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Nitric oxide synthase inhibitors block behavioral sensitization to methamphetamine in mice

Masuo Ohno *, Shigenori Watanabe

Department of Pharmacology, Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan

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Abstract

Repeated administration of methamphetamine (1.0 mg/kg) once daily for 7 consecutive days resulted in an augmentation of the locomotor-activating effect of methamphetamine (0.5 mg/kg) challenged 72 h after the last injection. Administration of the nitric oxide (NO) synthase inhibitor, N^G-nitro-L-arginine (10 and 30 mg/kg), before daily methamphetamine injections dose dependently prevented the development of behavioral sensitization to subsequent methamphetamine challenge. The mice given another NO synthase inhibitor, N^G-nitro-L-arginine methyl ester (100 mg/kg), before daily methamphetamine injections showed significantly less locomotor activity in response to 0.5 mg/kg methamphetamine challenge than the mice given daily methamphetamine alone. Such effects were not observed when the inactive isomer, N^G-nitro-D-arginine methyl ester (100 mg/kg), was administered daily prior to methamphetamine. Both NO synthase inhibitors exerted the acute effect to reduce spontaneous and methamphetamine-stimulated locomotor activity, while neither spontaneous locomotion nor hyperlocomotion in response to 1.0 mg/kg methamphetamine was altered 72 h after repeated administration of N^G-nitro-L-arginine (30 mg/kg) or N^G-nitro-L-arginine methyl ester (100 mg/kg) alone once daily for 7 days. On the other hand, pretreatment with the NMDA receptor antagonist, MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate), at 0.2 mg/kg also suppressed the development of sensitization to the locomotor-activating effect of methamphetamine. These findings suggest that NO formation possibly mediated by NMDA receptors is involved in mechanisms underlying the development of behavioral sensitization to methamphetamine.

Keywords: Methamphetamine; Locomotor activity; Sensitization; Nitric oxide (NO); N^G-Nitro-L-arginine; N^G-Nitro-L-arginine methyl ester; NMDA receptor

1. Introduction

It is well documented that activation of NMDA receptors is an absolute requirement for induction of hippocampal long-term potentiation, which models synaptic plasticity and is hypothesized to be a neural mechanism underlying memory formation (Collingridge and Bliss, 1987; Bliss and Collingridge, 1993). The sensitization, that refers to the increased responsiveness to certain drugs observed persistently after previous administration, can be considered to be a plasticity in the central nervous system (CNS) at the behavioral level. It appears that the NMDA receptor-dependent mechanism is also involved in behavioral sensitization since the NMDA receptor antagonists MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate) and CPP ((±)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) block the development of behavioral sensitization to locomotor activity and stereotypy induced in mice and rats by CNS stimulant drugs, such as amphetamine and cocaine (Karler et al., 1989, 1990, 1991; Wolf and Khansa, 1991; Kalivas and Alesdatter, 1993; Wolf and Jeziorsky, 1993). Recently, nitric oxide (NO) resulting from Ca^{2+} influx in response to NMDA receptor activation has been proposed to act as a retrograde neural messenger in long-term potentiation (O'Dell et al., 1991; Schuman and Madison, 1991; Fazeli, 1992). Processes mediated by NO formation also play a role in memory perfor-

* Corresponding author. Fax (81) (92) 632-2752.

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mance in some learning tasks (Chapman et al., 1992; Böhme et al., 1993; Estall et al., 1993; Ohno et al., 1993). In contrast to considerable evidence for the roles of NMDA receptors in behavioral sensitization to CNS stimulants, there are few studies concerning the involvement of NO synthesis in this phenomenon.

The purpose of the present study was to investigate the effecs of the NO synthase inhibitors, N^G-nitro-L-arginine and N^G-nitro-L-arginine methyl ester (Rees et al., 1990), on sensitization to the locomotor-stimulating effect of methamphetamine in mice.

2. Materials and methods

The animals used were male *ddY* strain mice (Japan SLC), weighing between 25–30 g at the start of the experiment. The mice were housed under constant temperature (23 ± 2°C) and a 12-h light/dark cycle (light period: 07.00–19.00 h). The mice were allowed free access to food and water throughout the experiment.

The locomotor activity of the mice was measured in a circular open-field apparatus (75 cm inner diameter and 40 cm height) equipped with a video camera above the center of the floor. The activity of each animal during a 3-min period was monitored by a video tracking system (Muromachi Kikai, BTA-2A), and the distance traveled was recorded. Locomotor activity was expressed as a percentage of that of the vehicle-injected group.

The drugs used in this study were methamphetamine hydrochloride (Dainippon Pharm. Co.), N^G-nitro-L-arginine (Sigma Chemical Co.), N^G-nitro-L-arginine methyl ester hydrochloride (Sigma Chemical Co.), N^G-nitro-D-arginine methyl ester hydrochloride (Sigma Chemical Co.) and MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate; Research Biochemicals International). Methamphetamine and MK-801 were dissolved in saline. N^G-Nitro-L-arginine, N^G-nitro-L-arginine methyl ester and N^G-nitro-D-arginine methyl ester were freshly prepared in saline for daily injections.

Methamphetamine (1.0 mg/kg i.p.) was administered once daily for 7 consecutive days. N^G-Nitro-L-arginine, N^G-nitro-L-arginine methyl ester, N^G-nitro-D-arginine methyl ester and MK-801 were administered i.p. daily 30 min before the methamphetamine injections. Locomotor activity was measured 20 min after methamphetamine was administered on day 1. The mice received no injection on days 8 and 9 of the experiment. Seventy-two hours after the last injection (on day 10), the mice were given open-field testing 20 min after they had the methamphetamine (0.5 mg/kg i.p.) challenge. Additional groups received a single injection of N^G-nitro-L-arginine, N^G-nitro-L-arginine methyl ester, N^G-nitro-D-arginine methyl ester and MK-801 50 min before test to evaluate the acute effect of these drugs on locomotor activity. Furthermore, the effects of repeated injections of N^G-nitro-L-arginine or N^G-nitro-L-arginine methyl ester alone on spontaneous locomotor activity and on hyperlocomotion induced by acute methamphetamine were examined: the mice received N^G-nitro-L-arginine or N^G-nitro-L-arginine methyl ester once daily for 7 consecutive days, and then they were tested for the open-field activities 20 min after saline or 1.0 mg/kg methamphetamine was administered on day 10. Drug administration and behavioral testing were performed between 10.00 and 14.00 h. After completion of the experiment, the animals were killed by exposure to a lethal level of ether anesthesia.

The significance of differences between the groups was determined by a one-way analysis of variance (ANOVA) followed by Dunnett's test when F ratios reached significance ($P < 0.05$).

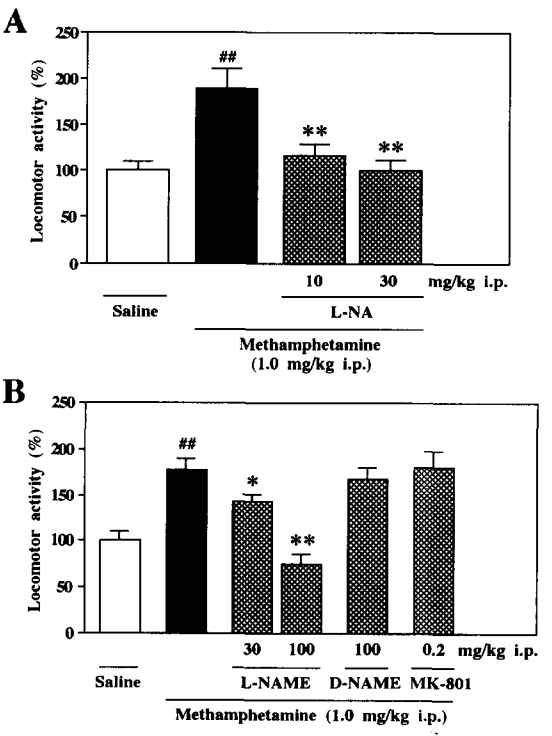

Fig. 1. Effects of NO synthase inhibitors and MK-801 on methamphetamine-induced increase in locomotor activity. The open-field activity was measured during a 3-min period, starting from 20 min after methamphetamine was administered. N^G-Nitro-L-arginine (L-NA), N^G-nitro-L-arginine methyl ester (L-NAME), N^G-nitro-D-arginine methyl ester (D-NAME) and MK-801 were administered 30 min before methamphetamine. Each column represents the mean ± S.E. of locomotor activity for 9–10 animals expressed as a percentage of that of the saline group. The significance of differences from the saline group ($^{\#\#} P < 0.01$) and from the methamphetamine group ($^{*} P < 0.05$, $^{**} P < 0.01$) was determined by means of a one-way ANOVA followed by Dunnett's test.

3. Results

Fig. 1A shows the acute effect of N^G-nitro-L-arginine on locomotor activity in response to 1.0 mg/kg methamphetamine on day 1. Methamphetamine at 1.0 mg/kg increased significantly locomotor activity ($F(1,17) = 14.32$, $P < 0.01$), as compared with that of the saline-injected group (1690 ± 93 cm, mean ± S.E.; $n = 10$). Pretreatment with N^G-nitro-L-arginine at doses of 10 and 30 mg/kg almost completely abolished the methamphetamine-induced increase in locomotor activity ($F(2,24) = 8.96$, $P < 0.01$). As shown in Fig. 1B, N^G-nitro-L-arginine methyl ester at 30 and 100 mg/kg also suppressed dose dependently the locomotor-activating effect of 1.0 mg/kg methamphetamine ($F(2,27) = 22.81$, $P < 0.01$). N^G-Nitro-D-arginine methyl ester at 100 mg/kg had no effect on locomotor activity in response to methamphetamine. As shown in Table 1, N^G-nitro-L-arginine at 10 and 30 mg/kg decreased locomotion in an open-field test when administered alone ($F(2,21) = 3.82$, $P < 0.05$), an effect that was significant only for the 30 mg/kg dose ($P < 0.05$). N^G-Nitro-L-arginine methyl ester at 30 and 100 mg/kg also reduced significantly locomotor activity when administered alone ($F(2,21) = 6.05$, $P < 0.01$), but N^G-nitro-D-arginine methyl ester at 100 mg/kg had no effect. MK-801 at 0.2 mg/kg produced almost as great a stimulation of locomotor activity as 1.0 mg/kg methamphetamine ($F(1,14) = 10.41$, $P < 0.01$). However, the combination of 0.2 mg/kg MK-801 and 1.0 mg/kg methamphetamine produced approximately the same increase in locomotion as either drug administered alone (Fig. 1B).

Fig. 2A shows the results obtained when rats given methamphetamine alone or together with N^G-nitro-L-arginine once daily for 7 days were challenged with 0.5 mg/kg methamphetamine on day 10. The 1.0 mg/kg methamphetamine-treated group exhibited significantly greater locomotor activity in response to 0.5 mg/kg methamphetamine than the saline-treated group ($F(1,17) = 40.31$, $P < 0.01$), indicating the development of behavioral sensitization to methamphetamine. Treatments with N^G-nitro-L-arginine (10 and 30 mg/kg) before daily injections of 1.0 mg/kg methamphetamine blocked dose dependently the development of sensitization to the locomotor-stimulating effect of methamphetamine ($F(2,24) = 9.50$, $P < 0.01$). As shown in Fig. 2B, the mice given N^G-nitro-L-arginine methyl ester (30 and 100 mg/kg) prior to daily methamphetamine injections showed less locomotor activity following 0.5 mg/kg methamphetamine challenge than the mice given daily methamphetamine alone ($F(2,27) = 4.77$, $P < 0.05$), an effect that reached significance only for the 100 mg/kg dose ($P < 0.05$). N^G-Nitro-D-arginine methyl ester (100 mg/kg), when administered repeatedly before 1.0 mg/kg methamphetamine, did not affect locomotor activity in response to 0.5 mg/kg methamphetamine challenge. Repeated treatment with MK-801 at 0.2 mg/kg before 1.0 mg/kg methamphetamine suppressed significantly the development of behavioral sensitization to subsequent challenge with 0.5 mg/kg methamphetamine ($F(1,18) = 23.36$, $P < 0.01$).

Repeated administration of N^G-nitro-L-arginine (30 mg/kg) or N^G-nitro-L-arginine methyl ester (100 mg/kg) alone once daily for 7 days did not affect spontaneous locomotor activity or hyperlocomotion in response to 1.0 mg/kg methamphetamine, as was assessed 72 h after the last administration of the NO synthase inhibitors (Fig. 3).

4. Discussion

The present study showed that the NO synthase inhibitors, N^G-nitro-L-arginine and N^G-nitro-L-arginine methyl ester, administered before daily methamphetamine injections, suppressed the development of sensitization to the locomotor-activating effect of methamphetamine in mice, whereas the inactive isomer, N^G-nitro-D-arginine methyl ester, had no effect. In contrast, Stewart et al. (1994) reported that N^G-

Table 1
Effects of NO synthase inhibitors and MK-801 on locomotor activity in an open-field test

Drug	mg/kg (i.p.)	n	Locomotor activity (%)
Saline	–	8	100.0 ± 9.0
N^G-Nitro-L-arginine	10	8	76.0 ± 9.8
	30	8	64.2 ± 9.2 [a]
N^G-Nitro-L-arginine methyl ester	30	8	62.3 ± 13.4 [a]
	100	8	55.1 ± 5.2 [b]
N^G-Nitro-D-arginine methyl ester	100	8	96.6 ± 13.0
MK-801	0.2	8	165.8 ± 18.3 [b]

Open-field activity was measured during a 3-min period, starting from 50 min after drugs were administered. Each value is the mean ± S.E. of locomotor activity expressed as a percentage of that of the saline group. The significance of differences from the saline group was determined by means of a one-way ANOVA followed by Dunnett's test, [a] $P < 0.05$, [b] $P < 0.01$.

nitro-L-arginine methyl ester (50 mg/kg) failed to interfere with the development of sensitization to the behavioral activating effect of amphetamine in rats. Recently, it has been demonstrated that N^G-nitro-L-arginine methyl ester acts not only as an inhibitor of NO synthase but also as a muscarinic receptor antagonist (Buxton et al., 1993). Blockade of muscarinic receptors augments amphetamine behavioral sensitization, since chronic administration of the muscarinic antagonist, scopolamine, enhances hyperlocomotion in response to amphetamine (Martin-Iverson et al., 1983). From these findings, it is reasonable to speculate that the antimuscarinic activity of N^G-nitro-L-arginine methyl ester offsets the ability of this compound to

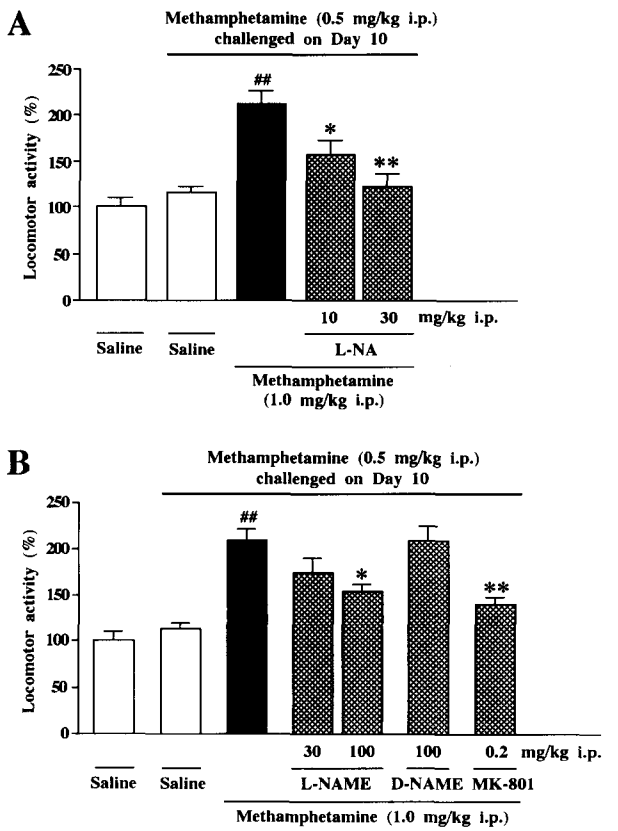

Fig. 2. Effects of NO synthase inhibitors and MK-801 on the development of behavioral sensitization to methamphetamine. The mice received saline or 1.0 mg/kg methamphetamine once daily for 7 consecutive days. N^G-Nitro-L-arginine (L-NA), N^G-nitro-L-arginine methyl ester (L-NAME), N^G-nitro-D-arginine methyl ester (D-NAME) and MK-801 were repeatedly administered 30 min before daily methamphetamine injections. After a 72-h period of abstinence (on day 10), the mice received a challenge dose of 0.5 mg/kg methamphetamine. The open-field activity was measured during a 3-min period, starting from 20 min after the methamphetamine challenge. Each column represents the mean ± S.E. of locomotor activity for 9–10 animals expressed as a percentage of that of the saline group. The significance of differences from the saline/methamphetamine challenge group ($^{\#\#}$ $P < 0.01$) and from the methamphetamine/methamphetamine challenge group (* $P < 0.05$, ** $P < 0.01$) was determined by means of a one-way ANOVA followed by Dunnett's test.

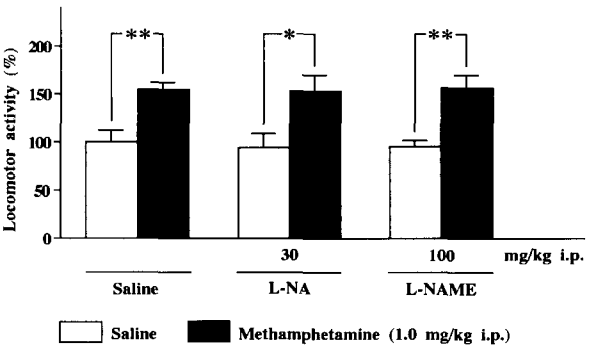

Fig. 3. Effects of repeated administration of NO synthase inhibitors on spontaneous locomotor activity and methamphetamine-induced hyperlocomotion. The mice received saline, N^G-nitro-L-arginine (L-NA) or N^G-nitro-L-arginine methyl ester (L-NAME) once daily for 7 consecutive days. After a 72-h period of abstinence (on day 10), the mice received saline or 1.0 mg/kg methamphetamine. The open-field activity was measured during a 3-min period, starting from 20 min after the administration. Each column represents the mean ± S.E. of locomotor activity for 8 animals expressed as a percentage of that of the saline/saline group. The significance of differences from the saline group was determined by means of a one-way ANOVA followed by Dunnett's test, * $P < 0.05$, ** $P < 0.01$.

prevent behavioral sensitization by inhibiting NO formation. In fact, another NO synthase inhibitor, N^G-nitro-L-arginine (30 mg/kg), which was devoid of antimuscarinic activity (Buxton et al., 1993), was able to almost completely attenuate methamphetamine behavioral sensitization, while N^G-nitro-L-arginine methyl ester significantly but only partially suppressed sensitization even when the higher dose of 100 mg/kg was administered in this experiment. Taken together, these results suggest that NO formation is involved in mechanisms underlying the development of behavioral sensitization to methamphetamine.

N^G-Nitro-L-arginine and N^G-nitro-L-arginine methyl ester, but not N^G-nitro-D-arginine methyl ester, decreased both spontaneous and methamphetamine-stimulated locomotor activity in mice. N^G-Nitro-L-arginine methyl ester has also been reported to reduce spontaneous locomotor activity and amphetamine- or cocaine-induced locomotor stimulation in rats (Pudiak and Bozarth, 1993; Stewart et al., 1994). Stewart et al. (1994) showed, using in vivo microdialysis, that N^G-nitro-L-arginine methyl ester did not reduce the basal or amphetamine-stimulated dopamine release in the nucleus accumbens, a brain structure known to be involved in the acute behavioral activating effects of CNS stimulants. Thus, it is not conceivable that the acute depressant effect of the NO synthase inhibitor on the CNS stimulant-induced hyperlocomotion results from reduced dopamine release; this effect may be caused by the independent motor suppression. In the present study, behavioral sensitization was evaluated by methamphetamine challenge 72 h after termination of the daily drug injections. It was unlikely that the

locomotor-depressant effects of N^G-nitro-L-arginine and N^G-nitro-L-arginine methyl ester accounted for their effectiveness to block methamphetamine behavioral sensitization, since the locomotor activity or hyperlocomotion in response to methamphetamine was not altered 72 h after repeated administration of the NO synthase inhibitors alone. On the other hand, the NMDA antagonist, MK-801, also prevented methamphetamine sensitization, but MK-801 by itself stimulated locomotor activity. Thus, it appears that the NO synthase inhibitors and MK-801 exert their acute effects on locomotion through different mechanisms for affecting methamphetamine sensitization.

The NMDA receptor antagonists, including MK-801 and CPP, have been reported to block the development of sensitization to locomotor-stimulant and stereotypic effects of amphetamine and cocaine in mice and rats (Karler et al., 1989, 1990, 1991; Wolf and Khansa, 1991; Kalivas and Alesdatter, 1993; Wolf and Jeziorski, 1993). In the present study, MK-801 was also effective to prevent methamphetamine behavioral sensitization. Thus, it appears that behavioral sensitization to CNS stimulants develops through activation of NMDA receptors. It has been found that some central effects of NMDA are likely to be mediated by the activation of NO synthase with the subsequent release of NO (Garthwaite, 1991; Snyder and Bredt, 1991; Bredt and Snyder, 1992). Pudiak and Bozarth (1993) recently reported that not only blockade of NMDA receptors but also inhibition of NO synthesis attenuated the development of sensitization to the locomotor-stimulating effect of cocaine in rats. In this study, similar results were obtained with regard to methamphetamine behavioral sensitization in mice. Furthermore, both NO synthase inhibitors and NMDA receptor antagonists have been demonstrated to block the development of morphine analgesic tolerance and dependence in mice and rats (Trujillo and Akil, 1991; Kolesnikov et al., 1993; Tiseo and Inturrisi, 1993; Majeed et al., 1994; Rauhala et al., 1994). Taken together, these findings suggest a common role for NMDA receptor activation followed by the subsequent NO release in mediating long-lasting changes in the neuronal responsiveness to CNS stimulants and morphine resulting from the repeated administration.

The NO synthase inhibitors were administered repeatedly before daily methamphetamine injections for 7 days, but were not given before the sensitization test challenged with methamphetamine on day 10. However, the inhibition of NO synthase activity may still be significant 72 h after the last administration, since it is found that the effect of N^G-nitro-L-arginine is irreversible, and that brain NO synthase activity does not return to normal levels for at least 5 days after intraperitoneal injections of N^G-nitro-L-arginine (Dwyer et al., 1991). Thus, it was possible that the NO synthase inhibition affected not only the development but also the expression of behavioral sensitization to methamphetamine in this experiment. Since a mechanism underlying the expression of behavioral sensitization to the CNS stimulant drugs is hypothesized to be an enhanced release of dopamine (Robinson and Becker, 1986), it is interesting to note that NO stimulates dopamine release from striatal slices (Zhu and Luo, 1992; Lonart et al., 1993). Likewise, Ishida et al. (1994) demonstrated that N^G-nitro-L-arginine, but not N^G-nitro-D-arginine, perfused through the microdialysis probe, substantially suppressed NMDA-evoked increase in striatal dopamine release in unanesthetized, freely moving rats, suggesting the involvement of NO formation in the dopamine release resulting from NMDA receptor activation. Taken together, these findings suggest that amphetamine or methamphetamine activates NMDA receptors by releasing glutamate (Moroni et al., 1981), which in turn leads to NO formation, releasing a quantity of dopamine in addition to that normally released by the CNS stimulant. Although further study will be necessary to clarify the precise mechanism, the functional interactions between the dopaminergic and excitatory amino acid systems via NO formation may, at least in part, contribute to the development and/or expression of behavioral sensitization to methamphetamine.

References

Bliss, T.V.P. and G.L. Collingridge, 1993, A synaptic model of memory: long-term potentiation in the hippocampus, Nature 361, 31.

Böhme, G.A., C. Bon, M. Lemaire, M. Reibaud, O. Piot, J.-M. Stutzmann, A. Doble and J.-C. Blanchard, 1993, Altered synaptic plasticity and memory formation in nitric oxide synthase inhibitor-treated rats, Proc. Natl. Acad. Sci. USA 90, 9191.

Bredt, D.S. and S.H. Snyder, 1992, Nitric oxide, a novel neuronal messenger, Neuron 8, 3.

Buxton, I.L.O., D.J. Cheek, D. Eckman, D.P. Westfall, K.M. Sanders and K.D. Keef, 1993, N^G-Nitro-L-arginine methyl ester and other alkyl esters of arginine are muscarinic receptor antagonists, Circ. Res. 72, 387.

Chapman, P.F., C.M. Atkins, M.T. Allen, J.E. Haley and J.E. Steinmetz, 1992, Inhibition of nitric oxide synthesis impairs two different forms of learning, Neuroreport 3, 567.

Collingridge, G.L. and T.V.P. Bliss, 1987, NMDA receptors: their role in long-term potentiation, Trends Neurosci. 10, 288.

Dwyer, M.A., D.S. Bredt and S.H. Snyder, 1991, Nitric oxide synthase: irreversible inhibition by L-N^G-nitroarginine in brain in vitro and in vivo, Biochem. Biophys. Res. Commun. 176, 1136.

Estall, L.B., S.J. Grant and G.A. Cicala, 1993, Inhibition of nitric oxide (NO) production selectively impairs learning and memory in the rat, Pharmacol. Biochem. Behav. 46, 959.

Fazeli, M.S., 1992, Synaptic plasticity: on the trail of the retrograde messenger, Trends Neurosci. 15, 115.

Garthwaite, J., 1991, Glutamate, nitric oxide and cell-cell signalling in the nervous system, Trends Neurosci. 14, 60.

Ishida, Y., R. Yamamoto and Y. Mitsuyama, 1994, Effects of L- and D-enantiomers of N^ω-nitro-arginine on NMDA-evoked striatal dopamine overflow, Brain Res. Bull. 34, 483.

Kalivas, P.W. and J.E. Alesdatter, 1993, Involvement of *N*-methyl-D-aspartate receptor stimulation in the ventral tegmental area and amygdala in behavioral sensitization to cocaine, J. Pharmacol. Exp. Ther. 267, 486.

Karler, R., L.D. Calder, I.A. Chaudhry and S.A. Turkanis, 1989, Blockade of 'reverse tolerance' to cocaine and amphetamine by MK-801, Life Sci. 45, 599.

Karler, R., I.A. Chaudhry, L.D. Calder and S.A. Turkanis, 1990, Amphetamine behavioral sensitization and the excitatory amino acids, Brain Res. 537, 76.

Karler, R., L.D. Calder and S.A. Turkanis, 1991, DNQX blockade of amphetamine behavioral sensitization, Brain Res. 552, 295.

Kolesnikov, Y.A., C.G. Pick, G. Ciszewska and G.W. Pasternak, 1993, Blockade of tolerance to morphine but not to κ opioids by a nitric oxide synthase inhibitor, Proc. Natl. Acad. Sci. USA 90, 5162.

Lonart, G., K.L. Cassels and K.M. Johnson, 1993, Nitric oxide induces calcium-dependent [^{3}H]dopamine release from striatal slices, J. Neurosci. Res. 35, 192.

Majeed, N.H., B. Przewłocka, H. Machelska and R. Przewłocki, 1994, Inhibition of nitric oxide synthase attenuates the development of morphine tolerance and dependence in mice, Neuropharmacology 33, 189.

Martin-Iverson, M.T., J.-F. Leclere and H.C. Fibiger, 1983, Cholinergic-dopaminergic interactions and the mechanisms of action of antidepressants, Eur. J. Pharmacol. 94, 193.

Moroni, F., R. Corradetti, F. Casamenti, G. Moneti and G. Pepeu, 1981, The release of endogenous GABA and glutamate from the cerebral cortex of the rat, Naunyn-Schmied. Arch. Pharmacol. 316, 235.

O'Dell, T.J., R.D. Hawkins, E.R. Kandel and O. Arancio, 1991, Tests of the roles of two diffusible substances in long-term potentiation: evidence for nitric oxide as a possible early retrograde messenger, Proc. Natl. Acad. Sci. USA 88, 11285.

Ohno, M., T. Yamamoto and S. Watanabe, 1993, Deficits in working memory following inhibition of hippocampal nitric oxide synthesis in the rat, Brain Res. 632, 36.

Pudiak, C.M. and M.A. Bozarth, 1993, L-NAME and MK-801 attenuate sensitization to the locomotor-stimulating effect of cocaine, Life Sci. 53, 1517.

Rauhala, P., J.J. Idänpään-Heikkilä, R.K. Tuominen and P.T. Männistö, 1994, *N*-Nitro-L-arginine attenuates development of tolerance to antinociceptive but not to hormonal effects of morphine, Eur. J. Pharmacol. 259, 57.

Rees, D.D., R.M.J. Palmer, R. Schulz, H.F. Hodson and S. Moncada, 1990, Characterization of three inhibitors of endothelial nitric oxide synthase in vitro and in vivo, Br. J. Pharmacol. 101, 746.

Robinson, T.E. and J.B. Becker, 1986, Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis, Brain Res. Rev. 11, 157.

Schuman, E.M. and D.V. Madison, 1991, A requirement for the intercellular messenger nitric oxide in long-term potentiation, Science 254, 1503.

Snyder, S.H. and D.S. Bredt, 1991, Nitric oxide as a neuronal messenger, Trends Pharmacol. Sci. 12, 125.

Stewart, J., S.-E. Deschamps and S. Amir, 1994, Inhibition of nitric oxide synthase does not block the development of sensitization to the behavioral activating effects of amphetamine, Brain Res. 641, 141.

Tiseo, P.J. and C.E. Inturrisi, 1993, Attenuation and reversal of morphine tolerance by the competitive *N*-methyl-D-aspartate receptor antagonist, LY274614, J. Pharmacol. Exp. Ther. 264, 1090.

Trujillo, K.A. and H. Akil, 1991, Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801, Science 251, 85.

Wolf, M.E. and M. Jeziorski, 1993, Coadministration of MK-801 with amphetamine, cocaine or morphine prevents rather than transiently masks the development of behavioral sensitization, Brain Res. 613, 291.

Wolf, M.E. and M.R. Khansa, 1991, Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine, Brain Res. 562, 164.

Zhu, X.-Z. and L.-G. Luo, 1992, Effect of nitroprusside (nitric oxide) on endogenous dopamine release from rat striatal slices, J. Neurochem. 59, 932.