Review article/*Artykuł poglądowy*

Neurotrophins, cognition and multiple sclerosis

Neurotrofiny i funkcje poznawcze w stwardnieniu rozsianym

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Neuropsychiatria i Neuropsychologia 2012; 7, 2: 51–56

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Abstract

Neurotrophins regulate neuronal survival and differentiation, and facilitate synaptic plasticity in the central nervous system (CNS). Although neurons are the major source of neurotrophic factors, they are also expressed within the peripheral blood mononuclear cell (PBMC) fraction of the immunological system. Multiple sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS), causing cognitive impairment in approximately half of the patients. In MS additional neurotrophic support from PBMCs might compensate the relative neurotrophin deficiency in the damaged CNS tissue that needs to be repaired. Neurotrophins, namely nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5), may exert a potentially neuroprotective role in MS-damaged CNS, influencing the structural brain atrophy rate and functional connectivity, with both these aspects contributing to cognitive performance in MS patients. So far a lot of evidence has been gathered based on animal model studies, and evidence from studying human disease is gradually emerging. The association between neurotrophins and the CNS cholinergic system has been underlined; however, the exact mechanism of neurotrophin-mediated neuroprotection is not yet fully understood. Neurotrophins have been considered as potential novel therapies for neurodegenerative diseases, especially those with cognitive involvement. The aim of this review is to present the role of neurotrophins in the context of MS-related cognitive impairment.

Key words: neurotrophins, multiple sclerosis, neuropsychology, neuroimmunology.

Streszczenie

Neurotrofiny odgrywają rolę w regulacji różnicowania i przetrwania neuronów w obrębie ośrodkowego układu nerwowego (OUN), a także w procesach plastyczności synaptycznej leżących u podstaw uczenia się i pamięci. Mimo że głównym źródłem czynników neurotroficznych są komórki nerwowe, produkować je mogą także komórki układu immunologicznego, w tym komórki jednojądrzaste krwi obwodowej. Stwardnienie rozsiane (łac. *sclerosis multiplex* – SM) to przewlekła, zapalna, demielinizacyjna i zwyrodnieniowa choroba OUN, w przebiegu której deficyt poznawczy pojawia się u około połowy pacjentów. Neurotrofiny, w szczególności czynnik wzrostu nerwów (*nerve growth factor* – NGF), czynnik neurotroficzny pochodzenia mózgowego (*brain-derived neurotrophic factor* – BDNF), neurotrofina 3 (*neurotrophin-3* – NT-3) i neurotrofina 4/5 (*neurotrophin-4/5* – NT-4/5), mogą pełnić funkcję neuroprotekcyjną w SM, zmniejszając tempo atrofii mózgowia oraz wpływając na funkcjonalną sieć połączeń neuronalnych, a tym samym warunkując sprawność funkcji poznawczych u pacjentów z SM. Dowody na potencjał neuroprotekcyjny neurotrofin uzyskano dotychczas przede wszystkim z badań przeprowadzonych na modelach zwierzęcych, które wykazały m.in. związek neurotrofin z układem cholinergicznym mózgowia. Coraz więcej doniesień sugeruje, że neurotrofiny mogą się okazać użyteczne jako nowe metody leczenia w chorobach neurodegeneracyjnych, w tym także w SM, szczególnie w zakresie funkcjonowania poznawczego. Celem niniejszej pracy jest przedstawienie roli neurotrofin w kontekście deficytu poznawczego w przebiegu SM.

Słowa kluczowe: neurotrofiny, stwardnienie rozsiane, neuropsychologia, neuroimmunologia.

Neurotrophins in the central nervous system

Neurotrophins are a group of secretory polypeptides, belonging to the neurotrophic factor family. Their primary biological role is mediating cell survival and differentiation in the developing and in the adult nervous system (Lewin and Barde 1996). Neurotrophins include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), also known

Table 1. Expression of neurotrophins and their receptors in the human immune system

Neurotrophin	Cellular source	Target	
		receptor	cell
β-NGF	mast cells, monocytes, macrophages, eosinophils, granulocytes, basophiles, T- and B-lymphocytes	TrkA	T-lymphocytes, macrophages
NT-3	T- and B-lymphocytes, mast cells, eosinophils	TrkC >> TrkA, TrkB	macrophages >> T- and B-lymphocytes
NT-4/5	T- and B-lymphocytes, granulocytes	TrkB	B-lymphocytes, macrophages
BDNF	T- and B-lymphocytes, mast cells, granulocytes	TrkB	B-lymphocytes, macrophages

as neurotrophin-4 (NT-4) or neurotrophin-5 (NT-5), with neurotrophin-6 (NT-6) and neurotrophin-7 (NT-7), the last two thus far not described in mammals (Huang and Reichardt 2001). Neurotrophins bind with high affinity to tropomyosin related kinase (trk) receptors, and with low affinity to $p75^{NTR}$ receptors (Kaplan and Miller 2000). Nerve growth factor binds primarily with TrkA; BDNF and NT-4 have the strongest affinity towards TrkB, and NT-3 has the strongest affinity towards TrkC, but it also binds TrkA and TrkB (Chao 2003). All neurotrophins bind to $p75^{NTR}$, which can act as a co-receptor for trk, or induce an independent signalling pathway. Acting via Trk, neurotrophins activate intracellular Ras/ERK and Akt/PI3K pathways, promoting cell survival (Huang and Reichardt 2001; Kaplan and Miller 2000). Binding to $p75^{NTR}$, they can lead to either survival (NF-κB), or cell death (Rac1/JNK, Harrington *et al*. 2002; Khursigara *et al*. 2001). Trk receptors may also interact with ion channels (Lin *et al*. 1998; Tucker and Fadool 2002), and $P75^{NTR}$ may act as a co-receptor for Nogo (Wong *et al*. 2002; Wang *et al*. 2002). The cellular source and targets for different neurotrophins are presented in Table 1.

It is undeniable that neurotrophins play a key role in maintenance of neuronal functional differentiation and their survival. Also, it has been confirmed that in the adult brain neurotrophins facilitate synaptic plasticity, which warrants adequate cognition, influencing memory and learning processes. Animal models have been especially useful in unravelling neurotrophins' functions. BDNF, NGF, NT-3 and their receptors were shown to be expressed at relatively high levels in the adult hippocampus (Lewin and Barde 1996), and NGF was found to be protective of the cholinergic system in animal models (Lewin and Barde 1996; Connor and Dragunow 1998; Chen *et al*. 1997). Heterozygous NGF+/– mice present with deficiency in memory acquisition and retention (Linker *et al*. 2009). Lewis rats with experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis (MS), present with cognitive deficits, which correlate with lower β-NGF mRNA expression in several brain structures, including hippocampus and cortex (D'Intino *et al*. 2005). When treated with acetylcholinesterase inhibitors, namely rivastigmine and donepezil, the rats improved in their cognitive performance, and β-NGF expression was restored (D'Intino *et al*. 2005). Exogenous NT-3 supply improves cognitive skills in rats (Mo *et al*. 2010), and BDNF deficiency results in reduction of hippocampal synaptic plasticity (Korte *et al*. 1995). Neurotrophin-4/5 deficient mice are defective in long-term memory (Xie *et al*. 2000). To sum up, animal models provide proof for neurotrophins' involvement in complex cognitive processes.

Ever since their first description, neurotrophins have raised expectations as potential therapies for CNS diseases with a neurodegenerative component, including Alzheimer's disease (Diniz and Teixeira 2011), amyotrophic lateral sclerosis (Yanpallewar *et al*. 2012), Parkinson's disease (Stahl *et al*. 2011), ischaemic stroke (Guan *et al*. 2012) and also multiple sclerosis (MS), where neuroinflammation is associated with a substantial neurodegenerative process.

Multiple sclerosis: clinical aspects

Multiple sclerosis is a chronic, inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS). Although we have come a long way since the original description of MS pathology by Jean Martin Charcot (1868), the exact aetiology of the disease is still unknown. More importantly, it remains one of

the most common causes of disability in young adults, as the treatment that we have to offer is not sufficient. Multiple sclerosis is characterized by dissemination of the destructive process in space and in time, which is consistent with relapses and remissions of different neurological symptoms in patients. The clinical presentation reflects localization of lesions (MS plaques) within the CNS, and typically includes pyramidal paresis, sensory deficits, cerebellar syndrome, optic neuritis, and many others. The disease is characterized by marked clinical heterogeneity. It is currently diagnosed by association of a typical clinical characteristic, supported by magnetic resonance imaging (MRI) findings, including multiple T2-hyperintense lesions in typical localizations, and cerebrospinal fluid (CSF) examination, which reveals intrathecal immunoglobulin synthesis. Cognitive deficit is found in 45-65% of MS patients (Rao *et al*. 1991; Ron *et al*. 1991).

Multiple sclerosis: cognition

Cognitive dysfunction may occur early in the course of MS and it does not necessarily correlate with neurological deficit or total lesion volume measured in MRI studies. It was Charcot who first noticed that memory and affect can be severely disturbed in the course of MS. For many years, the typical euphoria and emotional liability, with a relatively small cognitive deficit, was considered a hallmark of the disease. However, the very first systematic overview of cognitive disturbances in MS patients was published only in 1951 by Pratt.

The functions that are typically impaired in MS patients are attention (especially sustained and selective attention), visuo-spatial skills, abstract reasoning, multi-tasking, information processing speed, and working memory (Rao *et al*. 1991; Kujala *et al*. 1996). Language skills and general intelligence, described by Spearman's *g* factor, remain intact. Such pattern of dysfunction is typical for disconnection of cortical and subcortical white matter tracts (Piras *et al*. 2003). Traditionally it was considered to match the subcortical dementia profile. However, recent studies have shown that both cortical and white matter lesions contribute to cognitive dysfunction in MS (Sanfilipo *et al*. 2006). In an animal model for MS, namely EAE, hippocampal pathology has been suggested as the underlying cause of cognitive impairment associated with the disease (Ziehn *et al*. 2010), which was later confirmed in a small group of MS patients (Sicotte *et al*. 2008; Roosendaal *et al*. 2009). Using advanced MRI techniques, such as diffusion tensor imaging (DTI), Roca *et al*. (2008) demonstrated that cognitive deficit in the early stage of the disease correlates with the degree of fronto-subcortical tracts' disruption. Thalamic atrophy has also been suggested as a possible cognitive impairment correlate (Houtchens *et al*. 2007; Ramasamy *et al*. 2009).

Cognitive deficit in MS patients can vary from mild to severe, often impairing the quality of life more significantly than the neurological disability does. Therefore, early recognition and treatment of MS-related cognitive dysfunction is of utmost importance.

Neurotrophins and pathological mechanisms in multiple sclerosis

Interestingly, although neurotrophins exert their functions primarily in the nervous system, they are also expressed within peripheral blood mononuclear cells (PBMCs) of the immunological system. Under normal conditions neurons are the major source and target for neurotrophins; however, in pathological conditions the additional supply from PBMCs that cross the disabled blood-brain barrier may compensate the relative neurotrophin deficiency within the CNS (Kerschensteiner *et al*. 2003; Hohlfeld 2008). This is in line with evidence for neuroprotective autoimmunity within the central nervous system. It is widely accepted that MS is initiated by an inflammatory mechanism, and later develops a neurodegenerative component (Lassman 2010). A more radical hypothesis is that the underlying pathology in MS is in fact neurodegeneration, with superimposed inflammation. It is an indisputable fact that neurotrophins appear at the highest concentrations within immunologically active edges of newly formed plaques. In these hot-spots, neurotrophins' release might protect the nearby axons that are at the strongest risk of bystander damage (Kerschensteiner *et al*. 2003; Hohlfeld 2008).

A breakthrough finding that directed attention towards the therapeutic potential of neurotrophic factors in MS was the observation that leukaemia inhibitory factor (LIF), belonging to the neurotrophic factor family, reduces clinical disease activity in mice with EAE and promotes oligodendrocyte survival (Butzkueven *et al*. 2002). Such an effect was observed no matter whether LIF was injected systemically at the time of disease induction or in the clinically overt stage, which proves that it acts by facilitating neu-

roregeneration, and not by immunosuppression. This observation led to a series of experiments in animal models, trying to unravel neurotrophins' role and their therapeutic potential in MS.

In humans it has been shown that neurotrophin levels and secretion from immune cells are linked to axon-protective potential in MS patients (Weinstock-Guttman *et al*. 2007; Azoulay *et al*. 2008). Our group has previously reported that immune-cell NT-3 is associated with brain atrophy markers in relapsing-remitting MS patients (Kalinowska-Łyszczarz *et al*. 2011). Moreover, it was established that three of the immunomodulatory drugs available for MS, namely beta interferon, glatiramer acetate and alemtuzumab, increase serum and PBMC levels of BDNF in MS patients on these therapies, which might account for one of their mechanisms of action (Azoulay *et al*. 2005; Lalive *et al*. 2008; Jones *et al*. 2010).

Neurotrophins and cognitive functions in multiple sclerosis

Obviously, neurotrophins should also be considered in the context of MS-related cognitive dysfunction. So far there have only been a few studies regarding the potential link between neurotrophins and cognitive deficit in MS patients. In 2010 Patanella *et al*. described a correlation between lower immune-cell BDNF secretion and increased time of execution in a divided attention and visual scanning task (Patanella *et al*. 2010). In 2011 a protective function of C allele of BDNF rs2030324 was suggested (Weinstock-Guttman *et al*. 2011) in the context of visual cognitive processing deficits, and linked with thalamic volume in MS patients. In our study we have also found that MS-related cognitive deficit might be associated with PBMC-derived β-NGF levels (Kalinowska-Łyszczarz *et al*. 2012).

There is a substantial amount of indirect and circumstantial evidence for neurotrophins' relation to cognition in MS, obtained from animal model studies. Nerve growth factor, for instance, has been shown to exert a protective role in the cholinergic system in animal models (D'Intino *et al*. 2005, see earlier in the text). Although in a multicentre trial acetylcholinesterase inhibitors failed to show any benefit for MS-related cognitive impairment (Krupp *et al*. 2011), it does not exclude the possibility that NGF itself could prove beneficial. NGF-mediated acetylcholine release depends on the availability of extracellular choline (Auld *et al*. 2001). In MS patients choline availability differs within the group, as shown in 1H-MR spectroscopy studies (Gustafsson *et al*. 2007). Patients with low radiological activity of the disease show lower choline concentrations, which could be caused by a more effective consumption of this compound, facilitated by NGF. Obviously, more studies are needed in this aspect.

It is also important to consider neurotrophins in the context of mood disturbances that are common in MS patients, although there is no direct evidence for the role of neurotrophins in MS patients with depression. In animal models BDNF itself shows antidepressant-like properties (Siuciak *et al*. 1997). It can also be influenced by several psychiatric drugs (Rybakowski 2008), and has been associated with response to therapy in bipolar affective disorder (Rybakowski *et al*. 2007). In the context of MS-associated depression, since clinical and preclinical studies have revealed that immunomodulatory glatiramer acetate can enhance central BDNF activity (Blanco *et al*. 2006, also: see earlier), it was suggested as a potential antidepressant to be chosen in MS patients with depression (Tsai 2007).

Concluding remarks

Undoubtedly, neurotrophins play an important regulatory role in neuronal connectivity processes in both healthy and diseased brain. One can suspect that when the CNS is exposed to continuous destructive processes, like in MS-associated inflammation, there is a higher demand for neuroprotective mediators, such as neurotrophins. Neuroprotection can be perceived in the context of generalized structural brain atrophy, and functional plasticity. Cognition is probably related to both these aspects.

Based on the available studies one can speculate that neurotrophins might serve as a potential target of novel therapies for multiple sclerosis, especially in the context of cognitive impairment. Currently approved for MS immunomodulatory treatment decreases the annualized relapse rate, but is not sufficient, as it does not prevent cognitive decline and has only a small impact on accumulation of disability over time. Neuroprotective strategies might serve as potentially beneficial add-on therapies. Further studies are needed in this aspect. The relatively short plasma half-life of neurotrophins (several minutes) poses a practical difficulty in their clinical application (Pradat *et al*. 2001; Pradat *et al*. 2002). The possible strategies could include small-molecule selective trk receptor ago-

nists, monoclonal antibodies with agonistic functions towards trk receptors, and a cellular approach, with transfer of activated autoimmune cells modified *in vitro* in order to secret neurotrophins when re-injected. Also, since neurotrophic factor delivery to the CNS seems to be a key challenge, one could consider the use of drugs that are known to induce an increase of endogenous neurotrophins, such as lithium, which was shown to increase serum BDNF concentration in, among others, Alzheimer disease patients (Leyhe *et al*. 2009).

For many years MS-related cognitive impairment has been underestimated. To date, we are aware of the social and psychological burden for MS patients, that is associated with it. Therefore, it is of utmost importance to unravel the pathological basis of cognitive dysfunction in multiple sclerosis, using a comprehensive neuropsychological, neuroradiological and neuroimmunological approach. Based on the evidence we have gathered so far, neurotrophins seem to be a plausible candidate for future therapies directed against accumulation of cognitive deficits in multiple sclerosis patients.

Acknowledgments

The author has nothing to disclose.

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