Wild Ginseng Attenuates Repeated Morphine-Induced Behavioral Sensitization in Rats

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Many studies have suggested that the behavioral and reinforcing effects of morphine are induced by hyperactivation of the mesolimbic dopaminergic system, which results in increases in locomotor activity, c-Fos expression in the nucleus accumbens (NAc), and tyrosine hydroxylase (TH) in the ventral tegmental area (VTA). In order to investigate the effect of wild ginseng (WG) on treating morphine addiction, we examined the behavioral sensitization of locomotor activity and c-Fos and TH expression in the rat brain using immunohistochemistry. Intraperitoneal injection of WG (100 and 200 mg/kg), 30 min before administration of a daily injection of morphine (40 mg/kg, s.c.), significantly inhibited morphine-induced increases in c-Fos expression in NAc and TH expression in VTA as well as in locomotor activity, as compared with Panax ginseng. It was demonstrated that the inhibitory effect of WG on the behavioral sensitization after repeated exposure to morphine was closely associated with the reduction of dopamine biosynthesis and postsynaptic neuronal activity. It suggests that WG extract may be effective for inhibiting the behavioral effects of morphine by possibly modulating the central dopaminergic system and that WG might be a useful resource to develop an agent for preventing and treating morphine addiction.

Keywords: Morphine, ginseng, locomotor activity, c-Fos, tyrosine hydroxylase, dopamine

Morphine is widely used to relieve pain and to treat a number of other pathological indications. However, repeated exposure to morphine results in induction of tolerance, psychological dependence, and physical dependence, characterized by withdrawal symptoms after discontinuation of the drug administration [35]. Repeated administration of various psychoactive substances, including morphine, can produce a more robust effect than the first dose alone, even after an abstinence period [32]. This phenomenon, called behavioral sensitization, may play an important role in the development of drug addiction and drug-induced psychosis, as evidenced by an enhanced locomotor response to a subsequent injection of the drug [38]. Behavioral sensitization is the enhanced response to such psychostimulants as morphine or amphetamine, and this effect has been known to be mediated by the central dopaminergic system [23]. In particular, the mesolimbic dopamine system, which originates in the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc), has been implicated in the processes of drug addiction and behavioral sensitization [36]. Therefore, many studies have focused on the role of the mesolimbic dopamine system, which is known to play a critical role in the reinforcing effects of morphine [37]. Development of behavioral sensitization to morphine is presumed to depend on certain changes in the dopaminergic system via stimulation of µ-opioid receptors [14]. It is also established that sensitization to opioids directly affects rewarding pathways in the brain and acts to produce a large increase in dopamine (DA) release in the NAc, which plays a role in drug-seeking behavior [4, 5, 27]. For example, many studies demonstrated that the intra-NAc injection of the µ-opioid receptor antagonist d-Pen-Cys-Tyr-n-Trp-Orn-Thr-Pen-Thr-NH₂ (CTOP) blocks the development of motor sensitization to systemic morphine [8]. Moreover, behaviors evoked by repeated morphine administration reflect not only neurochemical actions at opioid receptors but also the actions of numerous other transmitters, such as glutamate, GABA, and DA that are under the indirect influence of opioid receptors [40].

Several studies have demonstrated that repeated morphine administration causes changes of gene expression profiles...
within brain reward systems and stimulates c-fos expression in dopaminergic target areas, such as the nucleus accumbens, striatum, and prefrontal cortex [37]. Many studies suggest that the alternations in the dopamine terminal areas might be critical in the long-term effects of morphine, and it is likely that the behavioral sensitization to morphine may reflect the alterations in extracellular dopamine release or postsynaptic gene expression [41]. Stimulation of dopamine transmission induces c-Fos protein [3, 6], a transcription factor that is often used as a neural marker for indicating pharmacologically induced functional changes in the selected brain areas. In addition, several studies have shown that repeated exposure to morphine produced the expression of tyrosine hydroxylase (TH) activity for DA biosynthesis in the mesolimbic DA pathway [1].

Wild ginseng (WG) is the ginseng (the root of *Panax ginseng* C.A. Mayer) that naturally grows but has not been field-cultivated domestically, and it is known to be pharmacologically more effective than field-cultivated ginseng. In the present study, WG specifies ginseng grown from seeds undisturbed in the Korean forest even though the seeds were initially scattered by humans [16]. In terms of seeding methods, it has been suggested that the seeds of truly wild ginseng have always been distributed through natural vectors such as birds. The major component of WG is ginsenosides, which have a hydrophobic steroid-like four-ring structure with sugar-attached moieties [19], and their concentrations are generally two to six times higher than those of field-cultivated ginseng [16]. Their chemical and pharmacological properties have been reported by investigators in many countries. Recently, several studies suggest that *Panax ginseng* (PG) and its ginsenosides can act on the central dopaminergic system [7, 13]. Many studies have also reported that *Panax ginseng* inhibited the hyperactivity and the conditioned place preference of morphine, cocaine, and methamphetamine [9–11]. Furthermore, *Panax ginseng* inhibits the development of postsynaptic dopamine receptor supersensitivity and the morphine-induced cAMP signaling pathway [12] and blocks nicotine-induced behavioral activity [11, 13].

However, there are still unresolved questions about the mechanism of action underlying WG’s effect as a therapeutic intervention in treating morphine addiction. Furthermore, the effect of WG on the morphine-induced neurochemical and behavioral alternations in animal models is poorly understood. Therefore, in the present study, we aimed to investigate whether WG could attenuate morphine-induced locomotor activity, as compared with PG. The expression of c-Fos in the nucleus accumbens and striatum and the expression of TH in the ventral tegmental area were also examined by immunohistochemical methods to explore the possible mechanism underlying the inhibitory effects of WG on the morphine-induced behavioral sensitization in rats repeatedly injected with morphine.

**Materials and Methods**

**Animals**

Adult male Sprague-Dawley (SD) rats (approximately 2 months of age, weighing 250–270 g) were purchased from Samtaco Animal Corporation (Osan, Korea). Animals were housed in groups of five rats per cage under controlled 12 h light/dark cycle and temperature (22–24°C) conditions. Food pellets purchased from a commercial vendor and tap water were provided ad libitum, unless otherwise stated. All animals were gently handled in the same way, for at least 7 days before the beginning of the experiments. Formal approval to conduct the experiments described was obtained from the animal subjects review board of our institution. All animal experiments were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals revised 1996. Efforts were made to minimize the numbers of animals used and to reduce their suffering.

**Preparation of the Drugs and the Methanol Extracts of WG and PG**

Wild ginseng roots (adventitious root culture of *Panax ginseng*, WG) was collected in Chonbuk Province in Korea and purchased from Baekjessayam Co. (Mr. Jong-Gu Lee, Jinan-kun, Jinan-up, Yeonjang-Ri #45-1, Chonbuk, 567-807, Korea). PG (*Panax ginseng*) was purchased from Dongwoodang Pharmacy Co., Ltd (Yeongcheon, Korea).

A voucher specimen of WG and PG has been deposited at the herbarium located at the College of Oriental Medicine, Kyung Hee University (No. KH-WG01 for WG and No. KH-PG01 for PG). WG and PG (100 g each) were cut into small pieces and extracted three times with 21% of 80% methanol by sonication in a reflux condenser for 24 h at room temperature (25±2°C), respectively. The solutions were combined, filtered through Whatman No. 1 filter paper, concentrated using a rotary vacuum evaporator (Rotavapor R-124; BÜCHI Labortechnik AG, Flawil, Switzerland) under reduced pressure, refrigerated in a recirculating chiller (EYELA CCA-1110; Tokyo Rikakikai Co., Tokyo, Japan) to obtain concentrated extracts, and then lyophilized (EYELO FD-800, Tokyo Rikakikai Co., Tokyo, Japan). The yields of aqueous phases of WG and PG were 11.6 and 20.6%, respectively. Morphine hydrochloride (Sigma-Aldrich Chemical Co., St. Louis, MO, USA) was obtained from the standard commercial suppliers. Morphine hydrochloride was dissolved in 0.9% saline solution.

**Morphine Treatment and Experimental Groups**

The procedure of morphine treatment consisted of three phases: (1) five days of addiction development (2) three days of withdrawal, and (3) one day for a morphine challenge. The rats were divided into eight groups. The development of morphine addiction was performed by repeated injection of morphine (40 mg/kg-body weight, s.c.) twice a day for 5 consecutive days, and the last challenge injection of morphine was performed on the 9th day (40 mg/kg, s.c.) after a 3-day withdrawal period (MOR group, n=6). The vehicle-treated rats (as a negative control of the addiction model development) were administered with saline (0.9% NaCl, s.c.) instead of morphine in the same way (SAL group, n=6). The yields of aqueous phases of WG and PG were 11.6 and 20.6%, respectively. The acute morphine-treated group received saline twice a day for 5 consecutive days and lastly a challenge injection of morphine on the 9th day after a 3-day withdrawal period (AcMOR group, n=6). Another group was pretreated with WG (200 mg/kg, i.p. WG group, n=6) intraperitoneally 30 min prior
to the injection of saline in the development phase. The WG- or PG-treated groups were divided as follows: 50 mg/kg WG plus morphine-treated group (WG50+MOR, n=6), 100 mg/kg WG plus morphine-treated group (WG100+MOR, n=6), 200 mg/kg WG plus morphine-treated group (WG200+MOR, n=6), and 500 mg/kg PG plus morphine-treated group (PG500+MOR, n=6). The WG or PG treatments were performed intraperitonically 30 min prior to the injection of morphine in the development phase.

Measurement of Locomotor Activity
Prior to behavioral testing, rats were individually housed to obtain more stable results. The measurement of locomotor activity was performed for 1 h after all morphine treatment. Measurements were conducted in a rectangular container (40×40×45 cm) equipped with a video camera above the center of the floor, as described previously [15]. The walls and floor of the container were made of clear acrylic plastic and painted black. Monitoring of locomotor activity was executed by a video tracking system with S-MART program (Panlab Co., Barcelona, Spain). The animals were allowed to adapt to the container for 1 h and the distance they traveled was recorded every 10 min for 2 h, 1 h for baseline adjustment and 1 h for recording. Locomotor activity was indicated in centimeters.

c-Fos and TH Immunohistochemistry
For immunohistochemistry studies, the animals were deeply anesthetized with sodium pentobarbital (80 mg/kg, i.p.), and then perfused through the ascending aorta with normal saline (0.9%), followed by 300 ml of 4% paraformaldehyde in 0.1 M phosphate-buffered saline (PBS). The brains were removed, post-fixed overnight, and cryoprotected in a 20% sucrose solution. Coronal sections, 30 µm thick, were cut through the striatum and ventral tegmental area using a cryostat (Leica CM1850; Leica Microsystems Ltd., Nussloch, Germany). The sections were obtained according to the rat atlas of Paxinos and Watson [21]. The sections were immunostained for Fos protein and TH protein expression using the avidin-biotin-peroxidase method. Briefly, the sections were rinsed three times for 5 min each in PBS, and then incubated with rabbit anti-c-Fos antibody (1:2,000 dilution; Chemicon International Inc., Temecular, CA, USA) and sheep anti-TH antibody (1:2,000 dilution; Chemicon International Inc.) in PBS containing 0.3% Triton X-100 (PBST) for 72 h at 4 °C, respectively. The sections were washed for 5 min in PBS and then incubated for 120 min at room temperature with biotinylated goat anti-rabbit IgG secondary antibody (for the anti-c-Fos antibody) or biotinylated goat anti-sheep IgG secondary antibody (for the anti-TH antibody). Both secondary antibodies were obtained from Vector Laboratories Co. (Burlingame, CA, USA) and diluted 1:200 in PBST containing 2% normal goat serum. To visualize immunoreactivity, the sections were incubated for 90 min in avidin–biotin complex (ABC) reagent (Vectastain Elite ABC kit; Vector Labs CO., Burlingame, CA, USA), washed three times for 5 min in PBS, and incubated in a solution containing 3,3′-diaminobenzidine (DAB; Sigma-Aldrich Chemical Co., St. Louis, MO, USA) and 0.01% H2O2 for 1 min. Finally, the tissues were washed in PBS, followed by a brief rinse in distilled water, and individually mounted onto slides. Slides were allowed to air dry, and then were cover-slipped. Images were captured using the AxioVision 3.0 imaging system (Carl Zeiss, Inc., Oberkochen, Germany) and processed using Adobe Photoshop (Adobe Systems, Inc., San Jose, CA, USA). The sections were viewed at 100× magnification and the number of cells within 100 ×100 µm2 grids was counted by an observer blinded to the experimental groups. The cells from the accumbal areas were obtained according to the stereotactic atlas of Paxinos and Watson [21]. The cells within the striatum and ventral tegmental areas were counted in at least three different sections for each rat.

Statistical Analysis
The experimental results were expressed as the mean ± standard error (SE). The behavioral data were calculated and analyzed by repeated measures analysis of variance (ANOVA) using SPSS (Version 13.0; SPSS, Inc., Chicago, IL, USA). The statistical significance of the differences among groups was further analyzed using Tukey’s post hoc test. Immunohistochemical data were also analyzed by one-way ANOVA followed by Tukey’s post hoc test. In all analyses, p < 0.05 was considered significant.

RESULTS
Effect of WG on Morphine-Induced Behavioral Sensitization
To observe behavioral sensitization induced by repeated morphine injection, we compared locomotor activity between the saline-treated rats (SAL group) and acute morphine-induced rats (AcMOR) on days 1, 5, and 9. When rats were treated with five consecutive daily morphine injections, but not with consecutive saline injection, behavioral sensitization was successfully produced. When the animals that were given repeated morphine treatments were challenged with systemic administration of morphine, their behavioral responses were significantly increased compared with those of the SAL group (p<0.001) and the AcMOR group (p<0.001). The locomotor activity traveled distance

Fig. 1. Locomotor activity following treatment with saline- and cocaine-pretreated rats during the challenge phase. Rats were pretreated with saline (SAL group, s.c. n=6) or morphine (40 mg/kg, s.c., MOR group, n=6) twice daily for five consecutive days, after which the rats were challenged with the same dose of saline or morphine, 72 h after the last treatment. The acute morphine-treated group (AcMOR group, s.c. n=6) received saline for 5 days, after which time the rats were challenged with morphine, 72 h after the last treatment. Significance with Tukey’s test following a repeated ANOVA is indicated as ***p<0.001 versus SAL group. The vertical lines indicate SE.
Repeated measures ANOVA (7×6, treatment×time) performed on all activity scores following the drug injections indicated a significant effect of a group difference [F(7, 40)=52.093, p<0.001]. However, there was not a significant activity increase over days [F(5, 200)=1.0.98, p=0.363], and interaction between experimental groups and days [F(35, 200)=0.859, p=0.697]. Tukey’s post-hoc comparisons indicated that the behavioral response to morphine challenge in the repeated morphine-treated group was significantly higher than those in both the saline-treated groups (p<0.001).

The administration of WG (100 and 200 mg/kg-body weight) before morphine injection, systemic morphine challenge, significantly inhibited the increase in the locomotor activity during a 60-min testing period as compared with the MOR group (Fig. 2). WG at doses of 50, 100, and 200 mg/kg administered 30 min before morphine injection decreased the morphine-induced locomotor activity to 5,657.7±108.2 (p=0.318), 4,835.8±384.2 (p<0.001), and 3,635.3±223.9 (p<0.001), respectively, whereas the locomotor activity of MOR group was 6,361.4±226.8. This finding indicates that administration of WG (100 and 200 mg/kg-body weight) significantly decreased the locomotor activity induced by a systemic morphine challenge. It was indicated that the locomotor activities of the WG100+MOR and WG200+MOR groups were higher than that in the PG500+MOR group.

**Effect of WG on Morphine-Induced Fos-Like Immunoreactivity**

Following the repeated injection of morphine, a massive amount of FLI was present in the NAc and striatum (Fig. 3). In the shell of NAc, measures of one-way ANOVA on the numbers of Fos-like immunoreactive cells revealed a significant difference among the experimental groups indicated by repeated injection of morphine.
Effect of Wild Ginseng on Morphine-Induced Sensitization

The post-hoc comparisons revealed that the MOR group showed a greater increase in Fos expression than the SAL group (p<0.01). The administrations of 50, 100, and 200 mg/kg-body weight WG, 30 min before the morphine injection, decreased the numbers of Fos-like immunoreactive cells to 27.39±1.10 (p=0.952), 22.83±0.76 (p<0.05), and 21.67±0.75 (p<0.01), respectively, as compared with Fos-like immunoreactive cells of 29.56±2.32 in the MOR group (Fig. 4A).

In the core of NAc, the measures of one-way ANOVA on the numbers of Fos-like immunoreactive cells revealed a significant difference among the experimental groups [F(6,125)=3.743, p<0.01]. The post-hoc comparisons revealed that the MOR group showed a significant increase in Fos expression compared with the SAL group (p<0.01). The administration of 50, 100, and 200 mg/kg-body weight WG, 30 min before the morphine injection, decreased the numbers of Fos-like immunoreactive cells to 25.06±1.11 (p=0.631), 22.44±0.80 (p<0.05), and 21.17±0.68 (p<0.01), respectively, as compared with Fos-like immunoreactive cells of 28.39±1.53 in the MOR group (Fig. 4A).

In the lateral and medial striatum, measures of one-way ANOVA on the numbers of Fos-like immunoreactive cells also revealed a significant difference among the experimental groups [F(6,125)=4.526, p<0.001 and F(6,125)=4.983, p<0.001, respectively] (Fig. 3). The post-hoc comparisons in each case revealed that the MOR group showed a greater increase in Fos expression than the SAL group (p<0.01). The WG administrations of 50, 100, and 200 mg/kg-body weight decreased the numbers of Fos-like immunoreactive cells to 23.67±1.34 (p=0.116), 22.67±1.34 (p<0.05), and 21.89±1.44 (p<0.05) in the lateral striatum, compared with the cell numbers (29.28±1.95) of the MOR group as a control (Fig. 4B). In the case of medial striatum, the decreased numbers of Fos-like immunoreactive cells were 26.39±1.12 (p=1.000), 20.89±1.11 (p<0.05), and 20.50±1.17 (p<0.05), compared with the number of 11.00±1.21 in the MOR group as a control (Fig. 4B). It was indicated that the c-Fos immunoreactivity of the WG100+MOR group was higher than that in the PG500+MOR group, and similar to that of the WG200+MOR group.

Effect of WG on Morphine-Induced TH-Like Immunoreactivity

Following the repeated injection of morphine, a massive amount of TH was present in the VTA (Fig. 5 and 6). In the

![Fig. 4. Effect of WG on the expression of Fos in the nucleus accumbens (A) and striatum (B) of morphine-treated rats. Values are presented as the mean ± SE of the total number of Fos-like immunoreactive neurons within a 100×100 µm grid over the areas at 100× magnification. Significance with Tukey’s test following a one-way ANOVA is indicated as **p<0.01 versus the SAL group; #p<0.05, ##p<0.01 versus the MOR group.](image_url)

![Fig. 5. Representative photographs showing TH expression in the ventral tegmental area of the SAL (A), MOR (B), and WG200+MOR (C) groups. The scale bar represents 50 µm.](image_url)
VTA, measures of one-way ANOVA on the numbers of TH-like immunoreactive cells revealed a significant difference among the experimental groups \( F(6,132)=3.800, p<0.01 \). The post-hoc comparisons revealed that the MOR group showed a greater increase in TH expression than the SAL group \( (p<0.01) \). The administrations of 50, 100, and 200 mg/kg-body weight WG, 30 min before the morphine injection, decreased the numbers of TH-like immunoreactive cells to \( 8.19\pm0.81 \) \( (p=0.929) \), \( 7.67\pm0.69 \) \( (p<0.05) \), and \( 6.17\pm0.60 \) \( (p<0.05) \), respectively, as compared with TH-like immunoreactive cells of \( 9.22\pm1.04 \) in the MOR group. It was indicated that the TH immunoreactivity of the WG100 +MOR and WG200+MOR groups were higher than that in the PG500+MOR group.

**DISCUSSION**

Our results clearly showed that WG extract significantly suppressed the morphine-induced locomotor activity, the increases in Fos expression in the NAc and striatum, and the increases in TH expression in the VTA. These results showed excellent agreement with previous findings [3]. Morphine challenge induced Fos-like immunoreactivity in the NAc and striatum and TH-like immunoreactivity in the VTA, which are the major projection areas of the central dopaminergic system. It could thus be suggested that the WG administration might attenuate the activated locomotor activity, the increases in c-Fos expression in the NAc and striatum, and the increases in TH expression in the VTA in response to repeated treatment of morphine by modulating the activities of dopamine neurons.

The significant induction of c-Fos protein in the NAc and striatum showed a good agreement with the previous findings that chronic injection of morphine altered several neurochemical and functional parameters including extracellular dopamine concentration [24, 31, 42] and local metabolic activity [18, 20] in the NAc and striatum. Therefore, the present study suggests that the behavioral sensitization to morphine is closely associated with the increased expression of a postsynaptic gene, c-fos, in the NAc and striatum. Previous studies have demonstrated that acute or chronic administrations of addictive drugs including morphine and nicotine produced the c-Fos expression in dopaminergic target areas, such as the NAc, striatum, and prefrontal cortex [22, 34, 39]. The behavioral sensitization to drugs might reflect alterations in postsynaptic gene expression and is closely associated with an activation of Fos-like immunoreactive cells in the NAc produced by repeated treatment with addictive drugs [26]. Repeated morphine treatment modifies neuronal circuits involved in the process of drug addiction, and the c-fos expression in the NAc and striatum generally reflects that those regions of the brain are important for developing drug dependence.

We observed that WG pretreatment significantly inhibited the morphine-induced behavioral sensitization and the dopaminergic system to repeated morphine challenge. The inhibition of repeated morphine-induced hyperactivity by WG pretreatment might be closely related with the suppression of the morphine-induced activation of dopaminergic systems in the VTA. It means that the inhibitory effect of WG reflects the blockade of dopaminergic biosynthesis or transmission. This hypothesis is strongly supported by previous studies elucidating that ginseng treatment significantly inhibited DA biosynthesis in the brain [17]. Therefore, it is possible that WG reduces the stimulation of locomotor activity due to morphine challenge by modulating dopamine signaling through the dopamine receptors in the NAc and striatum. Administration of WG inhibited the morphine-induced Fos-like immunoreactivity more effectively in the shell of NAc and lateral striatum than in the core of NAc and medial striatum. These results suggest that the WG effect could be mediated through neuronal cells within the limbic structures, which are involved in reward pathways of drug addiction, rather than within the nigrostriatal system, which can be associated with the control of motor function [28]. It can be possible that it suppresses the stimulation of locomotor activity in response to morphine challenge by modulating dopamine signaling in the mesolimbic dopaminergic system. The inhibitory effect of WG on the morphine-induced hyperactivity could thus be attributed to the substantial inhibition of the activated dopaminergic neurotransmission system by morphine.
We performed a dose-response experiment of WG (50, 100, or 200 mg/kg, i.p.) and the dose of 200 mg/kg produced a maximum inhibitory activity in the morphine-induced locomotor activity, and c-Fos and TH expressions. This dosage is highly coincident with those in other previous results that other researchers have reported in animal studies [10, 13].

WG has a long history of use in drug abuse therapy. Its therapeutic efficacy has been confirmed by many clinical studies in the Dong-Eu-Bo-Gam (a compendium of Korean traditional medicines compiled by Her Jun). WG is a well-known traditional medicine that has long been included in medical prescriptions for treating drug abuse. Although typical prescriptions including WG treatment are known to be clinically effective for alleviating psychostimulant-induced behavioral sensitization, the action mechanism of WG in drug abuse therapy has not been investigated. Some studies have demonstrated that ginseng total saponins (GTS) are effective for the treatment of cocaine dependence [17]. The administration of ginseng suppressed the expression of nicotine-induced release of dopamine in the mesolimbic system following repeated injections of nicotine [13]. Therefore, the current results demonstrated that the WG pretreatment exhibited a strong inhibitory effect on morphine-induced neurochemical and behavioral sensitization, which is consistent with previous studies showing that GTS suppressed the morphine-induced conditioned place preference in mice, and the behavioral activation was induced not only by morphine but also by other psychostimulants such as methamphetamine [33], cocaine [9], and nicotine [13].

We also verified the quantitative differences of 7 ginsenosides between WG and the field-cultivated ginseng (PG) using HPLC analysis [16]. It was observed that all ginsenosides analyzed in the study were present at higher levels in WG than in PG. In particular, the concentrations of Rb1 and Rg1 in WG were four to six times higher compared with PG. Meanwhile, the main molecular components responsible for the most medicinal activities of ginseng are the ginsenosides, which are also known as ginseng saponins. Approximately 30 different forms of ginsenoside have been isolated and identified from the root of PG. These molecules have a four-ring, steroid-like structure bearing sugar moieties, and can be classified into propanaxadiol (PD) or propanaxatriol (PT) ginsenosides according to the position of the sugar moieties at the 3- or 6-carbon [2]. Recently, some studies have reported that ginsenosides exerted powerful inhibitory actions on catecholamine secretion [29, 30], suggesting that ginseng saponins have the ability to selectively modulate dopaminergic activity at presynaptic sites. Other studies also found that a single treatment with the mixture of ginsenoside Rb1 and Rg1, PD and PT, inhibited the hyperactivity induced by morphine in mice, and that the inhibition activity was closely related with the inhibition of dopaminergic activation induced by morphine at the presynaptic DA receptors [11]. Despite this suggestion, the mechanisms mediating the effects of various ginsenosides have not yet been clearly elucidated. Therefore, we suggest that the investigations of the effects of differential types of the ginsenosides, PD and PT, on morphine-induced behavioral sensitization will be required for elucidating the mechanism of action in detail.

It was demonstrated that WG extract effectively suppressed the behavioral sensitization of locomotor activity, and c-Fos and TH expressions in the brains of the rats repeatedly injected with morphine. The inhibitory effect of WG on morphine-induced locomotor activity was closely associated with the reduction of dopamine biosynthesis and postsynaptic neuronal activity. These results suggest that WG could be effective for alleviating the behavioral responses of morphine dependence, possibly by modulating the central dopaminergic system, and might be a useful therapeutic resource for developing a novel drug for treating morphine addiction.

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References


