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ADIPOENDOCRINOLOGY AND ADIPOPARACRINOLOGY: EMERGING FIELDS OF STUDY ON THE ADIPOSE TISSUE

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Adipose tissue was conceived originally as merely passive, space-filling, fat storage tissue. However, in the last 10 years, investigations aimed at studying the endocrine secretion by adipose tissue have enjoyed explosive growth. The major secretory compartment of adipose tissue consists of adipocytes and stromal fibroblasts (adipofibroblasts). These cells secrete multiple bioactive molecules, conceptualized as adipokines or adipocytokines. Overall, this intellectual grown process framed an emerging field of study, adipoendocrinology. "Adipoendocrinology" connotes the study of the cellular and molecular biology of the endocrine function of adipose tissue in normal and diseased conditions. In humans, white adipose tissue is partitioned into a few large depots, including visceral and subcutaneous location, and many small depots, associated with heart, large blood vessels, major lymph nodes and other organs. The possibility that the endocrine secretory activity of large adipose depots may directly contribute to the elevated plasma levels of disease-associated adipokines has recently gained considerable attention. However, the paracrine secretory activity of organ-associated adipose tissue (the small adipose depots) has until now attracted little attention in the adipobiology of disease. Here we attempt to emphasize that studies aimed at evaluation of the paracrine secretion of organ-associated adipose tissue are becoming mandatory, since identification of the secreted molecules, particularly, adipokines, may yield clues to a possible transmission of pathogenic and/or protective stimuli, from the associated adipose tissue towards the interior of the associating organ. In this review we summarize most of the current information about adipoendocrinology and adipoparacrinology of various diseases.
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INTRODUCTION

In recent years, the simple paradigm of adipocytes as merely fat storage cells is rapidly evolving into a complex paradigm of these cells as multipotential secretory cells. Arguably, the most momentous changes that have occurred in the field of these studies have been the discovery of leptin, adipocyte-specific secretory protein, in the end of 1994 (1). Onwards, this seminal finding initiated a period of intense interest in the elucidation of the endocrine and paracrine roles of the

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adipose tissue and their potential involvement in the molecular mechanisms of obesity and related diseases. Overall, this intellectual grown process framed two emerging fields of study, adipoendocrinology and adipoparacrinology, respectively. These connote the study of the cellular and molecular biology of the endocrine/paracrine function of adipose tissue in normal and diseased conditions.

In humans, white adipose tissue (WAT) is partitioned into a few large depots, including visceral and subcutaneous location, and many small depots, associated with heart, large blood vessels, major lymph nodes (2-5), and even parasellar region in the brain (6), while, brown adipose tissue (BAT) is present around kidneys, adrenals, and aorta, and within the mediastinum and neck (7). Adipocytes are also located in bone marrow. Although adipose tissue has a similar uniform histological appearance in various parts of the human body, recent evidence suggests regional variations in the secretory protein production by adipose tissue (2-5,8).

Today we witness an increasing attention to the field of adipobiology, one of the most exciting examples being the rapidly growing interest in understanding the adipose tissue secretion and its involvement in the molecular mechanisms of a surprising variety of diseases besides obesity and related diseases. The major secretory compartment of adipose tissue consists of adipocytes and stromal fibroblasts (adipofibroblasts). Adipocytes are protein secreting cells that synthesize, (usually) store, and release proteins targeted to multiple secretory pathways (9-14). Adipofibroblasts are the major site of estrogen synthesis, mediated by the enzyme aromatase cytochrome P450 which converts androgens to estrogens (15-17). In effect, adipocytes and adipofibroblasts secrete a large number of multifunctional molecules, including cytokines, growth factors, enzymes, hormones, complement factors, and matrix proteins, conceptualized as adipokines (18-21) or adipocytokines (22-24). In addition to their importance in lipid, glucose and energy homeostasis, adipokines, using endocrine and/or paracrine pathways, exert important and often critical control over hematopoiesis (25-27), inflammation (25,27-30), hemostasis (31,32), complement activities (33), reproduction (34), angiogenesis (35,36), and feeding behavior (37,38). In a similar vein, adipokines now prove to be involved in mediating various diseased processes. Hence the development of adipoendocrinology and adipoparacrinology may indeed contribute to the understanding of pathogenesis and therapy of adipokine-associated diseases.

ADIPOSE TISSUE IS AN ENDOCRINE AND PARACRINE ORGAN PRODUCING ADIPOKINES

Since the isolation of the first known adipocyte-secreted protein, the serine protease adipsin (39), in 1987, the list of adipose tissue secretory proteins has greatly extended. Many, like tumor necrosis factor-alpha (TNF-α) (31,40,41), IL-8 (42), macrophage colony-stimulating factor (43), leukemia inhibitory factor (44), and also leptin itself (28), appeared to be cytokines or chemokines (IL-8), whereas others appeared to be growth factors, enzymes, and hormones (15-24,31-33,45-64), identical to those secreted by various other tissues. In obesity, for example, the plasminogen activator inhibitor-1 (PAI-1) secretory capacity of adipocytes may even exceed that of PAI-1-producing cells in other tissues (31). Likewise, in postmenopausal women, the estrogen production in whole body adipose tissue may be enough to effectively increase circulating levels of estrogens (15,16). Conceptually, to embody the secretory production by adipose tissue, the terms "adipokines" and "adipocytokines" were designated. Accordingly, their counterparts derived from nonadipose tissue sources are not in the scope of the present article. Note that mast cells, being an essential component of the adipose tissue, may also contribute to its secretory potential. Information about mast cell secretion and mast cell involvement in metabolic disorders may be found elsewhere (65-67).

Among adipokines discovered until now, leptin (from Greek *leptos*, means thin), encoded by the obese (*ob*) gene (1,25,26,28,30,34-38), and recently adiponectin (synonyms: Acrp30, adipocyte complement-related protein of 30 kD; apMl protein, encoded by adipose most abundant gene transcript 1; AdipoQ; GBP28, gelatin-binding protein of 28 kD) (22-24,68-71) have received intense scientific coverage. Other adipokines such as PAI-1, tissue factor (TF), TNF-α and transforming growth factor-beta (TGF-β) (31), and recently resistin (synonyms: ADSF, adipocyte secreted factor; FIZZ3, found in inflammatory zone 3) and resistin-like molecules (58,59) have also attracted great attention. A list of adipokines is presented in Table 1.

ADIPOBIOLOGY OF ADIPOKINE-ASSOCIATED DISEASES

As indicated in the Introduction, adipose tissue is partitioned into a few large depots, including subcutaneous and visceral location, and many small depots, associated with heart, large blood vessels, major lymph nodes, bone marrow, kidneys, adrenal glands, and even the brain (2-7). All these fat depots are potential sources of adipokines. The possibility that the endocrine secretory activity of large adipose depots may directly contribute to the elevated plasma levels of disease-associated adipokines has recently gained considerable attention (21-26,31,32,52-56,72-84). However, the paracrine secretory activity of the small adipose depots has until now attracted little attention in the adipobiology of disease. If signals can, *via* endocrine (systemic) pathway, be targeted from the large adipose depots through the bloodstream towards many organs in the body, and hence lead to various metabolic and cardiovascular disorders, then why not look for similar, but

Table 1. *A selected list of adipokines*

Adipokines
Adipsin
Leptin
Adiponectin (ADNC)
Plasminogen activator inhibitor-1 (PAI-1)
Tissue factor (TF)
Tumor necrosis factor-α (TNF-α)
Transforming growth factor-β (TGF-β)
Macrophage colony-stimulating factor (MCSF)
Nerve growth factor (NGF)
Estrogens
Interleukin-6 (IL-6)
Interleukin-8 (IL-8)
Leukemia inhibitory factor
Lipoprotein lipase (LPL)
Acylation stimulating protein
Angiotensin II
Cathepsin D/G
Metallothionein-1 (MT-1)
Bone morphogenetic protein GDF-2
Found in inflammatory zone 1 (FIZZ1)
Resistin (FIZZ3)
Heparin-binding epidermal growth factor (HB-EGF)
Osteonectin (SPARC)*
Hevin

* SPARC, secretory protein, acidic and rich in cysteine.

paracrine (local) reactions from the organ-associated adipose tissue represented by the small adipose depots? It was emphasized that studies aimed at evaluation of the molecular composition of the organ-associated adipose tissue become mandatory, since identification of these molecules, particularly, adipokines, may yield clues to a possible transmission of pathogenic and/or protective stimuli, from the associated adipose tissue towards the interior of the associating organ (2-4,18,19,21,85-88). In a similar vein, this defines a new field of study, adipoparacrinology. An intriguing example is the subepicardial adipose tissue (SEAT) that is conjunctioned to the adventitia of the most atherosclerosis-prone portions of the coronary artery, that is, the most proximal part of its left anterior descending (LAD) branch. In 1933, Smith and Willius (cited in 4) have pointed out a functional relationship between the SEAT and the LAD coronary artery, and stated that SEAT is "not a passive storehouse for fat". From metabolic point of view, the principle difference between SEAT and adipose tissue elsewhere in the body is its greater capacity for free fatty acid release and uptake, thus acting as a local energy supply for epimyocardium and coronary arteries and/or as a buffer against toxic levels of free fatty acids (4). Neglected for nearly 70 years, the possible involvement of SEAT in atherogenesis has been, at long last, currently addressed (18,86-88). Specifically, recent findings demonstrate that (*i*) the portion of the LAD coronary artery running in the SEAT develops atherosclerotic lesions, while the portion running in the myocardium is free of atherosclerotic lesions (86), and (*ii*) the "atherosclerotic" SEAT expresses an increased amount of nerve growth factor (NGF) and mast cells in human coronary atherosclerosis (21,77,87,88). Other examples of a potential pathogenic involvement of organ-associated adipose tissue include breast cancer (15,16), thyroid-associated ophthalmopathy (89,90), Crohn's disease (91), HIV-associated fat redistribution syndrome (see 2-5), and phaeochromocytoma (92). It is also worth noting that a recent work shows that subcutaneous adipocytes express NGF, supposedly involved in the process of wound healing (93), whereas topically applied NGF exerts beneficial effects in human skin ulcers (94,95). Another adipoparacrinological challenge might be studying the potential role of parasellar and epidural adipose tissue in pituitary gland and spinal cord pathology, respectively. Together, these findings strongly suggest that to further elucidate the potential physiological and pathogenic importance of organ-associated adipose tissue, we should no longer, as hitherto, cut it from the respective organ, but keep it attached and in place, and subject to thorough examination. Applying such an adipoprotective action, recent studies reported important findings on (*i*) the participation of perinodal adipose tissue (major lymph node-associated adipose tissue) in immune responses (2-5), and (*ii*) the modulation of contractile responsiveness of aorta by perivascular adipose tissue (96; see also 97 about leptin-induced nitric oxide release).

Figure 1 schematically illustrates endocrine (systemic) and paracrine (local) approach in studying the adipokine-associated diseases, whereas Table 2 presents a selective list of these diseases.

CONCLUSION

At birth, the average-size infant has approximately five billion adipocytes, whereas - approximately 80 billion in adult (6). Adding to them billions of fibroblasts and mast cells, makes the whole body adipose tissue, particularly WAT, a major human's secretory organ, topologically organized as visceral and subcutaneous adipose tissue (the large adipose depots) and organ-associated adipose tissue (the small adipose depots).

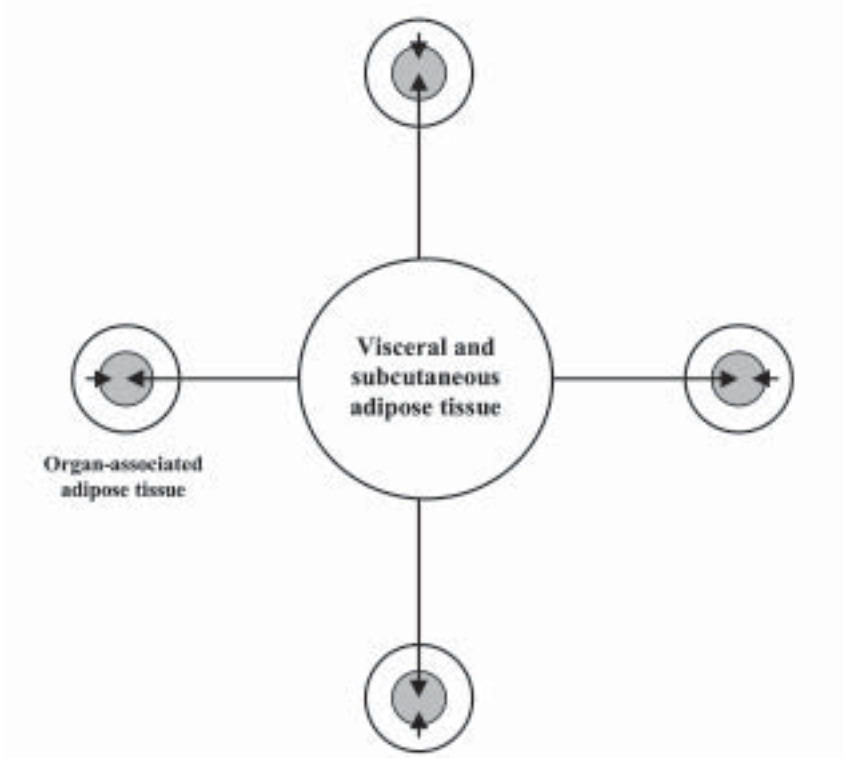

Figure 1. *Schematic illustration of large adipose depot (visceral and subcutaneous adipose tissue) and small adipose depots (organ-associated adipose tissue). Dual action of adipokines,* via *endocrine pathway (long arrows) and* via *paracrine pathway (short arrows), on adipose tissue-associated organs is depicted. Organ parenchyma is shown in grey.*

Table 2. *Selected list of adipokine-associated diseases**

Diseases	**Adipokines/Endocrine secretion**
Obesity	Leptin, ADNC, TNF-α, IL-6, PAI-1, TF, TGF-β, Resistin
Type II diabetes	ADNC, Leptin, TNF-α, PAI-1, TF, TGF-β
Metabolic syndrome	ADNC, TNF-α, IL-6, PAI-1, Leptin, NGF
Cardiovascular disease	ADNC, PAI-1, TF, TNF-α, TGF-β, Leptin, SPARC, HB-EGF, MT-1 (?)
Hypertension	Leptin, Angiotensin II
Hypertensive retinopathy	Leptin
Myocardial infarction	Leptin, ADNC (?)
Hemorrhagic stroke	Leptin
Diseases	**Adipokines/Paracrine secretion**
Coronary atherosclerosis	NGF
Breast cancer	Estrogens, IL-1,-6, TNF-α, NGF, FIZZ1 (?)
Crohn's disease	TNF-α
Skin wound	NGF
Thyroid-associated ophthalmopathy	IL-1, TNF-α
Osteoporosis	LPL, Estrogens
Phaeochromocytoma	?

* For abbreviations see Table 1.

Further study of both visceral and subcutaneous adipose tissue should certainly be continued. However, we should pay more attention to further elucidate the role of organ-associated adipose tissue in health and disease.

In recent years, the discovery that adipose tissue cells secrete a plethora of disease-related adipokines led to the development of major new insights into adipobiology at both the basic and clinical levels. For instance, a cluster of adipokines consisted of PAI-1, TF, TGF-β, TNF-α, IL-6, adiponectin, leptin, resistin, HB-EGF, NGF, osteonectin/SPARC, and MT-1 is differentially linked to obesity and related diseases. Since the actions of adipokines, like those of their relatives derived from nonadipose tissue sources, are complex and diverse, we need to design many new studies to determine how these bioactive molecules can, under different conditions, both promote and suppress various processes triggered by obesity, insulin resistance, and inflammation. The present challenge is thus to cultivate much a new thinking about how can we make adipokines work for the therapeutic benefit of patients. Although the development of novel therapies such as gene therapy, recombinant protein therapy, and stem cell-based therapy attracts great attention now, the search for small molecules as drugs remains prospective strategies in adipopharmacology. For instance, further studies may specifically upregulate some hidden, adipokine-associated actions of drugs that are already in clinical practice, like pentoxifylline, peroxisome proliferator-activated receptor-gamma agonists, and tamoxifen (41, 98-100). In this context, it is worth reminding that aspirin kept hidden its antiplatelet therapeutic action until the discovery of prostanoids, and so did, until the discovery of cytokines, pentoxifylline about its anti-TNF-α, antiinflammatory potential, and recently, antidepressants' action was related to the elevations of neurotrophin levels in the brain (101). Hence we could search some "old" drugs to disclose their adipokine-mediated therapeutic potential.

Finally, understanding the molecular biology and pharmacology of adipose tissue secretion could lead to novel ways to prevent and treat adipokine-associated diseases. Further progress in adipoendocrinology and adipoparacrinology holds much promise for the achievement of that goal.

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