

## Red Ginseng Supplementation More Effectively Alleviates Psychological than Physical Fatigue

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Red ginseng (RG, the extract of *Panax ginseng* Meyer) has various biological and psychological activities and may also alleviate fatigue-related disorders. The present study was undertaken to evaluate what kind of fatigue red ginseng alleviate. Animals were orally administered with 50, 100, 200, 400 mg/kg of RG for 7 days. Before experiments were performed. Physiological stress (swimming, rotarod, and wire test) are behavioral parameters used to represent physical fatigue. Restraint stress and electric field test to a certain degree, induce psychological fatigue in animals. Plasma concentration of lactate and corticosterone (CORT) were also measured after these behavioral assays. RG supplementation (100 mg/kg) increased movement duration and rearing frequency of restrained mice in comparison with control. 100 and 200 mg/kg of RG increased swimming time in cold water (8±4°C) while at 100 mg/kg, RG increased electric field crossing over frequencies. 50, 100 and 200 mg/kg RG prolonged running time on the rotarod and at 100 mg/kg, it increased balancing time on the wire. RG at those doses also reduced falling frequencies. RG supplementation decreased plasma CORT levels, which was increased by stress. Lactate levels were not significantly altered. These results suggest that RG supplementation can alleviate more the damages induced by psychological than physical fatigue.

**Keywords:** *Panax ginseng*, Red ginseng water extract, Restraint stress, Swimming test, Behavior

### INTRODUCTION

Ginseng (*Panax ginseng* Meyer) which contains a series of tetracyclic triterpenoid saponins (ginsenosides) is one of the most popular medicinal plants throughout the world because of its beneficial effects [1]. Red ginseng (RG) is prepared by steaming the root prior to drying. RG is widely known to contain more pharmacologically active effects than white ginseng [2,3]. Ginsenosides can be classified into three groups on the basis of the chemical structure of their sapogenins (aglycones): the panaxadiol group (e.g., Rb<sub>1</sub>, Rb<sub>2</sub>, Rb<sub>3</sub>, Rc, Rd, Rg<sub>3</sub>, Rh<sub>1</sub>); the panaxatriol group (e.g., Re, Rf, Rg<sub>1</sub>, Rg<sub>2</sub>, Rh<sub>1</sub>); and

the oleanolic acid group (e.g., Ro) [4,5]. Ginsenosides Rg<sub>3</sub>, Rg<sub>5</sub>, and Rk<sub>1</sub> were the most abundant ginsenosides in the ginseng steamed at higher temperature [6]. Jin *et al.* [7] suggested that the ratio of ginsenosides may be an important factor in the pharmacological effects of ginseng extracts [5]. Pharmacological effects of ginseng have been demonstrated in the central nervous system and in cardiovascular, endocrine, and immune systems. In addition, ginseng and its constituents have been ascribed antineoplastic, anti-stress, and antioxidant activity [8]. It enhances resistance to temperature stress, physical

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exercise, and increases swimming time in rats [9]. It has also long been used traditionally for the treatment of psychiatric diseases such as anxiety and depression [6]. It has long been considered to act as an adaptogen, but the mechanisms underlying its effect are still unclear. It is also unclear which kind of fatigue it counteracts more effectively.

Adaptogens have been defined as “natural metabolic regulators that increase the ability of organism to adapt to environmental factors and to avoid damage from such factors” [10,11]. The mode of action of adaptogens is not completely understood, but modulation of catecholamines and other stress mediators (e.g., cortisol and nitric oxide) has been proposed [11,12]. Tonic and adaptogenic effects of ginseng are believed to enhance physical performance and general vitality in healthy individuals, to increase the body’s ability to fight stress in stressful circumstances and to support resistance to diseases by strengthening normal body function as well as to reduce the detrimental effects of the aging processes [13]. Bhat-tacharya and Muruganandam [14] suggested that *P. ginseng* had significant antistress adaptogenic activity. The antistress activities of ginseng may account for its observed clinical efficacy in stress-related disorders like depression and anxiety [15,16]. Some of the ‘adaptogenic’ effects of ginseng are attributed to its actions on the hypothalamic-pituitary-adrenal axis, resulting in elevated plasma corticotrophin and corticosteroids levels [9].

In previous studies, we reported that RG and sun ginseng attenuated the response to stress through physiological effects and enhancement of physical capacity [17,18]. The role of RG in stressed animals remains to be determined, although there are a few reports stating that RG reduces the behavioral signs of fatigue-related disorders.

Our experiments were performed to identify what kind of fatigue RG supplementation alleviates. To measure the ability of RG to counteract physiological fatigue, mice were subjected to physiological stress (swimming, rotarod, and wire test), on the other hand restraint stress and electric field test represent psychological fatigue.

## MATERIALS AND METHODS

### Materials

RG water extract standard preparation was obtained from Korea Ginseng Corporation (Seoul, Korea). Corticosterone (CORT) were obtained from Sigma (St. Louis, MO, USA). Other unstated chemicals and reagents were of analytical grade.

### Animals and treatments

The male ICR mice (17-20 g) were supplied by Hanlim Laboratory Animals Co. (Hwaseong, Korea). They were housed in animal room which was maintained at temperature (22±2°C) and humidity (55±5%) under a 12/12-h light/dark cycle with lights on from 7:00 AM. Food and water were available *ad libitum*. After this stabilization period, animals were orally administered with 50, 100, 200 and 400 mg/kg of RG for 1, 3 or 7 days. Enduring activities after restraint, hanging on the wire, running on the rotarod, swimming in the cold water and crossing frequency over an electric field were noted. Animal treatment and maintenance were carried out in accordance with the Principles of Laboratory Animal Care (National Institutes of Health publication no. 85-23, revised 1985), Korea and the Animal Care and Use Guidelines of Sahmyook University, Korea.

### Psychological stress

#### Overcoming electroshock

The electroshock test was performed in a Plexiglas box (42×27×15 cm) with a stainless steel grid floor. The box was composed of two parts: an electric stimulator and a glass operation box. At the top of the box, there was a water bottle with its mouth 5 cm away from the stainless steel floor. Mice were deprived of water for 24 h and were then individually placed in the test chamber for 20 min at 0.5 mA with free access to the drinking bottle. RG was given 30 min prior to the test. Mice were put into the box and the frequency crossing over an electroshock was recorded.

#### Induction of stress

Mice were exposed to restraint stress (RS) after having been orally administered with RG 30 min before the tests. Mice were subjected to RS by being placed once in a translucent, well ventilated, conical propylene holder (3 cm in diameter and 7 cm in length) for 120 min [18]. After loading stress, stress-related behavioral changes of the animals were recorded and plasma CORT was measured.

### Physical stress

#### Cold swimming test

The mice were forced to swim in cold water maintained at 8±2°C. The apparatus is a circular water tank (diameter, 150 cm; height, 50 cm) made of stainless steel. The pool was filled with water to a depth of 15 cm. The mice were allowed to swim in the pool until they're exhausted to the point of drowning. After the test, the mice

were gently dried by patting their bodies with paper towel. The time spent swimming in the water was recorded manually using a stopwatch [19].

#### *Rotarod test*

The previous day of the experiment, all mice were habituated to running on a rotarod at a speed of 36 rpm for 120 s. Next morning, the latency time to fall and falling frequency for 20 min were recorded.

#### *Balanced wire test*

Like the rotarod test, mice were habituated to grasp horizontal wires (5 mm diameter, 150 cm length) with their forepaws and tails elevated 80 cm above the floor. The balanced wire test was carried out for 20 min, and the latency time to fall and falling frequency were recorded.

#### *Locomotor activity*

Computerized EthoVision system (Noldus Information Technology, Wageningen, The Netherlands) was used to evaluate changes in locomotor activity. The observation apparatus consisted of nine plastic boxes (42×42) with a field bordered by 42-cm-high sidewalls. The total distance moved and total movement times were monitored for 10 min after stress [20].

#### *Elevated plus-maze test*

The plus maze was elevated to a height of 50 cm and consisted of a black plastic area in the shape of a plus, with two open arms (50×10 cm for rats) and two closed arms (50×10×30 cm for rats) alternating at right angles. The central crossing point (10×10 cm) of the arms was not enclosed. Mice were placed in the central square facing the open arm and allowed to explore the maze freely for 5 min. The time spent in the open arms and the closed areas were automatically recorded by the computerized EthoVision system [20].

#### *Stress-related rearing behavior*

Rearing was defined as rearing around the wall. Rearing frequency was recorded automatically by EthoVision system for 10 min.

#### *Plasma corticosterone assay*

After monitoring behavioral assays, the mice were sacrificed immediately. Blood samples (1.5 mL) were collected through heart puncture. The plasma CORT level was measured by a modified method [19] using HPLC system composed of SI-2 3001 pum, SI-2 3002 UV-

Visible detector, SI-2 3004 column oven, separation (Shiseido, Tokyo, Japan), and column Capcell Pak C8 MG 120 (5 μm, 1.5 mmØ×250 mm). CORT was used as the internal standard. Twenty microliters of treated sample solution were injected into the HPLC column using acetonitrile: 50 mM NaH<sub>2</sub>PO<sub>4</sub> (33:67) as the mobile phase at a flow rate of 500 μL/min. CORT level was determined from the absorbance at 240 nm using the dsCHROM-computing program (Shiseido, Tokyo, Japan).

#### *Plasma lactate analysis*

Levels of lactate in plasma were determined by double antibody technique using a commercial kit (BioVision, Mountain View, CA, USA). Enzymeimmuno assay was performed according to the manufacturer's instructions.

#### **Statistical analysis**

Data were expressed as the mean±SEM. For statistical evaluation of data, one-way ANOVA was used. When statistically significant differences were found, Newman-Keul's test was used as a post-hoc test to determine the statistical differences between groups. Differences were considered statistically significant when  $p < 0.05$ .

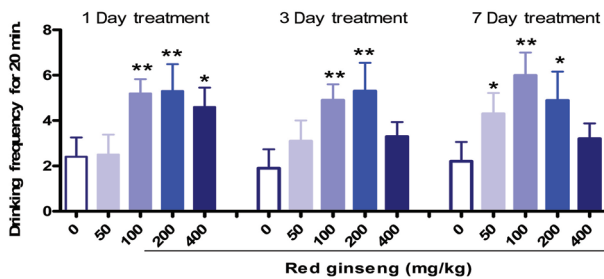
## **RESULTS AND DISCUSSION**

### **Effects of red ginseng on psychological fatigue-resistance activities**

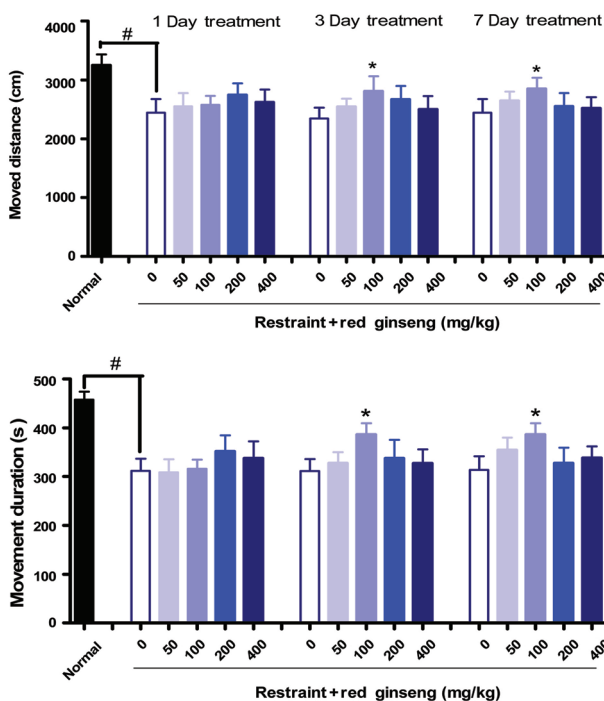
The electric field test was conducted to evaluate overcoming of psychological stress. RG supplementation significantly increased crossing frequency over an electric field (Fig. 1) most especially at the dosages of 100 and 200 mg/kg. Some studies have demonstrated a reduction of stress or its physiological accompaniments in animals. Nguyen *et al.* [21] suggested that Vietnamese ginseng crude saponin suppresses psychological and electroshock stress (ES)-induced antinociception. RG and white ginseng reduced conflict behavior in thirsty and ES-induced fighting in paired mice [22].

### **Effects of red ginseng extract on locomotor activity**

As shown in Fig. 2, stress significantly decreased locomotor activity in the open-field. RG supplementation (100 mg/kg for 3 or 7 d) significantly increased locomotor activity ( $p < 0.05$ ). Without stress, the water extract of RG (100 mg/kg) did not alter the locomotor activity in the open-field [6]. Pilot studies indicated that single-dose administration of ginseng had little to no acute behavior effects [22]. In our study, long term rather than single administration of RG had significant effects on locomotor



**Fig. 1.** Effect of red ginseng on psychological fatigue-resistant activities in mice ( $n=10$ ). Each bar represents the mean $\pm$ SEM of crossing frequency of electric field for 20 min. Control group vs. red ginseng extract. \* $p<0.05$ , \*\* $p<0.01$ .

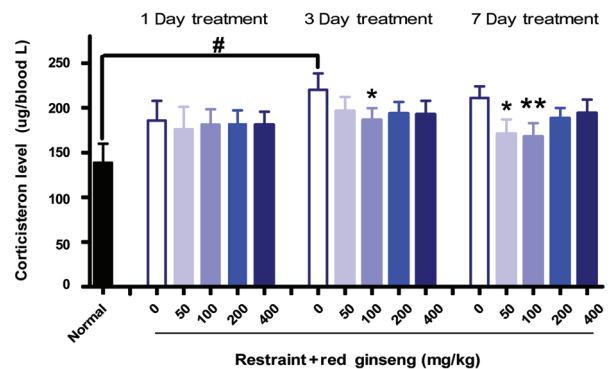


**Fig. 2.** Effects of red ginseng extracts on locomotor activity after loading restraint for 2 hours in mice ( $n=9-10$ ). Each bar represents the mean $\pm$ SEM of moved distance and movement duration for 10 minutes ( $^{\#}p<0.05$ , \* $p<0.05$  vs. control group).

activities in mice.

### Effects of red ginseng extract on plasma corticosterone levels

Psychological fatigue comes with depression, anxiety, and other psychological conditions. Corticosteroids play extremely important roles in fear and anxiety. Glucocorticoid secretion serves both to alert the organism to environment or physiologic changes and to maintain homeostasis under stressful conditions [23]. RG has diverse effects on the central nervous system, promotes



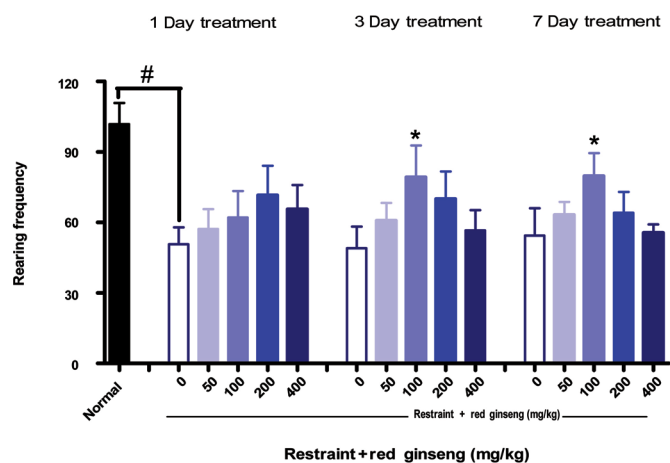
**Fig. 3.** Effects of red ginseng extracts on plasma corticosterone level after restraint for 2 h in mice ( $n=9-10$ ). Each bar represents the mean $\pm$ SEM of the corticosterone levels ( $^{\#}p<0.05$ , \* $p<0.05$ , \*\* $p<0.01$  vs. control group).

stimulation as well as inhibits cortical activity [6]. Total ginseng Saponin (TGS) administered intraperitoneally increased plasma CORT and adrenocorticotrophic hormone (ACTH) level in basal state, but pretreatment of animals with TGS (5 and 20 mg/kg) significantly attenuated the immobilization stress-induced increase in plasma CORT levels [23]. Such effects of TGS in rodents indicate that the inhibitory effects of TGS administered on stress-induced plasma CORT level appear to be mediated by blocking of ACTH action peripherally in adrenal gland [16]. As shown in Fig. 3, stress increased CORT release but RG supplementation (100 mg/kg) for 3 ( $p<0.05$ ) or 7 d ( $p<0.01$ ), significantly suppressed the production of CORT after loading RS.

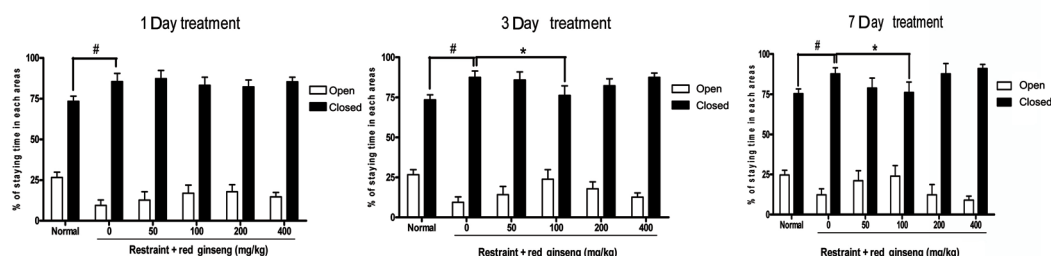
### Effects of RG extract on exploratory activity in the elevated plus maze and rearing behavior

Behaviors on the elevated plus maze (EPM) reflect anxiety or curiosity in mice. Animals exposed to stress spend less time in the open arms, exhibiting anxiogenic-like effects [24]. Ginseng has long been used traditionally for the treatment of psychiatric diseases such as anxiety and depression. Park *et al.* [6] showed that the water extract of RG did not influence activities on the EPM. However, Carr *et al.* [25] found that crude saponin ginseng fraction and ginsenoside RB<sub>1</sub> significantly increased the percentage time of open area in EPM in a dose-dependent manner. Wei *et al.* [26], also demonstrated that American ginseng had anxiolytic-like effect, which increased the percentage of time in open arms. Our results showed that RG had a partial anxiolytic-like activity. As shown in Fig. 4, stress decreased the staying percentage in the open arms of the EPM. RG supplementation (100 mg/kg) increased staying times in the open arms of the

A



B



**Fig. 4.** Effects of red ginseng extracts on stress-related specific behaviors induced by restraint stress in mice ( $n=8-10$ ). Each bar represents the mean $\pm$ SEM of rearing frequency for 10 min (A), % of time spent in each area over 5 min (B) ( $\#p<0.05$ ,  $*p<0.05$  vs. control group).

EPM after 3 or 7 d of treatment.

“Normal” behaviors of an animal (e.g., rearing) are affected with anxiety [27]. In our previous study, we confirmed that rearing behavior was decreased by stress but RG supplementation alleviated it [18]. As shown in Fig. 4, stress significantly decreased rearing frequency but RG (100 mg/kg) significantly increased it after 3 or 7 d of treatment. RG treatment may counteract stress-induced anxiety-related behaviors. The anxiolytic-like effects of ginseng may involve GABAergic mechanisms [6]. Our results support that ginseng may be useful for treatment of stress-related disorders.

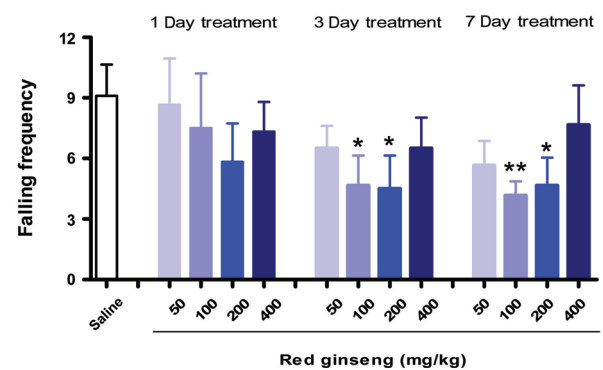
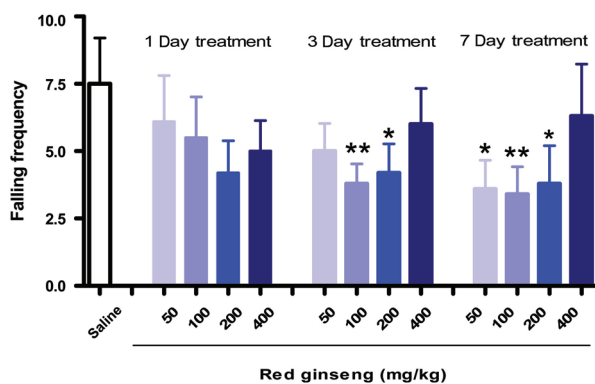
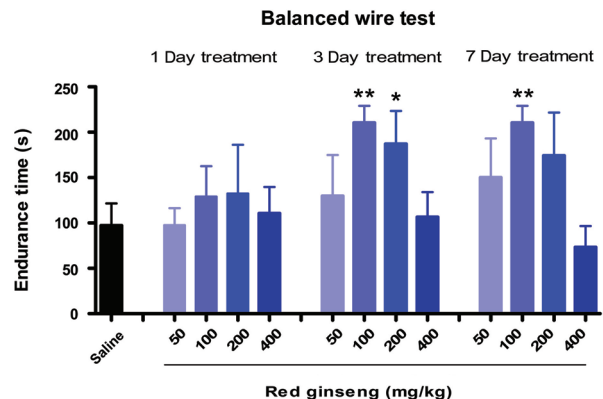
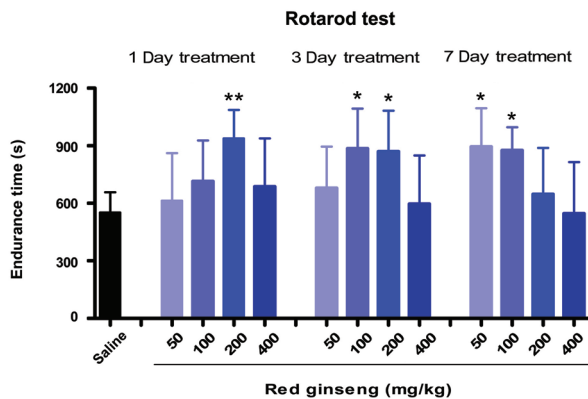
#### Effects of red ginseng extract on activities on the rotating rod and the balanced wire

As shown in Fig. 5, a single dose of RG (200 mg/kg) significantly increased endurance time on the rotating rod. RG supplementation (100 mg/kg) significantly increased endurance time and decreased falling frequency after 3 or 7 d of treatment. Endurance times on the rotarod were also increased by RG treatment at these doses

and corresponding durations: 50 mg/kg for 7 d and 200 mg/kg for 3 d. As shown in Fig. 6, the 100 mg/kg RG dose significantly increased endurance time and decreased falling frequency on the wire after 3 or 7 d of treatment. RG (200 mg/kg) also significantly increased endurance times after 3 d of treatment and decreased falling frequency after 3 or 7 d of supplementation. Filaretov *et al.* [28] showed that a single administration of ginseng leads to significant increases of working capacity up to 132% in a treadmill running test, and up to 179% with 7 d administration.

#### The effects of red ginseng extract on activity in the swimming pool in mice

Fig. 7 showed that RG (200 mg/kg) significantly increased swimming time in cold pool after treatment for 1 or 3 d, whereas at the dosage of 100 mg/kg, swimming times were increased after 3 or 7 d of treatment. Wang *et al.* [29] found that ginseng polysaccharides had anti-fatigue activities. The physiological effect of fatigue is on energy metabolism of muscular activity, and the im-



**Fig. 5.** Effects of red ginseng extract on activity on the rotating rod in mice ( $n=9-10$ ). Each bar represents the mean $\pm$ SEM of endurance time on the rotating rod (\* $p<0.05$ , \*\* $p<0.01$  vs. control group).

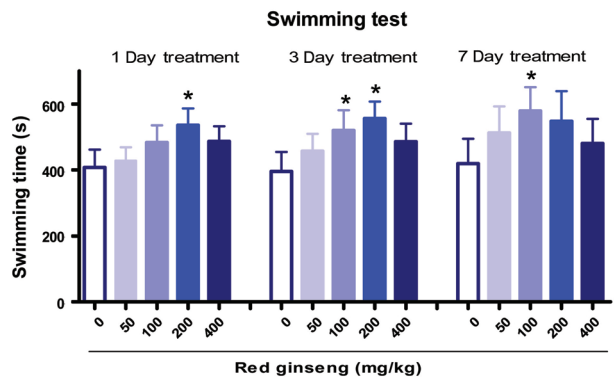
**Fig. 6.** Effects of red ginseng extract on activity on the balanced wire in mice ( $n=9-10$ ). Each bar represents the mean $\pm$ SEM of endurance time on the balanced wire (\* $p<0.05$ , \*\* $p<0.01$  vs. control group).

provement of exercise endurance is the most powerful representation of anti-fatigue enhancement [30]. Grandhi *et al.* [31] reported a significant increase in mice swimming time after ginseng administration.

**Effects of red ginseng extract on plasma lactate levels**

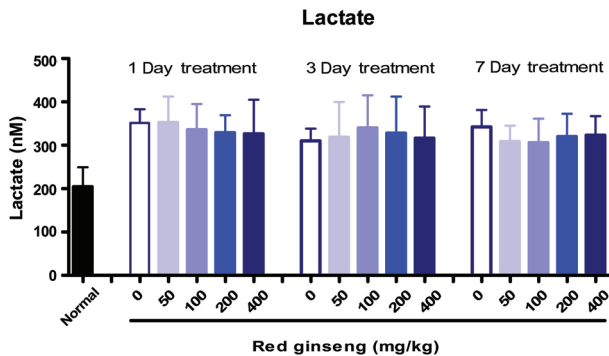
Lactic acid levels represent blood biochemical parameters related to fatigue. Physical fatigue can come from muscle weakness. The muscle produces some amount of lactic acid when doing high-intensity exercise. The increase of lactic acid level will induce many side effects in various physiological processes. Therefore, rapid removal of lactic acid is beneficial in relieving fatigue. Mice administered 20(R)-ginsenoside Rg<sub>3</sub> (0.05 mg/kg) showed reduction in blood lactic acid levels after swimming [30]. Avakian *et al.* [32] demonstrated that ginseng saponin-treated animals had markedly lower concentrations of lactic acid after swimming for 30 or 60 min. In our experiments, however, RG treatment did not change blood lactate levels (Fig. 8).

In summary, we found that psychological fatigue-re-



**Fig. 7.** Effects of red ginseng extract on activity in the swimming pool in mice ( $n=10$ ). Each bar represents the mean $\pm$ SEM of endurance time in the swimming pool (\* $p<0.05$ , \*\* $p<0.01$  vs. saline treated group).

lated responses were attenuated by RG supplementation. We also found that RG had effects on physiological fatigue (swimming, rotarod, and wire test). All these effects were produced by high (200 mg/kg) and low RG doses (100 mg/kg) in short and long-term treatment, respectively. We propose that the anti-fatigue effects of RG are



**Fig. 8.** Effects of red ginseng on blood lactate concentration after swimming in the pool in mice ( $n=10$ ). Each bar represents the mean $\pm$ SEM of mM of lactate.

caused by indirect effect that results in an enhancement of physical capacity or stamina.

The effect of RG on psychological fatigue is attributed to its actions on the hypothalamic-pituitary-adrenal axis, resulting in a decrease of plasma corticosteroids levels. Our results indicate that RG might enhance resistance to fatigue via a psychological rather than physical action. We suggest that present findings have potential implications for the clinical use of red ginseng in the treatment of stress-related disorders.

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