Insulin and muscle protein turnover in humans: stimulatory, permissive, inhibitory, or all of the above?

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In 1969, Pozefsky et al. (8) reported on the effects of systemic insulin infusion on forearm amino acid and glucose uptake. They noted that a large increase in insulin from 12 to 157 μU/ml resulted in a significant lowering of forearm (muscle) “. . . alpha amino nitrogen release by 74%. . . declines in output were seen for leucine, isoleucine, tyrosine, phenylalanine, threonine, glycine . . .”. They concluded that “. . . declines in amino acid levels after systemic insulinization are due to inhibition of muscle release.” A number of landmark investigations since that original report by Pozefsky et al. have reached a similar conclusion (3, 5, 7). As such, it seems that one definitive effect of insulin with respect to muscle protein turnover is a suppression of proteolysis. The tougher part of the puzzle has been unraveling the effect that insulin has on muscle protein synthesis. When combining hyperinsulinemia and hyperaminoacidemia a number of reports have documented an apparent augmentation of protein balance (protein synthesis minus protein breakdown) due to a stimulation of synthesis and possibly an inhibition of breakdown (1, 2, 4, 9). In this issue of the Journal, Greenhaff et al. (6) report in an elegantly controlled study how graded doses of insulin with hyperaminoacidemia affect muscle protein synthesis, breakdown, and balance. Using both stable-isotope approaches with direct muscle protein incorporation, arterial-venous balance, and molecular mechanistic data, a potentially clearer picture emerges. The authors’ main conclusions are that amino acids are, in and of themselves, remarkably anabolic and can stimulate a marked rise in muscle protein synthesis even in the face of basal (i.e., 5 μU/ml) insulin. Thus, hyperaminoacidemia does not require hyperinsulinemia to exert a powerful anabolic effect. Infusion of insulin, in general, produced substantial rises in phosphorylation of the “usual suspects” thought to be related to protein synthesis: protein kinase B (Akt), mammalian target of rapamycin (mTOR), ribosomal protein p70 S6 kinase p70S6K, and eIF4E-binding protein-1 (4EBP-1), but no further rise in muscle protein synthesis was observed with insulin concentrations from 30 up to 167 μU/ml. Instead, muscle protein breakdown was suppressed (an effect fully manifested at 30 μU/ml), which was accompanied by reductions in some proteosomal pathway components. Hence, insulin is not even mildly anabolic with increasing doses above 5 μU/ml and is definitely antiproteolytic; however, beyond even moderate hyperinsulinemia (i.e., 30 μU/ml), there is no further effect on muscle protein balance. Thus, can we say at this point that insulin is simply permissive for protein synthesis and suppressive for protein breakdown, but you don’t need much of it to see this effect? These statements are perhaps a little premature? However, Greenhaff et al. (6) are to be congratulated for their combination of some powerful methods and for a well-conceived and conducted study. No doubt further work will shed even greater insight into insulin’s role in regulating muscle protein turnover.

REFERENCES