SCAFFOLDING 2:

NEUROADIPOLOGY

Ask yourself for each of your thoughts: is it a new one?

Carl Gustav Jung (1875-1961)

High fat/high caloric consumption and sedentary life are linked to the initiation and development of obesity and related diseases. 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, demonstrating that the adipose tissue is the body’s largest endocrine and paracrine organ producing numerous signaling proteins collectively designated adipokines (1-3). The most momentous changes that have occurred in these studies have been the discovery of leptin and its role in regulating energy homeostasis (4) as well as memory and learning (5).

Both WAT and BAT (white and brown adipose tissue, respectively) are morphological and functional expressions of a dynamic system, consisting of adipocytes and non-adipocytes (stromal, vascular, nerve and immune cells). Adipose tissue-derived cells have the ability to differentiate into several lineages including neuronal cells (6, also see Tonchev et al in this volume of Biomedical Reviews). Adipose tissue is also located in cavernous sinus/parasellar region of the brain (7). 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) (8-16), (ii) new molecules (adipokines, lipid droplet-associated proteins, nitric oxide, hydrogen sulfide), and (iii) new implications in the pathogenesis of a variety of diseases (8).

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

Historically, Nikolai Konstantinovich Kulchitsky (1856-1925) has identified the enterochromaffin cells found in the crypts of Lieberkühn 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 Hellen Zellen (clear cells) in pancreas and gut, hepatic stellate cells (Ito cells) and other cells disseminated throughout the body (12 and references therein). Proudworthy, my classmate, Michail Davidoff, has innovatively contributed to the neuroendocrine nature of testicular Leydig cells (17).

While numerous studies have demonstrated that brain can control adipose tissue functions, it is only now becoming apparent that the control is bidirectional, that is, the adipose tissue can affect brain functions. For instance, (i) many neuropeptides and neurotrophic factors and their receptors are shared by the adipose tissue and brain (13,14), (ii) most pituitary hormones and hypothalamic releasing factors, termed “adipotrophins”, are expressed in adipose tissue (15), and (iii) the adipokines leptin, adiponectin, resistin and fasting-induced adipose factor (angiopoietin-like protein 4) and their receptors are found in the brain (12). While nerve growth factor (NGF), discovered by the Nobel laureate Rita Levi-Montalcini, was found in largest amount in the mouse sub-mandibular 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 (13-15), metallothioneins, and neuroprotectin D, a derivative of docosahexaenoic acid, an essential fatty acid (16). Altogether, the possible neuroendocrine potential of adipose tissue is illustrated in Tables 1 and 2, suggesting that adipose tissue might be a member of DNES.

Does our adipose tissue tell our brain what to do?

Today (dnes, in Bulgarian), adipose tissue is “getting nervous” (18). Metaphorically, this talented tissue is increasing dramatically its intelligence quotient (IQ) (6). As well as the gut is considered a second brain, the adipose tissue may likely function as a third brain (12).
Continuing Medical Education (CME)

Table 1. Neuroendocrine factors in adipose tissue

Neuropeptides
- Agouti protein, Neuropeptide tyrosine (NPY), Calcitonin gene-related peptide
- Adrenomedullin, Somatostatin, Substance P, Kisspeptin, Neuromedin B
  Neurotensin, Apelin

Neurotrophic factors
- Nerve growth factor, Brain-derived neurotrophic factor, Leptin
- Ciliary neurotrophic factor, Glial cell line-derived neurotrophic factor
- Insulin-like growth factor 1, 2, Angiopoietin-1, Vascular endothelial growth factor

Hypothalamic factors
- Mineralocorticoid-releasing factors
  Corticotropin-releasing hormone (CRH)
- Stresscopin, Urocortin (CRH-like peptides)

Table 2. Neural and neuroendocrine markers in adipose tissue

| Neuronal nuclear antigen, Nestin, Neuron-specific enolase |
| Neuronal nuclear antigen, Nestin, Neuron-specific enolase |
| Glial fibrillary acidic protein, Vimentin, Stathmin-like 2 |
| NF70, S100, Musashi-1 genes, Beta3 tubulin |
| Acetylcholinesterase and choline acetyltransferase |
| Amyloid precursor protein/Abeta peptides |

In 1999, Albee Messing has published Editorial entitled “Nestin in the Liver – Lessons from the Brain” (Hepatology 1999; 29: 602-603). He wrote therein: “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. And a step forward but not the whole journey into neophilia, herein designated neuroadipology, a novel component of neuroendocrinology (19).

In the preparation of this Scaffolding as well as our review published in Cell Biology International (19), I have had the cooperation of my colleague-friends Michail Davidoff (Hamburg, Germany), Anton Tonchev (Varna, Bulgaria), Marco Fiore and Luigi Aloe (Rome, Italy), and Maria Staykova (Canberra, Australia). If the Scaffolding has positive features suggesting new field in connecting adipose and neural tissue, these should be regarded as the results of the collaborative dialogue between my colleague-friends and myself. I retain responsibility for all deficiencies present.

REFERENCES

10. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam Horm 2006; 74:443-477.


