Caloric balance and insulin action

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Decreased skeletal muscle insulin sensitivity is a common metabolic disorder of aging and obesity. Significantly, this muscle insulin "resistance" is a key contributor to the etiology of T2D, and increases an individual's risk of developing other metabolic diseases, such as cardiovascular disease and certain cancers. Considering the alarming increase in obesity and T2D in recent decades and the burgeoning aged population, understanding the cellular signals underlying muscle insulin resistance has the potential to significantly impact health.

Moderate caloric restriction (CR) robustly retards the onset of muscle insulin resistance during aging, and also reverses insulin resistance in the already aged or obese. Interestingly, brief CR (several days to a week) is equally as effective at improving muscle insulin action as long-term (month-to-years) CR, despite minimal weight loss. Similarly, brief overfeeding rapidly induces muscle insulin resistance, despite minimal weight gain. The fact that skeletal muscle is acutely sensitive to changes in nutrient flux suggests there are signaling changes and pathways intrinsic to the cell (in this case skeletal muscle) that translate perturbations in energy flux into a metabolic adaptation, such as altered insulin sensitivity.

In recent years, reversible acetylation, which is a post-translational modification (PTM) in which an acetyl group is added to a lysine residue, has been proposed to link metabolic flux to cellular signaling and the adaptive response. This is due to the fact that two fundamental metabolites central to cellular/energy metabolism, NAD^+ and acetyl CoA, are key substrates for the sirtuin (SIRT) deacetylases (DACs) and acetyltransferases (ACTs), respectively. DACs remove acetyl groups from lysine residues, whilst ACTs add them. Thus, it is generally thought that when NAD^+ is increased, such as when metabolic flux is reduced (*e.g.* during CR), that the activity of SIRTs is increased, thereby favouring increased protein deacetylation. In contrast, when acetyl CoA is increased, such as when metabolic flux is increased (*e.g.* during hypercaloric feeding), protein acetylation is favoured. In fact, mass spectrometry-based studies reveal that reversible protein acetylation is in essence as common a PTM as phosphorylation and ubiquitination, with many of the enzymes involved in glycolysis, the Kreb's cycle, fatty acid metabolism and the electron transport chain being reversibly acetylated. This has served to further emphasize the potential importance of reversible acetylation to cellular homeostasis. Despite an exponential increase in our understanding of the contribution of acetylation to cellular function, the precise role of acetylation to cellular metabolism and metabolic balance is only just been revealed, and much remains to be learned.