AN INTEGRATED VIEW: NEUROADIPOCRINOLOGY OF DIABESITY

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INTEGRISANI PRIKAZ: NEUROADIPOKRINOLOGIJA DIABESITY (DIJABETES TIP 2 UDRUŽEN SA GOJAZNOŠĆU)

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ABSTRACT

Today's achievements in systems biology *and -omics sciences have facilitated a shift from studying individual molecules and tissues to characterising molecules and cells holistically. In this article, we attempt to discuss the status of a much-needed coherent view that integrates studies on neurobiology and adipobiology, as well as those on diabetes and obesity. Globally, cardiometabolic diseases (atherosclerosis, hypertension, type 2 diabetes mellitus, obesity, diabesity, and metabolic syndrome) are the most prevalent pathologies. In 2000, Astrup and Finer (Obes Rev 1: 57-59) wrote the following: "Since type 2 diabetes is obesity dependent, and obesity is the main aetiogical cause of type 2 diabetes, we propose the term 'diabesity' should be adopted." Arguably, the research field of adipobiology has witnessed three major paradigm shifts since the discovery of leptin, an adipose-derived hormone, in 1994. Various neuroendocrine and neurotrophic factors are included in the growing list of endocrine and paracrine adipose-secreted signaling proteins collectively designated adipokines. These findings open a novel field of research known as neuroadipocrinology, a component of neuroendocrinology. Adipokines, including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), mediate multiple biological processes, such as food intake, immunity, inflammation, memory, mood, and metabolism. The effects on metabolism involve the maintenance of glucose, lipid and energy homeostasis as well as cardioprotection, neuroprotection, and aging. In this article, we highlight the role of metabotrophic factors (MTF) and the adipose- and nonadipose-derived biomolecules that mediate these effects. Recent results demonstrate that circulating and tissue levels of certain MTFs, e.g., adiponectin, NGF, BDNF, glucagon-like protein-1, sirtuin-1, interleukin-10, and aquaporin-7, are altered in cardiometabolic diseases, including diabesity. Overall, this may cultivate*

SAŽETAK

Današnja dostignuća u biologiji sistema i povezanim biološkim naukama omogućila su prelazak sa proučavanja pojedinačnog molekula i tkiva na holistički prikaz molekula i ćelija. Ovde pokušavamo da objasnimo koherentan prikaz koji integriše studije neurobiologije i adipobiologije, kao i one o dijabetesu i gojaznosti. Uopšteno, kardiometaboličke bolesti (ateroskleroza, hipertenzija, dijabetes melitus tip 2, gojaznost, diabesity (dijabetes melitus tip 2 udružen sa gojaznošću), i metabolički sindrom) predstavljaju najčešća oboljenja današnjice. 2000. godine Astrup i Finer (Obes Rev 1: 57-59) su napisali : "Obzirom da dijabetes melitus tip 2 zavisi od gojaznosti, a gojaznost je glavni etiološki uzrok dijabetesa tip 2, predlažemo da se termin 'diabesity' usvoji." Verovatno je polje istraživanja adipobiologije svedočilo o tri velike promene od otkrića leptina, hormona adipoznog porekla, 1994.godine. Različiti neuroendokrini i neurotrofični faktori su takođe bili uključeni u povećanje liste endokrinih i parakrinih signalnih proteina sekretovanih od strane adipocita koji zajedno čine adipokine. Ovi nalazi otvaraju novu oblast istraživanja, neuroadipokrinologiju, deo neuroendokrinologije. Adipokini, uključujući faktor rasta nerava (NGF) i neurotrofični faktor poreklom iz mozga (BDNF), posreduju u višestrukim biološkim procesima kao što su unos hrane, imunitet, inflamacija, pamćenje, raspoloženje i metaboliza. Efekti na metabolizam uključuju održavanje glukoze, lipida i energetske homeostaze, kao i kardioprotekciju, neuroprotekciju i starenje. Ovde izdvajamo ulogu metabotropnog faktora (MTF), biomolekula poreklom iz masti, kao i biomolekula koji ne vode poreklo iz masti, koji posreduju ove efekte. Nedavni rezultati pokazuju da se cirkulišući i/ili tkivni nivoi nekog MTF, na primer adiponektin, NGF, BDNF, glukagonu sličan protein-1, sirtuin-1, interleukin- 10, akvaporin-7, menjaju u kardiometaboličkim bolestima, uključujući diabesity. Uopšteno, ovo može otvoriti nov pristup u razmišljanju o dijabetesu tip 2

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a novel thinking for diabesity, herein also referred to as Homo diabesus.

Key words: *adipobiology, adipokines, diabetes, obesity, neurobiology, NGF, BDNF, metabotrophins*

udruženim sa gojaznošću, koji se takođe ovde označava kao i Homo diabesus.

Ključne reči: a*dipobiologija, adipokini, dijabetes, gojaznost, neurobiologija, NGF, BDNF, metabotrofini.*

ABBREVIATIONS

AD-Alzheimer's disease
AQP-aquaporin
BAT-brown adipose tissue
BDNF-brain-derived neurotrophic factor
MTF-metabotrophic factor
NGF-nerve growth factor
NT-neurotrophin
PPAR-peroxisome proliferator-activated receptor
Trk-tropomyosin-related kinase/receptor tyrosine kinase
UCP-uncoupling protein WAT, white adipose tissue

Thus, the task is not so much to see what no one has yet seen, but to think what nobody has yet thought about that which everybody sees.

Arthur Schopenhauer

INTRODUCTION

In the second half of the 20th century, holism (from the Ancient Greek word *holos,* meaning whole, entire, or total) led to thinking in terms of systems and their derivatives, such as systems biology. Life at both the local and systemic levels requires nutritional, immune, neurotrophic and metabotrophic support. Any dysfunction of or deficit in this support may result in a disease phenotype, such as type 2 diabetes or obesity, or a combination of the two, diabesity.

Type 2 diabetes mellitus is largely responsible for the prediction that the number of diabetics worldwide will double within a period of 30 years, increasing from 150 million people in 1995 to over 300 million by 2025 (1).

At its core, obesity may be briefly classified as the accumulation and inflammation of adipose tissue (Fig. 1), and the adipose-derived pro-inflammatory signals are disseminated to many organs of the body, leading to the subsequent development of cardiometabolic and neurodegenerative diseases (the scope of the present short review), as well as non-alcoholic steatohepatitis, polycystic ovarian syndrome, obstructive sleep apnoea, inflammatory bowel disease, thyroid-associated ophthalmopathy, cancer and many other diseases outside the scope of present review.

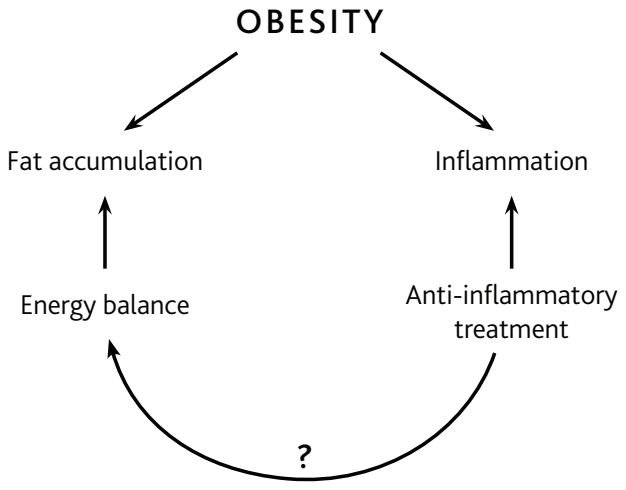

Figure 1. A drawing showing an oversimplified view of the possible pathogenesis of and therapies for obesity.

Obesity is the most prevalent disease in the world. 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) (1). Although the pathogenesis of obesity is not yet completely understood, there is now solid evidence that type 2 (non-insulin dependent) diabetes is strongly associated with the obese man (*Homo obesus*) (2). Therefore, diabesity (3) or *Homo diabesus* (4) has moved to centre stage as one of the most challenging biomedical and social threats, with its rising prevalence and impacts on both health and economics, in the present century. The health impact of diabesity includes a reduction of both quality of life and life expectancy due to complications such as myocardial infarction, stroke and end-stage renal disease. The burden of diabetes on the world economy has been rising in the last decade, as costs reached 376 billion dollars in 2010 and are expected to reach 490 billion dollars by 2030 (3). These latter authors wrote: "This century is the unprecedented diabetogenic era in human history. It is thus urgent to take steps including screening, prevention and early management in an attempt to control this evolving epidemic of diabesity." Furthermore, there is an "interaction" between diabesity and Alzheimer's disease, which will be highlighted below.

Adipobiology: a field marked by three paradigm shifts

One of biggest recent advances in studying cardiovascular diseases is associated with the "rediscovery" of a neglected tissue, adipose tissue.

In 1962, Thomas S. Kuhn published his book *The Structure of Scientific Revolutions* (1st edition, University of Chicago Press, Chicago, USA). Its publication was

Table 1. A paradigm shift: never before has adipose tissue been so active

FROM
Adipose tissue is a lipid and energy storage and is involved in obesity
TO
Adipose tissue is an endocrine and paracrine organ
Adipose tissue is a neuroendocrine organ
Adipose tissue is a steroidogenic organ
Adipose tissue is an immune organ
Adipose tissue is a source of and target for inflammatory mediators
Adipose tissue produces all components of the rennin-angiotensin system
Adipose tissue is therefore involved in numerous diseases beyond obesity

a landmark event in both the 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 often to *epistemological paralysis*, or neophobia. Kuhn argued for a model in which a period of such conceptual continuity in *normal science* was interrupted by a period of *revolutionary science,* leading to a new paradigm, an event he designated the *paradigm shift*.

At an epistemological level, adipose tissue has undergone three major paradigm shifts in the last 20 years, and has risen above the horizon and taken centre stage in a number of syndromes and that astonishes most scientists and medical doctors.

The first paradigm shift says: 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 discovery of leptin, an adipose-secreted hormone, published on 1 December 1994 in *Nature* 1994, 372:425–432 by Jeffrey Friedman and colleagues, marked this revolutionary event. This discovery was based on the pioneering contributions of Douglas Coleman (1931-2014). His work established the first clues regarding a genetic component to 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 the development of obesity and type 2 diabetes among laboratory mice.

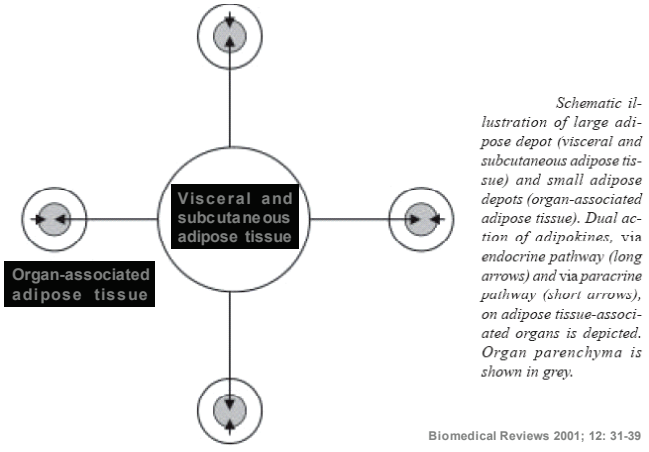

Figure 2. As indicated above/right.

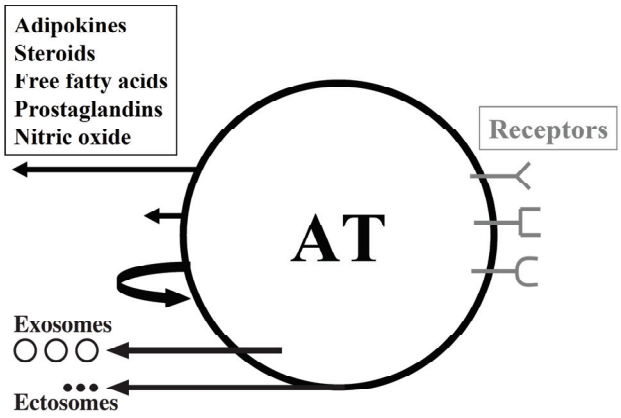

Figure 3. A drawing illustrating both the secretory and receptor nature of adipose tissue (AT) cells. At the secretory level, AT-derived signaling molecules communicate via multiple pathways, such as endocrine (arrows 1, 4 and 5, from top to bottom), paracrine (arrow 2) and autocrine (arrow 3, curved) pathways. Also depicted is that AT cells express receptors for various ligands. From (24).

The second paradigm shift derived from a study by Jeffrey Bell and colleagues (5), who have scanned nearly 800 people with magnetic resonance imaging (MRI) to obtain a map of white adipose tissue (WAT). The authors demonstrated that as many as 45 percent of women and nearly 60 percent of men have normal body mass index (BMI, 20-25 kg/m^2) scores and appear thin outside (TO), but actually have excessive levels of internal adipose tissue:, i.e., they are fat inside (FI). Therefore, they have the TOFI phenotype of body fat. The TOFI phenotype was also found among professional models. TOFI may therefore be considered an, "invisible" expression of both *Homo obesus* (2) and *Homo diabesus* (4).

The third paradigm shift features the increasing significance of brown adipose tissue (BAT) in both health and disease (see below).

Accumulation of adipose tissue in visceral and subcutaneous abdominal tissue, as well as near internal organs (Fig. 2), is a major risk factor for the development of numerous disorders, including diabesity and other related diseases. *Metaflammation* (metabolically induced inflammation) has emerged as a pivotal process in these disorders (6).

Adipose tissue is very plastic tissue and is constantly remodelled with weight gain and weight loss. It is a dynamic cellular and extracellular matrix assembly of adipocytes, fibroblasts, immune cells and matrix components and is also rich in sympathetic nerve fibres, blood vessels, and stem cells. There are two major subtypes of adipose tissue, WAT and BAT.

By sending and receiving different types of protein and non-protein signals, adipose tissue communicates with

many organs in the body (Fig. 3), therefore contributing to the control of energy, lipid and glucose homeostasis, as well as inflammation, immunity, learning and memory, among other biological functions.

In the human body, WAT stores energy and BAT dissipates energy by producing heat. BAT-mediated increases in energy expenditure are realised by uncoupling respiration from ATP synthesis via uncoupling protein 1 (UCP1), which is expressed in brown adipocytes, subsequently generating heat, a process known as adaptive thermogenesis. Animal studies have shown that the activation of BAT counteracts the effects of diet-induced weight gain and related disorders such as type 2 diabetes and metabolic syndrome: this may also be the case in humans (7). Recently, knowledge regarding WAT and BAT was enriched by information about their relatives, namely *brite* (brown in white) and *bruscle* (brown in skeletal muscle) adipocytes (8). Hence, brown adipobiology is emerging as a new focus in biomedicine.

In effect, such an adipocentric approach has revealed that although BAT is major thermogenic organ, whereas WAT is the body's largest endocrine and paracrine organ and produces multiple signaling proteins, which are collectively termed adipokines (9-12). Nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) are also produced by both WAT and BAT (13).

Multifunctionality of neurotrophins and adipokines

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, an idea that has never been proven. The proof was obtained through a rare combination of scientific reasoning and intuition by Rita Levi-Montalcini (1909-2012) in the early 1950s, in Saint Louis, MO, USA, when the first cell growth factor, NGF, was discovered. Levi-Montalcini was awarded the Nobel Prize in Medicine or Physiology 1986. The discovery of NGF has been embodied in a conceptual framework known as the neurotrophic theory. It reveals a pivotal role of effector (target) cells in the control of neuronal differentiation, survival and function via the production of NGF and other neurotrophic factors (14).

The neurotrophin family of proteins consists of NGF, BDNF, neurotrophin-3 (NT-3), NT-4/5, NT-6, and NT-7. Neurotrophins mediate their effects via ligation of (i) the panneurotrophin receptor, $p75^{NTR}$, and (ii) the receptor tyrosine kinases (tropomyosin-related kinase) (Trk), TrkA (for NGF), TrkB (for BDNF and NT-4), and TrkC (for NT-3) (reviewed in 12,14,15).

The past three decades have witnessed a number of breakthroughs regarding Rita Levi-Montalcini's NGF. Studies have revealed that NGF and BDNF not only are stimulators of nerve growth and survival but they also exert trophic effects on (i) immune cells, acting as immunotrophins; (ii) keratinocytes, enterocytes, and prostate and breast epithelial cells, acting as epitheliotrophins; and (iii) endothelial cells, acting as angiogenic factors (reviewed in 12,14-15).

From neurotrophins to metabotrophins

In 2003, additional phenotypic expressions of NGF were revealed, including metabotrophic actions on glucose, lipids, energy, pancreatic beta cells and cardiovascular homeostasis, and subsequently designated (analogous to neurotrophic factors and neurotrophins) as metabotrophic factors (MTF) or metabotrophins (from the Greek words *metabole* and *trophe*, meaning "nutritious for metabolism") (12,15-18), a family to which BDNF also belongs. The proof-of-hypothesis was based on results demonstrating that circulating and tissue levels of both NGF and BDNF are (commonly) decreased in atherosclerosis, metabolic syndrome (19), type 2 diabetes (20) and Alzheimer's disease (15), which currently is considered type 3 diabetes (21).

Neuroadipocrinology

As a multiplex of biological systems, life requires an interaction between its molecular and cellular components. One of the biggest recent achievements of neurobiology and adipobiology is the studies on neurotrophic factors (e.g., NGF and BDNF) and adipokines (e.g., leptin and adiponectin).

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 the case with neurotrophic factors and adipokines. For instance, in the more than 30 years following the discovery of NGF, there have been few indications that it acts on non-neuronal cells. Therefore, it was remarkable when Aloe and Levi-Montalcini discovered that treatment of newborn rats with NGF caused a systemic increase in mast cells, in 1977. This seminal finding paved the way for a novel research field, neuroimmunology (22, 23 and references therein).

As indicated above (9-13), WAT is a dynamic endocrine and paracrine organ, producing a large number of adipokines. Some of them, e.g., leptin, mediate cross-talk between adipose tissue and the hypothalamus in regulating food intake and energy expenditure. However, the hypothalamus is not the only brain target for leptin, and the regulation of food intake is not this adipokine's only biological action. Rather, some adipokines support various cognitive functions and have neurotrophic activity. Current data regarding adipose-derived neuroendocrine and neurotrophic factors are summarised in Tables 2 and 3. This finding raises an intriguing question as to whether WAT may be a peripheral counterpart of the hypothalamus-hypophysis axis. Cumulatively, linking neurobiology and adipobiology resulted in neuroadipology (24), herein renamed *neuroadipocrinology*.

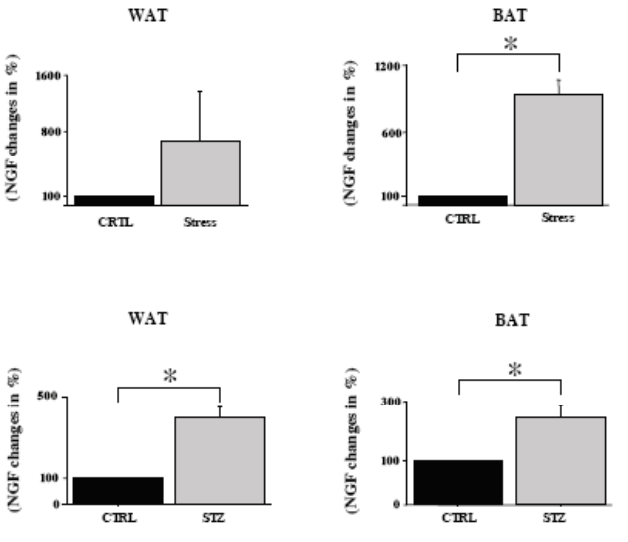

Figure 4. Changes in the amount of nerve growth factor (NGF) in white adipose tissue (WAT) and brown adipose tissue (BAT) of controls (CTRL) compared to the concentration of NGF in stressed mice (Stress) and streptozotocin-induced diabetic rats (STZ), expressed as a percentage of the controls. Note the enhanced presence of NGF in WAT and BAT in stressed mice, as well as in diabetic rats. The vertical lines in the figure indicate pooled S.E.M. derived from the appropriate error mean square in the ANOVA. * Significant differences between groups ($p < 0.05$). From (13).

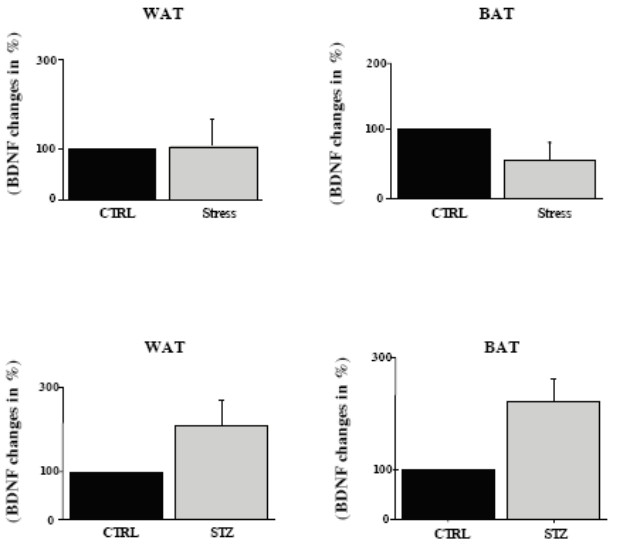

Figure 5. Changes in the amount of brain-derived neurotrophic factor (BDNF) in epicardial white adipose tissue (WAT) and brown adipose tissue (BAT) of controls (CTRL) compared to the concentration of BDNF in stressed mice (Stress) and in streptozotocin-induced diabetic rats (STZ), expressed as a percentage of the controls. The vertical lines in the figure indicate pooled S.E.M. derived from the appropriate error mean square in the ANOVA. From (13).

In an attempt to "close" the metabotrophic "loop" in cardiometabolic disease, we have measured circulating levels of NGF and BDNF in patients with acute coronary syndrome, and found that they are significantly reduced (25, cf. 26). Another study revealed altered levels of NGF in the 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 (Fig. 4,5); for mast cells see Figure 6.

Table 2. Selected list of adipose-derived neuroendocrine factors

Neuropeptides
Neuropeptide tyrosine (NPY)
Substance P
Calcitonin gene-related peptide
Agouti-related protein
Adrenomedullin
Somatostatin
Kisspeptin
Neuromedin B
Neurotensin
Apelin
Nesfatin-1
Hypothalamic factors
Mineralocorticoid-releasing factors
Corticotropin-releasing hormone (CRH)
Stresscopin, urocortin (CRH-like peptides)

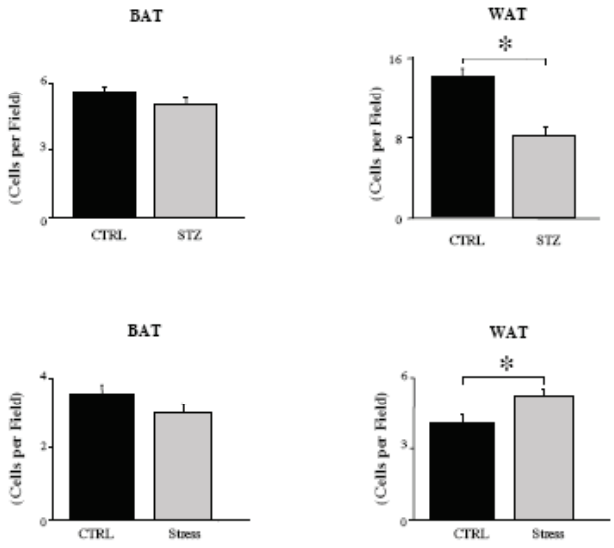

Figure 6. Changes in the number of mast cells in brown adipose tissue (BAT) and epicardial white adipose tissue (WAT) of controls (CTRL) compared to streptozotocin-induced diabetic rats (STZ) and stressed mice (Stress), expressed as a percentage of the controls. The vertical lines in the figure indicate pooled S.E.M. derived from the appropriate error mean square in the ANOVA.

PERSPECTIVE

Examples of proof-of-metabotrophic hypothesis derived from other laboratories include the following: *(i)* pancreatic beta cells secrete NGF and express its receptor TrkA, findings implicated in the pathogenesis of diabetes mellitus (28), and (ii) mutations affecting the *Bdnf* gene

Table 3. Selected list of adipose-derived neurotrophic factors

Leptin
Nerve growth factor
Brain-derived neurotrophic factor
Angiopoietin-1
Vascular endothelial growth factor
Ciliary neurotrophic factor
Glial cell line-derived neurotrophic factor
Steroids
Metallothioneins

(encoding BDNF) in mice or the *Ntr2k2* gene (encoding the high-affinity BDNF receptor TrkB) in humans are associated with hyperphagia and severe obesity (15 and references therein). Lists of selected metabotrophins (Table 4) and the metabotrophic effects of NGF and BDNF (Table 5) are provided in the aforementioned tables.

In this context, the recent discovery of (i) humanin, a mitochondria-derived peptide expressing neuro-metabotrophic effects (29,30), and (ii) irisin, a myokine/adipokine involved in the browning of WAT (31,32), may lead to the development of a novel approach in therapy for *Homo diabesus*. It may open new paths in the search for *exogenous* MTF, such as (i) small molecules that boost the secretory or signaling pathways of MTF (15) 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 effects (33,34). Furthermore, (i) transgenic mice with Alzheimer's disease fed J147, a new compound, demonstrate improved memory, a finding correlated with reduced soluble levels of beta-amyloid and increased hippocampal levels of NGF and BDNF, in addition to the

Table 4. Selected list of endogenous metabotrophic factors*

Secretory proteins
Nerve growth factor, Brain-derived neurotrophic factor
Ciliary neurotrophic factor, Neuron-derived neurotrophic factor
Adiponectin, Irisin, Humanin, Omentin, Chemerin, Apelin, Otopetrin 1
Interleukin-10, Interleukin-1 receptor antagonist, Metalothioneins
Glucagon-like peptide-1
Intracellular proteins
Sirtuin-1, PPAR-gamma, Uncoupling protein-1 (UCP-1)
Aquaporin-7**

* Modified from (12). For references, see the text, and also (43-55).

** Discovered in 1986 by Gheorghe Benga (56) as the water channel integral membrane protein, in erythrocytes, the family of proteins designated the aquaporins (AQP) was appreciated when the Nobel Prize in Chemistry was awarded in 2003 to Peter Egre, whereas its original discovery by Gheorghe Benga has been ignored. Today, the AQP family consists of more than 10 members, AQP7 being expressed in adipocytes and related to obesity (57,58).

Table 5. Metabotrophic effects of NGF and BDNF*

NGF shares homology with proinsulin
NGF and BDNF are produced by pancreatic beta cells and exert insulinotropic effects
NGF and BDNF are trophic factors for pancreatic beta cells, and also improve beta cell transplantation
NGF up-regulates the expression of LDL receptor-related protein
NGF up-regulates the expression of PPARgamma
NGF inhibits glucose-induced down-regulation of caveolin-1
NGF improves skin and corneal wound healing
NGF may improve vascular (atheroma) 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 circulating levels of NGF and BDNF
An atherogenic diet decreases brain BDNF levels
BDNF-deficient mice develop abnormalities similar to metabolic syndrome
BDNF improves cognitive processes

Modified from (15). For references, see the text, and also 36, 39, 47, 48, 50-53, 66, 67.

BDNF-responsive synaptotrophic proteins Homer-1 and Egr3 (35): (ii) an ATP-NGF complex, but not NGF itself, appears to be the active neuroprotective mediator (36): (iii) NGF is related to enhanced expression of the purinergic P2X(3) receptor (37): (iv) metformin, a widely prescribed drug for type 2 diabetes, may exert neuroprotective effects by increasing BDNF levels (38), and (v) vitamin A may exert antidiabetic effects via NGF expression (39). Likewise, the role of microRNA in diabetes development has been recognised (40, also see 41 and 42 for sirtuin-1). A possible therapeutic pathway for the management of diabesity is shown in Figure 7.

The present integrated view also suggests that understanding the precise role of MTF in the origin of *Homo diabesus* may lead to new therapies for diabesity and related diseases, including Alzheimer's disease (AD). The use of transcript clustering to identify molecular mecha-

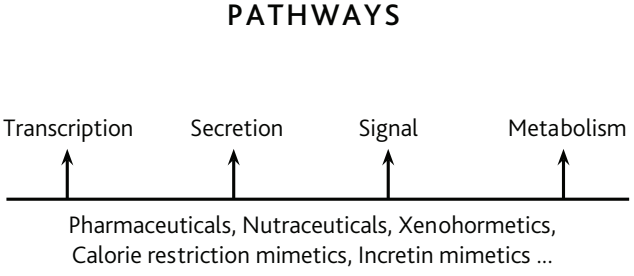

Figure 7. A drawing presenting a possible therapeutic pathway for diabesity.

nisms contributing to the early stages of AD in mice has identified changes in the insulin signaling pathway, including the down-regulation of insulin receptor substrate 4 (Irs4), an early event in AD (59). Insulin and MTF signaling are strongly associated with diabesity, which has recently been identified as a potential risk factor for AD (60-66; also see 67).

CONCLUSION

In 1999, Albee Messing published in an editorial entitled "Nestin in the liver - lessons from the brain" in *Hepatology* (29: 602-603). He wrote the following: "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. Future *new thinking* in neuroadipocrinology of diabesity may lead to a deeper insight about how we can make MTF secretion and signaling work for the improvement of physical and mental quality of life of *Homo diabesus* who is expressing now in more than a trillion earthians.

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