

CONTINUING ADIPOBIOLOGY EDUCATION (CAE)

*“To a man who knows nothing,
Mountains are mountains
Water is water and
Trees are trees.
When he has studied and knows a little,
Mountains are no longer mountains
Water is no longer water and
Trees are no longer trees.
When he has thoroughly understood,
Mountains are again mountains
Water is water and
Trees are trees.”*

Here, we introduce in *Adipobiology* a new section termed Continuing Adipobiology Education (CAE), a form of “classical” Continuing Medical Education (CME). We will present “scaffolding” - a metaphor that describes the way a teacher provides assistance to the students during the learning process in much the same way that the construction scaffolding serves as a temporary support until the building can stand on its own, which, in terms of neurocognition, is conceptualized as scaffolding theory of aging and cognition (1,2).

Today, a plethora of publications is disseminating globally. In a “think globally-act locally” manner, each of us, mostly in a group with others, focuses on her/his research topic. “It is our view that this has brought us only from stage 1 to stage 2 in terms of the three stages of knowledge presented by our Zen epigraph” written by the great scientist Oscar Hechter (3). First expressed in 1964, it sounds true also today. We – teachers, researchers and

students - are, nevertheless, a curious entity. Hence, to further move on the route of fascination with the different aspects of biomedical science, “we have some suggestions to offer regarding routes to stage 3” (3), presenting two Scaffolding entitled (i) Neuroadipology, and (ii) *Tunica adiposa*, as constructed by the Editor-in-Chief.

1. Park DC, Reuter-Lorenz P. The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol* 2009;60:173-196.
2. Goh JO, Park DC. Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. *Restor Neurol Neurosci* 2009; 27: 391-403.
3. Hechter O, Halkerston IDK. On the action of mammalian hormones. In: *The Hormones*. Volume 5, Academic Press Inc., New York, 1964. pp 697-816.

SCAFFOLDING 1: 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 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 crosstalk is an important 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 in 1994, 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 *Adipobiology*). 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 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 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 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 (13-15), metallothioneins, and neuroprotectin D, a derivative of decosahexaenoic acid, an essential fatty acid (16). Altogether, the possible neuroendocrine potential of adipose tissue is illustrated in Tables 1 and 2, suggesting adipose tissue membership in DNES.

Does our adipose tissue tell our brain what to do?

Today (*dnēs*, 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).

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

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)

From reference 19.

Table 2. Neural and neuroendocrine markers in adipose tissue

Semaphorin (Sema3A), Neuropilin-1, Pantophysin
 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

From reference 19.

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.

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SCAFFOLDING 2: TUNICA ADIPOSA



...two roads diverged in a wood, and I -
I took the one less traveled by,
And that has made all the difference.

Robert Frost, from *The road not taken*

Recently, obesity and related cardiometabolic diseases are among the major physical, social and economic burdens, globally. The World Health Organization has predicted a “globesity epidemic” with more than one billion adults being overweight (BMI over 25 kg/m²) and at least 400 million of these being clinically obese (BMI over 30 kg/m²). Arguably, we have learned more about the molecular control of food intake and energy homeostasis, particularly, the role played by adipose tissue in the pathogenesis of various diseases, including cardiometabolic diseases (atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, metabolic syndrome).

A long standing paradigm holds that the vascular wall consists of three coats: *tunica intima*, *t. media*, and *t. adventitia*. However, a paradigm shift comes of age: adipose tissue can express not only lipid-storage, but also secretory phenotype, particularly in the adipobiology of disease (*Curr Pharm Des* 2003; 9: 1023-1031). Hence we have forwarded the following message: “to further elucidate the potential role of periadventitial adipose tissue (PAAT) in atherosclerosis, we should no longer, as hitherto, cut it from the artery wall, but keep it attached and in place,

and subject to thorough examination” (*Int Med J* 2000; 7: 43-49; *Atherosclerosis* 2001; 154: 237-238). We thus conceptualized that the PAAT may indeed be the forth, outermost vascular coat, hence, *tunica adiposa* (*Ser J Exp Clin Res* 2008; 9: 81-88; *Obes Metab* 2010; 6: 46-49). Figure 1 presents a schematic illustration of vascular wall.

In 1983 at the seminar at the Department of Anatomy, University of Chicago Medical School, Chicago, IL, I delivered a lecture about secretion in vascular smooth muscle cells, a key cell type implicated in atherogenesis. During the discussion, a question whether adventitial fibroblasts may migrate into the intima was raised. The answer of the lecturer was “I do not know. It seems impossible”. However, what seemed “impossible” in 1983 was proven possible in 1996 (1) and later extended “outward” to PAAT (2-12).

Atherosclerosis, with its manifestation coronary artery disease, is the major cause of morbidity and mortality, globally. In atherogenesis, the response-to-injury paradigm of Russell Ross (*N Engl J Med* 1999; 340: 115-126) is not yet shifted, but significantly enriched. It proposes that lymphocyte and monocyte

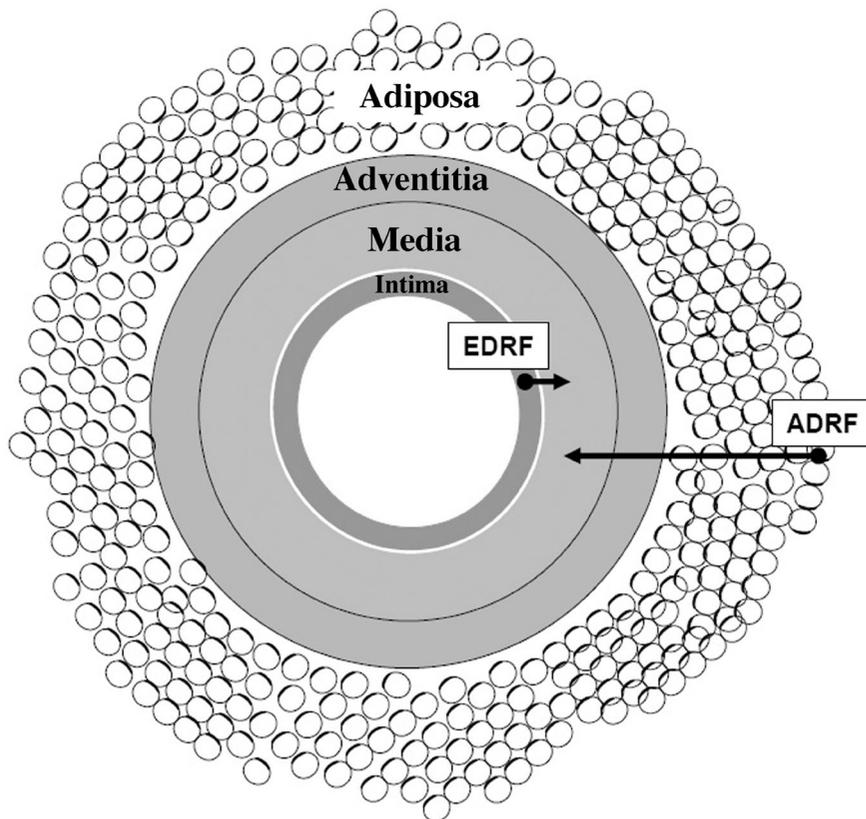


Figure 1. Schematic illustration of four-coated composition of the vascular wall. EDRF, endothelium-derived relaxing factor. ADRF, adipose-derived relaxing factor. From reference 11.

extravasation into the intima and vascular smooth muscle cell proliferation and oversecretion of matrix molecules are the key events in the development of atherosclerotic plaques. Because advanced intimal lesions lead to luminal loss, resulting in infarction, the intima is considered the most important vascular area involved in atherogenesis. However, it is unlikely that a single, linear pathway can mediate such a multiplex pathological process. Arguably, an interactive approach targeting all structural components of the vascular wall is required.

As indicated above, an extensive body of work has revealed that adipose tissue expresses not only metabolic, but also endo-, auto-, and paracrine/“vasocrine” (4) activity (Fig. 2). This new biology is achieved through secretion of more than 100 highly active signaling proteins, collectively termed adipokines (13-21), abundantly secreted by inflamed adipose tissue.

One aspect of the role of *tunica adiposa* is whether it facilitates or inhibits the process of atherogenesis. It is known that the proximal segments of coronary arteries are surrounded by (sub)epicardial adipose tissue (EAT), and these are atherosclerosis-prone as compared to the distal, intramyocardial, *tunica adiposa*-free, atherosclerosis-resistant coronaries (20). However, when EAT are totally absent, as in congenital generalized lipodystrophy, coronary atherosclerosis can still occur, suggesting that a homeostatic presence of adipose tissue is required for coronary artery health.

Given the key role of inflammation in the development of

atherosclerotic lesions, what role might *tunica adiposa* play in the process of atherogenesis (Fig. 3)? The expansion of adipose tissue seen in obesity is associated with an imbalanced secretion represented by an enhanced release of proinflammatory adipokines and by decreased release of anti-inflammatory adipokines (Table 1). Such an “enemy-or-friend” secretory capacity of *tunica adiposa* requires specific pharmacological manipulation, aiming at boosting the production and/or receptor sensitivity of anti-inflammatory adipokines. Further, recent evidence shows that plasma and tissue levels of the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which are also produced by adipose tissue (16), are altered in coronary atherosclerosis and metabolic syndrome (20).

“So what does it mean if” (18) adipoparacrinology is indeed a biological rationale in cardiovascular health and disease? First, in basic research, as indicated above, we should no longer cut *tunica adiposa*, but keep it attached and in place, and subject to thorough examination. Second, echocardiography, computer tomography, magnetic resonance imaging and other imaging technologies of heart-associated adipose tissue may identify high-risk population susceptible to atherosclerosis, and monitor vascular wall changes during follow-up studies and therapeutic trials (22-24). Third, *tunica adiposa* and, in general, heart-associated adipose tissue may represent a new therapeutic target in cardiovascular disease (6,9,16).

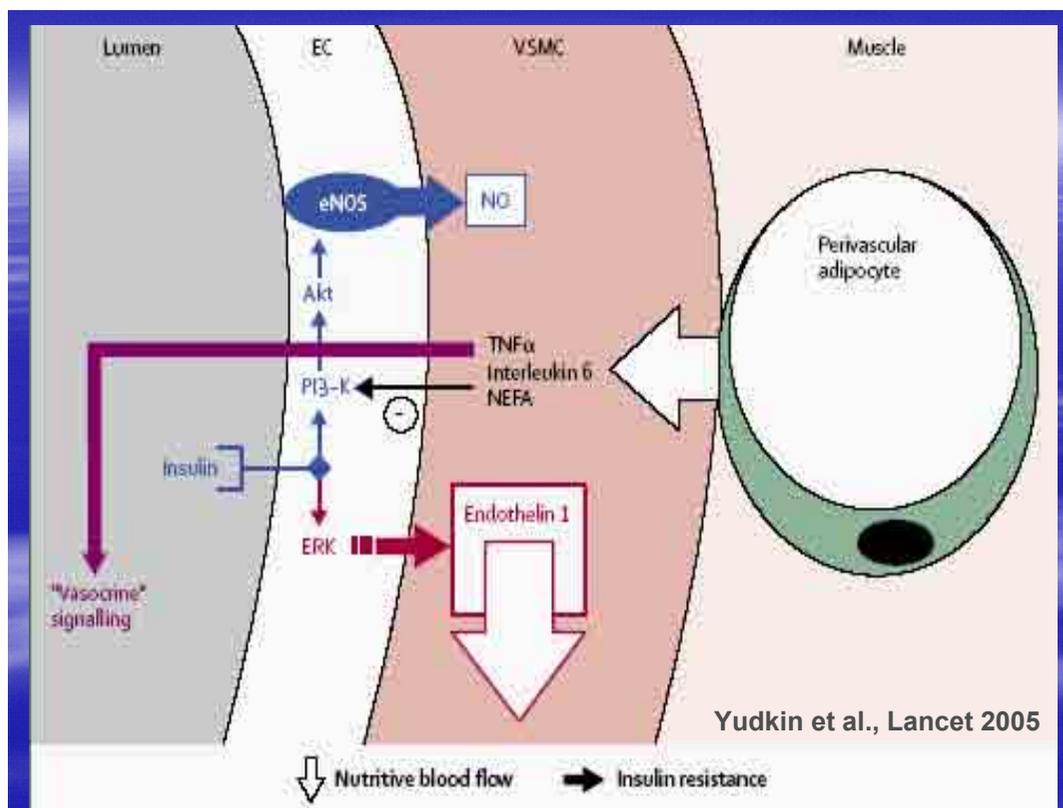


Figure 2. Schematic illustration of vascular wall, including perivascular adipocyte and respective "vasocrine" signaling (red arrow). From reference 4.



Figure 3. Human coronary artery affected by atherosclerotic plaque (below). Both adventitia and *tunica adiposa* (above) are enlarged. From reference 20.

Table 1. A selected list of adipose tissue-derived mediators, as related to cardiovascular disease

Pro-inflammatory adipokines

Leptin, IL-1, IL-6, IL-18, IL-8/CXCL8, TNF- α , PAI-1, angiotensin II, chemerin, visfatin, homocysteine*

Anti-inflammatory and metabotropic adipokines

Adiponectin, IL-1 receptor antagonist, IL-10, metallothioneins, NGF, BDNF, TGF- β , cardiac natriuretic peptide, adrenomedullin, angiopoietin-like protein 4

Vasodilators

Adipocyte-derived relaxing factor, nitric oxide (NO), hydrogen sulfide (H₂S)**, adiponectin, cardiac natriuretic peptide, adrenomedullin

Vasoconstrictors

Superoxide anion, angiotensin II, endothelin-1

* Today, hyperhomocysteinemia is in the list of global cardiometabolic risks. This sulfur-containing amino acid deriving from the metabolism of methionine may also be considered “adipokine” - all enzymes involved in the synthesis and metabolism of homocysteine are expressed in adipose tissue, suggesting that adipose tissue may be an important source of circulating homocysteine (19).

** See Bełtowski *et al* in this volume of *Adipobiology*.

Take brain message

Here I have “scaffolded” an adipose road in vascular biology, focusing on the possible paracrine role of *tunica adiposa* in an “outside-in” signaling related to atherosclerosis.

Traditional concept of atherogenesis focuses on the intimal road, where “inside-out” inflammatory processes and endothelial dysfunction trigger atherosclerotic plaque formation. Here we *took* the adipose road, which is *less traveled*.

Until recently, physicians have looked upon obesity as accumulation of external adipose tissue. This was routinely evaluated by various anthropometric measurements including BMI and waist, hip and, recently, neck circumference. However, recent non-invasive techniques, such as echography, computed tomography, MRI and positron emission tomography, reveal a new picture of adipose distribution. Hence, we should appreciate not only anthropometric values of external adipose tissue,

but – more importantly - the “weight” of internal adipose tissue, particularly, *tunica adiposa* as well as epicardial and pericardial adipose tissue, in cardiovascular disease.

“And that has made *some* difference”, paraphrasing Robert Frost’s *The road not taken*.

Acknowledgments

I would like to express my cordial thanks to my former student research associates (1992-1998): Kamen Vachanov, Anton Tonchev, Rouzha Pancheva, Wale Sulaiman, Galya Marinova and Yuliya Yosifova, some of them shown in the “micrograph” below. Their professional prosperity has been encouraging me to further work!



This photograph was taken by Nick Chaldakov in 1994. From left-to-right, Anton Tonchev, MD, PhD, now Associate Professor of Anatomy and Histology, Medical University, Varna, Bulgaria; Wale Sulaiman, MD, PhD, FRCS, now Head of Department of Neurosurgery, Ochsner Medical Center, New Orleans, LA, USA; George Chaldakov; Rouzha Pancheva, MD, PhD (and, more importantly, mother of three kids), now Assistant Professor, Department of Pediatrics, University St Mariana Hospital, Varna, Bulgaria, and Kamen Vachanov, MD, Consultant, Department of Anaesthesia, Papworth Hospital, Cambridge, UK.

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