Lifelong protein restriction induces denervation and increases proteasomal activity in skeletal muscle

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Early life environment plays a pivotal role in the development of age-related skeletal muscle disorders. Our group recently reported that lifelong protein restriction starting from birth accelerates skeletal muscle loss. However, the long-term effects of early life protein restriction on innervation and mitochondrial dynamics are still unknown. In this study, we investigated the effects of lifelong protein restriction on the neuromuscular system, examining potential correlations with alterations in mitochondrial dynamics and antioxidant enzymes.

Within 24h after birth, new-born male litters were transferred to different lactating dams (maintained on a 20% (NN) or 8% diet (NL)). At 21 days, pups were weaned on to either a 20% or 8% protein diet, resulting in three groups: control (NNN), Normal-Low-Normal (NLN), and Normal-Low-Low (NLL). Mice were maintained for up to 18 months.

NLL mice displayed significantly reduced body weight and tibialis anterior muscle weight, alongside diminished myelin sheath area in sciatic nerve, decreased innervated muscle fibres, and reduced overlap between pre- and post-terminals of the neuromuscular junctions compared to the control group. Additionally, elevated mRNA levels of atrophy markers MuRF1 and atrogin-1, coupled with increased centralized nuclei in the gastrocnemius muscle, indicated heightened atrophic processes. NLL mice had significantly increased 26s proteasome. There was no significant difference in the protein abundance of markers involved in the regulation of mitochondrial dynamics and markers regulating redox homeostasis in mitochondria, except for peroxiredoxin 3, which was significantly downregulated in NLL mice compared to the control group. In contrast, NLN mice exhibited comparable body weight, muscle metrics, mitochondrial content, and gene expression levels to the control group. In summary, lifelong protein restriction induces denervation and activates proteasomal activity, potentially contributing to the development of sarcopenia after 18 months of age when the sarcopenic phenotype is fully developed.

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