Calcineurin activation can enhance the structure and function of regenerating muscles following myotoxic injury

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Whilst calcineurin signalling is essential for successful muscle regeneration, it is not known whether upregulating calcineurin activity can enhance muscle repair after injury. Tibialis anterior (TA) muscles from adult wild-type (WT) and transgenic mice expressing high-levels of the constitutively active calcineurin-Aα transgene (MCK-CnA*) were injected with a myotoxin (Notexin) to destroy all muscle fibres; with the TA muscle of the contralateral limb serving as the uninjured control. Muscle structure was assessed at 5 and 9 days after notexin injury and function was assessed *in situ* at 9 days post-injury. To induce myotoxic injury and assess muscle function, mice were anaesthetised with 100 mg/kg Ketamine and 10 mg/kg Xylazine, intraperitoneal injection, such that they were unresponsive to tactile stimuli. At the conclusion of testing, deeply anaesthetised mice were sacrificed by cardiac excision. Calcineurin stimulation enhanced muscle regeneration and altered myoregulatory factor protein expression. Recovery of myofibre size and force producing capacity was faster and degeneration was reduced in injured muscles of MCK-CnA* compared to WT mice. Myogenin and MEF2A levels were greater in muscles of MCK-CnA* than WT mice at 5 and 9 days post-injury, respectively. Higher MEF2A expression in regenerating muscles of MCK-CnA* mice at 9 days post-injury may be related to an upregulation of slow fibre genes. Calcineurin activation in uninjured and injured muscles slowed the time course of the isometric twitch, reduced fatiguability, and enhanced recovery of force production after four minutes of intermittent maximal stimulation. Calcineurin activation can confer structural and functional benefits to regenerating skeletal muscles, which are mediated in part by differential expression of myoregulatory factors.

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