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Adipose tissue as source and target for novel therapies

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The physiology of adipose tissue has a key role in the pathogenesis of the metabolic syndrome and related cardiovascular disorders. Three main functions of adipocytes have been proposed to explain this role: the secretion of adipocyte-derived hormones (so-called adipokines), energy dissipation/thermogenesis, and energy storage. There is mounting evidence that this repertoire of actions and reactions contributes to whole-body glucose and energy homeostasis, the control of blood pressure, immune-system function, haemostasis and atherosclerosis. In this article we highlight the most recent examples of adipocyte-based therapies and discuss future pharmacological options for exploiting this triad of adipocyte functions.

Introduction

The capacity for storing and releasing energy on demand has been crucial for survival and successful reproduction in most phases in evolution. Close communication between multiple physiological systems of an organism appears to be a prerequisite for efficient energy management. The functions of adipose tissue meet these essential criteria: (i) adipocytes have a large capacity to store energy in the form of lipids; (ii) stored lipids can be metabolized rapidly and either released as fatty acids or used to increase thermogenesis by uncoupling fuel oxidation from ATP generation [1,2]; (iii) adipocytes communicate with other systems including the CNS, and reproductive, immune and cardiovascular systems by secreting hormones, so-called adipokines, in either an endocrine or a paracrine manner [3]. Thus, alteration of adipocyte functions is crucial to the pathogenesis of multi-system disease such as disorders that constitute the metabolic syndrome and its cardiovascular complications. However, factors that are implicated intimately in the pathophysiology of these disorders might also harbour the potential for efficient remedies. In this review, we focus on advances in defining and exploiting the characteristic triad of adipocyte functions to treat human disease, and discuss future approaches.

Administering and regulating adipokines: multifaceted biological ramifications

Administration and regulation of hormones derived from adipose tissue might be one of the most attractive options for treating cardiometabolic disorders. Here, we highlight treatment-related data on adipokines that are either proved or thought to be of interest in clinical contexts (Figure 1, Table 1).

Leptin

Leptin, the product of the *ob* gene, is the prototypic adipokine that was discovered in a landmark study in 1994. Leptin administration induces dramatic weight loss in mice with a homozygous deletion of the *ob* gene. However, there is general agreement that recombinant leptin is not a promising treatment strategy because most cases of human obesity are characterized by central resistance to leptin. Leptin analogues that enhance leptin-receptor-signalling pathways in the CNS might be more effective [4]. By contrast, in rare cases, including individuals with congenital, complete leptin deficiency, subcutaneous administration of leptin induces significant weight loss and improves hypogonadism, type 2 diabetes and physical activity [5]. Similar effects are observed in morbidly obese children [6]. Furthermore, in lipodystrophy, an inherited or acquired condition characterized by abnormalities in body fat distribution, leptin treatment significantly reduces insulin resistance, dyslipidemia [7] and non-alcoholic steatohepatitis [8]. Finally, in an apparently different context, a recent report describes

Glossary

AdipoR: adiponectin receptor
aP2: fatty acid binding protein
AMPK: AMP-activated protein kinase
AR: angiotensin receptor
ATGL: adipose triglyceride lipase
CNTF: ciliary neurotrophic factor
EC: endocannabinoid
FATP: fatty acid transporter protein
GIP: glucose-dependent insulinotropic polypeptide
11β-HSD-1: 11β-hydroxy steroid dehydrogenase-1
HSL: hormone sensitive lipase
IL-6: Interleukin-6
IRS: insulin receptor substrate-1
PGC1α: PPARγ coactivator 1 α
PPAR: peroxisome proliferator-activated receptor
PAI-1: plasminogen activator inhibitor-1
RAS: renin angiotensin system
RBP4: retinol-binding protein 4
RXRα: retinoid X receptor α
SRC1: steroid receptor coactivator 1
SRM: steroid receptor modulator
TNF-α: tumour necrosis factor α
TZDs: thiazolidinediones
TIF2: transcription intermediary factor 2

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the benefits of administering leptin to women with hypothalamic amenorrhea. Recombinant leptin for three months either partially or completely restores ovulatory function, accompanied by improvements in thyroid and growth-hormone axes, and markers of bone formation [9]. This, seemingly unexpected, twist in the therapeutic applications of leptin serves to illustrate the interconnections between the control of energy homeostasis and other biological systems that regulate reproduction, immune system and cardiovascular function. Future treatment indications for this pleiotropic adipokine are conceivable in these areas.

Adiponectin

Adiponectin, which was cloned independently by four groups in 1995 and 1996, is an endogenous insulin-sensitizing factor in mice and humans [10]. Adiponectin reverses insulin resistance in mouse models of lipodystrophy and obesity. Adenoviral-mediated expression of adiponectin in the liver of rats enhances insulin sensitivity [11]. Furthermore, this adipokine normalizes lipid abnormalities and causes weight-loss in mice with diet-induced insulin resistance. Improvement in dyslipidemia induced by HIV protease inhibitors is also reported [12]. Moreover, a recent study demonstrates that intracerebroventricular administration of adiponectin increases energy expenditure and reduces weight, glucose levels and lipid levels but does not alter food intake [13]. Finally, several lines of evidence indicate an anti-inflammatory, anti-atherogenic role of adiponectin [10]. Thus, adiponectin might have potential for the treatment of cardiometabolic disease, but, to our knowledge, no clinical studies have been published. At least two circulating forms of adiponectin have been described, which probably have different modes of action at different receptor subtypes (AdipoR1 and AdipoR2). The development of potent, recombinant forms of adiponectin and AdipoR agonists might lead to new compounds to treat diabetes and obesity, and to prevent cardiovascular disease.

Resistin

Resistin was identified independently by three groups [14]. Steppan and co-workers found that this adipokine is downregulated during screening for adipocyte-derived products that are targeted by the thiazolidinedione (TZD) class of insulin-sensitizing drugs. Furthermore, recombinant resistin caused insulin resistance in mice, which was improved by anti-resistin antibodies. However, subsequent studies on resistin regulation have yielded conflicting results, and its role in human disease is unclear [15]. Resistin is a member of a new gene family that includes resistin-like molecule α (RELM-α) RELM-β, and RELM-γ, which might have a role in inflammation [14]. Whether resistin family members represent therapeutic targets for treating human disease remains to be determined.

Glucocorticoid metabolism

Changing cortisol metabolism in adipose tissue by over-expressing the glucocorticoid reamplifying enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD-1) reproduces the metabolic syndrome in mice [16]. By contrast, inactivation of glucocorticoids in adipose tissue protects against obesity [17]. Administration of carbenoxolone, a pharmacological inhibitor of 11β-HSD-1, to healthy men and patients with diabetes reduces hepatic output of glucose and enhances lipid metabolism. However, the induction of hypertension and the lack of action of

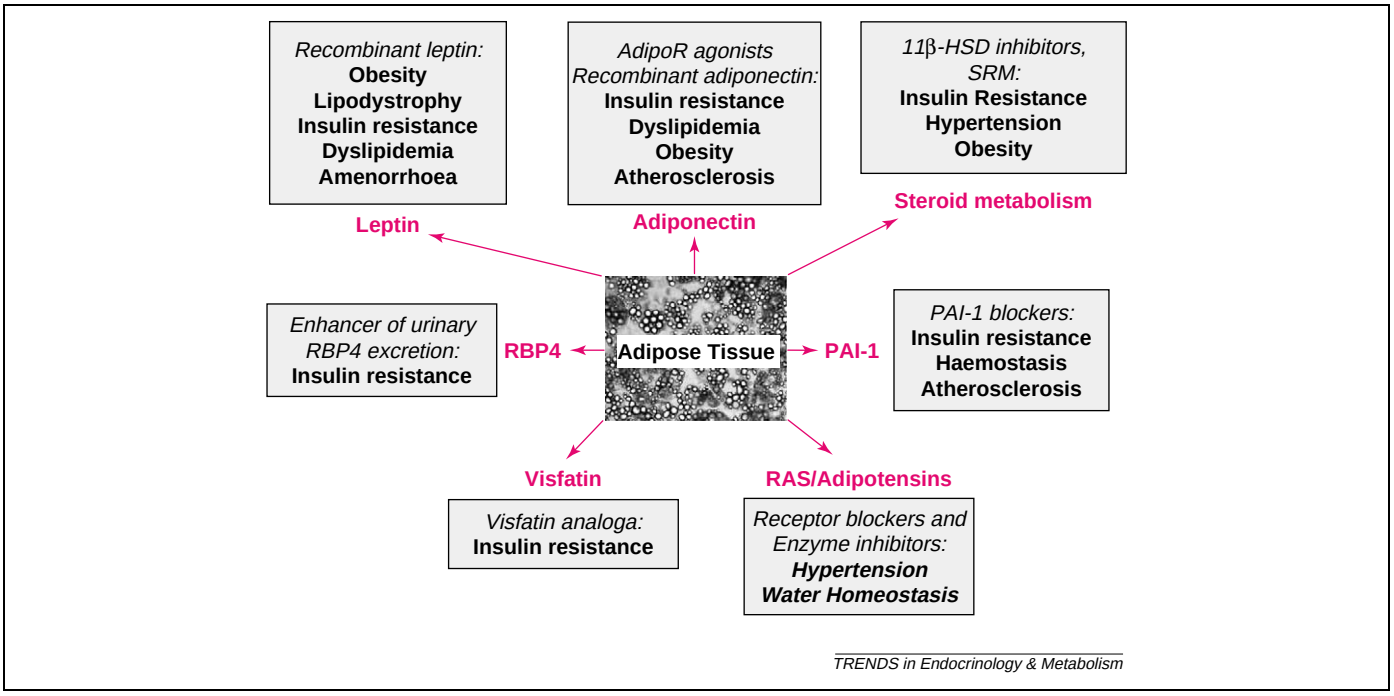

Figure 1. Therapeutic potential of human adipokines. Adipocyte-derived factors, including the glucocorticoid metabolism-regulating enzyme 11β-HSD, which have either been shown to be, or are being considered as, treatment options for human disease. Boxes contain actual and potential compounds (italics) and therapeutic indications (in bold).

Table 1. Regulation of adipokines by metformin and TZDs[a]

Adipokine	Effect on expression[b]	
	Metformin	TZD
Leptin	(↓)	(↓)
Adiponectin	(↑)	↑
Resistin	↑	↓
TNF-α	↔	↓
IL-6	↓	↔
PAI-1	(↓)	↓
RAS (angiotensinogen and angiotensin II)	N/A	↓, *ex vivo* data
Visfatin	N/A	N/A
RBP4	N/A	↓, mouse *in vivo* data

[a]Unless indicated, this table +summarizes data from human *in vivo* studies.
[b]↑, upregulation; ↓, downregulation; ↔, no regulation; N/A, no data available. Data in brackets indicates that the effect occurs in some but not all studies.

carbenoxolone in adipose tissue are concerns in this context [18]. A new class of selective inhibitors has been developed that lowers glucose levels in hyperglycemic mice and improves insulin sensitivity [19,20]. Another selective inhibitor, BVT3498, is in Phase II clinical trials [21]. Furthermore, analogous to selective receptor modulators of sex hormones, selective glucocorticoid receptor modulators might be a treatment option in future [22].

Tumour necrosis factor α

Tumour necrosis factor α (TNF-α) is a proinflammatory cytokine that was identified in 1985. It is produced in adipose tissue and has been implicated in the pathogenesis of insulin resistance and obesity in mice and humans [23]. Although neutralizing TNF-α in obese rodents improves glycemic control and dyslipidemia, these findings have not been confirmed in studies that use different strategies to antagonize TNF-α in obese humans with diabetes [24,25]. Adipocyte-derived TNF-α might act predominantly in a paracrine manner. To our knowledge, anti-TNF-α agents such as infliximab and etanercept, which are used to treat Crohn's disease and rheumatoid arthritis, are not associated with changes in insulin resistance and obesity in humans. Currently, a TNF-α-inhibiting pharmacotherapeutic strategy is not considered to be a promising approach to treat cardio-metabolic disease.

Interleukin 6

In humans, subcutaneous adipose tissue secretes ~30% of systemic interleukin 6 (IL-6), and omental adipose tissue appears to release more. Plasma levels of this proinflammatory cytokine correlate with fat mass and insulin resistance, and predict the development of diabetes and cardiovascular disease [26]. Peripheral administration of IL-6 induces insulin resistance and hyperlipidemia in rodents and humans. However, central concentrations of IL-6 correlate inversely with obesity in humans, and central application of this adipokine increases energy expenditure in rodents [27]. Adding further to this complexity, chronic treatment with relatively low doses of IL-6 reverses obesity and the associated metabolic disturbances in IL-6-deficient mice [28]. Whether IL-6-mimetic or antagonising strategies will eventually have a role in treating human disease remains unclear.

Plasminogen activator inhibitor 1

Plasminogen activator inhibitor 1 (PAI-1), the most important inhibitor of fibrinolysis, is synthesized predominantly in vascular tissues, liver and visceral adipose tissue. The source and mechanisms of increased PAI-1 in obesity are not fully understood. PAI-1-deficient mice are protected against insulin resistance and obesity [29], and many studies associate PAI-1 with cardiovascular disease in humans with these metabolic disorders [30]. Antagonists of angiotensin AT_1 receptors downregulate PAI-1 and ameliorate diet-induced obesity and hyperglycemia in mice [29]. Thus, regulators of PAI-1, which include regulators of the renin–angiotensin system (RAS), might have beneficial effects in the prevention and treatment of cardiometabolic disease. A novel, orally active PAI-1 antagonist reduces perivascular fibrosis in mice [31].

RAS and adipotensins

Adipose tissue produces all the components of the RAS. In humans, obesity is associated with increased circulating levels of components of the RAS. Angiotensinogen (AGT) and angiotensin II have local roles in the development of adipocytes. Transgenic mice release AGT that is derived from adipose tissue into the circulation [32]. However, a systemic role for adipose-tissue-derived RAS components in the control of blood pressure in humans is not established firmly [33]. A recent study found that weight loss in obese women is associated with decreases in circulating levels of AGT and changes in adipose tissue correlate with AGT expression [34].

Recently, it has been reported that human adipocytes secrete mineralocorticoid-releasing factors, called 'adipotensins', which might represent another molecular link between obesity and hypertension [35]. By analogy with the well established strategy of inhibiting the RAS, an adipotensin-antagonising strategy might be a potential therapeutic option that employs adipotensin inhibitors or adipotensin receptor blockers. However, these factors and putative receptors still need to be identified.

Visfatin

Visfatin, which was identified initially as pre-B-cell-colony-enhancing factor, is a novel adipokine that is produced preferentially in visceral adipose tissue of mice and humans [36]. Plasma levels of visfatin correlate with the mass of the visceral adipose tissue and increase in response to a high-fat diet. This adipokine stimulates markers of adipocyte differentiation *in vitro* and increases insulin sensitivity *in vivo* in diabetic mice via pathways that are insulin-receptor-dependent but independent of insulin-binding sites. This insulin-mimetic factor is considered to have both paracrine and endocrine modes of actions [37]. Therapeutic strategies must take into consideration that the visfatin-induced increase in insulin sensitivity might be accompanied by an increase in adipose-tissue mass. The potential of visfatin for treating human disease is unexplored to date.

Retinol-binding protein 4

Most recently, the adipocyte-derived factor retinol-binding protein 4 (RBP4) has been demonstrated to correlate with

obesity in mice and humans, and to mediate insulin resistance by interfering with insulin signaling in muscle and liver [38]. RBP4 is downregulated by insulin-sensitizing TZDs. Increasing the urinary secretion of RBP4 using fenretinide, a retinoic acid analogue, lowers RBP4 levels. The therapeutic perspectives of lowering RBP4 in humans are unclear.

Increasing energy dissipation: targeting thermogenesis

Another function of adipose tissue, thermogenesis (i.e. the dissipation of thermic energy) was identified before its endocrine activity. In brown adipose tissue, the mitochondrial uncoupling protein 1 (UCP-1) mediates uncoupling of the oxidation of fuel from the generation of ATP, releasing the energy as heat. Thermogenesis is important for the survival of small mammals in the cold, and for the control of energy homeostasis after food intake (diet-induced thermogenesis) [39]. The activation of β-adrenoceptors, in particular β_3-adrenoceptors, which are expressed predominantly in adipose tissue, is linked closely to the induction of UCP-1 in rodents and humans. Mice that lack each of the three known β-adrenoceptors have a reduced metabolic rate and develop massive obesity on a high-fat diet [40]. However, the role of brown adipose tissue in humans is a matter of debate. Brown adipose tissue is found in humans of all ages, however, in adults, unlike newborns, circumscribed tissue depots have regressed and brown adipocytes are disseminated in white adipose tissue [39]. In obese adults, the expression of UCP is reduced in intraperitoneal adipose tissue [41]. A brown-fat-specific 'basal' gene expression might be required to maintain insulin sensitivity [42]. Strategies to exploit the thermogenic function of brown adipocytes in humans have been studied for several years, but with limited success. An early study demonstrated increases in insulin action, lipolysis and fat oxidation in healthy individuals treated for 12 weeks with a β_3-adrenoceptor-selective compound [43]. However, several problems, including low affinity for the receptor and insufficient reactivation of 'dormant' brown adipocytes have slowed the development of potent pharmacologic inducers of thermogenesis. Some compounds are reported to be in clinical trials [21,44]. Conversion of human white adipocytes to thermogenic, brown adipocytes is another potential approach. Adenovirus-mediated overexpression of the transcriptional coactivator PGC1α in human adipocytes *in vitro* and in mouse adipose tissue *in vivo* increases expression of UCP-1 [45]. Molecular targets that are considered to be pivotal for induction of a brown-fat cell phenotype and thermogenic function are listed in Table 2. UCP-1 homologues (UCP-2 to UCP-5) have been identified. Their expression is not confined to adipose tissue, and their physiological role might be to limit oxidative damage [46]. Thyroid hormone and peripherally administered corticotropin-releasing factor [47] also increase thermogenesis. With respect to the former, selective receptor activators are under development [48]. Established and investigational drugs also directly influence the thermogenic functions of adipose tissue. Thus, treatment of human white adipocytes with TZDs induces UCP-1 [49]. Direct stimulation of UCP-1 might also contribute to the effects of ciliary neurotrophic factor (CNTF), an anorexigenic peptide that has effects on leptin-like pathways in the CNS. A second-generation variant of CNTF, axokine, promotes weight loss in early, small, clinical studies [50] and is being evaluated currently in larger, Phase III studies [4].

Table 2. Pharmacological targets for the induction of thermogenesis and alteration of lipid metabolism in adipocytes

	Refs
Thermogenesis[a]	
β_3-Adrenoceptor	[44]
PGC1α	[73]
SRC1	[74]
AMPK	[75]
UCP-1	[46]
Transcriptional regulators of lipogenesis	
PPARα, PPARγ, PPARδ	[76]
RXRα	[74]
TIF-2	[74]
Foxo1, Foxo4	[74]
Transport and metabolism of fatty acids	
aP2	[77]
ATGL	[77]
FATP1, FATP4	[78]
HSL	[77]
Perilipin	[77]

[a]Abbreviations: aP2, fatty acid binding protein; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; FATP, fatty acid transporter protein; HSL, hormone sensitive lipase; RXRα, retinoid X receptor α; SRC1, steroid receptor coactivator 1; TIF-2, transcription intermediary factor 2.

Inhibiting energy storage: targeting lipogenesis

Historically, the best known adipocyte function is to store energy in the form of lipids. This is regulated by several traditional and recently discovered hormone systems [51]. Here, we focus on membrane-receptor signalling systems that are interesting therapeutic targets. Transcriptional regulators that are crucial for lipogenesis, and molecular targets that control fatty acid metabolism are listed in Table 2.

Insulin receptor signalling

Lipogenesis is a classical adipocyte response to insulin stimulation. In mice, adipose-tissue-specific knockout of the gene that encodes the insulin receptor protects against obesity and age-dependent impairment of glucose tolerance [52]. Moreover, these animals live ~20% longer [53]. However, the molecular and functional consequences of an isolated defect in insulin signalling in adipocytes are complex. Differential effects of proximal insulin-signalling elements including insulin receptor substrate (IRS)-1, IRS-2, IRS-3 and IRS-4 on adipocyte biology have been shown in several *in-vitro* studies [54,55]. Furthermore, *in vivo* studies demonstrate that adipocyte-specific deletion of Glut4 renders mice insulin-resistant [56]. Finally, brown-adipocyte-specific knockout of the insulin receptor is characterized by a defect in insulin secretion, which progresses to impaired glucose tolerance [57]. The use of novel techniques, including immortalized cell lines, and microarray and proteomics approaches promises a better understanding of mechanisms that are responsible for inducing these phenotypes [54,55,58,59]. An inhibition of proximal insulin signalling in adipose tissue might

provide a pharmacological strategy to confer resistance to obesity and prolong life.

Endocannabinoid receptor signalling

The endocannabinoid (EC) system controls energy homeostasis by central and peripheral mechanisms, and represents a novel target for anti-obesity treatment strategies [60]. The CB_1 cannabinoid receptor is expressed in adipocytes. CB_1-receptor-knockout mice are resistant to diet-induced obesity [61], and a role for the CB_1-receptor antagonist rimonabant in regulating adipose lipid metabolism has been demonstrated recently in mice [62]. Rimonabant reduces weight and improves cardiovascular risk factors in overweight patients in large clinical trials [63], and it is expected to be on the market in 2006 in Europe and the USA. The significance of CB_1-receptor-mediated regulation of adipocyte function is little explored to date.

GIP receptor signalling

Glucose-dependent insulinotropic polypeptide (GIP) acts as an incretin hormone (i.e. it augments pancreatic insulin secretion when released from the gut in response to food intake). GIP receptors have been described on adipocytes, and a role in lipogenesis is reported in several studies *in vitro* and *in vivo* [64]. The most compelling evidence *in vivo* comes from GIP-receptor-knockout mice, which are protected from obesity induced by a high-fat diet [65]. Adipocyte lines from these mice have severe deficits in lipid accumulation (J. Klein and D.J. Drucker, unpublished). Because of its divergent tissue-specific effects, both, augmenting and antagonising GIP action, are currently discussed as therapeutic strategy to treat diabetes and obesity, and both, GIP agonists and antagonist are under development [66,67]. The role of GIP in adipose tissue in humans remains to be determined.

A note of caution

There are two general concerns about strategies that aim to prevent lipid storage in adipose tissue. The first is that blocking adipocyte lipogenesis might increase plasma levels of free fatty acids and lipid deposition in liver and muscle, both of which are associated with insulin resistance. Excessive loss of adipose tissue mass, as occurs in different forms of lipodystrophy, is linked to severe metabolic abnormalities. Conversely, TZDs, which activate PPARγ, a key promoter of adipogenesis, improve insulin sensitivity and dyslipidemia, and increase adipose tissue mass. Selective PPARγ antagonists are under development as anti-obesity drugs which might help to improve endocrine function without increasing adipose mass [4]. The second concern relates to the concept of 'adiposopathy', which emphasizes selective dysfunction of adipose tissue. Reducing adipose mass by inhibiting adipocyte differentiation might not correct, and might even make worse, endocrine adipose dysfunction and induce multi-system side-effects. In addition, differences in metabolic and endocrine function between visceral and subcutaneous fat depots further complicate the issue [37].

Selectively targeting adipose tissue: a difficult problem to solve?

From a pharmacotherapeutic viewpoint, a 'tailored', adipose-tissue-specific approach seems attractive, but difficult to achieve. Angiogenic processes are crucial for the development and remodelling of adipose tissue. Predominant effects on adipose tissue mass by targeting factors which are involved in angiogenesis have been reported in a number of recent studies [68–71]. Novel treatment perspectives might also come from employing advanced RNA-interference technologies [72]. However, identifying cell-surface markers and physico-chemical traits, which are specific to adipocytes and might be exploited by circulating drugs, represents a major challenge in the development of strategies that selectively target adipose tissue function.

Future directions

Many recent discoveries have prepared the ground for a paradigm shift in the appraisal of adipocyte function and its contribution to multi-system disease. Knowledge of the mechanisms that regulate different functions of adipose tissue is beginning to result in the development of therapeutic options for a broad range of disorders (Figure 2). Further elucidation of the biology of adipokines promises new discoveries. Modulation of the dissipation and storage of energy in adipose tissue is part of the activity profile of established and investigational drugs. The refinement of therapies might depend on the development of techniques that selectively target adipose tissue.

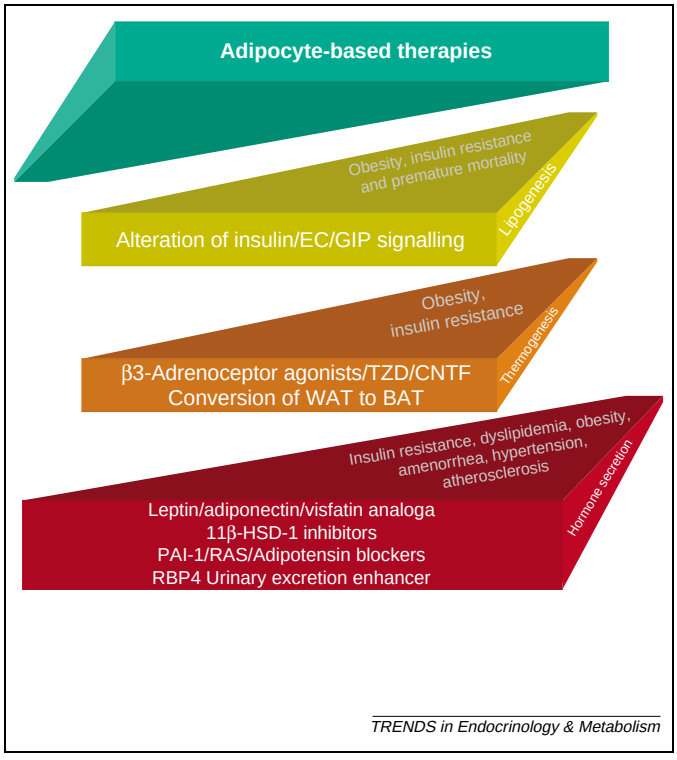

Figure 2. Adipocyte-based strategies to treat human disease. Functional characteristics of adipose tissue are indicated on the right face of each three-dimensional rectangle; the front face includes either actual or potential pharmacotherapeutic approaches to treat the disorders given on the top.

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