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Visions & Reflections

Newly discovered endocrine functions of white adipose tissue: possible relevance in obesity-related diseases

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Abstract. During recent years our view of adipose tissue has been revolutionized. White adipose tissue (WAT) is no longer seen as mere energy store or provider of thermal and mechanical insulation. Neglect of WAT has been overcome by surprising discoveries in recent years, changing the view of this tissue towards a highly endocrine organ that is involved in a wide variety of physiological and pathophysiological processes. In this brief article we will focus on new developments in adipocyte and WAT biology. The appreciation of WAT as an endocrine organ will provide the basis for new and promising perspectives in the management of obesity and obesity-related diseases including diabetes, mellitus type II and arterial hypertension.

Key words. Adipose tissue; adipocyte; obesity; endocrine; adipokines; inflammation; hypertension.

White adipose tissue is a highly complex endocrine organ

It is well established now that in addition to its role in the deposition and release of fatty acids, WAT produces and secretes several major hormones and signalling factors. Without receiving much attention, the enzymes lipoprotein lipase and adipsin, a component of the complement pathway, were introduced as adipocyte-secreted substances (adipokines) during the 1980s [1, 2]. The discovery of adipose tissue expression of tumor necrosis factor alpha (TNFα) in 1993 [3] and leptin in 1994 [4] initiated an explosive acceleration in adipocyte and obesity research. Predominately synthesized by WAT, serum leptin levels correlate to total body fat mass, but are in addition influenced by a wide range of factors that regulate food and energy balance. These include e.g. exercise, sleep pattern, ambient temperature and food composition. Conversely, leptin levels adjust the systems that regulate feeding, substrate utilization and energy balance to the nutritional status. Simply but, leptin reduces food intake and increases, at least in rodents, energy expenditure. Thus, WAT responds to changing metabolic situations in an endocrine manner and is directly involved in maintaining of the body's homeostasis. To date, numerous secretory products from adipocytes have been characterized, and the list is still growing (table 1). In characterizing proteins secreted by adipocytes, a proteomic approach is useful. Thus, two recent systematic studies examining the profile of proteins secreted by preadipocytes compared with adipocytes led to the identification of novel proteins secreted by adipocytes [5, 6]. A few recently characterized factors are discussed as examples of the high complexity of adipose tissue.

Fasting-induced adipocyte factor (FIAF) is one of the recently discovered adipocytic proteins that is likely to play an essential role in the organism's adaptation to fasting [7]. FIAF was identified as a circulating lipoprotein lipase inhibitor whose production is suppressed by the gut microbiota. This suppression enhances deposition of triglycerides in adipocytes, and it is speculated that

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Table 1. Selected secretory products of adipocytes.

α1-acid glycoprotein	[22]
Acylation stimulating protein (ASP)	[23]
Adiponectin	[24]
Adiponutrin	[25]
Angiotensinogen	[26]
Apelin	[10]
Fasting-induced adipocyte factor (FIAF)	[8]
Haptoglobin	[27]
Interleukin 1, 6, 8, 10	[11]
Leptin	[4]
Lipocalin 24p3	[22]
Lipoprotein lipase (LPL)	[28]
Macrophage migration inhibitory factor (MIF)	[16]
Nerve growth factor (NGF)	[29]
Plasminogen activator inhibitor-1 (PAI-1)	[30]
Resistin	[31]
Serum amyloid A3 (SAA3)	[22]
Sex steroids/glucocorticoids from precursors	[32]
Transforming growth factor β (TGFβ)	[11]
Tumor necrosis factor α (TNFα)	[3]
TNF-soluble receptors	[33]
Visfatin	[9]

changes in microbial ecology caused by Western diets and interindividual differences in gut microbiota might be crucial factors in the development of obesity [8].

Fukuhara et al. characterized a new adipocytokine, visfatin, which turned out to be identical to pre-B cell colony-enhancing factor (PBEF). The name 'visfatin' indicates its predominant expression in visceral compared with subcutaneous fat, and its serum levels are thus positively correlated to the amount of visceral but not subcutaneous fat in both mice and humans. Characterization of the possible physiological role of visfatin in vivo and in vitro revealed that visfatin mimics insulin signalling by binding to the insulin receptor. It may therefore be important for regulation of the body's glucose homeostasis. In addition, its characterization might provide the basis for the development of new and promising anti-diabetic drugs [9]. Apelin is yet another very recent addition to the list of endocrinologically active peptides produced by adipocytes. Its serum levels are related to the nutritional status of the body and parallel the serum levels of insulin. The expression of apelin is regulated by insulin, and its involvement in the regulation of food intake is discussed [10].

In the Western world overweight and obesity have reached alarmingly epidemic proportions. Obesity is a major risk factor for lipid abnormalities, atherosclerosis, high blood pressure, type 2 diabetes mellitus and certain types of cancer. At the cellular level, obesity correlates with an increase in adipocyte seize (hyperplasia) and number (hypertrophy). This is the consequence of an imbalance between energy uptake and energy expenditure. The sole increase in weight and fat mass is the cause of one category of obesity-associated medical problems. These include e.g. psychological dysfunctions resulting from stigmatization but also bodily diseases such as sleep apnoea, osteoarthritis and alterations of the skin such as acanthosis nigricans. Moreover, obesity is associated with disorders that result from hypersecretion by hypertrophic and hyperplastic adipocytes. In this context, the release of free fatty acids, and a disturbed blood fat composition and enhanced secretion of endocrinologically active factors must be considered as relevant pathophysiological factors in the development of obesity-associated disorders.

Inflammation and obesity

Recent studies indicate that in addition to the above-mentioned problems, a subclinical proinflammatory state may play a substantial role in the etiology of obesity-associated disorders such as insulin resistance, type 2 diabetes, atherosclerosis and the metabolic syndrome. Obesity is now considered to be a state of chronic inflammation due to elevated plasma levels of inflammatory markers such as interleukin (IL)-6, TNFα or C-reactive protein (CRP). One source of inflammatory cytokines is adipocytes themselves. They produce and secrete several cytokines, including TNF-α, IL-6 and IL-8 (table 1) (for review, see [11–13]). In addition, it has been shown that obesity is associated with macrophage infiltrations in WAT that amplify the effect [14, 15]. Human adipocytes produce and secrete macrophage migration inhibitory factor (MIF) in a body mass index-related manner [16]. This factor regulates macrophage accumulation in tissues and hence may be an obesity-dependent mediator of macrophage infiltration of adipose tissue.

Obesity and high blood pressure

Obesity, especially the visceral type of obesity, is strongly associated with arterial hypertension. Although the association between obesity and elevated blood pressure is unquestioned, the exact pathogenetic mechanisms are poorly understood. Activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, peroxisome proliferator-activated receptor gamma (PPARγ) activation, leptin and insulin are discussed as pathogenetic factors. In addition, the increase in total blood volume in obesity might be responsible for the long-term elevation of blood pressure (for reviews on obesity and high blood pressure, see [17, 18]).

The mineralocorticoid aldosterone is the most potent hormone enhancing renal sodium and water retention, and consequently elevating blood pressure. Increased aldosterone levels are a frequent observation in obesity. Interestingly, elevation of aldosterone levels does not always correlate with an increase in plasma renin activity,

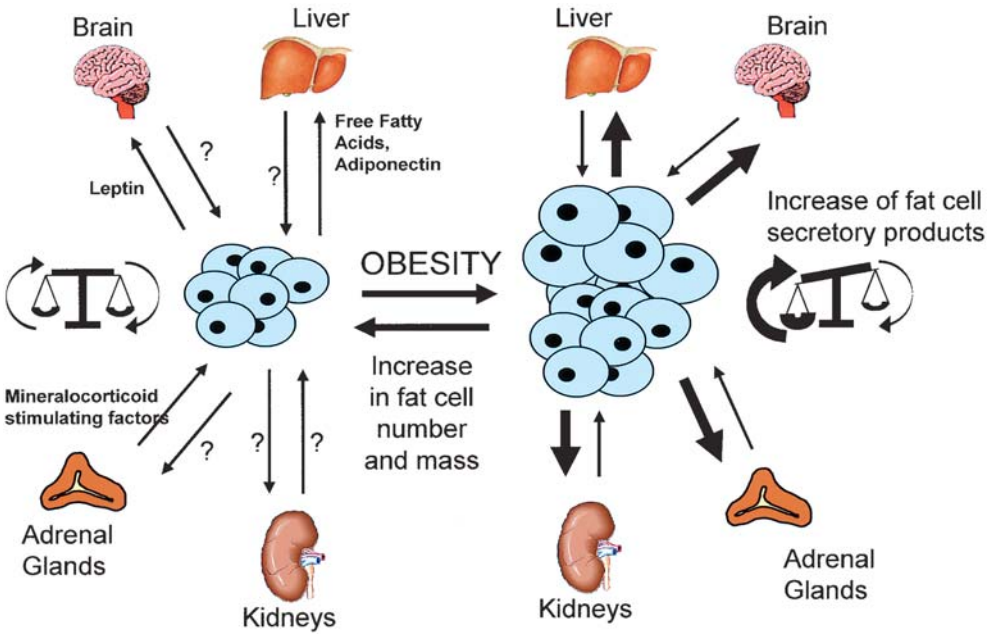

Figure 1. Adipose tissue is now considered a highly active endocrine organ that is involved in the body's metabolism and homeostasis. Overweight and obesity are accompanied by an overproduction of many adipokines, leading to an imbalance in these complex interactions, and consequently to metabolic problems.

suggesting renin-independent stimulation of aldosterone synthesis [19, 20]. We therefore tested the hypothesis that adipocytes secrete factors that directly influence aldosterone secretion from adrenocortical cells. In vitro cell culture and co-culture experiments indeed demonstrated a direct interaction of adipocytes with adrenocortical cells. Adipocyte secretory products stimulated adrenocortical hormone secretion with a predominant effect on aldosterone production. This effect was independent of the adipokines leptin, TNFα, IL-6, adiponectin and angiotensin II secreted from adipocytes. Our study indicates that adipocytes secrete factors that directly stimulate the release of aldosterone from the adrenal gland, further supporting the view that WAT is an endocrine organ that communicates with and influences other organ systems [21]. We therefore propose a direct link between obesity and elevated plasma aldosterone levels leading to hypertension, and speculate that WAT might play a hitherto unknown role in the process of water and electrolyte homeostasis by directly influencing adrenal and renal functions in an endocrine manner. In further studies we aim to explore in more detail the underlying nature of the mineralocorticoid stimulating factors (adipotensins).

Adipose tissue is no longer viewed merely as a lipid storage medium but as a highly complex endocrine organ involved in manifold physiological and pathological processes. We are only beginning to understand adipocyte and WAT biology and its role in health and disease. Recent studies on the endocrine function of adipocytes may provide the prerequisites for new and promising treatment strategies in obesity and obesity-associated disorders.

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