Study of the expression profile and pharmacological role of the CB1 receptor in Duchenne Muscular Dystrophy (DMD) muscles: a new opportunity to reinforce muscle repair and locomotor activity

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Duchenne muscular dystrophy (DMD) is a hereditary myopathy that causes the progressive degeneration of skeletal muscle tissue. It represents one of the most common forms of muscular dystrophy, which mainly affects young males since it is determined by alterations present in the gene, located on the X chromosome, encoding for the structural protein dystrophin. The loss of dystrophin function causes irreversible muscle damage (1). Prognosis is still poor, given that death of affected patients occurs in most cases within 10-15 years of age due to respiratory failure.
We recently showed that, in both murine and human skeletal muscle cells, stimulation of the CB1 receptor impairs myotube formation and increases the rate of myoblast proliferation (2). The purpose of this study was to investigate the potential role of CB1 signaling during DMD progression. Towards this aim, we examined CB1 expression and function in skeletal muscles of Dmdmdx mice, an animal model of DMD, and in biopsies of patients with this disease (3). We found that, in murine samples, the Cnr1 gene encoding for the CB1 receptor showed the highest degree of up-regulation at weeks 5-6, and correlating with the disease onset. Similar changes were observed for the selective marker of satellite cells, Pax7 (4). Similar changes were also detected in the muscles of children affected by DMD at both 3 and 7 years of age. Intriguingly, using bio-informatic analysis, we found putative consensus sites for PAX7 upstream of both the murine and human Cnr1 gene promoter. Using the luciferase assay, we showed that functional PAX7 binding sites are located proximal to, and hence regulate the expression of, Cnr1. Importantly, the pharmacological treatment of Dmdmdx mice with the CB1 inverse agonist, rimonabant (0.5mg/kg, IP, 3 times a week for 3 weeks), resulted in a marked increase in locomotor skills such as coordination, strength and resistance. Remarkably, the number of regenerated myofibers (cross-sectional area - CSA) was significantly increased in rimonabant-treated mice compared with control mice. By qPCR analysis we confirmed that in the muscles of DMDmdx mice treated with rimonabant, the mRNA expression of skeletal muscle differentiation markers was increased, whereas the transcript levels of genes encoding for inflammatory or fibrosis markers were reduced when compared to the vehicle group. In contrast, in Dmdmdx mice, treatment with ACEA (2.5 mg/Kg IP, 3 times a week for 3 weeks), a selective CB1 agonist, did not produce significant changes.
We suggest that pharmacological blockade of CB1 receptor, rather than its activation, may ameliorate locomotor activity in distrophic mice. The findings summarized here indicate a novel role for CB1 in the development of degenerative muscle diseases, by affecting muscle differentiation and repair processes, thus highlighting this receptor as a potential therapeutic target for the treatment of such disorders.

References:
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