Available online at www.sciencedirect.com
ScienceDirect
Behavioural Brain Research 186 (2008) 197–207
BEHAVIOURAL BRAIN RESEARCH
www.elsevier.com/locate/bbr

Research report

Lurasidone reverses MK-801-induced impairment of learning and memory in the Morris water maze and radial-arm maze tests in rats

Takeshi Enomoto *, Tadashi Ishibashi, Kumiko Tokuda, Takeo Ishiyama, Satoko Toma, Akira Ito

Discovery Pharmacology II, Pharmacology Research Laboratories, Dainippon Sumitomo Pharma Co., Ltd., 3-1-98, Kasugade Naka, Konohana-ku, Osaka 554-0022, Japan

Received 11 May 2007; received in revised form 8 August 2007; accepted 10 August 2007
Available online 19 August 2007

Abstract

We have previously shown that lurasidone, a novel atypical antipsychotic, potently reverses learning impairment induced by the *N*-methyl-D-aspartate receptor antagonist MK-801 in the rat passive avoidance test. However, the effects of lurasidone in other learning and memory tasks remain to be investigated. We investigated the effects of lurasidone and other marketed antipsychotics (risperidone, clozapine, aripiprazole, and haloperidol) on MK-801-induced impairment of learning and memory in the Morris water maze (MWM) and radial-arm maze (RAM) tests in rats. Learning and memory impairment in the MWM test, as measured by escape latency, escape distance, and diving behavior, and in the RAM test, as measured by reference and working memory errors, was induced by MK-801 (i.p.) at doses of 0.15 and 0.2 mg/kg, respectively. In the MWM test, lurasidone (1 and 3 mg/kg p.o.) potently reversed MK-801-induced learning impairment. In the RAM test, lurasidone (1 and 3 mg/kg p.o.) potently reversed MK-801-induced reference memory impairment and moderately but not significantly attenuated MK-801-induced working memory impairment. Risperidone (0.3 and 1 mg/kg p.o.), clozapine (3 and 10 mg/kg p.o.), aripiprazole (0.3 and 1 mg/kg p.o.), and haloperidol (0.3 and 1 mg/kg p.o.) did not reverse MK-801-induced impairment of learning and memory in both tasks. Lurasidone, but not the other antipsychotics tested in this study, reverses MK-801-induced impairment of learning and memory in both the MWM test and the RAM test. These results suggest that lurasidone would be more effective in treating schizophrenics with cognitive dysfunction than current antipsychotics.

Keywords: Antipsychotics; Learning and memory; Morris water maze; NMDA receptor antagonist; Radial-arm maze; Schizophrenia

1. Introduction

Schizophrenic patients suffer from widespread impairment in cognitive function, which is closely related to functional outcomes [11,33]. While typical antipsychotics lack the ability to improve cognitive dysfunction in schizophrenics, atypical antipsychotics have some beneficial effects on cognitive dysfunction in schizophrenia [18,36]. However, the efficacy of current atypical antipsychotics is still limited and in most cases is insufficient to return patients to normal condition [36].

In humans, non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine and ketamine, induce schizophrenia-like symptoms including positive, negative, and cognitive symptoms [14]. It has been hypothesized that insufficient glutamate neurotransmission is involved in the neuropathophysiology of schizophrenia [6]. Therefore, NMDA receptor antagonist-treated animals have been used as models for schizophrenia [8,10,21,22,29].

Lurasidone is a novel atypical antipsychotic drug that has moderate to potent binding affinity for dopamine D_2, serotonin 5-HT_{1A}, 5-HT_{2A}, 5-HT_7, and adrenaline α_{2C} receptors, but has very low binding affinity for acetylcholine muscarinic M_1 and histamine H_1 receptors [12]. Lurasidone has very low potential for inducing extrapyramidal side effects, despite its potent antipsychotic effects in rats and mice [28]. Consistent with preclinical findings, clinical studies have shown that lurasidone is effective in the treatment of schizophrenia with a favorable safety profile [23].

We have previously shown that lurasidone potently reverses learning impairment induced by the NMDA receptor antagonist

* Corresponding author. Tel.: +81 6 6466 5207; fax: +81 6 6466 5182.
E-mail address: takeshi-enomoto@ds-pharma.co.jp (T. Enomoto).

0166-4328/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2007.08.012

MK-801 in the passive avoidance test in rats [13]. However, the effects of lurasidone in other learning and memory tasks remain to be investigated. In this study we examined the effects of lurasidone and other marketed antipsychotics (risperidone, clozapine, aripiprazole, and haloperidol) on MK-801-induced impairment of learning and memory in the Morris water maze (MWM) and radial-arm maze (RAM) tests in rats.

2. Materials and methods

2.1. Animals

Male Wistar rats aged 7 weeks were obtained from Japan SLC (Shizuoka, Japan). They were quarantined and acclimatized for 1 week before use. The rats were housed in a controlled environment (23 ± 2 °C, 55 ± 10% humidity) with a 12-h light:12-h dark cycle (light on at 8:00 a.m.). Animals were allowed free access to food (CE-2, CLEA Japan) and filtered water, except for rats used in the RAM test, which were kept on a restricted diet in order to maintain a body weight 80–90% of the animals' free-feeding weight. All procedures for the use of animals were reviewed and approved by the Institutional Animal Care and Use Committee at Dainippon Sumitomo Pharma Co., Ltd., Research Division.

2.2. MWM test

The water maze was a round pool of 150 cm in diameter with 45 cm high walls (Neuroscience, Osaka, Japan) surrounded by several extra-maze cues. The extra-maze cues were kept constant throughout the testing period. The tank was filled to a height of 27 cm with tap water of approximately 22 °C. The transparent escape platform (12 cm in diameter) was placed 1 cm below the surface of water in the middle of one of the quadrants. The position of the platform was not changed throughout the experiment.

The MWM test was performed as previously described with a minor modification [15]. Rats were trained four trials per day for 5 days. Each antipsychotic (p.o.) or vehicle was daily administered 60 min before the first trial of the day. MK-801 (0.15 mg/kg i.p.) or saline was daily administered 30 min before the first trial of the day. In each trial, rats were put into the water, facing the pool wall at one of the three starting positions, and then released. If a rat failed to find the platform within 60 s, the rat was manually guided to the platform by the experimenter. Rats were allowed to rest on the platform for 30 s after each trial (inter-trial time). The behavior of rats was recorded with a digital TV system and analyzed using Ethovision video tracking system (Noldus, Wageningen, The Netherlands). For each trial, we measured the rats escape latency, swimming distance, and swimming speed to reach the platform. To assess the effect of compounds on the diving behavior (animal starts to swim away from the platform during the inter-trial time), both the frequency of diving behavior (FDB) and cumulative frequency of diving behavior (cFDB) were calculated. The FDB of the treatment group was calculated as follows: the total number of diving behavior incidence observed during four trials of the day were divided by the total number of animals of the day (i.e. number of animals per group multiplied by four which is the number of trials per day). The cFDB of the treatment group is calculated as follows: the total number of diving behavior incidence observed during the 5 days were divided by the total number of animals (i.e. total number of animals of the day described above multiplied by five).

2.3. RAM test

The RAM consisted of eight arms (48 cm × 12 cm) radiating from a central area (32 cm in a diameter). Training for the reference and working memory task was performed as previously described with a minor modification [9]. A food cup was attached to the end of each radiating arm. Before the actual training, rats were shaped to run to the ends of the radiating arms. The baits were initially available throughout the maze, but were gradually restricted to the food cups (shaping period). Following this shaping period, rats were trained by performing either four or eight trials per day. Four identical arms of the maze were baited with a single 45-mg food pellet, while the remaining four arms were left unbaited. Each trial continued until all four baits had been consumed or until 5 min had elapsed. The number of reference memory errors (entering an arm that was not baited), number of working memory errors (re-entering a bait-containing arm where the bait had been consumed or an arm not baited), number of eating failures (entering an arm containing a bait and leaving the arm without consuming the bait), and latency per arm entry were recorded.

In a pilot RAM test, rats showed relatively high response to MK-801 on the first administration. Therefore, in this study, rats received a single injection of MK-801 (0.2 mg/kg, i.p.) followed by a test before evaluating the effects of antipsychotics to exclude any artificial effect caused by higher response of rats to MK-801 first administration. The effects of antipsychotics were evaluated using rats that satisfied the following criteria: working memory errors being zero and reference memory errors being less than one in all four trials 1 day before the tests. Each antipsychotic or vehicle was orally administered 60 min before the tests, while MK-801 (0.2 mg/kg i.p.) or saline was administered 30 min before the tests. Rats performed only one drug test per day. When rats were unable to accomplish four correct choices within 5 min, they were excluded from further analysis. Drug tests were performed with an interval of at least 3 days. The doses of each antipsychotic were administered in a semi-random order. Each rat received only one kind of antipsychotic and performed no more than four tests.

2.4. Drug treatment

Lurasidone and risperidone were synthesized in Dainippon Sumitomo Pharma Co., Ltd. Aripiprazole was extracted and purified from Abilify (Bristol-Myers Squibb, NY, USA). Haloperidol and (+)-MK-801 hydrogen maleate were purchased from Sigma–Aldrich (St. Louis, Mo, USA). All antipsychotics were suspended in 0.5% methylcellulose. Based on a preliminary dose–response study of MK-801, we selected 0.15 mg/kg i.p. for the MWM test and 0.2 mg/kg i.p. for the RAM test. We chose the doses of 1 and 3 mg/kg p.o. for lurasidone, and 0.3 and 1 mg/kg p.o. for risperidone and clozapine. These doses were selected based on the results of a previous study where the three antipsychotics, at the selected doses, produced no learning impairment *per se* but ameliorated MK-801-induced learning impairment in the passive avoidance test [13]. For aripiprazole and haloperidol, we chose the doses of 0.3 and 1 mg/kg p.o. These doses were the second maximum and maximum doses that caused no passive avoidance learning impairment and no sedation in a previous study [13]. For each antipsychotic, the selected doses were near or lower than its ED_{50} for anti-dopaminergic effect in methamphetamine-induced hyperlocomotion test (ED_{50} values; 2.3 mg/kg p.o. for lurasidone, 1.8 mg/kg p.o. for risperidone, 65 mg/kg p.o. for clozapine, 9.7 mg/kg p.o. for aripiprazole, 0.88 mg/kg p.o. for haloperidol, unpublished data). In the case of clozapine, however, we found in a pilot MWM test that the doses of 0.3 and 1 mg/kg produced neither ameliorating nor impairing effect on the performance of MK-801-treated rats. Therefore, we increased the doses of clozapine to 3 and 10 mg/kg in the present study. Since risperidone (1 mg/kg; Figs. 1B, 3B, 4B, 5B and 6B), clozapine (10 mg/kg; Fig. 7C), aripiprazole (1 mg/kg; Figs. 1D, 2D and 4D), and haloperidol (1 mg/kg; Figs. 1E and 3E) tended to worsen the performance of MK-801-treated rats in MWM or RAM test, these doses were considered to be the maximum tolerable doses for these tests in MK-801-treated rats and higher doses were not used in this study.

2.5. Statistical analysis

In the MWM test, escape latency and swimming distance were totalled for 5 days and compared by unpaired *t*-test ("vehicle + saline" vs. "vehicle + MK-801") or Dunnett test ("vehicle + MK-801" vs. "antipsychotics + MK-801"). Mean swimming speed in the 5 experimental days was compared in the same way. The cFDB was compared by chi-square test with Bonferroni correction. In the RAM test, the number of reference memory errors, number of working memory errors, and latency per arm entry were compared by unpaired *t*-test ("vehicle + saline" vs. "vehicle + MK-801") or Dunnett test ("vehicle + MK-801" vs. "antipsychotics + MK-801").