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Short communication

The effect of combined treatment with risperidone and antidepressants on the MK-801-induced deficits in the social interaction test in rats

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ABSTRACT

Background: Several clinical reports have suggested that augmentation of atypical antipsychotics' activity by antidepressants may efficiently improve the treatment of negative and some cognitive symptoms of schizophrenia.
Methods: The aim of the present study was to investigate the effect of antidepressant mirtazapine or escitalopram and risperidone (an atypical antipsychotic), given separately or jointly, on the MK-801-induced deficits in the social interaction test in rats. Antidepressants and risperidone were given 60 and 30 min before the test, respectively. The social interaction of male Wistar rats was measured for 10 min, starting 4 h after MK-801 (0.1 mg/kg) administration.
Results: In the social interaction test, MK-801-induced deficits in the parameters studied, i.e. the number of episodes and the time of interactions. 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 mirtazapine (2.5 or 5 mg/kg) or escitalopram only at a dose of 5 mg/kg (but not 2.5 and 10 mg/kg) abolished the deficits evoked by MK-801.
Conclusion: The obtained results suggest that especially mirtazapine, and to a smaller degree escitalopram may enhance the antipsychotic-like effect of risperidone in the animal test modeling some negative symptoms of schizophrenia.

Introduction

Schizophrenia is a devastating psychiatric disorder that impairs mental and social functioning and affects approximately 1% of the world's population. The typical symptoms of schizophrenia can be divided into: positive (e.g. hallucinations, delusions), negative (e.g. deficits in social interaction, emotional expression and motivation), and also cognitive dysfunction (e.g. impaired attention and information processing, verbal and visual learning, memory and working memory) [1–3]. Although schizophrenia has been long known as a serious disease, its etiology and pathophysiology are still unknown. It is known that in contrast to pharmacotherapy with typical antipsychotics, the atypical antipsychotic agents alleviate not only the positive symptoms of schizophrenia but also the negative ones. Moreover, the role of antidepressant drugs as an adjunct in therapy of schizophrenic patients with negative symptoms has been described in several studies [4,5].

Atypical antipsychotic agents, e.g. risperidone (RIS), which target the serotonin (5-HT) signaling pathway in addition to the dopamine system, alleviate not only the positive symptoms of schizophrenia but also the negative ones; furthermore, they bring considerable benefits compared to the conventional antipsychotic drugs [6,7]. RIS at low doses blocks mainly serotonin 5-HT_{2A} receptors while at higher doses inhibits dopamine D_2 receptors, in addition, it is known to produce minimal extrapyramidal side-effects compared to classic antipsychotics [8,9]. Moreover, mirtazapine (MIR), enhances noradrenergic and 5-HT_{1A}-mediated serotonergic neurotransmission *via* antagonizing central α_2-auto- and hetero-adrenoreceptors. It also blocks 5-HT_2 and 5-HT_3 receptors and displays very low affinity for dopaminergic and high affinity for histamine H_1 receptors [10]. Escitalopram (ESC), a selective serotonin reuptake inhibitor, enhances serotonergic neurotransmission. Although the atypical antipsychotic drugs have some efficacy in alleviating social dysfunction [11] this effect

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are small and mechanisms of this action are still unknown. Several clinical reports have suggested that the MIR-induced augmentation of RIS activity may efficiently improve the treatment of negative and some cognitive symptoms of schizophrenia [12,13]. It was also recently shown that ESC enhanced the antipsychotic-like effect of a low dose of RIS in the conditional avoidance response test in rats, this test is used to evaluate negative symptoms of schizophrenia in animals [14].

To understand the mechanism of the clinical efficacy of a combination of an antidepressant and RIS in the therapy of schizophrenia, the present study was undertaken to examine the effect of the antidepressant MIR or ESC and the atypical antipsychotic RIS, given separately or jointly, on the NMDA receptor antagonist, MK-801-induced deficits in the social interaction test in rats, i.e. an animal test modeling some negative symptoms of schizophrenia. The effect of co-treatment with MIR or ESC and RIS on the MK-801-induced deficits in the social interaction in rats had not been studied before.

Materials and methods

Animals

The experiments were carried out on male Wistar rats (185–200 g) derived from Charles River Laboratories, Sulzfeld (Germany). The animals were housed 6 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 rats had free access to food and water before the experiments. Each experimental group consisted of 12 animals/dose. All the experiments were conducted 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, Sigma–Aldrich, Saint Louis, USA) and (+)-MK-801 maleate (MK-801, Tocris Bioscience, Bristol, UK) were dissolved in a 0.9% NaCl or risperidone (RIS) and mirtazapine (MIR, Tocris Bioscience, Bristol, UK) were dissolved in 0.1 M tartaric acid and the solution was adjusted to pH 6–7 with 0.1 N NaOH. Antidepressants and RIS were given intraperitoneally (*ip*) and MK-801 subcutaneously (*sc*) in a volume of 2 ml/kg.

MK-801-induced deficits in social interaction in rats

The social interaction test was performed using a black PCV box (67 cm × 57 cm × 30 cm, length × width × height) divided into six symmetrical sectors. The arena was dimly illuminated with an indirect light of 18 lux. Each social interaction experiment involving two rats was carried out during the light phase of the light/dark cycle. The rats were selected from separate housing cages to make a pair for the study. The paired rats were matched for body weight within 15 g. The social interaction was measured 4 h after the subcutaneous (*sc*) administration of MK-801 at a dose of 0.1 mg/kg, and 60 or 30 min after administration of MIR (2.5 and 5 mg/kg, *ip*) or ESC (2.5, 5 and 10 mg/kg, *ip*) and RIS (0.01 mg/kg, *ip*), respectively. Each pair of rats was diagonally placed in opposite corners of the box facing away from each other. The behavior of the animals was measured over a 10-min period. The test box was wiped clean between each trial. Social interaction between two rats was expressed as the total time spent in social behavior, like such as sniffing, genital investigation, chasing and fighting with each other. The number of episodes was counted as a separate paradigm. Moreover, the number of sector line crossings (ambulation) was also determined as a measure of locomotor activity of those rats. Each group consisted of 12 animals (six pairs).

Statistical analysis

The data were evaluated by an analysis of variance (ANOVA) followed by individual comparisons using Dunnett's test.

Results and discussion

The glutamatergic therapy of psychosis was based on the behavioral results indicating psychomimetic properties of NMDA receptor antagonists (e.g. phencyclidine, ketamine or MK-801), which induced positive, negative, and cognitive abnormalities in animals, similar to those observed in patients with psychosis [15].

The present results showed that in the social interaction test in rats, MK-801 (0.1 mg/kg) evoked deficits in the parameters studied (decreased the number of episodes and the time of interactions by c.a. 50%). Moreover, RIS at a higher dose (0.1 mg/kg) reversed that effect of MK-801, although, at a lower dose (0.01 mg/kg) it did not change those deficits [$F(3,20) = 24.37$; $p < 0.001$ and $F(3,20) = 138.46$; $p < 0.001$], respectively (Fig. 1). In addition, co-treatment with an

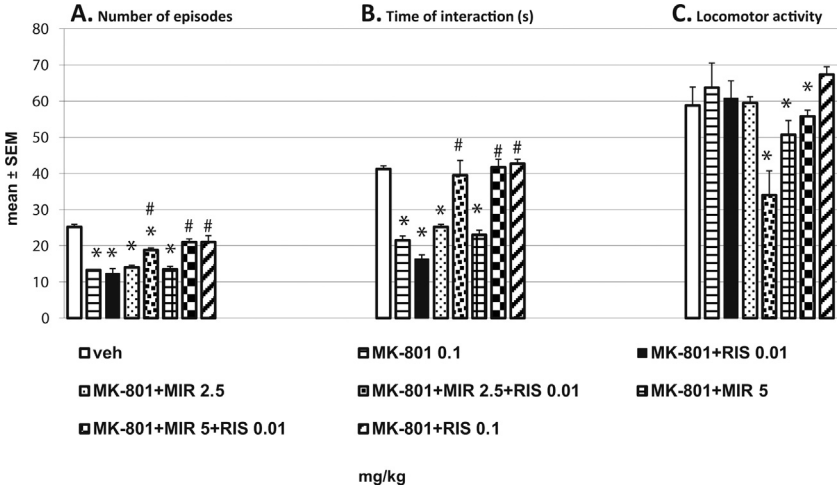

Fig. 1. The effect of mirtazapine (MIR, 2.5 and 5 mg/kg, *ip*) given alone or in combination with risperidone (RIS, 0.01 mg/kg, *ip*) on the MK-801-induced deficits in the social interaction test: (A) the number of social episodes, (B) the total duration of episodes (s), (C) the locomotor activity. MIR was given 60 and RIS 30 min before the test. The social interaction was measured 4 h after the MK-801 (0.1 mg/kg, *sc*) administration. Data are presented as the mean ± SEM of 6 pairs/group. The data were statistically evaluated by ANOVA, followed by individual comparisons using Dunnett's test. $^{*}p < 0.001$ *vs.* control group: $^{\#}p < 0.001$ *vs.* MK-801 and MK-801 + MIR or MK-801 + RIS group.