Nicotinic Modulation of Mesoprefrontal Dopamine Neurons: Pharmacologic and Neuroanatomic Characterization

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ABSTRACT

Schizophrenics have cortical dysfunction that may involve mesoprefrontal dopamine (DA) systems. Rates of nicotine dependence approach 90% in schizophrenia, and nicotine administration through cigarette smoking may ameliorate cortical dysfunction, which may be related to cortical DA dysregulation. We have shown that repeated, but not acute, nicotine pretreatment (0.15 mg/kg daily s.c.) reduces footshock stress-induced mesoprefrontal DA metabolism and immobility responses. This effect of repeated nicotine is dependent on mecamylamine (MEC)-sensitive nicotinic acetylcholine receptor (nAChR) stimulation and endogenous opioid peptides. In the present study, we have further characterized these effects of repeated nicotine on the stress reactivity of mesoprefrontal DA neurons by using the following: 1) local infusion of MEC into cell bodies (ventral tegmental area) and terminal fields (medial prefrontal cortex) to determine the site of action of nicotine; and 2) systemic administration of selective nAChR antagonists. Results of bilateral local infusions of MEC (0.1–1.0 μg/side) into ventral tegmental area or medial prefrontal cortex in saline- and nicotine-pretreated rats suggests a modulatory role for somatodendritic versus terminal field nAChRs on mesoprefrontal DA neurons under stress-induced states. Experiments with dihydro-β-erythroidine (a β2-subunit-selective blocker; 0.0–3.0 mg/kg) and methylycaconitine (an α7-subunit-selective blocker; 0.0–8.4 mg/kg) suggest that both α4β2- and α7-containing nAChRs modulate mesoprefrontal DA neurons. Thus, complex regulation of mesoprefrontal DA neurons by nAChRs is suggested, which may have relevance to prefrontal cortical DA dysfunction and the high comorbid rates of nicotine dependence in schizophrenia.

Nicotine exerts diverse psychopharmacologic effects and is thought to be the key component in tobacco responsible for habitual smoking (Balfour and Fagerstrom, 1996). The initial site of nicotine's actions is nicotinic acetylcholine receptors (nAChRs). Nicotine's diverse psychopharmacologic effects likely relate to nAChR modulation of dopaminergic, serotonergic, adrenergic, glutamatergic, and endogenous opiate peptide pathways (McGehee and Role, 1995; Picciotto, 1998). In particular, the effects of nicotine on the dopamine (DA) system and its relationship to psychiatric disorders, including schizophrenia, has received considerable attention (Nisell et al., 1995; Ziedonis and George, 1997; George et al., 1998, 2000). Schizophrenia is thought to be mediated, at least in part, by dysregulation of mesolimbic and mesocortical DA pathways, and clinically, prevalence rates of nicotine dependence in schizophrenic patients approach 90% in some studies (Hughes et al., 1986; Ziedonis and George, 1997).

In particular, schizophrenia is associated with cognitive deficits related to prefrontal cortical dysfunction, and schizophrenics may smoke heavily to ameliorate such cognitive dysfunction (George et al., 1998). There is evidence that auditory gating deficits (P50 responses) that are normalized by cigarette smoking are linked to deficits in the α7 nAChR (Freedman et al., 1997). Furthermore, mice with knockout of the β2 subunit of the nAChR have deficits in associative memory and nicotine-stimulated mesolimbic DA release (Picciotto et al., 1998). There is strong physical and functional evidence for the presence of nAChRs on nigrostriatal and mesolimbocortical DA neurons (Clarke and Pert, 1985; Vezina et al., 1992; George et al., 1998; Picciotto et al., 1998).

Schizophrenic disorders are often exacerbated by stress, and the mesoprefrontal DA in the rat is preferentially activated (increased DA metabolism and release) by acute stress, including that induced by acute inescapable electrical footshock stress (Horger and Roth, 1996). Furthermore, acute footshock stress leads to freezing behavior (immobility responses) in rats. Nicotine appears to have anxiolytic effects in smokers and in animal models as well as mood-elevating, nociceptive-, and cognitive-enhancing effects (Aceto et al., 1997; Zuckerman et al., 1997).

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ABBREVIATIONS: nAChR, nicotinic acetylcholine receptor; DA, dopamine; MEC, mecamylamine; VTA, ventral tegmental area; mPFC, medial prefrontal cortex; MLA, methyllycaconitine; DHBE, dihydro-β-erythroidine; DOPAC, dihydroxyphenylacetic acid.
Given the hypothesized clinical relationships between schizophrenia, the cortical DA system, stress, and nicotine use, we have studied how nicotine administration could modify mesoprefrontal DA responses to acute stress in rats.

In our previous studies (George et al., 1998), we have examined the effects of acute and repeated nicotine pretreatments on mesoprefrontal and subcortical DA systems under basal (no stress) and stress-induced states. Repeated, but not acute, nicotine pretreatment reduced stress-induced cortical DA and immobility responses. These effects were present at low (0.15 mg/kg), but were abolished with high dose (0.60 mg/kg) nicotine pretreatments, suggesting an “inverted-U” dose-response pattern. Experiments with the nonselective nAChR antagonist mecamylamine (MEC) suggested that the stress-reducing effects of nicotine were dependent on MEC-sensitive nAChR stimulation (George et al., 1998). However, MEC is a nonselective nAChR antagonist and also may bind to N-methyl-D-aspartate receptors (O’Dell and Christensen, 1988), and thus the role of subtype-specific nAChR regulation of mesoprefrontal DA neurons in these studies was not addressed. In addition, nicotine could exert its modulatory effects on the mesoprefrontal DA system by stimulation of nAChRs at the level of DA cell bodies in the ventral tegmental area (VTA) or at DA terminals in the medial prefrontal cortex (mPFC); hence, the site of action of nicotine in these studies was also unclear.

Accordingly, the present study sought to answer two questions: 1) What is the site(s) of action of nicotine on the mesoprefrontal DA pathway through which repeated nicotine administration modulates cortical DA responses to stress? and 2) What subtypes of the nAChR may mediate the effects of repeated nicotine on the cortical DA stress response?

In the present experiments, we have used local infusions of the nonselective nAChR antagonist MEC and systemic administration of the more selective nAChR antagonists dihydoro-β-erythroidine [DHBE, a competitive antagonist of high-affinity (~4.92 subunit-containing) central nAChRs; Stolerman et al., 1997] and methyllycaconitine (MLA, an antagonist of α7 nAChRs; Brioni et al., 1996) to characterize the pharmacology and site of action of repeated nicotine’s modulation of mesoprefrontal DA function.

**Experimental Procedures**

**General Procedures**

**Materials.** Male Sprague-Dawley rats initially weighing 250 to 274 g were obtained from Camm (Rutgers, NJ). The weights of rats at the conclusion of the experiments was 300 to 350 g. S-(−)-nicotine bitartrate and MEC hydrochloride were obtained from Sigma Chemical Co. (St. Louis, MO). DHBE and MLA were obtained from Research Biochemicals International (Natick, MA).

**Treatment Paradigm.** Rats were given daily injections for 5 days with either saline (1 ml/kg) or nicotine bitartrate (0.15 mg/kg, expressed as the freebase). All injection solutions were freshly prepared on a daily basis, and the pH of the saline and nicotine solutions was adjusted to 7.4 with NaOH. MEC, DHBE, and MLA were dissolved in saline. Biochemical measures were obtained 0.5 h after nicotine challenge injection.

**Antagonist Studies.** For MEC infusion experiments, rats were given an infusion of MEC (0.1–1.0 μg/side) or saline over a 1-min period at the time of nicotine challenge, 0.5 h before sacrifice. DHBE (0.0–3.0 mg/kg) was injected s.c. 0.5 h before challenge injection, and MLA (0.0–8.4 mg/kg) was injected i.p. at the time of challenge injection. Doses of DHBE (Stolerman et al., 1997) and MLA (Brioni et al., 1996) chosen were based on published reports with systemic administration of these antagonists.

**Surgical Procedures**

Rats were anesthetized by using an i.p. injection of 1 ml/kg equithesin (9.72 mg/ml phenobarbital, 44.4 mg/ml chloral hydrate in 44% propylene glycol carrier). Body temperature was maintained at 37°C by a thermostatically controlled electric heating pad. Surgical procedures have been described in details elsewhere (Murphy et al., 1997). Guide cannulae were prepared by using 25-gauge tubing (Small Parts, Inc., Miami, FL) and inserted bilaterally into the VTA (from bregma, −5.3 mm AP; ±2.0 mm ML; −6.7 mm DV at an 8° angle) or mPFC (from bregma, +2.2 mm AP; ±1.0 mm ML; −3.2 mm DV). After surgery, animals were housed individually in Plexiglas cages until local infusion experiments were performed. Saline or MEC (0.1 μg/side) was infused by using a Hamilton syringe connected to a Harvard Apparatus infusion pump at a rate of 2.0 μl/min over a 1-min period. After decapitation and fresh tissue dissection for biochemical analysis of mPFC, brains were then fixed for 24 h in 4% paraformaldehyde. Regions of interest (i.e., PFC and brainstem) were cut into 50-μm coronal sections with a vibratome. These sections were then stained with cresyl violet to facilitate visualization of cannulae tracks for cannulae tip localization.

**Behavioral Procedures**

**Acute Footshock Stress Procedure.** On day 5, rats were given a final injection of saline and nicotine, and then placed in a sound-attenuated chamber in which the grid floor of the chamber was connected to a shock generator (BRS/LVE Division of Tech Serv Inc., Beltsville, MD) and a pulse stimulator (Grass Medical Instruments, Quincy, MA) that delivered mild footshocks (0.8-mA shocks of 160-ms duration, every 10 s for 20 min). Rats received either the footshock paradigm or no shocks.

**Behavioral Procedures.** All footshock sessions were recorded by videotaping. The percentage of time spent immobile (% immobility) during each 1 min interval of the footshock session was scored by blinded examiners (T.P.G., C.D.V.) who manually rated the taped sessions post hoc. There was excellent inter-rater reliability (κ = .80) in the scoring of immobility. Results for immobility responses in MEC, DHBE, and MLA experiments are presented for the 1-min period, where effects of nicotine on immobility responses were maximal.

**Neurochemical Procedures**

At the conclusion of the footshock period, rats were sacrificed by decapitation. Samples of mPFC (+2.7 to 1.7 mm from bregma) were harvested by block dissection (Fig. 1; adapted from Paxinos and Watson, 1986).

DA and its major metabolite, dihydroxyphenylacetic acid (DOPAC), were quantified by using HPLC with electrochemical detection with a glassy carbon electrode set at +0.7 V and an Ag/AgCl reference electrode. The procedure involved alumina extraction before HPLC analysis as previously described (Morrow et al., 1995). A reversed phase 3-μm C18 HPLC column (Ranin Instruments, Woburn, MA) was used. The mobile phase, delivered at 0.65 ml/min, comprised of sodium citrate (30 mM), sodium dihydrogen phosphate (14 mM), sodium octanesulphonate (2.3 mM), EDTA (0.025 mM), acetoni-tile (6.5%), tetrahydrofuran (0.6%), and diethylamine (0.1%), adjusted to pH 3.10 with concentrated phosphoric acid. Dihydroxybenzamine was used as an internal standard and was used to calculate percentage of recovery of DOPAC and DA. Results are expressed as the ratio of DOPAC to DA, with levels in nanograms per
milligram of protein. Protein determination was done with the method of Lowry et al. (1957) with BSA as standard.

Statistical Procedures

One- and two-factor ANOVAs were used to analyze main effects, whereas repeated measures ANOVA with one within- and one between-factors comparison used to analyze dose-response data in DHBE and MLA experiments. Post hoc testing with Fisher's least-significant difference procedure was done when interactions were significant; post hoc differences were considered significant when $P < .05$.

Results

Verification of Cannulae Placement (Fig. 1). In VTA-cannulated rats analyzed for cortical DA biochemistry and behavior, tips of bilateral cannulae were located within 2 mm of the VTA (−5.3 mm from bregma; Fig. 1, top). Animals with
cannulae tips more than 2 mm from the VTA were excluded from further analysis. Similar localizations were obtained in the target area for the mPFC (+2.2 mm from bregma; Fig. 1, bottom).

**Biochemical Analysis.** Baseline metabolite levels (mean ± S.E.) for DOPAC and DA in mPFC were 0.234 ± 0.025 and 0.679 ± 0.071, respectively (DOPAC/DA ratio, 0.344 ± 0.007). Data are expressed as percentage of saline controls for the DOPAC/DA ratio. There were no differences in DA levels between treatment groups in all regions examined (data not shown), indicating that changes in DOPAC/DA ratios reflect true DA utilization.

**Effects of MEC Infusion into the VTA on Repeated Nicotine Modulation of Stress-Induced Cortical DA and Immobility Responses (Fig. 2).** In experiments involving infusion of the nonselective nAChR antagonist MEC into VTA-cannulated rats, there were no significant effects of pretreatment (F = 0.89; df = 1.24; P = .36) or antagonist (F = 3.14; df = 1.24; P = .09), but there was a significant pretreatment × antagonist interaction (F = 9.91; df = 1.24; P < .01) on stress-induced cortical DA utilization. Repeated nicotine (0.15 mg/kg s.c.) reduced stress-induced mesoprefrontal DA responses by 25 to 30% (P < .05). MEC infusion (0.1 μg/side) was without effects in saline-pretreated rats, but at higher doses (1.0 μg/side) reduced stress-induced mesoprefrontal DA responses by itself (data not shown). In rats pretreated with repeated nicotine, MEC infusion into the VTA blocked the reduction in the cortical DA stress response by repeated nicotine administration (P < .05 versus nicotine controls).

In VTA-cannulated rats, there were significant effects of

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**Fig. 2.** Effects of bilateral local infusion of MEC (0.1 μg/side) into VTA on 1) stress-induced mesoprefrontal DA utilization (top), and 2) stress-induced immobility responses (bottom). Location of cannulae tips is given in Fig. 1. n = 6 to 8 rats for each group.
pretreatment ($F = 10.14; \text{df} = 1.24; P < .01$) and antagonist ($F = 13.14; \text{df} = 1.24; P < .01$), and a significant pretreatment \times antagonist interaction ($F = 16.27; \text{df} = 1.24; P < .01$) for data on stress-induced immobility responses. Repeated nicotine (0.15 mg/kg s.c.) reduced stress-induced immobility responses by 40\% ($P < .01$). MEC (0.1 \mu g/side) was without effects in saline-pretreated rats, but at higher doses (1.0 \mu g/side) reduced stress-induced immobility responses by itself (data not shown). In rats pretreated with repeated nicotine, MEC infusion into the VTA blocked the reduction in stress-induced immobility responses by repeated nicotine administration ($P < .01$ versus nicotine controls).

**Effects of MEC Infusion into mPFC on Repeated Nicotine Modulation of Stress-Induced Cortical DA and Immobility Responses (Fig. 3).** In experiments involving infusion of MEC into mPFC-cannulated rats, there was a significant effect of pretreatment ($F = 15.19; \text{df} = 1.24; P < .01$), but not antagonist ($F = 0.52; \text{df} = 1.24; P = .48$) and no significant pretreatment \times antagonist interaction ($F = 0.15; \text{df} = 1.24; P = .90$) on stress-induced cortical DA utilization. Repeated nicotine (0.15 mg/kg s.c.) significantly reduced stress-induced mesoprefrontal DA responses ($P < .05$). MEC (0.1 \mu g/side) infusion into the mPFC was without effects in saline-pretreated rats, but at higher doses (1.0 \mu g/side) reduced stress-induced mesoprefrontal DA responses by itself (data not shown). In rats pretreated with repeated nicotine, MEC infusion into the mPFC did not block the reduction in the cortical DA stress response by repeated nicotine administration ($P = .58$ versus nicotine controls).

In mPFC-cannulated rats, there was a significant effect of pretreatment ($F = 44.00; \text{df} = 1.24; P < .01$), but not antagonist ($F = 1.50; \text{df} = 1.24; P = .23$) and no significant pretreatment \times antagonist interaction ($F = 0.09; \text{df} = 1.24; P = .76$) for data on stress-induced immobility responses. Repeated nicotine (0.15 mg/kg s.c.) significantly reduced stress-induced immobility responses ($P < .01$). MEC (0.1 \mu g/side) infusion into the mPFC was without effects in saline-pretreated rats, but at higher doses (1.0 \mu g/side) reduced

![Fig. 3. Effects of bilateral local infusion of MEC (0.1 \mu g/side) into mPFC on 1) stress-induced mesoprefrontal DA utilization (top), and 2) mPFC on stress-induced immobility responses (bottom). $n = 6$ to 8 rats for each group.](image-url)

* $p < 0.05$ vs. saline control

![MECAMYLLAMINE INFUSED (ug/side)](image-url)

* $p < 0.05$ vs. saline control
stress-induced immobility responses by itself (data not shown). In rats pretreated with repeated nicotine, MEC infusion into the mPFC did not block the reduction in the stress-induced responses by repeated nicotine administration ($P = .55$ versus nicotine controls).

**Effects of DHBE on Repeated Nicotine Modulation of Stress-Induced Cortical DA and Immobility Responses** (Fig. 4). In experiments with the competitive high-affinity nAChR antagonist DHBE, repeated measures ANOVA revealed significant effects of pretreatment ($F = 4.87; \text{df} = 1.44; P < .05$) and dose ($F = 3.27; \text{df} = 2.44; P < .05$), and a significant pretreatment $\times$ dose interaction ($F = 8.73; \text{df} = 2.44; P < .01$) for data on stress-induced cortical DA utilization. Repeated nicotine significantly decreased stress-induced DA metabolism ($P < .05$). DHBE pretreatment (1.0–3.0 mg/kg s.c.) was without effect on stress-induced cortical DA responses. A single DHBE pretreatment 0.5 h before the saline or nicotine challenge injection dose-dependently blocked the effects of repeated nicotine on the stress-induced cortical DA response, with a significant blockade of the effects of repeated nicotine administration at the 3.0-mg/kg, but not the 1.0-mg/kg DHBE dose ($P < .05$ versus nicotine controls).

In experiments with DHBE, repeated measures ANOVA revealed significant effects of pretreatment ($F = 16.41; \text{df} = 1.28; P < .01$) and dose ($F = 5.47; \text{df} = 2.28; P < .01$), and a significant pretreatment $\times$ dose interaction ($F = 4.97; \text{df} = 2.28; P < .05$) for data on stress-induced immobility responses. The immobility response during the first minute of the footshock session was significantly reduced by repeated nicotine versus saline pre-exposure ($P < .05$). DHBE (1.0–3.0 mg/kg) pretreatment did not alter the immobility stress response by itself, but dose-dependently blocked the inhibitory effects of repeated nicotine on 1-min immobility responses, with significant effects at the 3.0-mg/kg, but not the 1.0-mg/kg dose ($P < .05$ versus nicotine controls).

**Effects of MLA on Repeated Nicotine Modulation of Stress-Induced Cortical DA and Immobility Responses** (Fig. 5). In experiments with the competitive low-affinity nAChR antagonist MLA, repeated measures ANOVA revealed significant effects of pretreatment ($F = 135.35; \text{df} =$
1.56; \(P < .01\) and dose \((F = 8.86; df = 2.56; P < .01)\), and a significant pretreatment \(\times\) dose interaction \((F = 42.55; df = 2.56; P < .01)\) for data on stress-induced cortical DA utilization. Repeated nicotine significantly reduced stress-induced cortical DA responses \((P < .05)\). A single MLA cotreatment \((4.2–8.4 \text{ mg/kg i.p.})\) with the saline or nicotine challenge injection was without effect on stress-induced cortical DA responses by itself, but dose-dependently blocked the suppressive effects of repeated nicotine administration on cortical DA stress responses with significant effects at both the 4.2- and 8.4-mg/kg doses \((P < .05\) versus nicotine controls). In experiments with MLA, repeated measures ANOVA revealed significant effects of pretreatment \((F = 32.14, df = 1.28; P < .01)\) and dose \((F = 10.63; df = 2.28; P < .01)\), and a significant pretreatment \(\times\) dose interaction \((F = 9.66; df = 2.28; P < .01)\) for data on stress-induced immobility responses. Repeated nicotine pretreatment significantly reduced 1-min stress-induced immobility responses compared with saline controls \((P < .05)\). MLA \((4.2–8.4 \text{ mg/kg})\) did not affect the immobility stress response by itself, but blocked dose-dependently repeated nicotine’s reduction of stress-induced immobility responses at 1 min, with significant effects at both the 4.2- and 8.4-mg/kg doses \((P < .05\) versus nicotine controls).

**Discussion**

Our previous studies have found that pretreatment with the nonselective nAChR antagonist MEC blocks repeated nicotine’s reduction of the stress-induced mesoprefrontal DA and immobility responses (George et al., 1998). This suggests that these modulatory effects of repeated nicotine pretreatment are dependent on MEC-sensitive nAChR stimulation. In the present study, we sought to define the site of action of nicotine in modulation of stress-induced mesoprefrontal DA activation. Our experiments with local infusions of MEC into the VTA or mPFC suggest that MEC-sensitive somatodendritic nAChRs in the VTA, but not in the mPFC terminal
fields, mediate these actions of repeated nicotine administration. These results are consistent with the findings of Nisell et al. (1994) who implicated nAChRs in the VTA versus nucleus accumbens terminal fields in mediating the effects of nicotine's enhancement of DA release in the nucleus accumbens. The dose of MEC infused (0.1 µg/side, ~250 µM) in the present studies is within the MEC concentration range used by Nisell et al. (1994) (100–1000 µM), which did not affect nucleus accumbens DA release by itself, but blocked nicotine augmentation of DA release. Higher doses of MEC (1.0 µg/side, ~2500 µM) inhibited stress-induced cortical DA utilization by itself, and is consistent with MEC interacting with other neuroreceptors (e.g., N-methyl-D-aspartate receptors; O'Dell and Christensen, 1988), which have been show to reduce the cortical DA stress response (Goldstein et al., 1994; George et al., 1998).

Furthermore, studies with systemic pretreatment with the selective nAChR antagonists DHBE and MLA suggest that repeated nicotine's effects on mesoprefrontal DA neurons involve stimulation of both high-affinity (α4β2 subunit-containing) and low-affinity (α7 subunit-containing) nAChRs, respectively. It is important to note that because these antagonists were administered systemically, effective drug concentrations at central nAChRs are not known, and because both of these agents are less selective for nAChR subtypes at higher concentrations (Williams and Robinson, 1984; Yum et al., 1996), our results with DHBE and MLA should be interpreted cautiously. Nonetheless, there is evidence for the presence of α4 and β2 subunits, and, to a lesser extent, α7 subunits, on mesocorticolimbic DA neurons (Piciotto, 1998). α7 Subunits appear to be enriched in the cortex, where there are also high levels of α4 and β2 nAChR subunits (Hill et al., 1993; Zoli et al., 1995). Thus, it is possible that MLA could exert its actions on nicotine's modulation of stress-induced mesoprefrontal DA function at either the level of the VTA or mPFC. Future studies with local infusions of these selective antagonists into the VTA and mPFC are warranted to establish the exact anatomic sites of action of these agents in nAChR subtype-specific regulation of stress-induced mesoprefrontal DA function.

Our results suggest a complex regulation of stress-evoked mesoprefrontal DA neuronal activity by multiple nAChR subtypes. There is evidence for a role of high-affinity (α4β2) nAChRs in mediating nucleus accumbens DA release (Nisell et al., 1994), and low-affinity (α7) nAChRs in nicotine-induced nucleus accumbens DA release (Schistrom et al., 1998) and nicotine withdrawal-related changes in accumbens DA release (Nomikos et al., 1999) at the level of the VTA, and such nAChR regulation appears to extend to mesoprefrontal DA neurons, which also originate in the VTA. Our results also are consistent with recent evidence suggesting interactions between high-affinity (α4β2) and low-affinity (α7) nAChRs in the VTA (Pidoplichko et al., 1997) and hippocampus (Alkondon et al., 1999). These results may have implications for our understanding of the interactions between nicotine use, acute stress, and prefrontal cortical DA deficits with disorders characterized by prefrontal cortical DA dysfunction, such as schizophrenia. Furthermore, our results suggest that selective pharmacologic treatments targeting nAChR subtypes could be of importance for the treatment of both schizophrenia and nicotine dependence.

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References


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