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Effects of modulation of nitric oxide on acoustic startle responding and prepulse inhibition in rats

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Abstract

The nitric oxide-arginine pathway is intimately connected to the release of dopamine and glutamate, two neurotransmitter systems that may be dysfunctional in schizophrenia. In addition, nitric oxide synthase inhibitors share several behavioral effects with the psychotomimetic drug, phencyclidine. Previous research has found that phencyclidine-like drugs disrupt prepulse inhibition of the acoustic startle response, an animal model of sensorimotor gating, an attentional process that is disrupted in certain neuropsychiatric disorders in humans (e.g., acute schizophrenia). The purpose of the present study was to examine the effects of nitric oxide modulators in this model. Following injection with a nitric oxide modulator or phencyclidine, rats were placed in startle chambers in which they were exposed to acoustic pulses presented alone or preceded by a prepulse. As in previous reports, phencyclidine disrupted prepulse inhibition at doses that did not affect startle during pulse alone trials. In contrast, the nitric oxide synthase inhibitors, N^G-nitro-L-arginine (L-NOARG) and N^G-nitro-L-arginine methyl ester (L-NAME), dose-dependently decreased startle during pulse alone trials, but neither drug affected prepulse inhibition. A nitric oxide precursor, L-arginine, produced similar results. Sodium nitroprusside (a nitric oxide releaser) and 7-nitroindazole (a third nitric oxide synthase inhibitor) did not affect startle amplitudes during pulse alone or prepulse + pulse trials. The present results suggest that modulation of nitric oxide synthesis or availability does not disrupt sensorimotor gating of the acoustic startle response and is probably not involved in mediation of this type of attentional deficit in humans. © 1997 Elsevier Science B.V.

Keywords: Nitric oxide (NO); Startle; Prepulse inhibition; Startle reaction; Schizophrenia

1. Introduction

The intracellular messenger, nitric oxide, plays an important role in a number of physiological processes, including maintenance of normal cardiovascular function (Moncada et al., 1991), memory formation (Bohme et al., 1993), responses to neurotrauma and stroke (Lipton et al., 1993; Reif, 1993) and tolerance to drugs of abuse (Babey et al., 1994; Bhargava, 1995). Nitric oxide may also be implicated in schizophrenia. First, nitric oxide is intimately connected with dopamine and glutamate, two neurotransmitter systems that may be dysfunctional in schizophrenia. Nitric oxide has been shown to increase the release of dopamine and inhibit its uptake in the striatum (Lonart et al., 1993; Pogun et al., 1994). Glutamate stimulation of NMDA receptors results in release of nitric oxide which may mediate the effects of NMDA receptor stimulation and/or may result in feedback inhibition of the presynaptic neuron via a redox modulatory site (Garthwaite, 1991; Lipton, 1993; Manzoni et al., 1992; Montague et al., 1994). Second, previous research has found that levels of nicotinamide adenine dinucleotide diaphorase (NADPH), a co-factor of the nitric oxide synthase and arginine reaction, and activity of nitric oxide synthase are altered in postmortem brains or platelets, respectively, of schizophrenic patients (Akbarian et al., 1993a,b; Das et al., 1995; Karson et al., 1991).

Prepulse inhibition of the acoustic startle response is an animal model that has been used to investigate deficits in attentional processing. The acoustic startle response is a reflexive movement exhibited following sudden exposure to a loud noise. Prepulse inhibition is the phenomenon whereby exposure to a weak acoustic stimulus presented a few milliseconds before the sudden loud noise will de-

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crease the magnitude of the resulting startle response (Hoffman and Ison, 1980). This phenomenon occurs in both humans and animals. The degree of prepulse inhibition reflects integration of sensory and motor processes in the brain, including level of functioning of attentional processing systems, and has been shown to be disrupted in patients with acute schizophrenia and certain other neuropsychiatric disorders (Braff et al., 1978). In animals, a similar deficit can be produced by administration of dopamine agonists or phencyclidine-like noncompetitive NMDA receptor antagonists (Geyer et al., 1990). Interestingly, phencyclidine can produce psychosis-like subjective effects in humans who abuse this drug (Javitt and Zukin, 1991), as can high doses of amphetamine (Angrist and Gershon, 1970).

The purpose of the present project was to examine the effects of modulators of nitric oxide on prepulse inhibition of the acoustic startle response. In the present study, we examined the effects of N^G-nitro-L-arginine (L-NOARG), N^G-nitro-L-arginine methyl ester (L-NAME) and 7-nitroindazole (nitric oxide synthase inhibitors), L-arginine (nitric oxide precursor) and sodium nitroprusside (nitric oxide releaser) on startle amplitudes during pulse alone trials and on prepulse inhibition of the acoustic startle response. Phencyclidine was also tested as a positive control in this procedure.

2. Materials and methods

2.1. Subjects

Drug naive adult male Sprague-Dawley rats (weighing between 225–249 g at the beginning of the study), obtained from Harlan (Dublin, VA, USA), were weighed and handled daily for one week after delivery before testing began. The rats were individually housed in wire cages in a temperature-controlled (20–22°C) environment with 12-h light-dark cycle (lights on at 7 a.m.). They were transported to the laboratory for startle sessions. Water and standard rodent chow were freely available in the home cages.

2.2. Apparatus

Each startle chamber (San Diego Instruments, San Diego, CA, USA) enclosed a clear Plexiglas cylinder (8.2 cm diameter) which rested on a Plexiglas panel (10×20 cm). Acoustic stimuli were produced by a super tweeter, mounted 24 cm above the cylinder. Each of the three chambers was illuminated by a 15-watt houselight mounted in the ceiling above the cylinder. An IBM-compatible computer with SR-Lab software and interface (San Diego Instruments) was used to present stimuli and to record data.

2.3. Surgical procedure

Rats were injected with atropine (0.4 mg/kg, i.p.) and were anesthetized with 60 mg/kg ketamine (i.m.) and 32 mg/kg pentobarbital (i.p.) and placed in a standard rat stereotaxic apparatus. Guide cannulae were implanted in the right lateral ventricle in 6 of the 12 rats and in the left lateral ventricle in the other 6 rats (coordinates: 0.8 mm caudal to bregma, 1.4 mm lateral from midline and 3.9 mm ventral from dura; Paxinos and Watson, 1986). Penicillin (30 000 units, s.c.) was injected before surgery for prophylactic purposes.

2.4. Startle procedure

Rats were transported to the laboratory at least 30 min before startle sessions. After being injected with the test drug, they were returned to their home cages for the remainder of the pre-session injection interval. Before the start of the startle session, rats were placed in the startle chambers for a 5-min adaptation period, during which they were exposed to 69 dB[A] background noise. This background noise continued throughout the session. Each startle session consisted of 61 trials (average intertrial interval = 15 s). During the first trial, rats were exposed to a 120 dB[A] acoustic stimulus. Subsequent trials were of four types, presented in mixed order, for a total session duration of approximately 20 min. On one type of trial, the rats were exposed to a 120 dB[A] acoustic stimulus (pulse trials). Startle amplitudes during these trials indicate the degree of sensorimotor reactivity. A second type of trial consisted of a 85 dB[A] prepulse (20 ms duration) followed by a 120 dB[A] pulse (prepulse + pulse trials). The degree to which startle amplitudes during this type of trial was decreased as compared to responding during the 120 dB[A] pulse alone trials is a measure of prepulse inhibition or sensorimotor gating. The other two types of trials consisted of exposure to a 85 dB[A] prepulse alone (prepulse trials) or to 69 dB[A] background noise (nostim trials). Startle amplitudes during these trials were typically very low. These trials were control trials used to measure the degree of 'noise' in the procedure. A startle session was comprised of a first trial and three blocks of 20 trials (five of each of the four types). Startle pulse duration was held constant at 40 ms. A 100 ms delay was imposed between prepulse and pulse stimuli.

The dose–effect curve for each test drug was determined in a within-subjects design with 12 rats per drug. The order of doses was randomized across the rats in each group, according to a latin square design. At least 72 h intervened between test sessions for each rat. One rat died during the L-NAME dose–effect curve due to causes unrelated to this study; hence, only 11 rats were tested at some doses of this drug. In addition, the cannulae used to administer L-arginine i.c.v. became blocked before completion of the L-arginine dose–effect curve in some rats.

2.5. Drugs

L-NAME HCl (Research Biochemicals International, Natick, MA, USA), L-NOARG (RBI), L-arginine (RBI), sodium nitroprusside (Sigma, St. Louis, MO, USA) and phencyclidine (National Institute on Drug Abuse, Rockville, MD, USA) were mixed in sterile water or physiological saline. 7-Nitroindazole (Sigma) was dissolved in dimethyl sulfoxide (DMSO). With the exception of L-arginine, all nitric oxide modulators were administered i.p. at a volume of 1 ml/kg, 30 min before the start of the startle session. L-Arginine was injected i.c.v. at a volume of 5 μl over a period of 2 min, 15 min pre-session. Phencyclidine was injected s.c. at a volume of 1 ml/kg, 20 min before the start of the session.

2.6. Statistical analysis

Startle score was defined as the average of 100 1-ms voltage readings. Prepulse inhibition was calculated for prepulse + pulse trials as a percentage of pulse alone scores [(mean startle amplitude for pulse alone trials − mean startle amplitude for prepulse + pulse trials)/mean startle amplitude for pulse alone trials] × 100. For each dose–effect curve, separate SAS repeated measures GLM procedures (SAS Institute, Cary, NC, USA) were used to analyze percent prepulse inhibition and average startle amplitudes during pulse alone trials. Tukey post-hoc tests ($\alpha = 0.05$) were used to specify differences revealed by significant GLMs. (Startle amplitudes during prepulse alone trials and nostim trials were consistently low and are not shown.)

3. Results

As reported in previous studies, phencyclidine (3 mg/kg) significantly disrupted prepulse inhibition ($F(4,44) = 11.15$, $P = 0.0001$) without affecting startle during pulse alone trials at any dose (Fig. 1, left panels). Sodium nitroprusside (0.3–3 mg/kg, i.p.) did not affect startle amplitudes during pulse alone trials at the doses tested (Fig. 1, center panels). One rat that was tested with a 10 mg/kg dose of sodium nitroprusside died soon after receiving the drug; hence, additional rats were not tested at this higher dose. Although L-arginine (30–300 μg, i.c.v.) did not produce statistically significant changes in startle amplitudes during pulse alone trials, responding at the 300 μg concentration was lower (compared to water), suggesting a dose-dependent trend toward decreases with higher doses of the drug ($F(3,21) = 1.93$, $P = 0.16$) (Fig. 1, right panels). Unlike phencyclidine, neither of the positive modulators of nitric oxide affected prepulse inhibition.

The nitric oxide synthase inhibitors, L-NOARG (3–100 mg/kg, i.p.) and L-NAME (30–560 mg/kg) dose-dependently decreased startle amplitudes during pulse alone trials ($F(4,44) = 4.20$, $P = 0.006$ and $F(4,42) = 3.12$, $P = 0.02$, respectively) (Fig. 2, left and center panels). In contrast, 7-nitroindazole (3–100 mg/kg, i.p.) did not affect startle amplitudes during pulse alone trials, although

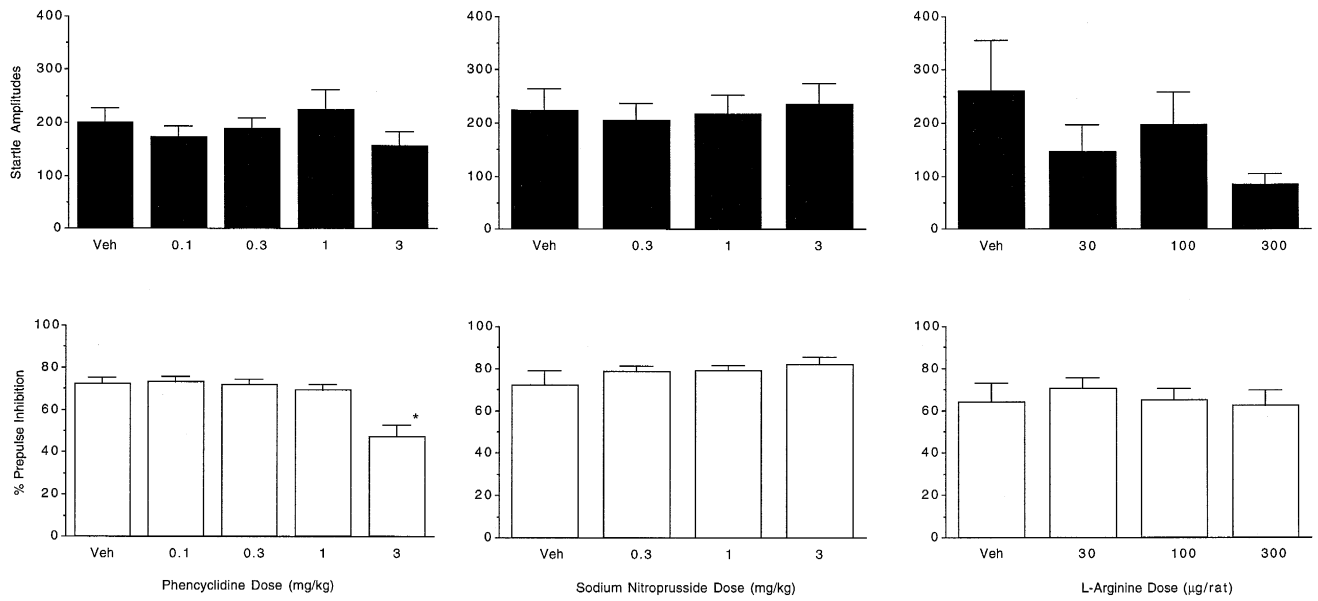

Fig. 1. Effects of phencyclidine (left panels), the nitric oxide releaser sodium nitroprusside (center panels) and the nitric oxide precursor L-arginine (right panels), on acoustic startle amplitudes during pulse alone trials (filled bars, top panels) and on percent prepulse inhibition during prepulse + pulse trials (open bars, bottom panels). Values at each concentration represent means (±S.E.M.) for 8–10 rats (L-arginine) and 12 rats (phencyclidine and sodium nitroprusside). Phencyclidine was injected s.c.; L-arginine was administered i.c.v.; sodium nitroprusside was administered i.p.

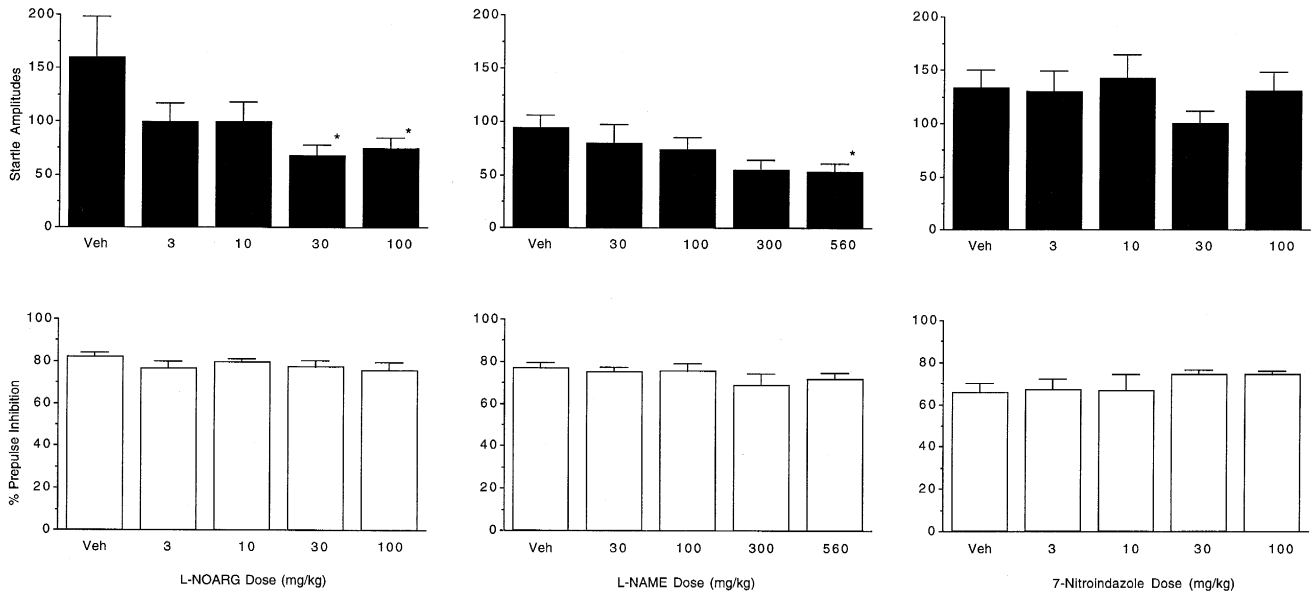

Fig. 2. Effects of the nitric oxide synthase inhibitors, L-NOARG (left panels), L-NAME (center panels), and 7-nitroindazole (right panels), on acoustic startle amplitudes during pulse alone trials (filled bars, top panels) and on percent prepulse inhibition during prepulse + pulse trials (open bars, bottom panels). Values at each dose represent means (±S.E.M.) for 11–12 rats. All drugs were administered i.p.

there was a trend for the 30 mg/kg dose to decrease startle amplitudes ($F(4,44) = 2.09$, $P = 0.10$) (Fig. 2, right panels). None of these three nitric oxide synthase inhibitors affected prepulse inhibition at any dose.

4. Discussion

L-NOARG and L-NAME, two of the three nitric oxide synthase inhibitors tested in the present study, dose-dependently decreased startle amplitudes during pulse alone trials. Although 7-nitroindazole, a third nitric oxide synthase inhibitor, did not significantly affect startle amplitudes during pulse alone trials, the 30 mg/kg dose produced a nonsignificant trend of decreased startle amplitudes. None of the nitric oxide inhibitors affected the degree of prepulse inhibition during prepulse + pulse trials. A previous study demonstrated that a 30 mg/kg dose of 7-nitroindazole administered intraperitoneally crossed the blood-brain barrier and was distributed to various brain areas, including the striatum, hippocampus and cerebral cortex, and that peak inhibition of nitric oxide synthase occurred at 30 min post-injection (MacKenzie et al., 1994), the time at which test sessions were conducted in the present study. Further, 7-nitroindazole has exhibited activity in other behavioral tests at comparable doses (Connop et al., 1994; Jewett et al., 1996; Vaupel et al., 1995). Hence, the time of administration or degree of CNS penetrability of 7-nitroindazole do not offer ready explanations of the relative lack of behavioral activity of this drug in the startle model. It also is possible that nitric oxide synthase inhibitors may not represent a homogeneous class of drugs in terms of their behavioral effects.

Behavioral pharmacology research with nitric oxide synthase inhibitors has been limited to date, although this situation is rapidly changing. Based on the results of this research, the profile of behavioral effects produced by nitric oxide synthase inhibitors most resembles that of NMDA receptor antagonists. Similar to NMDA receptor antagonists, nitric oxide synthase inhibitors have been shown to produce anxiolytic effects (Volke et al., 1995), anticonvulsant effects (De Sarro et al., 1991) and neuroprotective effects (Nagafusi et al., 1995; Schulz et al., 1995), to impair learning and/or memory (Chapman et al., 1992; Yamada et al., 1995) and to prevent the development of tolerance or sensitization to certain drugs of abuse (Khanna et al., 1993; Kolesnikov et al., 1992; Majeed et al., 1994; Pudiak and Bozarth, 1993). At high doses, L-NAME and 7-nitroindazole produced phencyclidine-like discriminative stimulus effects (Jewett et al., 1996). On the other hand, not all studies have found that the effects of nitric oxide synthase inhibitors mimic those of NMDA receptor antagonists (e.g., Connop et al., 1994; Deutsch et al., 1996; Stewart et al., 1994; Wiley et al., 1995). These conflicting results may be due, in part, to the dual role of nitric oxide. The nitric oxide that is released upon glutamate stimulation of the NMDA receptor serves as a second messenger that produces effects that mimic those of glutamate agonists; however, it may also serve as a retrograde messenger that acts on a NMDA receptor-associated redox modulatory site to produce feedback inhibition of the receptor (Garthwaite, 1991; Lipton, 1993; Manzoni et al., 1992; Montague et al., 1994). Hence, the actions of nitric oxide synthase inhibitors may depend upon their effect upon the balance between excitatory and inhibitory influ-

ences in the NMDA receptor-associated nitric oxide system. In fact, Rundfeldt et al. (1995) have shown that the propensity of nitric oxide synthase inhibitors to produce anticonvulsant vs. proconvulsant effects in the same seizure model is dependent upon dose and time of administration.

In the acoustic startle procedure, the effects of nitric oxide synthase inhibitors resemble those of competitive and glycine-site NMDA receptor antagonists or NMDA (versus those of phencyclidine-like drugs). Whereas phencyclidine-like NMDA receptor antagonists disrupt prepulse inhibition (e.g., present study), drugs that are antagonists at other sites within the NMDA receptor complex decrease startle amplitudes at higher doses without affecting prepulse inhibition (Balster et al., 1995; Mansbach, 1991). NMDA itself does not affect startle responding at non-convulsive doses (Mansbach, 1991). Yet, although the effects of nitric oxide inhibitors are more similar to those of competitive and glycine-site NMDA receptor antagonists than to those of phencyclidine, decreases in startle amplitudes without effect on prepulse inhibition can also be produced by drugs that do not affect glutamate neurotransmission (Johansson et al., 1995; Kokkinidis and McCarter, 1990).

The effects of positive modulators of nitric oxide synthesis and availability on acoustic startle responding and prepulse inhibition are similarly nonspecific. L-Arginine produced a trend toward dose-dependent decreases in startle amplitudes during pulse alone trials, but did not alter prepulse inhibition. Sodium nitroprusside (0.3–3.0 mg/kg) did not affect startle amplitudes or prepulse inhibition over the dose range tested. The ability to test higher doses of sodium nitroprusside was severely limited by its toxicity. The one rat in which a 10 mg/kg dose was injected died within 30 min of drug administration. In mice, the LD_{50} for sodium nitroprusside is 12 mg/kg (Yamamoto, 1992).

The present results suggest that modulation of nitric oxide synthesis or availability either decreases sensorimotor reactivity at higher drug doses (L-NAME, L-NOARG and L-arginine) or has no effect on it (7-nitroindazole and sodium nitroprusside), but does not affect sensorimotor gating. These patterns of startle responding are seen with competitive and glycine-site NMDA receptor antagonists as well as with NMDA itself, but differ from the pattern of dose-dependent disruption of sensorimotor gating produced by phencyclidine and other open NMDA channel blockers. In a phencyclidine discrimination study, however, high doses of nitric oxide synthase inhibitors substituted for phencyclidine. These results, in combination with those of the present study, suggest that the propensity for nitric oxide modulators to produce phencyclidine-like behavioral effects may be task-specific. Further, since drug-induced disruption of prepulse inhibition of the acoustic startle response models certain attentional deficits that have been observed in schizophrenia, the present results suggest that direct involvement of the nitric oxide-arginine pathway in mediation of these deficits is not likely.

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References

Akbarian, S., Bunney, W.E., Potkin, S.G., Wigal, S.B., Hagman, J.O., Sandman, C.A., Jones, E.G., 1993a. Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch. Gen. Psychiatry 50, 169.

Akbarian, S., Vinuela, A., Kim, J.J., Potkin, S.G., Bunney, W.E., Jones, E.G., 1993b. Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Arch. Gen. Psychiatry 50, 178.

Angrist, B., Gershon, S., 1970. The phenomenology of experimentally induced amphetamine psychosis: preliminary observations. Biol. Psychiatry 2, 95.

Babey, A.-M., Kolesnikov, Y., Cheng, J., Inturrisi, C.E., Trifilletti, R.R., Pasternak, G.W., 1994. Nitric oxide and opioid tolerance. Neuropharmacology 33, 1463.

Balster, R.L., Mansbach, R.S., Shelton, K.L., Nicholson, K.L., Grech, D.M., Wiley, J.L., Li, H., Weber, E., 1995. Behavioral pharmacology of two novel substituted quinoxalinedione glutamate antagonists. Behav. Pharmacol. 6, 577.

Bhargava, H., 1995. Attenuation of tolerance to, and physical dependence on, morphine in the rat by inhibition of nitric oxide synthase. Gen. Pharmacol. 26, 1049.

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

Braff, D., Stone, C., Callaway, E., Geyer, M., Glick, I., Bali, L., 1978. Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiology 15, 339.

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

Connop, B.P., Rolfe, N.G., Boegman, R.J., Jhamandas, K., Beninger, R.J., 1994. Potentiation of NMDA-mediated toxicity on nigrostriatal neurons by a low dose of 7-nitro indazole. Neuropharmacology 33, 1439.

Das, I., Khan, N.S., Puri, B.K., Sooranna, S.R., De Belleroche, J., Hirsch, S.R., 1995. Elevated platelet calcium mobilization and nitric oxide synthase activity may reflect abnormalities in schizophrenic brain. Biochem. Biophys. Res. Commun. 212, 375.

De Sarro, G.B., Donato di Paola, E., De Sarro, A., Vidal, M.J., 1991. Role of nitric oxide in the genesis of excitatory amino acid-induced seizures from the deep prepiriform cortex. Fundam. Clin. Pharmacol. 5, 503.

Deutsch, S.I., Rosse, R.B., Paul, S.M., Tomasino, V., Koetzner, L., Morn, C.B., Mastropaolo, J., 1996. 7-Nitroindazole and methylene

blue, inhibitors of neuronal nitric oxide synthase and NO-stimulated guanylate cyclase, block MK-801-elicited behaviors in mice. Neuropsychopharmacology 15, 37.

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

Geyer, M.A., Swerdlow, N.R., Mansbach, R.S., Braff, D.L., 1990. Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res. Bull. 25, 485.

Hoffman, H.S., Ison, J.R., 1980. Reflex modification in the domain of startle
I. Some empirical findings and their implications for how the nervous system processes sensory input. Psychol. Rev. 87, 175.

Javitt, D.C., Zukin, S.R., 1991. Recent advances in the phencyclidine model of schizophrenia. Am. J. Psychiatry 148, 1301.

Jewett, D.C., Butelman, E.R., Woods, J.H., 1996. Nitric oxide synthase inhibitors produce phencyclidine-like behavioral effects in pigeons. Brain Res. 715, 25.

Johansson, C., Jackson, D.M., Zhang, J., Svensson, L., 1995. Prepulse inhibition of acoustic startle, a measure of sensorimotor gating: effects of antipsychotics and other agents in rats. Pharmacol. Biochem. Behav. 52, 649.

Karson, C.N., Garcia-Rill, E., Biedermann, J., Mrak, R.E., Husain, M.M., Skinner, R.D., 1991. The brain stem reticular formation in schizophrenia. Psychiatry Res. Neuroimaging 40, 31.

Khanna, J.M., Morato, G.S., Shah, G., Chau, A., Kalant, H., 1993. Inhibition of nitric oxide synthesis impairs rapid tolerance to ethanol. Brain Res. Bull. 32, 43.

Kokkinidis, L., McCarter, B.D., 1990. Behavioral evidence implicating dopamine in sensorimotor arousal and norepinephrine in the sedative effects of antidepressant drugs. Psychopharmacology 100, 542.

Kolesnikov, Y.A., Pick, C.G., Pasternak, G.W., 1992. N^G-Nitro-L-arginine prevents morphine tolerance. Eur. J. Pharmacol. 221, 399.

Lipton, S.A., 1993. Prospects for clinically tolerated NMDA antagonists: open-channel blockers and alternative redox states of nitric oxide. Trends Neurosci. 16, 527.

Lipton, S.A., Choi, Y.-B., Pan, Z.-H., Lel, S.Z., Chen, H.-S.V., Sucher, N.J., Loscaizo, J., Singel, D.J., Stamler, J.S., 1993. A redox-based mechanism for the neuroprotective and neurodestructive effects of nitric oxide and related nitroso-compounds. Nature 364, 626.

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

MacKenzie, G.M., Rose, S., Bland-Ward, P.A., Moore, P.K., Jenner, P., Marsden, C.D., 1994. Time course of inhibition of brain nitric oxide synthase by 7-nitro indazole. NeuroReport 5, 1993.

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

Mansbach, R.S., 1991. Effects of NMDA receptor ligands on sensorimotor gating in the rat. Eur. J. Pharmacol. 202, 61.

Manzoni, O., Prezeau, L., Marin, P., Deshager, S., Bockaert, J., Fagni, L., 1992. Nitric oxide-induced blockade of NMDA receptors. Neuron 8, 653.

Moncada, S., Palmer, R.M.J., Higgs, E.A., 1991. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol. Rev. 43, 109.

Montague, P.R., Gancayco, C.D., Winn, M.J., Marchase, R.B., Friedlander, M.J., 1994. Role of NO production in NMDA receptor-mediated neurotransmitter release in cerebral cortex. Science 263, 973.

Nagafusi, T., Sugiyama, M., Muto, A., Makino, T., Miyauchi, T., Nabata, H., 1995. The neuroprotective effect of a potent and selective inhibitor of type I NOS (L-MIN) in a rat model of focal cerebral ischaemia. NeuroReport 6, 1541.

Paxinos, G., Watson, C., 1986. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York, NY.

Pogun, S., Baumann, M.H., Kuhar, M.J., 1994. Nitric oxide inhibits [^{3}H]dopamine uptake. Brain Res. 641, 83.

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

Reif, D.W., 1993. Delayed production of nitric oxide contributes to NMDA-mediated neuronal damage. NeuroReport 4, 566.

Rundfeldt, C., Koch, R., Richter, A., Mevissen, M., Gerecke, U., Loscher, W., 1995. Dose-dependent anticonvulsant and proconvulsant effects of nitric oxide synthase inhibitors on seizure threshold in a cortical stimulation model in rats. Eur. J. Pharmacol. 274, 73.

Schulz, J.B., Matthews, R.T., Muqit, M.M.K., Browne, S.E., Beal, M.F., 1995. Inhibition of neuronal nitric oxide synthase by 7-nitroindazole protects against MPTP-induced neurotoxicity in mice. J. Neurochem. 64, 936.

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

Vaupel, D.B., Kimes, A.S., London, E.D., 1995. Comparison of 7-nitroindazole with other nitric oxide synthase inhibitors as attenuators of opioid withdrawal. Psychopharmacology 118, 361.

Volke, V., Koks, S., Vasar, E., Bourin, M., Bradwejn, J., Mannisto, P.T., 1995. Inhibition of nitric oxide synthase causes anxiolytic-like behaviour in an elevated plus-maze. NeuroReport 6, 1285.

Wiley, J.L., Cristello, A.F., Balster, R.L., 1995. Effects of site-selective NMDA receptor antagonists in an elevated plus-maze model of anxiety in mice. Eur. J. Pharmacol. 294, 101.

Wiley, J.L., Golden, K.M., Bowen, S.E., 1996. Effects of modulation of nitric oxide on acoustic startle and prepulse inhibition in rats. Soc. Neurosci. Abstr. 22, 1677.

Yamada, K., Noda, Y., Nakayama, S., Komori, Y., Sugihara, H., Hasegawa, T., Nabeshima, T., 1995. Role of nitric oxide in learning and memory and in monoamine metabolism in the rat brain. Br. J. Pharmacol. 115, 852.

Yamamoto, H.A., 1992. Nitroprusside intoxication: protection of alpha-ketoglutarate and thiosulphate. Food Chem. Toxicol. 30, 887.