Cell Metabolism
Previews

Adipose Tissue Lipolysis Revisited (Again!): Lactate Involvement in Insulin Antilipolytic Action

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DOI 10.1016/j.cmet.2010.03.003

Lactate is produced from glucose by adipose tissue. In this issue of *Cell Metabolism*, Ahmed et al. (2010) show that the metabolite is involved in the antilipolytic effect of insulin, providing a new link between fat and carbohydrate metabolism.

Adipose tissue is the body's largest energy reservoir and a major source of metabolic fuel. In periods of food supply, energy is stored as triglycerides, whereas in periods of energy demand, triglycerides are hydrolyzed to release nonesterified fatty acids into the bloodstream. Adipose tissue lipolysis is an exquisitely controlled process (Figure 1). Catecholamines, natriuretic peptides, and insulin are considered to represent the major regulators of lipolysis in humans (Lafontan and Langin, 2009). When catecholamines, the hormone adrenaline and the neurotransmitter noradrenaline, bind β-adrenergic receptors, seven-transmembrane domain receptors coupled to stimulatory Gs proteins, there is an activation of adenylylcyclase leading to a rise in intracellular cAMP levels. Activated protein kinase A phosphorylates the lipid droplet protein perilipin and hormone-sensitive lipase, thereby promoting hydrolysis of triglycerides. Atrial and brain natriuretic peptides stimulate lipolysis via activation of type A natriuretic peptide receptor but through a different intracellular route which involves cGMP and protein kinase G. Insulin is the major antilipolytic hormone in the fed state acting to limit release of fatty acids. The signal transduction pathway results in activation of phosphodiesterase 3B, which hydrolyzes cAMP into inactive 5′AMP and thereby diminishes protein kinase A-mediated phosphorylations. Besides insulin, a large number of antilipolytic receptors negatively coupled to adenylylcyclase through inhibitory Gi proteins have been described. With the exception of the α_2-adrenergic receptors stimulated by catecholamines, most ligands for these receptors are thought to act in a paracrine manner, and their physiological roles remain elusive. Recently, several new Gi protein-coupled receptors with high expression in adipose tissue have been identified. The endogenous ligands of these previously orphan receptors may be metabolites. The first to be characterized was GPR109A, the receptor for nicotinic acid or niacin, an old lipid-lowering drug (Ahmed et al., 2009). The ketone body, β-hydroxybutyrate, specifically activates the receptor at concentrations observed in serum during fasting. The receptor for L-lactate, GPR81, is closely related to the β-hydroxybutyrate receptor. In the physiological concentration range, L-lactate inhibits lipolysis in adipocytes from humans, mice, and rats (Ahmed et al., 2009). In the present issue of *Cell Metabolism*, Ahmed et al. provide compelling evidence for an involvement of lactate and GPR81 in the antilipolytic action of insulin (Ahmed et al., 2010).

As lactate is produced in large amounts by skeletal muscle during anaerobic physical exercise, it was first hypothesized that the metabolite provides a negative feedback when other factors potently stimulate lipolysis. The rationale could be to limit fatty acid release during times when glycolysis rates exceed mitochondrial respiration rates in skeletal muscle. However, Ahmed et al. found no evidence for lactate-mediated inhibition of lipolysis during various conditions of intensive exercise in mice (Ahmed et al., 2010), thus confirming earlier data in humans (Trudeau et al., 1999). It therefore appears that lactate produced by skeletal muscle during physical exercise does not act on adipose tissue. Early studies revealed that fat cells produced lactate in significant amounts, especially when glucose uptake is stimulated by insulin or during α_1-adrenergic receptor-mediated catecholamine stimulation (DiGirolamo et al., 1992; Faintrenie and Geloen, 1996; Hagstrom et al., 1990). In mice, increased plasma glucose level was accompanied by more release of lactate and less of fatty acids by adipose tissue (Ahmed et al., 2010). The antilipolytic effect was blunted in GPR81-deficient mice despite a similar increase in lactate production. This observation could be reproduced in vitro on adipose tissue. Insulin-induced decrease of cAMP levels and inhibition of lipolysis were both diminished in adipose tissue lacking GPR81. The authors also analyzed the impact of GPR81 deficiency on body composition and insulin sensitivity. Compared to wild-type mice, animals without GPR81 gained less weight during high-fat diet without modification in glucose tolerance. This study offers a new paradigm for insulin antilipolytic action, revealing an unappreciated link between glucid and lipid metabolic pathways. Besides the now-classical intracellular route leading to phosphodiesterase 3B activation, the decrease in cAMP levels may also result from lactate activation of GPR81 and subsequent inhibition of adenylylcyclase (Figure 1). Furthermore, it shows that lactate chiefly acts on adipose tissue metabolism in an autocrine/paracrine manner.

The new roles of lactate and GPR81 are raising a flurry of questions and will undoubtedly foster research in different

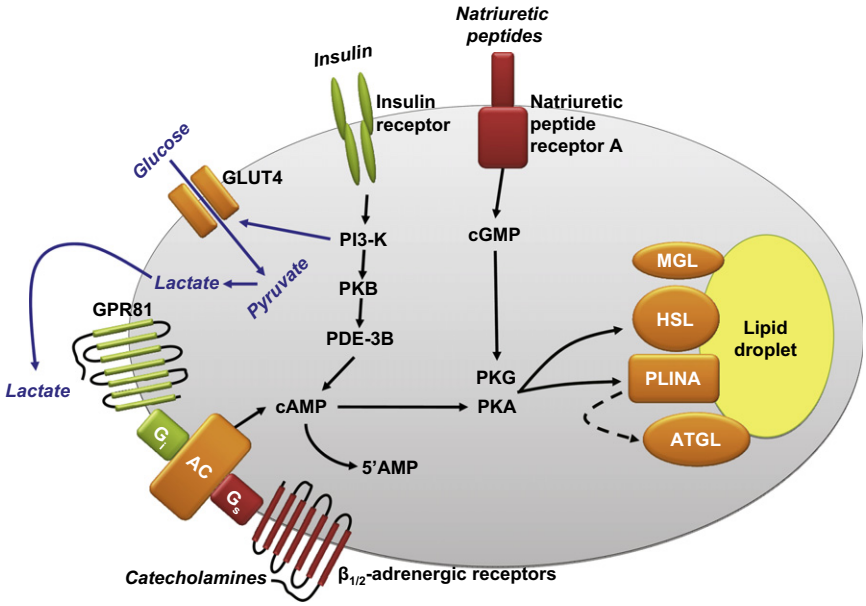

Figure 1. Control of Human Adipocyte Lipolysis

Binding of catecholamines to Gs protein-coupled $\beta_{1/2}$-adrenoceptors stimulates cAMP production by adenylyl cyclase (AC) and activates protein kinase A (PKA) while, conversely, stimulation of Gi protein-coupled α_2-adrenergic receptors (data not shown) 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 monoglyceride lipase (MGL) are also participating in the hydrolysis of triglycerides. Ahmed et al. (2010), in this issue, propose a new pathway shown by blue arrows involving the glucose transporter GLUT4; glycolysis-mediated lactate production; and the Gi protein-coupled lactate receptor, GPR81, in insulin-induced antilipolytic effect.

directions. There are several queries related to the physiological and pathological importance of this new pathway at the interface between fat and carbohydrate metabolism. Demonstration of the relevance in human physiology is now warranted. Important species differences have been described in the control of lipolysis (Lafontan and Langin, 2009). The natriuretic peptide pathway is a lipolytic pathway operational in humans in various conditions but not in rodents. As the second messenger of this pathway is cGMP, it is likely that lactate does not inhibit natriuretic peptide-induced lipolysis. Moreover, do catecholamines inhibit lipolysis not only through α_2-adrenergic receptor activation but also via α_1-adrenergic receptor-stimulated production of lactate, and does this latter process play a role in the crosstalk between catecholamines and insulin (Faintrenie and Geloen, 1996)? The involvement of lactate in insulin-mediated antilipolysis implies stimulation of glucose uptake by insulin. Therefore, alteration in the adipose tissue expression of the insulin-sensitive glucose transporter GLUT4 as reported in obesity and type 2 diabetes (Shepherd and Kahn, 1999) can be expected to result in diminution of insulin inhibition of lipolysis. However, insulin injection led to a normal suppression of fatty acid levels in mice with specific adipose tissue ablation of GLUT4 (Abel et al., 2001). In addition, it needs to be assessed whether alteration of adipose tissue insulin-stimulated glucose uptake, i.e., development of local insulin resistance, contributes to diminished insulin-mediated antilipolysis and enhanced fatty acid release that may lead to systemic insulin resistance and dyslipidemia. No difference in glucose and insulin tolerance was observed between wild-type and GPR81-deficient mice fed high-fat diet. As the decrease in insulin-mediated antilipolysis could lead to sustained plasma nonesterified fatty acid levels, a deterioration of insulin sensitivity was expected. However, the lower weight and supposedly fat mass of GPR81-deficient mice may have counterbalanced the expected increase of insulin resistance. Understanding the influence of GPR81 inactivation on insulin sensitivity is also important in a pharmacological perspective. GPR81 shows a highly restricted tissue distribution. It therefore constitutes a target amenable to drug development to limit deleterious fatty acid release from adipose tissue and improve the metabolic profile of dyslipidemic patients. In that respect, GPR81 may prove a better therapeutic target than GPR109A, as the expression of the nicotinic acid receptor in Langerhans cells has impaired the widespread use of nicotinic acid due to upper-body skin flushing. In a previous issue of *Cell Metabolism*, a cell-cycle protein was shown to be a regulator of adipose triglyceride lipase (Yang et al., 2010). A classic of biochemistry textbooks, lipolysis proves an ever-revisited pathway.

ACKNOWLEDGMENTS

D.L. is funded by Inserm, Université Paul Sabatier, Fondation pour la Recherche Médicale, Agence Nationale de la Recherche, Région Midi-Pyrénées and European Commission framework programs ADAPT and HEPADIP.

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