Muscle specific kinase protects mdx mouse muscles against eccentric contraction-induced loss of strength

J. Ban, S. Trajanovska and W.D. Phillips , Physiology and Bosch Institute, University of Sydney, NSW 2006, Australia.

Muscles of mdx mice lack dystrophin, providing a mouse model for Duchenne muscular dystrophy (DMD). Eccentric contractions applied to mdx muscles cause an acute drop in their maximum force, reflecting the vulnerability of dystrophin-deficient muscles to damage. It has been reported that mdx muscles express less Muscle Specific Kinase (MuSK) than wild-type muscles and that this might predispose the neuromuscular junction to eccentric contraction-induced damage. To test this we injected the *tibialis anterior* muscles of 8-week old male mdx mice with adeno-associated viral vector (AAV) so as to increase the level of expression of MuSK. Contralateral control muscles were injected with empty AAV vector. One month later the mice were anaesthetized with 2-3% inhaled isoflurane/oxygen and maximum tetanic force was recorded in response to direct muscle stimulation or stimulation *via* the nerve. After a series of four eccentric contractions (ECs), mdx muscles retained only 73 ± 2% (mean ± SEM) of their original (pre-stretch) maximum isometric force. Mdx muscles expressing MuSK-GFP retained significantly more of their original force after identical ECs (84 ± 1%; $P<0.01$). Rapsyn, an established downstream effector of MuSK signaling, conferred similar protection to mdx muscles. The protective effect was evident even when force was elicited by direct muscle stimulation, suggesting that the MuSK/rapsyn pathway acts downstream of neuromuscular transmission.