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REVIEW

Neurotrophic and metabotrophic potential of nerve growth factor and brain-derived neurotrophic factor: Linking cardiometabolic and neuropsychiatric diseases

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Abstract

One of biggest recent achievements of neurobiology is the study on neurotrophic factors. The neurotrophins are exciting examples of these factors. They belong to a family of proteins consisting of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5, NT-6, and NT-7. Today, NGF and BDNF are well recognized to mediate a dizzying number of trophobiological effects, ranging from neurotrophic through immunotrophic and epitheliotrophic to metabotrophic effects. These are implicated in the pathogenesis of various diseases. In the same vein, recent studies in adipobiology reveal that this tissue is the body's largest endocrine and paracrine organ producing multiple signaling proteins collectively termed adipokines, with NGF and BDNF being also produced from adipose tissue. Altogether, neurobiology and adipobiology contribute to the improvement of our knowledge on diseases beyond obesity such as cardiometabolic (atherosclerosis, type 2 diabetes, and metabolic syndrome) and neuropsychiatric (*e.g.*, Alzheimer's disease and depression) diseases. The present review updates evidence for (1) neurotrophic and metabotrophic potentials of NGF and BDNF linking the pathogenesis of these diseases, and (2) NGF- and BDNF-mediated effects in ampakines, NMDA receptor antagonists, antidepressants, selective deacetylase inhibitors, statins, peroxisome proliferator-activated receptor gamma agonists, and purinergic $P2X_3$ receptor up-regulation. This may help to construct a novel paradigm in the field of translational pharmacology of neuro-metabotrophins, particularly NGF and BDNF.

Key words: Neurotrophins; Metabotrophins; Adipose tissue; Adipokines; Disease; Therapy

Core tip: Previously we reviewed an enlarged list of metabotrophins including the adipose-produced nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), leptin and adiponectin as relevant to cardiometabolic, neurological and psychiatric diseases (*Riv Psichiatr* 2009; 44: 79-87). Now we update the growing body of evidence that NGF-BDNF/TrkA, B dysfunction may synergistically leads to both cardiometabolic and neuropsychiatric diseases. This may help to construct a conceptually novel therapeutic approach for future studies in the field of translational pharmacology of NGF and BDNF.

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INTRODUCTION

At the end of the nineteenth century, it was envisaged by Santiago Ramon y Cajal but has not been proven that life at the neuronal level requires trophic support. By a rare combination of scientific reasoning and intuition, the proof was obtained by Levi-Montalcini[1,2], Viktor Hamburger and Stanley Cohen in the early 1950's in the Washington University in St Louis, MO, United States, where the first cell growth factor, namely nerve growth factor (NGF), was discovered. This was embodied in a conceptual framework of the neurotrophic theory, which reveals a pivotal role of effector cells in the control of neuronal differentiation, survival and function via production of NGF. More importantly, Levi-Montalcini's NGF determined a new concept of biology: cells require specific protein signals for differentiation and survival, that is, the general theory of cell growth factors. All this resulted in the discovery of hundreds of growth factors that affect almost all facets of cell biology. Today, NGF and its relative molecules collectively designated neurotrophins are well recognized as mediators of multiple biological phenomena in health and disease, ranging from the neurotrophic through immunotrophic and epitheliotrophic to metabotrophic effects. Thus the evidence indicates that not only at neuroimmune level[1-6], but also at cardiometabolic level life requires NGF and/or brain-derived neurotrophic factor (BDNF)[7-15] (see[16] for NGF sharing structural homology with proinsulin). Consequently, NGF and BDNF are implicated in the pathogenesis of a large spectrum of neuronal and non-neuronal diseases, ranging from Alzheimer's and other neurodegenerative diseases to atherosclerosis and other cardiometabolic diseases. Likewise, recent studies demonstrated the therapeutic potentials of NGF in other diseases including ocular and cutaneous diseases, whereas NGF TrkA receptor antagonists emerged as novel drugs for pain, prostate and breast cancer, and urinary bladder syndromes (reviewed in[17]).

The present review updates evidence for neurotrophic and metabotrophic potentials of NGF and BDNF linking the pathogenesis and therapy of cardiometabolic, neurodegenerative and psychiatric diseases.

NEUROTROPHINS

The discovery of NGF triggered an unprecedented search for a family of related proteins now commonly called neurotrophins. The neurotrophin family of proteins includes NGF, BDNF, neurotrophin-3 (NT-3), NT-4/5, NT-6, NT-7; they mediate their effects via ligation of pan-neurotrophin 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)[1-5]. Noteworthy, transactivation of Trk receptors by G protein-coupled receptor[18] has recently emerged as a novel horizon 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 finding. 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 non-neuronal cells. Thus, it was remarkable to discover that the treatment of newborn rats with NGF caused a systemic increase in the number of mast cells[19]. Today there is compelling evidence that NGF, in addition to its neurotrophic function, enhances survival and activity of a large number of non-neuronal cells including immune cells[3-6], pancreatic beta cells[13], cardiomyocytes[15], endothelial cells[20,21], epithelial cells[22], and adipocytes[14,23]. The secretory proforms of NGF and BDNF, pro-NGF and pro-BDNF[24] respectively, are as active as their respective mature forms. Pro-NGF and pro-BDNF are released 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 pro-BDNF[25,26].

Elucidating the molecular mechanisms that maintain and modify (1) synaptic structure and function; and (2) vascular and metabolic homeostasis 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 (1) immune cells[3-6,19]; (2) blood vessels/angiogenesis[20,21,27,28]; (3) synaptic plasticity and consolidation[29,30] involved in learning and memory[31]; (4) wound healing and tissue repair[27,32];and (5) glucose, lipid and energy "homeodynamics"[2,9-11,33,34]; for neuron-derived neurotrophic factor as a novel secreted hypothalamic protein that regulates food intake, see[35]. Note that insulin[36-39], vascular endothelial growth factor[20,21,28], and the adipokine leptin[40] initially discovered as hypoglycemic, angiogenic, and anorexigenic factors, respectively, also exert neurotrophic effects, and thus may contribute to cognitive processes (for antidepressant effect of leptin, see[41]. Further, cardiometabolic biomarkers such as cholesterol[42,43], insulin[44] and the incretin glucagon-like peptide-1[45], also NGF and BDNF (Tables 1 and 2) are recently found to associate with the development of various neuropsychiatric disorders[46-52], also suggesting that Alzheimer's disease might be viewed as type 3 diabetes mellitus[53] (see also[54-64]). Noteworthy, it has 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[65].

BDNF AND SYNAPTIC PLASTICITY

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

Table 1 Potential role of nerve growth factor and brain-derived neurotrophic factor in the pathogenesis and therapy of diseases

Neurological diseases	Alzheimer's disease, mild cognitive impairment, Huntington's disease, Parkinson's disease, human immunodeficiency virus-associated dementia, amyothrophic lateral sclerosis, multiple sclerosis, epilepsy, Down syndrome, WAGRO syndrome (Wilms tumor, aniridia, mental retardation, genitourinary anomalies, obesity), cluster headache, diabetic neuropathy, diabetic retinopathy, diabetic erectile dysfunction
Psychiatric diseases	Depression, schizophrenia, eating disorders (anorexia nervosa; bulimia nervosa), pervasive developmental disorders (Autism, Rett syndrome, Fragile X syndrome)
Cardiometabolic diseases	Atherosclerosis, hypertension, obesity, type 2 diabetes mellitus, metabolic syndrome, heart failure, myocardial infarction, sudden cardiac death in diabetes mellitus (silent myocardial ischemia in diabetes mellitus), Kawasaki disease
Ocular diseases[1]	Glaucoma, retinitis pigmentosa, diabetic retinopathy, peripheral ulcerative keratopathy, dry eye
Skin diseases[1]	Diabetic wounds, pressure ulcers, chronic vasculitic ulcers
Malignant diseases[1]	Prostate cancer, breast cancer, melanoma
Urinary system diseases[1]	Overactive bladder syndrome, benign prostatic hyperplasia
Chronic pain-associated disorders[1]	Osteoarthritis, low back or spinal injuries, cancer, urological chronic pelvic pain syndromes

[1]For references see[17].

Table 2 Metabotrophic nerve growth factor and brain-derived neurotrophic factor

NGF and BDNF are synthesized and released from pancreatic beta cells
NGF and BDNF exert insulinotropic effect
NGF improves transplantation of Langerhans' islet
BDNF improves glucose and lipid profile in experimental diabetes and obesity
NGF upregulates expression of LDL receptor-related protein
NGF upregulates expression of PPAR-γ
NGF upregulates expression of purinergic $P2X_3$ receptors
NGF exerts antioxidant effect
NGF and BDNF suppress food intake
Mutation of *TrκB* gene results in hyperphagia and obesity
BDNF-deficient mice develop metabolic abnormalities similar to the metabolic syndrome
Atherogenic diet decreases brain BDNF levels
Treatment with NGF improves experimetally-induced cardiac ischemia
Caloric restriction and exercise increases brain BDNF levels and improves the metabolic profile in experimental metabolic syndrome
Tissue levels of NGF are reduced in atherosclerotic coronary artery and in heart failure myocardium
Circulating blood levels of NGF and BDNF are decreased in patients with metabolic syndrome and with acute coronary syndromes

NGF: Nerve growth factor; BDNF: Brain-derived neurotrophic factor.

and memory[29-31]. Today, growing evidence indicates that BDNF and *TrκB* signaling are uniquely important for the process of activity-dependent synaptic plasticity including long-term potentiation and long-term depression[66], dendritic spine density and cytoskeletal dynamics[67,68], underlying various cognitive functions such as learning and memory encoding and storage[69,70]; synaptotrophic activity of neurotrophins was conceptualized more than 10 years ago[71].

In brief, BDNF is an activity-dependent modulator of neuronal structure and function in the adult brain. Localization of BDNF and its *TrκB* 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[30,72].

NGF AND BDNF AS METABOTROPHIC FACTORS (METABOTROPHINS)

Recently, NGF and BDNF are increasingly implicated in the control of carbohydrate and lipid metabolism (reviewed in[9-12]). They are also considered anorexigenic signals in the central control of food intake[33,34,73-76]. Conversely, mice heterozygous for targeted disruption of BDNF show hyperphagia and obesity. The same phenotype was observed in mice with a reduced expression of *TrκB* receptor[77]. 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[78]. Conceptually, NGF and BDNF as well as other neurotrophic factors were for the first time viewed as metabotrophic factors (metabotrophins)[9-11]. Hence, it has been recognized that altered expression of NGF and/or BDNF and their respective Trk receptors may be implicated in the pathogenesis of cardiometabolic and neuropsychiatric diseases[64,79-83], cf[84] (Tables 1 and 2).

SECRETION OF SIGNALING PROTEIN BY ADIPOSE TISSUE

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[85] that focused many studies on the endocrine function of adipose tissue, thus defining a new field of study, adipobiology[8,86,87]. Hence numerous studies results have indeed shifted the paradigm of adipose tissue from simple energy storage to a major endocrine and paracrine organ of the body. 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, angiogenesis, neuronal growth and survival, and lipid, glucose and energy metabolism. Recent transcriptomic and proteomic analyses revealed that more than a hundred adipokines are secreted by adipose tissue cells including leptin, adiponectin, resistin, tumor necrosis factor-α, interleukins, chemokines, renin, angiotensin, visfatin, omentin, retinol-binding protein, plasminogen activator inhibitor-1, pigment epithelium-derived factor, hepatocyte growth factor, transforming growth factor-beta, vascular endothelial growth factor, and Agouti protein[8].

Likewise, adipose tissue cells also secrete NGF, BDNF, ciliary neurotrophic factor and other factors with neurotrophic action (*e.g.*, glial cell line-derived neurotrophic factor, leptin, adiponectin, metallothioneins, and vascular endothelial growth factor) as well as various neuropeptides and pituitary-hypothalamic hormones[87]. 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[88], whereas leptin[40] and adiponectin[89] exerts neuroprotective action, and leptin has antidepressant effect[41].

NGF- AND BDNF-BASED THERAPIES

In cardiometabolic and neuropsychiatric diseases (Tables 1 and 2), NGF- and BDNF-based therapeutic approaches may include (1) applying NGF and/or BDNF[8,27,32,90]; (2) targeting the secretory and signaling pathways using existing or novel drugs[91-94]; (3) *TrkB* transactivation[18]; (4) ampakines, small molecules that stimulate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptors[72,95,96]; (5) selective deacetylase inibitors[55,97,98]; (6) neuroprotective nutrients including calorie restriction[99,100]; and (7) physical activity[101] (see also[102,103]). Likewise, resveratrol[104,105] and olive polyphenols[106] require a novel research evaluation as "neurometabotrophic" nutraceuticals. Interestingly, some widely used drugs such as the cholesterol-lowering statins[42,107] and peroxisome proliferator-activated receptor gamma agonists[108] as well as two novel common players, acetylcholine[109] and glucagon like peptide-1[45,110], have been introduced into cholesterol-diabetes-obesity-dementia link[46-53,57,111]. Last not least, (1) transgenic mice with Alzheimer's disease fed J147, a new compound, in diet improve their memory correlated with reduced soluble levels of beta-amyloid and increased hippocampal levels of NGF and BDNF as well as the BDNF-responsive synaptotrophic proteins Homer-1 and Egr3[112]; (2) ATP-NGF complex, but not NGF itself, appears to be the active neuroprotective factor[113]; (3) NGF is related to an enhanced expression of the purinergic P2X(3) receptor[114], and (4) metformin, a widely prescribed drug for type 2 diabetes, may exert neuroprotective effect via increasing BDNF level[115].

Moreover, neurodegenerative hypothesis of depression is based on decreased hippocampal level of BDNF, NGF, NT-3 and GDNF in patients with depression. Accordingly, biogenic amine-based antidepressants as well as glutamate-based drugs such as the NMDA antagonist ketamine and a combination of ketamine and AMPA agonist increase synthesis of BDNF and activate its *TrkB* signaling pathway, and the antidepressant effects of these molecules are abolished in BDNF deficient mice[116-120]. Further, (1) adipose-derived mesenchymal stem cells, which can differentiate into neurons in BDNF enriched cultures[121]; and (2) BDNF-producing haematopoietic cells, which can control appetite and energy homeostasis by migrating to the brain[122], may represent useful tools to treat neuropsychiatric and cardiometabolic disorders respectively.

Collectively, 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 additional answers to the question of how NGF-BDNF/TrkA, B dysfunction may synergistically lead to both neuropsychiatric and cardiometabolic diseases. This may help to construct a conceptually novel therapeutic basis for future studies in the field of translational pharmacology of NGF and BDNF.

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