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Inhibition of kynurenine aminotransferase II reduces activity of midbrain dopamine neurons

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ABSTRACT

Kynurenic acid (KYNA), a neuroactive metabolite of tryptophan, is elevated in the brain of patients with psychotic disorders. Therefore, lowering brain KYNA levels might be a novel approach in the treatment of psychotic disorders. The present *in vivo* electrophysiological study aimed to investigate the effect of an inhibitor of kynurenine aminotransferase (KAT) II, the primary enzyme for KYNA synthesis, on dopamine (DA) neurons in the ventral tegmental area (VTA). Acute administration of the KAT II inhibitor PF-04859989 (5 or 10 mg/kg) was associated with a short-onset, time-dependent decrease in firing rate and burst activity of DA neurons, both parameters reaching a 50% reduction within 45 min. Furthermore, PF-04859989 reduced the number of spontaneously active DA cells as measured 4–6 after administration. Pretreatment with D-cycloserine (30 mg/kg) or CGP-52432 (10 mg/kg) prevented the inhibitory action of PF-04859989 (5 mg/kg) on firing rate and burst firing activity. In contrast, pretreatment with methyllycaconitine (MLA, 4 mg/kg) did not change the response, whereas picrotoxin (4.5 mg/kg) partially prevented the inhibitory effects of PF-04859989 (5 mg/kg, i.v.). Our results show that a specific inhibition of KAT II is associated with a marked reduction in VTA DA firing activity. This effect appears to be specifically executed by NMDA-receptors and mediated indirectly via a GABA(B)-receptor-induced disinhibition of DA neurons. Our findings are in line with the view that endogenous KYNA, by modulation of the NMDA-receptor, exerts important physiological roles in the brain.

1. Introduction

During the past decade tryptophan metabolism along the kynurenine pathway has attracted increasing interest with regard to the pathophysiology of a large variety of psychiatric and neurological diseases (Erhardt et al., 2009; Schwarcz et al., 2012). This pathway, mainly located in the astrocytes and microglia, appears strongly influenced by the immune system where the initial and rate-limiting enzymes indoleamine 2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) can be induced as a result of immune activation (Guillemin et al., 2001; see Schwarcz et al., 2012; Kozak et al., 2014). Notably, this major tryptophan degrading metabolism give rise to neuroactive compounds, such as kynurenic acid (KYNA) and quinolinic acid, the former blocking the glycine site of the N-methyl-D-aspartate (NMDA) receptor as well as the α7* nicotinic receptor, the latter stimulating the NMDA receptor (see Schwarcz et al., 2012; Stone et al., 2013).

For long KYNA has been implicated in schizophrenia and a central elevation of the compound is one of the most consistently found biochemical aberrations of the disease (Erhardt et al., 2001; Nilsson et al., 2005; Linderholm et al., 2012; Schwarcz et al., 2001; Sathysuikumar et al., 2011). In addition, cerebrospinal fluid (CSF) KYNA is also elevated in euthymic bipolar patients with a history of psychosis (Olsson et al., 2010, 2012). An involvement of KYNA in the pathophysiology of psychotic disorders is further supported by experimental studies showing that elevated levels of KYNA disrupt prepulse inhibition (PPI) in rats (Erhardt et al., 2004), which is considered as an analogue behavioral model of disrupted sensorimotor gating present in patients with schizophrenia (Geyer et al., 2001). In addition, increased brain levels of KYNA impair spatial working memory, attentional processing, contextual learning, social interaction and reward circuitry in rats (Chess and

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Bucci, 2006; Chess et al., 2007, 2009; Trecartin and Bucci, 2011; Alexander et al., 2012; DeAngeli et al., 2015). Importantly, it has recently been reported that CSF KYNA is associated with cognitive impairment seen in patients with bipolar disorder (Sellgren et al., 2015). Electrophysiological findings show that brain KYNA has an important role in the regulation of neuronal activity of midbrain dopamine (DA) neurons. Whereas elevated levels of brain KYNA are associated with increased firing rate and burst firing activity of these neurons, lowered levels diversely lead to a reduction in firing activity (Erhardt et al., 2001, 2003; Erhardt and Engberg, 2002; Schwieler and Erhardt, 2003; Nilsson et al., 2006; Schwieler et al., 2004, 2006, 2008; Linderholm et al., 2007; Olsson et al., 2009). Altogether, these data imply a reduction in brain KYNA levels as a novel therapeutic approach for psychotic and cognitive disorders. Inhibition of kynurenine aminotransferases (KATs), catalyzing the final step in the synthesis of KYNA, would provide a viable option in this regard. Four KATs have been characterized so far, i.e. KAT I and KAT II, both preferentially localized in glial cells (Guidetti et al., 1997), KAT III (Yu et al., 2006) and mitochondrial aspartate aminotransferase (Guidetti et al., 2007). Under physiological conditions KAT II appears to account for ~75% of the production of KYNA in the mammalian brain (Guidetti et al., 1997) and specific inhibition of this enzyme should significantly affect brain KYNA levels (Rossi et al., 2008). Previous studies have shown that mice with a targeted deletion of KAT II exhibit decreased brain KYNA levels that are associated with increased performance in cognitive paradigms (Potter et al., 2010). Further, a recent study show that administration of PF-04859989, a selective KAT II inhibitor, prevents amphetamine- or ketamine-induced disruption of sensory processing and improve cognitive function in rodents and nonhuman primates (Kozak et al., 2014).

In the present *in vivo* electrophysiological study, we investigate the effects of PF-04859989 on the firing activity of DA neurons in the ventral tegmental area (VTA). Furthermore, a series of electrophysiological experiments was conducted to study the mechanism by which KYNA exerts its regulatory effects on DA cell firing, including analysis of the role of γ-aminobutyric acid (GABA)(A)-, GABA(B)-, NMDA- and α7* nicotinic receptors in this regard.

2. Materials and methods

2.1. Animals

Experiments were performed on male Sprague–Dawley rats (B&K Universal AB, Sollentuna, Sweden; weighing between 200 and 420 g). The animals were housed in groups of five, and free access to food and water was provided. Environmental conditions were checked daily and maintained under constant temperature (25 °C) and 40%–60% humidity in a room with a regulated 12 h light/dark cycle (lights on at 06.00). Experiments were approved by and performed in accordance with the guidelines of the Ethical Committee of Northern Stockholm, Sweden, and all efforts were made to minimize the number of animals used and to optimize their well-being.

2.2. Single unit recording

Rats were anesthetized (chloral hydrate, 400 mg/kg, i.p. or, in a few pilot experiments, pentobarbital, 60 mg/kg, i.p.) and mounted onto the ear bars of a conventional stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA) so that the skull was set in a horizontal plane and the nose was secured using a clamp at the front of the frame. For i.v. administration, a cannula was inserted into a lateral tail vein and additional injections of chloral hydrate were given as needed to maintain a stable level of anesthesia. Drugs were also given through the lateral tail vein cannula. Throughout the experiments, the body temperature of the animals was maintained at 37 °C by means of a thermostatic heating pad. The skull surface was exposed and a 3 mm burr hole was drilled with its center located approximately 3.0 mm anterior to the lambda and 0.7 mm lateral to the midline. Following careful removal of the dura, a glass microelectrode with a tip diameter of approximately 1–2 μm (filled with 0.5 M sodium acetate saturated with Pontamine Sky Blue) was lowered by means of a hydraulic micro drive (David Kopf Instruments, Tujunga, CA, USA) into the region of VTA, according to the stereotaxic coordinates from the atlas of Paxinos and Watson (1998).

The in vitro impedance of the electrode was between 6 and 8 MΩ, measured at 135 Hz in 0.9% saline. Single unit potentials were passed through a high input-impedance amplifier and filters. The impulses were discriminated from background noise and fed into a computer, and simultaneously displayed on a digital storage oscilloscope, monitored on an audio monitor and on a strip chart recorder (Gould). All DA neurons were found 7.5–8.5 mm from the brain surface and fulfilled the neurophysiological characteristics (i.e. triphasic action potentials with a duration more than 2.0 ms, basal firing rates between 1 and 10 Hz and frequent occurrence of burst firing including progressively decreasing spike amplitude) previously described for DA neurons in the VTA (Grace and Bunney, 1984a, b). To further confirm that recordings had been made exclusively from DA neurons, the inhibitory action of a single dose of the DA agonist apomorphine (100 μg/kg, i.v.) was verified at the end of the experiments when the experiments allowed.

In order to determine the number of spontaneously active DA neurons a microelectrode was lowered 2.8 mm anterior to the lambda and 0.7 mm lateral to the midline. The electrode was subsequently moved in a predetermined grid pattern with each grid separated by 200 μm, 2.8–3.6 mm anterior to the lambda and 0.7–0.9 mm lateral to the midline. The mean number of DA cells found in each track as well as their firing characteristics was assessed between 4 and 6 h after administration of PF-04859989 or vehicle. All recorded VTA DA neurons were found 7.5–8.5 mm from the brain surface and fulfilled the neurophysiological characteristics as described above.

2.3. Data analysis

The distribution of spikes was analyzed on line utilizing a Spike II software program. In order to avoid artifacts in the sampling procedure, the program was set to ignore time intervals below 20 ms. The onset of a burst was determined as an inter-spike interval shorter than 80 ms and the termination of a burst by the next interval longer than 160 ms (Grace and Bunney, 1984a, b). Cells were considered to be bursting if at least one interspike time interval of 100 recorded spikes was below 80 ms. The intervals were analyzed with regard to the number of bursts that occurred during a sampling period of 100–500 spikes along with a calculation of the percentage of spikes fired in bursts.

2.4. Analysis of kynurenic acid

Brains were homogenized in 0.4 M perchloric acid (containing 0.1% sodium metabisulfite, 0.05% EDTA) using a disperser (Ultra-Turrax®, IKA, Stauffen, Germany). For analysis of KYNA, an isocratic reversed-phase high-performance liquid chromatography (HPLC) system was used, including a dual piston, high pressure liquid delivery pump (Bischoff, Leonberg, Germany), a ReproSil-Pur C18 column (4 × 150 mm, Dr. Maisch GmbH, Ammerbuch, Germany) and a fluorescence detector (Jasco Ltd, Hachioji City, Japan) with an excitation and emission wavelength of 344 nm and 398, respectively). A mobile phase of sodium acetate (50 mM, pH 6.20, adjusted

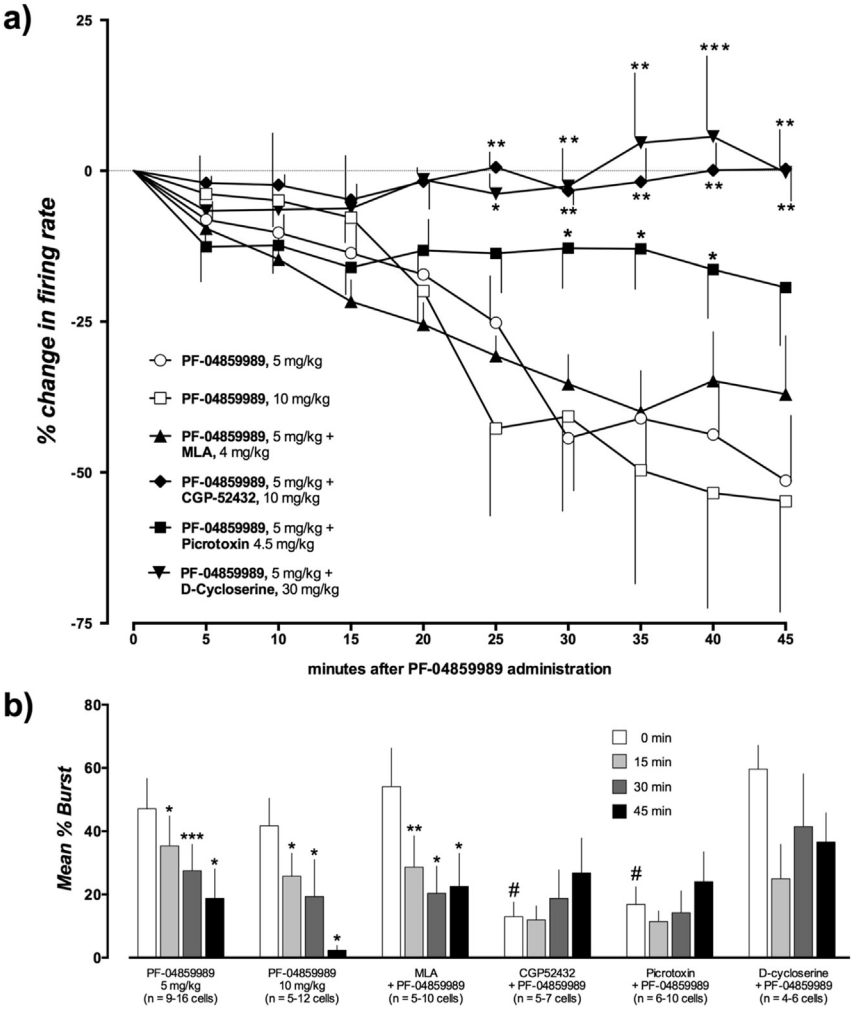

Fig. 1. Effect of the KAT II-inhibitor PF-04859989 (5 or 10 mg/kg, i.v.) on a) firing rate and b) burst activity of VTA DA neurons in controls (n = 9–15) and in rats pretreated with MLA (4 mg/kg, i.p., 15–32 min, n = 5–10), CGP-52432 (10 mg/kg, i.p., 21–33 min, n = 5–7), picrotoxin (4.5 mg/kg, i.p., 20–55 min, n = 5–8) or D-cycloserine (30 mg/kg, i.p., 21–50 min, n = 4–6). In a) comparisons were made versus corresponding value from PF-04859989 treated control rats (5 mg/kg; *P < 0.05, **P < 0.01, ***P < 0.001, Mann–Whitney U test). In b) changes in burst firing activity for each treatment group were compared to basal value and control value prior to the administration of PF-04859989 (5 mg/kg; *P < 0.05, **P < 0.01, ***P < 0.001 vs. corresponding value before administration of PF-04859989, Wilcoxon matched-pairs sign ranked test. #P < 0.05 vs. controls, Mann–Whitney U test). Each value represents mean ± SEM.

with acetic acid) and 7% acetonitrile was pumped through the reversed-phase column at a flow rate of 0.5 ml/min 30 μl samples were manually injected (Rheodyne, Cotati, CA, USA). Zinc acetate (0.5 M, not pH adjusted) was delivered post column by a syringe pump (P-500, Pharmacia, Uppsala, Sweden) at a flow rate of 10 ml/h. The signals from the fluorescence detector were transferred to a computer for analysis utilizing Datalys Azur (Grenoble, France). The retention time of KYNA was about 7 min.

2.5. Statistics

All data are expressed as mean ± SEM. Statistically significant differences were established using two-way ANOVA followed by Mann–Whitney U-Test. Differences in per cent spikes fired in bursts were established using two-way ANOVA followed by Mann–Whitney U-Test or Wilcoxon signed rank test. Significance was assumed for all values where $p < 0.05$.

2.6. Drugs and chemicals

The following drugs were used: chloral hydrate (Merck, Darmstadt, Germany), PF-04859989 (Kindly donated by Pfizer, USA), CGP-52432 (kindly donated by Dr Olpe, Novartis Pharma Inc.), methyllycaconitine (MLA, Tocris, Avonmouth, UK), isoflurane (Forene®, Abbott Scandinavia, Solna, Sweden), KYNA, Picrotoxin and D-cycloserine (Sigma, St. Louis, MO, USA). The chemicals used were: zinc acetate (Sigma, St. Louis, MO, USA), sodium acetate (Riedel-de Haen, Germany), perchloric acid (Kebo Lab, Stockholm, Sweden) and acetonitrile (Labasco, Partille, Sweden).

3. Results

3.1. VTA DA firing following acute administration of PF-04859989

The electrophysiological characteristics of VTA DA neurons were monitored for 45 min. Administration of PF-04859989, a selective KAT II-inhibitor, (5 mg/kg, i.v., n = 9–15) was associated with a time-dependent decrease in firing activity observed within 5 min and a decrease in per cent burst firing observed within 15 min (Fig. 1a and b). Both firing rate and burst firing activity was reduced to about 50 per cent 45 min after administration. The higher dose of PF-04859989 (10 mg/kg, i.v., n = 5–11) did not significantly differ in effect on firing rate or burst firing activity from the lower dose. In a few experiments, pentobarbital was used for anesthesia instead of

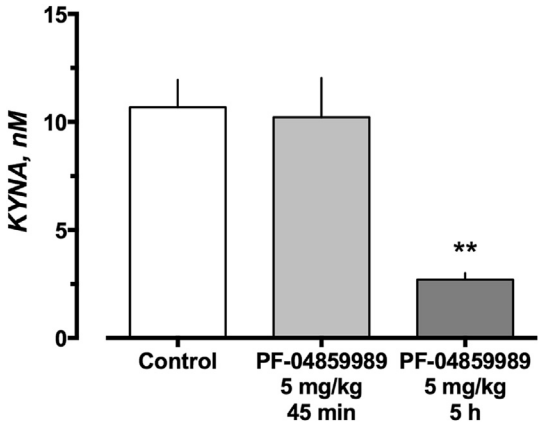

Fig. 2. Whole brain KYNA levels after administration of PF-04859989, (5 mg/kg) at 45 min, (i.v.) or 5 h (i.p). Bars represent mean ± SEM, **P < 0.01 vs. controls, Mann–Whitney U test.

chloral hydrate. DA VTA neurons of these rats (n = 3, data not shown) showed practically identical electrophysiological responses to PF-04859989 as compared to those recorded in rats anesthetized with chloral hydrate, indicating that the inhibitory action of the KAT II inhibitor is not restricted to chloral hydrate anesthesia.

Pretreatment with D-cycloserine, a partial agonist at the glycine site of the NMDA-receptor, (30 mg/kg, i.p., n = 4–5, 21–50 min) prevented the inhibitory action of PF-04859989 (5 mg/kg, i.v.) on firing rate (Fig. 1a) and burst firing activity (Fig. 1b, Mann–Whitney U-test). Similarly, pretreatment with CGP-52432, a selective inhibitor of the GABA(B) receptor, (10 mg/kg, i.p., n = 5–7, 21–33 min) inhibited the action of PF-04859989 (5 mg/kg, i.v., Fig. 1). Pretreatment with picrotoxin, a noncompetitive antagonist of the GABA(A) receptor, (4.5 mg/kg, i.p., n = 5–8, 20–55 min) was found to partially prevent the inhibitory effect on firing rate and burst firing activity of PF-04859989 (5 mg/kg, i.v.), whereas MLA, an antagonist of α7* nicotinic receptors, (4 mg/kg, i.p., n = 5–10, 15–32 min) was without effect in this regard (Fig. 1).

Pretreatment with D-cycloserine, MLA, CGP-52432 or picrotoxin did not significantly alter basal cell firing rates (6.2 ± 0.9 Hz; 6.8 ± 0.8 Hz; 5.6 ± 0.7 Hz; 5.7 ± 1.0 Hz, respectively) compared to controls (6.1 ± 0.5 Hz). Animals pretreated with CGP-52432 or picrotoxin showed significantly lower per cent burst activity compared to controls but this difference was absent already 5 min after administration of PF-04859989 (Fig. 1b).

3.2. Brain KYNA concentration following administration of PF-04859989

Intravenous administration of PF-04859989 (5 mg/kg, 45 min) in a chloral hydrate anesthetized rat (n = 6) did not change whole brain KYNA concentrations compared to saline controls (Fig. 2). In contrast, analysis 5 h after the administration of PF-04859989 (5 mg/kg, i.p) revealed a marked reduction in whole brain KYNA levels (mean value: 2.70 nM ± 0.31, n = 6), compared to saline treated control rats (10.7 nM ± 1.3, n = 6; p < 0.01).

3.3. VTA DA firing following 5 h pretreatment with PF-04859989

Rats receiving saline (i.p., 5 h, n = 5 rats, 41 cells) showed an average of 2.4 ± 0.32 spontaneously active DA neurons per electrode track, with a mean firing rate of 3.6 ± 0.26 Hz and 20.2 ± 3.2% of action potentials fired in bursts (Fig. 3). Rats receiving PF-04859989 (5 mg/kg, i.p., 5 h, n = 5 rats, 16 cells) exhibited a significantly lower number of spontaneously active DA neurons per track (0.69 ± 0.08, p < 0.01) compared to controls, although the remaining active DA neurons showed no difference in average firing rate (4.2 ± 0.69 Hz) and action potentials fired in bursts (31.0 ± 8.2%) compared to controls (Fig. 3).

4. Discussion

Inhibition of KAT II may serve as a potentially valuable pharmacological strategy in the treatment of diseases that are associated with an excess of KYNA, including psychiatric disorders like schizophrenia and bipolar disorder. PF-04859989 is a KAT II inhibitor that has been extensively studied with regard to potency and selectivity (Kozak et al., 2014). The results of the present study show that administration of this compound, in doses that produce a reduction in extracellular fluid of KYNA (Kozak et al., 2014) decreased firing rate and burst firing activity of VTA DA neurons in rats anesthetized with chloral hydrate. Our electrophysiological findings are in line with previous studies from our laboratory showing that a decrease in brain KYNA by the selective cyclooxygenase (COX)-2 inhibitor parecoxib, results in a decreased firing rate and burst firing activity of midbrain DA neurons (Schwieler et al., 2006, 2008). Correspondingly, these neurons show increased firing rate and burst firing activity in rats with pharmacologically elevated brain levels of KYNA (Erhardt et al., 2001; Erhardt and Engberg, 2002; Nilsson et al., 2006; Schwieler et al., 2006; Linderholm et al., 2007; Olsson et al., 2009).

The afferent control of VTA DA neurons emanates from a variety of different sources (see Grace et al., 2010). The increase in firing rate and burst firing activity of VTA DA neurons observed following elevated brain KYNA concentrations are possibly mediated through disinhibition of GABAergic afferent regulation of the VTA. Major regulators of the mesolimbic DA system are local interneurons (Tan et al., 2012; van Zessen et al., 2012) and the medial prefrontal cortex (Christie et al., 1985; Carr and Sesack, 2000; Sesack and Carr, 2002) that directly, or indirectly via the basolateral amygdala, project to VTA DA neurons (Patton et al., 2013). Notably, our present results

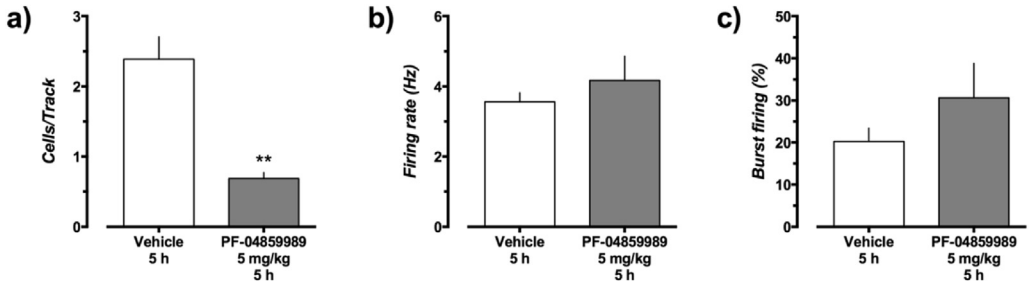

Fig. 3. Effect of pretreatment with PF-04859989 (5 mg/kg, i.p, 4–6 h) on VTA DA cell activity compared to vehicle. a) Numbers of spontaneously active cells found per electrode track, b) firing rate and c) burst activity. Bars represent mean ± SEM, **P < 0.01 vs. controls, Mann–Whitney U test.

following a longer exposure to PF-04859989 show a marked reduction in spontaneously active DA cells concomitant with an apparently unaffected firing rate and burst firing activity of the remaining cells. This phenomenon is in line with a recent study utilizing pharmacological stimulation of the infralimbic medial PFC (Patton et al., 2013). In analogy with this, the presently observed suppression in neuronal DA activity in the VTA by a KAT II inhibitor would reflect an activation of GABAergic afferents as a result of an increased glutamatergic tone induced by a lowering of endogenous level of KYNA. Indeed, pretreatment with GABA receptor antagonists attenuated or blocked the decrease in firing rate seen after reduced levels of KYNA. This inhibition was most prominent using the CGP52432, a GABA(B)-receptor antagonist, whereas the GABA(A)-receptor antagonist picrotoxin was less effective. Although it was recently shown that GABA(A) receptors preferably regulates firing of VTA DA neurons by local GABAergic interneurons (Tan et al., 2012), present results principally indicate a more prominent role of the GABA(B)-receptor in this regard. Our findings are in line with previous observations demonstrating that GABA(B) receptors in the VTA are predominantly localized on DA neurons (Xi and Stein, 1999) and directly inhibit VTA DA neurons (Engberg et al., 1993; Margolis et al., 2012).

Although previous studies have shown that local administration of KYNA in the rat striatum decreases terminal DA release via a specific blockade of the α7* nicotinic receptor (Rassoulpour et al., 2005) the interaction between KYNA and α7 nACh receptors is still a matter of controversy (for review see Albuquerque and Schwarcz, 2013). Furthermore, our previous studies have repeatedly shown that increase in firing of midbrain DA neurons is specifically mediated by blockade of the glycine-site of the NMDA receptors (Erhardt and Engberg, 2002; Schwieler et al., 2004; Linderholm et al., 2007). The present study provides further support for this hypothesis: the decrease in VTA DA neuron firing rate following reduced brain levels of KYNA was prevented by pretreatment with D-cycloserine, a glycine-site agonist of NMDA receptors. In contrast, pretreatment with MLA, an antagonist of the α7* nicotinic receptor failed to block the effects of the KAT-II inhibitor on DA firing activity. Although only one dose of MLA was administered (4 mg/kg) our results support the notion that blockade of the glycine site of the NMDA receptor, rather than antagonism of the α7* nicotinic receptor, is the mechanism by which KYNA modulates firing rate on midbrain DA neurons. Furthermore, these results are in line with previous studies where systemic administration of NMDA receptor antagonists, such as PCP, MK-801, and L-701,324, are associated with increased firing rate and percent burst firing in midbrain DA neurons (French et al., 1991, 1993; Zhang et al., 1992; Schwieler et al., 2006).

In the present study, administration of PF-04859989 was associated with a marked lowering (75%) in whole brain KYNA (5 mg/kg, i.p. n = 5) 5 h after administration. This is comparable to a previous microdialysis study in freely moving rats showing that systemic administration of PF-04859989 is associated with a dose-related reduction in striatal or cortical extracellular KYNA to a similar extent (Kozak et al., 2014). However, in contrast to the relatively instantaneous effects of PF-04859989 on VTA DA firing and on brain KYNA observed by Kozak et al., present results show no effect of the drug on whole brain KYNA within the time course of the electrophysiological experiment (45 min). A conceivable explanation for this discrepancy may be that whole brain analysis would also include a considerable intracellular pool of KYNA not detectable by microdialysis. Although the mechanisms of KYNA storage and release are not fully understood, the existence of two distinct intracellular KYNA pools has been suggested, which are preferentially responsible for KYNA storage and its rapid mobilization (Wu et al., 1992; Schwarcz et al., 2012). Therefore, measurement of total brain concentration of KYNA may not faithfully indicate its concentration at the sites of the receptors that mediate the pharmacological effects reported here.

5. Conclusions

In this study, the novel blood–brain barrier penetrating KAT-II inhibitor PF-04859989, which effectively reduces brain levels of KYNA, decreases firing activity of midbrain DA neurons. Thus, our results support a physiological role of KYNA to control DA firing, preferentially by modulating the number of spontaneously active cells. Hereby, a reduction in brain KYNA levels has a potential to treat hyperdopaminergic conditions that are generally associated with schizophrenia and bipolar disorder. Given the role of glutamate and acetylcholine signaling in memory processing, the pharmacological profile of KYNA, including blockade of both NMDA- and α7* nicotinic receptors, principally indicate that this endogenous compound may be of pathophysiological relevance also in cognitive impairments seen in several mental disorders.

Acknowledgments

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