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Dopamine–*N*-methyl-D-aspartate interactions in the modulation of locomotor activity and memory consolidation in mice [1]

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Abstract

This study explores the functional interaction between glutamatergic and dopaminergic systems in the modulation of two behavioral responses: locomotor activity and memory consolidation assessed with one-trial inhibitory avoidance. In agreement with previous reports, the NMDA receptor antagonist, (+)-MK-801 ((+)-5-methyl-10,11-dihydro(*a,d*)cyclohepten-5,10-imine hydrogen maleate), dose dependently enhanced locomotor activity in mice. The selective dopamine D_1 receptor antagonist SCH 23390 at doses up to 0.05 mg/kg was unable to affect MK-801-induced locomotor activity, while (−)-sulpiride, but only at high doses (30 mg/kg), and haloperidol (0.05 mg/kg) blocked the MK-801 effect. Hypermotility induced by MK-801 was enhanced by repeated administration of haloperidol (once daily administration for 14 days of 4 mg/kg) or (−)-sulpiride (125 mg/kg), but not SCH 23390 (0.5 mg/kg). Dopamine D_1 (SKF 38393)- and D_2 (quinpirole)-selective agonists enhanced retention of one-trial inhibitory avoidance performance whilst NMDA receptor antagonists 3-(2-D-carboxypiperazin-4-yl)propyl-1-phosphoric acid (CPP) and MK-801 impaired it. Moreover we observed that the NMDA receptor antagonist-induced impairment of memory consolidation was attenuated by subeffective doses of SKF 38393 (5 mg/kg) and quinpirole (0.25 mg/kg). Impairment of the response induced by post-trial injections of CPP and MK-801, in the one-trial inhibitory avoidance test, was highly enhanced by 14 days of daily administration of haloperidol (4 mg/kg), sulpiride (25 mg/kg) but also SCH 23390 (0.5 mg/kg). These results suggest that different neural mechanisms underlie the functional interaction between the two neural systems in the modulation of these behavioral responses. Further, the results of the chronic study revealed a possible heterologous regulation of NMDA receptors.

Keywords: NMDA receptor antagonist; Dopamine; Neuroleptic, chronic; Locomotor activity; Memory; (Mouse)

1. Introduction

The glutamatergic system has a role in a number of different neurological disorders. A therapeutic use of NMDA receptor antagonists has been suggested for example in Parkinson disease (Carlsson and Carlsson, 1990; Porter et al., 1994). Overactive excitatory amino acid transmission in different brain structures, in fact, has been found to characterize this pathology (Porter et al., 1994). Moreover a malfunctioning corticostriatal glutamatergic pathway has been envisaged as a possible cause of schizophrenia (Grace, 1991). A reduced activity of this pathway is suggested by the increased [^{3}H]MK-801 binding in striatum found in schizophrenic patients (Kornhuber et al., 1989) as well as reduced glutamate levels in cerebrospinal fluids of schizophrenics (Kim et al., 1980).

NMDA receptors have been shown to be involved in the modulation of a variety of behavioral responses. Peripheral administration of NMDA non-competitive antagonists like MK-801 ((+)-5-methyl-10,11-dihydro(*a,d*)cyclohepten-5,10-imine hydrogen maleate), phencyclidine or ketamine induces locomotor activation (Liljequist, 1991) and stereotypy (Tiedtke et al., 1990). The same effect is exerted by drugs acting as competitive antagonists at the same receptors (Svensson et al., 1991). In situ injection of NMDA receptor antagonists in the nucleus accumbens or more generally in the ventral striatum enhances locomotor activity in rats (Raffa et al., 1989; Maldonado-Irizarry and Kelley, 1994), while focal injection in the striatum induces

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increased stereotyped behavior (Schmidt, 1986).

NMDA receptors seem also to play an important role in the modulation of learning and memory processes. Systemic injection of NMDA receptor antagonists induces an impairment in spatial learning (Morris et al., 1986), as well as in one-trial inhibitory avoidance (Venable and Kelly, 1990; Mondadori and Weiskrantz, 1993; Mele et al., 1995a,b). The sites for the action of these drugs in modulating memory processes have been suggested to involve limbic structures like hippocampus and amygdala.

An involvement of dopamine transmission in NMDA receptor antagonist-induced effects has been envisaged by some groups on the basis of non-competitive or competitive NMDA receptor antagonist-induced dopamine release, as assessed with in vivo microdialysis (Imperato et al., 1990; Kiss et al., 1994). Functional interactions between the two systems are also supported by behavioral data. MK-801 – induced hypermotility has been shown to be blocked by D_1 and D_2 antagonists (Dall'Olio et al., 1992; Ouagazzal et al., 1993; Willins et al., 1993). Behavioral studies are however not univocal in showing an impairing effect of dopamine antagonists on NMDA receptor antagonist-induced activity (Raffa et al., 1989). Functional interactions between the two neural systems have also been shown in the modulation of the one-trial inhibitory avoidance response. Ketamine induces an impairment in one-trial inhibitory avoidance performance which has been suggested to depend upon dopamine mechanisms (Uchihashi et al., 1994). Moreover we have recently shown in C57BL/6 mice an enhancement of the impairing effects of the competitive NMDA receptor antagonist 3(2-D-carboxypiperazin-4-yl)propyl-1-phosphoric acid (CPP) by selective D_1 and D_2 antagonists (Mele et al., 1995b).

It is interesting to note that while a functional antagonism seems to emerge in the modulatory action of the two systems on locomotor activity, the opposite happens for the one-trial inhibitory avoidance response. In fact, both dopamine agonists and NMDA receptor antagonists enhance locomotor activity (Carlsson and Carlsson, 1989), whilst dopamine agonists and NMDA receptor antagonists have opposite effects on one-trial inhibitory avoidance performance in mice (Castellano et al., 1991; Mele et al., 1995a,b). Therefore we used these two behavioral paradigms in order to further investigate the possible interactions between the dopaminergic and the glutamatergic systems.

In a first series of experiments we used selective dopamine D_1 and D_2 receptor agonists and antagonists to see whether they were able to modify the behavioral response to NMDA receptor antagonists. It has been shown, by us as well as others, that the chronic manipulation of the dopamine system through lesions (Lindefors et al., 1987; Porter et al., 1994) or pharmacological treatments (Ulas et al., 1993; Yamamoto and Cooperman, 1994; Mele et al., 1995b) induces marked changes in NMDA receptor sensitivity or glutamate brain levels. We therefore also verified whether subchronic treatment with dopamine antagonists, which are able to induce changes in dopamine receptor sensitivity, induces changes in the behavioral response to NMDA receptor antagonists.

2. Materials and methods

2.1. Animals

Male NMRI mice (Plaisant, Rome) weighing 24–32 g were used. The animals were housed eight per cage and allowed a 1 week acclimatization period after arrival before being tested or before the pharmacological treatment was started. They had free access to food and water and were maintained under a 12/12 h cycle (lights on from 07:00 to 19:00 h) at constant temperature (22 ± 2°C). Groups of at least eight animals were used in all experiments, with each group being tested only once. This study was conducted in accord with Italian national laws and regulations on the use of animals in research and NIH guidelines on animal care.

2.2. Motor activity recording

The apparatus consisted of eight toggle floor boxes divided into two 20×10 cm compartments. For each mouse the number of crossings from one compartment to the other one was recorded by means of a microswitch connected to the tilting floor of the boxes. This test is widely used to discriminate drugs effects on horizontal activity (Cabib et al., 1991). All experiments were carried out in soundproof cubicles with a 30 W lamp as source of illumination. The animals were acclimated to the cubicles for 1 h before testing.

2.3. One-trial inhibitory avoidance

Mice were trained on a step-through inhibitory avoidance apparatus, as previously described (McGaugh and Landfield, 1970). On the training day each mouse was placed in the light compartment, facing away from the dark compartment. When the mouse turned around, the door leading to the dark compartment was opened. When the mouse had stepped with all four paws into the dark side, the door was closed, a foot-shock (0.2 mA, 50 Hz, 1 s) was delivered, and the step-through latency was recorded. The mouse was removed from the apparatus and injected intraperitoneally with test compounds in a volume of 10 ml/kg. Retention was tested 24 h later following a similar procedure, except that no shock was administered. A maximum step-through latency of 180 s was considered.

2.4. Drugs and chronic treatments

CPP (3(2-D-carboxypiperazin-4-yl)propyl-1-phosphoric acid) and (+)-MK-801 ((+)-5-methyl-10,11-dihy-

dro(*a,d*)cyclohepten-5,10-mine hydrogen maleate, purchased from RBI, USA), quinpirole (Eli Lilly, USA), SKF 38393 (Smith, Kline & French Laboratories), SCH 23390 (Schering, USA) were all dissolved in distilled water. (−)-Sulpiride (Ravizza, Italy) and haloperidol (Sigma Chemical Co.) were dissolved in a 15% v/v acetic acid solution, diluted with saline and the pH was adjusted to 7.4 with NaOH. All the drugs were injected intraperitoneally (i.p.) in a volume of 10 ml/kg. In the motor activity experiments MK-801 was always injected immediately before testing. In the acute association experiments sulpiride and haloperidol were administered 30 min before testing while SCH 23390 was injected 15 min before. In the one-trial inhibitory avoidance test all the drugs were injected immediately after training. In the experiments in which two drugs were administered, two consecutive injections were given. Control animals received the same number of saline injections.

In the repeated treatment study the animals were injected once a day for 14 days. A 4 day washout period was allowed before testing or drug analysis. SCH 23390 was injected at the dose of 0.5 mg/kg, haloperidol at 4 mg/kg, and sulpiride at 25 mg/kg and 125 mg/kg. The doses of dopamine antagonists were chosen on the basis of reports in the literature (Creese and Chen, 1985; Rupniak et al., 1984; Laruelle et al., 1992; Lindefors et al., 1987). Control animals were repeatedly injected with an equivalent volume of saline. Body weights of these groups were measured at the beginning of the chronic treatment and on the test day. The increase in body weight in the dopamine antagonist-treated animals was comparable to that of vehicle-treated animals.

2.5. Pharmacokinetic study

In the MK-801 concentration study, chronically treated animals, after a 4 day washout period, were injected with 0.25 mg/kg of MK-801. 30 min later the brains were rapidly removed, frozen in dry ice and stored at −20°C until analysis. MK-801 was extracted from brain homogenates and quantified by high-performance liquid chromatography with ultraviolet detection as described by Vezzani et al., 1989. The limit of detection, precision and reproducibility in mouse brain were similar to those reported for rat tissue (Vezzani et al., 1989).

2.6. Statistical analysis

To analyse the data of the dose-response experiments, a one-way analysis of variance (ANOVA) was used; a two-way analysis of variance was used for all other experiments. Whenever an interaction between factors was found, a post-hoc comparison was performed using the Newman-Keul's test. In the presence of a significant main effect but without an interaction between the factors, simple effects were considered.

3. Results

3.1. Effects of NMDA receptor antagonists on locomotor activity

Habituated control mice showed an average score of 30.5 in the 1-h activity test. As shown in Fig. 1, the non-competitive NMDA receptor antagonist (+)-MK-801

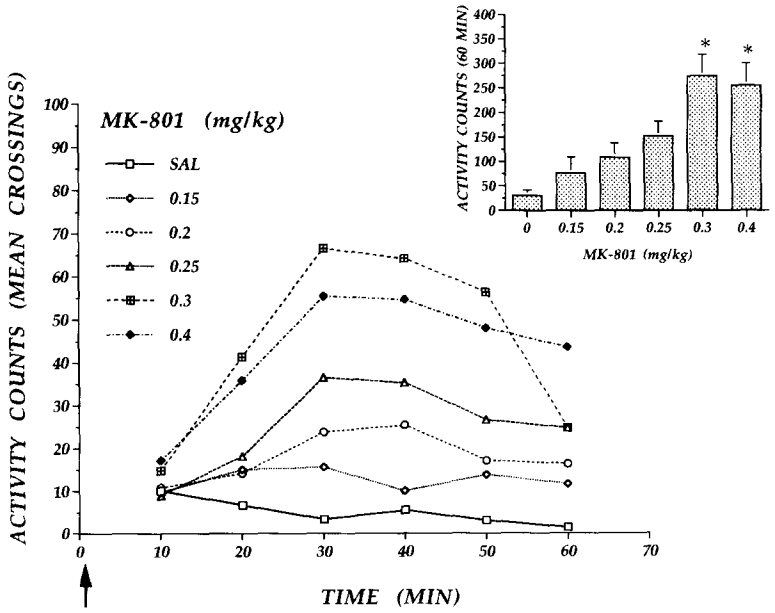

Fig. 1. Effect of systemic injection of MK-801 on horizontal activity of NMRI mice. The arrow shows the time of the injection. The insert shows the effect of different doses of the NMDA receptor antagonist on total counts in the 1 h test. * $P < 0.01$ compared to saline-injected mice (Newman-Keul's post-hoc comparison).

induced a clear-cut dose-dependent increase in locomotor activity. At the highest dose (0.4 mg/kg), however, mice started to show signs of ataxia and loss of posture. The one-factor ANOVA revealed a significant treatment effect $F(5,75) = 6.47$, $P < 0.0001$. The peak effect of the drug was reached 30 min after the injection for all the doses used (Fig. 1), with a maximum of 67 ± 11 crossings in 10 min for the 0.3 mg/kg dose.

The competitive NMDA receptor antagonist CPP was unable to induce any change in locomotor activity at any of the doses tested (data not shown). At the very high dose (CPP 10 mg/kg) a decrease in sector crossings was shown. The ANOVA was not significant ($F(4,35) = 1.56$, n.s.).

3.2. Effects of dopamine antagonists on MK-801 induced locomotor activity

In order to examine the role of the dopamine system in MK-801 induced locomotor activity, we administered different doses of D_1 and D_2 antagonists before injecting MK-801. As shown in Fig. 2A the dopamine D_1 receptor antagonist SCH 23390 did not affect MK-801-induced locomotor activity. Even the high dose of SCH 23390, which was able to induce a clear-cut decrease in locomotor activity (the mean crossings in 1 h being 51 ± 12 and 12 ± 2 respectively for sal-sal and SCH 0.05-sal injected groups), was unable to affect in any way MK-801-induced locomotor activity. The two-way analysis of variance revealed only a significant treatment effect $F(2,77) = 22.8$, $P < 0.001$, but no pretreatment effect $F(2,77) = 0.17$, n.s. or interaction between the factors $F(4,77) = 0.49$, n.s..

Fig. 2B shows the effects of (−)-sulpiride pretreatment on MK-801-induced locomotor activity. At both doses the drug induced a similar inhibition of locomotor activity in control mice. However only the highest dose of the D_2 antagonist was able to reduce MK-801-induced locomotion. This effect was also evident at the higher MK-801 dose. The two way ANOVA revealed both a significant pretreatment effect $F(2,87) = 5.23$, $P = 0.0072$ and a significant treatment effect $F(2,87) = 9.42$, $P = 0.0002$; however the interaction between the two factors was not significant $F(4,87) = 1.64$, n.s..

The effects of haloperidol on MK-801-induced locomotion are shown in Fig. 2C. The high dose of haloperidol (0.1 mg/kg) induced a significant attenuation of locomotor activity, the mean ± S.E. being 46 ± 16 vs. 12 ± 2.7 for saline-saline and haloperidol 0.1-saline groups respectively, while the low dose of haloperidol did not affect spontaneous locomotor activity (44.5 ± 8.9). However haloperidol at both doses was able to reduce MK-801-induced locomotion and was the most effective among the drugs used in affecting MK-801-induced locomotor activity. The two-way ANOVA revealed both a significant main pretreatment effect $F(2,63) = 5.6$, $P = 0.0057$ and a main treatment effect $F(2,63) = 7.03$, $P = 0.0018$; however the interaction between the two factors was found to be not significant $F(4,63) = 1.16$, n.s..

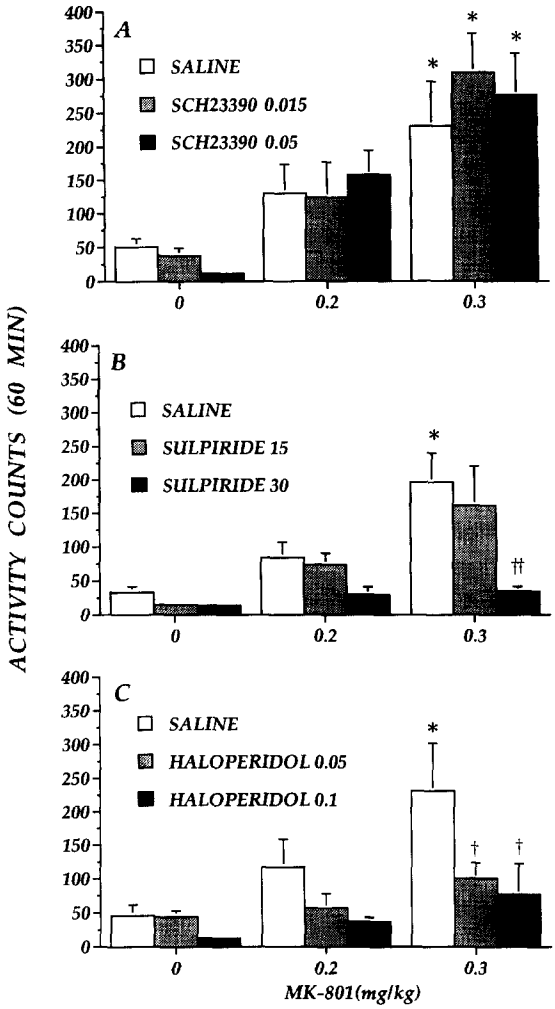

Fig. 2. Effects of systemic administration (i.p.) of different doses of dopamine antagonists on MK-801-induced locomotor activity. A: The dopamine D_1 receptor-selective antagonist SCH 23390 at the highest dose used reduced the spontaneous locomotor activity of NMRI mice. None of the doses used (0.015 and 0.05 mg/kg) however was able to attenuate MK-801-induced hyperactivity. B: Both doses of the dopamine D_2 receptor antagonist, (−)-sulpiride (15 and 30 mg/kg), reduced the spontaneous activity of NMRI mice. Only the highest dose (30 mg/kg), however, was able to reduce MK-801-induced locomotor activity. C: The classical neuroleptic haloperidol attenuated MK-801-induced hyperactivity at either dose used (0.05 and 0.01 mg/kg). * $P < 0.01$ compared to sal-sal, † $P < 0.05$ and †† $P < 0.01$ compared to mice injected with saline and the same dose of MK-801 (Newman-Keul's post-hoc comparison).

3.3. Effects of repeated dopamine antagonists on MK-801 induced locomotor activity

14 daily injections of a high dose of the dopamine D_1 receptor antagonist, SCH 23390 (0.5 mg/kg once a day), were unable to affect MK-801-induced locomotor activity (Fig. 3A). The two-way ANOVA showed a significant

effect only for the challenge factor $F(3,128) = 38.07$, $P = 0.0001$).

Repeated administration of haloperidol (4 mg/kg) induced a shift of the dose-response curve to the left, indicating a clear increase in the efficacy of MK-801 in inducing locomotor activity (Fig. 3B). At the dose of 0.25 mg/kg of MK-801, haloperidol-pretreated animals were less active than the control animals. The two-way analysis of variance revealed a significant main pretreatment effect $F(1,126) = 8.59$, $P = 0.004$, a significant main treatment effect $F(3,126) = 13.58$, $P = 0.0001$ and a significant interaction between the two factors $F(3,126) = 8.04$, $P = 0.0001$.

Fig. 3C shows the effect of repeated (−)-sulpiride (125 mg/kg) on locomotor activity induced by a low dose of MK-801 (0.15 mg/kg). As observed for haloperidol, there was an increased response to MK-801 in the mice repeatedly administered the dopamine antagonist; however, the effect was not as evident as with haloperidol. The two-way ANOVA, in fact, showed a significant pretreatment effect ($F(1,58) = 5.21$, $P = 0.026$), but no significant treatment effect ($F(1,58) = 2.97$, n.s.) or significant interaction between the two factors ($F(1,58) = 2.73$, n.s.).

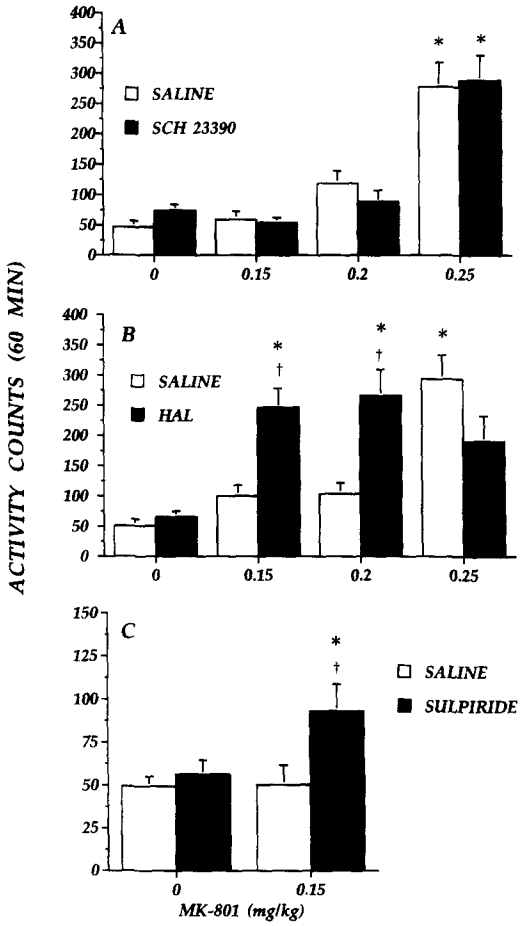

Fig. 3. Effects of repeated administration (14 days) of saline or different dopamine antagonists on MK-801-induced locomotor activity. None of the treatments induced any change in the locomotor activity of saline-injected mice. A: 14 daily injections of SCH 23390 (0.5 mg/kg) did not change the MK-801-induced locomotor response. B: 14 daily injections of haloperidol (4 mg/kg) enhanced MK-801-induced hyperactivity. C: 14 daily injections of the dopamine D_2 receptor antagonist (−)-sulpiride (125 mg/kg) enhanced the locomotor response to a low dose of MK-801. * $P < 0.01$ compared to sal-sal; † $P < 0.01$ compared to mice repeatedly injected with saline and challenged with same dose of MK-801 (Newman-Keul's post-hoc comparison).

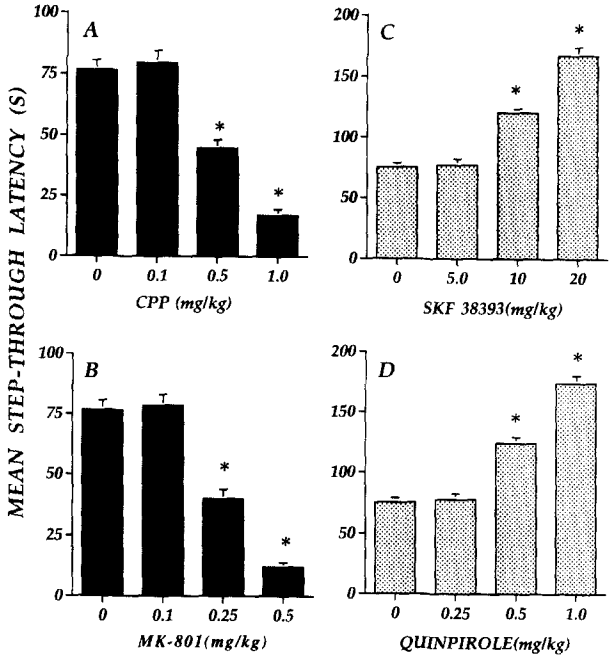

Fig. 4. Effects of immediate post-trial i.p. injection of NMDA receptor antagonists, CPP (A), and MK-801 (B), and selective dopamine D_1 (SKF 38393) (C) and D_2 (quinpirole) (D) receptor agonists, on step-through latency on the test day. * $P < 0.01$ compared to saline-injected mice (Newman-Keul's post-hoc comparison).

3.4. Effects of post-trial administration of NMDA receptor antagonists and dopamine agonists on one-trial inhibitory avoidance

Post-trial injections of both competitive ($F(3,28) = 76.4$, $P = 0.0001$) and non-competitive ($F(3,28) = 57.1$, $P = 0.0001$) NMDA receptor antagonists impaired memory consolidation in a dose-dependent fashion, the lower doses of both drugs being ineffective (Fig. 4A and B).

Fig. 4 shows also the effects of post-trial administration of dopamine agonists on one-trial inhibitory avoidance test performance. D_1 and D_2 agonists both enhanced memory consolidation in a dose-dependent fashion. The one-way ANOVA revealed for both drugs a main treatment effect $F(3,28) = 73.24$, $P = 0.0001$ for the D_1 agonist SKF 38393 (Fig. 4C) and $F(3,28) = 80.86$, $P = 0.0001$ for the D_2 agonist quinpirole (Fig. 4D).

3.5. Ineffective doses of dopamine agonists on NMDA receptor antagonist-induced response on one-trial inhibitory avoidance

In order to assess whether NMDA receptor modulation of memory retention was affected by the dopaminergic

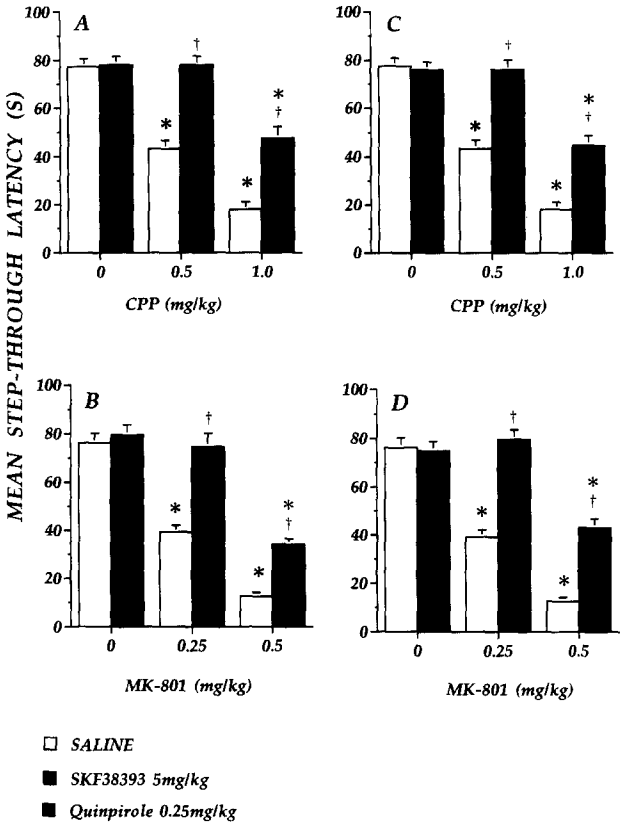

Fig. 5. Effects of subeffective doses of selective D_1 (SKF 38393 5 mg/kg) and D_2 (quinpirole 0.25 mg/kg) dopamine receptor agonists on NMDA receptor antagonist-induced impairment of memory consolidation. A: CPP-induced reduction of step-through latency on the test day was attenuated by subthreshold doses of SKF 38393. B: MK-801-induced reduction of step-through latency on the test day was attenuated by subthreshold doses of SKF 38393. C: CPP-induced reduction of step-through latency on the test day was attenuated by subthreshold doses of quinpirole. D: MK-801-induced reduction of step-through latency on the test day was attenuated by subthreshold doses of quinpirole. * $P < 0.01$ compared to sal-sal-injected mice; † $P < 0.01$ compared to mice injected with saline and the same dose of NMDA receptor antagonist (Newman-Keul's post-hoc comparison). For complete statistical analysis see Table 1.

system, low, ineffective doses of SKF 38393 and quinpirole, dopamine D_1 and D_2 receptor agonists, respectively, were injected post-trial in association with different doses of NMDA receptor antagonists.

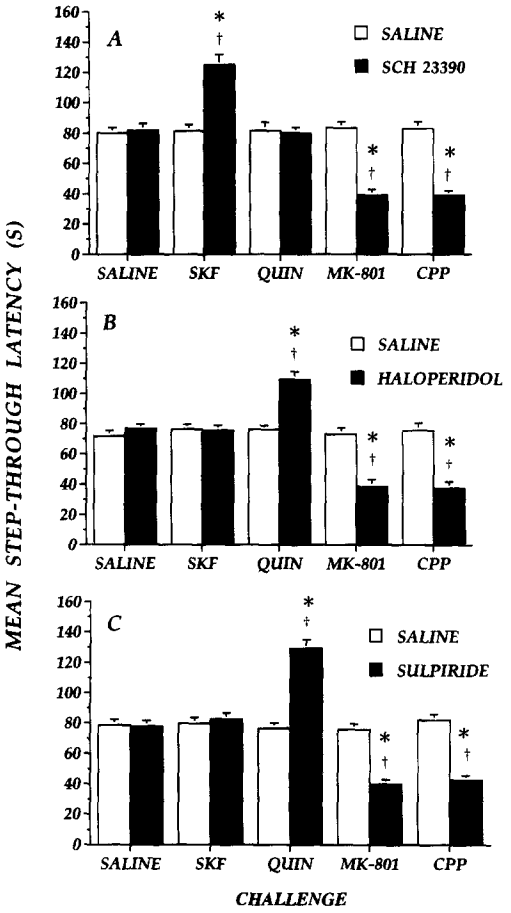

Fig. 6. Effects of post-trial injection of saline or subeffective doses of SKF 38393 5.0 mg/kg (SKF), quinpirole 0.25 mg/kg (QUIN), MK-801 0.1 mg/kg and CPP 0.1 mg/kg in mice repeatedly injected with different dopamine receptor antagonists. A: 14 days of repeated administration of SCH 23390 (0.5 mg/kg) enhanced the behavioral response to post−trial administration of SKF, MK-801 and CPP but not to QUIN. B: 14 days of repeated administration of sulpiride (25 mg/kg) enhanced the behavioral response to post-trial administration of QUIN, MK-801 and CPP but not to SKF. C: 14 days of repeated administration of haloperidol (4 mg/kg) enhanced the behavioral response to post-trial administration of QUIN, MK-801 and CPP but not to SKF. * $P < 0.01$ compared to sal-sal mice; † $P < 0.01$ compared to mice repeatedly injected with saline and challenged with the same drug (Newman-Keul's post-hoc comparison). For complete statistical analysis see Table 2.

Table 1
Summary of statistical analysis of results of one-trial inhibitory avoidance performance, following post-trial administration of subthreshold doses of D_1 and D_2 agonists in association with NMDA antagonists.

	Pretreatment	Treatment	Interaction
SKF 38390			
CPP	$F(1,52) = 51.2$ $P = 0.0001$	$F(2,52) = 75.3$ $P = 0.0001$	$F(2,52) = 13.6$ $P = 0.0001$
MK-801	$F(1,52) = 49.9$ $P = 0.0001$	$F(2,52) = 124.2$ $P = 0.0001$	$F(2,52) = 10.5$ $P = 0.0002$
Quinpirole			
CPP	$F(1,52) = 42.1$ $P = 0.0001$	$F(2,52) = 79.7$ $P = 0.0001$	$F(2,52) = 14.3$ $P = 0.0001$
MK-801	$F(1,52) = 71.5$ $P = 0.0001$	$F(2,52) = 104$ $P = 0.0001$	$F(2,52) = 20.2$ $P = 0.0001$

Table 2
Summary of statistical analysis of results of one-trial inhibitory avoidance performance, following administration of D_1, D_2 agonists and NMDA antagonists in mice repeatedly administered DA antagonists

	Pretreatment	Challenge	Interaction
SCH 23390 (0.5 mg / kg)			
SKF 38390	$F(1,28) = 21.4$ $P = 0.0001$	$F(1,28) = 20.3$ $P = 0.0001$	$F(1,28) = 17.8$ $P = 0.0002$
Quinpirole	$F(1,27) = 0.001$ n.s.	$F(1,27) = 0.004$ n.s.	$F(1,27) = 0.19$ n.s.
MK-801	$F(1,27) = 26.9$ $P = 0.0001$	$F(1,27) = 23.8$ $P = 0.0001$	$F(1,27) = 32.2$ $P = 0.0001$
CPP	$F(1,28) = 27.2$ $P = 0.0001$	$F(1.28) = 25.3$ $P = 0.0001$	$F(1,28) = 32.6$ $P = 0.0001$
Sulpiride (25 mg / kg)			
SKF 38390	$F(1,28) = 0.07$ n.s.	$F(1,28) = 0.5$ n.s.	$F(1,28) = 0.2$ n.s.
Quinpirole	$F(1,28) = 35.4$ $P = 0.0001$	$F(1,28) = 32.4$ $P = 0.0001$	$F(1,28) = 37.1$ $P = 0.0001$
MK-801	$F(1,29) = 26.6$ $P = 0.0001$	$F(1,29) = 32.8$ $P = 0.0001$	$F(1,29) = 24.8$ $P = 0.0001$
CPP	$F(1,28) = 26.5$ $P = 0.0001$	$F(1,28) = 16.4$ $P = 0.0004$	$F(1,28) = 24.9$ $P = 0.0001$
Haloperidol (4 mg / kg)			
SKF38390	$F(1,28) = 0.35$ n.s.	$F(1,28) = 0.23$ n.s.	$F(1,28) = 0.72$ n.s.
Quinpirole	$F(1,28) = 24.7$ $P = 0.0001$	$F(1,28) = 23.1$ $P = 0.0001$	$F(1,28) = 13.6$ $P = 0.001$
MK-801	$F(1,28) = 13.6$ $P = 0.001$	$F(1,28) = 21$ $P = 0.0001$	$F(1,28) = 23.97$ $P = 0.0001$
CPP	$F(1,27) = 16.7$ $P = 0.0004$	$F(1,28) = 19.1$ $P = 0.0002$	$F(1,27) = 27.9$ $P = 0.0001$

The effect of a low dose of SKF 38393 (5 mg/kg) on CPP and MK-801-induced memory impairment is shown in Fig. 5. The ineffective dose of the dopamine D_1 receptor agonist was able to partially reverse CPP induced memory impairment (A). Similarly the effect of the non-competitive antagonist, MK-801, was largely reduced by SKF 38393 (B) (see Table 1 for statistics).

Fig. 5 also shows the effect of quinpirole pretreatment on NMDA receptor antagonist-induced memory impairment. The dopamine D_2 receptor agonist was as potent as the dopamine D_1 receptor agonist in antagonizing the effects of CPP (Fig. 5C) and MK-801 (Fig. 5D) in the one-trial inhibitory avoidance (see Table 1 for statistics).

3.6. Effects of repeated dopamine antagonists on NMDA receptor antagonist-induced response in the one-trial inhibitory avoidance response

Fig. 6 shows the response to ineffective doses of dopamine agonists and NMDA receptor antagonists after repeated administration of dopamine D_1 and D_2 receptor antagonists in the one-trial inhibitory avoidance test. None of the treatments resulted in changes in latency to step-through on the training day. The latencies in s (mean ± SEM) were saline (4 ± 0.3), SCH 23390 0.05 mg/kg (5 ± 0.3), (−)-sulpiride 25 mg/kg (7 ± 0.39), and haloperidol 4 mg/kg (5 ± 0.3).

Fig. 6A shows the effects of repeated administration of the dopamine D_1 receptor antagonist, SCH 23390 (0.5 mg/kg). The compound did not induce changes in step-through latency on the test day in mice injected post-training with saline, means (± S.E.) being 80 ± 3.8 and 82 ± 4.5 s respectively in the saline and in the SCH 23390-treated groups. Post-trial injection of an ineffective dose of SKF 38393 (5 mg/kg) induced a significant enhancement of memory consolidation in the SCH 23390 chronically treated group. A post-trial injection of an ineffective dose of the dopamine D_2 receptor agonist quinpirole (0.25 mg/kg) was unable to affect step-through latency on the test day of mice treated chronically with SCH 23390. Repeated administration of the dopamine D_1 receptor antagonist was, instead, able to potentiate the response to both competitive and non-competitive NMDA receptor antagonists. Ineffective doses of both CPP (0.1 mg/kg) and MK-801 (0.1 mg/kg), in fact, induced a reduction in the time to step-through only in the chronic SCH group (see Table 2 for statistics).

The effects of a subchronic treatment with haloperidol (4 mg/kg) are shown in Fig. 6B. The haloperidol treatment did not induce any change in step-through latency in mice injected after training with saline, means ± S.E. being 72 ± 3.7 and 77 ± 3.2 for saline and haloperidol groups respectively. Haloperidol was also ineffective in modulating the response to subthreshold doses of SKF 38393. The effects of post-trial injection of ineffective doses of quinpirole (0.25 mg/kg) were, instead, potentiated by haloperidol. This drug was also able to enhance the behavioral response to the NMDA receptor antagonist. For both drugs, the doses ineffective in mice repeatedly treated with saline were able to decrease the step-through latency in haloperidol-treated animals (see Table 2 for statistics).

As shown in Fig. 6C repeated administration of (−)-sulpiride induced a behavioral response to challenge drugs that was very similar to the response induced by haloperidol. At 25 mg/kg/day, in fact, it was not able to induce any change in the response to post-trial injection of either saline or SKF 38393, while it induced a clear-cut increase in step-through latency of mice administered an ineffective dose of the dopamine D_2 receptor agonist quinpirole. As with the other dopamine antagonists used, we found an increased sensitivity to both the NMDA receptor antagonists, CPP and MK-801 (see Table 2 for statistics).

MK-801 brain concentrations in SCH 23390-(46 ± 6 ng/g), (−)-sulpiride-(43 ± 10 ng/g) and haloperidol-pretreated mice (35 ± 7 ng/kg) were comparable to those of vehicle-treated mice (44 ± 10 ng/g), 30 min after i.p. injection of MK-801 (0.25 mg/kg). Previous studies have established that the drug is uniformly distributed in various regions of the rat brain (Vezzani et al., 1989).

4. Discussion

In this study we investigated the role of dopamine receptor active drugs on NMDA receptor antagonist-induced behavioral response in two behavioral paradigms: locomotor activity and one-trial inhibitory avoidance. The results show that dopamine D_2 receptor antagonists, (−)-sulpiride and haloperidol, attenuated MK-801-induced locomotor activity. Both dopamine D_1 and D_2 receptor agonists were able to attenuate MK-801- and CPP-induced impairment in memory consolidation. Finally repeated administration of dopamine antagonist enhanced NMDA antagonist-induced responses in both tests. MK-801-induced locomotor activity was affected only after repeated haloperidol or sulpiride. The MK-801- or CPP-induced response in the one-trial inhibitory avoidance test was enhanced by sulpiride, haloperidol but also SCH 23390.

4.1. Locomotor activity

In agreement with previous studies (Carlsson and Carlsson, 1989; Ouagazzal et al., 1993, 1994) MK-801 induced a dose-dependent increase in locomotor activity. Since MK-801 has been demonstrated to be a potent antagonist of the NMDA receptors, acting at the channel site (Wong et al., 1988), this effect is possibly due to the blockade of these receptors. The lack of effect of low doses of competitive NMDA receptor antagonists on locomotor activity has also been previously described by some authors (Liljequist, 1991), but not by others (Svensson et al., 1991). The discrepancy between the effects of competitive and non-competitive antagonists on locomotor activity is difficult to explain, apart from the poor blood-brain barrier penetration of CPP compared to MK-801. However, Carlsson, 1993 suggested that if the binding of competitive antagonists is inhibited by endogenous glutamate and the opposite happens for non-competitive antagonists, the behavioral effects of the two classes of compounds could depend upon the state of activity – i.e. tonic vs. phasic – of the glutamatergic pathways mediating the locomotor response. This hypothesis however needs the support of experimental evidence.

This study also investigated the effects of dopamine antagonists on MK-801-induced activity. The dopamine D_1 receptor-selective antagonist tested, SCH 23390, was not able to affect the hyperactivity induced by MK-801, and this even at doses that decreased locomotion in saline-injected mice. The selective dopamine D_2 receptor antagonist sulpiride decreased MK-801-induced locomotor activity only at very high, sedative doses. The classical neuroleptic haloperidol reduced MK-801-induced activity also at doses without effect in naive mice. Several studies suggest that dopamine-selective antagonists are able to antagonize MK-801-induced locomotor effects only at rather high doses (Martin et al., 1994; Ouagazzal et al., 1993). They also suggest that dopamine D_2 receptor ligands are more efficacious in antagonizing MK-801 effects than dopamine D_1 receptor ligands are (Ouagazzal et al., 1993). The effects of the classical neuroleptic haloperidol on MK-801-induced locomotor activity that we found are in good accord with previous data (Tiedtke et al., 1990). Haloperidol has been described as a preferential dopamine D_2 receptor antagonist, its D_1/D_2 selectivity being, however, lower than that reported for sulpiride (Waddington and O'Boyle, 1989 for review). Blockade of both dopamine D_1 and D_2 receptors is much more efficacious in antagonizing MK-801 effects than the blockade of only a single class of receptors (Ouagazzal et al., 1993; Willins et al., 1993). Thus it is possible that the better efficacy of haloperidol, compared to the other dopamine antagonists used, in antagonizing MK-801 effects is due to an action of this drug on both receptors and that blockade of MK-801 locomotor effects occurs only when dopamine transmission is largely inhibited.

Our results do not support the view that MK-801-induced locomotion is dependent upon enhanced dopamine release. The locomotor effects of cocaine, amphetamine or other drugs able to enhance synaptic dopamine concentration, in fact, are preferentially antagonized by dopamine D_1 receptor antagonists (Cabib et al., 1991; Ouagazzal et al., 1993). In our study the dopamine D_1 receptor antagonist was devoid of effect. It should be noted that an intact dopaminergic system has been shown not to be necessary for the expression of NMDA-induced locomotor activity. 6-Hydroxydopamine lesions of the n. accumbens are not able to affect MK-801 hyperactivity (Ouagazzal et al., 1994; Mele and Pert, unpublished observation). Finally, a lack of effect of systemic MK-801 administration on dopamine release has also been shown with the microdialysis technique (Kashihara et al., 1990; Fontana et al., 1993).

It has been suggested that dopamine influences the corticostriatal glutamatergic pathway through dopamine D_2 receptors (Maura et al., 1989), and a similar functional organization has been reported for the n. accumbens (Yang and Mogenson, 1986). Acute dopamine D_2 receptor agonists have been shown to decrease glutamate efflux in the striatum (Maura et al., 1989; Yamamoto and Davy, 1992). It is therefore to be expected that the opposite will happen after the administration of dopamine D_2 receptor antagonists. This mechanism could be an alternative explanation

for the reduction of MK-801-induced activity by preferentially D_2 acting substances like haloperidol and sulpiride.

An interesting finding of this study was the effect of repeated neuroleptics on MK-801-induced activity. Our behavioral results show that haloperidol and sulpiride, but not SCH 23390, induced an increased sensitivity to MK-801. The kinetic results of the present study also indicate that these effects were not due to pharmacokinetic interactions, as MK-801 brain concentrations were comparable under the different experimental conditions.

Repeated administration of dopamine D_2 receptor antagonists has been reported to induce increased D_2 receptor binding both in the n. accumbens and in the striatum without affecting D_1 receptor sensitivity (Laruelle et al., 1992). Similar specific changes have been reported after chronic treatment with the atypical neuroleptic sulpiride (Rupniak et al., 1984). Repeated administration of the dopamine D_1 receptor antagonist SCH 23390 selectively enhanced the B_{max} of D_1 receptors (Creese and Chen, 1985).

A possible explanation for the observed increased response to MK-801 after repeated administration of neuroleptics is that the effect is due to an increase in dopamine D_2 receptors. However, as mentioned, acute MK-801 administration does not increase dopamine release in the dopamine terminal region (Kashihara et al., 1990; Fontana et al., 1993). Moreover there are no reports in the literature of a direct interaction of this drug with dopamine receptors. Our results show that repeated dopamine D_1 receptor antagonist administration was ineffective on MK-801 – induced behavioral responses. Since subchronic SCH 23390 increases D_1 receptor sensitivity, as well as behavioral responses to dopamine D_1 receptor agonists (Hess et al., 1986), if MK-801 was acting through a dopamine – dependent mechanism, an increase in MK-801 sensitivity would have been expected also after SCH 23390 treatment and this was not the case. An alternative explanation for the augmentation of the behavioral effects of MK-801, after prolonged neuroleptic treatment, as reported in this paper, could be a change in NMDA receptor sensitivity. This suggestion is supported also by biochemical evidence showing changes in CPP and MK-801 binding in different basal ganglia structures after 6-hydroxydopamine lesions (Samuel et al., 1990; Porter et al., 1994). A possible hypothesis to explain changes in NMDA receptor subtype, after manipulation of the dopaminergic system, is that blockade of dopamine receptor functioning could suppress a regulatory function on NMDA receptor cellular expression. Such a mechanism would be linked through common second messenger pathways at a postsynaptic level (Nestler et al., 1984; Calabresi et al., 1996). Alternatively, a presynaptic influence of dopamine receptors on glutamate release could be suggested (Yamamoto and Davy, 1992). Such a mechanism could induce, in repeatedly treated animals, prolonged changes in glutamate transmission, thus producing NMDA receptor changes at a postsynaptic level.

4.2. One-trial inhibitory avoidance

The second part of this study considered the possible interactions between NMDA receptor antagonists and dopamine agents on the one-trial inhibitory avoidance response. The dose-response curve for CPP and MK-801 showed an inhibitory effect of both NMDA receptor antagonists in this behavioral paradigm. These results are in good accord with previous reports showing an impairing effect of NMDA receptor antagonists on one-trial inhibitory avoidance performance (DeNoble et al., 1990; Venable and Kelly, 1990; Mele et al., 1995a,b). In most of these studies the drugs were administered either pre-trial (DeNoble et al., 1990; Venable and Kelly, 1990) or before the retention test (Venable and Kelly, 1990), to assess the effects of blockade of NMDA receptors on learning or retrieval respectively. We report on the effects of these drugs when administered immediately post-trial in the step-through dark avoidance paradigm. Post-trial administration has the advantage of reducing the effects of the drug treatments on motivational, sensory or motor mechanisms. Moreover we have recently shown that high doses of NMDA receptor antagonists are unable to affect the performance on the test day if injected post-trial without administering the shock (Mele et al., 1995a,b). The effects of NMDA receptor antagonist on test day performance appear to be due to a specific action on memory consolidation. It should however be mentioned that the literature is not always consistent in indicating an impairing effect of NMDA receptor antagonists on passive avoidance performance, when injected post-trial (Venable and Kelly, 1990). These differences, however, can be partially explained on the basis of strain differences in the response to drugs (Cestari et al., 1992), or as extensively discussed by Mondadori (Mondadori et al., 1989; Mondadori and Weiskrantz, 1993), they can depend on the test used, i.e. step-through vs. step-down.

In a second series of experiments we investigated the effects of post-trial injections of different dopamine receptor agonists on one-trial inhibitory avoidance performance. Both drugs induced a dose-dependent improvement in memory performance on the test day. This result is in good accord with previous reports on the effects of selective dopamine D_1/D_2 receptor agonists (Castellano et al., 1991) and dopamine uptake blockers (Cestari et al., 1996). Also in this case strain differences have been reported on the effects of dopamine receptor active drugs on the one-trial inhibitory avoidance response (Cestari et al., 1992).

We also found that dopamine agonists, at subthreshold doses, and independently of the receptor subclass involved, antagonized the impairing effects of NMDA receptor antagonists on memory consolidation. Therefore also in the modulation of the behavioral response in this paradigm there is a functional interaction between dopamine and NMDA systems.

Finally, we show that repeated administration of

dopamine antagonists induced an enhanced response to NMDA receptor antagonists as well as dopamine agonists in the one-trial inhibitory avoidance test. To our knowledge this is the first report of such behavioral sensitization observed in this paradigm. It is interesting to note that when the animals were challenged with selective dopamine D_1 or D_2 receptor agonists it was possible to discriminate between the subchronic treatments. Repeated administration of SCH 23390 did not change the response to subeffective doses of quinpirole while it enhanced the sensitivity to the selective dopamine D_1 receptor agonist SKF 38393 and the opposite happened after repeated administration of haloperidol or sulpiride, with no change in the response to SKF 38393, but an increased response to quinpirole. As mentioned, repeated blockade of dopamine receptors with selective antagonists induces an upregulation of the receptors (Creese and Chen, 1985; Laruelle et al., 1992), and is an explanation for these results.

The response to NMDA receptor antagonists was also enhanced after repeated treatment with dopamine antagonists. This effect, as expected from the acute association experiment, was independent of the dopamine antagonist used: SCH 23390, sulpiride and haloperidol, which show different affinities for dopamine D_1 and D_2 receptors, in fact (Waddington and O'Boyle, 1989) all induced a similar change in the response to NMDA receptor antagonists. Although it is difficult to determine the neural substrate underlying the interaction between the two neural systems modulating this response, it should be stressed that a releasing action of MK-801 on dopamine neurons seems unlikely since dopamine agonists and MK-801 have opposite effects on memory consolidation. The behavioral sensitization to NMDA receptor antagonists that we observed after repeated administration of dopamine antagonists cannot be due to the observed upregulation of dopamine receptors. If CPP and MK-801 were to act through the dopaminergic system to affect memory consolidation, an enhancement of memory performance, or in other words a reduction of the effect of NMDA receptor antagonists, would have been expected and this was not the case. As already discussed for the increased sensitivity to MK-801 seen in the locomotor activity test, also in this case an explanation for the observed effect is a change in NMDA receptor sensitivity induced by the repeated administration of dopamine receptor antagonists. Repeated administration of haloperidol has indeed been shown to induce changes in L-[^{3}H]glutamate binding in cortex (Ulas et al., 1993).

4.3. General conclusions

There are several points that should be stressed on the basis of these results.

1. Pharmacological manipulation of the dopamine system is able to modify the response to NMDA receptor antagonists in both the behavioral paradigms used in this study.
2. The present results support the hypothesis that these drugs have different sites of action and that different neural networks are possibly involved in the modulation of locomotor activity and memory consolidation. For example, dopamine agonists and NMDA receptor antagonists acted in opposite ways to modulate memory consolidation, while both elicited a similar stimulatory action on locomotor activity. Moreover high, sedative doses of dopamine antagonists were needed to attenuate the MK-801-induced locomotor response, while the memory consolidation impairment induced by MK-801 was sensitive to ineffective doses of dopamine receptor active drugs. Finally, an enhanced dopamine transmission, independently of the dopamine receptor class affected, induced an enhanced performance in the one-trial inhibitory avoidance test, while different regulatory actions have been suggested for the two dopamine receptor classes in the modulation of locomotor activity (Cabib et al., 1991).
3. The effect of repeated administration of dopamine receptor antagonists on NMDA receptor antagonist-induced behavioral responses suggests a change in receptor sensitivity after these treatments. These changes would be generalized since we observe them in both paradigms. Further they are possibly due to some kind of receptor-receptor interaction at a post-synaptic level, with the possibility of a heterologous regulation of NMDA receptors by the dopamine system (Porter et al., 1994).

It is interesting that only sulpiride and haloperidol, but not SCH 23390, induced an increased sensitivity to the locomotor effects of MK-801. Sulpiride and haloperidol are used in clinical therapy as antipsychotic agents, and a common feature of these drugs is that they are therapeutically effective only after repeated administration. An involvement of the glutamatergic system in the development of schizophrenia has been suggested on the basis of postmortem studies of glutamate levels in schizophrenic patients (Kim et al., 1980) as well as on the psychotomimetic action of the non-competitive NMDA receptor antagonist phencyclidine (Javitt and Zukin, 1991). On the basis of our results, we suggest that a possible mechanism of action of these drugs is to induce enduring adaptation of glutamatergic transmission.

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