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Review

Adipocyte lipolysis and insulin resistance

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ABSTRACT

Obesity-induced insulin resistance is a major risk factor for the development of type 2 diabetes. Basal fat cell lipolysis (i.e., fat cell triacylglycerol breakdown into fatty acids and glycerol in the absence of stimulatory factors) is elevated during obesity and is closely associated with insulin resistance. Inhibition of adipocyte lipolysis may therefore be a promising therapeutic strategy for treating insulin resistance and preventing obesity-associated type 2 diabetes. In this review, we explore the relationship between adipose lipolysis and insulin sensitivity. After providing an overview of the components of fat cell lipolytic machinery, we describe the hypotheses that may support the causality between lipolysis and insulin resistance. Excessive circulating fatty acids may ectopically accumulate in insulin-sensitive tissues and impair insulin action. Increased basal lipolysis may also modify the secretory profile of adipose tissue, influencing whole body insulin sensitivity. Finally, excessive fatty acid release may also worsen adipose tissue inflammation, a well-known parameter contributing to insulin resistance. Partial genetic or pharmacologic inhibition of fat cell lipases in mice as well as short term clinical trials using antilipolytic drugs in humans support the benefit of fat cell lipolysis inhibition on systemic insulin sensitivity and glucose metabolism, which occurs without an increase of fat mass. Modulation of fatty acid fluxes and, putatively, of fat cell secretory pattern may explain the amelioration of insulin sensitivity whereas changes in adipose tissue immune response do not seem involved.

Contents

Abbreviations: ANP, atrial natriuretic peptide; AR, adrenergic receptor; AT, adipose tissue; ATGL, adipose triglyceride lipase; BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CGI-58, comparative gene identification-58; CMA, chaperone-mediated autophagy; DAG, diacylglycerol; DNL, *de novo* lipogenesis; FA, fatty acid; FABP4, fatty acid binding protein 4; GPCR, G-protein coupled receptor; HSL, hormone-sensitive lipase; IR, insulin resistance; LD, lipid droplet; MAG, monoacylglycerol; MGL, monoacylglycerol lipase; NEFA, non esterified fatty acid; NP, natriuretic peptide; NPR, natriuretic peptide receptor; PDE3B, phosphodiesterase 3B; PKA, protein kinase A; PKG, protein kinase G; PLIN, perilipin; TAG, triacylglycerol.

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1. Introduction

Obesity, characterized by an excess of fat mass, is increasing worldwide. It is two times more important than in the 80's and about 13% of population is estimated to be obese [1]. Obesity is a well-known risk factor for insulin resistance (IR) and development of type 2 diabetes [2]. Diabetes is associated with complications such as cardiovascular diseases, non-alcoholic fatty liver disease, retinopathy, angiopathy and nephropathy, which consequently leads to higher mortality risks. Obesity-associated diabetes is therefore a major public health problem. Paucity of available medication against IR requires the validation of new therapeutic targets.

Adipose tissue (AT) is the main organ for energy storage. In healthy people, AT represents about 20% of the body mass in men and about 30% in women. In obesity, it expands tremendously and may constitute more than 50% of the body mass in morbidly obese individuals. AT is composed of many cellular types. The majority are adipocytes, specialized cells for fat storage. Cells composing the stroma vascular fraction gather preadipocytes, stem cells, immune cells such as macrophages or lymphocytes, pericytes, endothelial cells and fibroblasts [3–5].

In periods of energy supplies, AT stores fatty acids (FA) that may have two distinct origins. Most of circulating FA are under the form of triacylglycerols (TAG) (i.e., 3 FA esterified on glycerol) carried by lipoproteins such as chylomicrons – derived from the gut – or very low density lipoproteins – produced by the liver. Circulating TAG are hydrolyzed into non-esterified fatty acids (NEFA) by the action of the lipoprotein lipase within vascular endothelium in AT. Lipoprotein lipase activity in the endothelium is stimulated by insulin. Released FA enter the adipocyte through FA transporters. Insulin also promotes glucose uptake through the translocation of the glucose transporter GLUT4 to the plasma membrane. FA are then re-esterified using glycerol 3-phosphate derived from glucose as a backbone to form TAG stored within lipid droplet (LD) [6]. To a lesser extent in human AT than in mouse AT, FA can also be directly synthesized into the adipocytes, with glucose as precursor, by a process called *de novo* lipogenesis (DNL) [7].

During periods of energy demands, such as fasting or physical exercise, adipocytes are able to mobilize their fat stores to fulfill other organ needs. Lipolysis consists in the hydrolysis of TAG into FA and glycerol. Three major lipases act sequentially. First, adipose triglyceride lipase (ATGL) hydrolyzes TAG into diacylglycerol (DAG) and FA. Then, hormone-sensitive lipase (HSL) cleaves DAG into monoacylglycerol (MAG) and, ultimately, monoacylglycerol lipase (MGL) converts MAG into FA and glycerol. Released FA may be oxidized in muscle and glycerol may be used as precursor for gluconeogenesis in liver. Catecholamines, natriuretic peptides and insulin are considered to be the major regulators of lipolysis *in vivo* [6,8].

In this review, we will first make an overview of the different regulators of fat cell lipolysis. We will also deal with dysregulation of lipolysis during obesity and its relationship with IR. Animal models of lipase inhibition – genetic or pharmacologic – will be presented. Finally, we will make a point on the relevance of the inhibition of fat cell lipolysis as a therapeutic strategy.

2. Lipolytic and antilipolytic factors and pathways

The neurohormonal control of lipolysis has previously been extensively reviewed [6,8] and is summarized in Fig. 1. Here, we present a global overview.

2.1. Prolipolytic signals

2.1.1. Catecholamines

Adrenaline and noradrenaline are considered as master regulators of lipolysis. They can both activate or inhibit lipolysis. In humans, $\beta_{1/2}$-adrenergic receptors (β-AR) induce a lipolytic response whereas α_2-adrenergic receptor (α_2-AR) transmits an antilipolytic signal. β-AR and α_2-AR belong to the G-protein coupled receptor (GPCR) family. β-AR are associated with Gαs protein promoting activation of adenylyl cyclase, cyclic adenosine monophosphate (cAMP) production and protein kinase A (PKA) activation. PKA then phosphorylates HSL and induces HSL translocation to the LD. PKA also favors LD fragmentation by phosphorylating perilipin 1 (PLIN1), a LD-associated protein. The wider surface of contact between lipases and LD enables an optimal lipolysis. PLIN1 sequestrates ATGL co-activator, comparative gene identification-58 (CGI-58) in basal conditions. Upon PKA-mediated phosphorylation of PLIN1, CGI-58 is released and interacts with ATGL to allow full activation of the lipase. On the opposite, α_2-AR are coupled with Gαi inhibitory subunit and promote an antilipolytic effect by inactivating adenylyl cyclase and PKA. Lipolysis activation or inhibition depends on the relative affinity of catecholamines for the different adrenergic receptors and on the respective enrichment in each receptor on the plasma membrane of adipocytes.

2.1.2. Natriuretic peptides

Other critically important stimulating factors of the lipolytic pathway are the atrial natriuretic peptide (ANP) and the brain natriuretic peptide (BNP) [9]. Physiologically, circulating natriuretic peptides (NP) levels rise during physical exercise. NP bind and activate type A natriuretic peptide receptors (NPR-A) which possess guanylyl cyclase activity. Increase in cyclic guanosine monophosphate (cGMP) levels activates protein kinase G (PKG) which phosphorylates the same targets as PKA. Type C natriuretic peptide

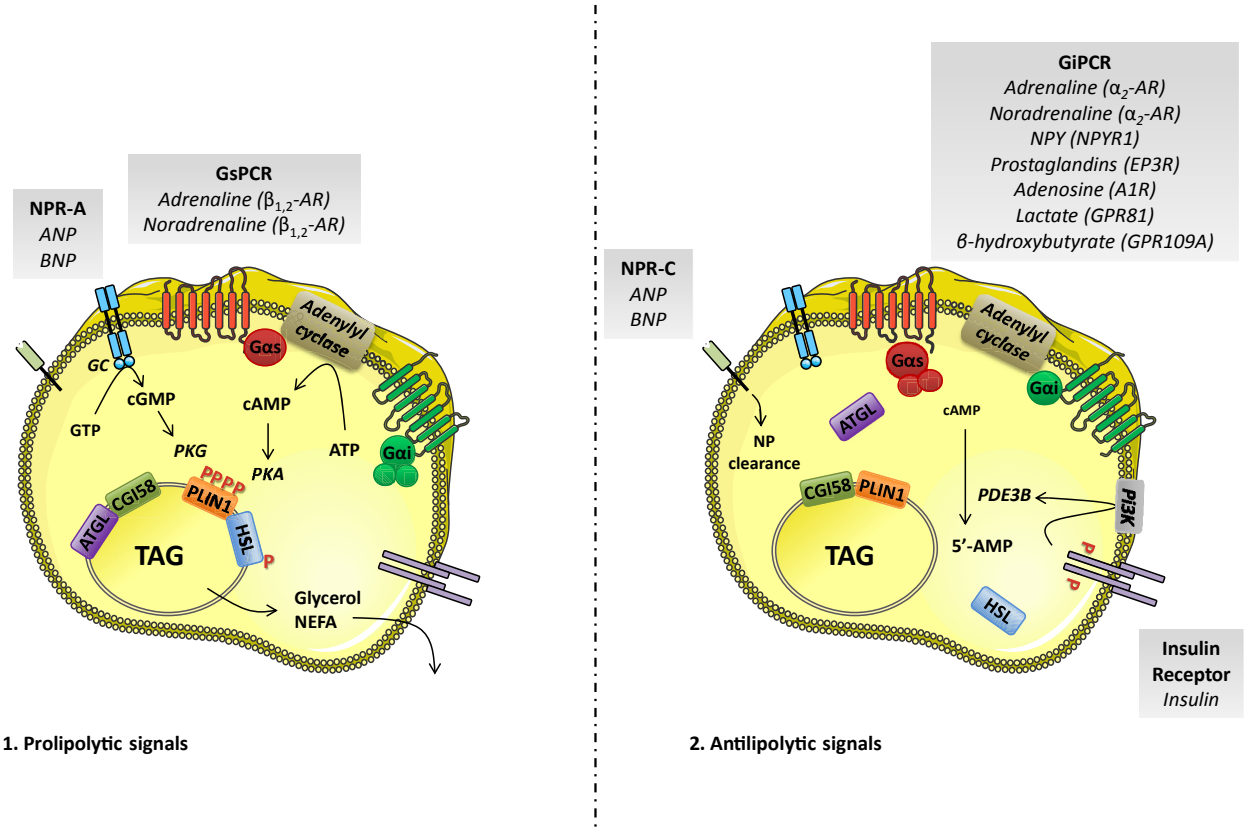

Fig. 1. Major regulators of AT lipolysis. Left panel: prolipolytic signals. Catecholamines and natriuretic peptides act through β-AR and NPR-A, respectively. PKA and PKG subsequent activation leads to HSL and PLIN1 phosphorylation. Phosphorylated HSL translocates to the LD surface to exert its action. PLIN1 phosphorylation promotes lipid droplet fragmentation and ATGL co-factor CGI-58 release. CGI-58 interacts with ATGL, conferring optimal activation of the lipase. Right panel: antilipolytic signals. Insulin activation of PDE3B through a Pi3K-dependent pathway and adenylyl cyclase inhibition through Gi protein-coupled receptor blunt cAMP production and PKA activation. Induction of NPR-C expression in antilipolytic conditions favors NP clearance impairing their lipolytic action. β-AR: β -adrenergic receptor; NPR-A: type A natriuretic peptide receptor; PKA: protein kinase A; PKG: protein kinase G; HSL: hormone sensitive lipase; PLIN1: perilipin 1; ATGL: adipose triglyceride lipase; CGI-58: comparative gene identification 58; PDE3B: phosphodiesterase 3B; Pi3K: phosphatidyl inositol 3 kinase; NPR-C: type C natriuretic peptide receptor; GC: guanylyl cyclase; GPCR: G-protein coupled receptor; TAG: triacylglycerol; NEFA: non esterified fatty acid; cGMP: cyclic guanosine monophosphate; cAMP: cyclic adenosine monophosphate; P: phosphate groups.

receptor (NPR-C) is also expressed on adipocyte plasma membrane and is responsible of NP internalization and degradation. NPRA and NPRC appear to be regulated in an opposite manner. While NPR-A gene expression increases in fasting conditions, energy supplies and insulin inhibit its expression. On the contrary, these latter conditions promote expression of the clearance receptor, NPR-C. As for catecholamines, potential of NP to activate lipolysis depends on the relative enrichment in each receptor on adipocyte plasma membrane.

2.1.3. Chaperone-mediated autophagy, a novel regulator of lipolysis

Recently, chaperone-mediated autophagy (CMA) has been identified as a new actor in the control of lipolysis and lipid storage [10,11]. CMA is activated during starvation and results in the recognition of PLIN 2 and 3 by the heat chaperone hsp70. Heat shock protein 70 promotes the trafficking of PLINs from LD to the lysosome through lysosomal-associated membrane protein 2A recognition and induces PLIN degradation. The decrease of PLIN on the LD surface allows ATGL recruitment and binding with CGI-58, leading to higher lipolytic rates. A role for CMA in macroautophagy-induced lipolysis has also been proposed. In addition to lipase-induced lipolysis, TAG breakdown can also occur through the formation of autophagosomes from the LD and their fusion with lysosomes [10,12]. To date, these studies were performed in murine fibroblasts and hepatocytes and in rodent liver. The involvement of CMA-induced lipolysis in the specialized fat cell remains to be determined. An important issue is to evaluate the effect of CMA on PLIN1 degradation as PLIN1 is the major perilipin coating LD in adipocytes.

2.2. Antilipolytic signals

2.2.1. Insulin

Insulin is considered as the main factor in the inhibition of lipolysis. Insulin receptor belongs to the tyrosine kinase receptor family and activates phosphoinositol-3-kinase signaling. Increase of PiP3 activates PKB/AKT and leads to activation of phosphodiesterase 3B (PDE3B). PDE3B converts cAMP into 5′-AMP and, consequently, counteracts the lipolytic effect of catecholamines but not that of natriuretic peptides.

2.2.2. Other negative regulators of lipolysis

In addition to the catecholamine α_2-AR, several other factors have been identified to activate an antilipolytic response through Gαi coupled receptors. They may be produced by cells from the stroma vascular fraction, sympathetic nerve terminals or adipocytes. Several of these factors have an autocrine/paracrine action, e.g., prostaglandins, adenosine and neuropeptides such as NPY. Two of the GPCRs coupled with Gαi, GPR109A and GPR81, raised special interest [13,14]. GPR109A, also called hydroxycarboxylic acid receptor 2 (HCA2), is highly expressed on adipocytes and binds ketone bodies, such as β-hydroxybutyrate, as endogenous ligands

which plasma levels are elevated during fasting [14]. Lactate binds GPR81 and counteracts the Gαs lipolytic pathway activated by catecholamines [13,15–17]. It has been postulated, from studies in rodents, that insulin-stimulated glucose uptake in fat cells leads to increased lactate production and activation of the receptor [13]. This would constitute another mechanism for insulin antilipolytic action [18].

3. Lipolysis and insulin resistance

3.1. Putative mechanisms for the control of insulin sensitivity by adipose tissue lipolysis

In obese and insulin resistant people, the lipolytic effect of catecholamines is reduced in subcutaneous AT but increased in visceral AT [19,20]. NP-induced lipolysis may be also decreased in the obese state since NPRA/NPRC ratio was reported to be lower in several animal models of obesity and in a few human studies [21]. However, basal (i.e., unstimulated) lipolysis is increased in the obese state [6,19]. Enlargement of fat cells may be one of the contributors to the increase of basal lipolysis. The latter was recently demonstrated to be closely associated with insulin-resistance, independently of BMI or age [22]. It was also observed that, after bariatric surgery-induced weight loss, obese people with the highest recovery of insulin sensitivity were those with the highest decrease in basal lipolysis [22]. Thus, dysregulation of basal fat cell lipolysis may be an important primary event contributing to the emergence of IR. Several hypotheses can be proposed. First, increased FA release by adipocytes may worsen lipid accumulation in insulin-sensitive organs such as liver and skeletal muscle and participate in the impairment of insulin sensitivity [23]. Second, increased lipolysis may modulate adipocyte secretions which can be either proteins named adipokines or lipids named lipokines, influencing insulin sensitivity [24]. Third, higher lipolysis may favor AT inflammation as FA may promote cytokine production by macrophages [25].

Increasing circulating NEFA levels by lipid infusion induce transient IR [26]. FA thereby accumulate in ectopic tissues such as liver or skeletal muscle. The relationship between ectopic lipid accumulation and IR is well established and termed lipotoxicity [23]. DAG and ceramides are potential molecular intermediates impairing insulin signaling. Lipid infusion of healthy lean people promotes a transient increase in cytosolic DAG content and IR of skeletal muscle cells [27]. DAG activate novel PKC which directly counteract transmission of the insulin signal. In humans, the relationship between DAG accumulation and PKC activation is also suggested in the liver from insulin resistant patients suffering from non-alcoholic fatty liver disease [28]. The contribution of AT lipolysis in ectopic lipid storage and IR was shown in several animal studies. Reduced hepatic and/or muscle lipid content in parallel with an improvement of insulin sensitivity has been reported in several models of lipase deficiencies [22,29,30]. Moreover, the increase of circulating NEFA and glycerol may also serve as precursors for gluconeogenesis and worsen hyperglycemia in mice [31]. Accordingly, ablation of AT lipolysis results in normalization of hepatic glucose production [31].

In addition to increasing circulating NEFA levels, AT lipolysis can also modulate fat cell secretions. AT is a well-known endocrine organ releasing adipokines [32] or lipokines [33,34] which act remotely on other organs such as muscle and liver. Regulation of the adipocyte secretome modulates IR [32]. In this context, Ertunc et al. recently demonstrated a direct relationship between lipolysis and aP2/FABP4 secretion by adipocytes, a deleterious adipokine which favors neoglucogenesis and IR [24,35]. Stimulation of lipolysis and increased lipid bioavailability increase aP2 secretion. On the contrary, inhibition of lipases impairs aP2 secretion by adipocytes. Consequently, despite the paucity of studies available, it appears that lipolysis may control IR through the modulation of adipocyte secretory factor production.

Inflammation also plays a role in the development of IR [23]. Adipocyte hypertrophy during AT expansion is associated with hypoxia and cell death [36]. In response, adipocytes release chemokines to recruit macrophages. Immune cell infiltration in AT is consequently a hallmark of obesity. For a long time, it was considered that obesity is associated with a switch from anti-inflammatory M2 macrophages to proinflammatory M1 macrophages. Nevertheless, the association between M1 macrophages and IR is increasingly debated since M2-like macrophages have been found to be increased in AT from overweight individuals [37]. Release of proinflammatory cytokines such as tumor necrosis factor α may worsen IR [38]. Cytokines activate c-Jun N-terminal kinase and directly interfere with insulin signaling. Moreover, tumor necrosis factor α increases basal lipolysis and may exacerbate ectopic lipid accumulation [39]. Numerous studies have shown that saturated FA can directly activate proinflammatory macrophages through Toll-like receptor 4 and worsen AT inflammation [25,40]. Consequently, one may postulate that increased basal lipolysis may exacerbate inflammation and IR. However, recent studies invalidated this hypothesis [22,30,41,42]. We demonstrated *in vivo* and *in vitro* that lipolysis-derived FA are stored within macrophages but do not modify cytokine or interleukin production by these cells [41]. Moreover, HSL haploinsufficient and adipocyte-specific ATGL knockout mice have better glucose and insulin tolerance than control animals without change in AT inflammation [22,30]. Mice submitted to high fat diet present macrophage infiltration into AT and develop IR within 3 days [42]. However, pharmacologic or genetic suppression of macrophages and inflammation does not improve IR and does not modify intrahepatic lipotoxic species content. These observations are also supported by human studies [43,44]. Healthy people submitted to overfeeding develop IR before any changes in circulating cytokines levels and immune cell infiltration into AT. Altogether, these studies suggest that adipocyte dysfunction may be a primary event in the pathogenesis of IR and that AT inflammation does not appear as a significant actor in the relationship between lipolysis and IR.

3.2. Genetic lipase deficiencies and insulin resistance

3.2.1. ATGL deficiency

Haemmerle et al. were the first to characterize mice with global deficiency in ATGL (ATGL−/−) [45]. These mice exhibit a strong increase of fat mass due to an accumulation of neutral lipids. Because of increased lipid content in other organs such as cardiac muscle, the majority of animals prematurely die of heart disease. Moreover, ATGL−/− mice also present pancreatic steatosis and impaired insulin secretion [46]. In terms of insulin sensitivity, ATGL−/− mice submitted to a normal or a high fat diet show an improvement of glucose and insulin tolerance and exhibit a better glucose uptake by insulin-sensitive tissues, suggesting that the absence of ATGL improves whole body insulin sensitivity [45,47]. Notably, ATGL−/− mice preferentially consume glucose as they cannot mobilize fat stores. This improvement of insulin sensitivity may be explained by a decrease availability of DAG in insulin-responsive organs. The same group later studied the link between accumulation of TAG and insulin sensitivity in ATGL−/− mice [48]. Surprisingly, insulin signaling was deteriorated in liver, not modified or slightly improved in AT and improved *in vivo* in skeletal muscle but deteriorated *ex vivo*. Understanding the mechanisms that link global ATGL deletion and insulin sensitivity is therefore complicate. It must be kept in mind that ATGL is expressed in

skeletal muscle and liver. Its ablation in these organs directly modify FA metabolism. Moreover, systemic factors may play a role since improvement of insulin sensitivity in muscle was only observed *in vivo*.

There are a few reports on people with defective ATGL due to homozygous mutations [49]. These individuals show impaired stimulated lipolysis but do not present lower plasma NEFA levels. As observed in ATGL−/− mice, they present increased fat mass and lipid content in skeletal muscle or pancreas. Despite impaired insulin secretion, whole body insulin sensitivity is preserved. The number of people studied is very low. Consequently, relationship between ATGL and insulin sensitivity in humans is still unclear.

To investigate the relationship between adipocyte ATGL and systemic IR, fat cell-specific knock out is a better model than global invalidation of the enzyme. Two groups produced AT ATGL-specific deletion by crossing animals carrying an aP2-Cre-recombinase with animals carrying a floxed allele of the ATGL gene [29,50]. These mice present an increase of fat mass. However, ectopic lipid storage is not modified or reduced compared to wild type littermates. Cardiopathy and premature death are not observed. Concerning insulin sensitivity, both groups reported an improvement of glucose and insulin tolerance associated with better hepatic insulin response. The improvement may be partly explained by the decrease of intrahepatic lipotoxic species content. However, this model shows limitations since aP2 and ATGL are also expressed in AT stroma vascular fraction, notably in macrophages [30,51]. Alternatively, adiponectin-driven Cre expression has recently been used to induce a specific deletion of ATGL in adipocytes [30]. These mice also exhibit a better glucose and insulin tolerance associated with better hepatic insulin sensitivity when fed chow or high fat diets. However, as mentioned above, no change or even a tendency to worsened AT inflammation was observed. Of note, the mice showed improvement of systemic insulin sensitivity with a fat mass similar to control mice. This latter observation may be explained by lower expression of proteins involved in lipid uptake, lipogenesis and adipogenesis in AT.

Altogether, these studies suggest that inhibition of ATGL in AT improves whole body insulin sensitivity through reduced FA fluxes and ectopic lipid deposit rather than change in AT inflammatory status. Improvement of the metabolic status does not seem to be related to weight gain.

3.2.2. HSL deficiency

Global HSL null mice were initially characterized by two groups [52,53]. These studies revealed an important role of HSL in DAG hydrolysis *in vivo* [52] and revealed that HSL is an essential enzyme for spermatogenesis since male HSL−/− mice were infertile [53,54]. Concerning insulin sensitivity, despite DAG accumulation in AT and in other organs such as skeletal muscle, HSL null mice only show moderate impairment of insulin sensitivity compensated by higher insulin secretion [55]. However, global HSL deficiency in genetically obese mice causes pancreatic islet steatosis and impaired insulin secretion [56]. HSL null mice present alteration of AT development with a large heterogeneity of adipocyte size and a pronounced AT inflammation and are resistant to high fat diet-induced obesity [53,57]. This may be explained by the fact that HSL is necessary for synthesis of endogenous peroxisome proliferator-activated receptor γ ligands and adipogenesis [58].

Recently, the phenotypes of a few individuals from the Amish community carrying a homozygous frameshift mutation of HSL were described [59,60]. As observed in HSL null mice, partial lipodystrophy appears during aging. In contrast to HSL-deficient mice, which are nondiabetic, all four homozygous carriers developed diabetes. Another difference was that a man with defective HSL had children suggesting different involvements of HSL in mouse and human spermatogenesis [61].

A better model for the study of HSL inhibition in the context of diet induced-obesity is provided by heterozygous HSL (HSL+/−) mice which express only half the content and activity of HSL in AT [22]. HSL+/− mice do not exhibit defect in adipogenesis. Fed high fat diet, unlike HSL−/− mice, HSL+/− mice develop the same obesity as wild type littermates. Indeed, the decrease of AT lipolysis is compensated by a decrease of plasma FA uptake by adipocytes which contribute to fat mass maintenance. HSL+/− mice exhibit a shift of respiratory quotient in favor of glucose consumption. These mice show better glucose uptake in AT and skeletal muscle and, improved insulin signaling in skeletal muscle and liver. HSL+/− mice present an improvement of whole body insulin sensitivity. Interestingly, AT inflammation is unchanged. In human adipocytes, RNAi-mediated HSL knock down results in an increase of insulin-stimulated glucose uptake which favors DNL. In accordance with these cell autonomous adaptations, negative correlations between lipolysis and DNL gene expression in AT were shown in several cohorts of patients. As adipose DNL has been demonstrated to be a determinant of whole body insulin sensitivity [62–64], it may constitute an important mechanism for the link between HSL inhibition and improvement of systemic insulin sensitivity.

In contrast to HSL heterozygous mice, Amish individuals heterozygous for frameshift mutation show very modest changes in blood lipid profiles and fasting plasma glucose concentrations but display a marked decrease in glucose tolerance and a higher risk of type 2 diabetes [59,60]. These heterozygous carriers show intact adipocyte lipolysis. Therefore, it is conceivable that the presence of the enzymatically inactive mutant protein provokes metabolic effects by unknown mechanisms that differ from those observed in HSL+/− mice.

Mouse models reveal that partial inhibition of HSL protects against IR without weight gain. As no change in the inflammatory status is observed, the beneficial effects may be mediated through changes in AT secretory profile and in FA flux. However, as for ATGL, specific genetic inhibition of HSL in AT is warranted since HSL is expressed in other metabolic organs. The relationship between HSL and IR in humans is still unclear and requires further investigation.

3.2.3. MGL deficiency

Only a few studies addressed the involvement of global MGL deficiency on lipolysis and insulin sensitivity [65,66]. MGL−/− mice show accumulation of MAG in AT, brain and liver [66]. As lower circulating glycerol levels are observed, MGL null mice may have a lower lipolytic capacity. Concerning insulin sensitivity, MGL null mice exhibit better insulin sensitivity under high fat diet. However, the mechanisms responsible for this improvement are not characterized to date and may be related to other roles of the enzymes, such as brain endocannabinoid metabolism.

4. Inhibition of lipolysis to alleviate insulin resistance: an overview of clinical studies

Preclinical studies suggest that inhibition of lipolysis may appear as an attractive therapeutic strategy in obese pre-diabetic people.

No pharmacological inhibitors of lipases have so far been used in humans. Specific ATGL inhibitors are in development. The only available compound, atglistatin inhibits lipolysis *in vitro* and *in vivo* in mice [67]. However, the compound does not inhibit human ATGL. Several series of inhibitors, potent and selective for both human and mouse HSL, have been synthesized. One of these compounds was shown to improve glucose and insulin tolerance in mice [22].

As mentioned above, activation of GPCR coupled to Gi results in lipolysis inhibition. GPR109A is the pharmacological target of

nicotinic acid, a well-known lipid lowering agent [68–70]. Acute treatment with nicotinic acid decreases circulating levels of NEFA and was reported to increase glucose clearance from plasma [71–73]. However, adverse effects on hepatic glucose production have been reported [71,72]. They may potentially be due to a receptor-independent direct action of nicotinic acid on hepatocytes. During chronic administration of nicotinic acid, there is deterioration of glucose metabolism and insulin sensitivity partly explained by a rebound effect on plasma NEFA levels due to tachyphylaxis [73,74]. Moreover, nicotinic acid treatment has poor compliance because of frequent flushing due to GPR109A expression on Langerhans cells [75,76]. Acipimox, an analog of nicotinic acid, show a more favorable profile on insulin sensitivity. Acute administration of acipimox decreases circulating NEFA and improves glucose clearance from plasma [77,78]. During chronic acipimox treatments, decreased [79–81], increased [82,83], or unaffected circulating NEFA levels have been reported [84]. However, all these studies conclude to an improvement of glucose metabolism control which is usually moderate. Chronic administration of acipimox was also reported to reduce glycated hemoglobin [82], increase glucose disposal and oxidation [79–81,83,84], increase insulin signaling in muscle [81], and decrease hepatic glucose production [79–81]. On these promising observations, new GPR109A agonists, such as GSK256073, are in development [85–87]. This compound showed encouraging effects during acute administration [86] with moderate adverse flushing effect [87]. Unfortunately, after a three month administration in diabetic patients, the inhibition of AT lipolysis was not maintained and IR was not diminished [85].

Receptors with a more restricted tissue expression profile may prove interesting alternatives. GPR81 is another antilipolytic GPCR specifically expressed in AT [15,16]. As mentioned above, lactate is an endogenous ligand of GPR81. Specific GPR81 agonists are in development but no clinical studies have been reported so far [17,88].

Drug tolerance appears as one of the challenges for the use of antilipolytic GPCR agonists. It has been illustrated in drug trials with chronic administration of nicotinic acid. Unlike continuous nicotinic acid infusion, an intermittent dosing strategy succeeded in retaining plasma NEFA lowering and improving insulin sensitivity in obese Zucker rats [89]. This promising approach has not been used so far in clinical trials.

5. Conclusion

There is now convincing evidence for an association between fat cell lipolysis and IR in humans. Studies in mouse models produced important information. First, partial inhibition of lipolysis is not accompanied by an increase of fat mass and body weight. Second, inhibition of lipolysis results in improvement of whole body glucose metabolism. This may be due to a decrease in FA-derived lipotoxic species in liver and skeletal muscle and to a more favorable secretory profile of the adipocytes. Data are currently missing concerning fat cell production of adipokines and lipokines during adipocyte lipolysis inhibition. The modulation of AT inflammation does not seem to be involved. Evaluation of the involvement of CMA-induced lipolysis in fat cell physiology and in obesity-induced IR also requires further studies. To conclude, the inhibition of fat cell lipolysis may be a promising therapeutic strategy for the treatment of IR. Understanding the mechanisms and deciphering the pathways is essential as are the identification of drugs with high potency and selectivity as well as specificity of action on fat cells, safety and sustained action during long-term treatments.

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