Swings and roundabouts for muscle gain and loss: differences between sexes?

MAINTENANCE OF MUSCLE MASS results from a balance between muscle protein synthesis and breakdown, with a greater amplitude of changes in synthesis (±2-fold) than breakdown (±0.25-fold) during the diurnal cycle. Furthermore, adaptive changes in human muscle mass also seem to be largely the result of modulations in the rate of muscle protein synthesis. Contractile activity increases synthesis by two- to threefold for up to 2 days, and protein breakdown rises too but to a lesser extent. Consequently, net muscle protein balance becomes positive. In starvation and many situations of slow wasting associated with chronic diseases such as heart failure, there appear to be adaptive falls in synthesis and to a lesser extent breakdown, so the net balance is negative. Excessive rates of protein breakdown are only observed in cases of extreme muscle wasting, such as sepsis and burn injury. Long-term immobilization of human muscle is not associated with rapid breakdown (2–4); however, in the early stages, components of the ubiquitin-dependent proteasome proteolytic pathway are upregulated (6). An important distinction between studies of muscle in humans and rats, which have a much higher protein turnover rate, is that the responses may be more extreme in the latter. In fact, 28 days of complete bed rest resulted in a loss of only ~5% leg muscle mass (8), whereas 28 days of hindlimb unloading caused a 30% loss of rat gastrocnemius in the study by Sitnick et al. reported in the January issue of Journal of Applied Physiology (11).

Women are at a disadvantage with regard to muscle mass: they possess less muscle than men and appear to gain it more slowly with strength training (5, 10), the most potent hypertrophic stimulus yet known. The reasons for the differences are not clear, but the lack of “sufficient” testosterone is probably very important. The male hormone stimulates the rate of muscle protein synthesis and increases muscle size in a dose-dependent manner. Nevertheless, women may do better under some circumstances. For example, the loss of muscle mass that occurs during detraining is less in women than in men (5). What is still not clear, however, is the extent of any direct influence the female sex hormones have on this response. Sitnick and colleagues (11) make a useful contribution to our knowledge here and help us to better understand sexual dimorphism in the regulation of muscle mass. The authors investigated the effects of ovariectomy (Ovx) on changes in the mass of gastrocnemius muscle and activities of signalling proteins involved in regulating the translational phase of muscle protein synthesis during 28 days of hindlimb suspension and 14 days of reloading. Although complete removal of the ovaries eliminates the female-specific hormonal milieu thought to be responsible for most of the metabolic differences between men and women (aside from nonhormone-driven regulation, such as maybe different gene-expression patterns), the relevance of this model to human physiology is nonetheless limited: 1) ovaries produce a variety of hormones, and the production of some of those fluctuates not only throughout the life span but also on shorter terms during a menstrual cycle, pregnancy, and lactation; and 2) ovaries produce not only typical female but also the male hormone testosterone, the production of which is not lost at the onset of menopause, unlike that of the typical female reproductive hormones.

The most striking finding of this new study was that ovarian hormones, despite having no benefit (or adverse effect) in preventing muscle loss itself during hindlimb suspension, appeared to protect muscle from permanent damage in response to disuse. Although the rates of muscle protein synthesis and breakdown have not been measured, it is probably safe to speculate that Ovx did not modulate the response to unloading but likely inhibited protein synthesis during recovery, as the reduced amounts and phosphorylation of Akt and p70S6K thought to be required for protein synthesis suggest. Surprisingly, Ovx actually diminished the capacity of anabolic signaling already during unloading, an apparent discrepancy that is not explained. One likely explanation is that, during the catabolic phase of unloading when muscle protein synthesis is probably reduced, a decrease in anabolic signaling has no impact on the actual rate of protein synthesis, whereas a diminished signaling capacity likely does not enable muscle to revitalize protein synthesis during recovery and therefore is rate limiting for regrowth. It is also possible, however, that protein synthesis during immobilization was reduced to a greater extent in rats with Ovx, and this was accompanied by a relatively more accelerated protein breakdown that then resulted in the same net change of muscle mass. Puzzlingly, it has recently been shown that muscle loss during short-term (5 day) hindlimb casting occurs probably only as a result of accelerated breakdown, with markers of the ubiquitin-dependent proteasome proteolytic pathway being upregulated, but without a defect in protein synthesis and essential regulators of translational initiation and elongation (7). Hence, we can only speculate that a depression of Akt and p70S6K signaling as found in the present study (11) develops later during chronic disuse and not already in the early days when protein synthesis is found to be normal.

A dissociation between cell signals thought to be crucial for the maintenance of muscle mass and the actual changes of muscle mass may on reflection not be entirely unexpected. There is indeed evidence that phosphorylation of signaling elements at sites that are considered important for their activation does not always correspond with the activity of the immunoprecipitated enzyme in vitro (9), and possibly also not in vivo. The lack of such an association may be related to the timing of measurements. If the elements under investigation are needed to initiate, but not maintain, a metabolic pathway (i.e., protein synthesis), then they may have already returned to their basal status once the metabolic pathway they promote is measurably upregulated. Last, given the large number of possible cellular control points, we should consider our present knowledge limited at best. The element(s) chosen for investigation may not be the ones that play a regulatory role in mediating the outcome of interest after all. In that respect, Anthony et al. (1) have shown that leucine enhances protein synthesis in skeletal muscle through both insulin-dependent and -independent mechanisms. The insulin-dependent mechanism was associated with increased phosphorylation of 4E-BP1 and S6K1, whereas this was not a feature of the insulin-independent effect. In any case, such findings highlight the need for simultaneous assay of a range of sensing and signaling
elements plus the physiological readouts of mass change and muscle protein turnover.

Although it appears that Ovx had no effect on the extent of muscle loss during unloading in the study by Sitnick et al. (11), we have to consider that 28 days of doing so is a long time given the life span of a rat. Alterations in the initial rate of loss (e.g., a faster rate in rats without ovaries) could easily be masked.

In summary, Sitnick and coworkers (11) provide an important framework for future research and clearly demonstrate the direct involvement of female sex hormones in the control of muscle mass. Further clarification is needed to see to what extent the observations regarding alterations in muscle mass and intracellular signaling events in rats with Ovx are attributable to the variety of hormones (including the highly anabolic “male” testosterone) produced by the ovaries and how the Ovx-induced changes in anabolic signaling translate into changes of muscle protein synthesis mediating the changes in muscle mass.

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