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Behavioral effects of NMDA receptor agonists and antagonists in combination with nitric oxide-related compounds☆

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Abstract

Responding of rats was maintained under a 120-response fixed ratio (FR) schedule of food delivery, and animals received individual and combined injections of *N*-methyl-D-aspartic acid (NMDA), phencyclidine hydrochloride, (+)-MK-801 hydrogen maleate (MK-801), (±)-2-amino-5-phosphonopentanoic acid (AP5), 7-chlorokynurenic acid (7CK), ifenprodil tartrate, N^G-nitro-L-arginine methyl ester hydorchloride (L-NAME), 7-nitroindazole, aminoguanidine hemisulfate, L-arginine, molsidomine, sodium nitroprusside, and 8-(diethylamino)octyl 3,4,5-trimethoxybenzoate hydrochloride (TMB-8). Behavioral suppression after NMDA was completely and dose-dependently reversed by MK-801, phencyclidine, AP5, and aminoguanidine; partially and dose-dependently attenuated by molsidomine, ifenprodil, and 7CK; and not attenuated at all by L-NAME, 7-nitroindazole, or TMB-8. These findings suggested that behavioral suppression after NMDA was associated with nitric oxide from the inducible synthase. In a second series of experiments, comparable behavioral suppression by 0.1 mg/kg MK-801, but not 3 mg/kg phencyclidine, was attenuated by nitroprusside, molsidomine, and L-arginine, suggesting that suppressions from MK-801 and phencyclidine were mediated by different final common pathways, and that behavioral suppression from MK-801, but not phencyclidine, may be associated with Ca^{2+}-dependent nitric oxide.
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1. Introduction

The NMDA-type glutamate receptor has been implicated in the behavioral processes of learning and memory (Land and Riccio, 1997; Morris and Davis, 1994; Sanger and Joly, 1991), opioid analgesia (Ben-Eliyahu et al., 1992; Marek et al., 1991), locomotion (Powell and Holtzman, 1998; Shoaib et al., 1997), and Parkinson's disease (Herrling, 1997); and there are reports that elevated Ca^{2+} is associated with clinically defined affective disorder (Helmeste and Tang, 1998; Yamawaki et al., 1998). In addition, there is evidence that administration of NMDA into hippocampal (Kojima et al., 1998) and striatal (Hanania and Johnson, 1998) tissue increases nitric oxide (NO) production, and it is generally considered that behavioral effects of NMDA—and related compounds—may involve a final common pathway that is influenced by the intracellular flow of Ca^{2+} and its subsequent role in production of NO (Brenman and Bredt, 1997; Christopherson and Bredt, 1997; Menéndez et al., 1997; Robbins and Grisham, 1997).

NO is characterized as a "free radical" diffusible gas and is perhaps best known for producing rapid cardiovascular vasodilation as a mechanism of action for clinical effects of sublingual nitro glycerin. NO also functions as a neurotransmitter in both the central and peripheral nervous systems (Brenman and Bredt, 1997; Prast and Philippu, 2001) and is implicated in opioid analgesia (Bhargava et al., 1997; Inturrisi, 1994; Kolesnikov et al., 1997; Machelska et al., 1997) and withdrawal (Capasso et al., 1998), locomotion (Johansson et al., 1997), feeding (Racotta et al., 1998), learning (Ingram et al., 1998), memory (Ohno et al., 1994; Prickaerts et al., 1997; Zou et al., 1998), discrimination (Green et al., 1997; Jewett et al., 1996), and immunosup-

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pressant processes that are perhaps related to neurodegenerative disease such as Huntington's and Parkinson's (Smith and Bennett, 1997; Snyder et al., 1998). NO is also implicated in cholinergic function for α7 nicotinic (Adams and Freedman, 1997; Fedele et al., 1998; Scheller et al., 1998; Shimohama et al., 1998; Smith et al., 1998) and M1 (Cuadra and El-Fakahany, 1997; Gómez-Vargas et al., 1999) and muscarininc M_2 (Wang et al., 1997) receptors, as well as in brain levels of adenosine (Delaney et al., 1998; Young et al., 1997), histamine (Nilsson et al., 1997), glutamate (McNaught and Brown, 1998; Pogun et al., 1994), and dopamine (Ali and Itzhak, 1998; Fleckenstein et al., 1997; Itzhak, 1997; Silva et al., 1998).

NO is produced from oxidation of L-arginine by one of at least three forms of the enzyme nitric oxide synthase (NOS; (Knowles, 1997; Robbins and Grisham, 1997). Endothelial (*e*NOS) and neuronal (*n*NOS) isoforms can be recruited by intracellular Ca^{2+} and calmodulin, and their resulting "constitutive" NO is considered a major influence on vasodilation and neurotransmission, respectively. A third isoform (*i*NOS) is not thought to be activated by Ca^{2+}, but to be induced in response to inflammatory stimuli, and its resulting "nonconstitutive" NO is considered a major influence on arthritis (Clancy et al., 1998; Fletcher et al., 1998), stroke (Christopherson and Bredt, 1997; Gobbel et al., 1997), toxic shock (Christopherson and Bredt, 1997), apoptosis (Mannick et al., 1997), and multiple sclerosis (Snyder et al., 1998).

Present experiments studied effects of NO-related drugs and NMDA-site agonists and antagonists on operant responding of rats maintained under a fixed-ratio (FR) schedule of food delivery, and then studied joint effects for combinations of selected NO-related compounds and drugs known to act at the NMDA receptor. The purpose of these experiments was to characterize interactions among drugs that control intracellular Ca^{2+} and drugs known to involve Ca^{2+}-dependent NO. Drugs studied were *N*-methyl-D-aspartic acid (NMDA; namesake receptor agonist), phencyclidine hydrochloride (channel-site indirect antagonist), (+)-MK-801 hydrogen maleate (channel-site indirect antagonist), (±)-2-amino-5-phosphonopentanoic acid (AP5; surface-site direct antagonist), 7-chlorokynurenic acid (7CK; glycine-site antagonist), ifenprodil tartrate (polyamine-site antagonist), N^G-nitro-L-arginine methyl ester hydorchloride (L-NAME hydrochloride; *e*NOS inhibitor), 7-nitroindazole (*n*NOS inhibitor), aminoguanidine hemisulfate (*i*NOS inhibitor), L-arginine (NO precursor), molsidomine (NO donor), sodium nitroprusside (NO donor), and TMB-8 (8-(diethylamino)octyl 3,4,5-trimethoxybenzoate hydrochloride; intracellular Ca^{2+} channel antagonist).

2. Materials and methods

Twenty-four experimentally naive male Sprague–Dawley rats were 120 days old at the beginning of experiments. Water was continuously available in both experimental and home cages, and animals were maintained at approximately 200 g body weight with a diet of Noyes Pellets Formula A and Purina Rodent Chow. Behavioral reinforcers were 45-mg food pellets and daily supplemental feeding always occurred at least 45 min after completion of experimental sessions (Bacotti, 1976).

Experiments were conducted with Gerbrands Model C Rat Chambers (23 cm long × 20 cm wide × 20 cm high; Gerbrands) containing a response lever (Gerbrands G6312 or LVE/BRS 121-05); a recessed food cup (F7020, Gerbrands) mounted on the same wall; three white lights centered above manipulanda on the front wall; and a single red light and speaker mounted on the rear wall. Reinforcers were delivered with a solenoid-operated dispenser (G5100 Gerbrands). Each chamber was enclosed in a larger sound attenuating box, and control and recording of all scheduled events used networked computers (Palya and Walter, 1993) and cumulative stepping recorders (Model C-3, Gerbrands).

Lever pressing was established by selectively reinforcing desired features of behavior, and responding was initially maintained under a 1-response FR schedule delivering reinforcers after each response in the presence of a 7-W white light and a distinctive tone. In the absence of the light and tone, responses had no scheduled consequences (TimeOut). After responding occurred reliably in the presence, but not in the absence, of the light and tone, reinforcers were delivered under increasingly larger FR requirements. Under final conditions, responding in the presence of the light and tone produced three food pellets after completion of each 120 responses (FR120), and responding in the absence of light and tone had no scheduled consequences (TimeOut). Daily experimental sessions comprised five 10-min periods of light and tone, each separated by a 1-min TimeOut. Animals responded under these conditions Monday–Friday without receiving any drug until variability of daily response rates was within 20% for two successive weeks.

After responding was stable, drugs were administered either 5 or 15 min prior to experimental sessions (i.p.) on Tuesdays and Fridays with a provision that the same drug was not administered more than once weekly. Phencyclidine was not administered more often than once every 2 weeks. Experiments studied at least three observations for at least four to five doses of NMDA (3–56 mg/kg in 0.1 N NaOH and saline; Sigma-Aldrich), AP5 (1–10 mg/kg in saline; Research Biochemicals), 7CK (1–30 mg/kg in 0.1N NaOH and saline; Research Biochemicals), ifenprodil (0.1–130 mg/kg in saline; Sigma), MK-801 HCl (0.01–0.17 mg/kg in saline; Research Biochemicals), phencyclidine HCl (0.3–5.6 mg/kg in saline; Research Biochemicals), L-arginine HCl (300–1700 mg/kg in saline; Sigma-Aldrich), L-NAME (3–40 mg/kg in saline; Research Biochemicals), 7-nitroindazole (3–30 mg/kg in dimethyl sulfoxide (DMSO) and saline; Research Biochemicals), aminoguanidine (10–72 mg/kg in saline; Research Biochemicals), TMB-8 HCl (1–10 mg/kg in saline; Research Biochemicals), molsido-

mine (1–10 mg/kg in propylene glycol; Alexis); and sodium nitroprusside (0.01–0.56 mg/kg in saline; Research Biochemicals). Doses of several drugs were selected on the basis of their reported safe physiological effects and not on the principal criteria that operant responding be decreased (e.g., Aleixandre et al., 1995; Kivastik et al., 1996; Mayer et al., 1994; Olney et al., 1991; Reynolds et al., 1991). When effects of combined drugs were studied, the first drug was administered 15 min, and the second drug 5 min, prior to sessions.

Twelve rats were used for experiments studying response suppression from NMDA, and 12 rats were used for experiments studying response suppression from phencyclidine and MK-801. Results are expressed as means ± the sample S.D. (*not* the standard error of the mean) for responses per second and percent change from control value, and effects were considered meaningful when there was no overlap in sample S.D.

3. Results

Responding was readily controlled and maintained under the FR120 schedule, and rates and patterns of both responding and food delivery were comparable to those reported in the archives for similar schedules and parameters (Ferster and Skinner, 1957). FR120 responding occurred at 1.42–1.66 responses/s and animals received all available reinforcers in each session.

FR responding was unaffected by doses studied for L-arginine, aminoguanidine, AP5, 7CK, ifenprodil, nitroprusside, and TMB-8, and responding was decreased at largest doses of NMDA, 7-nitroindazole, MK-801, and phencyclidine (Fig. 1).

After studying effects of individual drugs on FR responding, effects were studied for combined administrations of 56 mg/kg NMDA and selected doses of these other drugs. Responding had been markedly suppressed by 56 mg/kg

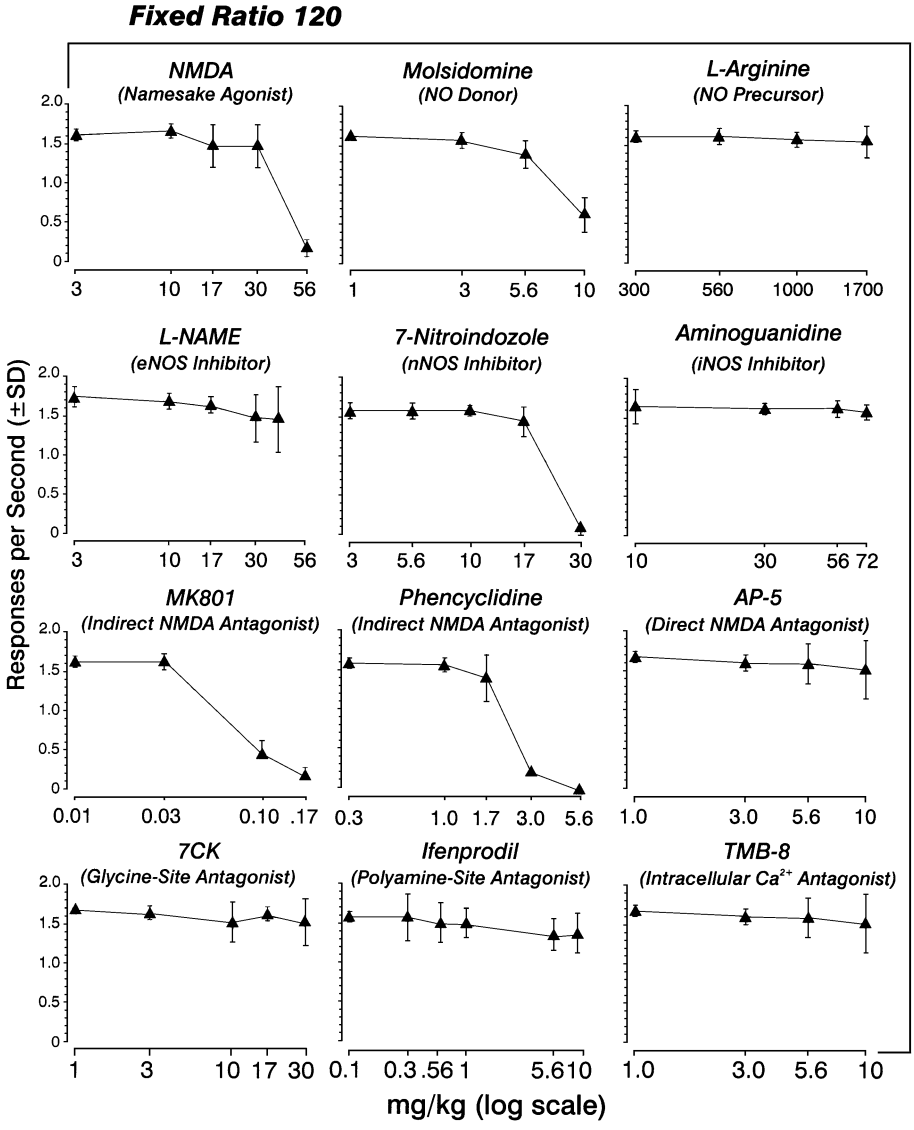

Fig. 1. Dose effects (3 determinations ± S.D.) of drugs on overall rate of responding maintained under the FR120 schedule of food delivery.

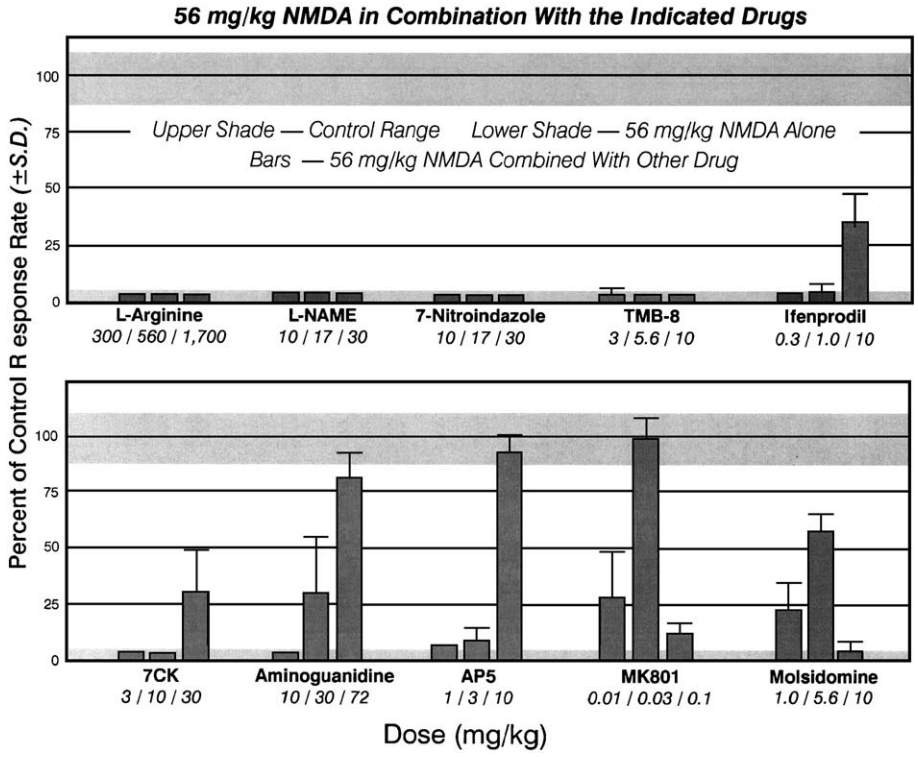

Fig. 2. Percent change in FR120 responding after 56 mg/kg NMDA, both alone and in combination with other drugs (3 determinations ± S.D.). The upper shade indicates non-drug control range; the lower shade indicates the range after NMDA alone; and vertical bars indicate joint effects of the labelled drug and NMDA.

NMDA, and results of combined drugs are reported as percent change from control responding (Fig. 2).

Suppression by 56 mg/kg NMDA was not affected by L-arginine, L-NAME, 7-nitroindazole, or TMB-8. In contrast, suppression by NMDA was completely and dose-dependently attenuated by AP5, MK-801, phencyclidine, and aminoguanidine. In comparison, suppression by NMDA was partially attenuated by molsidomine, ifenprodil, and

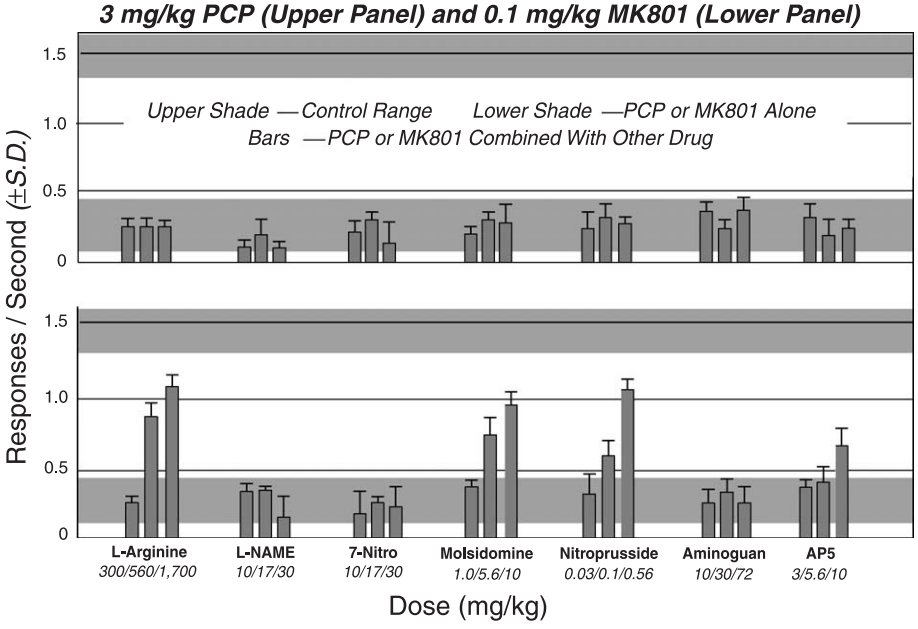

Fig. 3. Dose effects on FR120 responding after 3 mg/kg phencyclidine (upper panel) and 0.1 mg/kg MK-801 (lower panel), both alone and in combination with other drugs (3 determinations ± S.D.). The upper shade indicates non-drug control range; the lower shade indicates the range after either phencyclidine or MK-801 alone; and vertical bars indicate joint effects of the labelled drug and either phencyclidine (upper) or MK-801 (lower).

7CK. Suppression by NMDA was exacerbated by L-arginine and L-NAME, and some animals died after combined administration of 56 mg/kg NMDA and 40 mg/kg L-NAME. Additionally, animals who became prostrate after combined administration of NMDA and L-NAME recuperated quickly after administration of 72 mg/kg aminoguanidine.

Because phencyclidine and MK-801 interfere with intracellular flow of Ca^{2+} at the NMDA site, it is possible that their effects on operant responding resulted from reduced intracellular Ca^{2+} and a consequent reduction in Ca^{2+}-dependent levels of NO. Present experiments studied influences of L-arginine, L-NAME, 7-nitroindazole, molsidomine, nitroprusside, and aminoguanidine on effects of equi-suppressive doses of phencyclidine (3 mg/kg) and MK-801 (0.1 mg/kg). Sodium nitroprusside and molsidomine are direct, Ca^{2+}-independent donors of constitutive NO, whereas L-arginine generates NO provided that adequate stores of Ca^{2+} and calmodulin are available (Ogonowski et al., 2000).

FR responding suppressed by 3 mg/kg phencyclidine (Fig. 3, upper panel) was not altered by doses of any second drug. In comparison, responding suppressed by 0.1 mg/kg MK-801 (Fig. 3, lower panel) was markedly attenuated by L-arginine, molsidomine, and nitroprusside, and was partially attenuated by AP5.

4. Discussion

Present results are the first to characterize dose-effects of several NO-related drugs on operant responding and to describe their influence on behavioral effects of NMDA. Because intracellular flow of Ca^{2+} is a principal result of NMDA receptor activity, attenuation of NMDA suppression by both surface-site (AP5) and channel-site (phencyclidine and MK-801) antagonists, as well as partial attenuation by the polyamine-site (ifenprodil) and glycine-site (7CK) antagonists, suggested that behavioral suppression from 56 mg/kg NMDA resulted from excessive intracellular Ca^{2+}. Furthermore, because intracellular Ca^{2+} is essential for endogenous generation of endothelial and neuronal NOS, previous discussion has considered that neurotoxic effects of NMDA might be mediated in part by increased levels of NO produced by Ca^{2+}-fostered *e*NOS or *n*NOS (Farrell and Blake, 1996; Richter et al., 1997). However, NMDA-suppressed operant responding in the present experiment was not attenuated by intermediate doses of either L-NAME or 7-nitroindazole, and animals who were rendered prostrate by 56 mg/kg NMDA were made even worse by 30 and 40 mg/kg L-NAME. Thus, although it is well documented that exogenous NMDA can increase constitutive NO in the striatum, (Christopherson and Bredt, 1997; Menéndez et al., 1997), present results with L-NAME and 7-nitroindazole suggest that behavior suppressed from 56 mg/kg NMDA did not result from NO arising from constitutive *e*NOS or *n*NOS.

Results from previous in vitro experiments have suggested that increased NOS following administration of bradykinin or substance P can sometimes deplete intracellular L-arginine (Endres et al., 1998; Ogonowski et al., 1997). During such conditions of limited L-arginine, oxygen substitutes as a substrate for NOS and results in peroxynitrite as a byproduct which may mediate neural and cardiovascular toxicity (Ulrich et al., 1997). If excessive intracellular Ca^{2+} may also increase synthesis of NO and deplete L-arginine, supplemental L-arginine might have attenuated effects of NMDA in the present experiment. This did not occur, however, and a contrasting observation was that animals appeared qualitatively worse following NMDA and 1.7 g/kg L-arginine than after NMDA and smaller doses of L-arginine. These effects suggest that NMDA suppression did not result from depleted L-arginine and peroxynitrite in a manner similar to that suggested to occur after bradykinin and substance P.

In marked contrast to the absence of attenuated suppression after L-NAME, 7-nitroindazole, and L-arginine, NMDA-suppressed behavior was readily attenuated by the *i*NOS inhibitor aminoguanidine—which also consistently and quickly reversed severe prostration after combined administration of NMDA and 40 mg/kg L-NAME or NMDA and 1.7 g/kg L-arginine. Results from previous in vitro experiments have consistently shown that large amounts of *i*NOS-derived NO are generated independently of Ca^{2+} in response to the presence of bacterial lipopolysaccharides and cytokines. This *i*NOS-derived NO results in a cascading process of disruption of mitochondrial respiration, damaged DNA, activation of poly(ADP ribose) synthetase, and subsequent depletion of ATP (Almeida et al., 1999; Dalkara and Moskowitz, 1998). Present findings suggested that *i*NOS-derived NO can also result from stimulation of the NMDA receptor and that *i*NOS inhibitors can be an important adjunct to competitive and noncompetitive NMDA antagonists in cases of excitatory-amino acid toxicity.

In addition to the rapid and extensive reversal of suppression from 56 mg/kg NMDA after inhibition of *i*NOS, but not constitutive NOS, there was nevertheless substantial attenuation of suppression by small and intermediate doses of the constitutive NO donor molsidomine. On one hand, therefore, insensitivity of response suppression to inhibition of consititutive NOS—or application of an important precursor of constitutive NO—suggested that Ca^{2+}-dependent constitutive NO did not mediate response suppression after NMDA stimulation. Yet, on the other hand, response suppression from NMDA stimulation was paradoxically quite sensitive to a direct supply of constitutive NO. This apparent inconsistency of influences from constitutive NO on behavioral suppression from NMDA stimulation indicates a need for further study, but smaller doses of molsidomine may have resulted in an independent source of constitutive NO which relaxed peripheral endothelial tissue, sped blood flow, and thereby quickened the clearance of NMDA. A similar influence of blood flow has been sug-

gested to explain the attenuation of effects of ketamine by L-NAME (Mueller and Hunt, 1998).

In addition to studying influences of NO-related drugs on response suppression from NMDA stimulation, the present experiment also studied influences of these same NO-related drugs on response suppression from NMDA antagonism. If behavioral suppression after NMDA antagonism was mediated by reduced constitutive NOS after reduction of Ca^{2+} through the NMDA channel, then it was expected that Ca^{2+}-independent NO donors, and perhaps L-arginine as well, would reverse effects of NMDA antagonism. Nitroprusside, molsidomine, and L-arginine did attenuate suppression from 0.1 mg/kg MK-801, but did not attenuate comparable suppression from 3 mg/kg phencyclidine. There are numerous previous reports of different behavioral effects from surface-site and channel-site NMDA antagonists (Bespalov et al., 1998; Koek et al., 1987; Koek and Colpaert, 1990), and there is evidence as well that MK-801, but not phencyclidine, attenuates loss of brain cells after stroke (Olney et al., 1987). Present results are therefore consistent with earlier findings that important behavioral effects of NMDA antagonism are not always the same simply by virtue of decreased intracellular Ca^{2+}.

In summary, a principal finding of the present experiment was that inhibition of *i*NOS, and not *e*NOS or *n*NOS, attenuated behavioral suppression from 56 mg/kg NMDA. Previous findings have consistently reported that *i*NOS inhibitors can reverse toxicity resulting from Ca^{2+}-independent sources of NO (e.g., Brune et al., 1998), and present results suggest that this nonconstitutive NO is also influenced by NMDA stimulation.

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