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Review

The regulation of muscle protein turnover in diabetes☆

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ABSTRACT

Diabetes cannot be considered simply a disease of glucose dysregulation; it is a chronic inflammatory disease that affects nearly every biological process, including protein metabolism. Diabetes is associated with disturbances in muscle protein metabolism that results in decreased muscle mass and in some cases, loss in the activities of daily living, decreased productivity and diminished quality of life. Alteration in protein metabolism and its effect on muscle mass and function is one of the most challenging and least understood issues in the management of diabetes. Central among insulin action in muscle is suppression of protein degradation pathways and up-regulation of anabolic pathways. In type 1 diabetes, muscle wasting essentially results from insulin deficiency and this induces of genes involved in the ubiquitin proteasome pathway. On the other hand, the chief defect that leads to muscle atrophy in type 2 diabetes is decreased insulin responsiveness primarily in muscle. Decreased insulin responsiveness has been attributed to defects in the insulin signaling pathways secondary to inflammation (e.g., NF-κB activation and elevated levels of TNF-α, IL-1 and IL-6), metabolic acidosis, increased circulating free fatty acids and glucotoxicity. Furthermore, emerging pathways, such as myostatin/activin A system are beginning to be uncovered. We conclude with a discussion of possible interventions to slow, mitigate or reverse muscle wasting associated with diabetes.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

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1. Introduction

The first known reference to diabetes comes from the medical papyrus that has survived ancient Egypt from the 15th century B.C. Even at that time, diabetes was described as a 'shrinking' disease, most likely referring to the decrease in body water and muscle mass associated with this affliction (Carpenter et al., 1998). The term diabetes is ascribed to the Greek physician Aretaeus, a contemporary of Galen; his classic description begins (Major and Classics of Medicine Library, 1994):

> Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and the limbs into urine...

These early descriptions are perceptive and address perhaps an under-appreciated complication of diabetes, namely muscle wasting. There are over 350 million people world-wide with diabetes and the epidemic will grow as societies modernize and obesity rates continue to climb (Whiting et al., 2011). Beyond the devastating cardiovascular sequelae of diabetes, the muscle wasting associated with this disease contributes to the loss in the activities of daily living, decreased productivity and diminished quality of life (Guillet et al., 2012; Ryerson et al., 2003).

Protein metabolism does not have a binary architecture (i.e., protein synthesis or catabolism); it summation of a complex set of signals that vary over the course of several hours and manifest over several months or years. Protein metabolism is inextricably linked to the amount of lean mass and muscle homeostasis because there is no other stored form of this energy substrate. Muscle is the largest reservoir for protein and the source of amino acids in the fasted state. It is also the largest reservoir for insulin stimulated glucose transport in humans. The relationship between protein metabolism, insulin resistance and body composition is complex since one often influences the other to varying degrees. The implications of muscle wasting, especially in countries with high prevalence, is difficult to quantify, but there is little doubt that it represents a significant social burden, decreased economic potential and an added stress to healthcare systems (Muscaritoli et al., 2010). We can gain clues to the alterations in protein metabolism by examining the body composition of patients with diabetes. In a number conditions, the presence of diabetes mellitus as a co-morbidity is the strongest predictor of muscle loss independent of clinically relevant variables such as age, gender, markers of malnutrition (Castaneda et al., 2000; Pupim et al., 2005; Suskin et al., 2000). Thus, it is critical to examine how diabetes affects protein metabolism and to develop treatments to mitigate or reverse its devastating consequences. In this article, we will review insulin's role in muscle homeostasis and observations in type 1 and 2 diabetes. We will include a discussion of cell biology of insulin signaling and muscle, and possible interventions to slow, mitigate or reverse muscle wasting associated with diabetes.

2. Type 1 diabetes

Insulin was to be characterized late in the 19th century by Paul Langerhans and just decades later Frederick Banting and Charles Best made tremendous advancements in therapy of patients with diabetes. What has become increasingly clear in the last several decades however, is that in addition to its effects on whole body glucose disposal, insulin has significant pleotropic effects on a number of tissues including muscle. Central among insulin action in muscle is suppression of protein degradation pathways and up-regulation of anabolic pathways. Insulin achieves its anabolic effect through several mechanisms. Experimentally (i.e., in cultured muscle cells and rodents) and in human subjects it has been shown that insulin administration inhibits protein breakdown, enhances amino acid uptake and stimulates protein synthesis (Biolo et al., 1995; Fryburg et al., 1995). The classic experiments by Atchley et al. (1933) are particularly enlightening and illuminate the effect of insulin on muscle metabolism. They found that insulin withdrawal in type 1 diabetics is associated with negative nitrogen balance in a pair of insulin-dependent subjects. These careful balance experiments made clear that insulin withdrawal resulted in significantly negative nitrogen balance, which was normalized only after insulin was restored. Other investigators have shown that protein synthesis is increased with insulin withdrawal, but that it is exceeded by the rate of protein breakdown resulting in negative protein balance (Hebert and Nair, 2010; Umpleby et al., 1986).

It is instructive to examine branched chain amino acids (BCAA), which include leucine, isoleucine and valine because they are significant components of muscle and key markers of muscle turnover. An inverse relationship exists between circulating effective insulin levels and blood BCAA concentrations. The first step in oxidation of BCAA is by branched chain α-ketoacid dehydrogenase (BCKD) activity and this enzyme and its active form is increased significantly in the absence of insulin. Furthermore, *resistance* to the metabolic effects of insulin has been reported with regard to amino acid turnover even when diabetic subjects are euglycemic. In normal subjects, insulin suppresses leucine (KIC) oxidation and this effect is blunted in insulin deficiency states (Tessari et al., 1986).

It is generally recognized that patients with type 1 diabetes (T1DM) at the time of diagnosis are less likely to be overweight compared to type 2 patients, and in fact demonstrate decreased lean and fat mass compared to age-matched controls (Rosenfalck et al., 2002). Often there is significant recovery of weight after insulin therapy is started. This was demonstrated in subjects enrolled in the intensive therapy arm of the DCCT who gained 4.7 kg on average after the first year of therapy (DCCT, 2001). Patients with T1DM who demonstrate excessive weight gain do so as a result of improved glycemic control. It should be noted that despite weight gain, intensive insulin therapy is associated with reduced microvascular and possibly macrovascular complications. These studies establish a clear link between insulin deficiency and muscle protein degradation.

3. How are proteins degraded within cells in T1DM?

Growth factors are down-regulated and cachexia factors are induced in the diabetic state. There are at least four major proteolytic pathways contributing to the loss of muscle protein. The four pathways are: lysosome-mediated protein degradation; intracellular proteolysis by calcium-activated proteases (calpains); ATP-dependent proteases (UPS plays a key role in this pathway); and poorly understood proteases that do not require energy to break down cellular proteins (Rajan and Mitch, 2008). In all cells, including muscle, UPS is the major proteolytic system that degrades proteins. The current model of muscle wasting in diabetes is linked to decreased insulin signaling and induction of genes involved in the Ub–proteasome pathway (Merforth et al., 1999).

3.1. Ub–proteasome pathway

As a result of insulin deficiency, insulin receptor substrate-1 (IRS-1) associated phosphatidylinositol 3-kinase (PI3K) activity is reduced (Mitch and Goldberg, 1996). Decreased PI3K activity impairs phosphorylation of Akt (pAkt) in muscle. Decreased pAkt leads to reduced phosphorylation of forkhead transcription factors (Fox O) which enter the nucleus and stimulate expression of key muscle-specific E3 ubiquitin ligases: atrogin-1/MAFbx (muscle atrophy F box) and MuRF1 (muscle RING finger 1). Activation of MAFbx and MuRF results in ubiquitin conjugation to protein substrates and these are recognized and degraded by the proteasome