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Contributions Of Adipocyte Lipid Metabolism To Body Fat Content And Implications For The Treatment Of Obesity

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Abstract

Obesity is a chronic disease that increases susceptibility to various diseases, particularly cardiovascular dysfunction, type 2 diabetes and some types of cancer. In this review, we highlighted recent evidence in mouse models that support a potential benefit of increasing adipose lipid utilization through stimulating lipolysis in adipose tissue and fatty acid oxidation. Brown adipocyte development within white adipose tissue of humans suggests that mouse models may be applicable to human obesity. Consequently, new therapies should target adipose tissue to specifically reduce fat mass through controlled triglyceride utilization.

Introduction

In most mammals, adipose tissue can undergo hypertrophy, causing obesity, or pathological atrophy that leads to lipodystrophy. The obese state results from an imbalance between caloric intake and energy expenditure. Consequently, excess circulating fuel is mainly stored in adipose tissue but also in ectopic sites, such as liver (causing hepatosteatosis), muscle, pancreas and the kidneys. Excess triglyceride (TG) storage in these ectopic sites is clearly associated with insulin resistance, glucose intolerance, dyslipidemia and hypertension. Adipose metabolism acts to buffer nutrient excess in promoting lipid storage with increased adipogenesis and lipogenesis [1].

There are two morphologically distinct types of adipose tissue: the white adipose tissue (WAT) and the brown adipose tissue (BAT). The WAT is the predominant type, located in the subcutaneous region and distinct visceral regions surrounding the internal organs, such as the heart, intestine, kidneys and gonads. The major function of WAT is storage of energy as TG within lipid droplets to supply the whole organism in time of energy restriction. Additionally, secretion of adipokines from WAT (i.e. adiponectin, leptin) regulate overall energy balance. The BAT exists in rodents and humans, with its primary role as a thermogenic organ. Brown fat in normal adult humans has recently been shown to be functional in terms of responsiveness to beta adrenergic stimulation and heat generation [2].

Strategies that aim to increase TG hydrolysis (lipolysis) and subsequent fatty acid utilization might be useful in ameliorating or preventing obesity. Such a strategy of inducing preferential TG utilization would be highly desirable to preserve lean mass, as weight loss is typically

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associated with an obligatory loss of lean mass due to the inflexibility of substrate utilization [3] [4]. Nevertheless, elevated circulating free fatty acid (FFA) concentrations, and this has been associated with accumulations of TG in ectopic sites. Also, promoting increased fatty acid oxidation in skeletal muscle leads to myopathy [5] and favouring cardiac lipid utilization results in cardiomyopathy [6]. Consequently, these observations suggest that a balance of substrate oxidation is critically important to the long term health of various tissues. A concomitant increase in the rate of fatty acid oxidation can compensate for the increase in fatty acid release from adipose tissue, preventing an increase in circulating FFA concentrations [7]. Adipocyte fatty acid utilization is also triggered in some situations where WAT can acquire phenotypic and molecular features of BAT [8]. This phenotypic switch of WAT from an energy storing organ to an energy burning organ could be utilized as a therapeutic modality in disorders of energy balance and obesity.

Lipolysis in white adipose tissue

Switching between TG storage to TG hydrolysis

With excess caloric intake and low physical activity, energy balance is tipped into storage mode and adipose tissue functions as the major energy storage organ. Within the adipocyte, FFA are esterified into triglycerides that are packed into lipid droplets (Figure 1A). During times of increased energetic demand, WAT has the ability to switch to acting as a nutrient provider to the other organs [9]. In this context, induction of lipolysis is the essential mechanism that triggers the breakdown of triglycerides stored in fat cells and release of FFAs and glycerol (Figure 1B). The balance between lipogenesis and lipolysis is primarily under the control of insulin and leptin [10] [11] [12] [13]. While insulin has direct and indirect effects on adipocytes, leptin primarily uses central nervous system mediators to act upon the adipocyte. In the arcuate nucleus of the hypothalamus (ARH), leptin-responsive POMC neurons down-regulate food intake and promote lipolysis. Stimulation of the melanocortinergic system triggers WAT lipolysis independently of its effects on feeding behavior [14]. This melanocortinergic induction is mediated by the sympathetic system that separately innervates the different WAT and BAT depots [15]. In rodents as well as humans, the sympathetic nervous system is the primary initiator of lipolysis [9]. In the absence of leptin signaling, lipolysis is greatly inhibited while lipogenesis is enhanced, favoring triglyceride storage within adipocytes [16].

The lipolytic machinery

White fat cells are characterized by a large and unique lipid droplet (unilocular) that is mainly composed of triglycerides and cholesterol esters surrounded by a phospholipid and cholesterol monolayer coated with proteins [12]. The lipid droplet coat is a dynamic structure as some rearrangement and recruitment occurs in response to lipolytic stimuli. Adipocyte triglyceride lipase (ATGL) and hormone sensitive lipase (HSL) assume the triglyceride hydrolase activities in adipose tissue. Lipolysis typically occurs through catecholamine-stimulation of beta-adrenergic receptors and the subsequent activation of protein kinase A (PKA). The two major lipolytic targets of PKA in adipocytes are hormone-sensitive lipase (HSL) and perilipin A. HSL is the only known neutral lipid lipase regulated by PKA-mediated phosphorylation. Upon PKA activation, phosphorylated HSL translocates to the lipid droplet where HSL hydrolyzes triglycerides. In addition, activation of lipolysis is also strictly dependent on the PKA-mediated phosphorylation of perilipin A [17]. It is thought that perilipin A functions as a protective coat, surrounding the lipid droplet until phosphorylated by PKA, whereupon it undergoes a conformational change, leaving the lipid droplet as an open target for HSL [18]. Lipid droplet associated proteins are also important regulators of lipolysis. For instance, caveolin 1 (CAV-1), selectively associates with droplets in stimulated cells and may function as a bridge between perilipin A and PKA's catalytic site to facilitate perilipin A phosphorylation [19]. Regarding ATGL, neither PKA or other enzymatic modification has yet been shown to modulate its

activity. Expression level and binding to CGI-58 are the main determinants of ATGL activity [20]. More recently, G0S2 has been shown to attenuate ATGL TG hydrolase activity [21]. In mice, deletion of HSL does not alter basal (i.e. unstimulated) adipocyte lipolysis [22] [23] suggesting that HSL is not critical for basal TG hydrolysis. Meanwhile, ATGL loss of function only affects stimulated lipolysis [20] [24] and ATGL overexpression [25] increased both basal and stimulated lipolysis.

In humans, an HSL specific inhibitor was used to determine the relative contribution of HSL and ATGL in adipocyte lipolysis. Basal glycerol release but not basal fatty acid release was blunted by HSL inhibition. Additionally, in catecholamine-induced lipolysis, there was an almost complete absence of glycerol release and a blunted FFA release in the presence of the HSL inhibitor [26] [27]. Thus, ATGL and HSL appear to have complementary role in basal lipolysis. Additionally, ATGL hydrolase activity is crucial to provide diglycerides to HSL in both basal and stimulated conditions as HSL does not hydrolyze triglycerides efficiently.

Lipolysis in obesity

In mice, inhibiting [24] or enhancing lipolysis [25] has been shown to promote or prevent, respectively, diet-induced obesity and its associated metabolic defects. In humans, both HSL and ATGL protein expression are decreased in adipose tissue from obese patients compared to lean individual [27] [28]. Additionally, resistance to catecholamine-induced lipolysis in subcutaneous adipose tissue has been demonstrated in obese adults and children and is the likely cause of decreased expression of lipolytic β 2-adrenoreceptors and HSL [27]. Also, similar rates of lipid oxidation have been reported in lean and obese men following experimentally-induced increases of circulating FFA [29]. Thus, based on these observations in mouse and human, it is likely that impaired lipolysis, which fails to mobilize lipids stored in adipose tissue, is a contributing factor to obesity.

Fatty acid oxidation in adipocytes

Brown adipose tissue and its function in the overall energetic balance

Historically, brown fat tissue was mainly characterized in rodents and human infants. Combined positron-emission tomography and computed tomography (PET-CT) has been used to identify metabolically active adipose tissue with a high rate of uptake of ^{18}F -fluorodeoxyglucose (^{18}F -FDG) as putative brown adipose tissue in adult humans. As opposed to the white fat cells, brown adipocytes store lipid in multiple small lipid droplets (multilocular) and its main function is to participate in thermogenesis by burning its fat store in response to sympathetic nerve activation [30]. The numerous mitochondria of brown fat cells uncouple large amounts of fuel oxidation from membrane potential generation for the hydrolysis of ATP. This uncoupling is caused by the specific presence of uncoupling protein-1 (UCP1), located in the inner mitochondrial membrane, which catalyzes a leak of protons from the intramembranous space into the mitochondrial matrix [31].

The most common locations for brown adipose tissue that were detectable in adults by PET-CT were the cervical, supraclavicular, and superior mediastinal depots. Histological analyses reveal that UCP1-positive brown fat cells are clustered within white adipose tissue [32]. These brown-fat islands displayed other important brown-fat features, such as dense innervation and a dense capillary network, numerous mitochondria in the cytoplasm and small cytoplasmic lipid droplets [33].

Brown fat has been recognized for its potential to expend energy with demonstrated anti-obesity properties. Indeed, genetic ablation of the brown fat in mice results in obesity and metabolic defects [34]. According to the concept that energy intake is able to stimulate the expansion and activation of brown adipose tissue, it has been shown that UCP-1 ablated mice,

when maintained at thermoneutrality, developed obesity [35]. Conversely, hyperactivation of brown fat function led to a lean phenotype with higher energy expenditure and more active lipid metabolism [36] [37]. Human studies suggest a comparable function of the brown fat as BAT activity was significantly lower in the overweight or obese subjects relative to the lean subjects [38] [39].

Phenotypic switch of WAT into “brown like” adipose tissue and examples of therapeutic implication

Adipose fatty acid oxidation is mainly accomplished by the brown adipose tissue due to expression of a specific set of proteins. Nevertheless, it has been shown in mice that white adipocytes can also be converted into an energy consuming organ even in the absence of caloric restriction. Thus, these fat burning white adipocytes may play a significant role in reducing triglyceride storage and improving the metabolic defects associated to obesity. This shift can be induced *in vivo* in obese mice treated with a specific beta 3 adrenoreceptor agonist [8]. Indeed, adrenergic stimulation induces brown adipocytes to appear in WAT, marked by the expression of UCP1 and brown fat morphological characteristics [8].

Several studies using genetically modified mice have made valuable contributions to our understanding of adipocyte metabolism and have identified different molecular determinants that participate in this phenotypic shift. For example, *p107* deletion [40], increased FOXC2 expression [41], defective mTORC1 signaling [42], *Atg7* inactivation (autophagy modulation) [43], and hedgehog activation [44] have been shown to trigger a partial WAT transdifferentiation into BAT. Altogether, the histological, physiological and molecular features of BAT appearing in the WAT depot are accompanied with a high level of lipid utilization and a lean phenotype.

These mouse models are a critical tool for the design of a therapeutic strategy. For instance, autophagy represents an appealing therapeutic target as mouse models revealed its association with energetic metabolism. Indeed, inhibition of autophagy enhances intracellular lipid storage in hepatocytes [45]. In contrast, inhibition of autophagy in adipocytes using genetic and pharmacological methodologies inhibits adipocyte differentiation [43]. Small molecules known to influence the autophagic process do not act directly but involve indirect mechanisms or exert other parallel effects. Thus, to further analyze *in vivo* consequences of manipulating autophagy, more specific small molecules may be necessary [46].

On another front, the adipose tissue phenotype of genetic obesity models probably involve a developmental component. Predicting the consequences of targeting these pathways in a therapeutic manner to decrease established obesity is not a simple proposition. Indeed, some mechanistic differences can be found between a genetic model and the corresponding pharmacological treatment. For example, acute inhibition of mTORC1 signaling by rapamycin stimulates lipolysis primarily via activation of ATGL expression [47] while developmental lethality prevents analysis of adult mice with loss of mTOR signaling. Interestingly, mTOR inhibitors have been already developed for their immunosuppressive effect after organ transplantation. One of these, sirolimus, is associated with decreased body weight and reduced adipocyte size in rats [48]. Similarly, transplanted patients treated with sirolimus displayed a decreased BMI as compared to patients undergoing cyclosporine treatment [48]. Thus, inhibition of mTOR signaling may be a promising treatment for reducing adipose mass.

Conclusions

Major therapies that are in development target the central control of satiety. However, caloric reduction is accompanied by reductions in both fat and lean mass, which in turn, may contribute to the reduction in resting metabolism in the formerly obese [4]. Additionally, reductions in

both fat and lean mass rather than a specific loss of fat mass lowers the metabolic benefits of weight loss. Consequently, new therapies should target adipose tissue to specifically reduce fat mass. In this review, we highlighted evidence that supports the beneficial potential of increasing adipose lipid utilization through lipolysis and fatty acid oxidation. Evidence for functional β_3 adrenoreceptor (β_3 -AR) in human white adipose tissue that can promote the mobilization of fatty acids have led a number of pharmaceutical companies to design highly selective compounds. β_3 -AR agonists demonstrate benefits of stimulating fat oxidation in humans and rodents but the second-generation compounds had poor bioavailability or pharmacokinetics [49]. Consequently, further understanding of the positive regulators of these pathways may be useful. Indeed, the ability of exogenous growth hormone (GH) to stimulate the release and oxidation of FFA has been associated with fat loss in human [50]. Also, atrial natriuretic peptide (ANP) has been shown to promote human adipose tissue lipolysis and systemic post prandial lipid oxidation in human [51] [52]. IL-6 [53], TNF α [54] secreted from adipocytes can impact on adipocyte metabolism by stimulating lipolysis. Finally, inhibition of PGE2 production in WAT due to loss of *Adpla2* was shown to disinhibit adipocyte lipolysis and to protect against obesity induced by high-fat feeding or leptin deficiency [7].

In summary, mouse studies have highlighted new molecular actors that regulate adipocyte metabolism and further investigation is needed to evaluate their potential to prevent or reverse obesity.

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References

- Hofbauer KG. Molecular pathways to obesity. *Int J Obes Relat Metab Disord* 2002;26(Suppl 2):S18–27. [PubMed: 12174325]
- Seale P, Kajimura S, Spiegelman BM. Transcriptional control of brown adipocyte development and physiological function--of mice and men. *Genes Dev* 2009;23(7):788–797. [PubMed: 19339685]
- Levin N, Nelson C, Gurney A, Vandlen R, de Sauvage F. Decreased food intake does not completely account for adiposity reduction after ob protein infusion. *Proc Natl Acad Sci U S A* 1996;93(4):1726–1730. [PubMed: 8643697]
- Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, Klein S, Ehsani AA, Holloszy JO. Lower extremity muscle size and strength and aerobic capacity decrease with caloric restriction but not with exercise-induced weight loss. *J Appl Physiol* 2007;102(2):634–640. [PubMed: 17095635]
- 5*. Levak-Frank S, Radner H, Walsh A, Stollberger R, Knipping G, Hoefler G, Sattler W, Weinstock PH, Breslow JL, Zechner R. Muscle-specific overexpression of lipoprotein lipase causes a severe myopathy characterized by proliferation of mitochondria and peroxisomes in transgenic mice. *J Clin Invest* 1995;96(2):976–986. This study highlight the importance of balanced substrate utilization in skeletal muscle as over fatty acid oxidation can be deleterious. [PubMed: 7635990]
- Yagy H, Chen G, Yokoyama M, Hirata K, Augustus A, Kako Y, Seo T, Hu Y, Lutz EP, Merkel M, Bensadoun A, et al. Lipoprotein lipase (LpL) on the surface of cardiomyocytes increases lipid uptake and produces a cardiomyopathy. *J Clin Invest* 2003;111(3):419–426. [PubMed: 12569168]
- 7**. Jaworski K, Ahmadian M, Duncan RE, Sarkadi-Nagy E, Varady KA, Hellerstein MK, Lee HY, Samuel VT, Shulman GI, Kim KH, de Val S, et al. AdPLA ablation increases lipolysis and prevents obesity induced by high-fat feeding or leptin deficiency. *Nat Med* 2009;15(2):159–168. This work provides evidence that increased lipid utilization in adipose tissue can prevent excess TG accumulation due to high fat feeding or leptin deficiency. [PubMed: 19136964]
- Guerra C, Koza RA, Yamashita H, Walsh K, Kozak LP. Emergence of brown adipocytes in white fat in mice is under genetic control. Effects on body weight and adiposity. *J Clin Invest* 1998;102(2):412–420. [PubMed: 9664083]

- 9**. Lafontan M, Langin D. Lipolysis and lipid mobilization in human adipose tissue. *Prog Lipid Res* 2009;48(5):275–297. An extensive review that discuss both cellular and molecular aspects of lipolysis regulation in mouse and human. [PubMed: 19464318]
10. Buettner C, Muse ED, Cheng A, Chen L, Scherer T, Pocai A, Su K, Cheng B, Li X, Harvey-White J, Schwartz GJ, et al. Leptin controls adipose tissue lipogenesis via central, STAT3-independent mechanisms. *Nat Med* 2008;14(6):667–675. [PubMed: 18516053]
11. Choi YH, Park S, Hockman S, Zmuda-Trzebiatowska E, Svnnelid F, Haluzik M, Gavrilova O, Ahmad F, Pepin L, Napolitano M, Taira M, et al. Alterations in regulation of energy homeostasis in cyclic nucleotide phosphodiesterase 3B-null mice. *J Clin Invest* 2006;116(12):3240–3251. [PubMed: 17143332]
12. Duncan RE, Ahmadian M, Jaworski K, Sarkadi-Nagy E, Sul HS. Regulation of lipolysis in adipocytes. *Annu Rev Nutr* 2007;27:79–101. [PubMed: 17313320]
- 13**. Ahmed K, Tunaru S, Tang C, Muller M, Gille A, Sassmann A, Hanson J, Offermanns S. An autocrine lactate loop mediates insulin-dependent inhibition of lipolysis through GPR81. *Cell Metab* 11(4):311–319. This study highlight a regulatory mechanism that link carbohydrate and lipid metabolism. [PubMed: 20374963]
14. Nogueiras R, Wiedmer P, Perez-Tilve D, Veyrat-Durebex C, Keogh JM, Sutton GM, Pfluger PT, Castaneda TR, Neschen S, Hofmann SM, Howles PN, et al. The central melanocortin system directly controls peripheral lipid metabolism. *J Clin Invest* 2007;117(11):3475–3488. [PubMed: 17885689]
15. Brito MN, Brito NA, Baro DJ, Song CK, Bartness TJ. Differential activation of the sympathetic innervation of adipose tissues by melanocortin receptor stimulation. *Endocrinology* 2007;148(11):5339–5347. [PubMed: 17702843]
16. Siegrist-Kaiser CA, Pauli V, Juge-Aubry CE, Boss O, Permin A, Chin WW, Cusin I, Rohner-Jeanraud F, Burger AG, Zapf J, Meier CA. Direct effects of leptin on brown and white adipose tissue. *J Clin Invest* 1997;100(11):2858–2864. [PubMed: 9389752]
17. Brasaemle DL, Subramanian V, Garcia A, Marcinkiewicz A, Rothenberg A. Perilipin A and the control of triacylglycerol metabolism. *Mol Cell Biochem* 2009;326(1-2):15–21. [PubMed: 19116774]
18. Miyoshi H, Souza SC, Zhang HH, Strissel KJ, Christoffolete MA, Kovsan J, Rudich A, Kraemer FB, Bianco AC, Obin MS, Greenberg AS. Perilipin promotes hormone-sensitive lipase-mediated adipocyte lipolysis via phosphorylation-dependent and -independent mechanisms. *J Biol Chem* 2006;281(23):15837–15844. [PubMed: 16595669]
19. Cohen AW, Razani B, Schubert W, Williams TM, Wang XB, Iyengar P, Brasaemle DL, Scherer PE, Lisanti MP. Role of caveolin-1 in the modulation of lipolysis and lipid droplet formation. *Diabetes* 2004;53(5):1261–1270. [PubMed: 15111495]
20. Lass A, Zimmermann R, Haemmerle G, Riederer M, Schoiswohl G, Schweiger M, Kienesberger P, Strauss JG, Gorkiewicz G, Zechner R. Adipose triglyceride lipase-mediated lipolysis of cellular fat stores is activated by CGI-58 and defective in Chanarin-Dorfman Syndrome. *Cell Metab* 2006;3(5):309–319. [PubMed: 16679289]
21. Yang X, Lu X, Lombes M, Rha GB, Chi YI, Guerin TM, Smart EJ, Liu J. The G(0)/G(1) Switch Gene 2 Regulates Adipose Lipolysis through Association with Adipose Triglyceride Lipase. *Cell Metab* 2010;11(3):194–205. [PubMed: 20197052]
22. Osuga J, Ishibashi S, Oka T, Yagyu H, Tozawa R, Fujimoto A, Shionoiri F, Yahagi N, Kraemer FB, Tsutsumi O, Yamada N. Targeted disruption of hormone-sensitive lipase results in male sterility and adipocyte hypertrophy, but not in obesity. *Proc Natl Acad Sci U S A* 2000;97(2):787–792. [PubMed: 10639158]
23. Wang SP, Laurin N, Himms-Hagen J, Rudnicki MA, Levy E, Robert MF, Pan L, Oligny L, Mitchell GA. The adipose tissue phenotype of hormone-sensitive lipase deficiency in mice. *Obes Res* 2001;9(2):119–128. [PubMed: 11316346]
24. Haemmerle G, Zimmermann R, Strauss JG, Schoiswohl G, Birner-Gruenberger R, Riederer M, Lass A, Neuberger G, Eisenhaber F, Hermetter A, Zechner R. Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase. *Science* 2004;306(5700):1383–1386. [PubMed: 15550674]

25. Ahmadian M, Duncan RE, Varady KA, Frasson D, Hellerstein MK, Birkenfeld AL, Samuel VT, Shulman GI, Wang Y, Kang C, Sul HS. Adipose overexpression of desnutrin promotes fatty acid use and attenuates diet-induced obesity. *Diabetes* 2009;58(4):855–866. [PubMed: 19136649]
26. Bezaire V, Mairal A, Ribet C, Lefort C, Girousse A, Jocken J, Laurencikiene J, Anesia R, Rodriguez AM, Ryden M, Stenson BM, et al. Contribution of adipose triglyceride lipase and hormone-sensitive lipase to lipolysis in hMADS adipocytes. *J Biol Chem* 2009;284(27):18282–18291. [PubMed: 19433586]
27. Langin D, Dicker A, Tavernier G, Hoffstedt J, Mairal A, Ryden M, Arner E, Sicard A, Jenkins CM, Viguerie N, van Harmelen V, et al. Adipocyte lipases and defect of lipolysis in human obesity. *Diabetes* 2005;54(11):3190–3197. [PubMed: 16249444]
28. Steinberg GR, Kemp BE, Watt MJ. Adipocyte triglyceride lipase expression in human obesity. *Am J Physiol Endocrinol Metab* 2007;293(4):E958–964. [PubMed: 17609260]
29. Schifflers SL, Saris WH, van Baak MA. The effect of an increased free fatty acid concentration on thermogenesis and substrate oxidation in obese and lean men. *Int J Obes Relat Metab Disord* 2001;25(1):33–38. [PubMed: 11244455]
30. Jacobsson H, Bruzelius M, Larsson SA. Reduction of FDG uptake in brown adipose tissue by propranolol. *Eur J Nucl Med Mol Imaging* 2005;32(9):1130. [PubMed: 16133392]
31. Virtanen KA, Lidell ME, Orava J, Heglind M, Westergren R, Niemi T, Taittonen M, Laine J, Savisto NJ, Enerback S, Nuutila P. Functional brown adipose tissue in healthy adults. *N Engl J Med* 2009;360(15):1518–1525. [PubMed: 19357407]
32. van Marken Lichtenbelt WD, Vanhomerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ. Cold-activated brown adipose tissue in healthy men. *N Engl J Med* 2009;360(15):1500–1508. [PubMed: 19357405]
33. Zingaretti MC, Crosta F, Vitali A, Guerrieri M, Frontini A, Cannon B, Nedergaard J, Cinti S. The presence of UCP1 demonstrates that metabolically active adipose tissue in the neck of adult humans truly represents brown adipose tissue. *FASEB J* 2009;23(9):3113–3120. [PubMed: 19417078]
34. Lowell BB, V SS, Hamann A, Lawitts JA, Himms-Hagen J, Boyer BB, Kozak LP, Flier JS. Development of obesity in transgenic mice after genetic ablation of brown adipose tissue. *Nature* 1993;366(6457):740–742. [PubMed: 8264795]
35. Feldmann HM, Golozoubova V, Cannon B, Nedergaard J. UCP1 ablation induces obesity and abolishes diet-induced thermogenesis in mice exempt from thermal stress by living at thermoneutrality. *Cell Metab* 2009;9(2):203–209. [PubMed: 19187776]
36. Zhou Z, Yon Toh S, Chen Z, Guo K, Ng CP, Ponniah S, Lin SC, Hong W, Li P. Cidea-deficient mice have lean phenotype and are resistant to obesity. *Nat Genet* 2003;35(1):49–56. [PubMed: 12910269]
37. Pan D, Fujimoto M, Lopes A, Wang YX. Twist-1 is a PPARdelta-inducible, negative-feedback regulator of PGC-1alpha in brown fat metabolism. *Cell* 2009;137(1):73–86. [PubMed: 19345188]
- 38*. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, Kuo FC, Palmer EL, Tseng YH, Doria A, Kolodny GM, et al. Identification and importance of brown adipose tissue in adult humans. *N Engl J Med* 2009;360(15):1509–1517. The findings that BAT mass is inversely correlated with body mass index suggests a potential role of BAT in adult human metabolism. [PubMed: 19357406]
39. Saito M, Okamatsu-Ogura Y, Matsushita M, Watanabe K, Yoneshiro T, Nio-Kobayashi J, Iwanaga T, Miyagawa M, Kameya T, Nakada K, Kawai Y, et al. High incidence of metabolically active brown adipose tissue in healthy adult humans: effects of cold exposure and adiposity. *Diabetes* 2009;58(7):1526–1531. [PubMed: 19401428]
40. Scime A, Grenier G, Huh MS, Gillespie MA, Bevilacqua L, Harper ME, Rudnicki MA. Rb and p107 regulate preadipocyte differentiation into white versus brown fat through repression of PGC-1alpha. *Cell Metab* 2005;2(5):283–295. [PubMed: 16271529]
41. Cederberg A, Gronning LM, Ahren B, Tasken K, Carlsson P, Enerback S. FOXC2 is a winged helix gene that counteracts obesity, hypertriglyceridemia, and diet-induced insulin resistance. *Cell* 2001;106(5):563–573. [PubMed: 11551504]
42. Polak P, Cybulski N, Feige JN, Auwerx J, Rugg MA, Hall MN. Adipose-specific knockout of raptor results in lean mice with enhanced mitochondrial respiration. *Cell Metab* 2008;8(5):399–410. [PubMed: 19046571]

- 43*. Singh R, Xiang Y, Wang Y, Baikati K, Cuervo AM, Luu YK, Tang Y, Pessin JE, Schwartz GJ, Czaja MJ. Autophagy regulates adipose mass and differentiation in mice. *J Clin Invest* 2009;119(11):3329–3339. Autophagy can regulate lipid mass by controlling adipocyte differentiation and the ration brown versus white adipose tissue mass. [PubMed: 19855132]
44. Pospisilik JA, Schramek D, Schnidar H, Cronin SJ, Nehme NT, Zhang X, Knauf C, Cani PD, Aumayr K, Todoric J, Bayer M, et al. Drosophila genome-wide obesity screen reveals hedgehog as a determinant of brown versus white adipose cell fate. *Cell* 2010;140(1):148–160. [PubMed: 20074523]
45. Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. *Nature* 2009;458(7242):1131–1135. [PubMed: 19339967]
46. Rubinsztein DC, Gestwicki JE, Murphy LO, Klionsky DJ. Potential therapeutic applications of autophagy. *Nat Rev Drug Discov* 2007;6(4):304–312. [PubMed: 17396135]
47. Chakrabarti P, English T, Shi J, Smas CM, Kandror KV. Mammalian target of rapamycin complex 1 suppresses lipolysis, stimulates lipogenesis, and promotes fat storage. *Diabetes* 59(4):775–781. [PubMed: 20068142]
48. Rovira J, Marcelo Arellano E, Burke JT, Brault Y, Moya-Rull D, Banon-Maneus E, Ramirez-Bajo MJ, Gutierrez-Dalmau A, Revuelta I, Quintana LF, Campistol JM, et al. Effect of mTOR inhibitor on body weight: from an experimental rat model to human transplant patients. *Transpl Int* 2008;21(10):992–998. [PubMed: 18657090]
49. Arch JR. The discovery of drugs for obesity, the metabolic effects of leptin and variable receptor pharmacology: perspectives from beta3-adrenoceptor agonists. *Naunyn Schmiedebergs Arch Pharmacol* 2008;378(2):225–240. [PubMed: 18612674]
50. Franco C, Brandberg J, Lonn L, Andersson B, Bengtsson BA, Johannsson G. Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. *J Clin Endocrinol Metab* 2005;90(3):1466–1474. [PubMed: 15598680]
51. Birkenfeld AL, Budziarek P, Boschmann M, Moro C, Adams F, Franke G, Berlan M, Marques MA, Sweep FC, Luft FC, Lafontan M, et al. Atrial natriuretic peptide induces postprandial lipid oxidation in humans. *Diabetes* 2008;57(12):3199–3204. [PubMed: 18835931]
52. Sengenès C, Bouloumie A, Hauner H, Berlan M, Busse R, Lafontan M, Galitzky J. Involvement of a cGMP-dependent pathway in the natriuretic peptide-mediated hormone-sensitive lipase phosphorylation in human adipocytes. *J Biol Chem* 2003;278(49):48617–48626. [PubMed: 12970365]
53. Morisset AS, Huot C, Legare D, Tchernof A. Circulating IL-6 concentrations and abdominal adipocyte isoproterenol-stimulated lipolysis in women. *Obesity (Silver Spring)* 2008;16(7):1487–1492. [PubMed: 18451782]
54. Plomgaard P, Fischer CP, Ibfelt T, Pedersen BK, van Hall G. Tumor necrosis factor- α modulates human in vivo lipolysis. *J Clin Endocrinol Metab* 2008;93(2):543–549. [PubMed: 18029463]

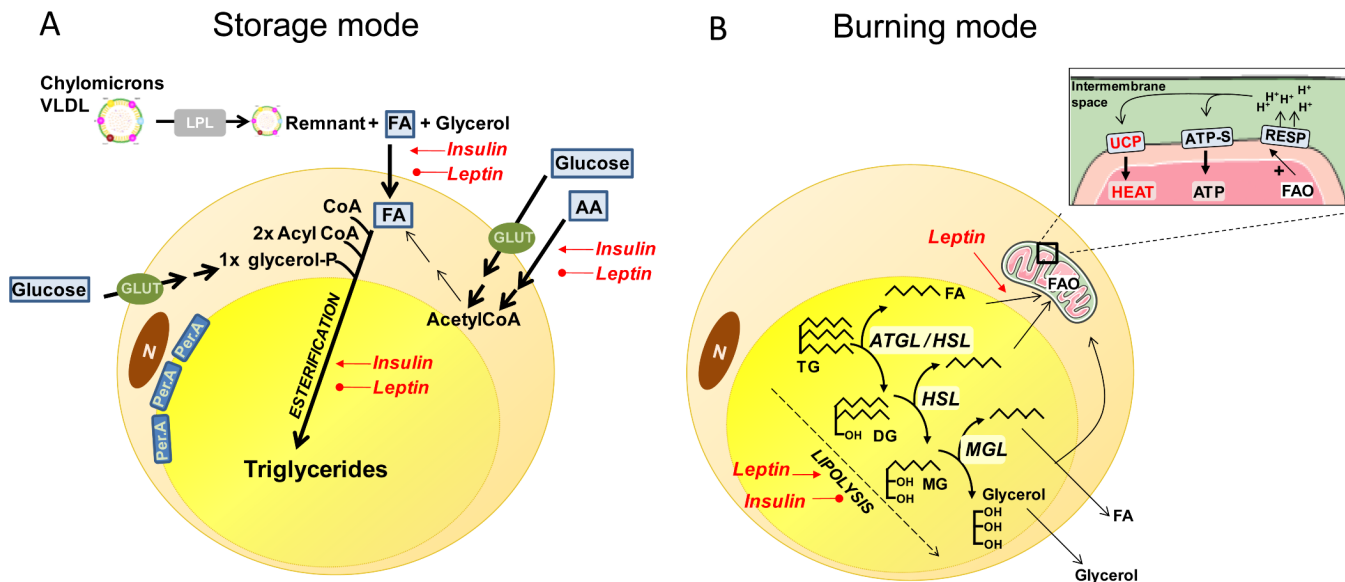


Figure 1. (A) Post-pandrial increase in insulin leads to induction of lipogenesis and inhibition of lipolysis. Lipoprotein lipase (LPL) is the rate-limiting enzyme for the import of triglyceride-derived fatty acids from VLDL or chylomicrons for storage by the adipose tissue. Uptake of free fatty acids (FA) involves passive diffusion through the lipid bilayer or protein-facilitated transfer. Within the adipocytes, FA are activated into acyl-CoA and 3 acyl-CoA are esterified with glycerol to form triglycerides (TG) stored into the lipid droplet. Additionally, insulin triggers glucose and amino acid (AA) transport into adipocytes that are metabolized into acetyl-CoA. ACC (Acetyl-CoA carboxylase) which converts acetyl-CoA to malonyl-CoA is the committed step of FA synthesis pathway. Leptin antagonizes lipogenesis and promotes lipolysis. (B) In some situations, white adipocytes can acquire brown adipocytes features and lipid stores are mobilized. Sequential breakdown of intracellular TG (lipolysis) provides FA and glycerol. Diglyceride formation (DG) is catalysed by HSL and ATGL, DG are hydrolysed by HSL and monoglyceride catabolizing involve MGL. Insulin and leptin have opposing action on lipolysis. FA and glycerol can be liberated in the circulation or FA can be oxidized in mitochondria. Fatty acid oxidation (FAO) forms substrates for the respiratory chain (RESP). ATP or heat can be produced by the discharge of the intermembrane space proton gradient via the ATP synthase or UCP, respectively. Leptin has been shown to exert direct and indirect stimulation in FAO. Abbreviations: CoA: coenzyme A, Glycerol-P: phospho-glycerol, PERA: perilipin A, GLUT: glucose transporter, VLDL: very low density lipoprotein, N: nucleus, ATGL: adipose triglyceride lipase, HSL: hormone sensitive lipase, MGL: monoglyceride lipase, DG: diglyceride, MG: monoglyceride, UCP: uncoupling protein, ATP-S: ATP-synthase, .