Journal of Neuroscience Research 84:299–305 (2006)

Nitric Oxide Donor Molsidomine Attenuates Psychotomimetic Effects of the NMDA Receptor Antagonist MK-801

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There is experimental evidence indicating that the non-competitive NMDA receptor antagonist MK-801 impairs cognition and produces a series of schizophrenia-like symptoms in rodents (hypermotility, stereotypies, and ataxia). The present study was designed to investigate the efficacy of the nitric oxide (NO) donor molsidomine in counteracting these MK-801-induced behavioral effects in the rat. In a first study, post-training administration of molsidomine (at 4 but not 2 mg/kg) successfully antagonized MK-801-induced performance deficits in a recognition memory test. In a subsequent study, molsidomine (2 and 4 mg/kg) was shown to be unable to reverse MK-801-induced hypermotility but attenuated stereotypies (continuous movement whole cage, body sway, and head weaving) produced by MK-801. Moreover, at 4 mg/kg this NO donor counteracted MK-801-induced ataxia. Our findings indicate that molsidomine attenuates behavioral effects related to the hypofunction of the NMDA receptor suggesting that NO might be involved in the psychotomimetic effects of non-competitive NMDA receptor antagonists.

Key words: recognition memory; motility; ataxia; stereotypies

Non-competitive antagonists of the N-methyl-D-aspartate (NMDA) receptor such as ketamine or phencyclidine (PCP) are known for their strong psychotomimetic effects in humans (Javitt and Zukin, 1991). MK-801 is also a non-competitive antagonist at the NMDA receptor complex that produces wide-ranging effects on rodent behavior, including working memory deficits (Verna and Moghaddam, 1996; De Lima et al., 2005), hypermotility (Willetts et al., 1990; Carlsson, 1993), stereotypy and ataxia (Tricklebank et al., 1989).

Nitric oxide (NO) a soluble, short-lived and freely diffusible gas, is an important intracellular messenger in the brain. Activation of NMDA receptors has been shown to induce NO synthesis (Garthwaite, 1991; Dawson and Snyder, 1994). Reportedly, NO is involved in the mechanisms of synaptic plasticity (O'Dell et al., 1991) and plays an important role in cognition (Prast and Philippu, 2001). Several behavioral studies carried out in rodents have demonstrated that compounds that block NO synthase (NOS) inhibit learning (Madison and Schuman, 1991; Chapman et al., 1992; Yamada et al., 1996; Pitsikas et al., 2002a) whereas compounds that generate NO (NO donors) reversed memory deficits (Fin et al., 1995; Huang and Lee, 1995; Meyer et al., 1998). Interestingly, it was found that the NO donor S-nitroso-*N*-acetyl penicillamine (SNAP) successfully antagonized MK-801-induced performance deficits in a spatial learning task in the mouse (Yamada et al., 1996).

Several lines of evidence suggest that NO is also implicated in various neuropathologic conditions including schizophrenia (Akbarian et al., 1993; Das et al., 1995; Karatinos et al., 1995; Khan et al., 1995; Karson et al., 1996). Contradictory results were reported however, concerning the exact role of NO in modulating NMDA receptor blockade and these discrepancies still need to be elucidated. It has been shown that several psychotomimetic effects of the NMDA receptor antagonist PCP were blocked either by the NO donor sodium nitroprusside (SNP) (Bujas-Bobanovic et al., 2000a) or by diverse NOS inhibitors (Johansson et al., 1997, 1999; Klamer et al., 2001). In another series of studies it has been shown that NOS inhibitors potentiated PCP-induced behavioral effects (Noda et al., 1995, 1996; Bujas-Bobanovic et al., 2000b).

The aim of the present study was to clarify the relationship between NO and NMDA receptor hypofunction. We investigated the role of the NO donor molsidomine on the behavioral effects produced by the NMDA antagonist MK-801. Among NO donors, molsidomine has a high bioavailability, a long-lasting duration of action (Boger et al., 1994) likely crosses the blood-brain barrier (BBB) (Maccario et al., 1997; Rigamonti et al., 2001) and increases its permeability (Mayhan, 2000). Molsidomine was found effective to antagonize memory

Contract grant sponsor: Research Committee of the University of Thessaly; Contract grant number: 2937.

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Received 27 January 2006; Revised 6 March 2006; Revised 23 March 2006; Accepted 24 March 2006

Published online 18 May 2006 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jnr.20889

deficits in different animal models (Meyer et al., 1998; Pitsikas et al., 2001, 2002a,b, 2003, 2005).

In the first set of experiments, we evaluated the efficacy of molsidomine in antagonizing MK-801-induced performance deficits in a recognition memory task in the rat. For this study, the object recognition task, a non-rewarded paradigm based on the spontaneous exploratory behavior of rats, which reflects non-spatial working memory, was selected (Ennaceur and Delacour, 1988). In the second set of experiments, the ability of this NO donor to antagonize MK-801-induced behavioral changes such as hypermotility, stereotypies and ataxia was assessed in a locomotor activity test.

MATERIALS AND METHODS

Animals

Male, 3-month-old Wistar rats (Hellenic Pasteur Institute, Athens, Greece) weighing 250–300 g were used in this study. The animals were housed in Makrolon cages (35 × 45 × 20 cm), three per cage, in a regulated environment (21 ± 1°C; 50–55% relative humidity; 12-hr light/dark cycle, lights on at 07:00 hr) with free access to food and water. Experiments were conducted in the room where only these animals where housed, and took place between 09:00 and 13:00. Behavioral observations and evaluations were carried out by experimenters who were unaware of the pharmacologic treatment.

Procedures involving animals and their care were conducted in conformity with the international guidelines, in compliance with National and International laws and policies (National Research Council, 1985; Council of the European Communities, 1986).

Object Recognition Test

The test apparatus consisted of an open box made of plexiglas (80 × 50 × 60 cm) that was illuminated by a 60 W lamp suspended 60 cm above the box. In the different parts of the apparatus the light intensity was equal. The objects to be discriminated (in triplicate) were in three different shapes: cubes, pyramids and cylinders 7 cm high; they could not be displaced by rats. The cubes were from metal, the pyramids were from glass and the cylinders were plastic. In addition, these objects had no genuine significance for rats and had never been associated with a reinforcement.

The object recognition test was carried out as described elsewhere (Ennaceur and Delacour, 1988). In the week preceding testing, the animals were handled twice daily. On the day before testing, they were allowed to explore the apparatus for 2 min, whereas on the testing day, a session of two 2-min trials was given. During the ''sample'' trial (T1) two identical samples (objects, e.g., 2 plastic cylinders) were placed in two opposite corners of the apparatus 10 cm from the side wall. A rat was placed in the middle of the apparatus and was left to explore these two identical objects. After T1, the rat was put back in its home cage and an intertrial interval (ITI) of 3 hr was given. Subsequently, the ''choice'' trial (T2) was carried out. During T2, a new object (N) different from the familiar object either as texture or as shape (e.g., a metallic cube) replaced one of the samples presented in T1. The rats were then re-exposed to two objects: a copy of the familiar (F) and the N. All combinations and locations of objects were used in a balanced manner to reduce potential biases due to preferences for particular locations or objects. To avoid the presence of olfactory trails, the apparatus and the objects after each trial were thoroughly cleaned.

Exploration was defined as follows: directing the nose toward the object at a distance of no more than 2 cm or touching the object with the nose. Turning around or sitting on the object was not considered as exploratory behavior. The times spent by rats in exploring each object during T1 and T2 were recorded manually by using a stopwatch. From this measure a series of variables was then calculated: the total time spent in exploring the two identical objects in T1, and that spent in exploring the two different objects, F and N in T2. To evaluate whether or not within each group, animals had manifested a preference either for an object or for a location, the exploration times were analyzed according to the nature of objects and locations of the apparatus. The discrimination between F and N during T2 was measured by comparing the time spent in exploring the F with that spent in exploring the N. As this time may be biased by differences in overall levels of exploration (Cavoy and Delacour, 1993) a discrimination index (D) was then calculated; $D = N - F/N + F$. D is the discrimination ratio and represents the difference in exploration time expressed as a proportion of the total time spent exploring the two objects in T2 (Cavoy and Delacour, 1993). In addition, motor activity of each animal expressed as total number of steps during each trial was also recorded.

Spontaneous Behavior

Spontaneous motor activity was assessed in the ANIMEX motility-meter (LKB, Farad, Sweden). Every movement of the animal produced a signal due to variation of inductance and capacity of the apparatus resonance circuit. Then, signals were automatically converted in numbers. The rats subjected to locomotor activity experiment were tested only once. After an initial 30-min habituation period in the apparatus, the animals received the appropriate pharmacologic treatment. After drug administration, the animals were immediately put back into the motility arena and spontaneous locomotion was recorded for 60 min. During this 60-min session, motility data were collected every 5 min.

Throughout the recording period, behavioral stereotypy was rated for 10 sec every 5 min. Animals received a score of 0 for absence or 1 for presence of each of the following behaviors: active, resting, continuous movement within the whole area of the cage (CMWC), body sway and head weaving. Ataxia was assessed accordingly to the simplified rating scale (Andine et al., 1999): 0, normal body posture; 1, falling tendency upon movement; 2, falling upon movement; and 3, almost unable to move.

Drugs

(+)-MK-801 maleate (Sigma, St. Louis, MO) was dissolved in saline (NaCl 0.9%) and administered intraperitoneally (i.p.) in a volume of 0.5 ml/rat. For the object recognition task, the dose of MK-801 (0.1 mg/kg) was chosen based

on a previous study in which MK-801 was found to impair rat performance in this task without producing side effects (De Lima et al., 2005). For the evaluation of animals spontaneous behavior, MK-801 was used at a dose (0.2 mg/kg) that causes major psychotomimetic effects (hypermotility, stereotypies, and ataxia) (Andine et al., 1999). This dose made it easier to detect any reduction in behavior caused by the interventional drug (i.e., molsidomine).

Molsidomine (Sigma Tau, Milan, Italy) was dissolved in saline (NaCl 0.9%) and administered i.p. in a volume of 0.5 ml per rat. Doses of molsidomine were chosen based on studies in which they were effective against learning impairments and did not produce adverse side effects (hypotension, sensorimotor deficits) (Meyer et al., 1998; Pitsikas et al., 2001, 2002a,b, 2003, 2005). Doses of compounds are expressed as bases. Control animals received isovolumetric amounts (0.5 ml) of the vehicle (NaCl 0.9%).

Effects of Molsidomine in Antagonizing MK-801-Induced Performance Deficits in the Object Recognition Task

Rats were divided randomly into six experimental groups (10 rats/group) as follows: vehicle + vehicle; vehicle + molsidomine 2 mg/kg; vehicle + molsidomine 4 mg/kg; vehicle + MK-801 0.1 mg/kg; MK-801 0.1 mg/kg + molsidomine 2 mg/kg; and MK-801 0.1 mg/kg + molsidomine 4 mg/kg. Compounds were administered immediately after T1.

Effects of Molsidomine in Antagonizing MK-801-Induced Psychotomimetic Effects

Rats were divided randomly into six experimental groups (8 rats/group) as follows: vehicle + vehicle; vehicle + molsidomine 2 mg/kg; vehicle + molsidomine 4 mg/kg; vehicle + MK-801 0.2 mg/kg; MK-801 0.2 mg/kg + molsidomine 2 mg/kg; and MK-801 0.2 mg/kg + molsidomine 4 mg/kg. Molsidomine and MK-801 were administered 15 and 5 min respectively before starting the 60-min testing session. Control rats were given the vehicle i.p., 15 and 5 min before starting the 60-min testing session.

Statistical Analysis

For the object recognition task results are expressed as mean ± SEM. Preference of animals for objects or locations was analyzed by the Student's *t*-test for each experimental group. Motor activity, total exploration times during T2, and discrimination index D data were assessed by the two-way analysis of variance (ANOVA). The factors were MK-801 (three levels) and molsidomine (three levels). Post-hoc comparisons were made by the Tukey's test.

Motor activity data are presented from 12 sequential 5-min measurement periods and expressed as mean ± SEM. Differences between groups were evaluated by the three-way ANOVA (two between, one within subjects). The first between subjects factor was MK-801 (three levels) and the second was molsidomine (three levels). There were 12 levels of the within factor time. Significant two-way interaction between MK-801 and molsidomine was examined by comparing treatment group means for the 12 time periods, using the Tukey's test.

For the overt behavior, and ataxia the cumulative behavioral scores for each animal from the observation period was totaled. Each behavioral category was then analyzed by determining the median and interquartile range. Data were subsequently analyzed by the Kruskal-Wallis non-parametric test. Post-hoc comparisons were made by the Newman-Keuls test.

RESULTS

Recognition Memory

No difference within any group when the exploration time was compared according to the nature of objects (cubes, pyramids, or cylinders) and their locations (left or right) in the apparatus was observed.

A two-way ANOVA analysis of motor activity results demonstrated a significant main effect of MK-801 [$F(5,54) = 91.3$, $P < 0.01$], but not of molsidomine [$F(5,54) = 0.3$, $P = 0.7$] and a significant MK-801–molsidomine interaction [$F(5,54) = 3.2$, $P < 0.05$]. Post-hoc comparisons have shown that treatment with MK-801 resulted in an increase of motility: MK-801 + vehicle vs. vehicle + vehicle, $P < 0.05$; MK-801 + molsidomine 2 mg/kg vs. vehicle + molsidomine 2 mg/kg, $P < 0.05$ and MK-801 + molsidomine 4 mg/kg vs. vehicle + molsidomine 4 mg/kg, $P < 0.05$ (Fig. 1A).

Total exploration levels were not different among the various experimental groups (Fig. 1B). Overall ANOVA did not show a main effect either of MK-801 [$F(5,54) = 1.8$, $P = 0.1$] or of molsidomine [$F(5,54) = 0.12$, $P = 0.9$] or a significant interaction between MK-801 and molsidomine [$F(5,54) = 0.7$, $P = 0.5$].

Data for D showed a significant main effect of MK-801 [$F(5,54) = 12.1$, $P < 0.01$] of molsidomine [$F(5,54) = 3.4$, $P < 0.05$] but not a significant interaction between MK-801 and molsidomine [$F(5,54) = 2.2$, $P = 0.1$]. Post-hoc comparisons have shown that the vehicle + MK-801-treated rats were unable to discriminate between N and F with respect to the vehicle + vehicle, and MK-801 + molsidomine 4 mg/kg-treated rats ($P < 0.05$). Moreover, MK-801 + molsidomine 4 mg/kg-treated rat performance was not different than that displayed by the vehicle + molsidomine 4 mg/kg-treated animals, and was significantly better than that exhibited by the MK-801 + molsidomine 2 mg/kg-treated animals ($P < 0.05$). In addition, the lower dose of molsidomine did not confer any protection in the MK-801-treated animals (MK-801 + molsidomine 2 mg/kg vs. MK-801 + vehicle, not significant; MK-801 + molsidomine 2 mg/kg vs. vehicle + molsidomine 2 mg/kg, $P < 0.05$, Fig. 1C).

Motor Activity

Overall ANOVA showed a nonsignificant three-way MK-801 × molsidomine × time interaction [$F(15,462) = 0.4$, $P = 1$] but a significant two-way interaction between MK-801 and molsidomine [$F(2,42) = 15.2$, $P < 0.01$] between MK-801 and time [$F(13,462) = 81.4$, $P < 0.01$] but not between molsidomine and time. A main effect

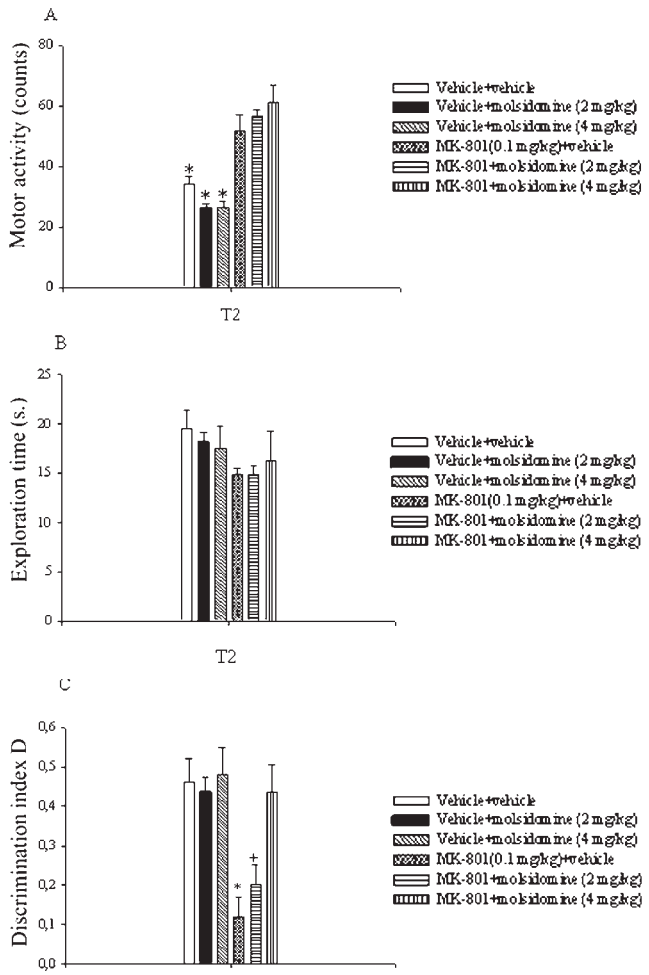

Fig. 1. Object recognition task. MK-801 and molsidomine were injected i.p., just after T1, respectively. Results are expressed as mean ± SEM. **A:** Total motor activity displayed by different groups of rats during T2. *$P <$ 0.05; vehicle + vehicle vs. MK-801 + vehicle; vehicle + molsidomine 2 mg/kg vs. MK-801 + molsidomine 2 mg/kg and vehicle + molsidomine 4 mg/kg vs. MK-801 + molsidomine 4 mg/kg-treated rats. **B:** Total exploration time displayed by different groups of rats during T2. **C:** Discrimination index D performance expressed by different groups of rats during T2. *$P < 0.05$ vs. the vehicle + vehicle and the MK-801 + molsidomine 4 mg/kg-treated rats. $^{+}P < 0.05$ vs. the vehicle + molsidomine 2 mg/kg and the MK-801 + molsidomine 4 mg/kg-treated rats.

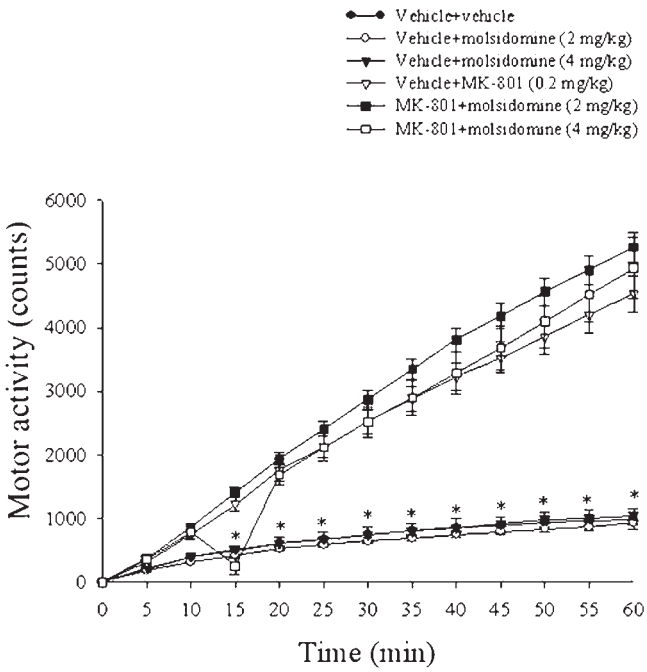

Fig. 2. Temporal effects of MK-801 and molsidomine on rats locomotor activity. Results are expressed as mean ± SEM. Molsidomine and MK-801 were injected i.p. 15 and 5 min respectively before starting the 60-min testing session. *$P < 0.05$; vehicle + vehicle vs. MK-801 + vehicle; vehicle + molsidomine 2 mg/kg vs. MK-801 + molsidomine 2 mg/kg; and vehicle + molsidomine 4 mg/kg vs. MK-801 + molsidomine 4 mg/kg-treated rats.

of MK-801 [$F(2,42) = 270$, $P < 0.01$] of molsidomine [$F(2,42) = 5.9$, $P < 0.05$] and of time [$F(11,42) = 156$, $P < 0.01$] has also been observed. Post-hoc comparisons have demonstrated that after 15 min all rats treated with MK-801 displayed increased motility throughout time. This hypermotility was not antagonized by molsidomine ($P < 0.05$, vs. all the respective control groups, Fig. 2).

Overt Behavior

With respect to control animals, MK-801 increased activity (H = 41.8, $P < 0.01$), abolished resting (H = 41.5, $P < 0.01$), increased CMWC (H = 35.2, $P <$ 0.01), body sway (H = 41.6, $P < 0.01$) and head weaving (H = 42.1, $P < 0.01$). Pretreatment with molsidomine (2 and 4 mg/kg) successfully antagonized certain signs of this MK-801-induced stereotypy, notably body sway, head weaving and CMWC ($P < 0.05$ vs. vehicle + MK-801-treated rats, Table I). Molsidomine at any dose, however, did not completely reverse these stereotypies in the MK-801-treated rats with respect to the control populations (MK-801 + molsidomine 2 mg/kg vs. vehicle + molsidomine 2 mg/kg, $P < 0.05$; MK-801 + molsidomine 4 mg/kg vs. vehicle + molsidomine 4 mg/kg, $P < 0.05$, Table I).

Ataxia results are illustrated in Table II. An effect of treatment with MK-801 was evident (H = 40.8, $P <$ 0.01). Molsidomine (4 mg/kg) attenuated this MK-801-induced ataxia ($P < 0.05$ vs. vehicle + MK-801-treated animals). Molsidomine did not completely eliminate ataxias' signs with respect to the control animals (MK-801 + molsidomine 2 mg/kg vs. vehicle + molsidomine 2 mg/kg; $P < 0.05$; MK-801 + molsidomine 4 mg/kg vs. vehicle + molsidomine 4 mg/kg, $P < 0.05$, Table II).

DISCUSSION

Our findings are in line with a previous study in which systemic administration of MK-801 at 0.1 mg/kg disrupted rats performance in the object recognition task (De Lima et al., 2005). Post-training treatment with 4 but not 2 mg/kg molsidomine attenuated the MK-801-

TABLE I. Behavioral Outcome

Treatment	Active	Resting	CMWC†	Body sway	Head weaving
Vehicle+vehicle	6.5 (4.5–7.0)	5.0 (4.5–7.0)	1.0 (0.5–2.5)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Vehicle+molsidomine (2 mg/kg)	9.5 (9.0–10.0)	2.5 (2.0–3.0)	0.5 (0.0–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Vehicle+molsidomine (4 mg/kg)	8.0 (7.5–10.0)	4.0 (2.0–4.5)	1.0 (0.5–1.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
MK-801 (0.2 mg/kg)+vehicle	12.0 (12.0–12.0)★	0.0 (0.0–0.0)★	12.0 (10.5–12.0)★	7.0 (6.5–7.5)★	9.5 (9.0–10.0)★
MK-801+molsidomine (2 mg/kg)	12.0 (12.0–12.0)★	0.0 (0.0–0.0)★	10.0 (8.0–11.5)★	4.0 (3.0–7.5)★,★★	6.0 (6.0–7.0)★,★★
MK-801+molsidomine (4 mg/kg)	12.0 (12.0–12.0)★	0.0 (0.0–0.0)★	7.5 (2.5–11.0)★,★★	2.5 (1.0–4.5)★,★★	3.0 (1.0–3.0)★,★★

†CMWC, continuous movement whole cage. Values are median (interquartile range), $n = 8$ rats per group.
★$P < 0.05$ vs. the respective control group.
★★$P < 0.05$ vs. MK-801+vehicle-treated rats.

TABLE II. Ataxia Outcome

Treatment	Median and interquartile range
Vehicle+vehicle	0
Vehicle+molsidomine (2 mg/kg)	0
Vehicle+molsidomine (4 mg/kg)	0
MK-801 (0.2 mg/kg)+vehicle	17.5 (12.5–20.5)★
MK-801+molsidomine (2 mg/kg)	13.5 (11–18)★
MK-801+molsidomine (4 mg/kg)	9 (2.5–12.5)★,★★

★$P < 0.05$ vs. the respective control groups.
★★$P < 0.05$ vs. MK-801+vehicle and MK-801+molsidomine 2 mg/kg-treated rats.

induced performance deficits in this recognition memory paradigm. MK-801 and molsidomine influenced rat performance during retention, seemingly reflecting a modulation of post-training mnemonic processes (storage or retrieval of information).

MK-801 and molsidomine were administered systemically, thus, it cannot be excluded that non-specific factors (attentional, sensorimotor) might have influenced animal performance. All animals that received MK-801 displayed higher levels of motility, but not of general exploration during T2, with respect to their control counterparts. Treatment with 4 mg/kg molsidomine did not antagonize the MK-801-induced hypermotility but successfully counteracted memory deficits. This implies that the effects of these compounds on rat cognitive performance were not related to the effects on motility.

The mechanism underlying molsidomine antagonism of MK-801-induced cognition effects deserves to be further investigated. At the moment there is no information that would support the hypothesis that NO donors can enhance cognition by improving cerebral blood flow (Patel, 1995). Among the potential mechanisms, a stimulatory effect of NO donors on central glutamatergic (Yamada et al., 1996), cholinergic (Prast and Philippu, 1992; Pitsikas et al., 2001), and GABAergic functions (Segovia et al., 1994; Segovia and Mora, 1998; Pitsikas et al., 2003), with promotion of long-term potentiation (LTP) has been proposed (Arancio et al., 1996).

In line with previous data (Tricklebank et al., 1989; Willetts et al., 1990; Carlsson, 1993) the present results indicate that MK-801 induced a characteristic behavioral syndrome consisting of hyperactivity, stereotyped behavior and ataxia. Treatment with molsidomine by itself produced no effect on any behavior assessed and did not antagonize the hypermotility induced by this NMDA antagonist. Molsidomine however, was able to attenuate a series of stereotypies (CMWC, head sway, and body weaving) and to antagonize but not eliminate ataxia.

In a previous report it was found that treatment with the NO donor SNP abolished PCP-induced hyperlocomotion, stereotypies, ataxia and c-fos expression (Bujas-Bobanovic et al., 2000a). Our results are in accordance with that study concerning the components of stereotypies and ataxia but not hypermotility. Task, strain, and drug variation across studies may play a role in differences in results obtained. A possible explanation of the different efficacy of these NO donors might be related to the fact that the hyperactivity induced either by PCP or MK-801 are mediated by different mechanisms (Ogren and Goldstein, 1994). In addition, molsidomine and SNP may generate NO in an altogether different mechanism that could also might explain this discrepancy (Darley-Usmar et al., 1992; Schuman and Madison, 1994).

Contradictory findings have been reported, however, concerning the exact role of NO in modulating NMDA receptor blockade. Antagonism of NMDA hypofunction has been related either to NO donors (Bujas-Bobanovic et al., 2000a) or to NOS inhibitors (Johansson et al., 1997, 1999; Klamer et al., 2001). In addition, other studies proposed that NOS inhibitors even potentiated PCP-induced behavioral effects (Noda et al., 1995, 1996; Bujas-Bobanovic et al., 2000b). Our findings support a beneficial role for this NO donor for the treatment of NMDA-induced psychotomimetic effects. The precise mechanism by which NO donors produce their effects on MK-801-induced behavioral deficits is not clear. It has been proposed that NO donors antagonize the effects of NMDA blockade through the activation of the NO-guanylyl cyclase signalling pathway (Bujas-Bobanovic et al., 2000a). This suggest that the effects of NMDA antagonists might be at least in part the result of a decrease in NO. Treatment with NO donors presumably reverses these effects by providing NO.

It is important, however, to underline that co-generation of superoxide anion might represent a limit to the therapeutical potential of molsidomine and its metabolites, e.g., 3-morpholinosydnonomine (SIN-1) can even be used as a peroxynitrite generator (Menconi et al., 1998).

Thus, to strengthen the role of NO in modulating MK-801-induced deficits, further studies can be carried out with different NO donors.

Our results demonstrate that a NO donor, molsidomine, is capable of influencing cognition and, although partially, some psychotomimetic effects of non-competitive NMDA receptor antagonists.

ACKNOWLEDGMENTS

This study was supported by a grant from the Research Committee of the University of Thessaly to N.P.

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