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NEW TRICK FOR OLD DOGS: CANNABINOIDS IN THE TREATMENT OF RARE SKELETAL MUSCLE DISORDERS

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The lack of efficient treatment for rare diseases represents an enormous unmet medical need. In this context, our work provides novel insights into the involvement of the gut microbiota-endocannabinoid system crosstalk in Duchenne muscular dystrophy (DMD), a rare hereditary myopathy for which there is no cure. Using the mdx mouse model of DMD, we found that faecal microbiota composition is significantly altered compared to healthy controls. Accordingly, the plasma levels of short-chain fatty acids (SCFAs) including acetate, propionate and butyrate along with their related metabolites are reduced, whereas ECS activity is increased in both plasma and skeletal muscle tissues. Remarkably, in mdx mice, oral supplementation with sodium butyrate (NaB) rescues locomotor activity and impaired muscle autophagy associated with inflammation to the same extent as deflazacort (DFZ), a standard of care for DMD. Additionally, both NaB and DFZ prevent ECS overactivity. In C2C12 myoblasts, NaB prevented endotoxin-induced up-regulation of pro-inflammatory genes as well as the miRNA dysregulation-mediated upregulation of the endocannabinoid CB1 receptor, in a manner depending on GPR109A and PPARγ receptor activation. Importantly, NaB exerts anti-inflammatory and pro-autophagic effects in primary myoblasts isolated from DMD donors. In conclusion, we provide novel insights into molecular pathogenic mechanisms underlying DMD, which may lead to new therapeutic approaches for rare and incurable skeletal muscle.

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