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NEURO-ADIPOSE INTERACTIONS (BIACTOME). IMPLICATION IN CARDIOMETABOLIC DISEASE

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Cardiometabolic diseases (CMD) are the number one cause of death globally, and the major CMD's phenotypes are atherosclerosis, hypertension, obesity, type 2 diabetes and metabolic syndrome. Arguably, since the leptin discovery in 1994 the field of study on adipose tissue, adipobiology, has been witnessing a number of paradigm shifts. One of them introduced the adipose tissue in the list of endocrine and paracrine organs of the human body. It was discovered a dazzling number of adipose-delivered secretory proteins, collectively termed adipokines. Among them are proteins improving glucose, lipid and energy metabolism, that is, metabotrophic factors (metabotrophins) (from Greek metabole, and trophe, nutrition, means "nutritious for metabolism"). Examples include adiponectin, apelin, visfatin, nerve growth factor, brain-derived neurotrophic factor and insulin-like growth factor-1, each of them mediating both metabotrophic and neurotrophic effects. Hence a novel field of research, neuroadipocrinology - a relative of neuroendocrinology, was launched. A piece of it designated biactome (neuro-adipose interactions) is herein highlighted. Its implications in the pathogenesis and therapy of major CMD (atherosclerosis, hypertension, obesity, type 2 diabetes, metabolic syndrome) are discussed.

Key words: adipose tissue, adipokines, adipobiology, BDNF, metabotrophic factors, NGF.

INTRODUCTION

In the postgenome time, many "-ome" projects have emerged including proteome, interactome, metabolome, adipokinome, exposome, connectome so much numerous to be listed. Perhaps, this prompted Jeff Lichtman and Joshua Sanes to entitle one of their connectome articles Ome sweet ome (Curr Opin Neurobiol 2008; 18:346–53).

Based on current knowledge of neuro-immunology and adipobiology, we previously published our hypothesis of neuro-immune-adipose interactions (triactome) in vascular biology[1]. The present review describes neuro-adipose interactions (biactome) in the patho-genesis and therapy of cardiometabolic diseases (CMD) – atherosclerosis, hypertension, obesity, type 2 diabetes and metabolic syndrome. Obesity, a major risk factor for CMD, is most prevalent human health disorder globally. In 2005, 800 million people were overweight (BMI 25.0–29.9 kg/m^2) and 400 million were obese (BMI over 30 kg/m^2). Although the pathogenesis is not yet completely understood, there is now solid evidence that type 2 diabetes mellitus is a disease strongly associated with the obesity, hence the term diabesity has been introduced[2,3].

Adipose tissue

One of the challenges in the study of CMD is associated with the "rediscovery" of a neglected tissue, the adipose tissue. Today, adipose tissue is recognized as a vital player not only in the "traditional" control of lipid and energy balance, but also inflammation, immunity, reproduction as well as cardiovascular and neuronal homeo-dynamic.

Adipose tissue is a cellular and extracellular matrix assembly composed of adipocytes, fibroblasts, immune cells and matrix components, also rich in sympathetic nerve fibers, blood vessels, and stem cells. There are two major subtypes of adipose tissue, white adipose tissue (WAT) and brown adipose tissue (BAT). White adipose tissue may grow and shrink dramatically to meet the energetic needs of an organism. However, severe metabolic consequences can result from excessive WAT gain, featuring diabesity and related CMD, or extreme loss of WAT mass, known as lipodystrophy.

Paradigm shifts in adipobiology

In 1962 Thomas S. Kuhn published his book The Structure of Scientific Revolutions (1st edition, University of Chicago Press, Chicago, USA). Its publication was a landmark event in history and philosophy of scientific knowledge (epistemology). Kuhn challenged the then prevailing view of "normal science" which was viewed as "development-by-accumulation" of accepted facts and concepts leading oftenly to epistemological paralysis, we dubbed it neophobia. Kuhn argued for a model in which a period of such conceptual continuity in normal science were interrupted by a period of revolutionary science leading to a new paradigm, an event he designated paradigm shift.

At epistemological level, the adipose tissue has undergone three major paradigm shifts in last 20 years. This rise it above the horizon to take center stage in so many diseases that it leaves most scientists and medical doctors astonished.

The first paradigm shift was: while considered as passive storage-release of lipids by most cell biologists and pathologists for a long period of time, adipose tissue is now considered the biggest endocrine and paracrine organ of the human body (Table 1). The publication of a ground-breaking article describing the discovery of leptin, an adipose-secreted hormone, by Jeffrey Friedman and colleagues, marked such a revolutionary event in the study of adipose tissue and obesity (Nature 1994; 372: 425–432. doi: 10.1038/372425a0). In this context, the pioneering contribution of Douglas Coleman (1931–2014) has to be acknowledged. His work established the first clues to a genetic component in obesity. In the 1970s, Coleman conducted a series of experiments that led him to propose the existence of a satiety factor that would account for obesity and type 2 diabetes among certain laboratory mice.

Onward, in 2000 the term adipokines instead of adipocytokines was introduced[4]. In 2003 the research field studying adipose tissue in health and disease was conceptualized as adipobiology and adipopharmcology[5].

The second paradigm shift derived from the study of Jeffrey Bell and colleagues [6] who have scanned nearly 800 people with magnetic resonance imaging (MRI) technique, aimed at obtaining map of WAT. The authors demonstrated that as many as 45 percent of women and nearly 60 percent of men scanned have normal scores of the body mass index (BMI, 20–25 kg/m^2). These people are thin outside (TO), while actually have excessive levels of internal adipose tissue – they are fat inside (FI), hence TOFI phenotype of body fatness. Noteworthy, TOFI phenotype was also found among people who are professional models. TOFI may thus be considered a specific, "invisible" expression of both Homo obesus and Homo diabesus[3].

The third paradigm shift features the increasing significance of brown adipose tissue in health and disease. In human body, WAT stores energy and secretes adipokines and other bioactive molecules, whereas BAT produces heat. BAT-mediated increase in energy expenditure is realized by uncoupling respiration from ATP synthesis, via uncoupling protein 1 (UCP1) expressed in the inner mitochondrial membrane of brown adipocytes, thus mediating a process known as adaptive thermogenesis. Animal studies have shown that activation of BAT counteracts diet-induced weight gain and related disorders such as type 2 diabetes and metabolic syndrome; it may also be the case for humans. Recently, the knowledge about WAT and BAT were enriched with their derivatives, namely brite (brown in white) and bruscle (brown in skeletal muscle) adipocytes[7]. Hence, brown adipobiology is emerging as a new challenge for biomedical research.

Cumulatively, BAT is the major thermo-genic organ, aslo expressing crinologic phenotype[8], whereas WAT is the body's largest lipid storage and the most productive crinologic (endo- and paracrine) organ delivering multiple signaling proteins collectively termed adipokines[4,5,8-12]. Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)[13] (see also 14) and other neurotrophic and neuroendocrine factors[15-20] are also secreted (synthesized, stored, and released) by both WAT and BAT, thus being incorporated in the progressively extended list of adipokines.

Table 1

A paradigm shift: never before has adipose tissue been so active*

FROM
Adipose tissue is a lipid and energy storage involved in obesity
TO
Adipose tissue is an endocrine and paracrine organ
Produces neurotrophic factors, neuropeptides, neurohormones
Produces steroid hormones
Adipose tissue is an immune organ
Adipose tissue is a source of and target for inflammatory mediators
Adipose tissue produces all components of rennin-angiotensin system
Adipose tissue produces and processes amyloid precursor protein (APP)
Adipose tissue is thus involved in numerous diseases beyond obesity

*Modified from reference 3.

Multiple life of neurotrophins

At the end of the 19th century it was envisaged by Santiago Ramon y Cajal but has not been proved that the nerves require trophic support. By a rare combination of scientific reasoning and intuition, Rita Levi-Montalcini (1909–2012) obtained the proof in the early 1950's in Saint Louis, MO, USA, where the first cell growth factor, namely NGF, was discovered, and 35 years later awarded Nobel Prize 1986 [14]. Data of NGF have been embodied in a conceptual framework well known now as neurotrophic (nerve-effector interaction) theory. It reveals a pivotal role of effector (target) cells in the control of neuronal differentiation, survival and function via production of NGF and other neurotrophic factors.

The past three decades has witnessed a number of breakthroughs in the study on Rita Levi-Montalcini's NGF and related neurotrophins, BDNF, neurotrophin-3 (NT-3), NT 4/5, NT-6 and NT-7. Studies have revealed that NGF and BDNF are not only stimulating for nerve growth and survival, but also exert trophic effects over (i) immune cells, acting as immunotrophins, (ii) keratinocytes, enterocytes, prostate and breast epithelial cells, acting as epitheliotrophins, and (iii) endothelial cells, acting as angiogenic factors (reviewed in 15).

How neurotrophins became metabotrophins

Recently, the functional signature of NGF and BDNF was enriched with one more expression, that is, metabotrophic action on glucose, lipid, energy and pancreatic beta cell, cardiovascular and neuronal homeostasis, and thus, together other neurotrophins, particularly BDNF, designated metabotrophic factors (MTF). In analogy with neurotrophins, MTF were named metabotrophins (from Greek metabole, and trophe, nutrition, means "nutritious for metabolism")[15,16,20]. The proof-of-hypothesis was based on results demonstrating that the circulating and/or tissue levels of NGF and BDNF are commonly decreased in atherosclerosis and metabolic syndrome [18], type 2 diabetes [19,20], depression and other psychiatric diseases [15], including Alzheimer's disease which increasingly is considered type 3 diabetes [21,22] (other references are indicated below). A selected list of metabotrophic factors (Table 2) and of metabotrophic effects of NGF and BDNF (Table 3) is presented.

Table 2

Selected list of endogenous metabotrophic factors

Secretory proteins
Leptin, Nerve growth factor, Brain-derived neurotrophic factor
Ciliary neurotrophic factor, Glial cell line-derived neurotrophic factor
Neuron-derived neurotrophic factor
Adiponectin, Apelin, Visfatin/SIRT-2, Omentin, Chemerin, Otopetrin 1
Irisin, Humanin, Interleukin-10, Metalothionein-I,-II, S100B
Glucagon-like peptide-1, Neuromedin-B, Kisspeptin-1, Estrogens
Intracellular proteins
SIRT-3, Uncoupling protein 1 (UCP1), GLUT4

Table 3

Metabotrophic NGF and BDNF

NGF shares homology with proinsulin
NGF and BDNF are produced by pancreatic beta cells and exert insulinotropic effect
NGF and BDNF are trophic factors for pancreatic beta cells, also improve beta cell transplantation
NGF up-regulates expression of LDL receptor-related protein
NGF up-regulates expression of PPARgamma
NGF inhibits glucose-induced down-regulation of caveolin-1
NGF improves skin and corneal wound healing*
NGF rescues silent myocardial ischemia in diabetes mellitus*
NGF improves diabetic erectile dysfunction
NGF and BDNF suppress food intake
Healthy lifestyle increases brain and/or circulating levels of NGF/BDNF
Atherogenic diet decreases brain BDNF levels
BDNF-deficient mice develop abnormalities similar to the metabolic syndrome
NGF and BDNF improves cognitive processes

*Viewing the atherosclerotic plaque as vascular wound, NGF TrkA and BDNF TrkB receptor agonists might be antiatherosclerotic drugs.

Neuroadipocrinology: the biactome hypothesis

Life of multicellular organisms requires the interaction between cells of nervous, endocrine, immune and other systems. Understanding how the precise interactions of nerves and adipose tissue account for cardiometabolic biolology is a central aim of biomedical research at present. In sensu stricto, adipokines mediate the cross-talk between adipose tissue and hypothalamus in regulating food intake and energy homoeostasis. However, the hypothalamus is not the only brain target for leptin, and food intake is not the only biological effect of this adipokine.

As often occurs, the framework of an initial concept of the physiological role of a newly discovered molecules extends in the light of emerging findings. This was also the case with both adipokines and neurotrophic and neuro-hormonal factors. By sending and receiving different types of protein and non-protein signals, adipose tissue communicates with many organs in the body (Fig. 1), thus contributing to the control of energy, lipid and glucose homeostasis as well as

inflammation, immunity, learning and memory among many other biological functions.

An example of such a communication might be the bioactome, a neuro-adipose „interactome". *Note*: we are focusing here on the interaction of nerves and WAT, which does not mean that BAT's participation in biactome is ignored; it needs further evaluation. The suggested diactome is mediated by adipokines (in the broader sense), including neurotrophic factors and hypothalamus-pituitary neurohormones.This is the language of biactome.

Noteworthy, adipose cells are able to secrete neurotrophic factors[13,19,20] as well as neuro-nal cells - adipokines[1,3,15,16] (and references therein). Moreover, most pituitary hormones and hypothalamic releasing factors, termed adipo-trophins, express their receptors in adipose tissue, creating hypothalamic-pituitary-adipose axis[24]. Likewise, a set of neuropeptides including neuro-peptide tyrosine (NPY), substance P, calcitonin gene-related protein as well as the neuro-transmitters glutamate and GABA and their corresponding vesicular glutamate transporters VGLUT1 and VGAT are also expressed in adipose tissue. And leptin and possibly adipo-nectin have neurotrophic action and are involved in memory and other cognitive functions at the level of dendritic spines (see [15, 16]). Altogether, such a brain-adipose „interactome" prompted us to publish a paper entitled „Adipose tissue as a third brain" (Obesity Metab 2009; 5: 94-96).

In an attempt to "close" the metabotrophic "loop" in CMD, we have measured circulating levels of NGF and BDNF in patients with acute coronary syndromes, and found they are significantly reduced [25,26]. Another study revealed altered levels of NGF in pancreas and brain in streptozotocin-induced diabetes[27]. Recently, it was demonstrated that in response to experimental stress or diabetes, the amount of NGF and BDNF was altered both in WAT and BAT (Figs. 2,3).

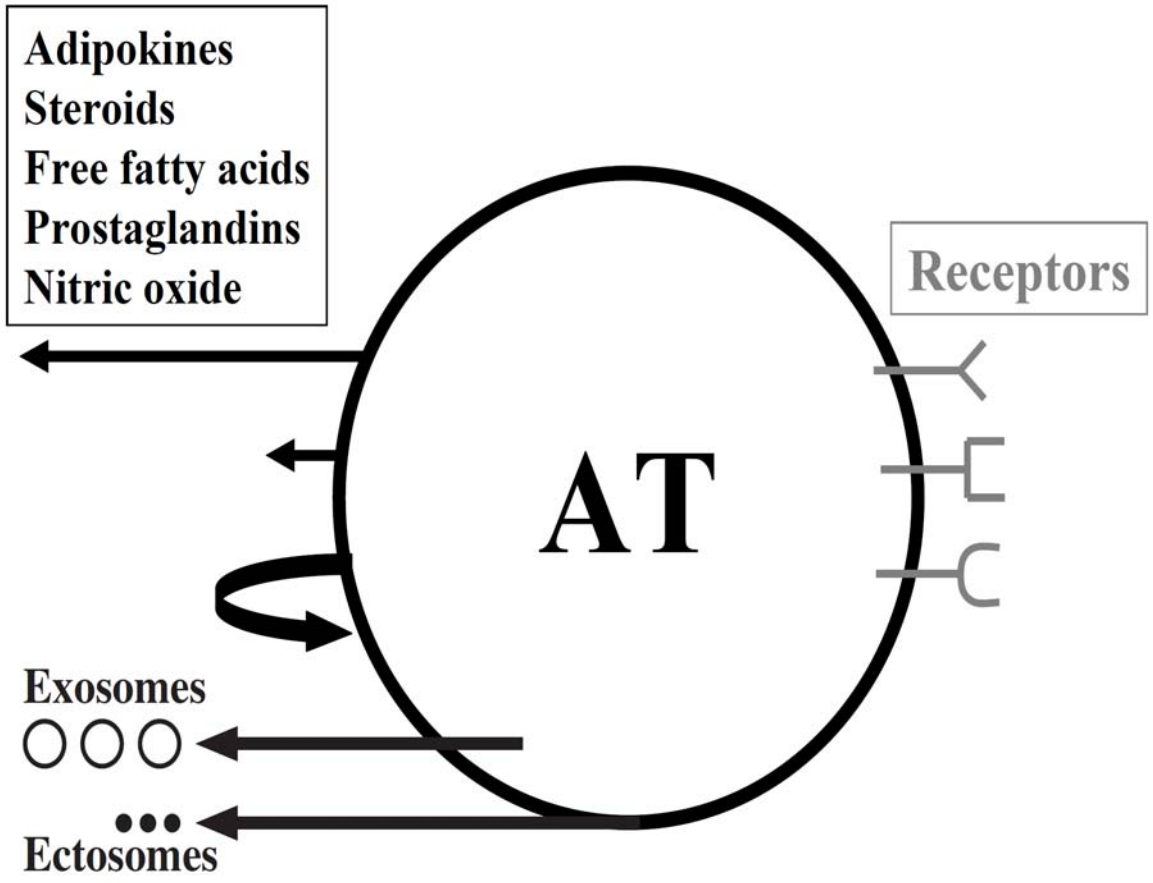

Figure 1. A drawing illustrating both secretory and receptor nature of adipose tissue (AT) cells. At the secretory level, AT-derived signaling molecules communicate via multiple pathways, such as endocrine (arrows 1, 4 and 5, from top to bottom), paracrine (arrow 2) and autocrine (arrow 3, curved). Also depicted is that AT cells express receptors for various ligands. From reference 16.

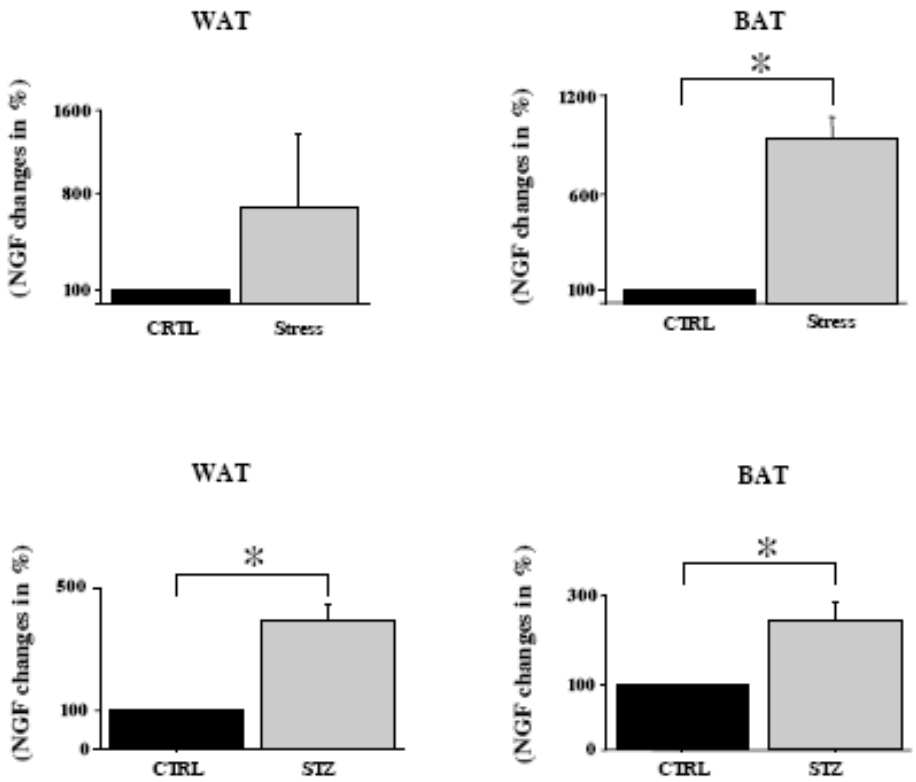

Figure 2. Changes in the amount of nerve growth factor (NGF) in white adipose tissue (WAT) and brown adipose tissue (BAT) of controls compared to the concentration of NGF in stressed mice (Stress) and streptozotocin-induced diabetic rats (STZ), expressed as percentage of controls. Note the enhanced presence of NGF in WAT and BAT in stressed mice as well as diabetic rats. The vertical lines in the figure indicate pooled S.E.M. derived from appropriate error mean square in the ANOVA. * significant differences between groups ($p < 0.05$). From reference [13].

Perspectives

The present biactome hypothesis of CMD is supported by data derived from other laboratories include: (i) pancreatic beta cells secrete NGF and express its high-affinity receptor TrkA, findings being implicated in the pathogenesis of diabetes mellitus[20,28], (ii) mutations affecting Bdnf gene (encoding BDNF) in mice or Ntr2k2 gene (encoding the high-affinity BDNF receptor TrkB) in patients are associated with hyperphagia and severe obesity, and (iii) topical application of NGF accelerates healing of human skin and corneal ulcers, glaucoma, retinopathies and other eye and brain diseases [39] (see also [15,40-45]). Further studies may open new windows for the search of exogenous MTF, such as (i) small molecules boosting secretory and/or signaling pathways of MTF, and (ii) incretin mimetics and receptor agonists, because the insulinotropic hormone glucagon-like peptide-1 (GLP-1) and exendin-4, a GLP-1 receptor agonist, exert neuro-metabotrophic effect[33,34].

In support of these perspectives might be the recent discovery of (i) humanin, a mitochondria-derived peptide[29,30], (ii) irisin, both myokine and adipokine, involved in the browning of WAT[31], (iii) SIRT2 (silent information regulator 2 protein, called sirtuin), NAD-dependent protein deacetylases related to visfatin[32], (iv) changes of the insulin signaling pathway including the down-regulation of insulin receptor substrate 4 (Irs4) as an early event in Alzheimer's disease (AD)[46] (also [47-54]), (v) the significant role of NGF in amyloid precursor protein (APP) processing in experimental models of AD[55], and (vi) exosomes and ectosomes, cell-derived extracellular signaling vesicles (signalosomes)[56]; the measurement of their presence in blood circulation as well as other body's fluid compartments has recently entered clinical and pharmacological laboratories for diagnostic and therapeutic purposes respectively[57,58]. Of note, the involvement of adipose tissue in the production of APP[59,60] and of S100B protein[61] needs further research evaluations.

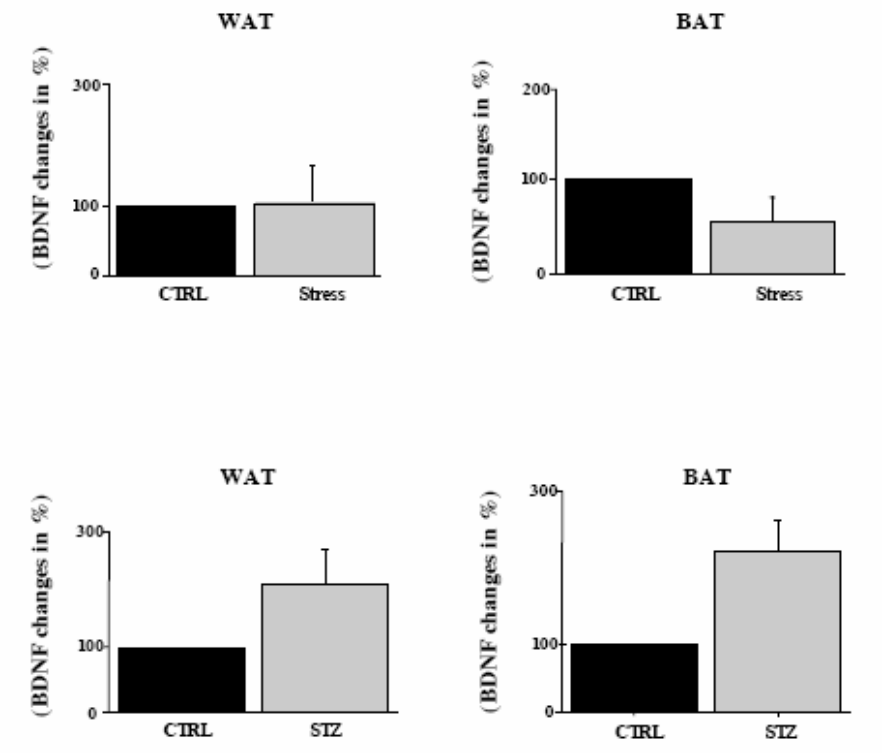

Figure 3. Changes in the amount of brain-derived neurotrophic factor (BDNF) in epicardial white adipose tissue (WAT) and brown adipose tissue (BAT) of controls compared to the concentration of BDNF in stressed mice (Stress) and streptozotocin-induced diabetic rats (STZ), expressed as percentage of controls. The vertical lines in the figure indicate pooled S.E.M. derived from appropriate error mean square in the ANOVA. From reference 13.

Coda

The present short review suggests that understanding precisely the neuro-adipose interactions (biactome) may provide new pharmacological approaches to be explored in the therapy of CMD and related disorders including AD. Further studies may lead to or exclude the possibility that adipose tissue also „suffers" from AD, or at least extend our knowledge of viewing AD as metabotrophin-deficit biactome disorder.

We hope the present hypothesis might be a better, not just different. Its relevance to BAT[62,63] also requires research attention. The future challenge is therefore to cultivate integrative thinking about how we can make biactome, also triactome[1], work for the benefit of cardio- and neurometabolic health.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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