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Anti-addictive actions of an *iboga* alkaloid congener: a novel mechanism for a novel treatment

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Abstract

18-Methoxycoronaridine (18-MC), 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 animal models, 18-MC reduced intravenous morphine, cocaine, methamphetamine and nicotine self-administration, oral alcohol and nicotine intake, and attenuated signs of opioid withdrawal, but had no effect on responding for a nondrug reinforcer (water) and produced no apparent toxicity [Brain Res. 719 (1996) 29; NeuroReport 11 (2000) 2013; Pharmacol. Biochem. Behav. 58 (1997) 615; Psychopharmacology (Berl.) 139 (1998) 274; NeuroReport 9 (1998) 1283; Ann. N. Y. Acad. Sci. 914 (2000) 369]. Consistent with a relationship among drug sensitization, mesolimbic dopamine, and drug-seeking behavior, 18-MC also blocked the sensitized dopamine responses to morphine and cocaine in the nucleus accumbens. An extensive series of receptor studies showed that 18-MC was most potent and somewhat selective as an antagonist at $\alpha3\beta4$ nicotinic receptors. Low-dose combinations of 18-MC with other drugs known to have this same action (e.g., mecamylamine, dextromethorphan, bupropion) decreased morphine, methamphetamine, and nicotine self-administration in rats at doses that were ineffective if administered alone. Together, the data support the hypothesis that diencephalic pathways having high densities of $\alpha3\beta4$ nicotinic receptors modulate mesocorticolimbic pathways more directly involved in drug reinforcement. Antagonists of $\alpha3\beta4$ nicotinic receptors may represent a totally novel approach to treating multiple addictive disorders, and 18-MC might be the first of a new class of synthetic agents acting via this novel mechanism and having a broad spectrum of activity.

Keywords: Ibogaine; *Iboga* alkaloids; 18-Methoxycoronaridine; $\alpha3\beta4$ Nicotinic receptors; Dorsal diencephalic conduction system; Habenulo-interpeduncular pathway; Mesocorticolimbic pathways; Dopamine; Addiction; Drug self-administration; In vivo microdialysis

1. Introduction

Ibogaine, one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga*, has a long history of use in Africa, in initiation rites and religious rituals of Bwiti and Mbiri cults as well as a stimulant to keep hunters awake and motionless while stalking prey. While studies conducted in France in the early 1900s showed that it had both hallucinogenic and stimulant properties, ibogaine attracted little scientific interest in the United States until the late 1980s. Despite a brief appearance on the illicit market in the 1960s, resulting in it being classified as a Schedule I substance by the U.S. Food and Drug Administration in 1970, ibogaine use was never widespread in this country. Indeed, ibogaine only became newsworthy when it was claimed to be an effective treatment for the abuse of other drugs.

In five U.S. patents (numbers 4,499,096; 4,587,243; 4,857,523; 5,026,697; 5,124,994) issued between 1985 and 1992, H. Lotsof claimed that ibogaine had antiaddictive properties, supposedly being effective in treating opiate (heroin) addiction, stimulant (cocaine and amphetamine) abuse, alcohol dependence, cigarette smoking (nicotine dependence), and polydrug abuse. Ibogaine was said to interfere with the ‘‘physiological and psychological aspects’’ of addiction, abolishing the craving for drugs; a single treatment was supposedly effective for 6 months and a series of four treatments for up to 3 years. To a limited extent, studies in animals corroborated these claims. In rats, ibogaine was reported to decrease intravenous morphine (Glick et al., 1991) and cocaine (Cappendijk and Dzoljic,

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1993; Glick et al., 1994) self-administration as well as the oral intake of alcohol (Rezvani et al., 1995) and nicotine (Glick et al., 1998). Most of these effects lasted for a day or more after ibogaine treatment, well beyond the presence of the drug, or its active metabolite noribogaine, in the brain (Hough et al., 1996; Pearl et al., 1997).

Although still used outside of the United States, reports of side effects of ibogaine have limited its potential therapeutic utility and markedly reduced the likelihood that it will ever be developed for use as an approved legal medication. Aside from having stimulant and hallucinogenic properties, ibogaine (20–40 mg/kg) induces tremors, manifested as whole body shaking in rats. The tremors are attributable to activation of an olivocerebellar pathway (O'Hearn and Molliver, 1997). At high doses ($\geq$100 mg/kg in rats), ibogaine overstimulates cerebellar Purkinje cells (O'Hearn and Molliver, 1993; Molinari et al., 1996) and produces damage to the cerebellar vermis. Another side effect that is not as well documented (Hajo et al., 1981; Glick and Maisonneuve, 2000b) but that might have more clinical significance is a pronounced bradycardia (decrease in heart rate).

Our intent in this article is not to review the sizeable literature on the pharmacology and toxicology of ibogaine. This was presented fairly exhaustively in 2001 (cf. Alper and Glick, 2001) and very little new information has emerged in the last couple of years. Rather, we will review our recent work concerned with the development of a safer and more efficacious structural derivative of ibogaine and with the mechanism(s) of action of this compound.

Our initial work with other *iboga* alkaloids demonstrated that decreases in drug self-administration could be dissociated from tremorigenic activity: R-ibogamine and R-coronaridine, two nontremorigenic *iboga* alkaloids, mimicked ibogaine's effects on morphine and cocaine self-administration (Glick et al., 1994). However, like ibogaine, these other alkaloids also had acute nonspecific effects, reducing responding for a nondrug reinforcer (water) during the first 1–2 h after administration. Noribogaine, the major metabolite of ibogaine (Mash et al., 1995), was tested too (Glick et al., 1996b); although nontremorigenic, it also reduced responding for water as well as for drugs (morphine, cocaine). Although several other synthetic analogues of ibogamine and coronaridine had similar profiles of activity, eventually we identified one that was quite different. 18-Methoxycoronaridine (18-MC, Fig. 1), which was also nontremorigenic, mimicked ibogaine's effects on morphine and cocaine self-administration but had no acute depressant

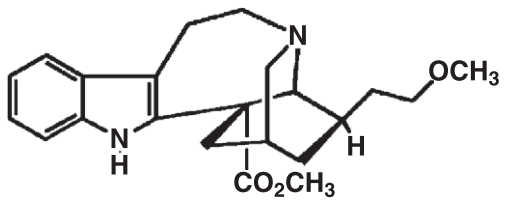

Fig. 1. Chemical structure of 18-MC.

effect on responding for water (Glick et al., 1996a). Further studies showed that 18-MC also reduced oral alcohol and nicotine intake as well as intravenous nicotine and methamphetamine self-administration (Rezvani et al., 1997; Glick et al., 2000a). 18-MC produced no cerebellar toxicity (Glick et al., 1996a). After establishing the efficacy and relative safety of 18-MC, most of our efforts were directed to elucidating its mechanism of action. This article will largely focus on these more recent studies.

2. Methods

2.1. Animals

Naïve female Long–Evans (250 g; Charles River, NY) or Sprague–Dawley derived (250 g; Taconic, Germantown, NY) rats were maintained on a normal 12-h light cycle (lights on at 7:00 a.m., lights off at 7:00 p.m.). Female rats were used because they have much slower growth curves and are therefore less likely to outgrow their intravenous catheters. For all experiments, the *Guide for the Care and Use of Laboratory Animals* (National Academy of Sciences, 1996) was followed.

2.2. Chemicals used in vivo

18-MC hydrochloride (Albany Molecular Research, Albany, NY) was dissolved in phosphate buffer. Ibogaine hydrochloride (Sigma/RBI, St. Louis, MO) was dissolved in water. Dextromethorphan hydrobromide, mecamylamine hydrochloride, and bupropion hydrochloride (all from Sigma/RBI) were dissolved in saline.

2.3. Self-administration procedure

The intravenous self-administration procedure has been described previously (e.g., Glick et al., 1996a, 2000a, 2002a,b). 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 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 (number 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 to 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 or a 50-μl infusion of drug solution (0.025 mg of methamphetamine sulfate, 0.02 mg of nicotine hydrogen bitartrate) in about 1 s. Since all rats generally weighed

250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine, 0.1 mg/kg of methamphetamine, or 0.08 mg/kg of nicotine (0.028 mg/kg free base). Experiments to assess the effects of experimental treatments were begun when baseline self-administration rates stabilized ($\leq 10\%$ variation from one day to the next across 5 days), usually after 2 weeks of testing. 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. Rotarod motor coordination test

Performance measures of motor behavior were conducted using a commercially designed and constructed accelerating rotarod (Rotamex 4/4, Columbus Instruments, Columbus, OH). Motor coordination was quantified as the animal's ability to remain in place on an accelerating rotating rod. Before drug dosing, rats were gradually trained to stay on the rod by providing them six to eight 3-min training periods per day. The rats were trained at increasing rod speeds of 3, 6, 9, 12, and 15 rpm for periods of 3 min. Electric shock (2 mA, AC) was present on the apparatus floor to encourage the animal to stay on the rod. The animal's time of falling was recorded automatically by photocell detection. An individual animal was considered trained when it reached a criterion of two successive trials at 15 rpm wherein it stayed on the rod for the full 3-min session. Only those rats that met this criterion after 2 days of training were used in these experiments. All testing was conducted at least 2 h after the final training trial. Drugs were given by intraperitoneal injection 30 min prior to the testing session. Animals were placed on the rod while it was rotating at 10 rpm. Upon placement, the rod's rotational speed was increased at a rate of 8.3 rpm/min. Total possible test session duration was 3 min. Time of falling and revolutions per minute at time of fall were recorded for each animal.

2.5. Plus maze procedure

The apparatus was made of black Plexiglas and consisted of two runways that intersected at the center at right angles. Each arm of the maze measured 40 × 10 cm (length by width). Two of the arms that were opposed to each other had walls that measured 40 cm in height (closed arms), whereas the other two arms had no walls (closed arms). The maze was elevated 52 cm above the floor. It was located in a darkened room so that only the open arms were illuminated, each with its own 40-W incandescent light. Animals were placed in the center of the maze (10 × 10 cm) and the number of entries into each type of arm was counted (all four paws in the arm defining an entry) as was the time spent on each type of arm. The test was terminated 5 min after the animal was placed in the center. The following measures were calculated: total number of arm entries, entries into open and closed arms, time in open and closed arms, and percent of total time spent in open arms. Changes in the total number of arm entries reflect a general index of activity, whereas changes in the percent measure constitutes an index of anxiety. Increased percent open-arm time reflects an anxiolytic state, while decreased percent open-arm time reflects an anxiogenic state. Animals' movements were recorded by using an overhead video camera and VCR. They were subsequently scored by a "blind" observer.

2.6. In vivo microdialysis and high-pressure liquid chromatography procedures

Under pentobarbital anesthesia (50 mg/kg ip), the rats were implanted stereotaxically with a microdialysis guide cannula (CMA: 8309010; Acton, MA) over the nucleus accumbens and with bilateral injector guides 0.5 mm above the interpeduncular nuclei (see Section 2.7). The coordinates of the microdialysis guide cannula were chosen such that, when inserted, the tips of the dialysis probes were located 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) (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 were placed in a cubical microdialysis chamber with free access to food and water. With the rats briefly anesthetized with Brevital (45 mg/kg ip), dialysis probes (CMA 8309502) 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 at a flow rate of 1 μl/min. Collection of perfusates began the next day. 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, 18-MC (10 μg) or vehicle was locally administered into the interpeduncular nucleus (see Section 2.7) and the rats received a dose of morphine (5 mg/kg ip) or saline. 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.

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 an ESA 540 autosampler, an ESA 580 solvent delivery system, an ESA C18 column (MD-150), and an ESA Coulochem II

electrochemical detector with a working electrode set at a potential of 0.25 V. The mobile phase was purchased from ESA (MD-TM) and consisted of 0.075 μM sodium dihydrogen phosphate, monohydrate, 0.0017 μM octane sulfonic acid, and 25 μM EDTA in 10% HPLC grade acetonitrile, adjusted to pH 3.0 with phosphoric acid. The flow rate was set at 0.53 ml/min. Chromatograms were integrated using Hewlett Packard ChemStation software.

2.7. Intracerebral drug administration methodology

Rats were stereotaxically implanted under sodium pentobarbital anesthesia (50 mg/kg) with bilateral 22-gauge injector guides (Plastics One, Roanoke, VA, USA) 0.5 mm above the interpeduncular nuclei (AP: −6.3 mm, ML: ±2.6 mm, DV: −9.2 mm, angled 14° from midline) (Paxinos and Watson, 1986). Obturators were screwed into the injector guides. The injector guides were fastened to the skull using stainless steel screws (Small Parts, Miami Lakes, FL) and cranioplastic cement (Plastics One). Rats were returned to individual cages and were provided with food and water ad libitum. The cages were kept on a heating pad overnight, and the following day the rats were returned to the colony room. Rats were allowed at least 4–5 days of recovery from surgery before being utilized in microinjection studies. Drugs (or vehicle) were locally administered into the interpeduncular nucleus using an infusion pump (Harvard Apparatus); all such treatments were administered in a 1-μl volume during a 1-min infusion to prevent reflux through the guide cannula; the injection cannula (26-gauge) was kept in place for an additional minute after a treatment was administered.

3. Results

3.1. Effects of 18-MC on drug self-administration and other behaviors

Fig. 2 shows that in rats, 18-MC reduced the self-administration of multiple classes of drugs of abuse; at 40 mg/kg, these effects generally lasted for 24–48 h (Glick et al., 1996a, 2000a; Rezvani et al., 1997). 18-MC (40 mg/kg) appeared to produce downward shifts, without any displacement to the left or right, in the entire unit infusion dose–response curve of a self-administered drug (Maisonneuve and Glick, 1999), indicating that reinforcing efficacy was reduced (i.e., drugs of abuse were less reinforcing in the presence of 18-MC). It should also be noted that 18-MC was most potent at reducing nicotine self-administration. The minimum effective dose of 18-MC that significantly decreased drug self-administration was 2 mg/kg for nicotine vs. 10 mg/kg for morphine, methamphetamine, and cocaine. This was perhaps an early hint that 18-MC might interact with nicotine receptors.

Testing in other behavioral contexts revealed that 18-MC's effects on drug self-administration are fairly selective.

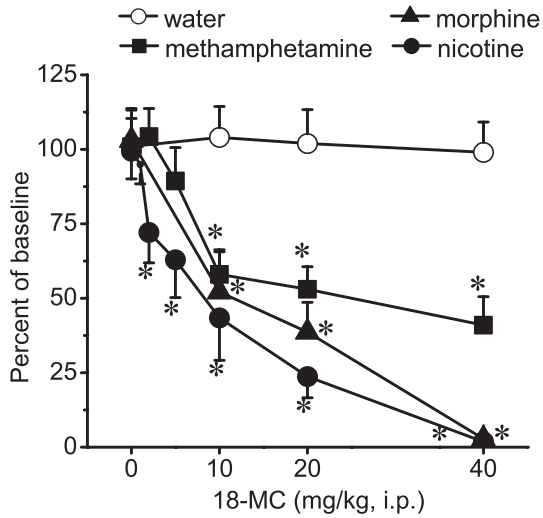

Fig. 2. Dose–response effects of intraperitoneally administered 18-MC on the self-administration of morphine, methamphetamine, and nicotine. Each data point represents the mean (±S.E.M.) of at least six rats. * Significant differences between baseline and treatment, $P < .05–.001$.

Unlike ibogaine (40 mg/kg), which produces tremors, depresses locomotor activity, and impairs rotarod performance, 18-MC (40 mg/kg) produced no motoric effects; it elicited no tremors (Glick et al., 1996a), did not affect rotarod performance (Fig. 3), and did not alter spontaneous locomotor activity (Glick et al., 1999). 18-MC was also inactive in the Porsolt Immobility Test (indicative of antidepressant activity) as well as in the Vogel Conflict Test (indicative of anxiolytic activity); however, in the plus maze, 18-MC was anxiolytic (significantly increasing open arm entries but not total arm entries), in contrast to ibogaine, which was anxiogenic (Fig. 4). As mentioned below, 18-MC has been shown to block α3β4 nicotinic receptors and interestingly, it was recently reported that mice lacking β4 nicotinic receptor subunits were also anxiolytic in the plus maze but not in other "anxiety" paradigms (Salas et al., 2002).

3.2. Pharmacokinetics

We used gas chromatography–mass spectrometry to develop a quantitative method for measuring 18-MC in plasma and tissues. Analysis of plasma levels after intravenous administration of 18-MC indicated that 18-MC had a short initial half-life (about 5–10 min); however, the data did not fit a one-compartment model and, using a two-compartment model, which did fit the data, there was a terminal half-life of over 100 min (Glick et al., 1999). Analysis of tissue levels after intraperitoneal and per os administration showed that 18-MC was highly sequestered in fat (Glick et al., 1999); this was consistent with the elimination data fitting a two-compartment model and with the fact that the calculated volume of distribution of 18-MC was very large (4–6 l in rats). However, in absolute terms,

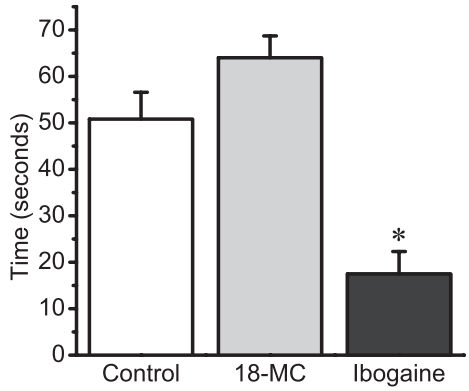

Fig. 3. Effects of 18-MC and ibogaine on rotarod performance. The drugs (40 mg/kg) were administered intraperitoneally 30 min prior to the testing session. Each data point represents the mean (±S.E.M.) of four rats. * Significant difference between control (vehicle) and treatment, $P < .05$.

even fat levels of 18-MC were low and the total amount of 18-MC measured in tissues accounted for less than 10% of the administered dose. This suggested that 18-MC might be rapidly metabolized, probably subject to a substantial first-pass effect. Although the deposition in fat could account for 18-MC's prolonged duration of action (i.e., fat being a natural depot), it was also possible that 18-MC might have an active metabolite, such that the drug deposited in fat served as a long-term depot of precursor for conversion to the active moiety. Subsequent studies showed that 18-MC does indeed have an active metabolite (18-hydroxycoronaridine; Zhang et al., 2002), but this metabolite appears to play a minimal role in mediating 18-MC's effects (i.e., tissue levels of 18-hydroxycoronaridine are very low; L.B. Hough, personal communication of preliminary data).

3.3. Receptor studies: antagonism of α3β4 nicotinic receptors

The results of an extensive receptor screen comparing the binding affinities of 18-MC and ibogaine showed that both drugs potentially interacted with several receptors (Glick et al., 1999, 2000b). Ibogaine had micromolar affinities for kappa- and mu-opioid receptors, NMDA receptors, 5-HT_3 receptors, muscarinic receptors, sigma-2 sites, sodium channels, and serotonin transporter. 18-MC had micromolar affinities at all three opioid receptors and at 5-HT_3 receptors but no affinity at NMDA receptors or the serotonin transporter. Because all of these affinities were low, it was difficult to envision how any of these actions could be responsible for "therapeutic" effects lasting 24–48 h. However, some of these actions might be relevant to side effects and be responsible for a potentially higher therapeutic index of 18-MC relative to ibogaine. Actions of ibogaine at muscarinic (M1 and M2) receptors and at sodium channels might be responsible for its cardiovascular toxicity (bradycardia); and ibogaine's affinity was two to three times greater than 18-MC at all of these sites. Ibogaine's action at sigma-2 sites has been related to its neurotoxicity (Bowen et al., 1995), and its sigma-2 affinity was approximately 30-fold greater than that of 18-MC. We have previously proposed that the hallucinogenic effect of ibogaine is attributable to serotonin release, an effect not exhibited by 18-MC (Wei et al., 1998); the NMDA antagonist action of ibogaine (Popik et al., 1994), also not shared by 18-MC, might also contribute to ibogaine's hallucinogenic effect.

Functional studies (Badio et al., 1997; Mah et al., 1998; Fryer and Lukas, 1999) indicating that ibogaine was a relatively potent noncompetitive antagonist at nicotinic receptors prompted us to pursue this as a potential mechanism of action for 18-MC as well. Initially, in functional assays ($^{86}Rb^+$ efflux from KXα3β4R2 cells) conducted by Dr. Kenneth Kellar (Georgetown University) as part of the NIMH Psychoactive Drug Screening Program, 18-MC was found to be an antagonist at α3β4 nicotinic receptors. However, this work did not establish whether 18-MC nicotinic antagonist action was specific to the α3β4 subtype or whether other nicotinic subtypes were also affected, for example the α4β2 subtype that is most prevalent in the brain (e.g., Flores et al., 1992). Hence, the actions of both 18-MC and ibogaine at both α3β4 and α4β2 receptors were subsequently determined using patch-clamp methodology (Glick et al., 2002a).

Both ibogaine and 18-MC were antagonists at α3β4 nicotinic receptors (IC50s = 0.22 and 0.75 μM, respectively), and both agents were more potent at this site than at α4β2 nicotinic receptors or at NMDA or 5-HT_3 receptors; 18-MC was more selective in this regard than ibogaine. Ibogaine was at least five times less potent at α4β2 than at α3β4 sites and even more times less potent at NMDA and 5-HT_3 receptors. 18-MC was approximately 25 times less potent at 5-HT_3 than at α3β4 receptors, and up to at least 20 μM was inactive at α4β2 and NMDA receptors. Hence, the data suggested that antagonism at α3β4 receptors was a potentially important and possibly the primary mechanism

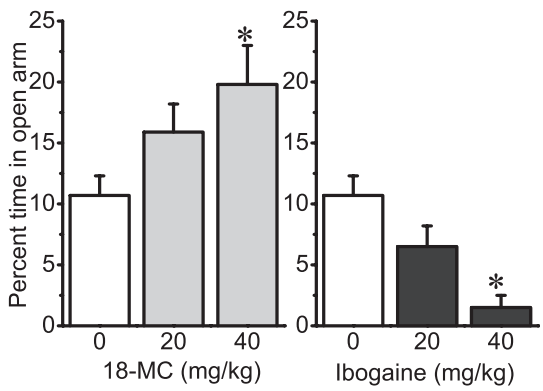

Fig. 4. Dose–response effects of 18-MC and ibogaine in the plus maze test. The drugs were administered intraperitoneally 30 min prior to the test. Each data point represents the mean (±S.E.M.) of at least five rats. * Significant differences between control (vehicle) and treatments, $P < .05$.

of action for both ibogaine and 18-MC. Consistent with this hypothesis, recent work (Pace et al., 2002) with a series of 18-MC derivatives (nine compounds) showed that potencies to block α3β4 receptors were significantly ($P<.05$) correlated ($r=.67$ and .75, respectively) with effects on morphine and methamphetamine self-administration. Moreover, the (+) and (−) enantiomers of 18-MC were equally potent in reducing morphine self-administration (Glick and Maisonneuve, 2000b) and equally potent in blocking α3β4 nicotinic receptors.

3.4. α3β4 Antagonism and self-administration

Totally selective antagonists of α3β4 receptors are unavailable, and hence it was difficult to further test our hypothesis that α3β4 receptor antagonists would reduce drug self-administration. 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 (doses of each agent that would be ineffective if administered alone) might produce additive effects at the α3β4 site and reduce drug self-administration without the involvement of other actions contributing to side effects. As a test of this idea, the effects of six such combined treatments on morphine, methamphetamine, and nicotine self-administration were assessed (Glick et al., 2002a,b). These treatments consisted of combinations of two of the following: 18-MC, mecamylamine, dextromethorphan, and bupropion.

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 (Hernandez et al., 2000); 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 vs. 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 as well as for 18-MC, 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.

All six drug combinations, but none of the drugs administered alone at the same doses, significantly decreased morphine, methamphetamine, and nicotine self-administration while having no effect on responding for water. The drug doses selected for the combination treatments were, in each instance, based on knowledge of the respective dose–response functions (i.e., the doses were approximately one-third of the lowest doses that would, if administered alone, significantly decrease drug self-administration). Fig. 5 shows the effects of the combination treatments on morphine self-administration. It should be noted that these same treatments had no effects on responding for water.

3.5. In vivo microdialysis studies

It is now well established that the rewarding effects of many drugs of abuse are, to some extent, all mediated by the mesolimbic dopaminergic pathway originating in the ventral tegmental area and innervating the nucleus accumbens. Although through different mechanisms, opioids, stimulants, ethanol, and nicotine all increase extracellular levels of dopamine in the nucleus accumbens. Consistent with an antiaddictive action, 18-MC (Glick et al., 1996a), like ibogaine (Maisonneuve et al., 1991), was found acutely (within the first 3 h of administration) to decrease dopamine release in the nucleus accumbens. Other studies at longer posttreatment intervals showed that 18-MC (Glick et al., 1998; Maisonneuve and Glick, 1999; Szumlinski et al., 2000a), like ibogaine (Maisonneuve et al., 1991, 1992a,b, 1997; Benwell et al., 1996; Sershen et al., 1996), could sometimes alter drug-induced increases in dopamine in the nucleus accumbens. However, these acute interactions differed in direction for different drugs. For example, although 18-MC pretreatment clearly blocked the acute dopamine response to nicotine (Glick et al., 1998), it actually potentiated the effects of morphine (Maisonneuve and Glick, 1999; Maisonneuve et al., 2001), both on dopamine and its metabolites (DOPAC and HVA). In contrast, in further

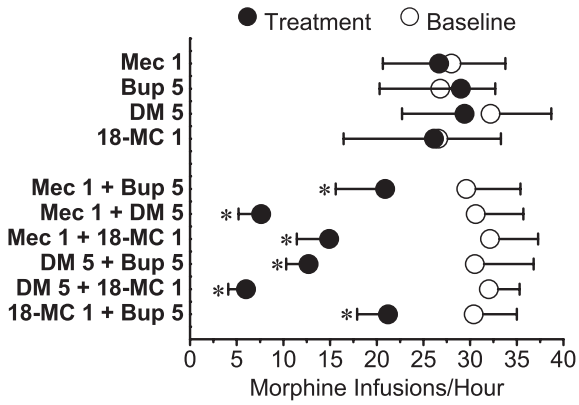

Fig. 5. Effects of drug combinations on morphine self-administration. Rats were administered two of the following treatments before testing: mecamylamine (MEC; 1 mg/kg ip, 30 min prior to test), 18-MC (1 mg/kg ip, 15 min prior to test), dextromethorphan (DM; 5 mg/kg, sc, 20 min prior to test), bupropion (Bup; 5 mg/kg ip, 15 min prior to test), or vehicle (saline for MEC, DM, and Bup; phosphate buffer for 18-MC). Each data point represents the mean (±S.E.M.) percent of baseline of six to eight rats. * Significant differences between baseline and treatments, $P<.01–.001$.

work (Szumlinski et al., 2000b), the effect of the same 18-MC pretreatment on the sensitized dopamine response to repeated morphine (20 mg/kg) administration was quite different: 18-MC (40 mg/kg ip, 19 h beforehand) blocked sensitization to morphine-induced dopamine release in the shell of the nucleus accumbens. Similar to 18-MC, dextromethorphan, another α3β4 nicotinic antagonist, was also found to enhance the acute dopamine response to morphine in the nucleus accumbens yet it blocks the sensitized dopamine response to chronic morphine (Steinmiller et al., 2002). Furthermore, 18-MC pretreatment (40 mg/kg ip, 19 h beforehand) also blocked the sensitized dopamine response to repeated cocaine administration (Szumlinski et al., 2000a), although the same 18-MC pretreatment had no effect on the acute dopamine response to cocaine (20 mg/kg ip). Substantial evidence supports a relationship between drug sensitization and drug-seeking behavior, and several investigators have theorized that the neuroadaptations mediating sensitization are responsible for the craving associated with addiction (De Vries et al., 1998, 1999; Vanderschuren et al., 1999; Robinson and Berridge, 1993, 2001). Hence, the attenuation of drug sensitization by 18-MC is consistent with its effects on drug self-administration and, to the limited extent studied, on "craving" in an animal model (Glick et al., 1999).

3.6. 18-MC and the habenulo-interpeduncular pathway

The evidence implicating antagonism of α3β4 nicotinic receptors as the primary mechanism of action of 18-MC was, at least superficially, difficult to reconcile with its effects on the mesolimbic dopamine system. 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 drug 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). The interpeduncular nucleus receives its major input from the medial habenula, forming the habenulo-interpeduncular pathway, and there are multiple avenues for interaction between this pathway and the mesolimbic pathway (cf. Section 4 and Fig. 8). Functional interactions between the habenulo-interpeduncular and mesolimbic pathways are therefore likely, and to some extent, have already been demonstrated (Nishikawa et al., 1986). We therefore began to directly test the hypothesis that 18-MC's action in the habenulo-interpeduncular pathway mediates its effects on the mesolimbic pathway and on drug self-administration.

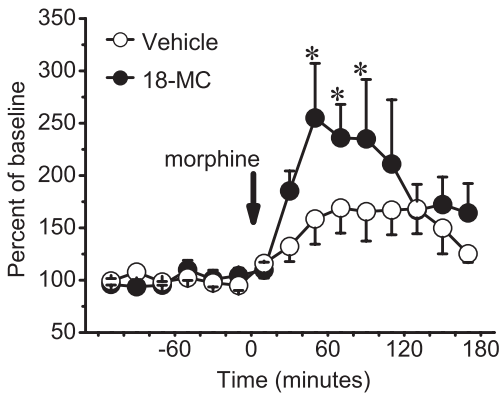

Fig. 6. Effects of interpeduncular administration of 18-MC on morphine-induced changes (means ± S.E.M.) in extracellular dopamine in the nucleus accumbens. 18-MC (10 μg in 1 μl) or vehicle was infused into both interpeduncular nuclei of rats ($N = 6–8$/group) immediately prior to morphine administration (5 mg/kg ip). * Significant differences between the two groups, $P < .05$.

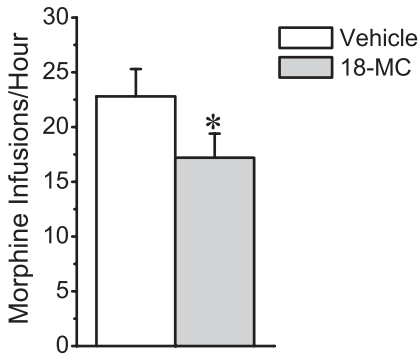

Fig. 7. Effect of interpeduncular administration of 18-MC on morphine self-administration (means ± S.E.M.). 18-MC (10 μg in 1 μl) or vehicle was infused into both interpeduncular nuclei of rats ($n = 6$/group) immediately prior to the session. * Significant difference between treatments, $P < .01$.

In preliminary studies, we first conducted an experiment to determine if the local administration of 18-MC (10 μg) into the interpeduncular nucleus could alter morphine-induced (5 mg/kg ip) dopamine release in the nucleus accumbens. As shown in Fig. 6, interpeduncular-administered 18-MC significantly enhanced morphine-induced increases in nucleus accumbens dopamine levels while having no effect on basal levels. Subsequently, the effect of the same dose of interpeduncular-administered 18-MC was assessed on intravenous morphine self-administration. As shown in Fig. 7, interpeduncular-administered 18-MC significantly reduced morphine self-administration by 25%. Thus, although much work remains to be done, the evidence supporting our hypothesis is mounting.

4. Discussion

A variety of new agents, including dopamine agonists and antagonists, GABA agonists, glutamate antagonists, opioid partial agonists, and catalytic antibodies, is being studied and/or developed as potential treatments for drug abuse (cf. Glick and Maisonneuve, 2000a). Most of these treatments are targeted at a specific drug or drug class of abuse. It would indeed be remarkable if a new agent was useful in treating multiple forms of drug abuse. Claims that the naturally occurring substance ibogaine had such effects

were intriguing. Prompted by the novelty of these claims, we initiated studies of ibogaine in rats. Single as well as repeated injections of ibogaine reduced rates of morphine self-administration in rats (Glick et al., 1991). Similar to our data on morphine self-administration, we and/or other investigators reported that ibogaine reduced intravenous cocaine self-administration (Cappendijk and Dzoljic, 1993; Glick et al., 1994) as well as oral alcohol (Rezvani et al., 1995) and nicotine intake (Glick et al., 1998).

Problems (e.g., neurotoxicity) associated with ibogaine led to attempts to develop a safer and still efficacious structural derivative. After testing many synthetic congeners, we eventually discovered 18-MC. 18-MC reduced morphine (Glick et al., 1996a), cocaine (Glick et al., 1996a), methamphetamine and nicotine self-administration (Glick et al., 2000a), oral alcohol (Rezvani et al., 1997) and nicotine intake (Glick et al., 1998), and attenuated signs of opioid withdrawal (Rho and Glick, 1998), but had no effect on responding for a nondrug reinforcer (water; Glick et al., 1996a, 1998) and produced no apparent toxicity (Glick et al., 1996a, 1999). Subsequent studies showed that 18-MC blocked $\alpha3\beta4$ nicotinic receptors without affecting NMDA receptors, sigma-2 receptors, serotonin uptake sites, or another subtype of nicotinic receptor ($\alpha4\beta2$). These results led us to hypothesize that the $\alpha3\beta4$ receptor was a viable as well as novel target around which to develop treatments for drug addiction (Glick et al., 2002a,b). Consistent with this hypothesis, low-dose combinations of 18-MC with other drugs known to have this same $\alpha3\beta4$ antagonist action (e.g., mecamylamine, Papke et al., 2001; dextromethorphan, Hernandez et al., 2000; bupropion, Fryer and Lukas, 1999) decreased morphine, methamphetamine, and nicotine 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 combinations of any two of the other three agents were similarly effective. In the brain, $\alpha3\beta4$ nicotinic receptors are mainly localized in the interpeduncular nucleus and the medial habenula (Quick et al., 1999; Klink et al., 2001). Again, consistent with our hypothesis, local administration of 18-MC in the interpeduncular nucleus decreased morphine self-administration.

The interpeduncular nucleus and habenula are part of a system referred to as the dorsal diencephalic conduction system (Sutherland, 1982). As originally described by Herkenham and Nauta (1977), most of the afferents to the habenular nuclei course through the stria medullaris. The major inputs to the medial habenula are from the septal area and use acetylcholine, glutamate, and ATP as neurotransmitters (Robertson and Edwards, 1998). Other inputs to the medial habenula include a projection from the nucleus accumbens, a GABAergic projection from the nucleus of the diagonal band (Contestabile and Fonnum, 1983) and a noradrenergic projection from the central gray area. The medial habenula also receives minor serotonergic inputs from the medial raphe nucleus via the fasciculus retroflexus. The major input to the lateral habenula comes from the entopeduncular nucleus (medial globus pallidus) and is in part GABAergic and somatostatin containing (Ellison, 1994). Other inputs include those from the nucleus accumbens and frontal cortex; dopaminergic inputs from both the ventral tegmental area and the substantia nigra have also been described (Skagerberg et al., 1984) as have serotonergic inputs from the raphe and noradrenergic inputs from the central gray. While the outputs of both nuclei travel in the fasciculus retroflexus, the medial habenula has its efferents in the core of the fasciculus retroflexus and projects principally to the interpeduncular nucleus, but also to the ventral tegmental area, substantia nigra, and raphe nuclei. These fibers are cholinergic, glutamatergic as well as substance P containing (Ellison, 1994). The lateral habenula, with its efferent in the mantle of the fasciculus retroflexus, has projections that are more widespread, including connections to the raphe nuclei, the ventral tegmental area, the substantia nigra, the central gray, the mediodorsal thalamus, and the lateral hypothalamus. There are connections between the two habenular nuclei (Iwahori, 1977; Cuello et al., 1978; Sutherland, 1982). In addition, many of the projections of these two nuclei have extensive interconnections. The interpeduncular nucleus receives major cholinergic inputs from the medial habenula and the septal areas and projects to the raphe nuclei, the central gray, and to a lesser extent, the mediodorsal thalamus (Groenewegen et al., 1986).

Since the 1980s, it has been known that the dorsal diencephalic conduction 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). Several studies, assessing local glucose utilization or expression of c-*fos*, have clearly demonstrated that drugs of abuse, after acute and chronic administration or during withdrawal, affect the habenulo-interpeduncular system (Martin et al., 1997; Wooten et al., 1982; Kimes et al., 1990; Porrino et al., 1988; Wilkerson and London, 1989; Engber et al., 1998; Brown et al., 1992; Pang et al., 1993; Seppa et al., 2001; Grunwald et al., 1988). Opioids may interact with mu-opioid receptors that exist in high densities in the habenula (Moriwaki et al., 1996). Stimulants may interact with dopamine uptake sites located on the dopaminergic projections to the lateral habenula from the ventral tegmental area or substantia nigra. Nicotine may interact with abundant nicotinic receptors, especially the $\alpha3\beta4$ subtype, present in the habenula and interpeduncular nucleus (Perry and Kellar, 1995; Quick et al., 1999; Klink et al., 2001). In addition, very large and sustained doses of some of these drugs have been proven to be toxic to the habenulo-interpeduncular system. Amphetamine and cocaine damage the lateral habenula and mantle of the fasciculus retroflexus (Ellison, 1992, 1994), whereas nicotine damages the medial habenula and

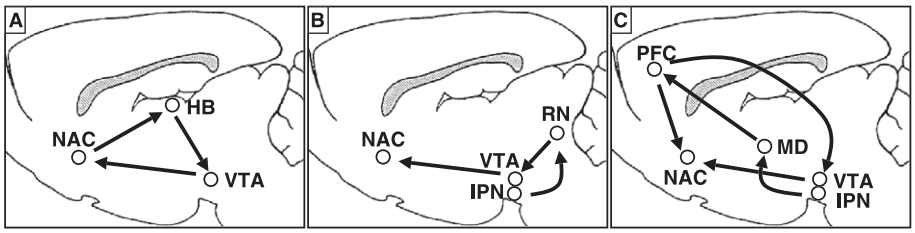

Fig. 8. Some of the connections between the dorsal diencephalic conduction and mesolimbic systems. HB = habenula; IPN = interpeduncular nucleus; MD = medial dorsal thalamic nucleus; NAC = nucleus accumbens; PFC = prefrontal cortex; RN = raphe nuclei; VTA = ventral tegmental area.

core of the fasciculus retroflexus (Carlson et al., 2000, 2001). In the case of cocaine, it was suggested that a decrease in inhibitory tone, which leaves the excitatory tone unopposed, was at the origin of the toxic effect (Meshul et al., 1998). Although toxicity occurs with doses much larger than those used by human addicts, it has been suggested that "alterations in this tract would be predicted to be especially important for the genesis of the symptomatology, which develops during drug binges, residual effects of such binges, and the processes underlying relapse" (Carlson et al., 2000). In fact, one study using a sensitization regimen of amphetamine administration revealed that the only region where c-*fos* expression was enhanced was the lateral habenula (Hamamura and Ichimaru, 1997).

Sutherland and Nakajima (1981) suggested that there is a mutual inhibitory relationship between the medial forebrain bundle and the dorsal diencephalic conduction system, since a lesion of one pathway enhanced self-stimulation of the other pathway. Dopamine agonists have been found to decrease glucose utilization in the lateral habenula while increasing glucose utilization in dopaminergic regions (e.g., ventral tegmental area, nucleus accumbens) (e.g., Wechsler et al., 1979; Trugman et al., 1989, 1991; Sharkey et al., 1991). Dopamine antagonists have had opposite effects (e.g., McCulloch et al., 1980; Pizzolato et al., 1984). The output of the dorsal diencephalic conduction system appears to inhibit dopaminergic activity. Lesions of the dorsal diencephalic conduction system, either of the stria medullaris, habenula, or fasciculus retroflexus, increased dopamine synthesis and/or metabolism in homogenates of nucleus accumbens, striatum, and frontal cortex (Lisoprawski et al., 1980; Nishikawa et al., 1986). Dopaminergic cells in the ventral tegmentum are inhibited by electrical stimulation of the habenula (Christoph et al., 1986), an effect possibly mediated by glutamate (Matsuda and Fujimura, 1992). Starting with GABAergic afferents in the stria medullaris to the habenula (Gottesfeld et al., 1977), the dorsal diencephalic conduction system may in fact function as a long-loop negative feedback pathway (Ellison, 1994) between limbic dopamine receptors and midbrain dopamine cell bodies (e.g., Sasaki et al., 1990).

There are several avenues by which functional interactions can occur between the dopamine containing mesocorticolimbic pathways and the dorsal diencephalic conduction system. For example, as shown in Fig. 8A, The habenula sends input to the ventral tegmental area, and the nucleus accumbens sends input to the habenula. As shown in Fig. 8B, the interpeduncular nucleus sends input to the raphe nuclei that in turn provides input to the ventral tegmental area. And as shown in Fig. 8C, the interpeduncular nucleus sends input to the medial dorsal thalamic nucleus that projects to the prefrontal cortex, which in turn has connections to the nucleus accumbens and ventral tegmental area.

Nicotinic $\alpha 3\beta 4$ receptor subtypes are thought to be located on the soma of the medial habenula efferents and on axon terminals of afferents to the interpeduncular nucleus (Clarke et al., 1986; Mulle et al., 1991). Activation of presynaptic nicotinic receptors in the interpeduncular nucleus has been shown to enhance glutamate (Girod and Role, 2001) and GABA release (Lena et al., 1993), thereby regulating the excitatory and inhibitory output of this structure. We propose that nicotinic $\alpha 3\beta 4$ receptor antagonists, by interfering with neuronal activity in the dorsal diencephalic conduction system, represent a truly novel class of antiaddictive agents. 18-MC, having apparently greater selectivity for $\alpha 3\beta 4$ sites than other agents (i.e., mecamylamine, dextromethorphan, bupropion, or ibogaine), may represent the first of this new class of synthetic agents acting via a novel mechanism and having a broad spectrum of activity to diminish multiple forms of addictive behavior.

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