PREVENTION AND THERAPY OF *PANAX GINSENG* ON THE ADVERSE ACTIONS OF DEPENDENCE-LIABLE DRUGS

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INTRODUCTION

Ginseng root has been used in Chinese medicine for thousands of years. The pharmacological effects of ginseng on various organ have been reviewed(Lee *et al.*, 1986). In 1959, Petkov demonstrated that ginseng played an important role in regulating the activity of the intergrating nervous system. His study also showed that Panax ginseng may promote stimulation as well as inhibition of the cortex in the cerebral hemisphere. Oh *et al.*(1966) showed that saponin and oil fraction of ginseng extract at low dose(10 ㎎/㎏) reduced the sedative effect of sodium pentobarbital and shortened sleeping time, whereas a higher dose of ginseng saponin delayed the convulsion time and the death caused by cocaine and pentylenetetrazol. It was also reported that ginseng extract exhibited supression of condition avoidance response(Nabata *et al.*, 1973 ; Saito *et al.*, 1973, 1977a ; Takagi *et al.*, 1972) and reduced sound discrimination (Saito *et al.*, 1977b). Recently, Lee et al.(1990) showed that chronic intake of *Panax ginseng* extract stabilized sleep and wakefulness in food-deprived M rats.

Neurochemical studies have been performed by Tsang *et al.*(1983) on the effects of ginsenosides on the uptake of radioactive gamma-aminobutyric acid(GABA), glutamate, dopamine, norepinephrine and serotonin in rat brain synaptosomes. Their results showed that one of the ginsenosides, Rd, was the most effective in reducing the uptake of norepinephrine > GABA > dopamine > glutamate > serotonin. Dainan *et al.*(1983) showed that a significant increase in the level of norepinephrine and dopamine was observed in the diencephalon and cerebral cortex in animals which had been treated with ginseng, 100 ㎎/㎏, s.c., for 10 days. It was also demonstrated that administration of ginseng total saponin(GTS) antagonizes morphine antinociception and inhibits the development of morphine tolerance and dependence in mice(Kim *et al.*, 1986 ; Kim *et al.*, 1987).

Dopaminergic and noradrenergic neurons in central nervous system play important roles in the behavioral effects of drugs. Methamphetamine and cocaine are compounds which act as central stimulants through an acceleration of release and/or an inhibition of uptake of dopamine and norepinephrine(McKim, 1986). Tatum and Seevers(1929) first reported an enhancement of the motor accelerating effect of cocaine after repeated administration in dogs. Similar enhancements 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), methamphetamine(Kashiwabara, 1983 ; Alam, 1981 ; Hirabayashi *et al.*, 1981) methylphenidate(Hirabayashi *et al.*, 1983), lisuride(Carruba *et al.*, 1985), 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 sensitizied to methamphetamine shows an enhanced response to apomorphine, a direct dopamine receptor agonist, and to nomifensine, a potent dopamine uptake blocker, suggesting the development of dopamine 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 evidence 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 readly self-administered in a variety of species and display conditioned place preference behavior.

It has been hypothesized recently that addictive drugs such as cocaine, methamphetamine and morphine derive 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 conditioned place preference(CPP) in mice were determined to examine the usefulness for the prevention and therapy of dependence-liable drugs-cocaine, methamphetamine and morphine.

MATERIALS AND METHODS

1. Animals and Meterials

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± 2℃), 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.), GTS (gift 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. Cocaine and morphine were administered to mice subcutaneously (s.c.), and methamphetamine, GTS and apomorphine were administered to mice intraperitoneally(i.p.).

2. Measurement of the ambulatory activity and the development of reverse tolerance to the ambulation - accelerating effect

Cocaine 15 ㎎/㎏ and morphine 10 ㎎/㎏ were administered to mice once a day for 7 days respectively. Methamphetamine 2 ㎎/㎏ was administered to mice every other day for 9 days. Administration of GTS 100 or 200 ㎎/㎏ was performed 1 hr prior to the injection of cocaine, and 3 hr prior to morphine and methamphetamine injection, respectively.

The motor activity of cocaine, methamphetamine and morphine was measured by their effects on mice ambulatory activity. 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 morphine and cocaine, and 2 hr after methamphetamine administration.

The development of reverse tolerance was evidenced by the enhanced ambulation - accelerating activity with repeated administration of the drugs and inhibition of the development of reverse tolerance, by lesser ambulatory activity.

3. Measurement of the development of dopamine receptor supersensitivity

The development of dopamine receptor supersensitivity was determined by measuring the enhancement of the hypothemic response to and of the ambulatory activity of a dopamine agonist, apomorphine, by repeated administration of cocaine, methamphetamine and morphine.

3 - 1. Measurement of the hypothermic response to apomorphine

Additional groups of mice that received the same chronic morphine, methamphetamine and cocaine, and GTS were used to determine the effects of these treatments on the hypothermic response to apomorphine.

The hypothermic response to an intraperitoneal injection of apomorphine(Ritzmann *et al.*, 1979) 1㎎/㎏, a dosage enough to produce hypothermia, was determined 24 hr after the final injection of cocaine, methamphetamine or morphine. Body temperature was determined by using telethermometer with a rectal probe (inserted 2.5 cm into the rectum). The measurements were made just prior to and 30 min after apomorphine injection. Data are expressed as the difference between the measurements before and after injection.

3 - 2. Measurement of the ambulatory activity of apomorphine

Other additional groups of mice that had received the same chronic morphine, methamphetamine and cocaine, and GTS were used to determine the effects of these treatments on the apomorphine - induced ambulation - accelerating activity.

The ambulation - accelerating activity of apomorphine(Bhargava, 1980) was measured 24 hr after the final injections of cocaine, methamphetamine and morphine. Mice were first allowed to preambulate for 10 min followed by a 20 min test period. After an interval of 30 min, mice were given apomorphine 4 mg/kg, a dosage which produced significant increase of ambulatory activity. Just after the administration, 10 min preambulation period and 20 min test period were repeated. Data are expressed as the difference between the test activity counts before and after injection.

4. Measurement of the conditioned place preference

4 - 1. Apparatus

The apparatus consisted of two square - base plexiglas compartment(15 X 15 X 15 cm), one with white and the other with black plastic boxes jointed by a grey tunnel (3 X 3 X 7.5 cm) which could be closed by guillotine doors. To provide tactile difference between compartments, the white compartment had a rough floor and the black compartment had a smooth floor. Removal of the guillotine doors during the pre - testing and the final testing phase allowed animals freely access to all two compartments connected with computer.

4 - 2. Procedures

The control mice received i.p. injection of saline, immediately before exposure to the white or black compatment. To study the effect of test drugs on place conditioning, the drugs dissolved in saline (0.1 ㎖/10g) were given immediately before the mice were placed in the white compartment. To test the effect of ginseng saponin(GTS, 50, 100 ㎎/㎏, 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 days 3, 5 and 7, the mice were injected with the test drugs before being confined in the white compartment, non - prefered side, for 40 or 60 min. On days 4, 6 and 8, the mice were injected with the saline before being confined in the black compartment, prefered side, for 40 or 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).

The scores were calculated by changes of the testing phase and the pre-testing phase in the white compartment.

5. Apomorphine-induced climbing behavior

The climbing behavior in mice was measured by modified Protais *et al.*'s method(1976). Apomorphine HCl(Sigma, USA) was used to dissolve in saline containing 0.1% ascorbic acid, just prior to the experiment. Immediately after a subcutaneous injection of apomorphine, the mice were put into cylindrical individual 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, the cilmbing behavior was measured by all or none score at 10, 20 and 30 min after apomorphine administration and the three scores were averaged. The scores of this behavior were evaluated as follows : four paws on the floor(0), four feet holding the wall(1), four paws holding the wall(2). GTS 50, 100 and 200 mg/kg were administered intraperitoneally to mice 1 hr prior to the injection of apomorphine.

6. Statistics

The data were expressed as Mean± S.E.. The significance of differences was analyzed by the Student's t-test.

RESULTS AND DISCUSSION

1. Inhibitory effects of GTS on the ambulatory activity and the development of reverse tolerance to the ambulation-accelerating effect

Cocaine, methamphetamine and morphine at the individual dose enhanced the ambulatory activity in comparison with the saline group. The ambulation-accelerating activities of these drugs were enhanced by repeated treatment ; that is, reverse tolerance was developed to the ambulation-accelerating effects of these drugs. Single or chronic treatment with GTS or saline alone did not influence the spontaneous motor activity of mice. GTS inhibits the ambulatory activity of cocaine, methamphetamine and morphine, and the development of reverse tolerance to the ambulation-accelerating effects of the test drugs.

2. Inhibitory effects of GTS on the development of dopamine receptor supersensitivity

2-1. Inhibitory effects of GTS on the enhanced hypothermic response to apomorphine

The hypothermic responses to apomorphine were enhanced in mice treated with cocaine, methamphetamine and morphine repeatedly, compared with saline control group. Chronic administration of cocaine, methamphetamine and morphine develops dopamine receptor supersensitivity and GTS blocks the development of dopamine receptor supersensitivity.

2-2. Inhibitory effects of GTS on the enhanced ambulatory activity of apomorphine

The ambulatory activities of apomorphine were enhanced in mice treated with cocaine, methamphetamine and morphine repeatedly, compared with saline control group. These results show another evidence that chronic administration of cocaine, methamphetamine and morphine develops dopamine receptor supersensitivity.

3. Inhibitory effects of GTS on conditioned place preference

In this study, cocaine, methamphetamine and morphine displayed their conditioned place preference. GTS also suppressed the development of cocaine, methamphetamine and morphine-induced conditioned place preference.

The present experiments showed that cocaine, methamphetamine and morphine increase the ambulatory activity of mice and the effects are progressively enhanced by repeated administration of these drugs indicating the development of reverse tolerance. These results are identical with those reported previously (Hirabayashi *et al.*, 1981 ; Kuribara *et al.*, 1989 ; Shuster *et al.*, 1977). The phenomenon of reverse tolerance is a model for studying the psychotoxicity of dependence-liable drugs. In addition, it has been hypothesized recently that addictive drugs such as cocaine, methamphetamine and morphine derive their reinforcing quality by stimulating the same neurochemical system that modulates psychomotor activity. The conditioned place preference is a procedure used to investigate potential reinforcing properties of drugs. So the conditioned place preference has been used as a model for studying the psychic dependence of drug abuse. In this experiment, cocaine, methamphetamine and morphine have been shown to produce conditioned place preference. Hence we studied here the effects of GTS on the phenomena in mice in order to estimate the usefulness for therapy of the adverse action of the drugs.

Morphine indirectly stimulates dopaminergic system through an agonistic action in opioid system, in particular, μ-receptor site(Matsumoto *et al.*, 1988 ; Rethy *et al.*, 1971) Chronic administration of morphine leads to the development of supersensitivity of postsynaptic dopamine receptors due to decreased dopamine contents (Puri *et al.*, 1973). Methamphetamine facilitates dopamine release and inhibits uptake of dopamine (Fischman, 1987). Cocaine inhibits reuptake of catecholamines at presynaptic terminals(Moore *et al.*, 1988). Chronic exposure to cocaine produces functional depletion of dopaminergic neuronal activity. In support of this, it has been demonstrated that such sensitization is blocked by neuroleptics(Beninger *et al.*, 1983 ; Gawinm *et al.*, 1984 ; Giannini *et al.*, 1986).

Then the responses to apomorphine, a direct-acting dopamine receptor agonist, should be enhanced since the postsynaptic dopamine receptor supersensitivity develops after the repeated administration of cocaine, methamphetamine and morphine. In the present experiments, the enhancement of the hypothermic

response to and ambulatory activity of apomorphine was observed in groups treated with cocaine, methamphetamine and morphine compared with control group suggesting the development of dopamine receptor supersensitivity. GTS inhibited the development of reverse tolerance to ambulation - accelerating effects of cocaine, methamphetamine and morphine. And GTS also inhibited the development of dopamine receptor supersensitivity by chronic treatment of these drugs. In support of these, Kim *et al.*(1990) demonstrated that standardized ginseng extract inhibited the development of reverse tolerance to the locomotor accelerating activity of morphine and the development of morphine - induced dopamine receptor supersensitivity. And Tokuyama *et al.*(1992) demonstrated that standardized ginseng extract suppressed the development of reverse tolerance to the ambulation - accelerating effect of methamphetamine.

The possible mechanisms underlying the inhibition by GTS of the development of reverse tolerance and dopamine receptor supersensitivity to cocaine, methamphetamine and morphine and the conditioned place preference of the drugs remain unclear. Kim *et al.*(1985) and Tsang *et al.*(1985) have shown that dopamine content is increased by ginseng saponin treatment ; and the ginseng saponin inhibits the uptake of dopamine into rat brain synaptosomes, suggesting that GTS has the ability to modulate the dopaminergic activity preferentially. It may be, therefore, plausible that the inhibitory effects of GTS on the development of reverse tolerance, dopamine receptor supersensitivity to cocaine, methamphetamine and morphine and the conditioned place preference of the drugs were related to the recovery of the dysfuction in the dopaminergic system.

In this study, the ambulatory stimulant effects of cocaine, methamphetamine and morphine exhibited not only sensitization but also the rewarding effects of the drugs following repeated administration. Meanwhile, GTS inhibited the ambulatory stimulant effects of the drugs and the sensitization as well as the rewarding effects. In support of these, Wise and Bozarth proposed psychomotor stimulant theory of addiction that neurochemical mechanisms underlying locomotor stimulation are the same as those underlying reward processes. Ginseng components not only inhibited the deveolpment of reverse tolerance to the ambulation accelerating effect of the drugs, but also prevented the development of dopamine receptor supersensitivity by chronic treatment of these drugs. The conditioned place preference of these drugs was also attenuated by ginseng components.

These results provide evidences that *Panax ginseng* may be useful for prevention and therapy of the adverse action of dependence - liable drugs - cocaine, methamphetamine and morphine.

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