Review article

Neurodegeneration and –protection in autoimmune CNS inflammation

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Abstract

Neurodegeneration in multiple sclerosis (MS) is the structural correlate of permanent neurological disability in patients. The histopathological features of neurodegeneration include destruction of axons as well as apoptotic cell death of neuronal cell bodies. Therapeutic efforts to control these clinically important aspects of MS pathology showed limited success so far. In this review article, we give an overview about the current knowledge concerning the molecular mechanisms of neurodegeneration in autoimmune inflammation that is mainly derived from animal models. Further, we critically discuss experimental neuroprotective strategies with respect to their functional relevance and differentiate between anti-apoptotic and axon protective treatment approaches.

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Keywords: Multiple sclerosis; Experimental autoimmune encephalomyelitis; Neurodegeneration; Neuronal apoptosis; Neuroprotection

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1. Neurodegeneration in multiple sclerosis: what can we conclude from clinical studies?

In multiple sclerosis (MS), non-remitting clinical disability is mainly caused by neuronal and axonal damage. In the past decade, post-mortem and magnetic resonance imaging (MRI) studies revealed that destruction of axons begins early during the disease course (Ferguson et al., 1997; Trapp et al., 1998; De Stefano et al., 2003). Although there is some evidence that axonal damage also occurs in apparently normal white matter, most axons that undergo transection are demyelinated and located within MS lesions (Ferguson et al., 1997; Trapp et al., 1998; Lovas et al., 2000). Furthermore, apoptotic neuronal cell bodies have been found in chronically active and inactive MS lesions (Peterson et al., 2001). Brain atrophy as the result of the overall tissue loss develops in early stages of MS as well and appears to be influenced by previous inflammatory activity (Simon et al., 1999). In particular in later stages of the disease, atrophy of grey and
white matter is more relevant for the accumulating irreversible disability of MS patients than the extent of demyelination (Kalkers et al., 2001; Lin et al., 2003; De Stefano et al., 2003). With respect to the development of irreversible deficits, the most favourable long-term treatment of MS should abolish the predominantly inflammation-induced demyelination and reduce ongoing axonal and neuronal loss. Interferon-β (IFN-β) and glatiramer acetate (GA) are the two most frequently applied long-term therapies in MS (Paty and Li, 1993; Johnson et al., 1995; PRISMS, 1998; Wolinsky, 2006) which are usually given during a disease stage when neuroprotection appears to be most relevant. For both substances, an early start of the treatment is recommended to delay the development of chronic disability. However, the question of whether these substances have sufficient influence on neurodegenerative aspects in MS causes controversial discussion. The observed decrease of amount and size of T1-lesions as well as the reduction of brain atrophy reported for both agents (Rovaris et al., 2001; Hardmeier et al., 2005) only indirectly reflects the preservation of axons and neuronal cell bodies, as these MRI parameters represent the overall loss of tissue. In contrast, the level of N-acetylaspartate (NAA) is a more specific parameter for axonal damage that can be determined by magnetic resonance spectroscopy (MRS; Arnold, 1999). In respective studies, application of IFN-β and GA were shown to improve NAA values in MS patients in comparison to placebo-treated controls (Narayanan et al., 2001; Khan et al., 2005). However, other trials revealed no influence on axonal damage determined by MRS in subjects which had received immunomodulatory therapy, although the development of new lesions in T2-weighted images was considerably decreased (Sarchielli et al., 1998; Parry et al., 2003). Moreover, experience from daily clinical practice often reveals progressive disability in patients under immunomodulatory treatment. As a conclusion, the established treatment strategies of MS, which all aim at modifying the pathological immune reaction, might have certain effects on neurodegeneration (Jacobs et al., 1996; PRISMS, 2001; Wolinsky, 2004, 2006) but, in general, therapeutic efforts preventing chronic disability need to be substantially improved. For developing additional (primary) neuron/axon protective therapies, a better understanding of the underlying mechanisms by which the autoimmune reaction induces axonal and neuronal degeneration is essential. Further, the intracellular signaling steps that mediate neurodegeneration have to be characterized in detail in order to reveal potential targets for a neuroprotective therapy.

2. Studying neurodegeneration in animal models of multiple sclerosis

Due to the limited availability of human brain tissue during active stages of the disease, much of the present knowledge about apoptotic neuronal cell death and axon degeneration in MS is derived from studies in animal models. Experimental autoimmune encephalomyelitis (EAE) is the common animal model of MS, mimicking many of the histopathological hallmarks of the human disease (Hohlfeld and Wekerle, 2001; Gold et al., 2006). However, the available EAE models do not reproduce each aspect of the MS pathogenesis: The involvement of CD8+ cytotoxic T cells is underrepresented and no models mimicking primary progressive MS are available (Gold et al., 2006). In addition, cortical lesions, which have recently been characterized to give a major contribution to the accumulating disability of MS patients in chronic progressive disease stages (Kutzelnigg et al., 2005), are not well reproduced in the common EAE models. By the use of different immunization protocols and animal strains, EAE models mimicking a wide histopathological spectrum of the human disease were established, but the genetic heterogeneity of MS patients is still not sufficiently reflected (Storch et al., 1998; Wekerle et al., 1994; Weisert et al., 1998).

To study neurodegeneration under autoimmune inflammatory conditions, the rat model of myelin oligodendrocyte glycoprotein (MOG)-induced EAE has several advantages. It includes the encephalitogenic T-cell activation as well as the demyelinating humoral immune response, which are both present in MS patients (Storch et al., 1998; Stefferl et al., 1999). In mouse models of EAE in contrast, the humoral immune response, which is most relevant for the induction of demyelination (Limington et al., 1988), is underrepresented in comparison to the situation in humans. Further, in MOG-EAE in rats the amount of axonal damage is similar to the one occurring in the human disease (Kornek et al., 2000; Wujek et al., 2002). About two weeks after immunization with MOG, approximately 90% of female Brown Norway (BN) rats develop acute optic neuritis (Storch et al., 1998) which is also a frequent incident in early MS stages. In MOG-induced optic neuritis in BN rats, inflammatory infiltration and demyelination of the optic nerve is accompanied by severe axonal degeneration and consecutive apoptotic cell death of retinal ganglion cells (RGCs) (Meyer et al., 2001; Hobom et al., 2004). Fig. 1 shows the respective histopathological changes within the optic nerve of a MOG-induced rat in comparison to a sham-immunized control animal. Due to its long axonal projections, the optic system is a suitable anatomical structure for a separate investigation of RGC bodies in the retina and the associated axons within the optic nerve. Additionally, recordings of visual evoked potentials (VEPs) and electroretinograms (ERGs) can be used to differentiate between optic nerve and RGC function under in vivo conditions (Meyer et al., 2001).

3. Neuronal apoptosis in EAE and its intracellular mechanisms

In MS and EAE lesions, transection and swelling of axons as well as changes in axonal cytoskeleton and impaired axonal transport are frequently observed (Ferguson et al., 1997; Trapp et al., 1998; Kornek et al., 2000; Meyer et al., 2001; Wujek et al., 2002; Zhu et al., 1999, 2003; Schneider
et al., 2004). These pathological events within axons are considered to be responsible for the induction of secondary apoptosis of the neuronal cell body (Diem et al., 2005a).

Originally, the term “apoptosis” was used as a morphological description of dying vertebrate cells, which includes features such as cell shrinkage and chromatin condensation (Kerr et al., 1972). Apoptotic cell death is an energy-consuming process that involves the activation of several genes within a suicide cascade. During development, neuronal apoptosis provides an efficient strategy for eliminating unwanted neurons or those which have lost their function. In the adult CNS, however, apoptosis of neuronal populations contributes to manifestation of clinical symptoms. Under pathological conditions, apoptosis results in an irreversible loss of neurons which are involved in the normal function of the CNS. Apoptosis of neuronal cell bodies as a result of traumatic axonal injury has previously been characterized in detail (Isemann et al., 1997; Diem et al., 2001; Ugolini et al., 2003). Despite clear differences concerning the primary stimulus which induces neuronal cell death under traumatic versus autoimmune inflammatory conditions, remarkable similarities in the molecular mechanisms are present. These biochemical events executing programmed cell death include the interaction of different signaling cascades and are highly conserved.

3.1. The Bcl-2 family of proteins

In EAE, alterations of the Bcl-2 family of proteins are involved in early stages of neurodegeneration (Offen et al., 2000; Lev et al., 2004; Hobom et al., 2004; Diem et al., 2005b). The Bcl-2 family of apoptosis regulatory proteins consists of at least 15 Bcl-2 homologues, which are categorized based on the presence or absence of conserved structural motifs, the Bcl-2 homology domains (Benn and Woolf, 2004). Although all members of the Bcl-2 family share a high homology, they have major functional differences, acting either as agonists or antagonists of apoptotic cell death (Bähr, 2000). For example, conformational changes of the pro-apoptotic Bax protein induce cytochrome c release out of mitochondria and consecutively the formation of the apoptosome, whereas the anti-apoptotic member of the Bcl-2 family, Bcl-XL, prevents the release of cytochrome c (Parsadanian et al., 1998) as indicated in Fig. 2. The functional relevance of Bcl-XL for neuronal survival in MOG-induced optic neuritis was shown in a recent study (Diem et al., 2005b). To avoid unwanted anti-apoptotic effects of Bcl-XL on T-lymphocytes, which could increase inflammatory infiltration (Waiczies et al., 2002), a local protein delivery approach via a “Trojan horse peptide” was used (Diem et al., 2005b). Therefore, Bcl-XL was linked to the protein transduction domain of the HIV transactivator of transcription, which facilitates the delivery of macromolecules into cells (Dietz and Bähr, 2004). Using transgenic mice over-expressing the Bcl-2 gene demonstrated in addition the functional importance of the anti-apoptotic Bcl-2 protein in reducing axonal degeneration in EAE (Offen et al., 2000). Furthermore, ablation of the bax gene improved axonal damage in this neuro-inflammatory animal model (Lev et al., 2004). In MOG-induced optic neuritis in BN rats, a simultaneously occurring, inverse regulation of Bcl-2 and Bax was observed during the early and severe apoptosis of RGCs: An increase in the protein level of Bax as well as a reduced expression of Bcl-2 were shown to precede the major loss of RGCs (Hobom et al., 2004).

3.2. Mitogen-activated kinases

Neurotrophin-induced neuroprotection, which also seems to be endogenously relevant under autoimmune inflammatory conditions (Kerschensteiner et al., 1999), involves an
additional pathway, the phosphorylation of mitogen-activated protein kinases (MAPKs). A schematic drawing of this pathway including its activation steps is given in Fig. 2. Activation of MAPKs by phosphorylation can be induced by different neurotrophic factors, including nerve growth factor (NGF), ciliary neurotrophic factor (CNTF), or brain-derived neurotrophic factor (BDNF) (Segal and Greenberg, 1996). In vitro, the phosphorylation of MAPKs was observed to depend on the Janus tyrosine kinase/signal transducers and activators of transcription (Jak-STAT) pathway (Bonni et al., 1997; Rajan and McKay, 1998). In addition, multiple second messengers such as cyclin adenosine monophosphate, protein kinase A, or the small G protein Ras contribute to the regulation of MAPK signaling (Grewal et al., 1999). In different neuronal cell types, phospho-MAPK levels are increased during exposure to chronic stress, brain injury, or during development of neurodegenerative diseases (Ferrer et al., 2001; Trentani et al., 2002; Dash et al., 2002). Inhibition of MAPK kinase (MEK), the upstream kinase which induces the phosphorylation of MAPKs, decreased the survival of RGCs in MOG-induced optic neuritis in rats (Diem et al., 2003). This observation suggests that the phosphorylation of MAPKs could serve as an endogenous rescue mechanism which is involved in the preservation of neurons under autoimmune inflammatory conditions. This hypothesis is corroborated by data showing pro-apoptotic effects of methylprednisolone, the standard treatment of acute MS relapses, on RGCs during experimental autoimmune optic neuritis. In this study, neuronal apoptosis caused by methylprednisolone was mediated via a calcium-dependent inhibition of MAPK phosphorylation independent of the cytosolic glucocorticoid receptor (Diem et al., 2003). In contrast, an increased phosphorylation of MAPKs led to improved neuronal survival in MOG-EAE. Daily systemic application of erythropoietin (Epo), a neurotrophin-like cytokine, substantially ameliorated survival and function of RGCs during MOG-induced optic neuritis, despite severe inflammation in the optic nerve (Sättler et al., 2004). This anti-apoptotic effect of Epo has been shown to be, in part, mediated via an increase of the phosphorylation of MAPKs (Sättler et al., 2004). CNTF, another cytokine with pleiotropic neuroprotective effects stimulated MAPK phosphorylation via the Jak/STAT pathway in the same model and thereby led to a functionally relevant increased survival of RGCs (Maier et al., 2004).

3.3. The phosphatidylinositol 3-kinase/Akt pathway

Similar to the MAPK cascade, the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway has originally been described as a signal transduction step involved in growth-factor-induced neuroprotection against different apoptotic stimuli in vitro as well as in vivo (Dudek et al., 1997; Kermer et al., 2000). In general, interaction of neurotrophins or cytokines with their highly specific receptors activates PI3-K which generates various phosphorylated phosphatidylinositides. These second messengers lead to activation of protein kinase B, also called Akt (Coffer et al., 1998). Phospho-Akt in turn can phosphorylate and thereby inactivate the pro-apoptotic protein Bad (Datta et al., 1997) as well as unprocessed or active caspase-9 (Cardone et al., 1998). This inhibition of...
caspase-9 results in decreased levels of the downstream effector caspase-3 (Li et al., 1997). Fig. 2 shows this cascade of anti-apoptotic signaling within a neuronal cell. In a model of surgical axotomy of the optic nerve, it has been demonstrated that phospho-Akt levels in RGCs were down-regulated (Kermer et al., 2000) and that these neurons could be rescued by therapies which re-increase the phosphorylated form of this protein (Diem et al., 2001). Similarly, decreased levels of phospho-Akt were observed in the retina during induction and manifestation of MOG-induced optic neuritis (Hobom et al., 2004), indicating that autoimmune inflammatory damage to the optic nerve suppresses the same cascades as a primarily traumatic stimulus. During MOG-EAE, phospho-Akt levels in RGCs re-increased around one week after manifestation of general clinical symptoms suggesting a temporary breakdown of this intracellular endogenous rescue mechanism simultaneously with the highest rate of apoptotic neuronal cell death. In contrast to CNTF which did not lead to increased phosphorylation of Akt in this model (Maier et al., 2004), Epo strongly activated PI3-K in RGCs and thereby decreased caspase-3 activation and neuronal apoptosis (Sättler et al., 2004). Application of specific inhibitors of both upstream kinases MEK and PI3-K indicated that an interaction of the MAPK and Akt pathway does not play a role in Epo-induced neuroprotection during MOG-EAE. Further, these experiments revealed that the PI3-K/Akt pathway is more relevant for protecting RGCs from secondary apoptosis during MOG-induced optic neuritis than the activation of MAPKs (Sättler et al., 2004).

3.4. Ionic changes and energy depletion

Recently, it has been hypothesized that the molecular mechanisms of axonal/neuronal injury in hypoxia as well as in inflammatory demyelinating diseases share a final common pathway: Under both pathophysiological conditions, a mismatch of the cellular demand and the production of energy can occur which results in depletion of adenosine triphosphate (ATP). After destruction of myelin, axons have a high demand of ATP due to the re-distribution of sodium channels along the demyelinated segments. Compared to physiological conditions, each action potential is accompanied by a higher sodium influx, resulting in an increased energy demand to keep the resting potential and the sodium concentration within the normal range (Poliak and Peles, 2003). Additionally, increased levels of nitric oxide produced in inflammatory lesions (Smith and Lassmann, 2002) have been shown to reduce the cellular ATP production by interfering with the mitochondrial electron transport (Brown and Borutaite, 2002; Garthwaite et al., 2002). ATP depletion, in turn, induces a failure of the Na/K-ATPase with an increase of the intracellular sodium concentration and changes in the resting potential of the neuronal membrane. This rising membrane potential can inhibit the inactivation of sodium channels with a further augmentation of sodium influx into neurons occurring in parallel with an efflux of potassium (Taylor, 1993; Styx et al., 1993; Styx, 2004, 2005). As a result, calcium is released from intracellular stores and, additionally, calcium influx occurs via voltage-gated calcium channels (Brown et al., 2001; Nikolaeva et al., 2005). Furthermore, the rising sodium concentration reverses the direction of the Na/Ca-exchanging ATPase, which additionally carries calcium into the neuron in order to reduce the concentration of sodium (Styx, 2004, 2005). A subsequent activation of various ionotropic and metabotropic glutamate receptors follows, resulting in a finally lethal increase of intracellular calcium which then activates a variety of calcium-dependent enzymes and further inhibits the energy production in mitochondria (Stys and Jiang, 2002; Styx, 2004). The functional relevance of the increased sodium and calcium influx into neurons under autoimmune inflammatory conditions has been shown by different studies testing respective channel blockers in EAE. Sodium channel blockade with phenytoin or flecainide led to significant axon protection within the spinal cord and improved the functional outcome of mice during MOG-induced EAE as assessed by in vivo electrophysiology (Lo et al., 2002; Lo et al., 2003; Bechtold et al., 2004). Inhibiting voltage-gated calcium channels, which have been shown to be subtypically up-regulated in EAE (Kornek et al., 2001), also protected spinal cord axons from EAE-induced degeneration (Brand-Schieber and Werner, 2004).

Increased calcium influx into neurons after activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)/kainate receptors seems to be another important mechanism for neuronal degeneration in MS and EAE. These receptors mediate toxicity induced by the excitatory neurotransmitter glutamate which has been shown to contribute to neuronal apoptosis in neurodegenerative disorders such as Alzheimer’s disease, Huntington’s disease and amyotrophic lateral sclerosis (Mattson, 2000). The sources of increased glutamate concentrations under chronic inflammatory conditions are supposed to be activated leukocytes and macrophages/microglia which have been shown to produce large amounts of the excitotoxin by up-regulating glutaminase (Piani et al., 1991). Down-regulation of glutamate dehydrogenase and glutamine synthetase, enzymes involved into glutamate transport or glutamate metabolism, further contributes to increased glutamate levels as shown in an adoptive transfer EAE model in mice (Hardin-Pouzet et al., 1997). The relevance of glutamate toxicity for the human disease as well has been suggested by the observation of increased glutamate levels in the cerebrospinal fluid of patients during an acute MS relapse (Stover et al., 1997). Additionally, high expression levels of glutaminase were detected in macrophages and microglia of active MS lesions in close proximity to damaged axons (Werner et al., 2001). Therapeutic administration of different AMPA/kainate receptor antagonists in rats suffering from myelin basic protein (MBP)-induced EAE improved neurological outcome and limited apoptotic cell death of spinal cord neurons (Smith et al., 2000). Not only neurons, also oligodendrocytes which
express the AMPA/kainate type of excitatory glutamate receptors can be damaged by glutamate (Pitt et al., 2000) which would lead to secondary axonal and neuronal degeneration due to the loss of myelin sheaths.

4. Neuroprotective treatment approaches

Current research on neurodegenerative aspects in EAE or MS is focused on developing treatment strategies that inhibit degeneration of axons as well as protect the neuronal cell body from apoptotic cell death by directly targeting the neuron itself. The concept of achieving neuroprotective effects as a secondary phenomenon resulting from the treatment of inflammation and autoimmunity was supported by studies showing a close association of axonal damage and inflammation (Trapp et al., 1998). However, trials evaluating anti-inflammatory therapies in MS patients have revealed that elimination of the inflammatory component of the disease does not necessarily stop progression of brain and spinal cord atrophy (Paolillo et al., 1999). Methylprednisolone, the standard treatment of autoimmune optic neuritis (Brusaferri and Candelise, 2000), accelerates visual recovery, but it does not influence the final visual outcome (Beck et al., 1993). Using MRI techniques, it has been shown that treatment with methylprednisolone did not limit ongoing lesion lengthening triggered by an episode of acute optic neuritis in subgroups of MS patients (Kapoor et al., 1998) nor did it prevent optic nerve atrophy (Hickman et al., 2003). In MOG-induced optic neuritis, even detrimental effects of anti-inflammatory treatment with methylprednisolone on the survival of RGCs have been described (Diem et al., 2003).

An increased secretion of NGF was recently reported to be induced by IFN-β in brain endothelial cells (Biernacki et al., 2005), nevertheless, the effects of this cytokine on neuronal apoptosis in MOG-induced EAE appear to be limited (Sättler et al., 2006; Maier et al., 2006).

On the other hand, blocking apoptosis signals in neurons without simultaneously treating inflammation-induced axon degeneration does not lead to functionally relevant results: Although application of Epo as well as CNTF increased survival rates of RGCs during MOG-induced optic neuritis, visual acuity in these animals remained poor due to severe and ongoing degeneration of optic nerve axon fibers (Sättler et al., 2004; Maier et al., 2004). Even anti-apoptotic treatment approaches that have been shown to improve the functional outcome in rodent models of cerebral ischemia, led to disappointing results after translation into clinical trials (Muir and Lees, 2003; Hoyle et al., 2004). These observations led to a hypothesis that can easily be transferred to the situation in MS: Due to the much larger proportion of white matter in the human brain, preventing apoptosis of neuronal cell bodies alone might not find its expression in clinical scores and neurological function (Ransom and Brown, 2003). Therefore, neuroprotective approaches in combination with the established disease-modifying therapies might be promising. Recently, it has been demonstrated in different EAE models that simultaneous anti-inflammatory and neuroprotective therapies were beneficial with respect to clinical outcome and neurodegeneration. Combined treatment with an anti-inflammatory antibody, an AMPA/kainate receptor antagonist, and the N-terminal tripeptide of insulin-like growth factor (IGF) led to decreased paralysis, inflammation, and

![Diagram](image-url)
neuron/axon degeneration in mice (Kanwar et al., 2004). Simultaneous application of methylprednisolone and Epo in MOG-induced optic neuritis resulted in a functional, electrophysiological improvement of optic nerves and RGCs as demonstrated in Fig. 3 as well as in increased neuronal and axonal survival (Diem et al., 2005c). The advantage of the "atypical" neurotrophin Epo in this context lies in its application mode and the good tolerability which makes it a promising candidate for transfer into a clinical trial. In a study of acute ischemic stroke in humans, intravenous treatment with Epo was well tolerated and an improvement in clinical outcome as well as a reduction in infarct size was observed (Ehrenreich et al., 2002).

The concept of "benign autoimmunity" might help to explain the effectiveness of combining anti-inflammatory treatment with application of neurotrophin-like substances such as IGF or Epo in EAE. According to this hypothesis, autoimmune inflammatory conditions can promote neuronal survival via a transient reduction of energy requirement (Moalem et al., 1999) or increased secretion of neurotrophic factors by cells of the immune system. Production of BDNF upon antigen stimulation was shown in a study on T cell lines specific for myelin autoantigens such as MBP or MOG (Kerschensteiner et al., 1999). In this study, immune-cell derived BDNF was demonstrated to support the survival of sensory neurons in vitro. BDNF immunoreactivity was also detected in inflammatory cells in lesional areas within the brain of MS patients (Kerschensteiner et al., 1999). Behind this background, delivery of exogenous neurotrophin-like substances might compensate for the lack of endogenous neurotrophic factor support resulting from anti-inflammatory treatment of EAE or MS.

In summary, it is evident that characterization of the molecular mechanisms, kinetics and pathogenesis of neurodegeneration in chronic inflammatory autoimmune CNS diseases is the basis for the development of future neuroprotective therapies. However, these neuroprotective treatment approaches should cover neuronal cell bodies threatened by apoptotic cell death as well as degenerating axons within inflammatory lesions. Otherwise, "protective" effects without functional relevance can be the consequence. As this therapeutic aim might not be reached by a mono-therapy, the combination of anti-inflammatory/immunomodulatory therapies with primary neuroprotective agents seems to be reasonable. In parallel, diagnostic tools able to detect neurodegeneration in early stages of MS are needed which can be used during clinical routine. Further, prognostic markers which help to identify patients endangered by early conversion into progressive disease stages would allow individually adjusted neuroprotective intervention.

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