NGF and BDNF: from nerves to adipose tissue, from neurokines to metabokines.

NGF e BDNF: dai nervi al tessuto adiposo, dalle neurochine alle metabochine

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SUMMARY. While neurotrophins are widely studied in neuroimmune links, their implications in vascular, metabolic and cognitive biology have recently emerged. The present overview addresses the significance of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in the pathogenesis and therapy of neuropsychiatric and cardiometabolic diseases. Neurotrophins, particularly, NGF and BDNF are now well recognized to mediate a dizzying number of trophobiological effects, ranging from the Rita Levi-Montalcini's neurotrophic through immunotrophic to metabotrophic effects. These are implicated in the pathogenesis of various diseases including neuropsychiatric and cardiometabolic diseases, where dementia, depression, type 2 diabetes and obesity may express a common phenotype and coexistence. Recently, adipobiology (adiposcience) became a focus of numerous studies showning that the adipose tissue is the body's largest endocrine organ producing multiple signaling proteins, including NGF and BDNF, all these dubbed adipokines. On the basis of our and other authors' evidence that low NGF and/or BDNF levels are found in cardiometabolic diseases (atherosclerosis, obesity, type 2 diabetes, metabolic syndrome), a hypothesis of a critical role of neuro-metabotrophic deficit in the pathogenesis of these diseases has been raised. Since NGF and BDNF also exerts various synaptotrophic effects involved in cognitive enhancement, this hypothesis might also be related to neuropsychiatric diseases such as dementia, depression, schizophrenia, autism, Rett syndrome, anorexia nervosa, and bulimia nervosa. Finally, NGF- and BDNF-based therapeutic approach, including ampakines, antidepressants, selective deacetylase inhibitors, statins, peroxisome proliferator-activated receptor gamma agonists, and "brain food" and calorie restriction, is outlined.

KEY WORDS: adipokines, neurotrophins, synatotrophic effects, metabotrophic effects, ampakines, deacetylase, calorie restriction.

RIASSUNTO. Mentre le neurotrofine sono state largamente studiate nei rapporti neuroimmunitari, solo recentemente sono emerse le loro implicazioni nella biologia vascolare, metabolica e cognitiva. La presente overview esprime il ruolo del nerve growth factor (NGF) e del brain-derived neurotrophic factor (BDNF) nelle patogenesi e terapia delle malattie neuropsichiariche e cardiometaboliche. Le neurotrofine, in modo particolare NGF e BDNF, sono ben riconosciute per mediare un numero da capogiro di effetti trofobiologici, partendo da quelli neurotrofici di Rita Levi-Montalcini attraverso quelli immunotrofici e metabotrofici. Tutte queste funzioni sono coinvolte nella patogenesi di diverse malattie, incluse quelle neuropsichiatriche e cardiometaboliche, quali la demenza, la depressione, il diabete di secondo tipo e l'obesità, malattie che potrebbero esprimere un fenotipo comune e una coesistenza. Recentemente, l'adipobiologia (adiposcienza) è diventata il focus di numerosi studi che hanno dimostrato che il tessuto adiposo è l'organo endocrino più grande del corpo, che produce proteine di segnale multiplo, incluse il NGF e il BDNF, con un significato anche di adipochine. Sulla base dell'evidenza nostra e di altri autori che livelli bassi di NGF e/o di BDNF sono stati ritrovati nelle malattie cardiometaboliche (arteriosclerosi, obesità, diabete di secondo tipo, sindrome metabolica), è stata formulata un'ipotesi sul ruolo critico del deficit neurometabotropico nella patogenie di queste malattie. Da quando si è visto che il NGF e il BDNF esercitano anche effetti sinaptotrofici coinvolti nel miglioramento cognitivo, si è ipotizzato che queste neurotrofine potrebbero essere implicate nella patogenesi di malattie neuropsichiatriche come ad esempio la demenza, la depressione, la schizofrenia, l'autismo, la sindrome di Rett, l'anoressia ner-

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INTRODUCTION

Growing body of evidence indicates that not only at neuronal (1-6), but also at cardiometabolic level life requires both NGF and BDNF (7-22).

The present review clusters neurotrophic and metabotrophic potentials of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) relevant to the pathogenesis and therapy of neuropsychiatric and cardiometabolic diseases. In other words, NGF and BDNF are herein appreciated as a pleiotrophic signaling molecule, both neurokines (2) and metabokines (metabotrophic factors) (10,23). Note that (i) Angeletti and Levi-Montalcini (24) pointed out to NGF's "metabolic effects", (ii) NGF share structural homology with proinsulin (25), and (iii) the term "metabokine" was, as referring to adenosine, introduced by Lukashev, et al. (26).

NEUROTROPHINS

In retrospect, 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, the proof was obtained by Rita Levi-Montalcini, Viktor Hamburger and Stanley Cohen in the early 1950's in Saint Louis, MO, USA, where the first cell growth factor, namely NGF, was discovered (1-4). This was embodied in a conceptual framework now well known as neurotrophic theory, which 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 neurotrophin family of proteins consisted of NGF, BDNF, neurotrophin-3 (NT-3), NT-4/5, NT-6, and NT-7 (6). Neurotrophins mediate their effects via ligation of panneurotrophin receptor, p75^{NTR}, and of receptor tyrosine kinase (tropomyosin-related kinase) (Trk), namely, TrkA (for NGF), Trk B (for BDNF and NT-4), and TrkC (for NT-3) (27). Noteworthy, transactivation of Trk receptors by G protein-coupled receptor (27,28) and by adenosine receptors (29) has recently emerged as a novel biology of neurotrophin actions.

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 NGF. During some 30 years after its discovery, there have been few reasons given to indicate that NGF acts on noneuronal cells. Thus, it was remarkable to discover that treatment of newborn rats with NGF caused a systemic increase in the number of mast cells (30). Today there is compelling evidence that NGF, in addition to its neurotrophic function, enhances survival and activity of a large number of nonneuronal cells (5,6,31), including immune cells (32), pancreatic beta cells (15), vascular smooth muscle cells (33), cardiomyocytes (22), endothelial cells (34,35), epithelia cells (36), and adipocytes (37-39).

The secretory proforms of NGF and BDNF, pro-NGF and pro-BDNF (40), respectively, are cleaved extracellularly through the tissue type plasminogen activator (tPA)-serine protease plasmin pathway; note that today's widely administrated cholesterol-lowering drugs, collectively named statins, can induce tPA, hence releasing a mature form of BDNF (41). As discussed below, these cardiometabolic drugs may also be therapeutic for Alzheimer's disease and possibly other types of dementia. While NGF is upregulated (18,42), BDNF is downregulated by stress and upregulated by learning, antidepressants, histone deacetylase inhibitors, physical activity, and dietary calorie restriction (see below). And disruption of NGF and/or BDNF signaling is a characteristic feature of many central and peripheral nervous system disorders, such as dementia, depression, amyotrophic lateral sclerosis, multiple sclerosis, stroke, neuropathy and eating and nociceptive disorders (**Table 1**).

Elucidating the molecular mechanisms that maintain and modify (i) neural including synaptic structure and function, and (ii) vascular and metabolic homeodynamics is required for understanding nervous, cognitive and cardiometabolic systems in health and disease. Indeed, NGF and BDNF initially discovered as neural growth factors are also affecting (i) immune cells (32), (ii) blood vessels/angiogenesis (34,35,43,44), (iii) synaptic plasticity and consolidation (45,46) involved in learning and memory (47), (iv) wound healing and tissue repair (9,13,43,48,49), and (v) glucose, lipid, antioxidant and energy metabolism (50,51). Whereas insulin (52,53), vascular endothelial growth factor (34,35,44,54), cytokines (55,56) and the adipokine leptin (57) initially discovered as hypoglycemic, angiogenic, immunotrophic, and anorexigenic factors, respectively, also exert neurotrophic effects, and thus may contribute to cognitive processes (for antidepressant effect of leptin, see 58). Further, cardiometabolic biomarkers such as cholesterol (59,60) and insulin (61) and the incretin glucagon-like peptide-1 (62), respectively atherosclerosis, type 2 diabetes and obesity, are recently found to associate with the development of Alzheimer's disease (53,58,63-71), also suggesting that Alzheimer's disease might be viewed as type 3 diabetes mellitus (72). Noteworthy, it has

Table 1. Selected list of NGF- and BDNF-related diseases

Neuropsychiatric diseases
Alzheimer's disease
Mild cognitive impairment
Huntington's disease
Parkinson's disease
Human immunodeficiency virus-associated dementia
Amyothrophic lateral sclerosis
Epilepsy
Primary headache
Migraine
Cluster headache
Diabetic neuropathy
Diabetic retinopathy
Diabetic erectile dysfunction
Depression
Schizophrenia
Pervasive developmental disorders
Autism
Asperger syndrome
Rett syndrome
Eating disorders
Anorexia nervosa
Bulimia nervosa
Williams syndrome
Down syndrome
Cardiometabolic diseases
Atherosclerosis
Obesity*
Metabolic syndrome
Type 2 diabetes mellitus
Kawasaki disease

*Recently, the American Psychiatric Association recognizes obesity not just as a metabolic disorder but also as mental, "food addiction" disorder.

been estimated that 40-60% of individuals with schizophrenia and 55-68% of individuals with depression in the United States are overweight or obese due to combination of disease-related factors and/or use of antipsychotic drugs (reviewed by Kolotkin, et al.) (73).

Here we conceptualize available data of NGF and BDNF as related both to cardiometabolic (see below) and neuropsychiatric diseases (74-93; for a re-evaluation of BDNF hypothesis of depression, see 94).

Synaptotrophic neurotrophins

Changes in the stability and density of dendritic spines and the efficacy of synaptic transmission, known as synaptic plasticity, are believed to be general mechanisms underlying many brain functions, specifically learning and memory (45-47).

Today, there is compelling evidence indicating that in addition to their actions on neuronal differentiation and survival, BDNF and TrkB signaling are uniquely important for the process of activity-dependent synaptic plasticity including long-term potentiation and long-term depression (95), dendritic spine density and cytoskeletal dynamics (96,97), synaptic vesicle neurotransmitter release and retrieval (98) underlying various cognitive functions such as learning and memory encoding and storage (87,99,100); synaptotrophic activity of neurotrophins was conceptualized more than 10 years ago (101).

In brief, BDNF is an activity-dependent modulator of neuronal structure and function in the adult brain. Localization of BDNF and its TrkB receptor to glutamate synapses makes this system intriguing as a dynamic, activity-dependent regulator of excitatory transmission that is implicated in the mechanisms of memory storage and mood control (46,102).

Metabotrophic neurotrophins

Recently, NGF and BDNF are increasingly implicated in the control of glucose, lipid and antioxidant metabolism – reviewed by Chaldakov, et al. (103) and Töre, et al. (19). They are also considered anorexigenic signals in the central control of food intake (50,51,104-108). Conversely, mice heterozygous for targeted disruption of BDNF show hyperphagia and obesity. The same phenotype was observed in mice with a reduced expression of TrkB receptor (109). Likewise, it was demonstrated that BDNF is an important downstream effector of melanocortin signaling in the hypothalamus, thus can, synergistically with leptin, modulate food intake (110).

Conceptually, NGF and BDNF as well as other neurotrophic factors were for the first time viewed as metabotrophic factors (10), recently also designated metabokines (23). Hence, over the last 10 years it has been recognized that altered expression of NGF and/or BDNF and their TrkA receptors has also been implicated in the pathogenesis of cardiometabolic diseases (111-117) (**Table 1**), which were not appreciated in otherwise excellent review on neurotrophins published recently (118).

ADIPOSE TISSUE AND NEUROTROPHIC FACTORS

Although the discovery of first adipose-derived endocrine factor, the serine protease adipsin, is traced back to 1986, it was the discovery of leptin in 1994 (119) that focused many studies on the endocrine function of adipose tissue, thus defining a new field of study, adipobiology (10,120-123). These studies' results have indeed shifted the paradigm of adipose tissue from a simple energy storage to a major body's endocrine organ.

In mammals including humans, there are two major subtypes of adipose tissue: white and brown adipose tissue, WAT and BAT, respectively. WAT has a couple of subdivisions, each with unique anatomic, metabolic and secretory properties: intraabdominal or visceral and subcutaneous adipose tissue. In addition to the subcutaneous and visceral compartments, there are many small visceral depots associated with heart, blood vessels, major lymph nodes, ovaries, mammary glands, eyes, bone marrow, also brain and spinal cord (10,122,123).

Secretion by adipose tissue

The adipose-secreted products include an increasing number of signaling proteins, collectively termed adipokines. Adipokines are involved in the regulation of a wide range of biological processes including inflammation, immunity, angeogenesis, neuronal growth and survival, and lipid, glucose and energy metabolism. Recent transcriptomic and proteomic analyses revealed that more than hundred adipokines are secreted by adipose tissue including leptin, adiponectin, resistin, tumor necrosis factor-alpha, interleukins, chemokines, renin, angiotensin, visfatin, retinol-binding protein, plasminogen activator inhibitor-1, tissue factor, C-reactive protein, haptoglobin, pigment epithelium-derived factor, hepatocyte growth factor, transforming growth factor-beta, vascular endothelial growth factor, and *agouti* protein –reviewed by Chaldakov, et al. (10), Trayhurn, et al. (120) and Töre, et al. (19). Likewise, adipose tissue cells also secrete NGF, BDNF, ciliary neurotrophic factor and other factors with neurotrophic action (**Table 2**), also various neuropeptides and pituitary-hypothalamic hormones (124,125,12). The adipokines provide communication between adipose tissue and the rest of the body including the brain. Moreover, brain also produces various adipokines such as leptin, adiponectin, and resistin (126,127), whereas leptin exerts neuroprotective action (57) as well as antidepressant-like effect (58).

Table 2. Adipose tissue-produced neurotrophic factors (11,19,104 and references therein)

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

THERAPY INSIGHT

NGF- and BDNF-based therapeutic pipeline for neuropsychiatric diseases discussed herein (except migraine, cluster headache, and probably epilepsy) may include (i) applying NGF itself (9,13,43,49,128), (ii) targeting the secretory and signaling pathways using existing or novel drugs (129-134), (iii) TrkB transactivation (27-29), (iv) ampakines, small molecules that stimulate Alpha-amino-3-hydroxy-5-Methyl-4-isoxazole Propionic Acid (AMPA)-type glutamate receptors (102,135,136), (v) selective deacetylase inhibitors (75,137-140), and (vi) "brain food" (21), that is, neuroprotective nutrients including calorie restriction (141-146), also physical activity (147). Whereas a high-fat diet reduces brain BDNF levels and declines cognitive capacity (148). Accordingly, the above mentioned classes of drugs, including calorie restriction mimetics – see, for example, O'Brian and Chu (149) and Nikolova (150) for resveratrol –, require a novel research evaluation as possible pharmaceuticals and nutraceuticals also for cardiometabolic diseases. Meanwhile, NGF and BDNF could be reasonable targets for resveratrol's therapeutic effects in both neuropsychiatric and cardiometabolic diseases. Further, recent findings have discovered that free fatty acids may influence brain development through binding to G protein-coupled receptor-40 expressed in the hippocampus (151). Interestingly, some widely used drugs for cardiometabolic diseases such as the cholesterol-lowering statins (59,152-155) and peroxisome proliferator-activated receptor gamma agonists (156,157) as well as two novel common players, acetylcholine (158,159) and glucagon like peptide-1 (62,160), have been introduced into diabetes-obesity-dementia link (53,63,66-69,72,81,161). Another crossroad of nerves and adipose tissue may be adipose-derived mesenchymal stem cells, which can differentiate into neurons in BDNF-enriched cultures (162), and thus representing useful tool to treat neuropsychiatric disorders. Note that pro-NGF can be cleaved proteolytically at dibasic residues and liberates two other peptides beside NGF, LIP1, a 29 amino acid (aa) peptide, and LIP2, a 38 aa peptide (163,164); their synthetic forms may be targets for new drugs in NGF-related diseases.

The challenge for the future is to understand to what extent the effects of NGF and BDNF are interrelated with regards to their neuro-, synapto-, vasculo- and metabotrophic potentials. Further studies should provide answers to the questions of when and how NGF-BDNF/TrkA,B dysfunction appears and leads to both neuropsychiatric and cardiometabolic diseases. It

is hope that by bringing the datasets together in these seemingly diverse disorders we can help develop a conceptual novel basis for future studies in the field.

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