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Targeting Kynurenine Aminotransferase II in Psychiatric Diseases: Promising Effects of an Orally Active Enzyme Inhibitor

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Increased brain levels of the tryptophan metabolite kynurenic acid (KYNA) have been linked to cognitive dysfunctions in schizophrenia and other psychiatric diseases. In the rat, local inhibition of kynurenine aminotransferase II (KAT II), the enzyme responsible for the neosynthesis of readily mobilizable KYNA in the brain, leads to a prompt reduction in extracellular KYNA levels, and secondarily induces an increase in extracellular glutamate, dopamine, and acetylcholine levels in several brain areas. Using microdialysis in unanesthetized, adult rats, we now show that the novel, systemically active KAT II inhibitor BFF-816, applied orally at 30 mg/kg in all experiments, mimics the effects of local enzyme inhibition. No tolerance was seen when animals were treated daily for 5 consecutive days. Behaviorally, daily injections of BFF-816 significantly decreased escape latency in the Morris water maze, indicating improved performance in spatial and contextual memory. Thus, systemically applied BFF-816 constitutes an excellent tool for studying the neurobiology of KYNA and, in particular, for investigating the mechanisms linking KAT II inhibition to changes in glutamatergic, dopaminergic, and cholinergic function in brain physiology and pathology.

Key words: kynurenic acid/microdialysis/Morris water maze/schizophrenia/spatial memory

Introduction

Over the past 30+ years, our laboratory at the Maryland Psychiatric Research Center (MPRC) has focused mainly on elaborating the neurobiological features of the kynurenine pathway (KP) of tryptophan degradation. This work initially revolved around our discovery that 2 KP metabolites ("kynurenines") capable of targeting glutamate receptors, the agonist quinolinic acid and the antagonist kynurenic acid (KYNA), have excitotoxic and neuroprotective properties, respectively.[1,2] These studies, in turn, had been prompted by the concept that endogenous excitotoxins may play a causative role in Huntington's disease and other neurodegenerative disorders, and evidence showing prevention of neuron loss by pharmacological blockade of glutamate receptors.[3] As a testament to the vision of Will Carpenter, who as MPRC Director promoted promising, novel—rather than established—research projects from the Center's inception, it soon became apparent, however, that kynurenines may also be involved in the pathophysiology of schizophrenia (SZ) and other psychiatric diseases. Key developments and discoveries at the time were the classification of ionotropic glutamate receptors into kainate, quisqualate, and *N*-methyl-D-aspartate (NMDA) subtypes,[4–6] a (later refuted) report of reduced glutamate levels in the cerebrospinal fluid of individuals with SZ,[7] and the demonstration that NMDA receptors play a critical role in learning and memory.[8,9] Most importantly, Lodge and collaborators showed that the psychotomimetic drug phencyclidine, which induces hallucinations and negative SZ symptomatology in humans,[10,11] is a potent NMDA receptor antagonist.[12] Taken together, these new insights led to the realization that reduced glutamatergic neurotransmission, and specifically NMDA receptor hypoactivity,[13,14] may be causally related to all 3 core domains of SZ psychopathology, namely positive, negative, and cognitive symptoms.[15,16]

KYNA, which is present in the human brain in high nanomolar concentrations,[17] was soon shown to

preferentially inhibit the NMDA receptor, and especially the receptor's glycine coagonist site.[18,19] We therefore conjectured that elevated levels of endogenous KYNA may contribute to glutamatergic hypofunction in SZ.[20] Subsequent studies revealed that, unrelated to antipsychotic medication, KYNA levels were indeed increased in the prefrontal cortex of individuals who died with the disease,[21] and that KYNA was also abnormally elevated in the patients' cerebrospinal fluid.[22] Around the same time, it was found that low concentrations of KYNA can also antagonize the α7 nicotinic acetylcholine receptor (α7nAChR),[23] which is critically involved in cognitive processes and the formation of excitatory neural networks, and may participate in the development and clinical manifestations of SZ.[24,25] This, together with more recent data showing that acute systemic administration of kynurenine, a pivotal KP metabolite and immediate bioprecursor of KYNA, causes cognitive dysfunction in rodents,[26–30] suggested that a reduction in KYNA function in the brain may benefit persons with SZ.[31,32]

In the brain as elsewhere, several distinct kynurenine aminotransferases (KATs) can catalyze the irreversible transamination of kynurenine to KYNA.[33–35] Of these, KAT II, which is distinguished over other KATs by its substrate specificity, preferentially controls a pool of KYNA that can be rapidly mobilized in the brain.[34,36] KAT II, which is preferentially localized in astrocytes,[37] is therefore an excellent target for pharmacological intervention. In recent years, selective KAT II inhibitors have been synthesized and used for hypothesis testing in rats.[31,36] These compounds, which needed to be applied intracerebrally because of poor brain penetration, not only caused a prompt reduction in extracellular KYNA but also improved cognitive functions—probably related to the rapid increase in the extracellular levels of glutamate,[38] acetylcholine,[39] and dopamine[40] that was found to be associated with KYNA synthesis inhibition.

Systemically active KAT II inhibitors are needed to advance research in KYNA neurobiology and to evaluate the possible therapeutic utility of these agents. As communicated in abstract form,[41] we recently identified such a compound, BFF-816. We describe here some of the in vivo properties of BFF-816 in rats, using neurochemical and behavioral outcome measures.

Methods

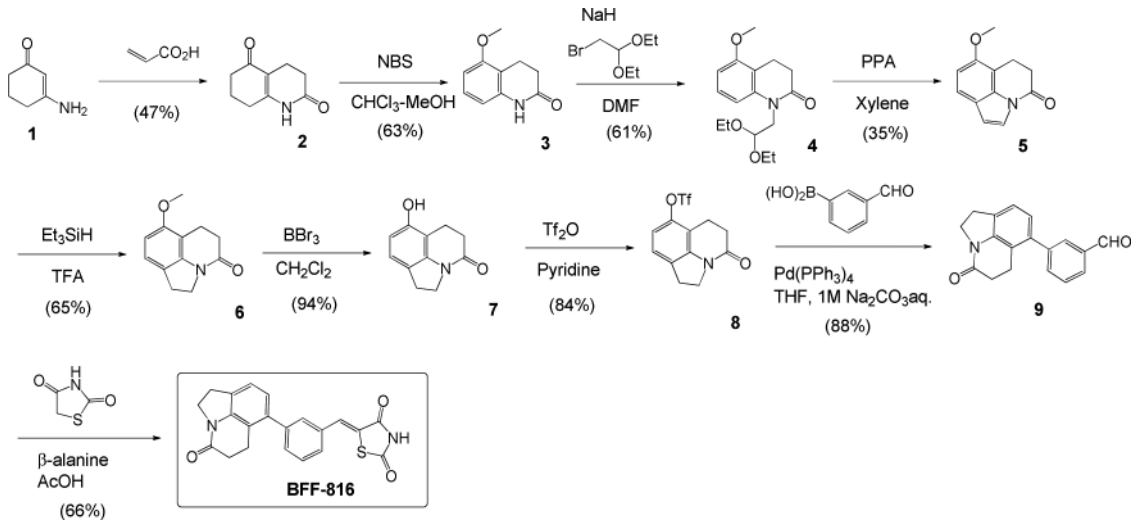
Animals

Adult, male Sprague-Dawley rats (250–300 g) were used in all experiments.

Chemicals

(5Z)-5-[(3-{11-oxo-1-azatricyclo[6.3.1.0{4,12}]dodeca-4(12),5,7-trien-7-yl}phenyl)methylidene]-1,3-thiazolidine-2,4-dione (BFF-816) was synthesized from 3-aminocyclohex-2-en-1-one in 9 steps as follows (yields in parentheses):

The purity of the final product, determined by high-performance liquid chromatography, was 98.6%. 400 MHz ^{1}H-NMR (DMSO-d6): δ 2.50 (m, 2H), 2.91 (t, J = 7.6 Hz, 2H), 3.18 (t, J = 8.5 Hz, 2H), 3.99 (t, J = 8.5 Hz, 2H), 6.94 (d, J = 7.6 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.48 (m, 1H), 7.57–7.64 (m, 3H), 7.86 (s, 1H), 12.65 (br s, 1H). MS (ESI): m/z 377 (M+1). NBS: *N*-bromosuccinimide; DMF: dimethylformamide; PPA: polyphosphoric acid; Tf_2O: trifluoromethanesulfonic anhydride.



KYNA and other biochemicals were purchased from Sigma (St Louis, MO). All other chemicals were of the highest commercially available purity.

Microdialysis

Rats were anesthetized and placed in a stereotaxic frame, and guide cannulae were implanted, respectively, on top of the striatum, dorsal hippocampus, or medial prefrontal cortex, as described.[38,40,42] On the next day, a microdialysis probe (CMA, Stockholm, Sweden) was lowered into the targeted brain region (probe length: 2 mm for striatum and hippocampus, 3 mm for medial prefrontal cortex) of the awake animals. Rats were then perfused at 1 µl/min with Ringer solution (pH 6.7) containing (in mM) NaCl, 144; KCl, 4.8; $MgSO_4$, 1.2; and $CaCl_2$, 1.7. After the establishment of a stable baseline, BFF-816, dissolved in 10% cyclodextrin (adjusted to pH 8.0 with 0.1 N NaOH), was administered by gavage. Microdialysate samples were collected every 30 minutes. Analytes were determined fluorimetrically (KYNA, glutamate) or electrochemically (dopamine), as described.[38,40] KYNA and dopamine (striatum), and KYNA and glutamate (dorsal hippocampus, medial prefrontal cortex), were always determined in the same samples. Data were not corrected for recovery from the microdialysis probe.

Morris Water Maze

In light of the conspicuous anatomical and functional changes seen in the hippocampus of individuals with SZ,[14] the Morris water maze task, a classical test designed to investigate hippocampus-mediated cognition, was used to study spatial navigation and reference memory. As described in detail previously,[42,43] each animal was tested on 4 trials on each of 4 consecutive days. BFF-816 or vehicle was administered to animals 90 minutes prior to the first trial of behavioral testing on each day.

Statistics

Two-way ANOVA with treatment group as a between-subject factor and time as a within-subject factor with appropriate post hoc analysis was used in all experiments. A P value of <.05 was considered significant.

Results

BFF-816 was identified by high-throughput screening using human recombinant KAT II, and subsequent lead optimization. Tested in rat liver homogenate at physiological kynurenine concentrations,[44] the IC_{50} of BFF-816 was determined to be 13.4 ± 0.2 µM (n = 3).

Preliminary in vivo microdialysis experiments were conducted in the rat striatum, using 3 doses of BFF-816 (orally [p.o.]) and monitoring effects on extracellular KYNA levels over time. In this pilot study, application of 10 mg/kg BFF-816 caused a maximal decrease of 12%, whereas 30 and 50 mg/kg of the compound resulted in almost identical, approximately 30% reductions in extracellular KYNA levels (nadir after 1.5 h at all doses; data not shown). Subsequent analysis, performed in the striatum using 30 mg/kg BFF-816 (p.o.) (n = 4), confirmed the reversible reduction in extracellular KYNA and revealed a concurrent reversible increase in extracellular dopamine levels compared with baseline values (KYNA: 2.8 ± 0.1 nM; dopamine: 2.7 ± 0.1 nM). Upon repeated administration of the same dose of the KAT II inhibitor, no difference in daily baseline levels was seen across the 5 days of experimentation with regard to both KYNA (P = .66) and dopamine (P = .91) (one-way ANOVA). Moreover, the effects of BFF-816 on the extracellular levels of the 2 analytes remained unchanged by daily application, causing maximal KYNA reductions of 25%–32% and maximal dopamine increases of 50%–70% on each day (figure 1).

In the dorsal hippocampus (n = 4), BFF-816 (30 mg/kg, p.o.) reversibly reduced extracellular KYNA and increased extracellular glutamate levels compared with respective baseline levels (KYNA 2.5 ± 0.1 nM, glutamate: 1.9 ± 0.2 µM, respectively). Maximal effects (~25% decrease in KYNA and ~60% elevation in glutamate) were seen between 90 and 150 minutes after BFF-816, and levels returned to control values after approximately 4 hours (figure 2A). In separate rats, BFF-816 administration caused qualitatively and quantitatively similar changes from baseline levels (KYNA: 1.9 ± 0.2 nM; glutamate: 3.2 ± 0.2 µM) in the prefrontal cortex (n = 4) (figure 2B). Thus, oral application of BFF-816 duplicated the effect of the compound on extracellular KYNA, and mimicked the elevation in extracellular dopamine, seen in the striatum (cf figure 1).

In a first attempt to evaluate possible procognitive effects of BFF-816 in healthy, adult rats, the compound was evaluated in the Morris water maze. In this model of spatial learning,[43] daily administration of the KAT II inhibitor 90 minutes prior to behavioral testing significantly improved behavioral performance (two-way repeated measures ANOVA, $F_{1, 17}$ = 8.86, P < .01) (controls: n = 9; BFF-816: n = 10) (figure 3). Retention of the newly learned task and spatial navigation strategy was assessed in 1 single probe trial 24 hours after the last training session. Animals treated acutely with BFF-816 crossed into the area formerly occupied by the platform more frequently than control animals (control: 2.6 ± 0.6 crosses; BFF-816: 5.0 ± 0.9 crosses; P < .05). Additionally, swim speeds did not differ significantly between the comparable groups during the probe trial (control: 36.4 ± 3.3 cm/s; BFF-816: 37.7 ± 2.9 cm/s; P = .71), and there were no differences in the escape latencies between the two experimental groups in a separate visible platform trial (control: 6.5 ± 0.7 s; BFF-816: 7.4 ± 1.3 s; P = .53), indicating no gross visual deficits.

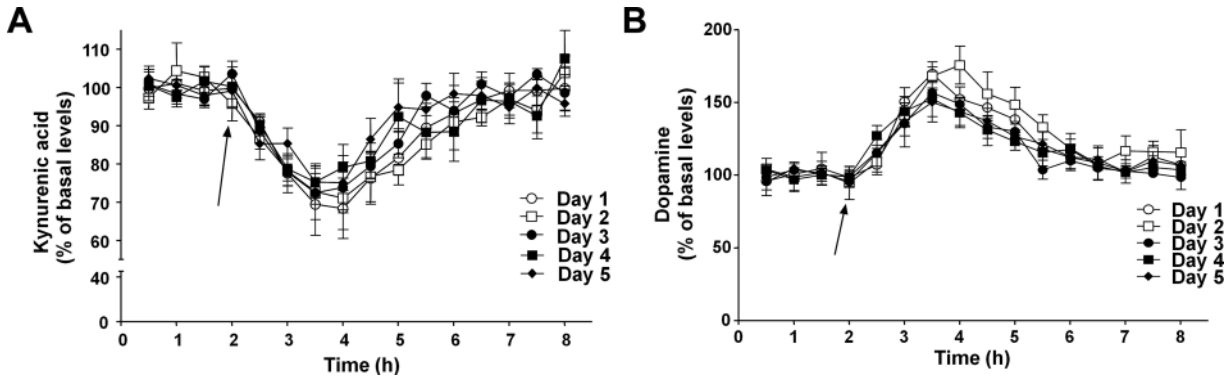


Fig. 1. Kynurenine aminotransferase II inhibition by BFF-816 (30 mg/kg, orally), administered 2 h after baseline collections (arrow), causes an acute reduction in extracellular kynurenic acid (A) and an acute increase in extracellular dopamine (B) levels in the rat striatum. No evidence of tolerance is seen when BFF-816 is administered daily for 5 d. See text for basal levels of the analytes. Data are the mean ± standard error of the mean ($n = 4$), $P < .05$ compared with baselines on each day; two-way repeated measures ANOVA.

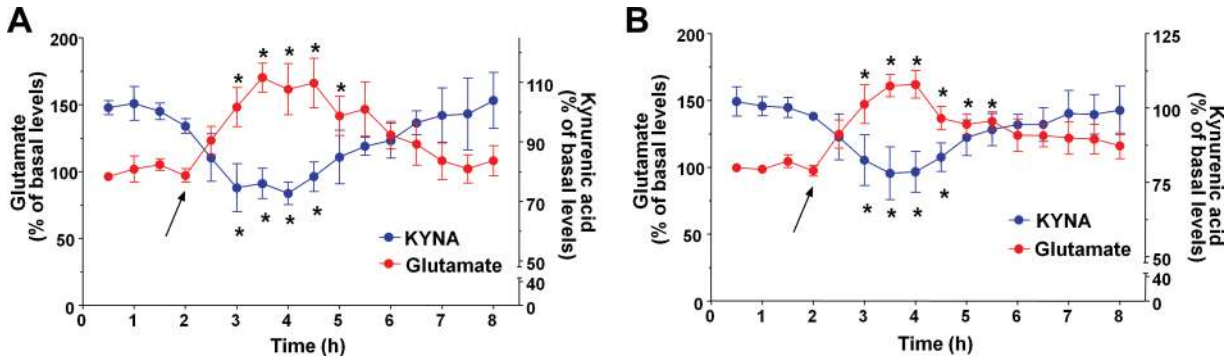


Fig. 2. Kynurenine aminotransferase II inhibition reduces extracellular kynurenic acid (KYNA) and increases extracellular glutamate levels in the rat brain in vivo. BFF-816 (30 mg/kg, orally) was administered 2 h after baseline collections (arrow). (A) Dorsal hippocampus; (B) medial prefrontal cortex. See text for basal levels of the analytes. Data are the mean ± standard error of the mean ($n = 4$ for each group). *$P < .05$ (two-way repeated measures ANOVA compared with baseline values followed by Bonferroni corrected paired t test; statistical significance set at $P < .05$).

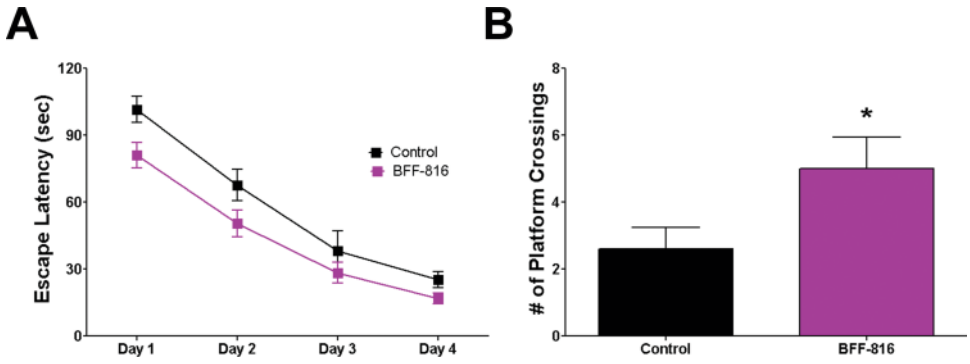


Fig. 3. BFF-816 enhances performance in the Morris water maze in healthy, adult rats. (A) Compared with controls, rats receiving BFF-816 (30 mg/kg, orally) daily 90 min prior to behavioral testing show an overall significant effect on escape latency across days in the maze ($P < .01$, two-way repeated measures ANOVA). (B) During the probe trial, animals receiving BFF-816 cross the area previously occupied by the platform significantly more frequently than controls (video-tracking analysis). *$P < .05$ vs control (t test). See text for additional details. Data are the mean ± standard error of the mean ($n = 9$ for control; $n = 10$ for BFF-816).

Discussion

In adult rats, oral administration of the novel KAT II inhibitor BFF-816 caused a transient reduction in the extracellular levels of KYNA in striatum, hippocampus, and prefrontal cortex. These effects were associated with elevations in extracellular dopamine levels in the striatum and with increases in the extracellular levels of glutamate in the hippocampus and the medial prefrontal cortex. In the striatum, daily administration of BFF-816 for up to

5 days did not appear to blunt or exacerbate its in vivo effects. By extrapolation to other brain areas, this allowed us to use this KAT II inhibitor in the Morris water maze, a behavioral assay that requires repeated application of a test compound for the assessment of effects on spatial and contextual memory.[42,43] Although the pharmacokinetics and pharmacodynamics of BFF-816 need to be elaborated in detail, the compound indeed enhanced performance in this model, supporting a role of endogenous KYNA in limiting performance in this cognitive task even under healthy conditions. The neurochemical effects of BFF-816 shown here are in remarkably good agreement with studies where selective, but not brain penetrant, KAT II inhibitors were infused directly into the rat brain. Thus, like systemically applied BFF-816, local KAT II inhibition causes an approximately 30% reduction in extracellular KYNA levels regardless of brain region.[38–41] The present study therefore confirms that KAT II accounts for the synthesis of a relatively small but rapidly mobilizable KYNA pool in the rat brain,[34,36] and that this proportion of endogenous KYNA is sufficient to regulate extracellular dopamine and glutamate levels.[38,40,41] Peripheral administration of a selective KAT II inhibitor therefore provides a suitable new approach for studying the neurobiology of KYNA and, in particular, for investigating mechanisms linking (a reduction in) brain KYNA to glutamatergic and dopaminergic, as well as cholinergic,[39] neurotransmission.

In the brain's extracellular milieu, newly released KYNA can act as an antagonist of α7nAChRs and, possibly, can also directly target NMDA receptors (NMDARs) and other receptors.[45] Reduced activity at α7nAChRs and NMDARs adversely affects the development of complex excitatory neural networks and, ultimately, the expression of cognition. As such, these changes may be causally linked to SZ pathology.[13,14,24,25,46] As impaired brain KP metabolism results in enhanced central KYNA levels in SZ,[21,22,47] and as increased brain levels of KYNA produce "SZ-like" cognitive impairments in experimental animals,[26–30,48,49] scientists in academia[32,45] and in the pharmaceutical industry[50,51] set out to explore the possible procognitive properties of pharmacological agents that reduce extracellular KYNA levels in the brain. This approach was validated by the finding that mice with a genomic deletion of KAT II show marked cognitive enhancement[52] and by the demonstration that the first generation KAT II inhibitor (*S*)-4-(ethylsulfonyl) benzoylalanine[31] improves performance in the Morris water maze after intracerebroventricular administration.[42] The present corroboration using the orally active compound BFF-816 bodes well for future developments using KAT II as a drug target. Notably, this pharmacological approach, which is currently being evaluated in detail using a variety of treatment regimens and outcome measures, may not only be useful under normal physiological conditions but could be especially effective for improving cognition in individuals with SZ and in other psychiatric diseases that are associated with cognitive deficits.[53]

In conclusion, it is worth remembering that the scientific developments described and alluded to here, and the future they may hold for clinical applications, are merely one example of the accomplishments of the extraordinary, long-lasting tenure of Will Carpenter as MPRC Director. Jointly, these achievements in psychiatric research, which are amply described in other contributions to this Festschrift, can be directly attributed to the translational composition of the MPRC faculty, and the exceptional collegiality and highly stimulating atmosphere that was generated under Will Carpenter's superb leadership.

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