Muscle damage in *mdx* mice is reduced after treatment with streptomycin

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Extensive research has been carried out on the cellular mechanisms underlying Duchenne Muscular Dystrophy (DMD) and a number of therapeutic options have been proposed for the treatment of this muscle disease. However, while much progress has been made, there are currently no effective therapies that significantly slow the progression of the disease. It has been hypothesised that dystrophin may be important in maintaining the normal function of certain membrane channels, in particular stretch-activated channels (SAC), and that calcium entry through these channels could initiate degradative pathways that leads to muscle fibre degeneration (Franco & Lansman, 1990). Recent research in our laboratory has focused on the role of SAC in muscle damage using *mdx* mice, an animal model of DMD. In single muscle fibres from *mdx* mice, it has been found that a component of the damage induced by a series of eccentric contractions can be prevented by two known SAC blockers, gadolinium and streptomycin (Yeung, Head & Allen, 2003; personal communication).

The current study aimed to investigate the role of SAC in muscle damage *in vivo* by using *mdx* mice that were given either normal drinking water (control) or water containing streptomycin (3mM). A previous study by McBride *et al*., (2000) showed that this concentration of streptomycin prevents the muscle fibre depolarisation caused by eccentric contractions, which has also been attributed to the entry of Na^+ through SAC. It is known that muscle damage in *mdx* mice begins at about 21 days after birth (McGeachie *et al*., 1993), and that the first signs of regenerating fibres, evident by the presence of centrally located nuclei, occurs at 24 days. Thus, the mice used in the current study began the streptomycin treatment at 18 days, that is, three days before the onset of any muscle damage. At various times after the onset of the treatment, mice were killed by cervical dislocation and the EDL muscles were dissected out and placed in a normal physiological solution. Each muscle was attached to steel frame on a cork pad and immersed in embedding medium (Tissue-Tek) before being frozen in liquid nitrogen. Muscle cross-sections (10μm thick) were stained with haematoxylin and eosin, and viewed under a light microscope, with digital images taken for analysis of the location (central or peripheral) of muscle fibre nuclei.

At 24 days, the number of fibres with nuclei that were centrally located was 25% for control *mdx* mice compared to 4% for the streptomycin treated *mdx* mice. Over the next three days, the number of fibres with central nuclei for the control mice remained fairly similar with a peak of 30%. Values for the streptomycin treated mice also increased, peaking at 20%, but always remained lower than those of their age-matched control mice. This difference was statistically significant ($P<0.05$; two-factor ANOVA). Other indicators of muscle damage, such as plasma creatine kinase levels and serum albumin localisation within muscle fibres, are currently being used in order to further investigate and quantify the effect of streptomycin in preventing damage in *mdx* muscle.

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