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Inhibition by Ginsenosides Rb_1 and Rg_1 of Cocaine-Induced Hyperactivity, Conditioned Place Preference, and Postsynaptic Dopamine Receptor Supersensitivity in Mice

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KIM, H.-S., K.-S., KIM AND K.-W. OH. *Inhibition by ginsenosides Rb_1 and Rg_1 of cocaine-induced hyperactivity, conditioned place preference, and postsynaptic dopamine receptor supersensitivity in mice.* PHARMACOL BIOCHEM BEHAV **63**(3)407–412, 1999.—A single or repeated administration of cocaine (15 mg/kg) in mice produced hyperactivity and conditioned place preference (CPP). Ginsenoside Rb_1 (Rb_1) and ginsenoside Rg_1 (Rg_1), prior to and during the cocaine treatment in mice, inhibited cocaine-induced hyperactivity and CPP. The development of enhanced postsynaptic dopamine (DA) receptor sensitivity in mice displaying a cocaine-induced CPP was evidenced by the enhanced response in ambulatory activity to the DA agonist, apomorphine (2 mg/kg). Rb_1 and Rg_1 inhibited the development of postsynaptic DA receptor supersensitivity. However, Rb_1 and Rg_1 did not show any antidopaminergic activity at the postsynaptic DA receptors, because the apomorphine-induced climbing behavior was not inhibited by Rb_1 and Rg_1. Therefore, it is presumed that Rb_1 and Rg_1 modulate DA activity induced by cocaine at the presynaptic DA receptors, and this modulation results in the inhibition of postsynaptic dopaminergic activation. These results suggest that the cocaine-induced CPP may be associated with enhanced DA receptor sensitivity. The inhibition by Rb_1 and Rg_1 of cocaine-induced hyperactivity and CPP may be closely related with the inhibition of dopaminergic activation induced by cocaine at the presynaptic DA receptors. © 1999 Elsevier Science Inc.

Ginsenoside Rb_1 Ginsenoside Rg_1 Cocaine Hyperactivity Conditioned place preference Postsynaptic dopamine receptor supersensitivity

COCAINE produces hyperactivity (6,10) and acts as a stimulant on the central nervous system (CNS) by inhibiting the uptake of dopamine (DA) (1,28), norepinephrine (8,15), and serotonin (7) at the presynaptic terminals. The reinforcing effect is exhibited after a single or repeated exposure to cocaine (22). The conditioned place preference (CPP) test is a procedure used to investigate potential reinforcing properties of drugs. Therefore, the CPP has been used as a model for studying the psychological dependence (3,4,34).

Some neuropharmacological investigations suggest an involvement of the mesolimbic and mesocortical dopaminergic system in the neuronal mechanisms mediate cocaine-induced hyperactivity (6,10,11) and reinforcement (15,22,27). It has been reported that a DA receptor antagonist, haloperidol, inhibited cocaine-induced hyperactivity (21), and that pimozide (18) and haloperidol (29) antagonized cocaine-induced CPP. Pimozide has also been reported to attenuate cocaine self-administration in rats. Therefore, these results showed that the dopaminergic system might be involved in the mediation of the rewarding effect of cocaine.

On the other hand, numerous reports have provided evidence that ginseng has various effects of CNS (20,23–25). Tsang et al. (33) reported that ginsenosides, active components of ginseng saponin, inhibited the uptake of radioactive gamma-aminobutyric acid (GABA), glutamate, DA, noradrenaline, and serotonin in rat brain synaptosomes. These results

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suggest the possibility that ginsenosides can also modulate the dopaminergic system.

Kim et al. (12) have demonstrated that ginseng total saponin (GTS) inhibits cocaine-induced reverse tolerance and the development of postsynaptic DA receptor supersensitivity, thereby suggesting that the inhibitory effect of the GTS on this action may be associated with the interruption of chronic cocaine action at the presynaptic terminals. It was reported that GTS prevented cocaine-induced CPP (12,13). GTS also inhibited the development of postsynaptic DA receptor supersensitivity in cocaine-induced CPP mice. Therefore, it was presumed that cocaine-induced CPP was associated with enhanced DA receptor sensitivity because GTS blocked both phenomena.

In a previous study, it was confirmed that GTS produced inhibitory effects on cocaine-induced hyperactivity and CPP. Because former studies were performed using GTS, a mixture of several components of ginsenosides, it is important to identify which components of ginsenosides are active.

For this reason, the present experiments were primarily undertaken to investigate the effects of Rb_1 and Rg_1 major protopanaxadiol and protopanaxatriol components of ginseng saponin fraction, respectively. Therefore, the inhibitory effects of Rb_1 and Rg_1 on the hyperactivity and the CPP induced by cocaine were studied. Moreover, to determine the neuropharmacological mechanisms underlying the CPP induced by cocaine, the enhanced DA receptor sensitivity was examined in CPP induced by cocaine and the enhanced DA receptor sensitivity was examined in CPP mice. In addition, to examine the acute effects of Rb_1 and Rg_1 on postsynaptic DA receptors, apomorphine-induced climbing behavior was also measured in mice treated with single doses of Rb_1 and Rg_1.

METHOD

Animals and Drugs

ICR male mice weighing 25–30 g, in groups of 10–15, were used in all experiments. As a matter of convenience to allow the handling of a large number of animals, groups of 10 mice were housed in cages with water and food available ad lib under an artificial 12 L:12 D cycle (lights at 0700 h) and at a constant temperature (22 ± 2°C). The drugs used were cocaine hydrochloride (National Institute of Safety Research, Seoul, Korea), apomorphine hydrochloride (Sigma, Chemical Co., St. Louis, MO), haloperidol (Whan-In Pharm. Co., Seoul, Korea), and Rb_1 and Rg_1 (supplied by Korea Ginseng and Tobacco Research Institute, Taejon, Korea). With the exception of the apomorphine, all drugs were dissolved in physiological saline (0.1 ml/10 g). Apomorphine was dissolved in saline containing 0.1% ascorbic acid just prior to the experiment.

Measurement of Hyperactivity Induced by Cocaine

The hyperactivity of the mice was measured by a tilting-type ambulometer (AMB-10, O'Hara Co., Ltd., Japan) as reported previously (12,13). Each mouse was placed in the activity cage (20 cm in diameter; 18 cm in height), and after an adoption period of 10 min, the drug administration was carried out. The dosage of cocaine used was chosen on the basis of a preliminary experiment. When the combined effects of cocaine and ginsenosides were investigated at various time intervals, the reliable inhibitory effects of ginsenosides were observed 1 h prior to the intraperitoneal (IP) injection of cocaine (data not shown). Therefore, Rb_1 and Rg_1 (50, 100, or 200 mg/kg) were injected IP in mice 1 h prior to the administration of cocaine. The preliminary experiments also indicated that the ambulatory activity of cocaine 15 mg/kg (IP) for 1 h produced consistent and reliable activity. Therefore, the ambulatory activity was measured for 1 h after the administration of cocaine.

Measurement of CPP Induced by Cocaine

Apparatus. The CPP apparatus was a modification of the apparatus used by Mucha et al. (19), as reported previously (12,13). It consisted of two square-base Plexiglas compartment (15 × 15 × 15 cm), one with white walls and the other with black walls joined by a gray tunnel (3 × 3 × 7.5 cm), which could be closed by guillotine doors. To provide a tactile difference between the floor of the compartment, the white compartment had a wire mesh floor and the black compartment had a metal grid floor. Removal of the guillotine doors during the pretesting and the final testing phase allowed animals free access to both compartments, and the time spent by the mice in each of the two compartments was recorded for 15 min using an IBM-compatible PC computer with infrared detectors. The tunnel was designed to be just small enough for a mouse to pass through. The time spent by the mice in the tunnel was ignored, because the time spent in the tunnel comprised less than 5% of the total time measured: all conditioned and test sessions were conducted under ambient light (20–30 lx).

Procedures. The control mice received an IP saline immediately before exposure to the white or black compartment. To test their effects, Rb_1 and Rg_1 were administered 1 h prior to the cocaine of saline injection, respectively.

Phase I (pretesting phase). On day 1, the mice were preexposed to the test apparatus for 15 min. The guillotine doors were raised and each animal was allowed to move freely between the two compartments. On day 2, baseline preference was determined for the nonpreferred side vs. the preferred side for 15 min.

Phase II (conditioned phase). On days 3, 5, 7, and 9, the mice were injected with the drug before confinement in the white compartment, the nonpreferred side, for 60 min. On days 4, 6, 8, and 10, the mice were injected with saline before confinement in the black compartment, the preferred side, for 60 min.

Phase III (testing phase). On day 11, the guillotine doors were raised. The mice were placed in the tunnel in the central part of the apparatus, and the time spent by the mice in the two compartments was recorded for 15 min.

Place preference data were expressed as the difference in time spent between the drug-paired compartment and the saline-paired compartment. Values from both pretest baseline and test conditions were shown. Animals that acquire a place shift their preference to the drug-paired compartment. An increase in time in the drug-paired compartment shows that the animals spent more time in the originally less-preferred compartment, presumable due to the reinforcing effects of the drug that were conditioned in this environment.

Measurement of the Development of Postsynaptic DA Receptor Supersensitivity in CPP Mice

Additional groups of mice subjected to the same conditioning regimen, as well as repeated injections of cocaine or ginsenosides according to the schedule of the CPP experiment, were used to determine whether the enhanced response to apomorphine resulted from the repeated administration of cocaine. Development of enhanced DA receptor sensitivity was evidenced by the increased responses in ambulatory activity to the

DA agonist, apomorphine, 24 h after the final CPP confinement. The ambulation-increasing activity of apomorphine was measured by a modification of Bhargava's (2) method as we reported previously (12,13). All mice were first allowed to preambulate for 10 min and were given apomorphine (2 mg/kg, SC), a dose of which produced a significant increase in ambulatory activity. Ambulatory activity following apomorphine treatment was measured for 20 min.

Measurement of Apomorphine-Induced Climbing Behavior

The climbing behavior in mice was measured by a modification of the method of Protais et al. (26), as reported previously (12,13). Immediately after a subcutaneous injection of apomorphine 2 mg/kg, a dose of which has been known to act as a postsynaptic D_1 receptor agonist (13), the mice were put into individual cylindrical cages (12 cm in diameter; 14 cm in height) with walls of vertical metal bars (2 mm in diameter; 1 cm apart). After a 5-min period of exploratory activity, climbing behavior was measured by an all-or-none score at 10, 20, and 30 min. After the administration of apomorphine, the three scores were averaged. The scores of this behavior were evaluated as follows; four paws on the floor (0 point), forefeet holding the wall (1 point), and four paws holding the wall (2 points). Rb_1 and Rg_1 (25, 50, 100, and 200 mg/kg) were administered IP to mice 1 h prior to the injection of apomorphine. Haloperidol (0.1 mg/kg) was also administered for comparison.

Statistics

The data was expressed as a mean ± SE. The statistical significant effects of the drug were analyzed of variance (ANOVA). In the case of significant variation, the significance between individual does conditions and the corresponding control group was analyzed by a Dunnett's test in all experiments, except for the climbing results, in which a Mann–Whitney *U*-test form the pharmacological calculations program (32) was used.

RESULTS

Inhibitory Effects of Rb_1 and Rg_1 on Cocaine-Induced Hyperactivity.

There was no significant difference in ambulatory activity in both groups of mice treated with saline and ginsenosides alone, respectively (Fig. 1). However, the group treated with cocaine showed a marked increase in ambulatory activity, yielding 1,780 counts, 1,466 counts more than the 314 counts of the naive group. In addition, the group pretreated with Rb_1 200 mg/kg showed a significant inhibition of ambulatory activity, yielding 820 counts, 960 counts less than the 1,780 counts of the cocaine control group and 420 counts more than the 400 counts of Rb_1 200 mg/kg alone (Fig. 1A). Meanwhile, the groups pretreated with Rg_1 200 mg/kg showed a significant inhibition of ambulatory activity, yielding 678 counts, 1,508 counts less than the 2,186 counts of the cocaine control group and 478 counts more than the 200 counts of Rg_1 200 mg/kg alone (Fig. 1B).

Inhibitory Effects of Rb_1 and Rg_1 on Cocaine-Induced CPP

The group treated with Rb_1 100 mg/kg did not show any CPP (Fig. 2A). The group treated with cocaine 15 mg/kg showed significant effects of CPP with 201 s, 237 s more than the −36 s of the naive group. Pretreatment with Rb1 100 mg/kg showed a marked inhibition of cocaine (15 mg/kg)-induced CPP yielding 13 s, 214 s less than the 201 s of the cocaine control group.

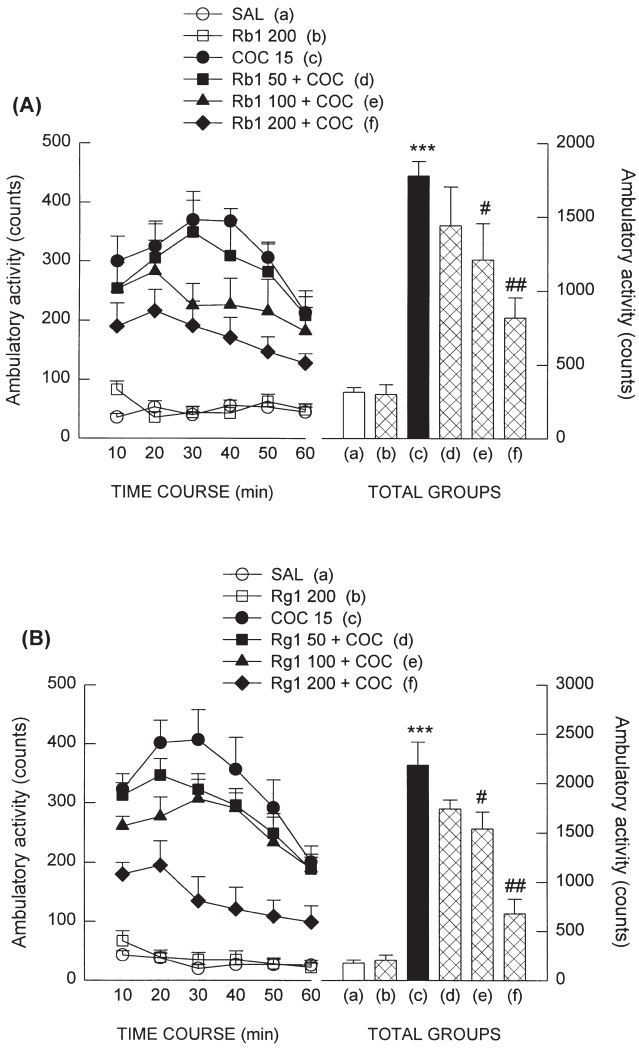

FIG. 1. Inhibitory effects of (A) Rb_1 and (B) Rg_1 on cocaine-induced hyperactivity in mice. Rb_1 and Rg_1 (50, 100, and 200 mg/kg, IP) were administered to mice 1 h prior to the injection of cocaine (15 mg/kg, SC). Ambulatory activity was measured every 10 min for 1 h after the administration of cocaine. The data are expressed as mean ± SE. ***$p < 0.001$, compared with that of the saline group. #$p < 0.05$, ##$p < 0.01$, compared with that of the cocaine group. SAL: saline; COC: cocaine; Rb_1: ginsenoside Rb_1; Rg_1: ginsenoside Rg_1.

Pretreatment with Rg_1 100 mg/kg showed a marked inhibition of cocaine (15 mg/kg)-induced CPP showing 25 s, 218 s less than the 243 s of the cocaine control group (Fig. 2B).

Inhibitory Effects of Rb_1 and Rg_1 on the Development of Postsynaptic DA Receptor Supersensitivity in Cocaine-Induced CPP Mice

The ambulatory activity produced by apomorphine was enhanced in mice treated with cocaine, compared with the ambulatory activity of the naive group. The group treated with cocaine showed a significant increase in ambulatory activity to apomorphine (2 mg/kg), yielding 364 counts, 242 counts more than the 122 counts of the naive group. Meanwhile, pretreatment with Rb_1 100 mg/kg showed a significant inhibition of cocaine 15 mg/kg, yielding 233 counts, 131 counts less than the

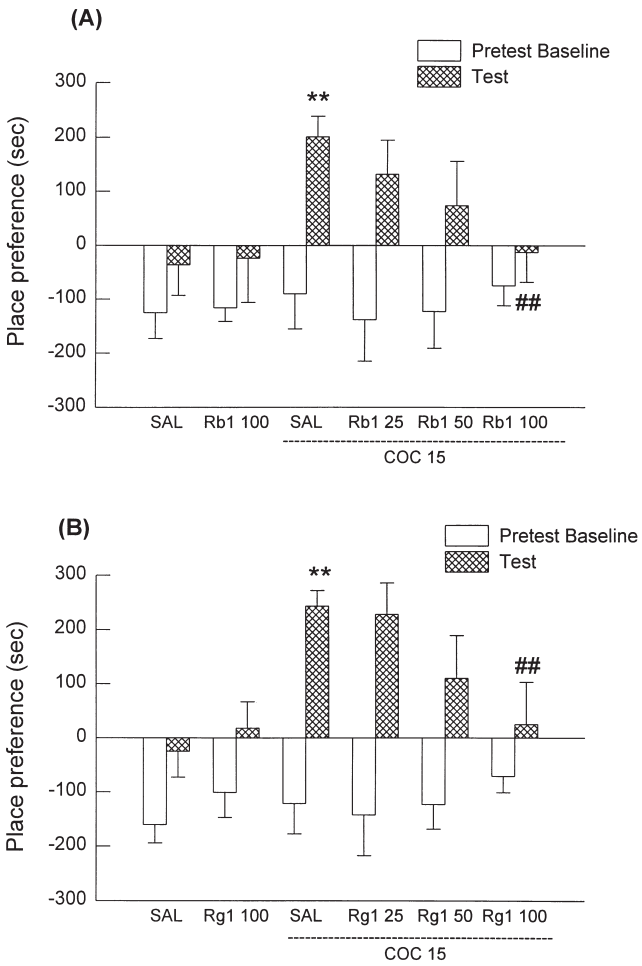

FIG. 2. Inhibitory effects of (A) Rb_1 and (B) Rg_1 on cocaine-induced CPP. Rb_1 and Rg_1 (25, 50), and 100n mg/kg IP) were administered to mice 1 h prior to the injection of cocaine (15 mg/kg, SC) or saline. In the conditioning phase, mice were injected with 60 min every day for 8 days. The data are expressed as mean ± SE. $^{**}p < 0.01$, compared with that of the saline group, $\#\#p < 0.01$, compared with that of the cocaine group. SAL: saline; COC: cocaine; Rb1: ginsenoside Rb_1: Rg_1: ginsenoside Rg_1.

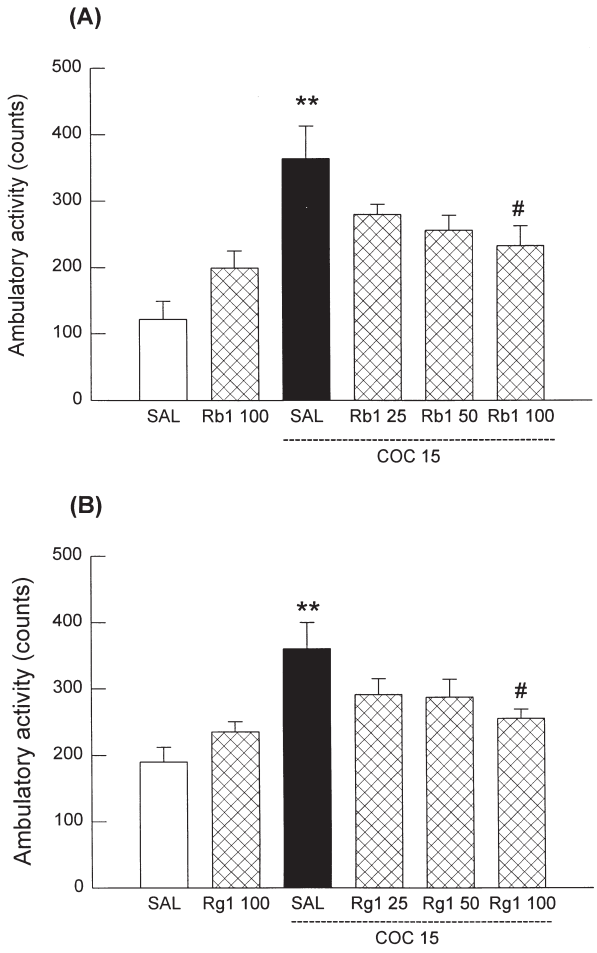

FIG. 3. Inhibitory effects of (A) Rb_1 and (B) Rg_1 and on the development of postsynaptic DA receptor supersensitivity in cocaine-induced CPP mice. The development of postsynaptic DA receptor supersensitivity was determined by the enhancement of ambulatory activity to apomorphine 24 h after the final CPP confinement. Mice were injected with apomorphine (2 mg/kg) and first allowed to ambulate for 10 min and then tested for 20 min. The data are expressed as mean ± SE. $^{**}p < 0.01$, compared with that of the saline group, $\#p < 0.05$, compared with that of the cocaine group. SAL: saline; COC: cocaine; Rb_1: ginsenoside Rb_1; Rg_1: ginsenoside Rg_1.

364 counts of the cocaine control group (Fig. 3A). The groups pretreated with Rg_1 25 and 50 mg/kg did not show any significant inhibition of enhanced ambulatory activity to apomorphine, yielding 290 counts and 287 counts, respectively, compared with the 360 counts of the cocaine control group. However, pretreatment with Rg_1 100 mg/kg showed a significant inhibition of cocaine 15 mg/kg, yielding 360 counts, 105 counts more the 255 counts of the cocaine control group (Fig. 3B).

Effects of Rb_1 and Rg_1 on Apomorphine-Induced Climbing Behavior

A dosage of apomorphine 2 mg/kg was used in this experiment because the submaximal response was observed with this dose in a preliminary experiment using 0.5, 1.0, 2.0, and 4.0 mg/kg of apomorphine (data not shown). The treatment with groups of Rb_1 and Rg_1 (25, 50, 100, and 200 mg/kg) did not show any inhibition of apomorphine-induced climbing behavior when compared to the apomorphine control group (Fig. 4A and B). However, the mice that received haloperidol (0.1 mg/kg) showed significant inhibition of climbing behavior compared to the apomorphine control group (Mann–Whitney *U*-test). These results suggest that Rb_1 and Rg_1 did not show any antidopaminergic activity at postsynaptic DA receptors.

DISCUSSION

A single or repeated administration of cocaine produced hyperactivity and CPP. This is in agreement with the theory that addictive substances such as cocaine derive their reinforcing quality by stimulating the same neurochemical system that mediates psychomotor activity (35). It has been demonstrated that cocaine-induced hyperactivity (6,10) and reinforcement (16,22) appear to be involved in the activation of the mesolimbic dopaminergic system. Cocaine inhibited the uptake of monoamines at the presynaptic terminals (1,7,8). Therefore,

repeated administration of cocaine results in the depletion of catecholamines at the presynaptic site (1,7,8) and then in the development of postsynaptic DA receptor supersensitivity (5,17). In conjunction with this fact, it has been presumed that behavioral sensitization produced by repeated administration of cocaine is accompanied by a change in dopaminergic neuronal activity (31).

On the other hand, ginseng saponin inhibits the uptake of DA into the rat brian synaptosomes (33) and DA content is increased in the mouse brain by a ginseng saponin treatment (14). Furthermore, it has been reported that ginsenosides exerted powerful inhibitory actions on catecholamine secretion (30), suggesting that ginseng saponin has the ability to modulate dopaminergic activity preferentially at the presynaptic site. Ginseng saponin has been known as a mixture of more than 11 ginsenosides (13), and the exact action mechanisms mediating the effects of ginsenosides have not been made clear yet. In this study, a single treatment with ginsenosides Rb_1 and Rg_1 inhibited the hyperactivity induced by cocaine in mice. Accordingly, it is hypothesized that the inhibition of cocaine-induced hyperactivity by Rb_1 and Rg_1 may be closely related with the inhibition of dopaminergic activation induced by cocaine at the presynaptic DA receptors.

Repeated treatment with cocaine produces CPP (19,29). Many investigations have implicated the dopaminergic system in the reinforcing effect produced by cocaine (15). The present study showed that CPP induced by cocaine was also inhibited by Rb_1 and Rg_1. The inhibitory effects of Rb_1 and Rg_1 on this action might be associated with the interruption of chronic cocaine-induced dopaminergic activation at the reinforcing dopaminergic system. In connection with this result, there are reports that ginseng saponin or ginseng extracts inhibits the development of sensitization to the locomotor accelerating effect of cocaine (12) and ginseng saponin inhibits hyperactivity and CPP induced by cocaine (13).

The dose 100 mg/kg of ginsenoside used in this study may be regarded as quite large when compared with ginseng or other drugs. However, a single or repeated administration of this 100 mg/kg of Rb_1 and Rg_1 did not show any toxicological symptoms or behavioral side effects such as ataxia, sedation, or place-aversive effects that might interrupt the performance of CPP (data not shown). Furthermore, it has been reported that the lethal doses (LD_{50}) of Rb_1 and Rg_1 were 1,110 and 1,250 mg/kg (IP), respectively (9). Thus, the involvement of any special side effects with this high dose of ginsenosides that may interrupt the performance of cocaine-induced dopaminergic behaviors can be ruled out in the present experiment. Meanwhile, preliminary studies indicated that different dose ranges of ginsenosides produced consistent and reliable inhibitory effects on the cocaine-induced hyperactivity and CPP experiments, respectively. Therefore, the different dose ranges were used on the cocaine-induced hyperactivity and CPP experiments, respectively.

In addition, the postsynaptic DA receptor supersensitivity to apomorphine developed in cocaine-induced CPP mice. DA receptor sensitivity in increased in the postsynaptic sites following the repeated administration of cocaine. Pretreatments with Rb_1 and Rg_1 inhibited the development of the postsynaptic DA receptor supersensitivity in cocaine-induced CPP mice. In support this result, ginseng saponin inhibited the development of the postsynaptic DA receptor supersensitivity to apomorphine in sensitized mice as well as in CPP mice treated with cocaine (12,13). It is suggested that ginsenosides may alter postsynaptic dopaminergic function through the modulation of dopaminergic activity at the presynaptic site.

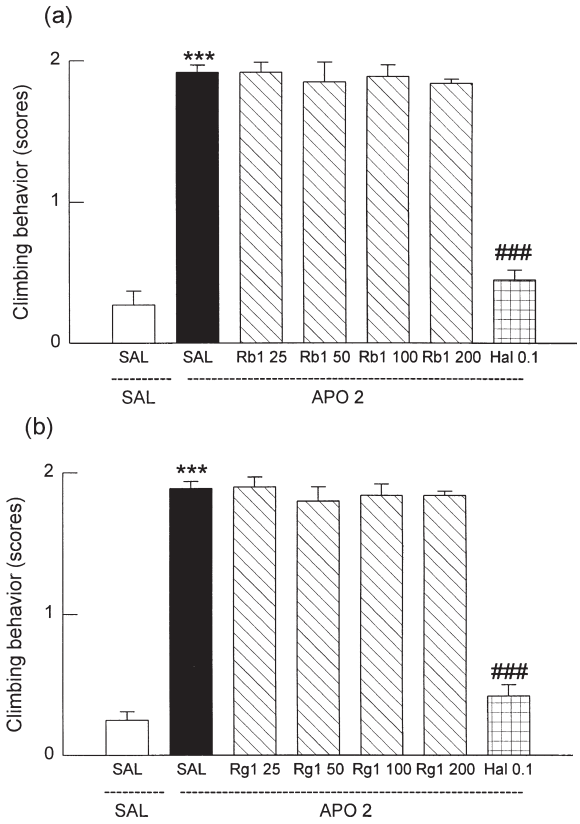

FIG. 4. Effects of (A) Rb_1 and (B) Rg_1 on apomorphine-induced climbing behavior. Rb_1 and Rg_1 (25, 50, 100), and 200 mg/kg, IP) were administered to mice 1 h prior to the injection of apomorphine (2 mg/kg, SC). Haloperidol (0.1 mg/kg, IP) was administered to mice 30 min prior to the injection of apomorphine. Immediately after the injection of apomorphine, the mice were put into individual cylindrical cages. After a 5-min period of exploratory activity, the climbing behavior was measured by all-or-none score at 10, 20, and 30 min after the administration of apomorphine, and the three scores were averaged. The data are expressed as mean ± SE. $***p < 0.001$, compared with that of the saline group, $###p < 0.001$, compared with that of the cocaine group. SAL: saline; COC: cocaine; Rb_1: ginsenoside Rb_1; Rg_1: ginsenosides Rg_1; APO: apomorphine; HAL: haloperidol.

However, it was somewhat surprising that a single administration of Rb_1 and Rg_1 did not inhibit apomorphine-induced striatal dopaminergic behavior, cage climbing, suggesting that Rb_1 and Rg_1 had no antidopaminergic activity at the postsynaptic DA receptor when determined by a cage-climbing behavior model. This results are not consistent with our previous findings (13) that apomorphine-induced climbing behavior was blocked acutely by a single administration of ginseng saponin. The main reasons for this result is not clear.

However, this discrepancy might be produced by the differences in intrinsic in vivo activity against postsynaptic DA receptor between ginseng saponin and ginsenosides Rb_1 or Rg_1, because it has been reported that ginsenosides had the ability to modulate dopaminergic activity preferentially at the presynaptic site (30). The magnitude of inhibitory effects of Rb_1 and Rg_1 on cocaine-induced dopaminergic behaviors might be somewhat smaller than that of ginseng saponin (13).

From these results, it is likely that the inhibitory effects of ginsenosides on cocaine-induced sensitization or CPP may be

closely related to recovery from dysfunction in the dopaminergic system as well as a direct modulation of dopaminergic receptor. Therefore, the present results suggest that Rb_1 and Rg_1 may be the active components of ginseng saponin in mediation of cocaine-induced dopaminergic behaviors such as hyperactivity. It is presumed that Rb_1 and Rg_1 modulate DA activity induced by cocaine at the presynaptic DA receptors, and these modulation results in the inhibition of postsynaptic dopaminergic activation. Furthermore, the degree of the development of postsynaptic DA receptor supersensitivity might be associated with the dopaminergic activation modulated by ginsenosides, because the development of postsynaptic DA receptor supersensitivity that developed in cocaine-induced CPP mice was inhibited by both Rb_1 and Rg_1.

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