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RESPONSE TO COMMENT ON SMITH ET AL.

Protein Ingestion Induces Muscle Insulin Resistance Independent of Leucine-Mediated mTOR Activation. Diabetes 2015;64:1555–1563

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We appreciate Dr. Dioguardi's critical assessment (1) of our recently published article (2). We are a bit perplexed that he considered the outcome from our study predictable. Prompted by the results from intravenous amino acid infusion studies in people that demonstrated that amino acids blunt insulin-mediated glucose disposal (3,4) and studies conducted in cultured myotubes and isolated rat skeletal muscles that demonstrated that leucine can impair insulin-mediated glucose uptake (5,6), presumably mediated by mTOR-p70S6K phosphorylation and subsequent serine phosphorylation of insulin receptor substrate-1 (6), we tested the hypothesis that protein ingestion impairs insulin-mediated glucose disposal by leucine-mediated muscle mTOR signaling in people. We demonstrated that protein ingestion impairs whole-body and leg glucose disposal during a hyperinsulinemic-euglycemic clamp and found (rather unexpectedly) that the insulin-desensitizing effect of protein ingestion is not due to inhibition of AKT by leucine-mediated muscle mTOR signaling in people (2).

Dr. Dioguardi (1) suggests potential alternative mechanisms that could be responsible for the adverse effects of protein on glucose disposal (i.e., alanine- and arginine-mediated inhibition of glucose disposal) and argues that chronic supplementation with essential amino acids (including leucine) will actually improve insulin sensitivity. Although theoretically possible and to some degree supported by the results from studies of in vitro and animal models, the proposed mechanisms and potential beneficial effect of chronic amino acid supplementation remain speculation until rigorously tested in people, who, as we have shown, are always here to surprise us.

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