the cervical part of the trigemino-cervical complex . These results pointed to the role of KYNA and its derivatives in the modified activation of the second-order neurones in the TNC.

Preclinical findings indicated that KYNA acts on the "migraine generators", such as the LC, DRN, NRM and PAG . In animal experiments, noxious stimulation strongly activated the central noradrenergic neurones in the LC, which was abolished by pretreatment with KYNA . Activation of the serotonergic neurones in the DRN was inhibited by substance P microinfusion, which was prevented by KYNA microinfusion . Neuroanatomical tracing studies revealed that the NRM sent a direct projection to the lateral reticular nucleus (LRN) in the caudal ventrolateral medulla . Microinjection of Glu into NRM significantly altered the discharge of the majority of the LRN cells, which was partially antagonized by KYNA . Anatomical studies demonstrated a connection from the medial preoptic nucleus of the hypothalamus (MPO) to the PAG and NRM . The interaction between the MPO and the NRM can be modulated by inhibition of both the neuronal transmission and the Glu-ergic system in the PAG. Injection of KYNA into the PAG blocked both inhibitory and excitatory responses in the different cell types in the PAG to chemical and electrical stimulation of the MPO . Glu and NMDA can trigger CSD . KYNA was found to inhibit K<sup>+</sup>-triggered CSD in rat neocortical slices and in an *in vitro* preparation of the turtle cerebellum . It was recently reported that the systemic administration of L-KYN suppressed CSD in rats . Peripherally administered KYNA reduced the number of CSD waves and decreased the permeability of the BBB during CSD in rats .

All of the above-mentioned results clearly confirmed that KYNA and its derivatives exert effects on the functional anatomical structures of the nervous system participating in the leading hypothesis of migraine .

### **Neurodegenerative disorders (AD, PD and HD)**

Glu-induced excitotoxicity is an important factor in the pathomechanisms of both migraine and neurodegenerative disorders . Although the complete inhibition of Glu-ergic neurotransmission is not feasible, and is accompanied by severe side-effects, prevention of the overactivation of NMDA receptors and restoration of the normal Glu-ergic balance might offer neuroprotection. The KP produces both NMDA agonist and antagonist molecules, and might therefore have a modulatory role in Glu-ergic neurotransmission. Elevation of the neuroprotective KYNA level, and reduction of the amounts of neurotoxic KP metabolites might offer a valuable therapeutic option. NMDA antagonism and modulation of the KP metabolism have been suggested to be of therapeutic value in AD, PD and migraine (reviewed by ). Modulation of the KP can be achieved by three main methods: the administration of prodrugs or of synthetic KYNA derivatives that may cross the BBB, or influencing the enzymatic processes of the KP . KYN administered together with probenecid (PROB), a non-selective organic anion transporter inhibitor, results in an elevation of the brain KYNA level . This combination effectively prevented trigeminal activation in the nitroglycerol (NTG)-induced and in the electrical stimulation-induced migraine model, and reduced the frequency of CSD too . Moreover, KYN+PROB treatment exerted a neuroprotective effect in an AD animal model, and prevented both the cognitive decline and the histopathological changes . In the 6-hydroxydopamine model of PD, KYN+PROB was able to reduce the histochemical changes and prevent neuronal damage .

KMO inhibition leads to increased KYNA production. This treatment has been demonstrated to prevent histopathological changes and behavioural symptoms in animal models of AD and HD . Another research group demonstrated that the KMO inhibitor Ro 61-8048 prevented levodopa-induced dyskinesia in a primate model of PD .

The KYN derivative 4-chlorokynurenine successfully prevented QUIN-induced neurotoxicity . This compound, which has the ability to cross the BBB, is converted in the brain to 7-chlorokynurenic acid, which is an antagonist of the Gly-binding site of the NMDA receptor .

The KYNA analogue, *N*-(2-*N,N*-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride, proved to prolong survival and prevent neuronal damage in a transgenic HD model . One important concern regarding the use of NMDA antagonists is the possibility of inducing systemic side-effects. Behavioural studies have confirmed that, in the dose at which it exerted a neuroprotective effect, the KYNA-amide did not exhibit any significant cognitive side-effect .

In an epilepsy model induced by pentylenetetrazole, another novel KYNA-amide (SZR104) prevents seizures . These promising results allowed the conclusion, that modulation of the KP, and especially the development of KYNA derivatives with a beneficial pharmacological profile, appears to be a promising therapeutic option for future drug development.

### **Medicinal chemistry strategy of the synthesis of novel kynurenic acid analogues**

The transformations of KYNA derivatives can be achieved through modification of the aromatic ring, the synthetically active 4-OH group, or conversion of the 2-carboxylic function to pharmacologically interesting ester or amide derivatives of KYNA. These transformations, together with the pharmacological applications of the resulting KYNA derivatives, were earlier reviewed .



The amides of KYNA are pharmacologically and synthetically highly promising synthons in the patent literature. The KYNA amides were designed with regard to the following structural properties:

1. the presence of a water-soluble side-chain;
2. the inclusion of a new cationic centre;
3. side-chain substitution to facilitate brain penetration.

Coupling between KYNA and 2-dimethylaminoethylamine was achieved by using *N,N'*-diisopropylcarbodiimide (DCI) in the presence of 1-hydroxybenzotriazole hydrate (1-HOBT), yielding 2 (Figure 3).

The excellent biological activity of 2 led the authors to regard it as the basic amide and to design further KYNA amides by modifying 2. To lengthen the side-chain by one CH<sub>2</sub> group, KYNA was reacted with 3-dimethylamino-1-propylamine, resulting in 3. Compound 3 proved not to reduce the population spike amplitudes significantly. Its biological effects were not valuable.

By using 2-diethylaminoethylamine as starting amine, 4 was synthesized as a diethyl analogue of 2, and analogues 5, 6 and 7, containing the tertiary nitrogens in different ring systems, were prepared by reacting KYNA with 2-morpholinoethylamine, 2-piperidinoethylamine and 2-pyrrolidinoethylamine, respectively.

## Conclusions

Neuronal hyperexcitability and glutamate excitotoxicity are important factors contributing to the pathomechanism of neurodegenerative disorders and migraine. The KP involves several neuroactive compounds which are capable of influencing glutamatergic neurotransmission. Alterations in the KP have additionally been implicated in neurodegeneration and in the nociceptive process, and targeting the KP might therefore provide novel future therapeutic

options. Synthetic KYNA analogues with a favourable pharmacological profile might be well promising candidates for drug development.

## **List of abbreviations**

3-OH-KYN: 3-hydroxy-kynurenine

AD: Alzheimer's disease

BBB: blood-brain barrier

Ca<sup>2+</sup>: calcium ion

CGRP: calcitonin gene-related peptide

CNS: central nervous system

CSD: cortical spreading depression

CSF: cerebrospinal fluid

DRN: dorsal raphe nucleus

Gln: glutamine

Glu: glutamate

Gly: glycine

HD: Huntington's disease

IDO: indoleamine-2,3-dioxygenase

K<sup>+</sup>: potassium ion

KAT: kynurenine aminotransferase

KMO: kynurenine 3-monooxygenase

KP: kynurenine pathway

KYNA: kynurenic acid

LC: locus coeruleus

L-KYN: L-kynurenine

LRN: lateral reticular nucleus

Mg<sup>2+</sup>: magnesium ion

MPO: medial preoptic nucleus of the hypothalamus

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MRS: magnetic resonance spectroscopy

NMDA: *N*-methyl-D-aspartate

NO: nitric oxide

nNOS: neuronal nitric oxide synthase

NOS: nitric oxide synthase

NRM: nucleus raphe magnus

NTG: nitroglycerol

PAG: periaqueductal grey matter

PD: Parkinson's disease

PET: positron emission tomography

PROB: probenecid

QUIN: quinolinic acid

TNC: trigeminal nucleus caudalis

TRIG: trigeminal ganglion

Trp: tryptophan

TS: trigeminovascular system

**Conflict of interest**

The authors declare that they have no conflict of interest and have received no payment in preparation of their manuscript.

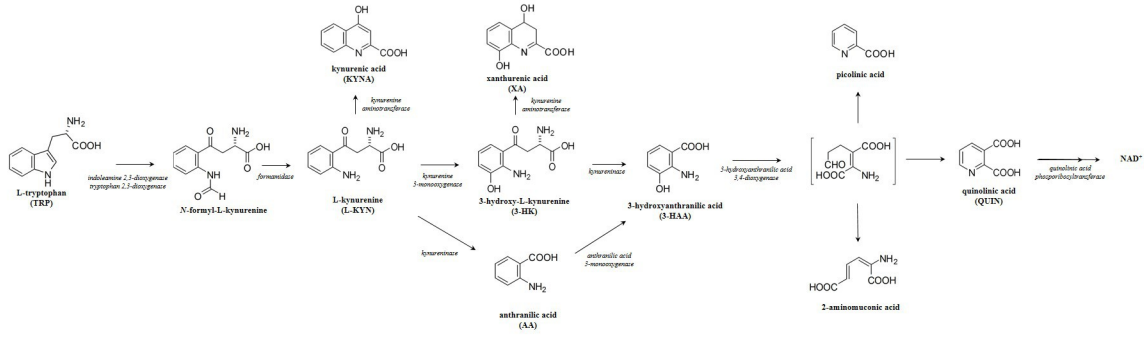
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# Figures

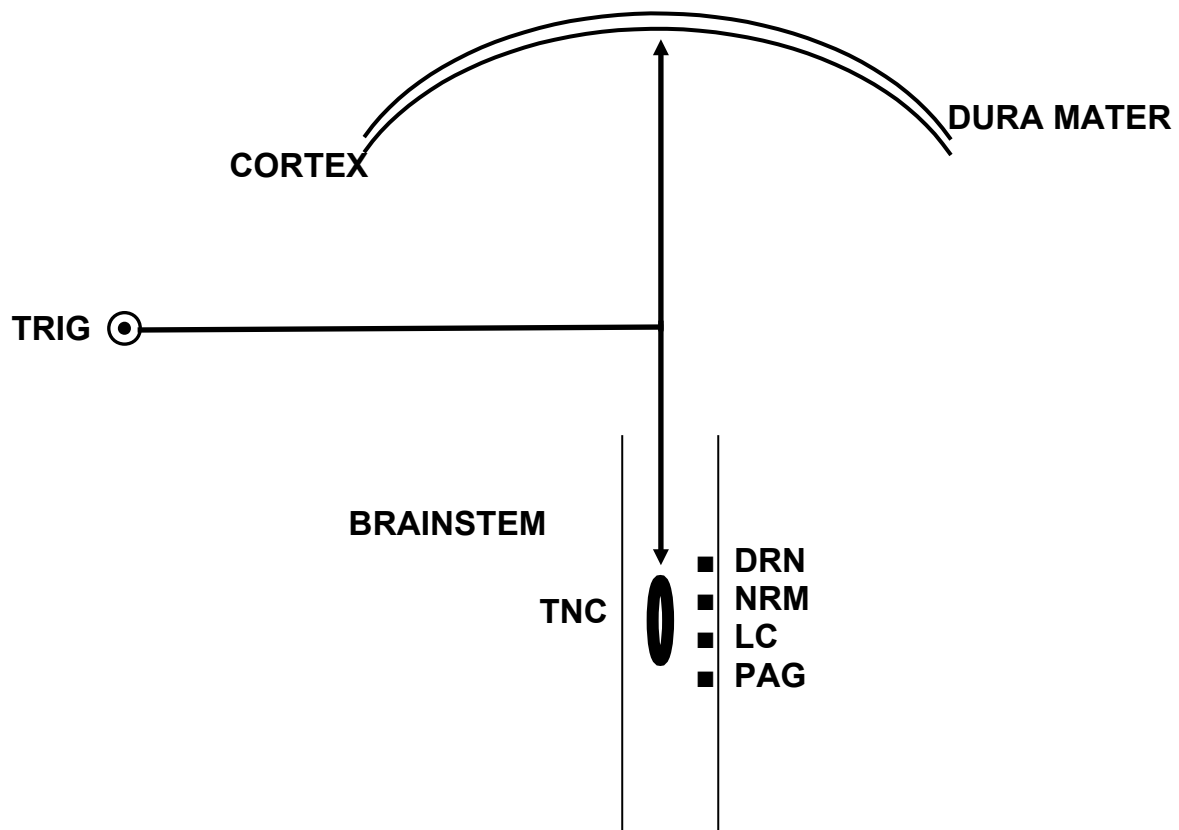
Figure 1.

The kynurenine pathway (modified ref.)



**Figure 2.**

**Scheme of the trigeminovascular system and the possible sites of action of kynurenine-related substances**



**KYNA: TNC, LC, DRN, NRM, PAG, cortex**

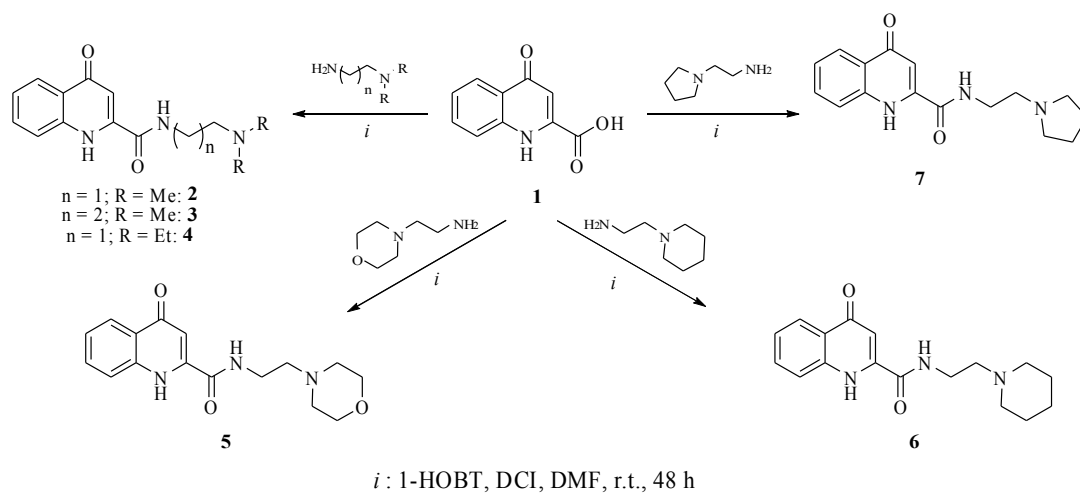
**KYNA derivatives 1: TRIG, TNC**

**L-KYN: TRIG, TNC, cortex**

Abbreviations: DRN: dorsal raphe nucleus, KYNA: kynurenic acid, KYNA derivatives: (2-(2-*N,N*-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride); (*N*-(2-*N*-pyrrolidinyloethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride), LC: locus coeruleus, L-KYN: L-kynurenine, NRM: nucleus raphe magnus, PAG: periaqueductal grey matter, TNC: trigeminal nucleus caudalis, TRIG: trigeminal ganglion

**Figure 3.**

**Synthesis of several kynurenic acid analogues**





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