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The metabotrophic NGF and BDNF: an emerging concept

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ABSTRACT

The field of neurotrophins, particularly, nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), has witnessed a number of breakthroughs in recent years. There is evidence now that NGF and BDNF mediate multiple biological phenomena, ranging from the Rita Levi-Montalcini's neurotrophic through immunotrophic to epitheliotrophic and nociceptive effects. In 2003 we have enriched the "NGF-ome" with one more expression presented in our concept of NGF metabotrophicity, also that of BDNF. This envisages that these two factors may operate as metabotrophins, that is, involved in the maintenance of cardiometabolic homeostasis (glucose and lipid metabolism as well as energy balance, cardioprotection, and wound healing). Recent results also demonstrated that the circulating and/or tissue levels of NGF and BDNF are altered in cardiometabolic diseases (atherosclerosis, obesity, type 2 diabetes, metabolic syndrome, and type 3 diabetes). Altogether, a hypothesis of metabotrophic deficit due to the reduction of NGF/BDNF availability and/or utilization was raised, and implicated in the pathogenesis of cardiometabolic diseases. This may cultivate a novel pathogenic and therapeutic thinking for these diseases.

Key words

NGF • BDNF • Metabotrophins • Cardiometabolic diseases

Introduction

Discovered in 1951, "the submerged areas of the NGF iceberg loom very large", Rita Levi-Montalcini stated in her Nobel prize lecture reviewing 35 years of research on nerve growth factor (NGF) (Levi-Montalcini, 1987). Paraphrasing Emily Dickinson's poem *The brain is wider than the sky*, this may sound like "the NGF is wider than the neuron". Indeed, growing body of evidence indicates that not only neuronal life (Levi-Montalcini, 1987, 2003; Levi-Montalcini et al., 1996), but also life of many other cells (Aloe and Calzà, 2004; Fiore et al., 2009) depend on the trophic support of NGF and other neurotrophins including brain-derived neurotrophic factor (BDNF) (Table 1).

Here we summarize our recent concept of metabotrophic potentials of NGF and BDNF, implicating their deficit in the pathobiology of cardiometabolic diseases (CMD) (Table 2).

Cardiometabolic diseases

Recent studies provide evidence that morbid obesity is a major evil of human health, because plays a pivotal role in the development of CMD as well as non-alcoholic steatohepatitis, obstructive sleep apnea syndrome, and polycystic ovary syndrome. Thus CMD are among the major physical, social and economic burdens of *Homo sapiens recens*, globally. The World Health Organization has predicted

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Table 1. - Members of the protein family of neurotrophins.
NGF
Pro-NGF
LIP-1, LIP-2*
BDNF
Pro-BDNF
Neurotrophin (NT-3, NT 4/5, NT-6, NT-7)
* These derived from the pro-NGF: LIP1 is a 29-amino acid peptide, LIP2 is a 38-amino acid peptide (Dicou, 2006). They affect both PC12 cells and brain cholinergic enzymes in a NGF-like manner.

a "globesity epidemic" with more than one billion adults being overweight (BMI over 25 kg/m^2) and at least 400 million of these being clinically obese (BMI over 30 kg/m^2). Moreover, CMD are associated with cognitive and mood disorders including Alzheimer's disease and depression (Frisardi et al., 2010; de la Monte and Wands, 2008; Milionis et al., 2008; Chaldakov et al., 2009a). Arguably, we have learned more about the molecular control of food intake and energy homeostasis, particularly, the role played by adipose tissue in the pathogenesis of various diseases, including CMD. Since the adipose-secreted hormone leptin was discovery in 1994, increasing evidence has been demonstrating that adipose tissue is a very active endocrine and paracrine organ (Chaldakov et al., 2003a; Renes et al., 2009), also producing NGF and BDNF (Chaldakov et al., 2001a, 2004; Trayhurn and Wood, 2004; Sornelli et al., 2009; Duhne et al., 2009). Cumulatively, such an adipocentric approach (Chaldakov et al., 2003a, 2004; Catalán et al., 2006; Chaldakov et al., 2007; Duhne et al., 2009, Wójcicka et al., 2011) has integrated the traditional cardiovascular risks (age, sex, smoking, hypertension, dyslipidemia, homocysteinemia) and abdominal obesity and related features of the metabolic syndrome, hence, global cardiometabolic risk (Després et al., 2008; Shimabukuro 2009). For instance, the Italian "Progetto CUORE" collected a database of risk factors from studies started between the mid 1980's and 1990's and followed up the participants for cardiovascular mortality and morbidity to estimate the Italian global cardiovascular risk (first coronary or cerebrovascular event) for men and women (Donfrancesco et al. 2010, also see www.cuore.iss.it).

"NGF-OME", or the multitrophic NGF

At the beginning of this century the Human Genome Project was finalized estimating over 30,000 genes encoding more than 100,000 functionally distinct proteins. As happened usually, one solved problem delivered many unsolved ones. Thus in the postgenome time, many "-ome" projects have emerged including proteome, transcriptome, interactome, metabolome, adipokinome, connectome. In this vein, the cumulative data of NGF's multitrophic potential is herein designated "NGF-ome" (reminding "Ome sweet ome", the title of review article

Table 2. - Selected list of cardiometabolic diseases.
Atherosclerosis
Hypertension
Obesity
Type 2 diabetes mellitus
Metabolic syndrome
Metabolic-cognitive syndrome*
Type 3 diabetes mellitus**
* See Frisardi et al., 2010. ** Recent hypotheses suggest that Alzheimer's disease is type 3 diabetes (de la Monte and Wands, 2008; Milionis et al., 2008).

by Lichtman and Sanes published in *Curr Opin Neurobiol* 18: 346-353, 2008).

As often occurs, the framework of an initial conception of the role of a newly discovered biomolecule extends in the light of emerging findings. This was also the case for NGF. During some 25 years after its discovery, there have been few reasons given to indicate that NGF acts on nonneuronal cells. Thus, in 1975, Aloe and Levi-Montalcini have made an experiment demonstrating that treatment of newborn rats with NGF caused an increase in the number of mast cells in various organs. These findings (Aloe and Levi-Montalcini, 1977) have triggered the study on neuroimmune interaction, leading to today's accumulation of evidence that NGF is not only for neuronal life.

Cumulatively, studies in the past three decades have revealed that the *neurotrophins* NGF and BDNF are not only stimulating for nerve growth and survival, but also exert trophic effects over (i) immune cells, acting as *immunotrophins* (Aloe and Levi-Montalcini, 1977; Leon et al., 1994; Fainzilber and Carter, 2002), (ii) keratinocytes, enterocytes, prostate and breast epithelial cells, acting as *epitheliotrophins* (see Aloe and Calzà, 2004), (iii) endothelial cells, acting as *angiogenic factors* (Lazarovici et al., 2006), and (iv) glucose, lipid and energy homeostasis, pancreatic beta cell and cardiovascular system, and thus designated *metabotrophins* (from Greek *metabole*, and *trophe*, nutrition, means "nutritious for metabolism") (Chaldakov et al., 2003b, 2007, 2009a).

Implication of NGF and BDNF in cardiometabolic diseases: results of a dream

During my student life at the Medical University, Varna, Bulgaria, I used to work four years (1962-1966) as research associated at the Department of Pharmacology. It was that period of time when I for the first time "met" Professor Rita Levi-Montalcini, reading her first papers on NGF. Since then I have being infected by this talented molecule, and thought how to reach her Institute in Rome, Italy. Although some colleagues told me that it is a very much difficult pursuit, I continued to believe more in the art of dream as presented by Emily Dickinson's *To Make a Prairie* (*To make a prairie it takes a clover and one bee, / One clover, and a bee, / And revery. / The dream alone will do, / If bees are few*).

Although in 1986-1987 (in Japan) as well as in 1991-1992 (in England) I liked to study the effect of NGF on vascular smooth muscle cells in culture (see Donovan et al., 1995) and the presence of NGF in perivascular (adventitial) mast cells (see Aloe and Montalcini, 1977), the host scientists have ignored these hypotheses. But not my dream! On its road, I, in 1995 contacted Luigi Aloe and invited him to contribute to *Biomedical Reviews*, an international journal of cell biology of disease. In 1997 I have applied for NATO-CNR Research Fellowship, which required acceptance letter by the host institution. Obviously, my dream asked Luigi Aloe about and he provided me with such a letter, consequently awarded the Fellowship. And in June 1998 appeared in the Institute of Neurobiology, CNR, Rome. During this first four months there as well as almost each year further on, I was pleased, more importantly, honored of meeting *in vivo* many times the Nobel laureate Rita Levi-Montalcini; the road she traveled "from Turin to Stockholm via St. Louis and Rio de Janeiro" (Levi-Montalcini, 2000) being a charismatic model for many generations pursuing scientific research.

NGF, p75NTR and mast cells in human coronary atherosclerosis

In 2001 (Chaldakov et al., 2001a,b), we have, for the first time, published results about altered amount of NGF in human coronary vascular walls affected by advanced atherosclerosis, investigating simultaneously the expression of NGF and its $p75^{NTR}$ also in the surrounding subepicardial adipose tissue (SEAT) and in the adjacent myocardium. The content (pg/g) of NGF was measured by a highly sensitive two-site immunoenzymatic assay (ELISA) which recognizes human and murine NGF and does not cross react with BDNF. We found that the amount of NGF in atherosclerotic coronary wall was significantly reduced as compared to control, non-affected coronaries. This was accompanied by an elevated amount of NGF in SEAT, whereas NGF amount in the adjacent myocardium was comparable with that of controls (Chaldakov et al. 2001a; also see Fig. 1 in Chaldakov et al., 2004). These data represent the first quantitative evidence for NGF

in both human coronary vascular wall and SEAT, and strongly suggest that NGF is produced locally. Likewise, that NGF synthesis is processed in a tissue specific manner in different compartment of the human cardiovascular tissue. Moreover, we, for the first time, focused a NGF study to the significance of SEAT in human coronary atherosclerosis.

To further assess whether NGF is locally and differentially produced and to identify possible NGF-responsive areas, parallel immunohistochemical analyses of coronaries were undertaken. The results revealed that coronary vascular wall, particularly the adventitia, also SEAT, expressed a stronger $p75^{NTR}$ immunoreactivity in atherosclerotic compared to control arteries.

Since mast cells (MC) are known to be a cellular component of the coronary artery, and since MC not only respond to NGF action (Aloe and Montalcini, 1977), but also produce NGF (Leon et al., 1994), we investigated the presence and distribution of MC in atherosclerotic and control coronaries. In atherosclerotic vessels, MC (number/mm^2) were significantly increased and found mainly in both adventitia and SEAT (Chaldakov et al. 2001a; also see Fig. 1 in Chaldakov et al., 2004). Whether these MC populations, via their potential to synthesize and release NGF, attempt to compensate the reduced NGF in the coronary wall, remains to further be studied.

NGF and BDNF in human metabolic syndrome

In our CMD pursuit, we have published data of reduced circulating levels of NGF and BDNF in patients with *advanced stage* of metabolic syndrome as compared with healthy subjects (Chaldakov et al., 2001b; reviewed in Chaldakov et al., 2004). Contrary, the circulating levels of NGF and BDNF are significantly elevated in patients with *early stage* of metabolic syndrome (our unpublished data). Whether the metabotrophic reserve of the organism is discharged with the progression of metabolic syndrome, remains to be elucidated.

NGF and BDNF in acute coronary syndromes

In an attempt to "close" the metabotrophic "loop" in CMD, we have measured circulating levels of NGF and BDNF in patients with acute coronary syndromes, and found they are significantly reduced (Manni et al., 2005). Another own study revealed altered levels of NGF in pancreas and brain in streptozotocin-induced diabetes (Sposato et al., 2007). Recently, we found that in response to experimental stress or diabetes, the amount of NGF and BDNF was altered in white and brown adipose tissue (Sornelli et al., 2009), adding a further evidence for adipose-derived neurotrophic factors (Chaldakov et al., 2010)

Altogether, we have introduced the concept of metabotrophic potentials of NGF and BDNF, these being involved in the maintenance of cardiometabolic homeostasis (Chaldakov et al., 2003b; reviewed in Chaldakov et al., 2007, 2009a,b).

Further proof-of-concept

Selected proof-of-metabotrophic-concept examples derived by other laboratories are: (i) pancreatic beta cells secrete NGF and express its receptor, tyrosine-kinase A (TrkA), these findings being implicated in the pathogenesis of diabetes mellitus (Rosenbaum et al., 1998; Larrieta et al., 2006; Duhne et al., 2009; Cabrera-Vásquez et al., 2009), (ii) systemic and/or local levels of the major metabotrophins, NGF and BDNF, are altered in CMD (Molteni et al., 2002; Suwa et al., 2006; Geroldi et al., 2006; Bulló et al., 2007; Krabbe et al., 2007; Yamanaka et al., 2008; Fujinami et al., 2008; Golden et al., 2010; Wang et al., 2010), including acute coronary syndromes (Ejiri et al., 2005), and (iii) mutations affecting *Bdnf* gene (encoding BDNF) in mice or *Ntr2k2* gene (encoding the high-affinity BDNF receptor TrkB) in patients are associated with hyperphagia and severe obesity (see Han et al. 2006; Lebrun et al., 2006). Metabotrophic effects of NGF and BDNF are summarized in Table 3.

The new pipeline and the near future

As indicated above, a hypothesis of metabotrophic deficit of NGF and BDNF in the pathogenesis of CMD has been raised. It may open new windows for the search of *exogenous* metabotrophic factors, such as (i) small molecules/"drugs" boosting secretory and/or signaling pathways of NGF and BDNF (Chaldakov et al., 2009a,b; also see Lazarovici et

Table 3. - Metabotrophic effects of NGF and BDNF.
NGF shares homology with proinsulin
NGF/BDNF are produced by pancreatic beta cells and exert insulinotropic effect
NGF/BDNF are trophic factors for pancreatic beta cells, also improve beta cell transplantation
NGF up-regulates expression of LDL receptor-related protein
NGF exerts anti-lipolytic, niacin-like effects
NGF inhibits glucose-induced down-regulation of caveolin-1
NGF improves antioxidant homeostasis
NGF/BDNF decrease food intake
NGF supplementation rescues silent myocardial ischemia in diabetes mellitus*
Healthy lifestyle increases brain and/or circulating levels of NGF/BDNF
Atherogenic risk factors (e.g., high fat diet) decrease NGF/BDNF levels
NGF improves diabetic erectile dysfunction**
* See Ieda and Fukuda, 2009, also Abe et al., 1997; note: cf. Wernli et al., 2009 for the nerve sprouting hypothesis of sudden cardiac death. ** Chen et al., 2007. References for other items are listed in Chaldakov et al., 2009a,b.

al., 2006), 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 both neurotrophic and metabotrophic effects (Perry et al., 2002). Recombinant human NGF (Colangelo et al., 2005) requires special attention also in CMD.

The future challenge is therefore to cultivate a metabotrophic, neuroadipologic (see Chaldakov et al., 2010) and nutrigenomic thinking about how we can make NGF/BDNF secretion and signaling work for the benefit of human's health. Teleologically, this may help humans to enjoy both physical and mental health-related quality of life.

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