β2-ADRENOCEPTOR ACTIVATION IMPROVES PROTEIN QUALITY CONTROL IN DAMAGED SKELETAL MUSCLE

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The cellular protein quality control (PQC) machinery detects, repairs and disposes cytotoxic proteins through different proteolytic systems (i.e. ubiquitin-proteasome system and autophagy). We recently demonstrated that improving PQC protects against cardiac diseases. Here, we characterized the PQC profile as well as the benefits of sustained β2-adrenoceptor activation, a positive PQC modulator, during skeletal muscle atrophy in a rat model of sciatic nerve constriction (SNC). SNC rats present a drastic reduction in both skeletal muscle mass (55%) and contractility properties (92%) compared to sham group at day 14 after surgery. Of interest, PQC is disrupted in SNC rats, demonstrated by elevated proteasomal and lysosomal activities along with accumulation of small chaperones, polyubiquitinated (30%) and misfolded protein levels (80%). A sustained treatment of SNC rats with the β2-adrenoceptor agonist Formoterol (10 μg.kg⁻¹.day⁻¹) result in a further increase of proteasomal and lysosomal activities compared to saline-treated SNC animals. These changes are followed by reduction of polyubiquitinated protein levels and better skeletal muscle contractility properties, suggesting a positive effect of β2-adrenoceptor activation on PQC during skeletal muscle pathophysiology. We next test the role of ubiquitin proteasome system to PQC maintenance during skeletal muscle atrophy. Intriguingly, pharmacological proteasomal inhibition does not block the β2-adrenoceptor agonist benefits in skeletal muscle, suggesting a potential role of the autophagy-lysosomal system during β2-adrenoceptor activation in skeletal muscle PQC. In fact, β2-adrenoceptor agonist activates the autophagy-lysosomal machinery in SNC rats. Finally, as a proof of concept, mice lacking β2-adrenoceptor present a more severe PQC disruption and muscle dysfunction after SNC compared to wild-type littermates. Altogether, these findings suggest that PQC is disrupted during skeletal muscle atrophy. Moreover, sustained activation of β2-adrenoceptor activates PQC (mainly through autophagy-lysosomal machinery) and improves skeletal muscle contractility properties.

Key words: skeletal muscle atrophy, proteasome, autophagy
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