Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy Dovepress
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REVIEW

Anti-Lipolysis Induced by Insulin in Diverse Pathophysiologic Conditions of Adipose Tissue

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Abstract: As an important energy reservoir, adipose tissue maintains lipid balance and regulates energy metabolism. When the body requires energy, adipocytes provide fatty acids to peripheral tissues through lipolysis. Insulin plays an important role in regulating normal fatty acid levels by inhibiting lipolysis. When the morphology of adipose tissue is abnormal, its microenvironment changes and the lipid metabolic balance is disrupted, which seriously impairs insulin sensitivity. As the most sensitive organ to respond to insulin, lipolysis levels in adipose tissue are affected by impaired insulin function, which results in serious metabolic diseases. However, the specific underlying mechanisms of this process have not yet been fully elucidated, and further study is required. The purpose of this review is to discuss the effects of adipose tissue on the anti-lipolysis process triggered by insulin under different conditions. In particular, the functional changes of this process respond to inconsonantly morphological changes of adipose tissue.

Keywords: adipose tissue, insulin, anti-lipolysis

As an important endocrine organ and energy reservoir, adipose tissue is regulated by various esterases and hormones. Lipolysis, as the primary energy supply pathway, is involved in various metabolic processes, and the fatty acids released by lipolysis are important energy substrates and signal molecules.[1] Insulin plays an important role in regulating lipolysis and controlling the lipolysis of adipose tissues. When insulin binds to insulin receptors on the cytomembranes of adipocytes, it reduces the levels of cyclic adenosine phosphate (cAMP) through the phosphatidylinositol kinase-3/protein kinase B (PI3K/AKT) pathway, thereby inhibiting lipolysis.[2] At present, studies regarding insulin regulation of lipolysis have not yet established the anti-lipolysis process induced by insulin under distinct metabolic conditions, especially in terms of the functional differences due to morphological changes in adipose tissues. Therefore, it is necessary to further explore the underlying mechanism through which insulin regulates lipolysis when adipose tissues initiate functional changes to seek effective targets for the treatment of metabolic diseases.

Regulation of Lipolysis

Lipolysis is a biochemical pathway for the catabolism and metabolism of triglycerides (TAG) stored in lipid droplets in cells, and primarily occurs in adipocytes. In lipolysis, TAG is hydrolyzed into glycerol and free fatty acids (FFA) via lipases to mobilize stored energy during fasting or exercise. FFAs from the hydrolysis and cleavage of TAG are then used as energy substrates, being essential precursors for

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http://doi.org/10.2147/DMSO.S250699

lipid and membrane synthesis, or as media in the cell signal transduction process. Therefore, lipolysis plays an important role in maintaining the function of adipose tissue and the energy balance of the body.[3]

The Basic Process of Lipolysis

During fasting or starvation, lipolysis is activated to increase the concentration of fatty acids and glycerol in serum and meet the energy requirements of other metabolic tissues. Catecholamines trigger lipolysis during fasting. Catecholamine norepinephrine binds to the β-adrenergic receptors of adipocytes. These receptors bind to adenylate cyclase G protein and transmit the signal to adenylate cyclase to produce cAMP. cAMP binds to PKA and stimulates the activation of lipase.[4] In addition, when fasting, a lower plasma glucose level stimulates the secretion of glucagon. Glucagon elevates intracellular cAMP levels by increasing the activity of adenylate cyclase, thus, promoting lipolysis.[5] The lipolysis process requires the participation of a variety of lipases. When lipases are phosphorylated, they contact the lipid droplets and hydrolyze TAG into diacylglycerol (DAG), monoacylglycerol (MAG), glycerol, and FFAs.

Perilipin1A can be phosphorylated by PKA, which is a key protein regulator of adipose tissue lipolysis, releasing comparative gene Identification-58 (CGI-58) to promote phosphorylated lipase entry into lipid droplets.[6–8] CGI-58 can be further phosphorylated by PKA and diffused to the cytoplasm, activating adipose triglyceride lipase (ATGL) to initiate lipolysis.[9–12]

The first step in lipolysis is ATGL.[13–15] ATGL initiates lipolysis by specifically hydrolyzing the ester bond of TAG, but it has little effect on the hydrolysis of other lipids, which is, thus, considered the rate-limiting enzyme in the TAG hydrolysis process.[16,17] The reduced expression of ATGL leads to the increased accumulation of TAG in adipose cells and other tissues, which leads to obesity and other metabolic complications.[18] However, ATGL overexpression leads to increased lipolysis, fatty acid oxidation, decreased TAG deposition, and decreased adipocyte size.[19] In addition, the lipolysis involved by ATGL can promote the production of lipid signaling molecules to positively regulate glucose-stimulated insulin secretion.[20]

Subsequently, hormone-sensitive lipase (HSL), an intracellular neutral lipase, catalyzes the hydrolysis of DAG to MAG. Haemmerle[21] observed that HSL-deficient mice accumulated large amounts of DAG instead of TAG in adipose and other tissues. HSL knockout mice were found to have a lower lipolysis rate and TAG level in vivo as well as reduced FFA release and increased DAG accumulation. In vitro, HSL-deficient fat pads showed that isoproterenol-stimulated FFA release decreased and DAG accumulation and glycerol production in adipocytes were absent, indicating that HSL is a rate-limiting enzyme for DAG catabolism in adipose tissue.[22] HSL is strongly regulated by hormones, including catecholamine, ANP, and growth hormones, in which insulin is an important inhibitor of HSL.[23] HSL-deficient mice showed low hormone-stimulated lipolysis levels.[21] However, HSL-overexpressing mice showed normal basal lipolysis activity but increased excitatory lipolysis.[24]

Finally, monoglyceride lipase (MGL), which is located in the cytoplasm, plasma membranes, and lipid droplets, catalyzes the hydrolysis of MAG to glycerol and FFAs. MGL belongs to the serine hydrolytic enzyme superfamily[25] and is considered the rate-limiting enzyme for MAG hydrolysis.[26] Taschler[27] found that MGL-deficient mice exhibited reduced diet-induced insulin resistance despite altering the lipolysis levels. MGL is also an important component of the endocannabinoid system, which regulates peripheral lipogenesis.[28] After treatment with rosiglitazone, white adipose tissue (WAT) lipolysis in rats increased, as did the mRNA transcriptional level of MGL.[29] However, no relevant studies have shown that MGL activity is affected by hormones.

Regulation of Lipolysis

Lipolysis is regulated by various hormones and cytokines. The activity of lipases is strictly regulated by hormones. During fasting, elevated levels of glucocorticoids upregulate the ATGL transcription level.[15] Catecholamine promotes the phosphorylation of HSL by binding to the β-adrenoreceptor, increasing cAMP levels, and activating protein kinase A(PKA).[30] When refeeding, insulin binds to insulin receptors in adipocytes and reduces cAMP and ultimately inhibits lipolysis by phosphorylation and the activation of PDE3B.[31] Additionally, insulin may inhibit the expression of ATGL through FoxO1.[32]

Local autocrine/paracrine cytokines secreted from adipocytes also regulate lipolysis. For example, tumor necrosis factor-α (TNF-α) induces lipolysis via p44/42 and Jun kinases, while endogenous adenosine produces an antilipolytic effect through the adenosine A1 receptor.[33,34] Certain prostaglandin types affect lipolysis to a greater or lesser degree depending on concentration.[33] Jaworski[35] found that aliphatic specific phospholipase A2 (AdPLA) can regulate the level of prostaglandin PGE2, and the functional loss of AdPLA leads to a decrease in PGE2 levels, thereby increasing the levels of cAMP through

PKA-mediated HSL phosphorylation and the activation of lipolysis. In addition, other factors from the peripheral organs or central nervous system regulate lipolysis. NPY is involved in visceral adipose obesity induced by stress: knockdown of the NPY receptor reduces visceral adipose mass. Nicotinic acid inhibits lipolysis through PUMA-G, a Gi/o-coupled seven-transmembrane domain receptor expressed in mouse adipocytes.[36]

Anti-Lipolysis Effects of Insulin

Insulin plays a crucial role in regulating glucose and lipid metabolisms. Insulin promotes lipid synthesis and storage, reduces plasma FFAs, and inhibits the catabolism of lipids and FFA oxidation. Insulin is the most important hormone that inhibits lipolysis. As early as 1960, in vitro experiments showed that adding glucose and insulin to a culture medium inhibited the release of FFAs in adipocytes, while adrenalin stimulated the release of FFAs, suggesting that the lipolysis of adipocytes negatively responds to insulin.[37]

Insulin Mechanism of Action Against Lipolysis

The anti-lipolysis mechanism induced by insulin is relatively well understood. Insulin regulates the glucose uptake of adipocytes and triggers the transport of fatty acid transporters and the FFA uptake of adipocytes.[38] Insulin binds to specific membrane insulin receptors to initiate and activate tyrosine phosphorylation, then receptors interact with insulin receptor substrates (IRS-1 and IRS-2) to activate the phosphatidylinositol 3-kinase (PI3K) complex.[39] Subsequently, phosphodiesterase 3B (PDE3B) is activated through the PKB/Akt pathway to inhibit basal and catecholamine-induced lipolysis.[40,41] Phosphodiesterase catalyzes the decomposition of cAMP, then inactive 5′ -amp, thereby reducing the activation level of PKA, thus, reducing the activity of HSL and inhibiting lipolysis[42] (Figure 1).

Scherer[43] found that injecting insulin into the middle brain hypothalamus (MBH) of SD rats increased the expression of adipogenic gene-related proteins in WAT, reduced the activity of HSL, and thus inhibited lipolysis. In contrast, mice lacking insulin receptors in neurons showed no significant inhibition of lipolysis and a decrease in adipogenesis. Therefore, it is believed that in the brain, especially in the hypothalamus, insulin maintains the function of WAT.[43] In addition, the insulin signaling pathway in POMC neurons controls the lipolysis of adipose tissues.[44] In addition, previous studies have shown that cerebral insulin acts primarily on non-subcutaneous

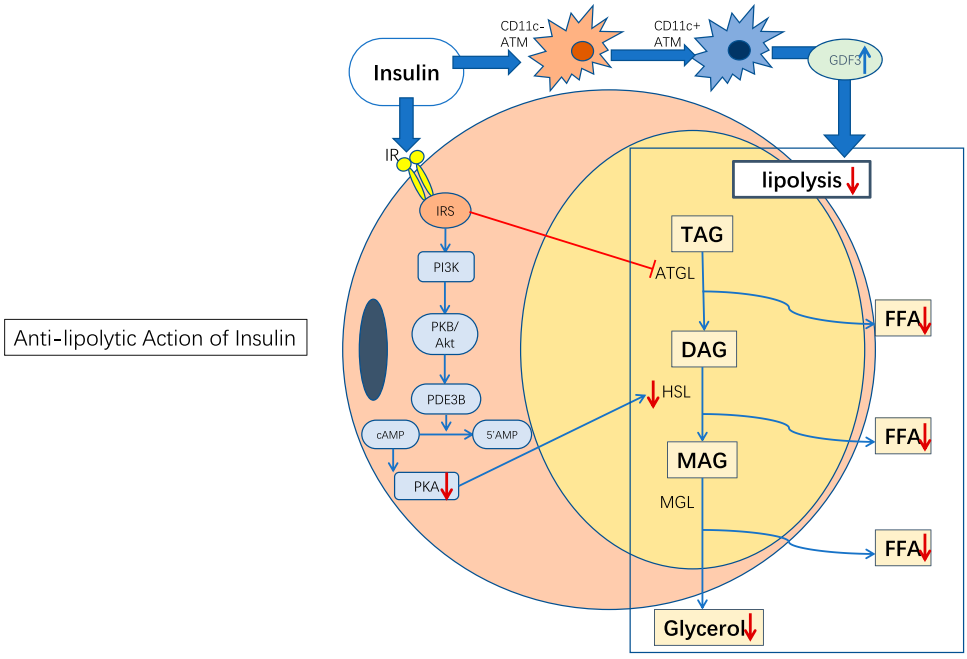

Figure 1 Anti-lipolytic action of insulin. Insulin inhibits lipolysis primarily through the PI3K/Akt signaling pathway. In addition, insulin inhibits lipolysis independently of Akt under certain conditions, such as through the regulation of adipose tissue macrophages (see description below). Blue→: promotion; Red →: inhibition; Red↓: reduction; Blue↑: increase.

Abbreviations: ATM, adipose tissue macrophage; IR, insulin receptor; IRS, insulin receptor substrate; FFA, free fatty acid; TAG, triglycerides; DAG, diacylglycerol; MAG, monoacylglycerol.

adipose tissue to control systemic lipolysis in healthy individuals.[45]

Recent studies have shown that the α/β-hydrolase domain containing protein 15 (ABHD15) is necessary for anti-lipolysis via insulin in WAT. It has also been found that neither insulin nor glucose treatment can inhibit fatty acid mobilization in ABHD15 knockout mice. Insulin signaling was impaired in ABHD15 knockout adipocytes along with reduced AKT phosphorylation, decreased glucose uptake, and lower adipogenesis. In vitro experiments showed that ABHD15 can bind and stabilize phosphodiesterase 3B (PDE3B); accordingly, PDE3B expression was reduced in the WAT of ABHD15 knockout mice. This explained the lack of decrease in FFA efflux despite increasing protein kinase A(PKA) activity and phosphorylation levels of hormone-sensitive lipase (HSL).[46] Insulin may also inhibit lipolysis through the regulatory subunit of phosphorylated protein phosphatase-1 (PP-1), which, once activated, rapidly dephosphorylates and deactivates HSL, thereby reducing the lipolysis rate.[47,48]

In addition, insulin appears to inhibit lipolysis independently of Akt under certain conditions. Akt2-deficient mice developed glucose intolerance and hyperinsulinemia, but still showed normal serum NEFA and glycerol levels. During the insulin tolerance test (ITT) and hyperinsulin-hyperglycemia clamp test, insulin partially inhibited lipolysis in akt2-deficient mice. Consistent with the in vivo results, insulin antagonized the lipolysis of primary brown adipocytes from Akt2-deficient mice induced by catecholamines. These data suggest that insulin inhibits lipolysis in the absence of Akt2 in hyperinsulinemia conditions.[49] Studies have shown that zinc finger protein transcription factor (Snail1) in adipocytes inhibit ATGL expression and lipolysis, while insulin increases the levels of Snail1 in mouse and human adipocytes, thereby regulating lipolysis.[50] A recent study found that physiologically low levels of insulin converted CD11c- adipose tissue macrophages (ATMs) into CD11c+ATMS that produce GDF3 and increase lipid accumulation dependent on ALK7 in vivo. In ALK7-intact obese mice, depletion of ATMs by clodronate upregulated lipase activity and reduced fat mass, but in ALK7 deficient mice, the opposite was observed. Meanwhile, ALK7 intact mice showed attenuated effects of insulin on lipolysis and lipid accumulation in vivo after ATMS removal or bone marrow transplantation from mice lacking GDF3, which represents a new mechanism of insulin regulating lipid metabolism.[51]

In addition, genes encoding various enzymes involved in adipogenesis, such as fatty acid synthetase (FASN), are transcribed and activated by insulin to stimulate adipogenesis.[52] Chakrabarti[53,54] found that insulin can reduce ATGL transcription through the mTORc1-mediated pathway, thereby inhibiting lipolysis and promoting triglyceride storage. High plasma insulin levels lead to the dephosphorylation of acetyl-CoA carboxylase, thereby promoting acetyl-CoA converting to malonyl-CoA and the conversion of carbohydrates into fatty acids.[55–57] Campbell[58] found that the re-esterification process of FFAs had marked insulin sensitivity. When increasing insulin concentration, although the absolute rate of FFA re-esterification in adipocytes remains unchanged, the amount of FFAs involved in re-esterification is twice that in the basal state, indicating that insulin can promote FFA re-esterification and indirectly inhibit lipolysis.

Insulin Resistance Results in Abnormal Lipolysis

The abnormal function of insulin leads to unstable systemic lipolysis. In obese individuals, the increase in basal lipolysis is closely related to insulin resistance, but not to BMI or age.[48,59] Studies have shown that insulin reduces the outflow of signals from the sympathetic nervous system to WAT, while excessive diets may impair insulin function in the hypothalamus, which may lead to uncontrolled lipolysis in patients with obesity and type 2 diabetes.[60] To study the relationship between lipolysis and insulin sensitivity in humans, Langin[61] studied 367 subjects and measured spontaneous glycerol release in vitro after overnight fasting. The results showed a positive correlation between glycerol release and the homeostasis model assessment of insulin resistance (HOMA-IR). When adjusting for age, sex, and body mass index, 8% of HOMA-IR variation was still explained by lipolysis, suggesting a relationship between the high lipolysis of adipose tissues and insulin resistance. Meanwhile, insulin tolerance was assessed in 126 subjects after intravenous insulin administration. A negative association was identified between insulin tolerance and lipolysis. Next, lipolysis and HOMA-IR were measured in 25 patients with morbid obesity who had previously undergone bariatric surgery. The results showed that the lower the lipolysis rate, the more significant the improvement in insulin resistance. Previous studies have shown that the production of endogenous glucose and the lipolysis rate of adipose tissue are very sensitive to circulating insulin. For individuals with

obesity but normal glucose tolerance, hyperinsulinemia within the normal physiological range can compensate for the insulin resistance of the liver and adipose tissue.[62] This indicates that there may be a mutual regulatory relationship between adipose lipolysis and insulin.

Anti-Lipolysis Regulation by Insulin for Morphological Differences in Adipose Tissue

The abnormal morphology of adipose tissue leads to changes in the microenvironment of the tissue, which impairs the function of insulin. The morphology of adipose tissue is positively correlated with lipolysis and inversely correlated with insulin-stimulated adipogenesis.[63] At present, studies have found that insulin resistance is not dependent on insulin, but is instead primarily driven by the morphological changes of adipose tissue.[64] However, the mechanism through which adipose tissues act on the anti-lipolysis process in insulin has not yet been clarified. The deletion of FSP27, which is related to the formation of lipid droplets in human adipocytes, increases lipolysis and inhibits insulin signal transduction by suppressing the phosphorylation of AKT.[65,66] Hypertrophy and lipodystrophy represent two abnormal morphologies of adipose tissue, both resulting in the dysfunction of lipolysis and lipid metabolism. The functional alterations induced by morphological changes in adipose tissue might impair the anti-lipolytic function of insulin directly or indirectly (Figure 2).

Anti-Lipolysis Induced by Insulin in Adipose Hypertrophy

In individuals with obesity, basal lipolysis increases but lipolysis stimulated by catecholamine decreases. Impaired sensitivity to insulin signals in adipocytes may be a cause of the increased basal lipolysis.[67] Clinical studies have shown that in adults with obesity, insulin poorly inhibits lipolysis, which may indicate that the hypertrophy of adipose tissue is resistant to insulin anti-lipolysis.[68] Clinically, it showed less insulin sensitivity in young adults with obesity accompanied by impaired glucose tolerance, including insufficient insulin action inhibiting lipolysis and lipid oxidation, as well as β-cell dysfunction in lipid and glucose metabolism.[69]

Wueest[70] showed that adipose tissue lipolysis mediated by glycoprotein 130 (gp130) promotes liver steatosis and insulin resistance. Kuang[71] found that adipose-specific SIRT6 knockout (FKO) was sensitive to diet-induced obesity, in which adipocyte hypertrophy exists, rather than adipocyte hyperplasia. Specific knockout of SIRT6 in adipose tissues increased the phosphorylation and acetylation of FoxO1, thereby reducing the transcriptional activity of ATGL, leading to reduced lipolysis levels in vivo. The increased inflammation of adipose tissue in FKO mice may also lead to insulin resistance in a high-fat diet. A recent study[72] showed that, compared to the adipocytes of lean individuals, anti-lipolysis and adipogenesis activities sensitive to insulin in adipocytes from individuals who are overweight or obese significantly receded. In particular, anti-

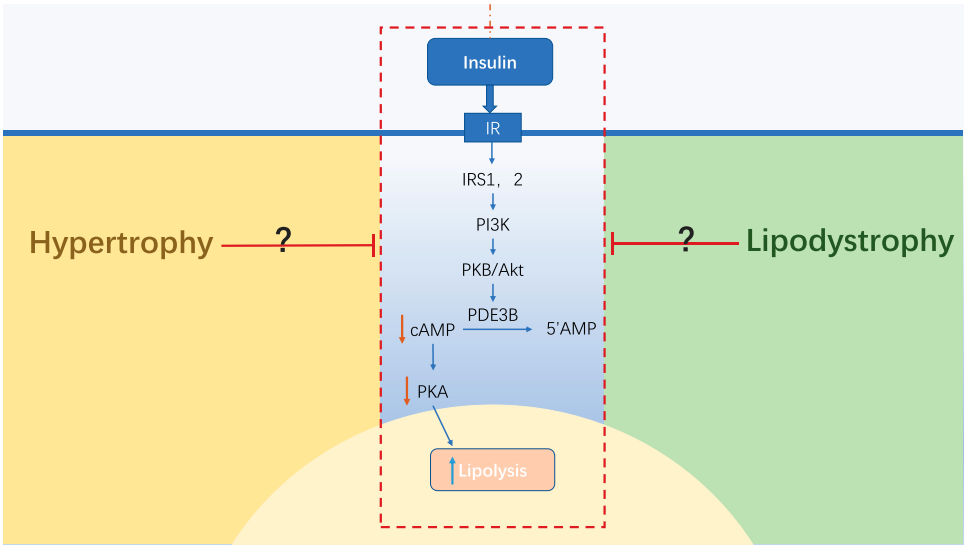

Figure 2 Anti-lipolysis regulation by insulin on the morphological differences of adipose tissue. The abnormal morphology of adipose tissues leads to changes in its microenvironment, which impairs the anti-lipolytic function of insulin by inhibiting the insulin signaling pathway. However, the mechanism through which adipose tissue acts on the anti-lipolysis process in insulin has not yet been clarified. Blue→: promotion; Red →: inhibition; Red↓: reduction; Blue↑: increase.
Abbreviations: IR, insulin receptor; IRS, insulin receptor substrate.

lipolysis sensitivity correlated with systemic insulin sensitivity. These differences were already evident in the overweight state, were only slightly worse in the unhealthy obese state, and were not related to adipocyte size. The following analysis showed that the epigenetic dysregulation of AKT2 is involved in disturbed adipocyte insulin signaling.

Insulin inhibits lipolysis in adipose tissue through the PI3K/Akt pathway. However, in patients with obesity, the PI3K signaling pathway is inhibited. When insulin/PI3K signaling is blocked, β-cells produce more insulin to maintain normal glucose and lipid levels, but the adipose tissues fail to efficiently respond to insulin, leading to increased circulation levels of FFAs and subsequent obesity-related metabolic diseases.[73,74] This indicates that the unhealthy expansion of adipose impairs insulin sensitivity, in which the anti-lipolysis effect of insulin is altered by adipose tissue hypertrophy.

Previous studies have found that TGF-β is related to obesity in humans and mice.[75–79] The TGF-β/Smad3 pathway is upregulated in obese adipose tissue, and TGF-β signaling factor Smad3 occupies the promoter of the insulin gene and inhibits insulin gene transcription. In Smad3 knockout mice fed a high-fat diet, it was found that mice showed increased insulin sensitivity without the obesity phenotype, suggesting that the absence of Smad3 enhances insulin sensitivity and prevents diet-induced obesity and insulin resistance.[80] These results suggest that, via the inhibition of the TGF-β pathway, upregulating the PI3K/Akt signal is a potential strategy to improve insulin sensitivity in adipose tissue hypertrophy.

Anti-Lipolysis Induced by Insulin in Lipodystrophy

According to previous studies, compared to the adipocytes found in patients with obesity, smaller adipocytes have higher sensitivity to insulin-stimulated glucose uptake, higher glucose oxidation levels, and lower sensitivity to anti-lipolysis.[81–83] However, when adipocytes are deficient in lipid storage and catabolism, they are insufficient to maintain homeostasis. Adipocyte-specific insulin receptor gene knockout mice display lipodystrophy with severe insulin resistance, hyperglycemia, organ enlargement, and adipokine secretion disorders, suggesting the indispensable role of insulin signaling in adipose tissue development,[84] and that the dysfunction of insulin might also give rise to lipodystrophy.

Lipodystrophy is a rare disease characterized by the selective loss of body fat, although the extent of fat loss varies and can be caused by genetic defects or acquired diseases. Adipocytes of lipodystrophy individuals are generally smaller, and fat loss is proportional to the total adipocyte amount. Insulin resistance, dyslipidemia, hypertension, and diabetes mellitus are often associated with lipodystrophy, and the extent of fat loss determines the extent of the metabolic disease.[85]

Studies have shown that the abnormal mitochondrial function of white adipose tissue may be related to the secretion of lipid metabolites and lactic acid, which leads to insulin resistance in peripheral tissues.[86] However, the correlation between the energy metabolism of adipose tissue and insulin sensitivity remains to be elucidated. It is notable that the double deficiency of Cidea and Cidec activates both WAT and BAT to consume more energy and increase insulin sensitivity.[87] Wei[88] found that Plin1 knockout mice had reduced lipid accumulation and increased adipose lipid catabolism and fatty acid efflux, thus, impairing insulin sensitivity in adipose tissue, suggesting that Plin1 may be a potential target for regulating insulin function in adipose tissue. In clinical practice, Brown[89] regarded lipodystrophy as a human model of leptin deficiency and found that recombinant leptin (Metrelptin) can improve insulin sensitivity, reduce liver steatosis, and lower circulating triglycerides independently of food intake restriction induced by leptin, suggesting that leptin may be a regulatory site of insulin resistance in lipodystrophy. In individuals with obesity, treatment with partial leptin reduction restores hypothalamic leptin sensitivity and leads to reduced food intake, increased energy expenditure, and improved insulin sensitivity.[90] However, how leptin affects insulin resistance in the case of lipodystrophy remains unclear.

Lipolysis activity in patients with lipodystrophy is currently ambiguous. The A-ZIP/F-1 "leanness" mouse is a model for studying lipodystrophy that has notable dyslipidemia and insulin resistance and lower levels of lipolysis.[91] AP2-SREBP1c overexpressing mice are another model of lipodystrophy that show significant insulin resistance. Overexpression of nSREBP1c in adipose tissue leads to systemic fat loss and severe metabolic syndrome. In a previous study, the mRNA levels of PPARγ, C/EBPα, and some lipoproteins related to adipocyte differentiation were significantly decreased. The mRNA levels of insulin receptor, insulin receptor substrate, and GLUT4, which are related to insulin function, were also significantly decreased.[92–94]

As an insulin-sensitive organ, the atrophy of WAT impacts the function of insulin, which is largely reflected in the

inhibition of insulin's anti-lipolytic action. In theory, imperfect insulin function leads to increased levels of WAT lipolysis, but in the case of lipodystrophy, lipolysis is more complicated. On the one hand, due to the loss of WAT, fewer adipocytes respond to insulin. On the other hand, as a result of the metabolic disorder caused by lipodystrophy, insulin loses its function in anti-lipolysis, leading to an imbalance in lipolysis that impairs metabolic stability. Therefore, it is necessary to understand the mechanism by which immature adipose tissue impacts insulin function, especially the lipolysis levels, in insulin-resistant adipose tissue in the lipodystrophic state.

Discussion

Obesity and lipodystrophy seem to be opposing diseases, yet both share similar pathological features, including insulin resistance, hepatic steatosis, and unstable adipokine levels.[95] These pathological differences might in turn alter the morphology and function of adipose tissue, leading to abnormal FFA levels, impairing normal lipid metabolism. As mentioned above, excess circulating FFA may accumulate in insulin-sensitive tissues, impairing insulin sensitivity. Increased basal lipolysis may also alter the microenvironment of adipose tissue and worsen systemic insulin sensitivity. Meanwhile, excessive release of FFAs may increase inflammation in adipose tissue, leading to insulin resistance (Figure 3).

As previously discussed, lipolysis levels in adipose tissue are theoretically elevated in insulin resistance due to the inability of insulin to function properly against lipolysis, but this does not appear to be the case. Relevant in vitro studies have shown that insulin has a biphasic effect on lipolysis,[96,97] indicating that the effect of insulin on lipolysis is equivalent to a superposition of synergistic and inhibitory effects, all of which are related to the synthesis of new proteins and the activation of cAMP.[98] In a recent study, mature adipocytes collected from adult women with and without diabetes reached the same conclusion.[99] However, these conclusions are based on in vitro studies and lack corresponding in vivo studies. This suggests that insulin regulates anti-lipolysis depending on adipose tissue state through a specific pathway that is not yet fully understood.

Metabolic diseases, including obesity and diabetes, seriously affect human health. Insulin resistance, as the most important pathological process of metabolic diseases, is needed for effective control. In general, insulin resistance leads to increased levels of lipolysis, and improvement in insulin sensitivity inhibits excessive lipolysis in adipose tissue. Currently, insulin sensitizers, such as TZDs and metformin,

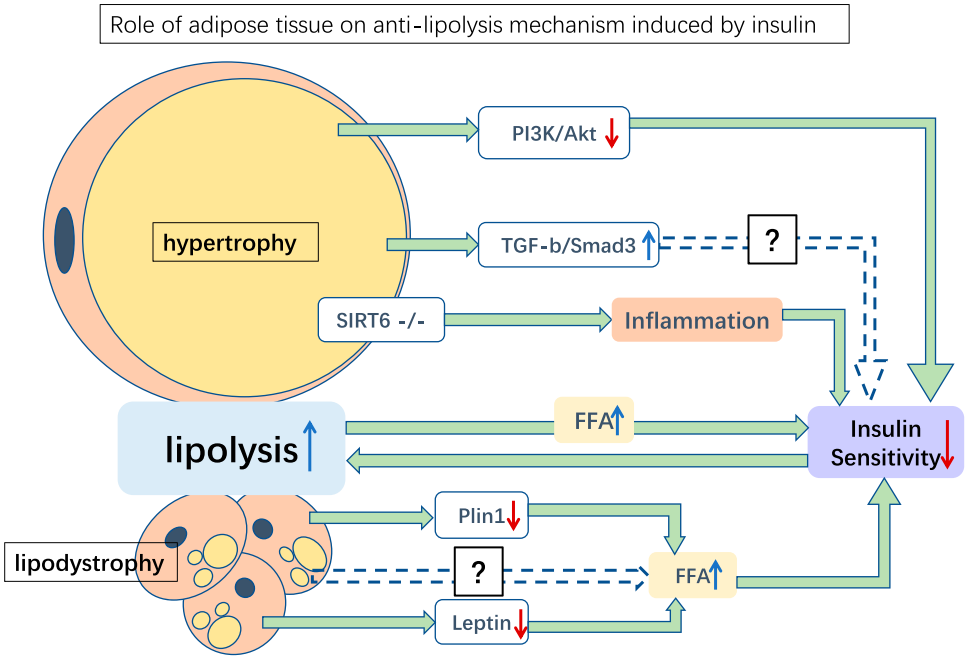

Figure 3 Role of adipose tissue on anti-lipolysis mechanism induced by insulin. Several possible mediations of the anti-lipolysis effect of insulin in hypertrophy and lipodystrophy adipose tissues. Hypertrophy of adipose tissue may damage insulin sensitivity by inhibiting PI3K/Akt, upregulating TGFβ/Smad3, and inhibiting SIRT6, resulting in increased lipolysis. Meanwhile, lipodystrophy adipose tissue downregulates the expression of Plin1 and leptin, thereby increasing FFA levels and reducing insulin sensitivity. Increased lipolysis releases more FFA and aggravates insulin sensitivity damage. Green→: promotion; blue dotted→: potential pathways; red ↓: reduction; blue ↑: increase.
Abbreviation: FFA, free fatty acid.

are widely used in the treatment of insulin resistance. Studies have shown that biguanides and thiazolidinediones inhibit stimulated lipolysis in human adipocytes through the activation of AMP-activated protein kinase.[100] TZDs may attenuate lipolysis and FFA efflux by activating Akt signaling to decrease cAMP levels, thereby reducing lipase activity in adipocytes.[101] The PPARγ receptor agonist troglitazone increases insulin sensitivity in visceral adipocytes, increases fat mass, and interferes with Beta-3-triggered lipolysis.[102] Pioglitazone can mitigate glucocorticoid receptor-induced excessive lipolysis in adipocytes.[103] Clinically, in well-controlled T2DM patients, whole body lipolysis is insulin resistant, pioglitazone improves the insulin sensitivity of lipolysis,[104] and thiazolidinediones can modify GH-induced insulin resistance by suppressing lipolysis.[105] Metformin inhibits lipolysis by preventing PKA/HSL activation by decreasing the accumulation of cAMP by preserving PDE3B.[106] It has also been found that metformin decreases cellular cAMP production, reduces the activities of PKA and MAPK1/3, and attenuates the phosphorylation of perilipin during isoproterenol-stimulated lipolysis.[107] These studies have shown that insulin sensitizers effectively inhibit excessive lipolysis by stimulating the insulin signaling pathway.

Obesity and lipodystrophy are two different abnormal morphologies of adipose tissue that both affect insulin function. Recent studies have confirmed that improving lipolysis in adipose tissue can enhance insulin sensitivity, but the mechanism is not presently clear, especially in the two extreme states. Preclinical studies have shown that inhibiting lipolysis may be an effective treatment strategy for patients with obesity or early stages of diabetes.[108,109] However, at present, there is no effective inhibitor applicable to the human body. Therefore, identifying targets acting on the insulin antilipolysis pathway (to improve insulin sensitivity by regulating lipolysis levels) to effectively rescue morphological and functional conversion will provide a new direction for our future research regarding the treatment of insulin resistance.

Acknowledgments

This study was sponsored by the National Natural Science Foundation of China (No: 81274156), the Natural Science Foundation of Guangdong Province (No: 2015A0303 11033), and the Science and Technology Planning Project of Guangdong Province (No: 2017B050504005).

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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