Nitric Oxide 67 (2017) 75–80

Contents lists available at ScienceDirect

Nitric Oxide

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

Effect of nitric oxide to axonal degeneration in multiple sclerosis via downregulating monocarboxylate transporter 1 in oligodendrocytes

Xiaoyi Tang [a, b, 1], Minghong Lan [a, b, 1], Mao Zhang [a], Zhongxiang Yao [a, *]

[a] Department of Physiology, Third Military Medical University, Chongqing 400038, China
[b] Battalion 5 of Cadet Brigade, Third Military Medical University, Chongqing 400038, China

ARTICLE INFO

Article history:
Received 6 January 2017
Received in revised form
5 April 2017
Accepted 5 April 2017
Available online 7 April 2017

Keywords:
Nitric oxide
Monocarboxylate transporter 1
Oligodendrocyte
Axonal degeneration
Multiple sclerosis
Lactate

ABSTRACT

Multiple sclerosis (MS) is a neurodegenerative disease of the central nervous system (CNS). Axonal degeneration, one of the main pathological characteristics of MS, is affected by nitric oxide (NO). In turn, NO induces mitochondrial dysfunction of neurons and glial cells. Inadequate glucose causes monocarboxylate transporter 1 (MCT1) to transfer lactate from oligodendrocytes (OLs) to neurons, which decreases MCT1 and results in energy substrate deficit (mainly lactate) in axons. The condition gradually leads to axonal degeneration. This study proposes that NO-induced MCT1 down-regulation in OLs may be involved in the pathological process of axonal degeneration, which eventually leads to MS.

© 2017 Elsevier Inc. All rights reserved.

Contents

1. Introduction 75
2. Nitric oxide may be involved in the pathogenesis of multiple sclerosis 76
3. Nitric oxide can induce the mitochondrial dysfunction in neurons and glial cells 76
4. Monocarboxylate transporter 1 is a crucial transporter to transfer lactate from oligodendrocytes into axons 78
5. Monocarboxylate transporter 1 accelerates mitochondrial energy metabolism 78
6. Nitric oxide may influence the expression of monocarboxylate transporter 1 in oligodendrocytes 78
7. Nitric oxide may contribute to axonal degeneration in multiple sclerosis through decreasing monocarboxylate transporter 1 in oligodendrocytes 79
8. Perspectives 79
Conflict of interest 79
Acknowledgements 79
References 79

1. Introduction

Since1986, after its identification as an endothelium-derived relaxing factor [1], nitric oxide (NO) was generally considered a messenger molecule in the central nervous system (CNS), as it transfers messages among neurons and glial cells [2]. In fact, NO also contributes to the pathogenesis of many diseases, including multiple sclerosis (MS) [3,4].

Multiple sclerosis is a chronic inflammatory demyelinating disease of the CNS with high morbidity rates, especially among young adults [5,6]. Several studies have confirmed inflammation, demyelination, and axonal degeneration as the main pathological features of MS [7]. Leukocytes penetrate the CNS through breakouts of blood–brain barriers (BBB), which then causes local

* Corresponding author.
E-mail address: yaozhx@yahoo.com (Z. Yao).
[1] Xiaoyi Tang and Minghong Lan contributed equally to this work.

http://dx.doi.org/10.1016/j.niox.2017.04.004
1089-8603/© 2017 Elsevier Inc. All rights reserved.

Abbreviation

4-CIN	a-cyano-4-hydroxycinnamate
ALS	amyotrophic lateral sclerosis
AMB	amphotericin B
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
ATP	adenosine-5'-triphosphate
BBB	blood-brain barrier
CNS	central nervous system
CNP	2′, 3′-Cyclic Nucleotide 3′-Phosphodiesterase
COX	cytochrome oxidase
D-Cys NO	D isomer of S-nitrosocysteine (Cys NO)
DRG	dorsal root ganglion
EFV	efavirenz
ERDF	endothelium-derived relaxing factor
HIF-1	hypoxia-inducible factor-1
iNOS	inducible nitric oxide synthase
IL-1	interleukin-1
L-arg	L-arginine
L-Cys NO	S-nitroso-L-cysteine
LDH	lactate dehydrogenase
MBP	myelin basic protein
MCT1	monocarboxylate transporter 1
MCTs	monocarboxylate transporters
MMP	mitochondrial membrane potentials
mNOA1	mitochondrial NO-associated protein 1
MPT	mitochondrial permeability transition
MRI	magnetic resonance imaging
MS	multiple sclerosis
NO	nitric oxide
NOX-2	nicotinamide adenine dinucleotide phosphateoxidase 2
NF-κB	nuclear factor kappa-B
NMDA	*N*-methyl-D-aspartic acid
OLs	oligodendrocytes
OXPHOS	oxidative phosphorylation
ROS	reactive oxygen species
siRNA	small interfering RNA
SNAP	S-nitroso-*N*-acetylpenicillamine
TNF-α	tumor necrosis factor-α

inflammation, demyelination, and decrease of axonal conductance velocity of MS [8]. Other studies have confirmed significant axonal degeneration in MS autopsy [9].

A number of studies have pathologically characterized axonal degeneration in MS [10], but the involved mechanisms were not clearly explained. A previous study has reported that metabolism of adenosine-5′-triphosphate (ATP)-generating phosphocreatine is reduced in white matter astrocytes in MS [11]. Therefore, as the main source of ATP in axons, mitochondria is significant for energy metabolism of neurons, while neuronal dysfunction may contribute to axonal degeneration, further leading to MS [6,7].

Monocarboxylate transporters (MCTs) are vital in lactate from glial cells to neurons, and lactate is considered as an energy substrate when glucose is inadequate [12]. Moreover, decrease in MCTs may cause energy substrate deficit (mainly lactate) in axons, which gradually leads to axonal damage and MS [12]. NO can also induce mitochondrial dysfunction of neurons [11]. The present study aims to explain how NO leads to MS and to determine how MCTs contribute to this process.

2. Nitric oxide may be involved in the pathogenesis of multiple sclerosis

NO plays a dual role in the CNS, namely, neuroprotective and, in certain conditions, neurodestructive. By increasing both the generation of cyclic guanosine monophosphate (cGMP) and the activation of CREB (i.e., cAMP-responsive element-binding protein) transcription factor and protein kinase B, the oligodendrocyte growth and maturation are enhanced and signals associated with myelinogenesis are mediated by NO [13–16]. NO can also clear damaged tissues and fight the CNS infection [17]. However, the destructive effect of NO should be considered. Some studies have reported that NO may be involved in the pathogenesis of MS [3,4,18]. Increase in NO concentration was observed among patients with MS, where NO level was measured by magnetic resonance imaging (MRI), and clinical progression was consolidated for MS patients over a three-year follow-up period [19,20]. Thus, NO may be regarded as an activity marker of MS pathogenesis [21,22]. However, available data to fully demonstrate the effect of NO to MS are limited.

The pathological process of NO in MS can be demonstrated in four aspects, namely: (1) NO behaves as an essential stimulator of local inflammatory response to MS [23]. NO can disturb the structure of BBB [24] and directly increase barrier permeability [25], which can lead to inflammatory response, one of the main pathological characteristics of MS; (2) NO causes neuronal apoptosis or necrosis and superoxide-triggered DNA damage [26]. Furthermore, NO affects the structural and functional injury of axons, e.g., axonal swellings and transections [10], although the accurate mechanism has not yet been detailed [27,28]; (3) NO induces impairments of mitochondrial function and energy metabolism, especially in OLs [29–31]; and (4) NO inhibits the expression of genes related to myelin formation and then indirectly accelerates death of OLs [32]. All these findings suggest that NO plays a crucial role in the pathogenesis of MS [Fig. 1].

Experimental autoimmune encephalomyelitis (EAE) is an established cell-mediated autoimmune disease of the CNS, and it has been used as an animal model for MS [33,34]. Endogenous NO synthase (NOS)-deficient mice experiment exhibited a delayed onset of EAE, which suggests that NO has a pro-inflammatory role and triggers the onset of disease [35]. In addition, compared with the wild-type control experiment, the inducible NOS (iNOS) knockout mice that suffered from EAE presented a less severe disease condition, which suggests that NO contributes to the pathogenesis of acute EAE [36].

3. Nitric oxide can induce the mitochondrial dysfunction in neurons and glial cells

NO has both protective and destructive effects on mitochondria. Firstly, NO can reversibly alter both respiratory oxygen availability and oxygen consumption, which can provide short-term protection [37]. NO also regulates oxygen delivery to tissues by regulating the combination and release of oxygen from hemoglobin [38]. Mitochondrial NO-associated protein 1 (mNOA1) can adjust mitochondrial oxidative phosphorylation for oxygen availability, hence controls mitochondrial metabolism [39]. Secondly, NO can stabilize hypoxia-inducible factor 1 (HIF-1). The HIF-1 transcriptional system, which can sense decrease in oxygen availability, transforms

Download English Version:

https://daneshyari.com/en/article/5514225

Download Persian Version:

https://daneshyari.com/article/5514225

Daneshyari.com