Soyasaponins protects against physical fatigue and improves exercise performance in mice

Yanli Xu1,2, Fengli Liu3, Zhongxin Xu4, Zhijun Liu2, Jianzhong Zhang5

Departments of 1Preventive Medicine, 3Nursing, 4Anatomy, Medical College of Hebei Engineering University, Handan, P. R. China; 2Clinical Skills Training Center, Affiliated Hospital of Hebei Engineering University, Handan, P. R. China; 5National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, P. R. China

Received March 16, 2016; Accepted September 5, 2016; Epub August 15, 2017; Published August 30, 2017

Abstract: This study aims to evaluate the effect of soyasaponins on physical fatigue and exercise performance and the underlying molecular mechanism. Body mass, forelimb grip strength, exhaustive swimming time, serum lactate, serum blood urea nitrogen (BUN), hepatic and muscle glycogen, and morphology of liver and skeletal muscle were determined. Results presented that soyasaponins could enhance the grip strength and endurance of mice, decrease serum levels of lactate and BUN and reduce tissue glycogen depletion. Besides, according to the morphological examination, soyasaponins indicated no significantly side effect on the major organs like liver, skeletal muscle, heart and kidney of mice. We also found that the metabolic regulator phosphorylated AMPK (P-AMPK) and PGC-1α, as well as antioxidant genes NRF-2 and SOD1, were all up-regulated in skeletal muscle tissue with soyasaponins treatment. Therefore, soyasaponins had an anti-fatigue effect and could improve exercise performance via the activation skeletal muscle metabolic regulators and antioxidant defense system.

Keywords: Soyasaponins, anti-fatigue, exercise performance, molecular mechanism

Introduction

Fatigue is the symptom that one feels the exhaustion of energy and has to reduce or even stop the performance physiologically and psychologically [1]. It can not only affect the physical functional ability but also impair quality of life including emotion, social skill, occupation and family interaction [2]. As a multidimensional and complex phenomenon that contains physical, mental and disease aspects, the origin of fatigue can be classified central or peripheral [3]. Central fatigue is regarded as the failure of the central nervous system drives to the muscular activities adequately, resulting from inadequate sleep, depressive mood, drug side effects, and so on. Physical fatigue, also named peripheral fatigue, is derived from high-intensity or excessive physical exercise that induced depletion of energy, accumulation of energy metabolic byproducts, free radicals overproduction of oxygen consumption in the development of fatigue [4].

For a long time, how to prevent fatigue and improve physical exercise capacity has become a focus in various researches. Regular physical exercise and nutritional food or supplement may be the most effect way in relieving fatigue and improving exercise duration or intensity [5]. Although there are many pharmacological drugs or therapies used to ameliorate fatigue, side-effects and low effectiveness lead to the interest of researchers in the safe and effective anti-fatigue alternatives. Recently, more and more investigators pay attention to the anti-fatigue effect of natural substance supplements. Several studies have that reported medicinal plant extracts, such as resveratrol [6], Angelica sinensis [7], Gastrodia elata Blume [8], curcumin [9] and Astragalus membranaceus [10] have beneficial effect on treating physical fatigue and improving exercise performance [5, 11]. The anti-fatigue effects of these tonic is conducted mainly by decreasing fatigue-related metabolites, enhancing muscular power and endurance, increasing motor skill performance and even improving recovery after exercise.

Studies have reported that certain skeletal muscle metabolic regulators like AMP-activ-
Soyasaponins protect against physical fatigue. The goal of this study was to investigate the potential effect of soyasaponins on physical fatigue and exercise performance by evaluation of forced swimming capacity, forelimb grip strength and biochemical parameters and at the same time to investigate the underlying molecular mechanism of this effect.

Materials and methods

Experiment design

The soyasaponins used in this study was purchased from Chengdu Purify Technology Development Co., Ltd (Chengdu, China). Male Kunming mice (6 weeks old, weighting 18-22 g) were purchased from Laboratory Animal Center of Hebei province (Shijiazhuang, China). Animals were cultured under standard animal house with 12 h light/dark cycle, room temperature (24 ± 1°C) and 40%-60% humidity. Food and water were provided ad libitum. All animal experiments were approved by local ethics committee and conformed to the guidelines of Hebei University of Engineering.

After one week of acclimatization to environment, all animals were randomly divided into four groups with 8 mice in each group and fed with the same volume of vehicle or soyasaponins by stomach intubation once a day for 30 continuous days. The experimental design was as follows: the control group (CG) were treated with vehicle, the low dose group (LG) were treated with soyasaponins at 20 mg/kg body weight per day; the middle dose group (MG) were treated with 40 mg/kg body weight per day; the high dose group (HG) were treated with 60 mg/kg body weight per day. The concentration of soyasaponins treated mice was determined by pre-experiment. Body weight was measured every five days in the whole experiment to adjust the quantity of the soyasaponins supplement.

Determination of biochemical parameters

To detect the effect of soyasaponins on biochemical variables of mice, blood and tissue biochemical parameters were determined. Serum levels of BUN and lactate were measure by autoanalyzer (Mindray BS 800, Mindray, Shenzhen, China). At the last day of the experiment, mice were assigned to swim without weight loading for 30 min after the last treatment of soyasaponins. After the swimming exercise, eyeballs were removed immediately under general anesthesia with a pair of tissue forceps and the blood samples were centrifuged at 4°C and 2000×g for 8 min. Following the collection of blood, hepatic glycogen, muscular glycogen were collected from the tissue homogenate of liver and gastrocnemius muscles respectively and determined by Assay Kit (Sigma-Aldrich, Shanghai, China).

Endurance measurement

The endurance of the mice was performed by exhaustive swimming, which was conducted as previously described with some modifications [22]. After 1 hour of the last administration of soyasaponins, mice, with loads equaled to 5% of body weight attached to the tail, were placed in their individual cages of a swimming pool (height 60 cm and radius 25 cm) filled with water of 40 cm depth and maintained a temperature at 30 ± 1°C. The endurance of each
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Table 1. Effect of soyasaponins on body weight of mice

<table>
<thead>
<tr>
<th>Groups</th>
<th>Initial body weight (g)</th>
<th>Final body weight (g)</th>
<th>Increased body weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>21.5 ± 0.9</td>
<td>37.2 ± 2.3</td>
<td>15.1 ± 1.6</td>
</tr>
<tr>
<td>LG</td>
<td>21.7 ± 0.8</td>
<td>38.1 ± 2.9</td>
<td>16.5 ± 2.7*</td>
</tr>
<tr>
<td>MG</td>
<td>21.6 ± 1.0</td>
<td>37.3 ± 3.1</td>
<td>15.8 ± 1.9*</td>
</tr>
<tr>
<td>HG</td>
<td>21.5 ± 0.9</td>
<td>37.7 ± 2.4</td>
<td>16.2 ± 2.3*</td>
</tr>
</tbody>
</table>

Weights were measured every 5 days to adjust the dose of soyasaponins treatment. CG, control group (vehicle); LG, low-dose (20 mg/kg body weight); MG: medium-dose group (40 mg/kg body weight); HG: high-dose group (60 mg/kg body weight). Values are means ± SD (n=10 per group). *P<0.05 as compared with control group.

Results

Effect of soyasaponins on body weight of mice

To measure the body weight of the mice, we weighted the mice every five days one by one. The data showed that there was no significant difference in initial and final weights of soyasaponins-treated groups (LG, MG and HG) compared with control group (P>0.05). After 30 days administration of soyasaponins, there were no increased body weights among different doses in the experimental process (P>0.05). The results were represented in Table 1.

Effect of soyasaponins on forelimb grip strength

The forelimb grip strength of mice was 115 ± 14, 126 ± 18, 145 ± 21 and 156 ± 25 g in CG, LG, MG and HG, respectively. As represented in Figure 1A, compared with control group, LG showed marked higher grip strength (P<0.05), and MG and HG significantly
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Increased the forelimb grip strength ($P<0.01$). However, the forelimb grip strength between MG and HG was no significant difference ($P>0.05$). These data suggested that soyasaponins could enhance the grip strength of mice.

**Effect of soyasaponins on endurance**

The endurance of the mice was determined by weight-loaded swimming time. According to the swim test, exercise endurance time in mice exposed with vehicle, low dose (20 mg/kg), middle dose (40 mg/kg) and high dose (60 mg/kg) were $246 \pm 54$, $332 \pm 68$, $515 \pm 81$ and $536 \pm 98$ s, respectively. The exercise endurance of LG was significantly longer than control group ($P<0.05$). The MG and HG significantly increased the swimming time to exhaustion compared with the control group ($P<0.01$). Just as the results showed in Figure 1B, soyasaponins supplementation contributed to the extension of forced swimming time and showed marked anti-fatigue capacity.

**Effect of soyasaponins on serum levels of BUN and lactate**

After the 30-minutes swimming, blood urea nitrogen and lactate were detected to measure the levels of fatigue. Serum BUN levels were $16.52 \pm 2.86$, $13.33 \pm 2.21$, $10.59 \pm 1.86$ and $9.66 \pm 1.36$, and serum lactate levels were $9.46 \pm 2.16$, $7.58 \pm 2.09$, $7.46 \pm 1.46$, $7.27 \pm 1.12$ in CG, LG, MG and HG. Results showed that soyasaponins-treated groups (LG, MG and HG) decreased BUN and lactate compared with control group ($P<0.01$) (Figure 2). Therefore, these results showed that treatment of soyasaponins supplementation could relieve the production of BUN and lactate.

**Effect of soyasaponins on glycogen levels in liver and muscle**

Also, after exercise swimming, in CG, LG, MG and HG, hepatic glycogen levels were $33.54 \pm 3.85$, $41.83 \pm 6.8$, $753.58 \pm 7.8$ and $558.96 \pm 8.8$, and muscle glycogen levels were $3.56 \pm 0.58$, $4.53 \pm 0.98$, $5.26 \pm 0.87$ and $5.56 \pm 0.95$, respectively. Soyasaponins-exposed groups (LG, MG and HG) significantly increased glycogen contents compared with control group ($P<0.01$) (Figure 2). This indicated that soyasaponins treatment could increase hepatic glycogen and muscle glycogen of body.

**Effect of soyasaponins on the morphology of tissues**

To examine whether soyasaponins could induced negative effect on liver or skeletal muscle tissues of mice, we evaluated the morphology of liver and skeletal muscle tissues by HE staining (Figure 3). The results suggested that soyasaponins administration had no significantly deleterious effect on health mice.

**Effect of soyasaponins on skeletal muscle metabolism and antioxidant system**

To further understand the molecular mechanism of the observed effect, we measured the
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Discussion

Previously, the effect of soyasaponins on physical fatigue and exercise performance has not been clearly elucidated. In this study, the goal was to found the potential effects of soyasaponins on exercise-induced fatigue and exercise performance of mice and the underlying molecular mechanism. By treating mice with vehicle or soyasaponins for 30 days, we measured the body mass, exercise performance, physical fatigue-associated biochemical parameters and the morphology of tissues, we also measured the expression levels of skeletal muscle metabolic regulators AMPK, P-AMPK and PGC-1α and the antioxidant genes NRF-2 and SOD1 by western blot. The data showed that soyasaponins supplementation could enhance mice’s grip strength and endurance, decrease serum lactate and BUN and lower tissue glycogen depletion, thereby protect against physical fatigue and elevate exercise performance. Furthermore, soyasaponins had few negative effects on mice. We also found the elevation of the expression levels of P-AMPK, PGC-1α, NRF-2 and SOD1 by soyasaponins treatment.

During the 30-days administration of soyasaponins, body mass was recorded every five days. According to the data of Table 1, among the initial, final and gained body mass, there was no significant difference between the control group and each soyasaponins treatment group (P>0.05). This result indicated that soyasaponins had no effect on the body mass.
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In this study, the exercise performance was measured by forelimb grip strength and exhaustive time after a 30-days period of soyasaponins or vehicle treatment. Grip strength has been widely used as the measurement of skeletal muscular system and indicator of anti-fatigue effect for novel compounds [9, 23]. The forced swimming test, previously used as animal model to predict antidepressant treatment, has recently been used to evaluate the anti-fatigue capacity of new agents [4]. The longer swimming time in water, the better exercise endurance of a mouse. Just as shown in Figure 1, soyasaponins administration remarkably increased the forelimb grip strength and exhaustive swimming time compared with control group by dose-dependent relation. These results suggested that soyasaponins possessed efficient anti-fatigue activity and could enhance the exercise tolerance of mice. Previous studies have reported that soyasaponins have many physiological activities including antioxidation, anti-inflammatory effect and enhancement of immune function [17, 21, 24].

Figure 3. Effect of soyasaponins on the morphology of liver (A), skeletal muscle (B), heart (C), and kidney (D) tissues. Specimens were photographed with a light microscope (Olympus BX51). (H&E stain, magnification: ×400, Scale bar, 40 μm).
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During strenuous or durable exercise, muscle damages commonly occur because of unnatural movement [25], reactive oxygen species (ROS) from the mitochondria among exercise due to increased oxygen consumption is considered deleterious to diverse cells and as one cause of fatigue [26, 27]. Therefore, it is possible to say that soyasaponins elevate the exercise performance and lessen fatigue by decreasing inflammation and enhancing immunity to reduce exercise-induced muscle damage and antioxidative effect to release oxidative stress and oxidized damage among fierce or prolonged exercise.

Lactate is an important biochemical indicator of exercise-induced fatigue. During intensive exercise challenge, muscles need enough energy from anaerobic glycolysis of carbohydrates, which products a large amount of lactate. The accumulation of lactate level could result in reduced pH value of muscular tissues and blood, which induces harmful effects on many biochemical and physiological activities and eventually induces fatigue of physical exercise, therefore, it is one of the beneficial and direct pathways to relieve fatigue by removing lactate rapidly [28]. Serum BUN is the metabolic product of protein and amino acid, acting as the indication of many physical disorder including renal disease, dehydration, stress, fatigue, and so on [29]. The BUN value was reported to increase markedly after fierce exercise, so it is positive correlated with exercise tolerance and regarded as the other important index related to fatigue [30]. In other words, BUN represents the level of fatigue after exercise and the recovered status. In our study, after a 30-days treatment of soyasaponins, data showed that the treated groups significantly decreased serum levels of lactate and BUN compared with control group after the swimming for 30 min (P<0.05). This indicated that soyasaponins could eliminate or delay the formation of lactate and BUN, lower the protein metabolism for energy, and elevate the capacity to adapt a physical load, which ultimately ameliorates the physical fatigue and improve exercise performance.

During the exercise, rapid ATP consumption and energy depletion are part of the main causes of physical fatigue [31]. At the initial stage of exercise, energy mainly originates from the breakdown of muscle glycogen, and then it is obtained from the hepatic glycogen following the energy expenditure [32]. For the reason that glycogen is the crucial resource of energy production through glycolysis, glycogen storage is another directly factor related to exercise capacity. In the present study, the soyasaponins treatment significantly increased the contents of liver and muscle glycogen (Figure 2). This indicated that soyasaponins might promote glycogen storage in liver and muscle to improve endurance in exercise by reducing glycogen consumption or glycogenolysis, or by increasing gluconeogenesis, or both.

Moreover, morphology of liver and skeletal muscle tissues suggested that soyasaponins had no significantly side effect on health mice (Figure 3). Therefore, we can conclude that it is safe to treat the mice with soyasaponins supplementation.

In line with the above results, the molecular mechanism was also investigated to support the beneficial effect of soyasaponins in anti-fatigue activities. We obtained the skeletal muscle from gastrocnemius and then detected the metabolic regulators AMPK and PGC-1α as well as antioxidant proteins NRF-2 and SOD1 of

Figure 4. Effect of soyasaponins on skeletal muscle regulators (A) and antioxidant defense system (B). Protein levels of skeletal muscle regulators AMPK, P-AMPK and PGC-1α as well as antioxidant genes NRF-2 and SOD1 were detected by western blot. GADPH was used as control for normalization.
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Skeletal muscle by western blot. AMPK is an evolutionarily conserved fuel sensor in many tissues [33]. By AMP activation and phosphorylation at Thr172 in the catalytic α-subunit, AMPK in muscle could prevent energy depletion and promote the expression of PGC-1α [33-35]. In skeletal muscle, PGC-1α stimulates mitochondrial biogenesis, impedes the fiber formation and promotes oxidative capacity via p38 MAPK pathway [36]. AMPK and PGC-1α were also reported to enhance the exercise endurance [37, 38]. In addition, under oxidative stress, NRF-2 was activated and translocated to nucleus [39]. Cellular antioxidant system is tightly regulated by NRF-2 and its down-stream antioxidant genes [40]. SOD1 is regarded as the catalyst of the dismutation of superoxide radical and the effect of SOD1 involves NRF-2 protein during biological oxidations and environmental stress [41]. NRF-2-ARE pathway, including NRF-2, SOD1 has been reported recently to mediated the antioxidant capacity [12, 42]. Similarly, results in our study represented that soyasaponins treatment significantly increased the expression levels of P-AMPK, PGC-1α, NRF-2 and SOD1 of mice. This suggested that the skeletal muscle metabolic regulators and antioxidant genes were activated in the anti-fatigue effect and endurance capacity of mice.

Conclusion

The results of the present study suggested that soyasaponins possessed anti-fatigue activities and enhanced exercise performance, including forelimb grip strength and swimming time to exhaustion, by decreasing serum levels of lactate and BUN, and increasing glycogen in liver and muscle. Besides, soyasaponins had no indication of negative effect on the major organs like liver, skeletal muscle, heart and kidney of mice. This observed effect was regulated by the activation of skeletal metabolic regulators AMPK and PGC-1α and the NRF-2-ARE pathway involved NRF-2 and SOD1. However, the detailed mechanism of effect of soyasaponins on anti-fatigue and exercise performance is not clear and needs to be further studied.

Acknowledgements

This work was supported by the grants from the National Natural Science Foundation of China (Project No. 81373095).

Disclosure of conflict of interest

None.

Address correspondence to: Zhijun Liu, Clinical Skills Training Center, Affiliated Hospital of Hebei Engineering University, Handan, P. R. China. E-mail: liuzhij1207@163.com; Jianzhong Zhang, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, P. R. China. E-mail: jmzhang@163.com

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