Inhibition of Nitric Oxide Synthase Disrupts Inhibitory Gating of Auditory Responses in Rat Hippocampus

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ABSTRACT

The amplitude of the hippocampal evoked response to the second of two identical auditory stimuli is suppressed relative to the response to the first stimulus. This inhibitory gating of sensory response has been linked to α-bungarotoxin-sensitive nicotinic receptors, which are found primarily on γ-aminobutyric acid (GABA) neurons in rat hippocampus. A recent study showed a high level of colocalization of α-bungarotoxin binding with immunoreactivity for nitric oxide synthase, the catalytic enzyme which produces nitric oxide, in rat hippocampus. To determine if loss of enzyme activity would alter normal sensory inhibition, N\(^\text{-nitro-}\)arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor, was continuously perfused through the ventricular system of anesthetized rats as they were tested for response to paired auditory stimuli. L-NAME, but not N\(^\text{-nitro-}\)arginine methyl ester (D-NAME), the inactive enantiomer, produced a loss of sensory inhibition. To determine if the effect of nitric oxide was presynaptic or postsynaptic to nicotinic receptors, rats with lesions of the fimbria/fornix, which removes the medial septal projection to the hippocampus, were tested with nicotine in the presence of L- or D-NAME. Fimbria/fornix lesions normally reduce sensory inhibition, which is restored with systemic nicotine injections. Lesioned rats treated with D-NAME showed normal sensory inhibition upon injection of nicotine; lesioned rats treated with L-NAME did not. These data support the hypothesis that stimulation of a nicotinic receptor releases nitric oxide, which in turn mediates sensory inhibition. The nicotine-induced release of nitric oxide may explain why some of the behavioral effects of nicotine have a longer time course than predicted from desensitization of nicotinic receptors.

Hippocampal neurons exhibit a rapid reduction in response to repetitive sensory stimulation (Vinogradova, 1975; Wilson et al., 1984). This hippocampal sensory inhibition appears to depend on an intact septohippocampal pathway, because lesions of the fimbria/fornix abolish the decrement of response to repetitive sensory stimulation typical of hippocampal neurons (Vinogradova, 1975). Axons from two subsets of medial septal neurons—those containing GABA and those containing acetylcholine—course through the septohippocampal pathway. The cholinergic contribution to hippocampal sensory inhibition was examined in anesthetized rats by Luntz-Leybman et al. (1992). They assessed the effects of intracerebroventricular infusion of cholinergic receptor antagonists on the amplitude of hippocampal evoked potentials elicited by paired auditory stimuli. Before drug infusion, the rats displayed inhibition of the response to the second stimulus; however, infusion of the nicotinic neuromuscular receptor antagonists α-BTX or d-tubocurarine produced similar amplitude responses for both stimuli, i.e., sensory inhibition was disrupted. Infusions of the muscarinic receptor antagonist, scopolamine, or the nicotinic ganglionic receptor antagonist, mecamylamine, did not change the amplitudes of the responses to either stimulus relative to baseline, i.e., sensory inhibition was not affected. Other studies have demonstrated normalization of fimbria/fornix-lesion-induced loss of sensory inhibition by nicotine (Bickford and Wear, 1995), and production of normal sensory inhibition in DBA/2 mice (a strain that normally shows deficient inhibition) by administration of either nicotine (Stevens and Wear, 1997) or 4-OH-MeO-benzylidine anabaseine (referred to as either DMXB or GTS-21), an agonist for the α-bungarotoxin-sensitive nicotinic receptor (Stevens et al., 1998). These pharmacological data suggest not only that nicotinic receptors participate in the rapid inhibition of hippocampal cells to repetitive auditory stimulation, but also that the α7 subtype

Abbreviations: GABA, γ-aminobutyric acid; L-NAME, N\(^\text{-nitro-}\)arginine methyl ester; D-NAME, N\(^\text{-nitro-}\)arginine methyl ester; GTS-21 or DMXB, 4-OH-MeO-benzylidine anabaseine; α-BTX, α-bungarotoxin; N40, identified as the maximum negativity in the auditory evoked potential between 20 and 60 msec after the auditory stimulus; P30, identified as the positivity in the auditory evoked potential immediately preceding the N40 wave; TC ratio, test/conditioning ratio; EBSS, Earle’s balanced salt solution; NO, nitric oxide; NADPH, diaphorase-nicotinamide-adenine dinucleotide phosphate-diaphorase; AChE, acetylcholinesterase.
Effects of nicotine in the sensory inhibition paradigm (Adler et al., 1993) and in other studies of performance on a variety of learning and memory tasks (Buccafusco and Jackson, 1991; Levin et al., 1992; Wilson et al., 1995) persist much longer than would be predicted from the rapid time course of activation and desensitization of the \( \alpha_7 \) nicotinic receptor (Couturier et al., 1990). The mechanism underlying the persistent effects of nicotine in each of these instances is unknown. One possibility is that activation of nicotinic receptors leads to the release of a neurotransmitter/neuromodulator that exerts a prolonged effect, either directly, via second messenger systems, or by regulation of transcription and/or translation processes (Arneric et al., 1995). Therefore, a crucial question is what substances might be released upon activation of the \( \alpha_7 \) receptor that could account for the persistent effects of nicotine.

\( \alpha \)-BTX binds to a subset of inhibitory neurons containing GABA in rat hippocampus (Freedman et al., 1993), including a population of neurons immunoreactive for nitric oxide synthase (Adams and Freedman, 1997), the catalytic enzyme for the production of nitric oxide (Bredt, 1995). The observation that some neurons immunoreactive for nitric oxide synthase also possess the \( \alpha_7 \) receptor led to the hypothesis that \( \alpha_7 \)-stimulated release of nitric oxide may mediate the effects of nicotine in rat hippocampus. Initial examination of this hypothesis entailed two experimental approaches. The first experiment examined whether release of nitric oxide is required for hippocampal sensory inhibition in intact rats. The second experiment examined whether release of nitric oxide is required for nicotine-mediated restoration of hippocampal sensory inhibition in rats with fimbria/fornix lesions. Both questions were addressed by determining the effect of intracerebroventricular infusion of the nitric oxide synthase inhibitor L-NAME on inhibition of hippocampal auditory evoked potentials, using intact rats in the first experiment and rats with fimbria/fornix lesions in the second experiment. The results of the two experiments provide the first evidence that sensory inhibition in rat hippocampus is mediated by nicotine-stimulated release of nitric oxide.

### Materials and Methods

Male Sprague-Dawley rats weighing 300 to 350 g were anesthetized with chloral hydrate (400 mg/kg i.p.) and pyrazole (400 mg/kg i.p.) to retard the metabolism of the chloral hydrate. The rats were intubated and placed in a stereotaxic apparatus with hollow ear bars to which miniature earphones were attached. Body temperature was maintained at 37°C with a heating pad. A tungsten microelectrode, impedance 8 to 10 megohms at 100 Hz, was inserted into the pyramidal layer of hippocampal area CA3 through a small burr hole in the skull. The recording electrode was placed 4 mm posterior to bregma, 3.5 mm lateral to the midline and 2.7 to 3.2 mm below the surface of the dura. A tungsten reference electrode was placed on the dura, contralateral to the recording electrode, just anterior to bregma. Neuronal activity was monitored continuously during lowering of the recording electrode into the hippocampus. The presence of multiple-unit discharges, often containing complex spikes, indicated placement of the recording electrode in the CA3 cell layer. The evoked potentials were amplified 1000 times with a 1 to 500 Hz filter and led to an analog-to-digital converter for computer averaging and storage. Tones, 300 Hz, 10 msec, 70 decibels (sound pressure level), were presented in pairs with an intertone interval of 500 msec and 10 sec between tone pairs. Responses to 16 tone pairs were averaged at 5- or 10-min intervals. Each average was filtered digitally with a filter that eliminates 90% of activity >250 and <10 Hz (Nagamoto et al., 1989).

The N40 component of the auditory-evoked potential was identified as the maximum negativity in the potential between 20 and 60 msec after the auditory stimulus. The P20 wave was identified as the positivity in the auditory evoked potential immediately preceding the N40 wave. The amplitude of the N40 wave was measured relative to the peak of the P20 wave. This complex has greater reproducibility for repeated measurements than either component alone (Cook et al., 1968). The amplitude of the response to the first tone stimulus (conditioning stimulus) and to the second tone stimulus (test stimulus), as well as the ratio of the amplitudes of the test to the conditioning responses (TC ratio), were calculated for each set of trials. A TC ratio of 0.4 or less is within the 95% confidence limits for outbred rats (Miller et al., 1992) and is defined as normal sensory inhibition.

Intracerebroventricular infusions were carried out by inserting a cannula, comprised of a 26-gauge needle attached to polyethylene tubing, into the lateral ventricle at 0.8 mm anterior to bregma, 1.2 mm lateral to the midline and 3.5 mm ventral to the dura, ipsilateral to the evoked potential recordings. EBSS was infused through this cannula at a rate of 4 \( \mu \)l/min by a microsyringe pump. Drugs (L-NAME or D-NAME, 5 mg/ml, Sigma Chemical Co., St. Louis, MO) were administered at various periods in EBSS so that reversibility of any effects could be observed. An opening was made in the membrane covering the cisterna magna to allow for continuous drainage of cerebrospinal fluid. This infusion procedure does not lead to dilation of the lateral ventricles (Luntz-Leybman et al., 1992). After completion of the study, the position of the cannula tip was verified histologically.

To assess the level of hippocampal function during drug infusion, a tungsten stimulating electrode coated with nonconducting varnish (8–10 megohm impedance) was inserted into the ventral hippocampal commissure/anteor hippocampal area CA3 at 1.3 mm posterior to bregma, 1.0 mm lateral to the midline and 3.2 to 3.7 mm below the surface of the dura, contralateral to the recording electrode. A ground screw for the commissural stimulation was placed in the skull, in contact with the dura, over the cerebellum. Commisural stimulation consisted of single pulses of 0.8 to 1.5 \( \mu \)A stimulation. Amplitude of the population spike produced by the stimulus was recorded by the same electrode that recorded the auditory evoked potentials.

In some rats, lesions of the fimbria/fornix were produced under sevoflurane (50 mg/kg i.p.) anesthesia, at least 2 wk before recording for auditory evoked potentials. The lesions were performed according to the aspiration protocol described in Bickford and Wear (1995). Briefly, a rectangular opening was made in the skull at 1 mm caudal to bregma and 1 to 4 mm lateral to the midline on the same side from which the hippocampal evoked potentials would be recorded. A modified Pasteur pipette was used to aspirate cerebral cortical and fimbria/fornix tissues from the cortical surface to 4 mm ventral to dura. Sham lesions of the overlying cortical tissue at the same rostrocaudal and mediolateral coordinates, but at 0 to 1 mm ventral to the dural surface have been previously shown to have no effect on hippocampal auditory inhibition (Bickford and Wear, 1995). At the end of the recording experiments, the brains were removed, frozen in dry ice snow and stored at −70°C.

To determine the degree of loss of the cholinergic input to the hippocampus produced by the fimbria/fornix lesions, acetylcholinesterase staining was performed on the frozen brain tissue. The acetylcholinesterase staining protocol was modified from Koelle (1955) and was carried out on coronal cryostat sections (40 \( \mu \)m) from four intact rat brains as well as from the frozen brains of rats with fimbria/fornix lesions. Sections were collected from the decussation of the anterior commissure through the caudal tip of the hippocampus and mounted onto gelatin coated slides. The tissue was incu-
Results

Blockade of nitric oxide formation by the nitric oxide synthase inhibitor L-NAME (5 mg/ml, 4 μl/min) produced a significant loss of sensory inhibition as evidenced by a significant increase in TC ratio (F(20,80) = 2.50, P = .002) (figs. 1 and 2). The loss of inhibition was sustained throughout the delivery of L-NAME (P < .05, Tukey’s HSD a posteriori analysis), but washed out upon resumption of EBSS alone (P > .05, Tukey’s HSD a posteriori analysis). The loss of sensory inhibition occurred primarily through a significant increase in test amplitude (F(20,80) = 2.19, P = .007) with no significant change in conditioning amplitude (F(20,80) = 1.27, P = .221). In contrast to the effect of L-NAME, D-NAME (5 mg/ml, 4 μl/min) the inactive enantiomer, failed to produce any change in sensory response or its inhibition (F(8,16) = 0.74, P = .660, conditioning amplitude; F(8,16) = 1.28, P = .321, test amplitude; F(8,16) = 1.06, P = .437, TC ratio).

To demonstrate that the loss of sensory inhibition was not simply due to an overall loss of hippocampal function, hippocampal commissural stimulation was performed to evoke population spikes in the CA3 region of the hippocampus. Population spike amplitude during the baseline period of EBSS flow through the ventricular system was compared with the amplitudes obtained 70 min after commencement of L-NAME infusion and 70 min after return to EBSS alone. There was no significant change in population spike amplitude during administration of L-NAME or during washout (F(2,6) = 0.32, P = .739) (fig. 5) indicating unimpaired functioning of pyramidal neurons in the hippocampus.

To determine if the effects of nitric oxide were postsynaptic to nicotinic receptors in the hippocampus, fimbria/fornix-lesioned animals were administered nicotine (3 mg/kg, s.c.) after continuous infusion of either L- or D-NAME (5 mg/ml, 4 μl/min). Lesions of the fimbria/fornix produced a loss of sensory inhibition as evidenced by significantly higher TC ratios (t = 3.60, df = 6, P = .006) during infusion of EBSS (TC ratio 1.25 ± 0.14, lesioned; 0.37 ± 0.02, nonlesioned). The fimbria/fornix lesions also resulted in a mean 79% loss of acetylcholinesterase staining in the various regions of the hippocampus (range = 73–86%) (t = 14.7, df = 4, P < .001) (fig. 4; table 1). Administration of nicotine after L-NAME failed to produce normal sensory inhibition in the lesioned rats. There were no significant changes in any parameter tested (F(19,45) = 1.66, P = .122, conditioning amplitude; F(9,45) = .50, P = .868, test amplitude; F(9,45) = 1.14, P = .358, TC ratio).

However, normal inhibition was restored by nicotine when the inactive enantiomer, D-NAME was infused through the ventricles (F(11,44) = 6.04, P < .001) (fig. 5). This decrease in TC ratio was produced by a significant increase in conditioning amplitude (F(11,44) = 2.87, P = .006) and a nonsignificant decrease in test amplitude (F(11,44) = 1.78, P = .088).
Discussion

This study demonstrates that intracerebroventricular infusion of the nitric oxide synthase inhibitor L-NAME disrupts hippocampal sensory inhibition in intact rats and prevents the restoration of normal hippocampal inhibition by nicotine in rats with fimbria/fornix lesions. These results support the hypothesis that release of nitric oxide mediates the effects of exogenous nicotine and endogenous acetylcholine on inhibitory gating of sensory response in rat hippocampus. Coupled with the immunohistochemical and autoradiographic colocalization studies (Adams and Freedman, 1997), they support a possible role for the α7 subtype of the nicotinic receptor in inhibitory gating.

A wide range of doses of L-NAME have been used to inhibit NOS in the central nervous system. Salter et al. (1995) used intracerebroventricular doses of L-NAME ranging between 0.03 and 1.0 mg/ml, based upon an approximate ventricular volume of 100 μl. Their highest dose, injected over a 2-min period, was sufficient to suppress nitric oxide synthase activity in the ipsilateral striatum, hippocampus and thalamus by more than 95%. This level of nitric oxide synthase inhibition was maintained for at least six hours. However, Ayers et al. (1997) used intracerebroventricular doses of L-NAME ranging from 2.0 to 50.0 mg/ml, with the highest dose providing prolonged (24-hr) inhibition of hippocampal nitric oxide synthase activity. We elected to use an intermediate dose of 5 mg/ml L-NAME in our study, a concentration that should have been more than sufficient to achieve a near-total inhibition of nitric oxide synthase. The more rapid time course of recovery following cessation of L-NAME infusion observed in our study may be due to our use of a continuous infusion paradigm, which allowed switching between the L-NAME solution and the vehicle alone, whereas, the Salter et al. (1995) and Ayers et al. (1997) studies did not washout the L-NAME. However, measurement of enzymatic activity would be required to adequately assess this possibility.

A possible explanation for the loss of sensory inhibition during L-NAME intracerebroventricular infusion is a non-specific loss of normal hippocampal cellular function. However, normal hippocampal function was verified by the lack of change in commissural stimulation-induced population spike activity before, during and after L-NAME infusion. These data suggest that loss of hippocampal sensory inhibition is

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**TABLE 1**

<table>
<thead>
<tr>
<th>Region</th>
<th>Control (n = 4) Mean (Range)</th>
<th>Lesion (n = 16) Mean (Range)</th>
<th>Percent Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior blade dentate gyrus</td>
<td>47.84 (37.52–53.51)</td>
<td>11.48 (5.83–18.70)</td>
<td>76</td>
</tr>
<tr>
<td>Superior blade dentate gyrus</td>
<td>59.17 (49.01–64.38)</td>
<td>8.36 (4.01–15.68)</td>
<td>86</td>
</tr>
<tr>
<td>Hilus</td>
<td>58.90 (47.73–68.28)</td>
<td>9.74 (7.92–17.34)</td>
<td>83</td>
</tr>
<tr>
<td>CA3</td>
<td>67.00 (57.27–72.51)</td>
<td>14.06 (1.57–18.47)</td>
<td>79</td>
</tr>
<tr>
<td>CA1</td>
<td>56.82 (48.16–64.16)</td>
<td>15.58 (9.06–24.44)</td>
<td>73</td>
</tr>
</tbody>
</table>

Data are inverted gray scale normalized to the corpus callosum, an area with no acetylcholinesterase.

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Fig. 3. A, Effects of L-NAME on population spike amplitude recorded in hippocampal region CA3 in response to hippocampal commissural stimulation. The arrowhead indicates the population spike. 1, Population spike amplitude during the EBSS baseline period. 2, Population spike amplitude 70 min after initiation of L-NAME infusion. 3, Population spike amplitude 70 min after resumption of EBSS alone. B, Mean ± S.E.M. for four animals, during the EBSS baseline period (pre), 70 min after L-NAME (during) and 70 min after resumption of EBSS (post). L-NAME produced a small, nonsignificant increase in population spike amplitude which declined with washout. Calibration: 500 mV, 25 msec.

Fig. 4. Representative section through the hippocampus of (A) a control animal and (B) a fimbria/fornix lesioned animal, stained for acetylcholinesterase (AChE). The fimbria/fornix lesioned animal shows a nearly complete loss of AChE in the hippocampus, indicating loss of cholinergic hippocampal input produced by removal of the fimbria-fornix. Abbreviations: CA1, hippocampal area CA1; CA3, hippocampal area CA3; D, dentate gyrus; M, molecular layer of the dentate gyrus; G, granule cell layer of the dentate gyrus; H, hilus of the dentate gyrus; P, stratum principale of the hippocampus; O, stratum oriens of the hippocampus; L, stratum lucidum of the hippocampus; R, stratum radiatum of the hippocampus; LM, stratum lacunosum/molecular of the hippocampus. Calibration mark = 300 μm.
due specifically to a loss of nitric oxide and not a nonspecific effect of L-NAME on hippocampal function.

The intracerebroventricular infusion paradigm permits diffusion of the infused drug to numerous brain regions adjacent to the ventricular system. Salter and colleagues (1995) demonstrated L-NAME-induced inhibition of nitric oxide synthase in many of these regions. Two of the areas within the diffusion range of the lateral ventricles, the nucleus of the lateral lemniscus and the brainstem reticular formation, have been shown to be involved in sensory inhibition. Both of these brain regions contain nitric oxide synthase-positive neurons (Vincent and Kimura, 1992) and studies have shown a diminution of evoked response to auditory stimuli in rat hippocampus upon stimulation of either area (Bickford et al., 1993). Thus, nitric oxide synthase inhibition in these or other areas could account for the disruption in sensory inhibition observed in the hippocampus in our study. However, the hippocampus receives information from the brainstem reticular formation and lateral lemniscus via the medial septum (Vertes, 1988). Therefore, any influence of these regions on hippocampal auditory gating would be removed by lesions of the fimbria/fornix. Because nicotine administration restores hippocampal sensory inhibition in rats with fimbria/fornix lesions (Bickford and Wear, 1995) and intracerebroventricular infusion of L-NAME prevented nicotine's normalization of the inhibition in this same preparation although D-NAME did not, the implication is that the hippocampus itself is the critical site of nitric oxide release with regard to sensory inhibition.

Nicotine exerts variable effects on the amplitude of conditioning and test responses evoked by auditory stimulation, influencing primarily the amplitude of the test response in some cases, the amplitude of both responses in other cases and primarily the conditioning response in still others (Adler et al., 1993; Bickford and Wear, 1995; Stevens and Wear, 1997). In our data, even though the primary effect of nicotine in fimbria/fornix-lesioned rats was on the conditioning response, examples were found where nicotine decreased the amplitude of the test response without a change in the conditioning response. The observed variability in the effects of nicotine on hippocampal auditory gating parameters is likely due to the fact that the hippocampus contains multiple subtypes of nicotinic, cholinergic receptors (Hill et al., 1993; Freedman et al., 1993; Lobron et al., 1995). In a study that used the α7-selective agonist GTS-21 (aka DMXB) rather than nicotine, a significant effect of the agonist was observed only on the test response (Stevens et al., 1998), suggesting that the effect of nicotine on the test response is primarily mediated by the α7 receptor, while the effect of nicotine on the conditioning response is mediated by nicotinic receptors other than or in addition to the α7 receptor. Therefore, a primary effect of L-NAME on the amplitude of the test response is in accord with the results of the GTS-21 study and with the hypothesis that stimulation of the α7 receptor leads to the release of NO.

The site or sites of presumed nicotine- and acetylcholine-stimulated nitric oxide release in rat hippocampus are unknown. Although some of the neurons labeled for both nicotinic oxide synthase and α-BTX are found in hippocampal area CA3 (the site of auditory evoked potential recording), a greater percentage of colocalized cells is found in area CA1 (Adams and Freedman, 1997). This finding raises the possibility that the “backprojection cells” observed in stratum oriens of area CA1 (Sik et al., 1994) may play a role in the inhibition of auditory evoked responses. An individual backprojection cell may contact principal cells in area CA1, area CA3, and on occasion, even in the dentate gyrus. Such broad synaptic contacts make the backprojection cells likely candidates for regulation of a population response such as the auditory evoked potential.

Nitric oxide is thought to increase the release of a number of neurotransmitters in rat hippocampus, including GABA, glutamate, norepinephrine, acetylcholine and adenosine (Lonart et al., 1992; Segieth et al., 1995; Fallahi et al., 1996; Getting et al., 1996; Suzuki et al., 1997). Of these neurotransmitters, an increase in GABA release is one plausible explanation for how nitric oxide mediates inhibitory gating of auditory response in rat hippocampus. Such a mechanism would be consistent with the established role of GABA_α receptors in hippocampal auditory gating (Hershman et al., 1995). The source of GABA release might well be the nitric oxide-producing cells themselves, as these neurons are a subset of hippocampal GABAergic neurons. However, recordings in CA3 by another group (Wulffert and Margineanu, 1996) showed an interaction between GABA_α-mediated inhibition of pyramidal neuron excitation and nitric oxide. Thus, the mechanism of nitric oxide’s interaction with the neurotransmitter and neurons involved in the nicotinic cholinergic activation of sensory inhibition remains to be elucidated.

Schizophrenics exhibit a deficit in auditory sensory inhibition that can be transiently (15–30 min) normalized by smok-
ing cigarettes (Adler et al., 1993). The deficit in auditory sensory inhibition displayed by schizophrenics may be due, at least in part, to a disruption of a7-mediated NO release. Postmortem hippocampal tissue from schizophrenic donors is characterized by reduced numbers of NADPH-diaphorase-positive neurons (Akbarian et al., 1993), a marker for NO synapse (Bredt, 1995), as well as reduced levels of α-BTX binding (Friedemann et al., 1995) relative to hippocampal tissue from control donors. Either of these abnormalities could result in decreased levels of NO release secondary to stimulation of the a7 receptor, thus potentially disrupting auditory sensory inhibition.

As mentioned above, the effects of nicotine in the sensory inhibition paradigm are more persistent (15–30 min) than would be predicted based upon the time course of nicotinic receptor activation alone (Adler et al., 1993). The possibility that NO might mediate this persistent effect is supported by recent electrochemical measurements of NO in rat brain. Application of a saturated solution of NO into rat striatum resulted in NO levels significantly greater than baseline for at least 7 min (Friedemann et al., 1996). Even more striking is local application of acetylcholine into area CA1 of rat hippocampus that resulted in NO levels significantly above baseline for at least 21 min (Stevens et al., 1997). Thus, NO in rat brain is degraded or removed relatively slowly, providing support that it may underlie the prolonged effects of nicotine on auditory sensory inhibition.

In summary, our studies demonstrate that inhibition of nitric oxide synthase by intracerebroventricular infusion of the nitric oxide synthase inhibitor L-NAME results in a disruption of hippocampal sensory inhibition in intact rats and prevents the restoration of hippocampal sensory inhibition by nicotine in rats with fimbria/fornix lesions. These data support the hypothesis that nicotinic receptor stimulation may induce the release of NO and suggest that the release of NO may be a mechanism through which nicotine, which produces very rapid receptor desensitization, may produce longer lasting effects on sensory inhibition.

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References


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