Increased calcineurin phosphatase activity improves fatigue resistance whilst maintaining specific force in diaphragm muscles from dystrophic *mdx* mice

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The calcineurin signalling pathway is essential for successful muscle regeneration in young *mdx* mice and this pathway is differentially activated in limb and diaphragm muscles from adult *mdx* and wild type mice. We tested the hypothesis that upregulation of a constitutively active calcineurin-A transgene (CnA Tg) would improve muscle function in *mdx* mice. Female *mdx* mice were mated with male CnA-Tg-MCK mice. All F1 male offspring were dystrophic and 50% expressed the transgene (*mdx*-CnA Tg). Muscle function was assessed in EDL, soleus, and diaphragm in 3 mo old *mdx*-CnA Tg mice and *mdx* littermates. Mice were anaesthetised with sodium pentobarbital and EDL, soleus, tibialis anterior, and diaphragm muscles surgically excised. Animals were killed by cardiac excision whilst still anaesthetised deeply. Muscle sections were stained with H&E for basic morphology and Van Gieson's to assess collagen infiltration. Muscles from *mdx*-CnA Tg mice exhibited prolonged twitch contraction and relaxation times, greater fatigue resistance, and improved recovery from fatigue, compared with mdx littermates. These parameters are indicative of a slower muscle phenotype. Furthermore, mean fibre cross-sectional area (CSA) was smaller in muscles from *mdx*-CnA Tg mice than *mdx* littermates. Differences in fibre CSA and type may account for the decrease in absolute (P_o) and specific force (sP_o) in EDL and soleus muscles from *mdx*-CnA Tg mice. Despite having a smaller fibre CSA and slower phenotype, diaphragm muscles from *mdx*-CnA Tg maintained sP_o. In contrast to hindlimb muscles, increased calcineurin activity was not associated with reduced sP_o in the diaphragm. This was not attributed to differences in collagen infiltration or diaphragm thickness. Whether this was due to increased fibre survival or integrity due to increased expression of utrophin and dystrophin associated proteins remains to be determined. Further investigation will determine whether over-expression of activated calcineurin may protect dystrophic muscles from contraction-induced injury.

Supported by the Muscular Dystrophy Association (USA).