Divergent Roles for 12/15-Lipoxygenase and 5-Lipoxygenase Lipid Metabolic Pathways in Neurogenic Muscle Atrophy

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Aging is associated with progressive decline in muscle mass and function which significantly impacts the quality of life in the elderly population. Studies by our group and others have shown that decline in neuromuscular junction integrity (i.e. loss of innervation) during aging plays a causative role in age-related loss of muscle mass and function. However, little is known about the pathways and/or mediators that induce muscle atrophy during age-related loss of skeletal muscle during denervation. We previously showed that muscle atrophy during aging and surgical denervation is associated with increase in the expression of cytosolic phospholipase A2, the rate limiting step for release of arachidonic acid from membranes which then acts as a substrate for lipid metabolic pathways catalyzed by 12/15-lipoxygenase (12/15-LO), 5-lipoxygenase (5-LO) and cyclooxygenase and leads to the generation of bioactive lipid metabolites that are important mediators of inflammation and/or oxidative stress. In this study, we report that the expression and activity of 5- and 12/15-LO pathways are significantly elevated in atrophied muscles from denervated mice. While genetic ablation/pharmacological inhibition of 12/15-LO confers protection against denervation-induced muscle atrophy, genetic ablation/pharmacological inhibition of 5-LO tends to increase muscle atrophy. We find that the activation of 12/15-LO pathway during denervation-atrophy increases NADPH oxidase mediated oxidative stress which leads to oxidative damage to lipids and proteins and increased proteolytic degradation by the ubiquitin-proteasome pathway. These findings reveal for the first time divergent roles for 5-LO and 12/15-LO lipid signaling pathways in muscle atrophy during loss of innervation.


Primary Astrocytes from Adult and Old Rats are able to Activate an Antioxidant Response via NRF-2 when Pretreated with Low Levels of Oxidative Stress

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Oxidative stress plays a critical role in the establishment of neurodegenerative diseases during aging. Astrocytes are known to be important players in the brain physiology, by producing and releasing antioxidants and glutathione precursors, which support neuronal survival. They are also involved in responses to damage and stress in a multifactorial manner, by secreting cytokines and chemokines during the so called reactive astrogliosis. For this reason, comprehending astrocytes response to damage and oxidative stress during aging is essential to understand the brain function and pathology.

Nrf-2 is a central regulator of the antioxidant response; therefore, pharmacological inducers are often used to activate it in order to induce cellular protection. However, it is still unknown if cells from aged animals are capable of developing this response. Hence, our purpose was to determine if cortical astrocytes derived from adult and old rats are able to respond to IBHQ pretreatment and stimulate the Nrf-2-ARE pathway to induce an antioxidant protection against MPP+ toxicity, (a commonly used molecule to model Parkinson’s disease) after a IBHQ pretreatment. For this purpose, astrocytes isolated from 3 d, 9 and 24 m old rats were treated with different MPP+ concentrations. Viability and oxidative stress levels were measured. Our results showed that, although astrocytes from adult and old rats were more susceptible to MPP+ than astrocytes from newborn rats, when pretreated with IBHQ, they were able to transactivate Nrf-2, increasing antioxidant enzymes and Nrf-2 expression.