The contractile characteristics of a novel dystrophin-negative mouse strain with enhanced voluntary exercise capability

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Introduction: Duchenne muscular dystrophy (DMD) is a devastating X-linked disease resulting from a mutation in the gene encoding the protein dystrophin. The lack of dystrophin leads to progressive skeletal muscle damage and wasting, which significantly decreases locomotory ability, and patients are usually wheel-chair bound by 12 years of age. The disease ultimately results in death from respiratory and/or cardiac failure in early adulthood and no cure is currently available. The mdx mouse, the main animal model of DMD, exhibits significantly lower levels of voluntary wheel running exercise than control mice. In this study, we cross-bred the mdx mouse line with a mouse strain from the Collaborative-Cross (CC) breeding program that exhibited an extremely high exercise capacity ('CC' mouse). Dystrophin-deficient progeny of this cross (mdx/CC mouse) displayed significant improvements in maximum running distance ($P<0.001$) and velocity ($P<0.01$) compared to mdx mice. In this study we investigated the contractile properties of fast and slow-twitch muscles from control mdx and mdx/CC mice in order to investigate the physiological mechanisms responsible for the increased exercise ability of the dystrophin-negative mdx/CC mouse.

Methods: Control C57BL/10 (WT; n=14), mdx (n=17) and mdx/CC (n=15) mice were anaesthetized, and the fast-twitch *extensor digitorum longus* (EDL) and slow-twitch *soleus* hind-limb skeletal muscles surgically removed and attached to an *in vitro* muscle test system. Maximum force production, twitch parameters, fatigability and response to damaging eccentric contractile activity was evaluated.

Results: Maximum specific force was similar in EDL muscles from mdx/CC and mdx controls ($P=0.62$). However, *soleus* muscles from mdx/CC had significantly higher maximum specific force values compared to mdx *soleus* muscles (mdx; 15.09 ± 0.27 N/cm^2, mdx/CC; 16.63 ± 0.56 N/cm^2, $P<0.05$). EDL muscles from mdx/CC mice contracted more rapidly than mdx EDL controls (twitch force time-to-peak: mdx; 26.75 ± 0.15 ms, mdx/CC; 22.24 ± 0.5 ms, $P<0.01$) (maximum rate of force development: mdx; 686.07 ± 18.72 g/s, mdx/CC; 792.73 ± 25.93 g/s, $P<0.01$). However, the *soleus* twitch responses were similar in both groups ($P>0.05$). The fatigability of mdx/CC EDL and *soleus* muscles was similar to respective mdx controls ($P>0.05$). EDL and *soleus* muscles from mdx/CC showed a significantly greater resistance to eccentric-contraction induced damage (% of loss of force: EDL mdx; 48.52 ± 4.40 %, mdx/CC; 39.95 ± 3.36 %, $P<0.05$) (% of loss of force: *soleus* mdx; 15.97 ± 0.57 %, mdx/CC; 13.17 ± 1.35 %, $P<0.05$) compared to muscles from control mdx mice.

Conclusion: The increase in contractile speed of the fast-twitch EDL and increased resistance to eccentric-contraction induced damage in the EDL and slow-twitch *soleus* of the dystrophin-negative mdx/CC mice compared to control mdx, could both play a role in the mdx/CC mice enhanced exercise ability. Elucidating the genes and proteins responsible for the shifts in muscle performance of these dystrophin-negative mdx/CC could lead to novel interventions to improve the quality of life in patients with DMD.