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18-Methoxycoronaridine acts in the medial habenula and/or interpeduncular nucleus to decrease morphine self-administration in rats

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Abstract

The novel iboga alkaloid congener 18-methoxycoronaridine (18-MC) is a putative anti-addictive agent that has been shown, in rats, to decrease the self-administration of morphine and other drugs of abuse. Previous work has established that 18-MC is a potent antagonist at α3β4 nicotinic receptors. Because α3β4 nicotinic receptors in the brain are preferentially located in the medial habenula and the interpeduncular nucleus, the present study was conducted to determine if 18-MC could act in these brain areas to modulate morphine self-administration in rats. Local administration of 18-MC into either the medial habenula or the interpeduncular area decreased morphine self-administration while having no effect on responding for a non-drug reinforcer (sucrose). Similar results were produced by local administration into the same brain areas of two other α3β4 nicotinic antagonists, mecamylamine and α-conotoxin AuIB. Local administration of 18-MC into the ventral tegmental area had no effect on morphine self-administration. These and other data are consistent with the hypothesis that 18-MC decreases morphine self-administration by blocking α3β4 nicotinic receptors in the habenulo-interpeduncular pathway.

Keywords: 18-Methoxycoronaridine; α-Conotoxin AuIB; Mecamylamine; Morphine; Medial habenula; Interpeduncular nucleus; Nicotine receptors; Drug addiction

1. Introduction

The results of several studies have indicated that 18-methoxycoronaridine (18-MC), an iboga alkaloid congener, may have unique potential to treat multiple forms of drug abuse. In rats, 18-MC has been shown to decrease the self-administration of morphine (Glick et al., 1996), cocaine (Glick et al., 1996), methamphetamine (Glick et al., 2000a), nicotine (Glick et al., 2000a) and alcohol (Rezvani et al., 1997) without altering responding for a non-drug reinforcer (water; Glick et al., 1996; sucrose, Pace et al., 2004). The precise mechanism of action of 18-MC remained elusive for a long time despite evidence that it modulated dopamine release in the nucleus accumbens (Glick et al., 1996) and bound, with low affinity, to several types of receptors (Glick and Maisonneuve, 2000; Glick et al., 2000b). However, in functional assays ($^{86}Rb^{+}$ efflux from KXα3β4R2 cells) conducted as part of the NIMH Psychoactive Drug Screening Program (unpublished data; K. Kellar, Georgetown University), 18-MC was found to be a potent antagonist at α3β4 nicotinic receptors. In subsequent patch-clamp studies of transfected *HEK293* cells expressing specific subtypes of nicotinic receptors, 18-MC was found to have a selective antagonist action in that it blocked α3β4 but not α4β2 nicotinic receptors (Glick et al., 2002a; Pace et al., 2004). The dose–response relationship of 18-MC's effects at α3β4 receptors had a Hill slope of unity, consistent with a single site of action. The inhibition developed rapidly in the presence of acetylcholine and reversed more slowly following 18-MC's removal, perhaps providing a correlate of prolonged effects on drug self-administration (Glick et al., 1996).

For most of the past two decades, the dopaminergic mesolimbic system has been the major focus of research regarding mechanisms of action of drugs of abuse; however, new treatments based on this research have been slow to develop and new approaches are needed. In addition to 18-MC, we recently reported that other agents (dextromethorphan, mecamylamine and bupropion) blocking cholinergic α3β4 nicotinic receptors also reduced morphine, methamphetamine and nicotine self-administration in rats (Glick et al., 2002a,b). In

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the brain, α3β4 nicotinic receptors are preferentially localized in the medial habenula and interpeduncular nucleus. Although low densities of α3β4 receptors reside in the dopaminergic nuclei of the ventral tegmental area, 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 main input from the medial habenula, forming the habenulo-interpeduncular pathway, there are multiple avenues for interaction between this pathway and the mesolimbic pathway. For example, 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.

The habenula, the interpeduncular nucleus, and the habenulo-interpeduncular pathway in the fasciculus retroflexus are part of what has been referred to as the dorsal diencephalic conduction system (Sutherland, 1982). Since the 1980s, it has been known that this system functions as a reward system separate from the mesolimbic pathway in the medial forebrain bundle. Rats will electrically self-stimulate all of the major structures of the dorsal diencephalic conduction system, including the stria medullaris, habenula, fasciculus retroflexus and interpeduncular nucleus (e.g., Sutherland and Nakajima, 1981; Rompre and Miliaressis, 1985; Blander and Wise, 1989; Vachon and Miliaressis, 1992). Although it has long been known that the dorsal diencephalic conduction system and the medial forebrain bundle interact and probably modulate each other (Sutherland and Nakajima, 1981; Nishikawa et al., 1986), few studies have explored the possibility of developing novel treatments based on such interactions. In the present study, we have begun to consider this idea by determining if local administration of 18-MC to either the medial habenula or interpeduncular nucleus will decrease morphine self-administration.

2. Materials and methods

2.1. Treatment drugs

Treatment drugs included 18-methoxycoronaridine hydrochloride (1–20 μg; Albany Molecular Research, Inc., Albany, NY), mecamylamine hydrochloride (10 μg; Sigma/RBI, St. Louis, MO), and α-conotoxin AuIB (25 pmol; generously provided by Dr. J. Michael McIntosh, University of Utah). All treatments were injected intracerebrally immediately before behavioral testing.

2.2. Animals

Naïve female Long-Evans derived rats (250 g; Charles River, NY) were maintained on a normal 12-h light cycle (lights on at 7:00 a.m., lights off at 7:00 p.m.). For all experiments, the "Guide for the Care and Use of Laboratory Animals" (Guide for the Care and Use of Laboratory Animals, 1996) was 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, Inc. interface. The 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 (0.025 mg of morphine sulfate) in about 1 s. Since all rats generally weighed 250±20 g, each response delivered approximately 0.1 mg/kg of morphine. Surgery to implant cannulae for intracerebral drug administration was performed when baseline self-administration rates stabilized (±20% 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 sucrose (15% solution; 0.01 ml orally) on a comparable schedule (continuous reinforcement; 1-h sessions).

2.4. Intracerebral drug administration

Rats were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and secured in a stereotaxic instrument. A midline incision was made, the bone was exposed, and bilateral holes for the microinjection guide cannulae were drilled. Microinjection guide cannulae (22-gauge; Plastics One, Roanoke, VA, USA) were lowered into place such that, when inserted, the tips of injectors would be located in the medial habenula or interpeduncular nucleus. The coordinates for the medial habenula and interpeduncular nucleus injections were, respectively, as follows: AP −4.2 mm, ML ±2.9 mm, DV −5.4 mm, using a 24° angle; AP −6.3, ML ±2.6 mm, DV −9.2 mm, using a 14° angle (Paxinos and Watson, 1986). Some injections were also made into the ventral tegmental area; coordinates were as follows: AP −6.0 mm, ML ±2.6 mm, DV −8.5 mm, angled 14° from midline. The microinjection guide cannulae were permanently secured with stainless steel screws and cranioplastic cement; and the incision was closed with staples. Rats were allowed to recover for at least 24 h before resuming self-administration testing. Intracerebral injections were made with the use of microsyringe (Hamilton; Reno, NV). Treatment drugs (or vehicle) were administered in a volume of 1 μl over 1 min to prevent backflow through the microinjection guide; the injection cannula (26 gauge) was kept in place for an additional minute after drug infusion. All intracerebral injections were

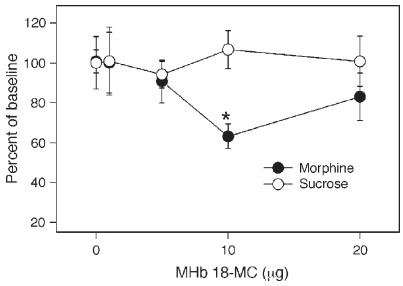

Fig. 1. Effects of local infusion of 18-MC into the medial habenula on morphine self-administration and responding for sucrose. Baseline morphine infusions averaged (±S.E.M.) 21.5±1.1 while baseline responding for sucrose averaged (±S.E.M.) 25.5±3.4. Each data point represents the mean (±S.E.M.) percent of baseline of 6–9 rats. *Significant difference between drug and vehicle (ANOVA, $P<0.03$; LSD test, $P<0.025$) and between drug and baseline (paired t-test, $P<0.01$).

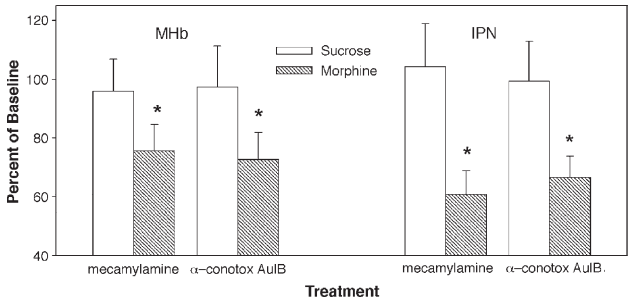

Fig. 3. Effects of local infusion of mecamylamine (10 μg) and α-conotoxin AuIB (25 pmol) into the medial habenula and interpeduncular nucleus on morphine self-administration and responding for sucrose. Baseline morphine infusions averaged (±S.E.M.) 22.1±1.4 while baseline responding for sucrose averaged (±S.E.M.) 23.9±3.8. Each data point represents the mean (±S.E.M.) percent of baseline of 5–7 rats. *Significant difference between drug and baseline (paired t-tests, $P<0.05$–0.01).

made bilaterally, immediately before starting a self-administration session.

3. Results

Figs. 1 and 2 show the effects of local administration of 18-MC into the medial habenula and interpeduncular nucleus on morphine self-administration and responding for sucrose. Infusion of 18-MC into either site decreased morphine self-administration [interpeduncular nucleus: $F(5,29)=6.89$, $P<0.0001$; medial habenula: $F(4,28)=3.07$, $P<0.03$] while having no effects on responding for sucrose. 18-MC appeared to be more potent, and possibly more effective, in the interpeduncular nucleus than in the medial habenula: 5 μg had a significant effect in the interpeduncular nucleus while 10 μg was required to produce a significant effect in the medial habenula (and the effect of the former was somewhat greater than the effect of the latter). In both sites, the dose–response function was U-shaped, with the highest dosage (20 μg) having no effect. In contrast, when infused into the ventral tegmental area, 18-MC had no effect (percent of baseline: vehicle=95.4±7.4, 18-MC=90.5±8.1, Ns=5) on morphine self-administration at a dose (10 μg) that was effective in both the interpeduncular nucleus and medial habenula.

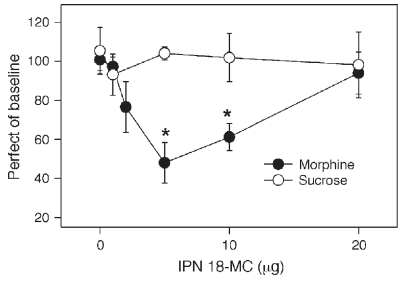

Fig. 2. Effects of local infusion of 18-MC into the interpeduncular nucleus on morphine self-administration and responding for sucrose. Baseline morphine infusions averaged (±S.E.M.) 22.7±1.2 while baseline responding for sucrose averaged (±S.E.M.) 24.3±2.5. Each data point represents the mean (±S.E.M.) percent of baseline of 5–10 rats. *Significant difference between drug and vehicle (ANOVA, $P<0.0001$; LSD tests, $P<0.005$–0.002) and between drug and baseline (paired t-tests, $P<0.01$–0.005).

Fig. 3 shows effects of locally administered mecamylamine (10 μg) and α-conotoxin AuIB (25 pmol). Both agents significantly decreased morphine self-administration when infused into either the interpeduncular nucleus or medial habenula while having no effects on responding for sucrose.

4. Discussion

The results of this study suggest that 18-MC acts in both the medial habenula and interpeduncular nucleus to modulate morphine self-administration. This action appears to be functionally specific in that sucrose responding was not affected by the same treatments. The comparable effects of mecamylamine and α-conotoxin AuIB in the medial habenula and interpeduncular nucleus are consistent with the premise that 18-MC's primary mode of action is to block α3β4 nicotinic receptors (Glick et al., 2002a; Pace et al., 2004). Although mecamylamine blocks all nicotinic receptor subtypes, it has some selectivity for the α3β4 subtype (Papke et al., 2001). On the other hand, α-conotoxin AuIB is an entirely specific antagonist of α3β4 nicotinic receptors (Luo et al., 1998). Along with the prevalence of α3β4 nicotinic receptors in the medial habenula and interpeduncular nucleus (e.g., Quick et al., 1999; Perry et al., 2002), the results of this study also suggest that cholinergic neurons in the habenulo-interpeduncular pathway participate in reward mechanisms responsive to morphine and possibly to other drugs of abuse as well.

The dose–effect relationship for 18-MC was non-monotonic in both the medial habenula and interpeduncular nucleus. The lack of effect of the highest dose (20 μg) suggests that 18-MC has an opposing but less potent action at another receptor. Importantly, a dosage (10 μg) of 18-MC that was effective when administered into the interpeduncular nucleus had no effect when administered bilaterally into the ventral tegmental area—this indication of selectivity is particularly significant in that it rules out the possibility that, when injected into the interpeduncular nucleus, 18-MC might have diffused to the ventral tegmental area to produce its effect.

Substantial evidence indicates that the habenulo-interpeduncular and dopaminergic mesolimbic pathways are reciprocally related, with the former inhibiting the latter and vice versa (e.g., Nishikawa et al., 1986; Ellison, 1994). However, there is also evidence that habenular output can stimulate ascending dopamine neurons in the ventral tegmental area (Christoph et al., 1986). How 18-MC alters the interaction between the habenulo-interpeduncular and mesolimbic pathways may depend on the activity of these pathways and on how drugs of abuse exert their effects; that is, an action of 18-MC in the habenulo-interpeduncular pathway may in fact modulate rather than simply inhibit the activity of the mesolimbic pathway. Thus, 18-MC enhances the acute effect of morphine while attenuating the sensitized effect of repeated morphine administration on dopamine release in the nucleus accumbens (Maisonneuve and Glick, 1999; Maisonneuve et al., 2001; Szumlinski et al., 2000).

Patch clamp studies have indicated that 18-MC blocks α3β4 nicotinic receptors by acting as a non-competitive allosteric modulator (Pace et al., 2003). In the presence of 18-MC, α3β4 nicotinic receptors will desensitize faster and recover slower from desensitization. α3β4 receptors are located on the soma of cholinergic projection neurons in the medial habenula, on their axon terminals in the interpeduncular nucleus, and on terminals of GABA neurons in the interpeduncular nucleus and possibly in the medial habenula as well (cf. Margeta-Mitrovic et al., 1999; Quick et al., 1999). When cholinergic neuronal activity is tonically low, 18-MC should reduce the activity of cholinergic habenulo-interpeduncular neurons in two ways: by blocking excitation in the medial habenula and by blocking the presynaptic facilitatory effect (positive feedback; cf. Grady et al., 2001; Wonnacott, 1997) of acetycholine in the interpeduncular nucleus. A different situation may prevail when cholinergic neuronal activity is tonically high. In this instance, released acetylcholine might spill over and activate presynaptic α3β4 receptors on GABA neurons, releasing GABA (Lena et al., 1993). By promoting desensitization of these receptors, 18-MC might reduce an inhibitory GABAergic influence (e.g., Lena et al., 1993) and paradoxically enhance the output of the habenulo-interpeduncular pathway. After acute administration of morphine, the habenulo-interpeduncular pathway may be inhibited due to the release of dopamine in the mesolimbic pathway. After repeated administration of morphine, the habenulo-interpeduncular pathway may be hyperactivated as a compensatory response to the increasingly high mesolimbic dopamine release (i.e., sensitization) or perhaps by a direct action of morphine. In this situation, possibly by blocking presynaptic α3β4 receptors on GABA neurons, 18-MC might further enhance the output of the habenulo-interpeduncular pathway and this effect would then severely dampen the mesolimbic dopamine response (i.e., abolish sensitization) to morphine and result in decreased morphine self-administration. Alternatively, it is possible that drugs of abuse may directly affect the habenulo-interpeduncular pathway, with the latter action in part contributing to and/or mediating drugs' rewarding effects. In this instance, the putative "anti-addictive" action of 18-MC might occur solely and locally in the habenulo-interpeduncular pathway. We have just begun to consider this latter possibility in recent experiments.

In summary, along with other data from this laboratory (Glick et al., 2002a; Pace et al., 2004; Taraschenko et al., 2005), the present data indicate that 18-MC acts in the habenulo-interpeduncular pathway, via antagonism of α3β4 nicotinic receptors, to decrease morphine self-administration. This behavioral effect is presumably mediated by an interaction between the mesolimbic and habenulo-interpeduncular pathways, although other mechanisms may also be involved.

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