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-Dmd^{mdx}/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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