

News Release

Title

Exercise attenuates polyglutamine-mediated neuromuscular degeneration

–Toward the development of early exercise therapy for polyglutamine diseases
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Key Points

- Exercise therapy is generally considered effective for neurological and muscular disorders, but the effective timing and intensity of exercise remain to be elucidated.
- Early-life exercise reduced abnormal protein accumulation and attenuated neuromuscular degeneration in a mouse model of spinal and bulbar muscular atrophy, an inherited neuromuscular disorder.
- Reduction of the abnormal protein was associated with exercise-induced AMPK signaling activation in skeletal muscles.
- This study suggests that AMPK signaling activation in skeletal muscles by early exercise has a therapeutic potential for the treatment of neuromuscular disorders caused by abnormal protein aggregation.

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine revealed that early exercise attenuates polyglutamine-mediated neuromuscular degeneration in a mouse model of spinal and bulbar muscular atrophy (SBMA). This work was published online in *Journal of Cachexia, Sarcopenia and Muscle*, on November 8, 2023.

Exercise therapy is generally considered effective for neurological and muscular disorders. However, the effective timing and intensity of exercise remain to be elucidated. In many neurodegenerative and muscular disorders, the nervous system and skeletal muscles are affected by the accumulation of abnormal proteins in neurons and muscle cells, but the impact of exercise therapy on the abnormal protein accumulation has not been fully investigated.

In this study, Prof. Katsuno and colleagues investigated the effect of exercise during the presymptomatic and early symptomatic stages in a mouse model of SBMA. The results showed that the low-intensity exercise during the early stages attenuated neuromuscular degeneration and improved survival and motor performance of the mice. The early exercise activated AMPK signaling in

skeletal muscle and suppressed abnormal polyglutamine protein accumulation in skeletal muscle cells and motor neurons. In addition, pharmacological activation of AMPK also reduced polyglutamine protein accumulation in cultured muscle cells.

This study suggests that early exercise-induced AMPK signaling activation in skeletal muscles has a therapeutic potential for the treatment of neuromuscular disorders, such as SBMA, caused by abnormal protein aggregation.

Research Background

Exercise therapy is generally considered effective for neurological and muscular disorders, but excessive or prolonged exercise may worsen symptoms. The effective timing and intensity of exercise remain to be elucidated. In many neurodegenerative and muscular disorders, the nervous system and skeletal muscles are affected by the accumulation of abnormal proteins in neurons and muscle cells, but the impact of exercise therapy on the abnormal protein accumulation has not been fully investigated.

The aim of this study is to investigate the effect of exercise therapy in a mouse model of SBMA, which belongs to polyglutamine diseases. SBMA is a neuromuscular disorder that causes atrophy and progressive muscle weakness of the face, tongue, and limbs, and usually occurs only in males. Leuprorelin acetate, which suppresses the production of the male hormone androgen, is approved in Japan. However, its efficacy is not sufficient, and thus the development of novel therapies is needed. SBMA is caused by abnormal CAG repeat expansion in the *androgen receptor (AR)* gene, which is translated into polyglutamine. By binding to androgen, abnormal AR translocates to the nucleus and forms nuclear aggregates that affect motor neurons and skeletal muscle cells. In our previous study, we generated a mouse model of SBMA (SBMA mice), which expressed human AR with expanded CAG repeats. Male SBMA mice show abnormal AR accumulation in the nucleus of motor neurons and skeletal muscle cells, resulting in progressive neuromuscular degeneration. In this study, we investigate the effect of wheel-running exercise on abnormal AR accumulation and neuromuscular degeneration in SBMA mice.

Research Results

First, we investigated the optimal intensity of wheel running exercise in SBMA mice. Early -stage mice (presymptomatic to early symptomatic) were able to exercise at low intensity (5 m/min) for one hour without interruption, but advanced-stage mice were unable to continue exercise at the same intensity.

Both early- and advanced-stage mice were unable to continue high intensity exercise (10 min/m). Therefore, exercise was started at presymptomatic 5 weeks of age and stopped at early symptomatic 9 weeks of age. The early exercise extended the survival (Figure 1, left) and improved motor function measured with rotarod task (Figure 1, right). This improvement in motor function continued after the end of the exercise period.

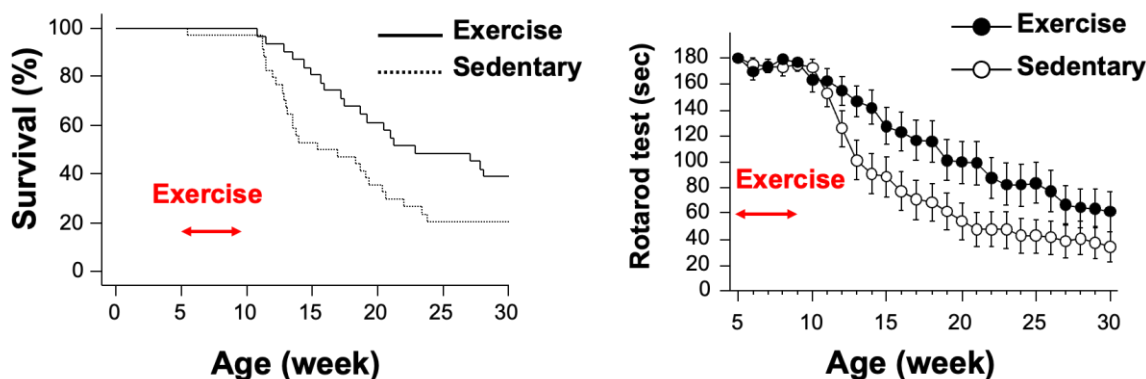


Figure 1. Early exercise improves survival and motor performance in SBMA mice

Western blotting showed a reduction of AR aggregates and monomers in the skeletal muscle and spinal cord of the exercised mice at 13 weeks of age compared to the sedentary mice (Figure 2, left). Immunohistochemistry using an antibody against polyglutamine protein showed a reduced number of nuclear AR aggregates in the skeletal muscle and motor neuron of the exercised mice (Figure 2, right). These results suggest that the early exercise reduced abnormal AR protein and inhibited protein aggregation, leading to attenuation of neuromuscular degeneration.

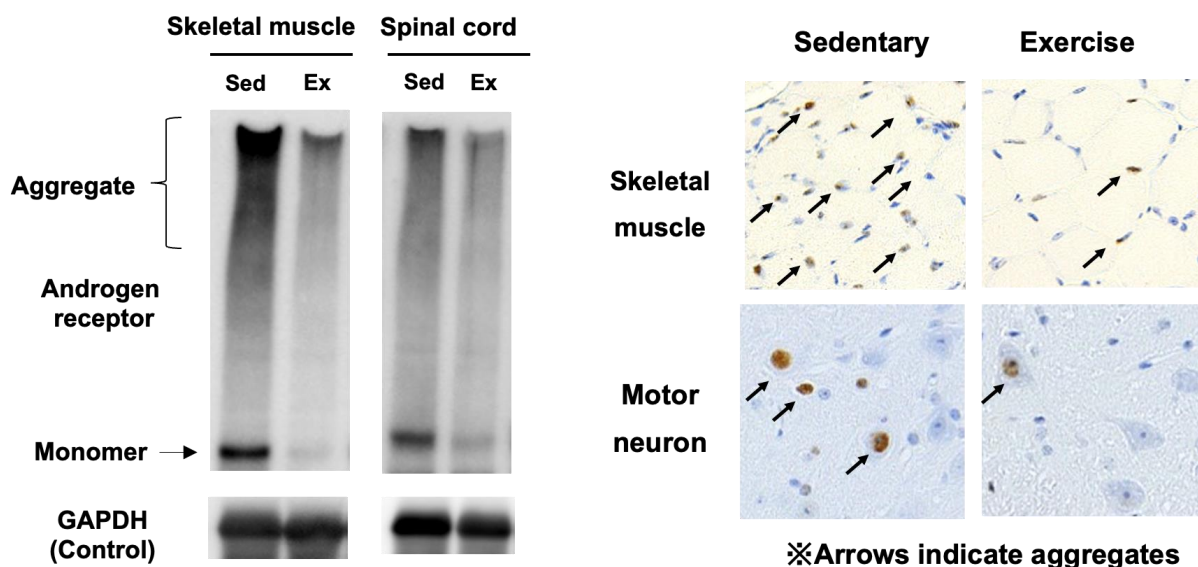


Figure 2. Exercise attenuates abnormal polyglutamine protein aggregation

To investigate the primary effects of the early exercise, we evaluated AR accumulation at 9 weeks of age, at the timing of termination of the exercise. Immunoblots for AR showed marked reduction of high molecular weight complex and monomeric AR in skeletal muscles of the exercised mice, whereas there was no change of those in the spinal cord. Therefore, we hypothesized that the early exercise would first ameliorate skeletal muscle degeneration and performed a comprehensive gene expression analysis in the skeletal muscle of SBMA mice at 9 weeks of age. The gene expression analysis showed upregulation of mitochondrial genes in the skeletal muscle of the exercised mice compared to the sedentary mice. Since previous studies have reported that activation of AMPK signaling is important for exercise-induced mitochondrial biogenesis, we examined AMPK in the skeletal muscle using Western blotting and found increased phosphorylation levels of AMPK in the exercise group. Interestingly, we also found inhibition of protein synthesis pathways in the skeletal muscle of the exercised mice, suggesting that exercise-induced AMPK signaling activation attenuates abnormal protein accumulation by inhibiting global protein synthesis (Figure 3, left). Indeed, pharmacological activation of AMPK inhibited protein synthesis and reduced AR protein aggregation in C2C12 muscle cells (Figure 3, right).

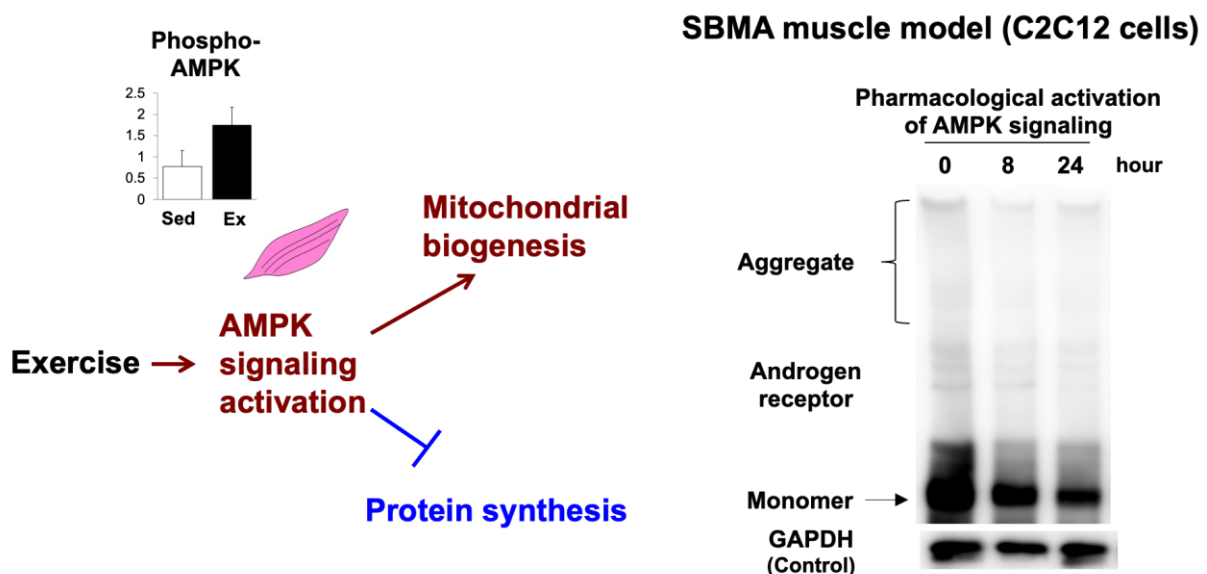


Figure 3. Exercise-induced AMPK signaling activation in skeletal muscle attenuates abnormal protein aggregation

In summary, this study demonstrated that low-intensity exercise during the early stage activated AMPK signaling in the skeletal muscle of SBMA mice, resulting in attenuation of abnormal AR aggregation. In addition, our results suggest that amelioration of skeletal muscle degeneration attenuates motor neuron degeneration and AR aggregation in motor neurons, which leads to a

long-term beneficial effect on motor performance and survival (Figure 4).

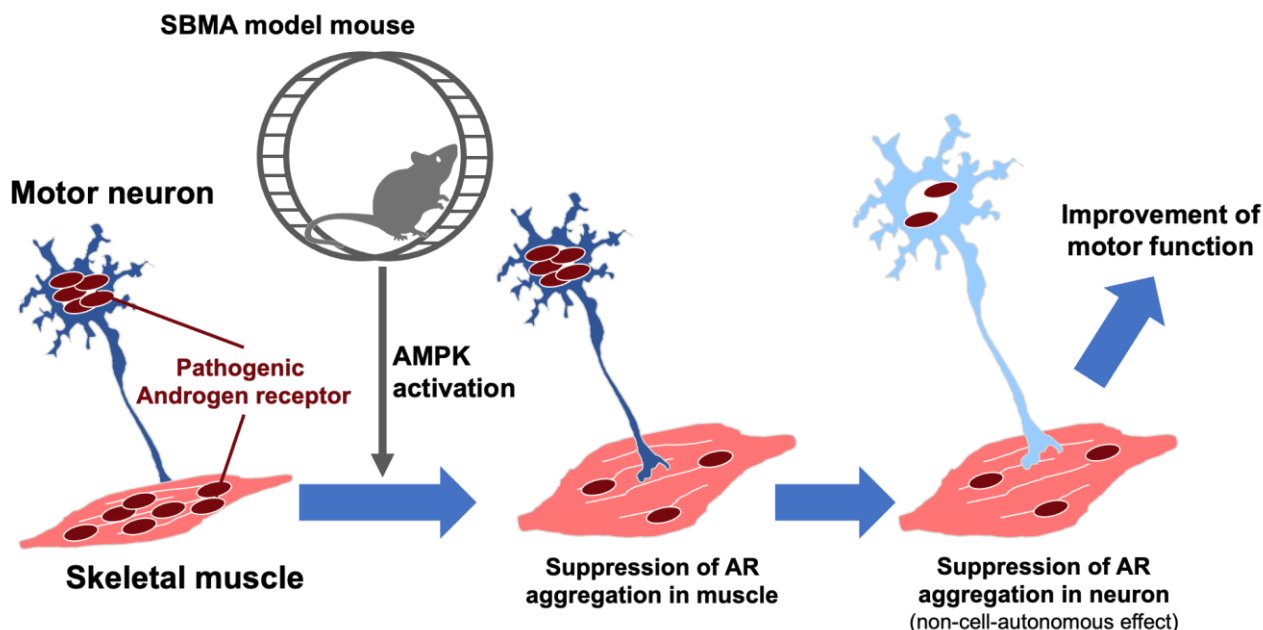


Figure 4. Summary of this study

Research Summary and Future Perspective

This study shows that low-intensity exercise during the early stages may attenuate neuromuscular degeneration caused by polyglutamine protein accumulation in SBMA. On the other hand, the results also suggest that even low-intensity exercise is difficult to continue in the advanced stages. Identifying objective indicators of exercise tolerance, such as specific biomarkers or clinical scores, may be necessary for implementing exercise therapy in individual patients. This study also suggests that AMPK signaling activation has a therapeutic potential for the treatment of polyglutamine diseases including SBMA.

Publication

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