

7-Nitroindazole and Methylene Blue, Inhibitors of Neuronal Nitric Oxide Synthase and NO-Stimulated Guanylate Cyclase, Block MK-801-Elicited Behaviors in Mice

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We examined the abilities of 7-nitroindazole and methylene blue, inhibitors of the neuronal isoform of nitric oxide synthase (NOS) and nitric oxide-stimulated guanylate cyclase activity respectively, to attenuate explosive episodic jumping behavior(s) ("popping") elicited by MK-801 in mice. MK-801, like phencyclidine (PCP), is a high-affinity, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor. We have postulated that MK-801-elicited popping behavior in mice represents an animal model of schizophrenia, because popping behavior is markedly inhibited/antagonized by both typical and atypical antipsychotic drugs. In the present study, popping behavior induced by MK-801 was measured using an automated detection system that quantifies

vertical displacements on the testing platform. 7-Nitroindazole (100 mg/kg) and methylene blue (32 and 100 mg/kg) significantly reduced the number and force of MK-801-elicited popping behavior. Mouse rotorod performance did not differ between animals receiving 7-nitroindazole, methylene blue, or their respective vehicles, suggesting that attenuation of MK-801-elicited popping behavior was not due to either sedation or ataxia caused by 7-nitroindazole or methylene blue. Our findings suggest that nitric oxide may, in part, mediate behaviors induced by NMDA receptor antagonists, like MK-801, and that inhibitors of NOS may have antipsychotic actions. [Neuropsychopharmacology 15:37-43, 1996]

KEY WORDS: 7-Nitroindazole; Methylene blue; MK-801; Phencyclidine; Antipsychotic; Popping behavior

In certain neurons, glutamate-stimulated Ca^{2+} conductance via the N-methyl-D-aspartate (NMDA) receptor-

associated ion channel leads to the production of nitric oxide (NO), a freely diffusible gaseous intercellular messenger (Dawson et al. 1992; Moncada and Higgs 1993). Effects attributed to NMDA receptor stimulation may, in some instances, be mediated by NO production and the resultant cascade of intracellular biochemical events induced by NO. For example, NO increases cyclic GMP synthesis by activating the soluble heme-containing form of guanylate cyclase (Dawson et al. 1992; Moncada and Higgs 1993; Murad 1994). NO is one product of a reaction catalyzed by nitric oxide synthase (NOS) that utilizes arginine as its substrate. NOS activity is due to multiple isoenzymes, which are both constitutively active and inducible depending on the tissue

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and cell type (Snyder and Bredt 1992; Moore et al. 1993). The distribution of immunohistochemically positive NOS-containing neurons is similar to that of neurons stained with nitro-blue-tetrazolium (NBT) used for the detection of nicotinamide adenine dinucleotide diaphorase (NADPH) activity (Dawson et al. 1992). Although NOS/NADPHd-staining neurons comprise only 1% to 2% of all neurons in the brain (Dawson et al. 1992), their neuronal processes have extensive ramifications throughout the brain.

Commonly used preclinical screening methods for identifying antipsychotic compounds generally involve testing the ability of such compounds to antagonize dopamine-mediated rodent behaviors elicited by direct or indirectly acting dopaminergic mimetics (Ferris et al. 1982). A limitation of these preclinical tests is that they identify compounds whose primary pharmacologic action involves antagonism of dopamine-stimulated behaviors. Although such methods have proven effective in identifying many of the currently used typical antipsychotic medications, they may be ineffective in identifying atypical medications that produce few, if any, extrapyramidal side effects (EPS) and appear to be more efficacious in treating the "deficit" symptoms of schizophrenia (see Meltzer 1991 for review).

Given the many similarities between phencyclidine (PCP)-induced behaviors in humans and schizophrenia (Javitt and Zukin 1991; Deutsch et al. 1989; Javitt 1987), several investigators have examined the ability of both typical and atypical drugs to antagonize PCP-induced behaviors in rodents (Deutsch and Hitri 1993; Schmidt 1991). In our laboratory, we have studied the behavioral effects of MK-801 ([+]-5-methyl-10,11-dihydro-5H-dibenzo [a,d] cyclohepten-5, 10-imine maleate; dizocilpine), an analogue of PCP that binds with high-affinity to the NMDA receptor complex, in mice (Foster and Wong 1987; Deutsch and Hitri 1993). MK-801 elicits hyperactivity, stereotypic behaviors, and an episodic explosive jumping behavior ("popping") in mice (Deutsch and Hitri 1993). Both typical and atypical antipsychotic medications have been reported to block MK-801-elicited behaviors in mice in a dose-dependent manner (Deutsch and Hitri 1993; Schmidt 1991).

In the current study, we examined whether 7-nitroindazole (7-NI) and methylene blue (MB), two drugs known to interfere with NO-mediated signal transduction (da Silva et al. 1994; Mayer 1993; Martin et al. 1985), would affect MK-801-elicited popping behavior in mice (Deutsch and Hitri 1993; Rosse et al. 1995). 7-NI has been shown to dose-dependently inhibit the neuronal isozyme of NOS, and to be centrally active when administered peripherally to rats (Babbedge et al. 1993; Moore et al. 1993). MB antagonizes the ability of NO to stimulate cyclic GMP production by binding to the heme moiety of the NO-sensitive soluble guanylate cyclase (Mayer et al. 1993; Martin et al. 1985); MB may

also interfere with other steps along the NO "cascade" (Mayer et al. 1993). We anticipated that these compounds, whose actions effectively antagonize NO-mediated signal transduction, would exacerbate behaviors elicited by MK-801. Unexpectedly, 7-NI and MB were shown to markedly reduce MK-801-elicited popping behavior(s). These data suggest that inhibitors of NO synthase or NO function may have antipsychotic activity.

METHODS

Animals

An outbred strain of male NIH Swiss Webster mice weighing approximately 25 g were obtained from the National Cancer Institute (Frederick, MD) and used in all experiments. Mice were housed in hanging wire mesh cages in groups of five and maintained on a 12-hour light/12-hour dark cycle with free access to food and water. Animals were weighed individually prior to drug injection and automated assessment of platform motor behaviors and rotorod performance.

Drugs

MK-801 (Research Biochemicals International; Natick, MA) was dissolved in 0.9% saline. 7-NI (Biomol, Plymouth Meeting, PA) was suspended by ultrasonic agitation in 2-hydroxypropyl- β -cyclodextrin (Research Biochemical International; Natick, MA). MB was obtained from Sigma Chemical Co. (St. Louis, MO) and dissolved in distilled water. All drugs were injected intraperitoneally (IP) in a volume of 0.01 ml/g of body weight.

Computerized Assessment of MK-801-Elicited Popping

An automated system for measuring explosive episodic popping behaviors was used to study the effects of 7-NI and MB on MK-801-induced popping behavior. This method is based on the detection and measurement of small vertical displacements of a platform induced by motor movements (Rosse et al. 1995). These vertical displacements are detected and converted to electrical signals (S72-25 Type A Transducer Coupler and S76-01 [Modified] Contour Following Integrator; Coulbourn Instruments, Inc., Allentown, PA) and transformed into a digital signal (L25-12 A/D Converter; Coulbourn Instruments, Inc., Allentown, PA). The digitized data are stored and later analyzed on an IBM compatible computer. In the present study, a popping count was identified as a vertical displacement of the platform of more than 150% of body weight. The computer also determines the strength of individual pops in gram equivalents of force exerted against the platform. Reverbera-

tions or "aftershock" movements of the platform, which occur after vigorous movements or jumps, were removed automatically in a manner similar to that used in measuring startle responses in laboratory animals (Coulbourn Instruments, Inc., Allentown PA).

The recording of MK-801-elicited popping behavior was divided into two phases: a 5-minute baseline period after pretreatment with either 7-NI (40 minutes prior), MB (10 minutes prior), or appropriate vehicle. The baseline period was then followed by administration of MK-801 and 30 minutes of recording. All mice were individually weighed and put into separate cages that were placed on the pressure platforms. The platforms were then calibrated so that the force on each platform including the cage and weight of the animal was measured as "0"; all forces from animal movements resulting in downward displacements of the platform were measured.

Rotorod Assessment

To evaluate possible sedative/ataxic properties of 7-NI and MB we used a rotorod (Biological Research Apparatus, Model 7600, Comerio Varese, Italy) rotating at a constant speed of 16 rpm. Rotorod assessment was divided into two phases: a baseline period of 5 minutes, during which the animals were replaced on the rotating rod in the event of failure to maintain balance. Subsequent to this, a 5-minute testing period began after the administration of either 7-NI (40 minutes), MB (10 minutes), or appropriate vehicle.

RESULTS

All analyses were performed on an IBM-compatible computer using Statistica (StatSoft, Inc., Tulsa, OK). In experiments examining the interaction of 7-NI and MK-801, the results of a two-way ANOVA revealed two significant main effects and a significant interaction. As predicted, MK-801 significantly induced popping in a dose-dependent manner ($F = 9.2$, $df = 3,88$, $p = .00002$). Additionally, a significant main effect for 7-NI ($F = 19.4$, $df = 1,88$, $p = .00002$) indicates that 7-NI (100 mg/kg) significantly attenuated MK-801 induced popping. The average peak force of these pops was also subjected to a two-way ANOVA, revealing two significant main effects (7-NI pretreatment, $F = 16.5$, $df = 1,88$, $p = .0001$; MK-801 dose, $F = 14.9$, $df = 3,88$, $p = .000001$; interaction not significant) (see Figure 1).

MB at 10 mg/kg was found to reduce only marginally the average number of pops (two-way ANOVA; MB pretreatment, $F = 3.2$, $df = 1,88$, $p = .08$; MK-801 dose, $F = 10.9$, $df = 3,88$, $p = .000004$; interaction was not significant). The average peak force of pops was not significantly influenced by MB at 10 mg/kg (two-way

ANOVA; MB pretreatment, $F = 0.2$, $df = 1,87$, $p = .6$; MK-801 dose, $F = 25.4$, $df = 3,88$, $p < .000001$; the interaction was not significant) (see Figure 2). However, at a dose of 32 mg/kg, MB was found to reduce the average number of pops significantly (two-way ANOVA; MB pretreatment, $F = 6.9$, $df = 1,88$, $p = .01$; MK-801 dose, $F = 9.5$, $df = 3,88$, $p = .00002$; interaction not significant). The average peak force of pops was also significantly influenced by MB at the 32 mg/kg dose (two-way ANOVA; MB pretreatment, $F = 52.2$, $df = 1,88$, $p < .0000001$; MK-801 dose, $F = 12.96$, $df = 3,88$, $p < .000001$; the interaction was not significant) (see Figure 3). At the higher dose (100 mg/kg), MB was found to have a significant effect on both the average number of pops (two-way ANOVA, factor 1, MB pretreatment, $F = 20$, $df = 1,88$, $p = .00002$; factor 2, MK-801 dose, $F = 4.9$, $df = 3,88$, $p = .003$; interaction significant, $F = 4.3$, $df = 3,88$, $p = .0076$) and the average peak force of these pops (two-way ANOVA; factor 1, MB pretreatment, $F = 38$, $df = 1,88$, $p = .000001$; factor 2, MK-801 dose, $F = 8.5$, $df = 3,88$, $p = .00005$; interaction significant, $F = 4.2$, $df = 3,88$, $p = .007$) (See Figure 4).

7-NI (100 mg/kg) and MB (10, 32, 100 mg/kg) failed to alter rotorod performance (one-way ANOVA, 7-NI, $F = 2.61$, $df = 1,1$; MB, $F = 0.46$, $df = 1,3$) compared to their respective vehicles (see Figure 5).

DISCUSSION

The recognition that NO production can be an important "downstream" consequence of glutamate-induced elevations of intraneuronal Ca^{2+} has prompted considerable interest in the possible development of NO interventions for therapeutic purposes (Bredt and Snyder 1992; Dawson et al. 1992). Excessive stimulation of NMDA receptors has been shown to mediate many of the neuropathologic consequences of hypoxic, hypoglycemic, or traumatic insults to brain (Iversen et al. 1989). NMDA antagonists are under consideration for development as neuroprotective and antiseizure agents.

There is also a growing interest in the role of the NO pathway in the idiopathic psychotic disorder of schizophrenia. Recently, Karson and colleagues (1991) have reported differences in the number of NOS-containing neurons in the brainstem of schizophrenic patients compared to appropriately matched controls. In this study, patients with schizophrenia were reported to have increased numbers of NADPHd-stained neurons in the pedunculopontine (PPN) nucleus (Karson et al. 1991). These cholinergic PPN neurons send excitatory signals to thalamus and midbrain, structures critical to sensory gating processes (Karson et al. 1991). Problems with sensory gating at the level of the thalamus have been proposed as important in the pathophysiology of schizophrenia (Andreassen et al. 1994). In another recent

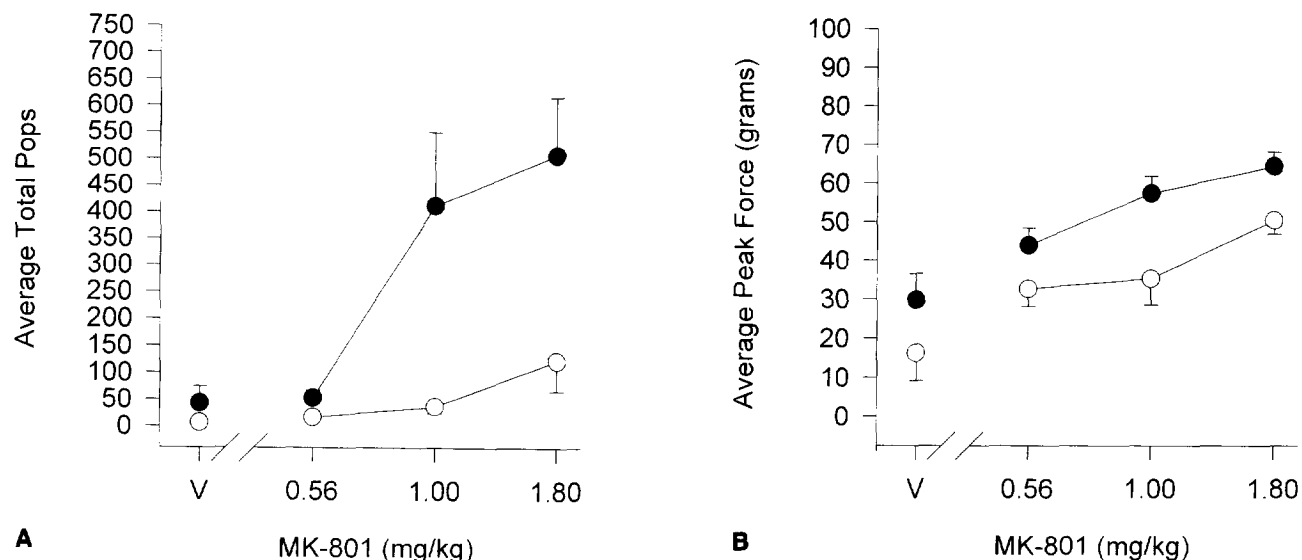


Figure 1. (A) Mean (\pm SEM) number of pops during a testing session for groups of mice ($n = 12$ /group) injected with 0.9% saline (the MK-801 vehicle, points above V) and either 100 mg/kg of 7-nitroindazole (open circles) or its vehicle (cyclodextrin) (solid circles). (B) The details are identical to A, with the exception that the data are depicting the force of pops.

study, an increase in the number of NADPHd-stained neurons in the deep layers of the white matter of the dorsolateral prefrontal cortex (DLPFC) were reported in schizophrenic patients (Akbarian et al. 1993a). Patients with schizophrenia also had greater numbers of NADPHd-stained neurons in the parahippocampal and lateral temporal lobe white matter (Akbarian et al. 1993b). Interestingly, it has been reported that NO may enhance both dopamine and serotonin release in certain brain regions (Lorrain and Hull 1993). The possible rela-

tionship between NO synthesis and the release of dopamine and serotonin is interesting in light of evidence that atypical antipsychotic drugs such as clozapine have both antidopaminergic and antiserotonergic properties (Meltzer et al. 1989). Additionally, NO, through a cGMP pathway, has been shown to stimulate the phosphorylation of DARPP-32, resulting in the amplification of dopamine neural transmission through certain dopamine receptors (Tsuo et al. 1993). Finally, reports of elevated platelet NOS activity and plasma cit-

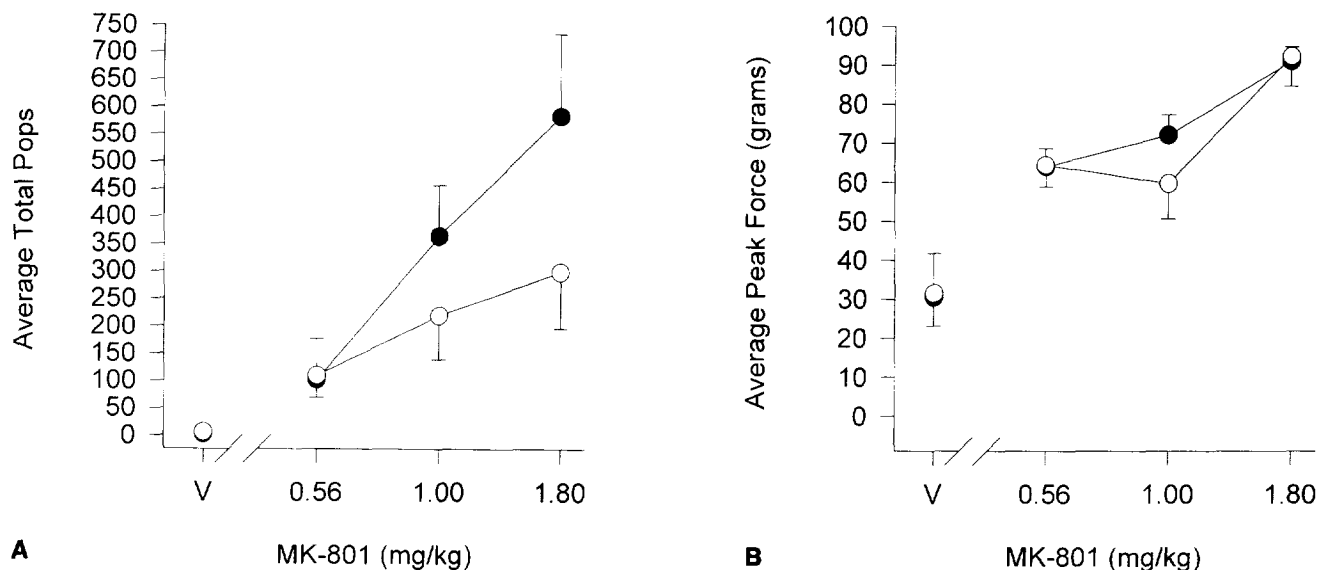


Figure 2. All details are the same as in Figure 1, with the exception that data are presented for 10 mg/kg of methylene blue (open circles), whose vehicle was distilled water (solid circles). Also note that the group size for mice injected with 0.9% saline and distilled water (closed circle above point V) was 11 in (A).

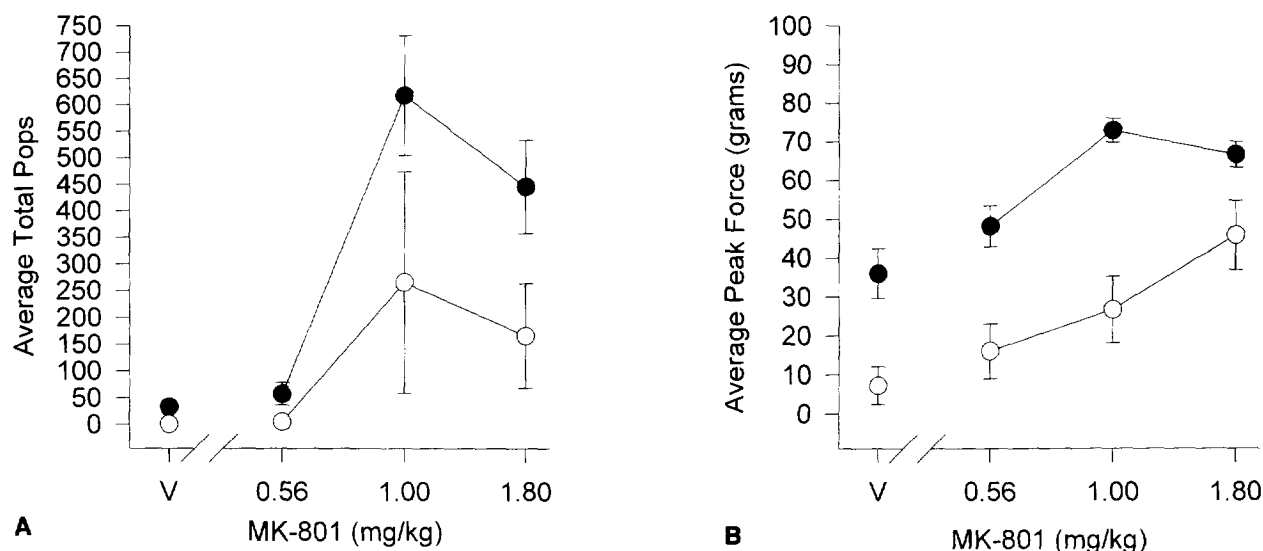


Figure 3. All details are the same as in Figure 1, with the exception that data are presented for 32 mg/kg of methylene blue (open circles), whose vehicle was distilled water (closed circles).

rutine/arginine ratios in patients with schizophrenia have been interpreted as possibly representing heightened brain NOS activity in schizophrenia (Das et al. 1995; Khan et al. 1995). Hence, the ability to attenuate the downstream consequences of the NO cascade might be of therapeutic benefit in patients with schizophrenia.

The ability of PCP to precipitate a schizophreniform psychosis coupled with its well-described pharmacologic action as an uncompetitive antagonist of NMDA receptors has led to a "glutamatergic deficiency hypothesis" of the pathophysiology of schizophrenia (Javitt and Zukin 1991; Deutsch et al. 1989; Javitt 1987). In light of the evidence that 7-NI and MB antagonize NMDA re-

ceptor-mediated activation of the NO cascade (i.e., NO synthesis and NO-induced cyclic GMP production, respectively), one would anticipate that the intensity of MK-801-elicited popping behaviors should be enhanced by their administration. Contrary to this prediction, in the current report, 7-NI and MB markedly inhibited MK-801-induced popping behaviors at doses that were by themselves devoid of significant sedative/ataxic effects. There is no clear explanation as to why an inhibitor of either NOS or NO function would antagonize MK-801-induced motor behaviors in mice that would be compatible with the glutamatergic deficiency hypothesis of schizophrenia. Conceivably, interference with

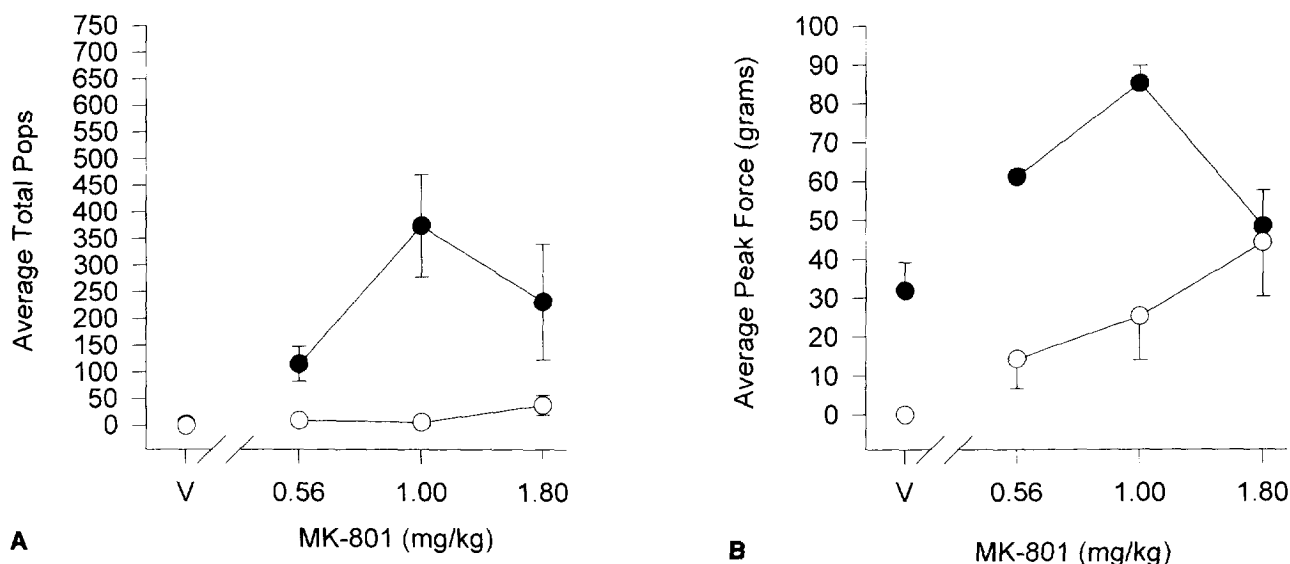


Figure 4. All details are the same as in Figure 1, with the exception that data are presented for 100 mg/kg of methylene blue (open circles), whose vehicle (solid circles) was distilled water.

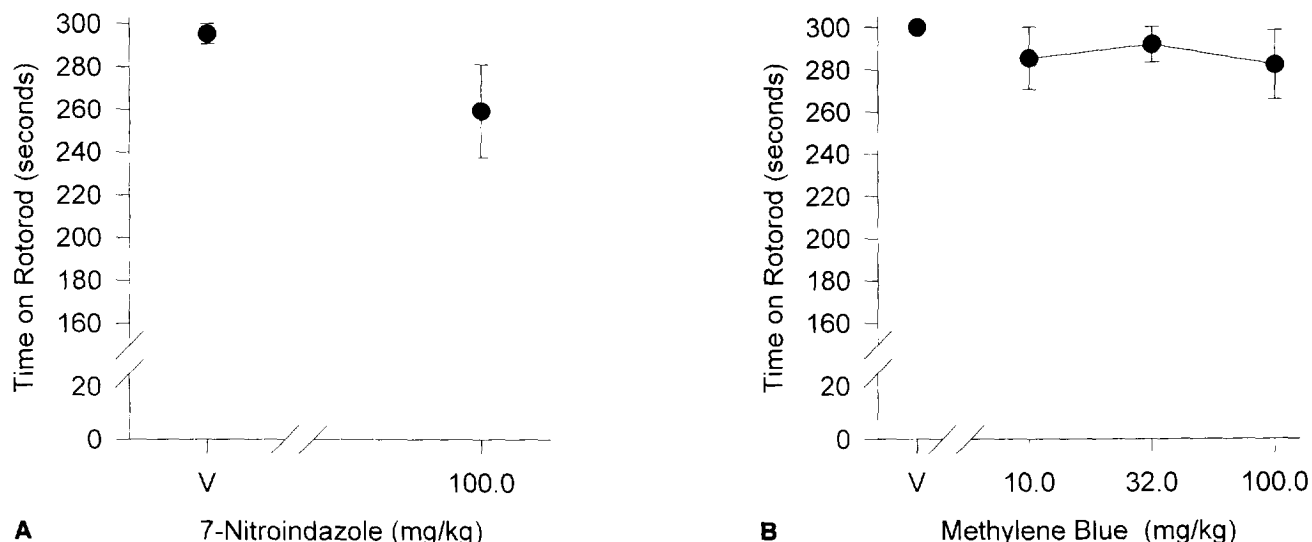


Figure 5. (A) Mean (\pm SEM) time on the rotarod for groups of mice ($n = 15$ /group) injected with either 100 mg/kg of 7-nitroindazole (point above 100) or its vehicle (cyclodextrin, point above V). (B) The details are identical to A, with the exception that data are presented for a range of doses of methylene blue.

NO production (or function) could relieve the NMDA receptor complex from the "feedback" inhibition that would result from an oxidized state of NO binding to the redox modulatory site on the NMDA receptor complex (Lipton et al. 1993a, 1993b). The existence of this redox modulatory site has been proposed to be a mechanism of dampening NMDA-mediated depolarization/neurotransmission under circumstances of excessive NO production. It is also possible that the effects of 7-NI and MB in antagonizing MK-801-induced popping behaviors are unrelated to NO-mediated signal transduction. However, given their structural dissimilarity and common actions with respect to NO function, this seems unlikely.

Finally, beneficial effects of MB in the treatment of psychosis and mania were reported by Bodoni almost 100 years ago (Bodoni 1899). Because MB possesses a phenothiazine nucleus and has been postulated to affect electron transfer reactions, it has more recently been tried empirically for the treatment of manic-depressive illness with some limited therapeutic success (Narsapur and Naylor 1983). Moreover, some antipsychotic drugs such as trifluoperazine and fluphenazine are capable of binding and sequestering calmodulin. Drugs capable of sequestering calmodulin have been shown to inhibit NOS activity and decrease NO production (Dawson et al. 1995). However, it is not known whether the ability of certain antipsychotic drugs to bind to calmodulin (and consequently decrease NO production) contributes to their antipsychotic profile. Nonetheless, our data suggest that inhibitors of NOS or NO-induced activation of guanylate cyclase may have antipsychotic actions in humans.

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