Cardiovascular and skeletal muscle responses in orchidectomized rats following short-term chronic formoterol administration

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Sarcopenia the age-related loss of muscle mass and function is a major public health problem (Lynch 2011). Exercise, particularly resistance training, has been shown to slow the rate of sarcopenia, but such an intervention is not realistic for frail elders unable to walk or to rise from a chair unaided. Safe and effective pharmacological interventions that can attenuate the loss of muscle mass, promote strength and improve quality of life are needed urgently to address the problem of sarcopenia. We have identified that the β_2-adrenoceptor (β_2-AR) agonist, formoterol, has therapeutic potential for muscle wasting disorders, including sarcopenia, but off-target effects on the cardiovascular system currently limit its clinical application (Leger *et al*., 2011). A deeper understanding of the cardiovascular effects of these drugs will potentially allow us to selectively manipulate β-AR signalling in skeletal muscle without off-target effects on the heart, and is an important research question. In previous studies we have investigated effects of β-agonists on intact rats with normal circulating levels of androgens and anabolic hormones that contribute to the maintenance and growth of skeletal muscle. Circulating levels of these hormones decrease during ageing which may affect the skeletal muscle response to anabolic stimuli. In this study we investigated the effect of chronic formoterol administration on cardiovascular parameters in orchidectomised adult male rats and tested the hypothesis that the usual anabolic effects of formoterol on heart and skeletal muscle would be attenuated.

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. Male 15 week old castrated Sprague Dawley rats (from the Animal Resources Centre, Canning Vale Western Australia) were anaesthetized deeply with an intraperitoneal (*i.p.*) injection of ketamine (100 mg/kg) and xylazine (10 mg/kg) and instrumented with a surgically implanted radiotelemeter to study the cardiovascular effects of acute and chronic formoterol administration. Following a 14 day recovery period, rats received a daily injection of saline (1 $ml \cdot kg^{-1} \cdot day^{-1}$; n=4) for a period of seven days (control period) followed by 28 days of formoterol administration (100 $\mu g \cdot kg^{-1} \cdot day^{-1}$; n=4). Cardiovascular parameters measured included: mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP) and heart rate (HR). A second non-instrumented group of castrated rats were treated with saline (n=8) or formoterol (n=8) for 28 days to study effects on heart and skeletal muscle morphology. Twenty four hours after the final formoterol treatment rats were anaesthetized deeply with sodium pentobarbitone (60 mg/kg, i.p.) and selected hindlimb muscles and the heart were excised and weighed. All animals were killed as a consequence of cardiac excision while still anaesthetized deeply.

Formoterol administration increased absolute mass of the heart, *tibialis* anterior (TA), *soleus* and *gastrocnemius* muscles ($P<0.05$), but when normalized to body mass, heart, TA and *soleus* mass were not different from control. Formoterol administration acutely increased heart rate, an effect which was consistent throughout the entire treatment period ($P<0.05$). In contrast, formoterol acutely decreased blood pressure on day 1 of treatment ($P<0.05$); but the acute effect on blood pressure rapidly diminished with subsequent treatments and was completely absent by the end of the treatment period. These data reveal that contrary to our hypothesis, formoterol administration can increase skeletal muscle mass in orchidectomized rats to similar levels as we have reported previously in intact rats (Ryall *et al*., 2008). However, formoterol caused some cardiovascular alterations, even in the absence of changes in normalized heart mass.

Formoterol has powerful anabolic effects on striated muscle with obvious therapeutic potential for muscle wasting conditions. Understanding the mechanisms underlying these cardiovascular effects will help identify novel approaches to selectively manipulate β-AR signalling in striated muscles for clinical application .

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.

Ryall, J.G., Schertzer, J.D., Murphy, K.T., Allen, A.M. and Lynch, G.S. (2008). *American Journal of Physiology. Heart and Circulatory Physiology* **294**, H2587-H2595.

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