Anabolic effect of formoterol administration on skeletal muscle is not impaired by co-treatment with the β1-adrenoceptor antagonist CGP-20712A

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Skeletal muscle wasting and weakness is associated with numerous conditions and pathologies and poses a major public health problem (Lynch, 2011). We have determined that the β_2-adrenoceptor (β_2-AR) agonist formoterol has therapeutic potential for muscle wasting conditions, but off-target cardiovascular effects currently limit its clinical application (Leger, 2011). These off-target effects may be mediated through activation of β_1-ARs which are highly expressed in the myocardium and so blockade of β_1-ARs concurrent with formoterol treatment may obviate these effects (Molenaar, Chen & Parsonage, 2006). In this study we investigated the effect co-treatment of formoterol with the selective β_1-AR antagonist CGP-20712A on skeletal muscle. We tested the hypothesis that co-treatment of formoterol with CGP-20712A does not impair the normal anabolic effects of formoterol on skeletal muscle.

All experiments were approved by the Animal Ethics Committee of The University of Melbourne and conducted in accordance with the current Code of practice for the care and use of animals for scientific purposes, as stipulated by the National Health and Medical Research Council. Twelve week old male C57BL/6 mice (from the Animal Resources Centre, Canning Vale, Western Australia) were treated with saline (subcutaneous, *s.c.*, n=12), formoterol (*s.c.*, 100 $\mu g \cdot kg^{-1} \cdot day^{-1}$, n=12), CGP-20712A (1.5 $mg \cdot kg^{-1} \cdot day^{-1}$, via osmotic mini pump, n=12) or formoterol together with CGP-20712A (100 $\mu g \cdot kg^{-1} \cdot day^{-1}$ and 1.5 $mg \cdot kg^{-1} \cdot day^{-1}$ respectively, n=11) for 28 days to study the effects of co-treatment of these two drugs on cardiac and skeletal muscle morphology. At the end of treatment, mice were anaesthetized deeply with an intraperitoneal injection of sodium pentobarbital (60 $mg \cdot kg^{-1}$) and selected hindlimb muscles and the heart were excised and weighed. The mice were killed while anaesthetized deeply.

Preliminary results from these experiments show that CGP-20712A administration alone does not alter *tibialis anterior* (TA) and *gastrocnemius* (GAS) muscle mass compared with saline treated controls (TA: 55±0.3 *vs* 57.4±1.1 mg, P=0.19; and GAS: 158.4±4.4 *vs* 164.7±4.4 mg, P=0.32). Formoterol administration increased TA and GAS muscle mass by 20% and 23%, respectively (P<0.05), compared with saline treated controls. Co-treatment of formoterol with CGP-20712A increased muscle mass of TA and GAS by 16% and 19%, respectively (P<0.05), compared with CGP-20712A treated controls. No differences were observed in TA and GAS mass between formoterol and formoterol/CGP-20712A co-treated mice (TA: 66±0.9 *vs* 66.6±0.8 mg, P=0.66; GAS: 195±2.4 *vs* 196.7±3.3 mg, P=0.67). Heart mass was unaffected by treatment and averaged 141.9±4.3 mg in saline treated, 147.4±3.1 mg in formoterol treated, 141.1±5 mg in CGP-20712A treated and 157.4±6.3 mg in formoterol/CGP-20712A co-treated animals.

Our preliminary results suggest that co-treatment of mice with formoterol and CGP-20712A does not affect the normal anabolic response of skeletal muscle following formoterol administration.

Lynch, G.S. (Ed). (2011). *Sarcopenia Age-Related Muscle Wasting and Weakness: Mechanisms and Treatments*, Springer (Heidelberg) 480 p.

Leger, B., Koopman, R., Walrand, S., Gehrig, S. M., Murphy, K. T. and Lynch, G. S. (2011). *International Journal of Cardiology* **146**, 270-2.

Molenaar P, Chen L, Parsonage WA. (2006) Cardiac implications for the use of β2-adrenoceptor agonists for the management of muscle wasting. *British Journal of Pharmacology* **147:** 583-6.

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