Low dose formoterol treatment reverses sarcopenia and improves muscle function in fast- but not slow-twitch skeletal muscles of aged rats

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Ageing is associated with progressive muscle wasting (sarcopenia) and weakness and in the frail elderly, the loss of muscle mass can be so severe it impacts on the ability to perform the tasks of everyday living (Lynch, 2004). There is a profound need for strategies to ameliorate sarcopenia and improve quality of life. One strategy is treatment with β_2-adrenoceptor agonists (β_2-agonists). Although traditionally administered at low doses for treating asthma, at higher doses, β_2-agonists have potent muscle anabolic effects. We have shown previously that treatment with the β_2-agonist fenoterol can reverse muscle wasting and weakness in old rats (Ryall *et al.*, 2004a). However, fenoterol was also associated with impaired cardiac function, likely mediated through actions at the β_1-adrenoceptor (Gregorevic *et al.*, 2005).

The β_2-agonist formoterol has a greater duration of action than the most widely used asthma drugs, and has an increased selectivity for the β_2-adrenoceptor (Anderson, 1993). Having found formoterol to be more potent and efficacious than fenoterol, with respect to its effects on skeletal muscle mass, (Ryall *et al.*, 2004b), we tested the hypothesis that low dose formoterol treatment would reverse the atrophy and weakness in skeletal muscles of old Fischer 344 rats, whilst having minimal unwanted effects on the heart (due to reduced actions at the 1-adrenoceptor). Young (3 months/age, n = 8), adult (16 months/age, n = 8) and old (28 months/age, n = 6) rats were treated daily with either formoterol (25 μg/kg/day, i.p ~0.5 mL total volume) or saline vehicle for 4 weeks. Following treatment, rats were anaesthetised with sodium pentobarbitone and the fast-twitch extensor digitorum longus (EDL) and predominantly slow-twitch soleus muscles were surgically excised from the hindlimb for determination of isometric contractile properties *in vitro*. Following completion of the functional measurements the deeply anaesthetised rats were killed by surgical excision of the heart.

Muscle mass was greater in adult than young rats, indicative of normal growth, whilst old rats exhibited a significant reduction in muscle mass compared to both young and adult rats (EDL (in mg): young 125 ± 3 *vs* adult 142 ± 2 *vs* old 80 ± 7, $P < 0.05$; soleus (in mg): young 113 ± 4 *vs* adult 129 ± 2 *vs* old 94 ± 9, $P < 0.05$). Similarly, maximum force of EDL and soleus muscles was greatest in adult rats, and significantly reduced in old rats (EDL (in mN): young 2737 ± 80 *vs* adult 3019 ± 40 *vs* old 1902 ± 210, $P < 0.05$; soleus (in mN): young 1373 ± 95 *vs* adult 1576 ± 35 *vs* old 1009 ± 159, $P < 0.05$). Treatment increased EDL muscle mass in young, adult and old rats by 23%, 23% and 40% respectively, with a concomitant increase in maximum force producing capacity. Treatment increased soleus muscle mass and maximum force producing capacity in young, but not adult or old rats.Treatment was associated with a significant increase in heart mass in young rats (743 ± 31 *vs* 868 ± 50 mg, $P < 0.05$), but not in adult or old rats.

Our findings indicate a muscle specific decrease in β-adrenergic responsiveness with age, with fast- but not slow-twitch skeletal muscle responding to low-dose administration of formoterol. We conclude that formoterol can restore muscle mass and strength of fast-twitch skeletal muscles in old rats without cardiac hypertrophy.

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