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Superior effects of quetiapine compared with aripiprazole and iloperidone on MK-801-induced olfactory memory impairment in female mice

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Abstract. Cognitive dysfunction is commonly observed in schizophrenic patients and the administration of antipsychotic treatments results in different outcomes. Although the typical antipsychotic treatments, such as haloperidol, appear to be unable to improve cognition dysfunction, the atypical antipsychotic drugs (quetiapine, aripiprazole and iloperidone) exert a beneficial effect. The purpose of the current study was to investigate the effects of atypical antipsychotics on olfactory memory in mice, utilizing the social transmission of food preference (STFP) tests to evaluate the effects of drugs on MK-801-induced cognitive dysfunction. Female BALB/c mice were treated with quetiapine (5 and 10 mg/kg), aripiprazole (3 and 6 mg/kg), iloperidone (0.5 and 1 mg/kg) or MK-801 (0.1 mg/kg) alone or concurrently prior to retention sessions of STFP tests. In the STFP tests, quetiapine (10 mg/kg; $P<0.05$), aripiprazole (3 and 6 mg/kg; $P<0.01$ and $P<0.001$, respectively), iloperidone (0.5 and 1 mg/kg; $P<0.01$ and $P<0.001$, respectively) and MK-801 ($P<0.001$) significantly decreased cued/total food eaten (%). Quetiapine (5 mg/kg; $P<0.05$) significantly increased MK-801-induced decreases in cued/total food eaten (%), while aripiprazole and iloperidone demonstrated no significant effects. The results revealed that all of the drugs disturbed olfactory memory in the naive mice; however, only quetiapine reversed MK-801-induced memory impairment in the STFP test.

Introduction

Cognitive impairment is the result of schizophrenia and influences the quality and function of life (1). Learning and attention are the most affected aspects of working memory disruptions. Furthermore, an impaired mental status renders self-care more difficult and results in increased frequency of hospitalization with significant costs to society (2).

One of the prevailing hypotheses is that cognitive impairments are caused by the hypofunction of the N-methyl-D-aspartate (NMDA) receptor (3). The antagonists of the NMDA receptor, such as ketamine, MK-801 and phencyclidine, provoke a schizophrenia-like syndrome in normal subjects, and positive, negative and cognitive symptoms may be observed (3). In addition, the NMDA receptor antagonists disrupt learning and cause memory impairments in animals that have similar psychosis conditions; therefore, these agents are used as a model to demonstrate cognitive dysfunctions (4,5).

Currently, various atypical antipsychotic drugs demonstrate improved efficacy when compared with classical antipsychotics to treat cognitive dysfunction. Recent clinical studies indicated that second generation atypical antipsychotic agents (clozapine, ziprasidone, quetiapine and olanzapine) improve cognitive impairment, whereas typical agents, such as haloperidol, exerted no effect (6,7). The cognitive tests of the atypical antipsychotics in preclinical studies demonstrate normal cognitive functions, which is in contrast to the classical antipsychotics. Previous studies reported the influences of the classical antipsychotics on cognitive functions, with controversial results (8-10).

The atypical antipsychotic drugs, quetiapine and aripiprazole are widely administered worldwide; however, iloperidone is a recently developed atypical antipsychotic drug that is only administered in the USA. The aim of the current study was to determine the effects of atypical antipsychotics, such as quetiapine, aripiprazole and iloperidone, on olfactory memory in naive and MK-801-treated mice using the social transmission of food preference (STFP) test.

Materials and methods

Animals. The main subjects of the experiments were 144 female, inbred BALB/cByJ mice (age, 7-8 week;

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Uludag University, Bursa, Turkey). They were housed with 8 mice per cage. The mice were maintained under standardized laboratory conditions (12-h light/dark cycle, lights on at 7:00 a.m.; temperature, 21±1˚C) with access to food and water *ad libitum*, for two weeks before commencing the tests. All procedures were conducted in accordance with the European Community Council's Directive for the ethical treatment of animals (Directive 86/609/EEC) and with approval from the Kocaeli University Medical Faculty (Kocaeli, Turkey; approval no. 4/3/2015).

Experimental groups and drug administration. Quetiapine was provided by Santa Farma Ilac (Istanbul, Turkey). Aripiprazole was purchased from Bal Pharma Ltd. (Bangalore, India) and iloperidone was purchased from AuSun Gaoba Pharmaceutical Co., Ltd. (Hebei, China). Quetiapine and aripiprazole were dissolved in saline plus 1% acetic acid. Iloperidone was dissolved in saline supplemented with 1% dimethyl sulfoxide. Quetiapine, aripiprazole and iloperidone were administered at a dose of 0.01 ml/g. Three control groups (n=8 per group) received the same volume of excipients. The animals were grouped randomly (n=8 per group) and treated intraperitoneally with the following: Quetiapine (5 and 10 mg/kg) for 60 min; aripiprazole (3 and 6 mg/kg) for 30 min; iloperidone (0.5 and 1 mg/kg) for 60 min or MK-801 (0.1 mg/kg) for 30 min alone or concurrently with quetiapine, aripiprazole and iloperidone, before the retention session of the STFP test. The effective doses of each drug were administered according to previous behavioral and neurochemical studies (11).

STFP test. The STFP test evaluates the hippocampus-dependent non-spatial olfactory memory (12). According to the test design, the scent of food, which was smelled on the muzzle of a demonstrator mouse 24 h before, is remembered by the observer mice with normal olfactory memory who will eat a greater proportion of the familiar cued food compared with a novel food.

The experiment was designed in three phases as follows: i) Flavored food habituation; ii) interaction between 'demonstrator' and 'observer' mice; and iii) test of the food preference in the 'observer' mice (12). Mice were kept at a ratio of 3-4 observer mice to 1 demonstrator mouse. In the habituation phase, a demonstrator mouse was selected from each cage. Demonstrators were housed alone in a separate cage for 3 h, with access to water *ad libitum*, but restricted food consumption. After 3 h of food restriction, the demonstrators were allowed to consume the ground chow scented with either cinnamon (1% w/w) or cocoa (2% w/w) flavored powder (12). Half of the demonstrators received cocoa-flavored food and the other half received cinnamon-flavored food. The demonstrators were allowed to eat the flavored food for 2 h. The pellets were weighed before and after being given to the demonstrators. The inclusion criterion was the consumption of at least 0.2 g. The demonstrators were housed with their observer mates for flavor interaction for 30 min (12). Subsequent to the interaction period, the demonstrator mouse was removed from the interaction cage and placed in its individual cage.

In the final phase of the experiment, the 24-h food preference of the observer mice was evaluated following the interaction with the demonstrator. Five hours prior to the test, the observer mice were caged individually with free access to water and a pair of food pellets. One pellet contained the flavor of food eaten by the demonstrator (cued) and the other contained the novel flavor (novel). Therefore, half of the observers were tested with the cinnamon-flavored cued food eaten by their demonstrator versus the novel cocoa-flavored food; the other half of the observers were tested with the cocoa flavored cued food eaten by their demonstrator vs. the novel cinnamon-flavored food (12). After 2 h, all of the food pellets were removed and weighed to quantify the food consumption of the observer mice at 3 h prior to the preference test. The weight ratio of the eaten cued food and the total eaten food were determined as a measure of food preference (12).

Statistical analysis. IBM SPSS Statistics 22.0 (IBM SPSS, Armonk, NY, USA) was used for statistical analysis. A two-way variance analysis and post hoc Tukey test were used to analyze the cued food/total food eaten percentage during the STFP test. The associated data are expressed as the mean values ± standard error of the mean and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Effects of quetiapine on olfactory memory in naive and MK-801-treated mice during the STFP test. When quetiapine (5 and 10 mg/kg) and MK-801 (0.1 mg/kg) were administered alone or concurrently before the retention session of the STFP test, the percentage of cued food/total food eaten was significantly different [$F(5,42)=7.53$; $P<0.0001$; Fig. 1]. Treatment with quetiapine (10 mg/kg; $P<0.05$) and MK-801 ($P<0.001$) significantly decreased the percentage of cued food/total food eaten when compared with the control group (Fig. 1). Treatment with quetiapine (5 mg/kg; $P<0.05$) significantly increased the percentage of cued food/total food eaten when compared with the MK-801 alone group; however, quetiapine (10 mg/kg) treatment resulted in no significant effect (Fig. 1).

Effects of aripiprazole on olfactory memory in naive and MK-801-treated mice during the STFP test. When aripiprazole (3 and 6 mg/kg) and MK-801 (0.1 mg/kg) were administered alone or concurrently before the retention session of the STFP test, a significant difference was observed among the groups for the percentage of cued food/total food eaten [$F(5,42)=8.61$; $P<0.0001$; Fig. 2]. Aripiprazole (3 and 6 mg/kg; $P<0.01$ and $P<0.001$, respectively) and MK-801 ($P<0.001$) treatment significantly decreased the percentage of cued food/total food eaten compared with the control group (Fig. 2). Aripiprazole (3 and 6 mg/kg) treatment partially increased the percentage of cued food/total food eaten compared with the MK-801 alone group, although the effect was not significant (Fig. 2).

Effects of iloperidone on olfactory memory in naive and MK-801-treated mice during the STFP test. When iloperidone (0.5 and 1 mg/kg) and MK-801 (0.1 mg/kg) were administered alone or concurrently before the retention session of the STFP test, a significant difference among groups for the percentage of cued food/total food eaten was demonstrated [$F(5,42)=11.31$; $P<0.0001$; Fig. 3]. Treatment with iloperidone

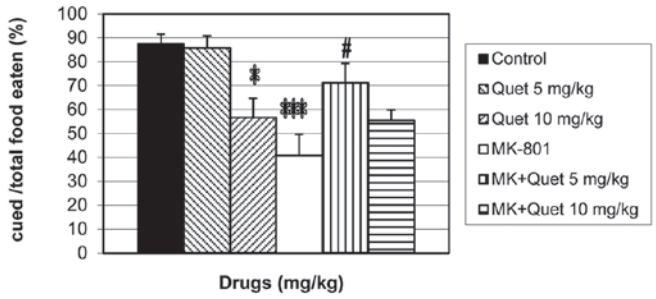

Figure 1. Effect of quetiapine (5 and 10 mg/kg) and MK-801 (0.1 mg/kg; n=8 per group) administered alone or concurrently on the percentage of cued/total food eaten (in which quetiapine and MK-801 were administered for 60 and 30 min, respectively, prior to the retention trial) in the social transmission of food preference test in mice. The data are expressed as the mean ± standard error of the mean. *P<0.05 and ***P<0.001 vs. control group, #P<0.05 vs. MK-801 alone group. Quet, quetiapine; MK, MK-801.

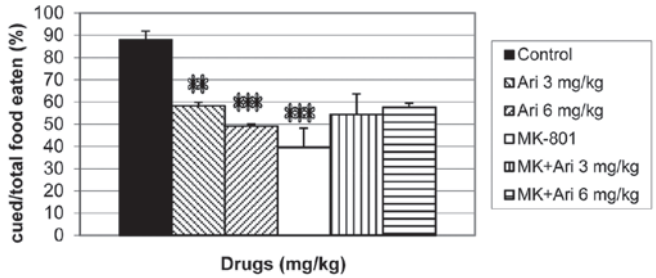

Figure 2. Effect of aripiprazole (3 and 6 mg/kg) and MK-801 (0.1 mg/kg; n=8 per group) administered alone or concurrently on the percentage of cued/total food eaten (in which aripiprazole and MK-801 were administered 30 min prior to the retention trial) in the social transmission of food preference test in mice. The data are expressed as the mean ± standard error of the mean. **P<0.01 and ***P<0.001 vs. control group. Ari, aripiprazole; MK, MK-801.

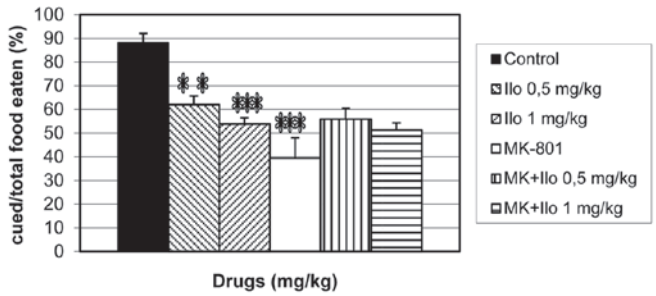

Figure 3. Effect of iloperidone (0.5 and 1 mg/kg) and MK-801 (0.1 mg/kg; n=8 per group) administered alone or concurrently on the percentage of cued/total food eaten (in which iloperidone and MK-801 was administered 60 and 30 min, respectively, prior to the retention trial) in the social transmission of food preference test in mice. The data are expressed as the mean ± standard error of the mean. **P<0.01 and ***P<0.001 vs. control group. Ilo, iloperidone; MK, MK-801.

(0.5 and 1 mg/kg; P<0.01 and P<0.001, respectively) and MK-801 (P<0.001) significantly decreased the percentage of cued food/total food eaten when compared with the control group (Fig. 3). Iloperidone (0.5 and 1 mg/kg) treatment partially increased the percentage of cued food/total food eaten compared with the MK-801 alone group although the effect was not significant (Fig. 3).

Discussion

In the current study, treatment with quetiapine (10 mg/kg), aripiprazole (3 and 6 mg/kg), iloperidone (0.5 and 1 mg/kg) and MK-801 (0.1 mg/kg) decreased the percentage of cued/total food eaten during the STFP test. Quetiapine (5 mg/kg) significantly increased the MK-801-induced decreases in the percentage of cued/total food eaten; however, aripiprazole and iloperidone treatment exerted no significant effects.

The effects of antipsychotics on learning and memory remain controversial. Although haloperidol and risperidone are strongly associated with cognition impairment from the effective dosage that is required to treat psychosis, clozapine and sertindole efficiently treat psychosis without negative effects on cognition (6,9,10). Skarsfeldt (10) reported the impaired performance of rats in a water maze associated with haloperidol usage (10) and in a delayed non-matching to position test (8). According to previous studies, atypical antipsychotics offered greater efficacy for improving cognitive function when compared with typical antipsychotics; however, certain studies reported controversial effects from associated drugs (13-15). For example, administration of atypical antipsychotics, such as clozapine and olanzapine, more effectively attenuates the cognitive deficits in schizophrenic patients when compared with haloperidol administration (16). In the present study, the atypical antipsychotic drug quetiapine improved MK-801-induced olfactory memory impairment; however, aripiprazole and iloperidone administration exerted no effects.

Quetiapine is a dopamine, serotonin and adrenergic antagonist, and is a potent antihistamine with clinically negligible anticholinergic properties. Aripiprazole is an atypical antipsychotic with a novel pharmacological profile that acts as a partial agonist of dopamine D_2 and D_3 and serotonin (5-HT) 5-HT_{1A} receptors, and as an antagonist for 5-HT_{2A} receptors (17,18). Aripiprazole has moderate affinity for histamine, α-adrenergic, and D_4 receptors, as well as the serotonin transporter; however, it has no appreciable affinity for cholinergic muscarinic receptors (17,18). Iloperidone is an antagonist of serotonin, D_2, D_3, D_4, 5-HT_6, and noradrenaline α1 receptors and has low affinity for the serotonin 5-HT_{1A}, dopamine D_1 and histamine H1 receptors. The effects of quetiapine, aripiprazole and iloperidone that are associated with these receptors modify the positive and negative symptoms of schizophrenia.

Antipsychotic drugs that target the D_2 receptors may treat the positive symptoms of schizophrenia while modification on non-D_2 receptors (D_1, D_3 and D_4), serotonin receptors (5-HT_{2A}, 5-HT_{1A}, 5-HT_3, 5-HT_6 and 5-HT_7) and α-adrenergic receptors affect the negative symptoms of schizophrenia (19,20). The impact on particular receptors is important for the reversal of MK-801-induced cognitive impairment by quetiapine.

The 5-HT_{2A} receptor regulates mesocortical dopamine projections. The atypical antipsychotic drugs diminish the cognitive impairments in schizophrenic patients. The underlying mechanism is the blockage of 5-HT_{2A} receptors within the prefrontal cortex and enhancement of dopamine transmission. The success on controlling the negative symptoms of schizophrenia is correlated with the enhanced affinity on 5-HT_{2A}/dopamine D_2 receptors; therefore, the reported interaction may be valuable for relieving cognitive deficits (21).

Different NMDA receptor antagonist-induced experimental models have been investigated to demonstrate the cognitive impairments, and selective ligands for serotonin and adrenoceptors have been examined in these models (22,23). In addition, post-training administration of the specific 5-HT7 receptor antagonists, SB-269970 and DR-4004, improved MK-801-induced memory impairments in rat auto-shaping tasks (22). Quetiapine reversed MK-801-induced deficits in the current study and this may be linked via the interactions between serotonin receptors and adrenoceptors.

The antihistaminic and anticholinergic effects of drugs also result in changes in cognitive performance. Increased histamine occupancy on the receptors may disturb cognitive performance. The olfactory memory disturbing effects of quetiapine, aripiprazole and iloperidone in naive mice may be associated with their antihistaminergic and anticholinergic activities. The present study identified the beneficial effects of quetiapine administration at a low dose (5 mg/kg); however, this activity disappeared at a high dose (10 mg/kg). This may be due to certain non-specific effects of quetiapine on motor activity and total food consumption at the high dose.

In conclusion, quetiapine, aripiprazole and iloperidone disturbed olfactory memory in naive mice; however, only quetiapine reversed MK-801-induced memory impairment during the STFP test. This study demonstrates the superior effect of quetiapine administration, compared with aripiprazole and iloperidone, for cognitive dysfunctions of schizophrenic patients. The superior effects of quetiapine compared with aripiprazole and iloperidone in the present study may be associated with the different features of olfactory memory, drug doses, administration time, strain and gender differences of the animals used in the current study. Further studies with different doses and learning tasks are required to determine the underlying mechanisms of these drugs.

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