Effects of ziprasidone, SCH23390 and SB277011 on spatial memory in the Morris water maze test in naive and MK-801 treated mice

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A B S T R A C T

Introduction: Patients with schizophrenia have cognitive dysfunctions; positive psychotic symptoms are the primary purposes for schizophrenia treatment. Improvements in cognitive function should be a characteristic of all newly developed drugs for the treatment of schizophrenia with dementia. Thus, we investigated the effects of the second-generation antipsychotic ziprasidone, dopamine D1 antagonist SCH-23390 and dopamine D3 antagonist SB-277011 on spatial learning and memory.

Materials and methods: Male inbred mice were used. The effects of ziprasidone, SCH-23390 and SB-277011 were investigated using the Morris water maze test.

Results: Ziprasidone (0.5 and 1 mg/kg), SCH-23390 (0.05 and 0.1 mg/kg) and SB-277011 (10 and 20 mg/kg) had no effect on the time spent in the target quadrant in naive mice. MK-801 (0.1 mg/kg) significantly decreased the time spent in the target quadrant. The time spent in the target quadrant was significantly prolonged by Ziprasidone (0.5 and 1 mg/kg) and SCH-23390 (0.1 mg/kg), but not with SB-277011 (20 mg/kg) in MK-801-treated mice.

Ziprasidone (0.5 and 1 mg/kg), SCH-23390 (0.05 and 0.1 mg/kg) and SB-277011 (10 and 20 mg/kg) had no effect on the mean distance to the platform in naive mice. MK-801 significantly increased the mean distance to the platform. Ziprasidone (1 mg/kg) and SCH-23390 (0.1 mg/kg) significantly decreased the mean distance to the platform in MK-801-treated mice, but SB-277011 (20 mg/kg) didn’t.

MK-801 significantly increased the total distance moved. Ziprasidone (0.5 and 1 mg/kg), SCH-23390 (0.05 and 0.1 mg/kg) and SB-277011 (10 and 20 mg/kg) had no effect on the total distance moved in naive mice. Ziprasidone (1 mg/kg) and SCH-23390 (0.1 mg/kg) significantly decreased the total distance moved in MK-801-treated mice, but SB-277011 (20 mg/kg) didn’t.

Conclusions: The second-generation antipsychotic drug ziprasidone and D1 antagonist SCH23390, but not the D3 antagonist SB277011, might be clinically useful for the treatment of cognitive impairments in patients with schizophrenia.

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1. Introduction

The impairment of cognitive function is a core feature of schizophrenia, and it diminishes quality of life (Addington and Addington, 1999). These impairments include deficits in attention, working memory, verbal learning, memory, and executive functions to varying degrees (Hoff et al., 1992 and Saykin et al., 1994). Currently used conventional antipsychotic drugs exhibit little benefit across cognitive domains. Furthermore, these drugs cause extrapyramidal side effects that require anticholinergic treatment, which impairs memory (Lieberman JA 3rd., 2004). The frequency of hospitalization increases because of these aforementioned problems, which increases the cost to society (Sevy and Davidson, 1995). Accordingly, effective treatment of cognitive deficits in schizophrenic patients may enormously influence the patient’s quality of life.

The N-methyl-D-aspartate (NMDA) receptor is an ionotropic glutamate receptor. NMDA receptor antagonists block hippocampal long-term potentiation and impair hippocampal-dependent behaviors (Bischoff and Tiedtke, 1992). Non-competitive antagonists of the NMDA receptor, such as ketamine or phencyclidine (PCP), exert psychotomimetic effects in humans (Boulay D et al., 2013; Javitt and Zukin, 1991). MK-801 is a noncompetitive antagonist that binds to the PCP binding site within the NMDA receptor-ion complex (Wong and Nielsen, 1989). It impairs animal performance in various learning and...
memory paradigms (Riedel et al., 2003). MK-801 also produces various effects on rodent behavior, including deficits in sensory processing, hypermotility, stereotypy and ataxia (Al-Amin and Schwarzkopf, 1996; Trickelbank et al. 1989). MK-801 is widely used as an animal model of psychosis because it induces a variety of cognitive disturbances that are related to schizophrenia. MK-801 corrupts Morris water maze performance, and treatment induces cognitive deficits that are observed in schizophrenic patients (Enomoto et al., 2008).

Hypofunction of the N-methyl-d-aspartate (NMDA) receptor causes cognitive impairments. NMDA receptor antagonists, such as ketamine and phencyclidine, induce schizophrenia-like symptoms in healthy subjects, including positive, negative, and cognitive symptoms (Boulay D et al., 2013; Krystal et al., 1994). NMDA receptor antagonists also decay learning and memory functions. Therefore, these agents are used to establish animal models of cognitive impairment (Boulay D et al., 2013; Wass et al., 2006; Didriksen et al., 2007).

Ziprasidone is a novel antipsychotic with a high affinity for the dopamine D2 and D3 and serotonin (5HT) 5HT1A, 5HT2C, and 5HT1D receptors. It also exhibits a high affinity for the 5HT1A receptor, where it acts as a potent agonist (Seeger et al. 1995). Ziprasidone (CP-88059) is a combined 5HT and dopamine receptor antagonist that exhibits potent effects in preclinical assays that are predictive of antipsychotic activity. It has been shown that drugs with serotonin 5HT2A blocking properties produce better cognitive function in patients with schizophrenia than drugs that have a predominantly dopamine D2 blocking activity (Weinberger and Gallhofer, 1997). SCH23390 is a selective dopamine D1 receptor antagonist (Bradford et al. 2010). SB-277011-A is a dopamine D3 receptor antagonist with a high affinity and selectivity for D3 receptors in humans and rats, and it exhibits good bioavailability and CNS penetration (Reavill et al. 2000).

Limited studies investigated the effects of atypical antipsychotics on memory processes in animal models. In the present study, the effects of the second generation atypical antipsychotic ziprasidone, dopamine D1 antagonist SCH-23390 and dopamine D3 antagonist SB-277011 on spatial learning and memory in naïve and MK-801-treated mice are investigated using the Morris water maze test.

2. Materials and methods

2.1. Animals

Male inbred BALB/c ByJ mice (Animal Research Center, Bursa-Turkey) aged 7 weeks upon arrival to the laboratory were used in this study. The animals (4–5 per cage) were maintained in the laboratory at 21 ± 1.5°C with 60% relative humidity under a reverse 12-h light/ dark cycle (lights on at 8.00 p.m.) for 2 weeks before experiments. Tap water and food pellets were available ad libitum. All procedures involving animals complied with the European Community Council Directive of November 24, 1986, and the Kocaeli University Ethics Committee granted ethical approval (Number: AEK 7/6, Kocaeli, Turkey).

2.2. Morris water maze test

The Morris water maze is a circular pool (90-cm diameter and 30-cm height) filled with water (22 °C) to a depth of 14 cm that is rendered opaque by the addition of small black balls (Mutlu O et al., 2015; Mutlu O et al., 2011). The pool was located in a dimly lit, soundproof test room with various visual cues, including a white and black-colored poster on the wall, a halogen lamp, a camera and the experimenter. The maze was divided into four quadrants, and three equally spaced points served as starting positions around the edge of the pool. The order of the release positions varied systematically throughout the experiment. A circular escape platform (6-cm diameter and 12-cm high) was located in one quadrant 1 cm above the water surface during the familiarization session and 1 cm below the water surface during the other sessions.

Video tracking was conducted using a video camera that focused on the full diameter of the pool. The navigation parameters were analyzed using the Ethovision 3.1 video analysis system (Noldus, The Netherlands). The mice were trained in the Morris water maze five times daily (Familiarization session, S1, S2, S3, S4). One familiarization session and four acquisition sessions were performed using the Morris water maze. Each mouse was given three trials during the familiarization session and acquisition phase of the experiment. The delay between trials was 60 s, and a 1-day interval was used between each session. The mouse was taken from the home cage and was placed into the water maze at one of three randomly determined locations with its head facing the center of the water maze for each trial. The trial was stopped after the mouse found and climbed onto the platform, and the escape latency was recorded. The trial was stopped if the mouse did not climb onto the platform in 60 s, and the experimenter guided the mouse to the platform. An escape latency of 60 s was recorded.

A ‘probe trial’ assessed the spatial memory retention of the location of the hidden platform 24 h after the last acquisition session. The platform was removed from the maze during this trial, and the mouse was allowed to search for the pool for 60 s. The following parameters were evaluated during the probe trial: the time spent in the target quadrant(s), the mean distance to the platform (cm), and the swim speed (cm/s). The “mean distance of the zone platform” measure means “the mean of the distance to the zone platform during a 60-s probe trial performance. If this value was smaller, it means that the mice swim closer to the zone platform during the probe test”.

The time spent in the target quadrant and the distance to the platform calculations were used as measures for the development of spatial memory, and swim speed was used to evaluate motor functions.

2.3. Open-field test

Compounds that alter motor activity may yield false positive/negative effects in the Morris water maze test. Therefore, mouse spontaneous locomotor activity was evaluated by monitoring activity in an open field (33 × 33 × 30 cm square box). Animals were placed in the center of the apparatus, and their behaviors were recorded for a period of 5 min using the Etovision-XT video tracking system. Locomotor activity was evaluated by measuring the total distance traveled in the apparatus.

2.4. Experimental design

Ziprasidone (0.5 and 1 mg/kg), SB-277011 (10 and 20 mg/kg) and MK-801 (0.1 mg/kg) were administered intraperitoneally (i.p.) 60, 30 and 30 min before the probe trial, respectively. SCH-23390 (0.05 and 0.1 mg/kg) was injected subcutaneously (s.c.) 60 min before the probe trial of the MWM test. The probe trial was performed on the sixth day of the test. Each animal was tested in the probe trial only once. MK-801 and other drugs were administered only on the probe trial day. Each drug was only tested in the probe trial on day 6. Animals that received MK-801 + drug x received two injections, and animals that received only a single drug similarly received two injections. The number of animals per group ranged from 8 to 10.

2.5. Drugs

Ziprasidone, SB-277011, SCH-23390 and MK-801 were purchased from Sigma (St. Louis, USA). All of the drugs were dissolved in saline. All of the drugs were freshly prepared on the day of the experiment and were administered in a volume of 0.1 ml per 10 g body weight. The control groups received the same volume of vehicle. All of the doses were chosen based on previous behavioral studies (Fedotova and Saponov, 2012, Bespalov et al. 2007, Bradford et al. 2010, Skarsfeldt, 1996).
2.6. Statistics

Two-way analysis of variance (ANOVA) and a post-hoc Tukey test were used to analyze the MWM. The data are expressed as the mean values ± SEM. Differences were considered statistically significant when a p value less than 0.05 was obtained.

3. Results

3.1. Effects of ziprasidone, SCH-23390 and SB-277011 on the time spent in the target quadrant in naïve and MK-801-injected mice in the Morris water maze test

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey test; F(4,41) = 17,850; p < 0.0001; Fig. 1a] in the time spent in the target quadrant during the probe trial of the MWM test when the ziprasidone groups were evaluated. Ziprasidone had no effect on the time spent in the target quadrant in naïve mice. MK-801 (0.1 mg/kg) significantly decreased the time spent in the target quadrant (p < 0.001). Ziprasidone (0.5 and 1 mg/kg) significantly prolonged the time spent in the target quadrant in MK-801-treated mice (p < 0.01) (Fig. 1a).

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey test; F(4,43) = 30,214; p < 0.0001; Fig. 1b] in the time spent in the target quadrant during the probe trial of the MWM when the SCH-23390 groups were evaluated. SCH-23390 had no effect on the time spent in the target quadrant in naïve mice. SCH-23390 (0.1 mg/kg) significantly prolonged the time spent in the target quadrant in MK-801-treated mice (p < 0.001) (Fig. 1b).

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey test; F(4,43) = 20,214; p < 0.0001; Fig. 1c] in the time spent in the target quadrant during the probe trial of the MWM test when the SCH-23390 groups were evaluated. SCH-23390 (0.05 and 0.1 mg/kg) had no effect on the time spent in the target quadrant in naïve mice. SCH-23390 (0.1 mg/kg) significantly prolonged the time spent in the target quadrant in MK-801-treated mice (p < 0.05) (Fig. 1c).

3.1.1. Effects of ziprasidone, SCH-23390 and SB-277011 on the distance to the platform in naïve and MK-801-injected mice in the Morris water maze test

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; F(4,41) = 56,260; p < 0.0001; Fig. 2a] in the mean distance to the platform in the probe trial of the MWM test when he ziprasidone groups were evaluated. Ziprasidone (0.5 and 1 mg/kg) had no effect on the mean distance to the platform in naïve mice. MK-801 significantly increased the mean distance to the platform (p < 0.001). Ziprasidone (1 mg/kg) significantly decreased the mean distance to the platform in MK-801-treated mice (p < 0.01) (Fig. 2a), which suggests that it exerted some beneficial effects on disturbed learning and memory.

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; F(4,43) = 30,507; p < 0.0001; Fig. 2b] in the mean distance to the platform in the probe trial of the MWM test when the SCH-23390 groups were evaluated. SCH-23390 (0.05 and 0.1 mg/kg) had no effect on the mean distance to the platform in naïve mice. SCH-23390 (0.1 mg/kg) significantly decreased the mean distance to the platform in MK-801-treated mice (p < 0.05) (Fig. 2b), which suggests that it exerted some beneficial effects on disturbed learning and memory.

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; F(4,43) = 20,141; p < 0.0001; Fig. 2c] in the mean distance to the platform in the probe trial of the MWM test when the SB-277011 groups were evaluated. SB-277011 (10 and 20 mg/kg) had no effect on the mean distance to the platform in naïve mice. SB-277011 (20 mg/kg) also had no effect on the mean distance to the platform in MK-801-treated mice (p > 0.05) (Fig. 2c).

3.2. Effects of ziprasidone, SCH-23390 and SB-277011 on motor function in naïve and MK-801-treated mice

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; F(4,41) = 11,382; p < 0.0001] in swimming speed when the ziprasidone groups were evaluated. MK-801 significantly increased the swimming speed (p < 0.001). Ziprasidone (0.5 and 1 mg/kg) had no effect on swimming speed in naïve mice. Ziprasidone (1 mg/kg) significantly decreased the swimming speed in MK-801-treated mice (p < 0.001) (Fig. 3a).

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; F(4,43) = 14,374; p < 0.0001] in the swimming speed when the SCH-23390...
groups were evaluated. SCH-23390 (0.05 and 0.1 mg/kg) had no effect on swimming speed in naïve mice. SCH-23390 (0.1 mg/kg) significantly decreased the swimming speed in MK-801-treated mice ($p < 0.001$) (Fig. 3b).

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; $F(4,43) = 15.267; p < 0.0001$] in the swimming speed when the SB-277011 groups were evaluated. SB-277011 (10 and 20 mg/kg) had no effect on swimming speed in naïve mice, and SB-277011 (20 mg/kg) had no effect on swimming speed in MK-801-treated mice ($p > 0.05$) (Fig. 3c).

### 3.3. Effects of ziprasidone, SCH-23390 and SB-277011 on locomotor activity in naïve and MK-801-treated mice

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; $F(4,41) = 11.382; p < 0.0001$] in the total distance traveled when the ziprasidone groups were evaluated. MK-801 significantly increased the total distance moved ($p < 0.0001$). Ziprasidone (0.5 and 1 mg/kg) had no effect on the total distance traveled in naïve mice. Ziprasidone (1 mg/kg) significantly decreased the total distance traveled in MK-801-treated mice ($p < 0.001$) (Fig. 4).

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; $F(4,43) = 14.374; p < 0.0001$] in the total distance traveled when the SCH-23390 groups were evaluated. SCH-23390 (0.05 and 0.1 mg/kg) had no effect on total distance traveled in naïve mice. SCH-23390 (0.1 mg/kg) significantly decreased the total distance traveled in MK-801-treated mice ($p < 0.001$) (Fig. 4).

There was a significant difference between drug groups or their combination [two-way ANOVA post-hoc Tukey’s test; $F(4,43) = 15.267; p < 0.0001$] in the total distance traveled when the SB-277011 groups were evaluated. SB-277011 (10 and 20 mg/kg) had...
no effect on total distance traveled in naïve mice, and SB-277011 (20 mg/kg) had no effect on total distance traveled in MK-801-treated mice (p > 0.05) (Fig. 4).

4. Discussion

Ziprasidone has antagonist activity at dopamine (DA) D2 and serotonin (5-HT) 5-HT1D, 5-HT2A, and 5-HT2C receptors and partial agonist activity at 5-HT1A receptors (Stahl and Shayegan, 2003). Ziprasidone inhibition of the firing of dorsal raphe 5-HT neurons was antagonized by the selective 5-HT1A antagonist WAY-100,635. In vitro functional dopamine receptor antagonist using ziprasidone results in a concentration-dependent blockade of the effects induced by the D2 agonist quinpirole (Seeger et al., 1995).

Limited studies investigated the effects of atypical antipsychotics on memory processes in animal models; thus, we investigated the effects of the second-generation antipsychotic drug ziprasidone, the dopamine D1 antagonist SCH-23390 and the dopamine D3 antagonist SB-277011 on spatial memory in naïve and MK-801-treated mice in the MWM test.

The main finding of this study is that the second-generation atypical antipsychotic drug ziprasidone, the dopamine D1 antagonist SCH-23390 and the dopamine D3 antagonist SB-277011 had no effect on spatial memory in naïve mice in the MWM test. Ziprasidone (1 mg/kg) and SCH-23390 (0.1 mg/kg) reversed MK-801-induced impairments in learning and memory in the MWM test, but SB-277011 (20 mg/kg) did not. In previous studies, the cognitive impairment caused by the muscarinic antagonist scopolamine is reversed by the dopaminergic (DA) antagonist selective D1 antagonist SCH-23390 on radial arm maze performance (Levin and Rose, 1991; Levin, 1988; McGurk et al., 1989). These results show that ziprasidone and SCH23390 may be effective for the treatment of cognitive dysfunctions in schizophrenia.

Antipsychotic agents alter glutamatergic neurotransmission via the modulation of glutamate release or alterations in the density or subunit composition of glutamate receptors (Goff and Coyle, 2001). NMDA glutamate receptor inhibition leads to working memory impairment and a GABAergic deficit (Timofeeva and Levin, 2011). However, a decrease in nicotinic receptor activity can improve learning by attenuating learning impairment that are induced by NMDA glutamate blockade in cognitive tests that demonstrate that nicotinic antagonists can improve cognitive function (Burke et al., 2014). Animals treated with moderate doses of NMDA receptor antagonists, such as PCP, ketamine, or MK801, are used to model various aspects of schizophrenia (Rezvani et al., 2008; Timofeeva and Levin, 2008; Larrauri and Levin, 2012). The NMDA receptor antagonists phencyclidine and MK-801 impaired acquisition learning and reference memory in the MWM test (Wass et al., 2006). MK-801 decreased the time spent in the target quadrant, increased the mean distance traveled to the platform during the probe test and increased the swimming speed of mice in our study. The increase in swimming speed is the limitation of this study because it introduces a hyperactivity element to the Morris water maze task. An increase in swimming speed because of MK-801 was shown in previous studies (Marcos et al., 2008; Chen et al., 2010). Accordingly, our study suggests that ziprasidone and SCH-23390 improved MK-801-induced spatial memory deficits in mice, but SB-277011 had no effect.

In one study, it was determined that ziprasidone (0.1, 0.32 and 1.0 mg/kg, i.p.) had no effect on habituation that was shown in a previous study, but it dose-dependently attenuated MK-801-induced hyperactivity (Bradford et al., 2010). The selective dopamine D1 receptor antagonist SCH23390 (0.01, 0.032 and 0.1 mg/kg, s.c.) had no effect on habituation in this same study, but it dose-dependently attenuated MK-801-induced hyperactivity (Bradford et al., 2010). In our study, ziprasidone (0.5 and 1 mg/kg), SCH-23390 (0.05 and 0.1 mg/kg) and SB-277011 (10 and 20 mg/kg) had no effect on swimming speed in naïve mice. Again, ziprasidone (1 mg/kg) and SCH-23390 (0.1 mg/kg) significantly decreased swimming speed in MK-801-treated mice, but SB-277011 (20 mg/kg) had no effect on swimming speed in MK-801-treated mice, which is consistent with a previous study (Bradford et al., 2010).

In a previous study, the D1 antagonist SCH 23390 caused a modest though significant decrease in reference memory errors (Levin et al., 1996). Moreover, the selective dopamine D3 receptor antagonist SB-277011 (10, 30 and 45 mg/kg) had no effect on locomotor activity during habituation or following an MK-801 challenge (Bradford et al., 2010). Dopamine D2 receptors appear to play a key role in the hyperactivity induced by 0.32 mg/kg MK-801, but dopamine D3 and D4 receptors exhibited no role in previous studies (Bradford et al., 2010).

Additionally, in our study, we observed that SB-277011 had no effect on spatial memory and locomotion. Thus, hyperactivity induced by NMDA antagonists or psychostimulants does not appear to require dopamine D3 activity in rodents.

In conclusion, ziprasidone, SCH-23390 and SB-277011 had no effect on cognition in naïve animals in the MWM test. Ziprasidone and SCH-23390 reversed MK-801-induced impairments in learning and memory, but SB-277011 did not. Thus, ziprasidone and D1 antagonist SCH-23390 might be clinically useful for treatment of cognitive impairments in patients with schizophrenia; however, the D3 antagonist SB-277011 might not be useful.

4.1. Limitations

This manuscript has poor relevance for humans; it does not provide novel and/or potential insights into the neurobiology of schizophrenia nor does it provide the pharmacology of relevant drugs that could be used in the clinical setting. Further studies at the cellular and molecular levels are needed to support our results.

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