Muscle weakness in a mouse model of nemaline myopathy can be reversed with exercise and reveals a novel myofibre repair mechanism

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Nemaline myopathy (NM) is an inherited muscular disorder characterised by muscle weakness and the presence of distinct rod-shaped accumulations of sarcomeric proteins (nemaline rods) in muscle fibres. We previously generated a transgenic mouse model for nemaline myopathy that expresses in all skeletal muscles a mutant α-tropomyosin-slow (Met9Arg) protein that causes NM in humans (Laing *et al.*, 1995). This mouse shows all of the features of the human disease including late-onset muscle weakness (4-6 mo of age) and nemaline rods, the defining feature of the disease (Corbett *et al.*, 2001). A debilitating feature of NM in humans is prolonged muscle weakness after periods of inactivity. In the present study, we have examined endurance exercise as means of improving recovery following muscle inactivity in the transgenic NM mouse model. Physical inactivity was induced by bilateral hind limb immobilisation (using surgical tape) in a maximal dorsoflexed position that stretches the ventral muscles (e.g. soleus) and shortens the dorsal muscles (e.g. extensor digitorum longus, EDL). Mice were fully anaesthetised during the immobilisation procedure with ketamine/xylazine (100 and 10 mg/kg body weight, respectively). The mice were then subjected to one of three, 4 week recovery regimens: 1) minimal physical activity (cage rest), 2) low intensity voluntary free-wheel exercise, or 3) high intensity treadmill exercise (1.5h/day; 5 days/week; 20 m/min; 5% incline). Fours weeks of immobilisation resulted in muscle fibre atrophy and severe muscle weakness in both wild-type (WT) and NM mice. However, NM mice were weaker than the WT mice after immobilisation, and exercise, not cage-rest, was required to regain whole body strength. Immobilisation of the EDL in the shortened position, led to an increase in the number of nemaline rods in the NM mice and surprisingly these rods that were formed with immobilisation appeared to be resolved with endurance exercise. Together these results suggest that nemaline rods may have a role in muscle weakness in NM. Chronic stretch-immobilisation of the soleus muscle for 10 days resulted in myonecrosis and continued stretch-immobilisation for a further 18 days resulted in complete regeneration of the damaged fibres. Although muscle regeneration did occur in NM mice during immobilisation it occurred without the classical features of regeneration (centrally located myonuclei) indicating an alteration in the normal repair process of muscle in NM. In conclusion, exercise is effective at attenuating disuse-induced muscle weakness in the NM mouse model. The novel muscle repair process in the NM maybe a response to primary myofibrillar damage that occurs in NM and maybe distinct from the classical repair observed in muscular dystrophies.

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