Ginseng Saponins Prevent the Adverse Effects of Dependence-liable Drugs

Hack-Seang Kim and Hwa-Kyung Lim

College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

ABSTRACT

A single administration of cocaine (CO), morphine (MOR) and methamphetamine (MA) showed hyperactivity in mice. Ginseng total saponin (GTS), ginsenosides Rb_1 and Rg_1 inhibited the hyperactivity induced by the drugs.

The repeated administration of CO, MOR and MA showed the development of psychological dependence showing as the development of conditioned place preference (CPP) in mice and the development of dopamine (DA) receptor supersensitivity showing as sensitization of the drugs. GTS and Rg_1 inhibited the development of not only psychological dependence but also of DA receptor supersensitivity induced by CO and MA. Rb_1 prevented also the development of psychological dependence and DA receptor supersensitivity induced by CO and MA but not by MOR. These results suggest that the development psychological dependence induced by the drugs is closely related with the development of DA receptor supersensitivity since both phenomena were inhibited by them.

Apomorphine induced climbing behavior was also inhibited by GTS but not by both of Rb_1 and Rg_1, indicating that GTS modulate dopaminergic action at both of pre and postsynaptic sites, but both of Rb_1 and Rg_1, only at the presynaptic site. These results suggest that active components acting at the postsynaptic site exist in GTS. In this study, it was found that GTS, ginsenosides Rb_1 and Rg_1 inhibited tyrosine hydroxylase (TH) and these components exerted inhibitory effects on both Ca^{2+} currents and ΔC_m in rat adrenal chromaffin cells. These results suggest that GTS and ginsenosides regulate catecholamine synthesis and secretion.

Meanwhile, it has been demonstrated that Rb_1, at high doses has more powerful inhibition of catecholamine secretion at the presynaptic site than Rb_1. Therefore, it was presumed that inhibition of morphine induced psychological dependence by Rg_1, but not by Rb_1 results from differences in the extent of this inhibitory action on dopaminergic synthesis and secretion.

Introduction

Dopaminergic and noradrenergic neurons in central nervous system play important roles in the behavioral effects of drugs. Methamphetamine (MA) and cocaine (CO) are compounds which act as central stimulants through an acceleration of release and/or an inhibitioin of uptake of dopamine

(DA) and norepinephrine (Mckim, 1986). Tatum and Seevers (1929) first reported an enhancement of the motor accelerating effect of CO after repeated administration in dogs. Similar enhancement of the ambulation-accelerating effect by repeated administration have been evidenced with many other drugs such as d-amphetamine (Hayashi *et al.*, 1980; Kilbey *et al.*, 1977), MA (Kashiwabara, 1983; Alam, 1981; Hirabayashi *et al.*, 1981), methylphenidate (Hirabayashi *et al.*, 1983), lisuride (Carruba *et al.*, 1975), morphine (Hayashi *et al.*, 1980; Shuster *et al.*, 1975; Lizuka *et al.*, 1983) and the phenomenon is called reverse tolerance. It was also reported that rats sensitized to MA shows an enhanced response to apomorphine, a direct DA receptor agonist, and to nomifensine, a potent DA uptake blocker, suggesting the development of DA receptor supersensitivity (Hunt *et al.*, 1974). It has been demonstrated that the behavioral sensitization after repeated administration of these drugs is attributable to the dopaminergic hyperfunction in the central nervous system (Puri *et al.*, 1973; Robinson *et al.*, 1986; Taylor *et al.*, 1979). A variety of drugs of abuse have been shown to have positive rewarding properties in a number of paradigms. There are now abundant evidences that the rewarding properties of both the psychostimulants and the opioids involve central DA-containing neuronal systems. Initial support for an involvement of DA was provided by the finding that DA receptor antagonists attenuate the rewarding effects of psychostimulants and heroins. In addition, direct DA receptor agonists such as apomorphine and bromocriptine possess rewarding properties. Both of the psychostimulants and the opioids are readily self-administered in a variety of species and display conditioned place preference behavior. It has been hypothesized recently that addictive drugs such as CO, MOR and MA derive their reinforcing quality by stimulating the same neurochemical system that mediates psychomotor activity (Wise and Bozarth, 1987).

It is generally known that *Panax ginseng* has been used as tonics for thousand years. But Kim and his coworkers reported that a folk medicine prescribed by seven herbal drugs including *Panax ginseng* has been used as antinarcotics in the treatment of morphine tolerant-dependent patients, and its effective component was keratin of *Manis squama*. But there were no reports that discussed the effects of *Panax ginseng* in the treatment of morphine tolerant-dependent patients. We hypothesized that ginseng saponins might counteract the reinforcing effects of CO, MOR and MA, since ginseng saponins inhibited the locomotion stimulant actions of CO, MOR and MA. For this reason, we started to work with *Panax ginseng* in the antinarcotic aspects. The traditional prescription for the treatment of morphine tolerant-dependent patient is included in Ginseng Radix, Euphorbiae Pekinensis, Manis squama, Zizyphi Spinosi Semen, Angelicase Gigantis Radix, Cnidii Rhizoma, and Paeoniae Radix.

Methods

1) Animals and Materials

ICR male mice weighing 18-22 g in a group of 10-20, were used in all experiments. They were housed in acrylfiber cage in a controlled room (temperature, $22 \pm 2°C$), and were freely given solid diet and tap water. The drugs used were cocaine hydrochloride (Dae-Won Pharm. Co., Ltd.), methamphetamine hydrochloride (National Institute of Safety Research, Korea), morphine hydrochloride (Dae-Won Pharm. Co., Ltd.), ginseng total saponin (GTS) and ginsenoside Rb_1 and Rg_1 (supplied from Korea Ginseng and Tobacco Research Institute) and apomorphine hydrochloride (Sigma, USA). Except for apomorphine, the drugs were dissolved in physiological saline. Apomorphine was dissolved in saline containing 0.1% ascorbic acid, just prior to the experiment. CO and MOR were administered to mice subcutaneously (s.c.), and MA, GTS and apomorphine were administered to mice intraperitoneally (i.p.).

2) Measurement of the hyperactivity and the development of reverse tolerance

CO 15 mg/kg and MOR 10 mg/kg were administered to mice once a day for 7 days respectively. MA 2 mg/kg was administered to mice every other day for 9 days. Administration of GTS 100 or 200 mg/kg was performed 1 hr prior to the injection of CO, and 3 hr prior to MOR and MA injection, respectively. The motor activity of CO, MOR and MA was measured by their effects on mice ambulatory. The ambulatory activity of mice was measured by the tilting-type ambulometer (AMB-10, O' hara & Co., Ltd., Tokyo). The daily ambulatory activity was measured for 1 hr after CO and MOR, and 2 hr after MA administration. The development of reverse tolerance was evidenced by the enhanced ambulatory activity with repeated administration of the drugs and inhibition of the development of reverse tolerance, by lessor ambulatory activity.

3) Measurement of the conditioned place preference (CPP)

The control mice received i.p. injection of saline, immediately before exposure to the white or black compartment. To study the effect of test drugs on place conditioning, the drugs dissolved in saline (0.1 ml/10 g) were given immediately before the mice were placed in the white compartment. To test the effect of GTS (50, and 100 mg/kg, i.p., in saline) alone or in combination with test drugs, GTS was administered 1 hr prior to test drugs or saline injection.

Phase 1. On day 1, the mice were preexposed to the test apparatus for 5 min. The guillotine doors were raised and each animal was allowed to move freely between two compartments. On day 2, the time spent by the mice in each of the two compartments was recorded for 15 min (Pre-testing phase).

Phase 2. On day 3, 5 and 7, the mice were injected with the test drugs before being confined in the white compartment, non-preferred side, for 60 min. On day 4, 6 and 8, the mice were injected with the saline before being confined in the black compartment, preferred side, for 60 min (Conditioning phase).

Phase 3. On day 9, the guillotine doors were raised, the mice were placed in the tunnel of central

part and the time spent by the mice in each of the two compartments was recorded for 15 min (Testing phase).

4) Measurement of the development of dopamine receptor supersensitivity

The development of dopamine receptor supersensitivity was determined by measuring the enhancement of the ambulatory activity of a dopamine agonist, apomorphine, by repeated administration of CO, MOR and MA.

Results and Discussion

A single administration of CO, MOR and MA showed hyperactivity in mice. GTS and ginsenoside Rb_1 and Rg_1 inhibited the hyperactivity induced by the drugs (Kim *et al.*, 1998a; 1998b). It was also demonstrated that administration of GTS antagonizes MOR antinociception and inhibits the development of MOR tolerance and dependence in mice (Kim *et a...* 1986; 1987). It has been hypothesized recently that addictive drugs such as CO, MOR and MA deriv their reinforcing quality by stimulating the same neurochemical system that mediates psychomotor activity (Wise and Bozarth, 1987).

For these reasons, the effects of GTS on the development of reverse tolerance and the CPP in mice were determined to examine the usefulness for the prevention and therapy of adverse actions of CO, MOR and MA. Daily repeated administration of CO, MOR and MA developed reverse tolerance to the ambulation accelerating effects of the drugs, showing as psychotoxicity. Intraperitoneal administration of GTS prior to and during chronic administration of the drugs inhibited the development of reverse tolerance. The degree of the development of dopamine receptor supersensitivity in mice which had received the same drugs as in that of the development of reverse tolerance was evidenced by the enhanced ambulatory activity of the dopamine agonist, apomorphine. GTS also prevented the development of dopamine receptor supersensitivity induced by the chronic administration of the drugs.

The four times of conditioning of CO, MOR and MA alternative daily produced CPP showing as psychic dependence. The CPP of these drugs was attenuated by the administration of GTS, Rb_1 and Rg_1 prior to and during the conditioning of the drugs (Kim *et al.*, 1998a; 1998b). All of the results provide evidence that *Panax ginseng* may be useful for prevention and therapy of the adverse actions of CO, MOR and MA.

Apomorphine induced climbing behavior was also inhibited by GTS but not by both of Rb_1 and Rg_1, indicating that GTS modulate dopaminergic action at both of pre and postsynaptic sites, but both of Rb_1 and Rg_1, only at the presynaptic site. These results suggest that active components acting at the postsynaptic site exist in GTS. In this study, it was found that GTS, Rb_1 and Rg_1 inhibited

tyrosine hydroxylase (TH) and exerted inhibitory effects on both Ca^{2+} currents and ΔC_m in rat adrenal chromaffin cells (Kim *et al.*, 1998c). These results suggest that GTS, Rb_1 and Rg_1 regulate catecholamine synthesis and secretion. Therefore, it was presumed that the preventive and therapeutic effects of GTS, Rb_1 and Rg_1 on the adverse actions of dependence-liable drugs are mediated partially by the modulation of catecholamine synthesis and secretion.

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