

Antidepressant-like Effects of Kynurenic Acid Analogues †

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- † Presented at the 1st International Electronic Conference on Biomedicine, 1–26 June 2021; Available online: <https://ecb2021.sciforum.net/>.

Published: 3 June

Abstract: Kynurenic acid (KYNA) is a metabolite of the L-tryptophan (TRP)-kynurenine (KYN) pathway, which has been shown to possess neuroprotective and antidepressant-like properties. The intracerebroventricular (i.c.v.) administration of KYNA triggered antidepressant-like effects at least in part through the serotonin 5-hydroxytryptamine (5-HT) type 2 receptors, D₂, D₃, D₄ dopamine receptors, and gamma-aminobutyric acid subunit A receptors in modified forced swimming test (FST) of mouse. However, KYNA is impermeable to the blood-brain-barrier (BBB) and thus it is probably a cause that the peripheral administration of KYNA did not exhibit an antidepressant-like effect. New KYNA analogues were designed to overcome the BBB in attempt to deliver neuroprotective KYNA molecules to the central nervous system (CNS). The antidepressant-like effects of KYNA analogues SZR72, SZR81, and SZR104 were studied i.c.v. and intraperitoneally (i.p.) in a modified FST. The modified FST revealed that i.c.v. administration of SZR81 significantly decreased immobility and significantly increased swimming time, which suggested that its antidepressant-like effects were triggered at least in part through the serotonin 5-HT nervous system. SZR72 and SZR104 did not significantly change either immobility, climbing, or swimming time, suggesting SZR72 and SZR104 did not show antidepressant-like effects at tested dose in FST. Furthermore, i.p. administration of SZR81 did not change either immobility, climbing, or swimming time like i.c.v. administration. This study showed that SZR72 and SZR104 may not have the antidepressant-like properties at tested dose in FST and SZR-81 may not cross the BBB in vivo or be modified on the way to the CNS at least at tested dose. Novel KYNA analogues are expected to be designed and biologically characterized in search of potent antidepressants which reserve antidepressant properties, cross the BBB, and target KYNA effectors in the CNS.

Keywords: depression; antidepressant; kynurenines; kynurenic acid; analogues; drug design; blood-brain-barrier

1. Introduction

The tryptophan (TRP)-kynurenine (KYN) metabolic pathway attracts increasing attention as a diagnostic marker as well as a therapeutic target in a broad range of diseases from cancer and metabolic, neurodegenerative, and psychiatric diseases [1,2]. The pathway is a major branch of the essential amino acid L-TRP metabolism and the upregulation of TRP-KYN metabolic activity was observed in various illnesses [2]. L-TRP is catabolized through the methoxyindole or KYN pathway producing serotonin or nicotinamide adenine dinucleotide (NAD⁺), respectively. While serotonin has been a major subject of depression research, over 95% of L-TRP is catabolized in the TRP-KYN pathway into a number of bioactive molecules with diverse properties, including oxidant, antioxidant, neurotoxic, neuroprotective, and immunomodulant [4].

Kynurenic acid (KYNA) is one of the metabolites, catalyzed in a non-reversible step by kynurenine aminotransferase (KAT) from L-KYN to KYNA (Figure 1). KYNA is generally considered to be a neuroprotective molecule with antioxidant, anticonvulsant, metabolic, and immunomodulant activities [1]. However, a relative increase of KYNA to quinolinic acid (QUIN) was strongly linked to the cognitive impairment of schizophrenia (SCZ). The actions of KYNA in SCZ are supposed to be through the inhibition of the N-methyl-D-aspartate (NMDA) neurotransmission, either through the potentiation of dopaminergic activity or the inhibition of dopaminergic neurotransmission via its inhibitory response to $\alpha 7$ nicotinic acetylcholine ($\alpha 7$ nACh) receptor activation, and/or through the decrease of the gamma-aminobutyric acid (GABA) receptor neurotransmission [5]. KYNA reciprocally regulates glutamate, dopamine, and GABA concentrations [5]. Furthermore, sleep deprivation-induced depression was implicated with the activity of α -ketoglutarate dehydrogenase which is closely related to that of KAT [6,7]. Therefore, KYNA is considered to be a central coordinator of neurotransmissions in the central nervous system (CNS) [5]. Recently, the antidepressant-like effects of KYNA were reported in force swim test (FST) of mouse, an animal model of depression. The antidepressant-like actions were found to be triggered at least in part through serotonin (5-hydroxytryptamine, 5-HT), dopamine, and GABA receptor neurotransmissions [8].

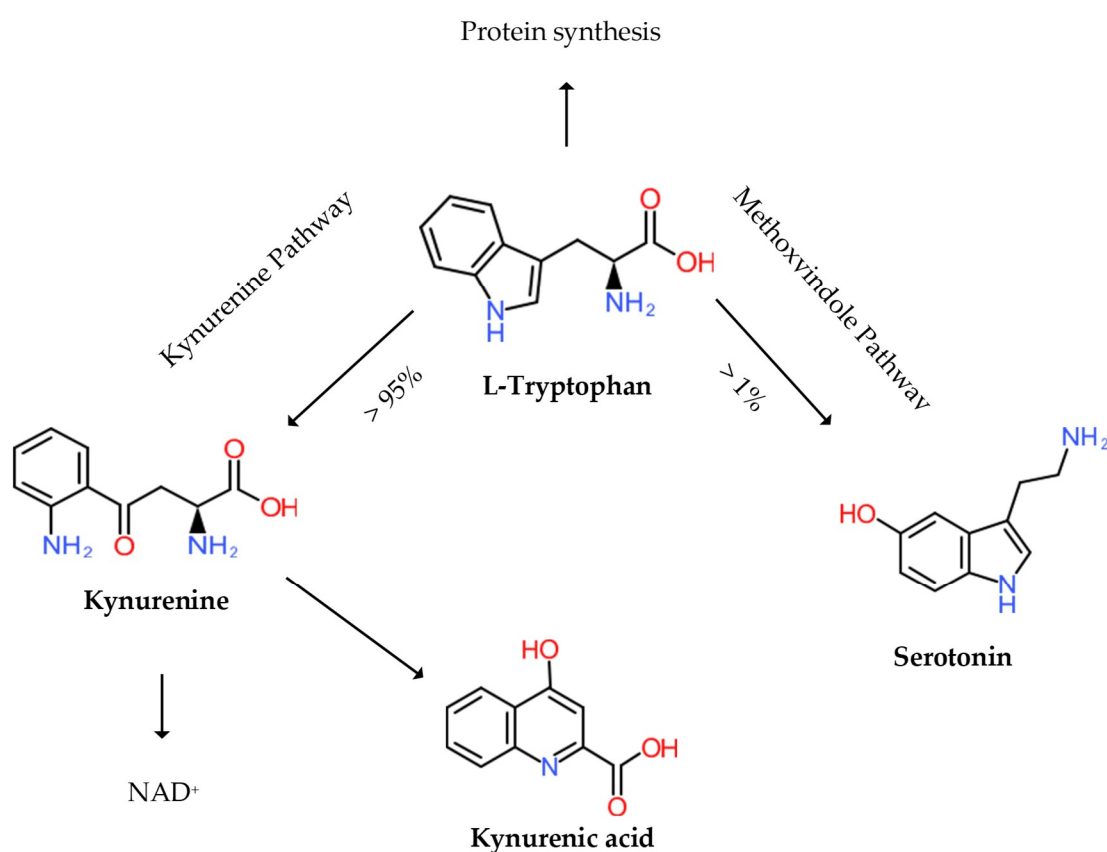


Figure 1. The tryptophan kynurenine metabolic pathway. L-tryptophan (TRP) is catabolized through the kynurenine or methoxyindole pathway, producing nicotinamide adenine dinucleotide (NAD⁺) or serotonin. Kynurenic acid is one of the metabolites, which is considered to possess a beneficial property.

KYNA is scarcely permeable to the brain-blood-barrier (BBB) [9]. The design of prodrugs which become active in the CNS and analogues permeable to the BBB is under extensive study [10]. The KYNA analogues SZR-72 (2-(2-N, N-dimethylaminoethylamine-1-carbonyl)-1H-quinolin-4-one hydrochloride), SZR-81 (N-(2-(pyrrolidin-1-yl)ethyl)-4-hydroxyquinoline-2-carboxamide hydrochloride), and SZR-104 (N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-hydroxyquinoline-2-carboxamide) were studied for their antidepressant-like effects in modified FST of mouse (Figure 2). The analogues were administered intracerebroventricularly (i.c.v.) to compare with the antidepressant-like effects of KYNA and then they were administered intraperitoneally (i.p.) to examine their BBB permeability.

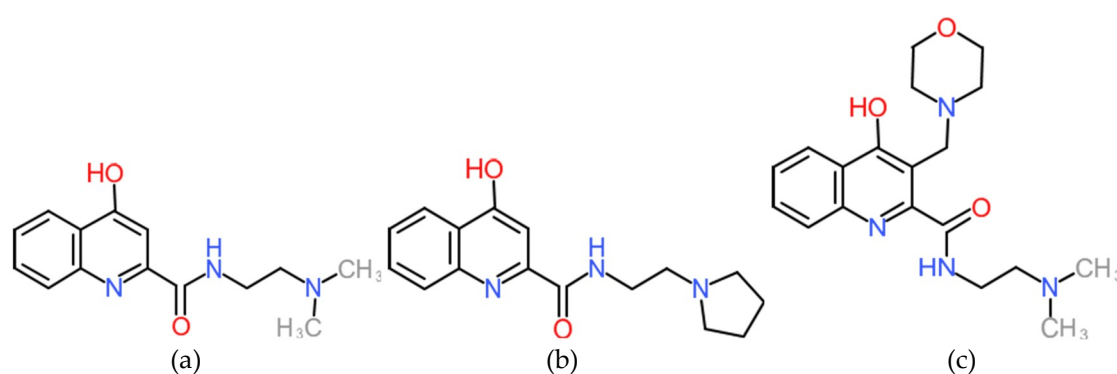


Figure 2. The chemical structures of kynurenic acid analogues (a) SZR72 (2-(2-N,N-dimethylaminoethylamine-4-hydroxyquinoline-2-carboxamide hydrochloride), (b) SZR81 (N-(2-(pyrrolidin-1-yl)ethyl)-4-hydroxyquinoline-2-carboxamide hydrochloride), and (c) SZR104 (N-(2-(dimethylamino)ethyl)-3-(morpholinomethyl)-4-hydroxyquinoline-2-carboxamide).

2. Materials and Methods

Charles Dawley (CD) 1 male mice were kept and handled during the experiments in accordance with the guidelines of the 8th Edition of the Guide for the Care and Use of Laboratory Animals and the Use of Animals in Research of the International Association for the Study of Pain and the directive of the European Economic Community (86/609/ECC). The experiments were approved by the Committee of Animal Research at the University of Szeged (I.74-24/2018) and the Scientific Ethics Committee for Animal Research of the Protection of Animals Advisory Board (XI./240/2019). Each animal was used only once in the experiments. The animals were weighed between 28 and 35 g. They were housed under standard laboratory conditions at constant temperature (25 ± 1 °C) and on a 12-h dark–light cycle (lights on at 06:00–18:00 h) with free access to tap water and standard laboratory food [8].

2.1. Surgery

To allow i.c.v. administration, a polystyrene cannula was implanted into the right lateral brain ventricle of each mouse at the coordinates 0.2 mm posterior, 0.2 mm lateral to the bregma, and 2.0 mm deep from the dural surface [11]. The cannula was fixed with cyanoacrylate (Ferrobond) (Budapest, Hungary). The suffering of the animals and the number of animals used were kept to a minimum. The i.c.v. administration was performed 5 days after the surgery.

2.2. Materials

KYNA was purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA). SZR72, SZR81, and SZR104 was synthesized in the Institute of Pharmaceutical Chemistry, University of Szeged. KYNA, SZR72, SZR81, and SZR104 was dissolved in sterile pyrogen-free 0.9% saline and administered i.c.v. via the cannula in a volume of 2 μ l. Physiological saline (0.9% NaCl) was used as a control [12].

2.3. Forced swimming test

The modified mouse FST was performed as reported previously [13]. The mice were placed individually in a glass cylinder of 12 cm in diameter and 30 cm in height. Water (25 ± 1 °C) was filled to a height of 20 cm. Fresh water was used for each mouse. A 15-min pretest was carried out 24 h before the 3-min test session. 30 min prior to the test session, SZR72, SZR81, SZR104, or KYNA was injected at a volume of 2 μ l 2.0 mM solution for i.c.v. administration. SZR72, SZR81, SZR104, or KYNA was injected at a volume of 10 ml/kg 2.0 mM solution for i.p. administration. A time-sampling technique was conducted to count the duration of climbing, swimming, and immobility times. The climbing time is influenced at least in part through the adrenergic nervous system, while the swimming time is influenced at least in part through serotonergic nervous system.

2.4. Open field test

Locomotor activity was measured by the open field test. The mice were placed individually in the center of a 35 cm \times 35 cm open-field box consisting of 49 squares. SZR72, SZR81, SZR104, or KYNA (2 μ l 2.0 mM i.c.v. or 10 ml/kg 2.0 mM) was administered 30 min before the exploratory test session, which lasted 5 min. The total number of floor units entered, the number of occasions on which the animals stood on their hind legs and the number of occurrences of face washing, forepaw licking and head stroking, each of which indicated the ambulatory activity, the total number of rearing and the grooming frequency were monitored [8].

2.4. Statistical analysis

The analysis of variance (two-way ANOVA) test was followed by Tukey's test for multiple comparisons with unequal cell size. Probability values (p) of less than 0.05 were regarded as indicative of significant differences.

3. Results

Compared to controls, i.c.v. the administration of SZR81 or KYNA significantly decreased immobility time [$p < 0.05$], suggesting the presence of the antidepressant-like effects of SZR81 and KYNA (Figure 3 (a)).

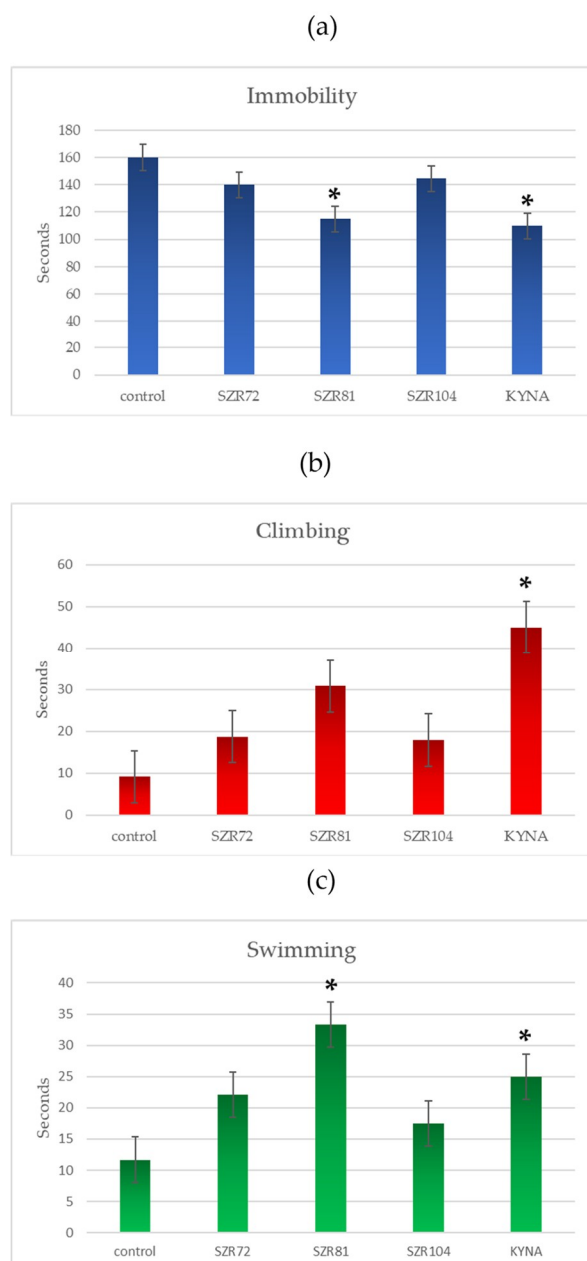


Figure 3. The effects of kynurenic acid and its analogues on immobility, climbing, and swimming times in modified forced swim test in mice. *: $p < 0.05$.

Compared to controls, the i.c.v. administration of KYNA significantly increased climbing time [$p < 0.05$]. It suggests that the antidepressant-like effect to KYNA is triggered by the adrenergic nervous system, while the participation of the adrenergic nervous system in the antidepressant-like effect of SZR81 remain inconclusive (Figure 3 (b)). Compared to controls, the i.c.v. administration of SZR81 or KYNA significantly increased swimming time [$p < 0.05$]. It suggests that the antidepressant-like effects of SZR81 and KYNA are triggered by the serotonergic nervous system (Figure 3 (c)).

No significant changes were observed following i.p. administration of KYNA or its analogues (data not shown). No significant changes were observed in locomotive, rearing or grooming activities following the i.c.v. or i.p. administration of KYNA or its analogues (data not shown).

4. Discussion

The various beneficial effects of KYNA have been attracting growing attention amongst other metabolites of the TRP-KYN pathway partly because the activation of the pathway is a common

finding in many illnesses and thus KYN metabolites are considered to participate in the pathogenesis of a wide range of diseases from cancer to psychiatric disorders [1-4].

The biosynthesis of KYNA depends largely on the activity of KAT enzyme, which is determined by the availability of a substrate KYN and the active form of vitamin B₆, pyridoxal 5'-phosphate (PLP) [9]. The phase 1 clinical trial reported that the intravenous infusion of L-KYN was safe and well-tolerated. The study showed a possible option to increase KYNA levels and proposed the potential therapeutic intervention of the TRP-KYN pathway for CNS disorders [14]. Around 20% of the elderly have lower dietary vitamin B₆ intakes and vitamin B₆ supplements were observed to improve cognitive performance in the elderly. The potentiation of KYN transferase enzyme by PLP is another option to increase KYNA levels and it was implicated for the treatment of cognitive impairment in Alzheimer's diseases [15,16].

KYNA is poorly permeable to the BBB and thus the delivery of KYNA to the CNS is one of the biggest challenges [10]. A prodrug permeable to the BBB and metabolized into an active molecule upon the entry to the CNS, has been designed. 4-chloro-KYN or 4,6-dichloro-KYN becomes 7-chloro-KYNA or 5,7-dichloro-KYNA in the brain. AV-101 (L-4-chloro-KYN) has entered phase 2 clinical trials, but the efficacy remains unknown for major depressive disorder [17]. KYNA analogues capable of crossing the BBB and retaining biological activities have been synthesized. Thiokynurenate 4-thio-KYNA, urea 4-urea-5,7-di-Cl-KYNA, glucose-KYNA, and KYNA amide derivatives are some examples [9].

KYNA analogues studied in this article exhibited a wide range of biological activities. SZR72 was found to affect inflammation, behavior, thermal regulation, and mitochondrial respiration [18-22]. SZR81 showed one of the best beneficial physiologic attenuators in bdelloid rotifers [23]. SZR104 inhibited drug-induced seizure, microglial activation, and is highly permeable to the BBB [24-26]. In addition, SZR104 influenced the production of inflammatory cytokines, but its action was contrary to that of KYNA [27]. SZR72, SZR81, and SZR104 were shown to cross the BBB in the *in vivo* model of the BBB permeability, SZR104 being the most permeable and, furthermore, the permeability of SZR104 is higher than that of KYNA [26,28].

KYNA acts on many targets in the CNS and possesses a broad range of bioactive properties. Its analogues may possess even a wider range of biological actions and may have contrary effects at a certain target. The antidepressant-like effects of KYNA were reported in several doses [8]. The limitation of this study is that a single dose was applied based on the previous study and, especially, there needs more doses to be tested for *i.p.* administration. In addition to their chemical and biological properties regarding their metabolism and the BBB permeability, further investigation is expected to characterize their beneficial use and to develop a novel lead compound.

5. Conclusions

KYNA and three KYNA analogues were assayed and compared *in vivo* for their antidepressant-like actions in modified FST of mouse. SZR81 retains an antidepressant-like activity like KYNA. However, *i.p.* administration of KYNA or its analogues failed to show any positive finding. Further fine drug design, the investigation of their possible metabolic transformation, and *in vivo* study are expected to successfully target the KYNA effectors in search of potent antidepressant drugs.

Author Contributions: conceptualization, M.T., F.F. and L.V.; methodology, M.T.; software, M.T.; validation, M.T.; formal analysis, M.T.; investigation, M.T. and Á.S.; resources, B.T., I.S. and F.F.; data curation, M.T.; writing—original draft preparation, M.T.; writing—review and editing, M.T. and L.V.; visualization, M.T.; supervision, L.V.; project administration, F.F. and L.V.; funding acquisition, L.V.

Funding: The current work was supported by the Economic Development and Innovation Operational Programme (GINOP) GINOP 2.3.2-15-2016-00034, GINOP 2.3.2-15-2016-00048, TUDFO/47138-1/2019-ITM, and TKP2020 Thematic Excellence Programme 2020.

Conflicts of Interest: The authors declare no conflict of interest.

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