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Modulation of nicotine self-administration in rats by combination therapy with agents blocking α3β4 nicotinic receptors

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Abstract

18-Methoxycoronaridine, a novel *iboga* alkaloid congener that decreases drug self-administration in several animal models, may be a potential treatment for multiple forms of drug abuse. In previous work, 18-methoxycoronaridine was found to be a somewhat selective antagonist at α3β4 nicotinic receptors; and low dose combinations of 18-methoxycoronaridine with other drugs known to have the same action (e.g., mecamylamine, dextromethorphan) decreased both morphine and methamphetamine self-administration in rats at doses that were ineffective if administered alone. In the present study, similar drug combinations (but including bupropion as well) were found to decrease nicotine self-administration in rats. The data further support the hypothesis that diencephalic pathways having high densities of α3β4 nicotinic receptors modulate mesocorticolimbic pathways more directly involved in drug reinforcement. Antagonists of α3β4 nicotinic receptors may represent a totally novel approach to treating polydrug abuse.

Keywords: 18-Methoxycoronaridine; Dextromethorphan; Mecamylamine; Bupropion; Nicotine; Nicotine receptor; Drug addiction

1. Introduction

18-Methoxycoronaridine, a novel *iboga* alkaloid congener being studied as a potential treatment for multiple forms of drug abuse, decreases the self-administration of morphine (Glick et al., 1996; Maisonneuve and Glick, 1999), cocaine (Glick et al., 1996), methamphetamine (Glick et al., 2000a), nicotine (Glick et al., 2000a) and ethanol (Rezvani et al., 1997) in rats. Although it is known that 18-methoxycoronaridine reduces dopamine release in the nucleus accumbens (Glick et al., 1996) and binds with low affinity to several types of receptors (Glick and Maisonneuve, 2000; Glick et al., 2000b), its precise mechanism of action has been uncertain for a long time. Recently, however, using patch-clamp methodology, 18-methoxycoronaridine was found to be a somewhat selective antagonist at α3β4 nicotinic receptors (Glick et al., 2002). Evidence pointing to the importance of this action was provided by data showing that low dose combinations of 18-methoxycoronaridine with other drugs known to have this same action (e.g., mecamylamine, Papke et al., 2001; dextromethorphan, Hernandez et al., 2000) decreased both morphine and methamphetamine self-administration in rats at doses that were ineffective when administered alone. Not only were combinations of 18-MC with each of these agents effective, but a dextromethorphan–mecamylamine combination was similarly effective. Because there are no agents available that are entirely specific for α3β4 receptors, the use of combinations of low doses of unrelated agents that act at this site was thought to be a potentially practical way of enhancing therapeutic efficacy (attributable to additive effects at the α3β4 site) while reducing side effects (attributable to actions unique to each agent).

Together, many of our previous findings (Glick et al., 2002; also cf. Glick et al., 2001) suggested that antagonism of acetylcholine's actions at α3β4 nicotinic receptors may constitute an important mechanism for reducing the rewarding effects of multiple drugs; and α3β4 receptors are localized in brain areas that are well suited to modulate, both directly (e.g., Klink et al., 2001) and indirectly (e.g., Nishikawa et al., 1986; Quick et al., 1999), the mesocorticolimbic system involved in drug reward. Thus, in the present study, the foregoing rationale was extended to the study of nicotine self-administration. 18-Methoxycoronaridine (Glick et al., 2000a), dextromethorphan (Glick et al., 2001), and mecamylamine (e.g., Corrigall

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and Coen, 1989; Watkins et al., 1999) have all been shown to decrease nicotine self-administration in rats. Another drug that blocks α3β4 nicotinic receptors (Fryer and Lukas, 1999) and that decreases nicotine self-administration (smoking) in humans is the atypical antidepressant bupropion (e.g., Holm and Spencer, 2000); hence, bupropion was also included here. Following dose–response determinations of each drug's effects alone on nicotine self-administration in rats, the effects of combinations of low (i.e., ineffective alone) doses of each pair of drugs were assessed. The drug pairs included all possible combinations, i.e., 18-methoxycoronaridine with either dextromethorphan, mecamylamine or bupropion as well as dextromethorphan–mecamylamine, dextromethorphan–bupropion, and mecamylamine–bupropion.

2. Materials and methods

2.1. Treatment drugs

18-Methoxycoronaridine hydrochloride (Albany Molecular Research, Albany, NY) was dissolved in phosphate buffer and injected intraperitoneally 15 min before behavioral testing. Dextromethorphan hydrobromide (Sigma/RBI, St. Louis, MO) was dissolved in saline and injected subcutaneously 20 min before testing. Mecamylamine hydrochloride (Sigma/RBI) was dissolved in physiological saline and injected intraperitoneally 30 min before testing. Bupropion hydrochloride (Sigma/RBI) was dissolved in saline and injected intraperitoneally 15 min before testing. All rats received two injections (for rats that received a single drug, half of them also received the appropriate saline/vehicle injection corresponding to one of the other three drugs).

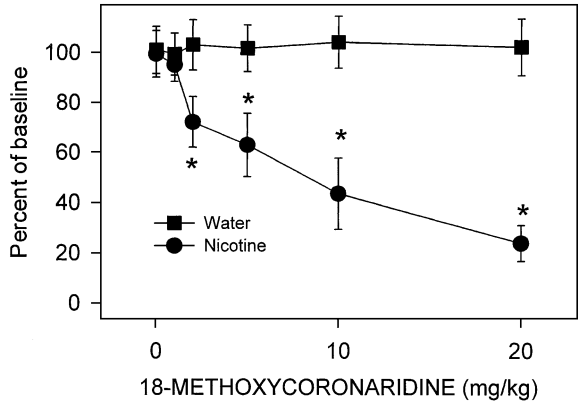

Fig. 1. Effects of 18-methoxycoronaridine on nicotine self-administration (0.028 mg/kg/infusion) and on responding for water. Baseline nicotine infusions averaged (± S.E.M.) 27.7 ± 2.6 and baseline responses for water averaged (± S.E.M.) 869.32 ± 68.1. Each data point represents the mean (± S.E.M.) percent of baseline of five to six rats. * Significant differences between drug and vehicle (ANOVA, $P<0.00005$; post-hoc Newman–Keuls, $P<0.02$–0.0001).

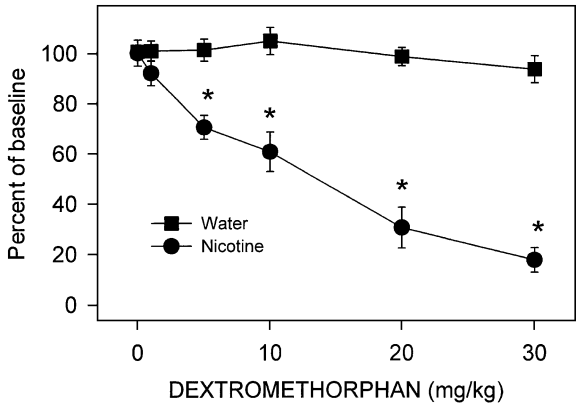

Fig. 2. Effects of dextromethorphan on nicotine self-administration (0.028 mg/kg/infusion) and on responding for water. Baseline nicotine infusions averaged (± S.E.M.) 26.0 ± 1.8 and baseline responses for water averaged (± S.E.M.) 845.32 ± 29.1. Each data point represents the mean (± S.E.M.) percent of baseline of five to six rats. * Significant differences between drug and vehicle (ANOVA, $P<0.00001$; post-hoc Newman–Keuls, $P<0.01$–0.0001).

2.2. Animals

Naive female Long–Evans derived rats (250 g; Charles River, NY) were maintained on a normal 12-h light cycle (lights on at 7:00 AM, lights off at 7:00 PM). For all experiments, the "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed.

2.3. Self-administration procedure

The intravenous self-administration procedure has been described previously (e.g., Glick et al., 1996, 2000a). Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM compatible computer with a Med Associates interface. The

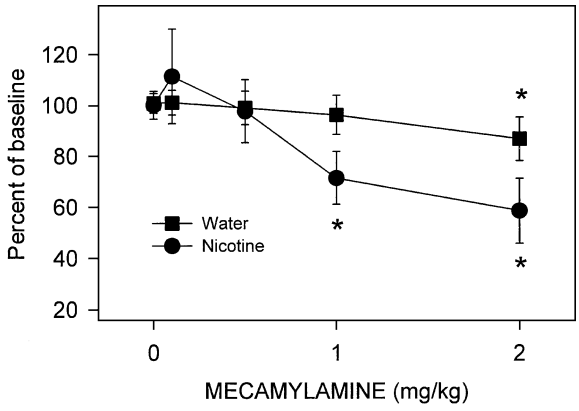

Fig. 3. Effects of mecamylamine on nicotine self-administration (0.028 mg/kg/infusion) and on responding for water. Baseline nicotine infusions averaged (± S.E.M.) 25.6 ± 1.7 and baseline responses for water averaged (± S.E.M.) 858.32 ± 36.6. Each data point represents the mean (± S.E.M.) percent of baseline of five to six rats. * Significant differences between drug and vehicle (ANOVA, $P<0.05$–0.02; post-hoc Newman–Keuls, $P<0.05$).

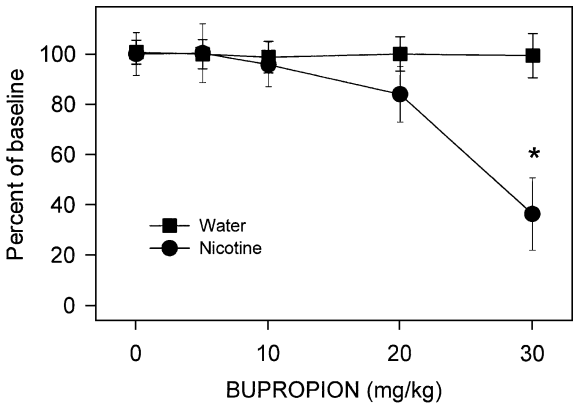

Fig. 4. Effects of bupropion on nicotine self-administration (0.028 mg/kg/infusion) and on responding for water. Baseline nicotine infusions averaged (± S.E.M.) 25.3 ± 2.2 and baseline responses for water averaged (± S.E.M.) 873.2 ± 48.1. Each data point represents the mean (± S.E.M.) percent of baseline of five to six rats. * Significant differences between drug and vehicle (ANOVA, $P<0.05$; post-hoc Newman–Keuls, $P<0.05$).

intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks (1972), Instech harnesses and swivels, and Harvard Apparatus infusion pumps (#55-2222). Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks (1972). Self-administration testing began with a 16-h nocturnal session followed by daily 1-h sessions, 5 days (Monday–Friday) a week. A lever-press response produced a 50-μl infusion of drug solution (0.02 mg of nicotine hydrogen bitartrate) in about 1 s. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.08 mg/kg of nicotine (0.028 mg/kg free base). A 20-s time-out followed each nicotine infusion, during which time responses were not rewarded or counted. Experiments to assess the effects of experimental treatments were begun when baseline self-administration rates stabilized (< 10% variation from 1 day to the next across 5 days), usually after 2 weeks of testing. Each rat typically received two or three different treatments spaced at least 1 week apart. In order to provide an indication of the specificity of treatment effects on drug self-administration, all treatments were also administered to other rats bar-pressing for water (0.01 ml orally) on a comparable schedule (continuous reinforcement; 1-h sessions).

2.4. Statistical analysis

All dose–response functions were analyzed with one-way analysis of variance (ANOVA) followed by post-hoc Newman–Keuls tests to determine which dose–effects differed significantly from vehicle. Paired *t*-tests were used to compare the effects of drug combinations to their respective baselines (average rate during the two preceding test sessions).

3. Results

Figs. 1–4 show dose-related effects of 18-methoxycoronaridine, mecamylamine, dextromethorphan, and bupropion on nicotine self-administration and on responding for water. Analyses of variance showed significant ($P<0.05$–0.00001) effects of each drug alone on nicotine self-administration; only mecamylamine (ANOVA, $P<0.05$) had a significant effect on responding for water. Figs. 5 and 6 show the effects of the combination treatments on nicotine self-administration and on responding for water. All six drug combinations, but none of the drugs administered alone at the same doses, significantly decreased nicotine self-administration while having no effect on responding for water. The drug doses selected for the combination treatments were, in

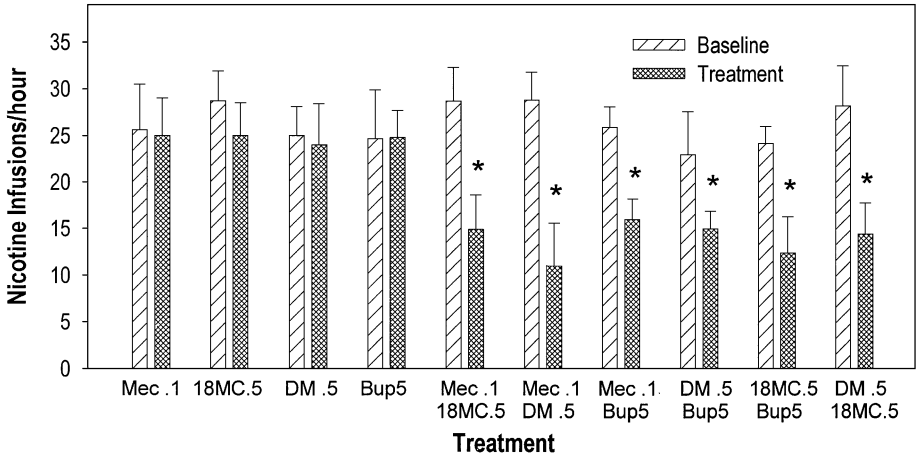

Fig. 5. Effects of drug combinations on nicotine self-administration (0.028 mg/kg/infusion). Rats were administered two of the following treatments before testing: mecamylamine (MEC; 0.1 mg/kg i.p., 30 min), 18-methoxycoronaridine (18 MC; 0.5 mg/kg i.p., 15 min), dextromethorphan (DM; 0.5 mg/kg s.c., 20 min), bupropion (Bup; 5 mg/kg i.p., 15 min), or vehicle (saline for MEC and DM; phosphate buffer for 18MC). Each data point represents the mean (± S.E.M.) infusions per hour of five to eight rats. * Significant differences between baseline and treatment (paired *t*-test, $P<0.01$).

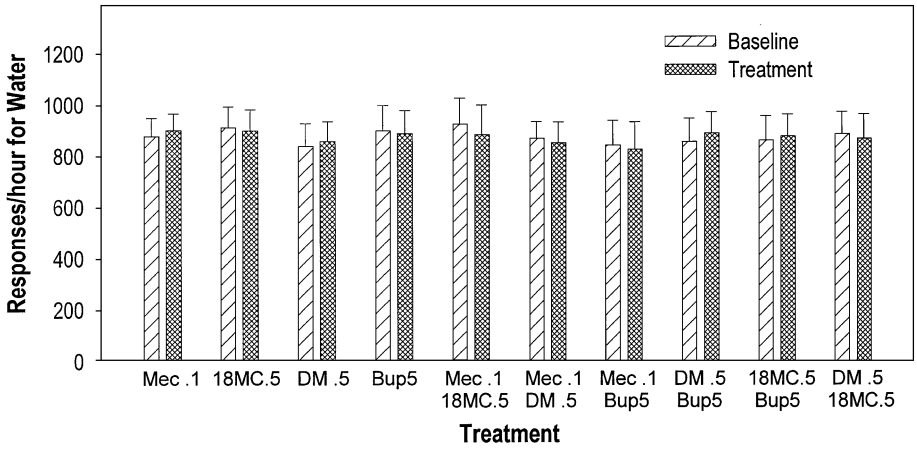

Fig. 6. Effects of drug combinations on responding for water. Rats were administered two of the following treatments before testing: mecamylamine (MEC; 0.1 mg/kg i.p., 30 min), 18-methoxycoronaridine (18 MC; 0.5 mg/kg i.p., 15 min), dextromethorphan (DM; 0.5 mg/kg s.c., 20 min), bupropion (Bup; 5 mg/kg i.p., 15 min), or vehicle (saline for MEC and DM; phosphate buffer for 18MC). Each data point represents the mean (± S.E.M.) responses per hour of five to six rats.

each instance, based on knowledge of the respective dose–response functions. The doses of 18-methoxycoronaridine, dextromethorphan, and bupropion were approximately one-fourth of those required to decrease nicotine self-administration when administered alone. Because of its non-specific effect (i.e., on responding for water), the dose of mecamylamine in the combination treatments was chosen to be about one-tenth of that required to decrease nicotine self-administration when administered alone.

4. Discussion

Low dose combinations of 18-methoxycoronaridine with either mecamylamine, dextromethorphan or bupropion, or of mecamylamine with dextromethorphan or bupropion, or of dextromethorphan with bupropion all significantly reduced nicotine self-administration without affecting responding for water. Although baseline rates of responding for water were much higher than baseline rates of nicotine self-administration, previous work (e.g., Glick et al., 1991) has established that higher rates are more rather than less sensitive to nonspecific treatment effects. Due to the inverted U shape that is characteristic of drug self-administration dose–effect functions, treatment-induced decreases in drug self-administration at a single infusion dosage could conceivably reflect either potentiation (leftward shift of dose–effect function) or antagonism (rightward shift of dose–effect function) of the self-administered drug. However, unlike other drugs self-administered by rats, antagonists of nicotine appear to shift the nicotine dose–effect function downward rather than to the right (i.e., compensatory increases in responding after antagonists are not typically observed; cf. Corrigall and Coen, 1989; Watkins et al., 1999). Furthermore, previous work involving the effects of 18-methoxycoronardine on morphine self-administration (Maisonneuve and Glick, 1999) and of dextromethorphan on methamphetamine self-administration (Jun and Schindler, 2000) indicated that, in both instances, the infusion dose–effect function was also shifted downward without displacement to the left or right, suggesting that these treatments reduced the reinforcing efficacy of the self-administered drugs. Thus, both the individual and combination treatments assessed in the present study may have similarly reduced the reinforcing efficacy of nicotine.

As in previous self-administration studies from this laboratory (e.g., Glick et al., 1991, 1996, 2000a, 2002), female rats were used. We primarily use female rats because they have much slower growth curves and are therefore less likely to outgrow their intravenous catheters. Although some sex differences in drug self-administration have been reported, such differences appear to be minimal using a fixed ratio schedule similar to the one used here. Roberts et al. (1989) reported no significant effect of sex on fixed ratio rates of cocaine self-administration but, in contrast, a significant sex effect on breaking points when the same rats were subsequently trained on a progressive ratio schedule. There was also an estrous effect on the progressive ratio but not on the fixed ratio schedule. More recently, Lynch and Carroll (1999) and Lynch et al. (2000) reported that female rats acquire cocaine self-administration at a faster rate than male rats, and differ from male rats in the variability of spacing between infusions; however, the sexes did not differ in total intake of cocaine per session. And most pertinent to the present study, Donny et al. (2000) reported that female rats acquired nicotine self-administration faster and reached higher break points than males on a progressive ratio schedule, but females did not differ from males in total nicotine intake per session during stable fixed ratio self-administration; and there was no effect of estrous cycle on either progressive ratio or fixed ratio nicotine self-admin-

istration. We therefore have no reason to suspect that our conclusions regarding female rats would not generalize, at least qualitatively, to male rats.

Antagonism at α3β4 sites is the only known action that 18-methoxycoronaridine, mecamylamine, dextromethorphan, and bupropion have in common. Although 18-methoxycoronaridine binds with low affinity to several receptor sites (e.g., opioid, 5-HT_3; cf. Glick and Maisonneuve, 2000; Glick et al., 2000b), we have recently demonstrated that 18-methoxycoronaridine is relatively selective for α3β4 nicotinic sites versus other ionotropic receptors (e.g., α4β2, NMDA, 5-HT_3; cf. Glick et al., 2002). Dextromethorphan and its metabolite dextrorphan are both antagonists at NMDA glutamate receptors (Murray and Leid, 1984; Ebert et al., 1998) as well as at α3β4 nicotinic receptors; however, in studies comparing their effects on drug self-administration (Glick et al., 2001), the relative potencies of dextromethorphan and dextrorphan were more consistent with actions at α3β4 receptors than at NMDA receptors. Mecamylamine is a well known and prototypical nonspecific nicotinic antagonist (e.g., Martin et al., 1993); however, Papke et al. (2001) recently reported that mecamylamine has preferential affinity for α3β4 receptors versus other nicotinic subtypes (e.g., α4β2). Bupropion, long known to be a weak inhibitor of dopamine reuptake (e.g., Ferris et al., 1982; Ascher et al., 1995), was more recently discovered to block nicotinic receptors (Fryer and Lukas, 1999; Slemmer et al., 2000); and it has been estimated that bupropion concentrations in human brain are likely to be more than sufficient to block α3β4 nicotinic receptors (Fryer and Lukas, 1999). Thus, for each of these drugs, there is a reason to believe that the α3β4 nicotinic receptor may be an important site of action despite the fact that all of these drugs have multiple actions.

Although all the treatment agents used in this study have a common action at the α3β4 nicotinic receptor, it is difficult to make a clear correlation between α3β4 antagonist potency and potency to reduce nicotine self-administration. However, some reasonable inferences can be made. Reported IC50s at the α3β4 nicotinic receptor indicate that mecamylamine (IC50 = 0.64 μM; Papke et al., 2001) is slightly more potent than 18-methoxycoronaridine (IC50 = 0.75 μM; Glick et al., 2002) which in turn is more potent than dextromethorphan (IC50 = 8.9 μM; Hernandez et al., 2000). In the present study, in fairly close agreement with these IC50s, doses of 1, 2 and 5 mg/kg of mecamylamine, 18-methoxycoronaridine and dextromethorphan, respectively, significantly decreased nicotine self-administration by approximately 30%. The outlier is bupropion, which has an IC50 of 1.4 μM at the α3β4 nicotinic receptor (Fryer and Lukas, 1999) and which, from Fig. 4, would take between 20 and 30 mg/kg to decrease nicotine self-administration by 30%. However, while metabolism should play a minor role in mediating the effects of mecamylamine (which is excreted mostly unchanged; cf. Hardman et al., 2001), 18-methoxycoronaridine (which has an active but minor metabolite with a similar IC50 for the α3β4 site; Zhang et al., 2002; Fleck, personal communication), and dextromethorphan (via the subcutaneous route; cf. Wu et al., 1995), bupropion is extensively metabolized (with several metabolites known to be active; cf. Hardman et al., 2001). Thus, if bupropion itself is responsible for its effects on nicotine self-administration (and smoking in humans; cf. Fryer and Lukas, 1999), its systemic potency would indeed be expected to be much lower than that predicted by its IC50 for the α3β4 nicotinic receptor.

Previous studies of nicotine self-administration and reward have focused on roles for the α4β2 and α7 nicotinic receptors. While involvement of the α7 receptor is controversial (e.g., Panagis et al., 2000; Grottick et al., 2000), there is substantial evidence supporting a role for α4β2 receptors (e.g., Picciotto et al., 1998; Watkins et al., 1999; Grottick et al., 2000). Indeed, α4β2 receptors are highly localized in the ventral tegmental area (e.g., Klink et al., 2001), the origin of neurons comprising the dopaminergic mesolimbic pathway that is thought to be the common mediator of the reinforcing properties of most drugs of abuse, nicotine included (e.g., Corrigall and Coen, 1991; Corrigall et al., 1992, 1994). While the present self-administration results are consistent with our hypothesis implicating antagonism of α3β4 receptors as a potential mechanism for reducing nicotine seeking behavior, only relatively low densities of α3β4 receptors reside in the ventral tegmental area (e.g., Klink et al., 2001), making it unlikely that α3β4 antagonists modulate nicotine self-administration directly via this route. In fact α3β4 nicotinic receptors are mainly located in the medial habenula and the interpeduncular nucleus (e.g., Klink et al., 2001; Quick et al., 1999). While the interpeduncular nucleus receives its major input from the medial habenula, forming the habenulointerpeduncular pathway, there are multiple avenues for interaction between this pathway and the mesolimbic pathway. The medial habenula receives input from the nucleus accumbens and has efferents to the ventral tegmental area; and the interpeduncular nucleus has efferent connections to the brainstem raphe nuclei and the medial dorsal thalamic nucleus, both of which directly or indirectly (e.g., via the prefrontal cortex) connect to the ventral tegmental area. Functional interactions between the habenulointerpeduncular and mesolimbic pathways are therefore likely, and to some extent, have already been demonstrated (Nishikawa et al., 1986).

Totally selective antagonists of α3β4 receptors are unavailable, and hence it was difficult to directly test our hypothesis that α3β4 antagonists would reduce the self-administration of nicotine and other drugs (Glick et al., 2002). However, we reasoned that if two agents had the common action of blocking this site but also had other actions that were unique to each agent, the combination of low doses of such agents might produce additive effects at the α3β4 site and reduce drug self-administration without the involvement of other actions contributing to side effects. In the present study, as a further test of this idea, the effects

of six such combined treatments on nicotine self-administration were assessed; and the results were similar to our previous results with morphine and methamphetamine self-administration (Glick et al., 2002). Inasmuch as 18-methoxycoronardine reduces alcohol intake in rats (Rezvani et al., 1997), the present rationale may be applicable to alcohol as well. Supporting this possibility is a report that mecamylamine also reduces alcohol intake but that dihydro-β-erythroidine, a potent α4β2 nicotinic antagonist, does not reduce alcohol intake (Lê et al., 2000). Thus, antagonism of α3β4 nicotinic receptors may be a truly novel mechanism through which multiple forms of addictive behavior can be influenced. 18-Methoxycoronaridine, having apparently greater selectivity for α3β4 sites than either mecamylamine, dextromethorphan or bupropion, may be the first of a new class of synthetic agents having this broad spectrum of activity.

Acknowledgements

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