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Dietary supplementation with alkylresorcinols prevents muscle atrophy through a shift of energy supply

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Abstract

It has been reported that phytoextracts that contain alkylresorcinols (ARs) protect against severe myofibrillar degeneration found in isoproterenol-induced myocardial infarction. In this study, we examined the effect of dietary ARs derived from wheat bran extracts on muscle atrophy in denervated mice. The mice were divided into the following four groups: (1) sham-operated (control) mice fed with normal diet (S-ND), (2) denervated mice fed with normal diet (D-ND), (3) control mice fed with ARs-supplemented diet (S-AR) and (4) denervated mice fed with ARs-supplemented diet (D-AR). The intake of ARs prevented the denervation-induced reduction of the weight of the hind limb muscles and the myofiber size. However, the expression of ubiquitin ligases and autophagy-related genes, which is associated with muscle proteolysis, was slightly higher in D-AR than in D-ND. Moreover, the abundance of the autophagy marker p62 was significantly higher in D-AR than in D-ND. Muscle atrophy has been known to be associated with a disturbed energy metabolism. The expression of pyruvate dehydrogenase kinase 4 (PDK4), which is related to fatty acid metabolism, was decreased in D-ND as compared with that in S-ND. In contrast, dietary supplementation with ARs inhibited the decrease of PDK4 expression caused by denervation. Furthermore, the abnormal expression pattern of genes related to the abundance of lipid droplets-coated proteins that was induced by denervation was improved by ARs. These results raise the possibility that dietary supplementation with ARs modifies the disruption of fatty acid metabolism induced by lipid autophagy, resulting in the prevention of muscle atrophy.
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Keywords: Alkylresorcinols; Muscle atrophy; Fatty acid metabolism; Lipid autophagy; Phenolic compounds

1. Introduction

A decline in muscle mass termed muscle atrophy has been observed under the conditions of disuse (*e.g.*, immobilization, denervation, muscle unloading), fasting, aging and several disease states including cancer cachexia, sepsis, diabetes mellitus and chronic renal failure [1,2]. Muscle atrophy can be caused by decreased protein synthesis and/or increased proteolysis. We previously reported that an accumulation of ubiquitinated proteins was observed in the quadriceps femoris muscle of bedridden volunteers and the gastrocnemius (GA) muscle of spaceflight-exposed rats, indicating that the ubiquitin proteasome system plays an important role in the degradation of proteins in atrophied muscle [3,4]. It is true that mice deficient in the muscle-specific ubiquitin ligases MuRF-1 and atrogin-1/MAFbx showed resistance against denervation-induced muscle loss [5,6]. The expression of ubiquitin ligases and autophagy-related genes such as LC3 and Gabarap in muscle was reported to be induced by denervation or fasting [7]. Furthermore, it has been reported that denervation-induced protein loss in muscles involved proteolysis rather decreased protein synthesis [8,9]. Thus, the inhibition of proteolysis is important in the prevention of muscle loss in some atrophy models.

Under the condition of disuse, muscle atrophy causes a switch in muscle fiber type. Previous studies have demonstrated that denervation induces the transformation of slow oxidative fibers to fast glycolytic fibers in rat soleus muscle [10,11]. In addition, we have previously reported that mitochondrial dislocation and dysfunction were found in disused muscle [12]. Furthermore, the results of gene ontology data showed that the expression of genes associated with “fatty acid catabolic process” had significantly decreased after denervation [13]. Thus, it appears that muscle atrophy induces a metabolic shift from oxidative to glycolytic metabolism.

Phenolic compounds derived from plants have several benefits to human health and reduce the risks of developing cardiovascular disease and cancer [14]. Whole grains contain various phenolic

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Table 1
Changes in body weight and food intake of denervated mice fed a normal or ARs diet

Groups	S-ND	D-ND	S-AR	D-AR
n	5	6	5	6
Body weight (g)	28.0±0.6^{ab}	29.7±0.7^{a}	26.8±0.4^{bc}	25.4±0.5^{c}
Food intake (g)	3.8±0.6^{a}	3.1±0.4^{a}	3.4±0.2^{a}	3.8±0.5^{a}

Data are mean±S.E.M. (n=5–6). Different letters indicate significant differences (P<.05) based on ANOVA and Tukey–Kramer test. S-ND, sham-operated (control) mice fed with normal diet; D-ND, denervated mice fed with normal diet; S-AR, control mice fed with ARs-supplemented diet; D-AR, denervated mice fed the ARs-supplemented diet.

compounds, and an increased intake of whole grains in patients with obesity, type II diabetes and cardiovascular disease has been shown to lower blood pressure, increase insulin sensitivity, and improve glucose and lipid metabolism [15–17]. One of the major groups of phenolic compounds in whole-grain cereals is the 5-n-alkylresorcinols (ARs), which comprise approximately 0.015%–0.3% of the dry weight of wheat and rye grains [18]. It has been reported that the intake of ARs suppressed obesity and glucose intolerance induced by a high-fat, high-sucrose diet by increasing insulin sensitivity and cholesterol excretion in mice [19]. Meanwhile, phenolic compounds obtained from olive oil are known to have a protective effect against muscle atrophy and also improve high-fat-diet-induced insulin resistance in skeletal muscle [20,21]. In the present study, we examined the effect of ARs, phenolic compounds derived from wheat bran extracts, on denervation-induced muscle atrophy.

2. Materials and methods

2.1. Isolation of ARs

ARs were isolated from wheat bran M (Nisshin seifun, Tokyo, Japan) as described in a previous report [19].

2.2. Animal model (denervation)

Male C57BL/6N mice (Kyudo, Kumamoto, Japan) aged 6 weeks were housed in a room maintained at 24°C±1°C on a 12-h light/dark cycle with food (Oriental Yeast Company, Tokyo, Japan) and water available *ad libitum*. The mice were divided into four groups: (1) sham-operated (control) mice fed with normal diet (S-ND, n=5), (2) denervated mice fed with normal diet (D-ND, n=6), (3) control mice fed with ARs diet (S-AR, n=5) and (4) denervated mice fed the ARs diet (D-AR, n=6). Briefly, after acclimatization for 1 week, an ARs-supplemented diet (0.4%, w/w) or normal diet was given to the mice for 4 weeks. After then, the sciatic nerve of the right leg was cut, and a 5-mm piece was excised under anesthesia. During the development of disuse-induced muscle atrophy, the mice continued to receive the normal or ARs-supplemented diet until the termination of the experiment 6 days later. The α-starch content of the ARs-supplemented diet was reduced to adjust for the composition of other nutrients and comprised the normal diet (based on AIN-93M) mixed with purified ARs (0.4% w/w). The hind limb skeletal muscles [the tibialis anterior (TA), extensor digitorum longus (EDL), GA and soleus (SO)] were isolated at the time of sacrifice. After measuring their wet weight, the skeletal muscles were immediately frozen in chilled isopentane and liquid nitrogen and were stored at −80°C until analysis. All animal experiments involving denervation were approved by the Committee on Animal Experiments of Nagasaki University and were performed according to the guidelines for the care and use of laboratory animals prescribed by the University.

2.3. Quantitative reverse transcription (RT)-polymerase chain reaction (PCR)

Total RNA was extracted from mouse GA muscle using an acid guanidinium thiocyanate-phenol-chloroform mixture (ISOGEN; Nippon Gene, Tokyo, Japan). Quantitative RT-PCR was performed with the appropriate primers and SYBR Green dye using a real-time PCR system (ABI Real-Time PCR Detection System; Applied Biosystems, Foster City, CA, USA), as described previously [22]. The oligonucleotide primers used for PCR are shown in Supplemental Table 1. We used 18S ribosomal RNA as an internal standard gene.

2.4. Immunoblotting

The mouse GA muscle was prepared in 50 mM Tris–HCl buffer, pH 7.5, containing 150 mM NaCl, 1% Triton X-100 and a protease inhibitor cocktail containing ethylenediaminetetraacetic acid (Roche Diagnostics, Tokyo, Japan), and the samples were homogenized using a sonicator. The Pierce BCA assay (Pierce, Rockford, IL, USA) was used to quantify proteins. Protein samples were combined with 4× sample buffer (250 mM Tris–HCl, 8% sodium dodecyl sulfate, 40% glycerol, 8% β-mercaptoethanol and

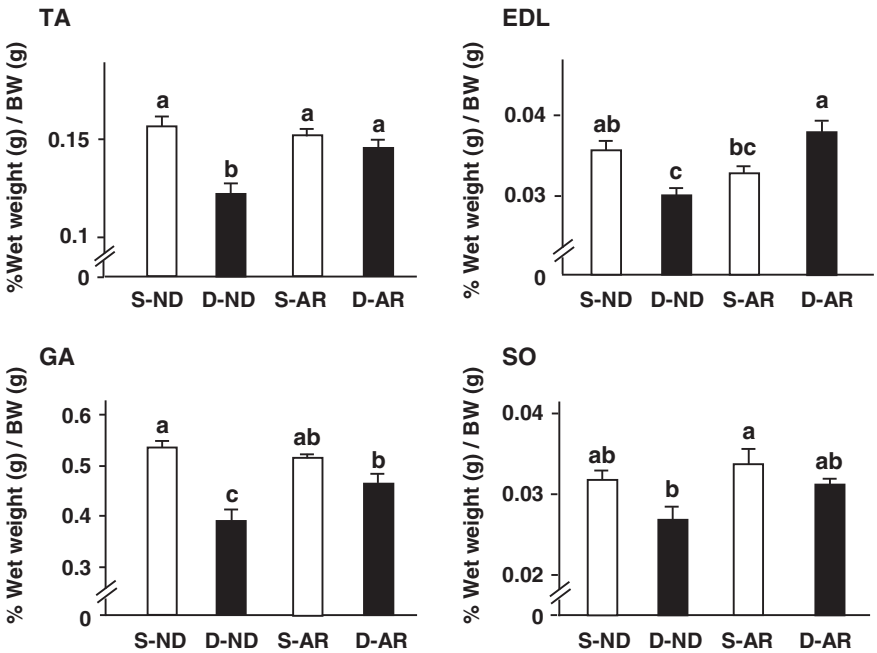

Fig. 1. The effect of dietary alkylresorcinols (ARs) on the denervation-induced decrease in the wet weight of skeletal muscle. An ARs-supplemented diet or a normal diet was given to mice for 4 weeks, and then their skeletal muscles were isolated 6 days after denervation. The wet weights of the TA, EDL, GA and SO muscles were measured. Data are mean±S.E.M. (n=5–6). Different letters indicate significant differences (P<.05) based on ANOVA and Tukey–Kramer test. S-ND, sham-operated (control) mice fed the normal diet; D-ND, denervated mice fed the normal diet; S-AR, control mice fed the ARs-supplemented diet; D-AR, denervated mice fed the ARs-supplemented diet.

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