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Differential Effects of NMDA Receptor and Dopamine Receptor Antagonists on Cocaine Toxicities

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SHIMOSATO, K., R. J. MARLEY AND T. SAITO. *Differential effects of NMDA receptor and dopamine receptor antagonists on cocaine toxicities.* PHARMACOL BIOCHEM BEHAV **51**(4) 781–788, 1995.—Cocaine produces not only euphoric effects but also a wide range of detrimental effects, including seizures and lethality. The present study examined the involvement of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptors and the dopamine D_1 and D_2 receptors in seizure activity and lethality observed following single and repeated injections of cocaine in ddY mice. Repeated injections of 60 mg/kg cocaine resulted in the development of sensitization to the convulsant effects of cocaine during an initial 3 or 4 days, followed by the development of tolerance at day 5 and day 6. Repeated injections of 90 mg/kg cocaine augmented the lethal effect of cocaine progressively over the course of treatment. Treatment with 0.1–0.4 mg/kg of the noncompetitive NMDA receptor antagonist, MK-801, prevented the development of sensitization to cocaine-induced seizures in a dose-dependent manner, and attenuated partially the cocaine-induced lethality. In contrast, treatment with 10–50 mg/kg of the dopamine D_2 receptor antagonist, sulpiride, had no effects on the development of sensitization and tolerance to cocaine-induced seizures. On the other hand, treatment with 0.1–0.5 mg/kg of the dopamine D_1 receptor antagonist, SCH 23390, not only prolonged the latency to 90 mg/kg cocaine-induced seizures but also delayed the development of sensitization to the convulsant effects of cocaine. The increased lethality observed following repeated injection of cocaine was unaffected by treatment with SCH 23390, but was severely aggravated by treatment with sulpiride. These results suggest that the development of sensitization to cocaine-induced seizures and lethality is primarily associated with NMDA receptor-mediated mechanisms, but that the dopamine D_1 and D_2 receptors may also be involved subordinately in cocaine-induced seizures and lethality, respectively, in mice.

Cocaine Sensitization Toxicity Seizures Lethality MK-801 SCH 23390 Sulpiride

COCAINE is a widely abused drug that has many adverse consequences including the induction of seizures and lethality. A survey on cocaine abusers reported that 11% of those abusers complained of seizures and loss of consciousness (34). Another retrospective survey documented that 65% of emergency room admissions for illicit drug-induced seizures were associated with cocaine abuse (1). Furthermore, it has been noted that intermittent cocaine use may result in the kindling of a complex partial seizure and subsequent adverse cardiac dysfunction leading to cocaine-related death (17). Acute injection of sufficiently high doses of cocaine produces convulsant and lethal effects in mice and rats. However, even subthreshold doses of cocaine result in a progressive increase in sensitivity to its convulsant and lethal effects when injected repeatedly (5,12,19).

The psychostimulant and euphoric actions of cocaine are associated with a blockade of dopamine uptake in the central nervous system (7,21). A number of investigators have examined the possible role of the dopaminergic mechanisms in cocaine-induced seizures and death. There were no differences in sensitivity to the acute, convulsant effects of cocaine between rats depleted of brain dopamine and control animals (14). However, the dopamine D_2 receptor antagonist, sulpiride, potentiated the convulsant effects of cocaine in spontane-

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ously hypertensive rats (23), whereas another D_2 antagonist haloperidol decreased the incidence of seizures after acute cocaine injection in rats (3). In addition, the lethal effects of cocaine were suppressed by the D_1 receptor antagonist, SCH 23390 (4,36), but not by haloperidol (3,36). Thus, there is still controversy regarding the involvement of dopamine receptors in the convulsant effect of an acute injection of cocaine. Similarly, little is known about the role of the dopamine receptors in cocaine-induced seizures and lethality following repeated injection of the drug.

Repeated injection of low doses of cocaine results in the development of sensitization to locomotor- and stereotypy-inducing effects in animals (19,27). The phenomenon has been termed behavioral sensitization or reverse tolerance. A number of studies have shown that the development of behavioral sensitization caused by psychomotor stimulants is effectively blocked by MK-801, a potent, indirect antagonist of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors (9,37). It has been proposed that common mechanisms may mediate various manifestations of neuronal plasticity such as memory, long-term potentiation, the development of increased seizure susceptibility (kindling), and behavioral sensitization, as well as drug addiction and mental illness (22,35). MK-801 has been shown not only to block acute seizures induced by a variety of agents (29), but also to suppress the development of amygdala kindled seizures (16,26). NMDA receptor antagonists, including MK-801, decrease the incidence of both seizures and mortality caused by a single injection of cocaine (24) and completely abolish the development of sensitization to cocaine-induced seizures and lethality (8). These findings suggest that the NMDA receptor-mediated mechanisms may be associated with the development of increased susceptibility to cocaine-induced seizures and lethality.

The present study was designed to investigate further the effects of treatments with SCH 23390, sulpiride, and MK-801 on seizure susceptibility and mortality following single and repeated injections of cocaine among ddY mice.

METHOD

Animals

Male ddY mice were obtained from Japan SLC, Inc. (Hamamatsu, Shizuoka) at the age of 5 weeks. Mice were housed four to a cage in the animal facilities under conditions on a constant light : dark cycle (illuminated at 7:00–21:00 h) and 24°C for at least 10 days before testing. Food and water were freely available except during the test sessions. Prior to seizure testing, subjects were placed in a quiet, air-conditioned testing room for at least 30 min. All testing was carried out between 9:00–15:00 h.

Cocaine-Kindled Seizure Test

Cocaine HCl (Shionogi & Co., Osaka, Japan) in physiological saline was injected IP in an injection volume of 0.01 ml/g of body weight at doses of 60 and 90 mg/kg. MK-801 (Merck & Co., Rahway, NJ) was dissolved in physiological saline and injected, SC, at doses of 0.1, 0.2, and 0.4 mg/kg in the same injection volume. SCH 23390 (Schering Corp., Bloomfield, NJ), dissolved in physiological saline, was injected, SC, at doses of 0.1, 0.2, and 0.5 mg/kg in the same injection volume. (−)Sulpiride (Sigma Chemical Co., St. Louis, MO) was dissolved in a minimum quantity of acetic acid, followed by dilution with 5% of glucose, and injected at doses of 10, 20, and 50 mg/kg in the same injection volume. Thirty minutes after pretreatment with the various antagonists and their respective vehicles, sets of four mice were injected, IP, with either saline, 60, or 90 mg/kg of cocaine. They were placed individually in a plastic cage (30 × 40 × 40 cm) for observation of seizure activity. Occurrence of seizures was assessed for at least 12 min after injection of cocaine, and the latency to onset of seizures was recorded for each mouse. The latency value for mice showing no convulsions was defined as 720 s. Cocaine kindling was assessed using a once daily injection regimen for 6 successive days. The numbers of mice used for each pretreatment dose were 12 for the MK-801 experiment, 10 for the SCH 23390, and 9 for sulpiride experiments.

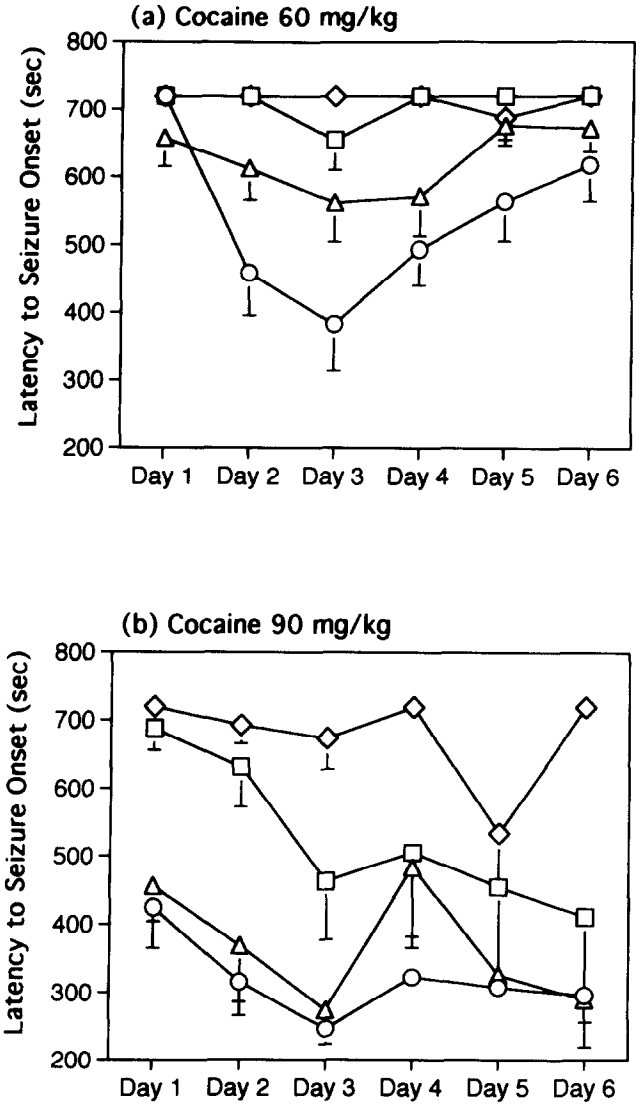

FIG. 1. Effects of MK-801 on cocaine-induced seizures following repeated injections of 60 (a) or 90 (b) mg/kg cocaine among ddY mice. Animals were injected IP with 60 or 90 mg/kg cocaine daily, 30 min after pretreatment with either saline (○) or 0.1 (△), 0.2 (□), or 0.4 (◇) mg/kg of MK-801. Panels illustrate the data presented as the latency to onset of seizures on each day of treatment. Each point and bar represent the mean value of the latency and the standard error, respectively.

Cocaine-induced seizures were defined, as in previous studies (12,13), as either the loss of body posture with convulsant movements in all extremities or as a bout of running and bouncing clonus in which episodes of violent and dramatic uninhibited running and bouncing occurred. At a high dose or following repeated injections, cocaine also produced tonus, a stage of seizure activity characterized by extreme muscle rigidity and the caudal extension of fore- and hindlimbs. Because tonus was always preceded by a clonic seizure, evaluation of cocaine-induced seizures here reflects the occurrence exclusively of clonic seizure activity.

Lethality Test

In order to examine the effects of MK-801, SCH 23390, and sulpiride on cocaine-induced lethality, animals were injected, IP, with 60 or 90 mg/kg of cocaine 30 min after the antagonist treatment. Survival was recorded within 24 h after the cocaine injection.

Statistics

Statistical analyses of the percent seizure and percent lethality data were conducted using the Fisher's exact probability test. The data for the latency to seizure onset were analyzed using a one- or two-factor analysis of variance (ANOVA) followed by posthoc Scheffe's *S*-test.

RESULTS

Blockade of Cocaine-Induced Seizures by MK-801

Figure 1a shows the time course changes in the latency to onset of seizures after injection of 60 mg/kg cocaine in vehicle-pretreated control and MK-801-pretreated mice. The latency to seizures in the control mice progressively decreased during the initial 3 days. This was followed by gradual prolongation of seizure latency on the 4th to 6th days of treatment. A one-factor ANOVA revealed significant decreases in the latency on days 2 and 3 in the control mice as compared to day 1, $F(5, 62) = 5.04$, $p < 0.001$. Pretreatment with 0.1 mg/kg of MK-801 partially suppressed this decrease in latency, while pretreatment with 0.2 and 0.4 mg/kg almost completely blocked it, $F(3, 256) = 29.11$, $p < 0.0001$.

On day 1, 60 mg/kg cocaine produced little or no seizures in the control and MK-801-pretreated mice. Repeated administration of 60 mg/kg cocaine to the control mice resulted in a rapid increase in number of mice seizing with 67% (8 of 12) or 73% (8 of 11) on days 2-4. This was followed by a gradual decrease in percent seizures on days 5 and 6. MK-801 dose dependently decreased the occurrence of kindled seizures across the course of treatment. On day 3, the cocaine treatment produced seizures in only 50% (6 of 12), 17% (2 of 12) and 8% (1 of 12) of animals pretreated with 0.1, 0.2, and 0.4 mg/kg of MK-801, respectively. Statistical analyses verified the significance of the inhibition of seizures in the mice pretreated with 0.2 mg/kg MK-801 at days 2-5 (Fisher's exact $p < 0.001$ or 0.05) and 0.4 mg/kg MK-801 at days 2-4 (Fisher's exact $p < 0.001$).

The effects of pretreatment with MK-801 on seizures induced by 90 mg/kg cocaine were also examined using the data for the latency to onset of seizures (Fig. 1b). A one-factor ANOVA with the Scheffe's *S*-test noted a significant prolongation of the latency on day 1 in the mice pretreated with 0.2 or 0.4 mg/kg MK-801 as compared to mice pretreated with vehicle or 0.1 mg/kg MK-801, $F(3, 44) = 13.11$, $p < 0.0001$. Repeated injection of 90 mg/kg cocaine produced no change in latency during the course of the session in the control mice, $F(5, 32) = 1.26$, $p = 0.31$, in the mice pretreated with 0.1 mg/kg, $F(5, 27) = 0.89$, $p = 0.50$, and 0.2 mg/kg of MK-801, $F(5, 35) = 2.13$, $p = 0.08$. A two-factor ANOVA with the Scheffe's *S*-test clearly demonstrated a significant dose-dependent inhibition of seizures by MK-801 pretreatment across the days of 90 mg/kg cocaine, $F(3, 140) = 28.67$, $p < 0.0001$.

Acute injection of 90 mg/kg cocaine produced convulsions in 75% (9 of 12) of the mice pretreated with vehicle on day 1. Although pretreatment with 0.1 mg/kg MK-801 had no effect on convulsant activity after 90 mg/kg cocaine on day 1, pretreatment with 0.2 and 0.4 mg/kg MK-801 completely blocked the occurrence of seizures after 90 mg/kg cocaine (Fisher's exact $p < 0.01$ and 0.001, respectively). Following repeated injections, percent seizures were almost unchanged in the con-

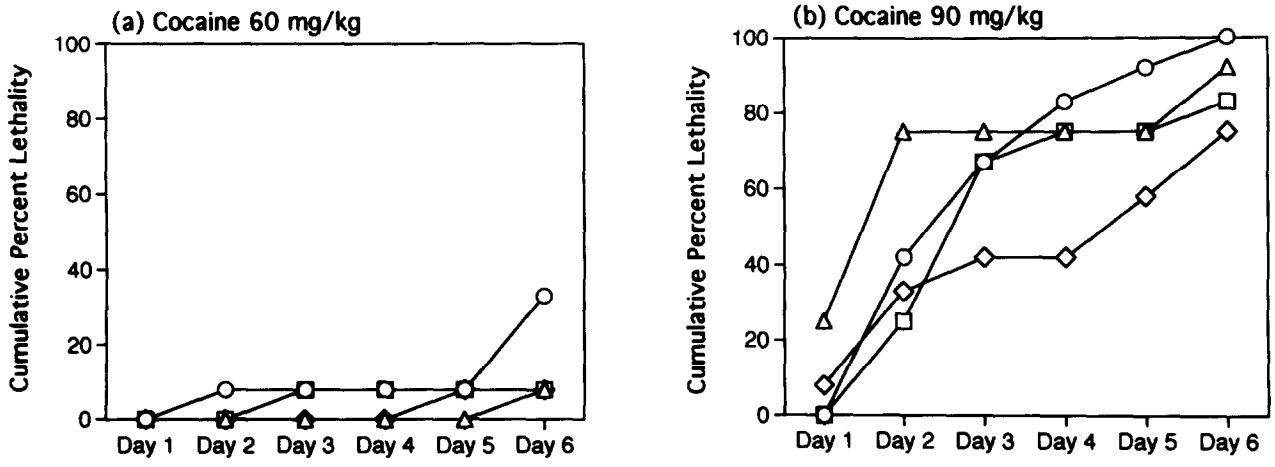

FIG. 2. Effects of MK-801 on cumulative mortality following repeated injection of 60 (a) and 90 (b) mg/kg cocaine in ddY mice. Animals were injected IP with 60 or 90 mg/kg cocaine at each session, 30 min after SC treatment with either saline (○) or 0.1 (△), 0.2 (□) or 0.4 (◇) mg/kg of MK-801. Survival was recorded 24 h after injection of cocaine.

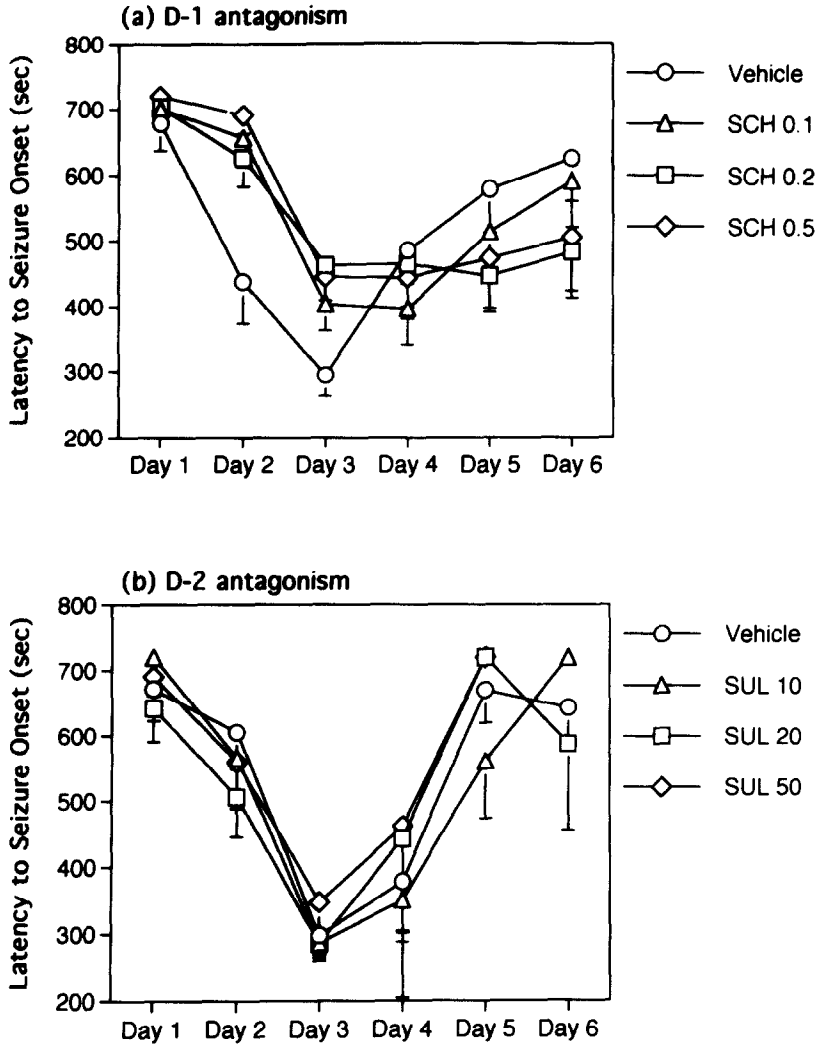

FIG. 3. Effects of SCH 23390 (a) and sulpiride (b) on seizure activities following repeated injection of 60 mg/kg cocaine in ddY mice. Animals were injected IP with 60 mg/kg cocaine daily, 30 min after either pretreatment with vehicle (○), 0.1 (△), 0.2 (□), or 0.5 (◇) mg/kg of SCH 23390 or pretreatment with vehicle (○), 10 (△), 20 (□), or 50 (◇) mg/kg of sulpiride. Each point and bar represent the mean value of the latency and the standard error, respectively.

trol mice and the mice pretreated with 0.1 and 0.4 mg/kg MK-801. In contrast, the percent seizures progressively increased from 8% on day 1 to 67% on day 6 among the mice pretreated with 0.2 mg/kg MK-801, though the difference did not reach a statistical significance. The percent seizures were significantly decreased in the mice pretreated with 0.2 mg/kg MK-801 on day 2 (Fisher's exact $p < 0.001$) and in the mice pretreated with 0.4 mg/kg MK-801 on days 2-4 (Fisher's exact $p < 0.0001$ or 0.01), as compared to the control mice on respective days.

Attenuation of Cocaine Lethality by MK-801

Figure 2 illustrates the cumulative percent lethality for the four pretreatment groups following repeated injections of 60 and 90 mg/kg cocaine. No lethality was observed after a single injection of 60 mg/kg cocaine among the vehicle pretreated mice on day 1 (Fig. 2a). Following repeated injection of 60 mg/kg cocaine, only four mice died over the course of treatment. Pretreatment with MK-801 neither attenuated nor augmented the lethal effects of 60 mg/kg cocaine. A single injection of 90 mg/kg cocaine also had no lethal effects in the vehicle-pretreated mice on day 1 (Fig. 2b). Treatment with 0.1, 0.2, and 0.4 mg/kg of MK-801 resulted in the death of animals of three, none, and one out of 12, respectively, after the first injection of cocaine. The Fisher's exact test, however, found no significant difference in percent lethality on day 1. Repeated injection of 90 mg/kg cocaine resulted in a progressive increase in cumulative lethality in the vehicle-pretreated mice. Following repeated injection of 90 mg/kg cocaine, cumulative lethality progressively increased in the mice pretreated with 0.1 or 0.2 mg/kg MK-801 in the same manner as in the vehicle-pretreated mice. However, treatment with 0.4 mg/kg MK-801 significantly attenuated the lethal effect of

repeated injections of 90 mg/kg cocaine (Fisher's exact $p < 0.05$ on day 4).

Differential Effects of Dopamine Receptor Antagonism on Cocaine-Induced Seizures and Lethality

We have also examined the effect of treatments with various doses of SCH 23390 and sulpiride on cocaine-induced seizures. Figure 3a shows the latency to seizure onset following repeated injections of 60 mg/kg cocaine in mice pretreated with either vehicle, 0.1, 0.2, or 0.5 mg/kg of SCH 23390. We have examined the effects of antagonism of NMDA and dopamine receptor function using data for both the percent seizures and the latency to the onset of these seizures. The time course changes for these two measures essentially mirrored each other. Accordingly, only the latency to seizure onset data are presented for the effects of the dopamine antagonists on cocaine-induced seizures. The latency in the vehicle-pretreated control mice decreased sharply during the initial 3 days and thereafter increased gradually to the levels seen on day 1. Pretreatment with any dose of SCH 23390 shifted the curves to the right. Although the main effect of pretreatment was not significant, $F(3, 199) = 0.41$, $p = 0.74$, a two-factor ANOVA indicated that the pretreatment × session interaction was significant, $F(15, 199) = 1.94$, $p < 0.05$. On the other hand, as depicted in Fig. 3b, pretreatment with sulpiride had no effect on the time course changes in the latency to seizure onset.

Because coadministration of 90 mg/kg cocaine and either SCH 23390 or sulpiride produced severe lethal effects over the course of treatment, the number of animals was too small to be meaningful. Accordingly, we only examined the effects of the dopamine antagonists on the latency to seizure onset after injection of 90 mg/kg cocaine on day 1 (Fig. 4). A one-factor ANOVA demonstrated a significant effect of the treatment on the latency among the groups pretreated with either vehicle or SCH 23390, $F(3, 32) = 3.77$, $p < 0.05$, reflecting inhibition of cocaine-induced seizures by 0.1 mg/kg SCH 23390. In contrast to the effect of SCH 23390, pretreatment with sulpiride had no effect on seizure latency after acute injection of the high dose of cocaine on day 1, $F(3, 32) = 1.58$, $p = 0.21$.

A single injection of 60 or 90 mg/kg of cocaine produced little or no lethality in the vehicle-pretreated mice on day 1 (Fig. 5). Pretreatment with 50 mg/kg sulpiride potentiated the lethal effect of 90 mg/kg cocaine on day 1 (Fisher's exact $p < 0.05$), whereas the other pretreatments had no effect on the lethality resulting from the acute administration of 60 or 90 mg/kg cocaine. There was no significant effect of the treatment with SCH 23390 on the time course changes in cumulative lethality following repeated injection of 60 or 90 mg/kg cocaine (Fig. 5a,b). In contrast, pretreatment with sulpiride substantially increased the percent lethality observed following repeated injection of 60 mg/kg cocaine (Fig. 5c). Statistical analyses demonstrated significant increases in the cumulative percent lethality in mice pretreated with 10 mg/kg sulpiride on day 5 (Fisher's exact $p < 0.05$), 20 mg/kg on days 3–5 (Fisher's exact $p < 0.05$), and 50 mg/kg on days 3–5 (Fisher's exact $p < 0.01$). Pretreatment with sulpiride increased the cumulative percent lethality following repeated injection of 90 mg/kg cocaine (Fig. 5d). There was a significantly higher rate of mortality in the mice pretreated with 50 mg/kg of sulpiride on days 2 and 3 than in the control mice (Fisher's exact $p < 0.05$).

DISCUSSION

The present study investigated the effects of MK-801, SCH 23390, and sulpiride on seizure susceptibility and mortality following not only single but repeated injections of cocaine in ddY mice. The results suggest that the development of sensitization to cocaine-induced seizures and lethality is primarily associated with NMDA receptor-mediated mechanisms, but that D_1 and D_2 receptors may also be involved subordinately in cocaine-induced seizures and lethality, respectively. However, receptor binding studies have shown that cocaine binds to the transporters of dopamine, serotonin, and noradrenaline, but

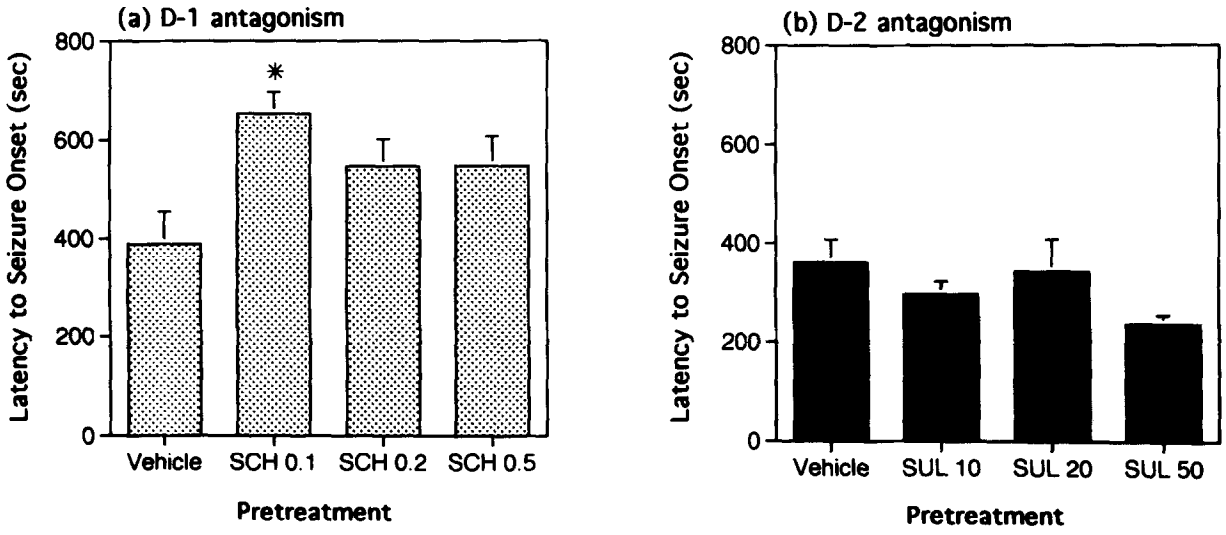

FIG. 4. Effects of SCH 23390 (a) and sulpiride (b) on seizures induced by the injection of 90 mg/kg cocaine in ddY mice on day 1. Animals were injected IP with 90 mg/kg cocaine, 30 min after pretreatment with vehicle, 0.1, 0.2, or 0.5 mg/kg of SCH 23390 or pretreatment with vehicle, 10, 20, or 50 mg/kg of sulpiride. Each column and bar represent the mean value and the standard error, respectively. The asterisk denotes a significant difference in the latency as compared to that in vehicle-pretreated mice.

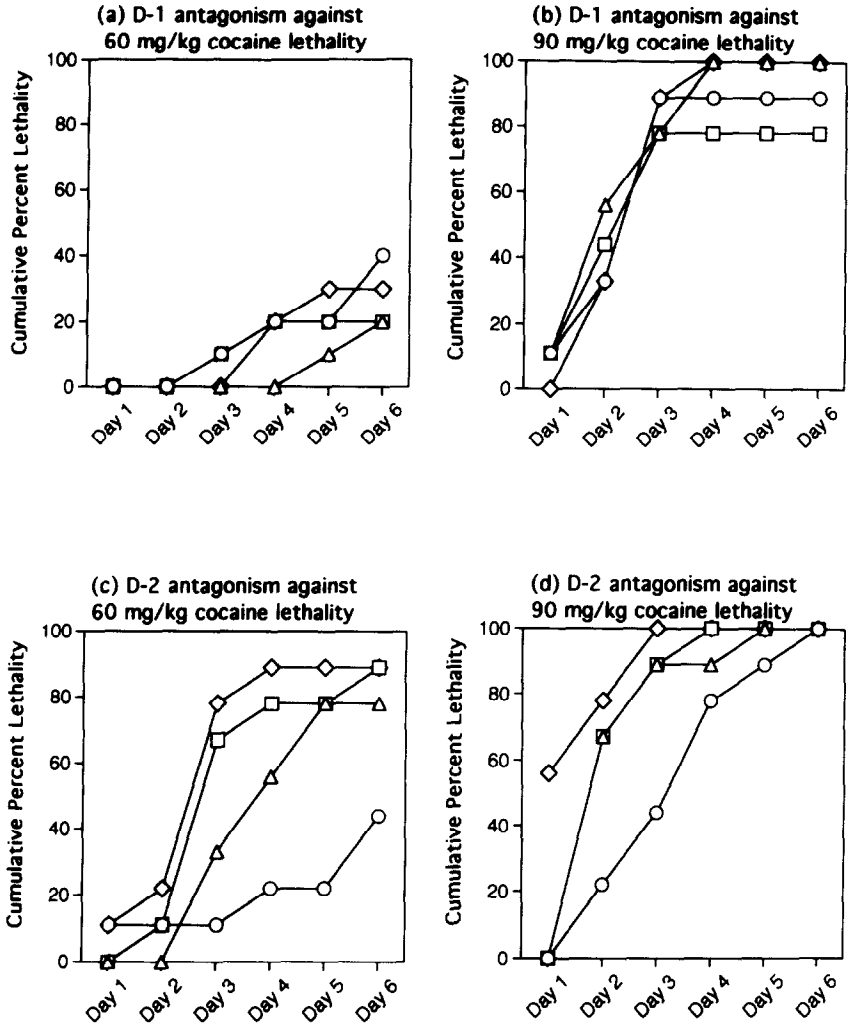

FIG. 5. Effects of SCH 23390 (a,b) and sulpiride (c,d) on cumulative percent lethality following repeated injection of 60 (a,c) and 90 (b,d) mg/kg cocaine in ddY mice. Animals were injected IP with cocaine daily, 30 min after pretreatment with vehicle (○), 0.1 (△), 0.2 (□), or 0.5 (◇) mg/kg of SCH 23390 or pretreatment with vehicle (○), 10 (△), 20 (□), or 50 (◇) mg/kg of sulpiride. Survival was recorded 24 h after injection of cocaine.

not to glutamate receptors (21). It is unlikely, therefore, that cocaine acts directly on the NMDA receptor to produce convulsant and lethal effects. Recently, it was suggested that convulsant and lethal effects of cocaine clearly depend on the serotonergic, muscarinic and sigma receptor sites as well as the dopaminergic site (20). In addition, α_1-adrenergic antagonist prazosin was reported to prevent cocaine-induced death in rats (30). Thus, further investigations will be required to elucidate the mechanism underlying the toxic effects of cocaine.

In the present study, repeated injection of 60 mg/kg cocaine caused the development of sensitization to the convulsant effect of the drug during an initial 3 or 4 days in ddY mice. Thereafter, tolerance to the convulsant effect was developed. We have previously reported the development of both sensitization and tolerance to the convulsant effect of 50 mg/kg cocaine in the BALB, C57BL, and DBA mice (12). It has also been shown that while the repeated injection of 40 mg/kg cocaine initially raises the threshold for electrical convulsions, the threshold is lowered after 16 days of treatment (10). These findings suggest that more than one mechanism may be associated with changes in sensitivity to the convulsant effect of cocaine following repeated injections.

Besides its effect on dopamine uptake, cocaine has local anesthetic actions that appear to be mediated by its blocking actions at voltage-dependent sodium channels (11,33). Other local anesthetics, including lidocaine, also produce seizures and cause the development of sensitization to seizures when repeatedly injected (19). Accordingly, the convulsant actions of cocaine could be related to its local anesthetic properties (19). However, previous studies have shown that there are apparent differences in the rank order of a number of mouse strains for susceptibility to seizures following single and repeated injections of cocaine and lidocaine (13). In addition, it has recently been demonstrated that a group of compounds known to inhibit seizures induced by a variety of agents also blocked the voltage-gated sodium channel in a frequency- and voltage-dependent manner (6,38,39). Therefore, cocaine's local anesthetic properties alone are unable to account for its seizure inducing properties. Other systems are conceivably associated with the convulsant and epileptogenic properties of cocaine.

The NMDA receptor is generally considered to be implicated in a number of phenomena associated with neuronal plasticity, including memory, long-term potentiation, kindling, behavioral sensitization, and neuronal degeneration (15). For instance, MK-801 blocks the development of behavioral sensitization resulting from repeated injection of cocaine, amphetamine, and morphine in rats (37). In the present study, we revealed that MK-801 completely blocked the convulsant effect of 90 mg/kg cocaine after a single injection on day 1, dose dependently inhibited the development of sensitization to the convulsant effects following repeated injections of 60 mg/kg cocaine, and partially attenuated the increased lethality associated with repeated injections of 90 mg/kg cocaine. These results are evidently consistent with the findings made by a number of investigators (8,16,24,29). MK-801 has been reported to inhibit the acute seizures induced by NMDA, pentylenetetrazol, electric shock, and audiogenic stimuli (29). MK-801 has also been shown to suppress the development of amygdala kindling and the resultant generalized seizures in rats (16). With respect to the cocaine's actions, 0.3 mg/kg of MK-801, but not 0.1 mg/kg, almost completely blocked seizures induced by a single injection of 90 mg/kg cocaine, and 0.1–10 mg/kg of MK-801 drastically decreased the incidence of death caused by 90 mg/kg of cocaine (24). Recently, MK-801 (0.35 mg/kg) has been shown to block completely the development of sensitization to the convulsant and lethal effects following repeated injection of 45 mg/kg cocaine (8). The present results, together with the findings discussed above, suggest that NMDA receptors probably mediates the induction of seizures by cocaine, as well as the development of the sensitization to cocaine's convulsant and lethal effects.

Cocaine's psychomotor stimulant effects are associated with its inhibition of dopamine uptake (7,21). Dopamine antagonists, especially for D_2 receptors, have been shown to prevent the development of behavioral sensitization (19,32). However, neither depletion of noradrenaline nor dopamine in the brain affected seizures induced by a single injection of cocaine (60–80 mg/kg) in Wistar rats (14), suggesting no involvement of the catecholaminergic mechanism in cocaine-induced seizures. In contrast, sulpiride (50 mg/kg) increased susceptibility to cocaine-induced seizures in spontaneously hypertensive rats, but not in Wistar-Kyoto rats (23). Another study found that haloperidol (10, 20 mg/kg) decreased the incidence of cocaine-induced seizures in Sprague–Dawley rats (3). These results suggest the involvement of D_2 receptors in cocaine seizures. On the other hand, whereas SCH 23390 (0.5–2.5 mg/kg) had no effect on the incidence of cocaine-induced seizures, the latency to cocaine-induced seizures was significantly prolonged by 0.5 mg/kg SCH 23390 (4). The present study demonstrated not only a prolongation of the latency to 90 mg/kg cocaine-induced seizures on day 1, but also a delay of the development of sensitization to the convulsant effects of 60 mg/kg cocaine in SCH 23390-pretreated mice, suggesting that D_1 receptors may also be associated with the convulsant action of cocaine. Thus, there is no consensus concerning a possible role of the dopaminergic mechanisms in convulsant actions of cocaine at present. This discrepancy may be accounted for by the differences in species or strains of animals used in the experiments, the lack of selectivity for binding site of the dopamine receptor antagonists, and/or the dose of cocaine. There is also controversy over involvement of the dopaminergic mechanism in the seizure activity induced by other chemoconvulsants (2,18,25,28,31). The inconsistencies seem to indicate that the dopaminergic mechanism, if involved, exerts only minor effects on cocaine-induced seizures.

SCH 23390 (0.3 or 0.5 mg/kg) has been shown to protect rats against the acute lethal effect of cocaine (>70 mg/kg) while haloperidol (0.3–20 mg/kg) failed to prevent it (3,4,36). In the present study, injection of 90 mg/kg cocaine produced no lethal effect on day 1. Accordingly, we are unable to determine the effect of blockade of the D_1 or D_2 receptor on the lethality resulting from a single injection of a high dose of cocaine. On the other hand, the present study revealed that although increased mortality following repeated injection of cocaine was unaffected by pretreatment with SCH 23390, it was markedly aggravated by pretreatment with sulpiride. These results suggest a protective role of D_2 receptors against the lethality resulting from repeated cocaine injections.

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