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Cocaine: Evidence for NMDA- and Opioid-Mediated Antinociception in the Tail-Flick Test

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USHIJIMA, I. AND A. HORITA. *Cocaine: Evidence for NMDA- and opioid-mediated antinociception in the tail-flick test.* PHARMACOL BIOCHEM BEHAV 44(2) 365-370, 1993.—Cocaine (20–40 mg/kg, IP) produced in a rat tail-flick test a bimodal antinociceptive effect, the first peak appearing 5–30 min and the second 3–6 h after injection. The secondary, but not the initial, cocaine antinociception was blocked by naloxone (2 mg/kg, IP). The secondary antinociceptive action was also increased by a dose of the κ-receptor agonist, trans-(±)-3,4-di-chloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl) cyclohexyl]-benzene-acetamide methane sulfonate (U-50,488H) (5 mg/kg, IP), which by itself had no antinociceptive effect. Both the initial and secondary antinociceptions were increased following daily cocaine (20 mg/kg, IP) administration for 4 days. 3-(2-Carboxy-piperazin-4-yl) propyl-1-phosphonic acid (CPP) and (+)-5-methyl-10,11-dihydro-5*H*-dibenzo [*a,d*] cyclohepten-5,10-imine (MK-801), competitive and noncompetitive NMDA antagonists, respectively, inhibited both the initial and secondary cocaine antinociceptions. Although neither NMDA (5 mg/kg, IP) nor cocaine in lower doses (10 mg/kg, IP) alone produced antinociception, cocaine administered after NMDA produced antinociception. The dopamine D_1 receptor agonist 1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepin-7-*ol* (SK&F38393) enhanced both initial and secondary cocaine antinociceptions, while the D_1 receptor antagonist *R*(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-*ol* (SCH23390) reversed this potentiating effect. The D_2 receptor agonist quinpirole and its antagonist sulpiride exerted opposite effects of their respective D_1 counterparts. Both D_2 agonist and antagonist were without activity by themselves. These results suggest that the initial cocaine antinociception may be produced via an activation of the NMDA receptor-Ca^{++} ionophore complex and modulated by a dopaminergic system that does not by itself exert intrinsic activity. The secondary cocaine antinociception may be mediated by an activation of an opioid system, in particular the κ-receptors. The initial activation of the NMDA-Ca^{++} ionophore complex may trigger subsequent activation of the opioid system, which results in the long-lasting secondary cocaine antinociception.

Cocaine   Bimodal antinociception   NMDA complex   Opioid system   Dopaminergic system   Rats

THE CENTRAL pharmacological action of systemically administered analgesic drugs is thought to be mediated primarily through neural mechanisms involving opiate receptors (5,17). Cocaine has been reported to produce nonopioid antinociception which is attenuated by dopamine D_1 and D_2 antagonists, and is unaffected by naloxone, an opiate antagonist. The antinociceptive effect of cocaine is rapid in onset (within 5 min) and shorter in duration (18). Cocaine, however, potentiates opiate analgesia (22), and this potentiation is inhibited by naloxone. Cocaine also stimulates the secretion of opioid peptides such as β-endorphin (7,23) and dynorphin (28,29). Subchronic administration of cocaine (20 mg/kg/day for 4 days) increased the level of striatonigral dynorphin, which is a κ-receptor activator (28).

The periaqueductal gray (PAG) has been shown to be an important CNS site for the analgesic action of morphine. An injection of morphine (15) or of β-endorphin (16) into this brain site results in a naloxone-reversible analgesic action, presumably mediated by opiate receptors that have been demonstrated to be present autoradiographically (11). Autoradiographic studies have also shown the presence of *N*-methyl-D-aspartate (NMDA) receptors in the PAG (9,10). Administration of NMDA into the rat PAG results in a potent and rapid analgesia (14). NMDA given with morphine potentiated

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morphine analgesia, which was blocked by AP-7, an NMDA competitive antagonist (14). NMDA receptors have attracted considerable attention for their potential roles in various CNS disorders such as epilepsy, spasticity, and ischemic neuronal degeneration (21,27). The NMDA receptor is coupled to a calcium permeable ion channel (6,19) that is gated by Mg ions in a voltage-dependent fashion (24,20). Recently, it was reported that the NMDA receptor played a facilitatory role in the regulation of nigrostriatal and mesolimbic dopaminergic systems (3,13). We found that cocaine-induced antinociception produced a bimodal pattern of antinociception (after 10 min and 3-6 h after cocaine administration). The present study was undertaken to elucidate the functional roles of the NMDA-ionophore complex, the opioid and dopaminergic systems on the cocaine-induced bimodal antinociception.

METHOD

Animals

Healthy, male Wistar rats (300–380 g) were permitted food and water ad lib except during the time of the experiments. All trials and breeding were carried out at an environmental temperature of 23 ± 1°C with a 12 L : 12 D cycle.

Measurement of Antinociception

The tail-flick test was used to measure antinociception. It consisted of measuring the latency period at which a rat whose body was wrapped in a towel flicked its tail away from a beam of focused light (i.e., noxious heat, cut-off time = 20 s). Values were expressed according to the equation: the latency for tail flick (seconds) after drug − the latency for tail flick before drug = value (seconds) (in all figures).

Administration of Drugs

In the acute treatment, cocaine (10–40 mg/kg) was injected IP. To examine influences of drugs on cocaine antinociception, we administered naloxone (2.0 mg/kg) and trans-(±)-3,4-di-chloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl) cyclohexyl]-benzene-acetamide methane sulfonate (U-50,488H) (5.0 mg/kg) 5 min and 3-(2-carboxy-piperazin-4-yl) propyl-1-phosphonic acid (CPP) (5.0 and 10 mg/kg), (+)-5-methyl-10,11-dihydro-5*H*-dibenzo [*a,d*] cyclohepten-5,10-imine (MK-801) (0.1 and 0.4 mg/kg), NMDA (5.0 mg/kg), 1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepin-7-*ol* (SK&F38393) (5.0 mg/kg), quinpirole (1.0 mg/kg), and *R*(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepin-7-*ol* (SCH23390) (0.2 mg/kg) 15 min before cocaine. Sulpiride (30 mg/kg) was administered 60 min before cocaine (20 mg/kg).

In the subchronic treatment, rats received subchronic treatment of cocaine (20 mg/kg/day, IP, for 4 days). The long-lasting antinociceptive effect of subchronic cocaine was measured 24, 48, and 72 h and 1 week after the last cocaine administration (Table 1). A challenge dose of cocaine (20 mg/kg, IP) was administered 48 h after its last injection (Fig. 1). Naloxone (2 mg/kg, IP) and U-50,488H (5 mg/kg, IP) were also administered 48 h after the last cocaine (20 mg/kg) injection (Table 2).

Drugs

Drugs used were cocaine HCl (Takeda Ltd. Osaka, Japan), morphine HCl (Takeda), naloxone HCl (Sigma Chemical Co., St. Louis, MO), U-50,488H (Upjohn Co., Kalamazoo, MI), CPP (Tocris, Bickhurst Hill), MK-801 hydrogenmaleate [Research Biochemicals, Inc. (RBI), Natick, MA], NMDA (Sigma), SK&F38393 HCl (RBI), SCH23390 HCl (RBI), quinpirole HCl (RBI), and sulpiride HCl (Sigma). SK&F38393 and quinpirole were dissolved in ethanol (0.1 ml) and subsequently diluted with saline. Sulpiride HCl was suspended in 3% Tween-80 solution, and the other drugs were dissolved in saline. These drugs were injected IP in a volume of 1 ml/kg. Doses are expressed as the salt form. Injection of vehicle did not produce any abnormal symptoms.

Statistical Analysis

The latency of antinociception was measured three times and expressed as medians. Statistical analysis was done using

TABLE 1

TIME COURSE OF EFFECTS OF WITHDRAWAL OF SUBCHRONIC ADMINISTRATION OF COCAINE (20 mg/kg/DAY FOR 4 DAYS) ON ANTINOCICEPTION

Treatments	Latency of Tail Flick (seconds)	*n*
24 h after the last dose		
Saline group	4.9 ± 0.2	16
Cocaine group	8.2 ± 0.5*	21
48 h after the last dose		
Saline group	4.3 ± 0.2	16
Cocaine group	8.5 ± 0.4*	21
72 h after the last dose		
Saline group	5.0 ± 0.3	8
Cocaine group	9.2 ± 0.5*	8
1 week after the last dose		
Saline group	4.5 ± 0.2	8
Cocaine group	8.0 ± 0.4*	8

Values are means ± SEM of the sample number.
*$p < 0.05$ as compared to the respective saline-treated group.

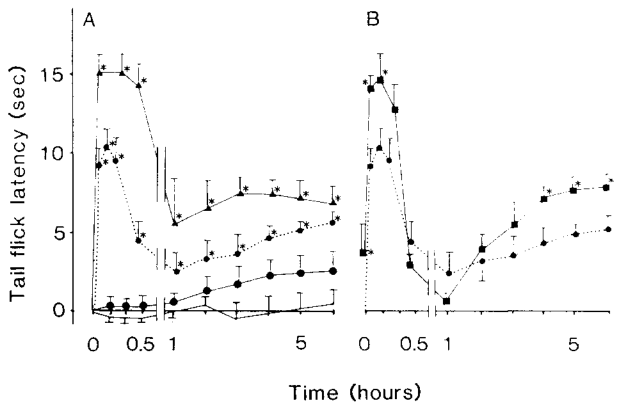

FIG. 1. Time-effect relationships of the antinociceptive effect of several doses of cocaine in (A) acutely treated rats and (B) rats that had received a subchronic pretreatment with cocaine. Each value is mean ± SEM. (A). Cocaine 10 mg/kg (●) (n = 8), cocaine 20 mg/kg (broken line) (n = 18), cocaine 40 mg/kg (▲) (n = 8). *$p < 0.05$ as compared to saline (solid line) (n = 6). (B). Cocaine (20 mg/kg) effect in rats readministered 48 h after the last injection of cocaine IP/day for 4 days (■) (n = 10). *$p < 0.05$ as compared to cocaine 20 mg/kg (broken line). All drugs were given by IP injection.

TABLE 2

EFFECTS OF OPIOID DRUGS ON THE INCREASED ANTINOCICEPTION IN 48 h WITHDRAWAL OF SUBCHRONIC ADMINISTRATION OF COCAINE (20 mg/kg/DAY FOR 4 DAYS)

Treatments (mg/kg)	Interval before testing (min)	Latency of tail flicks (seconds)	n
Subchronic saline group			
Saline	30	4.3 ± 0.2	16
Naloxone (2)	30	4.5 ± 0.2	8
U-50,488H (5)	30	4.8 ± 0.3	8
Subchronic cocaine group			
Saline	30	8.5 ± 0.4*	21
Naloxone (2)	30	3.9 ± 0.2†	8
U-50,488H (5)	30	13.8 ± 0.8†	10
Naloxone + U-50,488H	30, 30	4.1 ± 0.3‡	8

Each value is expressed as mean ± SEM.

*†‡$p < 0.05$, significant difference from subchronic saline group (control), subchronic cocaine group (control), and subchronic group (U-50,488H), respectively.

Kruskal-Wallis one-way analysis of variance (ANOVA) and the two tailed Mann-Whitney *U*-test.

RESULTS

Time-Effect Relationship of Cocaine Antinociception

Cocaine injected IP produced two antinociceptive peaks at doses of 20 and 40 mg/kg, but not at 10 mg/kg. The initial antinociception showed a rapid onset and transient duration, whereas the secondary response had a slower onset and longer duration of action (Fig. 1A). Cocaine readministered to cocaine-pretreated rats (20 mg/kg, IP, for 4 days, last dose 48 h previously) exhibited markedly increased initial and secondary antinociceptive responses. Part of this increase may have resulted from the higher baseline (time 0) in cocaine-pretreated rats (Fig. 1B), which showed a doubling of the antinociceptive threshold. This increased threshold persisted for at least 1 week, as shown in Table 1. During the antinociceptive period, rats showed an increase in exploratory and stereotypical behaviors, but these did not interfere with execution of the tests.

Effects of the Opioid System on Cocaine Antinociception

Pretreatment of rats with naloxone (2 mg/kg, IP) completely inhibited the secondary, but not the initial, antinociceptive peak of cocaine (20 and 40 mg/kg, IP) (Figs. 2A and 2B). Moreover, U-50,488H (5 mg/kg, IP) administered before cocaine (20 mg/kg, IP) increased the secondary antinociceptive response, although U-50,488H itself had no activity (Fig. 2C). Naloxone completely inhibited this potentiation of cocaine antinociception by U-50,488H (Fig. 2D).

The increased antinociceptive threshold seen 48 h after subchronic administration of cocaine (20 mg/kg/day, IP, for 4 days) was inhibited by naloxone but potentiated by U-50,488H. Naloxone also blocked this potentiation by U-50,488H and restored antinociceptive threshold levels to those of saline controls. These results are summarized in Table 2.

Involvement of NMDA-Ion Complex System in Cocaine Antinociception

When administered after CPP (5 mg/kg, IP) or MK-801 (0.1 and 0.4 mg/kg, IP), both the primary and secondary components of cocaine antinociception were reduced in a dose-dependent manner (Figs. 3A and 3B). Although neither NMDA (5 mg/kg, IP) nor cocaine (10 mg/kg, IP) alone produced antinociception, cocaine administered after NMDA exerted antinociception (Fig. 3C) while CPP (10 mg/kg, IP) antagonized this potentiating effect (Fig. 3D). Figures 4A and 4B show the stimulatory effect of U-50,488H (5 mg/kg, IP) on the secondary antinociceptive effect of cocaine and its inhibition by CPP and MK-801.

Effects of Dopaminergic Drugs on Cocaine Antinociception

SK&F38393 (5.0 mg/kg, IP) potentiated the initial and secondary components of cocaine antinociception, and SCH23390 (0.2 mg/kg, IP) blocked this potentiation but not the cocaine antinociception itself (Figs. 5A and 5B).

In contrast, quinpirole (2 mg/kg, IP) inhibited both components of cocaine antinociception. Sulpiride (30 mg/kg, IP) increased the initial antinociception of cocaine but decreased the secondary component (Fig. 5C). The combined treatment with sulpiride and quinpirole antagonized the inhibitory effect of quinpirole and stimulatory effect of sulpiride on initial cocaine antinociception and tended to reverse the inhibitory effect of quinpirole on secondary cocaine antinociception (Fig. 5D). Neither SK&F38393 nor sulpiride alone produced antinociception, nor did SCH23390 or quinpirole exert any nociceptive effect (data not shown).

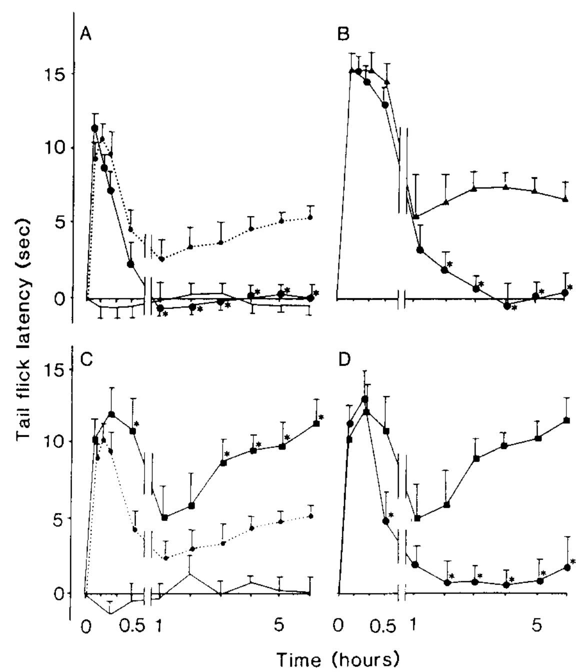

FIG. 2. Effects of opioid system on cocaine antinociception. (A). Naloxone 2 mg/kg (solid line) ($n = 6$), naloxone 2 mg/kg + cocaine 20 mg/kg (●) ($n = 8$). *$p < 0.05$ as compared to cocaine 20 mg/kg (broken line). (B). Naloxone 2 mg/kg IP + cocaine 40 mg/kg (●) ($n = 8$). *$p < 0.05$ as compared to cocaine 40 mg/kg (▲). (C). U-50,488H 5 mg/kg (solid line) ($n = 6$), U-50,488H 5 mg/kg + cocaine 20 mg/kg (■) ($n = 8$). *$p < 0.05$ as compared to cocaine 20 mg/kg (broken line). (D). Naloxone 2 mg/kg + U-50,488H 5 mg/kg + cocaine 20 mg/kg (●) ($n = 8$). *$p < 0.05$ as compared to U-50,488H 5 mg/kg + cocaine 20 mg/kg (■).

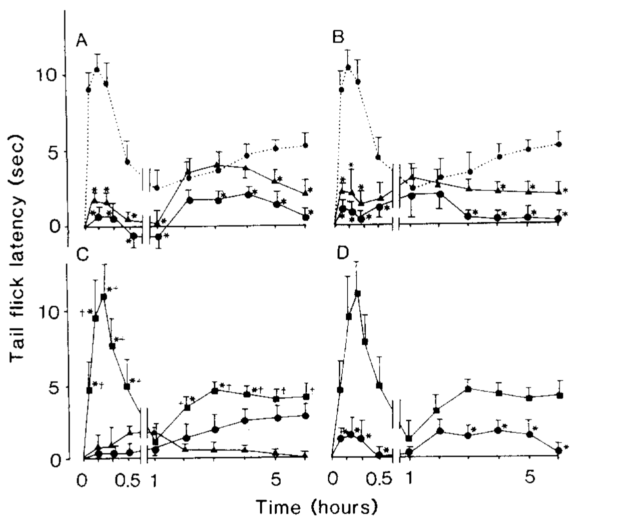

FIG. 3. Involvement of NMDA-ionophore complex in cocaine antinociception. (A). CPP 5 mg/kg + cocaine 20 mg/kg (▲) (n = 8), CPP 10 mg/kg + cocaine 20 mg/kg (●) (n = 8). $*p < 0.05$ as compared to cocaine 20 mg/kg (broken line). (B). MK-801 0.1 mg/kg + cocaine 20 mg/kg (▲) (n = 8), MK-801 0.4 mg/kg + cocaine 20 mg/kg (●) (n = 8). $*p < 0.05$ as compared to cocaine 20 mg/kg (broken line). (C). Cocaine 10 mg/kg (●) (n = 8), NMDA 5 mg/kg (▲) (n = 8), NMDA 5 mg/kg + cocaine 10 mg/kg (■) (n = 10). $*\dagger p$ = 0.05 as compared to cocaine 10 mg/kg and NMDA 5 mg/kg, respectively. (D). CPP 10 mg/kg + NMDA 5 mg/kg + cocaine 10 mg/kg (●) (n = 10). $*p < 0.05$ as compared to NMDA 5 mg/kg + cocaine 10 mg/kg (■).

DISCUSSION

Acute systemic administration of cocaine to rats produced in a dose-dependent manner two types of antinociceptive effects that could be differentiated by their temporal and pharmacological properties. The initial antinociception had a rapid onset but a short duration, and the secondary response had a slower onset with a weaker and longer duration. Naloxone exerted no effect on initial response but inhibited secondary antinociception. The initial nonopiate antinociception could be interpreted as occurring in response to sudden pain, while the latter opiate-mediated antinociception could occur more slowly as a reinforcement of the former in response to continuous nociception.

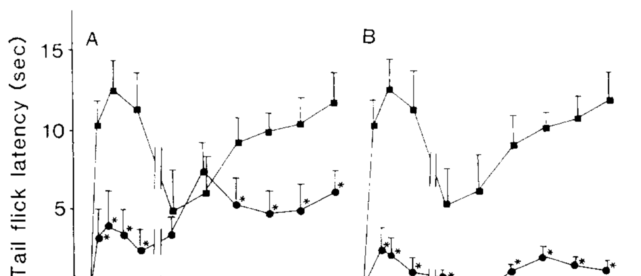

FIG. 4. Interaction between NMDA and opioid systems on cocaine antinociception. (A). U-50,488H 5 mg/kg + cocaine 20 mg/kg (■) (n = 8), CPP 10 mg/kg + U-50,488H 5 mg/kg + cocaine 20 mg/kg (●) (n = 10). $*p < 0.05$ as compared to U-50,488H (5 mg/kg) + cocaine (20 mg/kg) (■). (B). MK-801 0.4 mg/kg + U-50,488H 5 mg/kg + cocaine 20 mg/kg (●) (n = 10). $*p < 0.05$ as compared to U-50,488H 5 mg/kg + cocaine 20 mg/kg (■).

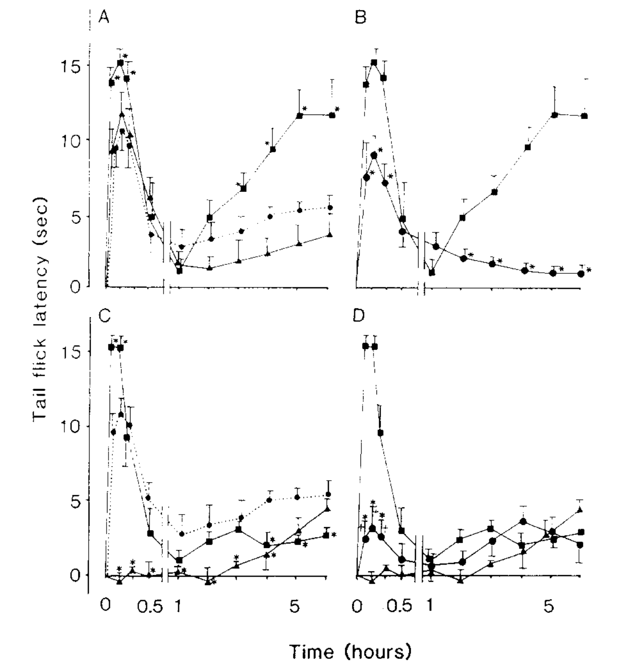

FIG. 5. Effects of dopamine agonists and antagonists on cocaine antinociception. (A). SK&F38393 5 mg/kg + cocaine 20 mg/kg (■) (n = 8), SCH23390 0.2 mg/kg + cocaine 20 mg/kg (▲) (n = 8). $*p < 0.05$ as compared to cocaine (20 mg/kg) (broken line). (B). SCH23390 0.2 mg/kg + SK&F38393 5 mg/kg + cocaine 20 mg/kg (●) (n = 10). $*p < 0.05$ as compared to SK&F38393 (5 mg/kg) + cocaine (20 mg/kg) (■). (C). Quinpirole 2 mg/kg + cocaine 20 mg/kg (▲) (n = 8), sulpiride 30 mg/kg + cocaine 20 mg/kg (■) (n = 8). $*p < 0.05$ as compared to cocaine (20 mg/kg) (broken line). (D). Sulpiride 30 mg/kg + quinpirole 2 mg/kg + cocaine 20 mg/kg (●) (n = 10). $*\dagger p < 0.05$ as compared to quinpirole 2 mg/kg + cocaine 20 mg/kg and sulpiride 30 mg/kg + cocaine 20 mg/kg, respectively.

Sivam (28) reported that a single dose of cocaine did not affect the levels of met-enkephalin, substance P, or dynorphin A (1-8) in the striatum and substantia nigra. However, a subchronic treatment regimen of cocaine increased the striatal and nigral content of dynorphin without affecting the substance P or met-enkephalin levels 24 h after the last dose of the drug. The effects persisted for at least 4 days. Further, extrapyramidal and limbic dynorphin-like immunoreactivity content markedly increase after cocaine treatment (20 and 30 mg/kg, IP). In the present study, the secondary antinociception produced by 20–40 mg/kg IP cocaine was slow in onset but persisted for a longer period of time (3–6 h). Following daily cocaine (20 mg/kg, IP) administration for 4 days, the increased antinociceptive response persisted for at least 1 week. This secondary antinociception was inhibited by naloxone and potentiated by U-50,488H, a κ-receptor agonist (4), at a dose ineffective by itself. These results suggest that the secondary antinociceptive effect of cocaine is mediated by an opioid system, possibly by κ-receptor activation. In this procedure, repeatedly measuring tail-flick latency, which includes restraint, may introduce a stress component that can induce antinociceptive effects. These effects may be opioid sensitive depending upon the conditions of the imposed stress (1). There is evidence that dynorphin content in the nucleus accumbens was not elevated at 1 h after cocaine (30 mg/kg, IP); it significantly increases by 8 h and returned to control levels within 24 h. Consequently, dynorphin systems were substantially influenced by cocaine (29).

The present study further suggests that the NMDA-ionophore system was important in mediating the initial cocaine antinociception because NMDA potentiated and the competitive and noncompetitive NMDA antagonists, CPP and MK-801, respectively, inhibited the response. Moreover, neither NMDA nor cocaine alone produced antinociception, but their combined treatment did, indicating that the initial cocaine effect might involve an activation of the NMDA-ionophore complex. The opioid-mediated secondary antinociceptive effect was inhibited by CPP and MK-801, suggesting that an activation of the NMDA-ionophore complex may be a triggering factor for inducing subsequent opioid antinociceptive effect.

In this study, D_1 and D_2 receptor agonists exerted differential effects on the initial and secondary components of cocaine antinociception, that is, an increase for the D_1 agonist SK&F38393 and a decrease for the D_2 agonist quinpirole. These effects of dopamine agonists were reversed by their respective antagonists. Because of the opposite effects of the D_1 and D_2 dopamine systems on cocaine antinociception, we may conclude that these two receptor subtypes were independent of each other in influencing cocaine antinociception. Because neither drug induced antinociception nor nociception by themselves, it may be assumed that the dopamine system is not exerting an intrinsic "tone" in mediating nociception thresholds. With regard to the interaction between opioid (dynorphin) and the dopamine systems, there is evidence that neostriatal dynorphin levels are decreased by D_2 agonists while stimulation of the D_1 receptors result in an increase in nigral dynorphin levels (25). In this study, because this is certainly not the case for the locomotor and dopamine releasing effects of cocaine (12), which are back to normal by 2 h, the dopaminergic effects of cocaine on initial NMDA-mediated antinociception may reflect the secondary opioid-mediated antinociception.

It is unlikely that the antinociceptive effect of cocaine may be due to its peripheral actions, such as through release of adrenal steroids or because of its local anesthetic effect. Our findings that cocaine antinociception is dependent upon dopamine, the NMDA-ion complex, and the opioid mechanisms suggests the participation of dopamine-, glutamate-, and opioid-containing mesolimbic structures. These structures have been shown to be important for maintaining cocaine-induced behaviors, that is, self-stimulation, motor stimulant, and reinforcing properties (2,8), and convulsion (26) in the rat and mouse.

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