Kynurenine pathway dysregulation in Duchenne muscular dystrophy

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New Directions Conference Abstract April 2021
Category: Expanding Concepts in Muscle Pathophysiology

The loss of dystrophin protein manifests as a fatal muscle wasting disease, Duchenne muscular dystrophy (DMD). The *mdx* mouse model of DMD exhibits unique and severe stress response phenotypes upon routine scruff handling and social stress exposure. Scruff handling leads to acute *mdx* inactivity, while social defeat stress invokes significant *mdx* mortality within 24 hours, preceded by a counterintuitive hypotensive response to stress-induced tachycardia. Stress phenotypes observed in *mdx* mice are relevant to the significant proportion of DMD patients who suffer from chronic life stress autonomic dysfunction.

The kynurenine pathway (KP), a major tryptophan degradation route in the liver, becomes hyperactive in extrahepatic tissues under pathological inflammatory conditions. Neurotoxic kynurenine metabolites are implicated in affective mental disorders and chronic stress pathology. Additionally, a vasodilatory kynurenine precursor generated in the presence of reactive oxygen species could link stress-induced *mdx* hypotension with KP dysfunction in dystrophic skeletal muscle, which is subject to chronic inflammation and oxidative stress. Preliminary evidence has revealed elevated kynurenine in urine from both *mdx* mice and DMD patients. KP hyperactivity is counteracted by kynurenine aminotransferases (KATs), which catabolize kynurenine to a neuroprotective by-product, kynurenic acid (KYNA). KATs and their transcriptional regulators, peroxisome proliferator-activated receptor gamma coactivator 1 isoforms alpha and beta (PGC-1α and PGC-1β), exhibit reduced expression in *mdx* skeletal muscle. Notably, KAT and PGC-1α/β expression is restored in transgenic *mdx* mice expressing nearly full-length dystrophin, who are also protected from stress susceptibility. Concurrently, *mdx* skeletal muscle and liver display elevated KP rate-limiting enzymes after stress. Thus, skeletal muscle dystrophinopathy and acute stress may drive systemic KP metabolic dysregulation and contribute to *mdx* stress response phenotypes. Elucidating the impact of KP dysfunction in dystrophinopathy will advance understanding of *mdx* stress susceptibility and provide novel disease biomarkers that can be quantified in DMD patients via minimally invasive biofluid collection.