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Review

The NGF saga: From animal models of psychosocial stress to stress-related psychopathology

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ABSTRACT

The role of the neurotrophins Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF) has been expanding over the last years from trophic factors involved in brain growth and differentiation, to much more complex messengers, involved in psycho–neuro-endocrine adaptations. Much of this research stems from a series of studies inspired by the life-long work of the Nobel laureate Rita Levi-Montalcini. A new field of research started when NGF was found to be released in the bloodstream as a result of psychosocial stressors in male mice. Subsequent studies have shown that, in humans, highly arousing situations also result in increased blood levels of NGF, underlying the unique role of this neurotrophin, compared to other neuroendocrine effectors, and its sensitivity to environmental variables endowed by a social nature. Data are reviewed to support the hypothesis that this neurotrophic factor, together with BDNF, could be involved in the neurobiological changes underlying physiological and pathological reactions to stress that can result in increased vulnerability to disease in humans, including risk for anxiety disorders, or in the complex pathophysiology associated with mood disorders. Indeed, numerous data indicate that neurotrophins are present in brain hypothalamic areas involved in the regulation of hypothalamic-pituitary–adrenal axis, circadian rhythms and metabolism. In addition, there is now evidence that, in addition to the nervous system, neurotrophins exert their effects in various tissue compartments as they are produced by a variety of non-neuronal cell types such as endocrine and immune cells, adipocytes, endothelial cells, keratinocytes, thus being in a position to coordinate brain and body reactions to external challenges. Aim of this review is to discuss the evidence suggesting a role for neurotrophins as multifunctional signaling molecules activated during allostatic responses to stressful events and their involvement in the complex pathophysiology underlying stress-related psychopathology.

1. Introduction

Neurotrophic factors (NTs) are growth factors that act directly on neurons to support their growth, differentiation and survival. NTs belong to several families of structurally and functionally related molecules including the nerve growth factor (NGF) superfamily, the glial cell line-derived neurotrophic factor (GDNF) family, and the neurokine or neuropoietin superfamily [1]. The NGF superfamily includes NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5) and neurotrophin-6 (NT-6). NGF was discovered in the 1950s as a key player in target-mediated regulation of peripheral innervation [2]. The concept of cell death was first formulated in the course of transplantation and ablation experiments performed by Victor Hamburger and Rita Levi-Montalcini [3,4]. These studies revealed that the development of the nervous system is characterized by a remarkable amount of neuronal death and that neurons require an adequate supply of trophic factors from the environment for survival and development (Fig. 1). These studies identified the target as key to the development of neurons and suggested that it determined the size of its neuronal center by regulating cell death among neurons. In particular, the target tissue controls the innervating neurons making the neurotrophin available only in limited amounts. This results in the selection only of those neurons which have established the best connections with the target tissue, thereby optimizing the number of nerve cells required for target innervation. Successively, a direct demonstration of the involvement of specific factors in this process was obtained by injecting antibodies to NGF into perinatal mammals: the result was a complete destruction of peripheral sympathetic and sensory neurons [5]. Conversely, injection of NGF could rescue neurons that would be normally eliminated during development (for reviews, see [6,7]). Subsequent studies have demonstrated that, during nervous system development, NGF is released by the target tissue, taken up in responsive neurons by receptor-mediated endocytosis and transported retrogradely to the cell body where it exerts its trophic/differentiative effects [2,7–9].

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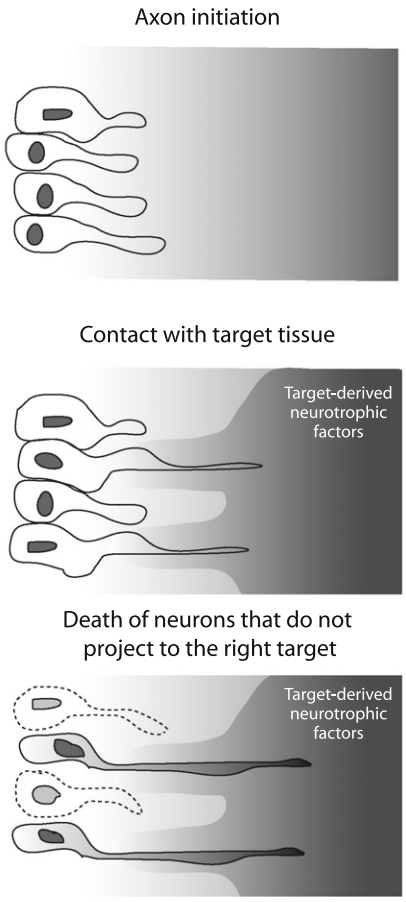

Fig. 1. Neuronal cell death is a regressive phenomenon that is widespread in the developing nervous system. It serves to provide for the survival only of those neurons with functionally appropriate contacts. The neurotrophic theory of cell death suggests that target tissues release the neurotrophic factor, which is taken up by receptor-mediated endocytosis and transported back to the cell body, promoting cell survival.

Since these first investigations on target-controlled neuronal survival, NGF has been one of the most thoroughly studied NTs, regulating the survival, development and trophism of specific neuronal populations in the peripheral and central nervous system [6] (Fig. 2). NGF, as all other NTs, binds with low affinity to a membrane spanning receptor molecule, known as the low-affinity NGF receptor (p75NTR) [9], a member of the TNF receptor family. P75NTR displays extracellular and transmembrane domains, but does not possess a cytoplasmatic kinase domain for signal transduction. The trophic effect of all neurotrophins, including NGF, requires binding to recognition molecules of the tyrosine kinase (Trk) family of receptors [9] activated in response to neurotrophin binding, although Trk-independent signal transduction through p75NTR can also occur [10]. NGF preferentially binds to TrkA, BDNF and NT-4/5 to TrkB and NT-3 to TrkC. Trk receptors display intracellular, transmembrane and extracellular domains, and transduce neurotrophin signaling through autophosphorylation, in turn resulting in increased tyrosine phosphorylation of cellular proteins [9,11]. Intracellular signaling cascades activated by Trk receptors include the Ras/ERK pathway, the phosphatidylinositol-3-kinase (PI3K)/Akt kinase pathway as well as the phospholipase Cγγ (PLCγγ) cascade [12]. While the p75NTR can cause apoptosis in a variety of systems, when co expressed with the appropriate Trk proteins, it can modify their ligand-binding activity, dose-responsiveness and kinase activity, leading to increased survival, neurite outgrowth and synaptic plasticity [13–17]. Some evidence indicates that NGF and BDNF may be secreted as pro-peptides. Interestingly, proneurotrophins often have biological effects that oppose those of mature neurotrophins, having a high affinity for p75NTR and inducing apoptosis in cultured neurons [18]. This piece of data suggests that the balance between cell survival and cell death might depend upon the relative quantity of mature vs. pro-NTs available to cells expressing TRK and p75NTR receptors.

The NGF isolated and purified from male mice submaxillary glands as a 2.5S form, is a dimer of two identical subunits linked together by non-covalent bonds and with a molecular weight of about 26 kD [19]. The amino acid sequence and primary structure of this NT has been characterized and indicates that NGF is a highly conserved molecule sharing a great homology between different species. [1,19]. There is evidence that Trk signaling mechanisms may be highly conserved between vertebrates and invertebrates [20]. While in the periphery this NT was first recognized for its action on the sympathetic ganglia, in the adult brain the highest levels of NGF are found in hippocampus, cortex and olfactory regions, which represent targets for basal forebrain cholinergic neurons [21,22]. NGF acts as a trophic factor for these neurons since its administration in vivo increases the levels of choline acetyltransferase [23,24] while rescuing from death basal forebrain neurons following transaction of the septo-hippocampal pathways [25]. BDNF, purified from pig brain [26], is more abundantly expressed and widely distributed than NGF in the CNS, acting as a trophic factor for dopaminergic neurons of the substantia nigra/ventral mesencephalon, in addition to cholinergic ones [27]. In addition to being retrogradely transported, BDNF is also anterogradely transported in the CNS and acts as both a target-derived neurotrophic factor and an autocrine/paracrine modulator [28]. At the synapse BDNF has been shown to play an important role in long-term potentiation (LTP) [29–31]. As an activity-dependent NT, with receptors densely distributed throughout the CNS, including the limbic system and midbrain [32,33], BDNF clearly has emerged as a major regulator of synaptic plasticity [34,35].

In addition to the nervous system, NTs exert their effects on various other tissue compartments [36–43]. The largest amount of NGF is produced in the salivary glands of adult male mice, which are the largest and best available source of this NT. Smaller concentrations of this NT can be found in snake venom, guinea pig prostate, the seminal fluid of guinea pigs and bulls, in the human skin and in numerous tissues and body fluids [6]. The presence of both NGF and BDNF in CNS limbic areas involved in mood and cognition and in the orchestration of neuroendocrine responses and circadian activities, as well as in cells of the immune and endocrine system, indicates a much wider role for these NTs than previously hypothesized and suggests that they might function as intercellular messengers or even humoral factors to help regulate endocrine responses to stress [37,44–48].

1.1. Neurotrophins, brain plasticity and psychiatric disorders

During development, NTs regulate naturally occurring cell death, synaptic connectivity, fiber guidance and dendritic morphology [49]. In addition, NTs contribute to brain plasticity, being involved in activity-dependent neuronal function [34,44,49,50].

Several lines of evidence suggest that reduced NTs signaling in the adult brain may be implicated in the pathophysiology of psychiatric disorders, such as depression [50–54]. NTs themselves do not control mood, but they play an important functional role in the modulation of networks which ultimately determine how a plastic change influences mood [51]. It has been, in fact, hypothesized that successful antidepressant treatments promote activity-dependent neuronal plasticity by activating NTs systems, possibly inducing proliferative or survival effects on neural stem cells [50].