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Invited review

The adipocyte as an endocrine organ in the regulation of metabolic homeostasis

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ABSTRACT

Over the past decade and a half it has become increasingly clear that adipose tissue is a much more complex organ than was initially considered and that its metabolic functions extend well beyond the classical actions of thermoregulation and of storage and release of fatty acids. In fact, it is now well established that adipose tissue plays a critical role in maintenance of energy homeostasis through secretion of a large number of adipokines that interact with central as well as peripheral organs such as the brain, liver, pancreas, and skeletal muscle to control diverse processes, such as food intake, energy expenditure, carbohydrate and lipid metabolism, blood pressure, blood coagulation, and inflammation. While many of these adipokines are adipocyte-derived and have a variety of endocrine functions, others are produced by resident macrophages and interact in a paracrine fashion to control adipocyte metabolism. It is also abundantly clear that the dysregulation of adipokine secretion and action that occurs in obesity plays a fundamental role in the development of a variety of cardiometabolic disorders, including the metabolic syndrome, type 2 diabetes, inflammatory disorders, and vascular disorders, that ultimately lead to coronary heart disease. Described herein are the traditional as well as endocrine roles of adipose tissue in controlling energy metabolism and their dysregulation in obesity that leads to development of cardiometabolic disorders, with a focus on what is currently known regarding the characteristics and roles in both health and disease of the adipocyte-derived adipokines, adiponectin, leptin, resistin, and retinol binding protein 4, and the resident macrophage-derived adipokines, tumor necrosis factor-α and interleukin-6.

This article is part of a Special Issue entitled 'Central Control of Food Intake'.

1. Introduction

The classical roles of adipose tissue are to insulate and cushion the body, to store free fatty acids (FFA) after food intake, and to release FFAs during periods of fasting to ensure sufficient energy availability (Hajer et al., 2008). Adipocytes are the only cells that are specifically adapted to store lipids without compromising their functional integrity and have all of the enzymatic machinery necessary to synthesize fatty acids, to store triglycerides during periods of abundant energy supply, and to mobilize them via lipolysis when there is a calorie deficit (Fonseca-Alaniz et al., 2007). For example, during the postprandial phase, FFAs are taken up from the blood by adipocytes, after hydrolysis of the triglycerides contained in circulating triglyceride-rich lipoproteins by extracellular lipoprotein lipase (LPL), and are then converted back to triglycerides intercellularly for storage (Hajer et al., 2008). Mobilization of this reserve during periods of fasting occurs through hydrolysis of these intracellular triglycerides by hormone-sensitive lipase (HSL) (Hajer et al., 2008). Insulin is the primary regulator of adipocyte fat content, since it is both a potent inhibitor of HSL and an important activator of LPL (Hajer et al., 2008).

The central nervous system takes part in regulation of these two processes by means of direct or indirect neural activity. The autonomic nervous system acts directly on adipose tissue through both the sympathetic and parasympathetic systems (Fonseca-Alaniz et al., 2007). The sympathetic system promotes catabolic actions

Abbreviations: AAPL1, adaptor protein containing pleckstrin homology domain, phosphotyrosine binding domain and leucine zipper motif; AdipoR, adiponectin receptor; AMPK, 5'-AMP-activated protein kinase; BAT, brown adipose tissue; CETP, cholesterol ester transfer protein; FFA, free fatty acid; HDL, high-density lipoprotein; HMW, high molecular weight adiponectin; HSL, hormone-sensitive lipase; IL6, interleukin-6; IRS, insulin receptor substrate; JAK, janus kinase; LDL, low-density lipoprotein; LMW, low molecular weight adiponectin; LPL, lipoprotein lipase; LR, leptin receptor; NFκB, nuclear factor kappa-light-chain-enhancer of activated B-cells; PI3, phosphoinositol-3; PTP1B, protein-tyrosine phosphatase-1B; RBP4, retinol binding protein-4; RELM, resistin-like molecule; SAT, subcutaneous adipose tissue; siRNA, small interfering RNA; SOCS3, suppressors of cytokine signaling-3; STAT, signal transducer and activator of transcription; T2DM, type 2 diabetes; TNFα, tissue necrosis factor-α; UCP1, uncoupling protein-1; VAT, visceral adipose tissue; VLDL, very low-density lipoprotein; WAT, white adipose tissue.

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(e.g. lipolysis) via β-adrenergic stimulation, which activates HSL (Penicaud et al., 2000), whereas the parasympathetic system promotes anabolic actions by increasing insulin production and increasing tissue glucose and fatty acid uptake (Kreier et al., 2002).

Adipose tissue contains adipocytes as well as many additional cell types, including endothelial cells, fibroblasts, pericytes, monocytes, macrophages, and preadipocytes (Ahima and Flier, 2000). These additional cells, which are collectively termed "stromal vascular cells", account for a significant portion of the total cell number in adipose tissue, and can be separated from adipocytes using protocols that involve collagenase digestion followed by flotation of the adipocyte fraction using low centrifugal force (Rodbell, 1964). These stromal vascular cells exert a number of important functions for adipose tissue homeostasis. For example, endothelial cells and pericytes make up the vasculature of tissues and enable processes such as adipose tissue growth and development (Brakenhielm et al., 2004; Rupnick et al., 2002), monocytes and macrophages present in adipose tissues are thought to aid in the clearance of necrotic adipocytes, a role of increasing importance in the adipose tissue of obesity (Cinti et al., 2005), and adipose tissue macrophages are responsible for the increased adipose tissue inflammatory cytokine production in obesity (Weisberg et al., 2003; Xu et al., 2003). Adipose tissue is also a reservoir of pluripotent stem cells (Zuk et al., 2002) that contribute to the pools of stromal vascular cells and adipocytes.

2. Adipose tissue type and distribution

In mammals, two fundamentally different types of adipose tissue can be differentiated histologically, white adipose tissue (WAT) and brown adipose tissue (BAT), and their adipocytes exhibit important differences. White adipocytes are found in WAT tissue and contain large unilocular lipid droplets, suggesting an enhanced capacity for lipid storage (Trujillo and Scherer, 2006). Mature white adipocytes store triglycerides in a single large lipid droplet that occupies the center of the cell and accounts for 85–90% of the mass of the cell (Fonseca-Alaniz et al., 2007). During their development, young adipocytes contain multiple small lipid droplets, that coalesce to form a single lipid inclusion as the cell matures (Fonseca-Alaniz et al., 2007). Although they have variable volume, mature white adipocytes are large cells, hundreds of times larger than, for example, immune cells, hepatocytes, and skeletal muscle cells, and their size can change dramatically depending on the quantity of triglycerides they accumulate (Fonseca-Alaniz et al., 2007). In contrast, brown adipocytes in BAT contain many cytoplasmic lipid droplets of varying sizes, relatively abundant cytoplasm, spherical and mildly eccentric nuclei, and many mitochondria that release heat via oxidation of fatty acids (Cannon and Nedergaard, 2004). Brown adipocytes are on average 30–40 μm in diameter and are smaller than those of WAT, which average 60–100 μm in diameter (Fonseca-Alaniz et al., 2007), and function primarily in non-shivering thermogenesis (Trujillo and Scherer, 2006). The expression of uncoupling protein-1 (UCP-1) and an increased presence of mitochondria in brown adipocytes are two distinguishing features of BAT.

2.1. Brown adipose tissue

BAT is specialized for heat production, which occurs through the action of UCP-1, which is located in the internal mitochondrial membrane and acts as a proton channel, discharging the potential generated by the accumulation of protons in the mitochondrial intermembrane space, diverting them from ATP synthase and allowing the potential energy to be dissipated as heat (Cannon and Nedergaard, 2004). The high concentration of cytochrome oxidase in the mitochondria of brown adipocytes contributes to their darker color (Fonseca-Alaniz et al., 2007).

Although the relevance of BAT for adult rodents is widely appreciated, it was originally thought that BAT, which is present in human fetuses and newborn infants, was absent in adult humans. It is now know that substantial amounts of brown adipocytes exist throughout life in human adipose tissue (Krief et al., 1993; Nedergaard et al., 2007). Whether the presence of brown adipocytes in WAT is a consequence of trans-differentiation of white adipocytes to brown adipocytes or is the result of *de novo* differentiation of preadipocytes to brown adipocytes within white adipocyte depots is unclear (Himms-Hagen et al., 2000).

2.2. White adipose tissue

WAT is the predominant type of adipose tissue in mammals (Flier, 2004). WAT is composed primarily of adipocytes, surrounded by loose connective tissue that is highly vascularized and innervated, and contains fibroblasts, macrophages, adipocyte precursors, and various other cell types (Ahima, 2006). While the largest WAT depots are found in the subcutaneous region and around viscera, WAT has a generalized distribution throughout the body, surrounding and infiltrating the subcutaneous region, visceral organs, and a variety of muscle groups where it offers mechanical protection, softening impacts and allows muscle fibers to slide over each other without compromising their functional integrity (Fonseca-Alaniz et al., 2007). While its participation in thermogenesis is negligible, WAT is an excellent thermal insulator, and therefore plays an important role in conservation of body temperature.

WAT provides a limitless capacity for the storage of triglycerides that is vital for survival. The concomitant rise in insulin, glucose, and lipids during meals stimulates triglyceride formation and storage in liver and WAT (Ahima, 2006). By contrast, the fall in insulin during fasting stimulates glycogen breakdown and lipolysis, through activation of the sympathetic nervous system and elevation of glucagon, epinephrine, and glucocorticoids (Ahima, 2006). Increased glycogen breakdown during fasting maintains glucose supply to the brain and vital organs, whereas fatty acids released from adipose tissue during fasting are partially oxidized by skeletal muscle and liver, generating ketone bodies that serve as an alternate source of fuel for the brain and peripheral organs (Ahima, 2006).

In addition to its important functions mentioned above, WAT also possesses an exceptionally active secretory system, whose function is not only to release products of a variety of housekeeping genes, but also to release many endocrine and paracrine factors that are commonly referred to as adipokines. These adipokines, whose actions are central to the dynamic control of energy metabolism, communicate the nutrient status of the organism to the tissues responsible for controlling energy intake and expenditure, thus allowing the adipocyte to regulate processes in peripheral tissues such as the liver and skeletal muscle, in tissues of the central nervous system such as the hypothalamus, and in neighboring adipocytes and other cell types contained within the adipose tissue (Galic et al., 2010; Trujillo and Scherer, 2006).

White adipose tissue is distributed across a large number of different depots in the body that are classified anatomically as subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT is primarily located in deposits below the skin in the abdominal, gluteus and femoral areas, whereas VAT includes depots of fat deposited close to or even within the viscera of the abdominal cavity (Fonseca-Alaniz et al., 2007). Examples of VAT are mesenteric, omental and retroperitoneal fat.

A variety of studies have reported depot-specific differences in the expression of developmental genes that are maintained after