

Research Paper: Effects of Pretreatment With Ginseng Extract on Dopamine D2 Receptor Analgesia



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ABSTRACT

Introduction: The ginseng extract is an herb that has been used for many purposes such as analgesic effect. Dopamine D2 receptors are involved in the regulation of pain in humans. Therefore, the present investigation aims to study how pretreatment with aqueous-alcoholic extract of ginseng can affect dopamine D2 receptors' pain sensitivity.

Methods: We used 45 adult male rats weighing 250 ± 20 for this study. Animals were maintained in a standard condition at a temperature of 21°C - 24°C . The experimental groups were as follows: 1. Sham 1 (intraperitoneal [IP] injection of normal saline); 2. Sham 2 (intracerebroventricular [ICV] injection of artificial cerebrospinal fluid [ACSF]); 3. Experimental 1 (IP injection of ginseng extract); 4 and 5. Experimental groups 2 and 3 (IP injection of ginseng extract + bromocriptine 10 and 30 $\mu\text{g}/\text{rat}$ by ICV injection); 6 and 7) experimental groups 4 and 5 (IP injection of ginseng extract + chlorpromazine 20 and 40 $\mu\text{g}/\text{rat}$ by ICV injection). Ginseng extract 100 mg/kg/d was used for 7 days. Pain sensitivity test was done in all groups with the formalin test. Lateral ventricles of the rats were cannulated unilaterally by the stereotaxic procedure.

Results: Our data showed that ginseng (100 mg/kg/d) significantly ($P < 0.05$) decreased pain sensitivity compared to the sham 1 group. Bromocriptine in two doses significantly decreased pain sensitivity compared to the sham 2 group. Chlorpromazine in high doses significantly increased pain sensitivity compared to the sham 2 group.

Conclusion: The present results indicate that ginseng can modulate the D2 receptor of the dopamine system in the control of pain sensitivity in the formalin test. Because bromocriptine and ginseng have similar effects, it seems that they had synergistic effects.

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Highlights

- Ginseng and bromocriptine had an analgesic effect.
- An analgesic effect of ginseng and bromocriptine is synergistic but no additive.
- Hyperalgesic effect of chlorpromazine is more potent than the analgesic effect of ginseng.

Plain Language Summary

Pain is physical and mental suffering that may arise by internal or external stimuli. Dopamine is one of the main chemical substances of the brain. It seems that the dopamine has analgesic effect. The analgesic effect of dopamine is through dopaminergic D2 receptors. On the other hand, Ginseng is an herbal plant and the roots of this plant contain a class of steroid that is responsible for its pharmacological activity. Ginseng has analgesic, antioxidant, anti-inflammatory, anti-apoptotic, and anti-aging properties. Some investigator stated that ginseng not only cause the release of dopamine directly or indirectly through the cholinergic system, but also can directly affect dopamine D2 receptors. According to the present results, ginseng administration (100 mg/kg/day) for 7 days had an analgesic effect, and bromocriptine (D2 receptor agonist) administration in two different doses after pretreatment with ginseng (100 mg/kg/day) had an analgesic effect the same as ginseng alone. Therefore, it seems that bromocriptine and ginseng had a synergistic but no additive effect. Finally, chlorpromazine (D2 receptor antagonist) administration in two different doses after pretreatment with ginseng (100 mg/kg/day) had hyperalgesic effects compared to ginseng alone. Therefore, the hyperalgesic effect of chlorpromazine is more potent than the analgesic effect of ginseng. According to our data ginseng and D2 receptor agonist had the same analgesic effect.

1. Introduction

Pain is physical and mental suffering that may arise by internal or external stimuli. Pain regulation is a complex process that depends on the interaction of many physiological, neurological, and hormonal factors. By changing the level of chemical mediators, some environmental events reduce or increase pain sensitivity. These chemical mediators are very effective in pain relief (Garland, 2012).

Dopamine is one of the main neurotransmitters of the central nervous system and many neurological and psychiatric diseases are related to its secretion and functions (Dauer & Przedborski, 2003). It seems that the analgesic effect of the dopaminergic system is through the endogenous opioid receptor (Volkow, 2010). These effects on pain processing are mainly done by striatal dopaminergic D2 receptors (Becker et al., 2013). Besides, it is reported that activation of dopamine D2 receptor through descending endogenous pain-control pathways is essential (Dauer & Przedborski, 2003).

Ginseng is an herbal plant belonging to the Panax genus of the family Araliaceae (Rhim, Kim, Lee, Oh, & Nah, 2002). The roots of this plant contain a class of ste-

roid glycosides called ginsenoside that is responsible for its pharmacological activity (Chang, Seo, Gyllenhaal, & Block, 2003). The scientific names of ginsenosides are triterpenoid saponins or sometimes panaxoside in ginseng root (Sun, 2004). Ginseng has antioxidant, anti-inflammatory, anti-apoptotic, and anti-aging properties. These effects include increased neuronal survival, growth, and development of neuron and prevention from neuronal death (Rausch, Liu, Gille, & Radad, 2006). Kim, Shim, Chung, and Lee (2006) stated that ginseng saponins not only cause the release of dopamine directly or indirectly through the cholinergic system, but also can directly affect dopamine D2 receptors (Kim et al., 2006). On the other hand, ginsenosides have partial neurotrophic and neuroprotective effects on dopaminergic neurons in culture. Therefore, they increase cell survival by decreasing the release of lactate dehydrogenase and preventing mitochondrial membrane potential loss (Sandoval-Avila et al., 2018).

Despite many investigations on dopamine D2 receptor and pain and the relation between ginseng extract and pain, the simultaneous analgesic effect of these two factors has not been evaluated. Therefore, we aimed to investigate the effect of dopamine D2 receptor agonist (bromocriptine) and antagonist (chlorpromazine) on

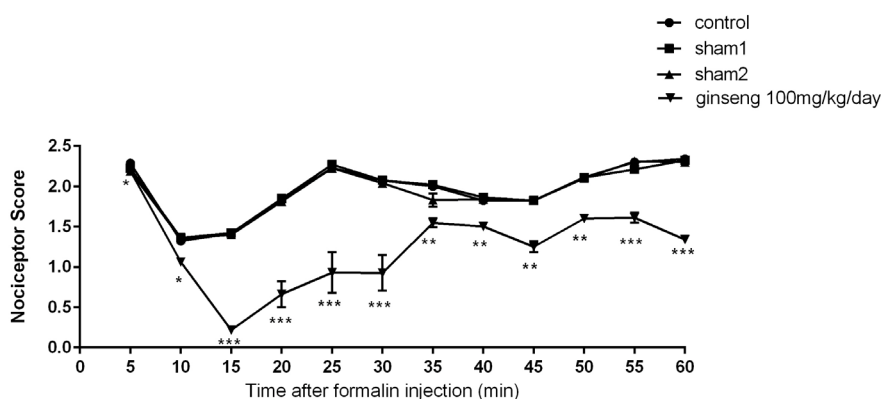


Figure 1. Effect of ginseng (100 mg/kg/d) on nociceptive scores (Mean±SE)

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* Difference between ginger group in comparison to control, sham 1 and sham 2 groups; * P<0.05, ** P<0.01, *** P<0.001.

pain sensitivity after ginseng extract administration (100 mg/kg/d) for 7 days.

results of all 15-s checks were averaged for every 5 minutes and considered for data analysis.

2. Materials and Methods

A total number of 56 adult male Wistar rats weighing approximately 250±20 g in standard conditions (12/12 hour light/dark cycle at 22±2°C) were used. They had access to food and water ad libitum.

The rats were randomly divided into 7 groups (n=8), as follows: 1. Sham 1: healthy rats received IP injection of normal saline; sham 2. Rats were unilaterally received Artificial Cerebrospinal Fluid (ACSF) by Intracerebroventricular (ICV) injection into the lateral ventricle; 3. experimental 1: rats received IP injection of ginseng extract; 4 and 5. Experimental 2 and 3: Rats received IP injection of ginseng extract + unilateral ICV injection of bromocriptine 10 or 30 µg/rat; 6 and 7. Experimental 4 and 5: rats received IP injection of ginseng extract + unilateral ICV injection of chlorpromazine 20 or 40 µg/rat.

IP injections of normal saline and ginseng extract (100 mg/kg/d) were done for 7 days. Formalin test was performed 30 min after IP injection of normal saline or ginseng extract in the sham 1 and experiment 1 groups and 30 min after ICV injection in groups that received drugs or ACSF. Hydro-alcoholic extract of ginseng was prepared according to Palaniyandi, Suh, and Yang (2017) study.

To evaluate the pain sensitivity, formalin solution (50 µL) was subcutaneously injected into the dorsal surface of the animal's right hind paw (2.5% in normal saline). The pain score was recorded every 15 seconds for 60 minutes. The score would be 0 if the animal showed no reaction, 1 if the animal did not rely on the injected paw, 2 if the animal holds its paw up, and 3 if the rat licks and/or bites the injected paw. The

For the stereotaxic procedure, the animals were anesthetized with an IP injection of ketamine 10% (100 mg/kg) and xylazine 2% (10 mg/kg). The rats were fixed in the stereotaxic apparatus using blunt ear bars. The skull was carefully exposed and stainless steel guide cannula (23-gauge needle) was inserted unilaterally into the lateral ventricle. The coordinates for lateral ventricle according to bregma were 0.5 mm anterior and 1.5 mm lateral to the midline and 3.5 mm below to cortex. The guide cannula via dental acrylic cement and two tiny stainless steel screws were fixed to the skull. In the end, the animals were given 7 days recovery period.

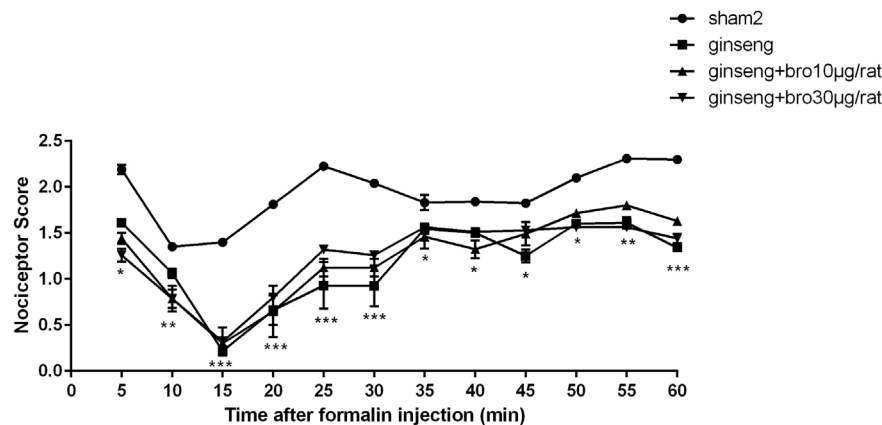
2.1. Statistical analysis

For data analysis, we used SPSS V. 21. The data were analyzed by One-way ANOVA, repeated measure ANOVA, and the Tuckey post-hoc test. P-values less than 0.05 were considered significant.

3. Results

According to ANOVA, IP injection of ginseng 100 mg/kg/d for 7 days significantly reduced pain sensitivity in the early phase ($F_9=61.2$, $P=0.0$), intermediate phase ($F_9=16.8$, $P=0.0$), and late phase ($F_9=92.8$, $P=0.0$) of formalin test compared to the control and sham1 groups (Figure 1).

One-way ANOVA results indicate that ICV injection of bromocriptine 10 µg/rat after IP injection of ginseng 100 mg/kg/d for 7 days significantly ($P<0.0001$) reduced pain sensitivity during 60 minutes of formalin test compared to the control and sham 1 groups. The ICV injection of bromocriptine 30 µg/rat after IP injection of ginseng (100 mg/kg/d) for 7 days had similar effects except that in the



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Figure 2. Effect of bro (bromocriptine) 10 and 30 µg/rat on nociceptive scores (Mean±SE) in rats pretreated by ginseng (100 mg/kg/d) for 7 days

* Significant difference between bro 10 and 30 µg/rat group in comparison to sham 2 group; * P<0.05, ** P<0.01, *** P<0.001.

25th and 45th minutes there was no difference compared to the control and sham 2 groups. Bromocriptine in two doses significantly decrease pain sensitivity in the early phase ($F_9=61.2$, $P=0.0$), intermediate phase ($F_9=16.8$, $P=0.0$), and late phase ($F_9=92.8$, $P=0.0$) of formalin test compared to the control and sham 2 groups but does not have any difference with ginseng group (Figure 2).

Chlorpromazine (20 µg/rat) had no significant effect on pain sensitivity compared to the control and sham 2 groups; while it significantly increased pain sensitivity in the early phase ($F_9=61.2$, $P=0.0$), intermediate phase ($F_9=16.8$, $P=0.0$), and late phase ($F_9=92.8$, $P=0.0$) of formalin test compared with the ginseng group (Figure 3). Chlorpromazine (40 µg/rat) significantly increased pain sensitivity in the early phase ($F=61.2$, $P=0.0$), intermediate phase ($F_9=16.8$, $P=0.0$) and late phase ($F_9=92.8$, $P=0.0$) of formalin test compared to the control, sham 2, and ginseng groups (Figure 3).

4. Discussion

The present study demonstrates that the hydro-alcoholic extract of ginseng 100 mg/kg/d has an analgesic effect in phase 1 and phase 2 of the formalin test. Previous studies revealed that ginseng saponins have analgesic effects in the writhing test and phase 2 of the formalin test (Nabata, Saito, & Takagi, 1973; Shin et al., 1997).

The mechanism of the analgesic action of ginseng by formalin test has not been specified, yet. Nevertheless, it is likely that saponins of ginseng attach to the nonopioid receptors at the cell surface and regulate the voltage-gated calcium channels. In other words, the calcium channels are inhibited by ginseng saponins. Volt-

age-gated calcium channels play a key role in releasing pain neurotransmitters in presynaptic nerve endings of efferent neurons and its blocking decreases pain to some extent (Nah & McCleskey, 1994).

The other analgesic mechanism of ginseng in the formalin test is that ginseng saponins or ginsenosides probably affect the dopaminergic activity of the central nervous system (Jun, Bae, Kim, Koo, & Kim, 2015). Besides the postsynaptic effect of ginseng on voltage-gated channels, it may also affect the presynaptic signal pathway in the dopamine system and thereby increasing dopamine release from nucleus accumbens, as a result, causes pain relief in the formalin test (Mancusoa & Santangelob, 2017; Nah, Bhatia, Lyles, Ellinwood, & Lee, 2009).

The present investigation demonstrates that the administration of bromocriptine (10 and 30 µg/rat) following to hydro-alcoholic extract of ginseng (100 mg/kg/d) for 7 days had an analgesic effect as great as ginseng alone in phases of formalin test. Therefore, ginseng extract may apply its analgesic effects through dopaminergic system receptors the same as dopamine. After the injection of a selective dopamine agonist in the nucleus accumbens core, it exerts analgesic effects of dopaminergic drugs in the formalin test (Faramarzi, Zendehdel, & Haghparast, 2016). Haghparast, Ghalandari-Shamami, & Hassanpour-Ezatti, (2012) suggested that dopamine D2 receptors in the nucleus accumbens had a critical role in the adjustment of acute and chronic inflammatory pain in the formalin test. Lintas et al. (2011) reported that bilateral microinjection of dopamine D2 receptor agonist in the nucleus accumbens inhibits the chronic phase caused by formalin test.

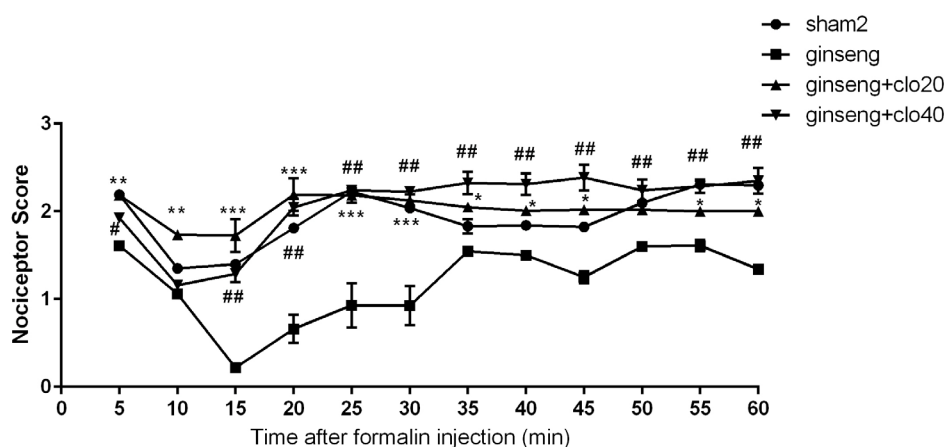


Figure 3. Effect of clo (chlorpromazine) 20 and 40 $\mu\text{g}/\text{rat}$ on nociceptive scores (mean \pm SE) in rats pretreated by ginseng (100 mg/kg/d) for 7 days

* Significant difference between clo 20 and 40 $\mu\text{g}/\text{rat}$ groups, in comparison to sham 2 group; # Significant difference between clo 20 and 40 $\mu\text{g}/\text{rat}$ groups, in comparison to ginseng (100 mg/kg/d) group.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; # $P < 0.05$, ## $P < 0.001$.

There are several mechanisms for analgesic effects of bromocriptine; one of them pointed out that it prevents Nitric Oxide (NO) release by affecting α_2 -adrenergic receptors (Beck et al., 2004). Some investigations suggest that NO is a modulator of the nervous system in many activities. One of the NO roles is related to pain, because following nerve damages in the affected area, the level of NO increases there (Cury, Picolo, Gutierrez, & Ferreira, 2011; Levy & Zochodne, 2004). Moreover, the production of NO, which increases following the formalin test, is inhibited by flavonoids and phenolic compounds of ginseng, thereby decreasing NO that leads to analgesic activity (Jang et al., 2016; Kim et al., 2015). Therefore, ginseng extract and bromocriptine synergistically reduce NO production.

5. Conclusion

The current study shows that chlorpromazine in two doses following to IP injection of ginseng (100 mg/kg/d) had a hyperalgesic effect compared to the ginseng group. However, its hyperalgesic effect compared to the control and sham 2 groups is seen at 40 $\mu\text{g}/\text{rat}$ but not 20 $\mu\text{g}/\text{rat}$ dose.

Various studies show that the raclopride (dopamine D2 antagonist) causes hyperalgesia in rats and pet animals (Da Silva et al., 2017; Dias et al., 2015). Prescription of dopamine antagonists can inhibit the analgesic effect caused by the release of dopamine (Yazdi-Ravandi, Razavi, Haghparast, & Goudarzvand, 2014). The selective prescription of dopamine D2 receptor antagonists

systematically reduces the analgesic effect caused by amphetamines, morphine, and cocaine in the formalin test (Pelissier, Laurido, Hernandez, Constandil, & Eschaliere, 2006). Quinpirole as a dopamine D2-like receptor agonist reduces pain in both phases of the formalin test and sulpiride as an antagonist can potentially reverse analgesic effects observed by this agonist (Shamsizadeh, Pahlevani, Haghparast, Moslehi, & Zarepour, 2013). These results supported our findings.

According to the present results, ginseng administration (100 mg/kg/d) for 7 days had an analgesic effect, and bromocriptine administration in two different doses after pretreatment with ginseng (100 mg/kg/d) had an analgesic effect the same as ginseng alone. Therefore, it seems that bromocriptine and ginseng had a synergistic but no additive effect. Finally, chlorpromazine administration in two different doses after pretreatment with ginseng (100 mg/kg/d) had hyperalgesic effects compared to ginseng alone. Therefore, the hyperalgesic effect of chlorpromazine is more potent than the analgesic effect of ginseng.

Ethical Considerations

Compliance with ethical guidelines

All animal procedures were performed according to the Institutional Research Ethics Committee of the School of Veterinary Medicine of Shiraz University, Shiraz, Iran.

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Authors' contributions

Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing – original draft preparation, writing – review & editing, visualization, supervision, and project administration, funding acquisition: Mahnaz Taherianfard; Methodology, investigation, resources, data curation: Somaye Aalam.

Conflict of interest

All authors declared no conflict of interest.

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