Blockade by Ginseng Extract of the Development of Reverse Tolerance to the Ambulation-Accelerating Effect of Methamphetamine in Mice

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ABSTRACT — Daily repeated administration of methamphetamine (MAP) developed reverse tolerance to its ambulation-accelerating effect. After pretreatment of mice daily with ginseng extract (GE) for 5 days, concomitant injections of MAP and GE suppressed the development of reverse tolerance to the effect of MAP, although GE itself did not affect the spontaneous motor activity of the naive mice. These results provide evidence that GE may be useful for prevention and therapy of the adverse action of MAP.

Keywords: Ginseng, Methamphetamine, Reverse tolerance

Much attention has been paid to ginseng saponins because of their multiple pharmacological actions. They also possess central actions such as suppression of exploratory and spontaneous movements (1), prolongation of hexobarbital sleeping time (2) and inhibition of conditioned avoidance response (3). Recently, Kim et al. (4, 5) have demonstrated that administration of ginseng saponins antagonizes morphine antinociception and inhibits the development of morphine tolerance and dependence in mice. Nonetheless, the effect of ginseng saponins on the development of reverse tolerance to the ambulatory activity of MAP, enhancement of the effect during its repeated administrations, has not been reported. The phenomenon of reverse tolerance is a model for studying the psychotoxity of MAP; hence, we have studied here the effect of GE on the phenomenon in mice.

Male mice of the ddY strain weighing 18–20 g (Otsubo Exp. Animals, Nagasaki) were used for the experiments. Standardized *Panax ginseng* extract powder (GE, G115 containing 18% of ginseng total saponins; Pharmaton SA, Switzerland) and methamphetamine-HCl (MAP; Dainippon Pharm. Co., Osaka) were dissolved in saline, in a volume of 0.1 ml/10 g body weight. Using the Ambulometer (O'hara & Co., Ltd., Tokyo), ambulatory activity was measured for 120 min after MAP administration. The statistical significance of differences between the control and each group was determined using repeated measures analysis of variance (ANOVA) followed by Dunnett's test. A difference was considered significant at $P < 0.05$.

MAP at the dose of 1 mg/kg, i.p. enhanced the ambulatory activity in comparison with the saline group. GE at 100 or 200 mg/kg, i.p. given 1, 2, 3 and 4 hr before MAP injection had no effect on the ambulation-accelerating effect of MAP (Fig. 1). On the other hand, daily treatment with MAP increased the ambulatory activity; that is, reverse tolerance was developed to the ambulation-accelerating effect. In mice daily pretreated with GE at 100 or 200 mg/kg, i.p., for 5 days, and from the 6th day, daily given GE 1 hr before MAP injection for another 6 days, GE dose-dependently suppressed the development of reverse tolerance to MAP (two-way, days x groups, ANOVA; days, $F(5,198) = 17.997$, $P < 0.001$; groups, $F(2,198) = 60.098$, $P < 0.001$), while no appreciable suppressive effect was observed in mice not pretreated with GE (Fig. 2). In this case, single or chronic (11 days) treatment with GE alone did not influence the spontaneous motor activity of mice (data not shown).

The possible mechanism underlying the inhibition by GE of the development of reverse tolerance to MAP remains unclear. The sensitization after repeated administration of amphetamine is attributable to the dopa-

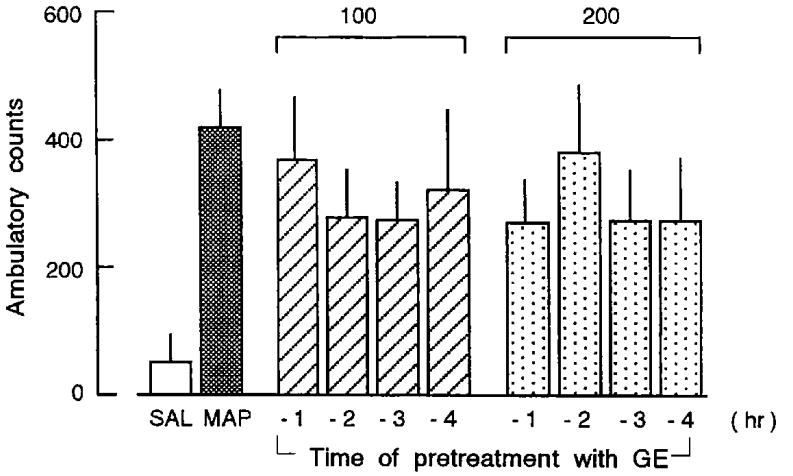

Fig. 1. Influence of ginseng extract given at various intervals prior to methamphetamine injection on the ambulation-accelerating effect. Ambulatory activity was measured using the Ambulometer for 120 min after metahamphetamin (MAP) injection. Ginseng extract (GE), 100 (▨) or 200 (▩) mg/kg, was administered i.p. 1, 2, 3 or 4 hr before 1 mg/kg of i.p.-MAP (▩). The control group (□) was given saline (SAL) alone. Each point is the mean ± S.E. (vertical bar) of the data obtained from 12–14 mice.

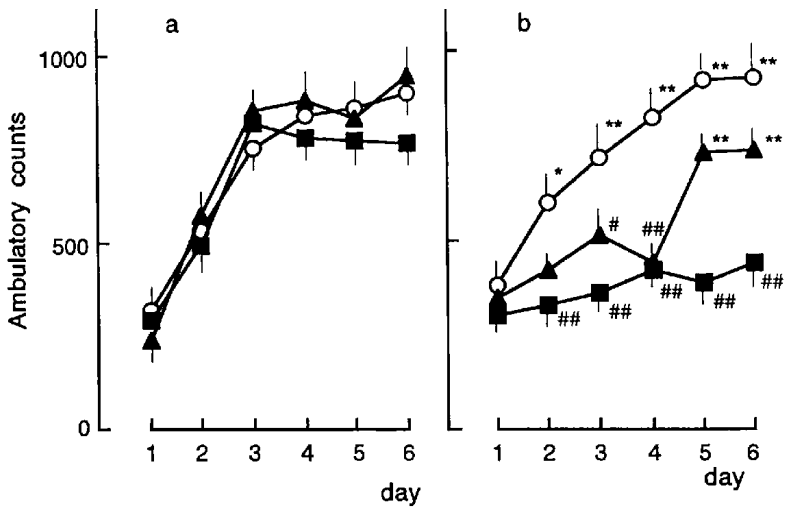

Fig. 2. Effect of ginseng extract (GE) on the development of reverse tolerance to the ambulation-accelerating effect of methamphetamine. a) GE 100 (▲) or 200 (■) mg/kg, i.p. was daily given 1 hr before 1 mg/kg of i.p.-MAP for 6 days. b) Mice were pretreated daily with GE, 100 (▲) or 200 (■) mg/kg, i.p., for 5 days, and from the 6th day, GE was daily given 1 hr before MAP injection for another 6 days. The control group (○) was given saline instead of GE. Each point is the mean ± S.E. (vertical bar) of the data obtained from 12–14 mice. $^{\#\#}P < 0.01$, $^{\#}P < 0.05$, compared with the saline pretreated group. $^{**}P < 0.01$, $^{*}P < 0.05$, compared with the value on the 1st day. For other details, refer to the legend of Fig. 1.

minergic hyperfunction in the central nervous system (6). In support of this, Beninger and Hahn (7) have reported that such sensitization is blocked by neuroleptics. It may be, therefore, plausible that the inhibitory effect of GE on MAP-induced reverse tolerance is related to the recovery of the dysfunction in the dopaminergic system. In fact, Kim et al. (8) and Tsang et al. (9) have shown that dopamine content is increased by ginseng saponin treatment; and the total ginsenoside fraction inhibits the uptake of dopamine into rat brain synaptosomes, suggesting that GE has the ability to modulate the dopaminergic activity preferentially. On the other hand, Kim et al. (5) have demonstrated that daily injections of ginseng saponin in mice prevent the development of reverse tolerance to the locomotor accelerating effect of morphine and suggested that the

inhibitory effect of ginseng saponin on this action may be associated with the interruption of chronic morphine action at the pre-synaptic dopamine receptors. We have previously indicated the difference in the underlying mechanisms among amphetamine, morphine and cocaine for the development of reverse tolerance to their ambulation accelerating- and swimming time prolonging-effect (10). In the present study, however, GE inhibited the development of reverse tolerance to MAP, in addition to Kim's report (5) that the reverse tolerance to morphine was suppressed by ginseng saponin.

By concomitant injections of MAP and GE after 5 daily pretreatments with GE, the development of reverse tolerance to MAP was dose-dependently suppressed; however, without pretreatment of GE, the suppressive effect was not observed. These results indicate that term and timing of drug medication are important factors in the action of GE. Indeed, several pharmacological actions of ginseng saponins are often observed by chronic treatment of these drugs. Accordingly, these results provide evidence that GE may be useful for prevention and therapy of the adverse actions of dependence-liable drugs.

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