Effects of Olanzapine and Clozapine on Radial Maze Performance in Naive and MK-801-Treated Mice

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Key words
- atypical antipsychotics
- MK-801
- mice
- radial arm maze task
- spatial memory

Abstract

Attention, working memory and long-term memory dysfunctions are the most commonly seen cognitive impairments in schizophrenic patients. Conflicting results exist regarding the effects of antipsychotics on cognitive abnormalities. The aim of this study was to investigate the effects of atypical antipsychotic drugs olanzapine (0.4, 0.8 and 1.25 mg/kg, i.p.) and clozapine (0.5 and 1 mg/kg, i.p.) on spatial working memory in naive and MK-801 (0.2 mg/kg, i.p.) treated BALB-c mice in an 8-arm radial arm maze (RAM) task. None of the antipsychotic drugs studied altered number of errors in naive mice, whereas MK-801 significantly increased working memory errors in RAM test. Olanzapine and clozapine potently reversed MK-801 induced increasement of working memory errors. Olanzapine and clozapine prolonged latency of the animals in naive mice. The MK-801-induced enhancement in the speed of mice in performing the RAM task was blocked by olanzapine but not clozapine. Our study shows that atypical antipsychotics olanzapine and clozapine might improve cognitive deficits in schizophrenic patients.

Introduction

For many years, positive psychotic symptoms have been considered the hallmark of schizophrenia and have been the target of pharmacological treatment. During the last decade, it has become increasingly evident that schizophrenia is also associated with cognitive dysfunction [1]. Attention, working memory and long-term memory dysfunctions are the most commonly seen cognitive impairments in schizophrenic patients [2,3].
The treatment by using typical antipsychotics has been reported to be ineffective [4,5] or even impairing cognitive functions [6]. Atypical antipsychotics, for example, olanzapine [7] and sertindole [8], have been shown to improve negative symptoms without inducing extrapyramidal syndrome.
One of the mechanisms responsible for cognitive impairments in schizophrenia is the hypofunction of N-methyl-D-aspartate (NMDA) receptors [9]. NMDA receptor antagonists such as ketamine and phencyclidine induce schizophrenia-like symptoms in healthy subjects, including positive, negative, and cognitive symptoms [9]. MK-801 is an NMDA receptor antagonist that is widely used in animal models of psychosis and induces a variety of cognitive disturbances related to schizophrenia. It impairs learning and memory functions that depend on the hippocampus and the amygdala [10].
Atypical antipsychotics have been established to be more effective in improving memory dysfunctions than conventional antipsychotics [11]. Effects of atypical antipsychotics on the cognitive function reported in the literature are inconsistent [4,5,12,13] although the results could be dependent on the type of the measured cognitive function [14].
Because the cognitively beneficial effects of a treatment may have a high impact on the patients' quality of life, the main area of investigation is research related to the efficacy of a new antipsychotic therapy in diminishing cognitive impairments. Thus, we aimed to investigate the effects of the atypical antipsychotic drugs olanzapine and clozapine on spatial working memory in naive mice as well as on MK-801-induced cognitive dysfunction in a radial arm maze (RAM) test in mice.

Materials and Methods

Animals

190 male inbred BALB/c ByJ mice (MAM TUBITAK, Gebze, Kocaeli-Turkey), aged 7 weeks at their

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arrival to the laboratory, were used in this study. They were kept in the laboratory for 2 weeks before the onset of the experiments. Mice were housed 4–5 per cage at 21 ± 1.5 °C under a 12 h light/dark cycle (light onset at 8.00 p.m.). Tap water and food pellets were available ad libitum. All procedures for the treatment of animals were in compliance with the European Community Council Directive of 24 November 1986, and ethical approval was granted by the Kocaeli University Ethics Committee (Number: AEK 1/2, Kocaeli, Turkey). All animals used were naive to the experimental apparatus. The experiments were conducted between 9:00 a.m. and 12:00 p.m. in a semi-soundproof and semi-dark laboratory. Different mice were used in each experiment.

Radial arm maze (RAM)

The experimental device was an elevated maze with 8 open arms (32-cm long and 5-cm wide) leading to an 8-cm square platform, which radiated from a central circular platform 44 cm in diameter with 1-cm high sides surrounding each arm. A small cup, 1 cm in diameter, was embedded in each distal platform, and it contained a hidden 10 mg noodle used as reinforcement. The maze was oriented in a small room, on the walls of which 4 large black, white or black and white striped patterns hung, which provided particularly salient visual extramaze cues. For further details on the apparatus, see Beuzen et al. [15]. 24 h prior to training, the mice were deprived of food but not water; their weight loss reached 15–20 % of the initial body weight by the start of testing.

Radial arm maze procedure was applied according to Belzung et al. 2000 [16]. Mice were first given 2 pretraining sessions at 24-h intervals. Groups of 4 mice were placed on the maze at the same time and for 20 min per session, and could freely explore the 8 arms, which contained abundant food. Following pretraining, mice were given 5 training sessions, at 90-min intervals.

After baiting the 8 arms with a 10 mg noodle, a mouse was placed on the central platform. Sessions were terminated when the animal had visited all 8 arms and eaten the rewards, after 16 arms were visited (regardless of which arms), or after a maximum of 15 min. The maze was quickly cleaned with ethanol to remove fecal deposits and urine after each mouse had completed testing. An error was recorded when the mouse entered an arm previously visited during the retention session. The total number of errors and the latency of retention session (time taken to complete the task) were scored. Since the effects of drugs on locomotor activity of the animals may cause false results, the speed of the animals was recorded using ethovision-XT (Noldus, Netherlands).

Drugs

MK-801 (CAS 77086-22-7) was purchased from Sigma (St. Louis, USA). Olanzapine (CAS 132539-06-1) was supplied as a gift by the Biofarma drug company (Istanbul, Turkey), clozapine (CAS 5786-21-0) was a gift from the Adeka drug company (Samsun, Turkey). Olanzapine and clozapine were dissolved in saline with the addition of a few drops of 0.1 M hydrochloric acid, and MK-801 was dissolved in saline. All drugs were freshly prepared and administered in a volume of 0.1 mL per 10 g body weight. Control groups received the same volume of vehicle. Olanzapine (0.4, 0.8 and 1.25 mg/kg, i.p.), clozapine (0.5 and 1 mg/kg, i.p.) and MK-801 (0.2 mg/kg, i.p.) were administered 60, 30 and 30 min before the fifth session (retention session) in the radial arm maze test, respectively. The number of animals per group ranged from 6–10. Doses of drugs were selected according to behavioral and neurochemical studies demonstrating the intended effect of the drugs [4,17,18].

Statistics

The number of working memory errors, latency and the speed of the animals in the radial arm maze test were analyzed by using 2-way analysis of variance (ANOVA) followed by Dunnett's post hoc test. Data are expressed as the means ± SEM. The level of significance was defined as $p < 0.05$.

Results

▼

Naive mice were trained during 4 trials and olanzapine (0.4, 0.8 and 1.25 mg/kg, i.p.), clozapine (0.5 and 1 mg/kg, i.p.) and MK-801 (0.2 mg/kg, i.p.) was administered 60, 30 and 30 min respectively, before the beginning of fifth trial. No sedation was applied to the MK-801 treated animals; none of the animals included in the experiment died.

Effects of olanzapine on spatial memory in the radial arm maze test

In the evaluation of the effects of acute treatment with olanzapine (0.4, 0.8 and 1.25 mg/kg), given 60 min before the retention trial, on the number of errors in naive or MK-801-treated mice in the RAM test, a significant difference between the groups was observed (2-way ANOVA post hoc Dunnett's test; $F(7,66) = 6.78$; $p < p < 0.001$). Olanzapine (0.4, 0.8 and 1.25 mg/kg) given alone had no effect on the number of errors, whereas MK-801 (0.2 mg/kg) significantly increased the number of working memory errors in the RAM test in mice ($p < 0.01$). Olanzapine at all doses significantly decreased the number of working memory errors in MK-801-treated mice ($p < 0.05$, $p < 0.01$, $p < 0.01$, respectively) in the RAM test (**Fig. 1a**).

When the effect of olanzapine on the latency (time taken to complete the task) of the animals in naive and MK-801-treated mice in the RAM test was evaluated, there was a significant difference between the groups (2-way ANOVA post hoc Dunnett's test; $F(7,66) = 3.72$; $p < 0.01$). Olanzapine significantly increased the latency of the animals at 0.8 and 1.25 mg/kg doses ($p < 0.05$ and $p < 0.01$, respectively), whereas MK-801 slightly but insignificantly increased this parameter ($p > 0.05$). Olanzapine at 1.25 mg/kg doses, but not at other doses, significantly increased the latency of MK-801-treated mice ($p < 0.05$) (**Fig. 1b**).

The speed of mice in performing the RAM task (which reflects the locomotor activity of the animals) after acute injection of the drugs in the retention trial of the RAM test was significantly different between the groups (2-way ANOVA post hoc Dunnett's test; $F(7,66) = 8.60$; $p < 0.001$). Olanzapine (1.25 mg/kg) significantly decreased the speed of the animals ($p < 0.05$), whereas MK-801 treatment significantly enhanced this parameter ($p < 0.01$). MK-801-induced enhancement in the speed of animals was reversed by olanzapine at all of the doses used (0.4, 0.8 and 1.25 mg/kg; $p < 0.01$, $p < 0.05$ and $p < 0.05$, respectively) in the RAM test (**Fig. 1c**).

Effects of clozapine on spatial memory in the radial arm maze test

The effect of acute injection of clozapine (0.5 and 1 mg/kg), administered 30 min before the retention trial, on the number of errors in naive and MK-801-injected mice in the RAM test was significantly different between the groups (2-way ANOVA post hoc Dunnett's test; $F(5,34) = 12.52$; $p < 0.001$). Clozapine (0.5 and 1 mg/kg) showed no effect on the number of errors, whereas MK-801 (0.2 mg/kg) significantly increased the number of errors

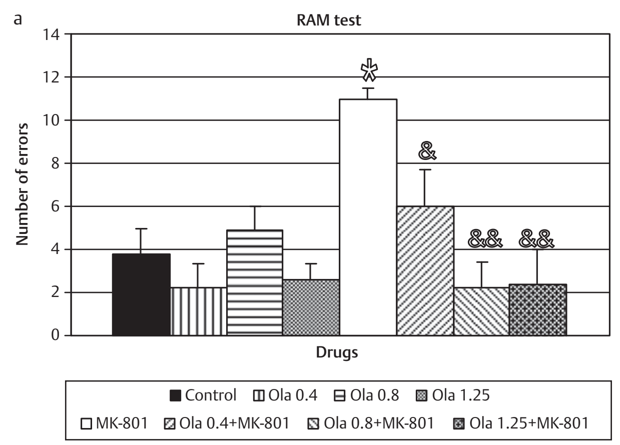

Fig. 1a Effects of olanzapine on working memory errors in the RAM test. Olanzapine (0.4, 0.8, or 1.25 mg/kg, i.p., n = 9–10) or vehicle (n = 10) was administered 60 min before the retention trial. MK-801 (0.2 mg/kg, i.p., n = 10) was administered 30 min before the test. $^*p < 0.05$ vs. control group, & $p < 0.05$, && $p < 0.01$ vs. MK-801 group.

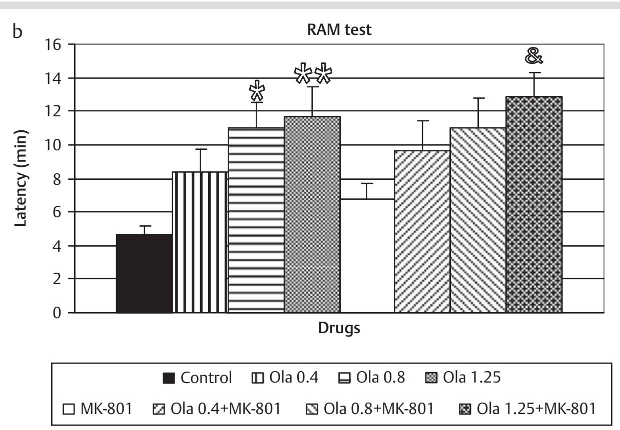

Fig. 1b Effects of olanzapine on latency per arm entry in the RAM test. Olanzapine (0.4, 0.8, or 1.25 mg/kg, i.p., n = 9–10) or vehicle (n = 10) was administered 60 min before the test. MK-801 (0.2 mg/kg, i.p., n = 10) was administered 30 min before the test. $^*p < 0.05$, $^{**}p < 0.01$ vs. control group, & $p < 0.05$ vs. MK-801 group.

in the RAM test in mice ($p < 0.01$). The MK-801-induced increase in the number of errors was reversed by clozapine (0.5 and 1 mg/kg) ($p < 0.05$) in the RAM test (▶ **Fig. 2a**).

There was a significant difference between the groups when evaluating the effects of clozapine on the latency (time taken to complete the task) of naive and MK-801-treated mice in the RAM test (2-way ANOVA post hoc Dunnett's test; $F(5,34) = 5.83$; $P = 0.001$). Clozapine significantly prolonged the latency of the animals at 1 mg/kg doses ($p < 0.01$), whereas MK-801 had no effect (▶ **Fig. 2b**).

The speed of mice in performing the RAM task was significantly different between the groups (2-way ANOVA post hoc Dunnett's test; $F(5,34) = 8.31$; $p < 0.001$). Clozapine failed to affect the speed of the animals, whereas MK-801 significantly increased this parameter ($p < 0.01$). Moreover, clozapine failed to reverse the MK-801-induced increase in the speed of animals in the RAM test (▶ **Fig. 2c**).

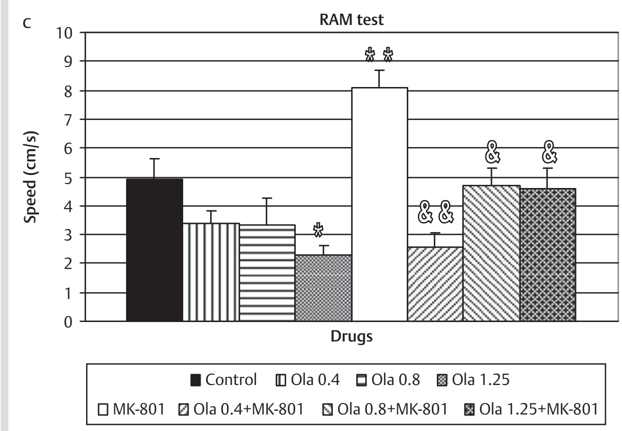

Fig. 1c Effects of olanzapine on speed of mice in the RAM test. Olanzapine (0.4, 0.8, or 1.25 mg/kg, i.p., n = 9–10), or vehicle (n = 10) was administered 60 min before the test. MK-801 (0.2 mg/kg, i.p., n = 10) was administered 30 min before the test. $^*p < 0.05$, $^{**}p < 0.01$ vs. control group, & $p < 0.05$, && $p < 0.01$ vs. MK-801 group.

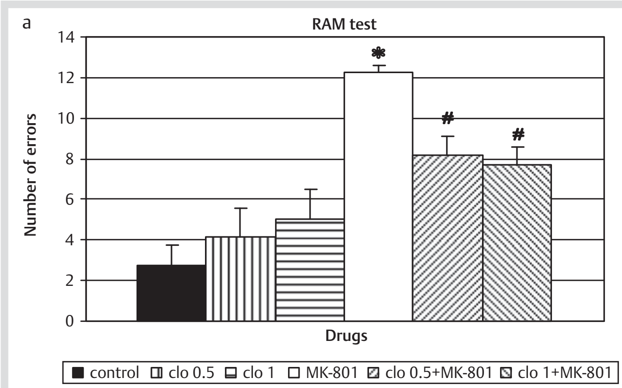

Fig. 2a Effects of clozapine on working memory errors in the RAM test. Clozapine (0.5 and 1 mg/kg, i.p., n = 6) or vehicle (n = 8) was administered 30 min before the retention trial. MK-801 (0.2 mg/kg, i.p., n = 8) was administered 30 min before the test. $^*p < 0.01$ vs. control group, # $p < 0.05$ vs. MK-801 group.

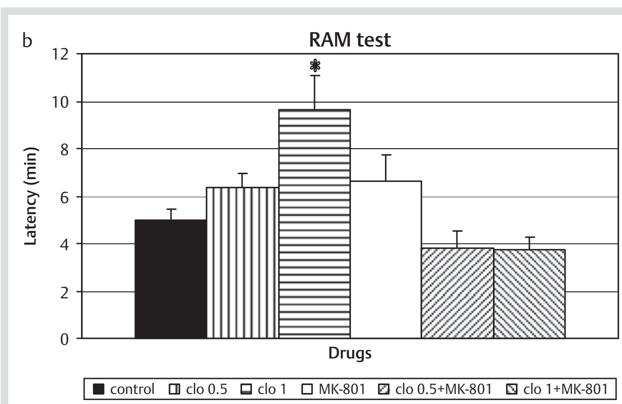

Fig. 2b Effects of clozapine on latency per arm entry in the RAM test. Clozapine (0.5 and mg/kg, i.p., n = 6) or vehicle (n = 8) was administered 30 min before the test. MK-801 (0.2 mg/kg, i.p., n = 8) was administered 30 min before the test). $^*p < 0.01$ vs. control group.

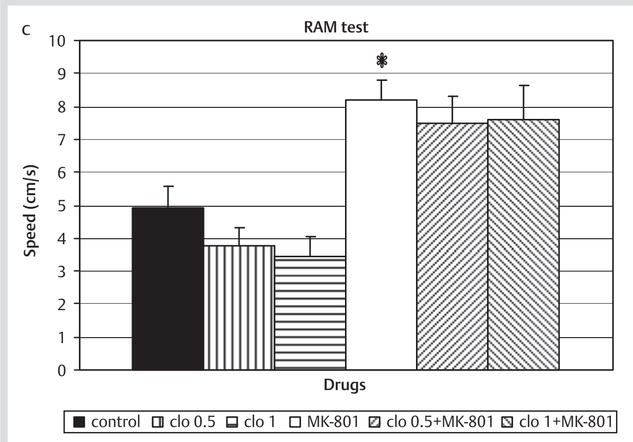

Fig. 2c Effects of clozapine on speed of mice in RAM test. Clozapine (0.5 and 1 mg/kg, i.p., n = 6) or vehicle (n = 8) was administered 30 min before the test. MK-801 (0.2 mg/kg, i.p., n = 8) was administered 30 min before the test. $^*p<0.01$ vs. control group.

Discussion

This study reveals that the second-generation atypical antipsychotic drugs olanzapine and clozapine both have beneficial effects on MK-801-induced memory impairment in the RAM test, although clozapine and olanzapine can exert side effects on locomotion in naive mice.

It has been shown that, in the RAM test, the ability to make a series of correct choices depends on spatial information from extramaze cues [19–21]. In our protocol, the effect of drugs on spatial memory is evaluated, because performance in the maze requires sufficient memory of the spatial environment. Each of the arms is baited with food, and the reentry to a previously visited arm is accepted as an error; thus, spatial working memory is thougt to be examined.

Conflicting results have been obtained for the effects of antipsychotics on learning and memory. In one study, clozapine failed to improve verbal working memory in patients with schizophrenia [22], although in another study, the drug reversed subchronic phencyclidine-induced impairment in spatial working memory in rats [23]. In a working memory test, a delayed response task in rats, low doses of haloperidol, clozapine and risperidone induced a delay-independent impairment, but sertindole treatment failed to exert an effect [24]. In a recent study, a novel atypical antipsychotic lurasidone reversed MK-801-induced impairment of learning and memory in both the MWM test and the RAM test [25].

Clozapine and olanzapine have affinities for numerous neurotransmitter receptors, such as dopaminergic, serotonergic, muscarinic, H_1, and α_1-, α_2-, and β-adrenergic receptors [26–28]. The most notable pharmacological difference between olanzapine and chlorpromazine (i. e., the feature that is thought to confer atypicality) is olanzapine's high affinity (as an antagonist) for $5HT_{2A}$ receptors [29]. $5HT_{2A}$ antagonists have been associated with improvements in information processing, attention, and working memory in rodents and in non-human primates [30, 31]. The positive effects of atypical antipsychotic drugs might be due to the ability of these drugs to enhance dopamine and acetylcholine efflux [13].

Olanzapine causes a dose-related increase in the extracellular concentration of dopamine in the rat prefrontal cortex [32], which may contribute to improved cognitive functioning. Olanzapine's high affinity and antagonistic activity at the $5\text{-}HT_6$ receptor [33] may also be important for its ability to improve memory. Pre-clinical evidence has suggested that $5\text{-}HT_6$ antagonists may improve cognitive function [34], possibly due to the selective enhancement of excitatory neurotransmission [35].

Clozapine and olanzapine may also influence cognitive performance due to antihistaminergic effects [29]. A strong correlation between increased histamine H_1 occupancy and decreased locomotion and cognitive performance was shown in human studies [36, 37]. The diminishing effect of olanzapine at 1.25 mg/kg on speed and prolonging effect of olanzapine and clozapine on latency of the animals at higher doses in naive animals in this study can be related to their histaminergic antagonistic effects. Both olanzapine and clozapine did not alter the number of errors compared to control group therefore we can not conclude the deterioration of memory by olanzapine and clozapine in naive mice.

The ability of atypical antipsychotics to block $5\text{-}HT_{2A}$ receptors within the prefrontal cortex may also lead to an increase in dopamine transmission and diminish some aspects of cognitive dysfunction associated with dopamine loss. A high 5 HT_{2A}/dopamine D_2 receptor affinity ratio seems to be related to successful treatment of the negative symptoms of schizophrenia [38], and this effect improves cognitive dysfunctions.

Animals treated with NMDA receptor antagonists, such as PCP, ketamine, or MK801, are used to model various aspects of schizophrenia. These animals show symptoms including hyperlocomotion, enhanced stereotypic behaviors, cognitive and sensorimotor gating deficits, and impaired social interactions [39]. Hyperactivity and many other behavioral abnormalities produced by noncompetitive NMDA receptor antagonists are blocked by most of the typical and atypical antipsychotics [40, 41]. Clozapine, olanzapine and sertindole have antagonistic effects on $5\text{-}HT_{2A}$, $5\text{-}HT_{2C}$, and α_1-adrenergic receptors, with higher potencies than the effects on dopamine D_2 receptors. It is known that selective ligands of these receptors (e. g., M100907 ($5\text{-}HT_{2A}$) and prazosin (α_1), respectively) can inhibit locomotor hyperactivity induced by MK-801 [42, 43]. Antipsychotics with potent $5\text{-}HT_{2A}$ and α_1-adrenergic antagonistic activity also block MK-801-induced hyperactivity [42], which was also demonstrated in the present study. Olanzapine reversed the MK-801-induced hyperactivity while clozapine had no effect in doses used in our study. It can be expected to observe the same effects by higher doses of clozapine in further studies.

As a conclusion, the second-generation antipsychotics olanzapine and clozapine seem to exert a beneficial effect on MK-801 induced cognitive dysfunction following acute treatment at the doses used similar to our previous studies [44, 45] in mice. Further research, including the assessment of neuronal and molecular factors and comparing effects of atypicals antipsychotics with a classical one, is needed to clarify the effects of atypical antipsychotics in various learning tasks on different forms of memory, and such approaches may facilitate the development of better antipsychotics for the treatment of cognitive deficits associated with schizophrenia.

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Conflict of Interest

Authors report no biomedical financial interests or potential conflicts of interests.

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