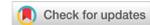**Neuroimmunology and Neuroinflammation**

Review

What is the role of Brain derived neurotrophic factor in Multiple Sclerosis neuroinflammation?

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Abstract

Multiple Sclerosis (MS) is a chronic, inflammatory and degenerative disease of the central nervous system (CNS) with an unknown etiology. The MS pathophysiology is due to altered bidirectional interactions between several immune cell types in the periphery (such as T and B cells, myeloid cells) and resident CNS cells (such as microglia and astrocytes). It is also known that inflammatory responses have both detrimental and neuroprotective effects. The release of brain derived neurotrophic factor (BDNF) by immune cells, in both peripheral blood and into inflammatory lesions in MS, but also by microglia and astrocytes, into the CNS, seems to be a possible mechanism for this neuroprotective effect. So far, the link between BDNF and neuroinflammation has been poorly investigated. A better understanding of this link could help in the development of new therapeutic strategies for MS. In this review, the role of BDNF in MS will be discussed as well as its possible alternative as an innovative therapeutic target.

Keywords: Multiple sclerosis, neuroinflammation, brain derived neurotrophic factor, neuroprotection, neurotrophin, therapeutic target

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, inflammatory and degenerative disease of the central nervous system (CNS)[1,2] of which the etiology is unknown. The clinical course of MS is characterized by fluctuating

neurological symptoms in most patients, with early clinical relapsing-remitting episodes and/or radiological worsening and different degrees of recovery (RRMS)[3]. The relapsing-remitting phase, in most patients, is subsequently followed by a chronic progressive phase; approximately 10%-15% of patients show a progressive form of the disease from onset.

For some authors, MS is an exclusive autoimmune inflammatory disease caused by dysregulated auto-reactive immune cells that traverse the blood-brain barrier (BBB) into the CNS parenchyma, attacking various cell types (the "outside-in" autoimmune hypothesis). For other authors it is a primary degenerative disease (the "inside-out" hypothesis) in which inflammation is secondary to the release of auto-antigens (components of myelin oligodendrocyte glycoprotein, myelin basic protein, and proteolipid protein), promoting autoimmunity[4]. Thus far, it is difficult to discern whether the inflammatory processes of MS are a product or a cause for neurodegeneration with a background autoimmune etiology. In all phases of the disease both immune and degenerative processes appear to coexist and this makes it difficult to definitively resolve the "outside-in" *vs.* "inside-out" controversy.

Despite this, there is well-documented evidence that, in MS, an uncontrolled inflammatory response in the CNS (neuroinflammation) causes destruction through high levels of pro-inflammatory cytokines, proteases, glutamate, and free radicals. Consequently, immunomodulatory drugs that reduce or suppress the activity of immune cells have been successfully used to reduce clinical relapses in MS and/or neuroradiological "activity", which are associated with the entry of leukocytes through the BBB[5]. Sustained disability, however, is due to a progressive neurodegenerative process, ending with axonal loss and brain atrophy, primary or secondary to the peripheral and compartmentalized inflammation in the CNS[6]. To date, no approved therapy has provided marked neuroprotective effects nor have commonly anti-inflammatory therapies, used in the treatment of the disease, showed great efficacy in the progressive phase of MS.

Neuroinflammation have not only harmful but also neuroprotective effects[7,8]. In MS and other neurological diseases, the reparative activities of inflammatory response have been demonstrated[9]. Therefore, some authors introduced the concept of "neuroprotective autoimmunity"[10,11]. The release of neurotrophins by immune cells in both peripheral blood and directly into inflammatory lesions in MS[12,13], but also by microglia and astrocytes in the CNS, stimulating neuronal growth and survival, seems to be a possible mechanism for this neuroprotective effect[14]. Among neurotrophins, brain derived neurotrophic factor (BDNF) seems to be a good candidate in promoting the beneficial effects of inflammation in MS.

In this review, the role of BDNF in MS neuroinflammation and as a novel therapeutic target will be discussed.

NEUROINFLAMMATION: THE DETRIMENTAL EFFECT

MS pathophysiology is characterized by altered bidirectional interactions between several immune cell types in the periphery and resident cells of the CNS, such as microglia and astrocytes[15]. The MS relapses, typical in the early phases of disease, are characterized by the infiltration of pro inflammatory CNS-specific effector T cells (CD4+ and CD8+ T cells), B cells and myeloid cells into the CNS parenchyma, that are activated and/or regulated in an aberrantly way[16]. The altered function of regulatory T (Treg) cells and resistance of CNS-specific effector T cells to Treg cell-mediated regulation could be a possible cause of the neuroinflammation[17-21]. Furthermore, CNS-resident cells, that secrete many inflammatory mediators, recruit inflammatory cells into the CNS. Microglia and astrocytes in particular, can also produce cytokines, chemokines and reactive oxygen species in the presence of homeostatic disturbance, promoting and sustaining axonal damage and neurodegeneration in MS[16]. Therefore, both peripheral and CNS-compartmentalized inflammatory mechanisms contribute to MS pathogenesis[22].

In the advanced stages of the disease, the infiltration of immune cells into the CNS is reduced, whereas ongoing CNS-compartmentalized inflammation seems to dominate progressive phases of MS. During this progressive phase, the role of B cells in driving inflammation seems to be prominent, particularly within meningeal inflammation[23]. In this phase, the B cell functions are antibody production, cytokine secretion, antigen presentation and ectopic formation of follicle-like structures[23-25]. The latter seem to maintain a high level of humoral response and other autoimmune mechanisms, in the CNS, independently from peripheral inflammation. This is very relevant during progressive MS phase, with the BBB being relatively intact and the contribution to disease from entry of peripheral immune cells into the brain fairly exiguous[26].

Activated microglia also plays a central role in neuroinflammation because it can sustain ongoing inflammation[27]. Microglia activation, in MS, is diffusely present in the lesions, in normal-appearing white and in grey matter[28]. Activated microglia, secreting pro-inflammatory cytokines, such as IL-1, IL-6, TNF-alfa, and IFN, promoting phagocytic activity, and presenting antigens via MHC Class II to CD4+ T cells[27], causes damage to oligodendrocytes; moreover, microglia inducing mitochondrial dysfunction, through reactive oxygen and nitrogen species, contributes to neuronal damage[29].

In addition, activation of astrocytes into demyelinating lesions contribute to oligodendrocyte injury and axonal degeneration[30]. So far, theories of either innate immune cells in the CNS are dysregulated and drive primary degeneration, or react against an unidentified primary injury causing tissue damage remain unknown.

NEUROINFLAMMATION IN MS: THE NEUROPROTECTIVE EFFECT
Evidence for neuroprotective functions of immune cells
Some evidences have unexpectedly shown that some cells of the immune system might have a protective function during inflammation. This neuroprotective effect may be partially mediated with the production of anti-inflammatory cytokines (TGF-beta, IL-10 *etc*.) and secretion of pro-inflammatory cytokines (such as IL-6, IFN-gamma, TNF-alfa) in a dose- and time-dependent manner[31-33]. Immune cells also induce neuroprotection by production and local secretion of neurotrophic factors[11,12,34]. neural growth factor (NGF) was the first neurotrophin shown to be produced by T and B lymphocytes, macrophages, and mastcells[35]. The expression of BDNF by immune cells was also subsequently described[12]. In particular, CD4+ and CD8+ T lymphocytes, B lymphocytes, and monocytes in the human peripheral immune system can produce BDNF[12]. Moreover, neurotrophin receptors expressed by immune cells can also be targeted by autocrine or paracrine neurotrophin actions. Therefore, neurotrophins seem to mediate bidirectional cross-talk between the immune and nervous systems[11].

Evidence for neuroprotective function of microglia and astrocytes
Resident CNS cells also exercise a defensive action against immune-mediated attacks, aside from being involved in neuroinflammation. Microglia has an important role in neuroprotection and this action seems to be time-dependent. Acutely activated microglia produces inflammatory mediators that recruit other activated immune cells, amplifying the inflammatory damage, but chronically activated microglia may have a neuroprotective effect supporting the growth and survival of neural progenitor stem cells[31,36]. On oligodendrocyte precursor cells microglia seems to have always direct protective action, being the detrimental action mediated by astrocytes[37].

The neuroprotective function of microglia is mediated by different mechanisms such as debris clearance, production of growth factors (overall BDNF), production of the immunosuppressive cytokine IL-10 and neuronal circuit-shaping[27,38].

TGF-beta secretion and CTLA-4 expression produced by neurons induce CD4+CD25-effector T cells to take regulatory phenotype that exerts bystander suppression in experimental autoimmune
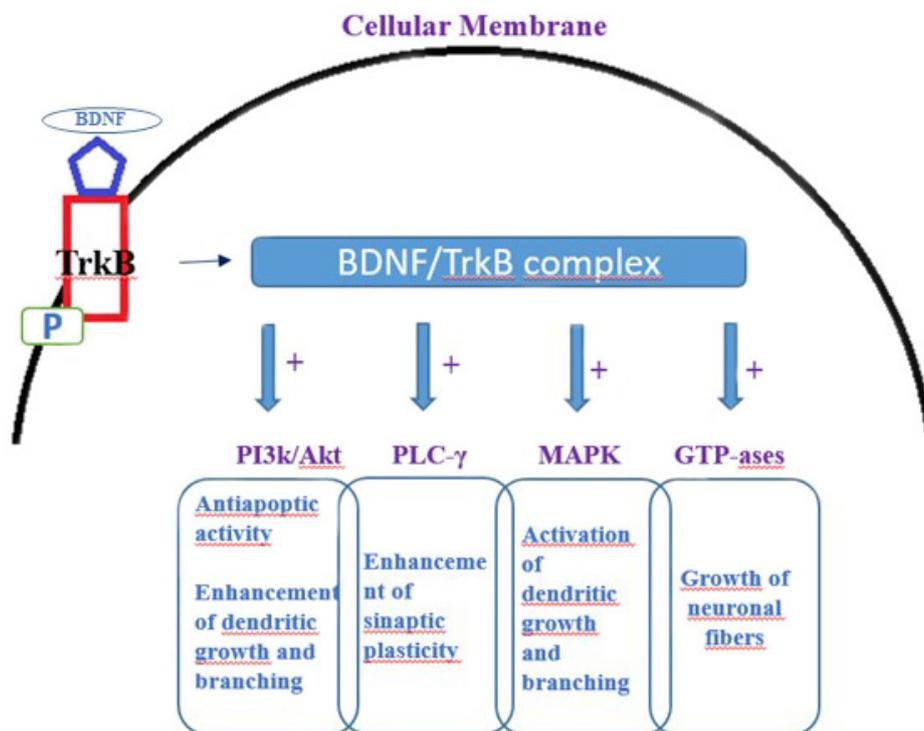
Figure 1. Intracellular signaling cascades induced by interaction of mature (m-)BDNF with TrkB receptor. Binding of BDNF to TrkB receptor induces its phosphorylation and translocation to cellular membrane. The BDNF/TrkB receptor complex triggers signaling pathways mediated by activation of PI3K, MAPK, PLC-γ, and GTP-ases. All these pathways induced by BDNF cause the enhancement/activation of dendritic growth and branching and growth of neuronal fibers. TrkB: tyrosine kinase B; BDNF: brain derived neurotrophic factor; PI3K: phosphoinositide 3-kinase; Akt: Protein kinase B; PLC: phospholipase C; MAPK: mitogen-activated protein kinase; TrkB: tropomyosin receptor kinase B

encephalomyelitis (EAE)[39]. Self-associated molecular patterns expressed by resident neurons and astrocytes drive innate cell immune responses toward a less inflammatory response[40]. Astrocytes also cause apoptosis of activated immune cells and drive microglial activity towards a less inflammatory pattern[41,42].

THE ROLE OF BDNF IN MS NEUROINFLAMMATION

BDNF

BDNF is a member of the neurotrophins gene family that includes also NGF and neurotrophins 3 and 4 (NT3 and NT4)[43] and is the neurotrophin most expressed in the brain by numerous cell types[44,45]. It plays a critical role on neuronal and oligodendroglial growth and survival, in healthy brains and in several neurologic diseases[46]. Interestingly, BDNF also modulates inflammatory homeostasis in the injured CNS[47,48].

The BDNF gene consist of a common 3′-exon that encodes the pro-BDNF region of the protein, and several species-dependent 5′-noncoding, promoter-regulated regions, terminating in a coding 5′-exon that contain the gene expression[49,50]. BDNF is translated as a proneurotrophin (pro-BDNF) that can be cut in the mature form. Both mature BDNF and pro-BDNF bind to the low affinity p75 neurotrophin receptor, activating the apoptosis cascade[51,52]. Mature BDNF binds to its high-affinity receptor tyrosine kinase B (TrkB), activating several signalling cascades[53,54] [Figure 1]. Among these, an increase in Ca^{2+} intake, phosphorylation of transcription factors, and *de novo* expression of the *BDNF* gene can be induced[53]. The nuclear factor-kappa B (NF-κB), a transcription factor with the ability to increase the expression of several pro- and antiapoptotic genes, including BDNF, is one of the main factors of inflammatory activation[55]. The

binding of BDNF to the TrkB receptor can also induce the expression of NF-κB but, the pathways for this modulation are not yet completely understood[54]. Thus, the role of BDNF in neuroinflammation, is strongly linked to its ability to induce, and being induced by, NF-κB.

Lai *et al.*[56] recently demonstrated that BDNF modulates inflammatory homeostasis, reducing inflammatory activity on microglia also through the erythropoietin and sonic hedgehog signalling pathways. BDNF may also influence the microglia inflammatory response differently in male and females probably by driving activated microglia responses toward a less inflammatory pattern in females[57].

The understanding of BDNF function in humans has greatly benefited from the identification of an SNP in the *BDNF* gene that causes a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met, c.196G>A, dbSNP: rs6265). In this Met variant form of BDNF carriers, that is, BDNF Val/Met heterozygotes and Met/Met homozygotes, the pro-domain structure of the gene is altered[58]. The polymorphism can potentially alter BDNF protein-protein interactions, binding affinities, localisation, or conformational stability of the protein. Whether the polymorphism has any significant impact on the proteome profile or posttranslational modifications of various proteins in the neuronal tissues or body fluids is currently unknown[58]. Several studies have emerged implicating the association or otherwise of this polymorphism with MS. So far, no conclusive data have been published[59]. New advances in the epigenetic field, highlight the role of BDNF antisense RNA (BDNF-AS), a naturally conserved long noncoding RNA, and of DNA methylation, in the regulation of BDNF expression in MS and in several neurological diseases[60-63]. So far, only few studies have been published on this argument[64].

BDNF in MS

BDNF is the neurotrophin which is expressed more in inflammatory brain lesions of MS patients[12,13]. A significant amount of BDNF was found in infiltrating immune cells, overall in T cells and macrophages, and in neurons and astrocytes[11]. BDNF is expressed by immune cells in actively demyelinating areas of MS lesions but not in lesions without ongoing myelin breakdown. Moreover, the neurotrophin is expressed more in the actively demyelinating edge of the plaque in the early phase of its development. It is released near to axons, not directly attacked by activated immune system cells but is at high risk of bystander damage[13]. Outside MS lesions, neurons are the major source of BDNF[13]. The literature data agree in showing that neurons are the major targets for neurotrophic interactions in the CNS. In particular, the full-length isoforms of TrkB (receptor for BDNF and NT4/5) and TrkC (receptor for NT3) are usually expressed on neuronal cells. Neurons close to MS plaques showed a prominent expression of full-length TrkB (gp145TrkB)[11]. Moreover, TrkB is upregulated in a part of damaged neurons. It is known that BDNF can be anterogradely transported and released by neurons. This process is up-regulated after axonal injury and transection[65]. The common occurrence of axonal damage in MS suggests that neuronal BDNF might contribute to endogenous neurotrophic support in MS plaques[66,67].

In older and chronic MS plaques, endogenous neurotrophins are low[13]. This may be one cause for the ongoing axonal degeneration in the chronic progressive stage of MS[68-70].

In the relapsing phase, levels of BDNF are generally reported to be increased in peripheral blood mononuclear cells (PBMC) and serum[71,72], but Azoulay *et al.*[73] found less BDNF in the serum of RRMS patients with no difference in remission and relapse phases. In MS patients, serum and CSF levels and PBMC secretion of BDNF are reduced compared to healthy controls[74,75]. In line with neuropathological findings[68-70], BDNF production by immune cells in RRMS patients is higher compared to progressive MS, suggesting again that progression of MS may be due to a failure of neuroprotection and neurorepair functions under chronic injury[72,75].

Numerous studies tried to correlate the role of rs6265 BDNF polymorphism with the prognosis of MS patients, with conflicting data so that other mechanisms could be involved in the modulation of BDNF gene[59]. Latest advances in the field of epigenetics highlight the role of epigenetic mechanisms, such as methylation, in controlling key biological processes. The presence of rs6265 SNP is not a prognostic factor for reaching a more severe Expanded Disability Status Scale (EDSS)[64]. When the percentage of methylation of the *BDNF* gene is considered, a lower percentage is associated with higher odds in achieving significant disability regardless of its polymorphism. Being a higher methylation a "silencer" of the gene, a lower inhibition of the gene correlates with a high probability in achieving an EDSS score of 6.0. Patients with more severe inflammation could appeal to a de-methylation to have a higher secretion of BDNF, preserving better CNS functions. The same patients tend to reach a more severe disability score by depleting the functional reserves of the brain at a faster rate[64]. If BDNF methylation is considered as an epiphenomenon of the disease activity (or better of the neuroinflammation status), it might help to differentiate patients with a higher degree of inflammation from patients with a lower ones. If these data will be confirmed by other studies, BDNF rs6265 polymorphism methylation could become a valid prognostic factor in MS to precociously recognise patients with a more severe disease from those with a milder one[64].

BDNF AS PROMISING THERAPY IN MS

MS, but also many other CNS diseases, are tricky to treat due to the difficulty of drugs to cross the BBB. To do this, a drug must have the appropriate physicochemical properties. Alternatively, some drugs may be directly injected into the CNS but these invasive procedures are not risk-free.

Most available MS treatment have an exclusive anti-inflammatory effect helpful in reducing clinical and neuroradiological relapses but ineffective in preventing axonal loss and neurodegeneration. On the other hand, neuroprotective and/or remyelinating molecules failed to achieve the primary endpoint in clinical trials[76,77]. Conversely, brain delivery of BDNF has a potential role in reversing neurodegenerative diseases[78,79] but, so far, not through systemic administration. Therefore, there is an urgent need for development of a non-invasive trans-BBB delivery method. All the therapeutic strategies designed for delivery of neurotrophins are well summarised in the review by Huang and Dreyfus[80].

Recently, the possibility to deliver BDNF in a non-invasive way into the CNS through a BBB modulator, the ADTC5, has been found[81]. BDNF + ADTC5 delivered to the brains of mice with RR-EAE via systemic administration, significantly improve the clinical body scores of EAE mice and induce remyelination, compared to controls. Further studies are needed to confirm these data and to definitively find the best way to delivery BDNF in CNS via systemic administration.

CONCLUSION

Few studies investigated the link between BDNF and neuroinflammation even if, in many brain disorders, neuroinflammation and altered BDNF expression are commonly found. Better understanding of the interaction between BDNF and neuroinflammation could help in improving the knowledge of diseases pathogenesis and in developing of new therapeutic strategies for CNS disorders.

In MS, a large body of neuropathological, experimental and clinical evidences shows that BDNF may play an important role in neuroinflammation modulation, neuroprotection and neurorepair. These data make BDNF a good candidate for new therapeutic strategies in MS. But, when growth factors are considered as possible treatments in brain disease, some issues have to be taken into account: first, how to increase growth factors levels within specific regions of the CNS; second, how to optimize entry of growth factors from the periphery; third, to define the rate at which BDNF is taken up by the brain; fourth, the need to better understand the pharmacological characteristics of BDNF-based substances. Further studies are needed to define these aspects.

However, the challenge for neuroprotection in MS is greater than in other brain disease, because MS requires the association of both neuroprotective and immunomodulation therapies. Any exclusive inflammatory suppression is likely required to abolish both destructive and protective components and any neuroprotective treatment cannot work without a powerful anti-inflammatory therapy.

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Conflicts of interest
The author declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

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