Exogenous administration of a PPARδ agonist to dystrophic *mdx* mice confers no protection from contraction-mediated muscle damage

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Duchenne muscular dystrophy (DMD) is an X-linked recessive disease caused by a variety of mutations in the dystrophin gene leading to the absence of dystrophin, a cytoskeleton protein implicated in muscle fibre stability. The lack of dystrophin renders muscle fibres highly susceptible to lengthening contraction-induced damage; a contributing mechanism to the dystrophic pathology (Lynch, 2004). Protecting dystrophic muscle fibres from injury is an important therapeutic strategy for DMD. Fast-twitch muscles are more susceptible to contraction-mediated damage than slow-twitch fibres in healthy and dystrophic mice (Consolino & Brooks, 2004), and so altering muscle fibre composition could potentially decrease injury susceptibility. Transgenic over-expression of peroxisome-proliferator activated receptor delta (PPARδ) in skeletal muscles increased the proportion of slow-twitch type I muscle fibres and treating mice with the PPARδ agonist, GW501516, promoted a slow-muscle phenotype and mitochondrial biogenesis, indicative of a shift to higher proportions of type I muscle fibres (Wang *et al*., 2004). We tested the hypothesis that treating dystrophic *mdx* mice with GW501516 would confer protection to muscles from contraction-induced injury by inducing a shift towards a slower muscle phenotype.

Dystrophic *mdx* mice (12 weeks old) were treated with GW501516 (10 mg/kg, oral gavage) for 4 weeks. Mice were anaesthetised deeply (60 mg/kg, sodium pentobarbital) for assessment of contractile function. Susceptibility to contraction-induced injury was examined *in situ* in the tibialis anterior (TA) muscle, and *in vitro* in soleus and diaphragm muscles. Muscle fatigability was examined *in vitro* in the *extensor digitorum longus* (EDL), *soleus*, and diaphragm muscles using a standard four-minute fatiguing stimulation protocol. The mice were killed by cardiac excision while anaesthetised.

Treating *mdx* mice with the PPARδ agonist did not alter the susceptibility to contraction-induced injury in the muscles tested. Maximum force (P_o) was reduced in the TA muscle after treatment. Muscle fatiguability was unchanged in the EDL and diaphragm muscles, however, the soleus muscles were more fatigue resistant after treatment ($p < 0.05$). These results indicate that a minor shift to a slower muscle phenotype does not confer protection to dystrophic muscles from contraction-induced injury.

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