Kynurenic Acid in the Brain

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Contributor: Tsutomu Fukuwatari

Kynurenic acid, a metabolite of the kynurenine pathway of tryptophan catabolism, acts as antagonist for both the α7 nicotinic acetylcholine receptor and glycine co-agonist sites of the N-methyl-D-aspartic acid receptor at endogenous brain concentrations. Elevation of brain kynurenic acid levels reduces the release of neurotransmitters such as dopamine and glutamate, and kynurenic acid is considered to be involved in psychiatric disorders such as schizophrenia and depression.

Keywords: tryptophan ; neurotransmitter ; schizophrenia

1. Introduction

In 1989, Kessler et al. found that KYNA competitively inhibited glycine coagonist site of the NMDA receptor at low concentration with an IC_{50} of 8 μmol/L[1]. A decade later, Hilmas et al. found that KYNA noncompetitively inhibited α7nAchRs with an IC_{50} of 7 μmol/L using the patch-clamp technique with cultured hippocampal neurons[2]. Furthermore, Wang et al. found that KYNA is ligand for GPR35, whose EC_{50s} are 10.7, 7.4, and 39.2 μmol/L in mouse, rat, and human, respectively[3]. Since physiological concentrations of brain KYNA are 5 pmol/g wet wt, 15 pmol/g wet wt, and 150 pmol/g wet wt in mouse, rat and human, respectively[4] [8], elevation of brain KYNA has been considered to affect these receptors. Effects of KYNA increase on the neurotransmitter release were investigated using microdialysis technique, and KYNA concentration-dependently and reversibly reduced extracellular glutamate, dopamine, and γ-aminobutyric acid (GABA) to less than 50% of baseline concentrations[5][6][7]. Conversely, inhibition of endogenous KYNA formation by reverse dialysis of KYNA synthesis inhibitor *(S)*-4-(ethylsulfonyl) benzoylalanine (*S*-ESBA) reversibly increases dopamine, glutamate, and GABA levels in the rodent brain[7][8][9]. Although these findings suggest that changes of brain KYNA levels affect neurotransmitter release via modulation of above receptors, understanding the mechanism of action of KYNA is difficult. There is disagreement about the interaction between KYNA and α7nAchRs, because several studies failed to reproduce evidence for action of KYNA on nicotinic receptors.[10]. Schematic representation of the interaction between KYNA and the receptors is shown in Figure 1.

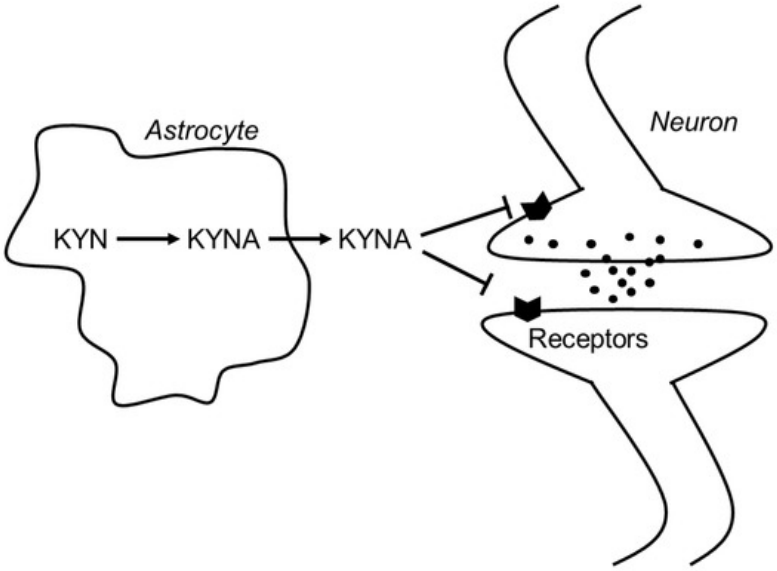

Figure 1. Schematic representation of the interaction between KYNA and neurotransmitters in the brain. Abbreviations: KYN: kynurenine; KYNA: kynurenic acid.

2. Function of Kynurenic Acid in the Brain

Behavioral studies showed that changes in brain KYNA levels affect several psychiatric functions in experimental animals. Elevation of endogenous KYNA concentration produces disruptions in prepulse inhibition[11] and habituation of auditory-evoked potentials[12], indicating that elevated KYNA levels interfere with normal reductions in processing and responding to irrelevant stimuli. Elevation of brain KYNA levels also affects cognitive function. For example, rats with elevations of endogenous KYNA exhibit spatial working memory deficits in a radial arm maze task[13]. These rats also exhibit impaired contextual fear memory consisting of two pairings of a tone and foot shock, and are slower to learn to discriminate between different contexts with or without foot shock[14]. On the other hand, reduction of endogenous KYNA levels by genetic and pharmacological manipulation improves cognitive functions. Mice with a targeted deletion of kynurenine aminotransferase II (KAT II), a major biosynthetic enzyme of brain KYNA, show reduced brain KYNA levels and significantly increased performance in three cognitive paradigms that rely in part on the integrity of hippocampal function, namely, object exploration and recognition, passive avoidance, and spatial discrimination[15]. Intracerebroventricular administration of selective KAT II inhibitor *S*-ESBA improves kynurenine-induced cognitive deficits on performance in the Morris water maze[16]. Systemic administration of KAT II inhibitor, PF-04859989, also dose-dependently reduces brain KYNA, prevents amphetamine- and ketamine-induced disruption of auditory gating, and improves performance in a sustained attention task[17]. It also prevents ketamine-induced disruption of performance in a working memory task and a spatial memory task in rodents and nonhuman primates, respectively. These findings support the hypotheses that endogenous KYNA impacts cognitive function and that inhibition of KAT II, and consequent lowering of endogenous brain KYNA levels, improves cognitive performance under conditions considered relevant for schizophrenia.

In humans, elevated KYNA levels are observed in the cerebrospinal fluid and cortex of patients with schizophrenia and bipolar disorder[18][19][20][21][22][23]. In the brain, kynurenine and KYNA levels in schizophrenic cases are 1.5 times higher than matched control subjects[20]. Similar observations reported that kynurenine and KYNA concentrations in the cerebrospinal fluid (CSF) were 2 and 1.5 times higher in patients with schizophrenia, respectively, than with healthy volunteers, whereas tryptophan concentrations did not differ between the groups[22]. Patients with bipolar disorder have 1.5 times increased levels of KYNA in their CSF compared with healthy volunteers, and the levels of KYNA are positively correlated with age among bipolar patients but not in healthy volunteers[24]. Haplotype analysis shows an association between kynurenine 3-monoxygenase (KMO) gene polymorphisms and CSF concentrations of KYNA in patients with schizophrenia[25]. In the bipolar disorder and schizophrenia patients, KMO mRNA levels are reduced in the brain compared with nonpsychotic patients and controls, and the KMO Arg452 allele is associated with increased levels of CSF KYNA and reduced brain KMO expression[26]. KMO is the primary enzyme responsible for kynurenine degradation. These results support the hypothesis that KYNA is involved in the pathophysiology of psychiatric diseases such as schizophrenia and bipolar disorder.

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