Review

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Lipolysis in lipid turnover, cancer cachexia, and obesity-induced insulin resistance

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Triglycerides in adipose tissue are rapidly mobilized during times of energy needs via lipolysis, a catabolic process that plays important role in whole body triglyceride turnover. Lipolysis is regulated through cell surface receptors via neurotransmitters, hormones, and paracrine factors that activate various intracellular pathways. These pathways converge on the lipid droplet, the site of action of lipases and cofactors. Fat cell lipolysis is also involved in the pathogenesis of metabolic disorders, and recent human studies have underscored its role in disease states such as cancer cachexia and obesity-induced insulin resistance. We highlight here topics and findings with physiological and clinical relevance, namely lipid turnover in human fat cells and the role of lipolysis in cancer cachexia and obesity-induced insulin resistance.

Adipose tissue lipolysis, a key process in energy balance and pathological states

Adipose tissue is the major body repository of energy. It exerts a buffering activity for energy imbalance at the cellular and whole-organism levels, storing energy in the form of triglycerides during periods of excess energy intake, and releasing it in the form of non-esterified fatty acids (FAs) for other organs during fasting. The understanding of the cellular and molecular factors regulating these metabolic processes is in constant evolution. Recent discoveries have dramatically altered the view of adipose tissue lipolysis (see Glossary) and have highlighted the importance of additional molecular factors regulating this process. Elucidating their mode of action may lead to novel therapeutic targets for the treatment of metabolic disorders [1–3]. This review is devoted to recent advances in the understanding of the role of lipolysis in normal and pathological states in humans.

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Short-term regulation of fat cell lipolysis

Over the years our understanding of the pathways involved in the short-term neural and hormonal control of lipolysis has dramatically increased (Figure 1). Sympathetic and sensory nerve fibers innervate white adipose tissue and modulate lipolysis, but the existence of parasympathetic innervation is a much-debated question [4]. Noradrenaline released from sympathetic nerves stimulates lipolysis through β-adrenoceptors, which are positively coupled to adenylyl cyclase through stimulatory G proteins (G_s proteins). This results in cAMP-dependent activation of protein kinase A (PKA). Another sympathetic nervous system neurotransmitter, neuropeptide Y, inhibits lipolysis through inhibitory G protein (G_i protein)-coupled receptors. Regarding endocrine factors, adrenaline, natriuretic peptides, and insulin are major regulators of lipolysis in human adipose tissue [2]. The ratio between lipolytic β- and antilipolytic

Glossary

Adipose tissue lipolysis: the catabolic pathway in the fat cell that leads to the sequential breakdown of triglycerides, diglycerides, and monoglycerides into one molecule of glycerol and three molecules of fatty acids.
Adipocyte triglyceride lipase (ATGL): an enzyme that catalyzes the first rate-limiting step in fat cell lipolysis, in other words the breakdown of triglycerides into diglycerides.
Cell death-induced DNA fragmentation-factor-α-like effector A (CIDEA): a protein associated with the lipid droplet in human fat cells. Enhanced expression of CIDEA may contribute to decreased basal lipolysis.
Comparative gene identification 58 (CGI58): a cofactor enhancing ATGL activity upon interaction with the enzyme. It also interacts with the lipid droplet binding protein, perilipin 1.
Familial combined hyperlipidemia (FCHL): a common, inherited metabolic disorder characterized by high blood cholesterol and triglyceride levels. Patients with this condition are at increased risk of early cardiac failure.
G0/G1 switch protein 2 (G0S2): a negative cofactor of ATGL and important regulator of lipolysis in adipocytes.
Hormone-sensitive lipase (HSL): an enzyme expressed at high levels in adipose tissues and displaying a high affinity for diglycerides as substrates.
Perilipin 1: the most abundant phosphorylated protein in the adipocyte. It is associated with lipid droplets and plays an essential role in the control of lipolysis. A decrease in perilipin 1 expression allows access of the lipases to the lipid droplet and leads to enhanced lipolysis.
Tumor necrosis factor α (TNFα): is produced by a wide variety of cell types, notably macrophages and adipocytes. It regulates several processes linked to immune response and inflammation as well as metabolic ones such as adipose tissue lipolysis.
Zinc-α2-glycoprotein (ZAG): is produced not only by some tumors but also by adipose tissue in conditions of cancer cachexia and calorie restriction. It modulates adipose tissue lipolysis.

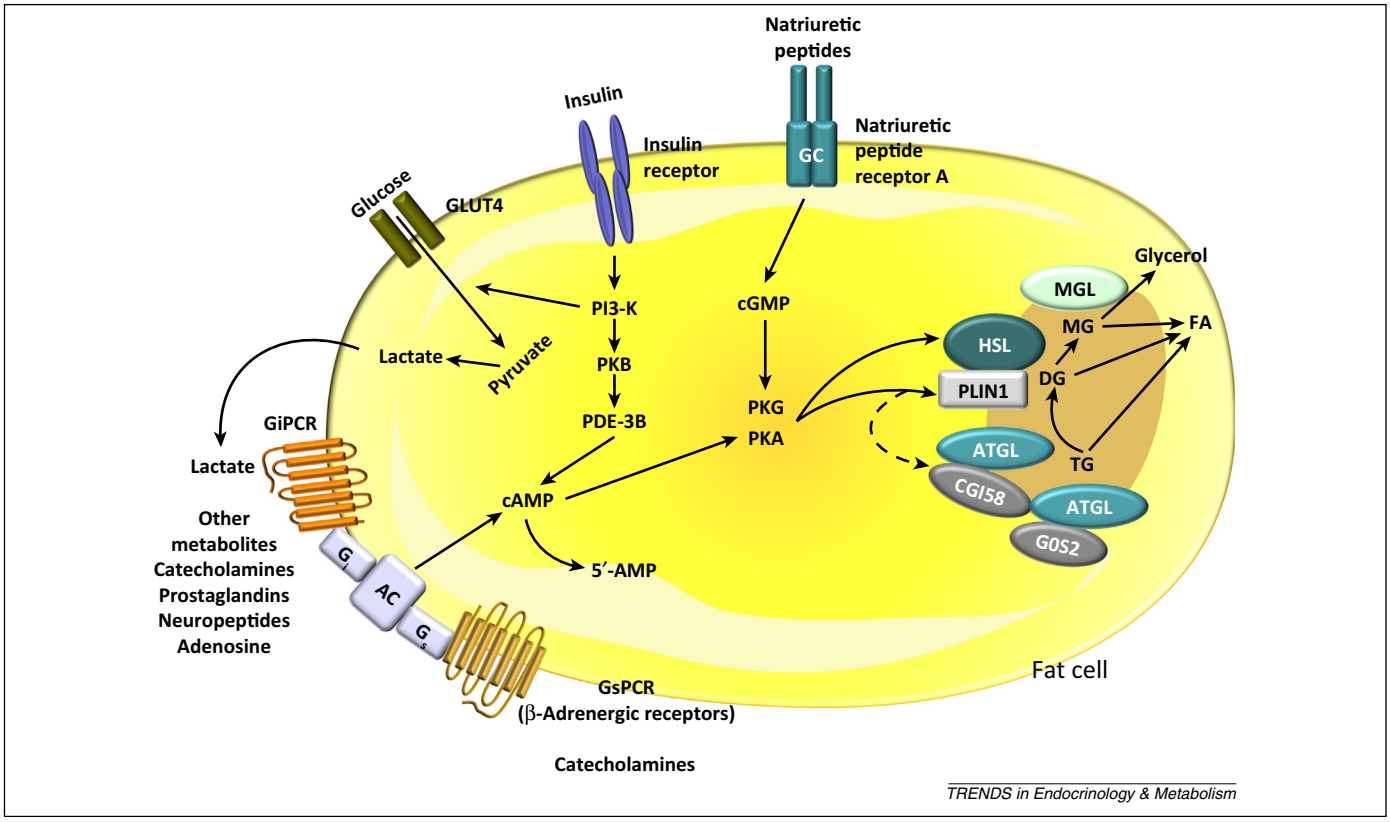

Figure 1. Overview of lipolysis regulation in human fat cells. Signal transduction pathways for catecholamines via adrenergic receptors, autacoid- and metabolite-driven inhibitory receptors, and atrial natriuretic peptides via type A receptor (NPR-A). Protein kinases A and G (PKA and PKG) phosphorylate target protein such as hormone-sensitive lipase (HSL) and perilipin 1 (PLIN). PLIN phosphorylation is a key event in the sequential activation of triglyceride (TG) hydrolysis involving adipose triglyceride lipase (ATGL), HSL, and monoglyceride lipase (MGL). Insulin, through activation of phosphodiesterase-3B (PDE-3B), inhibits catecholamine-induced lipolysis via the degradation of cAMP, whereas it is not active on cGMP-dependent pathways (natriuretic peptide pathway). Other abbreviations: AC, adenylyl cyclase; CGI58, comparative gene identification 58; DG, diglyceride; FA, fatty acid; G_i, inhibitory GTP-binding protein; GPCR, G protein-coupled receptor; G_s, stimulatory GTP-binding protein; G0S2, G0/G1 switch 2; GC, guanylyl cyclase; GLUT4, glucose transporter 4; MG, monoglyceride; PI3-K, phosphatidylinositol-3 phosphate kinase.

α2-adrenoceptors determines the net effect of adrenaline, which can stimulate or inhibit lipolysis. This ratio varies according to the location of the fat depots. For example, the predominance of α2- over β-adrenoceptors explains the marked resistance to adrenaline of femoral adipose tissue lipolysis [2,5].

Atrial and brain natriuretic peptides are potent activators of human fat cell lipolysis (Figure 1), acting through natriuretic peptide receptor A which possesses guanylyl cyclase activity [6]. The resulting production of cGMP activates protein kinase G (PKG). Physical exercise is a physiological condition with increased plasma atrial natriuretic peptide levels and stimulation of lipid mobilization. After a meal, the suppression of lipolysis is due to the rise in plasma insulin levels. The signal transduction pathway results in activation of phosphodiesterase 3B, which hydrolyzes cAMP into inactive 5′-AMP and thereby diminishes PKA-mediated phosphorylation. Recently, another mechanism involving lactate-mediated activation of an antilipolytic receptor was identified [7]. Fat cells produce lactate in significant amounts, especially when glucose uptake is stimulated. In an autocrine/paracrine loop, lactate activates the G_i protein-coupled hydroxycarboxylic acid receptor 1 (HCA1). Thereby, lactate counteracts the lipolytic effect of catecholamines mediated by β-adrenoceptors.

The physiological significance of several other antilipolytic receptors activated by paracrine factors revealed from *in vitro* studies remains to be elucidated. One of the G_i protein-coupled receptors, HCA2 (hepatocellular carcinoma-associated antigen 2, a nicotinic acid receptor; also known as MAGEC3, melanoma antigen C3), deserves special attention [8]. Its endogenous ligand is the ketone body, β-hydroxybutyrate, whose plasma levels rise during fasting. Activation of this receptor could serve as a negative feedback loop to mitigate the rate of lipolysis during long-term fasting and starvation, and prevent a massive efflux of FAs into the bloodstream that may be detrimental. Nicotinic acid and other antilipolytic analogs, which have been used as drugs to correct dyslipidemia, activate HCA2. The major side effect of nicotinic acid therapeutic use is skin flushing due to HCA2-mediated activation of epidermal Langerhans cells. New-generation agonists devoid of flushing effect targeting HCA1 or HCA2 have been identified [9,10].

Intracellularly, the lipolytic pathways converge on either PKA or PKG, which phosphorylate several proteins interacting with the lipid droplet. The unilocular cytosolic lipid droplet of white adipocytes is composed of a core of triglycerides surrounded by a monolayer of phospholipids and lipid droplet-associated proteins, including structural proteins and enzyme coactivators [11]. At the lipid droplet surface, triglycerides are sequentially hydrolyzed into diacylglycerol, monoacylglycerol, and glycerol, releasing one molecule of FA at each step. Three enzymes work in a stepwise fashion to ensure complete hydrolysis of triglyceride: adipose triglyceride lipase (ATGL), hormone-sensitive lipase