Arch Pharm Res Vol 28, No 9, 995-1001, 2005

Archives of Pharmacal Research
http://apr.psk.or.kr

Pharmacological Action of *Panax Ginseng* on the Behavioral Toxicities Induced by Psychotropic Agents

Hyoung-Chun Kim[1], Eun-Joo Shin[1], Choon-Gon Jang[2], Myung-Koo Lee, Jae-Soon Eun[3], Jin-Tae Hong, and Ki-Wan Oh

College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea, [1]Neurotoxicology Program, College of Pharmacy, Kangwon National University, Chunchon, 200-701, Korea, [2]College of Pharmacy, Sungkyunkwan University, Suwon, 440-746, Korea, and [3]College of Pharmacy, Woosuk University, Samrye 565-701, Korea

(Received July 7, 2005)

Morphine-induced analgesia has been shown to be antagonized by ginseng total saponins (GTS), which also inhibit the development of analgesic tolerance to and physical dependence on morphine. GTS is involved in both of these processes by inhibiting morphine-6-dehydrogenase, which catalyzes the synthesis of morphinone from morphine, and by increasing the level of hepatic glutathione, which participates in the toxicity response. Thus, the dual actions of ginseng are associated with the detoxification of morphine. In addition, the inhibitory or facilitated effects of GTS on electrically evoked contractions in guinea pig ileum (μ-receptors) and mouse vas deferens (δ-receptors) are not mediated through opioid receptors, suggesting the involvement of non-opioid mechanisms. GTS also attenuates hyperactivity, reverse tolerance (behavioral sensitization), and conditioned place preference induced by psychotropic agents, such as methamphetamine, cocaine, and morphine. These effects of GTS may be attributed to complex pharmacological actions between dopamine receptors and a serotonergic/adenosine A_{2A}/δ-opioid receptor complex. Ginsenosides also attenuate the morphine-induced cAMP signaling pathway. Together, the results suggest that GTS may be useful in the prevention and therapy of the behavioral side effects induced by psychotropic agents.

Key words: Ginseng total saponins, Morphine, Cocaine, Methamphetamine, Sensitization, Conditioned place preference.

INTRODUCTION

The repeated use of addictive drugs produces multiple unwanted changes in the brain that may lead to tolerance, sensitization, and dependence. Dependence is a biological phenomenon often associated with "drug abuse." Psychological dependence is manifested by compulsive drug-seeking behavior in which the individual uses drugs repeatedly for personal satisfaction, often in the face of known health risks. Cigarette smoking is an example in that deprivation for a short period of time typically results in a strong desire or craving. Physiological dependence is present when withdrawal of the drug produces symptoms and signs that are frequently the opposite of those sought by the user. It has been suggested that the body adjusts to a new level of homeostasis during the period of drug use and reacts in an opposite fashion when the new equilibrium is disturbed. Alcohol withdrawal syndrome is perhaps the best-known example, but milder degrees of withdrawal can be observed in people who drink large quantities of coffee every day. Psychological dependence almost always precedes physiological dependence but dose not inevitably lead to it. Addiction is usually taken to mean a state of both physiological and psychological dependence (Kosten and Hollister, 2001).

An enhanced response to repeated presentations of a drug is referred to as "sensitization" or "reverse tolerance" and occurs when repeated administration of the same drug dose elicits escalating effects. The reinforcing effects of addictive drugs are subject to sensitization. Similarly, locomotor sensitization has been observed in rodents, cats, dogs, nonhuman primates, and humans after repeated administration of opiates, nicotine, ethanol, or phencyclidine. Neurobiological findings in animal models have also been increasingly confirmed in human studies, in which radioligands have been used to examine dopamine

Correspondence to: Ki-Wan Oh, Department of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea
Tel: 82-43-261-2827 Fax: 82-43-268-2732
E-mail: kiwan@chungbuk.ac.kr

receptors and transporters, opioid receptors, and functional brain activity based on blood flow or glucose utilization (Di Chiara and Imperato, 1988a). These receptor neuroimaging studies have demonstrated that chronic drug abuse can produce tolerance, dependence, and behavioral sensitization, all of which may be associated with changes in the number of receptors (e.g., decreased dopamine D_2 receptors in cocaine abusers) and transporters (e.g., increased dopamine transporters in cocaine abusers) (Nicola *et al.*, 2000; Schultz, 1997).

For hundreds of years, efforts have been made to help people with drug addictions. Nevertheless, the body of knowledge regarding the nature of addictions and how to treat them is still incomplete. There are many alternative and widely divergent points of view concerning many treatment issues. Moreover, many forms of treatment have been either poorly evaluated or not evaluated at all, which makes it difficult for clinicians and drug therapists to make global recommendations. Nonetheless, medications can be used in the treatment of drug abuse in order to accomplish several goals. For example, the administration of a narcotic antagonist is a rational form of therapy because blocking the action of self-administered opioids should eventually extinguish the habit. The effects of naltrexone, a long-acting, orally administered, pure opioid antagonist, have been extensively studied, and narcotic antagonists such as naltrexone may be useful in treating addictions to other psychostimulants (Kosten and Hollister, 2001). Recent findings, such as the use of clonidine to aid in opioid withdrawal, have important treatment implications. Even though physical withdrawal is often mild, an addict knows that any discomfort can be relieved in minutes simply by taking a dose of the abused drug. Medications for withdrawal control can therefore be helpful in the short run for discouraging relapse.

A folk medicine composed of seven herbal drugs, including *Panax ginseng*, has been used as an antidote in the treatment of morphine-tolerant/dependent patients. The traditional form of this medicine consists of seven natural products: *Ginseng radix, Euphobiae pekinensis, Manis squama, Zizyphi spinosi semen, Angeliacase gigantis radix, Cniddi rhizoma*, and *Paeonia radix*. Ginseng's beneficial effects on the response to psychotropic agents were initially reported by Kim *et al.* (1986), who observed that *Panax ginseng* inhibited the analgesic tolerance and physical dependence induced by morphine. Here, we review the current knowledge regarding the effects of ginseng in the prevention and treatment of the adverse actions of dependence-liable drugs.

Pharmacological action of ginseng in responses to opioids

Previous investigations have demonstrated that the major component of ginseng, the saponin fraction (GTS), antagonizes morphine-induced analgesia in mice (Kim *et al.*, 1986, 1987a, 1990a). Some investigators have revealed the analgesic effects of GTS (Nabata *et al.*, 1973; Saito *et al.*, 1973). For example, Watanabe *et al.* (1988a, 1988b) demonstrated a non-opioid mechanism in the inhibitory effect of GTS on electrically evoked contractions of guinea pig ileum and mouse vas deferens. GTS also inhibited the exogenous ATP-elicited contraction of mouse vas deferens by inhibiting the action of the ATP released from sympathetic nerve terminals *via* P_2-purinoceptors (Kim *et al.*, 1993c, 1993d). However, it was recently reported that GTS has an affinity for opioid receptors in the CNS, because GTS inhibited opioid binding in some regions of the brain. In that study, specific [^{3}H]DAGO binding was decreased in the frontal cortex without changes in B_{max} (Oh *et al.*, 2002). The antinociceptive effect of U-50488H, a selective κ-agonist, was also prevented by GTS in the tail-flick test, suggesting the involvement of serotonergic mechanisms (Kim *et al.*, 1992a, 1993a). In addition, ginsenosides injected intrathecally or intracerebroventricularly antagonized morphine-induced antinociception (Suh *et al.*, 1997). Thus, GTS and ginsenosides may mediate morphine-induced antinociception by modulating GABA receptors. Similarly, we previously reported that ginsenosides decrease the binding affinity of $GABA_A$ and $GABA_B$ receptors without changing the number of binding sites (Kimura *et al.*, 1994). Furthermore, majonoside-R_2, from Vietnamese ginseng, was shown to attenuate opioid-induced antinociception by acting at the spinal and supraspinal levels, suggesting the involvement of the $GABA_A$ receptor complex at the supraspinal level (Huong *et al.*, 1997). Also, the systemic administration of GTS decreased pentazocine-induced analgesia dose-dependently and inhibited the development of analgesic tolerance to this compound and morphine (Kim *et al.*, 1992b, 1992c; Choi *et al.*, 2000).

The inhibitory effects of GTS on the development of morphine-induced analgesic tolerance and physical dependence appear to be associated with a ginseng-induced increase in hepatic glutathione levels (Schole, 1978; Kim *et al.*, 1987a, 1987b, 1989). When morphinone, a toxic metabolite of morphine, was conjugated with glutathione, its metabolism was tightly coupled to the detoxification process. However, the metabolism of morphinone into the morphinone-GSH conjugate plays an important role in the development of both morphine-induced analgesic tolerance and dependence by covalently binding to the sulfhydryl group of opioid receptors (Yamamoto *et al.*, 1985; Nagamatsu *et al.*, 1982, 1983). The inhibitory effect of GTS can be explained by its dose-dependent inhibition of morphine-6-dehydrogenase, the enzyme that catalyzes the synthesis of morphinone from morphine (Kim *et al.*, 1987b).

It was reported that the effects in mice of morphine 10 mg/kg were antagonized by pretreatment with reserpine 2.5 mg/kg. The antagonism was accompanied by reductions in the levels of brain biogenic monoamines (Takagi *et al.*, 1964; Verri *et al.*, 1967), consistent with the finding that neurotransmitters, such as dopamine and noradrenaline, and cAMP are implicated in abstinence syndromes (Di Chiara and Imperato, 1988b). Likewise, withdrawal symptoms are associated with increased levels of dopamine and cAMP in the brain (Iwamoto *et al.*, 1973; Collier *et al.*, 1975), and most studies have shown increases in noradrenaline, dopamine, and cAMP in GTS-treated animals (Joo, 1984; Park, 1984; Kim *et al.*, 1985). While brain levels of noradrenaline, dopamine, and serotonin were not changed after the administration of a single dose of GTS 100 mg/kg, locomotor activity was inhibited, confirming the depressive effects of GTS in mice. As noted above, the development of analgesic tolerance in response to U-50488H and pentazocine was inhibited by GTS in a serotonergic-related manner (Kim *et al.*, 1992a, 1993a). However, Watanabe *et al.* (1988b) reported that the inhibitory effect of GTS on isolated guinea pig ileum and mouse vas deferens provided evidence for a direct action of GTS on smooth muscle in the absence of cholinergic and/or serotonergic mechanisms involving opioid receptors.

Furthermore, the concurrent administration of GTS significantly diminished jumping, teeth chattering, and weight loss precipitated by naloxone in rats previously infused with morphine into the lateral cerebral ventricle via an osmotic minipump (Kim *et al.*, 1992c). Similarly, the development of physical dependence on nalbuphine and pentazocine was inhibited by GTS (Kim *et al.*, 1992b; Kim and Oh, 1994).

Pharmacological action of ginseng in responses to psychostimulants

It is well known that repeated administration of psychostimulants leads to an increase in ambulatory activity and rewarding behaviors, which, at least in part, may be consequences of the neurotoxicity associated with continuous exposure to such agents (Segal *et al.*, 1981; Segal and Geyer, 1985; Robinson and Becker, 1986). Dopaminergic systems play important roles in mediating responses to psychostimulants (Scheel-Kruger *et al.*, 1977; Roy *et al.*, 1978). For example, rats sensitized to psychostimulants show an enhanced response to apomorphine, a direct dopamine receptor agonist, suggesting the development of dopamine receptor supersensitivity (Hunt *et al.*, 1974).

After pretreatment with ginseng extract for 5 days, concomitant injections of methamphetamine and ginseng extract suppressed the development of reverse tolerance to methamphetamine, whereas ginseng extract did not affect the spontaneous activity of naïve mice (Tokuyama *et al.*, 1992). In addition, G115 (a standardized ginseng extract) significantly inhibited the development of morphine-induced analgesic tolerance and reverse tolerance to the locomotor-accelerating effect of morphine (Kim *et al.*, 1990b). GTS from ginseng extract prevented both the development of reverse tolerance to morphine, methamphetamine, and cocaine, and the dopamine receptor supersensitivity induced by those drugs, most probably by inhibiting dopamine receptor activation (Kim *et al.*, 1994;

Table I. Representative publications on the beneficial effects of abused drugs by ginseng

Drugs	Composition of ginseng	Pharmacological action	References
Morphine	Panax ginseng	Inhibition of tolerance	Bhargava *et al.*, 1991
Morphine	Panax ginseng	Inhibition of dependence	Kim *et al.*, 1992
Morphine	Ginseng total saponin	Inhibition of reverse tolerance	Kim *et al.*, 1995c
Morphine	Ginsenosides	Inhibition of antinociception	Suh *et al.*, 1997
Morphine	Ginseng total saponin	Inhibition of CPP	Kim *et al.*, 1998b
Opioids	Majonoside-R2	Inhibition of antinociception	Huong *et al.*, 1997
Opioid	Ginsenosides	Inhibition of tolerance	Choi *et al.*, 2000
U-50,488H	Ginseng total saponin	Inhibition of antinociception	Kim *et al.*, 1992a
Cocaine	Ginsneg total saponin	Inhibition of CPP	Kim *et al.*, 1996a
Cocaine	Ginseng total saponin	Inhibition of reverse tolerance	Kim *et al.*, 1995a
Cocaine	Ginsenosides Rb1 and Rg1	Inhibition of CPP	Kim *et al.*, 1999a
Methamphetamine	Pseudoginsenosides-F11	Inhibition of neurotoxicity	Wu *et al.*, 2003
Methamphetamine	Ginsenosides Rb1 and Rg1	Inhibition of CPP	Kim *et al.*, 1998a
Methamphetamine	Ginseng total saponin	Inhibition of CPP	Kim *et al.*, 1996b
Methamphetamine	Ginsenosides	Inhibitions of CPP and circular behavior by activation of adenosine A_{2A} receptor	Shin *et al.*,2005

Kim *et al.*, 1995a; Kim *et al.*, 1995b; Kim *et al.*, 1995c; Tokuyama *et al.*, 1996; Kim *et al.*, 1996a; Kim *et al.*, 1996b). Protection against methamphetamine-induced neurotoxicity was also observed with pseudoginsenoside-F-11 from American ginseng (Wu *et al.*, 2003). Taken together, these results provide evidence that ginseng may be useful in the prevention and therapy of drug-induced psychotoxicity or psychosis.

Amphetamine-like compounds facilitate the release of dopamine from synaptosomes and cocaine inhibits dopamine uptake by presynaptic neurons (Butcher *et al.*, 1988; Heikkila *et al.*, 1975; Heikkila *et al.*, 1979; Hadfield *et al.*, 1980). These enhanced neurotransmitter activities, particularly at dopamine receptors, have been implicated in the locomotor and stereotyped behaviors, as well as in the rewarding behaviors, mediated by psychostimulants such as amphetamine and cocaine. Multiple doses of amphetamines cause substantial and long-lasting depletions of striatal dopamine and its metabolites (Wagner *et al.*, 1980a). The neuropathological alterations that occur in response to high doses of methamphetamine parallel, at least in part, the pathology observed in Parkinson's disease (Wagner *et al.*, 1980a; Wagner *et al.*, 1980b).

Pretreatment with GTS exerted a significant neuroprotective effect against methamphetamine-induced dopaminergic damage (Oh *et al.*, 1997); GTS significantly restored the methamphetamine-induced decrease in 3,4-Dihydroxyphenylacetic acid (DOPAC). Similarly, pretreatment with two injections of GTS reduced the magnitude of methamphetamine-induced depletions of dopamine, DOPAC, and homovanillic acid (HVA), indicating that GTS prevents methamphetamine-induced striatal dopaminergic depletions (Oh *et al.*, 1997). It has been reported that ginsenosides exert powerful inhibitory actions on catecholamine secretion, suggesting that GTS modulates dopaminergic activity, preferentially at presynaptic sites (Takahashi *et al.*, 1993).

GTS from an extract of *Panax ginseng* suppressed conditioned place preference (CPP) induced by cocaine or methamphetamine (Tokuyama *et al.*, 1996). In this model, the repeated administration of psychostimulants also caused dopamine-receptor supersensitivity (Kim *et al.*, 1996a; Kim *et al.*, 1996b; Kim *et al.*, 1998a; Kim *et al.*, 1998b; Kim *et al.*, 1998c; Kim *et al.*, 1999a; Kim *et al.*, 1999b). Ginsenosides have been shown to inhibit tyrosine hydroxylase activity, which may at least partially explain their antidoapminergic action and the ability of ginseng to inhibit dopamine receptor activation (Kim *et al.*, 1999b). Recently, Shin *et al.* (2005) demonstrated that the stimulation of adenosine A_{2A} receptors by ginsenosides attenuated mouse behavioral changes as well as the increases in activator protein (AP)-1 DNA binding activity, Fos-related antigen immunoreactivity (FRA-IR), and proenkephalin gene expression in mouse striatum that were induced by methamphetamine. The behavioral data produced by Shin *et al.* (2005) are in line with those of Kim *et al.* (1996b). Taken together, these results are consistent with the notion that the stimulation of adenosine-receptive neural systems reduces the effects of psychostimulants on behavior (Justinova *et al.*, 2003).

CONCLUSIONS

Ginsenosides from GTS inhibit the development of reverse tolerance and psychological dependence induced by methamphetamine and cocaine (Kim *et al.*, 1998a; Kim *et al.*, 1999a). Ginseng simultaneously inhibits the analgesic effects mediated by morphine, the development of analgesic tolerance, and morphine dependence. It also inhibits hyperactivity, reverse tolerance, and CPP induced by psychostimulants. The beneficial effects of ginseng on psychotropic agent-induced behavioral toxicity deserve further attention in light of the potential for its clinical application. However, ginseng's precise pharmacological mechanism of action remains to be explored.

ACKNOWLEDGEMENTS

This is work was supported by the Regional Research Centers Program of the Korean Ministry of Education & Human Resources Development through the Center for Healthcare Technology and by Brain Korea 21 (2005).

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