Biochimica et Biophysica Acta 1862 (2016) 506–510

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Oxidative stress and its impact on neurons and glia in multiple sclerosis lesions☆

Hans Lassmann [a,*], Jack van Horssen [b]

[a] Center for Brain Research, Medical University of Vienna, Austria
[b] Dept. of Molecular Cell Biology and Immunology, VU University Medical Center Amsterdam, Neuroscience Campus Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 19 May 2015
Received in revised form 24 September 2015
Accepted 25 September 2015
Available online 8 October 2015

Keywords:
Oxidative stress
Multiple sclerosis
Neurons
Oligodendrocytes
Astrocytes
Microglia

ABSTRACT

Oxidative injury plays a major role in brain damage in many age-related human brain diseases and is particularly pronounced in the progressive stage of multiple sclerosis. In the latter it is related to the chronic inflammatory process and is amplified by brain changes due to aging and accumulation of disease burden. It induces demyelination and neurodegeneration by direct oxidation of lipids, proteins and DNA as well as by the induction of mitochondrial injury, which results in energy deficiency and further amplification of oxygen radical production. It affects neurons and all types of glia cells, but neurons and oligodendrocytes are most vulnerable. Difference in the susceptibility for oxidative injury between different cellular components of the central nervous system appears to be due to cell type specific differences in anti-oxidant defense mechanisms, iron loading, cellular susceptibility to apoptosis induction and energy demand. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

© 2015 Elsevier B.V. All rights reserved.

1. Introduction

Oxidative stress is a major driving force for tissue injury in brain aging as well as in chronic inflammatory, vascular and neurodegenerative disorders of the central nervous system [39]. It is induced through the production of reactive oxygen and nitric oxide species predominantly by microglia cells and macrophages, which in response to activation express the respective enzymes necessary for their production, such as different nicotinamide adenine dinucleotide phosphate (NADPH)-oxidases [12], myeloperoxidase [19,20] and inducible nitric oxide synthase [27,54]. Interaction of reactive oxygen species with nitric oxide leads to the formation of peroxynitrite, a highly reactive molecule involved in protein, lipid and DNA oxidation [11]. Reactive oxygen and nitrogen species, in particular peroxynitrite, also impair the function of the mitochondrial respiratory chain, leading to electron leakage and further propagation of oxidative injury [33]. Another amplification factor of oxidative injury is the liberation of divalent iron from degenerating cells into the extracellular space, which gives rise to the formation of highly reactive hydroxyl radicals through the Haber/Weiss/Fenton reaction [22,43]. Iron accumulates with age in the human brain, where it is mainly stored in oligodendrocytes and myelin. Thus, amplification of oxidative injury by iron is particularly important in inflammatory demyelinating diseases due to the widespread destruction of oligodendrocytes and the chronic microglia activation. Since the brain and spinal cord have a very limited potential for cell renewal and repair, chronic oxidative injury is detrimental and its consequences accumulate with aging and in chronic disease.

For this reason oxidative stress is under normal conditions limited by potent anti-oxidative defense mechanisms. Numerous enzymes and small molecules involved in anti-oxidant defense mechanisms, have been found up-regulated in active MS lesions, including superoxide dismutases [46], catalase [18], glutathione [8], heme oxygenase 1 [46], the Morbus Parkinson-associated molecules Parkin and PINK [50,51] and the mitochondrial anti-oxidants peroxiredoxin-3 and thioredoxin-2 [34]. Their expression appears to be regulated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [26,45] and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) [34]. The expression of these molecules has mainly been detected in astrocytes and macrophages and in vitro data suggest that the induction of anti-oxidant defense mechanisms in astrocytes may even protect neurons in co-culture [34]. However, in active demyelinating lesions immunoreactivity for some of these molecules was also found in oligodendrocytes [34,42]. As an example, Nrf2 is highly expressed in oligodendrocytes and in particular in injured or dying cells at sites of active demyelination in early MS as well as in slowly expanding lesions of patients with progressive MS [25].

☆ This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

* Corresponding author at: Center for Brain Research, Medical University of Vienna, Spitalgasse 4, A-1090 Wien, Austria.
E-mail address: hans.lassmann@meduniwien.ac.at (H. Lassmann).

http://dx.doi.org/10.1016/j.bbadis.2015.09.018
0925-4439/© 2015 Elsevier B.V. All rights reserved.

2. Mechanisms of oxidative tissue injury

Oxidative injury leads to tissue degeneration in the central nervous system by various different mechanisms. First it may directly oxidize lipids, proteins and DNA, thus interfering with the function of these molecules and propagating their degradation. This is mainly mediated by highly active species, such as hydroxyl radicals or peroxynitrite [11]. These molecules are rapidly inactivated, when diffusing from their site of production into the surrounding tissue. Thus these molecules have very short half-life times and act within very narrow half-life distances. In pathological conditions oxidized and nitrosylated proteins are mainly detected during a very short time window of lesion activity and in a close proximity to activated inflammatory cells [54]. As examples, neurons or oligodendrocytes with accumulation of oxidized lipids in multiple sclerosis lesions are only seen in highly active lesions and are present as single positive cells in close association with activated microglia and macrophages [13]. Oxidative injury can also induce the oxidation of nuclear DNA, triggering the induction of the apoptotic cell death program [21].

Mitochondria are highly vulnerable to the action of reactive oxygen species, which are able to interfere with multiple different components of the respiratory chain [33], with the heme-containing molecule COX1 of the complex 4 of the respiratory chain being the most vulnerable [31]. Oxidation of respiratory chain components results either in functional inhibition or in increased degradation of the respective proteins. Both mechanisms lead to partial dysfunction of energy metabolism, decreased ATP levels and consequently neuronal dysfunction or neurodegeneration. Due to the increased energy demand of demyelinated axons mitochondrial dysfunction is particularly deleterious in demyelinating diseases, such as multiple sclerosis [30]. Oxidative injury, however, may also induce mitochondrial DNA mutations and deletions [7]. With cell aging, the population of mitochondria with large gene deletions gradually expands on the expense of normal mitochondria [6]. This finally leads to progressive mitochondrial dysfunction in neurons, which is particularly prominent in the progressive stage of multiple sclerosis [7]. In addition, despite being associated with energy deficiency, mitochondrial damage can also induce neurodegeneration by other means. Liberation of cytochrome C and of apoptosis inducing factor from mitochondrial stores induces apoptosis [36], and apoptotic oligodendrocyte death can be seen as a primary mechanism of demyelination in multiple sclerosis lesions [3,29,48]. In neurons, mitochondrial dysfunction is deleterious in the course of impulse conduction. In the state of energy deficiency, sodium ions, which enter the axon during spiking, are not removed by the ATP-dependent sodium pump. Increased intra-axonal Na^{+} ions are then replaced by Ca^{++} through the inverse operation of the Na^{+}/Ca^{++} exchanger leading to an intra-axonal Ca^{++} overload and subsequent protease-induced axonal degeneration [15,44]. As will be discussed in detail below, the combination of oxidative and mitochondrial injury primarily affects the cell processes of neurons and glia, resulting in disturbance of cellular communication before actual cell loss is seen. Overall, these data show that the initial trigger of oxidative injury induces different cascades of molecular events, leading to cell death and cell process degeneration, which may be different in different cell types.

Oxidative injury, reflected by the accumulation of oxidized lipids, proteins and DNA, associated with cell degeneration, is seen in active and slowly expanding lesions, in the white and gray matter and in acute, relapsing or progressive MS. However, the mechanism leading to oxidative injury may differ in a stage dependent way. In early stages of MS it is mainly associated with inflammation and oxidative burst activation of microglia, while in the progressive stage additional age and lesion burden related amplification mechanisms, such as chronic mitochondrial injury or iron accumulation in the brain and its liberation in demyelinating lesions, appear to become increasingly important [30]

3. The response to oxidative injury differs between neurons and different glial cells

Although oxidative injury and mitochondrial damage play an important role in brain aging as well as in many different inflammatory, vascular and neurodegenerative diseases of the central nervous system [39], a direct comparison of gene expression in active lesions showed that in the progressive stage of multiple sclerosis these pathways of tissue injury are much more pronounced compared to lesions of other chronic inflammatory diseases or Alzheimer's disease [13]. The profound oxidative injury seen in MS lesions allows to study the response of individual cell populations in the central nervous system.

3.1. Neurons

Due to their electrical activity neurons have a very high energy demand and their capability to cope with oxidative stress seems to be limited. The latter may be due to a rather low expression of different regulators of anti-oxidant defense, such as Nrf2 [45] even under inflammatory conditions. PGC-1α, a transcription co-regulator of key mitochondrial anti-oxidant mechanisms is reduced in a subset of neurons in the cortex of progressive MS patients [52]. Furthermore, deletions of mitochondrially encoded genes are predominantly seen in neuronal cell bodies, where they appear to accumulate due to retrograde transport from axons, damaged by oxidative injury in white matter plaques, and to become clonally expanded within the affected cells [7,30]. Accumulation of oxidized lipids in neurons are present in active cortical lesions in MS patients and this is associated with fragmentation of their dendritic and axonal cell processes or with nuclear condensation and fragmentation, suggestive for apoptotic cell death [13] (Fig. 1). Mitochondrial injury results in energy deficiency and subsequent functional impairment of neuronal impulse conduction. When it exceeds a critical threshold it may lead to axonal and neuronal degeneration through the induction of ionic imbalance and Ca^{++} accumulation within affected cells or axons [44]. Thus, energy failure induced by oxidative injury and mitochondrial damage appears to be particularly important for neuronal dysfunction and demise.

3.2. Oligodendrocytes

The most specific feature of multiple sclerosis pathology is widespread primary demyelination with relative preservation of axons. Thus, myelin and oligodendrocytes are dominantly affected in the disease process. Demyelination in active MS lesions with severe oxidative and mitochondrial injury shows a pattern of distal “dying back” oligodendrogliopathy [1]. This is characterized by a primary degeneration in the most distal (peri-axonal) oligodendrocytes processes, reflected by a selective loss of myelin associated glycoprotein in initial lesion stages and later followed by oligodendrocyte apoptosis [3,29]. Accordingly, the most extensive oxidative injury in active MS lesions is seen within myelin and oligodendrocytes [21]. This is reflected by the accumulation of oxidized lipids in the cytoplasm and the presence of oxidized DNA within nuclei, some of them with features of apoptosis. Distal “dying back” oligodendogliopathy is also seen in initial stages of white matter stroke lesions and in a subset of virus-induced inflammatory diseases of the white matter [1]. Such classical active lesions are mainly seen in patients with acute and relapsing MS, but their incidence is low in the progressive stage of the disease [16]. In this stage slowly expanding lesions are prominent, which also reveal signs of oxidative injury, but do not reflect the full pathological spectrum of active demyelinating lesions with distal oligodendrogliopathy [5].

The high lipid content within the myelin sheaths may render it highly vulnerable for lipid peroxidation and its consequences. In addition, iron accumulates within the human brain with aging and iron storage mainly takes place in oligodendrocytes and myelin [10]. Although iron is mainly stored in its non-toxic trivalent form, bound to ferritin, it

Download English Version:

https://daneshyari.com/en/article/1904535

Download Persian Version:

https://daneshyari.com/article/1904535

Daneshyari.com