ELSEVIER

Pharmacology Biochemistry and Behavior, Vol. 53, No. 1, pp. 185–190, 1996
Copyright © 1995 Elsevier Science Inc.
Printed in the USA. All rights reserved
0091-3057/96 $15.00 + .00

0091-3057(95)00170-0

Effects of Ginseng Total Saponin on Cocaine-Induced Hyperactivity and Conditioned Place Preference in Mice

HACK-SEANG KIM,*[1] CHOON-GON JANG,* KI-WAN OH,* YEON-HEE SEONG,† HANG-MOOK RHEU,‡ DAE-HYUN CHO‡ AND SEOG-YOUN KANG‡

*Department of Pharmacology, College of Pharmacy, and
†College of Veterinary Medicine, Chungbuk National University, Cheongju 360-763, Korea
‡Department of Toxicology, National Institute of Safety Research, Seoul 122-040, Korea

Received 30 September 1994

KIM, H.-S., C.-G. JANG, K.-W. OH, Y.-H. SEONG, H.-M. RHEU, D.-H. CHO AND S.-Y. KANG. *Effects of ginseng total saponin on cocaine-induced hyperactivity and conditioned place preference in mice.* PHARMACOL BIOCHEM BEHAV **53**(1) 185–190, 1996. – Cocaine produced hyperactivity and conditioned place preference (CPP) following a single or repeated administration. A single or repeated administration of ginseng total saponin (GTS) (100 and 200 mg/kg) inhibited not only cocaine-induced (15 mg/kg) hyperactivity but also CPP in mice. These results suggest that GTS attenuates cocaine-induced CPP by inhibiting the same neurochemical system that mediates cocaine-induced hyperactivity. A single-dose administration of GTS inhibited both cocaine-induced hyperactivity and the apomorphine-induced (2 mg/kg) climbing behavior, suggesting that GTS inhibits cocaine- or apomorphine-induced dopaminergic activity at the postsynaptic DA receptor. Repeated administration of GTS before and during the treatment of cocaine inhibits the development of postsynaptic DA receptor supersensitivity. These results suggest that chronic treatment with GTS might modulate cocaine-induced dysfunction at both the pre- and postsynaptic DA receptors. We conclude that GTS may be useful in the prevention and therapy of the adverse action of cocaine.

Hyperactivity Conditioned place preference Dopamine receptor supersensitivity Cocaine Panax ginseng

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 of drug abuse (6,51). Many reinforcing drugs are known to induce CPP, including cocaine (33,45), morphine (2,40), amphetamines (15,19), and heroin (7,44).

Cocaine produces hyperactivity (10,20) and acts as a stimulant on the CNS by inhibiting the reuptake of dopamine (1,43), norepinephrine (17,27), and serotonin (11,29) at presynaptic terminals. The reinforcing effect is exhibited after chronic exposure to cocaine (28,36), showing a functional depletion of DA synthesis (25,31,49). Some neuropharmacologic investigations suggest an involvement of the mesolimbic and mesocortical dopaminergic system in the neuronal mechanisms mediating cocaine-induced hyperactivity (10,20) and reinforcement (28,36). It has been reported that the dopamine receptor antagonist haloperidol inhibited cocaine-induced hyperactivity (5,35), and that pimozide (32) and haloperidol (46) antagonized cocaine-induced CPP. Pimozide has also been reported to attenuate cocaine self-administration in rats, whereas the noradrenergic receptor blocker phentolamine does not; this suggests a role for the dopaminergic system more than the noradrenergic system in a reinforcing effect (8). Furthermore, 6-hydroxydopamine lesions were shown to decrease cocaine reinforcement (42), and the 5-hydroxytryptamine (5-HT; serotonin) reuptake inhibitor fluoxetine inhibited cocaine self-administration (41). Therefore, these results showed that not only the dopaminergic system but also the serotonergic system may be involved in the mediation of the rewarding effect of cocaine.

On the other hand, ginseng is well known as an herbal medicine and has been used in therapy for thousands of years. Recently, its chemical and pharmacologic properties have

[1] To whom requests for reprints should be addressed.

been reported by investigators in many countries. Numerous reports have made it evident that ginseng has various effects on the nervous system.

Kim et al. (21) reported that ginseng extract inhibited the development of reverse tolerance to the locomotor-accelerating effect of morphine and the development of morphine-induced dopamine receptor supersensitivity. They also reported that ginseng total saponin (GTS), as an active component of ginseng extract, inhibited the development of analgesic tolerance to and physical dependence on morphine (23). Tokuyama et al. (48) showed that standardized ginseng extract prevented the development of reverse tolerance to the ambulation-accelerating effect of methamphetamine. Recently, Kim et al. reported that GTS inhibited the development of reverse tolerance to the ambulation-accelerating effects of cocaine and the development of postsynaptic DA receptor supersensitivity induced by cocaine (22).

However, it has been hypothesized that addictive substances such as cocaine derive their reinforcing quality by stimulating the same neurochemical system that mediates psychomotor activity (52). Because GTS inhibited the locomotor stimulant action of cocaine, we hypothesized that GTS might also counteract the reinforcing effect of cocaine.

For these reasons, the present experiments were undertaken to investigate the inhibitory effects of GTS on cocaine-induced hyperactivity and CPP as an index of reinforcement in mice. Furthermore, the effects of GTS on the development of postsynaptic dopamine receptor supersensitivity were also examined in cocaine-induced CPP in mice. In addition, apomorphine-induced climbing behavior was determined in mice treated with a single dose of GTS to examine the acute effects of GTS on postsynaptic dopaminergic receptors.

METHODS

Animals and Drugs

We used male ICR mice, weighing 22–26 g, in a group of 10–20, in all experiments. They were housed in an acrylic fiber cage with water and food available ad lib under an artificial 12 L : 12 D cycle (light on at 0700 h) and at a constant temperature (22 ± 2°C).

The drugs used were cocaine hydrochloride (Han-Saem Pharm Co., Ltd., Seoul, Korea), apomorphine hydrochloride (Sigma, St. Louis, MO), and GTS [characterized saponin mixture quantatively containing at least 11 glycosides: Rb1 (18.26%), Rb2 (9.07%), Rc (9.65%), Rd (8.24%), Re (9.28%), Rf (3.48%), Rg1 (6.42%), Rg2 (3.62%), Rg3 (4.70%), Ro (3.82%), Ra (2.91%), and other minor ginsenosides and components (20.55%) from Panax ginseng, extracted and purified by the method of Namba et al. (34) and supplied by Korea Ginseng and Tobacco Research Institute, Taejon, Korea]. Except for apomorphine, the drugs were dissolved in physiologic saline. Apomorphine was dissolved in saline containing 0.1% ascorbic acid just before the experiment.

Measurement of Cocaine-Induced Hyperactivity

The ambulatory activity of mice was measured by the tilting-type ambulometer (AMB-10; O'Hara Co., Ltd., Tokyo, Japan). Each mouse was placed in an activity cage (20 cm in diameter and 18 cm in height), and after an adaptation period of 10 min, cocaine was administered subcutaneously (SC). The mice were pretreated with GTS intraperitoneally (IP) 1 h before the injection of cocaine. The ambulatory activity was measured every 10 min for 1 h after the administration of cocaine.

Measurement of Cocaine-Induced CPP

Apparatus. The CPP apparatus was made by modifying the method of Mucha et al. (33). It consisted of two square-base Plexiglas compartments (15 × 15 × 15 cm), one white and one black box joined by a grey tunnel (3 × 3 × 7.5 cm), which could be closed by guillotine doors. To provide tactile difference between compartments, the white compartment had a rough floor, whereas the black compartment had a smooth floor. Removal of the guillotine doors during the pretesting and final testing phase allowed animals free access to both compartments, and the time a mouse spent in each compartment was recorded for 15 min using a computer connected to infrared detectors.

Procedures. The control mice received an IP injection of saline just before entering the white or black compartment. Cocaine HCl (15 mg/kg, IP, of base) dissolved in saline (0.1 ml/10 g) was administered immediately before the mice were placed in the white compartment. To test the effect of GTS (50 and 100 mg/kg, IP) alone or in combination with cocaine, GTS was administered 1 h before the cocaine or saline injection.

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

Phase 2 (conditioning phase). On days 3, 5, and 7, the mice were injected with cocaine before being confined to the white compartment, the nonpreferred side, for 40 min. On days 4, 6, and 8, the mice were injected with saline before being confined to the black compartment, the preferred side, for 40 min.

Phase 3 (testing phase). On day 9, the guillotine doors were raised. The mice were initially placed in the tunnel and the time spent by the mice in the two compartments was recorded for 15 min using a computer.

The scores were calculated by changes in the testing phase and the pretesting phase in the white compartment.

Measurement of the Development of Dopamine Receptor Supersensitivity

Additional groups of mice with the same treatment of confinement and repeated injection of cocaine or GTS were used in this experiment. The development of dopamine receptor supersensitivity was determined by the enhancement of ambulatory activity to a dopamine agonist, apomorphine, 24 h after the final CPP confinement. The ambulation-accelerating activity to apomorphine was measured by modifying Bhargava's method (4). Mice were first allowed to preambulate for 10 min and were given apomorphine 2 mg/kg (SC), a dosage that produced a significant increase in ambulatory activity. The ambulatory activity of apomorphine was measured for 20 min.

Measurement of Apomorphine-Induced Climbing Behavior

In the previous experiment, chronic treatment with GTS inhibited the development of dopamine receptor supersensitivity induced by cocaine. Therefore, apomorphine-induced climbing behavior in mice treated with a single dose of GTS was determined to investigate the acute behavioral effects of GTS on the postsynaptic dopaminergic receptor. Climbing behavior in mice was measured by modifying the method of Protais et al. (39). Immediately after an SC injection of 2

mg/kg apomorphine, the mice were put into individual cylindrical cages 12 cm in diameter and 14 cm in height, with walls of vertical metal bars (2 mm in diameter and 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 intervals after the administration of apomorphine, and the three scores were averaged. The scores of this behavior were evaluated as follows: four paws on the floor = 0 points; forefeet holding the wall = 1 point; and four paws holding the wall = 2 points. GTS (50, 100, and 200 mg/kg) was administered IP to mice 1 h before the injection of apomorphine.

Statistics

The data are expressed as mean ± SE. The significance of drug effects was assessed by analysis of variance (ANOVA), and the significance between individual dose conditions and the corresponding control group was determined by Student's *t*-test.

RESULTS

Inhibitory Effect of GTS on Cocaine-Induced Hyperactivity

There was no significant difference in ambulatory activity between any groups of mice treated only with saline and GTS (Fig. 1). However, the cocaine-treated group showed a marked increase of ambulatory activity at 1237 counts, 1117 counts more than that of the saline control group ($p < 0.001$). Meanwhile, 100 mg/kg of the GTS-pretreated group showed a significant inhibition of ambulatory activity at 572 counts, 665 counts less than that of the cocaine control group ($p < 0.001$). The 200 mg/kg GTS-pretreated group also showed a marked inhibition at 321 counts, 916 counts fewer than that of the cocaine control group ($p < 0.001$).

Inhibitory Effect of GTS on Cocaine-Induced CPP

We used 15 mg/kg cocaine in this experiment because a preliminary experiment using 7.5, 15, and 30 mg/kg showed

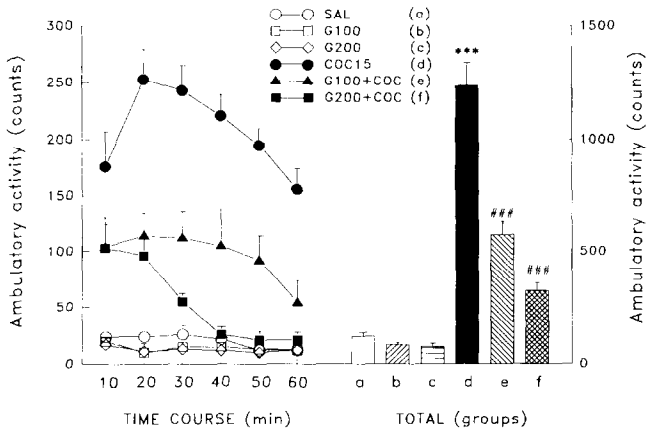

FIG. 1. Inhibitory effect of GTS on cocaine-induced hyperactivity in mice. GTS 100 or 200 mg/kg (IP) was administered to mice 1 h before the injection of 15 mg/kg cocaine (SC). Ambulatory activity was measured every 10 min for 1 h after the administration of cocaine. ***$p < 0.001$ compared with that of the saline group; ###$p < 0.001$ compared with that of the cocaine group. SAL, saline; G, GTS (ginseng total saponin); COC, cocaine.

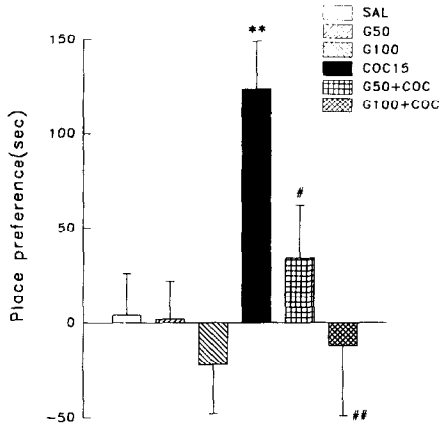

FIG. 2. Inhibitory effect of GTS on cocaine-induced CPP. GTS 50 and 100 mg/kg (IP) were administered 1 h before the injection of cocaine or saline (IP). In the conditioning phase, mice were injected with saline or cocaine before being confined to the black or white compartment for 40 min. The scores were calculated from the changes of the testing phase (15 min) and the pretesting phase (15 min) in the white compartment. **$p < 0.01$ compared with that of the saline group; #$p < 0.05$, ##$p < 0.01$ compared with that of the cocaine group.

that this dose produced the maximum response (data not shown). The 50 and 100 mg/kg GTS-treated groups showed no CPP compared with that of the saline control group (Fig. 2). The 50 mg/kg GTS-pretreated group showed a significant inhibition of 15 mg/kg cocaine-induced CPP at 34 s, 90 s fewer than 124 s of the cocaine control group ($p < 0.05$). Pretreatment with 100 mg/kg GTS showed a marked inhibition of 15 mg/kg cocaine-induced CPP at −12 s, 136 s less than that of the cocaine control group ($p < 0.01$).

Inhibitory Effect of GTS on the Development of Dopamine Receptor Supersensitivity in Cocaine-Induced CPP Mice

The ambulatory activities of apomorphine were enhanced in mice treated with cocaine compared with that of the saline group. The cocaine-treated group showed a significant increase of ambulatory activity to 2 mg/kg apomorphine at 230 counts, 100 counts more than the 130 counts of the saline control group. Meanwhile, 50 or 100 mg/kg of the GTS-pretreated groups showed significant inhibitions of enhanced ambulatory activity to apomorphine at 150 and 130 counts, 80 and 100 counts fewer than the 230 counts of the cocaine control group, respectively (Fig. 3). However, the GTS control group showed no significant effect.

The results suggest that dopamine receptor supersensitivity is developed in cocaine-induced CPP mice and that GTS blocks the development of dopamine receptor supersensitivity in cocaine-induced CPP mice.

Inhibitory Effect of GTS on Apomorphine-Induced Climbing Behavior

We used 2 mg/kg apomorphine in this experiment because a preliminary experiment using apomorphine 0.5, 1.0, 2.0, and 4.0 mg/kg showed that this dose produced the maximum response (data not shown). GTS 50, 100, and 200 mg/kg-treated groups did not show any climbing behavior compared with the saline control group in a preliminary experiment (data

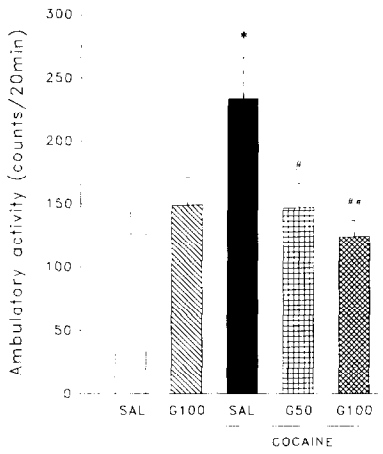

FIG. 3. Inhibitory effect of GTS on ambulatory activity from apomorphine in cocaine-induced CPP mice. Ambulatory activity from apomorphine was determined 24 h after the final confinement. Mice were injected with apomorphine 2 mg/kg (SC) and allowed to preambulate for 10 min; then, they were tested for 20 min. $*p < 0.05$ compared with that of the saline group; $\#p < 0.05$, $\#\#p < 0.01$ compared with that of the cocaine group.

not shown). Pretreatment with 100 or 200 mg/kg GTS showed significant inhibitions of apomorphine-induced climbing behavior at 1.14 and 0.95 scores, 0.78 and 0.97 scores fewer than the 1.92 scores of the apomorphine control group, respectively ($p < 0.05$ and $p < 0.01$) (Fig. 4). These results showed that a single-dose administration of GTS inhibits apomorphine-induced climbing behavior showing antidopaminergic activity at the postsynaptic dopaminergic receptor.

DISCUSSION

In this study, cocaine produced hyperactivity and CPP following a single or repeated administration. 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 (52). It has been demonstrated that cocaine-induced hyperactivity (10,20) and reinforcement (28,36) appear to involve the activation of the mesolimbic dopaminergic system. Cocaine inhibited the reuptake of monoamine at presynaptic terminals (1,11,17,31). Therefore, chronic administration of cocaine results in the depletion of catecholamine at the presynaptic site (25,31,49) and then in the development of dopamine receptor supersensitivity. In conjuction with these facts, it has been presumed that the behavioral sensitization produced by chronic administration of cocaine is accompanied by a change in dopaminergic neuronal activity. In support of this, it has been demonstrated that such sensitization is blocked by neuroleptics (14).

However, it has also been reported that rats sensitized to cocaine showed an enhanced response to apomorphine, a direct dopamine receptor agonist, suggesting the development of dopamine receptor supersensitivity (9,30). It has been demonstrated that behavioral sensitization after repeated administration of cocaine can be attributed to dopaminergic hyperfunction in the CNS (47).

In this experiment, dopamine receptor supersensitivity to apomorphine was developed in cocaine-induced CPP mice. However, a 5-HT-induced head twitch response (3,16) was not enhanced in cocaine-induced CPP mice, suggesting that postsynaptic 5-HT receptor supersensitivity did not develop in this experiment (data not shown). Therefore, the inhibitory effect of GTS on the development of 5-HT receptor supersensitivity was not determined in cocaine-induced CPP mice. These results suggest that the DA system, not the serotonergic system, is mainly involved in cocaine-induced CPP. In support of this, the psychotropic effects of cocaine are reported to contribute via its ability to block the reuptake of dopamine into mesocortical or mesolimbic neurons, rather than via its ability to block the reuptake of 5-HT and norepinephrine (12).

Pretreatment with GTS inhibited cocaine-induced hyperactivity as well as CPP in mice. This pretreatment also inhibited the development of postsynaptic DA receptor supersensitivity. These results suggest that GTS attenuates not only cocaine-induced CPP by inhibiting the same neurochemical system that mediates cocaine-induced hyperactivity, but also the development of DA receptor supersensitivity. In support of these findings, Kim et al. (21) demonstrated that standardized ginseng extract inhibited the development of reverse tolerance to the locomotor-accelerating effect of morphine and the development of morphine-induced dopamine receptor supersensitivity, suggesting that the inhibitory effect of ginseng extract on this action may be associated with the interrruption of chronic morphine action at the presynaptic dopamine receptor. Tokuyama et al. (48) demonstrated that ginseng extract inhibited the development of reverse tolerance to the ambulation-accelerating effect of methamphetamine and showed that the inhibitory effect of ginseng extract on methamphetamine-induced reverse tolerance was related to recovery from dysfunction in the dopaminergic system. However, the possible mechanisms underlying the inhibition, by GTS, of cocaine-induced hyperactivity, CPP, and DA receptor supersensitivity

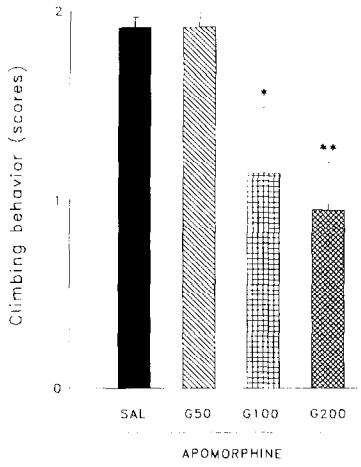

FIG. 4. Inhibitory effect of GTS on apomorphine-induced climbing behavior. GTS 50, 100, and 200 mg/kg (IP) were administered to mice 1 h before the injection of apomorphine (SC). Immediately after the injection of apomorphine, the mice were put into individual cylindrical cages. After a 5-min period of exploratory activity, climbing behavior was measured by all-or-none score at 10-, 20-, and 30-min intervals after apomorphine administration and the three scores were averaged. $*p < 0.05$, $**p < 0.01$ compared with that of the apomorphine group.

remain unclear. Kim et al. (24) and Tsang et al (50) showed that dopamine content is increased by ginseng saponin treatment, and that the ginseng saponin inhibits the uptake of dopamine into rat brain synaptosomes, suggesting that GTS has the ability to modulate dopaminergic activity preferentially. It has been reported that the inhibitory effects of GTS on the development of reverse tolerance and dopamine receptor supersensitivity to cocaine may be related to recovery from dysfunction at both the pre- and postsynaptic dopamine receptors (22), because the cocaine action on dopamine receptor is indirect, as Gawin (13), Gianini (14), and Moore (31) suggested; and a postsynaptic increase in D_1 dopamine receptor sensitivity following the chronic administration of cocaine has been demonstrated (18,26). In addition, ginseng extract has been reported to lower adenylate cyclase in a high dose (200 mg/kg) (38); and ginsenoside Rb2, one of the active components of GTS, inhibited adenylate cyclase activity (37). These results suggest that GTS may alter postsynaptic DA receptor supersensitivity through the modulation of adenylate cyclase activity.

Meanwhile, apomorphine-induced climbing behavior is a procedure used to examine the direct dopaminergic activity of drugs at the receptor. A single dose of GTS inhibited not only apomorphine-induced climbing behavior but also cocaine-induced hyperactivity, suggesting that GTS inhibits cocaine or apomorphine-induced dopaminergic activity at postsynaptic receptors. Therefore, it was also presumed that inhibitory effects of GTS on cocaine-induced hyperactivity, CPP, and DA receptor supersensitivity may be related to the recovery of the dysfunction at both the pre- and postsynaptic DA receptors.

In conclusion, administration of cocaine produced an exhibition of hyperactivity and CPP. Administration of GTS before and during the treatment of cocaine inhibited not only cocaine-induced hyperactivity and CPP in mice, but also the development of cocaine-induced postsynaptic DA receptor supersensitivity. These results suggest that GTS might modulate cocaine-induced dysfunction at both the pre- and postsynaptic DA receptors. From these results, we can conclude that GTS may be useful for the prevention and treatment of the adverse action of cocaine.

ACKNOWLEDGEMENT

This study was supported by the Nondirect Research Fund (1994-1995) from Korea Research Foundation, Ministry of Education, Korea.

REFERENCES

1. Akimoto, K.; Hamamura, T.; Otsuki, S. Subchronic cocaine treatment enhanced cocaine-induced dopamine efflux, studied by in vivo intracerebral dialysis. Brain Res. 490:339-344; 1989.
2. Bardo, M. T.; Miller, J. S.; Neisewander, J. S. Conditioned place preference with morphine: The effect of extinction training on the reinforcing CR. Pharmacol. Biochem. Behav. 21:545-549; 1984.
3. Bedard, P.; Pycock, C. J. Wet-dog shake behavior in the rat: A possible quantitative model of central 5-hydroxytryptamine activity. Neuropharmacology 16:663-670; 1977.
4. Bhargava, H. N. Cyclo(leucylglycine) inhibits the development of morphine induced analgesic tolerance and dopamine receptor supersensitivity in rat. Life Sci. 27:117-123; 1980.
5. Bhattacharyya, A. K.; Aulakh, C. S.; Pradhan S.; Ghosh, P.; Pradhan, S. N. Modification of behavioral and neurochemical effects of cocaine by haloperidol. Arch. Int. Pharmacodyn. Ther. 238:71-80; 1979.
6. Bozarth, M. A. Condition place preference: A parametric analysis using system heroin injection. In: M. A. Bozarth, ed. Methods of assessing the reinforcing properties of abuse drugs, New York: Springer; 1987:241-273.
7. Bozarth, M. A.; Wise, R. A. Heroin reward is dependent on a dopaminergic substrate. Life Sci. 29:1881-1886; 1981.
8. DeWit, H.; Wise, R. A. Blockade of cocaine reinforcement in rats with dopamine receptor blocker pimozide but not with noradrenergic blockers phentolamine and phenoxybenzamine. J. Psychol. 31:195-203; 1977.
9. Dwoskin, L. P.; Peris, J.; Yasuda, R. P.; Philpott, K.; Zahnister, N. R. Repeated cocaine administration results in supersensitivity of striatal D_2 dopamine autoreceptors to pergolide. Life Sci. 42: 255-262; 1988.
10. Elliot, P. J,; Rosen, G. M.; Nemeroff, C. B. A comparison of cocaine and its metabolic norcocaine: Effect on locomotor activity. Pharmacol. Biochem. Behav. 26:573-575; 1987.
11. Friedman, E.; Gershom, S.; Rotrosen, J. Effects of acute cocaine treatment on the turnover of 5-hydroxytryptamine in the rat brain. Br. J. Pharmacol. 54:61-64; 1975.
12. Galloway, M. P. Neurochemical interactions of cocaine with dopaminergic systems. Trends Pharmacol. Sci. 9:451-454; 1988.
13. Gawin F. M.; Kleber, D. H. Cocaine abuse treatment: Open pilot trial with desipramine and lithium carbonate. Arch. Gen. Psychiatry 11:903-904; 1984.
14. Giannini, A. J.; Malone, D. H.; Giannini, M. C. Treatment of depression in chronic cocaine and phecyclidine abuse with desipramine. J. Clin. Pharmacol. 26:211-214; 1986.
15. Gilbert, D.; Cooper, S. J. Beta-phenylethylamine-, *d*-amphetamine- and *l*-amphetamine-induced place preference conditioning in rats. Eur. J. Pharmacol. 95:311-314; 1983.
16. Green, A. R. 5-HT-Mediated behavior. Neuropharmacology 23: 1521-1528; 1984.
17. Hadfield, M. G.; Mott, D. E. W.; Ismay, J. A. Cocaine: Effect of in vivo administration on synaptosomal uptake of norepinephrine. Biochem. Pharmacol. 29:1861-1863; 1980.
18. Henry, D. J.; White, F. J. Repeated cocaine administration causes persistent enhancement of D_1 dopamine receptor sensitivity within the rat nucleus accumbens. J. Pharmacol. Exp. Ther. 258:882-890; 1991.
19. Hoffman, D. C.; Beninger, R. J. The effect of selective dopamine D_1 or D_2 receptor antagonist on the establishment of agonist induced place conditioning. Pharmacol. Biochem. Behav. 33:273-279; 1989.
20. Kalivas, P. W.; Duffy, P.; DuMars, L. A.; Skinner, C. J. Behavioral and neurochemical effects of acute and daily cocaine administration in rats. J. Pharmacol. Exp. Ther. 245:485-492 ; 1988.
21. Kim, H. S.; Jang, C. G.; Lee, M. K. Antinarcotic effects of the standardized ginseng extract G115 on morphine. Planta Med. 56: 158-163; 1990.
22. Kim, H. S.; Kang, J. G.; Seong, Y. H.; Nam, K. Y.; Oh, K. W. Blockade by ginseng total saponin of the development of cocaine induced reverse tolerance and dopamine receptor supersensitivity in mice. Pharmacol. Biochem. Behav. (in press).
23. Kim, H. S.; Oh, K. W.; Park, W. K.; Choi, J. W.; Bae, D. S. Effects of panax ginseng on the development of morphine induced tolerance and dependence (VI). On the oral administration of ginseng ether fraction and saponins. Arch. Pharmacol. Res. 10:188-192; 1987.
24. Kim, Y. C.; Lee, J. H.; Kim, M. S.; Lee, N. G. Effect of the saponin fraction of panax ginseng on catecholamines in mouse brain. Arch. Pharmacol. Res. 8:45-49; 1985.
25. Kleven, M.; Woolverton, W. L.; Seiden, L. S. Lack of long-term monoamine depletions following repeated or continuous exposure to cocaine. Brain Res. 8:45-49; 1985.
26. Lakoski, J. M.; Galloway, M. P.; White, F. J. Cocaine: Pharmacology, physiology and clinical strateges. In: White, F. J.; Henry, D. J.; Hu, X.; Jeziorski, M.; Ackerman, J. M., eds. Electrophysi-

ological effects of cocaine in the mesoaccumbens dopamine system. Boca Raton, FL: CRC Press; 1992:262–293.
27. Langer, S. Z.; Enero, M. A. The potentiation of responses to adrenergic nerve stimulation in the presence of cocaine: Its relationship to the metabolic fate of released norepinephrine. J. Pharmacol. Exp. Ther. 191:431–443; 1971.
28. Mackey, W. B.; Van der Kooy, D. Neuroletics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. Pharmacol. Biochem. Behav. 22: 101–105; 1985.
29. McKim, W. A. Psychomotor stimulants and antidepressants. In: Drugs and behavior: An introduction to behavioral pharmacology. Englewood Cliffs, NJ: Prentice Hall; 1986:161–185.
30. Meno, M.; Pradhan, S.; Hanbauer, I. Cocaine-induced supersensitivity of striatal dopamine receptors: Role of endogenous calmodulin. Neuropharmacology 20:1145–1150; 1981.
31. Moore, K. E.; Chiuch, C. C.; Zelole, G. Release of neurotransmitters from the brain in vivo by amphetamine, methylphenidate and cocaine. In: Ellinwood, E. H., Jr.; Kilbey, M. M. Advances in behavioral biology. New York: Plenum; 1977:143–160.
32. Morency, M. A.; Beninger, R. J. Dopaminergic substrates of cocaine-induced place conditioning. Brain Res. 399:33–41; 1987.
33. Mucha, R. F.; Van der Kooy, D.; O'Shaughnessy, M.; Bucenieks, P. Drug reinforcement studied by the use of place conditioning in rat. Brain Res. 243:91–105; 1982.
34. Namba, T.; Yoshizaki, T.; Tominori, K.; Kobashi, K.; Mitsui, K.; Hasse, J. Fundamental studies on the evaluation of the crude drugs. 1. Planta Med. 32:588–594; 1974.
35. Nemeroff, C. B.; Luttinger, D.; Hernandez, D. E.; Mailman, R. B.; Mason, G. A.; Davis, SD; Widerlov E.; Frye, G. D.; Kilts, C. A.; Beaumont, K.; Breese, G. R.; Prange, A. J., Jr. Interactions of neurotensin with brain dopamine system: Biochemical and behavioral studies. J. Pharmacol. Exp. Ther. 225:337–345; 1983.
36. Nomikos, G. G.; Spyraki, C. Cocaine-induced place conditioning: Importance of route of administration and other procedual variables. Psychopharmacology 94:119–125; 1988.
37. Park, I. W.; Lee, Y. Y.; Lee, K. S.; Seo, K. L.; Chan, M. K. The reciprocal effects of several ginsenosides on the adenylate cyclase and guanylate cyclase. Proceedings of the 4th International Ginseng Symposium; 1984:107.
38. Petkov, V. W. Effects of ginseng on the brain biogenic monoamines and 3′,5′-AMP system. Experiments on rats. Arzneimittelforschung 28:388–393; 1978.
39. Protais, P.; Costentin, J.; Schwartz, J. C. Climbing behavior induced by apomorphine in mice: A simple test for the study of dopamine receptors in striatum. Psychopharmacology 50:1–6; 1976.
40. Reid, L. D.; Marglin, S. H.; Mattie, M. E.; Hubbell, C. L. Measuring morphine's capacity to establish a place preference. Pharmacol. Biochem. Behav. 33:765–775; 1989.
41. Richardson, N. R.; Roberts, D. C. Fluoxetine pretreatment reduces breaking points on a progressive ratio schedule reinforced by intravenous cocaine self-administration in the rat. Life Sci. 49: 833–840; 1991.
42. Roberts, D. C. S.; Koob, G. F. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacol. Biochem. Behav. 17:901–904; 1982.
43. Scheel-Kruger, J.; Braestrup, C.; Nielson, M.; Golembrowska, K.; Mogilnicka, E. Cocaine: Discussion on the role of dopamine in the biochemical mechanism of action. In: Elliwood, E. M.; Kilbey, M. M., eds. Cocaine and other stimulants. New York: Plenum; 1977:373–408.
44. Schenk, S.; Hunt, T.; Colle, L.; Amit, Z. Isolation vs. grouped housing: Differential effects of low doses of heroin in the place preference paradigm. Life Sci. 32:1129–1134; 1983.
45. Spyraki, C.; Fibiger, H. C.; Philips, A. G. Cocaine-induced place preference conditioning: Lack of effects of neuroleptics and 6-hydroxydopamine lesions. Brain Res. 253:195–203; 1982.
46. Spyraki, C.; Nomicos, G. G.; Varonos, D. D. Intravenous cocaine-induced place preference: Attenuation by haloperidol. Bahav. Brain Res. 26:57–62; 1987.
47. Taylor, D.; Ho, B. T.; Fager, J. D. Increased dopamine receptor binding in rat by repeated cocaine injections. Commun. Psychol. Pharmacol. 3:137–142; 1979.
48. Tokuyama, S.; Oh, K. W.; Kim, H. S.; Takahashi, M.; Kaneto, H. Blockade by ginseng extract of the development of reverse tolerance to the ambulation-accelerating effect of methamphetamine in mice. Japan J. Pharmacol. 59:423–425; 1992.
49. Trulson, M. E.; Ulissey, M. J. Chronic cocaine administration decreases dopamine synthesis rate and increases [^{3}H]-spiroperidine binding in rat brain. Brain Res. 19:35–38; 1987.
50. Tsang, D.; Yeung, H. W.; Tso, W. W.; Peck, H.; Lay, W. P. Effect of saponins isolated from ginseng on the uptake of neurotransmitter in rat brain synaptosomes. Neurosci. Lett 12(Suppl): S20; 1980.
51. Van der Kooy, D. Place conditioning: A simple and effective method for assessing the motivational properties of drugs. In: Bozarth, M. A., ed. Methods of assessing the reinforcing properties of abuse drugs. New York: Springer; 1987:229–240.
52. Wise, R. A.; Bozarth, M. A. A psychomotor stimulant theory of addiction. Psychol. Rev. 94:469–492; 1987.