β-adrenergic signalling in skeletal muscle regeneration after myotoxic injury

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β-adrenoceptor agonists (β-agonists) have therapeutic potential for skeletal muscle wasting disorders due to their potent muscle anabolic effects. β-agonist administration promotes skeletal muscle hypertrophy *via* cAMP-mediated increases in protein accretion (Navegantes *et al.*, 2001; Ryall *et al.*, 2002). We have shown previously that β-agonist administration can enhance functional repair of rat skeletal muscle after injury (Beitzel *et al.*, 2004). It has been suggested that adrenoceptor desensitisation may limit the therapeutic efficacy of β-agonists in skeletal muscle (Claing *et al.*, 2002), but little is known about β-adrenergic signalling during muscle regeneration. The aim of this study was to examine aspects of β-adrenergic signalling in skeletal muscle and test the hypothesis that during regeneration, β-agonist administration does not cause β-adrenoceptor desensitisation. Male rats (275-300g) were deeply anaesthetised (ketamine 100 mg/kg and xylazine 10 mg/kg, *i.p.*), and the extensor digitorum longus (EDL) and soleus muscles of the right hindlimb were surgically exposed and injected with a maximal volume of the myotoxic agent, bupivacaine hydrochloride, to cause complete destruction of all muscle fibres (Beitzel *et al.*, 2004). The EDL and soleus muscles of the contralateral hindlimb served as uninjured controls. Rats then received either the β-agonist, fenoterol (1.4 mg/kg/day, *i.p.*), or an equivalent volume of saline for 7 days post-injury. Following treatment, rats were anaesthetised deeply and the EDL and soleus muscles were excised for analysis. All rats were killed by cardiac excision whilst anaesthetised. β-adrenoceptor density was measured using radioligand binding assays on isolated muscle membranes (Beitzel *et al.*, 2004). In regenerating EDL muscles there was a ~2-fold increase in β-adrenoceptor density compared to control values. β-adrenoceptor density in regenerating EDL muscles from fenoterol treated rats was only 57% that for saline treated rats. In regenerating soleus muscles, β-adrenoceptor density was restored to control levels. Fenoterol treatment reduced β-adrenoceptor density during regeneration to 58% that for saline treated rats. Adenylate cyclase (AC) activity assays were performed on fresh isolated muscle membranes. Despite the marked reduction in β-adrenoceptor density in both regenerating EDL and soleus muscles with fenoterol treatment, receptor desensitisation did not occur, since AC activity was maintained during isoproterenol stimulation. Various AC stimulants (NaF, forskolin and Mn^{2+}) which act at different points in the AC signalling pathway were used to examine the underlying mechanisms responsible for these observations. The findings indicated compensation for homologous downregulation of the β-adrenoceptors by the heterologous sensitisation at the level of AC. These results highlight the unique β-adrenergic signalling responses of injured/regenerating muscles compared with uninjured muscles, so as to maximise functional recovery.

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