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Effects of the Ginsenosides Rg_1 and Rb_1 on Morphine-induced Hyperactivity and Reinforcement in Mice

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Abstract

Recent studies have demonstrated that ginseng saponin inhibits the hyperactivity and conditioned place-preference response induced by psychostimulants and opiates. This seems to occur by direct or indirect modulation of dopaminergic activity. However, it is not known which components of ginseng saponin are active. These experiments were conducted to determine the effects of the ginsenosides Rb_1 and Rg_1, major components of the protopanaxadiol and protopanaxatriol fractions of ginseng saponin, on morphine-induced hyperactivity and conditioned place-preference.

Morphine-induced hyperactivity, but not apomorphine-induced climbing behaviour, was inhibited by both Rb_1 and Rg_1. These findings confirm the hypothesis that ginsenosides modulate catecholaminergic activity preferentially at pre-synaptic sites. Morphine-induced conditioned place-preference was inhibited by Rg_1, but not by Rb_1. It has previously been shown that at low doses Rb_1 and Rg_1 are equally effective at inhibition of catecholamine secretion at the pre-synaptic site, but that at high doses Rg_1 is a more effective inhibitor. This observation might explain our finding that morphine-induced conditioned place-preference was inhibited by Rg_1 only.

Our findings suggest that Rg_1, a component of ginseng saponin with appropriate activity, might be a useful agent for prevention and treatment of the adverse effects of morphine.

Morphine is considered an addictive drug because drug-craving and psychological dependence are commonly associated with its abuse. A single treatment with morphine in animals induces hyperactivity and stereotyped behaviour (Shuster et al 1963). Chronic treatment with morphine influences behaviour in a conditioned place-preference paradigm which is regarded as one model for studying the reinforcing effect of morphine (Mucha et al 1982; Bardo et al 1984). These effects are considered to result primarily from activation of both pre- and post-synaptic dopaminergic receptors.

Panax ginseng is a well-known traditional oriental medicine which has been used therapeutically for thousands of years. Its chemical and pharmacological properties have been assessed recently by several investigators. There is evidence that ginseng has diverse effects on the nervous system, including both excitatory and inhibitory effects (Petkov 1959; Takagi et al 1972; Saito et al 1977a, b); it also modulates the effects of sedatives, hypnotics and convulsants (Oh et al 1969) and has been reported to antagonize morphine-induced anti-nociception and to inhibit the development of tolerance to, and dependence on, morphine (Kim et al 1990).

Recently, Tokuyama et al (1992) have demonstrated that ginseng extracts inhibit methamphetamine sensitization. These investigations with mice suggested that the inhibitory effects of ginseng extracts on methamphetamine-induced reverse tolerance is related to the recovery of dysfunction in the dopaminergic system. Ginseng total saponin (ginseng saponin) has also been reported to prevent both the development of reverse tolerance to the ambulation-accelerating effects and the development of dopamine receptor supersensitivity to morphine and methamphetamine (Kim et al 1995a, b). Kim et al (1995a, b) suggested that the development of reverse tolerance to the ambulation-accelerating effect of these drugs is associated with the enhanced dopamine receptor sensitivity, because both phenomena are blocked by ginseng saponin with similar time-dependence. It has also

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been reported that ginseng saponin inhibits hyperactivity and conditioned place-preference induced by both methamphetamine (Kim et al 1996) and morphine (Kim et al 1998). These previous studies were performed with ginseng saponin, a mixture of several components. It is important to determine which of these components are active. There is currently no indication which components inhibit the hyperactivity and conditioned place-preference induced by morphine.

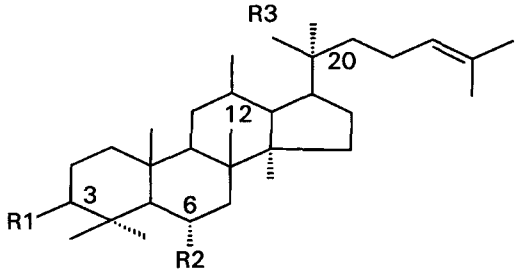
This work was undertaken primarily to determine the effects of the major active protopanaxadiol and protopanaxatriol components of the ginseng saponin fractions ginsenoside Rb_1 (Rb_1) and ginsenoside Rg_1 (Rg_1), respectively. The effects of each ginsenoside on the hyperactivity and conditioned place-preference induced by morphine were assessed. The effects of Rb_1 and Rg_1 on apomorphine-induced climbing behaviour were measured to assess the anti-dopaminergic activity of these ginsenosides.

Materials and Methods

Animals and drugs

Groups of 10–15 male ICR mice (Samyuk Laboratory Animal, Osan, Korea), 20–26 g, were used in all experiments. They were housed 10 to a cage under an artificial 12-h light–dark cycle (lights on 0700 h) and constant temperature (22 ± 2 °C) with water and food freely available.

The drugs used were morphine hydrochloride (Je-il Pharmaceutical, Seoul, Korea), apomorphine hydrochloride (Sigma, St Louis, MO), haloperidol (Whan-In Pharmaceutical, Seoul, Korea) and Rb_1 and Rg_1 (Figure 1; Korea Ginseng and Tobacco Research Institute, Taejon, Korea). Apomorphine was dissolved immediately before use in physiological saline containing 0·1% ascorbic acid. All other drugs were dissolved in physiological saline.



	R1	R2	R3
Ginsenoside Rb_1	-O-Glc^2-Glc	-H	-O-Glc^6-Glc
Ginsenoside Rg_1	-OH	-O-Glc	-O-Glc

Figure 1. The chemical structures of the ginsenosides Rb_1 and Rg_1.

Measurement of hyperactivity

Hyperactivity was measured by means of a tilting-type ambulometer (AMB-10; O'hara, Tokyo, Japan). Each mouse was placed in the activity cage (20 cm diam., 18 cm height) and after a period of acclimatization of 10 min, morphine (10 mg kg^{-1}) was administered subcutaneously. Ambulatory activity was monitored for 60 min after morphine administration. The doses of morphine and the observation period were chosen on the basis of preliminary experiments.

Assessment of conditioned place-preference

Apparatus. The apparatus was constructed as previously reported (Kim et al 1996). Briefly, it comprised two cubic plexiglas compartments ($15 \times 15 \times 15$ cm^3), one with white walls the other with black walls. The compartments were connected by a grey tunnel ($3 \times 3 \times 7{\cdot}5$ cm^3), which could be closed by guillotine doors. The white compartment had a wire-mesh floor and the black compartment had a metal grid floor to provide a tactile difference. Mice were allowed free access to both compartments when the guillotine doors were open during the pre-testing and final testing phase, and the time spent by the mouse in each compartment was recorded for 15 min using infrared detectors interfaced with a computer. The tunnel was designed to be just small enough for the mouse to pass through. Time spent in the tunnel generally represented less than 5% of the total observation period, and was disregarded. All conditioning and test sessions were conducted under ambient lighting (20–30 Lux).

Procedures for place conditioning. Preliminary data from our laboratory have indicated that naive mice spend more time in the black compartment than in the white compartment when given free access to the entire apparatus for 15 min. Thus, to establish conditioning, we paired morphine with the less favoured white compartment. Control mice received an intraperitoneal injection of saline immediately before being placed in the black compartment. Mice were placed in the white compartment immediately after intraperitoneal administration of morphine (5 mg kg^{-1}). The ginsenosides Rb_1 and Rg_1 (25, 50 and 100 mg kg^{-1}, i.p.) were given 1 h before morphine or saline injection, respectively, to test their effect alone or in combination with morphine.

Pre-testing phase. On day 1 mice were pre-exposed to the test apparatus for 5 min. The doors were opened and each animal was allowed to move

freely between the two compartments. On day 2 baseline preference between the two compartments was established during a 15-min observation period.

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

Testing phase. On day 11, the doors of the apparatus were opened and mice were placed initially in the tunnel between the two compartments. The time spent by each mouse in the two compartments was recorded during a 15-min observation period.

Place preference data are expressed as the difference (s) between the time spent in the drug-paired compartment (conditioning stimulus; least preferred initially) and the time spent in the saline-paired compartment.

Measurement of apomorphine-induced climbing behaviour

Apomorphine-induced climbing behaviour was evaluated in mice treated with a single dose of Rb_1 and Rg_1 to assess acute behavioural effects on the post-synaptic dopaminergic system. Haloperidol, a post-synaptic dopamine antagonist, was used as a positive control in this test.

Climbing behaviour in mice was measured by a modification of the method of Protais et al (1976). Immediately after subcutaneous injection of apomorphine ($2\,mg\,kg^{-1}$) mice were placed in individual cylindrical cages (12 cm diam., 14 cm height) with walls of vertical metal bars (2 mm diam., 1 cm apart). After a 5-min period of exploratory activity, the climbing behaviour was measured, as a graded score, 10, 20 and 30 min after administration of apomorphine. Scores for this behaviour were: all four paws on the floor, 0 points; fore feet holding the wall, 1 point; all four paws holding the wall, 2 points. Scores at the three different observation times were averaged. Rb_1 or Rg_1 (25, 50, 100 or $200\,mg\,kg^{-1}$) was administered intraperitoneally to mice 1 h before injection of apomorphine; haloperidol was administered intraperitoneally to mice 30 min before apomorphine.

Statistics

Data are expressed as the means ± s.e.m. The significance of drug effects on all responses except climbing behaviour was assessed by one-way analysis of variance with Dunnett's test for post-hoc comparisons. Climbing behaviour was analysed by use of a Mann-Whitney *U*-test. In all statistical analyses the criterion for significance was $P < 0.05$.

Results

Inhibitory effects of Rb_1 and Rg_1 on morphine-induced hyperactivity

The effects of the ginsenosides Rb_1 and Rg_1 on morphine-induced hyperactivity were evaluated in separate experiments. Preliminary studies established that the greatest effects were seen when the ginsenosides were administrated 3 h before morphine (data not shown). This time interval was used throughout the remaining experiments. Administration of Rb_1 and Rg_1 alone did not have any significant effect on ambulatory activity. Morphine, however, resulted in a marked increase in ambulatory activity compared with the saline control group in each study (Dunnett's test, $P < 0.001$) (Figure 2A and B). Pretreatment with 50, 100 or $200\,mg\,kg^{-1}$ Rb_1 significantly inhibited morphine-induced hyperactivity (Dunnett's test, $P < 0.05$ in each case). Pretreatment with Rg_1 at 50, 100 and

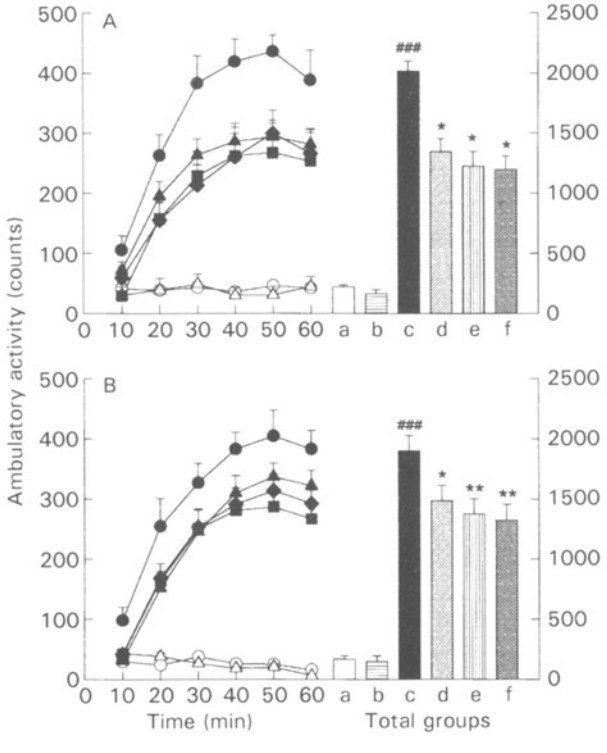


Figure 2. Inhibitory effects of Rb_1 and Rg_1 on morphine-induced hyperactivity in mice. The ginsenosides Rb_1 (A) or Rg_1 (B), 50, 100 or $200\,mg\,kg^{-1}$, were administered intraperitoneally to mice 3 h before subcutaneous injection of $10\,mg\,kg^{-1}$ morphine. Ambulatory activity was measured every 10 min for 1 h after administration of morphine. ### $P < 0.001$, significantly different from the result from the saline group. * $P < 0.05$, ** $P < 0.01$, significantly different from the result from the morphine group. ○, a Saline; △, b Rb_1 (A) or Rg_1 (B) 200; ●, c morphine; ▲, d Rb_1 or Rg_1 $50\,mg\,kg^{-1}$ + morphine; ◆, e Rb_1 or Rg_1 $100\,mg\,kg^{-1}$ + morphine; ■, f Rb_1 or Rg_1 $100\,mg\,kg^{-1}$ + morphine.

200 mg kg^{-1} significantly inhibited morphine-induced hyperactivity (Dunnett's test, $P < 0.05$, $P < 0.01$ and $P < 0.01$, respectively).

Effects of Rb_1 and Rg_1 on morphine-induced conditioned place-preference

Treatment with 100 mg kg^{-1} Rb_1 alone did not significantly influence the conditioned place-preference response compared with that of the saline control group. Furthermore, pretreatment with 25, 50 or 100 mg kg^{-1} Rb_1 did not significantly inhibit the conditioned place-preference response to 5 mg kg^{-1} morphine (Figure 3A). Treatment with 100 mg kg^{-1} Rg_1 alone also had no significant effect on the conditioned place-preference response compared with that of the saline control group (Figure 3B). Mice pretreated with 50 mg kg^{-1} or 100 mg kg^{-1} Rg_1 showed significant inhibition of the conditioned place-preference response to 5 mg kg^{-1} morphine (Dunnett's test, $P < 0.01$ in each case).

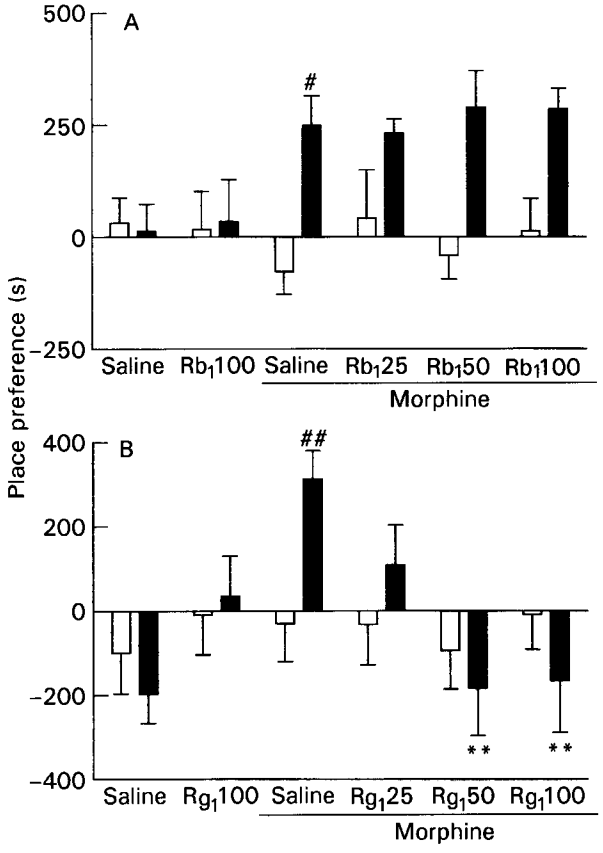


Figure 3. Effects of Rb_1 and Rg_1 on morphine-induced conditioned place-preference. Place preference data are expressed as the difference (s) between the time spent in the drug-paired compartment (conditioning stimulus; least preferred initially) and the time spent in the saline-paired compartment. The ginsenosides Rb_1 (A) or Rg_1 (B), 25, 50 or 100 mg kg^{-1}, were administered intraperitoneally to mice 1 h before intraperitoneal injection of morphine 5 mg kg^{-1} or saline in the conditioning phase. Mice were injected with saline or morphine before confinement in the black or white compartments, respectively, for 60 min every day during an 8-day period. # $P < 0.05$, ## $P < 0.01$, significantly different from the result from the saline group. ** $P < 0.01$, significantly different from the result from the morphine group. □ Pre-test baseline; ■ test.

Effects of Rb_1 and Rg_1 on apomorphine-induced climbing behaviour

Treatment with Rb_1 or Rg_1 (25, 50, 100 or 200 mg kg^{-1}) alone did not evoke any climbing behaviour (data not shown). However, treatment with 2 mg kg^{-1} apomorphine induced a marked increase in climbing behaviour. Pretreatment with Rb_1 or Rg_1 (Table 1) did not significantly inhibit apomorphine-induced climbing behaviour. Pretreatment with haloperidol, however, resulted in significant inhibition of this behaviour. These results suggest that Rb_1 and Rg_1 do not have anti-dopaminergic activity at post-synaptic dopamine receptors.

Discussion

A single administration of morphine induced hyperactivity. This result confirmed results from earlier studies (Shuster et al 1963; Kuschinski & Hornykiewicz 1974). Morphine indirectly stimulates the dopaminergic system by agonistic action on the opioid system, in particular the μ-receptor site (Matsumoto et al 1988); this indirect action results in the activation of the post-synaptic dopamine receptors. Specifically, morphine induces locomotor hyperactivity by releasing dopamine from the pre-synaptic terminals in the striatum (Kuschinski & Hornykiewicz 1974). Furthermore, it has been reported that dopamine receptor antagonists inhibit morphine-induced hyperactivity (Vezina & Stewart 1985). These results suggest that the dopaminergic system might play a primary role in the hyperactivity induced by morphine.

Recent studies have demonstrated that ginseng saponin inhibits the hyperactivity induced by methamphetamine (Kim et al 1996) and morphine (Kim et al 1997). In the current study morphine-induced hyperactivity in mice was inhibited by a single treatment with the ginsenosides Rb_1 and Rg_1, the major protopanaxadiol and protopanaxatriol components, respectively, of ginseng saponin. These findings suggest that the ginsenosides Rb_1 and Rg_1 inhibit the activation of the dopaminergic system induced by morphine. In support of this possibility, Kim et al (1985) have reported that the dopamine content of some brain regions is increased by ginseng saponin. Tsang et al (1985) have demonstrated that ginsenosides inhibit the uptake of dopamine into rat brain synaptosomes, which suggests that ginsenosides might modulate

the dopaminergic system. The mechanisms that underlie the inhibitory effects of ginsenosides on morphine-induced hyperactivity are unclear. It has been postulated that drugs that reduce the availability of catecholamines in the pre-synaptic neuron or block the action of catecholamines on the post-synaptic receptor attenuate the behavioural effects, such as hyperactivity, of stimulants in experimental animals (Wilson & Schuster 1972).

It has also been reported that ginsenosides exert a powerful inhibitory action on catecholamine secretion (Takahashi et al 1993), suggesting that ginseng saponin modulates dopaminergic activity preferentially at the pre-synaptic site. In the current study a single treatment with ginsenosides Rb_1 and Rg_1 inhibited the hyperactivity induced by morphine in mice. Accordingly, it is hypothesized that inhibition of morphine-induced hyperactivity by Rb_1 and Rg_1 is closely related to the inhibition by morphine of activation of pre- and post-synaptic dopamine receptors.

Repeated treatment with morphine in this study produced a conditioned place-preference response, a finding consistent with reports from other studies (Bardo et al 1984; Reid et al 1989). Many investigators have reported the involvement of the dopaminergic system in the reinforcing effects of morphine (Bozarth 1986). These observations imply that the reinforcing effects of opioids are a result of their enhancement of mesolimbic dopamine release and consequent activation of the mesolimbic dopaminergic pathway (Koob & Bloom 1988; Wise & Rompre 1989).

Pretreatment with Rg_1, but not with Rb_1, inhibited the conditioned place-preference response to morphine. The biological effects of ginsenosides differ depending on their structure and on the target examined. Rg_1 stimulates the secretion of adrenocorticotropin from cultured rat pituitary cells whereas Rb_1 does not (Odani et al 1986). Although low doses of Rb_1 and Rg_1 have been shown to cause almost the same amount of inhibition of catecholamine secretion at pre-synaptic sites, high doses of Rg_1 are more powerful in their inhibitory action than Rb_1 (Takahashi et al 1993). It is thus presumed that the inhibition of morphine-induced conditioned place-preference by Rg_1 but not Rb_1 results from differences in the extent of their inhibitory action on dopamine secretion.

The 100 mg kg^{-1} dose of ginsenoside used in this study might be regarded as quite a large dose compared with ginseng saponin or other drugs. However, administration of Rb_1 and Rg_1 at 100 mg kg^{-1}, in either single or repeated doses, did not cause any toxicological symptoms or adverse behavioural effects, such as ataxia, sedation or place aversive effects, that might disrupt the performance of conditioned place-preference testing (data not shown). Furthermore, the lethal doses (LD50) of Rb_1 and Rg_1 have been reported to be 1110 and 1250 mg kg^{-1}, respectively, when administered intraperitoneally (Kaku et al 1975). Thus it is unlikely that any adverse effects associated with this high dose of ginsenosides could have impaired the performance of the mice in the current study of morphine-induced dopaminergic behaviour.

It was somewhat surprising that a single administration of Rb_1 or Rg_1 did not inhibit apomorphine-induced striatal dopaminergic behaviour, such as cage-climbing. This finding suggests that the ginsenosides Rb_1 and Rg_1 have negligible anti-dopaminergic activity at post-synaptic dopamine receptors, at least in terms of cage-climbing behaviour. These results, however, are not consistent with our previous finding that apomorphine-induced climbing behaviour was blocked acutely by a single administration of ginseng saponin (Kim et al 1996). Although the reason for this discrepancy is not clear, it might arise from differences between ginseng saponin and ginsenosides Rb_1 and Rg_1 in intrinsic in-vivo activity against post-synaptic dopamine receptors. It has previously

Table 1. Effects of Rb_1 and Rg_1 on apomorphine-induced climbing behaviour.

Group (mg kg^{-1})	Score	Group (mg kg^{-1})	Score
Saline control	0·27 ± 0·10	Saline control	0·25 ± 0·06
Apomorphine control	1·92 ± 0·05###	Apomorphine control	1·89 ± 0·05###
Ginsenoside Rb_1 (25)	1·92 ± 0·07	Ginsenoside Rg_1 (25)	1·90 ± 0·07
Ginsenoside Rb_1 (50)	1·85 ± 0·14	Ginsenoside Rg_1 (50)	1·79 ± 0·10
Ginsenoside Rb_1 (100)	1·89 ± 0·08	Ginsenoside Rg_1 (100)	1·84 ± 0·08
Ginsenoside Rb_1 (200)	1·84 ± 0·03	Ginsenoside Rg_1 (200)	1·84 ± 0·03
Haloperidol (0·1)	0·45 ± 0·07***	Haloperidol (0·1)	0·42 ± 0·08***

The ginsenosides Rb_1 or Rg_1 were administered intraperitoneally to mice 1 h before subcutaneous injection of apomorphine. Immediately after injection of apomorphine mice were placed in individual cylindrical cages. After a 5-min period of exploratory activity, climbing behaviour was measured as a graded score 10, 20 and 30 min after apomorphine administration, and the three scores were averaged. ### $P < 0.001$, significantly different from the result from the saline group. *** $P < 0.001$, significantly different from the result from the apomorphine group.

been reported that these ginsenosides have the ability to modulate dopaminergic activity preferentially at pre-synaptic sites (Takahashi et al 1993).

It is unlikely that the inhibitory effects of ginseng saponin on morphine-induced dopaminergic behaviour were mediated only by Rg_1, because Rg_1 accounts quantitatively for only 6% of ginseng saponin (Kim et al 1996). In addition, the magnitude of the inhibition of morphine-induced dopaminergic behaviour by the ginsenoside Rg_1 was somewhat smaller than that by ginseng saponin and the effects of ginsenosides were to produce partial inhibition with little evidence of dose-dependency. Further studies employing several ginsenosides simultaneously, at full dose, are needed to ascertain the major active components of ginseng saponin against morphine-induced dopaminergic behaviour.

These results suggest that Rg_1, an active component of ginseng saponin, might be useful for the prevention and treatment of the adverse effects of morphine.

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