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Short communication

The effect of combined treatment with escitalopram and risperidone on the MK-801-induced changes in the object recognition test in mice

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ABSTRACT

Background: Atypical antipsychotic drugs have some efficacy in alleviating the negative and some cognitive symptoms of schizophrenia but those effects are small and mechanisms of this action are still unknown. A few clinical reports have suggested that the antidepressant drugs, especially selective serotonin reuptake inhibitors (SSRI) are able to augment the activity of atypical antipsychotic drugs, thus effectively improving treatment of the negative and some cognitive symptoms of schizophrenia.
Methods: In the present study, we evaluated the effect of escitalopram (SSRI) and risperidone (an atypical antipsychotic drug), given separately or jointly, on the effect of MK-801 (a NMDA receptor antagonist) given before to the first introductory session, in the object recognition memory test. The mice were tested for the ability to discriminate between an old, familiar and a novel object. Escitalopram and risperidone were given 30 min before MK-801, and MK-801 was administered 30 min before the first introductory session. Memory retention was evaluated 90 min after the introductory session.
Results: The obtained results showed that MK-801 (0.2 mg/kg) decreased memory retention when given before the introductory session. Risperidone at a higher dose (0.1 mg/kg) reversed that effect. Co-treatment with an ineffective dose of risperidone (0.01 mg/kg) and escitalopram (5 or 10 mg/kg) abolished the deficit of object recognition memory induced by MK-801.
Conclusions: The obtained results suggest that escitalopram may enhance the antipsychotic-like effect of risperidone in the animal tests used for evaluation of some cognitive symptoms of schizophrenia.

Introduction

In recent years, some clinical and preclinical studies have suggested that atypical antipsychotic drugs alleviate not only positive but also negative symptoms of schizophrenia and also bring improvement in signs cognitive dysfunction (*e.g.* impaired attention and information processing, verbal and visual learning and working memory) [1,2]. Although the currently available atypical antipsychotics have some efficacy in alleviating cognitive dysfunction, this effect is small and mechanism of this action is still unknown. A few clinical reports have suggested that the antidepressant drugs, especially selective serotonin reuptake inhibitors (SSRI) are able to augment the activity of atypical antipsychotic drugs, thus effectively improving treatment of the negative and some cognitive symptoms of schizophrenic patients [3,4].

It is known that risperidone at low doses blocks serotonin 5-HT_{2A} receptors while at higher doses inhibits dopamine D_2 receptors, and produces minimal extrapyramidal side-effects compared to classic antipsychotics [5]. Moreover, escitalopram (ESC), a selective serotonin reuptake inhibitor, enhances serotonergic neurotransmission, but did not block dopaminergic and noradrenergic receptors, that might be involved in the psychophysiological parameters of attention [6,7].

In the last years, the involvement of *N*-methyl-D-aspartate (NMDA) receptors in memory and learning processes, especially in the encoding stage has been intensely investigated. For example, MK-801 (a NMDA receptor antagonist) has been studied in a number of memory tests but it is still unknown whether it affects the whole strategy of memory formation [8].

The novel object recognition in rodents is analogous in some ways to human declarative (episodic) memory, one of a few cognitive domains which are abnormal in schizophrenic patients [9]. In this test, the animal (rat or mouse) is tested for its ability to discriminate an old, familiar, and a novel object in two sessions (introductory and recognition). It is known that an animal spends more time on exploration of a novel object in the recognition

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session than on examination of the object presented in the introductory session. All the earlier studies on the object recognition memory indicate a decreased memory retention when MK-801 is administered before the first, introductory session [10–13].

Thus, in the present study we investigated the effect of the antidepressant ESC and an atypical antipsychotic risperidone, given separately or jointly, on the effect of MK-801, given before the first introductory session, in the object recognition test in mice, in which animals were tested for their ability to discriminate between an old, familiar and a novel object. The effect of co-treatment with ESC and risperidone on the MK-801-induced changes in the object recognition memory in mice had not been studied before.

Materials and methods

Animals

The experiments were carried out on male Albino-Swiss mice (24 ± 2 g) (Charles River Laboratories, Sulzfeld, Germany). The animals were housed 10 per cage (57 cm × 35 cm × 20 cm) in a colony room kept at 21 ± 1 °C with a 40–50% humidity, on a 12-h light-dark cycle (the light on at 7 a.m.). The mice had free access to food and water before the experiments. Each experimental group consisted of 10–12 animals/dose. All the experiments were conduced during the light phase and were carried out according to the procedures approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences in Kraków.

Drugs administration

Escitalopram oxalate (ESC) and (+)-MK-801 maleate (MK-801, Tocris Bioscience, Bristol, UK) were dissolved in a 0.9% NaCl while risperidone (Tocris Bioscience, Bristol, UK) was dissolved in 0.1 M tartaric acid and the solution was adjusted to pH 6–7 with 0.1 N NaOH. All the drugs were given intraperitoneally (*ip*) in a volume of 10 ml/kg. ESC (2.5, 5 or 10 mg/kg) and risperidone (0.01 mg/kg) were given 30 min before MK-801, and MK-801 (0.2 mg/kg) was administered 30 min before the first introductory session.

The object recognition test

On the day of the experiment the mice were transferred to the laboratory, labeled and weighed, and, thereafter, left to acclimate to the new environment for approximately 2 h before the testing started. In the first, *i.e.* introductory session each mouse was placed in a white plastic box (57 cm × 35 cm × 20 cm). Objects to discriminate were: a black metal box (4 cm × 6 cm) and a green glass cone (4 cm × 6 cm). Objects were placed in two opposite corners with the center of the object 24 cm from the corner. A mouse was placed in the middle of the arena and presented with two identical object, A1 and A2, during 5 min (half of the animals were presented two black metal boxes and the other half two green glass cones). After a 90 min delay in the home cage, the mice were again placed in the same plastic box as earlier and presented with two objects, the old familiar A1, and a new object B during 5 min (recognition session). Object A2 was always the one that was replaced. Object exploration was defined as mice sniffing or touching the object with its nose and/or forepaws. The objects were cleaned with 10% ethanol between each mouse and session. Each group consisted of 12 mice.

Locomotor activity

The locomotor activity of mice was measured individually for each animal in OPTO-M3 locomotor activity cages (Columbus Instruments, Columbus, OH, USA) linked on-line to a compatible PC. Each cage (13 cm × 23 cm × 15 cm) was surrounded with an array of photocell beams. Interruptions of these photobeams resulted in a horizontal activity defined as ambulation scores. Locomotor activity was measured for 5 min (like in the object recognition test) starting 30 min after treatment with MK-801 (0.2 mg/kg) and 90 min later. Each group consisted of 10 mice.

Statistical analysis

The data were evaluated by a one-way analysis of variance (ANOVA) followed by individual comparisons using Dunnett's test. The discrimination index was calculated for each mouse [(time spent exploring the novel object – time spent exploring the familiar object)/(total time spent exploring both the object during the recognition session). The recognition index was expressed in percentages.

Results and discussion

In the present study we evaluated the effect of the antidepressant ESC and an atypical antipsychotic risperidone, given separately or jointly, on the effect of MK-801, given before the first introductory session, in the object recognition test in mice, in which animals were tested for their ability to discriminate between an old, familiar and a novel object.

Our data showed that during the introductory session mice receiving MK-801 (0.2 mg/kg) or saline 30 min before the test, spent alike time on exploring the two similar objects (Fig. 1A), which indicated that there was no preference for a certain position of the objects in the area. During the recognition session (Fig. 1B) control mice spent significantly more time exploring the novel object [$F(1,22) = 72.10$; $p < 0.001$], while mice receiving MK-801 at a dose of 0.2 mg/kg showed no preference for a particular object [$F(1,22) = 0.15$; *ns*]. During the introductory session mice receiving MK-801 at a dose of 0.2 mg/kg spent less total time by *ca.* 42.8 and 33.1% on exploring both objects (A1 + A2) compared with control group, respectively, while during the recognition session, there was no difference between the groups in the total object exploration time (Table 1A and B).

Our early data showed that in the locomotor activity test, where MK-801 (0.1 and 0.2 mg/kg) was given 30 min before the test (like in the object recognition test), the dose of 0.2 mg/kg only (but not 0.1 mg/kg) increased the total locomotor activity of mice. Moreover, in these mice 90 min later, MK-801 in both studied groups increased locomotor activity, what suggested that the impaired recognition at the higher dose of MK-801 was not connected with increased locomotor activity [13].

The above data are also in line with the previous studies which suggested that MK-801 decreased memory retention when given before the introductory session [10,11]. Moreover, another study demonstrated that MK-801 administered at both times, *i.e.* directly after the introductory session or before the recognition session, increased the exploration time of a novel object but did not decrease memory retention, what suggested that the activation of NMDA receptors was necessary for encoding of recognition memory in animals but not for consolidation and retrieval processes [14].

The present results also showed that risperidone at a higher dose (0.1 mg/kg) abolished the decrease in memory retention of the object recognition evoked by MK-801 (0.2 mg/kg) ($F(1,22) = 65.37$; $p < 0.01$, B group *vs.* A group, Fig. 1B), but it did not change the time spent on exploring the two similar object in the introductory session (Fig. 1A), while, the total time spent on the exploring two objects in both sessions was decreased, compared with control group (Table 1A). Moreover, risperidone at a lower dose (0.01 mg/kg) or ESC (2.5, 5 and 10 mg/kg) given alone did not change the effect of MK-801 (0.2 mg/kg) on the object recognition memory, while

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