Scientific Meeting
AuPS | ASB
HOBART · 2022

Abstract: 146P

The role of N-acetylcysteine (NAC) in reducing pathological skeletal muscle fibre branching in an mdx mouse model of human Duchenne Muscular Dystrophy

Asma Redwan[1], Leonit Kiriaev[1,3], Sindy Kueh[1], John W. Moley[1], Peter J. Houweling, Ben D. Perry[2], Stewart I. Head[1,3]

[1]*Myogenica Laboratory, School of Medicine, Western Sydney University, Sydney, NSW, Australia.*

[2]*School of Science, Western Sydney University, Sydney, NSW, Australia.*

[3]*Muscle Research Group, Murdoch Children's Research Institute, Melbourne, VIC, Australia.*

Introduction: DMD is a severe muscle wasting disorder caused by mutations in gene *DMD*, encoding sarcolemmal protein dystrophin. The *mdx* strain of mice is used as a model for DMD. Dystrophin deficiency raises $[Ca^{2+}]_{in}$, triggering muscle fibre necrosis and regeneration, resulting in aberrant fibre branching. When the number and complexity of branched fibers reaches a critical threshold, we call it "tipping point" - the branches rupture due to contraction, causing a force deficit. Oxidative stress contributes to dystrophic necrosis by increasing ROS level. Given that NAC has an established ROS scavenger mechanism, we hypothesize NAC treatment will lower pathogenic load of branching fibers in regenerated skeletal muscles.

Objective: To investigate the efficacy of the antioxidant NAC to reduce branched fibres in *mdx* mice below “tipping point” where normal skeletal muscle function is compromised.

Methods and Results: 3-week weaned *mdx* and littermate controls (n=6) were divided into two groups of treated vs untreated for 6 weeks chronic treatment of NAC. After 6-week, extensor digitorium (EDL) muscles were harvested and contractile electrophysiology experiments were performed. Muscles were then examined to see the morphology of the muscle fibres and assess if the degree of fiber branching is associated with any protective effect of NAC. Data shows statistical significance in NAC treated EDL and TA muscles have lower mass that untreated *mdx* muscles. Also, *mdx* muscles from NAC treated group show less complexity in fiber branching than untreated group indicating that NAC treatment may have reduced ROS activity thus less fiber degeneration occurred leads to less branched fibers. NAC untreated mdx animals show greater force loss after first eccentric contraction opposite to treated group indicating higher number and complexity of fiber branching have become site of contraction-induced rupture and force loss.

Conclusion: NAC reverses pseudohypertrophy and fiber branching in *mdx* mice comparing to untreated group.