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

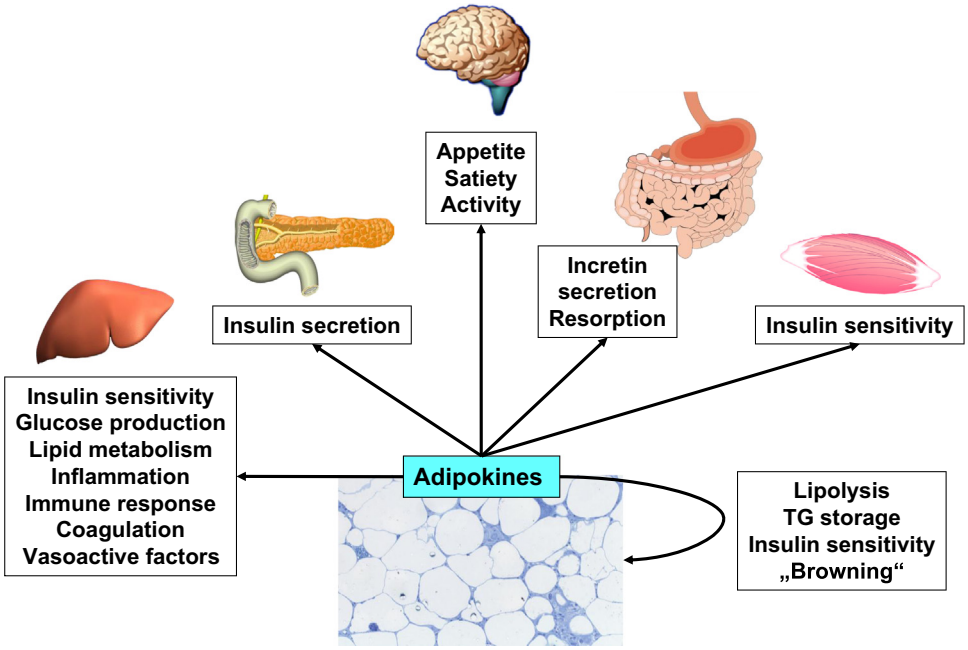

Figure 1: Adipokines regulate important physiologic processes. Secreted factors from adipose tissue play an important role in the regulation of appetite and satiety, energy expenditure, insulin sensitivity and insulin secretion, inflammation, blood pressure, hemostasis, endothelial function and others. 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.

