ADIPOBIOLOGY OF THE BRAIN: FROM BRAIN DIABETES TO ADIPOSE ALZHEIMER'S DISEASE

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Introduction

Accumulating evidence suggests that brain-adipose tissue bi-directional communications might be promising intervention point for cardiometabolic and neurodegenerative diseases (1). Alzheimer's disease (AD) is a progressive and yet incurable disorder characterized by memory loss and cognitive ability deterioration. It is the most common form of dementia, afflicting millions of humans globally. Although the progression of AD currently cannot be stopped or reversed, an increased understanding of its pathogenesis may give patients and their families chance for new therapies, which may at least delay the progress of the disease.

Although the human brain is nearly 50 percent lipids, the brain is the only organ which does not contain adipose tissue, except that located at the parasellar region, traditionally known as the cavernous sinus (Weninger WJ, Pramhas D. *J Anat* 2000; 197 (Pt 4): 681-686; Weninger WJ, Prokop M. *Clin Anat* 2004;17:112-117).

Today, we know that essential fatty acids, particularly the omega-3 fatty acids and docosahexaenoic acid (DHA), play important role for brain development and are among the most crucial molecules that determine a large spectrum of brain's functions (for brain GPR40, a receptor for free fatty acids, see Tonchev *et al* in the section "Abstracts from 4th ISAA" published in this volume of *Adipobiology*).

To maintain metabolic and anthropometric homeostasis, the brain must precisely monitor the peripheral energy state. This monitoring is also extremely important for the brain's survival, because the brain does not store energy but depends solely on a continuous supply of nutrients from the blood circulation.

Brain-adipose misunderstanding may lead to various metabolic diseases including obesity, type 2 diabetes mellitus, metabolic syndrome and AD. Here we *Dance Round* the hypothesis of *brain diabetes* and *adipose AD*, white adipose tissue (WAT) being in the scope of the hypothesis.

Neuroadipocrinology

Both phenotypes of human life, the health and the disease, require the interaction between the cells of nervous system and the cells of other systems. One of the biggest recent achievements of neurobiology and adipobiology is the study on neurotrophic factors, e.g. nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (2-4), insulin-like growth factor-1 (5), and adipokines, e.g. leptin, adiponectin, resistin and apelin (6-10; 11 for adipose-derived NGF and BDNF).

As often occurs, the framework of an initial concept of the role of newly discovered molecules extends in the light of emerging findings. This was also the case with neurotrophic factors and adipokines. For instance, for some 30 years after the discovery of NGF, there have been few hints to indicate that it may act

Received 3 December 2015, revised 8 December 2015, accepted 12 December 2015.

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on non-neuronal cells. Thus, it was remarkable when Aloe and Levi-Montalcini have discovered in 1977 that the treatment of newborn rats with NGF caused a systemic increase in the number of mast cells. This seminal finding paved the road of a novel research field, the neuroimmunology (12).

In the same context, the adipose tissue is no more considered mostly a lipid storage but a dynamic endocrine and paracrine organ producing a dazzling number of signaling proteins collectively termed adipokines (6). Currently, their number estimated to be over 600 (7). Some of them mediate the cross-talk between adipose tissue and brain in regulating food intake and energy homeostasis. However, the brain (mostly hypothalamus) is not the only target for leptin and other adipokines, as well as the food intake is not the only biological effect of these adipokines. Rather, some adipokines support various metabolic and cognitive functions and exert both metabo- and neurotrophic actions (13-24). Current data of adipose-derived neuroendocrine and neurotrophic factors are summarized in Tables 1, 2. This raises an intriguing question as to whether adipose tissue might be a peripheral counterpart of hypothalamus-hypophysis, a part of diffuse neuroendocrine system, or our third brain (*Obesity Metab* 2009; 5: 94-96). Cumulatively, linking neurobiology and adipobiology resulted in neuroadipocrinology, a novel component of neuroendocrinology (*Cell Biol Int* 2010; 34:1051-1053).

From brain diabetes to adipose Alzheimer's disease

Epidemiological evidence supports the observation that subjects with type 2 diabetes mellitus are at higher risk to develop AD. An estimated 312 million people suffer from type 2 diabetes while AD affects nearly 45 million people worldwide. Whether and how these two diseases are causally linked is not yet known.

Adipose tissue and brain of high fat diet fed animals expressed increased levels of proinflammatory cytokines and macrophage activation. Noteworthy, both brain and adipose tissue also have elevated amyloid precursor protein (APP) levels. Indeed, obesity, diabetes and/or metabolic syndrome may affect multiple cognitive functions including expression of APP, amyloid- β (A β) peptide and *tau* hyperphosphorylation - molecular signatures of AD pathology. In brief, an extraneuronal production of both APP and A β peptides including the adipose tissue was demonstrated (25-30). Accordingly, the administration of streptozotocin (STZ), a well known experimental model for diabetes, induces brain insulin resistance and cognitive alterations resembling those in AD patients (31-33). We have reported that STZ-induced diabetes is associated with changes in NGF levels in both pancreas and brain (34). In effect, STZ treatment became a new experimental tool in studying AD, which is increasingly evaluated as type 3 diabetes (33, 35). To focus on the

Table 1. Selected list of neuroadipokines (adipose-derived neuroendocrine factors)

Neuropeptides

Neuropeptide tyrosine (NPY), Substance P, Calcitonin gene-related peptide

Agouti protein, Adrenomedullin, Somatostatin, Kisspeptin

Neuromedin B, Neurotensin, Mineralocorticoid-releasing factors

Corticotropin-releasing hormone (CRH), Stresscopin and urocortin (CRH-like peptides)

Apelin, Nesfatin-1, S100B protein

Neurotrophic factors

Nerve growth factor, Brain-derived neurotrophic factor, Leptin, Adiponectin

Vascular endothelial growth factor, Ciliary neurotrophic factor

Glial cell line-derived neurotrophic factor, Insulin-like growth factor-1

Angiopietin-1, Steroids, Metallothionein-1, -2

Neurotransmitters

Glutamate, Gamma-aminobutyric acid, Acetylcholine

Table 2. Metabotropic effects of NGF, BDNF and adiponectin (APN)

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

APN is anti-obesity, anti-diabetogenic, anti-atherogenic adipokine

BDNF- and APN -deficient mice develop abnormalities similar to the metabolic syndrome

BDNF and APN improve cognitive processes

NGF up-regulates expression of LDL receptor-related protein

NGF up-regulates expression of PPAR-gamma

NGF inhibits glucose-induced down-regulation of caveolin-1

NGF improves skin and corneal wound healing

NGF and APN improve vascular (atheroma) wound healing

NGF rescues silent myocardial ischemia in diabetes mellitus

NGF improves diabetic erectile dysfunction

Healthy lifestyle increases brain and/or circulating levels of NGF, BDNF, APN

Atherogenic diet decreases brain BDNF levels

brain-metabolism link (36-55) the concept of *cognitive diabetes* and *brain diabetes* was recently introduced (56, 57; for the antidiabetic drug metformin and APP processing, see 58, 59). Again, many studies demonstrated that the adipokine leptin has a “therapeutic” effect on the APP processing and *tau* phosphorylation (16-24).

As mentioned above, AD is characterized by the accumulation of A β and hyperphosphorylated *tau*, a microtubule-associated protein. The deposit of A β is a result of an imbalance between A β production and clearance. Among several proteases involved in the proteolysis of A β , neprilysin (neutral endopeptidase, NEP), a type II membrane-associated metalloendopeptidase, appears to be the most important A β -degrading enzyme in the brain, thus exploration of possibilities for NEP delivery is required. Accordingly, it was reported that human adipose tissue-derived stem cells (ADSC) secrete exosomes carrying enzymatically active NEP. When ADSC-derived exosomes were transferred into cultured nerve cells a decrease both secreted and intracellular A β levels in the treated cells was found (60), suggesting the therapeutic relevance of these extracellular signaling vesicles for AD.

Altogether, our hypothesis of adipose tissue as a third brain working in tandem with that located “within the head” (Greek, *enkephalon*), herein referred to as *adipose AD*, might sound more plausible at present.

Further, diabetes mellitus and AD are both common and increasing incidence in the aging population. Recent evidence has demonstrated common pathogenic factors operating in both conditions. Some proof-of-hypothesis of *adipose AD* may also derive from the results demonstrating that the circulating and/or tissue levels of NGF, BDNF and adiponectin are commonly decreased in both cardiometabolic and neuropsychiatric diseases, including AD (reviewed in 3, 4, 15). Thus, adipobiology of the brain has emerged as a challenging area of biomedical research. Its relevance to brown adipose tissue (BAT) also requires research attention.

Conclusion

The present *Dance Round* suggests that understanding precisely the neuro-adipose interactions (61, 62) may provide new insights in the pathogenesis and the therapy of obesity, diabetes, metabolic syndrome and 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 a metabotropic disorder, as previously proposed for obesity and related diseases (63, 64).

In 1999 Albee Messing published in *Hepatology* (29: 602-603) 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.

Today, physicians must accordingly be aware of the increased risk of cognitive deficit in patients with cardiometabolic diseases. And *vice versa*, to look for alteration of glucose, lipid and adipokine metabolism in patients with AD. Moreover, recent genome wide association study (GWAS) findings provide information for the design of future novel therapeutic approaches for a subpopulation of type 2 diabetic subjects with genetic disposition to AD, that could benefit diabetes and reduce the risk for subsequent development of AD dementia (55).

Of note, after Alois Alzheimer’s clinical report of “presenile dementia” on 3 November 1906, the first Italian contributions to the histopathological and clinical description of AD dementia was published by Gaetano Perusini in three papers between 1906 and 1911 (Lucci B. The contribution of Gaetano Perusini to the definition of Alzheimer’s disease. *Ital J Neurol Sci* 1998; 19: 49-52). To appreciate the contribution of Perusini, our hypothesis should be named *adipose Alzheimer-Perusini’s disease*.

Acknowledgements

None of this review article would have been possible without the staunch support and creative collaboration of our brain-and-heart friends (BHF) Peter Ghenev, Danko Georgiev, Marcia Hiriart, Stanislav Yanev, Francesco Angelucci and many others. We apologise to the authors who were not quoted in this text, as their work was omitted for the sake of this *Dance Round*.

Conflict of interest

The authors declare no conflict of interest.

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