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Reviews

Cellular mechanisms regulating fuel metabolism in mammals: Role of adipose tissue and lipids during prolonged food deprivation

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ABSTRACT

Food deprivation in mammals results in profound changes in fuel metabolism and substrate regulation. Among these changes are decreased reliance on the counter-regulatory dynamics by insulin-glucagon due to reduced glucose utilization, and increased concentrations of lipid substrates in plasma to meet the energetic demands of peripheral tissues. As the primary storage site of lipid substrates, adipose tissue must then be a primary contributor to the regulation of metabolism in food deprived states. Through its regulation of lipolysis, adipose tissue influences the availability of carbohydrate, lipid, and protein substrates. Additionally, lipid substrates can act as ligands to various nuclear receptors (retinoid x receptor (RXR), liver x receptor (LXR), and peroxisome proliferator-activated receptor (PPAR)) and exhibit prominent regulatory capabilities over the expression of genes involved in substrate metabolism within various tissues. Therefore, through its control of lipolysis, adipose tissue also indirectly regulates the utilization of metabolic substrates within peripheral tissues. In this review, these processes are described in greater detail and the extent to which adipose tissue and lipid substrates regulate metabolism in food deprived mammals is explored with comments on future directions to better assess the contribution of adipose tissue to metabolism.

1. Introduction

Regulation of metabolism has been largely associated with the liver because it serves as a critical target for most hormones to mediate their functions. However, in recent years adipose tissue has received greater attention due to increased understanding of its endocrine capabilities and its influence over insulin sensitivity [1–4]. In addition to being the storage site for triacylglycerols (TAG), adipose tissue also secretes various adipokines such as leptin, adiponectin, and

Abbreviations: AMPk, AMP kinase; ATGL, Adipose Triglyceride Lipase; BCAA, Branched chain amino acid; CD36, Fatty acid Translocase; DAG, Diacylglycerol; DHA, Dihydroxyacetone; DGAT, Diglyceride acyltransferase; EGP, Endogenous glucose production; FAS, Fatty acid Synthase; FATP, Fatty acid Transport Protein; G3P, Glycerol-3-phosphate; GK, Glycerol Kinase; GLUT4, Glucose transporter type 4; HSL, Hormone-sensitive Lipase; LCFA, Long chain fatty acid;; LPL, Lipoprotein Lipase; LXR, Liver X Receptor; MAG, Monoacylglycerol; MGAT, Monoglyceride acyltransferase; MGL, Monoglyceride Lipase; MUFA, Monounsaturated fatty acid; PEPCK-c, Phosphoenolpyruvate Carboxykinase-cytosolic; PPAR, Peroxisome Proliferator-activated Receptor; RAR, Retinoic Acid Receptor; RQ, Respiratory Quotient; RXR, Retinoid X Receptor; SFA, Saturated fatty acid; SNS, Sympathetic nervous system; SREBP, Sterol regulatory element-binding protein; TAG, Triacylglycerol.

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apelin, which modulate insulin sensitivity by regulating the utilization of plasma lipids [4–6]. Through the breakdown of stored TAG, adipose tissue also releases free fatty acids (FFA) and glycerol. FFA can be directly oxidized to generate ATP while glycerol can be used as a substrate in gluconeogenesis or lipogenesis. In this manner, adipose tissue can directly and indirectly modulate the availability of other metabolic substrates.

When mammals endure food deprivation, significant changes to metabolism occur to promote the preservation of metabolic substrates [7]. These changes were identified as the three phases of starvation, and characterized by the predominant catabolism of a single class of substrate: 1) carbohydrate, 2) lipid, and 3) protein [8,9] (Fig. 1). Because carbohydrate stores are depleted within a matter of hours, metabolism must transition to reliance on lipids to meet energetic demands [7,9]. Mammals adapted to prolonged food deprivation, like seals and bears, transition to a metabolism primarily reliant on lipid oxidation as part of their natural life history [10–14]. However, other mammals (e.g., humans and rodents) that are not adapted are incapable of shifting to a completely lipid-dependent metabolism [15]. This can be due to either improper regulation of substrates during fasting (Phase I or II), or simply inadequate lipid stores.

Whatever the case, the inability to transition results in protein catabolism and lean tissue degradation (cachexia) for energy. If not prevented, cachexia can eventually lead to death. These distinctions in lipid metabolism during phase II and III of Cahill's model of starvation provide the basis for differentiating the adapted mammals' ability to fast versus the non-adapted mammals' endurance of starvation [16].

In the past, research concerning metabolic regulation during food deprivation focused on hormonal control at the systemic level, allowing for the characterization of the typical endocrine response to fasting [8,9,17]. However, because most endocrine factors that regulate metabolism postprandially have reduced roles in food-deprived mammals [18], considerable investigation has focused on the contributions of intracellular mechanisms of substrate regulation to metabolism [19–22]. Though the majority of this work has been done in humans and rodents during feeding or short term fasting, data from mammals that endure prolonged bouts of food deprivation, like seals, suggest that lipid substrates may have the same regulatory effects [10,13,23].

As the principal storage site of lipids, adipose tissue must contribute to metabolic regulation under food-deprived conditions. Therefore, understanding its contributions, from the systemic to the molecular level, is important to assess metabolic regulation during food deprivation in mammals. Because hepatic regulation of metabolism is prominent, a better understanding of the cross-talk between the liver and peripheral tissues would be useful.

Therefore, this review focuses on the regulation of substrate availability by adipose tissue, the influence by the liver on this regulation, and how this may assist in the regulation of fuel metabolism in prolong-fasted mammals.

2. Mechanisms regulating substrate availability

Most mammals suppress sympathetic nervous system activity [24,25], various endocrine factors that regulate postprandial metabolism [18], and the activity of adipokines [26], in order to reduce energy expenditure under food deprived states. Food deprivation also increases the concentrations of slow-acting hormones like cortisol or biomolecules like retinoic acid that control the expression of genes within the liver, adipose, and other peripheral tissues to generate metabolism-regulating proteins like lipases or fatty acid transporters [27,28]. These proteins are responsible for shifting metabolism and maintaining the availability and utilization of substrates within a tolerable range. Therefore, the regulation of their activity and expression is of critical importance to the survival of the organism.

2.1. *Lipolysis*

Intracellular lipases are responsible for breaking down the stored TAG molecules to release three FA and glycerol. Adipose triglyceride lipase (ATGL), hormone-sensitive lipase

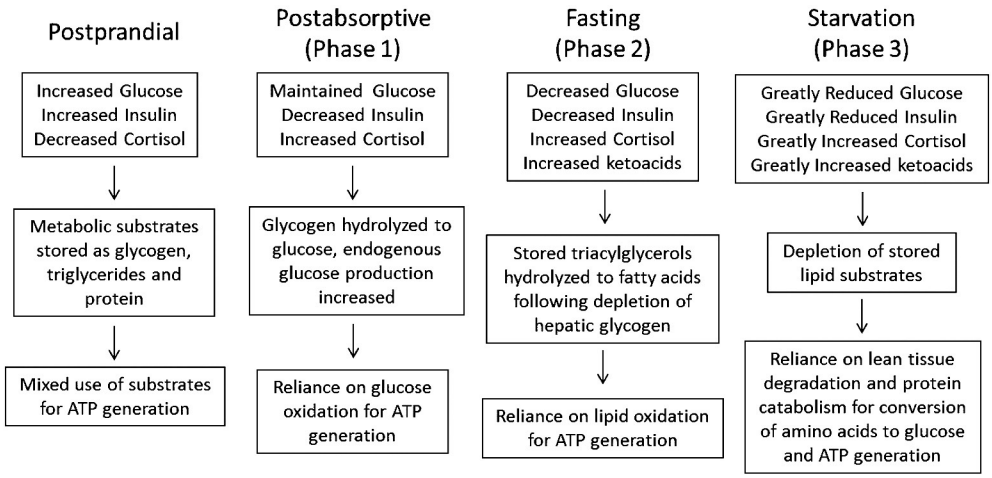

Fig. 1 – Comparison of the changes to key metabolic parameters in mammals under postprandial, postabsorptive, fasting, and starving conditions.