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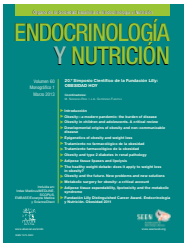

20.º SIMPOSIO CIENTÍFICO OBESIDAD HOY

Adipose tissue lipases and lipolysis

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White adipose tissue (WAT) is the major body energy repository in mammals. WAT exerts a buffering activity for energy imbalance at the cellular and whole-organism levels, storing energy in the form of triacylglycerol (TAG) in period of excess energy intake and releasing it in the form of non esterified fatty acids (NEFA) for other organs during fasting. While TAG synthesis occurs in various tissues, the release of fatty acids (FA) as energy provider for other tissues is unique to adipocytes. Lipolytic and antilipolytic molecules activate receptors present at the surface of the fat cell. Catecholamines (the neurotransmitter, noradrenaline, and the hormone, adrenaline), natriuretic peptides and insulin are considered to represent the major regulators of lipolysis in humans (Fig. 1). The physiological significance of a number of other lipolytic and antilipolytic agents, especially paracrine and autocrine factors, has yet to be established.[1]

During lipolysis, intracellular TAG is sequentially hydrolyzed into diacylglycerol (DAG), monoacylglycerol (MAG) and glycerol, releasing one molecule of FA at each step. Three major lipases are involved: adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MGL). Other lipases may play a minor role. NEFA and glycerol efflux from the fat cells is followed by transport of these metabolites in the bloodstream to other tissues (mainly liver for glycerol, and skeletal muscle, liver and heart for NEFA). Some of the NEFA that are formed during lipolysis do not leave the fat cell and can be re-esterified into intracellular TAG. The glycerol formed during lipolysis is not re-utilized to a major extent by white fat cells because they contain minimal amounts of the enzyme glycerol kinase necessary for its metabolism. However, expression of the enzyme can be stimulated thereby allowing a futile cycle of lipolysis and reesterification as observed in brown adipose tissue (BAT).[2,3]

The mature white adipocyte is composed of a large lipid droplet occupying the major part of the cell. Lipid droplets are considered dynamic organelles that are critical for the management of cellular lipid stores and lipolytic processes.[4] Lipolysis requires that soluble cytosol lipases (i.e., ATGL and HSL) can access the highly hydrophobic TAG substrates coated by proteins surrounding the lipid droplet. During lipolysis, adipocyte lipid droplets undergo an important structural reorganization involving lipid-droplet associated proteins (e.g., perilipin), lipases (e.g., ATGL and HSL) and cofactors (e.g., CGI-58/ABHD5, a coactivator of ATGL) (Fig. 1).

ATGL enzymology, gene and protein structure have recently been reviewed.[5] Structural domains of human ATGL have been described. The C-terminal protein region is essential for localization to the lipid droplet and interferes with ABHD5 interaction and enzyme activation.[6] ATGL exhibits 10-fold higher substrate specificity for TAG than DAG. Extensive studies of ATGL and HSL-deficient mice provided strong support for designating ATGL as the major TAG lipase in WAT, and assigned the primary function of HSL as a DAG lipase in vivo.[5,7] The pivotal role of ATGL in both basal and stimulated lipolysis has been demonstrated in human fat cells.[8] Moreover, translocation of ATGL from the cytosol to smaller lipid droplets increases its colocalization with HSL under stimulated conditions.[8]

ATGL-null mice show blunted fat cell lipolysis and rapidly become obese.[9] The major phenotypic consequence of ATGL

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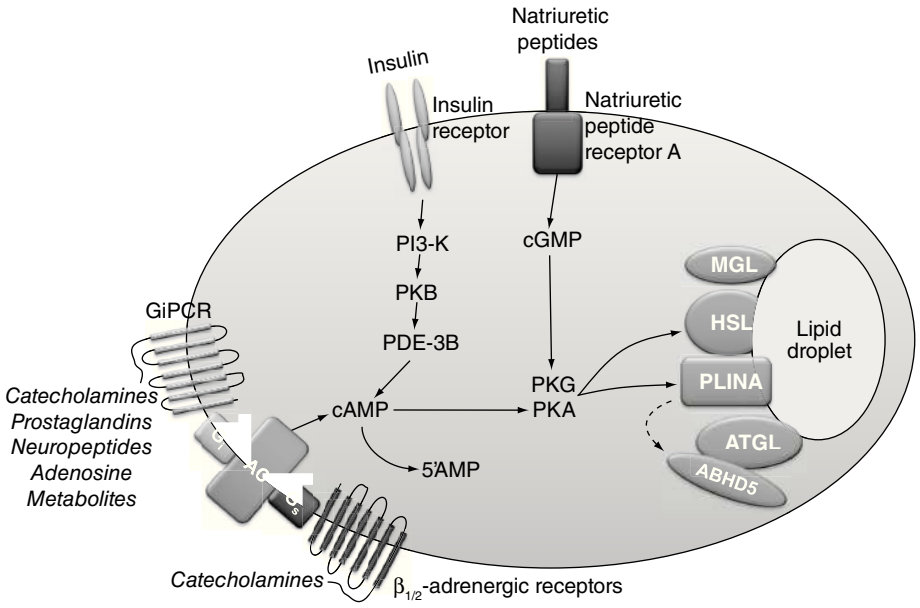

Figure 1 Control of human adipocyte lipolysis. Binding of catecholamines to Gs protein-coupled $\beta_{1/2}$-adrenoceptors stimulates cAMP production by adenylyl cyclase (AC) and activates protein kinase A (PKA). Conversely, stimulation of Gi protein-coupled receptors reduces cAMP and PKA-activation. Insulin favors cAMP degradation through activation of phosphatidylinositol-3 phosphate kinase (PI3-K) and protein kinase B (PKB), and stimulation of phosphodiesterase 3B (PDE-3B) activity. Natriuretic peptides promote cGMP accumulation and protein kinase G (PKG) activation. PKA and PKG phosphorylate hormone-sensitive lipase (HSL) and perilipin A (PLINA). Adipose triglyceride lipase (ATGL) and its cofactor ABHD5 and monoglyceride lipase (MGL) are also participating in the hydrolysis of triglycerides.

disruption is massive TAG accumulation in adipose and non adipose organs. Global energy metabolism is characterized by an inability to mobilize enough FA as fuel as exemplified by defective thermoregulation, reduced energy expenditure during fasting and impaired exercise-stimulated lipolysis.[10] Adipose-specific ablation of ATGL in mice converts BAT to a WAT-like tissue.[11] The mice exhibit severely impaired thermogenesis revealing the requirement of ATGL-catalyzed lipolysis for maintaining a brown fat phenotype.

Adipocyte HSL is composed of an N-terminal domain and a C-terminal catalytic domain that is identical in all known HSL isoforms.[1] This catalytic domain contains the active site, including residues of the catalytic triad (Ser, Asp, His), as well as a regulatory module with all the known phosphorylation sites of HSL. The N-terminal domain interacts with the molecular chaperone and fatty acid binding protein FABP4. In vitro, HSL catalyzes the hydrolysis of TAG into DAG and DAG into MAG. The relative acylglycerol hydrolase activity of HSL *in vitro* is tenfold greater against DAG than TAG and MAG.

Unlike other known mammalian TAG lipases, HSL is regulated by reversible phosphorylation of serine residues, being induced by protein kinase A and protein kinase G-mediated phosphorylations and inhibited by AMP-activated protein kinase-induced phosphorylation.[12] An important step in lipolysis activation is the translocation of HSL from a cytosolic compartment to the surface of the lipid droplet. Moreover, protein kinase A-induced phosphorylation promotes an increase in the hydrophobic surface area of HSL.

HSL disruption results in blunted stimulated lipolysis. However, when fed a high fat diet, HSL-null mice failed to become obese.[10] Growth curves indicated that HSL-null mice gain as much weight as the wild type mice during the early stages of the diet but suddenly stop putting on more weight suggesting a limitation in WAT expandability. HSL-null mice were also resistant to genetic-induced obesity when they were bred on the ob/ob background. Reduced weight gain in HSL-null mice is not a result of reduced food intake. Fat absorption was also reported to be unchanged in HSL-null mice whereas energy expenditure was significantly increased.[13] WAT shows metabolic brown adipocyte-like features. Reduced fat deposition could also result from impaired adipogenesis and/or adipocyte maturation due to a defect in production of PPARgamma ligands.[14] DAG accumulation, retinoic acid metabolites and local inflammation can also interfere with adipocyte differentiation.[15] HSL-null mice is indeed an unusual model of pronounced WAT inflammation not associated with obesity.

MGL belongs to the serine hydrolase superfamily with a catalytic triad composed of the active site serine, and aspartic acid and a histidine. The enzyme is required in the final hydrolysis of the 2-monoacylglycerols produced by HSL. It hydrolyses the 1(3) and 2-esters bonds of MAG at equal rates and is without in vitro catalytic activity against DAG and TAG. Due to its abundance in WAT, it was thought not to be limiting. However, ex vivo stimulated lipolysis is decreased in MGL-null mice.[16] In this mouse model, MAG hydrolase activity is not abolished due to partial compensation by HSL.

Against conventional wisdom, fasting plasma NEFA concentration is largely unrelated to body fat mass.[17] In the fasting state, plasma NEFA arises almost entirely from hydrolysis of TAG within the adipocyte. In the obese state, the lack of increase in plasma NEFA is partly explained by a decrease in subcutaneous WAT NEFA production; the

majority of NEFA originating from this depot. Impairment in the catecholamine-induced lipolysis and lipase expression in subcutaneous WAT is a common feature of obese subjects.[18-20]

The last decade has been marked by the discovery of a number of mechanisms able to clarify the control of lipid mobilization. Knowledge of the lipolytic pathways has fostered the identification of new targets for lipolysis modulators.[21] As HSL and ATGL are involved in TAG hydrolysis, selective inhibitors targeting this step are likely promising drugs, though a limitation could be the tissue distribution of these enzymes. The accumulating knowledge on the lipolytic pathways may hopefully lead to new chemical entities for the treatment of obesity-related problems such as insulin resistance, dyslipidemia and cardiovascular risk.

As proof of concept, we recently showed that partial inhibition of WAT lipolysis may prove beneficial in the treatment of obesity-related insulin resistance.[22]

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Conflicts of interest

The author declares that he has no conflicts of interest in this article.

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