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Full Length Research Paper

Stimulatory effects of soybean isoflavones on exercise performance

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The object of this study was to investigate stimulatory effects of soybean isoflavones (SI) on exercise performance based on swimming time to fatigue in mice. The mice were randomly divided into four groups: a control group and three treatment groups. The control group was administered with distilled water and the treatment groups were administered with SI of 50, 200 and 500 mg/kg body weight by gavage every day for 5 weeks. The swimming test was performed and the biochemical parameters related to fatigue were examined. The results showed that soybean isoflavones prolonged the exhaustive swimming time in mice, as well as increasing the hepatic glycogen, but decreased the serum urea nitrogen and blood lactic acid levels, which indicated that soybean isoflavones had stimulatory effects on exercise performance.

Key words: Stimulatory effects, soybean isoflavones, exercise performance, mice.

INTRODUCTION

Isoflavones, mainly derived from soybean, are a group of biologically active substances with a chemical structure similar to that of estrogen (Omoni and Aluko, 2005; Klejdus et al., 2005). Genistein (49, 5, 7-trihydroxyisoflavone) and daidzein (49, 7-dihydroxyisoflavone) (Figure 1). The most significant *soybean* isoflavones are heterocyclic phenols (Boersma et al., 1999; Vera et al., 2005; Han et al., 2007). Soybean isoflavones are natural dietary compounds widely marketed and consumed for their potential health benefits (Mahady et al., 2003). The physiologic effects of soybean isoflavones have been studied extensively in recent years. To date, various studies have demonstrated that soybean isoflavones possess a variety of characteristics such as antioxidant, antiproliferative, anti-inflammatory, anti-diabetic, enzyme-inhibitory effects and differentiation-inducing abilities (Anthony et al., 1998; Shyong et al., 2002; Yousef et al., 2004; Clair and Anthony, 2005; Sakai and Kogiso, 2008; Shu et al., 2009; Raju et al., 2009). But studies on whether soybean isoflavones have an effect on fatigue are very limited.

Intensive physical exercise is associated with increased production of reactive oxygen species (ROS), which induces an imbalance between ROS production and antioxidant defenses in the body. This leads to the development of damage to biological molecules and key cellular components (Polidori et al., 2000; Herzberg, 2004; Reid, 2008). Antioxidants protect against exercise-induced oxidative stress, which can contribute to reducing the degree of exhaustion caused by continuous physical activity (Rossi et al., 2000; Morillas-Ruiz et al., 2006; You et al., 2006). Since soybean isoflavones clearly exhibit antioxidant activity *in vitro* and *in vivo* (Kurzer and Xu, 1997) and Brandi (1997) surmised that soybean isoflavones might be responsible for the beneficial effect of lowering the incidence of diseases. Therefore, the object of this study was to investigate stimulatory effects of soybean isoflavones (SI) on exercise performance based on swimming time to fatigue in mice.

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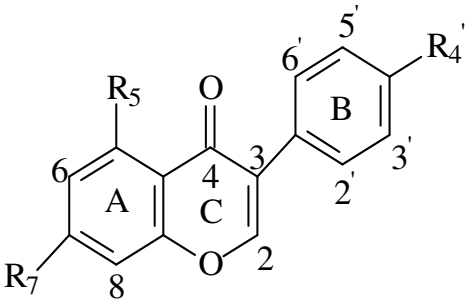

Isoflavone	R_4'	R_5	R_7
Genistein	OH	OH	OH
Daidzein	OH	H	OH

Figure 1. Structures of the isoflavones genistein and daidzein.

MATERIALS AND METHODS

Animals

Four-weeks-old male BALB/c mice (Grade 2) were purchased from Institute of Chinese Traditional Medicine of Zhejiang province, China. The animals were housed eight per cage in controlled temperature (23 ± 2℃), humidity (55 ± 10%) and light (12 h light/12 h darkness, without any ultraviolet emission). They were allowed ad libitum access to water and commercial mice diet. The mice rested for one week in the animal facility prior to the experiments. All animal experiments were performed in accordance with the National Institute of Health Guidelines under the protocols approved by the Institutional Animal Care and Use Committee of Zhejiang University.

Soybean isoflavones preparation

Whole *soybeans* were cracked, dehulled, and flaked by standard procedures, followed by a hexane extraction to remove the majority of lipid (Zhou et al., 1998). The resulting defatted soybean flour was extracted with aqueous ethanol (60%) to produce a mixture containing carbohydrates (60 to 70%), isoflavones (2%), fat (12%), ash (4%), and protein (5%). A proprietary extraction procedure was then used to remove the carbohydrates, and the remaining material was spray dried to form a powder called soybean isoflavones (SI) and analyzed for isoflavones according to published methods (Wang and Murphy, 1994; Zhou et al., 1998; Rostagno et al., 2003). The final soybean isoflavones (SI) used in our studies contained 32.47% isoflavones.

Experimental design

Experiment 1

Sixty-four mice were randomly divided into four groups, a control group and three treatment groups, of sixteen each. The first group designated as control group was administered with 2.5 ml distilled water by gavage every day for 5weeks. The second, third and fourth group designated as treatment groups were administered with SI of 50, 200 and 500 mg/kg body weight day for 5weeks, respectively. SI was dissolved in 2.5 ml of distilled water. The doses used in this study were confirmed to be suitable and effective in tested mice according to preliminary experiments. For exercise performance measurements, a swimming test was applied. The mice were submitted to weekly swimming exercise supporting constant loads (lead fish sinkers, attached to the tail) corresponding to 10% of their body weight. The mice were assessed to be fatigued when they failed to rise to the surface of the water to breathe within 5 s (Ikeuchi et al., 2005; Zhang et al., 2007). The apparatus used in this test was an acrylic plastic pool (90 × 60 × 60 cm) filled with water maintained at 28 ± 1℃. The water in the acrylic plastic pool was 40 cm deep. The swimming test was performed between 13:00 and 18:00.

Experiment 2

Thirty minutes after the last administration（5 weeks later）, 20 ml of blood was collected from the veins of the tails of mice (eight mice per group), then the mice were made to swim for 10 min without weight loading, and blood was collected immediately after 20 min after forced swimming, respectively (Zhang et al., 2006; Tang et al., 2008). The blood lactic acid levels were analyzed with commercial kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). And the increase ratio of blood lactic acid was calculated as following equation (Huang and Zou, 2001; Chen et al., 2006; Cao et al., 2009):

$$\text{Increase ratio} = \frac{b-a}{a}$$

$$\text{Reduce ratio} = \frac{b-c}{c}$$

a - The blood lactic acid level in mice before swimming.
b - The blood lactic acid level in mice after swimming immediately.
c - The blood lactic acid level in mice after swimming for 20 min.

The increase ratios of the blood lactic acid was the percentage of the increase of blood lactic acid after swimming and that of blood lactic acid before swimming, which can be used as an indicator of the degree of fatigue. And the reduce ration of blood lactic acid, reflecting the reducing of blood lactic acid after 20 min, represents the condition of recovery (Tang et al., 2009).

Experiment 3

Thirty minutes after the last administration, the mice (eight mice per group) were made to swim for 90 min without weight loading, after

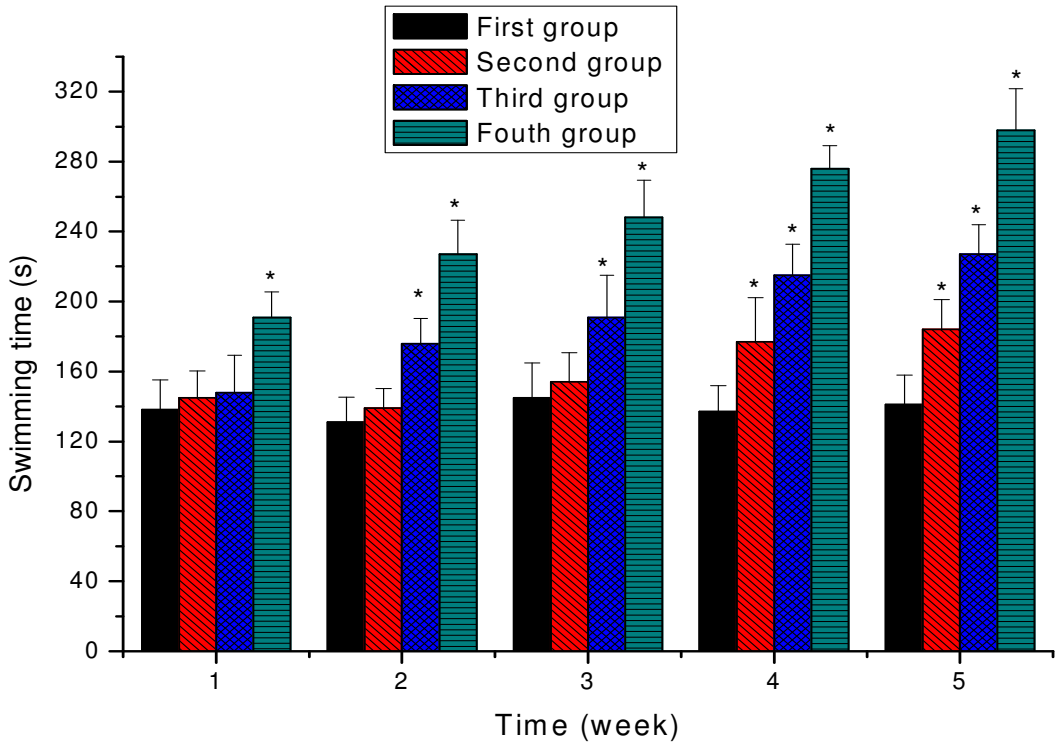

Figure 2. Effect of soybean isoflavones on swimming exercise in mice (Experiment 1).The first group administered with distilled water; the second, third and fourth group were administered with SI of 50, 200 and 500 mg/kg body weight (n= 16 mice per group). Each value represents mean ± SEM. * P<0.05 vs. first group.

resting for 60 min, the mice were anesthetized with ether and whole blood samples were collected in tubes by heart puncture (Kang et al., 2005; Tang et al., 2008). Blood samples were placed for about 1 h at 4℃ and centrifuged for 10 min at a speed of 3000 rpm. The supernatant was collected and contents of serum urea nitrogen (SUN) were analyzed with commercial kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China). In addition, immediately after the blood had been collected, the liver was dissected out quickly from the mice, washed with physiological saline and dried with absorbent paper. Then the content of hepatic glycogen was analyzed with commercial kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, China).

Statistical analysis

The statistical analyses were performed with the statistical software SPSS/Windows (SPSS 10.0. LNK). The results were expressed as the mean ± SEM to show variations in a group. Differences are considered significant at a P level <0.05.

RESULTS AND DISCUSSION

Effect of soybean isoflavones on exercise performance in mice

Exercise performance was investigated by swimming exercise. It has been selected here as a model of physical exercise (Venditti et al., 1996), because muscle trauma caused by other types of physical exercise like prolong running in treadmill, exercise stimulated electric shock, and plyometric contractions could be avoided (Misra et al., 2009). In Experiment 1, which involved a 10% body weight load as described in the methods. The data of swimming time were shown in Figure 2. The 500 mg/kg treatment group showed a significant increase in swimming time to exhaustion as compared to the control group from the first week ($P<0.05$). In the 200 mg/kg treatment group, a significant increase in swimming time to exhaustion as compared to the control group was evident after 2 weeks ($P<0.05$). In the 50 mg/kg treatment group, a significant increase in swimming time to exhaustion as compared to the control group was evident after 4 weeks ($P<0.05$). Data presented herein indicates that soybean isoflavones increased exercise performance.

Effect of soybean isoflavones on blood lactic acid in mice

Lactic acid, which is dissociated into H^+ and lactate ions, is commonly produced in the body during physiological (example, severe exercise) or pathological (example,

Table 1. Effect of soybean isoflavones on blood lactic acid in mice (Experiment 2).

Groups	The blood lactic acid levels (Mmol/l)			Increase ratio	Reduce ratio
	Before swimming (a)	After swimming immediately (b)	After swimming for 20 min (c)		
First	5.16±1.26	9.43±0.93	6.94±1.29	0.83±0.01	0.36±0.01
Second	5.08±0.76	8.57±1.36	5.89±0.87	0.69±0.01*	0.46±0.01*
Third	5.27±1.03	8.26±1.15	5.41±1.14	0.57±0.01*	0.53±0.01*
Fourth	4.93±1.17	7.42±1.08	5.07±0.98	0.51±0.01*	0.46±0.01*

The first group administered with distilled water; the second, third and fourth group were administered with SI of 50, 200 and 500 mg/kg body weight (n= 8 mice per group). Each value represents mean ± SEM. * P<0.05 vs. first group.

Table 2. Effect of soybean isoflavones on SUN and hepatic glycogen in mice (Experiment 3).

Groups	SUN (mol/l)	Hepatic glycogen (mg/g)
First	257.29±12.45	14.36±8.13
Second	199.12±19.83*	21.49±9.26*
Third	187.84±23.48*	26.94±8.51*
Fourth	181.76±17.89*	29.81±9.87*

The first group administered with distilled water; the second, third and fourth group were administered with SI of 50, 200 and 500 mg/kg body weight (n= 8 mice per group). Each value represents mean ± SEM. * P<0.05 vs. first group.

tissue hypoxia) anaerobic metabolism (Rokitzki et al., 1994; Hong et al., 1997; Akova et al., 2001). In both humans and a large number of animals, strenuous exercise is associated with accumulation of lactic acid (Sejersted and Sjøgaard, 2000; Nielsen et al., 2001). There is accumulating evidence that fatigue occurs when lactic acid builds up within the myocyte, which causes intracellular pH (pHi) to drop, inhibiting both glycolysis and contractile activity (Chase and Kushmerick, 1988; McCullagh et al., 1996; Wilson et al., 1998; Zhang et al., 2006; Allen et al., 2008). Therefore, Lactic acid is a key indicator of fatigue. In Experiment 2, the blood lactic acid levels were measured before swimming, after swimming immediately and after swimming for 20 min as described in the methods. The data of increase ratio and reduce ratio of blood lactic acid were shown in Table 1. It was found that the blood lactic acid levels of each group had no significant difference before swimming (P> 0.05). However, after swimming, the treatment groups showed a significant decrease in the increase ratios of the blood lactic acid as compared to the control group (P＜0.05). Meanwhile, the reduce ratios of the blood lactic acid of the treatment groups were higher than that of the control group (P ＜ 0.05). The current results indicates that soybean isoflavones can effectively retard and lower the blood lactic acid produced after swimming exercise, postpone the appearance of fatigue and accelerate the recovering from fatigue.

Effect of soybean isoflavones on serum urea nitrogen and hepatic glycogen in mice

Serum urea nitrogen (SUN) is an important blood biochemical parameter related to fatigue. The SUN test is a routine test used primarily to evaluate renal function. Urea is formed in the liver as the end product of protein-metabolism. During digestion, protein is broken down into amino acids. Amino acids contain nitrogen, which is removed as NH^{4+} (an ammonium ion), while the rest of the molecule is used to produce energy or other substances needed by the cell (Koo et al., 2004). There is a positive correlation between the urea nitrogen *in vivo* and the exercise tolerance (Wu et al., 2007; Tang et al., 2008). Energy for exercise is derived initially from the breakdown of glycogen, after strenuous exercise muscle glycogen will exhaust, and later, energy will from circulating glucose released by the liver (Schneiter et al., 1995; Vissing and Haller, 2003; Yue and Zhang, 2006; Di Mauro, 2007; Suh et al., 2007). Thus, the glycogen contents are sensitive parameters related to fatigue. In Experiment 3, contents of SUN and hepatic glycogen were determined after swimming. As shown in Table 2, content of the hepatic glycogen of treatment groups were higher than that of control group and content of SUN of the treatment groups were significantly lower than that of the control group (P<0.05). In this study, the data showed that soybean isoflavones may increase the hepatic glycogen content of mice post exercise by improving

glycogen reserve, or reducing the glycogen consume during exercise, or both. However, this detailed mechanism is not clear and needs the further studies.

Conclusions

In conclusion, soybean isoflavones prolong the exhaustive swimming time in mice, as well as increasing the hepatic glycogen, but decrease the serum urea nitrogen and blood lactic acid levels. These results indicate that soybean isoflavones have stimulatory effects on exercise performance. However, further studies are needed to clarify the detailed mechanisms involved in the anti-fatigue-like properties of soybean isoflavones in order to support present findings.

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