Restoration of pharyngeal dilator muscle force in dystrophin-deficient (mdx) mice following co-treatment with neutralizing IL-6R antibody and Urocortin-2

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Duchenne Muscular Dystrophy (DMD) is a fatal genetic disorder wherein patients lack the major structural protein dystrophin. DMD is characterised by severe muscle weakness. The mdx mouse, a model of DMD has impaired respiratory muscle function. Inflammation is a primary pathological feature of DMD and known to play an integral part in DMD muscle pathology. We hypothesise that co-treatment of anti-IL-6 receptor antibody & CRF receptor-2 agonist will alleviate respiratory muscle dysfunction in mdx mice.

Six week old mdx (C57BL/10ScSn-Dmdmdx/J; n=24) and wild-type (WT; C57BL/10ScSn; n=23) mice received either saline (0.9% w/v) or a co-treatment of neutralizing IL-6 receptor antibodies (xIL-6R; 0.2 mg/kg) and CRF receptor-2 agonist (Urocortin-2; 30μg/kg). Following treatment, sternohyoid muscle (pharyngeal dilator) contractile function was examined ex vivo. Muscle fibre nucleation and inflammatory cell infiltration were histologically examined. Muscle fibre type analysis was determined by myosin heavy chain immunofluorescence.

Peak specific force (Fmax) was significantly reduced in mdx compared with WT. Co-treatment restored Fmax for mdx to values equivalent to WT. Co-treatment also restored mechanical power production over the load continuum. The percentage of centrally-nucleated muscle fibres was significantly increased in mdx compared with WT, and was significantly reduced in mdx mice only, following co-treatment. The areal density of inflammatory cell infiltrates was significantly increased in mdx mice also, and unaffected by co-treatment. Fibre type transitions were apparent in the mdx sternohyoid muscle and were ameliorated by co-treatment.

Co-treatment with xIL-6R and Urocortin-2 had a positive inotropic effect, completely restoring mechanical force and power. Co-treatment reversed fibre transitions in mdx, as well as decreasing the proportion central nucleated muscle fibres. Preservation of MHCIIb fibres may underpin, at least in part, recovery of force production in the mdx co-treated mice. These data may have implications for the development of pharmacotherapies for DMD with relevance to respiratory muscle performance.

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