J Muscle Research and Cell Motility **14,** 255 (1993)

CONTRACTILE PROPERTIES AND MOLECULAR THERAPY

Structural basis for force decline in EDL-muscle from *mdx* mice after eccentric contraction

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EDL-muscles from *mdx* mice display an irreversible decline in maximal isometric force after eccentric contractions (Moens *et al.*, this Meeting). As only about 50% of the force decline could be explained by membrane-damaged fibres, we propose and test two hypotheses to explain the remaining 50% force decline.

The first hypothesis is that the observed force decline can be fully explained by membrane-damaged fibres, but the extent of the latter is underestimated. It is possible that the dye that we used to detect membrane-damaged fibres only stained a limited area around a membrane lesion. As we studied sections taken from the center of the muscle, we may have not counted fibres that were membrane-damaged more towards the tendon. To test this hypothesis, transverse sections were cut at 150 µm intervals along the length of an EDL muscle (*mdx*) with a large force decline. Then, the muscle was reconstructed and the longitudinal distribution of staining (membrane damage) was studied. It appeared that still the observed force decline could not be fully explained by the percentage of membrane-damaged fibres.

A second hypothesis is that the unexplained part of the force decline is caused by damage at the myotendinous junction (MTJ). It was reported earlier that eccentric contractions can cause separation of basement- and plasma membrane at MTJs of normal muscle (Miller (1977) *Am. J. Sports Med.* **5**, 191-3), and that dystrophin is present in abundance at the MTJ (Tidball and Law (1991) Am. *J. Pathol.* **138,** 17-21; Byers *et al.* (1991 *J. Cell Biol.* **115,** 411-21). Therefore, absence of dystrophin might render this location relatively more susceptible to mechanical strain in mdx mice. To study MTJs by electron microscopy, ultrathin longitudinal sections were cut at 100 µm intervals from blocks that contained both tendon and muscle. Preliminary results show no fibres that are both healthy and display separation of basement- and plasma membrane at the MTJ. So far, our results indicate yet another cause for the unexplained part of the force decline observed after eccentric contractions in EDL muscles from *mdx* mice. One possibility is that in *mdx* mice eccentric contractions give rise to a disruption of sarcomeres, without destruction of the fibres.