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REVIEW

A GROWING JOURNEY FROM NEUROTROPHINS TO METABOTROPHINS IN CARDIOMETABOLIC DISEASES

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Abstract

Currently, obesity has been recognized as a prime risk in the development of cardiometabolic diseases (CMD) and neurodegenerative diseases (NDD). The pathogenesis and therapy of CMD are immensely complex at the cellular and molecular levels. This scenario raises the question of how such a complexity may be grappled in a more tangible manner. Since 2003, we have been thinking "what nobody has yet thought about that everybody sees", namely, matabotrophic factors (MTF, metabotrophins). The latter include mainly (i) the neurotrophins nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), and (ii) the adipomyokines adiponectin, irisin, BDNF, fibroblast growth factor-21 alike as adipose- and skeletal muscle-derived signaling proteins (these latter discussed in another review in the present volume of *Adipobiology*). Herein, we argue that obesity and related CMD and NDD, particularly Alzheimer's disease, may be viewed as MTF-deficient diseases. Further studies on MTF signatures and ramifications in these diseases are required. These would provide greater insights on how we can make MTF work for the improvement of physiological and psychological quality of human life.

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Introduction

Life at both the local and systemic levels requires nutritional, immune, neurotrophic and metabotrophic support. Any dysfunction or deficit in this support may lead to illness, such as obesity and related cardiometabolic diseases (CMD) such as atherosclerosis, hypertension, type 2 diabetes mellitus (T2DM), metabolic syndrome, and metabocognitive syndrome, including Alzheimer's disease (AD). At its core, obesity may be classified as dysmetabolic disorder, featured by: (i) accumulation, hypoxia and inflammation of white adipose tissue (1-4), and (ii) dysfunction of brown adipose tissue (5-9). Then, the adipose-derived proinflammatory and dysmetabolic signals are disseminated to many organs of the body. This leads to the development of CMD and neurodegenerative diseases (NDD), particularly AD, which we shall discuss in the present review as a neurometabolic disease.

Neurotrophins

In the 1950s at Washington University Medical School, St Louis, MO, Rita Levi-Montalcini and Stanley Cohen discovered a protein with nerve growth-stimulating effect, and they named it nerve growth factor (NGF). This *Eureka* provided a conceptual framework for the formulation of the neurotrophic hypothesis: particular neuronal types require specific trophic factors for their differentiation, function and survival (10-13).

Today, NGF and brain-derived neurotrophic factor (BDNF) and their relatives are collectively designated neurotrophins. The latter include: NGF, BDNF, neurotrophin-3 (NT-3), NT-4/5, and NT-6, also pro-NGF and pro-BDNF which are as active as their respective mature forms. Neurotrophins, particularly NGF and BDNF, were recognized as mediators of multiple biological processes, ranging from the neurotrophic (10) through immunotrophic (14) to metabotrophic effects over glucose, lipid, energy and cardiovascular homeostasis (2, 13, 15-20). Consequently, NGF and BDNF were implicated in the pathogenesis of a large spectrum of neuronal and non-neuronal diseases.

Adipose cells (adipocytes and associated cells of the white adipose tissue/WAT) also secrete various neurotrophic factors (Table 1).

Table 1. A selected list of adipose-derived neurotrophic factors (ADNF)

NGF, BDNF, Glial cell line-derived neurotrophic factor
Ciliary neurotrophic factor, Vascular endothelial growth factor
Leptin, Adiponectin, Irisin, β-Klotho, Meteorin-like (Metrnl, also known as Cometin, Subfatin), Neprilysin (β-amyloid peptide-degrading enzyme)
Fibroblast growth factor- 21, Metallothionein-I, -II, Angiopoietin-1

Neurotrophins "became" metabotrophic factors and "make" CMD and AD metabotrophins-deficient diseases

In 2003 NGF-and-BDNF's physiological profile was enlarged with one more extra-neuronal activity, namely, the improvement of metabolism of glucose and lipids, also of pancreatic beta cell and cardiovascular homeostasis. Accordingly, these neurotrophins were also named *metabotrophic factors* (MTF) or *metabotrophins,* also *metabokines* (2, 15-17, 21; from Greek *metabole*, and *trophe*, nutrition, means "nutritious for metabolism").

The proof-of-concept was based on results demonstrating that the circulating and/or local NGF and BDNF levels are decreased in (i) human coronary atherosclerosis and in patients with *advanced stage* of metabolic syndrome (22), (ii) T2DM (23, 24), and (iii) AD which is considered recently T3DM (25-27; for adipose AD, see 28). In contrast, the circulating levels of NGF and BDNF were significantly elevated in patients with *early stage* of metabolic syndrome (29). It remains to be elucidated whether the metabolically protective reserve of the organism is limited with the progression of metabolic syndrome.

Furthermore, circulating levels of NGF and BDNF in patients with acute coronary syndromes were measured, and they were found to be reduced significantly (30, 31). It was reported that in response to experimental stress or diabetes, NGF and BDNF levels were altered, both in white and brown adipose tissue (WAT and BAT, respectively) (32). Further, it was demonstrated that pancreatic beta cells secrete NGF and express its receptor tyrosine kinase A ($TrkA^{NGF}$), findings being implicated in the pathogenesis of T2DM and metabolic syndrome (33-43). Synergistically with leptin, BDNF reduces food intake (44). Accordingly, mutations of *Bdnf* gene in mice or *Ntr2k2* (encoding $TrkB^{BDNF}$ receptor) in patients are associated with hyperphagia and severe obesity (45). Table 3 presents characteristics and a list of MTF-induced effects.

Table 3. Characteristics and 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 metabolic syndrome
NGF, 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
BDNF-deficient mice develop abnormalities similar to the metabolic syndrome
BDNF improves cognitive processes

Table 4 shows a list of endogenous metabotrophins.

Table 4. A selected list of endogenous metabotrophins

Nerve growth factor, Brain-derived neurotrophic factor
Ciliary neurotrophic factor, Vascular endothelial growth factor
Leptin, Adiponectin, Irisin, Fibroblast growth factor- 21, Meteorin-like (Metrnl),
Sirtuins (Visfatin/SIRT-2, SIRT-1), Klotho, Humanin, Omentin,
Chemerin, Apelin, Otopetrin-1, Interleukin-10, Metalothionein-I,-II,
Incretins (Glucagon-like peptide-1, Glucose-dependent insulinotropic polypeptide)
Neuromedin-B, Kisspeptin-1, Progranulin, Kallistatin, Aquaporin-7, Angiopoietin-like protein 4

Targeting metabotrophins in drug discovery NGF and BDNF

As discussed, obesity and related CMD are featured by reduced circulating and epicardial adipose tissue levels of NGF and BDNF. Most probably, hypometabotrophinemia induces a metabolic stress, thus staying in the heart of a complex network of factors orchestrated the pathobiology of CMD. If so, drugs facilitating (boosting) the intracellular secretory pathways (46, 47) of NGF, BDNF, adiponectin, irisin as well as other MTF may represent a novel pharmacotherapeutic approach in these diseases. However, our knowledge of secretory pathways (synthesis, translocation, folding, targeting, sorting, storage, and exocytosis) of MTF remains limited.

Neurotrophins ligated two different types of receptors on the surface of neurones and other target cells: (i) high-affinity neurotrophin receptors belong to the Trk (pronounced "track") family of tyrosine kinase receptors (TrkA, TrkB and TrkC) which bind to specific neurotrophins (e.g., $TrkA^{NGF}$, $TrkB^{BDNF}$), and (ii) low-affinity panneurotrophin receptor, $p75^{NTR}$, which lacks a tyrosine kinase endodomain. Hence, another approach for the discovery of novel therapeutics for obesity and its diseased relatives may indeed lie in exploring Trk^{NGF} and $TrkB^{BDNF}$ receptor agonists (for *trackins*, see 48, 49).

As reviewed (13, 50), increasing number of reports demonstrate that damage to some tissues can be cured by the administration of NGF. For instance, (i) wounded diabetic skin, characterized by increased levels of NGF, will benefit by additional exogenous local treatment with NGF, (ii) elevated local NGF levels in experimentally-induced cardiac ischemia is improved by exogenous administration of NGF, and (iii) NGF administration in diabetic rodents promotes repair of injured pancreatic islets.

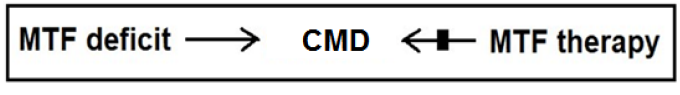
Metformin for thought or metformin 100 years latter

Metformin has its origin in the herb *Galega officinalis*, which was used for centuries to treat many diseases. In 1922, metformin (dimethylbiguanide) was synthesized, and the French physician Jean Sterne first reported the use of metformin to treat diabetes in 1957. It was demonstrated that metformin had the potential to decrease blood glucose with fewer gastrointestinal adverse effects than others drugs used for the same purpose. Today, this drug is a first-line therapy for T2DM as a monotherapy or in combination. Recent evidence suggests that metformin is a multi-therapeutic drug including its neuroprotective and procognitive actions. Observational studies of metformin-treated T2DM patients reported lower rates of dementia, reduced depressive symptoms, and a reduced risk of cognitive impairment, with the lowest risk seen in those patients with longer-term (>6 years) metformin use (51-54; also see 55, 56). Intriguingly, metformin increases brain expression of BDNF, a procognitive metabotrophin (57).

Noteworthy, (i) both brain and adipose tissue have elevated amyloid precursor protein (APP) levels in obesity, (ii) there is an extraneuronal production both of APP and amyloid β (Aβ) peptides, including in WAT, and (iii) the administration of streptozotocin, a well known experimental model for type 1 diabetes, induces brain insulin resistance and cognitive alterations resembling the status of AD patients (58). Hence, an intriguing question emerges: can these AD-associated molecules spread from adipose tissue to the brain? In the same stream-of-associations, a growing body of evidence suggested that metabolic syndrome (impaired glucose tolerance, abdominal obesity, hypertension, hypertriglyceridemia, and a reduced "good", HDL cholesterol) may be important in the development of cognitive impairment, including AD. With other words, metabodegeneration may pivotally be involved in the process of neurodegeneration of AD; this may clarify approaches valuable both in preventing and therapy of the disease. Hence, new diagnostic term were proposed: „metabolic-cognitive syndrome" (59, 60) and "T3DM" (25, 61-63).

Conclusion

Many basic and clinical studies have demonstrated that circulating and/or tissue levels of metabotrophins are reduced in individuals with obesity and related CMD. The scheme within the box below illustrates the possible involvement of metabotrophins both in the pathobiology and the therapy of CMD, including AD, viewed as metabotrophins-deficient diseases.



In this conn ection, Figure 1 illustrates our concept of the potential significance of MTF in the pathogenesis of CMD and NMD, particularly AD.

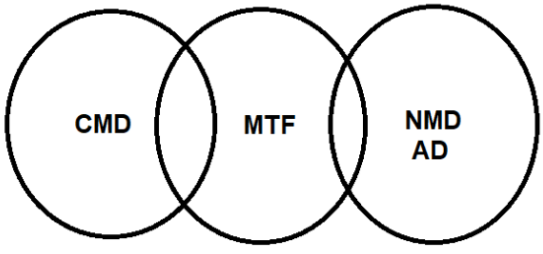


Figure 1. Metabotrophic factors (MTF) on the cross-road of cardiometabolic diseases (CMD) and neurometabolic diseases (NMD), particularly Alzheimer's disease (AD). Credit for Nikifor N. Chaldakov. From: (61, 62; also see 25, 63-65).

Since 2003 (2), we have been "thinking what nobody has yet thought about that which everybody sees" with respect to the concept of metabotrophins and their relevance for the cellular and molecular mechanisms of CMD and NMD (see also 12, 15, 16, 18, 28, 38, 58).

Yet, we have to keep in mind Robert Frost's poem *The Secret Sits*:

We dance round in a ring and suppose,
But the Secret sits in the middle and knows.

Future studies on metabotrophins signature in CMD and NMD, particularly AD and Parkinson's disease, may therefore cultivate a more relevant thinking about how we can make these talented biomolecules work for the improvement of physical and mental quality of life of *Homo sapiens*.

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Conflict of interest statement

The authors declare that no conflicts of interest exists.

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