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Leptin- The Central Regulator of Starvation

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Humans have evolved to store energy in three major forms: carbohydrate, fat, and protein. In the liver, insulin triggers the storage of circulating glucose as glycogen, which can be readily mobilized to glucose and is the fuel of choice where instantaneous energy is required, such as during conditions of stress and the onset of starvation. However, liver glycogen accounts for <1% of the total stored energy. Skeletal muscle is also a major site of storage of glycogen (about 2/3 of the total glycogen) and protein and accounts for 15% of the total stored energy. The majority of energy stores, >80%, are in the form of fat, stored as lipid droplets in adipocytes[1]. Teleologically, this makes a lot of sense given that humans have been hunter-gatherers and had to go for prolonged periods of starvation in search of food. On the contrary, the modern man is exposed to a much more nutrient replete environment. The human body, however, is still adapted for efficiently storing any ingested nutrients as energy reserves in different tissues for periods of critical need such as starvation.

The pioneering studies by George Cahill Jr. [1]have well characterized the metabolic response to starvation in humans. During transition from fed to the early fasting stage, the body enters a catabolic phase of fuel mobilization orchestrated by low insulin levels. Liver glycogen stores are rapidly mobilized and are not sufficient to keep up with the body's energy demands. As insulin levels drop with prolonged starvation, counterregulatory hormones such as catecholamines trigger fat breakdown[2] and stimulate hepatic gluconeogenesis (the synthesis of glucose from non-carbohydrate precursors) and ketogenesis in order to maintain glucose homeostasis and a steady supply of substrates for critical tissues, such as the brain, that mainly depend on glucose utilization. Triacylglycerols in adipocytes (TAGs) are hydrolyzed into glycerol which is used as a substrate for gluconeogenesis, and free fatty acids which can be shuttled to the liver to be stored as Acetyl CoA and further metabolized to ketone bodies[3]. Thus during prolonged starvation, there is a shift from carbohydrate to fat metabolism.

Prolonged starvation also causes a drop in the levels of leptin, the adipocyte derived hormone which centrally regulates feeding behavior in mammals. A larger body of work has highlighted that starvation induced metabolic changes are driven by very low insulin levels (insulinopenia)[1] and partly by increased glucagon levels[4]. However, recent studies from the Shulman lab have shown that insulinopenia, alone is not sufficient, and that hypoleptinemia is also required to mediate the starvation induced metabolic shift[3]. These studies elegantly show that leptin regulates the glucose to fatty acid oxidation shift by integrating signals from hepatic gluconeogenesis and adipocyte lipolysis to maintain euglycemia during starvation. On similar lines, their previous work demonstrated that hypoleptinemeia drives HPA axis and triggers adipocyte lipolysis, which leads to increased hepatic gluconeogenesis in Type 1 diabetes. Leptin replacement was also shown to suppress hyperglycemia and correct the metabolic derangements in Type I diabetes[5]. In this current issue, Perry and Shulman discuss the current literature on leptin and describe their pioneering work[3,5] on leptin in regulating glucose homeostasis during starvation. These studies demonstrate the therapeutic potential of leptin,

going beyond its classical function of regulating food intake, in maintaining glucose homeostasis. These studies confirm that leptin replacement is a very attractive and promising therapy for treatment of diabetes. Whether leptin will be a panacea for metabolic disorders remains to be further warranted.

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