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Inhibition of Kynurenine Aminotransferase II Attenuates Hippocampus-dependent Memory Deficit in Adult Rats Treated Prenatally with Kynurenine

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Abstract

A combination of genetic and environmental factors contributes to schizophrenia (SZ), a catastrophic psychiatric disorder with a hypothesized neurodevelopmental origin. Increases in the brain levels of the tryptophan metabolite kynurenic acid (KYNA), an endogenous antagonist of $\alpha 7$ nicotinic acetylcholine and NMDA receptors, have been implicated specifically in the cognitive deficits seen in persons with SZ. Here we evaluated this role of KYNA by adding the KYNA precursor kynurenine (100 mg/day) to chow fed to pregnant rat dams from embryonic day (ED) 15 to ED 22 (control: ECon; kynurenine treated: EKyn). Upon termination of the treatment, all rats received normal rodent chow until the animals were evaluated in adulthood (postnatal days 56–85). EKyn treatment resulted in increased extracellular KYNA and reduced extracellular glutamate in the hippocampus, measured by *in vivo* microdialysis, and caused impairments in hippocampus-dependent learning in adult rats. Acute administration of BFF816, a systemically active inhibitor of kynurenine aminotransferase II (KAT II), the major KYNA-synthesizing enzyme in the brain, normalized neurochemistry and prevented contextual memory deficits in adult EKyn animals. Collectively, these results demonstrate that acute inhibition of KYNA neosynthesis can overcome cognitive impairments that arise as a consequence of elevated brain KYNA in early brain development.

Cognitive dysfunctions, including deficits in hippocampus-mediated explicit memory and learning, are a core domain of the psychopathology of several mental disorders, including schizophrenia (SZ) (Tamminga et al., 2010). These impairments appear to be related to glutamatergic and nicotinic abnormalities, and excessive inhibition of NMDA and $\alpha 7$ nicotinic acetylcholine ($\alpha 7$ nACh) receptors are believed to play critical roles in these functional deficits (Levin et al., 2006; Robbins and Murphy, 2006). Kynurenic acid (KYNA), a metabolite of the kynurenine pathway (KP) of tryptophan degradation, antagonizes both these receptors and may thus modulate cognitive processes (Pocivavsek et al., 2016). As KYNA levels are significantly elevated in post-mortem brain tissue and cerebrospinal fluid of patients with SZ (Erhardt et al., 2001; Schwarcz et al., 2001),

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inhibition of the enzyme kynurenine aminotransferase (KAT) II, which is primarily responsible for the formation of neuroactive KYNA in the brain, has emerged as an attractive novel strategy to overcome cognitive deficits in the disease (Chang et al., 2018; Jayawickrama et al., 2015; Kozak et al., 2014; Pocivavsek et al., 2011; Wu et al., 2014).

In adult rats, even modest increases in hippocampal KYNA cause a reduction in the extracellular levels of glutamate via inhibition of presynaptic $\alpha 7$ nACh receptors located on glutamatergic terminals, and may therefore contribute to the cognitive impairments that are observed in these animals (Pocivavsek et al., 2011). Notably, and in line with leading hypotheses of SZ etiology (Murray and Lewis, 1987; Weinberger, 1987), the influence of KYNA on neurochemistry and behavior may also have a developmental dimension (Notarangelo and Pocivavsek, 2017). Thus, we demonstrated that raising KYNA levels in the fetal brain during the last week of gestation leads to elevated brain KYNA levels and impairs hippocampus-dependent memory and other cognitive functions in adulthood (Notarangelo and Pocivavsek, 2017; Pershing et al., 2015; Pocivavsek et al., 2014). Conceptually similar results were obtained, and identical conclusions were reached, independently by Stone and his collaborators (Forrest et al., 2013; Forrest et al., 2015).

Based on these findings, the present study was designed to test the hypothesis that *acute* inhibition of cerebral KYNA formation in adulthood, which does not affect the production of related metabolites such as 3-hydroxykynurenine and quinolinic acid (Amori et al., 2009), may overcome the learning impairments seen in animals that had received excessive amounts of KYNA's bioprecursor kynurenine *in utero* ("EKyn" rats; Pocivavsek et al., 2014). Reduction in KYNA levels was achieved pharmacologically by administering the orally active KAT II inhibitor BFF816 (Wu et al., 2014). The behavioral effects of this treatment were tested by applying the compound either prior to memory consolidation or prior to memory retrieval in the passive avoidance paradigm (PAP), a contextual memory task that relies on the functional integrity of the hippocampus (Dobryakova et al., 2015; Khakpai et al., 2016), a region known to be involved in the psychopathology of schizophrenia (Tamminga et al., 2010). The PAP was also selected because reductions in glutamate, as well as inhibition of $\alpha 7$ nACh and NMDA receptors, worsen performance in the task (Roesler et al., 1998; Marubio and Paylor, 2004), and because our previous work had demonstrated that elevations in brain KYNA, either during prenatal development (Pocivavsek et al., 2014; Notarangelo and Pocivavsek, 2017) or induced acutely in adulthood (Pocivavsek et al., 2017), impairs performance in this paradigm.

Pregnant Wistar rats (gestational age: 2 days) were obtained from Charles River Laboratories. All experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Maryland School of Medicine and followed the 'Principles of Laboratory Animal Care' (NIH publication No. 86-23, 1996). Animals were housed in a temperature-controlled facility, which is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), at the Maryland Psychiatric Research Center. The rats were kept on a 12h/12h light dark cycle and had free access to food and water.

Beginning on embryonic day (ED) 15, animals were fed daily with 100 mg of kynurenine (L-kynurenine sulfate, “kynurenine”; purity 99.4%, Sai Advantium, Hyderabad, India), which was mixed with wet rodent chow (embryonic kynurenine: EKyn), as previously described (Pocivavsek et al., 2014). Control animals (embryonic control: ECon) received wet mash alone. Dams were fed the diet daily from ED 15 to ED 22. After giving birth, each dam received normal rodent chow pellets *ad libitum*. On postnatal day (PD) 2, each ECon and EKyn litter was cross-fostered such that half of the pups were cared for by a dam from the alternate treatment condition. Male offspring were weaned on PD 21, pair-housed, and given normal rodent chow pellets *ad libitum*. To minimize the contribution of individual prenatal litters, a maximum of 3 offspring per litter were used in the experiments. Offspring were tested from PD 56 to PD 85 by an experimenter who was blind to the treatment conditions.

In the first experiment, microdialysis was conducted in the dorsal hippocampus of awake, freely moving animals, as previously described (Wu et al., 2014). Briefly, rats underwent a survival surgery procedure to position a guide cannula (outer diameter: 0.65 mm) over the dorsal hippocampus (AP: -3.4 from bregma; L: ± 2.3 mm from the midline; V: 1.5 mm below the dura). On the next day, a microdialysis probe (CMA/10, membrane length: 2 mm; Carnegie Medicin AB, Stockholm, Sweden) was inserted through the guide cannula, and the animals were perfused with Ringer solution (pH 6.7) at a flow rate of 1 μ l/min. The first 30-min fraction was discarded, and the next four 30 min fractions were collected to obtain baseline values. BFF816 (30 mg/kg, dissolved in 10% cyclodextrin, adjusted to pH 8.0) (kindly provided by Dr. H. Yasumatsu, Mitsubishi-Tanabe Pharma Corporation, Yokohama, Japan) was then administered by oral gavage (p.o.), and an additional 12 consecutive 30-min fractions were collected. Extracellular concentrations of both KYNA (excitation: 344 nm; emission: 398 nm) and glutamate (excitation: 390; emission: 460 nm) in the microdialysates were determined fluorimetrically by high performance liquid chromatography (HPLC), according to previously published methods (Wu et al., 2014), using 15 μ l of the microdialysate per analyte. Data were not corrected for recovery from the dialysis probe.

Basal extracellular KYNA levels were modestly but significantly elevated in adult EKyn rats (ECon: 2.3 ± 0.1 nM; EKyn: 2.8 ± 0.1 nM; $t(13) = 3.72$; Student's t test, $P < 0.01$) (Figure 1A). In contrast, extracellular glutamate was decreased (ECon: 1.9 ± 0.03 μ M; EKyn 1.6 ± 0.02 μ M; $t(7) = 7.47$; Student's t test, $P < 0.001$) (Figure 1B). BFF816 rapidly lowered extracellular KYNA levels in both ECon (to 29% below baseline) and EKyn (to 25% below baseline) rats (two-way repeated measures ANOVA, main effect of BFF816, $F_{15,195} = 29.62$, $P < 0.0001$) (Figure 2A). Notably, the treatment reduced KYNA in EKyn animals to 2.1 ± 0.1 nM, i.e. to levels that were not different from the baseline measured in ECon animals ($P = 0.1$). These results demonstrate that the elevation of KYNA seen in adult EKyn offspring can be overcome acutely with a single administration of a selective KAT II inhibitor. The reduction in KYNA lasted for only 4–5 hours after the administration of BFF816, and levels then reverted to their respective baseline in both ECon and EKyn animals. Measured in the same microdialysates as KYNA, glutamate levels were found to be *elevated* in both ECon (to 189% above baseline) and EKyn (to 169% above baseline) rats following the administration of BFF816 (two-way repeated measures ANOVA, main effect of BFF816: $F_{15,105} = 43.83$, $P < 0.0001$; BFF816 x prenatal condition interaction: $F_{15,105} =$

2.0, $P < 0.05$), and this effect, too, subsided after 4 hours (Figure 2B). Of note, the BFF816-induced increase in extracellular glutamate, though slightly larger in ECon than in EKyn animals, was not statistically different between the two groups (main effect of prenatal condition: $F_{1,7} = 1.96$, $P = 0.20$).

Behavior experiments were conducted in separate cohorts of adult offspring. Briefly, the PAP apparatus had two compartments of equal size (each 22 cm high, 18 cm wide and 16 cm deep), which were separated by a guillotine door. The right compartment was illuminated, and the left compartment remained dark. During the training trial, each animal was placed in the illuminated compartment, the door was opened, and the “approach latency” to enter the preferred dark compartment was recorded. Immediately upon entering, the door was closed, and an inescapable food shock (0.56 mA for 1 sec) was delivered through the grid floor (see cartoon; Figure 3A). Retention of the newly formed, one-trial, aversive foot shock memory was tested 24 hours later, when the rat was again placed in the illuminated compartment and the “avoidance latency”, i.e. the time to enter the dark compartment, was recorded.

This PAP was used to evaluate whether KYNA synthesis inhibition affects the consolidation of newly formed memory and/or memory retrieval. To this end, animals received BFF816 (30 mg/kg) or vehicle (10% cyclodextrin), applied by oral gavage (p.o.) at a concentration of 10 mg BFF816/ml, either 5 min prior to the training trial (Experiment A) or 90 min prior to the testing trial (Experiment B). Based on the biochemical results (Figure 2), this experimental design assured that extracellular KYNA was reduced both during consolidation of newly formed memory in Experiment A and during the retention of memory in Experiment B. There were no differences in approach latency between the various experimental groups (Figure 3B), demonstrating identical baseline performance during the training trial and intact acquisition. Importantly, task performance and the ability to significantly learn were not different in ECon offspring treated with either vehicle or BFF816 in both Experiment A and Experiment B. However, in line with previous studies (Notarangelo and Pocivavsek, 2017; Pocivavsek et al., 2014), vehicle-treated EKyn offspring showed significantly lower avoidance latency than ECon offspring during the retention trial (Student's *t* test, ECon vehicle vs. EKyn vehicle, $P < 0.05$) (Figure 3C). In contrast, EKyn offspring which had received BFF816 immediately prior to training demonstrated no such learning impairment during the retrieval test on Day 2 (two-way ANOVA, BFF816 x prenatal condition interaction: $F_{1,60} = 5.25$, $P < 0.05$), indicating that an acute reduction in KYNA during the memory acquisition phase was sufficient to overcome the cognitive deficit in these animals. Importantly, when KYNA levels were reduced only during the test trial, i.e. on Day 2, EKyn offspring remained significantly impaired in their PAP performance (two-way ANOVA, main effect of prenatal condition: $F_{1,41} = 12.61$, $P < 0.01$). These findings suggest a selective role for KYNA in the *acquisition and consolidation of contextual memory*.

Using the offspring of ECon and EKyn rats, the present study not only revealed that prenatal kynurenine treatment leads to a significant elevation in extracellular KYNA levels in the adult hippocampus, but also showed that extracellular glutamate levels are simultaneously reduced in the same samples. These results are in line with previous demonstrations that

acute fluctuations in KYNA levels reciprocally and bi-directionally influence extracellular glutamate levels in the adult rat brain (Konradsson-Geuken et al., 2010; Pocivavsek et al., 2011). This regulation of glutamate by KYNA, which may be mainly related to KYNA's inhibition of presynaptic $\alpha 7$ nACh receptors on glutamatergic nerve terminals, has been repeatedly proposed to be causally linked to the various behavioral changes that are observed in animals when KYNA levels are manipulated experimentally (Alexander et al., 2012; Chess et al., 2007; Pocivavsek et al., 2011; Pocivavsek et al., 2017; Potter et al., 2010).

As several of the impairments observed in adult EKyn rats resemble neurochemical and behavioral changes seen in persons with SZ (Tamminga et al., 2012; Wijtenburg et al., 2017), these animals have considerable construct validity in SZ research (see Pocivavsek et al., 2016, for review). The present demonstration that acute inhibition of KYNA synthesis prior to training is sufficient to overcome a translationally relevant learning deficit in these animals substantiates a functionally significant role of KYNA in the disease. Interestingly, the two best-established targets of endogenous KYNA in the mammalian brain, NMDA and $\alpha 7$ nACh receptors (Albuquerque and Schwarcz, 2013; Moroni et al., 2012; Stone et al., 2013), are both linked to the pathophysiology of SZ (Balu, 2016; Wallace and Bertrand, 2015) and are critically involved in hippocampal learning and memory (Levin et al., 2006; Robbins and Murphy, 2006). The BFF816-induced decrease in hippocampal KYNA levels shown here may therefore have improved memory consolidation by disinhibition of these receptors. The fact that a reduction in KYNA levels during the retention phase of the PAP failed to normalize the memory impairment in EKyn offspring provides further support for this hypothesis since intact cholinergic and glutamatergic activity is of critical importance specifically during the acquisition and consolidation of hippocampus-dependent memory (Dobryakova et al., 2015; Khakpai et al., 2016). Pharmacological agents targeting KAT II to reduce KYNA levels in the brain may therefore be a useful approach to treat cognitive dysfunctions in SZ (Chang et al., 2018; Jayawickrama et al., 2015; Kozak et al., 2014; Pocivavsek et al., 2011; Wu et al., 2014).

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Figure 1:

Effects of prenatal kynurenine treatment on extracellular KYNA and glutamate levels in the dorsal hippocampus of adult animals. Pregnant rats were exposed to kynurenine (100 mg/day) from ED 15–22 (EKyn). ECon: control rats fed normal chow prenatally. In adulthood (PD 56–85), 30-min microdialysate samples were collected consecutively for 2 hours. Averaged individual data as well as the mean ($\pm$ SEM) are shown for extracellular KYNA ($N = 7-8$ per group) (**A**) and glutamate ($N = 4-5$ per group) (**B**). Student's *t* test. ** $P < 0.01$, *** $P < 0.001$.

Figure 2:

Kynurenine aminotransferase II inhibition by BFF816 (30 mg/kg, p.o.), administered 2 hours after baseline collection (arrow), results in an acute reduction in extracellular KYN and an acute increase in extracellular glutamate levels in the rat hippocampus. Pregnant rats were exposed to kynurenine (100 mg/day) from ED 15–22 (EKyn). ECon: control rats fed normal chow prenatally. In adulthood (PD 56–85), 30-min microdialysate samples were collected from the dorsal hippocampus. Data (mean $\pm$ SEM) are shown for extracellular KYN (N = 7–8 per group) (A) and glutamate (N = 4–5 per group) (B). Bonferroni corrected paired t test vs. basal levels. ECon: * $P < 0.05$; EKyn: # $P < 0.05$.

Figure 3.

Administration of the kynurenine aminotransferase II inhibitor BFF816 (30 mg/kg, p.o.) prior to contextual memory task training attenuates memory impairment in adult EKyn rats. Rats were exposed to kynurenine (100 mg/day) from ED 15–22. In adulthood (PD 56–85), animals were tested in the passive avoidance paradigm. **(A)** Schematic: in Experiment A, animals received vehicle or BFF816 5 min prior to the training trial; in Experiment B, animals received vehicle or BFF816 90 min prior to the test trial; **(B)** Approach latency during the training trial; **(C)** Avoidance latency during the testing trial. Data are the mean $\pm$

SEM. N = 10–17 per group. Holm-Sidak's multiple comparison t test. * $P < 0.05$ vs. ECon. # $P < 0.05$ vs EKyn vehicle.

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