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Review

New adipokines☆

Nouvelles adipokines◊

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Abstract

Adipose tissue is now widely recognized as "an organ" able to synthesize and secrete hundred factors collectively called adipokines. These secreted molecules exert pleiotropic actions, notably on the regulation of glucose and lipid metabolism, inflammation, reproduction, or angiogenesis. Over the past two decades, a considerable amount of work was performed on the two "star" adipokines, leptin and adiponectin, particularly because of their involvement in energy metabolism. The present review is focused on the three most recently discovered adipokines that are clearly emerging as important actors in metabolism: apelin, fibroblast growth factor-21, and neuroregulin-4. Moreover, given a number of clinical and experimental data, these three adipokines represent promising targets in the context of metabolic disorders associated with obesity.

Keywords: Adipocyte; Adipokine; Apelin; Fibroblast growth factor-21; Insulin resistance; Neuroregulin-4; Obesity; Adipose tissue

Résumé

Le tissu adipeux est désormais largement reconnu en tant qu'« organe » capable de synthétiser et de sécréter de nombreux facteurs rassemblés sous le terme d'adipokines. Ce tissu sécrète vraisemblablement plusieurs centaines de molécules, qui exercent des actions pléiotropes, notamment sur la régulation du métabolisme glucido-lipidique, l'inflammation, la reproduction, ou l'angiogenèse. Au cours des deux dernières décennies, une somme considérable de travaux a été réalisée sur les adipokines « vedettes », la leptine et l'adiponectine, notamment en raison de leur implication dans le métabolisme énergétique. De parti pris, cette revue est focalisée sur trois adipokines de découverte plus récente, mais dont l'intérêt émerge clairement : l'apéline, le FGF21, et la neuroréguline-4. Au vu de plusieurs données cliniques et expérimentales, ces trois adipokines représentent des cibles prometteuses dans le contexte des désordres métaboliques associés à l'obésité.

Mots clés : Adipocyte ; Adipokine ; Apéline ; *Fibroblast growth factor-21* ; Insulinorésistance ; Neuroréguline-4 ; Obésité ; Tissu adipeux

1. Introduction

Over the last twenty years, considerable progresses have been made regarding the demonstration of the endocrine nature of adipose tissue (AT), dramatically illustrated in 1994 by the discovery of leptin, which exerts an anorectic effect on the central nervous system. Other adipokines have also been extensively investigated as adiponectin, interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1, resistin, omentin, or vaspin. However, we are

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far from understanding their pathophysiological implications. The complexity of this domain is documented by recent proteomic approaches, which indicate that human AT explants could secrete more than 700 distinct proteins. Therefore, the biology of AT will become more and more complicated.

Adipokines regulate important biological processes in target organs such as the brain, liver, skeletal muscle, cardiovascular and immune systems, and the endocrine pancreas (Fig. 1). This could explain the close link between obesity and the metabolic and cardiovascular complications [1,2]. The production of many adipokines is deregulated in obesity [3] and could participate into disturbances of appetite and satiety, and into changes in the distribution of AT, insulin secretion, insulin sensitivity, energy expenditure, endothelial function, angiogenesis, inflammation, blood pressure, haemostasis, osteoarticular functions and reproduction. Consequently, adipokines offer promising prospects for the management of obesity-related morbidities.

Moreover, adipokines are not necessarily derived from adipocytes, but also from other cell-types present in AT that contains not only adipocytes (that represent less than half of the total number of cells present in the tissue), but also various amounts of immune cells (macrophages, lymphocytes, granulocytes, mast cells), endothelial cells, and fibroblasts. Leptin and adiponectin are mainly derived from adipocytes, while the pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) are primarily produced by macrophages and immune cells. In addition, the secretory profiles of this heterogeneous and plastic tissue may be different according to the location of fat deposits.

Table 1
Summary of the main metabolic effects of apelin, FGF-21, and neuroregulin-4.

	Apelin	FGF-21	Neuregulin-4
Body weight	↘	↘	↘
Adiposity	↘	↘	↘
Insulin sensitivity	↗	↗	↗
Insulin secretion	↘	↗	?
Skeletal muscle glucose uptake	↗	↗	?
Thermogenesis	↗	↗	0

Finally, we must emphasize that new data and innovative concepts, well beyond the metabolic effects of these adipokines, have emerged over the last ten years. In this review article, we decided to focus on three "new" adipokines of interest which present potential therapeutic prospects: apelin, fibroblast growth factor (FGF)-21, and neuregulin-4. The main metabolic effects of these three adipokines are summarized in Table 1.

2. Apelin

2.1. Discovery, structure and main functions

In 1998, Tatemoto et al. purified from bovine stomach extracts a peptide recognizing a previously discovered G protein-coupled orphan receptor, APJ, now designated the apelin receptor. APJ

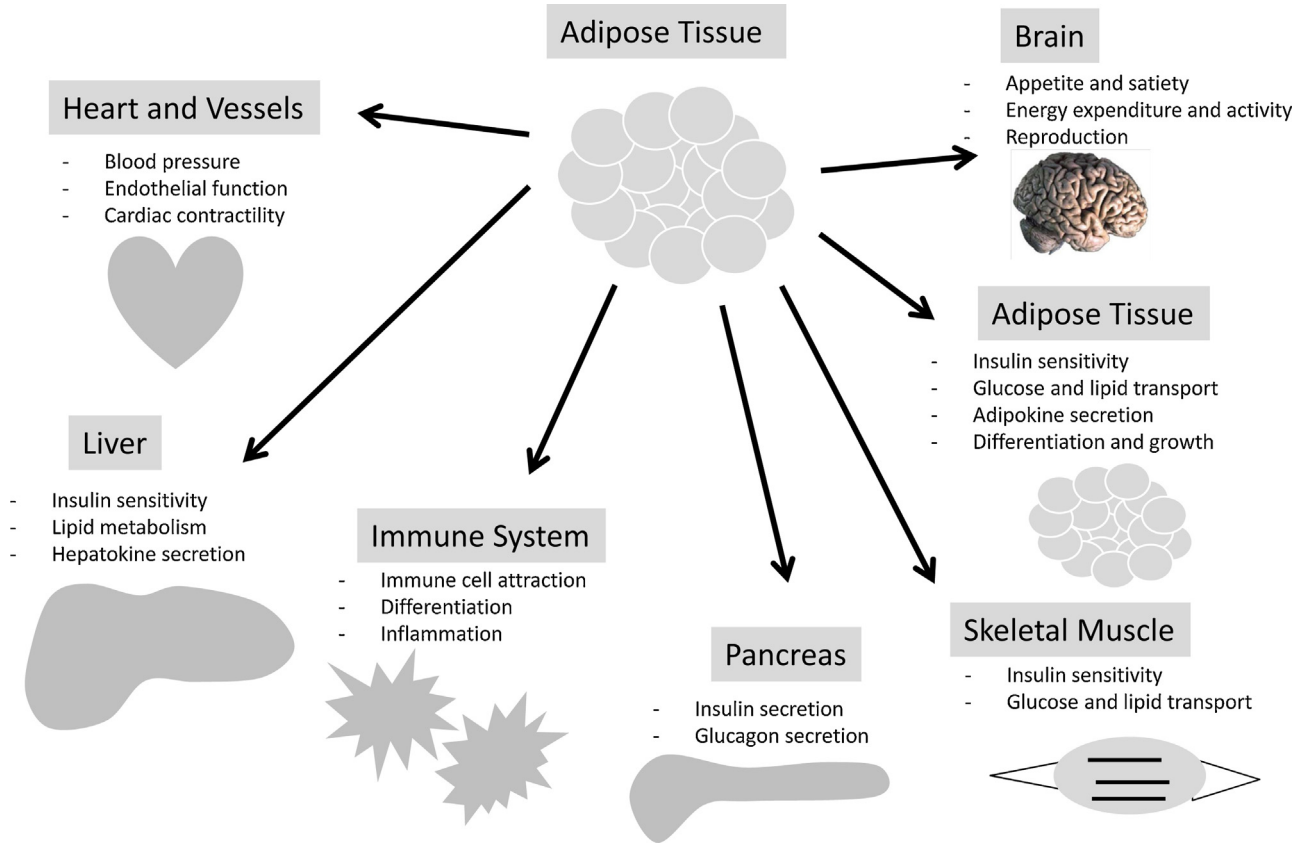

Fig. 1. Regulation of many biological functions by adipokines.