Targeting sarcopenia: muscle innervation and exercise

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With ageing, the progressive loss of muscle mass and function (sarcopenia) results in frailty, loss of independence and is a major cause of increased falls and fractures. The precise reasons for sarcopenia are unclear. Muscle function requires electrical stimulation by a nerve, yet impaired innervation as a cause for sarcopenia has barely been considered. While sarcopenia is widely studied in rats, there are very few studies in geriatric mice. We have previously described the time course of sarcopenia in female C57Bl/6J mice and showed significant loss of muscle mass at 24 and 27/29 months (Shavlakadze *et al.*, 2010). Here we assess the impact of life-long voluntary wheel running on sarcopenia and describe morphological changes in the neuromuscular compartment in geriatric compared to young mice. The impact of life-long voluntary exercise was investigated in a study carried out in New Zealand on 18 and 27/29 months old male FVB mice. Age-related changes in muscle innervation were assessed in a separate study using 3 and 29 month old female C57Bl/6J mice. All animal procedures were carried out in accordance with the guidelines of the National Health and Medical Research Council, Australia. Mice were anesthetized with a gaseous mixture of 1.5% isoflurane and sacrificed by cervical dislocation.

The impact of life-long exercise on sarcopenia was tested in a major study of 80 male FVB mice where half of the mice were subjected to voluntary wheel running for 2.5 years starting from 3 months of age. Exercising and sedentary (control) mice were aged to 18 and 27/29 months. We found that the life-long voluntary wheel running reduced the age-related loss of muscle mass in selected limb muscles. However, normalized grip-strength that decreased with age was not improved by exercise. Our data indicate that while life-long voluntary wheel running may help maintain the mass of aging skeletal muscles, the benefits of such exercise were not striking and did not extend to muscle strength.

The extent of muscle denervation in geriatric mice was examined using immunostaining of whole intact fast *extensor digitorum longus* (EDL) and slow *soleus* muscles to identify the contribution of both muscle and nerve to the maintenance of neuromuscular junctions (NMJ), and sections of lumbar spinal cord to quantify numbers of α-motoneurons. Our analyses show striking morphological changes of NMJs and innervation, with a significant loss (~20%) of innervation in NMJ of geriatric EDL but not *soleus* muscles. Myofibre type changes indicative of muscle denervation and re-innervation were observed in all muscles. There was no loss of α-motoneuron cell bodies in the spinal cord of geriatric mice at 27/29 months of age, compared with young 3 months old mice. Establishing these baseline data for geriatric mice is essential in order to take full advantage of the wealth of genetically modified mice available to study many aspects of sarcopenia, especially the molecular basis for pronounced denervation, and potential therapeutic interventions.

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