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Role of nitric oxide synthase inhibitors and NMDA receptor antagonist in nicotine-induced behavioral sensitization in the rat

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Abstract

Repeated injections of nicotine are well known to produce progressively larger increases in locomotor activity, an effect defined as behavioral sensitization. This study was carried out to investigate the role of nitric oxide (NO) and *N*-methyl-D-aspartate (NMDA) receptors in nicotine-induced behavioral sensitization. Rats were given repeated injections of nicotine (0.4 mg/kg, s.c., twice daily for 7 days) followed by one challenge injection on the fourth day after the last daily injection. Systemic challenge with nicotine produced a much larger increase in locomotor activity in nicotine-pretreated rats. Rats were pretreated with the nonselective nitric oxide synthase (NOS) inhibitor, N^G-nitro-arginine-methyl-ester (L-NAME; 75 mg/kg, i.p.), the selective constitutive NOS inhibitor, *N*-nitro-L-arginine (L-NNA; 15 mg/kg, i.p.), the prototypical selective inducible NOS inhibitor, aminoguanidine (100 mg/kg, i.p.) or NMDA receptor antagonist, MK-801 ((5*R*,10*S*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[a,d] cyclohepten-5,10-imine; 0.3 mg/kg, i.p.), 30 min before injections of nicotine during a 7-day development or a 3-day withdrawal phase after which challenged with nicotine on day 11. Pretreatment with L-NAME, L-NNA and MK-801, but not aminoguanidine, blocked the development of nicotine-induced sensitization to subsequent nicotine challenge. Injections of MK-801 twice daily during 3-day withdrawal periods after a 7-day induction period of nicotine attenuated nicotine-induced behavioral sensitization, whereas injections of L-NAME, L-NNA or aminoguanidine had no effects on the expression of sensitization produced by repeated nicotine. This study demonstrates that NMDA receptors can play a major role in the expression as well as development of nicotine-induced behavioral sensitization, and that NO is also involved in the development, but not critically involved in the expression of behavioral sensitization to nicotine.

Keywords: Behavioral sensitization; Nicotine; NMDA receptor; Nitric oxide (NO)

1. Introduction

Repeated injections of the psychostimulants, including amphetamine and cocaine, can produce behavioral sensitization, evidenced by an enhanced locomotor response to a subsequent injection of drug (Robinson and Becker, 1986; Kalivas and Stewart, 1991). Since behavioral sensitization has been known to be involved in the development of drug addiction and in drug-induced psychosis (Segal et al., 1981; Post and Contel, 1983; Robinson and Becker, 1986; Robinson and Berridge, 1993), there has been a great deal of interest in elucidating the neural mechanisms underlying behavioral sensitization. Several studies have shown that repeated injections of nicotine, an alkaloid agonist of nicotinic acetylcholine receptors, can produce behavioral sensitization (Clarke and Kumar, 1983; Shim et al., 2001). However, little is known about the neural mechanisms underlying the long-term behavioral effects produced by repeated injections of nicotine.

Recent studies have shown that nitric oxide (NO) plays an important role in drug-induced behavioral sensitization. For example, nitric oxide synthase (NOS) inhibitors have

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been shown to block cocaine or methamphetamine-induced behavioral effects (Pudiak and Bozarth, 1993; Ohno and Watanabe, 1995). Since several studies have demonstrated that nicotine has neurochemical as well as behavioral properties common to other psychostimulants, such as cocaine, amphetamine or methamphetamine (Byrne, 1988; Pontieri et al., 1996), it is likely that NO system may play a role in nicotine-induced behavioral sensitization. A recent study suggests that the NOS inhibitor *N*-nitro-L-arginine (L-NNA) attenuated nicotine abstinence syndrome (Malin et al., 1998), suggesting that NO system may play a role in nicotine-induced behavioral or reinforcing effects. However, the role of NO in nicotine-induced behavioral sensitization has not been examined.

It is well known that the neuronal glutamate–NO pathway modulates several important physiological processes, such as drug dependence, and NO is an intermediary in the action of glutamate (Fedele and Raiteri, 1999). Activation of *N*-methyl-D-aspartate (NMDA) receptors increases intracellular Ca^{2+} in the postsynaptic neuron and calcium binds to calmodulin and activates NOS, stimulating the formation of NO (Dawson et al., 1991). There are three types of isoforms of NOS: endothelial, neuronal and inducible NOS. Endothelial cells and neuronal tissues contain constitutively expressed NOS isoforms, which are Ca^{2+}/calmodulin-dependent, whereas inducible NOS is an isoform produced in macrophages and other cell types and is Ca^{2+}-independent (Ogden and Moor, 1995). It is suggested that the constitutive and inducible forms of NOS have distinct functions in mediating physiological processes of drug dependency. For example, the neuronal and endothelial constitutive isoforms of NOS, rather than the inducible form of NOS, were shown to inhibit morphine withdrawal, suggesting differential efficacy of isoforms in developing physical dependency of psychostimulants (Vaupel et al., 1997).

Therefore, in order to investigate the role of the NO systems in mediating nicotine-induced sensitization, we examined to determine which, if any, isoform of NOS affects the development of sensitization produced by repeated nicotine, and the expression of the response in sensitized animals.

Furthermore, it has been suggested that the neuronal glutamate–NO pathway may be critically involved in the psychostimulant-induced behavioral sensitization in that the administration of NMDA receptor antagonist, MK-801 ((5*R*,10*S*)-(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[a,d] cyclohepten-5,10-imine), during pretreatment with cocaine or amphetamine attenuated the development of behavioral sensitization (Karler et al., 1994; Wolf, 1998). Now, it is well established that noncompetitive and competitive NMDA receptor antagonists can block psychostimulant-induced sensitization. However, little is known about the role of NMDA receptors in the expression of behavioral sensitization produced by nicotine. Therefore, the effects of MK-801 on the development and expression of nicotine-induced behavioral sensitization were also examined in this study.

2. General methods

2.1. Subjects

Subjects were 56 male Sprague–Dawley rats weighing between 250 and 280 g at the start of the experiment. Rats were kept on a 12:12 h light:dark cycle in individual home cages with food and water available ad libitum. The experiments reported here were approved by the Kyung Hee Institutional Animal Care and Use Committee.

2.2. Measurements of locomotor activity

Locomotor activity was measured in a stabilimeter ($40 \times 40 \times 45$ cm) which was constructed in our lab according to the method Parreno et al. (1985) used. The polycarbonate animal containers were placed on stabilimeter with the sensitivity adjusted so as to record gross body movements. The walls and floor were made of a clear Plexiglas and were painted black. Activity counts cumulated in 20-min time bins. Three baselines were collected prior to treatments. Data were collected every 20 min for 2 h after all drug injections.

2.3. Experimental procedures

The experiment consisted of three phases: a 7-day development phase, withdrawal phase and testing phase. The rats were injected with (−)-nicotine hydrogen tartrate (Sigma, St. Louis, MO) (0.4 mg/kg, s.c., free base dissolved in saline at pH 7.2) twice daily for 7 consecutive days after which rats were challenged with systemic nicotine on day 11.

In order to examine the effects of the NOS inhibitors and NMDA receptor antagonist on the development of nicotine-induced sensitization, rats were pretreated with saline (1 ml/kg, 0.9 % NaCl), the nonselective NOS inhibitor, N^G-nitro-arginine-methyl-ester (L-NAME; 75 mg/kg, i.p.), the selective constitutive NOS inhibitor *N*-nitro-L-arginine (L-NNA; 15 mg/kg, i.p.), the prototypical selective inducible NOS inhibitor, aminoguanidine (100 mg/kg, i.p.) or NMDA receptor antagonists, MK-801 (0.3 mg/kg, i.p.), 30 min before injections of nicotine during a 7-day development phase. Drugs were not injected on days 8, 9 and 10 of the experiment and challenged with the same dose of nicotine 72 h after the last nicotine treatment in order to exclude residual effects of nicotine during the development test ($N=27$).

For the expression test, after repeated injections of nicotine for 7 days, animals were pretreated with saline, L-NAME, L-NNA or MK-801 during a 3-day withdrawal phase. The next day after 3-day withdrawal phase, animals

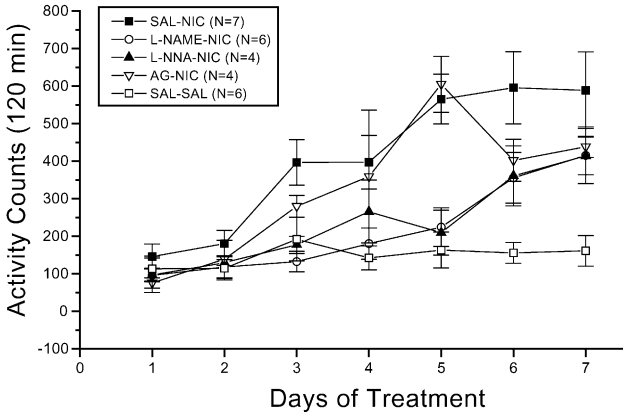

Fig. 1. Effects of NOS inhibitors on nicotine-induced locomotor activity during a 7-day development phase. Rats were pretreated with saline (1 ml/kg, ■ SAL-NIC), L-NAME (75 mg/kg, i.p., ○ L-NAME–NIC), L-NNA(15 mg/kg, i.p., ▲ L-NNA–NIC), or aminoguanidine (100 mg/kg, i.p., ▽ AG–NIC) 30 min before injections of nicotine twice daily for 7 consecutive days. The normal group was pretreated and challenged with only saline (□ SAL–SAL). Vertical lines indicate S.E.M. ($N=4-9$).

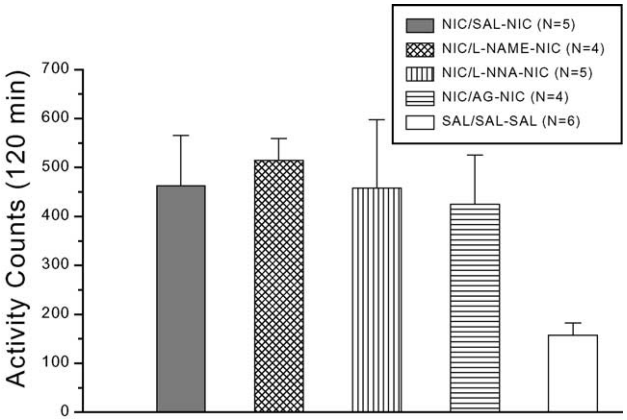

Fig. 3. Effects of NOS inhibitors on nicotine-induced expression of sensitization in response to nicotine challenge. Rats were pretreated with nicotine twice daily for 7 consecutive days and they were injected with saline (NIC/SAL–NIC), L-NAME (NIC/L-NAME–NIC), L-NNA (NIC/L-NNA–NIC) or aminoguanidine (NIC/AG–NIC) during a 3-day withdrawal phase and tested with a nicotine challenge on day 11. The normal group was pretreated and challenged with only saline (SAL/SAL–SAL) ($N=4-6$).

received the same treatment with saline or drugs 30 min before nicotine challenge ($N=23$). The last group received saline for 7 days and challenged with saline ($N=6$). Locomotor activity was measured for 2 h after every injection of nicotine or saline once a day at 10:00 a.m.

2.4. Statistical analysis

Behavioral data were statistically analyzed by two-way analysis of variance (ANOVA) with repeated measures on the time factor. The origin of significant effects was further examined by post hoc comparisons using the Bonferroni technique.

3. Results

3.1. Effect of NOS inhibitors on nicotine-induced behavioral sensitization

Cumulative locomotor activity counts for 2 h after injections of drugs during the 7-day development phase

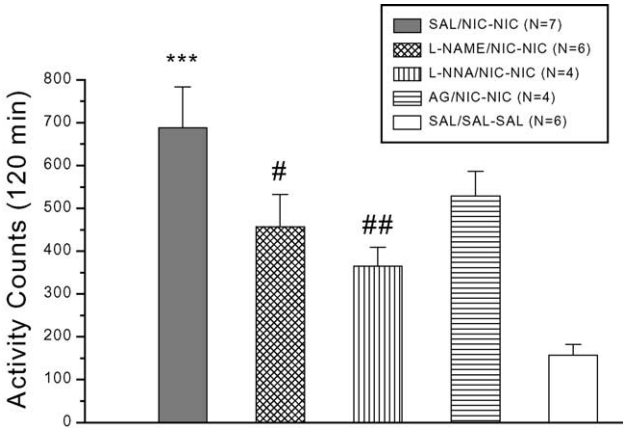

Fig. 2. Effects of NOS inhibitors on locomotor activity in response to nicotine challenge. Rats were pretreated with saline (SAL/NIC–NIC), L-NAME (L-NAME/NIC–NIC), L-NNA (L-NNA/NIC–NIC) or aminoguanidine (AG/NIC–NIC) 30 min before injections of nicotine during a 7-day development phase and tested with a nicotine challenge on day 11. The normal control group was pretreated and challenged with only saline (SAL/SAL–SAL). *=significant difference from normal control group and # from saline-pretreated and nicotine challenged group: ***, $P<0.001$; #, $P<0.05$; ##, $P<0.01$. Vertical lines indicate S.E.M. ($N=4-9$).

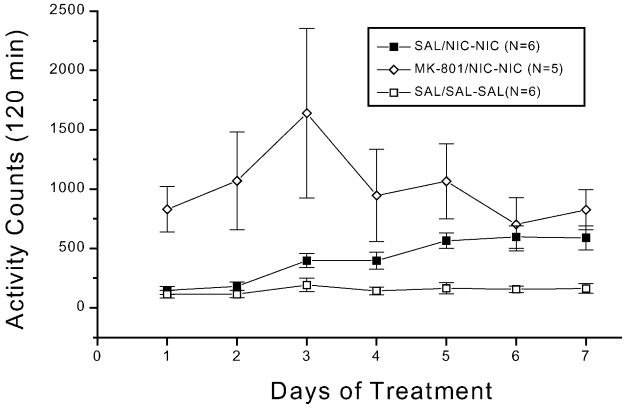

Fig. 4. Effects of MK-801 on nicotine-induced locomotor activity during a 7-day development phase. Rats were pretreated with saline (1ml/kg, ■ SAL/NIC–NIC) or MK-801 (0.3 mg/kg, i.p., ◇ MK-801/NIC–NIC) 30 min before injections of nicotine during a 7-day developmental phase. The normal group was pretreated and challenged with only saline (□ SAL/SAL–SAL). Vertical lines indicate S.E.M. ($N=5-6$).

are shown in Fig. 1. An ANOVA test (6 × 8, drug × time) performed on the activity scores after drug treatments for the development test indicated a significant effect of drug [$F(5,27) = 12.8$, $P < 0.001$], a significant effect of time [$F(7,21) = 10.3$, $P < 0.001$], and a significant interaction between drug × time [$F(35,125) = 1.6$, $P < 0.05$]. Post hoc comparisons indicated that repeated injections of nicotine produced a significant increase in locomotor activity, compared with those of saline-pretreated rats on day 11 ($P < 0.001$), reflecting that sensitization to nicotine was established and persisted on day 11. Pretreatment with L-NAME and L-NNA during the 7-day development phase, but not aminoguanidine, blocked the development of nicotine-induced sensitization during the 7-day nicotine treatments (Fig. 1) as well as in response to nicotine challenge on day 11 (Fig. 2). L-NAME ($P < 0.05$) and L-NNA ($P < 0.01$) injections significantly inhibited nicotine-induced locomotor activity, relative to saline treatment in response to nicotine challenge on day 11. There was, however, no a significant difference between aminoguanidine and saline pretreatment in response to nicotine challenge as shown in Fig. 2 ($P > 0.145$).

An ANOVA test (6 × 8, drug × time) performed on the activity scores after drug treatments for the expression test indicated a significant effect of drug [$F(5,23) = 8.3$, $P < 0.001$], a significant time effect [$F(7,17) = 13.5$, $P < 0.001$] and a significant interaction between drug × time time [$F(35,105) = 2.4$, $P < 0.01$]. Fig. 3 shows that none of the injections of L-NAME, L-NNA or aminoguanidine during 3-day withdrawal periods after the 7-day induction phase exerted an obvious effect on the expression of sensitization produced by repeated nicotine ($P > 0.66$, $P > 0.97$, $P > 0.75$ for L-NAME, L-NNA and aminoguanidine).

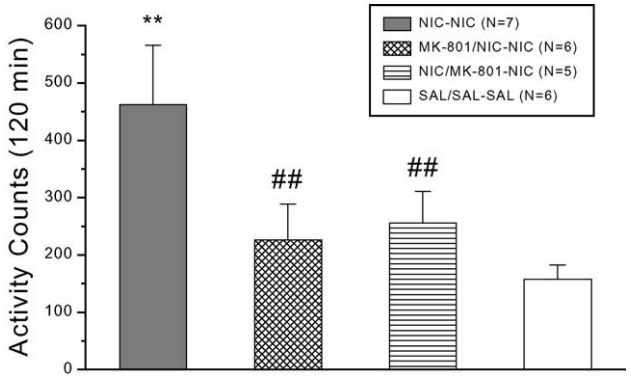

Fig. 5. Effects of MK-801 on nicotine-induced locomotor activity in response to nicotine challenge. Rats were pretreated with nicotine twice daily for 7 consecutive days and they were injected with saline or MK-801 during a 7-day developmental phase (MK-801/NIC – NIC) or during 3-day withdrawal phase (NIC/MK-801 – NIC) and locomotor activity was measured in response to nicotine challenge on day 11. * = significant difference from normal group and # from saline-pretreated and nicotine challenged group: **, $P < 0.01$; ##, $P < 0.01$. Vertical lines indicate S.E.M. ($N = 5–7$).

3.2. Effect of MK-801 on nicotine-induced behavioral sensitization

Injections of MK-801 plus nicotine produced a marked increase in locomotor activity for the first 4 testing days, compared with those of saline plus nicotine as shown in Fig. 4 ($P < 0.001$, $P < 0.01$, $P < 0.01$, $P < 0.05$ from day 1 to 4, respectively). However, in response to nicotine challenge on day 11, pretreatment with MK-801 during development phase ($P < 0.001$) or 3-day withdrawal period ($P < 0.001$) significantly blocked nicotine-induced behavioral sensitization in response to nicotine challenge as shown in Fig. 5.

4. Discussion

The present results clearly demonstrate that repeated daily injections of nicotine increase the locomotor response to a subsequent systemic challenge with nicotine. Since psychostimulant-induced sensitization consists of two components, development of sensitization and expression of the response in sensitized animals (Karler et al., 1990), we compared a variety of NOS inhibitors and NMDA receptor antagonist to nicotine-induced behavioral sensitization in two separate phases, development and expression. In the present study, it was shown that the induction of sensitization was blocked by pretreatment with L-NAME and L-NNA during development phase, but not with aminoguanidine. The behavioral responses to nicotine challenge in the L-NAME- and L-NNA-pretreated group were significantly lower than those in the saline-pretreated group. These findings suggest that constitutively produced NO may play an important role in the development of nicotine-induced behavioral effects although inducible NO was without effect on nicotine-induced behavioral sensitization. As far as we have known, this study is first to implicate the involvement of NO in nicotine-induced development of behavioral sensitization. Several studies have shown that NOS inhibitors markedly blocked the developmental phase of drug-induced sensitization. For example, L-NAME pretreatment inhibited the induction of sensitization produced by cocaine (Pudiak and Bozarth, 1993). However, pretreatment with L-NAME did not block the induction of the behavioral sensitization to amphetamine or methamphetamine (Stewart et al., 1994; Abekawa et al., 1995). These results suggest that the mechanism of nicotine-induced development of behavioral sensitization is similar to that of cocaine, but not that of amphetamine or methamphetamine. The neural mechanisms by which NO is involved in nicotine-induced induction of sensitization remain to be elucidated. Evidence suggests that the behavioral and reinforcing effects of nicotine may be mediated by central dopaminergic systems, especially the mesolimbic system from the ventral tegmental area to the nucleus accumbens (Fallon and Moore, 1978), and nicotine can act on nic-

otinic acetylcholine receptors localized both on dopaminergic cell bodies in the ventral tegmental area and on their nerve terminals in the nucleus accumbens (Clarke and Pert, 1985), leading in increased dopamine release in the nucleus accumbens (Shim et al., 2001). NO has been suggested as a retrograde neurotransmitter and may diffuse from the postsynaptic membrane to the presynaptic membrane (Snyder, 1992). Thus, repeated stimulation of postsynaptic receptors by nicotine may produce increases in release of presynaptic neurotransmitter including dopamine and glutamate. Since NOS inhibitors are shown to block methamphetamine-induced dopamine release in the striatum (Bowyer et al., 1995; Inoue et al., 1996), it is possible that inhibition of NO formation reduces development of locomotor activity to nicotine by modulating dopamine release or activation of postsynaptic dopamine receptors in the striatum or the nucleus accumbens. In the present study, even though L-NAME, known to act as a muscarinic receptor inhibitor as well as an NOS inhibitor (Buxton et al., 1993), produced larger decrease in nicotine-induced locomotor activity than did L-NNA, our results strongly suggest that NO formation during injections of nicotine is critical for the development of long-term behavioral changes. In addition, our results demonstrated that the induction of sensitization by nicotine was significantly blocked by a nonspecific constitutive NOS inhibitor, L-NAME and a neuronal and endothelial constitutive NOS inhibitor, L-NNA (Gross et al., 1990, 1991), but not by the selectively inducible NOS inhibitor, aminoguanidine. Even though there was a slight tendency to inhibit the development of sensitization in response to nicotine challenge with 100 mg/kg aminoguanidine chosen in the present study, pretreatment with 3, 30 and 100 mg/kg aminoguanidine in a pilot dose-dependent study had no significant effects on nicotine-induced development of sensitization (unpublished observations). It should be noted that the lack of effects with aminoguanidine in the present study may not be due to the selection of the noneffective ranges of the dose–response curve since many studies have demonstrated that aminoguanidine with this dosage produced significant biological and physiological effects. For example, administration of aminoguanidine (100 mg/kg, i.p.) significantly reduced alcohol-induced hepatotoxicity of rat (Alam et al., 2001) and histamine-induced contraction of the guinea pig small intestine (Kitanaka et al., 2002). Therefore, our results strongly suggest that constitutive isoforms of NOS, but not inducible isoform of NOS have an important role in NO-mediated behavioral sensitization produced by nicotine. This suggestion is strengthen by the fact that constitutive isoforms rather than inducible isoform of NOS blocked signs of morphine withdrawal (Vaupel et al., 1997).

Nicotine-induced behavioral sensitization was not affected by pretreatment with L-NAME, L-NNA or aminoguanidine during nicotine withdrawal period, indicating that NO production may be not critically involved in the expression of sensitization produced by nicotine. Thus, the current study clearly demonstrated that L-NAME and L-NNA inhibited the development, but not the expression of nicotine-induced sensitization. In contrast to our results, L-NAME was reported to block the expression of sensitization to methamphetamine (Inoue et al., 1996), in which multiple injections of the interfering drugs were given during withdrawal period. The multiple administrations of the interfering drugs, such as NOS inhibitors, are generally known to be more effective in blocking the expression of sensitization than the single acute administration before the challenge injection of the psychostimulant, which was not robust enough to prevent the expression of behavioral sensitization (Inoue et al., 1996; Yang et al., 2001). In the present study, nicotine-induced expression of sensitization was not blocked by pretreatments with NOS inhibitors, which were massively given during 3-day washout periods and just before nicotine challenge. These results suggest that NO formation may not be involved in mechanism underlying the expression of sensitization to nicotine and that its neural mechanism is different from that of methamphetamine.

The present study showed that pretreatment with the NMDA receptor antagonist, MK-801, during the nicotine induction phase also blocked the hyperactivity to subsequent nicotine challenge. These results are in good agreement with previous data showing that pretreatment with MK-801 blocked the development of sensitization to the drugs of abuse including nicotine, cocaine, amphetamine or methamphetamine (Kalivas and Alesdatter, 1993; Shoaib et al., 1994; Wolf, 1998). Furthermore, in the present study, it was shown that injections of MK-801 during the 3-day nicotine withdrawal period resulted in a pronounced decrease in locomotor activity in response to nicotine challenge, suggesting that the expression of behavioral sensitization to nicotine is also mediated by the activation of NMDA receptors. Taken together, the present results demonstrated that nicotine-induced behavioral sensitization requires the activation of NMDA receptors for not only its development, but also for its expression. Since NO is known to be formed as a results of the activation of NMDA receptors, followed by Ca^{2+} influx and stimulation of Ca^{2+}/calmodulin-dependent NOS (Dawson et al., 1991), long-term behavioral changes produced by nicotine can be mediated by activation of NMDA receptors followed by the formation of NO. Therefore, blockade of NMDA receptors and NO formation can result in prevention of the development of nicotine-induced sensitization.

In conclusion, NMDA receptors can play a major role in the expression as well as the development of nicotine-induced behavioral sensitization. NO is critically involved in the development, but not in the expression of the sensitization to nicotine. It suggests that the mechanisms of development to nicotine are different from that of expression. In addition, constitutively produced NO may play an

important role in the development of nicotine-induced behavioral effects, but inducible NO was without effect on nicotine-induced behavioral sensitization.

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