Available online at www.sciencedirect.com

SCIENCE DIRECT®

Brain Research Reviews 48 (2005) 185–195

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/brainresrev

Review

Macrophages and neurodegeneration

Jerome J.A. Hendriks, Charlotte E. Teunissen, Helga E. de Vries, Christine D. Dijkstra*

Department of Molecular Cell Biology and Immunology, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, The Netherlands

Accepted 9 December 2004
Available online 3 February 2005

Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). Demyelination is a classical feature of MS lesions, and neurological deficits are often ascribed to the reduced signal conduction by demyelinated axons. However, recent studies emphasize that axonal loss is an important factor in MS pathogenesis and disease progression. Axonal loss is found in association with cellular infiltrates in MS lesions. In this review, we discuss the possible contribution of the innate immune system in this process. In particular, we describe how infiltrated macrophages may contribute to axonal loss in MS and in experimental autoimmune encephalomyelitis (EAE), the animal model for MS. An overview is given of the possible effects of mediators, which are produced by activated macrophages, such as such as pro-inflammatory cytokines, free radicals, glutamate and metalloproteases, on axonal integrity. We conclude that infiltrated macrophages, which are activated to produce pro-inflammatory mediators, may be interesting targets for therapeutic approaches aimed to prevent or reduce axonal loss during exacerbation of inflammation. Interference with the process of infiltration and migration of monocytes across the blood–brain barrier is one of the possibilities to reduce the damage by activated macrophages.

Theme: Cellular and molecular biology
Topic: Neuroinflammation

Keywords: Macrophages; Neurodegeneration; Multiple sclerosis; Experimental allergic encephalomyelitis (EAE); Monocyte migration; Blood–brain barrier; Axonal loss

Contents

* Corresponding author. Fax: +31 20 444 8081.
E-mail address: cd.dijkstra@vumc.nl (C.D. Dijkstra).

0165-0173/$ - see front matter.
doi:10.1016/j.brainresrev.2004.12.008

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS). In the brain and spinal cord of MS patients, inflammatory lesions occur in association with blood vessels. Magnetic resonance imaging (MRI) studies revealed that gadolinium-enhancing lesions appear and disappear, even in clinically stable MS patients, indicating that the formation of new lesions is variable in place and time. Demyelination is a classical feature of MS lesions, and neurological deficits are often ascribed to reduced conduction capacity of demyelinated axons. However, it has already been recognized in the earliest MS studies by Charcot [28] that axonal loss is also an important feature of MS pathology. Nevertheless, in the century of research following these findings, MS was generally regarded as a demyelinating disease in which axons are relatively spared. Only recently, axonal loss has received renewed interest mainly due to the use of techniques detecting ongoing axonal damage. Now it becomes clear that axons are damaged during inflammation in MS which may eventually lead to substantial irreversible axonal loss [49,94,174]. Evidence for the contribution of cytotoxic $CD8^+$ T cells to axonal damage in an MHC class I dependent way is evolving [10,88,118,119,145] and mechanisms are being unraveled [111,114,144]. In addition, antibodies to axonal components like neurofilaments and gangliosides (predominantly located in neurons) are elevated in the CSF of MS patients [120,142,151] and may contribute to neuronal damage by directing macrophages to their neuronal and axonal targets. In this review, we will not discuss these antigen-specific contributions of the immune system to axonal loss. Our focus is on the possible contribution of the innate immune system in this process. In particular, we describe how infiltrated macrophages may contribute to axonal loss in MS and in experimental autoimmune encephalomyelitis (EAE), the animal model for MS.

2. Axonal damage in MS and EAE tissue

Axonal loss can be detected by classical histochemical methods such as Bodian silver impregnation or by electron microscopy. The percentage of axon loss is assessed by comparison of total numbers of axons in affected and unaffected tissue. After the early descriptions of Charcot, contradictory results have been reported, some claimed profound (50%) axonal loss [28] whereas others described unaltered axonal densities in most MS lesions [69]. These discrepancies were explained by differences in sensitivities of used methods, leaving the exact percentage of axonal loss unresolved. Recent, more detailed, studies show that there is indeed progressive axonal loss in MS lesions: up to 70% of axons can be lost in the spinal cord of MS patients [12]. Axonal loss correlates with neurological disability in MS [37,43,100] and chronic EAE [183], suggesting that axonal degeneration is at least partly responsible for disease progression. The classical methods, such as silverstaining on postmortem tissue, detect axonal loss that may be caused months or even years before. To fully understand the underlying mechanisms of axonal loss, it is important to detect axonal damage at an early stage.

Nowadays, the accumulation of the amyloid precursor protein (APP), a normal neuronal membrane-spanning glycoprotein transported by fast axonal transport [89], is used as a marker for acute axonal damage in the CNS [18,59,97,137,155,185]. In MS, the “age” of a lesion is indicated by various criteria, distinguishing early and late active lesions, both with signs of ongoing demyelination and inflammation, and inactive lesions [40,175]. Accumulation of APP was detected in axonal ovoids in active lesions and at the border of inactive lesions [49]. APP accumulation was more frequent in early and late active lesions compared to relatively ‘older’ inactive lesions in MS, but was unrelated to lesion age in EAE. In both EAE and MS studies axonal damage correlated with the location of cellular infiltrates [43,49,90,94].

Immunohistochemistry for non-phosphorylated neurofilaments is another method to detect axonal damage in MS lesions which was first described by Trapp et al. [174]. In healthy axons, phosphorylated neurofilaments are predominantly found in axons, whereas non-phosporylated neurofilaments are mainly localized in perikarya and dendrites [162]. Using this method, transected axons, caliber alterations and terminal ovoids have been identified in MS lesions. Also, discontinuous non-phosporylated neurofilament immunoreactivity was observed, which may indicate axonal degeneration distal from the sites of transection, as in Wallerian degeneration [22,174]. Whereas APP is confined to short axonal segments, non-phosporylated neurofilament staining is more diffuse and uniformly distributed along the damaged axon [104].

Recently, changes in dendritic and synaptic proteins have been found in EAE, indicating loss of contacts between neurons [189]. Besides this, a redistribution of ion channels in axons indicated neuronal deficits [31,32,141]. Due to demyelination, an increased expression or (re)distribution of certain types of ion channels is induced which may temporally restore axonal conduction. Eventually, this ion channel redistributrion may have a deleterious effect causing an influx of noxious levels of Ca^{2+} and subsequent axonal destruction [13,16,17,55]. In EAE, increased expression of specific types of sodium channels co-localized with APP immunoreactivity and the presence of a Na^+/Ca^{2+} exchanger [32,33]. The immunostaining for the pore-forming unit of the voltage-gated Ca^{2+} channel (N-type) was also increased in demyelinating lesions and co-localized with APP positivity, indicating altered Ca^{2+} transport [91]. In addition, expression of genes involved in Ca^{2+} homeostasis was found to be dysregulated during EAE, indicating early neuronal dysfunction [122].