The Journal of Applied Pharmacology, 14, 125-131(2006)

Inhibitory Effects of (-)-Epigallocatechin gallate on Morphine-Induced Locomotor Sensitization and Conditioned Place Preference in Mice

Jae-Soon EUN[1], Han-Na KWON[2], Jin-Tae HONG[2] and Ki-Wan OH[2]*

[1]*College of Pharmacy, Woosuk University, Samrye, 565-701 S. Korea*

[2]*College of Pharmacy, Chungbuk National University, Cheongju, 361-763, S. Korea*

(Received 23 August, 2006; Accepted 12 September, 2006)

Abstract – The inhibitory effects of (-)-epigallocatechin gallate (EGCG), a major compound of green tea, on the development of locomotor sensitization, conditioned place preference (CPP) and dopamine receptor supersensitivity induced by the repeated administration of morphine were investigated in mice. A single administration of morphine produces hyperlocomotion. The repeated administration of morphine develops sensitization, a progressive enhancement of locomotion, which is used as a model for studying the craving and drug-seeking behaviors characterizing addiction, and CPP, which is used as a model for studying drug reinforcement, respectively. EGCG inhibited morphine-induced hyperlocomotion, sensitization and CPP. In addition, EGCG inhibited the development of postsynaptic dopamine receptors supersensitivity, which may be an underlying common mechanism that mediates the morphine-induced dopaminergic behaviors such as sensitization and CPP. Apomorphine (a dopamine agonist)-induced climbing behaviors also were inhibited by a single direct administration of EGCG. These results provide evidence that EGCG has anti-dopaminergic activity, as inhibiting the development of dopamine receptor supersensitivity and apomorphine-induced climbing behaviors. Therefore, it is suggested that green tea may be useful for the prevention and therapy of these adverse actions of morphine.

Keywords □ (-)-Epigallocatechin gallate (EGCG), Morphine, Hyperlocomotion, Locomotor sensitization, Conditioned place preference (CPP), Dopamine receptor supersensitivity, Climbing behavior

INTRODUCTION

Morphine is considered to be an addictive drug because drug-craving and psychological dependence are commonly associated with its abuse liability. A single administration of morphine in rodents induces hyperlocomotion and stereotyped behaviors (Pollock and Kornetsky, 1989; Funada *et al.*, 1994). The repeated exposure to morphine produces progressive enhancement in behavior, a phenomenon known as behavioral sensitization or reverse tolerance (Kuribara and Tadokoro, 1989; Pierce and Kalivas, 1997; Trujillo *et al.*, 2004). Behavioral sensitization provides a useful animal model for drug-seeking behaviors (Robinson and Becker, 1986; Robinson and Berridge, 2001). In addition, the repeated intermittent administration of morphine to animals induces reinforcing properties. The paradigm known as conditioned place preference (CPP) has been widely used to investigate the drug reinforcement in animal research (Blander *et al.*, 1984; Bozarth, 1986; Tzschentke, 1998).

Repeated use of addictive drugs produces multiple changes in the brain that lead to sensitization and dependence. Both sensitization and CPP sends commonly dopaminergic projections to the ventral tegmental area of midbrain, and to the nucleus accumbens (Koob and Bloom, 1988; Porrino *et al.*, 1988; Rompre and Wise, 1989; Wood and Alter, 1998; Kalivas and Nakamura, 1999). In addition, the chronic administration of morphine lead to postsynaptic receptor changes such as increased sensitivity to dopamine receptor stimulation. In other word, both postsynaptic dopamine receptor supersensitivity and behavioral sensitization result from chronic administration of morphine, simultaneously (Bhargava, 1980). It has been demonstrated that several dopamine antagonists reversed sensitization and rewarding effects of the drugs of abuse (Shippenberg and Herz, 1987; Jeziorski and White, 1995; Serrano *et al.*, 2002). Recently, natural products for the treatment of adverse effects of the drugs of abuse have been of more interest because

*Corresponding author
Tel: +82-43-261-2827, Fax: +82-43-261-2827
E-mail: kiwan@chungbuk.ac.kr

of their own lower toxicity (Kim *et al.*, 1990; Kim *et al.*, 1995; Huong *et al.*, 1997; Kim *et al.*, 1998; Kim and Lim, 1999).

The chemical composition of green tea contains many polyphenolic compounds, generally known as catechins. The main catechins in green tea are (-)-epicatechin, (-)-epicatechin gallate, epigallocatechin, and (-)-epigallocatechin gallate (EGCG). Among them, EGCG is most active major polyphenol of green tea and primarily responsible for the green tea effect. EGCG has been known to have anti-oxidant, anti-cancer, anti-thrombotic and anti-neurodegenerative effects (Kang *et al.*, 1999; Lee *et al.*, 2005; Noguchi *et al.*, 2006).

These experiments were performed to evaluate the inhibitory effects of EGCG on morphine-induced locomotor sensitization and CPP, and to know whether these effects result in anti-dopaminergic activity. Therefore, we are very much interested in whether green tea is beneficial for the treatment of adverse effects induced by morphine, one of the drugs of abuse.

MATERIALS AND METHODS

Animals

ICR male mice weighing 22-27 g, in groups of 10-15 mice were used in all experiments. They were housed, 10-15 mice in a cage with water and food available *ad libitum* under artificial 12 hour (h) light/dark cycle (light at 07:00) and constant temperature (22±2°C).

Drugs

The drugs used are morphine hydrochloride (Dae-Won Pharm. Co., Seoul, Korea), apomorphine hydrochloride (Sigma, St. Louis, MO, USA) and EGCG (Sigma, St. Louis, MO, USA). Apomorphine was dissolved immediately before use in physiological saline containing 0.1% ascorbic acid. All other drugs were dissolved in physiological saline.

Measurement of locomotor sensitization

The locomotor activity of mice was measured by tilting-type ambulometer (AMB-10, O'Hara, Tokyo, Japan). Each mouse was placed in the activity cage (20 cm in diameter, 18 cm in height). Drugs were administered after an adaptation period of 10 min. EGCG (1.5, 3.0 and 6.0 mg/kg) was administered orally (p.o.) 60 min prior to the subcutaneous (s.c.) injection of morphine (10 mg/kg, Dae-Won Pharm. Co., Korea). Morphine (10 mg/kg. s.c.) was administered once a day for 7 days according to a previous method to induce locomotor sensitization (Kuribara and Tadokoro, 1989). EGCG (1.5, 3.0 and 6.0 mg/kg, p.o.) was administered once a day 60 min before the injection of morphine injection for 7 days. The morphine-induced locomotor activity was also measured for 60 min by using a tilting-type ambulometer. The mice were first allowed to perambulate for 10 min in the activity cages followed by a 60-min test period immediately after the morphine injection. The development of sensitization day after day was evidenced by an increased locomotor activity response to morphine as compared with that of at day 1. The inhibition of sensitization by EGCG was evidenced by a lesser locomotor activity produced by morphine.

Measurement of CPP

Apparatus: The CPP apparatus was made by a modification of the method of Mucha et al (Mucha et al., 1982). It consisted of two square-based Plaxiglas compartment (15×15×15 cm), one with a white and the other with a black box jointed by a gray tunnel (3×3×7.5 cm) that could be closed by guillotine doors. To provide tactile differences between the floors of the compartments, the white compartment had wire mesh and the black compartment had a metal grid. Removal of the guillotine doors during the pre-testing and the final testing phase allowed animals free access to both compartment was recorded for 15 min during photo-beam detector connected via electrical interface to an IBM-compatible PC computer.

Procedure: The control mice received saline immediately before the exposure to the white or black compartment. Morphine (5 mg/kg, s.c.) was given immediately before the mice were placed in the white compartment. To test the effect of EGCG alone or in combination with morphine, EGCG (1.5, 3.0 and 6.0 mg/kg, p.o.) was administered 60 min prior to the morphine or saline injection, respectively. Phase I (pre-testing phase): On day 1, the mice were pre-exposed to the test apparatus for 15 min. The guillotine doors were raised and each animal was allowed to move freely between the two compartments. On day 2, baseline preference was determined for the non-preferred side vs. the preferred side for 15 min. Phase II (conditioning phase): on day 3, 5, 7 and 9, mice were injected with the drug before being confined in the white compartment, the non-preferred side, for 60 min. On day 4, 6, 8 and 10, the mice were injected with saline before confinement in the black compartment, the preferred side, for 60 min. Phase III (testing phase): on day 11, the guillotine doors were raised. The mice were placed in the tunnel of the central part and the time spent by the mice in the two compartments was recorded for 15 min. The scores were calculated from the changes of the testing phase

and the pre-testing phase in the white compartment.

Measurement of dopamine receptor supersensitivity to apomorphine

Additional groups of mice that had received the same morphine (10 mg/kg, s.c.) as in the reverse tolerance experiment were used to determine the inhibitory effect of EGCG (1.5, 3.0 and 6.0 mg/kg, p.o.) on the development of behavioral sensitization to apomorphine (2 mg/kg, s.c.), a dopamine receptor agonist. Morphine was administered once a day for 7 days according to the paradigm of the reverse tolerance test. On day 8, 24 h after the final injection of morphine, the behavioral sensitization was evidenced by an increased locomotor activity induced by apomorphine. The apparatus and procedure used were the same as described in the reports (Bhargava, 1980; Kim *et al.*, 1995). The locomotor activity induced by apomorphine was measured for 10 min. The inhibitory effect of EGCG on the development of morphine-induced behavioral sensitization to apomorphine was evidenced by lesser locomotor activity to apomorphine.

Measurement of apomorphine-induced climbing behavior

The climbing behavior in mice was measured using the three point rating scale of Protais *et al.* (Protais *et al.*, 1976). The apparatus and procedure used were the same as described in our previous report (Kim *et al.*, 1998). Immediately, after a subcutaneous injection of apomorphine (2 mg/kg), the mice were put into cylindrical individual cages (12 cm in diameter and 14 cm in height) with the floor and wall consisting of vertical metal bars (2 mm in diameter and I cm apart). After a 5-min period of exploratory activity, climbing behavior was measured at 10, 20 and 30 min 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 point), fore feet holding the wall (1 point), and four paws holding the wall (2 points). EGCG (1.5, 3.0 and 6.0 mg/kg, p.o.) was administered to mice 60 min before the apomorphine injection.

Statistics

The data were expressed as mean±SEM. The significance of the hyperactivity, reverse tolerance, CPP and DA receptor supersensitivity results was assessed by an analysis of variance (ANOVA) followed by Dunnett's test. Non-parametric Mann-Whitney U-test analyzed climbing behavior results.

RESULTS

Inhibitory effects of EGCG on morphine-induced locomotor sensitization

Morphine (10 mg/kg, s.c.)-induced locomotor activity was progressively enhanced by the repeated administration of morphine once a day for 7 days when compared with that of saline group, suggesting the development of locomotor sensitization to morphine. Meanwhile, EGCG (1.5, 3.0 and 6.0 mg/kg, p.o.) inhibited morphine-induced locomotor sensitization for 7 days. In addition EGCG (3.0 and 6.0 mg/kg) inhibited about 26.7% (2,646 counts, $P<0.01$), and 25.6% (2,686 counts, $P<0.01$), respectively, compared with that of morphine group at day 6 (Fig. 1).

Effects of EGCG on morphine-induced CPP

Groups treated only with EGCG (6.0 mg/kg) did not show CPP, compared with that of the saline group. The group treated with morphine (5 mg/kg) showed significant effect of CPP with 121 sec, 158 sec less than the -37 sec of the saline group ($P<0.01$). The group pretreated with EGCG (6.0 mg/kg) showed a mark inhibition of morphine-induced CPP, yielding -75 sec, 196 sec less than the 121 sec of the morphine control group ($P<$

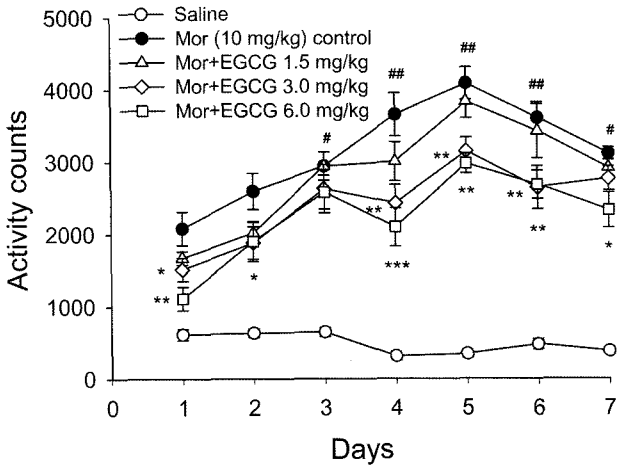

Fig. 1. Inhibitory effect of EGCG on the development of locomotor sensitization induced by morphine. Morphine (10 mg/kg, s.c.) was administered to the mice once a day for 7 days. EGCG (1.5, 3.0 and 6.0 mg/kg) was administered orally to the same mice 60 before the morphine injection. The locomotor activity was measured for 60 after the morphine injection. Each value is the mean ± SEM of at least 12 mice. *P<0.05, **P<0.01, compared with that of the morphine control group at day 1. #P<0.05, ##P<0.01, compared with that of morphine control group.

0.01). In addition, the group pretreated with EGCG (1.5 and 3.0 mg/kg) also showed significant inhibition of morphine-induced CPP, respectively (P<0.05 and P<0.01) (Fig. 2).

Inhibitory effects of EGCG on the dopamine receptor supersensitivity to apomorphine

The mice which received the same chronic administration of morphine (10 mg/kg) as in the reverse-tolerance test produced an enhanced locomotor activity to apomorphine (2 mg/kg), showing 151.0 counts (P<0.005), when compared with that saline group (45.9 counts), suggesting the development of postsynaptic dopamine receptor supersensitivity in morphine-induced reverse tolerant mice. However, EGCG (3.0 and 6.0 mg/kg) administration 1 h before the morphine injection inhibited about 54.0% (69.4 counts, P<0.05) and 60.9% (59.0 counts, P<0.01), respectively, compared with that of morphine control group (Fig. 3). These results suggest that EGCG inhibits the development of postsynaptic dopamine receptor supersensitivity in morphine-induced reverse tolerant mice.

Effects of EGCG on apomorphine-induced climbing behaviors

The maximum response of climbing behaviors by apomorphine (2 mg/kg) was observed in this experiment (P<0.005). The groups treated only with saline and EGCG themselves did not show any climbing behavior. Pretreatment with EGCG (3.0 and 6.0 mg/kg) produced a significant inhibition of apomorphine-induced climbing behavior resulting in less score than the apomorphine-induced climbing behavior score, yielding 3.57 and 2.96 scores, respectively (P<0.05 and P<0.01, Fig. 4). These results show that a single administration of EGCG inhibits its apomorphine-induced climbing behavior, demonstrating that EGCG has the anti-dopaminergic activity.

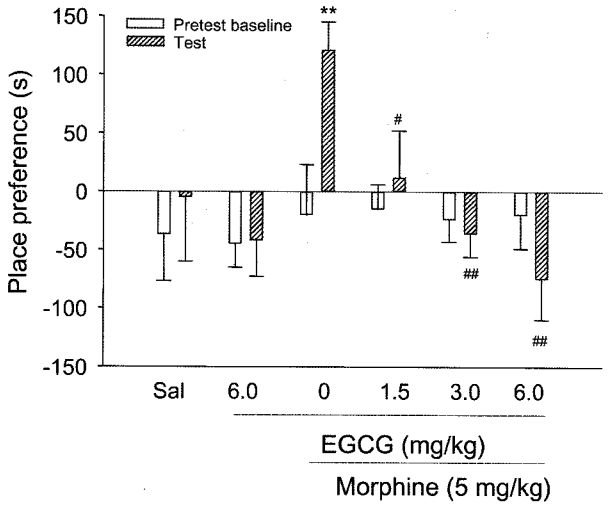

Fig. 2. Inhibitory effect of EGCG on morphine-induced CPP. In the conditioning phase, mice were injected with morphine according to the CPP test paradigm. EGCG (1.5, 3.0 and 6.0 mg/kg) was administered 60 before the morphine (5 mg/kg) injection. The scores were expressed as the differences in time spent by the mice between the testing phase and the pre-testing phase in the drug-paired compartment. Each value is the mean ± SEM of at least 12 mice. **P<0.01, compared with that of the vehicle group. #P<0.05, ##P<0.01, compared with that of morphine group.

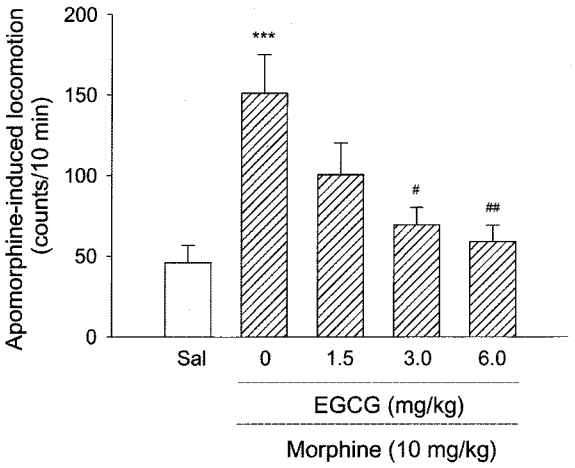

Fig. 3. Inhibitory effect of EGCG on morphine-induced dopamine receptor supersnsitivity. Additional groups of the mice that received the same repeated morphine were used to investigate the effect of EGCG on the development of supersensitivity to apomorphine. Morphine-induced locomotor sensitization was evidenced by measuring the enhanced locomotor activity to apomorphine. Each value is the mean ± SEM of at least 12 mice. ***P<0.005, compared with that of the saline group. #P <0.05, ##P<0.01, compared with that of morphine group.

DISCUSSION

In this experiment, Pretreatment of EGCG inhibited morphine induced hyperactivity. We suggest that EGCG antagonizes morphine-induced psychostimulant activity. In addition, EGCG also inhibited morphine-induced sensitization and CPP, suggesting that EGCG could reduce morphine-induced drug-seeking behavior and/or reinforcement. The effects of EGCG might be mediated by dopaminergic system as inhibited the dopamine receptor supersensitivity.

The primary goals of addiction treatment are the facilitation of abstinence and the prevention of relapse. Pharmacological treatment often is used to reduce withdrawal symptoms, but

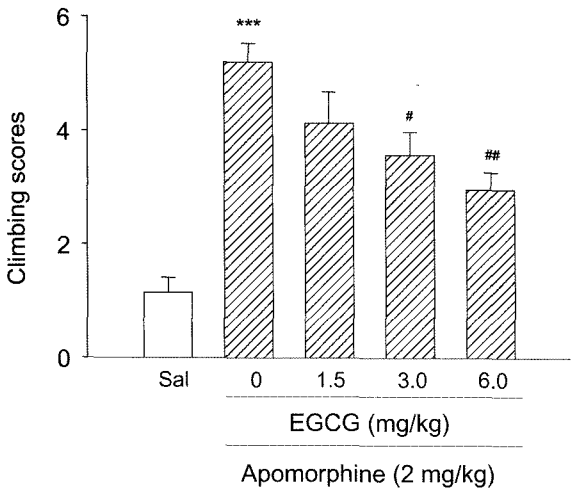

Fig. 4. Inhibitory effect of apomorphine-induced climbing behavior. EGCG (1.5, 3.0 and 6.0 mg/kg) was administered 1 h before the apomorphine (2 mg/kg) injection. Immediately, after the apomorphine injection, the mice were put into cylindrical individual cages. After a 5-min period of exploratory activity, climbing behavior was measured by all or non score at 10, 20 and 30 min after the administration of apomorphine, and the three scores were added and averaged. Each value is the mean ± SEM of at least 12 mice. ***P<0.005, compared with that of the saline group. #P<0.05, ##P<0.01, compared with that of morphine group.

thus far has not been effective in preventing relapse. Still, there has been considerable interest in the search of drugs that reduce and/or inhibit the adverse actions such as tolerance and dependence of abuse drugs. The effects of naltrexone, a long-acting, orally administered, pure opioid antagonist, have been extensively studied, and narcotic antagonists may be useful in treating addictions to other psychostimulants (Chiu *et al.*, 2005). However, the clinical use of naltrexone is limited because it is associated with low rates of compliance, which have been well documented. On the other hand, the use of clonidine to aid in opioid withdrawal, has important treatment implications. Medications for withdrawal control can be helpful in the short run for discouraging relapse.

Sensitization is a behavioral phenomenon associated with repeated administration of the drugs of abuse. Current theories suggest that sensitization is important in drug abuse, and may be responsible for the development of craving in addicts (Robinson and Berridge, 2001). In addition, Sesitization may be involved in the development of drug side effects such as drug-seeking behaviors (Robinson and Becker 1986). Drug-seeking behaviors that arise from repeated administration of psychomotor-stimulants such as morphine, cocaine and methamphetamine is thought to result from sensitization. The motor effects of morphine largely depend on the dopaminergic system, since dopaminergic antagonists block morphine-induced hyperactivity (Kuribara, 1995; Manzanendo *et al.*, 1999). It has been observed that dopamine receptor antagonists effectively inhibit the locomotor sensitization induced by morphine (Serrano *et al.*, 2002).

Drug-seeking behaviors with reinforcement do not enable the patients to maintain abstinence. Accordingly, we are much more interested in drugs that inhibit behavioral sensitization and/or CPP, because it is believed that the inhibition of sensitization and CPP may reduce drug-seeking behaviors of addicted patients. Morphine and heroin are among the most commonly abused opiates because of their effects on the brain reward circuitry. CPP produced by morphine is abolished by pretreatment with dopamine receptor antagonists. In addition, the reinforcing effects of abuse drugs are subject to sensitization. Sensitization resulting from repeated administration requires persistent activation of the mesolimbic dopaminergic systems. The activation of this system is also implicated in drug reinforcement. Therefore, a pivotal role for dopaminergic mechanisms in opioid-induced sensitization and CPP has been proposed (Bonarth, 1986; Shippenberg *et al.*, 1987; Beninger and Miller, 1998; Kalivas and Stewart, 1991). For example, the CPP produced by morphine is abolished by pretreatment with a dopamine receptor antagonist (Leone and Di Chihara, 1987). However, recently, natural products for the treatment of adverse effects have been of interest because of their own lower toxicity (Kim *et al.*, 1995; Huong *et al.*, 1997; Kim *et al.*, 1998; Kim *et al.*, 1999). Especially, ginseng's beneficial effects on the adverse actions of psychotropic agents were initially reported by Kim et al., who observed that *Panax ginseng* inhibited the analgesic tolerance and physical dependence induced by morphine (Kim *et al.*, 1990). *Panax ginseng* also attenuates hyperactivity, reverse tolerance, and CPP induced by psychotropic agents, such as morphine, cocaine, and methamphetamine, showing anti-dopaminergic activity (Leone and Di Chihara, 1985; Jeziorski and White, 1995; Kuribara, 1995).

There are no any reports about the therapeutic and/or preventive effects of EGCG isolated from green tea leaves on the adverse actions of morphine. From these experiments, EGCG, a major component of green tea, inhibited hyperactivity, reverse tolerance, CPP and dopamine receptor supersensitivity induced by morphine in mice. It is interesting that EGCG blocked the development of cocaine-induced locomotor sensitization and decreased dopamine receptor binding after cocaine treatment

(Park *et al.*, 2001). Moreover, we found that a single direct administration of EGCG inhibited apomorphine-induced climbing behavior. Therefore, it is suggested that these inhibitory effects of EGCG also might be mediated by dopaminergic transmission in the brain because EGCG inhibits the dopamine receptor supersensitivity and apomorphine-induced climbing behavior.

Natural products for the treatment of adverse effects of abuse drugs have been of more interest because producing their own lower toxicity clinically. It has been reported that ginsenosides from *Panax ginseng* inhibited reverse tolerance and CPP induced by abuse drugs such as morphine, cocaine and methamphetamine, suggesting they modulate dopaminergic function at the postsynaptic site (Kim *et al.*, 1995; Kim *et al.*, 1996a; Kim *et al.*, 1996b; Kim *et al.*, 1998). Paeonol from *Paeonia Radicis* inhibited not only morphine induced locomotor hyperactivity and reverse tolerance but also the development of CPP and dopamine receptor supersensitivity (unpublished data).

In conclusion, administration of morphine produced locomotor hyperactivity, locomotor sensitization and CPP in mice. Administration of EGCG inhibited not only morphine induced locomotor hyperactivity and sensitization but also the development of CPP and dopamine receptor supersensitivity. EGCG inhibited the development of postsynaptic dopamine receptors supersensitivity, which may be an underlying common mechanism that mediates the morphine induced dopaminergic behaviors such as sensitization and CPP. Therefore, these inhibitory effects of EGCG may be mediated by dopaminergic systems and drinking green tea may be beneficial for the treatment of the adverse actions of opiate dependent-patients.

ACKNOWLEDGEMENTS

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (the Center for Healthcare Technology Development, Woosuk University, Republic of Korea).

REFERENCES

Beninger, R. J., and Miller, R., (1998). Dopamine D1-like receptors and reward-related incentive learning. *Neurosci. Biobehav. Rev.* **22**, 335-345.

Bhargava, H. N., (1980). Cyclo (Leu-Gly) inhibits the development of morphine induced analgesic tolerance and dopamine receptor supersensitivity in rat. *Life Sci.* **27**, 117-123.

Blander, A., Hunt, T., Blair, R., and Amit, Z., (1984). Conditioned place preference: An evaluation of morphine's positive reinforcing properties. *Psychopharmacol.* **84**, 124-127.

Bozarth, M. A., (1986). Neural basis of psychomotor stimulant and opiate reward: evidence suggesting the involvement of a common dopaminergic system. *Behav. Brain Res.* **22**, 107-116

Chiu, C. T., Ma, T., and Ho, I. K., (2005). Attenuation of methamphetamine-induced behavioral sensitization in mice by systemic administration of naltrexone. *Brain Res.* **67**, 100-109.

Funada, M., Suzuki, T., and Misawa, M., (1994). The role of dopamine D1-receptors in morphine-induced hyperlocomotion in mice. *Neurosci. Letter,* **169**, 1-4.

Huong, N. T. T., Matsumoto, K., Yamasaki, K., Duc, N. M., Nham, N. T., and Watanabe, H., (1997). Majonoside-R2, a major constituent of Vietnamese ginseng, attenuates opioid-induced antinociception. *Pharmacol. Biochem. Behav.* **57**, 285-291.

Jeziorski, M., and White, F. J., (1995). Dopamine receptor antagonist prevents expression, but not development, of morphine sensitization. *Eur. J. Pharmacol.* **275**, 235-244.

Kalivas, P., and Nakamura, M., (1999). Neural systems for behavioral activation and reward. *Curr. Opinion Neurobiol.* **9**, 223-227.

Kalivas, P. W., and Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res. Rev.* **16**, 223-244.

Kang, W. S., Lim, I. H., Yuk, D. Y., Chung, K. H., Park, J. B., Yoo, H. S., and Yun, Y. P., (1999). Antithrombic activities of green tea catechins and (-)-epigallocatechin gallate. *Thrombosis Res.* **96**, 229-237.

Kim, H. S., Jang, C. G, and Lee, M. K., (1990). Antinarcotic effects of the standardized ginseng extract G115 on morphine. *Planta Med.* **56**, 158-163.

Kim, H. S., Kang, J. G., and Oh, K. W., (1995). Inhibition by ginseng total saponin of the development of morphine tolerance and dopamine receptor supersensitivity in mice. *Gen. Pharmacol.* **26**, 1071-1076.

Kim, H. S., Jang, C. G, Park, W. K., Oh, K. W., Rheu, H. M., Cho, D. H., and Oh, S., (1996a) Blockade by ginseng total saponin of methamphetamine-induced hyperactivity and conditioned place preference in mice. *Gen. Pharmacol.* **27**, 199-204.

Kim, H. S., Jang, C. G., Oh, K. W., Seong, Y. H., Rheu, H. M., Cho, D. H., and Kang, S. Y., (1996b). Effects of ginseng total saponin on cocaine-induced hyperactivity and conditioned place preference in mice. *Pharmacol. Biochem. Behav.* **53**, 185-190.

Kim, H. S., Hong, Y. T., and Jang, C. G., (1998). Effects of the ginsenosides Rg1 and Rb1 on morphine-induced hyperactivity and reinforcement in mice. *J. Pharm. Pharmacol.* **50**, 555-560.

Kim, H. S., Jang, C. G., Oh, K. W., Oh, S., Rheu, H. M., Rhee, G. S., Seong, Y. H., and Park, W. K., (1998). Effects of ginseng total saponin on morphine-induced hyperactivity and conditioned place preference in mice. *J. Ethnopharmacol.* **60**, 33-42.

Kim, H. S., and Lim, H. K., (1999). Inhibitory effects of velvet antler water extract on morphine-induced conditioned place preference and DA receptor supersensitivity in mice. *J. Ethnopharmacol.* **66**, 25-31.

Koob, G. F., and Bloom, F. E., (1988). Cellular and molecular mechanisms of drug dependence. *Science* **242**, 715-723.

Kuribara, H., and Tadokoro, S., (1989). Reverse tolerance to ambulation-increasing effects of MAP and MOR in 6 mouse strains. *Jpn. J. Pharmacol.* **49**, 197-203.

Kuribara, H., (1995). Modification of morphine sensitization by opioid and dopamine receptor antagonist: evaluation by studying ambulation in mice. *Eur. J. Pharmacol.* **275**, 251-258.

Lee, S. Y., Lee, J. W., Lee, H., Yoo, H. S., Yun, Y. P., Oh, K. W.,

Ha, T. Y., and Hong, J. T., (2005). Inhibitory effect of green tea extract on beta-amyloid-induced PC12 cell death by inhibition of the activation of NF-kB and ERK/p38 MAP kinase pathway through antioxidant mechanisms. *Mol. Brain Res.* **140**, 45-54.

Leone, P., and Di Chiara, G.., (1987). Blockade of D-1 receptors by SCH23390 antagonizes morphine- and amphetamine-induced place preference conditioning. *Eur. J. Pharmacol.* **135**, 251-254.

Manzanendo, C., Aguilar, M. A., and Minarro, J., (1999). The effects of dopamine D2 and D3 antagonist on spontaneous motor activity and morphine-induced hyperactivity in male mice. *Psychopharmacol.* **143**, 82-88.

Mucha, R. F., Van der Kooy, D., O'Shaughnessy, M., and Bucenieks, P., (1982). Drug reinforcement studied by the use of place conditioning in rat. *Brain Res.* **243**, 91-105.

Noguchi, M., Yokoyama, M., Watanabe, S., Uchiyama, M., Nakao, Y., Hara, K., and Iwasaka, T., (2006). Inhibitory effect of the tea polyphenol, (-)-epigallocatechin gallate, on growth of cervical adenocarcinoma cell lines. *Cancer Letters* **234**, 135-142.

Park, K., Vora, U., Darling, S. F., Kolta, M. G., and Soliman, K. F. A., (2001). The role of inducible nitric oxide synthase in cocaine-induced locomotor sentitization. *Physiol. Behav.* **74**, 441-447.

Pierce, R. C., and Kalivas, P. W., (1997). A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res. Rev.* **25**, 192-216.

Pollock, J., and Kornetsky. C., (1987). Evidence for the role of dopamine D1 receptors in morphine induced stereotypic behavior. *Neurosci. Letters* **102**, 291-296.

Porrino, L. J., Domer, F. R., Crane, A. M., and Sokoloff, L., (1988). Selective alterantions in cerebral metabolism within the mesocorticolimbic dopaminergic system produced by acute cocaine administration of rats. *Neuropsychopharmacol.* **1**, 109-118.

Protais, P., Costentin, J., and Schwartz, J. C., (1976). Climbing behavior induced by apomorphine in mice: A simple test for the study of dopamine receptors in striatum. *Psychopharmacol.* **50**, 1-6.

Robinson, T. E., and Becker, J. B., (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res. Rev.* **11**, 57-198.

Robinson, T. E., and Berridge, K. C., (2001). Incentive-sensitization and addiction mechanisms of action of addictive stimuli. *Addiction* **96**, 103-114.

Rompre, P., and Wise, R. A., (1989). Behavioral evidence for midbrain dopamine depolarization inactivation. *Brain Res.* **477**, 152-156.

Serrano, A., Aguilar, M. A., Manzanedo, C., Rodriguez-Arias, M., and Minarro, J., (2002). Effects of D1 and D2 antagonists on the sensitization to the motor effects of morphine in mice. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **26**, 1263-1271.

Shippenberg, T. S., and Herz, A., (1987). Place preference conditioning reveals the involvement of D1-dopamine receptors in the motivational properties of mu- and kappa-opioid agonists. *Brain Res.* **436**, 169-172.

Trujillo, K. A., Kubota, K. S., and Warmoth, K. P., (2004). Continuous administration of opioids produces locomotor sensitization. *Pharmacol. Biochem. Behav.* **79**, 661-669.

Tzschentke, T. M., (1998). Measuring reward with the CPP paradigm: a comparative review of drug effects, recent progress and new issue. *Prog. Neurobiol.* **56**, 613-672.

Wood, P. L., and Alter, C. A., (1998). Dopamine release in vivo from neostriatal mesolimbic and mesocortical neurons utility of 3-methoxytryamine measurement. *Pharmacol. Rev.* **40**, 163-187.