



Antidepressant-like effects of kynurenic acid in a modified forced swim test

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Abstract

Background Kynurenic acid (KYNA) is an L-tryptophan metabolite with neuromodulatory activities, regulating the release of neurotransmitters such as glutamate, dopamine (DA), and acetylcholine (ACh). Dysregulation of the kynurenine pathway has been associated with neurodegenerative, neurological, and psychological disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, major depressive disorder, and schizophrenia.

Methods The antidepressant-like effects of KYNA were studied with a modified mouse forced swimming test (FST), and the potential involvement of the serotonin (SER), norepinephrine, DA, ACh, *N*-methyl-D-aspartate, or gamma-aminobutyric acid subunit A (GABA_A) receptors in its antidepressant-like effect was assayed by modified combination mouse FST. In combination studies, the mice were pretreated with the respective receptor antagonist, cyproheptadine (CPH), phenoxybenzamine, yohimbine, propranolol, haloperidol (HPD), atropine, MK-801, or bicuculline (BCL).

Results The FST revealed that KYNA reversed immobility, climbing, and swimming times, suggesting the antidepressant-like effects of KYNA. Furthermore, the combination studies showed that CPH prevented the antidepressant-like effects of KYNA on immobility, climbing, and swimming times, whereas HPD reduced climbing time and BCL influenced immobility and climbing times and prevented the effects of KYNA on swimming time.

Conclusions The results demonstrated, for the first time, the presence of antidepressant-like effects of KYNA in a modified mouse FST. Furthermore, modified combination FST showed that the antidepressant-like actions of KYNA strongly interacted with 5-hydroxytryptamine type 2 SER-ergic receptors, weakly interacted with D₂, D₃, D₄ DA-ergic receptors, and interacted moderately with GABA_A receptors.

Keywords Tryptophan · Kynurenine · Kynurenic acid · Antidepressants · Neurotransmitter receptors · Depression

Introduction

Major depressive disorder (MDD) has been linked to imbalances of central nervous system (CNS) neurotransmitters such as serotonin (SER), norepinephrine (NE), dopamine (DA), acetylcholine (ACh), glutamate (Glu), and gamma (γ)-aminobutyric acid (GABA). Tryptophan

(TRP) metabolism has been observed to play a role in the pathophysiology of MDD. 1-month treatment with a low TRP diet significantly increased the immobility time in the forced swim test (FST) in rats, suggesting the induction of depression-like behavior. Meanwhile, TRP depletion studies showed exacerbated mood symptoms in remittantly depressed patients, familiarly risk patients, and patients on anti-depressant drugs. Furthermore, supplements containing TRP have been reported to improve mood symptoms in MDD [1].

Kynurenic acid (KYNA) is a metabolite in the kynurenine (KYN) pathway from the essential amino acid L-TRP, which is also a precursor of SER and melatonin in the melatonin pathway [2]. KYNA is a noncompetitive antagonist at the glycine site B of the *N*-methyl-D-aspartate (NMDA) Glu receptor, while quinolinic acid (QUIN) is an endogenous agonist at the NMDA receptor. Thus,

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the KYN pathway products, KYNA, and QUIN mutually influence neurotoxicity, excitotoxicity, cytotoxicity, and peroxidative actions at the NMDA receptor [3] (Fig. 1).

In this study, antidepressant-like effects of KYNA were studied and the potential involvement of the SER, NE, DA, Ach, NMDA, and GABA receptors in its antidepressant-like effect was investigated in a modified FST in mice. The mice were pretreated with a nonselective 5-hydroxytryptamine (5-HT)₂ SER-ergic receptor antagonist, cyproheptadine (CPH), a nonselective alpha (α)-adrenergic receptor (ADR) antagonist, phenoxybenzamine (PHB), an alpha-2 (α 2)-ADR antagonist, yohimbine (YHB), a beta (β)-ADR antagonist, propranolol (PPL), a D₂, D₃, D₄ DA receptor antagonist, haloperidol (HPD), a nonselective muscarinic Ach receptor antagonist, atropine (ATR), a noncompetitive NMDA receptor

antagonist, MK-801 or a GABA subunit A (GABA_A) receptor antagonist, bicuculline (BCL).

Materials and methods

Animals and ethical approval

CD₁ (Charles Dawley) male mice, generally employed as animal models in depression and kynurenine research, 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

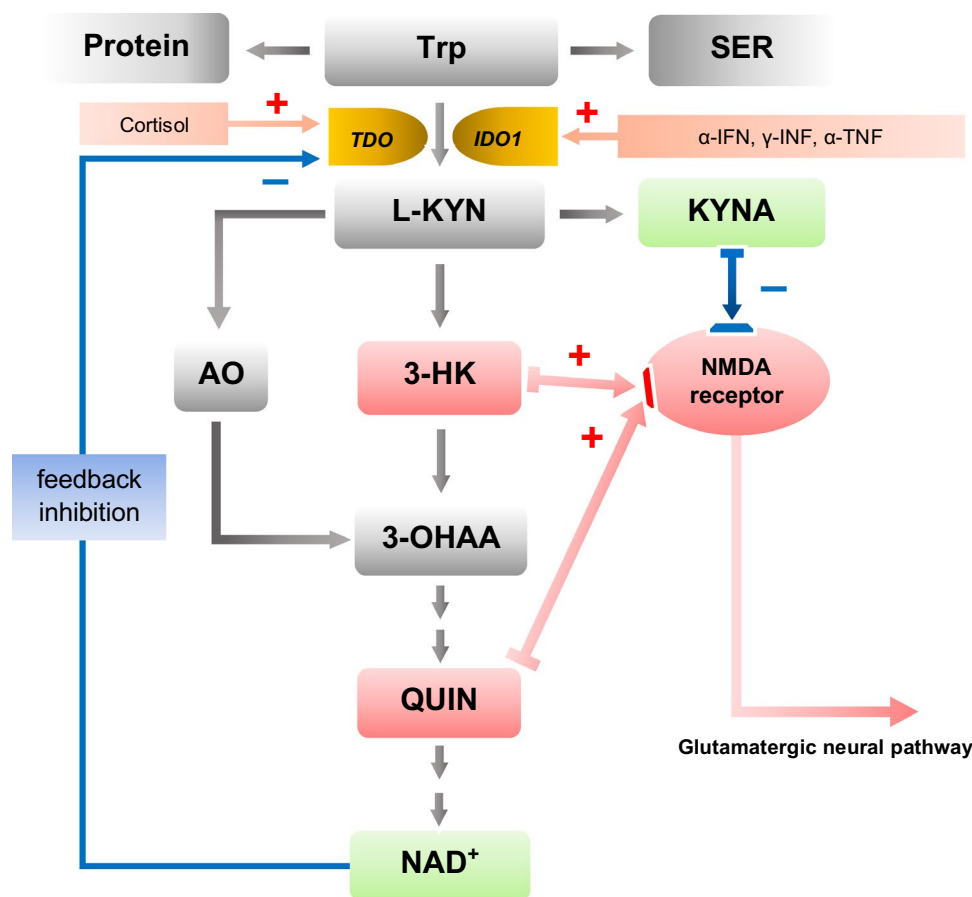


Fig. 1 The kynurenine pathway. More than 95% of TRP is metabolized in the KYN pathway except for protein synthesis. More than 95% of TRP is converted by the hepatic rate-limiting TDO and the rest of TRP, by ubiquitous rate-limiting IDO1 and IDO2 to KYN. Cortisol induces TDO, while α -IFN, γ -INF, and α -TNF induce IDO1. L-KYN is converted to AA, 3-HK, and KYNA. KYNA is an antagonist at NMDA receptor. AA and 3-HK are converted to 3-OHAA and further to QUIN. 3-HK and QUIN are agonists at NMDA receptor.

QUIN is converted to NAD⁺, which is a feedback inhibitor of TDO. TRP, tryptophan; SER, serotonin; TDO, tryptophan 2,3-dioxygenase; IDO, indoleamine 2,3-oxygenase; IFN, interferon; TNF, tumor necrosis factor; KYN, kynurenine; KYNA, kynurenic acid; AA, anthranilic acid; 3-HK, 3-hydroxykynurenine; NMDA, *N*-methyl-D-aspartate; 3-OHAA, 3-hydroxyanthranilic acid; QUIN, quinolinic acid; NAD⁺, nicotinamide adenine dinucleotide

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 about 6 weeks old and 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. At least 1 week of recovery post-surgery was allowed before the experiments. The suffering of the animals and the number of animals used were kept to a minimum.

Surgery

To allow intracerebroventricular (*icv*) 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 [4]. The cannula was fixed with cyanoacrylate (Ferrobond) (Budapest, Hungary). The *icv* administration was performed 5 days after the surgery.

Materials

KYNA was purchased from Sigma-Aldrich Corporation (St. Louis, MO, USA). CPH hydrochloride from Tocris (Bristol, UK); PHB hydrochloride from Smith Kline & French (Herts, UK); YHB hydrochloride from Tocris (Cologne, Germany); PPL hydrochloride from ICI Ltd. (Macclesfield, UK); ATR sulfate from EGIS (Budapest, Hungary); HPD from G. Richter (Budapest, Hungary); MK-801 from Sigma-Aldrich Corporation (St. Louis, MO, USA) and BCL methiodide from Sandoz (Basel, Switzerland). KYNA was dissolved in sterile pyrogen-free 0.9% saline and administered *icv* via the cannula in a volume of 2 μ l. Physiological saline (0.9% NaCl) was used as a control.

Forced swimming test

The modified mouse FST was performed as reported previously [5]. 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, KYNA was administered *icv* at a volume of 2 μ l, at doses of 0.1 mM, 0.5 mM, 1.0 mM, 1.5 mM or 2.0 mM.

In the modified combination FST, 30 min prior to KYNA (2.0 mM *icv*) administration, the following receptor blockers were administered intraperitoneally (*ip*): CPH (3 mg/kg *ip*) ($N=15$), PHB (2 mg/kg *ip*) ($N=15$), YHB (5 mg/kg *ip*) ($N=10$), PPL (5 mg/kg *ip*) ($N=10$), HPD (10 μ g/kg *ip*) ($N=15$), ATR (2 mg/kg *ip*) ($N=15$), MK-801 (2 mg/kg *ip*) ($N=10$) or, BCL (2 mg/kg *ip*) ($N=10$). Physiological saline was used for the control. A time-sampling technique was conducted to count the duration of climbing, swimming, and immobility times.

Open field test

Locomotor activity was assayed 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. KYNA (2.0 mM *icv*) was administered 30 min before the exploratory test session, which lasted 3 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.

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.

Results

Compared to controls, a dose of 1.0 mM KYNA significantly decreased immobility time [$F(3,35) = 10.68, p < 0.05$]. 1.5 mM significantly decreased immobility time [$F(3,35) = 13.93, p < 0.05$] and significantly increased swimming time [$F(3,35) = 6.73, p < 0.05$]. 2.0 mM significantly decreased immobility time [$F(3,35) = 14.98, p < 0.05$], significantly increased climbing time [$F(3,35) = 7.75, p < 0.05$], and significantly increased swimming time [$F(3,35) = 11.10, p < 0.05$]. The results suggest that KYNA induces antidepressant-like effects with doses of 1.0 mM, 1.5 mM, and 2.0 mM (Fig. 2).

Pretreatment with CPH significantly increased immobility time and significantly decreased swimming time compared to KYNA. It suggests the possible involvement of the SER receptor in KYNA-induced antidepressant-like effects. Pretreatment with PHB did not reverse immobility, climbing, or swimming times compared to KYNA, thus the NE receptor may not be involved in KYNA-induced antidepressant-like

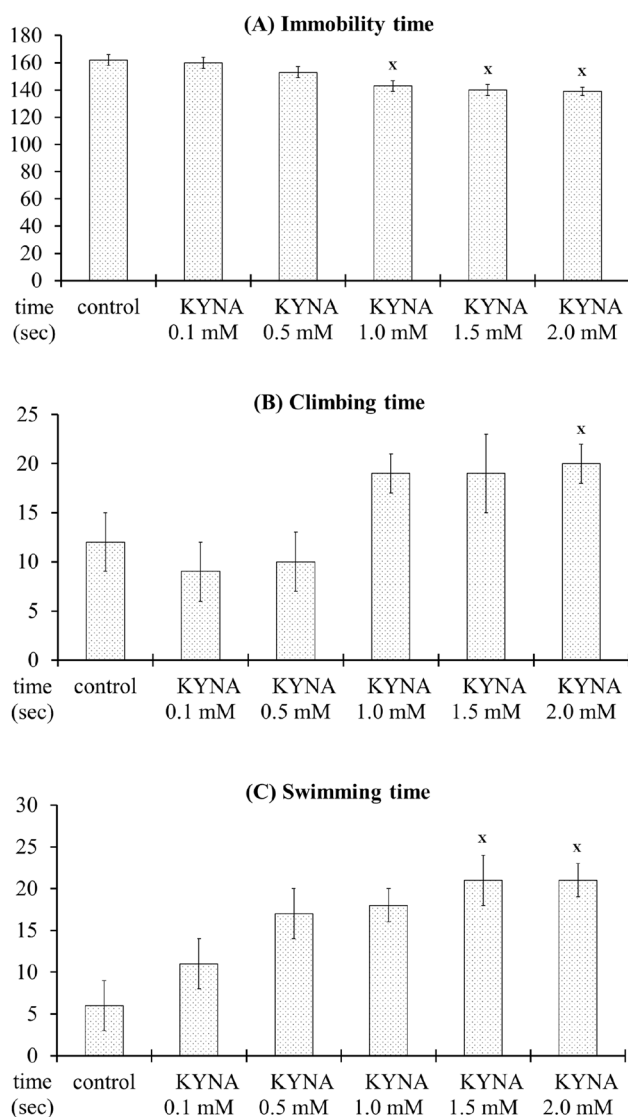


Fig. 2 The effect of kynurenic acid (KYNA) on immobility, climbing, and swimming times in a modified mouse forced swim test (FST). Compared to controls, KYNA significantly decreased immobility time in doses higher than 1.0 mM; significantly increased climbing time in a dose of 2.0 mM; significantly increased swimming time in doses of higher than 1.5 mM. Thus, KYNA showed the antidepressant-like effects in a modified mouse FST. Control ($N=12$), KYNA 0.1 mM *icv* ($N=12$), KYNA 0.5 mM *icv* ($N=12$), KYNA 1.0 mM *icv* ($N=12$), KYNA 1.5 mM *icv* ($N=12$), KYNA 2.0 mM *icv* ($N=12$). \times , $p < 0.05$ vs. control (N , the number of animals; p , probability)

effects. Likewise, pretreatment with YHB did not reverse immobility, climbing, and swimming times compared to KYNA, so the α 2-ADR receptor also may not be involved in KYNA-induced antidepressant-like effects nor did pretreatment with PPL reverse climbing, swimming, and immobility times compared to KYNA, so the β -ADR receptor is not involved in KYNA-induced antidepressant-like effects. Pretreatment with HPD did not change the immobility or

swimming times but did decrease climbing time compared to KYNA. It suggests a minimal involvement of the D_2 , D_3 , D_4 DA receptor in KYNA-induced antidepressant-like effects.

Pretreatment with ATR did not affect immobility, climbing, or swimming times compared to KYNA, so the muscarinic Ach receptor may not be involved in KYNA-induced antidepressant-like effects. Likewise, pretreatment with MK-801 did not affect climbing, swimming or immobility times compared to KYNA, thus the NMDA receptor may not be involved in KYNA-induced antidepressant-like effects. Pretreatment with BCL increased immobility time, decreased climbing time, and significantly decreased swimming time compared to KYNA, suggesting a possible involvement of the $GABA_A$ receptor in KYNA-induced antidepressant-like effects (Fig. 3).

No significant alterations in locomotive, rearing or grooming activities were observed following the *icv* administration of 2.0 mM KYNA (data not shown).

The above results revealed the presence of antidepressant-like effects of KYNA in a modified mouse FST, and the antidepressant-like actions of KYNA strongly interacted with $5-HT_2$ SER-ergic receptors, weakly interacted with D_2 , D_3 , D_4 DA-ergic receptors, and moderately interacted with $GABA_A$ receptors (Table 1).

Discussion

Disruption of the KYN pathway has been implicated in the pathophysiology of MDD [6]. The relationship between plasma KYN concentration and anxiety and depression in psychiatric patients has been studied. Plasma KYN concentration was increased in endogenous anxiety and decreased in endogenous depression. It was also observed that KYN, QUIN, and 3-hydroxy-KYN (3-HK) had anxiogenic effects, while KYNA was anxiolytic for mice in a dark–light chamber. Accordingly, it has been suggested that a group of KYN metabolites and neurokynurenes (NEKYs) are participants in depression [6, 7].

The SER hypothesis postulates that a deficit of SER in the CNS is the cause of MDD. TRP is the sole precursor of peripherally and centrally produced SER, and approximately 95 to 99% of dietary TRP not used in protein synthesis is metabolized in the KYN pathway. Thus, a small portion of TRP is available for SER-melatonin synthesis. Furthermore, it was proposed that SER deficiency in MDD was caused by a shunt of TRP metabolism from the formation of SER towards the production of KYN due to the activation of the hepatic rate-limiting enzyme, TRP 2,3-dioxygenase (TDO), which is activated by the primary stress hormone, cortisol. Activation of the ubiquitous rate-limiting enzyme, indoleamine 2, 3-oxygenase (IDO) 1 is induced by pro-inflammatory

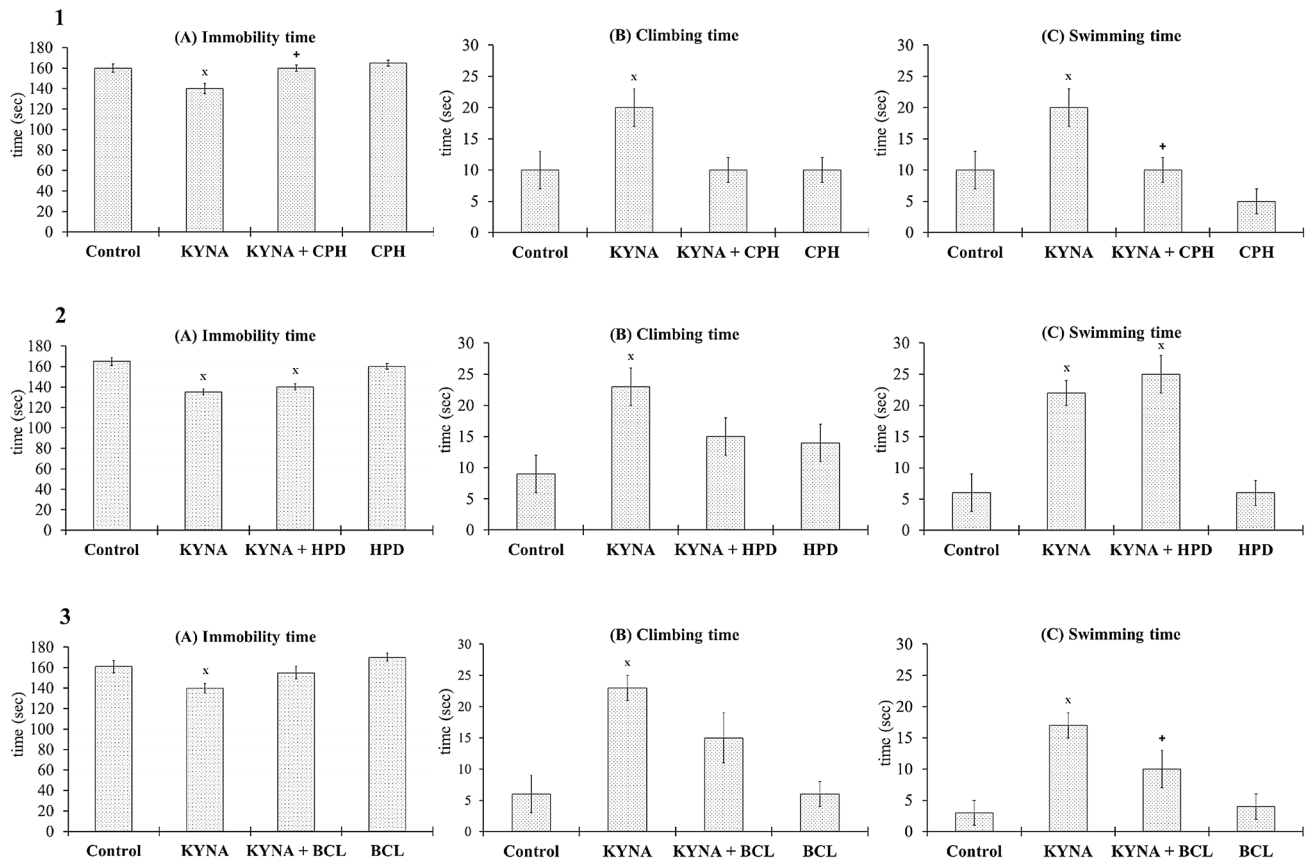


Fig. 3 The effect of a non-selective 5-HT₂ serotonergic receptor antagonist, cyproheptadine (CPH), a D₂, D₃, D₄ dopamine receptor antagonist, haloperidol (HPD) or a γ -aminobutyric acid subunit A receptor antagonist, bicuculline (BCL) in KYNA-induced antidepressant-like action in a modified forced swim test. **1**, CPH pretreatment significantly increased immobility time and significantly decreased swimming time compared to KYNA. This suggests a possible involvement of the SER receptor in KYNA-induced antidepressant-like effects. Control ($N=15$), KYNA 2.0 mM *icv* ($N=15$), CPH 3.0 mg + KYNA 2.0 mM *icv* ($N=15$), CPH 3.0 mg/kg *ip* ($N=15$). **2**, HPD pretreatment did not change immobility and swimming times, but decreased climbing time compared to KYNA. This suggests

a minimal involvement of the D₂, D₃, D₄ DA receptor in KYNA-induced antidepressant-like effects. Control ($N=15$), KYNA 2.0 mM *icv* ($N=15$), HPD 10.0 μ g/kg *ip* + KYNA 2.0 mM *icv* ($N=14$), HPD 10.0 μ g/kg *ip* ($N=15$). **3**, BCL pretreatment increased immobility time, decreased climbing time and significantly decreased swimming time compared to KYNA. This suggests a possible involvement of the GABA_A receptor in KYNA-induced antidepressant-like effects. Control ($N=10$), KYNA 2.0 mM *icv* ($N=10$), BCL 2.0 mg/kg *ip* + KYNA 2.0 mM *icv* ($N=10$), BCL 2.0 mg/kg *ip* ($N=10$), \times , $p < 0.05$ vs. control; $+$, $p < 0.05$ vs. KYNA, (N : the number of animals, p : probability)

cytokines such as α -interferon (IFN), γ -IFN, α -tumor necrosis factor, and so on [8, 9] (Fig. 1).

KYNA exhibited antidepressant-like effects by significantly decreasing immobility time, and significantly increasing climbing and swimming time in the modified FST in mice (Fig. 2). The *icv* administration of KYNA may overwhelm KYN, QUIN, and 3-HK actions at the NMDA receptors, resulting in the inhibition of the excitatory neuron pathway. The antidepressant-like effects of KYNA are reversed by the *ip* administration of SER antagonist, CPH. This suggests the possible involvement of SER receptors in the antidepressant-like effects of KYNA (Fig. 3; Table 1). It may also be assumed that the *icv* KYNA injection alters the KYN pathway balance, resulting in increased nicotinamide adenine dinucleotide (NAD⁺), which is responsible for the

feedback inhibition of TDO. Thus it facilitates the shunt of TRP metabolism from the KYN pathways toward the SER pathways to increase SER production [10].

The descending Glu-ergic neural pathway projects from the prefrontal cortex (PFC) toward the brain stem areas, innervating the substance nigra (SN), the ventral tegmental area (VTA), the midbrain raphe nuclei (MRN), and the locus coeruleus (LC). The VTA, MRN, and LC are the main brain areas where numerous serotonergic neurons originate [11, 12]. Thus, the inhibition of Glu-ergic neurotransmission may coordinate proper SER-ergic neuron firing, leading to antidepressant-like actions.

Anhedonia is one of the main symptoms of MDD and has been linked to dysfunction of the reward system in which DA neurotransmission plays a significant role. Animal models

Table 1 The involvement of receptors in KYNA-induced antidepressant-like action in modified combination mouse swim test

Receptors	Modified combination FST		
	Immobility	Climbing	Swimming
5-HT ₂ serotonin	High	Low	High
α -Adrenaline	–	–	–
α_2 -Adrenaline	–	–	–
β -Adrenaline	–	–	–
D ₂ , D ₃ , D ₄ dopamine	–	Low	–
Muscarinic acetylcholine	–	–	–
<i>N</i> -methyl-D-aspartate	–	–	–
Gamma-aminobutyric acid subunit A	Low	Low	High

The antidepressant-like actions of KYNA strongly interacted with 5-HT₂ SER-ergic receptors, weakly interacted with D₂, D₃, D₄ DA-ergic receptors, and moderately interacted with GABA_A receptors. “–”: A receptor antagonist did not modify KYNA-induced antidepressant-like effects. “low”: A receptor antagonist modified KYNA-induced antidepressant-like effects with $p > 0.05$ vs. KYNA. “high”: A receptor antagonist modified KYNA-induced antidepressant-like effects with $p < 0.05$ vs. KYNA

of depression also demonstrate changes in the function for the mesolimbic DA system. Altered DA receptor expression within the limbic structures was observed in different models of depression, such as the learned helplessness model and the chronic mild stress model [13]. A D₂, D₃, D₄ DA receptor antagonist, HPD, influenced the climbing time in the modified combination FST. This suggests that the KYNA-induced antidepressant-like action may possibly be involved in DA receptor function (Fig. 3; Table 1).

Main DAergic neural pathways involved in MDD originate in the SN and VTA, which project toward the striatum, PFC and amygdala. Glu-ergic neurons from the PFC innervate the SN and VTA and may influence the DA-ergic neurotransmission. Furthermore, Glu-ergic neural pathways innervate the striatum and amygdala as part of the cortico-striatum–thalamus loop, and thus may influence DA-ergic neural effectors [11, 12].

In humans, about 80% of neurons in the neocortex are spiny and excitatory and form 85% of the synapses, indicating that Glu neurons and synapses occupy the largest part of the brain governed by a Glu-ergic excitatory neurons. It was reported that 2-amino-7-phosphonoheptanoic acid, a competitive NMDA subtype of Glu receptor antagonist, MK-801, a noncompetitive NMDA antagonist and 1-aminocyclopropanecarboxylic acid showed antidepressant-like effects in animal models [14]. Significantly higher cerebrospinal fluid (CSF) glutamine (Gln) concentrations were observed in MDD patients [15]. The findings are in accordance with antidepressant-like effects of KYNA as a NMDA receptor antagonist, which inhibits excitatory Glu-ergic neurotransmission.

Antidepressant-like effects induced by KYNA may be triggered by inhibition of the $\alpha 7nAChR$, leading to the reduction of Glu neurotransmitter, and by antagonistic inhibition of ionotropic AMPA, NMDA, and kainate subtypes of Glu receptors, present on presynaptic and postsynaptic neurons, as well as on glial cells, inhibiting rapid ionotropic effects. Noncompetitive NMDA receptor antagonist MK-801 did not affect KYNA-induced antidepressant-like action, showing that KYNA and MK-801 are not synergistic action at the NMDA receptors. A high dose of MK-801 is a potent antidepressant per se in FST. A lower dose was calibrated to study the modified FST in combination with its MK-801, but did not show any antidepressant effect in FST.

About 20% of the neurons are smooth and inhibitory and 15% of the synapses in the neocortex are occupied by GABA, which mediates fast inhibitory transmission. Deficits in GABA neurotransmission may contribute to MDD according to the findings of reduced GABA levels in plasma, CSF, and resected cortical tissue of MDD patients [15]. A significantly reduced behavioral reactivity in the open field and reduced glutamic acid decarboxylase mRNA expression in the limbic system were found in male rats on reboxetine, a NE reuptake inhibitor [16]. A significant increase in the occipital cortex GABA concentration was observed by proton magnetic resonance spectroscopy in MDD patients on fluoxetine, a selective SER reuptake inhibitor [17].

The GABA-ergic deficit hypothesis of depression suggests that the activation of the hypothalamus–pituitary–adrenal glands (HPA) axis is triggered by reduced GABA release in the hippocampus and frontal cortex, both of which are projecting to the paraventricular nucleus of the hypothalamus. That is, it is caused by reduced GABA-ergic synaptic inhibition in the HPA axis [18]. Other GABA-ergic neurons projecting toward the hypothalamus originate in NAc, where numerous neural pathways transit or destinate, including Glu-ergic neurons originating from the prefrontal cortex, amygdala, and hippocampus [11, 12]. Marked alterations in GABA_A receptor signaling are reported in both anxiety and mood disorders [19].

A GABA_A receptor antagonist, BCL, influenced the immobility and climbing times and prevented the effects of KYNA on swimming time in the modified mouse FST. It suggests KYNA triggered antidepressant-like actions through the GABA_A receptors (Fig. 3; Table 1). KYNA-induced antidepressant actions may be generated by shifting the Glu/GABA-Gln cycle in favor of more GABA production. Inhibitory GABA-ergic neurotransmission may be fine-tuned by a panel of neurotransmitters in the NAc; thus, it may help induce KYNA’s antidepressant-like actions. But, the involvement of KYNA inhibition at presynaptic $\alpha 7nACh$ and the excitatory NMDA receptors triggering the

GABA-ergic neurotransmissions, and GABA production has yet to be investigated.

Meta-analysis of animal and human studies comparing metabolite levels of the KYN pathway between patients with depression and healthy controls showed that KYNA and KYN levels were slightly decreased in patients with MDD, ratios of KYNA/QUIN, as well as KYNA/3-HK, were lower in patients with depression, and there were no differences in QUIN and 3-HK levels between the two groups, presenting a strong evidence that the KYN pathway is involved in the pathophysiology of MDD [20].

Much evidence supports the involvement of KYN pathway products, KYNA, and NEKs in MDD. This work shows, for the first time, KYNA's antidepressant-like effects in a modified mouse FST. Furthermore, the antidepressant-like actions of KYNA interacted strongly with 5-HT₂ SER-ergic receptors, weakly with D₂, D₃, D₄ DA-ergic receptors, and in moderately with GABA_A receptors. KYNA's beneficiary antidepressant-like actions are to be explored further in the search for a potential novel therapeutic agent against MDD.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest regarding this work.

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