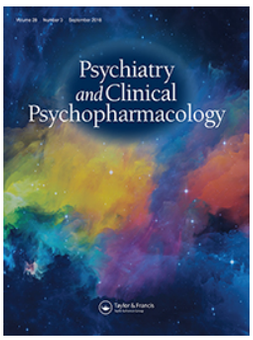

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

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To cite this article: Gokhan Unal, Alpay Ates & Feyza Aricioglu (2018) Agmatine-attenuated cognitive and social deficits in subchronic MK-801 model of schizophrenia in rats, Psychiatry and Clinical Psychopharmacology, 28:3, 245-253, DOI: 10.1080/24750573.2018.1426696

To link to this article: https://doi.org/10.1080/24750573.2018.1426696

Published online: 25 Jan 2018.

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2018, VOL. 28, NO. 3, 245–253
https://doi.org/10.1080/24750573.2018.1426696

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Agmatine-attenuated cognitive and social deficits in subchronic MK-801 model of schizophrenia in rats

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ABSTRACT

INTRODUCTION: Schizophrenia is one of the most severe psychiatric disorders with about 1% prevalence. It has been proved that glutamatergic *N*-methyl-D-aspartate (NMDA) receptor antagonists such as MK-801 and phencyclidine cause schizophrenia-like behaviours in rodents. Agmatine is an endogenous amine synthesized from decarboxylation of arginine and has been thought to be a neurotransmitter/neuromodulator. It binds to imidazoline and alfa adrenergic receptors and blocks cation channelled receptors, such as nicotinic acetylcholine, 5-HT3 serotonergic, and NMDA receptors. It is an endogenous inhibitor of nitric oxide synthase. A limited number of studies showed that agmatine attenuates sensorimotor gating deficit, which is an important parameter for schizophrenia, and improves cognitive deficits in rats. Despite this, it has also been shown that high doses of agmatine impaired sensorimotor gating. Herein, the aim of our study is to investigate the effect of subchronic agmatine treatment on sensorimotor gating, visual recognition memory, and social functions in subchronic MK-801 model of schizophrenia in rats.

METHODS: Wistar Hannover rats were divided into four groups as control (dimethyl sulphoxide), MK-801 (0.2 mg/kg), MK-801 + agmatine (20 mg/kg), and MK-801 + risperidone (0.5 mg/kg)($n = 8$ per group). MK-801 was subcutaneously injected once a day for 14 days. Agmatine and risperidone were administered intraperitoneally in the last seven days of MK-801 injections. On day 14, agmatine or risperidone was injected 15 minutes before MK-801 and MK-801 15 minutes before prepulse inhibition of the acoustic startle response (PPI) test. After the seven days washout period, social interaction (SI) test and novel object recognition test (NORT) were performed. One-way analysis of variance (ANOVA) or two-way ANOVA was used for statistical evaluation of NORT, SI, and PPI, respectively. Paired Student's *t*-test was used for the comparison of rat's affinity to a familiar and novel object in NORT.

RESULTS: MK-801 administration significantly decreased prepulse inhibition of rats in the PPI test ($p < .001$). In addition to this, MK-801 decreased startle response to pulse-alone trials and increased basal activity measured by the magnitude of no stimulus trials compared to the control group ($p < .05$). Agmatine treatment did not improve MK-801-induced PPI, startle response, or basal activity deficits while risperidone blocked the disruptive effect of MK-801 ($p < .05$). In NORT, the MK-801 group had significantly lower discrimination index ($p < .05$), whereas both the agmatine and risperidone treatments substantially increased this index ($p < .01$). Moreover, MK-801 injections not only decreased sniffing ($p < .01$) and following ($p < .01$) behaviours but also increased avoiding behaviour ($p < .001$) in SI. Agmatine partially treated social deficits ($p < .001$) while risperidone was reversed all of them ($p < .01$).

CONCLUSIONS: Subchronic MK-801 administration revealed sensorimotor gating, social and cognitive deficits in rats. Subchronic agmatine treatment improved cognitive deficits and increased socialization in rats although it was ineffective for sensorimotor gating deficits. Our results indicate that agmatine might be a modulator for negative and cognitive symptoms of schizophrenia, which are still unsolved issues for schizophrenia patients.

ARTICLE HISTORY
Received 2 January 2018
Accepted 9 January 2018

KEYWORDS
Agmatine; MK-801; risperidone; prepulse inhibition; schizophrenia

Introduction

Schizophrenia is one of the most severe psychiatric disorders with around 1% frequency in population, which significantly affects patient's quality of life. The pharmacotherapy is basically symptomatic and requires lifetime treatment. Besides, patients might have to leave the medicine due to serious adverse effects. Therefore, schizophrenia is one of the most important health problems waiting for a rational solution. Current drug treatment mainly acts through classical dopamine hypothesis and related changes in postsynaptic signal transduction or dopaminergic transmission and serotonergic system receptors. Accumulating data support that dysfunction of glutamate transmission regarding *N*-Methyl-D-Aspartate (NMDA) receptors might be associated with schizophrenia [1].

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Studies have demonstrated reduced glutamate levels in cerebrospinal fluid of schizophrenia patients [2]. It has been also indicated decreased NMDA receptor expressions in hippocampus and prefrontal cortex of post-mortem brains of patients [3,4]. It has been shown that NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, induce psychosis-like behaviours in healthy people [4]. On this basis, NMDA receptor antagonists (PCP, MK-801, and ketamine) have been used for inducing schizophrenia-like behaviours in rodents [5]. Acute injection of these antagonists is commonly used for modelling psychosis-like behaviours, while low-dose subchronic administrations (generally twice a day for seven days) create long-lasting negative and cognitive symptoms in rodents [6]. Studies showed that both acute and chronic administration of NMDA receptor antagonists disrupted prepulse inhibition paradigm, which is considered as an important marker for schizophrenia [7,8].

Pre-attentive information processing is a crucial component for processing of sensory information and cognitive functions. This process can be evaluated by certain specific tests such as prepulse inhibition of acoustic startle response (PPI) in human and rodents. The logic of PPI test can be described as a reduction in startle response of sudden and intense acoustic stimulus by presenting a weak prepulse stimulus just before (30–500 ms) the intense stimulus. It has been thought that PPI disruption results as sensorial flooding and attention deficits in schizophrenia patients [9]. Although PPI distuption is not specific for schizophrenia (also disrupted in Huntington disease and autism) it is well validated in human and rodent behavioural studies and it is one of the unique parameters evaluating the schizophrenia-like statement in human and rodents [10].

Cognitive deficits are one of the crucial symptom clusters of schizophrenia since two-thirds of the patients have impaired cognitive functions compared to healthy persons [11]. It has been shown that especially six types of memories including visual memory were impaired in schizophrenia. The Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative suggests that novel object recognition test (NORT) is a useful translational paradigm evaluating visual learning and memory in rodents [12]. The NORT has certain advantages such that it does not require any external motivation, reward, or punishment while it requires only little training or habituation period and it can be completed in a short time. The NORT is based on spontaneous exploratory behaviours of rodents. They commonly spend more time with novel object when they are exposed to a familiar and a novel object in NORT [13]. It has been indicated that NMDA receptor antagonism causes poor cognitive performance of rats in NORT. It has also been known that atypical antipsychotics ameliorate visual learning and memory deficits in rodents [14].

Negative symptoms are one of the five criteria for the diagnosis of schizophrenia according to Diagnostic and Statistical Manuel of Mental Disorders-5. Negative symptoms of schizophrenia consist of asocialization, amotivation, anhedonia, alogia, and affective flattening [15]. Even though all of the negative symptoms cannot be mimicked in preclinical studies, certain animal models such as low doses of subchronic NMDA receptor antagonism reveal social deficits in rodents. Certain behaviours showing sociality and social withdrawal such as sniffing, climbing, and avoiding were evaluated in the social interaction (SI) test [6]. In the light of this information, it can be said that the SI test demonstrates negative symptoms of schizophrenia in rodents.

Agmatine, an endogenous amine, which is formed by decarboxylation of L-arginine, synthesized by arginine decarboxylase, and degraded by agmatinase. It is widely distributed in the body including brain and interacts with a number of receptors, alpha-adrenergic and imidazoline receptors; blocks nicotinic cholinergic, serotoninergic 5-HT3, and glutamatergic NMDA receptors; and inhibits nitric oxide synthase. Agmatine can be defined as a putative neurotransmitter/neuromodulator [16–19]. Our research group and others have demonstrated that exogenously administered agmatine has a variety of pharmacological effects related with central nervous system, such as nociception, neuroinjury/neuroprotection, cognition, epilepsy, opioid tolerance/dependence, stress, anxiety, depression, and schizophrenia. Thus, agmatine can be a new candidate of novel therapeutic target by further revealing the underlying molecular mechanisms in related physiological and pathological conditions [20–27].

In spite of the given comprehensive pharmacological effects of agmatine, less is known about its role in schizophrenia. However, today, there is accumulating evidence that agmatine may have an effect on schizophrenia. The effect of agmatine has been examined in a limited number of studies in well-known PPI paradigm for schizophrenia in rodents. In the PPI model, agmatine has been shown to attenuate the disruptive effects of PCP [9]. Since agmatine does not produce extrapyramidal side effects, it has been suggested that it might be a therapeutic target for schizophrenia treatment. In the literature there are some conflicting reports indicating the effect of agmatine and it has been discussed that the alterations in data might be due to the levels of endogenous agmatine [9,19,28,29]. Agmatine mainly metabolized by a specific enzyme, agmatinase, into different polyamines, which can bind and block glutamatergic NMDA receptors. Both agmatine and polyamines, which are the end products of agmatine metabolism, interact with the glutamatergic system. Therefore, as postulated in previous studies, either agmatine and/or polyamines by

being a part of hypofunction of NMDA receptors may cause schizophrenia [30]. In a post-mortem study, a positive correlation was shown between metabolism of agmatine and the age of disease onset and the duration of schizophrenia [31].

In the light of above-mentioned evidence, we aimed to examine the effects of agmatine on sensorimotor gating, social, and cognitive deficits in subchronic MK-801 model of schizophrenia in rats.

Materials and methods

Animals and housing

All experiments documented in this study were conducted in accordance with the Regulation of Animal Research Ethics Committee in Turkey and was approved by GATA Haydarpasa Training Hospital Animal Research Ethics Committee. All experiments started after rats were allowed to habituate to the laboratory environment and the experimenters for two weeks. Male Wistar Hannover rats (8–12 weeks and 180–250 g) were housed under temperature-controlled (22 ± 1°C), 12/12 light and dark cycle room conditions. Animals were fed ad libitum bait and water. Experiments were conducted at the light phase of light/dark cycle. Animals were grouped as control (dimethyl sulphoxide), MK-801 (0.2 mg/kg), MK-801 + agmatine (20 mg/kg), and MK-801 + risperidone (0.5 mg/kg) ($n = 10$ in each group).

Drugs

MK-801 ((+)-MK-801 hydrogen maleate, Abcam) and agmatine sulphate (Sigma, USA) were dissolved in saline. Risperidon was dissolved in dimethyl sulphoxide (Merck, Germany) and diluted with saline. Dimethyl sulphoxide and drug treatments were administered at a volume of 0.1 ml/100 g.

Experimental design and treatments

After habituation and handling periods at the laboratory, MK-801 was subcutaneously injected once a day for 14 days. Agmatine and risperidone were treated intraperitoneally starting at day 8 for seven days. On day 14, treatments were administrated to rats 15 minutes before MK-801 injection and the PPI test was performed 15 minutes after MK-801. Agmatine and risperidone were injected into rats 30 minutes before the PPI test. After a seven-day washout period, NORT and SI were performed.

Prepulse inhibition of acoustic startle response

The SR-LAB systems (San Diego Instruments, San Diego, USA) were used for measurement of acoustic startle response of prepulse inhibition. The systems consist of soundproof chambers (39 × 38 × 58 cm), Plexiglas cylinders for restraining the rats in the chambers, piezoelectric sensors under the cylinders for detecting the startle of the rats, loudspeakers above the chambers for producing acoustic stimulus.

The test procedure of PPI has been described in the previous literature [8]. Before the testing day, rats were put into the chambers and exposed to the background noise for 5 minutes and five startle stimuli for adaptation to apparatus and testing of startle function, respectively. On the test day, rats were placed in the chambers and exposed to 70 dB background noise for 5 minutes. Then, rats were exposed to three trial blocks. Block 1 consisted of five presentations of 40 ms 120 dB pulse trials. Block 2 was 40 pseudo-random trials (average inter-trial intervals of 15 s) which consisted of eight presentations of each prepulse + pulse trials (74, 78, 86 dB 20 ms duration and 100 ms before 40 ms 120 dB pulse), eight presentations of 120 dB pulse-alone, and eight presentations of no stimulus trials. Block 3 had five presentations of pulse trials. Startle response was defined as the average of 100 readings (1 ms interval) of the acoustic startle stimulus. Only Block 2 was taken into account for percent prepulse inhibition. The percent prepulse inhibition of startle response was calculated for each rat as per following formula: $\%PPI = 100 - (PP + P)/(P) \times 100$. "PP + P" and "P" means the startle response after the presentation of prepulse + pulse stimulus and pulse-alone stimulus, respectively. Average PPI was calculated by the following formula: Average PPI = [PPI (74 dB) + PPI (78 dB) + PPI (86 dB)]/3. Startle response to pulse-alone trials and basal activity in no stimulus trials were also measured in this study.

Novel object recognition test

NORT consists of a black plexiglass open field arena (50 × 50 × 30 cm) and two different objects. The test apparatus was cleaned with 70% ethanol after using with each animal. The experiment was performed at dimly lit conditions. It was performed in a two-day protocol as habituation and test days. This process is well described in previous studies [32] and summarized as follows:

Habituation (Day 1): All animals in the same group were put into the plexiglass chamber and allowed to acclimate to the test environment for 60 minutes. No object was used in the habituation day. The process was performed for each group.

Test (Day 2): The test was conducted as two distinct 3-minute trials with 1-hour inter-trial interval. In trial 1 (Familiarization, T1), rats were allowed to explore two identical objects (A for each) for 3 minutes. The objects were placed into opposite corners of the chamber, which was 10 cm from the walls. At the end of 3 minutes, rats were returned their home cage for 1 hour. In trial 2 (Retention, T2), one of the

identical objects was changed with a novel object (B) and rats spent 3 minutes with objects. The familiar and novel objects had comparable size with each other (about10 cm high). Sniffing, licking, and touching behaviours were defined exploratory behaviour. All trials were recorded by a camera, which was placed above the apparatus. Exploration time (E) was scored by a researcher blinds to treatment groups. The discrimination index (DI) was calculated with the following formula: $DI = (E_B - E_A)/(E_B + E_A)$.

SI test

SI was performed in a black plexiglass open field arena (50 × 50 × 30 cm) at dimly lit conditions. The test apparatus was cleaned with 70% ethanol after usage with each animal.

In this test, two unfamiliar rats in the same treatment group allowed to interact with each other for 10 minutes. Before the test, one of them was painted with temporary and non-odour ink for discriminating from another one. Social behaviours were evaluated separately for each rat. All experiments were recorded with a camera. Spending time for sniffing, climbing, and following behaviours was measured as an indicator of socialization and spending time for avoiding was measured as an indicator of social withdrawal [33].

Statistical analysis

In this study, GraphPad Prism 6.0 for Mac was used to statistically analyse for all behavioural experiments. The most proper statistical and its *post hoc* tests were chosen for each experiment. Briefly, two-way analysis of variance (ANOVA) was used for the PPI test while one-way ANOVA was used for the NORT and SI tests. Dunnett's *post hoc* test was used to compare differences of groups in all experiments. Paired Student's *t*-test was also used for comparing exploration time of novel and familiar objects in NORT. Data were presented as mean ± standard error of mean (S.E.M) for all experiments. $p < .05$ was considered as a value of significance.

Results

Prepulse inhibition of acoustic startle response

It was found that 14 days MK-801 (0.2 mg/kg) administration significantly reduced PPI at +8 and +16 dB prepulse intensities ($p < .001$). Although MK-801 administration tended to decrease prepulse inhibition at +4 dB prepulse intensity, it was not statistically significant. Agmatine treatment did not change MK-801-induced PPI deficits in any prepulse intensities, while risperidone reversed PPI disruption at +16 dB prepulse intensity ($p < .05$, Figure 1).

MK-801 administration significantly decreased the startle amplitude of pulse-alone trials compared to the control group ($p < .05$). None of agmatine or risperidone treatments reversed the effect of MK-801 in PPI (Figure 2). In addition to this, it has been shown that MK-801 markedly increased basal activity compared to the control group ($p < .05$). Agmatine and risperidone did not reverse the effect of MK-801, while

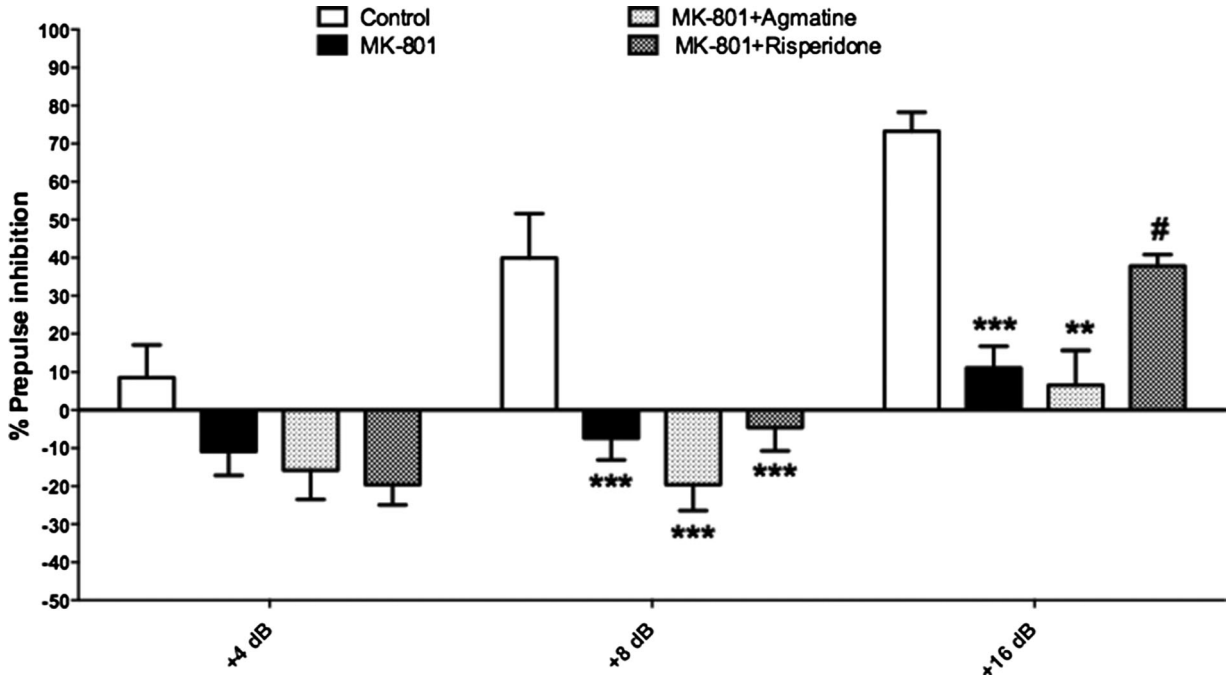

Figure 1. The effects of agmatine and risperidone treatments on MK-801-induced PPI deficits. Data are expressed as mean ± S.E.M and analysed by using two-way ANOVA followed by Dunnett's *post hoc* test. $^{**}p < .01$, $^{***}p < .001$ compared with the control group, $\#p < .05$ compared with the MK-801 group.

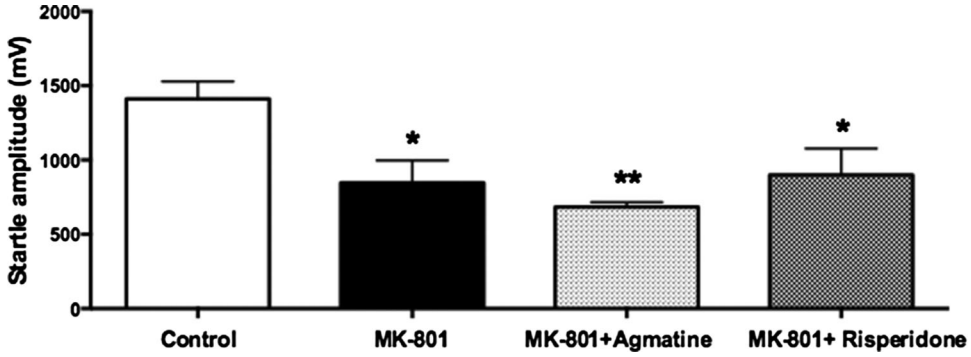

Figure 2. The effects of agmatine and risperidone treatments on MK-801 decreased startle amplitude in PPI. Data are expressed as mean ± S.E.M and analysed by using one-way ANOVA followed by Dunnett's *post hoc* test. *$p < .05$, **$p < .01$ compared with the control group.

agmatine potentiated the MK-801's effect on basal activity ($p < .05$, Figure 3).

Novel object recognition test

The time spent for novel object was not found different from the familiar ones within the MK-801 group. The exploration time of novel object was significantly higher than familiar object within control, MK-801 + agmatine and MK-801 + risperidone groups ($p < .01$, $p < .05$, and $p < .05$, respectively) (Figure 4).

We found that the MK-801 group had significantly lower DI than that of the control group ($p < .05$), while agmatine and risperidone treatments reversed the effect of MK-801 in NORT ($p < .01$ for each, Figure 5).

Social interaction

In this study, sniffing, climbing, following, and avoiding behaviours were measured in the SI test. For sniffing, time spent for this behaviour was significantly decreased in the MK-801 group compared to control

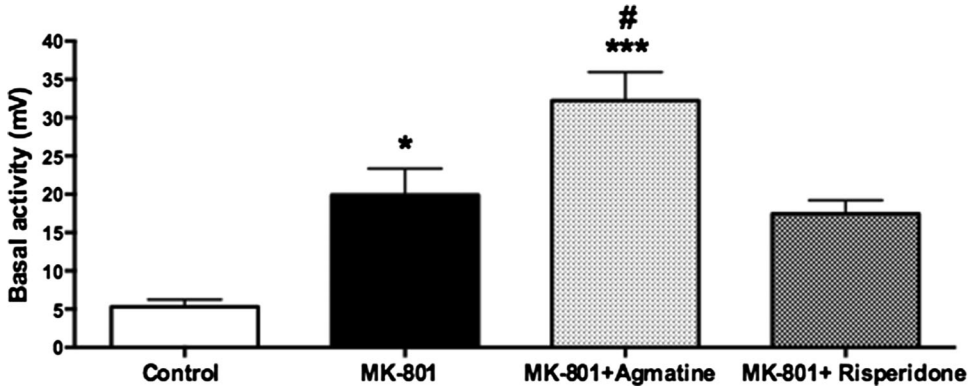

Figure 3. The effects of agmatine and risperidone treatments on MK-801-increased basal activity in PPI. Data are expressed as mean ± S.E.M and analysed by using one-way ANOVA followed by Dunnett's *post hoc* test. *$p < .05$, ***$p < .001$ compared with the control group, #$p < .05$ compared with the MK-801 group.

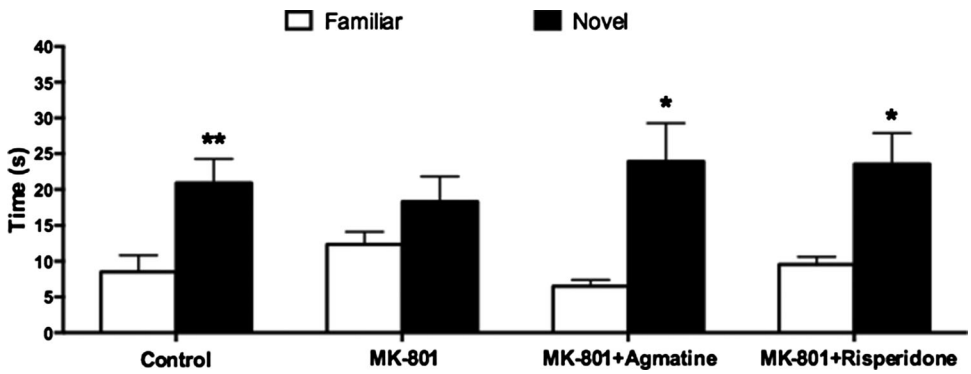

Figure 4. The time spent with familiar and novel objects in NORT. Data are expressed as mean ± S.E.M and analysed by using paired Student's *t*-test. *$p < .05$, *$p < .05$, and **$p < .01$ compared with a familiar object.

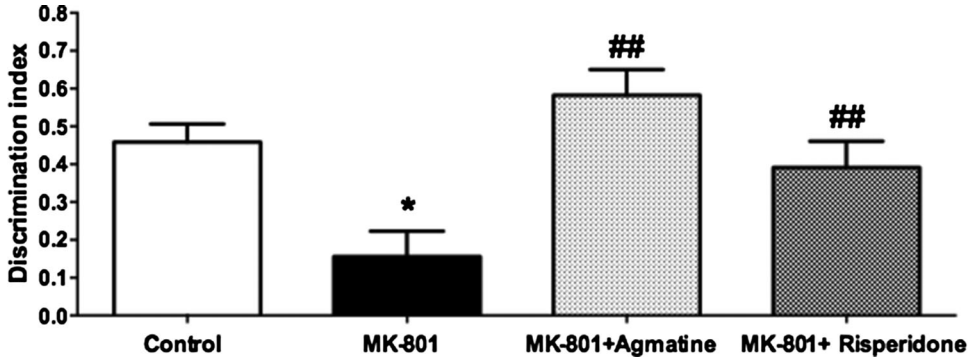

Figure 5. The effects of agmatine and risperidone treatments on MK-801 decreased the DI in NORT. Data are expressed as mean ± S.E.M and analysed by using one-way ANOVA followed by Dunnett's *post hoc* test. *$p < .05$, ##$p < .01$ compared with the control group, #$p < .05$ compared with the MK-801 group.

($p < .01$). Agmatine treatment did not change the effect of MK-801 in sniffing behaviour, while risperidone reversed this effect ($p < .01$, Figure 6(A)). In the following behaviour, MK-801-injected rats spent significantly less time than the control group ($p < .01$), risperidone reversed this effect ($p < .05$), while agmatine was not found to be effective (Figure 6(B)). MK-801 administration also increased avoiding behaviour compared to the control group ($p < .001$) and both agmatine and risperidone treatments reversed this effect of MK-801 in the SI test ($p < .001$ and $p < .01$, respectively). Although there was a tendency of increase in climbing behaviour, the difference was not found statistically significant (Figure 6(D)).

Discussion

Findings of the current study have demonstrated that subchronic MK-801 administration impaired sensorimotor gating, visual recognition memory, and social functions in rats. Treatment with agmatine attenuated MK-801-induced cognitive and social deficits, while it was found to be ineffective for disrupted sensorimotor gating in rats. Risperidone, an atypical antipsychotic, reversed all effects of MK-801 excluding startle response and basal activity.

It has been suggested that information processing and sensorimotor gating play roles in attention and cognitive functions, which were found disrupted in schizophrenia. PPI is a well-validated translational paradigm showing sensorimotor gating in both humans and rodents [34]. It has been thought that cortical, pallidal, striatal, and thalamic neuronal circuits have important roles for mediating the PPI paradigm. It has been indicated that psychotomimetic drugs such as dopaminergic agonists such as amphetamine and apomorphine, and glutamatergic NMDA receptor antagonists such as MK-801 and PCP induce PPI deficits via their acute effects and the effects are commonly transient [8,35]. In our study, we demonstrated that MK-801 administration induced PPI impairments and agmatine treatment did not ameliorate the disruptive effect of MK-801. In the literature there are only two studies showing the effect of agmatine on PPI. Palsson et al. [9] indicated that a low dose of agmatine (20 mg/kg) but not higher dose (40 mg/kg) attenuated PCP-induced PPI deficits in mice. They have also shown that single agmatine administration at the doses of 10, 20, and 40 mg/kg did not change PPI response in mice. In another study, a single administration of high-dose agmatine (160 mg/kg) but not lower doses (40 and 80 mg/kg) impaired sensorimotor gating. In addition to this, in the same study, it has been also demonstrated that agmatine treatment (40 and 80 mg/kg) could not reverse apomorphine-induced PPI deficits in rats [28]. In the light of these studies, the beneficial effect of agmatine showed by Palsson et al. [9] has not been confirmed while single effects of agmatine administration did not investigate in our study. According to above-mentioned findings, the beneficial effect of low-dose agmatine shown by Palsson et al. [9] is not in accordance with our findings might be explained at least a part due to the use of different animal strains. On the other hand, the mechanism beyond the effect of higher doses of agmatine still requires further research.

It has been demonstrated that startle amplitude of pulse-alone trials and the level of PPI are independent paradigms in rodents and thought that startle amplitude and PPI are mediated by different neuronal mechanisms in the brain [36]. In our study, MK-801 decreased startle amplitude of pulse-alone trials and neither agmatine nor risperidone reversed these effects of MK-801. Although the NMDA antagonist is not the same as that used in the previous study, results are compatible in terms of decrease in startle amplitude and insufficient effect of agmatine on this parameter [9]. Moreover, the other main issue was basal startle activity in these experiments, which were considered to be related with general activity in no stimulus trials. In previous studies, it was shown that drugs such as apomorphine and amphetamine increased basal activity in PPI [34]. In accordance with these previous

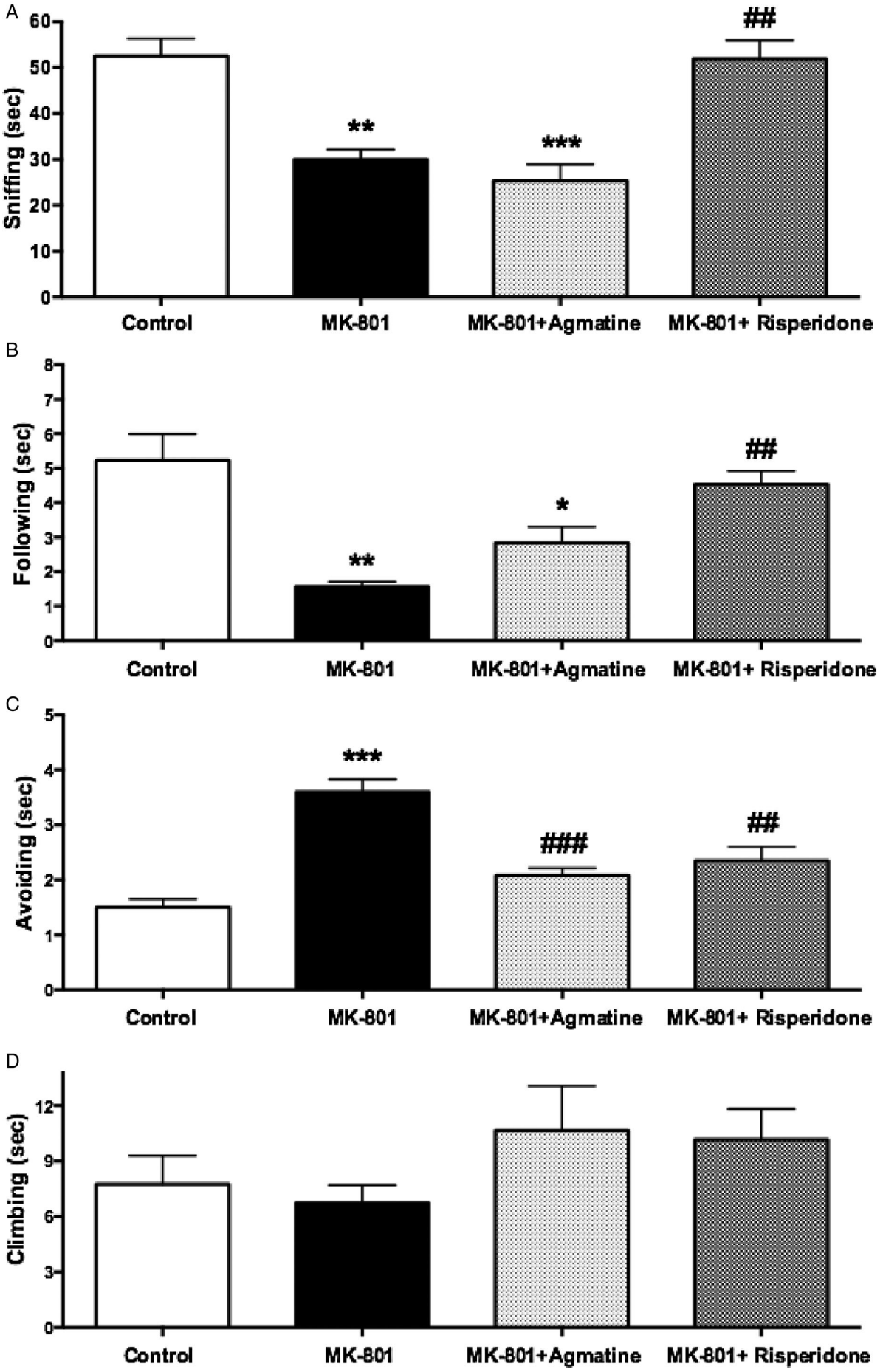

Figure 6. Time spent for sniffing (A), following (B), avoiding (C), and climbing (D) behaviours in the SI test. Data are expressed as mean ± S.E.M and analysed by using one-way ANOVA followed by Dunnett's *post hoc* test. *$p < .05$, **$p < .01$, and ***$p < .001$ compared to the control group and ##$p < .01$, ###$p < .001$ compared to the MK-801 group.

findings, our study indicated that MK-801 increased basal activity and none of the agmatine or risperidone attenuated this effect in PPI.

In our study, NORT was performed to assess visual recognition memory in rats. NORT is considered as a well-validated translational test in schizophrenia research and poor cognitive performance in NORT is a common finding in animal models of schizophrenia. It has been thought that perirhinal cortex and hippocampus have primer roles for mediating cognitive functions in NORT [37]. Therefore, the decreased discrimination ratio of novel and familiar objects in NORT due to the subchronic administration of MK-801 and PCP is one of the repeatable data to assess visual recognition memory in schizophrenia models [38,39]. In this study, we showed that subchronic MK-801 impaired visual recognition memory even after seven days of the washout period and both agmatine and risperidone attenuated this effect of MK-801 in NORT. To our current knowledge, there is no study investigating the effect of agmatine on schizophrenia-related visual memory deficits, though several studies have shown pro-cognitive effects of agmatine in different animal models [40–43]. This is the first time that the beneficial effect of agmatine has shown on MK-801-induced visual recognition memory deficit in NORT.

Negative symptoms are still one of the unsolved problems in schizophrenia. SI is a useful test to examine the effect of novel pharmaceutics on negative symptoms in rodents. Subchronic administration of NMDA receptor antagonists is a good approach to reveal social deficits in rats besides other symptoms seen in schizophrenia [6]. It has been well documented that both MK-801 and PCP can decrease social behaviours such as sniffing and following while they increased social withdrawal in SI. In contrast to low success of antipsychotic treatment in clinics, atypical antipsychotics were shown to ameliorate social deficits in rats [16,39]. In parallel to previous data, it has been found that MK-801 decreased sociality and increased social withdrawal in the SI test and risperidone totally but agmatine only partially reversed MK-801-induced social deficits in this study. Therefore, to our today's knowledge, this study is the first report that shows the beneficial effect of agmatine on negative symptoms of schizophrenia.

In conclusion, our results showed that agmatine ameliorated MK-801-induced negative and cognitive symptoms of schizophrenia but not disrupted sensorimotor gating in rats. Overall, our results showed that as an endogenous molecule agmatine might have a modulatory function on negative and cognitive symptoms of schizophrenia. It will be valuable to investigate the molecular mechanism beyond the effect of agmatine in schizophrenia, which might lead to future perspectives in the novel therapeutic approach.

Acknowledgements

The authors would like to thank Mustafa Isbir for his helpful assistance in this study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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