Nitric Oxide Synthase Inhibitors Attenuate Phencyclidine-Induced Disruption of Prepulse Inhibition

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Glutamate stimulation of N-methyl-D-aspartate (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. Results of a previous study showed that nitric oxide synthase (NOS) inhibitors blocked dizocilpine-induced behavior in mice. In the present study, NOS inhibitors were tested in combination with phencyclidine (PCP), a drug which typically dose-dependently disrupts prepulse inhibition of the acoustic startle response in rats. Alone, NOS inhibitors and promoters do not affect prepulse inhibition; however, when tested in combination with PCP,

the NOS inhibitors, L-NOARG, 7-nitroindazole and arcaine—but not the NR2B-selective polyamine site NMDA antagonist, eliprodil—attenuated PCP-induced disruption of prepulse inhibition of the acoustic startle response. These effects are similar to those produced by many atypical antipsychotics and suggests that this class of drugs should be investigated further for their potential utility as antipsychotics and as treatments for PCP abuse. [Neuropsychopharmacology 19:86-94] © 1998 American College of Neuropsychopharmacology. Published by Elsevier Science Inc.

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Nitric oxide is a soluble gas that is synthesized from the amino acid L-arginine by nitric oxide synthase (NOS). Nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH) is a required co-factor and citrulline is a co-product of the reaction. Constitutive and inducible forms of NOS have been identified, but it is the constitutive, Ca²⁺-calmodulin-dependent form that is found

in the brain and is hypothesized to be involved in the centrally mediated properties of nitric oxide (Lambert et al. 1991). These central effects may include roles in memory formation (Chapman et al. 1992; Yamada et al. 1995), development of tolerance or sensitization to drugs of abuse (Khanna et al. 1993; Kolesnikov et al. 1992; Majeed et al. 1994; Pudiak and Bozarth 1993), and response to stroke or neurotrauma (Nagafusi et al. 1995; Schulz et al. 1995).

Although NOS is not completely co-localized with any known neurotransmitter, a subset of N-methyl-D-aspartate (NMDA) neurons is associated with NOS (Garthwaite 1991). In these neurons, depolarization of the NMDA receptor by the endogenous excitatory amino acid neurotransmitter glutamate produces an influx of Ca²⁺ which binds to calmodulin. This Ca²⁺-calmodulin complex activates NOS directly, resulting in a brief "puff" of nitric oxide that diffuses out of the presynaptic terminal and into astrocytic processes to ac-

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tivate soluble guanylate cyclase (Garthwaite 1991); hence, nitric oxide may serve as an intracellular messenger that mediates glutamatergic effects at NMDA receptors. In addition, nitric oxide may also inhibit the actions of glutamate. Since nitric oxide is a gas that diffuses readily across cell membranes, its release may result in feedback inhibition of the presynaptic glutamate neuron via action at modulatory redox sites associated with NMDA receptors (Manzoni et al. 1992).

Consistent with the dual role of nitric oxide at NMDA receptors, previous research has shown that, although drugs that inhibit nitric oxide (NOS inhibitors) share some behavioral effects with NMDA antagonists, they also may attenuate other behaviors associated with NMDA antagonism. Shared properties include anxiolytic effects, memory impairment, and phencyclidine (PCP)-like discriminative stimulus effects (Chapman et al. 1992; Jewett et al. 1996; Volke et al. 1997). In contrast, Deutsch et al. (1996) found that NOS inhibitors blocked "popping" behavior in mice that was induced by the PCP-like noncompetitive NMDA antagonist, dizocilpine. Exploration of the effects of NOS inhibitors on other behavioral effects of NMDA antagonists, so far, has been minimal.

Another procedure in which PCP-like NMDA antagonists produce characteristic effects is prepulse inhibition of acoustic startle. The acoustic startle response is a reflexive movement that occurs upon abrupt presentation of a loud acoustic stimulus. Prepulse inhibition refers to a decrease in the magnitude of this startle response that is observed when the loud noise is preceded by a weak acoustic stimulus (a "prepulse"). Disruption of prepulse inhibition involves deficient capacity to "gate" or inhibit attention to incoming sensory information and occurs in certain disorders in humans such as schizophrenia, or can be induced by dopaminergic agonists or PCP-like noncompetitive NMDA antagonists in animals (Braff et al. 1978; Geyer et al. 1990). Previous research from this lab has shown that NOS inhibitors decreased startle amplitudes during pulse alone trials, but, unlike PCP, did not affect prepulse inhibition (Wiley et al. 1997).

The purpose of the present study was to examine the effects of NOS inhibitors on PCP-induced disruption of prepulse inhibition of the acoustic startle response in rats. The NOS inhibitors, N^G-nitro-L-arginine (L-NOARG), 7-nitroindazole, and arcaine, and their vehicles were tested alone and in combination with PCP. Since arcaine is not only a NOS inhibitor (Kabuto et al. 1995), but also an antagonist at the NMDA-associated polyamine site (Reynolds 1990), eliprodil was tested as a negative control in this study. Eliprodil shares arcaine's activity at NMDA-associated polyamine sites, but does not affect nitric oxide synthesis (Carter et al. 1989). A preliminary report of the results of this study was presented previously (Wiley 1997).

METHODS

Animals

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

Apparatus

A clear Plexiglas cylinder (8.2 cm diameter) resting on a Plexiglas panel (10 × 20 cm) was enclosed in each of three standard startle chambers (San Diego Instruments, San Diego, CA). Each chamber was illuminated by a 15-watt houselight mounted in the ceiling above the cylinder. Acoustic stimuli were produced by a super tweeter, mounted 24 cm 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.

Drugs

L-NOARG (Research Biochemicals International, Natick, MA), arcaine sulfate (RBI), and phencyclidine (National Institute on Drug Abuse, Rockville, MD) were mixed in sterile water or physiological saline. 7-Nitroindazole (Sigma Chemicals, St. Louis, MO) was dissolved in dimethylsulfoxide (DMSO). Eliprodil (Synthelabo Recherche, Bagneux, France) was mixed in 0.1% Tween 80 and saline. L-NOARG (all doses) and eliprodil (3 mg/kg) were administered at a volume of 1 ml/kg. Due to solubility-related issues, the 10 mg/kg dose of eliprodil was injected at a volume of 2 ml/kg; the 10 mg/kg dose of arcaine, at a volume of 1.2 ml/kg; and the 30 mg/kg dose of arcaine, at a volume of 3.6 ml/kg. 7-Nitroindazole (all doses) was given at a volume of 0.5 ml/kg. The NOS inhibitors, eliprodil, and their vehicles were injected i.p. 30 min before the start of the startle session. Phencyclidine or saline was injected s.c. at a volume of 1 ml/kg 20 min pre-session.

Procedure

Rats were transported to the laboratory at least 30 min before startle sessions. After being injected with the test drugs, 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 five-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 sec). 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 indicates the degree of sensorimotor reactivity. A second type of trial consisted of an 85 dB[A] prepulse (20 msec duration) followed by 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 an 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 five trials of each of the four types. Startle pulse duration was held constant at 40 msec. A 100 msec delay was imposed between prepulse and pulse stimuli.

The dose-effect curves for 7-nitroindazole, arcaïne and eliprodil were determined in a within-subjects design with 12 rats per drug. L-NOARG was tested in two groups of 12 rats each. The first group received vehicle, 1 and 3 mg/kg L-NOARG with and without PCP; the second group received vehicle, 10 and 30 mg/kg L-NOARG with and without PCP. Data from both groups were combined for the purposes of data analysis. A 3 mg/kg dose of PCP was used in all studies. In order to minimize the confound potentially produced by habituation or carry-over effects, the order of dose combinations was randomized across the rats in each group, according to a Latin Square design. At least 72 hrs intervened between test sessions for each rat.

Data Analysis

Startle score was defined as the average of 100 1-msec 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] $\times$ 100. For each dose-effect curve, separate two-factor (PCP vs. saline $\times$ drug dose) repeated measures GLM procedures (SAS Institute, Cary, NC) 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 GLM's. (Startle amplitudes during prepulse alone trials

and during trials in which there was not any auditory stimulation were consistently low and are not shown.)

RESULTS

Effects of NOS Inhibitors on PCP-Induced Disruption of Prepulse Inhibition of the Acoustic Startle Response

Figures 1 and 2 show the effects of tests with the NOS inhibitors, L-NOARG and 7-nitroindazole, alone and in combination with 3 mg/kg PCP on startle amplitudes during pulse alone trials (upper panels) and on % prepulse inhibition (lower panels). Startle amplitudes during pulse alone trials did not differ significantly across conditions for L-NOARG (Figure 1, upper panel), but were decreased by each dose of 7-nitroindazole [main effect $F(2, 22) = 6.32, p = .007$]. In each group of rats, PCP (3 mg/kg) disrupted prepulse inhibition compared to vehicle conditions [$F(1, 23) = 84.57, p = .0001$ and $F(1, 23) = 90.53, p = .001$, respectively], and there were significant interactions between PCP condition and NOS inhibitor dose on degree of prepulse inhibition [$F(4, 44) = 2.93, p = .03$ and $F(2, 21) = 7.95, p = .003$, respectively]. While PCP (3 mg/kg) disrupted prepulse inhibition (compared to the saline/vehicle condition) across every dose of L-NOARG or 7-nitroindazole, the degree of disruption varied dependent upon dose of NOS inhibitor. L-NOARG dose-dependently attenuated the effect produced by PCP on prepulse inhibition with significant reversal occurring at a dose of 30 mg/kg L-NOARG (compared to saline/PCP condition; Figure 1, lower panel). Similarly, a 10 mg/kg dose of 7-nitroindazole significantly increased the degree of prepulse inhibition following PCP administration (compared to saline/PCP condition), although a higher dose failed to do so (Figure 2, lower panel).

Effects of Polyamine Site NMDA Antagonists on PCP-Induced Disruption of Prepulse Inhibition of the Acoustic Startle Response

Figures 3 and 4 show the effects of tests with the polyamine site NMDA antagonists, arcaïne and eliprodil, alone and in combination with 3 mg/kg PCP on startle amplitudes during pulse alone trials (upper panels) and on % prepulse inhibition (lower panels). Startle amplitudes during pulse alone trials were decreased by 30 mg/kg of arcaïne [main effect $F(2, 22) = 3.67, p = .04$], but did not differ significantly across conditions for eliprodil (Figures 3 and 4, upper panels). Disruption of prepulse inhibition by 3 mg/kg of PCP occurred in each group of rats (Figures 3 and 4, lower panels). While a 10 mg/kg dose of arcaïne failed to alter the effect produced

Figure 1. Effects of L-NOARG (NOS inhibitor) alone and in combination with 3 mg/kg PCP on startle amplitudes during pulse alone trials (upper panel) and on % prepulse inhibition (lower panel). Each bar represents the mean ($\pm$ SEM) of data from 12 (each L-NOARG dose with saline or PCP) or 24 (saline/saline and saline/PCP conditions) rats. + $p < .05$ compared to sal/sal; * $p < .05$ compared to sal/PCP.

by PCP, a 30 mg/kg dose of arcaine completely reversed the PCP-induced disruption of prepulse inhibition [interaction $F(2, 22) = 13.55$, $p = .0001$]. The degree of PCP-induced disruption of prepulse inhibition was not affected by either dose of eliprodil; i.e., there was a significant main effect for PCP vs. saline [$F(1, 11) = 333.87$, $p = .001$], but no significant interaction.

DISCUSSION

The results of the present study showed that, when the NOS inhibitors, L-NOARG, 7-nitroindazole, or arcaine, were injected prior to PCP administration, each drug reduced PCP-induced disruption of prepulse inhibition. Although arcaine produced complete blockade of PCP-induced disruption of prepulse inhibition, L-NOARG and 7-nitroindazole only partially attenuated the effect produced by PCP on prepulse inhibition. At least a lim-

ited degree of selectivity of this attenuation was suggested by the fact that, the NR2B-selective polyamine site NMDA antagonist, eliprodil, failed to alter PCP-induced disruption of prepulse inhibition. Since eliprodil did not show obvious behavioral activity in the present study, it is possible that a higher dose might have affected PCP-induced disruption of prepulse inhibition in a manner similar to arcaine. This possibility is unlikely, however, as doses of 10 or 30 mg/kg eliprodil failed to alter the effects of 1 mg/kg PCP in a similar model, although the 30 mg/kg dose decreased startle amplitudes during pulse alone trials (unpublished data). The present results confirm and extend a previous finding that the NOS inhibitor, L-NAME, blocked disruption of prepulse inhibition induced by a 2 mg/kg dose of PCP (Johansson et al. 1997). In that study, pharmacological selectivity was suggested by the fact that L-NAME did not alter amphetamine-induced disruption of prepulse inhibition.

Figure 2. Effects of 7-nitroindazole (NOS inhibitor) alone and in combination with 3 mg/kg PCP on startle amplitudes during pulse alone trials (upper panel) and on % prepulse inhibition (lower panel). Each bar represents the mean ($\pm$ SEM) of data from 12 rats. + $p < .05$ compared to DMSO/sal; * $p < .05$ compared to DMSO/PCP; # $p < .05$ main effect for 7-nitroindazole dose.

A review of preclinical research examining pharmacological effects of NOS inhibitors reveals conflicting results. While some studies have reported that NOS inhibitors share behavioral effects with NMDA antagonists, including anxiolytic, anticonvulsant, and neuroprotective effects (Nagafusi et al. 1995; Volke et al. 1997), other studies have found that NOS inhibitors either do not mimic (Stewart et al. 1994; Wiley et al. 1995, 1997) and/or attenuate (Deutsch et al. 1996; Johansson et al. 1997) the effects of NMDA antagonists. For example, recent studies have shown that NOS inhibitors block the effects of PCP-like NMDA antagonists on "popping" behavior in mice (Deutsch et al. 1996) and locomotor activity and prepulse inhibition of the acoustic startle response in rats (Johansson et al. 1997). Potentiation of NMDA-induced neurotoxicity by 7-nitroindazole has also been reported (Connop et al. 1994). Although task and species variation across studies may play a role in differences in results obtained with these drugs, it is possible that the dual role of nitric oxide as

an intracellular messenger and as a retrograde messenger at the NMDA receptor complex may also help account for the divergent findings. Hence, NOS inhibitors may have both excitatory and inhibitory influences on NMDA receptor-associated events. In fact, Rundfeldt et al. (1995) have shown that the propensity of NOS inhibitors to produce anticonvulsant vs. proconvulsant effects in the same seizure model is dependent upon dose and time of administration. Although 7-nitroindazole was not tested in this seizure model, it showed a similar biphasic pattern of effects in the present study, in that a 10 mg/kg dose attenuated PCP-induced disruption of prepulse inhibition whereas a 30 mg/kg dose did not. Previous research has shown that this dose range of 7-nitroindazole is consistent with that which produces maximal inhibition of NOS in the brains of rats following acute i.p. injection (Connop et al. 1994).

To date, however, the effects of NOS inhibitors in the acoustic startle model have been consistent: without exception, this class of drugs have no effect on prepulse

Figure 3. Effects of arcaïne (NOS inhibitor and polyamine site NMDA antagonist) alone and in combination with 3 mg/kg PCP on startle amplitudes during pulse alone trials (upper panel) and on % prepulse inhibition (lower panel). Each bar represents the mean ($\pm$ SEM) of data from 12 rats. + $p < .05$ compared to sal/sal; * $p < .05$ compared to sal/PCP; # $p < .05$ main effect for arcaïne dose.

inhibition when administered alone, but attenuate PCP-induced disruption of prepulse inhibition (Johansson et al. 1997; Wiley et al. 1997). The only other class of drugs that has been shown to have a similar effect on PCP-induced disruption of prepulse inhibition is antipsychotics. Atypical antipsychotics (those that do not produce the motor impairment associated with typical antipsychotics such as haloperidol), including clozapine, olanzapine, and seroquel, reverse the disruptive effect produced by PCP on prepulse inhibition (Bakshi and Geyer 1995; Bakshi et al. 1994; Swerdlow et al. 1996), although there are exceptions (Hoffman et al. 1993; Johansson et al. 1994; Wiley 1994). These drugs also block the disruptive effects of dopamine agonists on prepulse inhibition (Swerdlow and Geyer 1993; Swerdlow et al. 1991, 1994) (L-NAME does not; Johansson et al. 1997). In contrast, haloperidol, a high potency typical antipsychotic, blocks amphetamine- or apomorphine-induced disruption of prepulse inhibition (Mansbach et al. 1988; Swerdlow

and Geyer 1993), but does not alter PCP-induced effects in this paradigm (Keith et al. 1991). Ellenbroek and Cools (1990) have suggested that prepulse inhibition of acoustic startle represents a valid animal model of attentional deficits that are present in schizophrenia. Hence, the present results suggest that additional investigation of the potential utility of NOS inhibitors as antipsychotics may be warranted.

Other types of evidence have strongly implicated nitric oxide in schizophrenia. First, nitric oxide is intimately connected with dopamine and glutamate, two neurotransmitter systems that are dysfunctional in schizophrenia (Lonart et al. 1993; Montague et al. 1994; Pogun et al. 1994). Further, nitric oxide's dual action as mediator and negative modulator of glutamate neurotransmission at the NMDA receptor complex give this system a unique role in regulating the balance of excitatory and inhibitory influences. It is this balance of excitatory and inhibitory processes that is likely to be

Figure 4. Effects of eliprodil (NR2B-selective, polyamine site NMDA antagonist) alone and in combination with 3 mg/kg PCP on startle amplitudes during pulse alone trials (upper panel) and on % prepulse inhibition (lower panel). Each bar represents the mean ($\pm$ SEM) of data from 12 rats. # $p < .05$ main effect for PCP (vs. saline).

disrupted in schizophrenia, as proposed by glutamate hypofunction and GABA predominance theories of this disorder (Squires and Saederup 1991). A second line of evidence that suggests a role for nitric oxide in schizophrenia is the finding that measures of nitric oxide metabolism are altered in platelets or postmortem brains of schizophrenic patients (Akbarian et al. 1993a,b; Das et al. 1995; Karson et al. 1991). Third, preliminary studies suggest that antipsychotics may decrease synthesis of nitric oxide (Hu et al. 1994).

In summary, attenuation of PCP-induced disruption of prepulse inhibition by NOS inhibitors is similar to the effects produced in this procedure by several antipsychotics. Consistent with the findings of previous studies which have reported that NOS inhibitors block characteristic behaviors produced by PCP-like drugs, the present results suggest that NOS inhibitors may

counteract some of the effects of PCP-induced glutamate hypoactivity. However, given that the behavioral effects of NOS inhibitors mimic those of PCP-like drugs in other preclinical procedures, further investigation of this class of drugs for potential utility as antipsychotics and as treatments for PCP abuse should proceed, but with caution.

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