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Review

Brain-derived neurotrophic factor and TrkB receptor in experimental autoimmune encephalomyelitis and multiple sclerosis

Lorenzo De Santi [a,*], Pasquale Annunziata [b], Edoardo Sessa [a], Placido Bramanti [a]

[a] IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy
[b] Department of Neurological, Neurosurgical and Behavioural Sciences, University of Siena, Siena, Italy

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ABSTRACT

The interaction between the immune and nervous systems can be both detrimental and beneficial. Experimental autoimmune encephalomyelitis (EAE) is an animal model of autoimmune demyelination that histologically and clinically mimics multiple sclerosis (MS). Myelin-reactive T cells produce and release brain-derived neurotrophic factor (BDNF) directly in the central nervous system, which stimulates tissue repair after traumatic injury. In EAE and MS, T cells in the vicinity of actively demyelinating lesions express BDNF, suggesting a neuroinflammatory reaction that is designed to limit brain damage and contribute to the repair process. Despite some evidence supporting MS therapies that enhance BDNF production by immune cells, no published reports have actually demonstrated that increased BDNF production can substantially ameliorate the clinical symptoms of MS. BDNF binds to a small subset of peripheral T cells that express TrkB, which is the BDNF receptor. This binding confers a partial resistance to apoptosis upon T cell activation, which could underlie the chronic nature of the inflammatory process.

Here we will review the main aspects of BDNF and TrkB receptor involvement in neuroprotective autoimmunity in both EAE and MS. We will also discuss the latest findings with respect to the role of the BDNF/TrkB axis in regulating the survival of autoreactive T cells, with a focus on potential selectively immunomodulating strategies that may favor neuroprotection in MS.

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that is characterized by episodes of acute neurological dysfunction during the relapsing–remitting (RR) phase, which can lead to partial or full recovery [1]. T cells infiltrating the CNS

* Corresponding author. IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, Contrada Casazza, 98124 Messina, Italy. Tel.: +39 090 3656756; fax: +39 090 3656750.
E-mail address: lorenzo.desanti@centroneurolesi.it (L. De Santi).

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cause myelin disruption and axonal damage [2]. These inflammatory events primarily target the myelin sheaths, which result in plaques of demyelination. These demyelinated axons are susceptible to injury even during the first stage of lesion formation [3]. During the progressive phase, MS pathology is dominated by microglial activation and axonal degeneration [4,5]. These injuries are independent of relapses, and their accumulation leads to progressive, permanent disability. The main goals of early intervention in MS are the treatment of inflammation and the prevention of axonal loss and cerebral atrophy [6]. Although the current MS immunomodulating and immunosuppressive treatments do control inflammation, their neuroprotective abilities have fallen short so far. The desire to prevent or reduce the irreversible progression of disability has spurred research on alternative therapeutic strategies. Inflammatory responses that target the CNS have shown not only detrimental, but also neuroprotective, effects in animal models [7]. The constellation of these effects is termed "neuroprotective autoimmunity" [8]. One possible method of intervention could involve shaping the autoimmune responses to focus on the beneficial, as opposed to the deleterious, components. Support for the reparative functions of the inflammatory response has been demonstrated in pathological conditions that involve the CNS, including trauma, stroke, MS, infection and the neurodegenerative diseases, such as Alzheimer's and Parkinson's [9]. One candidate molecular effector of neuroprotective autoimmunity is brain-derived neurotrophic factor (BDNF), which is a potent neurotrophin that promotes neuronal growth and survival. BDNF is produced by immune cells in peripheral blood and in MS lesions [10,11]. Furthermore, *in vitro* studies have shown that glatiramer acetate (GA), which is a currently approved treatment for MS, can increase the production and release of BDNF by T helper (Th) cells [12]. Although GA-specific Th1, Th2 and Th0 cells are all involved in BDNF production, larger *in vitro* studies have suggested that the Th2 cells have the predominant role [13]. Thus, GA could potentially have both anti-inflammatory and neuroprotective roles in MS therapy, by enhancing endogenous neurotrophic support. BDNF has been recently found to exert a beneficial effect on experimental autoimmune encephalomyelitis (EAE), which is an animal model that clinically and histopathologically mimics MS. The injection of BDNF-transfected bone marrow stem cells reduced demyelination and favored remyelination, which, in turn, delayed the onset and reduced the severity of clinical EAE symptoms [14]. BDNF has not yet been demonstrated to have a measurable effect on the clinical progression and quantitative magnetic resonance imaging (MRI) parameters, such as lesion load and brain atrophy, in MS [15].

In this review, we summarize the basic characteristics of neurotrophins and their receptors, with a focus on their potential roles in neuroinflammation and neuroprotective autoimmunity. In addition, we provide an update on the role of BDNF and its high-affinity full-length BDNF receptor, TrkB-TK, in the immune system, with respect to the immunopathogenesis of MS and EAE.

2. BDNF and neurotrophins: molecular and structural aspects

Nerve growth factor (NGF), a small protein with anti-apoptotic and trophic properties was the first known neurotrophin [16]. In 1989, BDNF was cloned [17]. In 1990, Barde and Lindsay discovered other proteins, neurotrophin 3 and neurotrophin 4/5, with structure and function similar to that of NGF. All these proteins are homodimers with a duplicate site for receptor binding and are all denoted as neurotrophins [16]. Recently, two other families of proteins showing neurotrophic properties have been described. The first family consists of the glial cell line-derived neurotrophic factor (GDNF), neurturin, artemin and persephin, the GDNF family ligands. The second family consists of the ciliary neurotrophic factor (CNTF) and the leukemia inhibitory factor (LIF), the neuropoietic cytokines (Table 1) [18]. All of these molecules show trophic effects not only during neural development [19] but also on mature neurons, especially after insults to the CNS [18,20]. Neurotrophins are synthesized as precursors, and mature molecules are produced by both intra- and extracellular cleavage [21]. Neurotrophins bind to a dual receptor system: the high-affinity tropomyosin-related kinase (Trk) receptors and the low-affinity p75 neurotrophin receptor ($p75^{NTR}$). The high-affinity receptor for NGF, TrkA, was the first tyrosine kinase receptor to be identified and characterized [22,23]. Subsequently, the high-affinity receptor for BDNF and NT-4/5, TrkB, was identified [24]. Trk receptors contain an extracellular domain with three leucin-rich motifs and two immunoglobulin-like C2 type domains (Ig-C2), a transmembrane domain, and an intracytoplasmic domain with kinase activity. Ig-C2 is responsible for ligand binding and for stabilization of the receptor, in order to avoid spontaneous dimerization and activation in the absence of neurotrophin binding [25]. Mutations altering Ig-C2 domain structure allow spontaneous receptor activation, as what occurs in neoplasias [26]. TrkB exists in three isoforms as the result of alternative splicing: the full-length signal-transducing receptor (gp145trkB or TrkB-TK), the truncated receptor (gp95trkB or TrkB-T1) lacking the intracytoplasmic catalytic domain, and a novel isoform lacking the tyrosine kinase domain but containing an Shc binding site, expressed only in brain [24,27,28]. When BDNF binds, dimerization and trans-autophosphorylation of the carboxyl-terminal intracellular domain of TrkB-TK occur. Several intracellular signaling pathways are triggered, involving Ras/Rap-MAPK, PI13K-Akt and PLCγ-PKC cascade. These pathways promote cell survival, differentiation, neurite outgrowth and plasticity on neurons (reviewed by Arevalo and Wu) [25]. In contrast, the Trk-T1 isoform induces inhibitory effects on BDNF-mediated signaling in neurons (Fig. 1) [29].

Table 1
Classification of neurotrophins and protein growth factors.

Neurotrophins	GDNF family ligands	Neuropoietic cytokines
NGF	GDNF	CNTF
BDNF	Neurturin	LIF
NT-3	Artemin	
NT-4/5	Persephin	

BDNF: brain-derived neurotrophic factor; CNTF: ciliary neurotrophic factor; GDNF: glial cell line-derived neurotrophic factor; LIF: leukemia inhibitory factor; NGF: nerve growth factor; NT-3: neurotrophin 3; NT-4/5: neurotrophin 4/5.

$p75^{NTR}$ is a receptor in the TNF family that contains a cysteine-rich domain and a cytoplasmic death domain [30]. Activation of $p75^{NTR}$ has been associated with multiple complex cell-specific functions, ranging from cell survival and proliferation to apoptosis [25]. In particular, apoptosis is mediated by $p75^{NTR}$ with the activation of sortilin, a co-receptor protein binding to pro-BDNF [31]. In addition, $p75^{NTR}$ can modulate the affinity of BDNF/TrkB interactions. $p75^{NTR}$ is also implicated in the interactions between immune cells and inflamed brain endothelium. $p75^{NTR}$ knock-out mice show greater clinical severity of EAE [32] and altered cellular composition of inflammatory infiltrates with T cell enrichment [33]. While human brain endothelial cell cultures produce active BDNF [34], they do not express TrkB and $p75^{NTR}$ *in vitro* [35].

In summary, pro-neurotrophins activate $p75^{NTR}$ causing apoptosis, as demonstrated *in vitro* for neuronal cultures [36], while mature neurotrophins, including BDNF, activate TrkB with pro-survival effects [37].

3. Expression and biological function of BDNF and TrkB-TK in the immune system

For several years, nerve tissue has been considered to be the only source of BDNF and other neurotrophins. In 1999, the production of BDNF by human T and B cells and macrophages was demonstrated *in vitro* (10). BDNF was found to be expressed by both CD4+ (Th1 and Th2) and CD8+ T cells. BDNF bioactivity has been demonstrated in neuronal cultures, with its expression enhanced upon stimulation. BDNF has also been found in cells that form perivascular infiltrates and in the invading lesions of acute disseminated encephalomyelitis [10] and MS