

Cocaine: evidence for supraspinal, dopamine-mediated, non-opiate analgesia

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Cocaine (25 mg/kg i.p.) produces analgesia in the rat within 5 min and for a duration of 90 min as determined by the formalin test or for 30 min as determined by the hot plate test. Cocaine analgesia is unaffected by doses of naloxone that are sufficient to attenuate morphine analgesia in both tests. Chlorpromazine (3 mg/kg i.p.), SCH 23390 (100 µg/kg i.p.; a D₁ dopamine receptor antagonist), and eticlopride (75 µg/kg i.p.; a D₂ dopamine receptor antagonist) each attenuate cocaine analgesia in both tests at doses that alone do not affect performance in either test. Measurements of blood pressure and heart rate indicate that cocaine analgesia is not due to the activation of baroreceptor reflex afferents. We conclude that cocaine is a supraspinally acting, dopamine-mediated, non-opiate analgesic in the rat.

INTRODUCTION

The central nervous system action of systemically administered analgesic compounds is thought to be mediated primarily, if not exclusively, by neural mechanisms also activated by opiate receptors^{12,18}. Neurons containing norepinephrine and serotonin form essential connecting links in the opiate-activated analgesia mechanism^{12,35}. Because cocaine blocks the deactivating re-uptake of biogenic amines in the central nervous system^{30,32}, we considered that cocaine might have potent systemic analgesic properties. Furthermore, cocaine's action could bypass opiate receptor mechanisms because it is not an opiate narcotic. It has long been known that sympathomimetic agents can produce analgesia^{5,25}, but we found only 3 short anecdotal reports on the analgesic effect of systemically administered cocaine in dogs^{20,27} and a human¹⁶. Yang et al.³⁶ showed that cocaine applied intranasally attenuated ischemic pain (tourniquet test) in humans, but this effect could not be related securely to a systemic action, and opiate

mediation was not tested. We therefore undertook a systematic investigation of cocaine as a systemic analgesic.

MATERIALS AND METHODS

All experiments were conducted using male Sprague-Dawley rats (250–400 g) maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care.

Analgesia was evaluated by both the formalin and hot plate tests. In the formalin test⁹, 0.05 ml of sterile 5% formalin was injected subcutaneously into the dorsum of one forepaw. Every 5–10 min, pain behavior was graded throughout a 3 min observation period according to the proportion of time (seconds) the paw was held up and licked (grade 3), held fully elevated (grade 2), partially weight bearing (grade 1), or fully weight bearing (grade 0). The sum of the products of each grade and the time spent in that grade was divided by 180 s to yield a pain intensity score. In the hot plate test²², each rat was placed

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within a clear plexiglass cylinder on a copper surface maintained at 52.5 °C by circulating water. The latency to hind paw lick or escape was determined and the test was terminated after 45 s. The baseline latency (*B*) was the average of 3 latency measurements made at 5 min intervals before administering drugs. Latencies (*L*) measured at intervals after drug administration were used to calculate % analgesia ($=[(L-B)/(45-B)] \times 100$). The significance of differences in pain scores (formalin test), % analgesia (hot plate test), or cardiovascular measurements was evaluated by computing the 95% confidence intervals about each mean. Compared means were considered significantly different when each fell outside the confidence limit of the other.

To determine if drug-induced motor deficits interfered with the hot plate test, we used the abnormal posture test of Fog¹³. One hindpaw of the rat was placed on a cork with a height of 3.5 cm, and the latency to movement off the cork was measured up to a maximum of 45 s.

Blood pressure and heart rate responses to cocaine or saline were determined in 13 rats. Five days before the experiment, rats were surgically implanted with a chronic polyethylene cannula (PE50) in the left internal carotid artery. The cannula was exteriorized at the scalp and passed through a stainless-steel spring, which was anchored to the skull with dental acrylic and screws. Blood pressure was recorded directly in conscious, freely-moving rats using a Grass Model 7

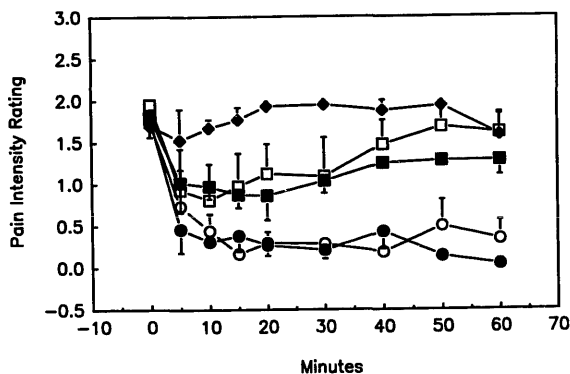


Fig. 1. Effect of different intraperitoneal doses of cocaine on averaged (\pm S.E.M.) pain intensity ratings in the formalin test. Formalin (5%, 0.05 ml) was injected subcutaneously into one forepaw 30 min before 0 time on the abscissa. Cocaine was administered at time 0. Four rats were in each dosage group. Filled diamonds, 5 mg/kg; open squares, 10 mg/kg; filled squares, 15 mg/kg; open circles, 20 mg/kg; filled circles, 25 mg/kg.

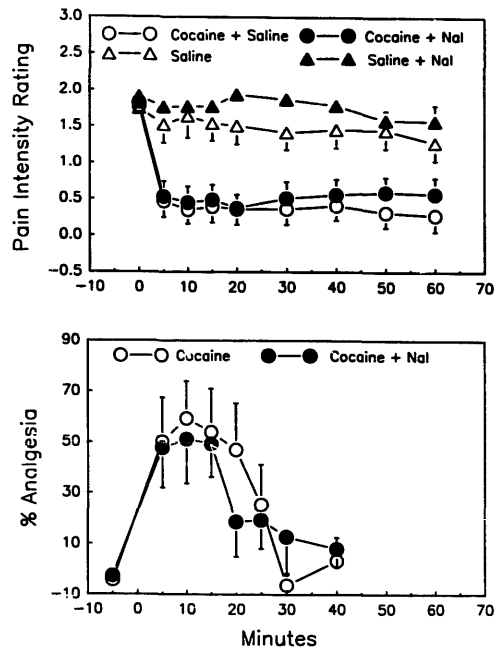


Fig. 2. Lack of effect of naloxone (1 mg/kg, i.p.) on cocaine (25 mg/kg, i.p.) analgesia. Top: formalin test in blinded format. At time 0, 30 min after subcutaneous formalin injection, each rat received 2 separate injections within 1 min. Average (\pm S.E.M.) pain ratings shown for each group of rats receiving cocaine and saline ($n = 9$), cocaine and naloxone ($n = 9$), saline and naloxone ($n = 10$), and saline only ($n = 8$). Bottom: hot plate test. Average (\pm S.E.M.) % analgesia (see Methods) shown for rats receiving cocaine ($n = 8$) or cocaine followed immediately by naloxone ($n = 8$) at time 0.

polygraph and Statham P23 pressure transducers. Heart rate was counted from the pressure tracing. Cardiovascular parameters were monitored for 15 min before administration of cocaine (25 mg/kg i.p.) or saline (1 ml/kg i.p.). Blood pressure was monitored continuously for 40 min after treatment and heart rate was sampled over 20 s epochs at 1, 5, 15, 25 and 40 min after treatment.

All drugs were given by intraperitoneal injection. Cocaine was prepared in sterile 25 mg/ml multiple injection vials by the pharmacy at the Veterans Administration Medical Center. The concentration of cocaine was independently verified on two occasions by the Toxicology Laboratory at the University of Michigan. The prototype dopamine D₁ and D₂ receptor antagonists, SCH 23390 and eticlopride, respectively, were both obtained from Research Biochemicals (Natick, MA). Fresh solutions in bacteriostatic saline were prepared daily; SCH 23390 was first dissolved in a minimum volume of 10% acetic acid.

RESULTS

Cocaine injected intraperitoneally produced a dose-dependent analgesia as determined in 20 rats by the formalin test (Fig. 1). At maximally effective doses (20–25 mg/kg, i.p.), analgesia was clearly detectable within 5 min and sustained for 1–1.5 h in most rats. During the analgesic period, rats showed a slight to moderate increase in exploratory behavior that did not interfere with execution of the test. Otherwise, behavior appeared normal and without evidence for weakness or ataxia. Cocaine (25 mg/kg, i.p.) also produced analgesia as determined by the hot plate test (Fig. 2). The response peaked at 5–10 min but, in contrast with the formalin test, the duration of analgesia was limited to approximately 30 min. In preliminary experiments using the tail flick test⁶, we found that the higher doses of cocaine produced, in the awake, restrained rat, enough increased spontaneous movement to make measurements unreliable (data not shown).

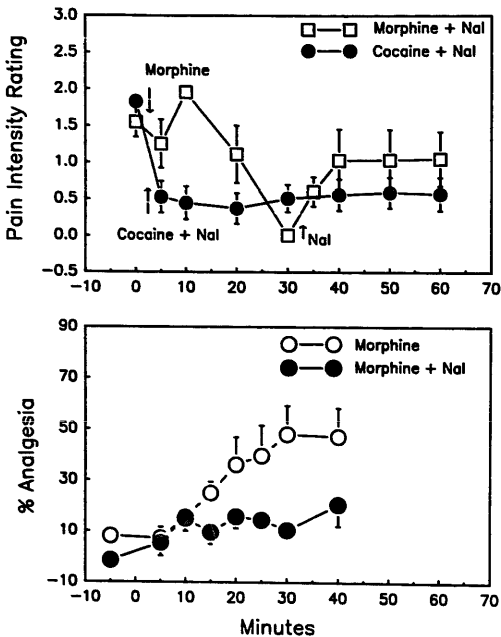


Fig. 3. Effect of naloxone (1 mg/kg, i.p.) on morphine analgesia. Top: formalin test. Arrows indicate time of drug injection. Morphine (6 mg/kg, i.p.; $n = 5$) produces analgesia more slowly than cocaine (25 mg/kg, i.p.; $n = 9$) and, unlike cocaine, morphine analgesia is attenuated by naloxone. Bottom: hot plate test. Morphine (12 mg/kg, i.p.) analgesia ($n = 7$) fails to develop when naloxone (1 mg/kg, i.p.) is injected immediately before morphine at time 0 ($n = 7$).

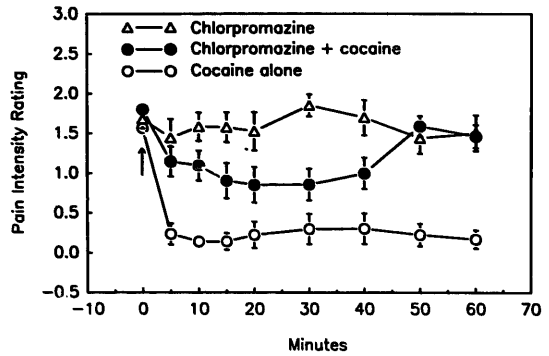


Fig. 4. Chlorpromazine (CPZ; 3 mg/kg, i.p.) attenuation of cocaine (25 mg/kg, i.p.) analgesia in the formalin test. CPZ and cocaine were separately administered within one minute after time 0. CPZ alone had no effect ($n = 6$). $n = 15$ (cocaine alone) and 12 (CPZ and cocaine).

Naloxone had no effect on cocaine analgesia in either the formalin or hot plate test (Fig. 2). In the formalin test, a blind format was used to test 36 rats divided into 4 groups; neither the person preparing the solutions nor the person performing the test knew which treatment any rat received. The dose of naloxone we used (1 mg/kg) was sufficient to attenuate morphine analgesia in both formalin and hot plate tests (Fig. 3).

Because of the evidence that other behavioral effects of cocaine are mediated in part by dopaminergic mechanisms³³, we determined the effect of the dopamine receptor antagonist, chlorpromazine (CPZ) on cocaine analgesia. When administered at a dose of 3 mg/kg, i.p., CPZ alone had no effect on the formalin test of pain behavior but significantly reduced the intensity and duration of cocaine analgesia (Fig. 4).

To examine further the dopamine receptor mechanisms that might mediate cocaine analgesia, rats were pretreated with either SCH 23390, a D_1 selective antagonist¹⁷ or eticlopride, a D_2 selective antagonist⁸. In the formalin test (Fig. 5), both SCH 23390 (100 μ g/kg, i.p.) and eticlopride (75 μ g/kg, i.p.) blocked the analgesic effect of cocaine at doses that alone had no effect on the test. In the hot plate test (Fig. 6), eticlopride and SCH 23390 both significantly attenuated cocaine analgesia; neither of these dopamine receptor antagonists interfered with the hot plate test when administered alone at the above doses. In addition, these compounds produced no evidence of motor impairment as assessed by the abnormal posture test (see Methods) at doses and times

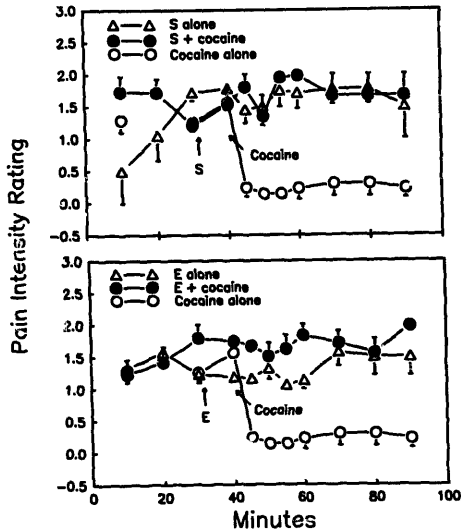


Fig. 5. D_1 receptor antagonist, SCH 23390 (SCH, 100 µg/kg, i.p., top panel), and D_2 receptor antagonist, eticlopride (E, 75.5 µg/kg, i.p., bottom panel), given 10 min before cocaine (25 mg/kg, i.p.), each prevent cocaine analgesia without affecting the formalin test when given alone. Arrows indicate time of drug injection. $n = 4$ (SCH alone), 3 (SCH + cocaine), 4 (E alone), 3 (E + cocaine), and 6 (cocaine alone).

corresponding to the block of cocaine analgesia.

There is evidence that acutely increasing arterial blood pressure in rats can produce an analgesia that is correlated with the reflex bradycardia mediated by baroreceptor activation^{10,25}. Analgesic doses of cocaine produced a significant increase in systolic blood pressure within the first minute after the injection, but subsequent measurements for 40 min thereafter

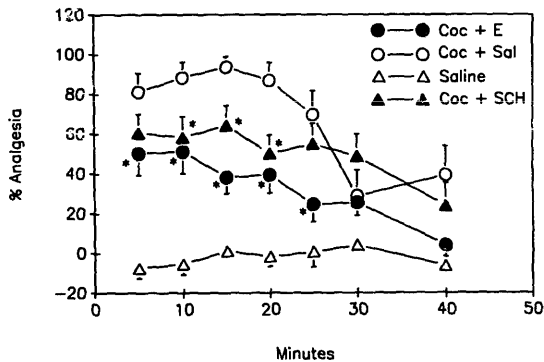


Fig. 6. Hot plate test. Eticlopride (E; 75.5 µg/kg, i.p.) and SCH 23390 (SCH; 100 µg/kg, i.p.) each block cocaine (25 mg/kg, i.p.) analgesia when given 10 min before cocaine injection at time 0. $n = 14$ (SCH + cocaine), 15 (E + cocaine), 12 (cocaine + saline), and 6 (saline). Asterisks indicate points of significant attenuation of cocaine analgesia.

showed no difference compared to animals injected with saline (Fig. 7). The transient hypertension was accompanied by a significant bradycardia for only 5 min.

DISCUSSION

The analgesic effect of systemically administered cocaine has been demonstrated in this study by two different measures of supraspinally organized nociceptive behaviors. The formalin test elicits a prolonged behavioral response to a chemically-induced inflammation, whereas the hot plate test elicits a short duration, abrupt response to a thermal stimulus. By both measures, analgesia elicited by 20–25

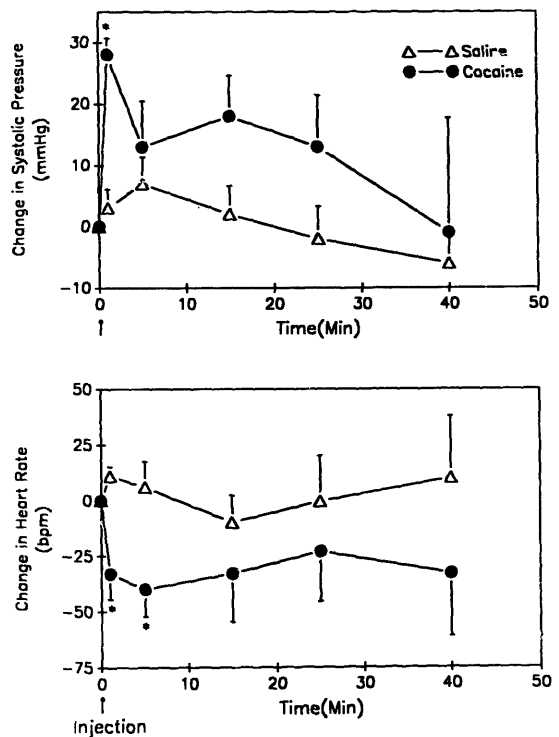


Fig. 7. Cardiovascular effects of cocaine (25 mg/kg, i.p.). Cocaine ($n = 7$) or saline ($n = 6$) was injected at time 0. Top: cocaine (circles) significantly increased systolic blood pressure at 1 min after injection compared to saline-treated controls (triangles). Systolic pressure before injection: cocaine group, 125 ± 9 mm Hg; saline group, 132 ± 7 mm Hg. Bottom: cocaine decreased heart rate at 1–5 min after injection compared to controls. Heart rate before injection: cocaine group, 369 ± 35 bpm; saline group, 423 ± 32 bpm. There were no significant differences in pretreatment blood pressure or heart rate between treatment groups. Asterisks indicate means that are significantly different from zero change and from the means of saline controls.

mg/kg of cocaine appears comparable in intensity to the analgesia produced by 6–12 mg/kg of morphine; at these doses, the analgesic effect of cocaine is more rapid in onset and, in the hot plate test, shorter in duration (Fig. 3). However, a definitive comparison of the potency and efficacy of these two analgesics will require additional studies using several dosage levels of each drug.

Our results indicate that the analgesia produced by parenterally administered cocaine is due to its action on nociceptive mechanisms within the central nervous system. We saw no evidence for motor deficits that would be expected if peripheral motor or kinesthetic mechanisms were affected by local anesthetic block. The attenuation and reversal of cocaine analgesia by dopamine antagonists also argues for a central effect on monoaminergic synaptic transmission rather than local anesthetic block of conduction in peripheral fibers. Furthermore, other experiments in our laboratory have shown that analgesic parenteral doses of cocaine do not affect the conduction of impulses into the cutaneous terminals of unmyelinated nociceptive afferents²³. The same dose of cocaine dramatically alters, over a time course paralleling the behavioral effects, the spontaneous and nociceptively evoked activity of bulboreticular neurons that project rostrally or to the spinal cord¹. It is possible, however, that the more prolonged analgesic effect of cocaine in the formalin, as compared to the hot plate, test is in part due to a peripheral anti-inflammatory effect of adrenal steroids in view of the recent finding that cocaine causes the release of adrenocorticotrophic hormone *in vitro*²⁸.

Systemic cocaine analgesia appears not to be caused by the activation of baroreceptors. In our experiments, cocaine produced a transient hypertension but did not induce the prolonged bradycardia associated with baroreceptor-activated analgesia^{10,25}. Similar results have been reported by others²⁴. A dissociation of cardiovascular responses and analgesia has recently been demonstrated during vaginocervical probing and phenylephrine injection in the rat³. Furthermore, naloxone reverses the analgesia of chronically hypertensive rats without affecting the blood pressure³⁷, but naloxone had no effect on cocaine analgesia in our experiments. We cannot, however, rule out the possibility that cocaine produces other somatic or visceral afferent activity that con-

tributes to the activation of central analgesic mechanisms^{26,38}.

Our results provide strong evidence that both D₁ and D₂ dopamine receptor mechanisms are important in mediating cocaine analgesia because both the D₂ receptor antagonist, eticlopride, and the D₁ receptor antagonist, SCH 23390, blocked cocaine analgesia in both the formalin and hot plate tests. In the formalin test, an anti-analgesic effect of both compounds might be seen if they each attenuated any anti-inflammatory effects of cocaine²⁸. Because of the evidence for synergistic interactions of D₁ and D₂ receptor mechanisms⁴, it is not possible to conclude that these two receptor types are acting independently in mediating cocaine analgesia. A more complete analysis of agonist and antagonist dose-response functions will be required to determine receptor selectivity. Furthermore, a spinal or supraspinal analgesic action of other monoamine systems cannot be excluded on the basis of our studies.

The central neural mechanisms of cocaine analgesia remain to be determined. De Jong et al.⁷ and Woolf and Wiesenfeld-Hallin³⁴ have presented evidence that systemically administered local anesthetics selectively block C-fiber-evoked polysynaptic reflex activity in the spinal cord. The results of other experiments in our laboratory, however, suggest a supraspinal site for cocaine analgesia because analgesic doses of cocaine either potentiate or have no effect on a nociceptive spinal reflex²³. The lack of evidence for spinal reflex inhibition and the lack of naloxone antagonism also argues against an opiate-mediated activation of supraspinal mechanisms that inhibit spinal nociceptive neurons by descending pathways^{12,14}. The dose of naloxone we used was sufficient to attenuate morphine analgesia in our tests and has been shown to block analgesia mediated by both μ - and δ -opiate receptors¹¹. Because cocaine is known to block the re-uptake deactivation of biogenic amines^{29,30}, it might potentiate opiate analgesia, as shown by Misra et al.²¹, by enhancing the bulbospinal, biogenic amine-mediated inhibition of nocifensive spinal reflexes³⁵. In contrast with our results, however, this potentiating effect of cocaine is blocked by naloxone²¹.

Evidence reviewed by Jensen¹⁹ shows that dopamine mechanisms can inhibit spinal nocifensive reflexes, but whether this inhibition is mediated by seg-

mental spinal or by supraspinal descending dopamine pathways is not known. Dopamine-mediated inhibition of spinal reflexes may be independent of supraspinal dopamine neurons; we have shown that extensive chronic partial myelotomies markedly reduce spinal serotonin and norepinephrine, but not dopamine, concentrations in the cat². The effect of cocaine on supraspinal mediated behaviors and the dependence of cocaine analgesia on dopaminergic mechanisms suggests the participation of dopamine-containing mesolimbic structures, which have been shown to be important for maintaining cocaine self-administration and reinforcement in the rat^{33,39}. The role of hypothalamic-related structures in dopamine-mediated analgesia deserves further investigation in

view of a recent report that cocaine causes the release of adrenocorticotrophic hormone (ACTH) through the activation of corticotropin releasing factor (CRF)²⁸. There are additional, though conflicting, reports about the analgesic effects of CRF^{15,31}.

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