Kynurenic Acid-Targeted Approaches in Dementia

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The blood–brain barrier (BBB) is poorly permeable to kynurenic acid (KYNA). The design of KYNA precursors that are highly penetrable across the BBB and convertible to an active form upon the entry has been under consideration. Another strategy is the administration of KYNA analogues that are highly penetrable to the BBB. The halogenation and conjugation of various side chains enables KYNA to cross the BBB easily, and the KYNA analogues have been shown to be more potent N-methyl-D-aspartate glutamatergic receptor (NMDAR) inhibitors. Meanwhile, inadequate nutritional status has been observed in patients with dementia. An active form of vitamin B_6, pyridoxal 5′-phosphate (PLP) is a cofactor of KYN aminotransferas (KAT) enzymes, which are responsible for KYNA production. Therefore, vitamin B_6 supplementation may be of important value to increase a level of KYNA in the brain. L-KYN is not only a precursor of KYNA, which is also produced at least partly from indole pyruvic acid (IPA) through redox reactions or the transamination of Tryptophan (TRP) . Little is studied about other routes of KYNA production and its influence on whole kynurenine (KYN) metabolism. In addition, D-enantiomers of amino acids and D-amino acid oxidase (DAAO) have been observed to contribute to L-amino acid concentration. D-TRP and D-KYN supplements and balancing the gastrointestinal microbiota responsible for conversion to L-enantiomers may be potential strategies to regulate KYN metabolism and maintain an adequate L-KYNA reservoir.

neuroprotective agents antioxidant molecules multitarget agents kynurenine tryptophan drug delivery analogue dementia depression

1. Prodrugs

The peripheral administration of kynurenic acid (KYNA) precursor, kynurenine (KYN) was found to lead to neuroprotection in hypoxic-ischemic animal models [1]. The peripheral administration of 4-chloro-KYN or 4,6-dichloro-KYN leads to the formation of 7-chloro-KYNA or 5,7-dichloro-KYNA in the brain and more potent antagonists at the glycine site of NMDARs than KYNA [2]. An orally active L-4-Cl-KYN known as AV-101 showed efficacy in animal models of Huntington's disease (HD) and neuropathic pain [3][4]. However, a Phase II clinical trial had shown negative results against major depressive disorder (MDD) in 2019 [5]. The development of other blood–brain barrier (BBB)-penetrating prodrugs is expected to be explored.

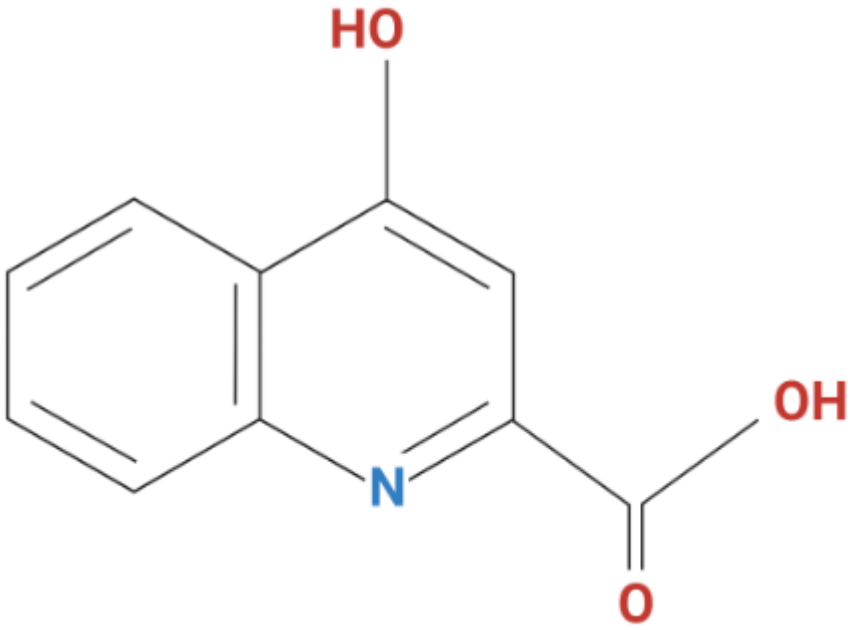

Figure 1. The chemical structure of kynurenic acid (KYNA).

2. Kynurenic Acid Analogues

More potent NMDAR-modulating KYNA derivatives have been synthesized in the search for promising new neuroprotective agents [6]. Halogenated KYNA analogues presented significantly lower IC50 values than the parent compound, and chlorination in position 7 of KYNA increased the affinity for the Gly site of the NMDARs [7][8]. Fluorination in position 5 and chlorination in position 5, 7, or 5 and 7 increased potency in the antagonism of glutamate-induced ileal contraction and for [^{3}H]Gly binding assay [9]. Hippocampal and entorhinal cortical applications of 7-Cl-KYNA attenuated magnesium-induced seizures in vitro. Intrahippocampal 5,7-di-Cl-KYNA injection prevented the behavioral and the electrographic manifestations in a rat model of status epilepticus [10]. The microinfusion of 5,7-di-Cl-KYNA suppressed the effect of both glutamate- and glycine-induced seizures of freely moving rats [11]. Bilateral 5,7-di-Cl-KYNA injection into the rostral striatum inhibited the haloperidol-induced muscle rigidity in rats, which is an animal model of parkinsonian-like muscle rigidity [12]. 4-trans-2-carboxy-5,7-dichloro-4-phenylaminocarbonylamino-1,2,3,4-tetrahydroquinoline, 5,7-di-Cl-KYNA, and 7-Cl-KYNA showed neuroprotective effects against glutamate-induced excitotoxicity in rat cortical neurons [13]. Thiokynurenates are also potent non-competitive antagonists of the NMDARs. Substitution of a thio group for the hydroxyl group in position 4 of KYNA increased the potency and chlorination of position 7 or 5 and 7 of 4-thio-KYNA and further increased potency in ileal myenteric plexus and for [^{3}H]Gly binding [14]. 4-urea-5,7-di-Cl-KYNA derivatives exerted anticonvulsant activity in maximal electroshock, subcutaneous pentylenetetrazole, and threshold tonic extension tests in mice [14].

BBB-penetrating KYNA derivatives have been synthesized by esterization. The methyl ester of diphenylureido-di-Cl-KYNA appeared to be protective against audiogenic seizures in DBA/2 mice [15]. d-Glucose or d-galactose esters of 7-Cl-KYNA penetrate the BBB and are converted to 7-Cl-KYNA or KYNA by astrocytes and neurons in the brain. d-Glucose esters of 7-Cl-KYNA and d-galactose esters of 7-Cl-KYNA attenuated the NMDA-induced seizures probably by increasing the BBB penetration [16]. The intraventricular and intravenous administration of glucose-KYNA induced stereotyped behaviors and ataxia and transient reductions of the amplitude of the somatosensory-evoked cortical potentials, suggesting that glucose-KYNA possesses similar activities to KYNA and crosses the BBB [17]. A KYNA amide derivative, *N*-(2-*N*,*N*-dimethylaminoethyl)-4-oxo-1*H*-quinoline-2-carboxamide hydrochloride showed electrophysiological properties similar to KYNA in vitro and showed a neuroprotective effect in models of cerebral ischemia (four-vessel occlusion) and an HD model of transgenic mice [18][19].

Nanotechnology-based approaches are under intensive study to overcome the blood–brain barrier and deliver the appropriate amount of drug to the specific brain site. Organic nanocarriers include polymeric nanoparticles, liposomes, dendrimers, and micelles, while inorganic nanocarriers include gold nanoparticles, silica nanoparticles, and carbon nanotubes [20]. Further research is expected to understand the blood–brain barrier crossing mechanisms and to improve the efficiency of brain delivery methods using nanotechnology.

3. Kynurenine Aminotransferases Enzyme Potentiation

KYN metabolism can be shifted toward KYNA production by enhancing KAT enzyme activity. KATs catalyzes the irreversible transamination of KYN to produce KYNA. The enzyme requires a cofactor, pyridoxal 5′-phosphate (PLP), the active form of vitamin B_6, and a cosubstrate, α-ketoacid. The kinetics of KATs depends on local KYN availability ascribed to its low affinity for their substrate. The active form of vitamin B_6, PLP, is a cofactor in many enzymes [21]. A main source of PLP is food and degraded PLP-dependent enzymes by salvage pathway enzymes in humans. Genetic dysfunction of the salvage pathway enzymes and drug interactions of PLP or pyridoxal kinase results in convulsions and epileptic encephalopathy, and a lower level of PLP has been associated with neurological disorders including AD, PD, and epilepsy [22][23]. About 20% of the elderly have been observed to have lower dietary vitamin B_6 intakes and other nutrients, and a daily intake of 20 mg vitamin B_6 improves vitamin B_6 status in healthy older men and vitamin B_6 supplementation improves cognitive performance in elderly men. It has been hypothesized that folate and vitamins B_6 and B_{12} are related to cognitive performance [24][25]. Vitamin B_6 emerged as a good predictor of cognitive performance across cognitive domains, but whether B_6 supplementation can improve cognitive performance is still to be demonstrated through ongoing longitudinal clinical trials. A correlation between blood levels of B vitamins and cognitive function has been documented, and high vitamin B_6 concentration has been correlated with better performance in memorization tests [26].

Nutrition status is relevant to the onset of dementia. Vitamin B_6 deficiency is prevalent in patients with AD, but it is not clear how low vitamin B_6 status directly influences AD pathogenesis or progression. Patients with AD are more likely to have low plasma PLP concentrations [27]. Combined high vitamin B_6 and magnesium supplementation was reported to improve verbal communication, non-verbal communication, interpersonal skills, and/or physiological function in children with autism spectrum disorders, but a systematic review concluded that the efficacy was

inconclusive [28]. Further studies are expected regarding vitamin B_6 status, KAT activity, and a KYNA level in patients with dementia.

4. Indole-3-Pyruvic Acid Precursor and Reactive Oxygen Species

KYNA is also formed at least partly from IPA, which is the transamination product of Tryptophan (TRP) by the TRP transaminase. It was reported that IPA administration increased 5-HT, 5-hydroxyindole-3-acetic acid, TRP, and KYNA levels in the brain [29]. IPA increases a KYNA level through TRP formation; furthermore, IPA can be converted to KYNA by redox reactions without enzymes. IPA is present in keto or enol tautomer. The latter cleaves the pyrrole ring by reactive oxygen radicals to form KYNA by spontaneous cyclization. IPA tautomerase increases the enol tautomer, favoring a greater formation of KYNA in the presence of free radicals [30].

In addition, KYNA is also produced from l-KYN in the presence of oxidants and peroxidase. KYN donates hydrogen, forming an unstable imino acid, which is the hydrolyzed to 2-oxo acid and ammonia. The 2-oxo acid spontaneously cyclizes to form KYNA [31]. The reaction takes place in the physiological pH ranges in the presence of H_2O_2. [32]. d-KYN was observed to produce KYNA with an interaction with hydroxyl radical and peroxynitrite in cerebellum homogenates. In vivo microdialysis studies showed that the KYNA level increases by intracerebellar infusion of l- or d-KYN, peroxynitrite infusion, and intracerebellar infusion of l- or d-KYN after peroxynitrite infusion. KYNA production from d-KYN was not influenced in the presence of a KAT inhibitor, aminooxyacetic acid, compared to one from L-KYN, suggesting that KAT is less responsible for KYNA production from d-KYN [33].

In the presence of peroxynitrite and aminooxyacetic acid, KYNA production from l-KYN decreased by 20%, but no significant change was observed with d-KYN. It suggests a minimal participation of KAT in the persistence of ROS. Furthermore, KYNA productions decreased from both enantiomers by 50% in the presence of an antioxidant, nordihydroguaiaretic acid, suggesting the oxidizing environments that facilitate KYNA production [34]. Both l-KYN and d-KYN are good ROS scavengers and lead to the production of KYNA. Oxidizing environments are in favor of producing KYNA, which may have relevance in brain development and aging and in neurological diseases that show redox environment alteration.

5. Amino Acid Oxidase and d-Amino Acids

DAAO oxidizes d-amino acids to the corresponding amino acids, producing ammonia and hydrogen peroxide. d-Serine is a physiological agonist at the NMDAR in the brain [35]. d-Enantiomers of amino acids are present at high concentrations in humans and to have biological functions. Derived from microorganisms or l-d racemization, d-amino acids are a pool of l-isomers that are necessary for protein synthesis and antagonists for l-isomers at biological sites. Bacterial pathogens and immune activation may cause an imbalance of d-amino acid concentrations [36].

D-TRP can be usable to promote growth in a TRP-deficient diet, and d-TRP and l-TRP were found to be equally effective in the growth of rats. d-TRP and d-KYN were metabolized slower than their l-enantiomers in rat liver. Small amounts of l-KYN, d-KYN, and KYNA were found converted from d-TRP [34]. KYNA and IPA were excreted from d-TRP or d-KYN-supplied rabbits [37]. d-Formyl-KYN was found to be the intermediate of d-TRP to d-KYN conversion, which was inhibited by l-TRP, and KYNA can be converted from d-KYN by DAAO in kidney homogenates [38]. Thus, KYNA can be produced from a d-TRP enantiomer. The intraperitoneal administration of d-TRP or d-KYN increased plasma KYNA levels in rats, which was inhibited by a DAAO inhibitor, 5-methylpyrazole-3-carboxylic acid [39]. KYNA was found to be produced from d-KYN in human brains, the KYN production being the highest in the cerebellum [40]. Microdialysis studies showed that increase in KYNA levels were observed after the intraperitoneal (i.p.) administration of d- or l-TRP or the infusion of d-KYN in the prefrontal cortex, which was inhibited by the DAAO inhibitor. In vitro studies showed that the KAT inhibitor inhibited KYNA production from d-KYN by 30% and the DAAO inhibitor inhibited it by 70% [34]. I.p. injection of d-TRP increased l-TRP levels in the plasma, forebrain, and cerebellum, confirming d-TRP to l-TRP conversion. KYNA levels were decreased by DAAO inhibitor in cerebellum, suggesting that DAAO takes a main role in KYNA production in cerebellum [41]. d-TRP and d-KYN are normally present in normal conditions by food intake and conversion by gastrointestinal microorganisms [34]. Thus, d-enantiomers influence a level of l-KYNA which may be affected by alteration of the cerebral DAAO activity in inflammation and neurological disorders.

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