J Mol Neurosci (2010) 40:204–210
DOI 10.1007/s12031-009-9235-2

The Astrocyte-Derived α7 Nicotinic Receptor Antagonist Kynurenic Acid Controls Extracellular Glutamate Levels in the Prefrontal Cortex

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Received: 13 July 2009 / Accepted: 20 July 2009 / Published online: 19 August 2009

Abstract The cognitive deficits seen in schizophrenia patients are likely related to abnormal glutamatergic and cholinergic neurotransmission in the prefrontal cortex. We hypothesized that these impairments may be secondary to increased levels of the astrocyte-derived metabolite kynurenic acid (KYNA), which inhibits α7 nicotinic acetylcholine receptors (α7AChR) and may thereby reduce glutamate release. Using in vivo microdialysis in unanesthetized rats, we show here that nanomolar concentrations of KYNA, infused directly or produced in situ from its bioprecursor kynurenine, significantly decrease extracellular glutamate levels in the prefrontal cortex. This effect was prevented by the systemic administration of galantamine (3 mg/kg) but not by donepezil (2 mg/kg), indicating that KYNA blocks the allosteric potentiating site of the α7AChR, which recognizes galantamine but not donepezil as an agonist. In separate rats, reduction of prefrontal KYNA formation by (*S*)-4-ethylsulfonyl benzoylalanine, a specific inhibitor of KYNA synthesis, caused a significant elevation in extracellular glutamate levels. Jointly, our results demonstrate that fluctuations in endogenous KYNA formation bidirectionally influence cortical glutamate concentrations. These findings suggest that selective attenuation of cerebral KYNA production, by increasing glutamatergic tone, might improve cognitive function in individuals with schizophrenia.

Keywords Cognition · Donepezil · Galantamine · Kynurenine · Microdialysis · Prefrontal cortex

Proceedings of the XIII International Symposium on Cholinergic Mechanisms

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Introduction

The cognitive deficits seen in individuals with schizophrenia (SZ) are now recognized as a core domain of the disease (Keefe et al. 2007). Several of these impairments affect executive functions (i.e., attention, cognitive flexibility), are mediated by the prefrontal cortex (PFC; Kerns et al. 2008; Moghaddam and Homayoun 2008), and may be causally related to abnormal glutamatergic and cholinergic neurotransmission within the PFC (Sarter et al. 2005; Lewis and Moghaddam 2006).

Dysregulation of prefrontal α7 nicotinic acetylcholine receptors (α7nAChRs) might be central to these behavioral and chemical abnormalities. Thus, α7nAChR protein levels are reduced in the PFC of individuals with SZ (Guan et al. 1999), and the α7nAChR gene and a SZ endophenotype (disrupted P50 evoked response to repeated auditory stimuli) are linked to the same locus and associated with disease transmission (Leonard and Freedman 2006). More-

over, specific cognitive improvements in SZ patients can be achieved by galantamine (Schubert et al. 2006; Buchanan et al. 2008), probably by activating the allosteric potentiating ligand (APL) site of the α7nAChR (Samochocki et al. 2003). Notably, α7nAChRs in the mammalian brain are frequently localized presynaptically on glutamatergic nerve terminals, where they regulate the release of glutamate (Albuquerque et al. 2009).

The endogenous metabolite kynurenic acid (KYNA) may play a substantive role in these prefrontal mechanisms and deficits. Initially described as a broad spectrum antagonist of ionotropic glutamate receptors (Perkins and Stone 1982), KYNA was later shown to block the glycine co-agonist ("glycine$_B$") site of the *N*-methyl-D-aspartate receptor with much higher potency (IC_{50} in the absence of glycine, ~10 μM; Kessler et al. 1989). However, KYNA is unlikely to inhibit this site under physiological conditions (IC_{50} in the presence of glycine, ~230 μM; Hilmas et al. 2001). Rather, endogenous KYNA appears to function as a preferential α7nAChR antagonist (Hilmas et al. 2001), targeting a site which closely resembles the APL site that is activated by galantamine (Lopes et al. 2007). Interestingly and unrelated to antipsychotic medication, KYNA levels are abnormally high in the brain and cerebrospinal fluid of SZ patients (Erhardt et al. 2001; Schwarcz et al. 2001).

The de novo synthesis of KYNA in the mammalian brain is catalyzed by the irreversible transamination of its bioprecursor kynurenine in astrocytes. Of two distinct astrocytic kynurenine aminotransferases (KAT I and KAT II), KAT II is the dominant isozyme in the rat brain (Guidetti et al. 1997). Newly formed KYNA is rapidly released into the extracellular milieu and eventually removed from the brain by probenecid-sensitive, passive efflux (Moroni et al. 1988; Turski et al. 1989). Recently, we reported the synthesis and biological characterization of (*S*)-4-ethylsulfonyl benzoylalanine (*S*-ESBA), the first potent and selective KAT II inhibitor (Pellicciari et al. 2006). Using locally administered KYNA, kynurenine or *S*-ESBA as tools, we now investigated the effects of fluctuations in brain KYNA levels on the extracellular concentrations of glutamate in the rat PFC. These studies, which were conducted using in vivo microdialysis in unanesthetized rats, also examined if α7nAChRs serve as functional targets of KYNA in the brain.

Materials and Methods

Animals

A total of 22 adult, male Sprague–Dawley rats (220–260 g) were used in the experiments. The animals were maintained on a 12:12-h light/dark cycle in a temperature- and humidity-controlled, Association for Assessment and Accreditation of Laboratory Animal Care-approved animal care facility and had free access to food and water. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Maryland in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Microdialysis

Rats were anesthetized with chloral hydrate (360 mg/kg, i.p.) and unilaterally implanted with a microdialysis guide cannula (0.38 mm o.d.; 3.0 mm membrane tip) into the medial PFC (*A*=3.2 mm in front of bregma, *L*=0.6 mm from the midline, *V*=1.0 mm below dura). The guide was fixed to the skull using stainless steel screws and dental acrylic, and the surgical site was swabbed with lidocaine (5%).

On the next day, a microdialysis probe (CMA/10, membrane length 3 mm, Carnegie Medicin, Stockholm, Sweden) was inserted through the guide cannula and connected to a microperfusion pump set to a speed of 1 μl/min. The freely moving animals were continuously perfused with Ringer solution, pH 6.7, containing (in millimolar): NaCl, 144; KCl, 4.8; $MgSO_4$, 1.2; and $CaCl_2$, 1.7. After the establishment of a stable baseline, KYNA (100 nM), kynurenine (2.5 μM) or *S*-ESBA (3 mM) was applied by reverse dialysis for 2 h. Subsequently, perfusion with Ringer solution continued for 4 h. Data were not adjusted for recovery from the microdialysis probe.

Analysis of KYNA and Glutamate

KYNA and glutamate were determined in the same microdialysate by high-performance liquid chromatography (HPLC) with fluorescence detection. To measure KYNA, 10 μL of the microdialysate were diluted with 5 μL of 0.1 M HCl, and 10 μL of the mixture was injected onto a 3-μm C_{18} reverse phase column (80×4.6 mm, ESA, Bedford, MA, USA). KYNA was isocratically eluted at a flow rate of 1 mL/min, using a mobile phase containing 200 mM zinc acetate and 5% acetonitrile, pH 6.2. In the eluate, KYNA was detected fluorometrically, using an excitation wavelength of 344 nm and an emission wavelength of 398 nm (fluorescence detector, Perkin-Elmer Series 200). The retention time of KYNA was approximately 5.0 min (Swartz et al. 1990).

Glutamate was measured in 8 μL of the microdialysate, as described by Shank et al. (1993). Briefly, *o*-phthalaldehyde/β-mercaptoethanol was added to each sample (2:1, *v*/*v*) to yield a fluorescent derivative. The mixture was applied to a reverse phase HPLC column

(C_{18}, 5 μm; 250×4.6 mm; Thermo Electron Corporation, Waltham, MA, USA) and eluted with a gradient composed of two mobile phases ((a) 20 mM sodium acetate, 7.5% acetonitrile, pH 6.1; (b) 30% acetonitrile, 30% methanol) set at a gradient elution program of 15 min at a flow rate of 1 mL/min. In the eluate, glutamate was detected fluorometrically (excitation wavelength 390 nm; emission wavelength 460 nm; Perkin-Elmer Series 200). The retention time of glutamate was approximately 4.0 min.

Chemicals

L-Kynurenine (sulfate) and galantamine were purchased from Sigma (St. Louis, MO, USA). All other biochemicals were of the highest purity available and were obtained from various commercial suppliers. Donepezil (hydrochloride) was purchased from A & A Pharmachem Inc. (Ottawa, Ontario, Canada).

Results

The basal extracellular levels of KYNA and glutamate in the PFC were 2.5±0.2 nM and 1.9±0.1 μM (n=18 and 22, respectively). Local perfusion of KYNA (100 nM) by reverse dialysis caused a significant 26% decrease in extracellular glutamate levels (n=4). This reduction was transient, and glutamate levels promptly reverted to baseline values following the removal of KYNA from the perfusion solution (Fig. 1).

Reverse dialysis of kynurenine (2.5 μM) resulted in an increase in extracellular KYNA, reaching a maximum of 220% of baseline values. In the same microdialysates, extracellular levels of glutamate were reduced, reaching a nadir of −28% compared to baseline levels. Both KYNA and glutamate levels gradually reverted to control values after kynurenine was removed from the perfusion solution (n=4; Fig. 2).

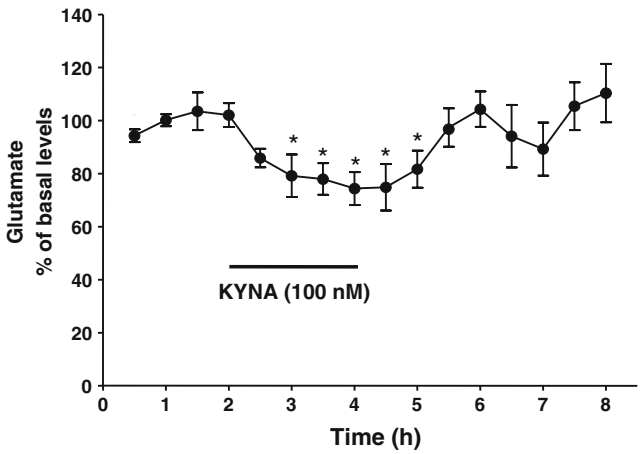

Figure 1 Effect of KYNA, applied by reverse dialysis (*bar*), on extracellular levels of glutamate in the PFC. Data are the mean ± standard error of the mean (n=4). *p<0.05 vs. the baseline (one-way ANOVA)

As illustrated in Fig. 3a, systemic administration of galantamine (3 mg/kg, i.p.) prevented the kynurenine-induced decrease in extracellular glutamate without, however, affecting the de novo production of KYNA (n=4). In contrast, a peripheral injection of donepezil (2 mg/kg, i.p.) did not affect either the increase in extracellular KYNA or the reduction in extracellular glutamate caused by the intracortical perfusion of kynurenine (n=6; Fig. 3b).

Intracortical perfusion of *S*-ESBA (3 mM) resulted in a significant 35% reduction in extracellular KYNA, which was accompanied by a 244% elevation of extracellular glutamate levels. The levels of both analytes gradually reverted to control values after the KAT II inhibitor was removed from the perfusion solution (n=4; Fig. 4).

Discussion

The present results demonstrate that nanomolar (i.e., endogenous) concentrations of KYNA exert bidirectional control over extracellular glutamate levels in the rat PFC and that these in vivo effects are mediated by α7nAChRs. More specifically, our experiments indicate that astrocytes, by generating and releasing KYNA, play a pivotal role in the modulation of extracellular glutamate via the allosteric potentiating site of the α7nAChR. Since both glutamate and α7nAChRs are linked to normal and impaired cognition involving the PFC (Hashimoto et al. 2008; Zahr et al. 2008), our study implies that fluctuations in endogenous KYNA may play a significant role in prefrontally mediated cognitive processes.

In subcortical regions, KYNA inhibition of α7nAChRs leads to a reduction in extracellular glutamate levels (Carpenedo et al. 2001; Rassoulpour et al. 2005; Grilli et al. 2006). We show here that KYNA, applied directly into the parenchyma or produced locally by perfusing physiological concentrations of kynurenine, also decreases glutamate levels in the PFC. Throughout the forebrain, this effect is presumably initiated mainly by the blockade of presynaptic α7nAChRs on glutamatergic nerve terminals (Gioanni et al. 1999; Marchi et al. 2002; Rousseau et al. 2005; Dickinson et al. 2008). However, α7nAChRs are also situated on postsynaptic, somatodendritic structures and on nonglutamatergic nerve endings (Csillik et al. 1998; Alkondon et al. 2000; Krenz et al. 2001; Albuquerque et al. 2009), so that it is conceivable that the inhibition of α7nAChRs receptors by KYNA reduces glutamate levels indirectly—either locally or through a distributed system involving brain areas with reciprocal links to the PFC (Del

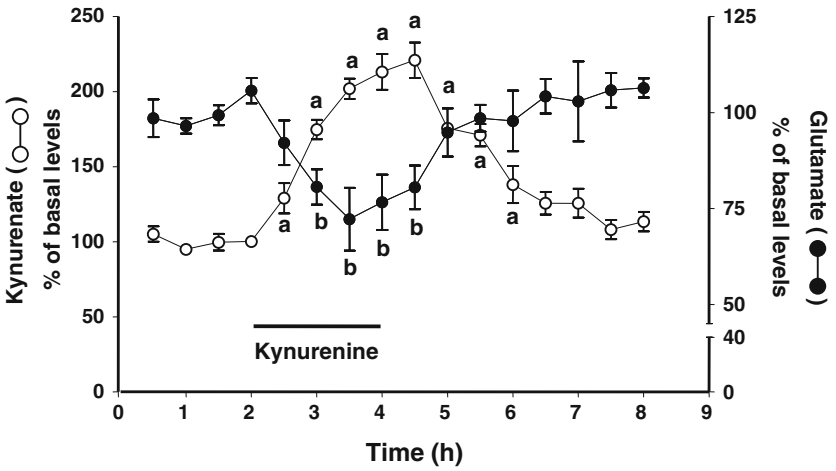

Figure 2 Effect of a local perfusion of kynurenine (2.5 μM; *bar*) on extracellular levels of KYNA and glutamate in the PFC. The two analytes were measured in the same microdialysates. Data are the mean ± standard error of the mean of four animals. *a*, *b* $p<0.05$ compared to the respective baseline values (one-way ANOVA)

Arco and Mora 2005, 2008; Biton et al. 2007; Couey et al. 2007). Jointly, these mechanisms, which clearly need to be elaborated in greater detail, probably account for the fact that even modest increases in cortical KYNA levels also influence extracellular dopamine and acetylcholine levels in the PFC (Wu et al. 2006; Zmarowski et al. 2009).

Regardless of the precise cellular or regional localization of the targeted receptors, our experiments with galantamine and donepezil demonstrated unambiguously that the KYNA-induced reduction in extracellular glutamate in the PFC is indeed α7nAChR dependent. Thus, systemic administration of galantamine, which acts as an agonist at

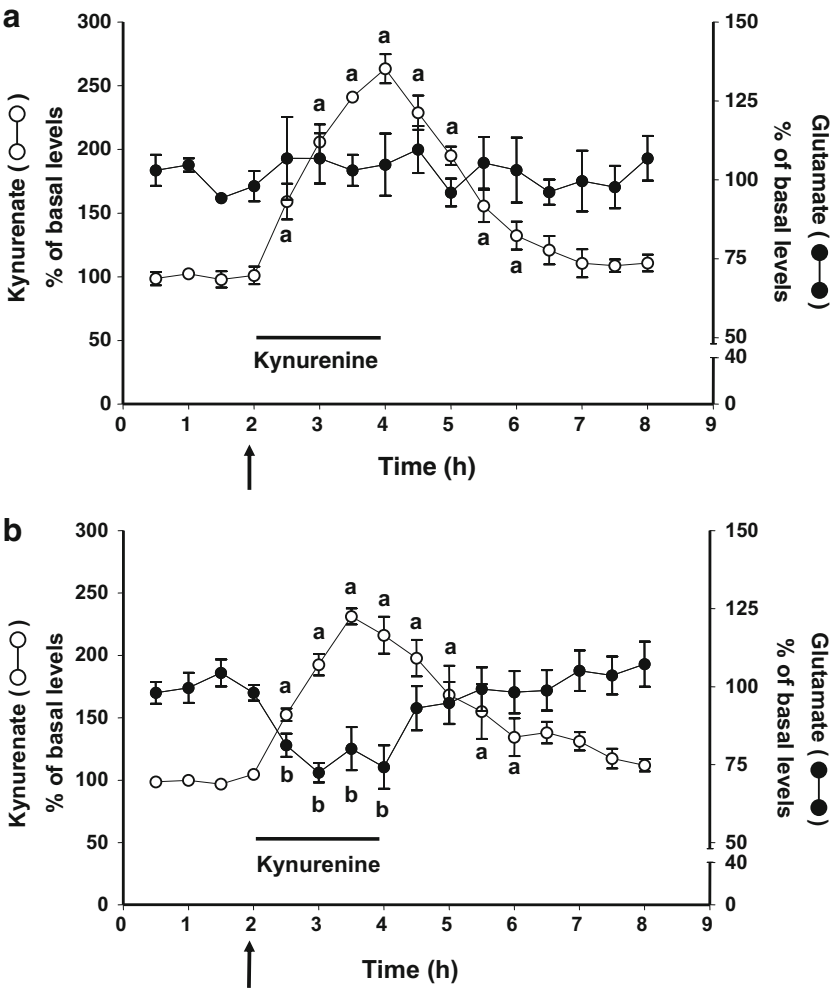

Figure 3 Galantamine (3 mg/kg; **a**) but not donepezil (2 mg/kg; **b**) blocks the reduction in extracellular glutamate caused by the local perfusion of kynurenine (2.5 μM; *bar*) in the PFC. Neither of the two drugs, injected i.p. (*arrows*), affected the de novo formation of KYNA from kynurenine. KYNA and glutamate were measured in the same microdialysates. Data are the mean ± standard error of the mean of four (**a**) and six (**b**) animals, respectively. *a*, *b* $p<0.05$ compared to the respective baseline values (one-way ANOVA)

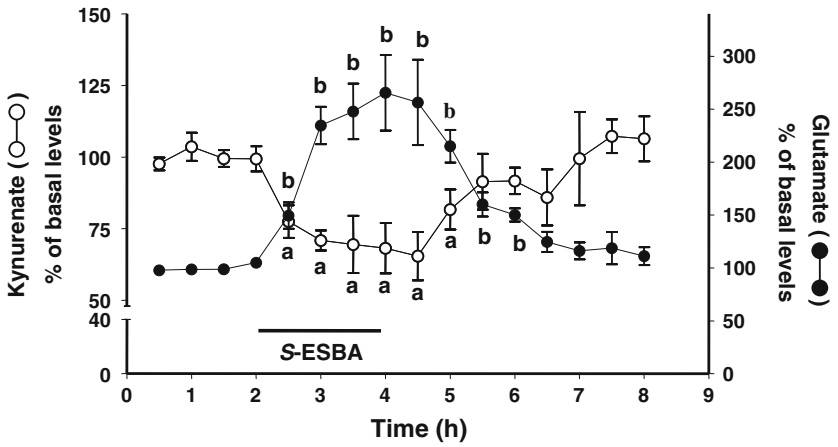

Figure 4 Effect of a local perfusion of *S*-ESBA (3 mM; *bar*) on extracellular levels of KYNA and glutamate in the PFC. The two analytes were measured in the same microdialysates. Data are the mean ± standard error of the mean of four animals. *a*, *b* $p<0.05$ compared to the respective baseline values (one-way ANOVA)

a site that is very similar or identical to the APL site of the α7nAChR that is inhibited by KYNA (Samochocki et al. 2003; Lopes et al. 2007), totally prevented the effect of KYNA. In contrast, no such neutralizing effect was observed after the peripheral application of a similar dose of donepezil, which is a substantially more potent acetylcholinesterase inhibitor than galantamine (Geerts et al. 2005). Moreover, donepezil does not function as an APL site agonist either in vitro (Samochocki et al. 2003) or in vivo (Schilström et al. 2007). These results, together with pharmacokinetic considerations (Geerts et al. 2005), suggest that the effect of galantamine shown here was in all likelihood due to selective α7nAChR stimulation rather than a nonspecific activation of cholinergic receptors by elevated acetylcholine levels.

As expected, intracortical perfusion of the KAT II inhibitor *S*-ESBA for 2 h transiently decreased the extracellular levels of KYNA, confirming that astrocytes, which contain KAT II almost exclusively (Guidetti et al. 2007), continuously produce KYNA from its endogenous bioprecursor kynurenine in vivo and steadily release newly formed KYNA into the extracellular milieu. In the same microdialysates, glutamate levels were elevated compared to baseline values, indicating a causal relationship between a reduction in KYNA synthesis and increased glutamate release. These results were the inverse of the effects of KYNA or kynurenine (see above and also Konradsson-Geuken et al. 2009), suggesting that astrocyte-derived KYNA, probably primarily by controlling the activation of presynaptic α7nAChRs, tonically modulates the release of glutamate in the PFC. Notably, as in the case of KYNA elevations, the effects of KYNA synthesis inhibition are not limited to the glutamatergic system since intracortical perfusion of *S*-ESBA also causes significant increases in extracellular dopamine and acetylcholine concentrations (Wu et al. 2006; Zmarowski et al. 2009). Moreover, similar bidirectional consequences of fluctuations in KYNA production are seen in subcortical brain areas such the striatum (Amori et al. 2009) and the hippocampus (Wu et al. 2007) and may therefore represent a more general, novel mechanism by which astrocytes influence neurotransmission in the mammalian brain.

The functional consequences of KYNA's neurochemical effects in the PFC are especially interesting in light of the fact that prefrontal KYNA levels are abnormally high in SZ (Schwarcz et al. 2001) and that debilitating polymorphisms in the regulatory region of the α7nAChR gene are associated with the disease (Stephens et al. 2009). Thus, enhanced inhibition of already dysfunctional α7nAChRs by KYNA and subsequent impairment of glutamatergic (and/or cholinergic and dopaminergic) neurotransmission within the PFC may be causally related to several of the cognitive deficits seen in individuals with SZ. This concept is supported by pharmacological studies in experimental model systems, where manipulations of α7nAChRs have been shown to predictably influence—exacerbate or ameliorate—disease-relevant, prefrontally mediated phenomena such as working memory (Chan et al. 2007; Chess et al. 2007), selective attention (Pichat et al. 2007), and cognitive flexibility (Zmarowski et al. 2008). Together, these data encouraged clinical investigators to use nicotinic agents such as galantamine or the partial α7nAChR agonist DMXB-A as adjunctive treatments in SZ, and first studies have revealed promising, selective cognitive improvements in patients (Olincy et al. 2006; Schubert et al. 2006; Buchanan et al. 2008). Based on our present results, it is tempting to speculate that these beneficial effects of α7nAChR stimulation are related to a secondary normalization of glutamatergic function, which is suspected to correct cognitive deficits in individuals with SZ (Buchanan et al. 2007). Notably, these considerations are also remarkably compatible with the increasingly propagated hypothesis that an activated immune system, resulting in impaired α7nAChR function and increased KYNA formation, plays a role in the pathophysiology of SZ (Wang et al. 2003; Müller and Schwarz 2007; Schwarcz and Hunter 2007; Holtze et al. 2008).

Establishment of a functional link between enhanced KYNA levels in the PFC and cognitive defects would support the hypothesis that attenuation of cerebral KYNA formation, for example by selective inhibition of KAT II, might improve cognitive abilities in patients afflicted with SZ (Schwarcz and Pellicciari 2002). Ongoing studies in our laboratories are therefore designed to investigate if experimental manipulations of KYNA levels in the PFC and beyond produce salient behavioral effects, which may provide insights into the pathophysiology and treatment of cognitive deficits in SZ.

Acknowledgment This work was supported by USPHS grant NS25296.

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