Inhibition of the renin-angiotensin system enhances whole body and skeletal muscle function in healthy and tumour-bearing mice

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Cancer cachexia describes the progressive skeletal muscle wasting and weakness in many cancer patients. Cancer cachexia impairs mobility, causes severe fatigue, and accounts for >20% of cancer-related deaths. The mechanisms underlying cancer cachexia are multifactorial and current treatments have proved ineffective as they have only targeted one of these mechanisms (Murphy & Lynch, 2009). Renin-angiotensin system (RAS) inhibition has typically been used in the treatment of hypertension, but recent evidence indicates that stimulation of RAS may contribute to skeletal muscle breakdown by a myriad of mechanisms, including inducing inflammation, causing insulin resistance, inducing skeletal muscle apoptosis, reducing protein synthesis and enhancing protein degradation. RAS inhibition may therefore preserve or enhance skeletal muscle strength and function and consequently, represents a potential therapeutic strategy for counteracting the skeletal muscle wasting and weakness associated with conditions such as cancer cachexia. We tested two hypotheses: i) that life-long RAS inhibition would enhance whole body and skeletal muscle function in healthy mice; and ii) that acute RAS inhibition would enhance whole body and skeletal muscle function in a commonly used murine model of cancer cachexia.

All experiments were approved by the Animal Experimental Ethics Committee of The University of Melbourne and conducted in accordance with the current codes of practice of the National Health and Medical Research Council (Australia). Animals were anaesthetised with sodium pentobarbitone (Nembutal, 60 mg/kg, *i.p.*) prior to assessment of muscle contractile properties and were later killed as a consequence of cardiac excision while anaesthetised deeply.

In study 1, 12 week old wild-type control mice (n=13) and those lacking the angiotensin type 1A receptor ($AT_{1A}^{-/-}$, n=15) were tested for whole body strength (grip strength) and function (rotarod), glucose sensitivity during a glucose tolerance test and maximum tetanic force production and fatiguability *in situ* of the *tibialis anterior* (TA) muscle (Murphy *et al.*, 2010). Compared with controls, $AT_{1A}^{-/-}$ mice exhibited a 17% higher grip strength (p<0.01) and a 49% prolonged latency-to-fall during a rotarod test (p<0.01). Glucose sensitivity was improved by 23-26% in $AT_{1A}^{-/-}$ mice (p<0.01). Maximum *in situ* forces (normalised to CSA) of TA muscles was higher by 25% in $AT_{1A}^{-/-}$ mice (p<0.05), but the force decline during fatiguing intermittent stimulation was not different between groups.

In study 2, 15 week old CD2F1 (Balb/c × DBA) mice bearing Colon-26 (C-26) tumour cells were treated for 14 days with the ACE inhibitor, Perindopril (4 mg/kg/day, n=4-7) *via* the drinking water. Control mice were given water alone (n=4-6). Perindopril prevented the decline in body mass in C-26 tumour-bearing mice (p<0.01), enhanced grip strength by 29% (p<0.05) and prolonged the latency-to-fall during a rotarod test by 56% (p<0.05). Glucose sensitivity was improved with Perindopril (p<0.01). Perindopril had no effect on maximum force of TA muscles *in situ* or of diaphragm muscle strips *in vitro*, but attenuated the decline in force during fatiguing intermittent stimulation in both TA muscles and diaphragm muscle strips (p<0.01).

RAS inhibition enhanced whole body and skeletal muscle function, and improved glucose sensitivity in healthy mice and in mice bearing C-26 tumours. These findings highlight the therapeutic potential of RAS inhibition for cancer cachexia and other diseases associated with skeletal muscle wasting and weakness.

Murphy KT & Lynch GS. (2009) *Expert Opinion on Emerging Drugs* **:** 619-632.

Murphy KT, Koopman R, Naim R, Léger B, Trieu J, Ibebunjo C & Lynch GS. (2010) *FASEB Journal* In Press (Jul 12, 2010) doi:2010.1096/fj.2010-158741.