

# Neuroadipology: a novel component of neuroendocrinology

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## Abstract

Adipose tissue is a dynamic endocrine and paracrine organ producing a large number of signalling proteins collectively termed adipokines. Some of them are mediators in the cross-talk between adipose tissue and the brain in regulating food intake and energy homeostasis. However, the hypothalamus is not the only brain target for adipokines, and food intake is not the only biological effect of these signals. Rather, some adipokines support various cognitive functions and exert neurotrophic activity. Current data on adipose-derived neuropeptides, neurotrophic factors, pituitary hormones and hypothalamic releasing factors is highlighted in this review. We propose that adipose tissue is a member of the diffuse neuroendocrine system. Cumulatively, this is conceptualized as neuroadipology, a new example of a link between neurobiology and other topics, such as neuroimmunology and neuroendocrinology. Because adipose tissue is a *bona fide* endocrine organ, neuroadipology may be considered a new discipline in neuroendocrinology. It may have a wide-ranging potential within a variety of neuronal and metabolic functions in health and disease.

Keywords: adipose tissue; diffuse neuroendocrine system; neurotrophic factor.

*Ask yourself for each of your thoughts: is it a new one?*  
Carl Gustav Jung (1875–1961)

## Introduction

High fat/high caloric consumption and respectively obesity and related diseases continue to increase globally. Arguably, we are learning more about the molecular mechanisms controlling food intake and energy homeostasis, in which the adipose tissue–brain cross-talk is an essential player. In the last 15 years, studies in the field of adipobiology have enjoyed explosive growth, indicating that the adipose tissue is the body's largest endocrine and paracrine organ, producing numerous signalling proteins collectively designated adipokines (Renes et al., 2009; Chaldakov et al., 2009a; Poulos et al., 2010). The most momentous change that has occurred in these studies has been the discovery of leptin and its role in regulating energy homeostasis (Friedman, 2009), as well as memory and learning (Greco et al., 2010).

White and brown adipose tissue (WAT and BAT respectively) are morphological and functional expressions of a dynamic system consisting of adipocytes and non-adipocytes (stromal, vascular, nerve and immune cells). Adipose tissue (referring to WAT hereafter) also contains cells that have the ability to differentiate into several lineages, including neuronal cells (Chaldakov et al., 2009b). In humans, WAT is partitioned into two large depots (subcutaneous and visceral), and many small depots associated with internal organs (e.g. heart, blood vessels, major lymph nodes, pancreas, prostate gland, ovaries). Noteworthy, adipose tissue is also located in the cavernous

sinus/parasellar region of the brain (Weninger and Prokop, 2004), as well as being associated with peripheral nerves and the epidural space of the spinal canal. In effect, adipobiology became an arena of many 'white' (and 'brown') novelties: (i) new functions (e.g. endo-, para-, auto- and intracrine secretion, inflammation, neuroprotection), (ii) new molecules (adipokines, lipid droplet-associated proteins, nitric oxide, hydrogen sulfide) and (iii) new implications in the pathogenesis of a variety of diseases (Chaldakov et al., 2009c).

We will deal with the current data of adipose-derived neuropeptides, neurotrophic factors, pituitary hormones, hypothalamic releasing factors and neurotransmitters. And we will also propose that adipose tissue may be a member of the DNES (diffuse neuroendocrine system). Altogether this is conceptualized as neuroadipology, a new example for a link between neurobiology and other topics, such as neuroimmunology, neuroendocrinology and neurogastroenterology.

## Adipose tissue secretion: adipokines, adipokinome and secretome

Recent adipoproteomic analyses identified over 100 adipokines, including cytokines, chemokines, growth factors and enzymes (Renes et al., 2009). They constitute a major part of the adipose secretome, which also includes free fatty acids, steroid hormones, prostaglandins, endocannabinoids, extracellular matrix proteins, lipid droplet-associated proteins and anti-inflammatory lipid mediators (resolvins, protectins, lipoxins and neuroprotectin D).

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**Abbreviations:** DNES, diffuse neuroendocrine system; GABA,  $\gamma$ -aminobutyric acid; NGF, nerve growth factor; WAT, white adipose tissue.

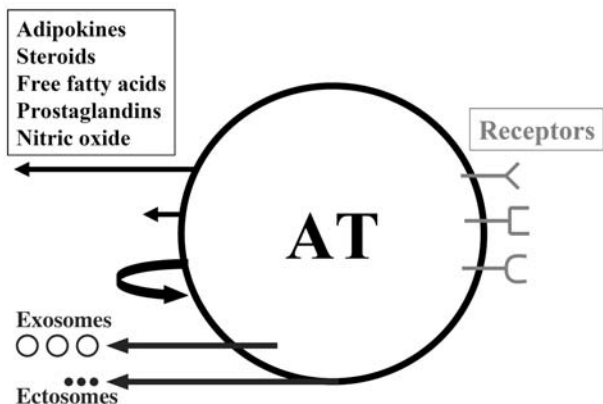
Indeed, Trayhurn and Wood (2004) called the secretory proteome of adipose tissue the ‘adipokinome’, whereas the whole spectrum of adipose secretory products was termed the ‘secretome’. Adipocytes are not the sole secretory cell type of adipose tissue; non-fat cells, especially in an inflamed adipose environment, secrete a major part of the known adipokines (Fain, 2006).

The current paradigm of cell protein secretion framed by the two Nobel winners, George Palade and Günder Blobel, focuses on the rough endoplasmic reticulum–Golgi complex pathway and the signal hypothesis respectively. It is also being explored in adipose tissue secretion (Töre et al., 2007). For instance, in human visceral adipose tissue in culture, 259 proteins were identified, of which 108 were secretory proteins (Alvarez-Llamas et al., 2007). Proteins, such as cytokines and those of the extracellular matrix, use unconventional endoplasmic reticulum–Golgi-independent secretion – via exosomes (multivesicular body-derived microvesicles) and ectosomes (plasma membrane-shedding microparticles) (Töre et al., 2007; Renes et al., 2009). The nature of adipose secretion and reception is illustrated in Figure 1.

## Adipose tissue and the diffuse neuroendocrine system

Historically, Kulchitsky (1856–1925) identified the ‘enterochromaffin’ cells found in the crypts of Lieberkuhn of gastrointestinal mucosa in 1897. This discovery formed the basis for the subsequent delineation of the DNES by Friedrich Feyrter in 1938; examples of DNES include Feyrter’s Helle Zellen (clear cells) in pancreas and gut, testicular Leydig cells, hepatic stellate cells (Ito cells), and other cells disseminated throughout the body (Chaldakov et al., 2009b, and references cited therein).

While numerous studies have demonstrated that brain can control adipose tissue functioning, it is only now becoming apparent that the control is bidirectional. For instance, (i) many



**Figure 1** A drawing illustrating both secretory and receptor nature of adipose tissue (AT)

At the secretory level, AT-derived signalling molecules communicate via multiple pathways, such as endocrine (arrows 1, 4 and 5, from top to bottom), paracrine (arrow 2) and autocrine (arrow 3, curved); also shown are exosomes and ectosomes. AT possesses receptors for various ligands (see Chaldakov et al., 2009d).

**Table 1** Neuroendocrine factors in adipose tissue

Modified from Chaldakov (2009b, 2009d)

Subdivision	Molecules
Neuropeptides	<i>Agouti</i> protein, neuropeptide tyrosine (NPY), calcitonin gene-related peptide Adrenomedullin, somatostatin, substance P, kisspeptin, neuromedin B Neurotensin, apelin
Neurotrophic factors	NGF, brain-derived neurotrophic factor, leptin Ciliary neurotrophic factor, glial cell line-derived neurotrophic factor Insulin-like growth factor 1, 2, angiotensin-1, vascular endothelial growth factor
Hypothalamic factors	Mineralocorticoid-releasing factors Corticotropin-releasing hormone (CRH) Stresscopin, urocortin (CRH-like peptides)

neuropeptides and neurotrophic factors and their receptors are shared by the adipose tissue and brain (Hausman et al., 2008; Chaldakov et al., 2009b; Sornelli et al., 2009), (ii) most pituitary hormones and hypothalamic releasing factors, termed ‘adipotrophins’, are expressed in adipose tissue (Schäffler et al., 2006), (iii) adipokines, e.g. leptin, adiponectin, resistin and fasting-induced adipose factor (angiopoietin-like protein 4), and their receptors are found in the brain (Chaldakov et al., 2009d) and (iv) glutamate and GABA ( $\gamma$ -aminobutyric acid) neurotransmitters, and NMDA (*N*-methyl-D-aspartate) and GABA receptors are expressed in adipose tissue (Nicolaysen et al., 2007). While NGF (nerve growth factor), discovered by the Nobel laureate, Rita Levi-Montalcini, was found in largest amount in the mouse submandibular glands, it appears today that the adipose tissue may also be a major biological source of NGF and other neurotrophic factors, such as brain-derived neurotrophic factor (Hausman et al., 2008; Sornelli et al., 2009), metallothioneins (Pedersen et al., 2009) and neuroprotectin D, a derivative of decosahexaenoic acid, an essential fatty acid (Zhang and Bazan, 2010). The neuroendocrine potential of adipose tissue is illustrated in Tables 1 and 2, suggesting that adipose tissue might be a member of the DNES.

## Does our adipose tissue tell our brain what to do?

Today (dnes, in Bulgarian), adipose tissue is ‘getting nervous’ (Fliers et al., 2003). Metaphorically, this talented tissue is seen as being increasingly dramatic its IQ (intelligence quotient) (Chaldakov et al., 2009b). Like the gut being considered a second brain, the adipose tissue probably functions as a ‘third’ brain (Chaldakov et al., 2009d).

**Table 2** Neural and neuroendocrine markers in adipose tissue

Modified from Chaldakov (2009b, 2009d)

Semaphorin (Sema3A), neuropilin-1, pantophysin Neuronal nuclear antigen, nestin, neuron-specific enolase Glial fibrillary acidic protein, vimentin, statthmin-like 2 NF70, S100, Musashi-1 genes, $\beta$ 3 tubulin Acetylcholinesterase and choline acetyltransferase Amyloid precursor protein/A $\beta$ peptides
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In 1999, Albee Messing published in *Hepatology* an editorial entitled “Nestin in the Liver - Lessons from the Brain”. He wrote: “Most neuroscientists manage to get through each day without thinking of the liver even once... but I think that is about to change.” This may also be the case for adipose tissue.

## Conclusions

Today, one of the challenges in cell biology may be to cultivate an adipocentric viewpoint about how we can make adipose-derived mediators work for the benefit of human health. This may indeed be a step forward, but not the whole journey into neophilia, herein designated neuroadipology.

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