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Modulation of Cocaine-Induced Antinociception by Opioid-Receptor Agonists

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WADDELL, A. B. AND S. G. HOLTZMAN. *Modulation of cocaine-induced antinociception by opioid-receptor agonists.* PHARMACOL BIOCHEM BEHAV **62**(2) 247–253, 1999.—Cocaine can produce antinociception in a number of animal models. The present experiments were designed to determine if opioid receptor agonists modulate cocaine-induced antinociception in rats. Cocaine produced a dose-dependent increase in antinociception in the hot-plate, but not paw-pressure, test. The combination of cocaine and morphine or [D-Pen^2, D-Pen^5]enkephalin (DPDPE) produced results no greater than simple additivity in the hot-plate test. However, the combination of cocaine and morphine produced greater antinociception than morphine alone in the paw-pressure test. A low dose of U69,593 potentiated the effects of cocaine in the hot-plate test. In contrast, cocaine attenuated the effect of U69,593 in the paw-pressure test. Both naltrexone and the selective κ-opioid receptor antagonist nor-binaltorphamine (nor-BNI) blocked the potentiation of cocaine-induced antinociception by U69,593. The combination of U69,593 and cocaine can produce superadditive or subadditive effects, depending upon the doses and antinciceptive assay used. © 1999 Elsevier Science, Inc.

Analgesia Hot plate Paw pressure U69,593 Morphine DPDPE

COCAINE, which is probably best known for its psychomotor stimulant properties, also produces antinociceptive effects in several types of tests and animal species. Antinociceptive effects following cocaine administration have been observed in several species, including rats (8), mice (16), and nonhuman primates (2), in a number of tests, including the hot-plate, formalin (8), tail-pinch (11), and tail-withdrawal (2) assays of antinociception. The antinociception effects produced by cocaine in the hot plate and formalin tests are attenuated by selective D_1 (SCH23390) and D_2 (eticlopride) dopamine receptor antagonists (8). A central, descending, dopaminergic pathway that is cocaine sensitive and suppresses pain-evoked dorsal horn nerve activity has been defined (7,15). Therefore, dopamine might play an important role in cocaine-induced antinociception, just as it is believed to do in the psychomotor stimulant effects of the drug (6,18).

Cocaine can also modify the effect of other analgesics. For example, subanalgesic doses of cocaine can change the antinociceptive effects of agonists for the three major classes of opioid receptors. Cocaine potentiates the antinociceptive effects of selective μ-opioid receptor agonists in mice (16), rats (4), and nonhuman primates (2). The antinociceptive effect of the selective δ-opioid receptor agonist [D-Pen^2- D-Pen^5]enkephalin (DPDPE) is potentiated by cocaine in mice (16); however, in rhesus monkeys, the combination of the selective δ-opioid receptor agonist BW373U86 and cocaine produces an antinociceptive effect no greater than the effect of cocaine alone (2). In contrast to the effects of δ- and μ-opioid receptor agonists, a low dose of cocaine attenuates the antinociceptive effect of U69,593, a selective κ-opioid receptor agonist, in rhesus monkeys (2). There is a clear interaction between the pathways controlling opioid-mediated and cocaine-mediated analgesia. However, the nature of the interaction varies, depending upon the species, particular agonist, and analgesic assay used.

Although there is relatively little data in the literature describing how subanalgesic doses of cocaine modify the analgesic effects of opioids, there is even less data on the converse situation: how subanalgesic doses of opioids modify the analgesic effect of cocaine. The first objective of the analgesia experiments in this project was to determine systematically the effect of subanalgesic doses of agonists selective for the three major opioid receptors upon the analgesic effect of cocaine. The opioid agonists tested were morphine (prototypic μ-opioid receptor agonist), DPDPE (selective δ-opioid receptor agonist), and U69,593 (selective κ-opioid receptor agonist). In

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addition, because cocaine blocks the reuptake of dopamine, norepinephrine, and serotonin, the second objective was to determine if the opioid agonists change the analgesic effects of other more selective inhibitors of neuronal reuptake for each of these neurotransmitters. In these experiments, GBR12909, nisoxetine, and fluoxetine were used to block the reuptake of dopamine, norepinephrine, and serotonin, respectively. Antinociception was measured using both the hot-plate and paw-pressure tests of analgesia. Both of these tests represents models of acute pain produced by noxious stimuli. However, because they employ different types of stimuli (i.e., thermal vs. mechanical), there may be detectable differences in the effect of the drugs tested alone and in combination.

METHODS

Subjects

Male Sprague–Dawley rats (Charles River, Inc., Raleigh, NC), weighing 250–325 g upon arrival, were used in all experiments. Animals were group housed in a temperature-controlled room and maintained on a 12 L:12 D cycle, with lights on between 0700 and 1900 h. There was no restriction on access to food and water. All experiments were performed between 1000 and 1600 h. The Institutional Animal Care and Use Committee of Emory University approved the procedures used in this study.

Experimental Procedure

Animals were randomly divided into eight groups; three groups for testing combinations of opioid agonists and cocaine ($n = 8$), two groups for testing antagonists ($n = 6$–8), and three groups for testing combinations of opioid agonists with selective inhibitors of monoamine reuptake ($n = 6$–8).

Because of the intersubject variability in the response to cocaine, the effect of cocaine alone was determined in all groups receiving cocaine in combination with an opioid agonist. At least 3 days separated successive drug tests on each animal.

Antinociceptive Testing

In the hot plate test (1,10), rats were placed on a surface that was maintained at 51°C and surrounded by walls of clear Plexiglas (26.5 × 29 × 28.5 cm). A trial ended following a response, which was either the licking of a rear paw or a jump with all four feet off of the hot plate, or after 35 s in the absence of a response. Each trial on the hot plate was followed by a trial in the paw pressure test [modified from (12)]. Rats were wrapped in a towel, to minimize movement, with the right rear paw exposed. The paw was placed on a 3.5-cm pedestal, and a blunt ended plastic cone was lowered onto the paw. Increasing pressure was applied by pressing a foot pedal that resulted in 210-g weight sliding across a numbered scale. A response was the withdrawal of the hind paw from the pedestal; the number on the scale indicated by the pointer at the time of the response was recorded. Rats were given two trials for habituation in both tests, and the third trial was taken as baseline. Baseline values did not vary across test groups or test days. At least 10 min separated each trial.

Initial testing of the opioid agonists was done to determine which doses would be tested in combination with cocaine. Morphine and U69,593 were administered subcutaneously (SC) and tested using a cumulative dosing schedule with 25 min between doses. For example, 1.0 mg/kg morphine was administered, followed 25 min later by a trial in each analgesic test. Immediately after testing, the next dose of morphine was injected (2.0 mg/kg resulting in a cumulative dose of 3.0 mg/kg), and 25 min later the animals were tested again. This cycle was repeated until all doses were tested. Cumulative dosing was not used with DPDPE due to the short duration of action; DPDPE was tested 25 min following a single dose administered intracisternally (IC). From these data, dose–response curves were constructed. Four doses of U69,593, three doses of morphine, and two doses of DPDPE were chosen for testing in combination with cocaine. The doses chosen represented different levels of analgesia in the hot plate test (i.e., no analgesic response, moderate response (35–50%), and maximum response seen achieved within the dose range tested). For DPDPE, the maximum response in the initial dose response curve fell within the 35–50% range, so only two doses were tested.

Single doses of morphine or U69,593 were tested with cumulative doses of cocaine administered intraperitoneally (IP), with 10 min separating test trials. After a baseline reading was obtained, one dose of morphine or U69,593 was administered, followed 15 min later with saline. After 10 min, the animals were tested for analgesia, then injected immediately with the lowest dose of cocaine. In pilot experiments, the highest doses of U69,593 and morphine were shown to produce consistent effects throughout the period when cocaine would be tested. The highest doses of morphine (5.2 and 10 mg/kg) and U69,593 (1.0 and 3.0 mg/kg) were tested with a maximum cumulative cocaine dose of 17.5 mg/kg, as opposed to 30 mg/kg in other experiments, due to concern about the possible toxicity of the drug combination. For DPDPE, a single dose was followed 15 min later by a single dose of cocaine. Ten minutes later, animals were tested for analgesia.

The experiments testing the ability of opioid antagonists to block the interaction between cocaine and an opioid were conducted in the same way as described above. The general opioid receptor antagonist naltrexone (0.3 mg/kg) was given SC 5 min prior to U69,593. The selective κ-opioid receptor antagonist nor-binaltorphamine (nor-BNI; 10 μg/10μl) was given IC, and animals were tested 1 and 4 days later (with and without U69,593). This dose blocks the antinociceptive effect of the selective κ-opioid receptor agonist spiradoline in the hot-place test for at least 21 days (3); therefore, only one dose was necessary.

In the experiments testing nisoxetine and fluoxetine, the dosing schedule was the same as the one used when testing U69,593 in combination with cocaine. For GBR12909, a single dose was tested with a single dose of U69,593, with a 40-min pretreatment for GBR12909 and 25 min for U69,593. The pretreatment time for all experiments was determined in pilot experiments. For the selective uptake inhibitors, it was the earliest time point that the maximum effect was achieved. All reuptake inhibitors were administered IP.

Intracisternal Injections

Animals were lightly anesthetized with a mixture of halothane and methoxyflurane in a 1:1 ratio. The back of the rat's neck and head was shaved and cleaned with alcohol. Animals were then placed in the earbars of a stereotaxic apparatus. The head was positioned at a 45° angle, and a 25-gauge needle, attached to a 50-μl Hamilton syringe, was inserted percutaneously 5 mm into the cisterna magna. The drug was delivered over 20–30 s in a volume of 10 μl. The needle was held in place for 20–30 s, to minimize leakage of injected drug.

Data Analysis

Latency to respond on the hot plate, in seconds, and scale reading following paw withdrawal, in arbitrary units (a.u.), were both expressed as percent maximum possible effect (%MPE).

$$\%\text{MPE} = \frac{\text{test value} - \text{baseline value}}{\text{cutoff value} - \text{baseline value}} \times 100\%$$

The cutoff value was 25 a.u. for paw pressure and 35 s for the hot plate. The maximum baseline value for paw pressure was 10 a.u. and 15 s for the hot plate. All comparisons between cocaine (or other reuptake inhibitor) and combinations of opioids and cocaine, were done using a two-factor ANOVA (pretreatment opioid × dose of cocaine), with repeated measures on both factors. A two-factor ANOVA with repeated measures on both factors was also used to compare the theoretical additive values of U69,593 in combination with cocaine with the observed values. Tukey's *t*-test for multiple pairwise comparisons was performed to determine if there were significant differences between two means for all data sets. The significance level for all tests was chosen as $p < 0.05$.

Drugs

Morphine sulfate (Penick Corp., Newark, NJ), U69,593, and GBR12909 hydrochloride were purchased from RBI (Natick, MA), naltrexone hydrochloride was purchased from Sigma (St. Louis, MO), nisoxetine hydrochloride and fluoxetine hydrochloride were a gift From Eli Lily (Indianapolis, IN), DPDPE was purchased from Bachem (King of Prussia, PA), and nor-binaltorphamine hydrochloride was provided by the National Institute on Drug Abuse (Rockville, MD). Morphine, naltrexone, and nor-binaltorphamine were dissolved in saline, U69,593 was dissolved in three parts 8.5% lactic acid and two parts 1 N sodium hydroxide, DPDPE was dissolved in 2% vol acetic acid and distilled water, nisoxetine and fluoxetine were dissolved in distilled water, and GBR12909 was dissolved in 30% vol DMSO and then brought to final volume with distilled water. All doses of drugs are expressed as percent base.

RESULTS

Morphine, U69,593, and DPDPE all produced dose-dependent increases in the response latencies in both tests of analgesia ($p < 0.001$) (Fig. 1). For all of the opioid agonists, the effects were similar in both tests. For example, the highest dose of morphine tested (10 mg/kg) produced 82.8 ± 12.4% and 83.2 ± 12.4% MPE in the hot-plate and paw-pressure tests, respectively. From these curves, doses were chosen for testing in combination with cocaine (see Table 1).

When administered alone, cocaine produced a dose-dependent increase in response latency in the hot-plate test, with a cumulative dose of 30 mg/kg producing a response significantly greater than that produced by vehicle. For example, in one group (morphine/cocaine; Fig. 2) 30 mg/kg cocaine produced a response of 37.0 ± 14.3% MPE. In contrast, no analgesic response was seen in the paw-pressure test at any dose of cocaine tested (Figs. 2–4).

Morphine, in combination with cocaine, produced no effects in the hot-plate test that were greater than simple additivity (Fig. 2A and C). In the paw-pressure test, the lower two doses of morphine, when combined with cocaine, produced an analgesic response no different than morphine alone (Fig. 2B and D). Although morphine did not affect cocaine-induced antinociception, the converse occurred. Cocaine potentiated the antinociceptive effect of 10 mg/kg morphine ($p < 0.001$) (Fig. 2D). The combinations of cocaine and this dose of morphine produced 100% MPE, an effect that was not graded by cocaine dose.

In both assays, 100 μg DPDPE produced a smaller antinociceptive effect than morphine or U69,593 with maximum

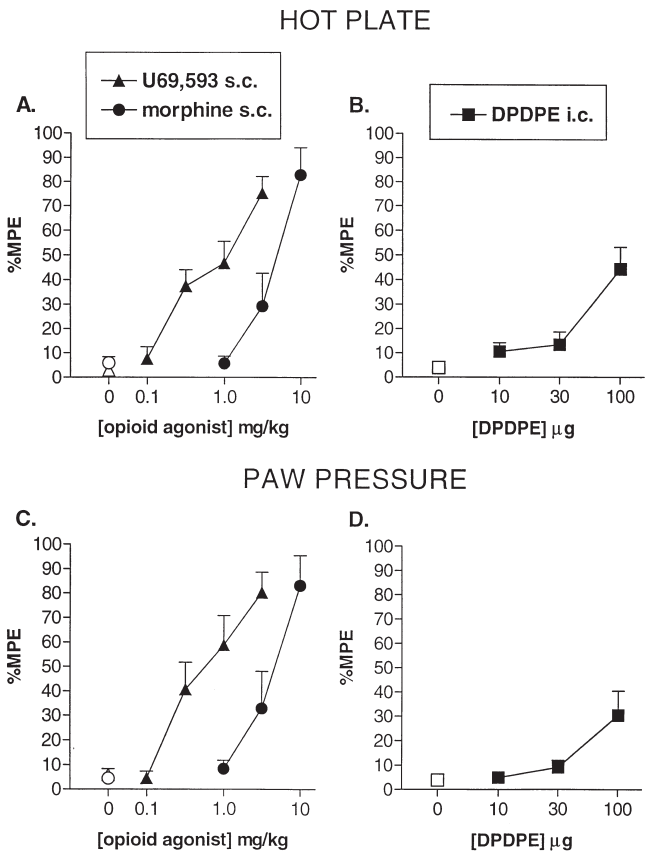


FIG. 1. Dose–response curves for (●) morphine, (■) DPDPE, and (▲) U69,593, in the (A) hot-plate and (B) paw-pressure tests of analgesia. Morphine and U69, 593 were tested using a cumulative dosing schedule, with 25 min between doses (SC). DPDPE was tested 25 min following a single dose (IC). %MPE = percent maximum possible effect. Data are presented as mean ± SEM.

TABLE 1

DOSES OF OPIOIDS TESTED IN COMBINATION WITH COCAINE

Opioid Agonist	*n*	10% MPE	35–50% MPE	Maximum
Morphine (mg/kg)	8	1.9	5.2	10
U69,593 (mg/kg)	8–16	0.1	0.3 & 1.0	3.0
DPDPE (μg)	8–16	10	100	*

These doses represent no analgesic response (10% MPE), moderate analgesic response (35–60%), and maximum response in dose range tested, which were determined from initial dose–response curves (Fig. 1).

*The maximum response produced by the doses tested fell within the 35–50% MPE range.

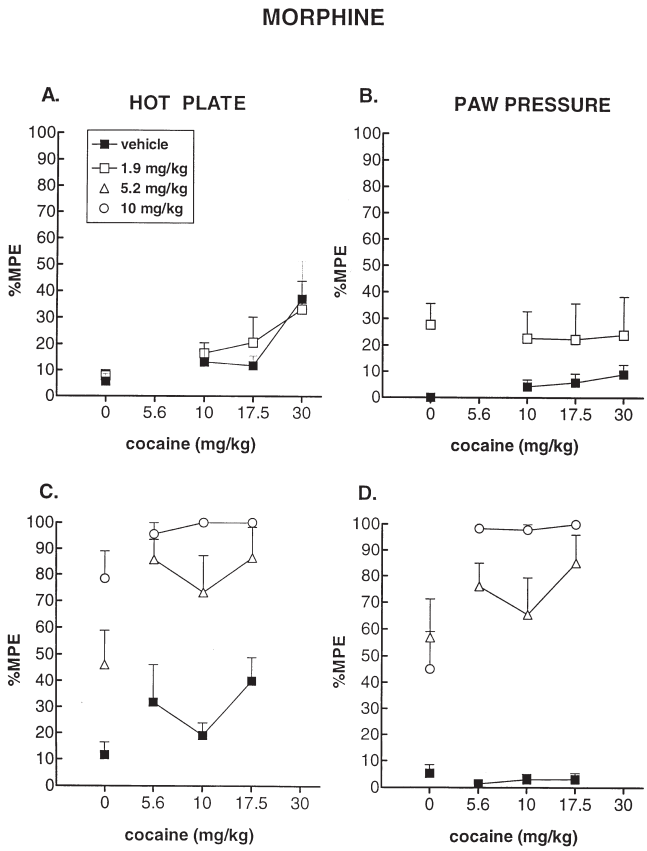


FIG. 2. Combinations of morphine (SC) and cocaine (IP), in the hot-plate (A,C) and paw-pressure (B,D) tests of analgesia. Open symbols = morphine + cocaine; closed square = vehicle + cocaine. There is no effect greater than additivity in the hot-plate test, while the effect of 10 mg/kg morphine is potentiated by cocaine in the paw-pressure test (D). For all figures, $n = 8$. %MPE = percent maximum possible effect. Data are presented as mean ± SEM.

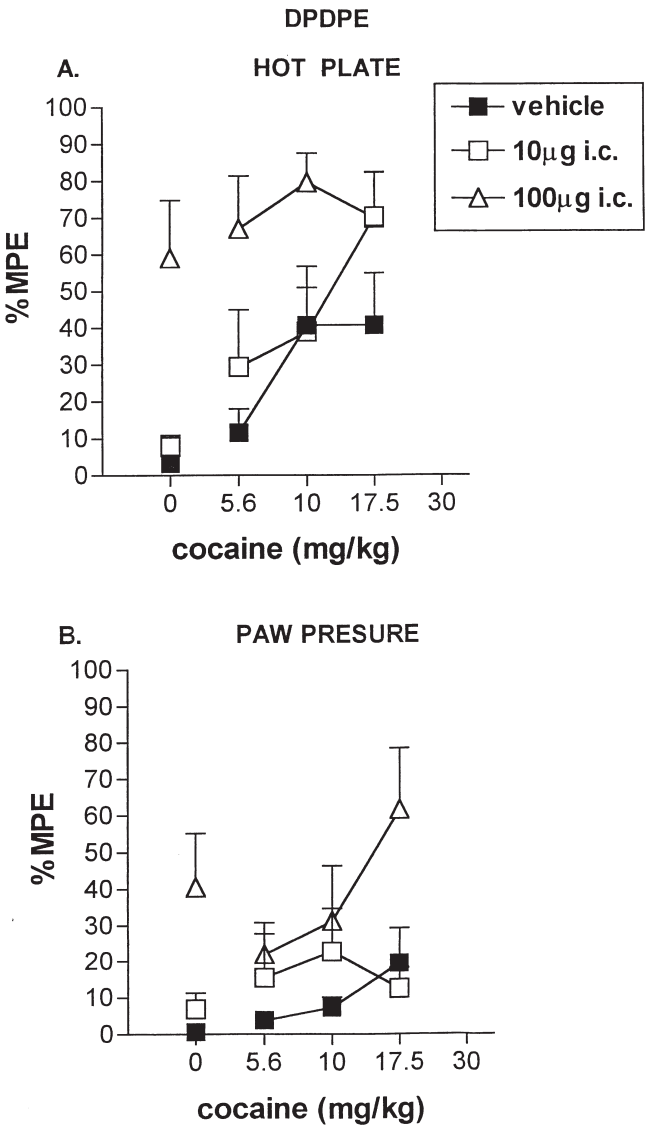


FIG. 3. Combinations of DPDPE (IC) and cocaine (IP) in the hot-plate (A,C), and paw-pressure (B,D) tests of analgesia. Open symbols = DPDPE + cocaine; closed squares = vehicle + cocaine. No combination tested produced an analgesic effect greater than that of cocaine or DPDPE alone. For all figures, $n = 8$. %MPE = percent maximum possible effect. Data are presented as mean ± SEM.

responses of 59.1±15.8% and 40.5 ± 14.7% MPE in the hot-plate and paw-pressure tests, respectively (Fig. 3A and B). An effect that was graded by the dose of cocaine occurred with 10 μg DPDPE in the hot-plate test and 100 μg in the paw-pressure test. However, the combination of DPDPE and cocaine, at the doses tested, did not produce antinociception greater than simple additivity in any experiments.

The κ-opioid receptor agonist U69,593 produced significant antinociception in the hot-plate test at all doses tested except for the lowest dose, 0.1 mg/kg (Fig. 4A and C). However, the two lower doses (0.1 and 0.3 mg/kg) of U69,593, when combined with cocaine, both produced effects greater than the effect of cocaine alone ($p = 0.023$ and 0.016, respectively) (Fig. 4A). When the observed values produced by the combination of 0.1 U69,593 and cocaine were compared with the theoretical values, as predicted by simple addition of the effect of 0.1 mg/kg U69,593 alone and cocaine alone, the observed values were significantly higher ($p = 0.035$). Post hoc analysis revealed that the combination of 0.1 mg/kg U69,593 and 10 mg/kg cocaine produced an antinociceptive effect significantly greater than was predicted. In contrast to the effects observed in the hot-plate test, the lower two doses of U69,593 did not produce any effect alone or in combination with cocaine in the paw-pressure test. As they did in the hot-plate test, the higher two doses (1.0 and 3.0 mg/kg) of U69,593 both produced an antinociceptive effect in the paw-pressure test ($p < 0.001$). However, results obtained with the drug combinations differed across tests. Specifically, cocaine did not change the antinociceptive effect of the higher two doses of U69,593 in the hot-plate test, but it did attenuate the effect of U69,593 in the paw-pressure test ($p = 0.008$ for 3.0 mg/kg dose U69,593).

To determine if the potentiation of cocaine's antinociceptive effect by U69,593 was mediated by κ-opioid receptors, the same experiment was performed following administration of the general opioid antagonist naltrexone (0.3 mg/kg SC 5-min pretreatment), or the selective κ-opioid antagonist nor-binal-

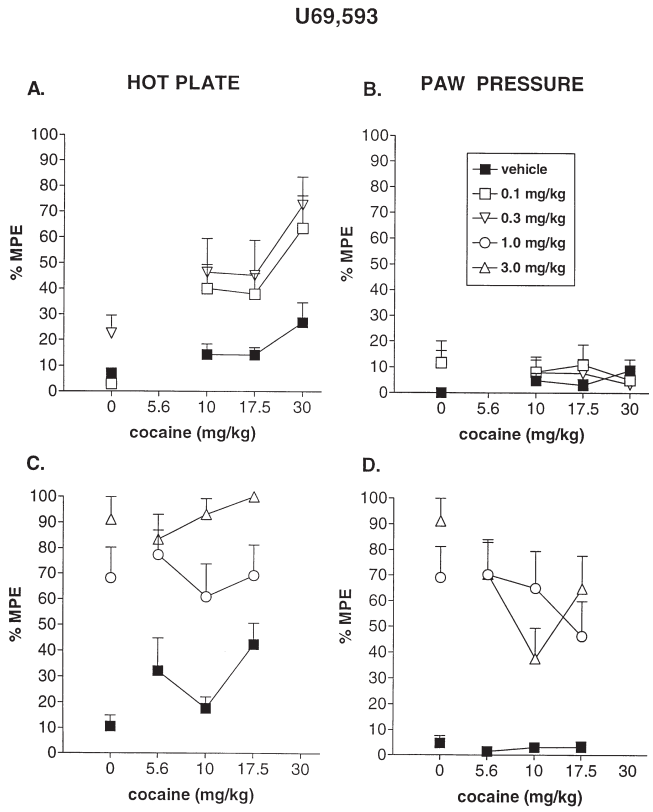


FIG. 4. Combinations of U69,593 (SC) and cocaine (IP) in the hot-plate (A,C), and paw-pressure (B,D) tests of analgesia. Open symbols = U69,593 + cocaine; closed squares = vehicle + cocaine. A low dose of U69,593 (0.1 mg/kg), potentiated the effect of cocaine ($p < 0.05$) in the hot-plate (A), but not paw-pressure (B) test of analgesia. In contrast, the combination of a high dose of U69,593 (3.0 mg/kg) and cocaine produces a subadditive effect ($p < 0.05$) in the paw-pressure test (D), with no change from the effect of U69,593 alone in the hot-plate test (C). For all figures, $n = 8$. %MPE = percent maximum possible effect. Data are presented as mean ± SEM.

torphamine (nor-BNI, IC, 24-h pretreatment). Both antagonists blocked the superadditive interaction of U69,593 with cocaine, without affecting the analgesic potency of cocaine alone (Fig. 5A and B).

The same low dose of U69,593 that potentiated the analgesic effect of cocaine was also tested with selective inhibitors of monoamine reuptake. Neither nisoxetine, which selectively blocks reuptake of norepinephrine, nor fluoxetine, which selectively blocks reuptake of serotonin, produced an analgesic response in the hot-plate test (Fig. 6A and B). GBR12909, which selectively blocks reuptake of dopamine produced a significant analgesic response in two of eight animals tested, producing 72% and 100% MPE, respectively. However, there was no significant effect in the group overall. U69,593 did not change the analgesic effect of any of the reuptake inhibitors tested (Fig. 6).

DISCUSSION

Cocaine produced an antinociceptive effect in the hot-plate test, consistent with earlier reports (8). However, it had no effect in the paw-pressure test of antinociception. The analgesic efficacy of cocaine is clearly assay specific.

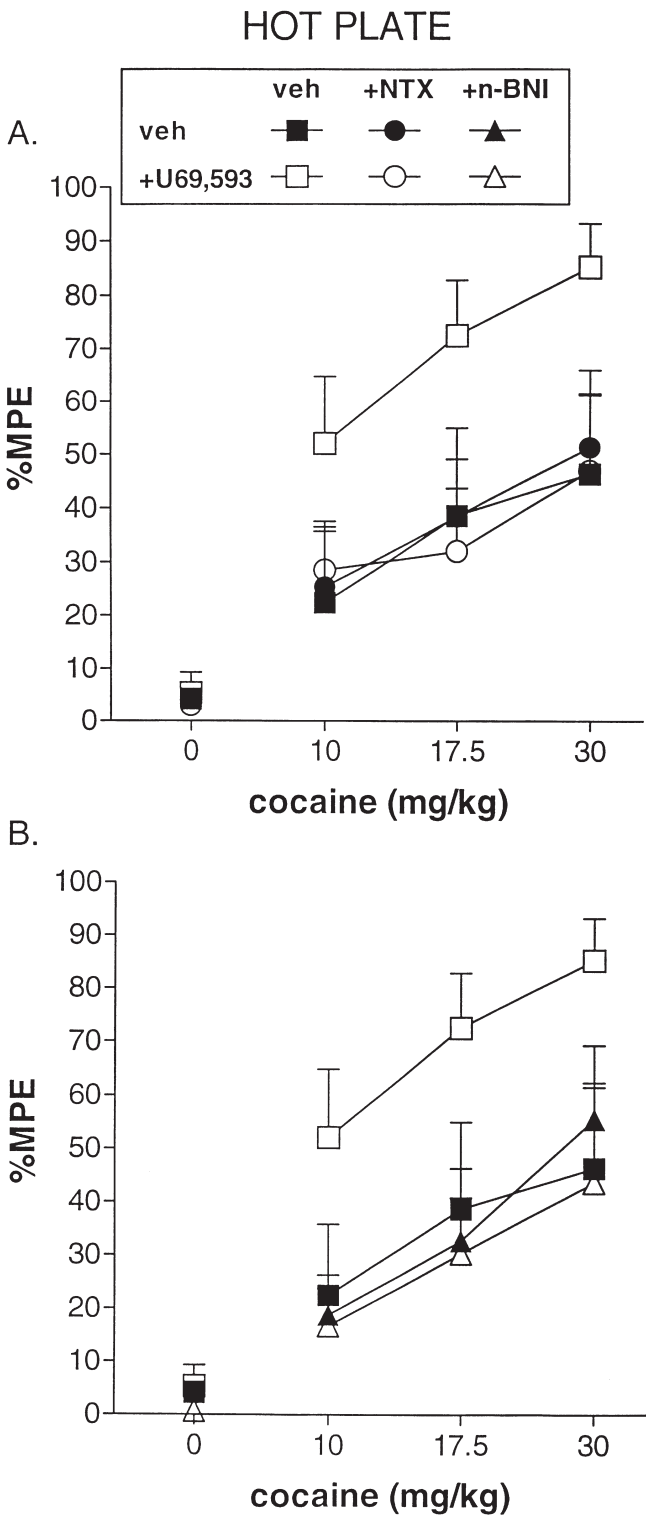
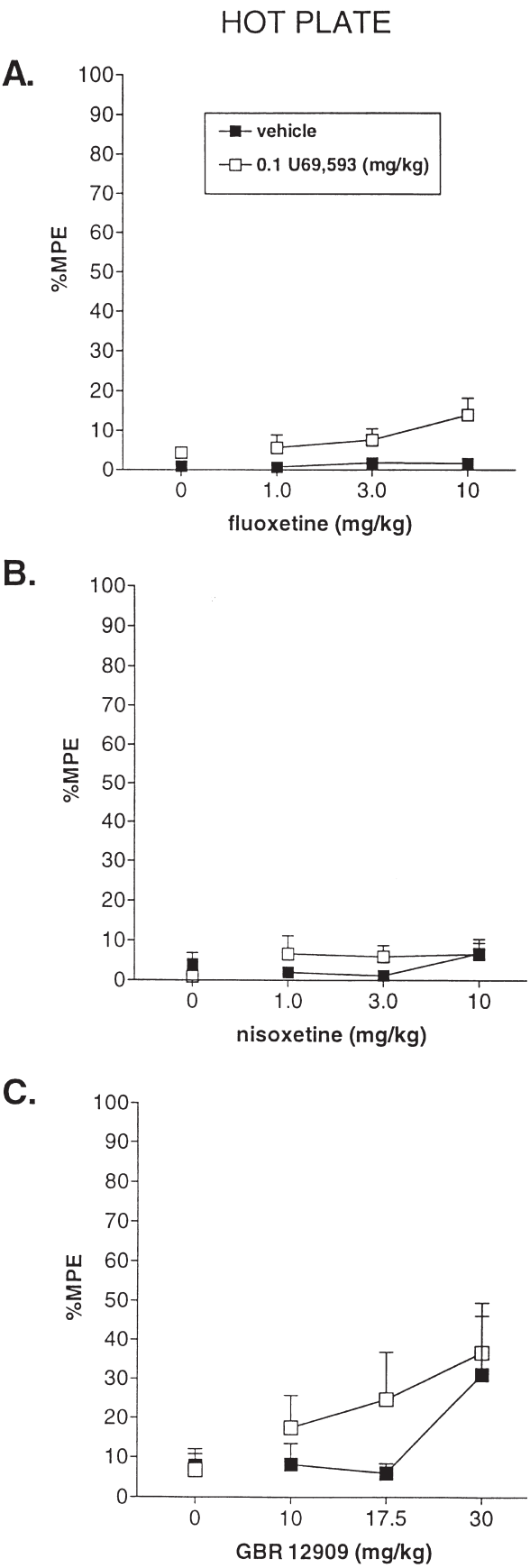


FIG. 5. The superadditive effect of 0.1 mg/kg U69,593 (SC) and cocaine (IP) was antagonized by both 1.0 mg/kg naltrexone SC (NTX; A), and 10 μg nor-binaltorphamine IC (nBNI; B). (A) $n = 6$; (B) $n = 8$. %MPE = percent maximum possible effect. Data are presented as mean ± SEM.



In contrast to cocaine, all three classes of opioid agonists tested produced significant antinociception in both assays. The potency of morphine, U69,593, and DPDPE were comparable in both tests. However, there was some intergroup variability in the antinociceptive response to the higher doses of these drugs. For example, in initial dose–response curves, 10 mg/kg morphine produced 83.2 ± 12.4% maximum possible antinociceptive response in the paw-pressure test. However, a single dose of 10 mg/kg morphine tested alone produced 45.2 ± 13.9% maximum possible antinociceptive effect. The variability could be accounted for by a procedural difference between the two groups, for example, single vs. cumulative dosing schedule. Because of the variability in antinociceptive response, all experiments were conducted within the same group. Therefore, the intergroup variability should not influence the overall results of these experiments.

The antinociceptive effect of morphine, as well as that of other μ-opioid agonists, is clearly potentiated by low doses of cocaine, in rats (4), as well as in other species (see the introduction). The converse was not true in the present study; a low dose of morphine did not potentiate the analgesic effect of cocaine. However, subantinociceptive doses of morphine can change other effects of cocaine. For example, 1.0 mg/kg morphine shifts the cocaine dose–response curve to the left in a drug discrimination procedure (17). However, there is variability in this interaction, because the same results were not seen in a study from this laboratory (19). The only significant interaction seen in this study between cocaine and morphine, potentiation of the antinociceptive effect of morphine by cocaine in the paw-pressure test, is consistent with what was previously shown in other antinociceptive assays (2,4,16). However, in the previous studies cited, when cocaine potentiated the antinociceptive effect of a μ-opioid receptor agonist, cocaine also produced an antinociceptive effect at higher doses alone. In this case, cocaine potentiated the effects of morphine in an assay where it did not produce any antinociceptive response alone up to a dose of 30 mg/kg.

The κ-opioid receptor agonist U69,593, produced different results with cocaine, depending upon dose and antinociceptive assay used. In the paw-pressure test, the antinocicepetive effect of a high dose of U69,593 was attenuated by cocaine. The same attenuation of the antinociceptive effect of U69,593 by cocaine was previously reported in rhesus monkeys using the tail-withdrawal assay (2). In contrast, a subeffective dose of U69,593 potentiated the antinociceptive effect of cocaine in the hot-plate test. This conclusion is based upon the "effect-addition" model of drug interaction. It should be noted that there are limitations in the conclusions that can be drawn when using this model of drug interaction (20); however, it is a reasonable way to address the question of drug synergy. In this case, the use of other statistical analysis methods (i.e., isobolographic analysis) was not possible because the relevant data did not share common points on the ordinate. Despite this, the fact that a very low dose of U69,593 (0.1 mg/kg) that had no antinociceptive activity alone produced such a dramatic increase in the antinociceptive effect produced by cocaine suggests that the effect produced by the combination of 0.1 mg/kg U69,593 and cocaine was superadditive. In addition,

FIG. 6. Combinations of 0.1 mg/kg U69,593 (SC) and (A) fluoxetine (IP; $n = 8$); (B) nisoxetine (IP; $n = 6$); and (C) GBR12909 (IP; $n = 8$). None of the combinations tested produced results greater than U69,593 alone. %MPE = percent maximum possible effect. Data are presented as mean ± SEM.

this effect is modulated through κ-opioid receptors, because it can be blocked with both the general opioid antagonist naltrexone, and the selective κ-opioid receptor antagonist norbinaltorphamine.

In contrast to the interactions between U69,593 and cocaine, no significant interactions were seen between U69,593 and the selective inhibitors of neuronal reuptake. However, each of the uptake inhibitors used can produce antinociception alone or change the response to analgesics. For example, 7.5 mg/kg GBR12909 did not produce an effect alone, but it did attenuate the antinociceptive effect of buspirone (14). Nisoxetine potentiated the antinociceptive effect of morphine (5), while fluoxetine produced antinociception in both the writhing (13) and the tail-flick tests (21). However, as much as 40 mg/kg fluoxetine was needed to produce a significant antinociceptive effect. Therefore, in this study, the doses of fluoxetine used were clearly in the subanalgesic range. Because the results in our experiments with the selective inhibitors of neuronal reuptake were negative, it is not clear what neurotransmitter system(s) is involved in the interactions between cocaine and U69,593. However, it is very interesting that, depending upon the dose combinations of U69,593 and cocaine, and the analgesic assay used, an apparent superadditive effect vs. a subadditive effect occurred.

The differences between opioid modulation of cocaine-induced antinociception and cocaine modulation of opioid-induced antinociception suggest a difference between the pathways controlling these effects. For example, cocaine reliably potentiates the analgesic effect of morphine in a number of tests, while a subanalgesic dose of morphine failed to alter the antinociceptive effect of cocaine in the current study. Based upon this, there is no apparent μ-opioid modulation of the supraspinal, descending, and dopaminergic pathway thought to control cocaine-induced analgesia. In contrast, cocaine is able to affect morphine-induced analgesia either through this dopaminergic pathway, or at sites in the pathway(s) mediating morphine-induced analgesia [see (9)].

In conclusion, the analgesic effect of cocaine was potentiated by a low dose of a κ-opioid receptor agonist, U69,593. Although cocaine has an analgesic effect in animals, the effect is not robust and is not consistently modified by doses of opioid agonists that modify other effects of cocaine in animals.

ACKNOWLEDGEMENTS

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REFERENCES

1. Eddy, N. B.; Leimbach, D.: Synthetic analgesics II. Dithienylbutenyl- and dithienylbutylamines. J. Pharmacol. Exp. Ther. 107:385–393; 1953.
2. Gatch, S. D.; Negus, S. S.; Butelman, E. R.; Mello, N. K.: Antinociceptive effects of cocaine/opioid combinations in rhesus monkeys. J. Pharmacol. Exp. Ther. 275:1346–1354; 1995.
3. Jones, D. N. C.; Holtzman, S. G.: Long term κ-opioid receptor blockade following nor-binaltorphamine. Eur. J. Pharmacol. 215:345–348; 1992.
4. Kauppila, T.; Mecke, E.; Pertovaara, A.: Enhancement of morphine-induced analgesia and attenuation of morphine-induced side-effects by cocaine in rats. Pharmacol. Toxicol. 71:173–178; 1992.
5. Kellstein, D. E.; Malseed, R. T.; Ossipov, M. H.; Goldstein, F. J.: Effect of chronic treatment with tricyclic antidepressants upon antinociception induced by intrathecal injection of morphine and monoamines. Neuropharmacology 27:1–14; 1988.
6. Kelly, P. H.; Iversen, S. D.: Selective 6-OHDA-induced destruction of mesolimbic dopamine neurons: Abolition of psychostimulant-induced locomotor activity in rats. Eur. J. Pharmacol. 20:45–56; 1976.
7. Kiritsy-Roy, J. A.; Shyu, B. C.; Danneman, P. J.; Morrow, T. J.; Belczynski, C.; Casey, K. L.: Spinal antinociception mediated by a cocaine-sensitive dopaminergic supraspinal mechanism. Brain Res. 644:109–116; 1994.
8. Lin, Y.; Morrow, T. J.; Kiritsy-Roy, J. A.; Terry, L. C.; Casey, K. L.: Cocaine: Evidence for supraspinal, dopamine-mediated, non-opiate analgesia. Brain Res. 479:306–312; 1989.
9. Lipp, J.: Possible mechanisms of morphine analgesia. Clin. Neuropharmacol. 14:131–147; 1991.
10. O'Callaghan, J. P.; Holtzman, S. G.: Quantification of the analgesic activity of narcotic antagonists by a modified hot-plate procedure. J. Pharmacol. Exp. Ther. 192:497–505; 1975.
11. Pertovaara, A.; Mecke, E.; Carlson, S.: Attempted reversal of cocaine-induced antinociceptive effects with naloxone, and opioid antagonist. Eur. J. Pharmacol. 192:349–353; 1991.
12. Randall, L. O.; Selitto, J. J.: A method for measurement of analgesic activity on inflamed tissue. Arch. Int. Pharmacodyn. Ther. 111:409–419; 1957.
13. Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D.: Absolute configurations and pharmacological activities of the optical isomers of fluoxetine, a selective serotonin-uptake inhibitor. J. Med. Chem. 31:1412–1417; 1988.
14. Rogers, L. W.; Giordano, J.: Effects of systemically administered monoamine reuptake blocking agents on patterns of buspirone-induced analgesia in rats. Life Sci. 47:961–969; 1990.
15. Shyu, B. C.; Kiritsy-Roy, J. A.; Morrow, T. J.; Casey, K. L.: Neurophysiological, pharmacological and behavioral evidence for medial thalamic mediation of cocaine-induced dopaminergic analgesia. Brain Res. 572:216–223; 1992.
16. Sierra, V.; Duttaroy, A.; Lutfy, K.; Candido, J.; Billings, B.; Zito, S. W.; Yoburn, B. C.: Potentiation of opioid analgesia by cocaine: The role of spinal and supraspinal receptors. Life Sci. 50:591–597; 1992.
17. Suzuki, T.; Mori, T.; Tsuji, M.; Misawa, M.: Interaction between discriminative stimulus effects of cocaine and morphine. Jpn. J. Pharmacol. 67:341–347; 1995.
18. Tella, S. R.: Possible novel pharmacodynamic action of cocaine: Cardiovascular and behavioral evidence. Pharmacol. Biochem. Behav. 54:343–354; 1996.
19. Woolfolk, D. R.; Holtzman, S. G.: μ-, δ-, and κ-opioid receptor agonists do not alter the discriminative stimulus effects of cocaine and d-amphetamine. Drug Alcohol Depend. 48:209–220; 1997.
20. Woolverton, W. L.: Analysis of drug interactions in behavioral pharmacology. In: Thompson, T.; Dews, P. B.; Barrett, J. E., eds. Neurobehavioral pharmacology. Hillside, NJ: Lawrence Erlbaum Associates; 1987:275–302.
21. Xu, W.; Qiu, X. C.; Han, J. S.: Serotonin receptor subtypes in spinal antinociception in the rat. J. Pharmacol. Exp. Ther. 269:1182–1189; 1994.