IGF-I overexpression in muscles of *mdx* mice improves excitation-contraction coupling in isolated mechanically skinned muscle fibres

C. Van Der Poel,[1] J.D. Schertzer,[1] T. Shavlakadze,[2] M.D. Grounds[2] and G.S. Lynch,[1] [1]Basic and Clinical Myology Laboratory, Department of Physiology, University of Melbourne, Victoria 3010, Australia and [2]School of Anatomy and Human Biology, The University of Western Australia, Crawley, Perth, Western Australia 6009, Australia.

Excitation-contraction coupling (ECC) is impaired in muscles of *mdx* mice, an animal model of Duchenne muscular dystrophy (DMD). Insulin-like growth factor-I (IGF-I) has therapeutic potential for DMD, and has been shown to enhance skeletal muscle dihydropyridine receptor function and gene expression. We tested the hypothesis that muscle specific overexpression of IGF-I in *mdx* mice (mIGF-I-*mdx*) improves ECC. Mechanically skinned fibres were prepared from EDL muscles excised from C57BL/10, *mdx*, and mIGF-I-*mdx* mice that were anaesthetised with pentobarbital sodium (60 mg/kg, i.p.). The mice were then killed by cardiac excision. The number of depolarization-induced contractions (DICR) before reaching a 50% reduction in DICR amplitude, was lower in fibres from *mdx* (7 ± 1, n = 15 fibres) than C57BL/10 mice (16 ± 2, n = 12 fibres), but there was no difference in SR Ca^{2+} loading or Ca^{2+} leak rates. In mIGF-I-*mdx* mice, rundown of DICR was improved significantly compared to *mdx* mice (14 ± 2 depolarizations, n = 14 fibres, $P < 0.05$). There was no change in SR Ca^{2+} loading, but the amount of releasable SR Ca^{2+} was increased, possibly due to the reduction in Ca^{2+} leak rate (*mdx*: $19 \pm 3\%$ reduction, n = 13 *vs* mIGF-I-*mdx*: $7 \pm 3\%$ reduction, n = 14). The results support the hypothesis that muscle specific overexpression of IGF-I improves ECC in *mdx* mice.

Supported by the Muscular Dystrophy Association (USA).