Review

MOLECULAR METABOLISM

Adipokines – removing road blocks to obesity and diabetes therapy

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ABSTRACT

Prevention of obesity and therapeutic weight loss interventions have provided only limited long term success. Therefore there is an urgent need to develop novel pharmacological treatment strategies, which target mechanisms underlying positive energy balance, excessive fat accumulation and adverse fat distribution. Adipokines may have potential for future pharmacological treatment strategies of obesity and metabolic diseases, because they are involved in the regulation of appetite and satiety, energy expenditure, endothelial function, blood pressure, insulin sensitivity, adipogenesis, fat distribution and insulin secretion and others. There are important road blocks on the way from an adipokine candidate to the clinical use a therapeutic compound. Such road blocks include an incomplete understanding of the mechanism of action, resistance to a specific adipokine, side effects of the adipokine and others. This review focuses on the potential of selected adipokines as therapeutic tools or targets and discusses important road blocks, which currently prevent their clinical use.

Keywords Adipokines; Obesity; Type 2 diabetes; Road blocks; Therapeutic compounds; Leptin; Adiponectin; DPP4; Vaspin; Nampt/visfatin; Nesfatin-1; Apelin; BMP7

1. INTRODUCTION

Obesity and fat accumulation predominantly in visceral depots are important risk factors for the development of type 2 diabetes, dyslipidemia, fatty liver disease, chronic subclinical inflammation, hypertension, and cardiovascular disease [1–3]. To develop novel etiology based strategies for the prevention and treatment of these diseases, a better understanding of the molecular mechanisms underlying obesity and its relationship to metabolic and cardiovascular diseases is essential. There are several open questions about the unresolved, pathogenic mechanisms of obesity and its comorbid disorders. Why is our food intake not regulated to keep the balance with energy expenditure? Why does overeating in some, but not all individuals lead to ectopic fat deposition? To what extent does adipose tissue contribute to the regulation of energy balance? What are the (missing?) signals from adipose tissue that may promote overeating and obesity related metabolic and cardiovascular diseases?

An effective treatment of obesity would require a systematic assessment of factors potentially affecting energy intake, metabolism and expenditure [4]. Since the factors (and their interaction) causing obesity are only incompletely understood, weight loss strategies may not address the root causes of energy imbalance [4,5]. Therefore, current therapeutic approaches frequently fail. The classical treatment of obesity, based on decreasing energy intake and increasing physical activity, has not been successful as a long term strategy. The majority of individuals who lose weight will regain it within 1 year, and almost all of them within 5 years [6]. In addition, social and environmental factors are critical modulators of the individual predisposition to develop obesity. The importance of socio-economic factors for obesity has recently been demonstrated by a population wide analysis of the consequences of weight loss and regain driven by an economic crisis in Cuba [7]. In this survey, an average population-wide ~5.5 kg weight loss was associated with rapid significant declines in diabetes and heart disease prevalence, whereas a weight rebound led to a diabetes prevalence that even exceeded pre-crisis levels [7].

At the individual level, anti-obesity interventions with the exemption of bariatric surgery [8] have provided very limited success. In my opinion, treatment of obesity (and its comorbidities) requires novel pharmacological therapeutics that targets the root causes of a sustained positive energy balance and the adverse signals from adipose tissue contributing to metabolic and cardiovascular diseases.

Obesity frequently leads to a dysregulation of adipokine secretion [1,9]. Since adipokines play important roles in the regulation of appetite and satiety, fat distribution, insulin sensitivity and insulin secretion, energy expenditure, inflammation, blood pressure, hemostasis, and endothelial function [10–14], they are promising candidate molecules for future treatment of obesity and obesity related diseases.

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2. POTENTIAL ROLE OF ADIPOKINES IN THE TREATMENT OF OBESITY AND METABOLIC DISEASES

In addition to the release of fatty acids, other lipids and metabolites, adipose tissue secretes more than 600 bioactive factors (adipokines) [15]. At the level of adipose tissue, adipokines contribute to the modulation of adipogenesis, immune cell migration into adipose tissue, adipocyte metabolism and function [1,11,14]. At the level of the whole body, adipokines modulate and regulate different biological processes in target organs including the brain, liver, muscle, vasculature, heart and pancreatic β-cells (Figure 1) [1,9,14]. The adipokine secretion pattern reflects adipose tissue function and seems to be important for determining the individual risk to develop metabolic and cardiovascular comorbidities of obesity [1,2,9]. When adipose tissue inflammation and dysfunction have developed, adipokine secretion is significantly changed towards a diabetogenic, proinflammatory, and atherogenic pattern [1,2,9]. The search for adipokines and their functional characterization was stimulated by the identification of adipose tissue as a major site for sex steroid metabolism [16] and production of adipsin, an endocrine factor that is negatively correlated with obesity in rodents [13]. The discovery that a deficiency of the adipokine leptin underlies hyperphagia and extreme obesity in the *ob*/*ob* mouse model [12] established adipokines as potential therapeutic tool in the treatment of obesity. Since then, the search for novel adipokines represents a major topic in obesity research. Recently, 44 novel adipokines with unknown function have been identified using an unbiased protein profiling approach of the secretome of primary human adipocytes [17,18]. Among the more than 600 adipokines [15], there are molecules which play a role in immune response (e.g. adipsin, ASP, SAA3, IL-17D, CSFs) and inflammation (e.g. IL-1β, IL-6, IL-8, IL-10, CrP, MCP-1, osteopontin, progranulin, chemerin), glucose metabolism (e.g. leptin, adiponectin, DPP-4, resistin, vaspin), insulin sensitivity (e.g. leptin, adiponectin, chemerin), hypertension (e.g. angiotensinogen), cell adhesion (e.g. PAI-1), vascular growth and function (e.g. VEGF), adipogenesis and bone morphogenesis (e.g. BMP-7), growth (e.g. IGF-1, TGFβ, fibronectin), lipid metabolism (e.g. CD36), regulation of appetite and satiety (e.g. leptin, vaspin) and other biological processes [1,9]. However, with the expanding number of newly identified adipokines there is an increasing need to define their function, molecular targets and potential clinical relevance in the treatment of obesity and metabolic diseases.

3. ROAD BLOCKS FOR THE THERAPEUTIC USE OF ADIPOKINES IN THE TREATMENT OF OBESITY AND METABOLIC DISEASES

The road from the discovery of a novel adipokine to its clinical use as either target or tool in the treatment of diseases contains several important barriers. In general, road blocks can be divided into biological and structural barriers (Figure 2). Structural road blocks include country specific patent restrictions, difficulties with material transfer agreements, seeking for (immediate) monetary reward, all delaying the advance of candidate therapeutics to the clinic. In addition, the funding and support infrastructure for clinical trials providing a successful translation of biomedical (bench) research into clinical practice is not always sufficient for the implementation of new therapeutic concepts, which do not guarantee a fast return in investment. In addition to these frequent structural deficits and obstacles, there are several biological road blocks. Some adipokines are considered as innovative biomarkers for the screening, diagnosis, and therapeutic monitoring of obese, insulin-resistant individuals and patients with diabetes, as well as for prediction of disease recurrence [19]. Because adipokines may represent the link between obesity and

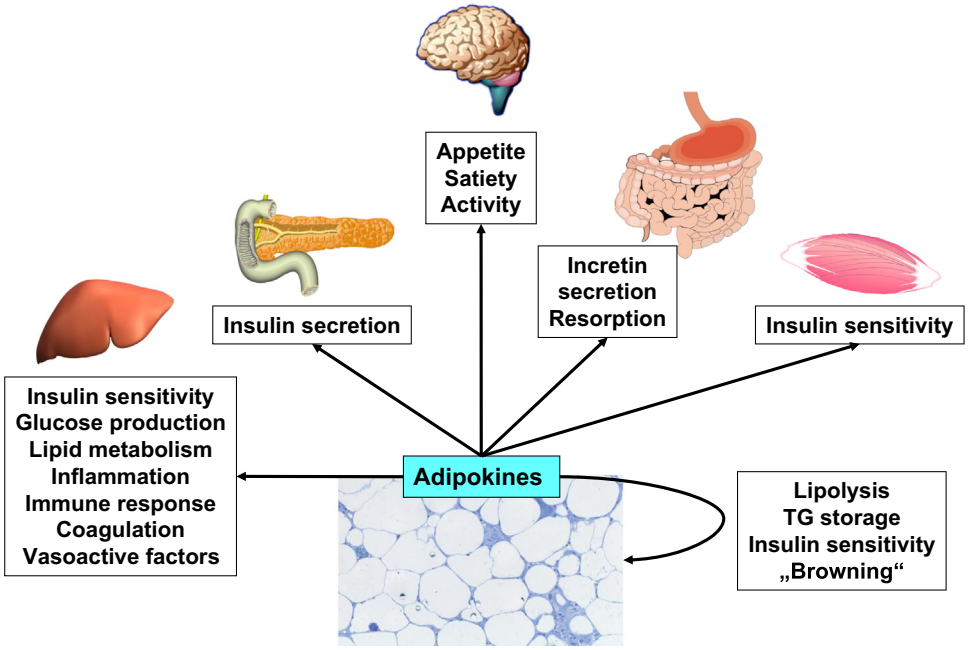

Figure 1: Adipokines regulate important physiologic processes. Secreted factors from adipose tissue play an important role in the regulation of appetite and satiety, energy expenditure, insulin sensitivity and insulin secretion, inflammation, blood pressure, hemostasis, endothelial function and others. In addition to an endocrine mode of action, adipokines contribute to the modulation of adipogenesis, adipose tissue lipolysis, adipocyte metabolism and function in an autocrine and paracrine manner.

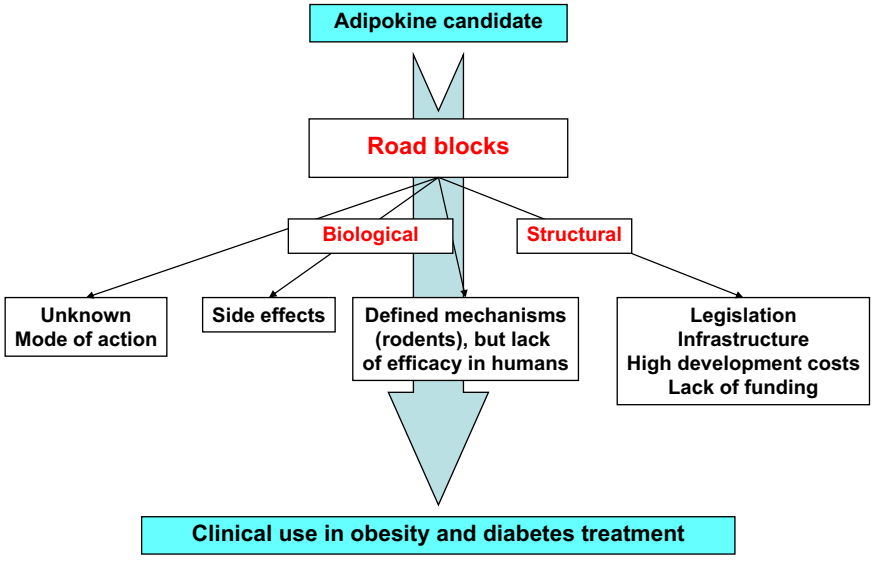

Figure 2: Current road blocks for the clinical use of selected adipokines. There are important obstacles on the road from an adipokine candidate to the clinical use as a therapeutic compound. Such road blocks include an incomplete understanding of the mechanism of action, a mechanistic concept derived from rodent studies does not translate into effective treatment in humans, lack of human data, development of adipokine resistance, side effects.

type 2 diabetes (e.g. leptin, adiponectin), hypertension (e.g., angiotensinogen), endothelial function (e.g., omentin, apelin), hemostasis (e.g., fibrinogen), chronic inflammation (e.g., TNFα, IL-6, IL-1β, MCP-1, progranulin, chemerin), they have great potential to be clinically relevant both as biomarkers and as therapeutic compounds [14]. Adipokines have the potential to predict individual treatment success and disease progression, to monitor clinical responses to therapeutic and lifestyle interventions, to early identify non-responders to specific interventions, or to monitor treatment adherence [20]. However, the validation of the impact of these adipokine markers, ultimately driving them toward approval by regulators and into clinical practice, is much more complex [19]. In the past, adipokines have been either systematically developed into a drug following their discovery (e.g. leptin) [21–24] or the importance of a molecule in the treatment of a specific disease has been appreciated before its identification as an adipose tissue secreted factor (e.g. DPP4) [25,26]. Noteworthy, the potential clinical use of adipokines may not be restricted to obesity and metabolic diseases: some adipokines have been already successfully introduced for other indications including lipodystrophy, infertility and bone growth (Table 1).

However, there are important road blocks on the way from an adipokine (drug) candidate to the clinical use as a therapeutic compound. As one of the initial road blocks, identification of the most promising adipokine candidates and characterization of the function, mode of action and molecular targets for a future therapeutic use remain major tasks (Table 1).

Additional road blocks include: (1) that a mechanistic concept derived from rodent studies does not translate into effective treatment in humans, (2) lack of human data, (3) an incomplete understanding of the mechanism of action, (4) adverse drug and side effects, (5) a very long drug development process which may take ~15 years from the discovery of a candidate adipokine to its clinical use or approval by authorities (Figure 3). After the preclinical identification of potentially important new therapeutic agents and several steps of mechanistic studies including *in vitro* and animal models, human pharmacotherapy trials have to undergo four phases of development [27]. In phase I, tolerability, safety and pharmacokinetics of drug is investigated; phase II provides proof of concept studies (mechanism, efficacy and safety); phase III focuses on confirmation of efficacy and side-effect profile in large-scale multi-centre trials; and phase IV represents long-term monitoring and data collection following governmental approval (Figure 3). Application for approval from the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA) is submitted after Phase III – the entire process takes ~15 years, the clinical phases alone ~8 years [27–30]. Taken together, the duration of the drug development process represents a major road block for novel therapeutics.

In the context of drug discovery, an incomplete understanding of the mechanism of action may represent a road block. The term mechanism of action refers to the specific biochemical interaction through which a molecule (potential drug) exerts its pharmacological effect. Usually the understanding of a mechanism of action includes identification of specific molecular targets. Interestingly, even for approved drugs, the mechanism of action may be still unknown. Despite their successful clinical application, 7% of approved drugs are purported to have no known primary target, and up to 18% lack a well-defined mechanism of action [31].

However, therapeutic effects of drugs including adipokines can indeed be demonstrated without understanding the actual mechanism of action, which suggests that not knowing the mechanisms of action may not necessarily be a major road block. For the majority of the recently discovered adipokines [17,18], the precise function and their main targets are still unknown.

Lack of human data still remains one of the major road blocks in drug discovery including establishing adipokines as novel drugs or drug targets. The preclinical development of drugs may take 4–5 years [30]. Therefore, for many of the very recently discovered adipokines including adiponectin, apelin, vaspin, omentin, STAMP2 (six transmembrane protein of prostase 2), nesfatin-1, cathepsins and others, the time

Adipokine	Effect or mechanism with (future) therapeutic potential or established use as therapeutic principle (TP)
Leptin	Decreases orexigenic and increases anorexigenic peptide synthesis in the hypothalamus: thereby decreasing appetite
	Improves hypertriglyceridemia and insulin sensitivity in patients with lipodystrophy (TP)
	Treatment of genetic leptin deficiency (TP)
Adiponectin	Has insulin sensitizing, anti-inflammatory and anti-apoptotic properties
	Reflects adverse fat distribution and adipose tissue dysfunction
	AdipoRon (small-molecule adiponectin receptor agonist) ameliorate insulin resistance and glucose intolerance[a]
TNFα	Pro-inflammatory, decreases insulin sensitivity
	Antagonists improve insulin sensitivity (TP)[a]
IL-6	Pro-inflammatory, decreases insulin sensitivity
Vaspin	Improves glucose metabolism[a], reduces food intake[a]
RBP4	Associated with insulin resistance and visceral fat distribution
Apelin	Improves glucose metabolism[a]
DPP-4	Degrades GLP-1 thereby contributing to impaired glucose metabolism
	Reflects visceral fat distribution
	Target of DPP-IV inhibitors – improved hyperglycemia (TP)
Progranulin	Pro-inflammatory properties
	Mutations in the progranulin gene cause familial frontotemporal lobar neurodegeneration
	Chemotactic molecule, contributing to macrophage infiltration into adipose tissue
IL-1β	Target for improved glycemia and β-cell function (TP)
MCP-1	Chemoattractant molecule, contributing to macrophage infiltration into adipose tissue
Chemerin	Correlate of systemic inflammation (recruitment of immune cells) and visceral fat accumulation
Resistin	May contribute to systemic inflammation and insulin resistance
FABP4	Suppresses cardiomyocyte contraction, predictor of cardiovascular events
	Antagonists improve myocardial function, glycemia and obesity (TP)[a]
FGF21	Improves insulin sensitivity and glucose metabolism[a]
	Promotes weight loss[a]
Fetuin-A	Related to liver fat content
Omentin	Marker of visceral fat mass; local regulator of visceral adipose tissue biology, promotes endothelial function[a]
Nampt/visfatin	Improves glucose metabolism[a], enzyme in NAD biosynthesis playing a role in β-cell function
Lipocalin-2	Component of the innate immune system, key role in acute-phase response to infections
Adipsin	Activation of the alternative complement pathway
TGFβ	Regulation of cell proliferation, differentiation and apoptosis
VEGF	Stimulates angiogenesis in adipose tissue
BMP7	Promotes "browning" of adipose tissue[a], improves fertility (TP), improves osteoblast differentiation and promotes bone injury healing (TP)
Cathepsins	Related to impaired glucose metabolism and obesity[a]
Nesfatin-1	Adaptation to stress, glucose-dependent insulinotropic effects[a]
	Reduces hyperglycemia[a]

Table 1: Systemic and tissue specific effects of adipokines establish these molecules as candidates or targets for the treatment of obesity-associated disorders. RBP4, retinol-binding-protein-4; DPP-4, dipeptidyl peptidase-4; IL, interleukin; FGF21, fibroblast growth factor 21; MCP-1, monocyte-chemotactic-protein-1; FABP4, fatty acid binding protein 4; VEGF, vascular endothelial growth factor; TGFβ, transforming growth factor β; BMP7, bone morphogenetic protein 7. [a]Effects shown in animal models only.

frame for further development was not sufficient to advance them from candidates to clinical phase I studies.

For several adipokines, there is a rationale to develop specific inhibitors rather than using the adipokine molecule itself. This approach could be useful for adipokines which are increasingly secreted in obesity and metabolic diseases including RBP4, nampt/visfatin, lipocalin-2, chemerin, progranulin, fetuin-A, resistin, MCP-1 and others (Table 1). Adipokine antagonists are in preclinical development for some of these molecules and their application may identify previously unrecognized functions of adipokines. For example the novel chemerin (ChemR23) antagonist CCX832 has been shown to protect against chemerin-related arterial contraction, thus linking higher chemerin concentrations in obesity to impaired vascular function [32]. Many more studies are required for potential drugs at this stage before they can be tested in clinical studies.

Adverse reactions and significant side effects are major road blocks in drug development in general, but also for adipokines. Ideally, an anti-obesity pharmacotherapy would produce sustained (if required extensive) weight loss with minimal side effects. Regulation of energy balance has substantial built-in redundancy, overlap considerably with other physiological functions, and are influenced by social, environmental, hedonic and psychological factors that limit the effectiveness of pharmacological interventions [27]. Moreover, our current incomplete understanding of the pathophysiology of obesity does not allow the design of etiology-based treatment strategies. In my opinion that is one major road block for the development of novel pharmacotherapies. Recent anti-obesity drug discovery programs have frequently failed or approved drugs had to be withdrawn from the market due to adverse effects that were not fully appreciated at the time of launch [27]. Systematically developed adipokine-based drugs have shown potential in preclinical studies but only leptin has reached further clinical study phases. For the DPP-4, approved inhibitors were already widely used in type 2 diabetes therapy before the notion that DPP-4 is also secreted from adipose tissue.

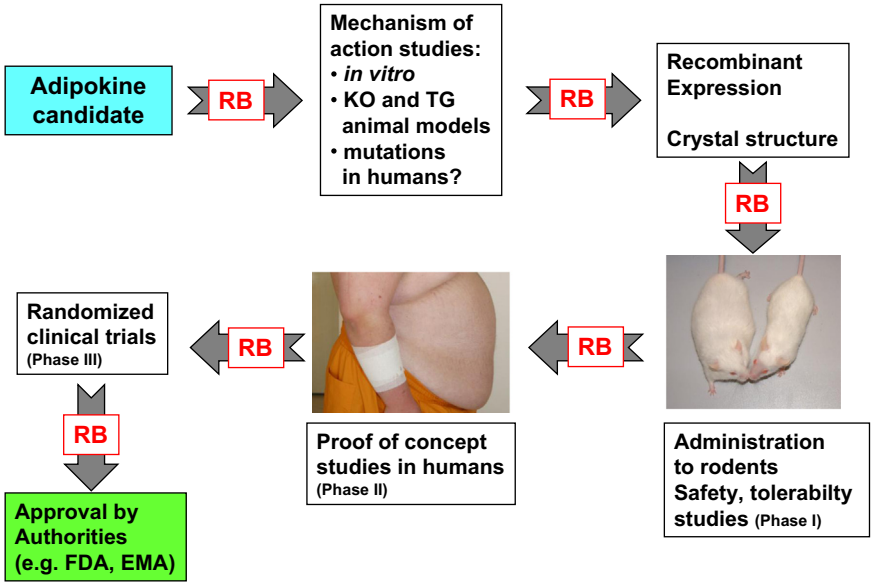

Figure 3: Schematic pathway of drug discovery from an adipokine candidate to its approval for clinical use as pharmacotherapy by the authorities. The path from candidates to an approved medication may take more than 15 years. At any step in the development there are potential road blocks (RB). Despite advances in technology and understanding of biological systems, drug discovery is a long, expensive, difficult, and inefficient process still with a low rate of new therapeutic discoveries. KO, knockout; TG, transgenic; FDA, Food and Drug Administration; EMA, European Medicines Agency.

Despite a high demand for efficacious, well tolerated and safe pharmacological anti-obesity drugs, there are only a few agents currently licensed for clinical use. Centrally acting amphetamine derivatives (e.g. desoxyephedrine, phentermine, diethylpropion) were widely used in the 1950s and 1960s, but were withdrawn from the market due to their abuse potential and increased cardiovascular risk [27]. Serotonin (5-HT)-releasing agents (e.g. fenfluramine) have been associated with the development of pulmonary hypertension and cardiac valvulopathy and have therefore been withdrawn too [27]. Sibutramine, a dual monoamine (noradrenaline and serotonin)-reuptake inhibitor, was introduced to clinical practice in the late 1990s. As a result of a post-marketing trial [28] showing increased cardiovascular risk upon sibutramine treatment, the drug has been suspended of marketing authorisations by the European Medicines Agency [27]. Rimonabant, a CB1-receptor-antagonist was licensed in Europe as an anti-obesity agent in 2006. However, by October 2008, burgeoning reports of serious psychiatric problems (such as anxiety, depression and suicide) led to suspension of marketing authorisations by the EMA [27]. The only anti-obesity drug, which is still on the market in Europe is orlistat, which has been approved by the FDA in 1998. Orlistat inhibits pancreatic lipases, thereby reducing fat absorption from the gut by ~30% resulting in a modest weight loss accompanied by several beneficial effects on cardiovascular risk, as reflected by a lowering of low-density-lipoprotein (LDL) cholesterol, blood pressure and glycemia [29]. Compared with other agents, adverse effects are limited, but include diarrhea, flatulence, bloating, abdominal pain and dyspepsia [27]. In the USA, lorcaserin (a serotoninergic drug) and a combination of phentermine and topiramate extended-release are approved as anti-obesity drugs. Significant side effects may also play an important role as a barrier for the further development of adipokine-based therapeutics. For the clinical development of the combination metreleptin/pramlintide, side effects such as antibody generation and skin reactions have been blocking the road to more advanced stages of clinical studies. Taken together, adverse drug effects are major road blocks in the development of anti-obesity drugs. In addition, it seems that authorities (as well as the public opinion) rank the tolerability of anti-obesity drugs in a risk-benefit-ratio higher than for any other diseases, most likely because obesity is still seen as a preventable disease.

Importantly, road blocks could be removed and adipokines may be introduced into clinical practice as it has been proven by the development of the prototypic adipokine leptin into a novel therapeutic strategy. The aim of this overview is to place the drug development of specific adipokines or adipokine-related compounds into context with major biological road blocks along this process. There are several adipokines with promising rodent efficacy data (Table 1) waiting for their validation in clinical studies.

4. LEPTIN

The relationship of leptin with insulin resistance, obesity, and cardiovascular disease has been extensively studied since its discovery [33]. Leptin is secreted from adipocytes and plays an important role in the regulation of satiety, appetite, food intake, activity and energy expenditure, fertility, atherogenesis and growth [34]. In the hypothalamus, leptin increases anorexigenic and decreases orexigenic peptide synthesis subsequently resulting in reduced appetite [34]. Leptin was discovered in 1994 as the protein product of the ob gene [12]. This discovery marked the identification of the mechanism underlying the extremely obese phenotype of the *ob*/*ob* mouse model, which carry a mutation in the ob gene subsequently leading to leptin deficiency [12]. Recombinant leptin is now available for compassionate use only for patients with congenital leptin deficiency [35]. Noteworthy, recombinant leptin treatment is only available in a few selected centers (e.g. US National Institutes of Health, University of Cambridge for the UK, University of Leipzig for Germany) on a research-protocol basis, i.e. not for routine clinical use. Metreleptin – an analog of the human hormone leptin – has been recently approved for the treatment of

lipodystrophy in Japan, but has not yet cleared the US and European regulatory agencies for approval [36]. Recently, the FDA Advisory Committee voted in favor of metreleptin for the treatment of diabetes and/or hypertriglyceridemia, in patients with rare forms of lipodystrophy. Because leptin is an important negative regulator of body weight, it has been suggested for the treatment of obesity. However, in individuals with obesity, serum leptin concentrations are increased and do not reduce food intake or improve hyperglycemia [34]. Moreover, exogenous administration of leptin does not significantly influence appetite and body weight in obese patients, a phenomenon which has been attributed to central leptin resistance [37]. Recent findings suggested that amylin is able to restore leptin sensitivity and when used in combination with leptin enhances body weight loss in obese rodents and humans [38]. This therapeutic concept using combined amylin/leptin agonism (with pramlintide and metreleptin) has been advanced to a clinical proof of concept study, which demonstrated a significant weight-lowering effect in a 24-week study in human obesity [39]. However, the latest randomized clinical trial on pramlintide/metreleptin as novel strategy in obesity treatment has been recently stopped because of significant problems with antibody generation and skin reactions (http://www.takeda.com/press/article_42791.html). The potential use of leptin-based treatment concepts gained further support by recent preclinical data demonstrating that optimized high activity, long-acting leptin analogs are additively efficacious when used in combination with exendin-4 and FGF21 [40]. Importantly, GLP-1 analogs like exendin-4 are approved drugs for the treatment of type 2 diabetes, but not for weight loss. Moreover, FGF21 has not been approved for any clinical purpose.

In summary, the drug discovery of leptin has shown that even if the mechanism of action is well established and the treatment concept has been successfully proven in rodent models, an efficacious and safe treatment of human diseases is not guaranteed. Leptin is effective in inducing weight loss in obese congenitally leptin-deficient mice [41] and humans [42], but in rodent models of diet-induced obesity [43] or in obese humans [44], leptin has only little weight loss efficacy. Moreover, treatment with higher doses of native leptin or leptin analogs with sustained pharmacokinetics failed to enhance weight loss and increased adverse effects [45]. The example of leptin, which made its way from the discovery (in 1994) to the approval of a leptin analog for human metabolic diseases (in 2013) further demonstrates the potential importance of adipokines as therapeutics, but also reveals important road blocks. In future translational studies it needs to be tested whether road blocks related to the clinical use of leptin for additional indications could be removed by the design of optimized adipokine analogs with improved efficacy and safety profile. In this context it has been recently demonstrated that the design and characterization of several site-specifically enhanced leptin analogs have high potency and sustained action in causing weight loss in diet induced obesity mice [40].

5. TNFα

TNFα is recognized as a multifunctional cytokine implicated in inflammation, apoptosis and cell survival as well as induction of insulin resistance [46]. Since TNFα is highly expressed in adipose tissue of obese animals [47] and humans [48], it may be considered as adipokine. Neutralization of TNFα in obese *fa/fa* rats caused a significant increase in the peripheral uptake of glucose in response to insulin [47]. In mice targeted disruption of the TNFα gene results in significantly improved insulin sensitivity in both diet-induced and monogenetic obesity models [49]. These data supported the hypothesis that blocking TNFα action may improve insulin sensitivity and its related traits. Indeed, in some rodent studies, administration of TNFα antibodies resulted in inhibited inflammatory activity, improved fatty liver disease [50], protection against diet induced obesity and insulin resistance [51]. However, in obese Zucker rats, anti-TNF treatment had no effect on insulin sensitivity or lipid profile [52]. The promising results from some of the rodent studies using anti-TNF treatment for improving metabolic diseases could not be proven to be successful in all clinical studies. A few studies reported some improvement of insulin sensitivity or glucose homeostasis in insulin resistant individuals during prolonged treatment with the anti-TNFα antibody infliximab [53] or etanercept [54]. In contrast to these reports, treatment with anti-TNFα antibodies such as infliximab or etanercept has not been associated with changes in insulin sensitivity and obesity in humans [55–60]. In a recent study, chronic TNF-α neutralization by infliximab led to improvements in inflammatory status, but did not improve insulin resistance or endothelial function in healthy, but obese, insulin-resistant volunteers [57]. Moreover, these studies question the concept that TNF-α is a causative link between obesity and insulin resistance. One potential explanation for the absent effect of anti-TNFα antibodies on insulin resistance in morbidly obese subjects may be the paracrine way of action of TNFα [58]. Because infliximab is predominantly distributed within the vascular compartment, its effectiveness in peripheral tissues of insulin resistance such as skeletal muscle and adipose tissue maybe low [58]. Therefore the major road block for the clinical use of anti-TNFα antibodies in the treatment of metabolic diseases is a lack of efficacy in human studies despite some promising preclinical data. Taken together, TNFα so far did not show to be a very promising drug target for insulin resistance or obesity related metabolic diseases in humans.

6. ADIPONECTIN

Adiponectin may be the most prominent example for the potential use of an adipokine in the treatment of obesity and obesity-associated metabolic diseases. Adiponectin has been discovered in 1995 and was originally named Acrp30 [61], adipoQ [62], and apM1 [63], until the consensus name 'adiponectin' found widespread acceptance [64]. There is consensus that adiponectin generally exerts insulin sensitizing, anti-inflammatory and anti-apoptotic actions on a number of different cell types [64]. Consistent with these properties, adiponectin release from adipocytes is down-regulated under adverse metabolic conditions, resulting in decreased adiponectin serum concentrations [64]. Interestingly, various hormones associated with insulin resistance and obesity including catecholamines, insulin, glucocorticoids, TNFα and IL-6 down-regulate adiponectin expression and secretion in fat cells *in vitro* [65]. Besides its peripheral effects, adiponectin acts in the brain to increase energy expenditure and cause weight loss [64]. The role of adiponectin as an endogenous insulin sensitizer was discovered in adiponectin knockout mice, which are characterized by impaired insulin sensitivity [66]. On the contrary, mice with transgenic adiponectin overexpression are protected against obesity, diabetes (*ob/ob* mice) and atherosclerosis (ApoE-deficient mice) [67,68].

In many (but not all) studies, administration of recombinant adiponectin results in improved (hepatic) insulin sensitivity, increased insulin secretion [69] and beneficial effects on body weight and hyperglycemia [reviewed in [19,64]]. In a recent study, no effect of recombinantly produced adiponectin on glucose levels, HbA1c, plasma lipids or body weight has been found [70]. However, this failure to lower blood glucose in animal models of type 2 diabetes could be due to ineffective recombinant adiponectin preparations [70]. Very recently, Okada-Iwabu and coworkers reported the production of an orally active, synthetic

small-molecule adiponectin receptor agonist that they have termed AdipoRon [71]. This molecule binds to adiponectin receptors and ameliorates insulin resistance and glucose intolerance in mice [71]. Importantly, AdipoRon ameliorates diabetes and prolonged lifespan of *db*/*db* mice on a high-fat diet [71]. Taken together, adiponectin or adiponectin receptor agonists are promising candidates for further development as therapeutic for insulin resistant states. The major road block for the further development of adiponectin-based treatment strategies is a lack of human data.

7. APELIN

Apelin is an adipokine which may play a role in the regulation of glucose homeostasis and may contribute to the link between increased adipose tissue mass and obesity related metabolic diseases [reviewed in [72]]. Higher apelin serum concentrations have been found in patients with obesity, insulin resistance, liver cirrhosis [72,73] and reduced adipose tissue apelin expression and serum concentration may contribute to improved insulin sensitivity independently of significant weight loss [73]. Apelin receptor antagonist treatment of rats showed diminished hepatic fibrosis and loss of ascites suggesting the hepatic apelin system as a novel therapeutic target in liver disease [74]. In obese and insulin-resistant mice, recombinant apelin injection has been shown to have glucose-lowering effects associated with enhanced glucose utilization in skeletal muscle and fat thereby restoring glucose tolerance [75]. Apelin treatment data from different rodent models indicate that apelin influences glucose homeostasis and may contribute to the link between increased adipose tissue mass and obesity related metabolic and inflammatory diseases. However, the exact mechanism how apelin may have a beneficial effect on glucose metabolism needs to be explored and human data are still not available.

8. VASPIN

Visceral adipose tissue-derived serpin (vaspin) may serve as another example for a promising adipokine in the therapy of obesity and diabetes. First identified in adipose tissue of a rat model of obesity and insulin resistance [76] and related to human obesity and type 2 diabetes [77], vaspin expression was also found in hypothalamus, stomach and rodent pancreatic islets [78]. So far, the mechanisms how vaspin secretion may be linked to deterioration of glucose metabolism and insulin sensitivity are not entirely understood. Administration of vaspin to obese mice improves glucose tolerance, insulin sensitivity and altered gene expression of candidate genes for insulin resistance [79]. Moreover, we could recently show that treatment of different mouse models with recombinant vaspin leads to sustained glucose lowering and reduction of food intake [78] which may at least in part be explained by an inhibition of kallikrein 7 [79]. Although these rodent studies suggest vaspin as a future pharmacological therapy of obesity and its related metabolic diseases, further molecular targets of vaspin have to be identified to fully understand its mechanism of action. Another road block in the drug development of vaspin is the lack of human data.

9. BMP-7

For another promising adipokine drug, BMP7, development to a therapeutic is more advanced. BMP7 has been suggested as a novel therapeutic approach for obesity and metabolic diseases since the discovery, that BMP7 induces brown adipogenesis, reduces food intake, increases energy expenditure and reduces weight gain [80,81]. Human recombinant BMP7 has surgical uses and is marketed under the brand name OP1 [82]. It can be locally used to aid in the fusion of vertebral bodies to prevent neurologic trauma, in the treatment of non-union after tibia fractures, particularly in cases where a bone graft has not been successful. Noteworthy, clinical application of recombinant BMP7 was not associated with local or systemic toxicity, ectopic bone production, or other adverse events [82]. However, as an important road block in the drug development, there are no clinical data available on the effects of BMP7 on obesity and metabolic diseases so far.

10. NAMPT/VISFATIN

Another example for a lack of human data blocking the road to a therapeutic use is the molecule nampt/visfatin and its related pathways. Nampt/visfatin has been first described as an adipokine predominantly secreted from visceral fat exerting insulin-mimetic effects [83], however, subsequent human studies revealed that other tissues and adipose tissue depots may also express nampt/visfatin and the effects of this molecule as an insulin mimetic are controversial [84–86]. However, nampt/visfatin has an important enzymatic function in synthesizing nicotinamide mononucleotide (NMN) from nicotinamide and phosphoribosylpyrophosphate (PRPP) [85]. Recently it has been demonstrated that hypercaloric feeding as well as aging compromise NAMPT-mediated NAD^+ biosynthesis and may therefore contribute to the pathogenesis of type 2 diabetes [85]. Yoshino et al. recently demonstrated that administration of NMN to mouse models of obesity and type 2 diabetes promotes NAD^+ biosynthesis thereby ameliorating glucose intolerance and improving hepatic insulin sensitivity [85]. The mechanism how nampt/visfatin contributes to alterations in glucose homeostasis may involve regulation of expression of genes related to oxidative stress, inflammatory response, β cell function [86] and circadian rhythm, at least in part via SIRT1 activation [85]. However, for the nampt/visfatin based treatment concept, there are no human data available yet.

11. NESFATIN-1

Another example for which lack of human data is still an obstacle is nesfatin-1, which has been proposed as novel satiety molecule acting through leptin-independent mechanisms [reviewed in [87]]. Nesfatin-1 is expressed in the central nervous system, the pituitary, stomach, pancreas, testis, and also adipose tissue [87], the latter may qualify nesfatin-1 to categorize as adipokine. In addition to its role in the adaptive response under stressful conditions, there is accumulating evidence that nesfatin-1 exerts direct glucose-dependent insulinotropic effects and increases preproinsulin mRNA expression in rodent isolated islets or cultured MIN cells [88,89]. Importantly, intravenous, but not central administration of recombinant nesfatin-1 to *db*/*db* mice significantly reduces hyperglycemia, supporting the hypothesis that nesfatin-1 has a direct glucose-dependent insulinotropic effect on β-cells [90]. However, in addition to mechanistic studies, clinical studies are necessary to translate the findings from rodent studies into the human situation.

12. DPP-4

Recently, it has been shown that dipeptidyl peptidase-4 (DPP-4) is secreted from adipose tissue [25]. DPP-4 secretion from adipose

tissue was also demonstrated *in vivo* with greater release in obese compared to lean individuals [26]. Moreover, insulin-sensitive obese patients [91] had significantly lower circulating DPP-4 than obesity-matched insulin-resistant patients [26]. Increased DPP-4 secretion from adipose tissue may therefore contribute to obesity and insulin resistance and inhibition of DPP-4 has been already an established type 2 diabetes treatment concept prior to the denomination of DPP-4 as adipokine. However, the contribution of adipose tissue derived DPP-4 to changes in endogenous GLP-1 levels has not been investigated *in vivo* so far. In addition, it is not known, whether DPP-4 inhibitors may disproportionately affect DPP-4 derived from adipose tissue or other sources. Further experiments including studying the effects of DPP-4 inhibitor treatment in adipocyte-specific DPP-4 knockout mice need to be performed to elucidate the contribution of DPP-4 secreted from adipose tissue to whole body incretin effects and glucose homeostasis.

DPP-4 inhibitors exert their hypoglycemic effect indirectly by increasing plasma concentration, duration and action of incretins [92–94]. Currently, the DPP4-inhibitors alogliptin, sitagliptin, linagliptin, saxagliptin and vildagliptin are in clinical use as anti-diabetic drugs to improve glycemic control by stimulating glucose-induced pancreatic insulin secretion and suppressing glucagon production [94]. Although research has focused on the role of DPP-4 in the degradation of GLP-1, recent data suggest that DPP-4 also exerts direct effects, as it is able to induce insulin resistance in adipocytes and skeletal muscle cells in concentrations that can be found in the circulation of overweight and obese subjects [25]. This notion is further supported by the notion that DPP-4 inhibitors might exert incretin-independent effects, further suggesting that DPP-4 might have direct metabolic effects [94]. The observation that circulating DPP-4 and adipose tissue *DPP-4* expression correlate with adipocyte size and adipose tissue inflammation [25,26] might also suggest that pro-inflammatory adipokines released from enlarged adipocytes could regulate DPP-4 release. Therefore, DPP4 might not only reflect adipose tissue function, but it may also have local effects within adipose tissue and systemic effects. Increased DPP-4 activity and serum concentrations in obesity may serve as a model how altered adipokine secretion may be successfully used as therapeutic target in the treatment of obesity related diseases. However, further work is needed to elucidate the functional role of DPP-4 within adipose tissue and to define whether higher DPP-4 expression and serum concentration may contribute to higher efficacy of DPP-4 inhibitors in patients with type 2 diabetes.

13. IL-1β

IL-1β is expressed in and secreted from adipose tissue [95]. IL-1β is a proinflammatory cytokine which has been proposed to play a role in inflammatory pancreatic β-cell destruction leading to type 1 diabetes [96]. IL-1β inhibits the function and promotes the apoptosis of β-cells [96]. The blockade of IL-1 with a recombinant human IL-1-receptor antagonist (anakinra) has been shown to improve glycemia and β-cell function and reduced markers of systemic inflammation in a double-blind, parallel-group clinical trial involving 70 patients with type 2 diabetes [96]. Therefore IL-1β represents a model that in addition to the direct use of adipokines as therapeutic strategy, adipokines may be indirectly used as target molecules for the treatment of obesity comorbidities.

14. FGF21

FGF21 is a member of the FGF superfamily that is primarily produced by the liver and adipose tissue and has been recently discovered as an important metabolic regulator [97]. FGF21 has significant glucose and lipid lowering as well as thermogenic effects through interaction with specific FGF receptors and a cofactor called β-Klotho. Administration of FGF21 produces beneficial metabolic effects in animal models [97]. Recently, the promising data from animal studies have been extended by a randomized, placebo-controlled, double-blind proof-of-concept trial on the effects of LY2405319, a variant of FGF21, in patients with obesity and type 2 diabetes [97]. The compound had beneficial effects on body weight reduction, fasting insulin and caused significant improvements in dyslipidemia, including decreases in low-density lipoprotein cholesterol and triglycerides and increases in high-density lipoprotein cholesterol and a shift to a potentially less atherogenic apolipoprotein concentration profile [97]. Noteworthy, the compound did not significantly improve glucose concentrations [97]. Despite that, the first clinical trial using FGF21 as a therapeutic concept suggested that FGF21-based therapies may be effective for the treatment of distinct obesity related metabolic disorders.

15. CONCLUSIONS

Anti-obesity interventions have provided only limited long term success (lifestyle changes, psychological interventions, pharmacotherapies) or are associated with a relatively high mortality risk (bariatric surgery). Therefore there is an urgent need to develop novel pharmacological treatment strategies which target the not entirely understood causative factors in the pathogenesis of obesity and obesity-related metabolic diseases. Because adipokines are involved in the regulation of appetite, satiety, energy expenditure and physical activity, they may represent tools for weight loss interventions in the future. A lack of understanding adipokines' actions (and potential side effects) especially for the more recently discovered adipokines are still road blocks in drug discovery, which need to be removed to generate more specific therapeutic targets.

However, reduction of body weight might not be the only or best approach to improve obesity related diseases. Novel treatment concepts for metabolic diseases may include the attempt to change a metabolically unhealthy into a metabolically healthy obese individual. Such a phenotype switch could be achieved by normalization of the pro-inflammatory, atherogenic and diabetogenic cytokine/adipokine profile, a reduction in visceral fat or an improvement of adipose tissue function. For these novel treatment concepts, adipokines are promising candidates for future pharmacological treatment strategies. For leptin, an analog (metreleptin) of the human hormone is already used as a pharmacotherapy in individuals with congenital leptin deficiency and lipodystrophies. Other adipokines such as FGF21 or adipokine-targeting compounds (IL-1 antagonists, adiponectin receptor agonists) may follow this successful example. Novel adipokine-related treatment strategies may offer exciting new opportunities in a spectrum of diseases with several unmet clinical needs.

CONFLICT OF INTEREST

None declared.

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