

The role of physiology in understanding muscle wasting, adaptation and plasticity

G.S. Lynch, Basic and Clinical Myology Laboratory, Department of Physiology, The University of Melbourne, VIC 3010, Australia.

Muscle wasting is an urgent and unmet health risk associated with many diseases and conditions, including: sarcopenia linked with ageing and frailty, cancer cachexia, sepsis and other forms of catabolic stress, denervation after nerve injury, disuse atrophy with plaster casting (unloading), inactivity and microgravity, burns, HIV-AIDS, chronic kidney or heart failure, chronic obstructive pulmonary disease and the muscular dystrophies, especially Duchenne muscular dystrophy (DMD). These conditions are linked by the inflammation, atrophy and weakness common to their pathophysiology. The consequences of muscle wasting can be devastating and include weakness, impaired mobility and fatigue, reduced functional independence, and in the worst cases death (Lynch & Ryall, 2008; Lynch, 2010; Murphy & Lynch 2009).

Therapeutic strategies for attenuating muscle wasting and improving muscle function vary in their efficacy. Exercise and nutritional interventions have merit for slowing the rate of muscle atrophy in some conditions, but usually they cannot halt or reverse the wasting process. Hormonal and/or other drug strategies are needed that can target key steps in the molecular pathways that ultimately regulate protein synthesis and protein degradation. GH, IGF-I, testosterone, SARMs, and anabolic steroids have received limited acceptance clinically because of potential serious side effects with hormonal manipulation, highlighting the urgent need to identify non-hormonal treatments for these conditions.

Physiology plays an important role not only in the discovery of novel therapeutic targets but in the rigorous evaluation of newly developed drugs. Unfortunately, the preclinical testing of many emerging compounds is often unsatisfactory and incomplete due to inadequate testing of a drug's efficacy to modulate muscle phenotype sufficiently to enhance muscle function. Even many published evaluations of drugs and targets for muscle wasting fail to assess whether there are true functional benefits, such as enhanced muscle strength or power or an improved resistance to muscle fatigue. Comprehensive physiological evaluation enhances the potential for new drugs to proceed to the next phase of development – ultimately towards safe and effective therapies.

DMD is a severe and progressive muscle wasting disorder caused by mutations in the dystrophin gene resulting in the absence of the membrane stabilizing protein dystrophin. Muscle fibers are fragile and susceptible to a loss of Ca^{2+} homeostasis which activates inflammatory and degenerative pathways. Although considerable efforts are being directed to the development of gene and cell therapies for DMD, many obstacles currently prevent their clinical application. In the interim, alternative therapies that preserve muscle mass, promote muscle growth and enhance muscle regeneration must be developed.

Our recent studies showed that increasing intramuscular heat shock protein 72 (Hsp72) expression preserved muscle strength and ameliorated the dystrophic pathology in two mouse models of muscular dystrophy (Gehrig *et al.*, 2012). Treatment with BGP-15 (a pharmacological co-inducer of Hsp72 used clinically for diabetes; *N-Gene*) improved muscle architecture, strength, and contractile function of severely affected diaphragm muscles in *mdx* mice. In *dko* mice, a phenocopy of DMD exhibiting severe kyphosis, muscle weakness and premature death, BGP-15 reduced kyphosis and improved the dystrophic pathophysiology of limb and diaphragm muscles and, most importantly, extended lifespan. The results provide evidence that increasing Hsp72 expression in muscle has therapeutic potential for DMD and related muscle wasting conditions, either as a standalone therapy or as an adjuvant with other treatments. That study also highlighted the importance of rigorous complementary physiological evaluations of cellular (single fibre) preparations, isolated muscles *in vitro* and working muscles *in situ* (with an intact nerve and blood supply), supported by comprehensive histological, immunohistochemical and molecular biochemical assessments that can better test the therapeutic potential of emerging drugs for muscle wasting disorders.

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