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Antinociceptive Effects of Cocaine in Rhesus Monkeys

MICHAEL B. GATCH, S. STEVENS NEGUS AND NANCY K. MELLO

Alcohol and Drug Abuse Research Center, McLean Hospital–Harvard Medical School, Belmont, MA

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GATCH, M. B., S. S. NEGUS AND N. K. MELLO. *Antinociceptive effects of cocaine in rhesus monkeys*. PHARMACOL BIOCHEM BEHAV **62**(2) 291–297, 1999.—The antinociceptive effects of (−)cocaine, (+)cocaine, and cocaine methiodide administered alone and in combination with the mu-opioid agonist morphine were evaluated in rhesus monkeys. The shaved tails of four rhesus monkeys were exposed to warm water (42, 46, 50, and 54°C), and tail-withdrawal latencies (20-s maximum) from each temperature were determined. (−)Cocaine (0.032–1.8 mg/kg, SC) produced dose-dependent antinociceptive effects and enhanced the antinociceptive effects of morphine. Neither (+)cocaine nor cocaine methiodide (0.1–10 mg/kg, SC) produced antinociception or altered the effects of morphine. Pretreatment with the serotonin receptor antagonist mianserin (0.1–0.32 mg/kg, IM) produced dose-dependent rightward shifts in the dose–effect curve for (−)cocaine alone, and attenuated (−)cocaine-induced enhancement of the antinociceptive effects of morphine. However, mianserin (0.32 mg/kg, IM) did not alter the antinociceptive effects of morphine alone. These results suggest that in rhesus monkeys, the effects of cocaine on nociception may be steroselective and centrally mediated. These findings further suggest that the antinociceptive effects of cocaine in primates may be mediated at least in part by cocaine's effects on serotonergic systems. © 1999 Elseiver Science Inc.

Antinociception Cocaine Serotonin receptors Opioids *Macaca mulatta* Mianserin Morphine

COCAINE and mu-opioid agonists such as morphine and heroin are used in combinations as drugs of abuse, and there is now considerable evidence that combinations of cocaine and mu agonists may produce effects that are qualitatively or quantitatively different from either cocaine or the mu agonist alone. For example, polydrug abuse involving the simultaneous or sequential administration of cocaine and opioids (i.e., a speedball) is often reported to produce greater pleasurable effects than either drug alone (30) and to attenuate the aversive side effects of each drug (23,24,44). In agreement with these anecdotal reports, methadone maintenance was found to increase cocaine's positive subjective effects under some conditions (9,37). Similarly, in preclinical studies, the discriminative stimulus effects of cocaine were potentiated by pretreatment with mu-opioid agonists in both squirrel monkeys (42,43) and some rhesus monkeys (34).

Combinations of cocaine and mu-opioid agonists have also been used clinically in analgesic preparations such as Brompton's mixture, which is used primarily to treat chronic pain in cancer patients (19,31,33). Moreover, many preclinical studies have investigated interactions between cocaine and opioids in animal models of nociception. For example, we recently extended our behavioral studies of cocaine and opioid interactions (30) to examine the antinociceptive effects of cocaine alone and in combination with mu agonists in a warm-water tail-withdrawal assay of thermal nociception in rhesus monkeys (13). Cocaine and the mu agonists nalbuphine, morphine, and fentanyl all produced dose-dependent antinociceptive effects in this procedure. The maximal antinociceptive effects of cocaine were similar to those produced by nalbuphine, but less than those produced by either morphine or fentanyl. When cocaine was administered in combination with the mu agonists, it was most effective in enhancing the antinociceptive effects of the partial agonist nalbuphine. Cocaine was less effective in potentiating the antinociceptive effects of morphine and ineffective in potentiating antinociception induced by fentanyl. These findings in rhesus monkeys are concordant with studies in rodents, which have consistently found that cocaine produces antinociceptive effects when administered alone and potentiates the antinociceptive effects of mu agonists (21,32,39,41).

The mechanisms responsible both for the antinociceptive

Requests for reprints should be addressed to Michael B. Gatch, Department of Pharmacology, University of North Texas, Health Science Center at Forth Worth, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107-2699. 817-735-2063 office 817 735 2091 fax

effects of cocaine and for cocaine's potentiation of antinociception induced by mu-opioid agonists in primates are unknown. Cocaine is thought to produce its effects primarily by blocking the reuptake of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine (3,10,14), whereas the effects of mu-opioid agonists are mediated by mu-opioid receptors (28,29). Despite these different mechanisms of action, cocaine and mu opioids may interact through their effects on a common neuroanatomical substrate. Acute pain and nociception are thought to be mediated by multisynaptic pathways composed of primary afferent nociceptors and secondary spinal and supraspinal neurons, and both monoaminergic and opioidergic systems regulate activity in these pathways (4,8). Furthermore, opioidergic and monoaminergic systems involved in antinociception may be anatomically and functionally integrated. For example, mu-opioid agonists may produce antinociceptive effects at least in part by stimulating descending serotonergic and noradrenergic systems (2,4,48).

We have shown previously that selective serotonin reuptake inhibitors, but not reuptake inhibitors of dopamine or norepinephrine, produce antinociception and enhance the antinociceptive effects of low-efficacy mu opioid agonists (12). These findings suggest that the blockade of serotonin reuptake is sufficient to produce antinociception in primates, and that the antinociceptive effects of cocaine itself may also result from a blockade of serotonin reuptake. The purpose of this study was to extend our evaluation of the pharmacologic determinants of the antinociceptive effects of cocaine administered alone or in combination with the mu-opioid morphine in rhesus monkeys. The steroselectivity of cocaine's effects alone and in combination with morphine was examined by comparing the effects of the (−) and (+) isomers of cocaine. In addition, the role of central vs. peripheral mechanisms was investigated by examining the effects of systemically administered cocaine methiodide, a quaternary derivative of cocaine that does not readily cross the blood–brain barrier (40). Finally, the role of serotonergic receptors in mediating the effects of cocaine was tested directly by evaluating the ability of the serotonin 5-HT_2 receptor antagonist mianserin to antagonize the effects of cocaine.

METHODS

Subjects

Four rhesus monkeys (*Macaca mulatta*), two females and two males, were housed in individual cages with free access to water. Weights ranged from 4.5 to 12.0 kg. The bottom 10 cm of their tails were shaved. All monkeys had extensive histories with drugs (cocaine, heroin, and/or alcohol) and behavioral procedures; however, monkeys were drug free for at least 1 month before beginning antinociception studies. All housing and procedures were in accordance with the guidelines of the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (Department of Health and Human Services, NIH Publication No. 86-23, revised 1985), and were approved by the McLean Hospital Animal Care and Use Committee.

Procedures and Apparatus

During test sessions, the monkeys were seated in acrylic restraint chairs so that their tails hung freely behind them. The bottom 10 cm of each monkey's shaved tail was immersed in a thermal container of warm water, and the latency to tail withdrawal was measured by a hand-held microswitch connected to an Apple IIe microcomputer (Apple Computers, Inc., Cupertino, CA). If the subject did not withdraw its tail within 20 s, the timer was stopped, and a latency of 20 s was assigned to that measurement. Tail-withdrawal latencies were measured using four different water temperatures: 42, 46, 50, and 54°C. These temperatures were presented in a pseudorandom order during each cycle of tail-withdrawal latency measurements. Sessions were conducted no more than two times per week, with at least 3 days between sessions.

The antinociceptive effects of (−)cocaine (0.032–1.8 mg/kg), (+)cocaine (0.1–10 mg/kg), cocaine methiodide (0.1–10 mg/kg), and the mu-opioid agonist morphine (0.1–10 mg/kg) were examined using cumulative dosing procedures. Cumulative dose–effect curves were designed to cover a range from ineffective doses to doses producing the maximal effect that could be safely studied without untoward effects (e.g., severe respiratory depression or convulsions).

Cumulative dosing test sessions consisted of multiple cycles. At the beginning of each test session, baseline latencies to tail withdrawal from 42, 46, 50, and 54°C water were determined. Subsequently, a dose of drug was administered at the beginning of each 30-min cycle, and each injection increased the total dose by 1/4 or 1/2 log increments. Fifteen minutes after each injection, tail-withdrawal latencies were recorded from different water temperatures as described above.

During pretreatment studies, a single dose of a cocaine analog [(−)cocaine 1.8 mg/kg; (+)cocaine 10 mg/kg; cocaine methiodide (10 mg/kg)], or mianserin (0.1–0.32 mg/kg) was administered during the first cycle, and cumulative doses of morphine or (−)cocaine began on the next cycle. Pretreatments were thus given 30 min before the first cumulative dose of the test compound and 45 min before the first tail-withdrawal latency measurements. This allowed adequate time for mianserin to take effect, and the effects of cocaine to be tested independent of its own antinociceptive effects.

Data Analysis

Tail-withdrawal latencies were transformed into a measure of change in baseline using the T10, the temperature at which the monkey removed its tail in 10 s, i.e., 50% of the maximal latency (13,35). For each monkey at each set of latencies, the temperature that corresponded to a 10-s latency was determined by fitting a line to the two points that fell immediately above and below 10-s and interpolating the temperature (T10) that corresponded to a 10-s latency. The T10 from each monkey's baseline was subtracted from the T10 determined from each subsequent test cycle, which provided a measure of change relative to the baseline of each animal, or ΔT10. The ΔT10s were then averaged across monkeys, and a standard error of the mean was calculated. The ΔT10 value was used as a measure of nociception in this study because it allows tail-withdrawal latency data across a range of temperatures to be summarized into a single dependent variable.

Mean ΔT10 values were plotted as a function of drug dose. The dose of each drug that produced a 4°C increase in the ΔT10 was interpolated from the linear portion of the dose–effect curve for each monkey and averaged to yield a mean ED_4° value (±SEM). The effects of cocaine analogs and mianserin on morphine-induced antinociception, and of mianserin on cocaine-induced antinociception were analyzed by repeated measures ANOVA. Post hoc comparisons between individual points on dose–effect curves were made by Duncan's multiple range test. Post hoc comparisons between ED_4°

values were made by Dunnett's test. The criterion for statistical significant was set a priori at $p < 0.05$.

Drugs

Drugs used were (−)cocaine hydrochloride, (+)cocaine base, cocaine methiodide, morphine sulfate (National Institute on Drug Abuse, Rockville, MD), and mianserin hydrochloride (Research Biochemicals International, Natick, MA). All drugs were dissolved in sterile water. Morphine and cocaine were injected subcutaneously in the back. Mianserin was injected IM in the thigh. Injection volumes ranged from 0.2–1.0 ml. All drug doses were expressed as salt weights, except (+)cocaine, which was free base.

RESULTS

Baseline Nociception

During baseline determinations, the subjects always kept their tails in 42°C water until the 20-s maximum. At a water temperature of 46°C, three of four monkeys consistently removed their tails in less than 10 s. All monkeys removed their tails in less than 2 s from 50°C water, and less than 1 s from 54°C water. The average baseline T10 over all experimental sessions was 45.09°C (±0.22).

Effects of Cocaine Analogs Alone

The top panel of Fig. 1 shows that cumulative doses of (−)cocaine administered alone produced a dose-dependent increase in the ΔT10 measure of antinociception. The maximum ΔT10 was 5.18°C (±1.62) at 1.8 mg/kg of cocaine. The ED_4° value was 0.56 (±0.15) mg/kg. In contrast, the (+)stereoisomer of cocaine (0.1–10.0 mg/kg) and the quaternary analog, cocaine methiodide (0.1–10.0 mg/kg), produced no change in the ΔT10 when administered alone. A single dose of cocaine (1.8 mg/kg) reached a maximum ΔT10 of 4.31°C (±0.39) at 15 min after administration and returned to baseline levels by 60 min (center panel, Fig. 1).

Effects of Cocaine Analogs in Combination with Morphine

The antinociceptive effects of morphine administered alone or in combination with (−)cocaine or its analogs are shown in the bottom panel of Fig. 1. There was a significant overall effect of drug, $F(3, 12) = 9.07$, $p = 0.002$. When morphine was administered alone, it produced a dose-dependent increase in ΔT10, and a dose of 10 mg/kg morphine produced a maximum ΔT10 of approximately 8°C. Pretreatment with 1.8 mg/kg (−)cocaine increased the antinociceptive effects ($p < 0.05$) of low doses of morphine alone (0.1–1.0 mg/kg), but did not alter the effects ($p > 0.05$) of higher doses of mor-

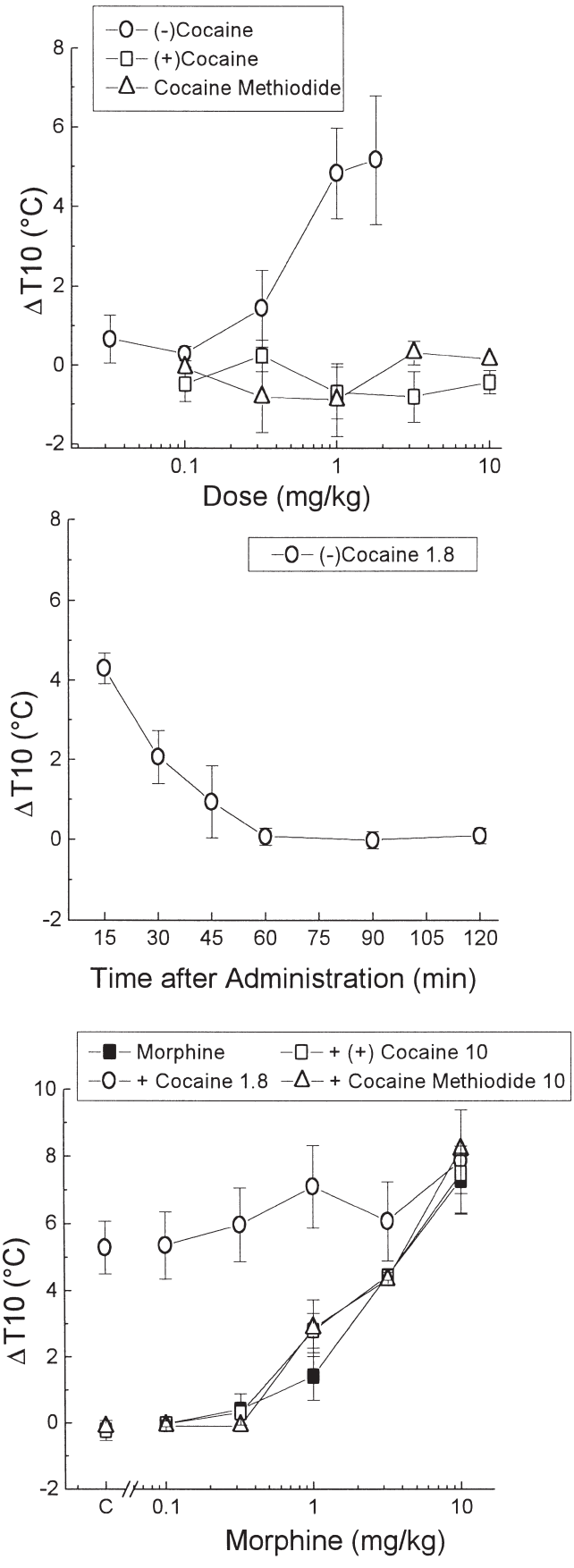

FIG. 1. Antinociceptive effects of (−)cocaine, (+)cocaine and cocaine methiodide alone (top panel). Abscissa: dose of drug in mg/kg (log scale), ordinate: ΔT10 in °C. Center panel shows the time course of a single dose of cocaine (1.8 mg/kg). Abscissa: time in minutes after administration of cocaine, ordinate: ΔT10 in °C. Bottom panel shows the antinociceptive effects of (−)cocaine, (+)cocaine and cocaine methiodide in combination with morphine (bottom panel). Abscissa: dose of drug in mg/kg (log scale), ordinate: ΔT10 in °C. Points over C indicate antinociceptive effects of cocaine analogues alone. In each panel, brackets show the standard error of the mean. The (−)cocaine and morphine dose–effect curves are the average of two determinations in each of four monkeys. All remaining points are the average of one determination in four monkeys.

phine (3.2 and 10.0 mg/kg). It is important to note that these increases in the effects of low doses of morphine could not be attributed simply to the effects of (−)cocaine alone. We have shown above that the antinociceptive effects of cocaine are transient. Maximum ΔT10 values were observed after 15 min, whereas after 45–60 min, the antinociceptive effects of 1.8 mg/kg cocaine were small (ΔT10 of 1°C) or no longer apparent. In the present study, the first tail-withdrawal measurements were not made until 45 min after cocaine was administered. Consequently, (−)cocaine pretreatment increased the antinociceptive effects of low doses of morphine at times when cocaine itself produced little or no antinociception. An $ED_4°$ value for the morphine/cocaine combination could not be calculated because △T10 values were greater than 4° for all morphine doses tested. In contrast to (−)cocaine, neither (+)cocaine (10.0 mg/kg) nor cocaine methiodide (10.0 mg/kg) significantly altered the antiociceptive effects of morphine ($p > 0.05$). The $ED_4°$ values for morphine were 2.55 (±0.17) mg/kg for morphine alone, 2.12 (±0.27) for morphine after (+)cocaine, and 1.93 (±0.18) mg/kg after cocaine methiodide.

Antagonist Effects of Mianserin

The upper panel of Fig. 2 shows the effects of the 5-HT_2–selective serotonin receptor antagonist mianserin on the antinociceptive effects of (−)cocaine. Mianserin (0.32 mg/kg) had no effect on nociception for as long as 120 min when administered alone (data not shown); however, mianserin (0.1–0.32 mg/kg) produced a dose-dependent and surmountable antagonism of the antinociceptive effects of (−)cocaine, [$F(2, 11) = 26.42$, $p < 0.001$]. The $ED_4°$ values for cocaine were 0.56 (±0.15) mg/kg for (−)cocaine alone, 1.31 (±0.14) for (−)cocaine after mianserin (0.1 mg/kg), and 1.92 (±0.22) mg/kg after mianserin (0.32 mg/kg). Mianserin (0.1 mg/kg) produced no significant change in the $ED_4°$ from that of morphine alone. A dose of 0.32 mg/kg mianserin produced a more than threefold rightward shift in the cocaine dose–effect curve ($p < 0.05$). The lower panel of Fig. 2 compares the antinociceptive effects of morphine administered alone and after pretreatment with mianserin (0.32 mg/kg). There was no difference between the curves, [$F(1, 6) = 2.70$, $p = 0.152$], or the $ED_4°$ values, [$F(1, 6) = 1.64$, $p = 0.248$], for morphine alone and morphine with 0.32 mg/kg mianserin.

Figure 3 shows the reduction of the antinociceptive effects of (−)cocaine on morphine by pretreatment with mianserin (0.32 and 1.0 mg/kg). Mianserin produced a significant, dose-dependent attenuation of antinociception produced by the morphine/cocaine combination, [$F(3, 12) = 5.43$, $p = 0.014$]. Mianserin (0.32 mg/kg) significantly reduced the effects of the morphine/cocaine combination ($p < 0.05$) at the low doses of morphine (0.1–1.0 mg/kg). These points were also significantly different from the low doses of morphine alone. Mianserin (1.0 mg/kg) also significantly reduced the effects of the morphine/cocaine combination ($p < 0.05$) at the low doses of morphine (0.1–1.0 mg/kg). The morphine/cocaine/mianserin 1.0 mg/kg combination was significantly different ($p < 0.05$) from the morphine-alone curve only at the dose of 1.0 mg/kg of morphine. There were no significant effects ($p > 0.05$) of cocaine or mianserin at the higher doses of morphine (3.2 and 10.0 mg/kg).

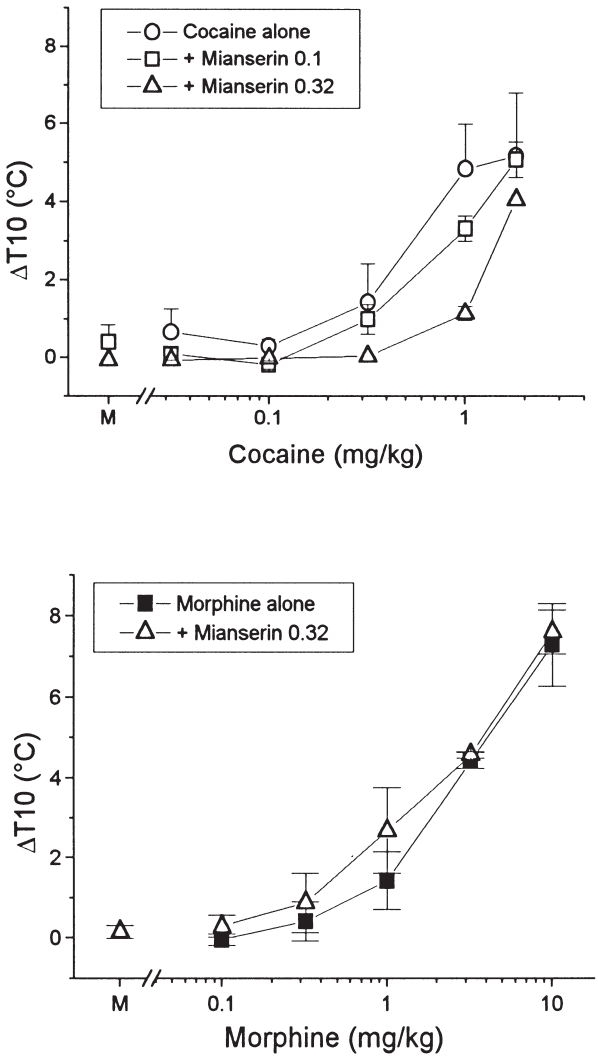

FIG. 2. Antinociceptive effects of (−)cocaine (top panel) and morphine (bottom panel) alone and following pretreatment with mianserin. Abscissas: dose of drug in mg/kg (log scale). Ordinates: ΔT10 in °C. Points over M indicate antinociceptive effects of mianserin alone. Brackets show the standard error of the mean. Dose–effect curves for (−)cocaine and morphine alone are the average of two determinations in each of four monkeys. All remaining points are the average of one determination in four monkeys.

DISCUSSION

The purpose of the present study was to extend our evaluation of the pharmacologic determinants of cocaine-induced antinociception and cocaine-induced enhancement of the antinociceptive effects of mu-opioid agonists in primates by examining the steroselectivity of cocaine isomers, the role of cocaine's central vs. peripheral actions, and the effects of a serotonergic antagonist on cocaine's effects. In agreement with our previous findings (13), (−)cocaine produced dose-dependent antinociceptive effects when administered alone, and increased the antinociceptive effects of low to medium doses of morphine (0.1–1.0 mg/kg) in rhesus monkeys. These results are concordant with the findings of previous studies that cocaine produces antinociceptive effects and enhances the antinociceptive effects of morphine and other mu-opioid agonists in rodents (21,36,39).

The effects of (−)cocaine alone lasted less than 60 min, but its enhancement of morphine dose–effect curve was apparent

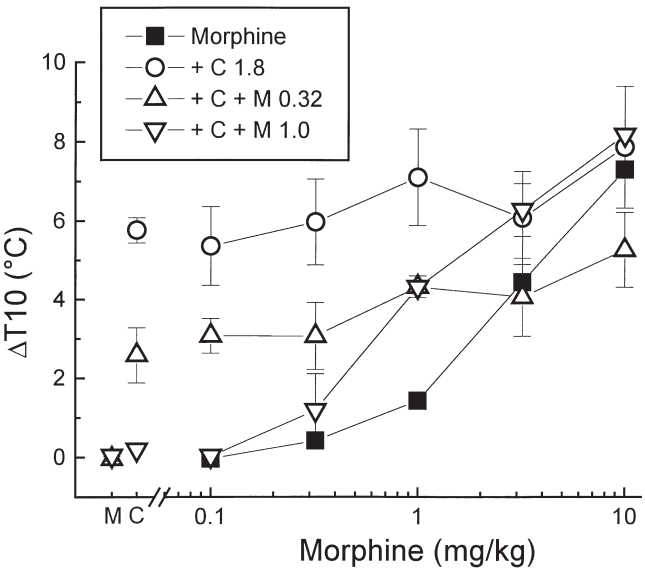

FIG. 3. Antinociceptive effects of morphine following pretreatment with 1.8 mg/kg (−)cocaine or both 1.8 mg/kg (−)cocaine and mianserin. Abscissa: dose of morphine in mg/kg (log scale). Ordinate: ΔT10 in °C. Points over M indicate antinociceptive effects of mianserin alone. Points over C indicate antinociceptive effects of (−)cocaine alone. Brackets show the standard error of the mean. Dose–effect curves are the average of one determination in four monkeys.

up to the 1.0 mg/kg of morphine, which was tested 105 min after administration of cocaine. This may seem paradoxical; however, in a recent study relating drug-discrimination performance to plasma levels of cocaine in rhesus monkeys, the authors reported that although the discriminative effects of cocaine (like its antinociceptive effects) were not apparent after 60 min, cocaine was still present in plasma for more than 120 min after administration (25).

(+)Cocaine at doses up to 30 times greater than the minimally effective dose of (−)cocaine produced no antinociception and did not enhance the antinociceptive effects of morphine. (+)Cocaine also failed to enhance the antinociceptive effects of mu-opioid agonists in rats (32). Taken together, these results indicate that the antinociceptive effects of cocaine alone and in combination with mu agonists are steroselective. Moreover, the (−) isomer of cocaine is at least 30 times more potent than the (+) isomer in producing antinociception. The (−) isomer of cocaine has also been found to be more potent than the (+) isomer in producing many of cocaine's other behavioral effects. For example, cocaine's discriminative stimulus effects in rats, as well as its effects on locomotor activity in mice, and on rates of behavior maintained under fixed-interval schedules of reinforcement in squirrel monkeys are all stereoselective. The (−)isomer was up to 340 times more potent than the (+)isomer of cocaine in each of these assays (20). However, (+)cocaine produced convulsions and lethality in mice at doses only 8- to 13-fold higher than convulsant and lethal doses of (−)cocaine (20). These findings suggest that the degree to which the behavioral effects of cocaine are stereoselective may vary as a function of the behavior under investigation.

Systemically administered cocaine methiodide at doses up to 30 times larger than the minimally effective dose of (−)cocaine also failed to produce antinociception or enhance the antinociceptive effects of morphine. Cocaine methiodide is a quaternary derivative of cocaine that does not readily cross the blood–brain barrier (40). Consequently, the failure of systemically administered cocaine methiodide to produce antinociception suggests that the antinociceptive effects of cocaine are mediated by cocaine binding sites located in the central nervous system and not in the periphery. This conclusion agrees with previous research in rats, which found that cocaine's enhancement of mu-opioid–induced antinociception also appeared to be centrally mediated (21,41). Cocaine methiodide has also been used to characterize the role of central and peripheral mechanisms in the mediation of other behavioral effects of cocaine. It produces local anesthesia, sympathetic activity, and lethality, but does not cross the blood–brain barrier (39,45). Systemically administered cocaine methiodide at doses 10–100 times higher than minimally active doses of cocaine failed to substitute for cocaine in rats trained to discriminate cocaine from saline (43, 46), suggesting that the discriminative stimulus effects of cocaine are also centrally mediated. Similarly, central mechanisms appear to mediate the effects of cocaine in place-conditioning procedures in rats (15). It was reported that systemic administration of cocaine methiodide failed to produce a conditioned place preference in rats, although systemic administration of a similar dose of cocaine did produce place-conditioning effects. Following ICV administration, however, cocaine methiodide was more potent than cocaine in producing place conditioning (15).

The 5-HT_2 serotonin receptor antagonist mianserin produced a surmountable antagonism of cocaine's antinociceptive effects and attenuated cocaine-induced enhancement of morphine antinociception. These results agree with our previous finding that selective serotonin reuptake inhibitors also produced mianserin-reversible antinociceptive effects, and enhanced the effects of low to intermediate efficacy mu-agonists in rhesus monkeys (12). Moveover, serotonin receptor agonists and serotonin reuptake inhibitors have been found to produce antinociceptive effects in both rodents and humans (1,5,45,47), and to enhance opioid-induced antinociception (5,7,18,26,45). Taken together, these results suggest that cocaine's antinociceptive effects may be mediated, at least in part, by the ability of cocaine to block serotonin reuptake and increase activity in serotonergic systems involved in modulating nociception. These findings also add to a growing literature describing a potential role for serotonergic systems in mediating some behavioral effects of cocaine (6,16,17,38,42).

It should be noted that mianserin was 10 times more potent in blocking the antinociceptive effects of the selective serotonin reuptake inhibitor clomipramine (12) than in blocking the effects of cocaine in the present study. For example, a dose of 0.032 mg/kg mianserin produced an approximately one-half log unit rightward shift in the clomipramine dose–effect curve, but a higher dose of 0.32 mg/kg mianserin was required to produce a significant rightward shift in the cocaine dose–effect curve. The relatively low potency of mianserin in blocking the antinociceptive effects of cocaine suggests that nonserotonergic mechanisms may also contribute to the antinociceptive effects of cocaine. Although the identity of these nonserotonergic mechanisms is not clear, it is known that cocaine also blocks the reuptake of dopamine and norepinephrine, and activity in both dopaminergic and noradrenergic systems has been found to modulate nociception (4,8). The effects of dopaminergic and noradrenergic receptor antagonists were not examined in the present study. However, we have previously reported that selective dopamine and norepinephrine

reuptake inhibitors failed to produce antinociceptive effects or alter opioid antinociception in rhesus monkeys (12). We concluded that the effects of cocaine on dopamine and norepinephrine reuptake do not play a major role in mediating its antinociceptive effects in primates.

Studies in rodents designed to examine the role of dopaminergic and noradrenergic systems in mediating the antinociceptive effects of cocaine have yielded conflicting results. For example, antagonists selective for D_1 (SCH23390) and D_2 (eticlopride) dopamine receptors blocked cocaine-induced antinociception in the rat formalin and hot-plate tests (27), and eticlopride blocked the effects of cocaine on C-fiber activity in the dorsal horn induced by noxious stimulation of the hindpaw (22). However, SCH23390 did not block cocaine-induced antinociception in the mouse-writhing assay (11). Preliminary data from this lab has found that the nonselective dopamine antagonist flupenthixol did not antagonize the antinociceptive effects of cocaine. However, when administered alone, flupenthixol produced changes in nonciception that complicate interpretation of the results (Gatch, unpublished observations). Similarly, the alpha-2 norepinephrine receptor antagonist yohimbine failed to block cocaine-induced enhancement of opioid antinociception in mice, which suggests that noradrenergic systems were minimally involved in cocaine's antinociceptive effects under those conditions (33).

In an earlier study (13), we reported that quadazocine (an opioid antagonist) failed to antagonize the antinociceptive effects of cocaine. This finding provides evidence that cocaine does not produce its antinociceptive effects at the mu-opioid receptor. In addition, mianserin had no effect on the antinociceptive effects of morphine alone, which suggests that morphine is not producing effects at serotonin 5-HT_2 receptors. Given that both the opioid and serotonin systems mediate antinociception, it is possible that cocaine and morphine produce their effects by completely separate and unrelated mechanisms. Alternatively, activity at serotonergic or opioid receptors may produce some sort of modulation of the effects of the other system. The mechanism by which cocaine and morphine interact (if at all) remains to be identified.

In summary, these results suggest that cocaine produces stereoselective and centrally mediated antinociceptive effects in rhesus monkeys. The antinociceptive effects of cocaine appear to be mediated at least in part by cocaine's effects on serotonergic systems; however, a role for other, nonserotonergic mechanisms of action cannot be ruled out. This study continues the characterization of cocaine's antinociceptive effects alone and in combination with opioids (12,13), and further supports the conclusion of earlier research, which suggests that the serotonergic system mediates these effects of cocaine (12). This study also adds to a growing body of evidence that serotonergic systems play a least a modulatory role in some of the behavioral effects of cocaine (6,16,17,38,42).

ACKNOWLEDGEMENTS

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