Arch. Immunol. Ther. Exp. (2013) 61:95–105
DOI 10.1007/s00005-012-0211-0

REVIEW

Brain-Derived Neurotrophic Factor in Neuroimmunology: Lessons Learned from Multiple Sclerosis Patients and Experimental Autoimmune Encephalomyelitis Models

Fred Lühder · Ralf Gold · Alexander Flügel · Ralf A. Linker

Received: 22 June 2012 / Accepted: 20 December 2012 / Published online: 3 January 2013

Abstract The concept of neuroprotective autoimmunity implies that immune cells, especially autoantigen-specific T cells, infiltrate the central nervous system (CNS) after injury and contribute to neuroregeneration and repair by secreting soluble factors. Amongst others, neurotrophic factors and neurotrophins such as brain-derived neurotropic factor (BDNF) are considered to play an important role in this process. New data raise the possibility that this concept could also be extended to neuroinflammatory diseases such as multiple sclerosis (MS) where autoantigen-specific T cells infiltrate the CNS, causing axonal/neuronal damage on the one hand, but also providing neuroprotective support on the other hand. In this review, we summarize the current knowledge on BDNF levels analyzed in MS patients in different compartments and its correlation with clinical parameters. Furthermore, new approaches in experimental animal models are discussed that attempt to decipher the functional relevance of BDNF in autoimmune demyelination.

Keywords Experimental autoimmune encephalomyelitis (EAE) · Neurotrophins · Brain-derived neurotropic factor (BDNF) · Multiple sclerosis (MS)

F. Lühder (✉) · A. Flügel
Department of Neuroimmunology,
Institute for Multiple Sclerosis Research
and The Hertie Foundation, University
Medical Center Göttingen,
Waldweg 33, 37073 Göttingen, Germany
e-mail: fred.luehder@med.uni-goettingen.de

R. Gold
Department of Neurology at St. Josef-Hospital/Ruhr-University
Bochum, Gudrunstr. 56, 44791 Bochum, Germany

R. A. Linker
Department of Neurology, Friedrich-Alexander University
Erlangen, Schwabachanlage 6, 91054 Erlangen, Germany

Introduction

Multiple sclerosis (MS) is a neurological disease which preferentially affects young adults between 20 and 40 years of age and is considered to be the foremost cause of disability of non-traumatic origin in this age group (Sospedra and Martin 2005). Although its etiology and pathogenesis is still incompletely understood, there is consensus that an autoimmune component plays a predominant role in most cases (Lutton et al. 2004; Noseworthy et al. 2000). Consequently, current and future therapeutic approaches including glucocorticoids, interferon (IFN)-β, glatiramer acetate (GA), natalizumab, mitoxantrone, rituxan, alemtuzumab and new oral drug developments such as laquinimod, fingolimod and BG00012 aim at immunomodulation, trying to reduce relapse rate and frequency to delay disease progression and disability development (recently reviewed in Buck and Hemmer 2011). However, this reduction of relapse rate and frequency has sometimes limited success in disability progression within the usual 2-year observation period of clinical trials, and the long term efficacy in this regard is still questionable and a definitive proof missing. Over the last decade, growing evidence has been accumulating that neurodegenerative processes are also involved in the pathogenesis of the disease (Trapp and Nave 2008). Axonal transection and loss as well as progressive brain atrophy are frequently observed in MS patients (Bjartmar et al. 2001; Lovas et al. 2000; Miller et al. 2002; Siffrin et al. 2010; Trapp et al. 1998). Degenerative processes rather than infiltration of mononuclear cells from the immune system correlate best with the disability status of individual patients (Wujek et al. 2002), and it also has been shown that key features of neurodegeneration can be observed in early stages of MS (Herz et al. 2010; Trapp et al. 1998) and its animal model experimental

autoimmune encephalomyelitis (EAE) (Herrero-Herranz et al. 2008; Vogt et al. 2009). Therefore, new therapeutic approaches directly aiming at neuroprotection or combining immunomodulatory and neuroprotective aspects are urgently warranted.

A potential therapeutic target is the group of neurotrophins and neurotrophic factors. Their classical function in the central nervous system (CNS) is the support of neurons and glia cells, including regulation of neuronal differentiation, survival, neurite growth and plasticity, synaptic structure and connections, neurotransmitter release and synaptic plasticity (Huang and Reichardt 2001; Linker et al. 2009). Most of the neurotrophins and neurotrophic factors additionally modulate functions of the immune system (Kerschensteiner et al. 1999; Kruse et al. 2007; Linker et al. 2008; Schuhmann et al. 2005; Scuri et al. 2010; Vega et al. 2003), providing a link between the nervous and immune system. Therapeutic intervention using neurotrophins and neurotrophic factors as a target for both immunomodulatory and neuroprotective drugs is a positive challenge, but can also be dangerous when modulating the systems in opposite directions and may have significant side effects at higher doses (Ochs et al. 2000).

This review focuses on brain-derived neurotropic factor (BDNF), a neurotrophin influenced by the natural disease course of MS as well as by several therapeutic approaches and for which neuroprotective effects have recently been shown in EAE.

BDNF as Neurotrophic Factor: Structure, Function and Receptors

After nerve growth factor, BDNF was discovered as second member of the neurotrophin family in 1982 (Barde et al. 1982). The protein is translated from the genome as a 32 kDa pro-form (Matsumoto et al. 2008) and recent evidence suggests that different enzymes may be involved in the conversion into its biologically active form of 14 kDa including furin, certain matrix metalloproteinases and tissue plasminogen activator (Lee et al. 2001; Mizoguchi et al. 2011; Yeh et al. 2012). It can form not only homodimers, but also heterodimers with NT3 and NT4/5 (Robinson et al. 1995; Wiesmann and de Vos 2001). Pro-BDNF induces neuronal apoptosis and a reduction of cholinergic fibers and hippocampal dendritic spines in cultures of basal forebrain cholinergic neurons, which point to an inhibitory role for pro-BDNF within the CNS (Koshimizu et al. 2009; Lee et al. 2001). In contrast, mature BDNF is more related to neuronal survival, differentiation and synaptic plasticity (Lewin and Barde 1996; Linker et al. 2009; Noble et al. 2011), playing a neuropromotional and protective role.

BDNF binds to two receptors, these being the relatively specific high-affinity tyrosine receptor kinase (Trk)B receptor and the low affine $p75^{NTR}$ receptor which is shared with other members of the neurotrophin family. TrkB can be expressed either as full-length receptor with signaling capacity or as two different truncated forms with limited signaling capacity and rather acting as decoy receptors or dominant negative receptors by the formation of heterodimers (De Santi et al. 2009a; Eide et al. 1996). TrkB is a tyrosine kinase receptor that is able to activate a number of intracellular signaling cascades, the most important activated downstream transcription factors being NF-κB and CREB (Favalli et al. 2012; Finkbeiner et al. 1997; Kaplan and Miller 2000).

BDNF is implicated in the pathogenesis of a number of neurological diseases. In Huntington's disease, BDNF seems to play a central role in the pathogenesis inasmuch as trophic support for striatal neurons by BDNF is disturbed by mutant huntingtin (Linker et al. 2009; Zuccato and Cattaneo 2007). Consequently, direct application of BDNF into the striatum is theoretically a possible therapeutic approach. The symptoms of patients with Alzheimer's disease (AD) are considered to be due to altered cholinergic function as a consequence of loss of cholinergic neurons and/or cholinergic transmission (Winblad et al. 1993). BDNF may act neuroprotectively on cholinergic neurons, and BDNF levels are decreased in the hippocampus and neocortex of brains from AD patients, but are up-regulated in activated glial cells surrounding senile plaques (Schindowski et al. 2008). Recently, it has been suggested that the onset of AD pathology is closely related to BDNF axonal transport deficits (Ye et al. 2012). It is hypothesized that abnormal amyloid precursor protein processing and amyloid β production in mitochondria disturb the axonal transport of BDNF by impairing mitochondrial function (Ye et al. 2012). In Parkinson's disease, BDNF levels are reduced in the substantia nigra of patients, where the loss of dopaminergic neurons is held responsible for disease pathology (Howells et al. 2000). Finally, BDNF has also been associated with the pathophysiology of schizophrenia. Here, topological differences of BDNF levels have been described, patients with schizophrenia having a higher level of BDNF expression in the neocortex and a lower expression in the hippocampus (Durany et al. 2001), a result which was corroborated later at the mRNA level where reduced BDNF expression levels were observed in the prefrontal cortex of schizophrenia patients (Hashimoto et al. 2005). In animal experiments, electroconvulsive seizures—which are applied as treatment for schizophrenia—resulted in increased BDNF levels in different brain regions, whereas the effects of electroconvulsive therapy and repetitive transcranial magnetic stimulation in human patients were less clear (reviewed in Favalli et al. 2012). Mechanistically,

reduced BDNF levels in the hippocampus could lead to hippocampal hyperactivity, resulting in a dysfunction of the dopamine system, the latter being a dominant hypothesis for the pathophysiology of schizophrenia (Favalli et al. 2012; Grace 2012; Lodge and Grace 2011). Furthermore, because of its central role in synaptic plasticity, BDNF is thought to be involved in the pathophysiology of affective disorders and used as biomarker for mood stages in bipolar disorders (Balanza-Martinez et al. 2011; Fernandes et al. 2011; Grande et al. 2010).

Although the most important functions of BDNF depend on its expression and action in various cell types in the CNS, BDNF is expressed in a number of other cell types including cells of the immune system. In addition, BDNF exerts different pleiotropic functions in both systems. In the thymus, BDNF mRNA is expressed in thymic stromal cells which could contribute to the survival of thymocytes in different developmental stages (Maroder et al. 1996). At the cellular level, BDNF mRNA and protein were detected in T cells, B cells and monocytes, predominantly in their activated stage (Kerschensteiner et al. 1999; Kruse et al. 2007). Additionally, a block in B-cell development at the Pre-BII stage was reported in young BDNF knock-out mice, suggesting a role for BDNF in B-cell development (Schuhmann et al. 2005). More recently, the expression of pro-BDNF and mature BDNF in B cells and the up-regulation of mature BDNF in stress culture conditions were confirmed (Fauchais et al. 2008). Additionally, an anti-apoptotic and survival-promoting effect of BDNF was recognized for B cells, an effect which is dependent on the intracellular transport protein and surface co-receptor sortillin (Fauchais et al. 2008). BDNF mRNA was also found in granulocytes, bone marrow cells (Laurenzi et al. 1998) and mast cells (Tam et al. 1997) and has been implicated in the regulation of eosinophilic inflammation in allergic asthma (Nassenstein et al. 2003). This highlights the potential of BDNF's effects outside the CNS and places it as a modulatory agent for cells of the immune system.

The importance of BDNF function is underscored by the premature death of BDNF-deficient mice which die at an age of 2–3 weeks after birth due to the degeneration of viscero-afferent neurons and resulting aspiration problems. For heterozygous $BDNF^{+/-}$ mice, a clear phenotype was described including behavioral deficits such as aggressiveness and hyperactivity combined with hyperphagia, obesity, loss of mechanosensitivity and loss of neurons of the peripheral nervous system (Carroll et al. 1998; Ernfors et al. 1994; Kernie et al. 2000; Rios et al. 2001). Based on these early observations, BDNF was recently implicated in regulating the energy balance and, therefore, impacting feeding behavior and body weight (Cordeira and Rios 2011; Noble et al. 2011).

The Role of BDNF in MS and EAE

The Value of Studying Serum BDNF Levels in Neuroinflammation

BDNF is mainly produced by neurons in the nervous system. However, as early as in the mid 1990s, protein chemical studies revealed that BDNF is also present in human serum (Rosenfeld et al. 1995). Similar data are available for rats, whereas the detection of BDNF in mouse serum is much more difficult (Radka et al. 1996). Given the neuroprotective properties of BDNF in neurobiological paradigms, the factor soon became an interesting candidate as a possible marker for several neuropsychiatric diseases as well as for the analysis of hypothetical neuroprotective capacities of different therapies. Lower BDNF serum levels were found in psychiatric diseases including depression, eating disorders and schizophrenia (Green et al. 2011; Karege et al. 2002; Nakazato et al. 2003). Several groups investigated serum BDNF levels in MS patients with conflicting results, describing in relapsing–remitting MS patients in the stable phase of the disease compared to healthy controls either a reduction of serum BDNF levels (Azoulay et al. 2005; Frota et al. 2009) or increased BDNF protein and mRNA levels (Liguori et al. 2009). In contrast, there is consistent information pointing to an increase of serum BDNF levels during MS relapses (Frota et al. 2009; Sarchielli et al. 2002). Furthermore, BDNF serum levels in MS patients may be modulated by therapeutic interventions like treatment with GA and hematopoietic stem cell transplantation, but also physical exercise (Azoulay et al. 2005; Blanco et al. 2005; Gold et al. 2003). Some studies even tried to correlate BDNF serum levels with magnetic resonance imaging (MRI) lesion load (Comini-Frota et al. 2012).

However, it should be mentioned that there are several caveats to the concept of correlating serum BDNF levels with neurodegeneration or neuroprotective effects, at least in MS. First, the source of serum BDNF needs some attention: It has been shown in humans and rodents that activated T cells, B cells and monocytes/macrophages express bioactive BDNF (Kerschensteiner et al. 1999; Kruse et al. 2007) which may contribute to BDNF levels in serum. Even more importantly, human platelets also contain significant amounts of BDNF (Yamamoto and Gurney 1990) and serum BDNF levels were shown to correlate with platelet counts (Iughetti et al. 2011). Indeed, the amount of BDNF produced by immune cells seems negligible to that stemming from platelets (Gonul et al. 2005; Shimizu et al. 2003). Interestingly, there is a wide range of BDNF concentrations in platelets which does not directly correlate with any baseline physiological parameter (Lommatzsch et al. 2005). BDNF is not directly synthesized by platelets or

their precursors, but rather actively taken up in these cells (Fujimura et al. 2002). In different diseases, the amount of platelet-stored BDNF is highly dynamic (Lommatzsch et al. 2007), thus contributing to the concept that platelets constitute a buffer storage of BDNF in the blood. Most importantly, platelet-derived BDNF may be released into the blood after thrombocyte activation or during clotting processes (Fujimura et al. 2002; Radka et al. 1996). Thus, the release of BDNF from platelets by activation or clotting (e.g. after contact with plastic material in syringes, tubes or monovettes) during handling of blood ex vivo after drawing may significantly alter measurable BDNF serum levels. Consequently, BDNF amounts as analysed ex vivo may not in all cases directly reflect the actual disease- or therapy-associated neurotrophin levels in vivo. This concept is underscored by an approximately 200-fold increase of BDNF levels in serum relative to plasma. Data from experiments using differential centrifugation indeed suggest that the source of this increase is due to release from platelets (Rosenfeld et al. 1995). In line with this, studies on patients with depression suggest that reduced serum BDNF levels are not due to direct changes in blood BDNF but are rather governed by altered mechanisms of BDNF release from platelets (Karege et al. 2005).

With regard to MS, it has not been shown that platelets cross the blood–brain barrier (BBB), home into actively demyelinated lesions and thus directly contribute to BDNF release in the CNS in situ. This situation might be different from inflammation in the periphery, where platelets may directly interact with pathophysiologically relevant targets, e.g. in the lung (Lommatzsch et al. 2007).

Second, BDNF is a very short-lived peptide with high affinity to membranes and a rather paracrine mode of action. While the target cells of BDNF in the circulation still remain poorly defined to date, it is known that in neurobiological paradigms, neurotrophins mainly act in a paracrine or autocrine manner on neurons (Robinson et al. 1996). Thus it also seems likely that in the periphery serum-derived BDNF acts on targets in the immediate vicinity within a limited time frame rather than recirculating for extended periods through the body. Therefore, the probability that serum BDNF eventually accumulates within the CNS is rather low, a conjecture underscored by the finding that even after a parenteral bolus injection, only a low amount of the neurotrophin is actually able to cross the BBB (Dittrich et al. 1996; Kishino et al. 2001). Recently, this concept was affirmed in a rodent ultrasound study revealing activation of BDNF signaling pathways after exogenous application of labeled BDNF only in CNS regions with non-invasive, ultrasound-mediated BBB disruption (Baseri et al. 2012).

In summary, all these facts point to the need for utmost caution when interpreting data on serum BDNF levels with regard to concepts of neuroprotective autoimmunity or neuroprotection. Better, such studies should be corroborated by directly proving serum findings in independent experimental paradigms. Such examples include effects of the oral immunomodulator laquinimod on serum and immune cell BDNF in MS patients and EAE knockout models (Thone et al. 2012).

The Role of Genetic BDNF Variations in MS

In a different approach, studies analyzed the influence of BDNF gene variations on clinical and MRI parameters in MS. Among different polymorphisms in the human BDNF gene, the Val66Met (rs6265) single nucleotide polymorphism (SNP) results in an exchange between valine and methionine at codon 66 which directly affects activity-dependent secretion of BDNF and consequently memory and hippocampal function (Egan et al. 2003). In 2007, a first study on the correlation of this genetic variant with MRI pointed to a preservation of gray matter volumes in MS patients (Zivadinov et al. 2007). These data were corroborated by different follow-up studies with variable group sizes linking the Val66Met SNP to a working memory task in a functional MRI study (Cerasa et al. 2010), regional gray matter volume (Ramasamy et al. 2011) and brain volumes (Dinacci et al. 2011), while the rs 2030324 BDNF SNP was associated with visual cognitive processing (Weinstock-Guttman et al. 2011). However, the clinical concept of such correlations was brought into question by a recent large-scale Norwegian study involving more than 2100 MS patients which failed to delineate any correlation of the Val66Met SNP with any demographic, clinical or neuropsychological parameters (Mero et al. 2012).

Studies on Immune Cell-Derived BDNF in Healthy Controls and MS Patients

In 1999, Kerschensteiner and co-workers described BDNF production by activated T cells, B cells and monocytes (Kerschensteiner et al. 1999) (Fig. 1). This work fitted very well into the previously described concept of neuroprotective autoimmunity which was based on improved neuronal function and reduced neuronal degeneration in a spinal cord injury model provoked by infiltration of CNS antigen-specific T cells or other immune cells (Hohlfeld et al. 2000; Moalem et al. 1999; Schwartz and Kipnis 2001). In view of these interesting data, investigations on BDNF production of peripheral blood mononuclear cells (PBMC) from healthy controls and MS patients were the focus of particular neuroimmunological interest. In several studies using GA-specific T-cell lines from healthy donors and GA-treated MS patients, BDNF production was observed in these T-cell lines at the mRNA and protein level

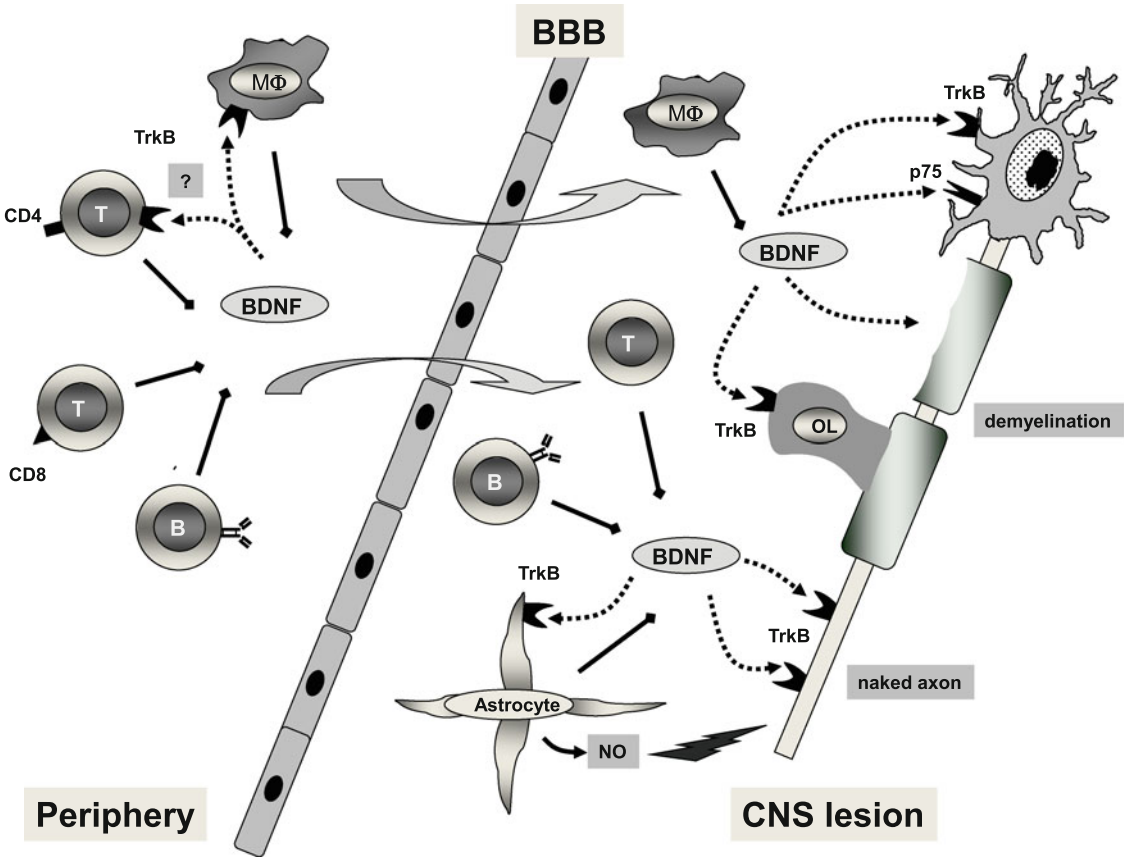

Fig. 1 BDNF in the process of autoimmune demyelination. Autoreactive T cells are activated in the periphery, cross the blood–brain-barrier (*BBB*) and pave the way for the subsequent infiltration of monocytes/macrophages and also *B* cells into the *CNS*. All these lymphocyte subpopulations are able to produce *BDNF* in their activated stage. In the *CNS*, additional *BDNF* is available secreted by neurons and astrocytes. *BDNF* acts via binding of its receptor *TrkB* on axons and oligodendrocytes in a presumably neuroprotective manner. Additionally, *BDNF* binds to *TrkB* on astrocytes, provoking nitric oxide production and leading to secondary neuronal degeneration. *BDNF* may also bind to *TrkB* expressed on immune cell subpopulations, but the outcome of this interaction is less clear. *Arrows* indicate *BDNF* secretion, *dotted arrows BDNF* binding to its receptors. *OL* oligodendrocytes, *NO* nitric oxide

irrespective of their Th1 and Th2 phenotypes (Chen et al. 2003; Ziemssen et al. 2002, 2005). In one study, GA-reactive T-cell lines showed a higher capacity to produce BDNF than MBP or tetanus toxoid-specific T-cell lines, but all activated T cells seem generally to be able to produce BDNF (Chen et al. 2003). In the animal model of EAE, GA-specific T cells were also shown to secrete BDNF in the CNS in situ (Aharoni et al. 2003).

Using more basic approaches, BDNF production from immune cells was also assessed ex vivo in unstimulated and stimulated peripheral PBMC from MS patients. Similar to the inconsistent results on serum BDNF levels, some studies on supernatants from cultured PBMC showed lower but others higher BDNF production in samples from MS patients compared to healthy controls (Azoulay et al. 2008; Petereit et al. 2003). These discrepancies might be explained by the higher BDNF levels in cell supernatants from MS patients under relapse (Blanco et al. 2005; Sarchielli et al. 2002). Significantly lower amounts of BDNF were found in secondary progressive MS patients (Hamamcioglu and Reder 2007; Sarchielli et al. 2002). Several studies also evaluated effects of immunomodulatory therapies on BDNF production in PBMC. While some investigations showed positive effects predominantly for GA (Sarchielli et al. 2002) and no other immunotherapies (Petereit et al. 2003), others also found effects in cells from patients treated with IFN-β (Hamamcioglu and Reder 2007). Further studies even aimed at correlating PBMC-derived BDNF levels with either cognitive performance (Patanella et al. 2010) or white matter volumes (Weinstock-Guttman et al. 2007). Recently, a comprehensive study investigated the expression of neurotrophic factors in cultured immune cells from MS patients treated in a phase II clinical trial with the anti-CD52 monoclonal antibody alemtuzumab. After therapy, T cells in PBMC culture produced increased concentrations of BDNF. Supernatants from these cultures promoted survival of neurons and increased axonal length, but also enhanced oligodendrocyte

precursor cell survival, maturation and myelination in vitro (Jones et al. 2010).

While there is a consensus about BDNF expression by immune cells, there is far less information available about its effect on immune cells as targets in the context of neuroinflammation. There are few studies describing dendritic cell activation and maturation mediated by BDNF binding to its receptor TrkB (Bratke et al. 2007; Noga et al. 2007). Studies on thymocytes show that expression of the high-affinity receptor TrkB in T cells is negatively correlated with their maturation stage (Maroder et al. 1996). Nevertheless, full-length TrkB could be detected in some human T-cell lines (Besser and Wank 1999; De Santi et al. 2009b) with a higher expression level reported in T-cell lines derived from relapsing–remitting MS patients compared to healthy controls (De Santi et al. 2009b). This was negatively correlated with the propensity of activated T cells to undergo apoptosis which would prevent the development of autoimmunity (De Santi et al. 2009b). These findings were interpreted to suggest that BDNF can rescue autoreactive T cells from apoptosis, thus contributing to their maintenance in the periphery and thereby rather promoting the development of autoimmune diseases (De Santi et al. 2011). However, direct protective effects of BDNF on T-cell apoptosis have not been shown to date (own unpublished observations). Finally, BDNF may also act in similar ways on granulocytes, as it was described as a survival and activation factor in eosinophilic granulocytes from asthma patients (Nassenstein et al. 2003).

Investigating the Functional Role BDNF in Animal Models of Autoimmune Demyelination

Secretion of BDNF by immune cells has also been shown in situ by immunohistochemical studies of MS lesions, where perivascular T cells and macrophages produce BDNF in the vicinity of TrkB positive neurons (Stadelmann et al. 2002). Whereas these studies strongly speak for the concept that BDNF may be a molecular basis for the concept of neuroprotective autoimmunity, the data are mainly descriptive in nature. Functional studies in animal models need to be carried out to better investigate the functional role of BDNF in autoimmune demyelination.

The first functional studies on BDNF in animal models were focused on the exogenous application of the factor. Negative data on the systemic application of BDNF in an experimental model of neuritis may be explained by the fact that the compound has a short half-life and does not readily cross the BBB (Felts et al. 2002). The next step saw application of genetically engineered bone marrow stem cells (BMSC) with BDNF over-expression in EAE (Makar et al. 2004).This strategy of neurotrophin over-expressing cell transfer had already been applied successfully beforehand to nerve growth factor in experimental autoimmune neuritis (Kramer et al. 1995) and EAE (Flügel et al. 2001). Intravenous application of BDNF over-expressing BMSC led to beneficial effects not only including reduced demyelination and increased remyelination, but also a reduction of inflammation and apoptotic cells in the CNS (Makar et al. 2008, 2009). Yet, this paradigm is somewhat complex since it requires the irradiation of mice, and BDNF may already alter the properties of immune cells derived from BMSC before effects on the CNS can be elucidated.

The most widely used murine animal model for MS is myelin oligodendrocyte glycoprotein-induced EAE in the C57BL/6 strain which mimics many degenerative features of MS (Gold et al. 2006; Herrero-Herranz et al. 2008). In this paradigm with axonal loss and extensive myelin damage, BDNF levels in the spinal cord are significantly reduced after EAE induction (Linker et al. 2010) and several knockout models on the C57BL/6 background are available for functional studies of neurotrophic factors (Linker et al. 2002, 2008). Conventional BDNF knockout mice cannot be used for EAE studies, since these mice die before or shortly after birth, depending on their genetic background (Korte et al. 1995). While studies in BDNF heterozygous knockout mice are feasible and show a less severe course of EAE (Javeri et al. 2010), these data are somewhat hampered by the complex behavioral and metabolic phenotype of these mice characterized by hyperactivity and obesity which may *per se* influence the immune response (Kernie et al. 2000). These problems can be overcome by the use of conditional knockout mice in which loxP sites flank the single coding exon, resulting in the deletion of BDNF when these mice are crossed with mice expressing Cre recombinase under control of a tissue-specific promotor or in an inducible manner (Matsumoto et al. 2008). In such a system, where BDNF is deleted in the CNS by Cre expressed by the tau locus, it could be shown that CNS-derived BDNF is not essential for prolonged postnatal survival of the animals, and that it is not a major factor either for the survival of most CNS neurons or for myelination (Rauskolb et al. 2010). To investigate the functional role of CNS-derived BDNF during autoimmune demyelination, floxed BDNF mice were bred with mice expressing Cre under the control of the glial fibrillary acidic protein (GFAP) promoter or timely regulated after tamoxifen injection (Lee et al. 2012; Linker et al. 2010). Mice with GFAP-Cre-driven BDNF deletion show a more severe course of the disease with increased axonal damage not only in demyelinated lesions, but also in the peri-lesional area and the normal appearing white matter. There was no influence on the immune reaction. In mice with timely regulated, tamoxifen-mediated BDNF deletion, early deletion of BDNF before the maximum of disease was needed to delineate similar clinical and histopathological effects (Lee et al. 2012; Linker et al. 2010). These data show that

CNS-derived BDNF is an important protective factor in autoimmune demyelination (Fig. 1). BDNF may particularly play a role early in the disease when functional axonal changes like focal axonal degeneration prevail (Nikic et al. 2011), but global neurodegeneration is not yet extensively present (Herrero-Herranz et al. 2008). In a setting of massive axonal loss, gliosis and tissue destruction at later disease stages, protective effects of BDNF may no longer be as pronounced since its regenerative capacity may be limited.

While data from mice with GFAP-Cre-mediated BDNF deletion suggest a protective role for astrocyte-derived BDNF in EAE, a recent study on mice lacking TrkB specifically in astrocytes showed that TrkB-mediated pathways in astroglia may also play a detrimental role involving nitric oxide production and secondary neuronal degeneration in EAE (Fig. 1) (Colombo et al. 2012). Given the wealth of data on the protective effect of BDNF in different settings (Linker et al. 2009), these results are surprising and not easily explained at the first glance. In general, when interpreting BDNF effects one has to consider that this neurotrophin may play a dual or Janus-like role, depending on the receptor involved. It is well known that binding of BDNF to TrkB or $p75^{NTR}$ has opposite effects, e.g. concerning cellular survival, axonal outgrowth, hippocampal synaptic plasticity and dendritic spine density and morphology (Chapleau and Pozzo-Miller 2012; Lu et al. 2005). This is due to the activation of different BDNF-receptor pathways, suggesting that the interplay of BDNF and other related neurotrophic factors and their precursors with distinct receptors on different CNS cell types may be complex and hard to predict. Additionally, different BDNF receptors are also expressed on peripheral cells, e.g. immune cells, and are subject to regulation by diverse factors. Therefore, the actual BDNF action is always the result of its binding to a certain receptor on a particular target cell. In the setting of TrkB deletion on astroglia, counter-regulatory up-regulation both of detrimental $p75^{NTR}$-mediated pathways and/or actions of pro-BDNF, the latter having been shown earlier to be important for neurodegeneration, may play a role.

In a next step, the role of immune cell-derived BDNF in EAE was investigated. Interestingly, the single conditional knockout of BDNF in T cells or cells of the myeloid lineage alone did not result in any effects on the course of EAE (Linker et al. 2010). These data are in line with a recent study showing that conditional lack of BDNF in T cells did not influence neuroprotection in a mouse model of facial nerve axotomy (Xin et al. 2012). Yet, effects in single conditional knockout mice may be masked by the persistent BDNF expression from other infiltrating immune cells: Mice lacking BDNF both in T cells and myeloid cells experienced a more severe clinical EAE course accompanied by a pronounced axonal loss specifically in demyelinated lesions in the chronic phase of the disease, but not in the perilesion or the normal appearing white matter in this stage (Linker et al. 2010). In a supplementary approach, co-injection of autoantigen-specific, non-activated T cells overexpressing BDNF in mice with ongoing myelin oligodendrocyte glycoprotein (MOG)-EAE led to an ameliorated disease course with axonal preservation, again without significant influences on the immune response (Linker et al. 2010). In summary, these data argue for the functional relevance of the concept of neuroprotective autoimmunity in neuroinflammatory conditions, with BDNF being an important molecular correlate.

Interestingly, BDNF may not only exert axon-protective effects, but also influence cells of the oligodendroglial lineage. Studies on the model of cuprizone-mediated demyelination in BDNF heterozygous knockout mice revealed that BDNF may play a role in regulating the number of oligodendrocyte progenitors as well as the expression of myelin proteins (VonDran et al. 2011). These data are well in line with a previous study on embryonal BDNF knockout mice and naïve BDNF heterozygous knockout mice which already disclosed deficits of oligodendrocytes in the basal forebrain in these mice (VonDran et al. 2010).

Finally, mice with a conditional BDNF deficiency may be employed to test the functional relevance of BDNF for the mechanism of action of MS therapies. Studies in mice lacking BDNF in immune cells or mice with a timely regulated BDNF deletion show that at least part of the effects of the immunomodulators GA and laquinimod involve BDNF produced by immune cells (Lee et al. 2012; Linker et al. 2010; Thone et al. 2012).

Concluding Remarks

There is increasing evidence that the concept of neuroprotective autoimmunity can be extended from injury conditions of the CNS to neuro-inflammatory conditions where the infiltration of autoantigen-specific T cells and other immune cells is part of the pathogenetic process. In such a situation, immune cells seem to play a dual role. On the one hand, they are clearly pathogenic by secreting pro-inflammatory cytokines, directly attacking neuronal structures and supporting glial cell populations. On the other hand, they secrete some factors which support regeneration and self-limit the on-going destructive inflammation. Neurotrophic factors and neurotrophins, among them BDNF, seem to play a pivotal role in the latter process. Whereas many studies have been conducted trying to correlate BDNF levels in the serum of MS patients and the amount of BDNF produced by their immune cells to clinical outcome, these results are partly contradictory and

have to be interpreted with caution. Sophisticated experimental studies in animal models in principle support the neuroprotective activity of BDNF in neuroinflammatory and demyelinating settings, presumably via BDNF-TrkB-mediated signaling pathways. While these data are very suggestive, the neuroprotective role of BDNF and its receptor pathways in neurological disease has not been definitely proven in humans so far. In particular, the short half-life of BDNF, restrictions in its distribution across the BBB and behavioral side effects at higher doses may limit the easy translation of experimental findings into clinical practice.

Acknowledgments We are grateful to M. Sendtner, Würzburg, for the longstanding good collaboration on the role of neurotrophic factors in autoimmune demyelination and to C. Ludwig for language correction. This work was supported by the Gemeinnützige Hertie-Stiftung (AZ 1.01.1/05/009), R. Gold and F. Lühder by the Deutsche Stifterverband, Fritz und Hildegard Berg-Stiftung, (AZ T 155-15.284) and F. Lühder was supported by the Deutsche Forschungsgemeinschaft (DFG, SFB-TR-43 TP B11).

References

Aharoni R, Kayhan B, Eilam R et al (2003) Glatiramer acetate-specific T cells in the brain express T helper 2/3 cytokines and brain-derived neurotrophic factor in situ. Proc Natl Acad Sci USA 100:14157–14162

Azoulay D, Vachapova V, Shihman B et al (2005) Lower brain-derived neurotrophic factor in serum of relapsing remitting MS: reversal by glatiramer acetate. J Neuroimmunol 167:215–218

Azoulay D, Urshansky N, Karni A (2008) Low and dysregulated BDNF secretion from immune cells of MS patients is related to reduced neuroprotection. J Neuroimmunol 195:186–193

Balanza-Martinez V, Fries GR, Colpo GD et al (2011) Therapeutic use of omega-3 fatty acids in bipolar disorder. Expert Rev Neurother 11:1029–1047

Barde YA, Edgar D, Thoenen H (1982) Purification of a new neurotrophic factor from mammalian brain. EMBO J 1:549–553

Baseri B, Choi JJ, Deffieux T et al (2012) Activation of signaling pathways following localized delivery of systemically administered neurotrophic factors across the blood-brain barrier using focused ultrasound and microbubbles. Phys Med Biol 57:N65–N81

Besser M, Wank R (1999) Cutting edge: clonally restricted production of the neurotrophins brain-derived neurotrophic factor and neurotrophin-3 mRNA by human immune cells and Th1/Th2-polarized expression of their receptors. J Immunol 162:6303–6306

Bjartmar C, Kinkel RP, Kidd G et al (2001) Axonal loss in normal-appearing white matter in a patient with acute MS. Neurology 57:1248–1252

Blanco Y, Saiz A, Costa M et al (2005) Evolution of brain-derived neurotrophic factor levels after autologous hematopietic stem cell transplantation in multiple sclerosis. Neurosci Lett 380:122–126

Bratke K, Maruschke L, Darowski M et al (2007) A role for the neurotrophin receptor TrkB on maturing dendritic cells. J Neuroimmunol 189:88–94

Buck D, Hemmer B (2011) Treatment of multiple sclerosis: current concepts and future perspectives. J Neurol 258:1747–1762

Carroll P, Lewin GR, Koltzenburg M et al (1998) A role for BDNF in mechanosensation. Nat Neurosci 1:42–46

Cerasa A, Tongiorgi E, Fera F et al (2010) The effects of BDNF Val66Met polymorphism on brain function in controls and patients with multiple sclerosis: an imaging genetic study. Behav Brain Res 207:377–386

Chapleau CA, Pozzo-Miller L (2012) Divergent roles of p75NTR and Trk receptors in BDNF's effects on dendritic spine density and morphology. Neural Plast 2012:578057

Chen M, Valenzuela RM, Dhib-Jalbut S (2003) Glatiramer acetate-reactive T cells produce brain-derived neurotrophic factor. J Neurol Sci 215:37–44

Colombo E, Cordiglieri C, Melli G et al (2012) Stimulation of the neurotrophin receptor TrkB on astrocytes drives nitric oxide production and neurodegeneration. J Exp Med 209:521–535

Comini-Frota ER, Rodrigues DH, Miranda EC et al (2012) Serum levels of brain-derived neurotrophic factor correlate with the number of T2 MRI lesions in multiple sclerosis. Braz J Med Biol Res 45:68–71

Cordeira J, Rios M (2011) Weighing in the role of BDNF in the central control of eating behavior. Mol Neurobiol 44:441–448

De Santi L, Annunziata P, Sessa E et al (2009a) Brain-derived neurotrophic factor and TrkB receptor in experimental autoimmune encephalomyelitis and multiple sclerosis. J Neurol Sci 287:17–26

De Santi L, Cantalupo L, Tassi M et al (2009b) Higher expression of BDNF receptor gp145trkB is associated with lower apoptosis intensity in T cell lines in multiple sclerosis. J Neurol Sci 277:65–70

De Santi L, Polimeni G, Cuzzocrea S et al (2011) Neuroinflammation and neuroprotection: an update on (future) neurotrophin-related strategies in multiple sclerosis treatment. Curr Med Chem 18:1775–1784

Dinacci D, Tessitore A, Russo A et al (2011) BDNF Val66Met polymorphism and brain volumes in multiple sclerosis. Neurol Sci 32:117–123

Dittrich F, Ochs G, Grosse-Wilde A et al (1996) Pharmacokinetics of intrathecally applied BDNF and effects on spinal motoneurons. Exp Neurol 141:225–239

Durany N, Michel T, Zochling R et al (2001) Brain-derived neurotrophic factor and neurotrophin 3 in schizophrenic psychoses. Schizophr Res 52:79–86

Egan MF, Kojima M, Callicott JH et al (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269

Eide FF, Vining ER, Eide BL et al (1996) Naturally occurring truncated trkB receptors have dominant inhibitory effects on brain-derived neurotrophic factor signaling. J Neurosci 16:3123–3129

Ernfors P, Lee KF, Jaenisch R (1994) Mice lacking brain-derived neurotrophic factor develop with sensory deficits. Nature 368:147–150

Fauchais AL, Lalloue F, Lise MC et al (2008) Role of endogenous brain-derived neurotrophic factor and sortilin in B cell survival. J Immunol 181:3027–3038

Favalli G, Li J, Belmonte-de-Abreu P, Wong AH et al (2012) The role of BDNF in the pathophysiology and treatment of schizophrenia. J Psychiatr Res 46:1–11

Felts PA, Smith KJ, Gregson NA et al (2002) Brain-derived neurotrophic factor in experimental autoimmune neuritis. J Neuroimmunol 124:62–69

Fernandes BS, Gama CS, Cereser KM et al (2011) Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res 45:995–1004

Finkbeiner S, Tavazoie SF, Maloratsky A et al (1997) CREB: a major mediator of neuronal neurotrophin responses. Neuron 19:1031–1047

Flügel A, Matsumuro K, Neumann H et al (2001) Anti-inflammatory activity of nerve growth factor in experimental autoimmune encephalomyelitis: inhibition of monocyte transendothelial migration. Eur J Immunol 31:11–22

Frota ER, Rodrigues DH, Donadi EA et al (2009) Increased plasma levels of brain derived neurotrophic factor (BDNF) after multiple sclerosis relapse. Neurosci Lett 460:130–132

Fujimura H, Altar CA, Chen R et al (2002) Brain-derived neurotrophic factor is stored in human platelets and released by agonist stimulation. Thromb Haemost 87:728–734

Gold SM, Schulz KH, Hartmann S et al (2003) Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. J Neuroimmunol 138:99–105

Gold R, Linington C, Lassmann H (2006) Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. Brain 129:1953–1971

Gonul AS, Akdeniz F, Taneli F et al (2005) Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 255:381–386

Grace AA (2012) Dopamine system dysregulation by the hippocampus: implications for the pathophysiology and treatment of schizophrenia. Neuropharmacology 62:1342–1348

Grande I, Fries GR, Kunz M et al (2010) The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Investig 7:243–250

Green MJ, Matheson SL, Shepherd A et al (2011) Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry 16:960–972

Hamamcioglu K, Reder AT (2007) Interferon-beta regulates cytokines and BDNF: greater effect in relapsing than in progressive multiple sclerosis. Mult Scler 13:459–470

Hashimoto T, Bergen SE, Nguyen QL et al (2005) Relationship of brain-derived neurotrophic factor and its receptor TrkB to altered inhibitory prefrontal circuitry in schizophrenia. J Neurosci 25:372–383

Herrero-Herranz E, Pardo LA, Gold R et al (2008) Pattern of axonal injury in murine myelin oligodendrocyte glycoprotein induced experimental autoimmune encephalomyelitis: implications for multiple sclerosis. Neurobiol Dis 30:162–173

Herz J, Zipp F, Siffrin V (2010) Neurodegeneration in autoimmune CNS inflammation. Exp Neurol 225:9–17

Hohlfeld R, Kerschensteiner M, Stadelmann C et al (2000) The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis. J Neuroimmunol 107:161–166

Howells DW, Porritt MJ, Wong JY et al (2000) Reduced BDNF mRNA expression in the Parkinson's disease substantia nigra. Exp Neurol 166:127–135

Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677–736

Iughetti L, Casarosa E, Predieri B et al (2011) Plasma brain-derived neurotrophic factor concentrations in children and adolescents. Neuropeptides 45:205–211

Javeri S, Rodi M, Tary-Lehmann M et al (2010) Involvement of brain-derived neurotrophic factor (BDNF) in MP4-induced autoimmune encephalomyelitis. Clin Immunol 137:181–189

Jones JL, Anderson JM, Phuah CL et al (2010) Improvement in disability after alemtuzumab treatment of multiple sclerosis is associated with neuroprotective autoimmunity. Brain 133:2232–2247

Kaplan DR, Miller FD (2000) Neurotrophin signal transduction in the nervous system. Curr Opin Neurobiol 10:381–391

Karege F, Perret G, Bondolfi G et al (2002) Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 109:143–148

Karege F, Bondolfi G, Gervasoni N et al (2005) Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57:1068–1072

Kernie SG, Liebl DJ, Parada LF (2000) BDNF regulates eating behavior and locomotor activity in mice. EMBO J 19:1290–1300

Kerschensteiner M, Gallmeier E, Behrens L et al (1999) Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? J Exp Med 189:865–870

Kishino A, Katayama N, Ishige Y et al (2001) Analysis of effects and pharmacokinetics of subcutaneously administered BDNF. NeuroReport 12:1067–1072

Korte M, Carroll P, Wolf E et al (1995) Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proc Natl Acad Sci USA 92:8856–8860

Koshimizu H, Kiyosue K, Hara T et al (2009) Multiple functions of precursor BDNF to CNS neurons: negative regulation of neurite growth, spine formation and cell survival. Mol Brain 2:27

Kramer R, Zhang YP, Gehrmann J et al (1995) Gene-transfer through the blood-nerve barrier—ngf-engineered neuritogenic T-lymphocytes attenuate experimental autoimmune neuritis. Nat Med 1:1162–1166

Kruse N, Cetin S, Chan A et al (2007) Differential expression of BDNF mRNA splice variants in mouse brain and immune cells. J Neuroimmunol 182:13–21

Laurenzi MA, Beccari T, Stenke L et al (1998) Expression of mRNA encoding neurotrophins and neurotrophin receptors in human granulocytes and bone marrow cells-enhanced neurotrophin-4 expression induced by LTB4. J Leukoc Biol 64:228–234

Lee R, Kermani P, Teng KK et al (2001) Regulation of cell survival by secreted proneurotrophins. Science 294:1945–1948

Lee DH, Geyer E, Flach AC et al (2012) Central nervous system rather than immune cell-derived BDNF mediates axonal protective effects early in autoimmune demyelination. Acta Neuropathol 123:247–258

Lewin GR, Barde YA (1996) Physiology of the neurotrophins. Annu Rev Neurosci 19:289–317

Liguori M, Fera F, Patitucci A et al (2009) A longitudinal observation of brain-derived neurotrophic factor mRNA levels in patients with relapsing–remitting multiple sclerosis. Brain Res 1256: 123–128

Linker RA, Maurer M, Gaupp S et al (2002) CNTF is a major protective factor in demyelinating CNS disease: a neurotrophic cytokine as modulator in neuroinflammation. Nat Med 8:620–624

Linker RA, Kruse N, Israel S et al (2008) Leukemia inhibitory factor deficiency modulates the immune response and limits autoimmune demyelination: a new role for neurotrophic cytokines in neuroinflammation. J Immunol 180:2204–2213

Linker R, Gold R, Lühder F (2009) Function of neurotrophic factors beyond the nervous system: inflammation and autoimmune demyelination. Crit Rev Immunol 29:43–68

Linker RA, Lee DH, Demir S et al (2010) Functional role of brain-derived neurotrophic factor in neuroprotective autoimmunity: therapeutic implications in a model of multiple sclerosis. Brain 133:2248–2263

Lodge DJ, Grace AA (2011) Hippocampal dysregulation of dopamine system function and the pathophysiology of schizophrenia. Trends Pharmacol Sci 32:507–513

Lommatzsch M, Quarcoo D, Schulte-Herbruggen O et al (2005) Neurotrophins in murine viscera: a dynamic pattern from birth to adulthood. Int J Dev Neurosci 23:495–500

Lommatzsch M, Niewerth A, Klotz J et al (2007) Platelet and plasma BDNF in lower respiratory tract infections of the adult. Respir Med 101:1493–1499

Lovas G, Szilagyi N, Majtenyi K et al (2000) Axonal changes in chronic demyelinated cervical spinal cord plaques. Brain 123(Pt 2):308–317

Lu B, Pang PT, Woo NH (2005) The yin and yang of neurotrophin action. Nat Rev Neurosci 6:603–614

Lutton JD, Winston R, Rodman TC (2004) Multiple sclerosis: etiological mechanisms and future directions. Exp Biol Med 229:12–20

Makar TK, Trisler D, Eglitis MA et al (2004) Brain-derived neurotrophic factor (BDNF) gene delivery into the CNS using bone marrow cells as vehicles in mice. Neurosci Lett 356:215–219

Makar TK, Trisler D, Sura KT et al (2008) Brain derived neurotrophic factor treatment reduces inflammation and apoptosis in experimental allergic encephalomyelitis. J Neurol Sci 270:70–76

Makar TK, Bever CT, Singh IS et al (2009) Brain-derived neurotrophic factor gene delivery in an animal model of multiple sclerosis using bone marrow stem cells as a vehicle. J Neuroimmunol 210:40–51

Maroder M, Bellavia D, Meco D et al (1996) Expression of trkB neurotrophin receptor during T cell development—role of brain-derived neurotrophic factor in immature thymocyte survival. J Immunol 157:2864–2872

Matsumoto T, Rauskolb S, Polack M et al (2008) Biosynthesis and processing of endogenous BDNF: CNS neurons store and secrete BDNF, not pro-BDNF. Nat Neurosc 11:131–133

Mero IL, Smestad C, Lie BA et al (2012) Polymorphisms of the BDNF gene show neither association with multiple sclerosis susceptibility nor clinical course. J Neuroimmunol 244:107–110

Miller DH, Barkhof F, Frank JA et al (2002) Measurement of atrophy in multiple sclerosis: pathological basis, methodological aspects and clinical relevance. Brain 125:1676–1695

Mizoguchi H, Nakade J, Tachibana M et al (2011) Matrix metalloproteinase-9 contributes to kindled seizure development in pentylenetetrazole-treated mice by converting pro-BDNF to mature BDNF in the hippocampus. J Neurosci 31:12963–12971

Moalem G, Leibowitz-Amit R, Yoles E et al (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. Nat Med 5:49–55

Nakazato M, Hashimoto K, Shimizu E et al (2003) Decreased levels of serum brain-derived neurotrophic factor in female patients with eating disorders. Biol Psychiatry 54:485–490

Nassenstein C, Braun A, Erpenbeck VJ et al (2003) The neurotrophins nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 are survival and activation factors for eosinophils in patients with allergic bronchial asthma. J Exp Med 198:455–467

Nikic I, Merkler D, Sorbara C, Brinkoetter M et al (2011) A reversible form of axon damage in experimental autoimmune encephalomyelitis and multiple sclerosis. Nat Med 17:495–499

Noble EE, Billington CJ, Kotz CM et al (2011) The lighter side of BDNF. Am J Physiol Regul Integr Comp Physiol 300:R1053–R1069

Noga O, Peiser M, Altenahr M et al (2007) Differential activation of dendritic cells by nerve growth factor and brain-derived neurotrophic factor. Clin Exp Allergy 37:1701–1708

Noseworthy JH, Lucchinetti C, Rodriguez M et al (2000) Multiple sclerosis. N Engl J Med 343:938–952

Ochs G, Penn RD, York M et al (2000) A phase I/II trial of recombinant methionyl human brain derived neurotrophic factor administered by intrathecal infusion to patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1:201–206

Patanella AK, Zinno M, Quaranta D et al (2010) Correlations between peripheral blood mononuclear cell production of BDNF, TNF-alpha, IL-6, IL-10 and cognitive performances in multiple sclerosis patients. J Neurosci Res 88:1106–1112

Petereit HF, Lindemann H, Schoppe S (2003) Effect of immunomodulatory drugs on in vitro production of brain-derived neurotrophic factor. Mult Scler 9:16–20

Radka SF, Holst PA, Fritsche M et al (1996) Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. Brain Res 709:122–301

Ramasamy DP, Ramanathan M, Cox JL et al (2011) Effect of Met66 allele of the BDNF rs6265 SNP on regional gray matter volumes in patients with multiple sclerosis: a voxel-based morphometry study. Pathophysiology 18:53–60

Rauskolb S, Zagrebelsky M, Dreznjak A et al (2010) Global deprivation of brain-derived neurotrophic factor in the CNS reveals an area-specific requirement for dendritic growth. J Neurosci 30:1739–1749

Rios M, Fan GP, Fekete C et al (2001) Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. Mol Endocrinol 15:1748–1757

Robinson RC, Radziejewski C, Stuart DI et al (1995) Structure of the brain-derived neurotrophic factor neurotrophin 3 heterodimer. Biochemistry 34:4139–4146

Robinson M, Buj-Bello A, Davies AM (1996) Paracrine interactions of BDNF involving NGF-dependent embryonic sensory neurons. Mol Cell Neurosci 7:143–151

Rosenfeld RD, Zeni L, Haniu M et al (1995) Purification and identification of brain-derived neurotrophic factor from human serum. Protein Expr Purif 6:465–471

Sarchielli P, Greco L, Stipa A et al (2002) Brain-derived neurotrophic factor in patients with multiple sclerosis. J Neuroimmunol 132:180–188

Schindowski K, Belarbi K, Buee L (2008) Neurotrophic factors in Alzheimer's disease: role of axonal transport. Genes Brain Behav 7(suppl 1):43–56

Schuhmann B, Dietrich A, Sel S et al (2005) A role for brain-derived neurotrophic factor in B cell development. J Neuroimmunol 163:15–23

Schwartz M, Kipnis J (2001) Protective autoimmunity: regulation and prospects for vaccination after brain and spinal cord injuries. Trends Mol Med 7:252–258

Scuri M, Samsell L, Piedimonte G (2010) The role of neurotrophins in inflammation and allergy. Inflamm Allergy Drug Targets 9:173–180

Shimizu E, Hashimoto K, Okamura N et al (2003) Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 54:70–75

Siffrin V, Vogt J, Radbruch H et al (2010) Multiple sclerosis—candidate mechanisms underlying CNS atrophy. Trends Neurosci 33:202–210

Sospedra M, Martin R (2005) Immunology of multiple sclerosis. Annu Rev Immunol 23:683–747

Stadelmann C, Kerschensteiner M, Misgeld T et al (2002) BDNF and gp145trkB in multiple sclerosis brain lesions: neuroprotective interactions between immune and neuronal cells? Brain 125:75–85

Tam SY, Tsai M, Yamaguchi M et al (1997) Expression of functional TrkA receptor tyrosine kinase in the HMC-1 human mast cell line and in human mast cells. Blood 90:1807–1820

Thone J, Ellrichmann G, Seubert S et al (2012) Modulation of autoimmune demyelination by laquinimod via induction of brain-derived neurotrophic factor. Am J Pathol 180:267–274

Trapp BD, Nave KA (2008) Multiple sclerosis: an immune or neurodegenerative disorder? Annu Rev Neurosci 31:247–269

Trapp BD, Peterson J, Ransohoff RM et al (1998) Axonal transection in the lesions of multiple sclerosis. N Engl J Med 338:278–285

Vega JA, Garcia-Suarez O, Hannestad J et al (2003) Neurotrophins and the immune system. J Anat 203:1–19

Vogt J, Paul F, Aktas O et al (2009) Lower motor neuron loss in multiple sclerosis and experimental autoimmune encephalomyelitis. Ann Neurol 66:310–322

VonDran MW, Clinton-Luke P, Honeywell JZ et al (2010) BDNF ± mice exhibit deficits in oligodendrocyte lineage cells of the basal forebrain. Glia 58:848–856

VonDran MW, Singh H, Honeywell JZ et al (2011) Levels of BDNF impact oligodendrocyte lineage cells following a cuprizone lesion. J Neurosci 31:14182–14190

Weinstock-Guttman B, Zivadinov R, Tamano-Blanco M et al (2007) Immune cell BDNF secretion is associated with white matter volume in multiple sclerosis. J Neuroimmunol 188:167–174

Weinstock-Guttman B, Benedict RH, Tamano-Blanco M et al (2011) The rs2030324 SNP of brain-derived neurotrophic factor (BDNF) is associated with visual cognitive processing in multiple sclerosis. Pathophysiology 18:43–52

Wiesmann C, de Vos AM (2001) Nerve growth factor: structure and function. Cell Mol Life Sci 58:748–759

Winblad B, Messamore E, O'Neill C et al (1993) Biochemical pathology and treatment strategies in Alzheimer's disease: emphasis on the cholinergic system. Acta Neurol Scand Suppl 149:4–6

Wujek JR, Bjartmar C, Richer E et al (2002) Axon loss in the spinal cord determines permanent neurological disability in an animal model of multiple sclerosis. J Neuropathol Exp Neurol 61:23–32

Xin J, Mesnard NA, Beahrs T et al (2012) CD4(+) T cell-mediated neuroprotection is independent of T cell-derived BDNF in a mouse facial nerve axotomy model. Brain Behav Immun 26:886–890

Yamamoto H, Gurney ME (1990) Human platelets contain brain-derived neurotrophic factor. J Neurosci 10:3469–3478

Ye X, Tai W, Zhang D (2012) The early events of Alzheimer's disease pathology: from mitochondrial dysfunction to BDNF axonal transport deficits. Neurobiol Aging 33:1122.e1–10

Yeh CM, Huang CC, Hsu KS (2012) Prenatal stress alters hippocampal synaptic plasticity in young rat offspring through preventing the proteolytic conversion of pro-brain-derived neurotrophic factor (BDNF) to mature BDNF. J Physiol 590:991–1010

Ziemssen T, Kumpfel T, Klinkert WE et al (2002) Glatiramer acetate-specific T-helper 1-and 2-type cell lines produce BDNF: implications for multiple sclerosis therapy. Brain 125:2381–2391

Ziemssen T, Kumpfel T, Schneider H et al (2005) Secretion of brain-derived neurotrophic factor by glatiramer acetate-reactive T-helper cell lines: implications for multiple sclerosis therapy. J Neurol Sci 233:109–112

Zivadinov R, Weinstock-Guttman B, Benedict R et al (2007) Preservation of gray matter volume in multiple sclerosis patients with the Met allele of the rs6265 (Val66Met) SNP of brain-derived neurotrophic factor. Hum Mol Genet 16:2659–2668

Zuccato C, Cattaneo E (2007) Role of brain-derived neurotrophic factor in Huntington's disease. Prog Neurobiol 81:294–330