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Attenuation of the reinforcing efficacy of morphine by 18-methoxycoronaridine

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Abstract

In previous studies, 18-methoxycoronaridine, a novel *iboga* alkaloid congener, has been reported to decrease the self-administration of morphine, cocaine, ethanol and nicotine, and to attenuate naltrexone-precipitated signs of morphine withdrawal. In the present study, the nature of the interaction between 18-methoxycoronaridine and morphine was further investigated. Using in vivo microdialysis, 18-methoxycoronaridine pretreatment (40 mg/kg i.p., 19 h beforehand) was found to markedly inhibit morphine-induced (5 mg/kg, i.p.) dopamine release in the nucleus accumbens and striatum; 18-methoxycoronaridine also enhanced morphine-induced increases in extracellular levels of dopamine's metabolites. These effects, which were more prominent in the nucleus accumbens than in the striatum, suggest that 18-methoxycoronaridine selectively interferes with morphine-induced dopamine release, without altering morphine-induced stimulation of dopamine synthesis. In intravenous morphine self-administration experiments, the effects of acute 18-methoxycoronaridine treatment (40 mg/kg, p.o.) were assessed in rats responding for one of several different unit infusion dosages of morphine (0.01-0.16 mg/kg/infusion). 18-Methoxycoronaridine produced a downward shift in the entire morphine dose–response curve without any displacement to the left or right. These results suggest that 18-methoxycoronaridine reduced the reinforcing efficacy of morphine without altering its apparent potency. Together, the microdialysis and self-administration data suggest that 18-methoxycoronaridine profoundly alters mechanisms crucial to the development and maintenance of opioid addiction.

Keywords: 18-Methoxycoronaridine; Ibogaine; Morphine; Self-administration; Microdialysis

1. Introduction

18-Methoxycoronaridine, a novel *iboga* alkaloid congener, has been reported to decrease morphine (Glick et al., 1996), cocaine (Glick et al., 1996), nicotine (Glick et al., 1998) and alcohol (Rezvani et al., 1997) self-administration in rats without inducing the adverse effects (Glick et al., 1996), such as tremor and loss of Purkinje cells in the cerebellum, that have impeded the development of a related alkaloid, ibogaine. It has also been reported to alleviate some of the withdrawal signs induced by interruption of chronic morphine treatment (Rho and Glick, 1998), and a recent study from our laboratory demonstrated its potential to decrease craving for cocaine (Glick et al., 1999). While these preclinical studies indicate that 18-methoxycoronaridine may be an effective treatment for drug addiction, its mechanism of action has yet to be definitively established. 18-Methoxycoronaridine interacts with several receptors (μ-, κ-, and δ-opioid, and 5-HT_3), but with low micromolar affinities (Glick et al., 1999).

As stated above, 18-methoxycoronaridine has been reported by our laboratory to decrease morphine self-administration without producing other non-specific responses. One question that was not addressed previously was how 18-methoxycoronaridine alters sensitivity to self-administered morphine. That is, for example, if 18-methoxycoronaridine behaved as an opioid receptor antagonist, it would be predicted that the unit infusion dose–response curve for self-administered morphine would be shifted to the right; because the dose–response curve is non-monotonic, its shape resembling an inverted U (e.g., Glick and Cox, 1977; Glick et al., 1975), an 18-methoxycoronaridine-induced decrease in the apparent potency of morphine

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would be reflected as decreased responding for low unit infusion doses and increased responding for high unit infusion doses of morphine. On the other hand, if 18-methoxycoronaridine behaved as an opioid receptor agonist, just the opposite result, a shift of the morphine dose–response curve to the left would be expected. The primary objective of the present study was to determine exactly how 18-methoxycoronaridine modulates the dose–response relationship for self-administered morphine.

It is well established that the mesolimbic dopaminergic pathway is involved in the rewarding property of drugs of abuse (Wise and Bozarth, 1987; Koob, 1992). Drug self-administration in rats is reduced after lesions of the mesolimbic dopamine system (Roberts and Koob, 1982; Smith et al., 1985) and all abused drugs, including opioids, enhance dopamine neurotransmission in the nucleus accumbens (Di Chiara and Imperato, 1988). Therefore, one possible mechanism by which 18-methoxycoronaridine could influence the rewarding effect of morphine is by altering the dopaminergic response to morphine. Presently, using in vivo microdialysis in awake and freely moving morphine-naive rats, we have determined if and how 18-methoxycoronaridine affects the mesolimbic dopamine response to acute morphine administration.

2. Methods

2.1. Chemicals

18-Methoxycoronaridine hydrochloride, obtained from Albany Molecular Research (Albany, NY), was dissolved in phosphate buffer at a concentration of 20 mg/ml. Morphine sulfate, purchased from Research Biochemicals International (Natick, MA), was dissolved in saline at the particular concentrations (0.25–5 mg/ml) required for each experiment.

2.2. Animals

For the microdialysis studies, animals were female Sprague–Dawley derived rats (Taconic, Germantown, NY), weighing 250–300 g. For the self-administration studies, they were female Long–Evans derived rats (Charles River, NY) weighing 225–250 g at the beginning of their training. The different choice of strains was attributable to the availability of rats at the time the experiments were conducted; previous work has found no differences between these strains in the effects of 18-methoxycoronaridine on morphine self-administration (e.g., Taconic Sprague–Dawley rats were used in Glick et al. (1996)). All animals were maintained on a normal 12 h light cycle (lights on at 0700 h; lights off at 1900 h) with food and water ad libitum. For all animal experiments, the ''Principles of Laboratory Animal Care'' (NIH publication No. 85-23, revised 1985) were followed.

2.3. In vivo microdialysis procedure

Under pentobarbital anesthesia (50 mg/kg, intraperitoneally (i.p.)), the rats were implanted stereotaxically with two microdialysis guide cannulas (CMA: 8309010; Acton, MA) over the nucleus accumbens and the striatum. The coordinates were chosen such that, when inserted, the tips of the dialysis probes were located either in the medial portion of the shell area of the nucleus accumbens (AP, +1.6 mm and L, ±0.8 mm from bregma; V, −8.6 mm from the surface of the skull) or in the striatum (AP, +0.5 mm; L, ±3.0 mm; V, −7.0 mm) (Paxinos and Watson, 1986). Animals were monitored for proper recovery but otherwise left undisturbed for 4 days after surgery. The afternoon prior to the in vivo microdialysis experiment, the rats received i.p., either 18-methoxycoronaridine (40 mg/kg) or vehicle. Later, the rats were placed in a cylindrical microdialysis chamber with free access to food and water. With the rats briefly anesthetized with Brevital (45 mg/kg, i.p.), dialysis probes (CMA 8309502 for the nucleus accumbens and CMA 8309503 for the striatum) were inserted through the guide cannulas. Artificial cerebrospinal fluid containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM $CaCl_2$ and 1.0 mM $MgCl_2$ was delivered continuously by a Harvard syringe pump. Collection of perfusates began the next day. The flow rate was set at 0.5 μl/min during the night prior to the experiment and changed to 1 μl/min 1 h prior to the collection of the first baseline sample. Twenty-minute fractions were collected in vials containing 2.0 μl of 1.1 M perchloric acid solution (containing 50 mg/l EDTA and 50 mg/l sodium metabisulfite). After 2 h of baseline collections, the rats received a stimulatory dose of morphine (5 mg/kg, i.p.; Maisonneuve et al., 1992; Pearl et al., 1995). The administration of morphine occurred exactly 19 h after the 18-methoxycoronaridine or vehicle pretreatment. The collection of dialysate samples was then continued for 3 h. Upon completion of an experiment, rats were killed by an overdose of pentobarbital. Each brain was removed, frozen and sliced (50 μm coronal sections) in a cryostat. The tracks left by the probes were identified and their exact positions determined by reference to the atlas of Paxinos and Watson (1986). Only the dialysates of animals whose tracks were within 0.5 mm of the correct placement were analyzed.

Previous work (Glick et al., 1996) showed that an acute dose (40 mg/kg) of 18-methoxycoronaridine decreased extracellular levels of dopamine in the nucleus accumbens for a few hours while the same dose of 18-methoxycoronaridine reduced morphine self-administration for 2 days. In the present study, we wanted to assess the neurochemical interaction between 18-methoxycoronaridine and morphine at a time when 18-methoxycoronaridine would not itself alter basal levels of dopamine but also at a time when 18-methoxycoronaridine would still be expected to inhibit morphine self-administration. We also wanted to be

able to compare the results to previous work examining the interaction between ibogaine (the prototypical *iboga* agent) and morphine (Maisonneuve et al., 1991). Thus, as in the ibogaine study, 18-methoxycoronaridine was administered 19 h prior to morphine.

2.4. Catecholamine assay

Dialysate samples were assayed for dopamine, dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA) by high-pressure liquid chromatography (HPLC) with electrochemical detection. The HPLC system consisted of a Waters 712 Wisp autosampler, a Waters 510 solvent delivery system, a Spherisorb C18 column and a Waters 464 electrochemical detector with a working electrode set at a potential of 0.79 V with respect to a silver–silver chloride reference electrode. The mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 500 to 560 mg/l heptane sulfonic acid, 100 mg/l disodium EDTA and 120 ml/l methanol and was adjusted with HCl to pH 3.6. The flow rate was set at 1.2 ml/min. Chromatograms were integrated using Hewlett Packard ChemStation software.

2.5. Self-administration procedure

The intravenous self-administration procedure has been described previously (e.g., Glick et al., 1991,1994). 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 486 computer with a Med Associates interface. The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks (1972), Instech harnesses and commutators, 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 10 μl infusion of drug solution (0.01 mg of morphine sulfate) in about 0.2 s. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine. Rats were administered saline (2 ml) by gavage 30 min prior to each daily 1 h test session. This was done to accustom rats to the gavage procedure that was to be used to administer 18-methoxycoronaridine. The p.o. route was selected in this instance to be more analogous to the route via which 18-methoxycoronaridine might eventually be administered to people.

Experiments to assess the effects of 18-methoxycoronaridine on responding for various infusion doses of morphine were begun when baseline self-administration rates stabilized, usually after 2 weeks of testing. All 18-methoxycoronaridine treatments (40 mg/kg, p.o.) and/or changes in unit infusion dose were performed on Wednesdays. Unit infusion doses of 0.02 mg/kg, 0.08 mg/kg and 0.16 mg/kg were accomplished by varying the infusion duration, whereas, for the lowest dose (0.01 mg/kg), the morphine concentration was changed. Each change in the unit infusion dose was assessed in a different group of rats. All cannulas were tested with methohexital (immediate ataxia in response to 5 mg/kg) on Fridays and only the data from rats having patent cannulas were included in the analysis of effects.

2.6. Statistical analysis

The data, expressed as infusions per hour, pmol/10 μl, or percent of baseline, were analyzed using analysis of variance (with repeated measures for microdialysis) followed by Newman–Keuls tests for post-hoc comparisons when appropriate.

3. Results

3.1. In vivo microdialysis

Basal levels of dopamine and its metabolites, that is levels that were measured during the 17–19 h interval following 18-methoxycoronaridine or vehicle pretreatment, were not different in the two pretreatment groups (Table 1).

Consistent with previous reports, in vehicle pretreated rats, morphine administration (5 mg/kg, i.p.) increased extracellular dopamine levels in nucleus accumbens and striatum [Time effect: $F(14,56) = 9.95$, $P < 0.00001$ (nucleus accumbens); $F(14,70) = 4.76$, $P < 0.00001$ (striatum)] as well as increased extracellular DOPAC [Time

Table 1
Basal levels (pmol/10 μl; mean ± S.E.M.) observed 17–19 h after vehicle or 18-methoxycoronaridine (18-MC) pretreatment

	Nucleus accumbens		Striatum	
	Vehicle ($N = 5$)	18-MC ($N = 6$)	Vehicle ($N = 6$)	18-MC ($N = 6$)
Dopamine	0.010 ± 0.002	0.011 ± 0.005	0.026 ± 0.0025	0.020 ± 0.0023
DOPAC	7.035 ± 1.12	7.17 ± 1.46	17.27 ± 4.17	16.85 ± 1.55
HVA	3.88 ± 0.97	3.53 ± 0.72	12.66 ± 2.92	11.78 ± 0.98

effect: $F(14,56) = 13.22$, $P < 0.00001$ (nucleus accumbens); $F(14,70) = 10.97$, $P < 0.00001$ (striatum)] and HVA levels [Time effect: $F(14,56) = 20.49$, $P < 0.00001$ (nucleus accumbens); $F(14,70) = 16.92$, $P < 0.00001$ (striatum)].

Although 18-methoxycoronaridine pretreatment did not abolish the increases in dopamine levels induced by morphine [Time effect: $F(14,70) = 7.86$, $P < 0.00001$ (nucleus accumbens); $F(14,70) = 3.32$, $P < 0.0004$ (striatum)], the effects were significantly attenuated (Figs. 1 and 2, left panels). In the nucleus accumbens, there was a significant pretreatment × time interaction [$(14,126) = 2.23$; $P < 0.01$]; post-hoc comparisons showed significant ($P < 0.05$) differences between 18-methoxycoronaridine and vehicle from 40 to 80 min following morphine administration. In the striatum, there was a significant pretreatment effect [$F(1,10) = 5.50$; $P < 0.04$].

In both the nucleus accumbens and striatum, 18-methoxycoronaridine pretreatment enhanced the increase in extracellular DOPAC levels (Figs. 1 and 2, top right panels) induced by morphine, indicated by significant treatment × time interactions [nucleus accumbens: $F(14,126) = 4.52$; $P < 0.0001$; striatum: $F(14,140) = 2.54$; $P < 0.005$]; post-hoc tests showed significant ($P < 0.05$) effects from 40 min after morphine administration to the end of the experiment in the nucleus accumbens, and during the 20 to 40 min and 140 to 160 min post-morphine intervals in the striatum. Similarly, in both regions, 18-methoxycoronaridine pretreatment enhanced the increase in extracellular HVA levels (Figs. 1 and 2, bottom right panels) induced by morphine [nucleus accumbens: $F(14,126) = 10.05$; $P < 0.0001$; striatum: $F(14,140) = 2.21$; $P < 0.01$]; in post-hoc tests, the effects were significant ($P < 0.05$) from 60 min after morphine administration to the end of the experiment in the nucleus accumbens, and from 140 to 160 min in the striatum.

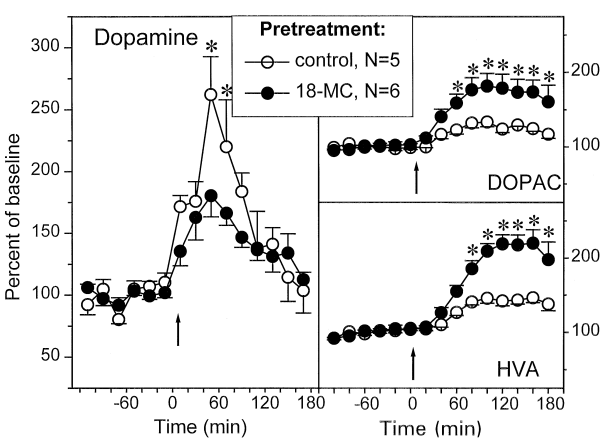

Fig. 1. Effects of 18-methoxycoronaridine pretreatment (40 mg/kg, i.p., 19 h beforehand) on morphine-induced (5 mg/kg, i.p.) changes (means ± S.E.M.) in extracellular dopamine, DOPAC and HVA levels in the nucleus accumbens ($N = 5–6$/group). $^*P < 0.05$, time points significantly different between 18-methoxycoronaridine and control groups.

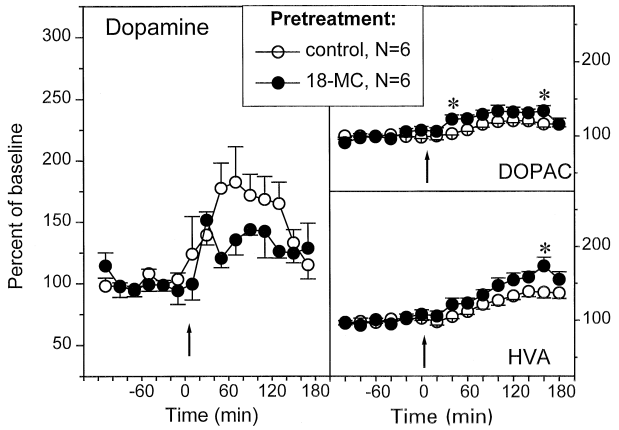

Fig. 2. Effects of 18-methoxycoronaridine pretreatment (40 mg/kg, i.p., 19 h beforehand) on morphine-induced (5 mg/kg, i.p.) changes (means ± S.E.M.) in extracellular dopamine, DOPAC and HVA levels in the striatum ($N = 6$/group). $^*P < 0.05$, time points significantly different between 18-methoxycoronaridine and control groups.

3.2. Morphine self-administration

Expressed as infusions per hour (Fig. 3, top panel), the analysis of variance showed that 18-methoxycoronaridine shifted the morphine dose–response curve downward [pretreatment effect: $F(1,67) = 5.99$; $P < 0.017$]. Because there is substantial variability among rats in their baseline rates of responding, the data were also analyzed as a percent of baseline (average infusion rate per hour on the 2 days preceding the test day). Again (Fig. 3, bottom panel), 18-methoxycoronaridine pretreatment shifted the entire morphine dose–response curve downward [pretreatment effect: $F(1,67) = 16.97$; $P < 0.00011$]. An analysis of in-

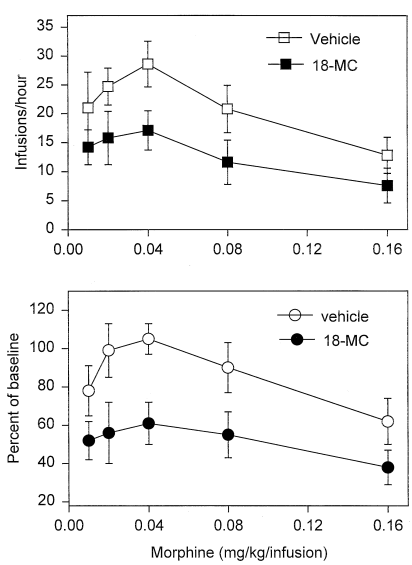

Fig. 3. Effects of 18-methoxycoronaridine (40 mg/kg, p.o., 30 min previously) on intravenous morphine self-administration (means ± S.E.M.; top, infusions per hour; bottom, percent of baseline) at different unit infusion dosages (0.01–0.16 mg/kg/infusion; $N = 5–12$/group).

terinfusion intervals showed that the 18-methoxycoronaridine-induced decreases in responding for morphine were largely accounted for by increases in the times between infusions. For the 0.04 mg/kg/infusion maintenance dosage of morphine, where it was possible to correlate within-animal baseline and 18-methoxycoronaridine data at the same morphine dosage, there was a significant relationship ($r = 0.82$, $P < 0.01$) between 18-methoxycoronaridine-induced decreases in responding and increases in interinfusion intervals.

4. Discussion

An intact nucleus accumbens appears to be required for morphine to exert its reinforcing effect (e.g., Smith et al., 1985; Zito et al., 1985). Opioid receptors are located both in the nucleus accumbens and in the ventral tegmental area, the terminal and cell body regions, respectively, of the mesolimbic dopamine pathway (Mansour et al., 1995). In the ventral tegmental area, morphine inhibits γ-aminobutyric acidergic (GABAergic) neurons and reduces the inhibition of dopaminergic neurons (Johnson and North, 1992; Bontempi and Sharp, 1997). This results in an increase in dopaminergic firing rate and an increase in dopamine synthesis, release and metabolism (Matthews and German, 1984). In the nucleus accumbens, morphine is thought to interact with efferent neurons (e.g., GABA, enkephalins) that project to the ventral pallidum (Chrobak and Napier, 1993). Dopamine may influence these same neurons via dopamine D1 receptors (Shippenberg et al., 1993; Liu et al., 1994). Therefore, studying the effect of morphine on dopamine release, while not a reflection of all of its actions in the nucleus accumbens, provides an indication of the functional net result of at least several important actions.

18-Methoxycoronaridine attenuated the increases in extracellular levels of dopamine induced by a stimulant dose of morphine. To our knowledge, no laboratory has fully characterized the dose–response curve for morphine-induced dopamine release in either the nucleus accumbens or the striatum. However, by assimilating the results from many microdialysis studies using various and different doses (Di Chiara and Imperato, 1988; Maisonneuve et al., 1991; Rada et al., 1991; Spanagel et al., 1993; Johnson and Glick, 1994; You et al., 1996; Enrico et al., 1998; Willins and Meltzer, 1998), it appears that morphine (i.p. and s.c.) increases extracellular dopamine levels in a dose related manner up to 10 mg/kg, depending on the strain of rats (e.g., Shoaib et al., 1995). With higher doses, the effect may plateau and then decrease such that, at 30 mg/kg, dopamine levels are unaffected (Maisonneuve et al., 1991; Johnson and Glick, 1994). The dose–response curve of morphine appears, therefore, to be inverted U-shaped, perhaps reflecting antagonistic actions of morphine on dopamine cell bodies and terminals (e.g., Rossetti et al., 1990; Leone et al., 1991). It is noteworthy that the dose–response curve for morphine on release of opioid peptides in the ventral pallidum has also been shown to be inverted U-shaped (Olive et al., 1995). Our observation that 18-methoxycoronaridine reduced the maximal increase in dopamine levels induced by a low dose of morphine is consistent with 18-methoxycoronaridine either shifting the morphine dose–response curve to the right or downward; a shift to the left is unlikely due to the plateau or ceiling of the morphine dose–response function.

What is the mechanism of the 18-methoxycoronaridine–morphine interaction? Acutely, 18-methoxycoronaridine, alone, decreases DA release and metabolism (Glick et al., 1996); this effect seems to dissipate in less than 17–19 h (see Table 1). However, the effect of administering morphine to 18-methoxycoronaridine pretreated animals at this time demonstrated that the dopaminergic system was still not responding appropriately. 18-Methoxycoronaridine inhibited morphine-induced dopamine release and enhanced the increases in extracellular levels of dopamine metabolites produced by morphine. These effects suggest that 18-methoxycoronaridine pretreatment selectively interfered with morphine's efficacy to stimulate release of dopamine, that is, without altering morphine's action to increase dopamine synthesis. The combination of reduced dopamine release and enhanced synthesis would result in an increased intracellular content of dopamine and this in turn would lead, in 18-methoxycoronaridine pretreated rats, to increased dopamine metabolism and eventual diffusion of the metabolites into the extracellular fluid. It is also noteworthy that this result was more prominent in the nucleus accumbens than in the striatum, consistent with its relevance to the substrate for morphine reinforcement.

Increases and decreases in drug sensitivity are, respectively, defined as leftward or rightward shifts in dose–response relationships. A competitive antagonist of a self-administered drug would be expected to shift the unit infusion dose–response curve to the right (Koob and Goeders, 1989), reflecting a decrease in the apparent potency of the self-administered drug. However, 18-methoxycoronaridine pretreatment produced a downward shift in the dose–response curve for morphine self-administration; rather than altering the potency of morphine, the results suggest that 18-methoxycoronaridine decreased the efficacy of morphine to function as a reinforcer. Borrowing the terminology of others (Koob and LeMoal, 1997; Ahmed and Koob, 1998), it would appear that 18-methoxycoronaridine increased the activity of homeostatic mechanisms that control or limit morphine intake, effectively decreasing the ''hedonic set point.'' Stated another way, morphine is simply less reinforcing in the presence of 18-methoxycoronaridine. Moreover, since at the same dose 18-methoxycoronaridine does not affect bar-press responding for water (Glick et al., 1996), this functional change in

the brain's reward pathway would appear to be selective for drug vs. other natural reinforcers.

While our understanding of how 18-methoxycoronaridine exerts its effects is still incomplete, several observations suggest that multiple mechanisms of action are likely to be involved. First, as noted in the Introduction, although 18-methoxycoronaridine has affinities for various receptor sites, all of these affinities are relatively low (Glick et al., 1999). Second, 18-methoxycoronaridine disappears quickly from plasma and brain tissue with an initial half-life of only 5–10 min (Glick et al., 1999). This, in combination with a prolonged duration of action in vivo, suggests that 18-methoxycoronaridine, like ibogaine, may have one or more active metabolites; like ibogaine, 18-methoxycoronaridine is also sequestered in fat and active metabolites might either persist in the body themselves or be produced via the slow release of 18-methoxycoronaridine from fat tissue. Third, in recent work (Glick et al., 1999), the (+) and (−) enantiomers of 18-methoxycoronaridine were found to have comparable efficacy and potency in decreasing morphine self-administration; however, the receptor binding profiles of the two enantiomers were somewhat different and only the (+) enantiomer acutely decreased dopamine release in the nucleus accumbens. These findings indicated that both enantiomers contribute to the efficacy of the racemate, and that the different actions of the enantiomers were likely to be additive with each other.

In conclusion, consistent with previous reports, the present results suggest that 18-methoxycoronaridine may reduce the rewarding effect of morphine and may be potentially useful as a treatment for opioid and other forms of drug addiction. Although the mode of action of 18-methoxycoronaridine is still an enigma, its complex pharmacology may be precisely the reason it has such a peculiarly novel efficacy.

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