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Nitric oxide might be an inducing factor in cognitive impairment in Alzheimer's disease via downregulating the monocarboxylate transporter 1

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ABSTRACT

Alzheimer's disease (AD) is a typical neurodegenerative disease in central nervous system (CNS). Generally speaking, patients with severe AD are often accompanied with cognitive impairment. Oligodendrocytes (OLs) are myelin-forming cells in CNS, and myelin injury potentially has something to do with the cognitive impairment in AD. Based on the previous experimental studies, it has been recognized that nitric oxide (NO), as a signaling molecule, might have an influence on the axon and myelin by affecting the energy transport mechanism of OLs through monocarboxylate transporter 1 (MCT1). Interestingly, a novel model of cell signaling——axo-myelinic synapse (AMS) has been put forward. In the context of this model, chances are that a new way is established in which NO can influence the pathogenesis of AD by down-regulating the expression of MCT1. As a consequence, it may provide attractive prospective and underlying drug targeting effects for the treatment of AD.

1. Introduction

Nitric oxide (NO), once an atmospheric pollutant, is now a magical signaling molecule. In 1986, endothelium-derived relaxing factor (EDRF) was proved to be NO, and it was found for the first time that gas molecules could play a signaling role in organisms [1]. Since it was discovered, much attention has been paid to it. In 1992, NO was chosen as the molecule of the year by Science. Subsequently, the discovery of NO and its biological significance were highly evaluated [2].

NO, which acts as an intercellular messenger throughout brain, produces a variety of physiological effects so that it could exert effects in many different brain functions [3]. In addition to physiological effects, NO also gives rise to cell damage and acts as a major mediator of neurodegeneration in neurological disorders, including Alzheimer's disease (AD), Parkinson's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease and stroke [4].

AD is a latent, progressive neurodegenerative disease in central nervous system (CNS). It is characterized by cerebral cortex atrophy with β-amyloid (Aβ) protein depositions, neurofibrillary tangles, decreased cholinergic neurons, and the formation of senile plaques. At the same time, AD is also a common cause of dementia whose clinical symptoms are manifested as progressive deterioration of cognitive impairment and mental problems. As a result, people with AD would gradually lose their memory and ability to learn, judge, communicate and even have difficulty in daily activities [5]. Unfortunately, there is neither targeted treatment nor a drug that can reverse the progression of the disease.

In most studies, NO has been reported to have beneficial effects on brain functions (such as learning and memory). However, there is also evidence that high NO production may lead to abnormal protein modification and affect the pathogenesis of neurodegenerative diseases [6,7]. High level of NO may affect synaptic plasticity, leading to cell death [8]. Animal model studies revealed that NO may affect aging and dementia, memory deficit, long-term memory and other cognitive tasks by regulating the activity of nitric oxide synthase (NOS). Importantly, elevated NO level has been reported to have a link with cognitive impairment in patients with AD [9].

From this point of view, as a possible reverse mediator of cognitive functions, NO may make a difference in the pathological process of AD, and to some extent, it has an important influence on the brain functions of patients with AD, which is worthy of exploration. Up to now, the scientific studies of NO as an AD target are relatively few, but it is a novel perspective which deserves more exploration.

2. Nitric oxide serves as a bidirectional regulation factor in the pathogenesis of Alzheimer's disease

In most cases, NO has two sides. In physiological level, NO is a

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Abbreviation

Aβ	β-amyloid
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
AMPAR	α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor
AMS	axo-myelinic synapse
APP	amyloid precursor protein
BACE1	β-site APP cleaving enzyme 1
Cdk5	cyclin-dependent kinase 5
CNS	central nervous system
EDRF	endothelium-derived relaxing factor
eNOS	endothelial nitric oxide synthase
iNOS	inducible nitric oxide synthase
LPC	lysophosphatidyl choline
LPS	lipopolysaccharide
LTP	long-term potentiation
MBP	myelin basic protein
MCT	monocarboxylate transporter
mPFC	medial prefrontal cortex
NMDAR	N-methyl-D-aspartic acid receptor
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
OLs	oligodendrocytes
PFC	prefrontal cortex
Pin1	peptidyl-prolyl cis-trans isomerases 1
RIP-3	receptor-interacting protein 3
RNS	reactive nitrogen species
ROS	reactive oxygen species
RyR	ryanodine receptor
TNFα	tumor necrosis factor α

molecule with neuroprotective effects, but it also has neurotoxicity when produced in large quantities [10]. Using hippocampal slices, it was confirmed that the synthesis of NO in postsynaptic neurons are induced by the activation of glutamate N-methyl-D-aspartic acid receptor (NMDAR), leading to influx of calcium and activation of nitric oxide synthase (NOS), and then, NO is diffused into the pre-synapses of the partner neurons to promote long-term potentiation (LTP) [11]. In the following years, the functions of NO had been established as a retrograde transmitter of LTP [11]. Moreover, drug therapies for AD may play a role by affecting NO/NOS related signaling pathways [12].

NO is produced from arginine and oxygen by NOS [13]. NOS includes NOS1, NOS2 and NOS3 which are encoded by neuronal, inducible and endothelial nitric oxide synthase (nNOS, iNOS and eNOS) respectively. nNOS is found in neurons, eNOS is found in vascular endothelial cells, and iNOS is activated in OLs, astrocytes and microglial cells [14]. Both nNOS and eNOS are expressed constitutively, and their activations depend on calcium ion/calmodulin, while iNOS expression is induced in astrocytes, microglial cells and blood-derived macrophages that respond to foreign bodies and tissue damage [15]. All of these cell types are altered in brain of AD, so these three subtypes of NOS are thought to take effects in the progression of AD [16]. eNOS plays an important part in neurocognitive functions. NO derived from

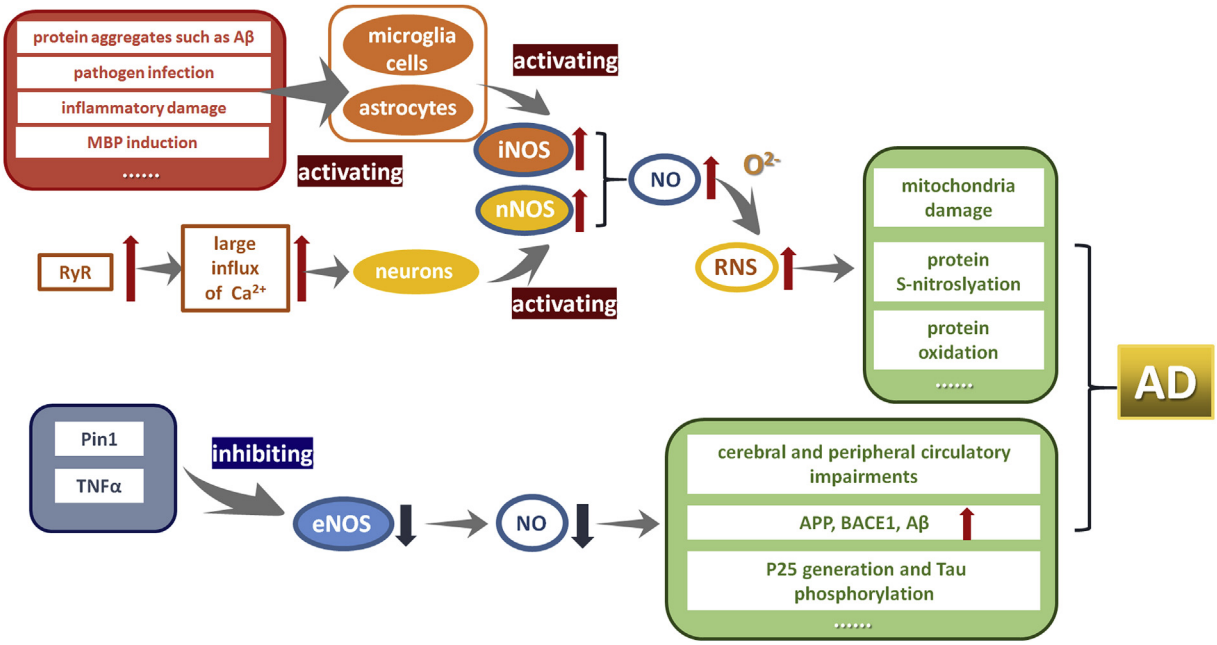

Fig. 1. The role of nitric oxide synthase (NOS) and nitric oxide (NO) in the progression of Alzheimer's disease (AD). In general, NO is produced by arginine and oxygen encoded by inducible nitric oxide synthase (iNOS), neuronal nitric oxide synthase (nNOS) and endothelial nitric oxide synthase (eNOS). All of these subtypes are altered in brain of AD, so they are thought to play an important role in the progression or prevention of AD. When protein aggregates such as amyloid-β (Aβ), pathogen infection and inflammatory damage occur, microglial cells and astrocytes are activated. Then the expression of iNOS is increased, resulting in NO production. In addition, myelin basic protein (MBP) could also induce microglial cells and astrocytes to activate iNOS, further releasing NO. Similarly, the expression of ryanodine receptor (RyR) increases in AD, resulting in a large influx of Ca^{2+}, which activates the expression of nNOS in neurons, leading to the synthesis of NO. Then, NO reacts with superoxide to produce peroxynitrite. Peroxynitrite oxidizes various macromolecules, such as DNA, lipids and proteins. eNOS plays an important role in neurocognitive functions. In blood vessels, tumor necrosis factor α (TNFα) and peptidyl-prolyl cis-trans isomerases 1 (Pin1) can inhibit the production of NO by changing the expression or activity of eNOS enzyme. When the bioavailability of NO in endothelial cells decreases, it leads to the disturbance of vascular endothelial function and the damage of cerebral circulation and peripheral circulation. In this case, the amyloid precursor protein (APP), β-site APP cleaving enzyme 1 (BACE1) and Aβ are increased. In addition, it is found that it also promotes p25 generation and Tau phosphorylation.

eNOS has neuroprotective effects [10]. In terms of vessels, tumor necrosis factor α (TNFα) and peptidyl-prolyl cis-trans isomerases 1 (Pin1) can inhibit the production of NO by changing the expression or activity of eNOS [17]. When the bioavailability of endothelial NO decreases, it brings about endothelial dysfunction, leading to cerebral and peripheral circulatory impairment [10]. In this case, for one thing, it increases amyloid precursor protein (APP), β-site APP cleaving enzyme 1 (BACE1) and Aβ [18]; for another, it could promote p25 generation and Tau phosphorylation [19]. P25 is an activator of cyclin-dependent kinase 5 (Cdk5) in hippocampus, while Cdk5 is the main kinase that induces Tau phosphorylation [20]. Chronic p25 generation induced by Aβ leads to persistent synaptic inhibition, synaptic plasticity impairment and decreased cognitive ability, which promotes the development of AD-like pathology [21].

Generally speaking, NO has been considered as an important factor in neurotoxic injury caused by neuroinflammation in AD [11]. AD is marked by senile plaque. The core of senile plaque is the deposition of Aβ, as well as the activated microglial cells and astrocytes surrounding the senile plaques [12]. In the pathological conditions of AD, astrocytes are activated by a variety of factors, such as Aβ and pro-inflammatory cytokines [15]. Similarly, when protein accumulation, pathogen infection and inflammatory damage occurred, the microglial cells should be activated. Reactive microglial cells and astrocytes tend to produce iNOS, further releasing a higher level of NO and enhancing inflammatory cascade reaction [12,15]. iNOS accounts for the inflammation/degeneration in CNS, and it derives from the production of excessive NO and the production of reactive nitrogen species (RNS) [22]. Physiologically, nNOS is activated by calcium entry into the cells, resulting in NO synthesis, which in turn affects the release of neurotransmitters. It was demonstrated that the expression of ryanodine receptor (RyR) (a calcium release channel in endoplasmic reticulum/sarcoplasmic reticulum) was increased in 3xTg-AD mouse model, resulting in the increase of calcium-induced calcium release in the early stage of AD. On the contrary, in the late stage of AD, the increase of nNOS activity due to calcium release induced by RyR led to the damage of macromolecules associated with oxidation and nitroso-stress [23]. In summary, the expression of RyR increases in AD, resulting in a large influx of calcium, which activates the expression of nNOS in neurons, leading to the production of NO. NO reacts with superoxide to produce peroxynitrite. Peroxynitrite oxidizes various macromolecules, such as DNA, lipids and proteins. Worse still, NO also deactivates the enzymes in respiratory chain of mitochondria, resulting in the reduced production of ATP, which is detrimental to bioenergy. In this way, neurons are damaged, directly facilitating the pathology of AD [16,23] (Fig. 1).

In light of the above evidences, it can be inferred that NO might participate in the mechanism of cognitive impairment in AD patients. Consequently, efforts are made to deduce the possible mechanism from the new perspective of energy metabolism.

3. Involvement of oligodendrocytes in the pathology of Alzheimer's disease

3.1. Oligodendrocyte and myelin injury are widely found in Alzheimer's disease

Over the past decade, it has been shown that OLs play a key role in maintaining and long-term survival of axons and neurons, which implied that OLs may participate in neurodegenerative diseases [24]. White matter lesions, especially damage in OLs and myelin sheath, can facilitate cognitive impairment and pathological changes of AD. As a result, OLs are targeted for the study and early treatment of AD [25].

Myelin basic protein (MBP) is the main protein of myelin sheath in CNS, which can maintain the structure and function of myelin sheath [26]. It was reported that the loss of myelin sheath and the destruction of MBP were found in pathological models of AD patients [27]. The MBP was proved to decrease in AD patients compared with the blank control group [28]. Interestingly, the activation of glial cells is a common phenomenon in neurodegenerative diseases [27], and it was suggested that MBP-activated Th1 cells could induce the expression of IL-1β and iNOS in microglial cells and astrocytes through similar T cell-microglial contact, resulting in NO production [29,30].

In 1964, Terry et al. first proposed the existence of myelin injury in AD. This kind of injury was different from that caused by nerve fiber damage and it was a kind of myelin injury without axonal degeneration, indicating that the myelin sheath around axons was interrupted, vacuolar, and granulated [31]. A loss of myelin integrity in AD patients had been revealed both in autopsy and imaging studies. Through an assessment of glial and temporal myelin injuries in AD mice, it was shown that myelin was vulnerable and the myelin damage was common in AD [32].

The loss of OLs, decreased myelin density, axonal loss and increased astrocytes were reported to be the main causes of changes in AD. Myelin injury in AD increases the likelihood that OLs should be attacked [25,32].

Premature dysfunction of OLs in AD may be the main reason for myelin injury. Heterogeneity of OLs is the primary cause of selective myelin injury in AD [33,34]. Partial recovery of myelin injury in transgenic model mice of AD was achieved by early treatment of OL/myelin pathology [35].

Donepezil is an acetylcholinesterase inhibitor used in the treatment of AD. It stimulates the differentiation of OLs and the maturation of OL progenitor cells derived from neural stem cells without affecting cell proliferation or cell viability. It has been demonstrated that Donepezil can promote OL differentiation and myelin-associated gene expression [36]. Although Donepezil improves the cognitive symptoms of AD patients, delays the decline of cognitive functions, and has good safety, it can only control or improve the symptoms for a period of time, and cannot prevent or significantly delay the progression of the disease. Frankly, the effective treatment for AD patients is still a tough problem [37,38].

3.2. Cognitive functions are facilitated by promoting the growth and development of OLs and myelination

The typical progression of AD starts with a decline in memory and learning, followed by language barriers, and ultimately cognitive impairment [39]. Both in AD patients and mouse models, the formation and development of OLs persist throughout the whole life and contribute to myelin formation and remodeling, thus it exerts an enormous functions on learning and memory, as well as cognitive functions [32].

Prefrontal cortex (PFC) is a brain region concerning complex emotions and cognitive behaviors. It has been further demonstrated that myelination is necessary for the cognitive processes depending on medial prefrontal cortex (mPFC) [40].

Multiple neurological diseases (such as multiple sclerosis, diffuse sclerosis, etc.) have myelin damages accompanied by cognitive impairment, and it was found that myelin injury was diffusely found in schizophrenia, depression, bipolar affective disorders and other mental diseases with cognitive disorders, and loss of cognitive functions may be linked with myelin injury [41]. To further demonstrate the role of myelination in mPFC dependent behavior, the mPFC was selectively demyelinated by lysophosphatidyl choline (LPC)-induced demyelination [42]. Severe demyelination occurred in rats at 7 days after local injection of LPC to mPFC. It was found that the mPFC-dependent function of demyelinating rats was severely impaired. Therefore, myelination is imperative for mPFC-dependent behaviors because the function of mPFC can be damaged for blocking the differentiation of OLs or lecithin induced demyelination. It has been suggested that maturation and myelination of OLs are essential for normal cognitive functions [42].

The maturation of complex neural circuits required for advanced cognitive and motor function depends on myelination. OLs promote

rapid and saltatory electrical pulse conduction through myelination and isolation of axons [42,43]. Myelination pushes forward an immense influence on promoting advanced cognitive functions, while abnormal myelination is related to neurological disorders and mental disorders [42].

How does myelin defect affect cognitive functions? In one case, the thinning of myelin sheath alters the conduction velocity of myelinated axons in mPFC, leading to abnormal information processing and loss of cognitive functions [42]. Considering abnormal plasticity of myelin sheath, the development and maintenance of myelin functional integrity may be the most important and vulnerable factor to obtain and maintain optimal cognitive functions [42].

3.3. Axo-myelinic synapse (AMS): a novel model of cell signaling

Myelin sheath, once regarded as the inert insulator layer around axons, is now considered to play an active and dynamic role in maintaining the structure and function of axons. Myelin sheath is able to transmit action potential rapidly by jumping conduction, provide nutritional support and maintain axon integrity. Myelin sheath determines the consistency of speed and the time of signals because it affects the distance between Ranvier's nodes. Hence myelin sheath is essential for advanced functions of brain. It is widely recognized that myelination of axons greatly enhances the speed of signal transmission [44].

Intercellular communication through signaling molecules is fundamental to the development of nervous system [45]. If the communication between axons and myelin sheath is vital to normal physiology, the interruption of this signal may bring about a variety of diseases, not only white matter lesions, but also axon-oligodendrocyte interactions in the cortex. Both axons and OLs are energy-consuming cells, they are susceptible to metabolic challenges [45]. Lactate produced by OL glycolysis is converted into pyruvate in axons and ATP is produced by aerobic respiration of axonal mitochondria. To support this process, OL specific clearance of monocarboxylate transporter 1 (MCT1) results in axonal damage rather than death of OLs, suggesting that lactate is exported from OLs to axons, which is key to the survival of axons [45].

Excitedly, there can be a dynamic communication between axons and myelin-forming OLs, including activity-dependent signals from axons to myelin sheath [46]. Using mature myelin calcium imaging, it was found that axons covered myelin sheath by releasing vesicles of glutamate and activating glutamate receptors in myelin sheath, which may contribute to dynamically regulate the physiology and structure of myelin sheath [44]. NMDARs expressed on myelin sheath have physiological functions and represent the potential synaptic signal interactions between axons and myelin sheath [45]. Recent studies have begun to reveal the molecular structure of the so-called “axo-myelin synapse (AMS)”. Accordingly, AMS may be an attractive target for the treatment of various neurological diseases [44,45]. OL myelin complexes may in turn regulate the spread of action potentials by providing metabolic support or changing subtle myelin properties [46].

It has been shown that training in a special task like learning new motor skills or spatial navigation resulted in changes in white matter in specific regions of brain, indicating the changes in axon caliber and/or myelination. AMS would be the ideal location to transmit this plasticity [47]. It is suggested that axons release transmitters along their internodes, signaling to the overlying myelin sheath, which forms the basis of what we call AMS [45].

Currently, AMS is understood only in the context of glutaminergic signals. It is assumed that the synapse plays a part in axon conduction and may affect all aspects of learning and memory, which in turn affects neurological and mental disorders [45,47]. A potential role of AMS is that it is a means of coupling action potential flow to oligodendroglia generation and transferring energy-rich substrates to axons, especially during periods of increased electrical activities [45]. Therefore, the possible function of AMS is to combine electrical activity with the

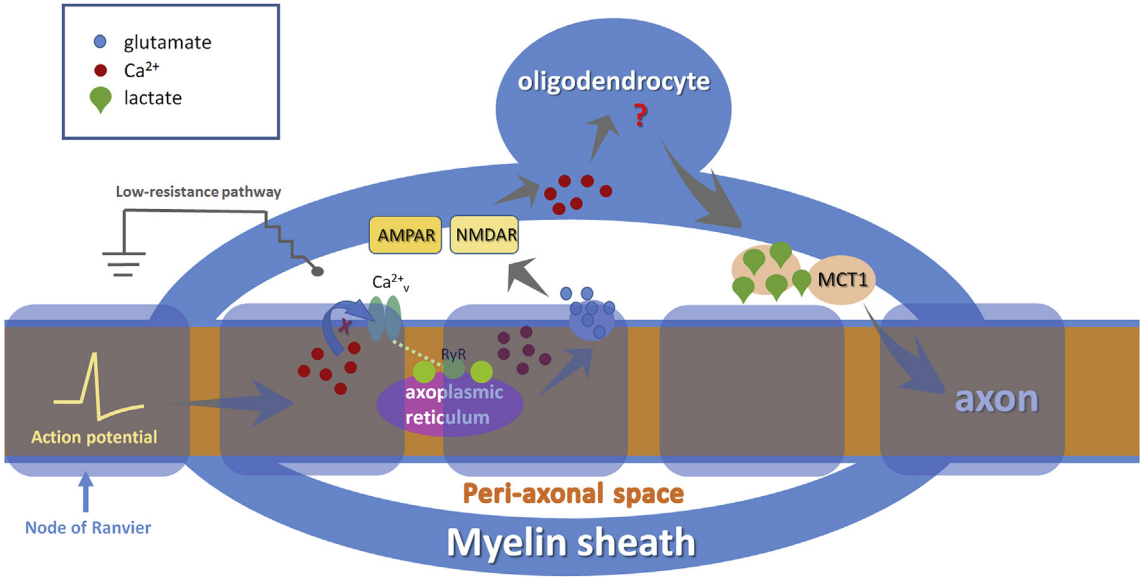

Fig. 2. Summary of the proposed axo-myelinic synapse (AMS). First, there is an action potential to induce internode membrane depolarization, which is detected by voltage-gated calcium channels. Because the internode axolemma is covered with a large number of insulated myelin sheath, a relatively low resistance pathway is necessary through myelin sheath, in order to enable the voltage-gated calcium channel to feel changes of electric field changes. There is evidence that there is a physical connection between voltage-gated calcium channel and ryanodine receptor (RyR) on the axoplasmic reticulum near the inner surface of axolemma. At this time, the voltage-gated calcium channel acts as a voltage sensor and transduces depolarization to activation of RyRs. As a result, the voltage-gated calcium channel results in Ca^{2+} acting on the RyRs and releasing Ca^{2+} from axons, rather than admitting the influx of a large number of Ca^{2+}. Then, Ca^{2+} promotes vesicular fusion in a tetanus-dependent manner and releases glutamate into the peri-axonal space. In turn, the α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptors (AMPARs) and N-methyl-D-aspartic acid receptors (NMDARs) in myelin sheath are activated, which leads to the influx of Ca^{2+} into the myelin cytoplasm. Glutamate is likely to be intaken by glutamate transporters and reloaded into vesicles. The consequences of an increase in myelin Ca^{2+} are unclear. It is assumed that it might regulate the myelin structure or signaling to oligodendrocytes (OLs). Then, monocarboxylate transporter 1 (MCT1), which is located on the inner surface of myelin sheath opposite to axonal membrane, is used to transport the lactate, so as to provide nutritional/metabolic support for axons.

metabolic output of OLs, that is, the action potential flow increases more, the glutamate releases more, thereby increasing myelinic calcium and triggering the release of OLs lactate. Lactate is a metabolic fuel, thus this process increases the energy efficiency of axons [44,45]. The disturbance of this basic new pattern of intercellular signal may support the onset of some important CNS diseases, in which myelin and white matter lesions are important pathophysiological events [45] (Fig. 2).

Although AMS is a concept for the present, it is rapidly accumulating to support a mechanism that allows the axon to communicate with its overlying myelin sheath. The presence of AMS may account for the underlying disorders in CNS [45]. In addition, the concept emphasizes the dynamic nature of axons and their myelin sheath, which may continue to undergo important plasticity not only during early development, but also throughout adult life [47]. In consequence, AMS may serve as a remarkable target for treatment of neurological diseases [44].

4. Effects of nitric oxide on cognitive impairment in Alzheimer's disease for deficiency of lactate

4.1. Nitric oxide impairs the energy metabolism in oligodendrocytes

It has been realized that mitochondrial dysfunction is an important factor in the pathogenesis of many degenerative diseases [48]. In CNS, mitochondrial dysfunction is mainly manifested in mitochondrial DNA damage [49], mitochondrial respiratory chain complex inhibition [50–52] and mitochondrial membrane dysfunction [53]. Cells are thought to experience three major forms of cell death: apoptosis, necrosis, and autophagy [54]. When the level of ATP is below a certain threshold, mitochondria can induce necrosis, and mitochondria can also induce apoptosis by releasing cytochrome C into the cytoplasm [55]. Autophagy is a clear process, but its function as an active cell death mechanism remains controversial [54]. Additionally, there is an alternative form of programmed cell death called necroptosis, which is mainly concentrated in the activation of receptor-interacting protein 3 (RIP-3) [56]. Under certain conditions, the mitochondria are not required for the execution of necroptosis [57]. The production of NO in neurons plays an important role in mitochondrial dysfunction [50,58]. It has been shown that mitochondrial dysfunction leads to cell degeneration, resulting from the formation of reactive oxygen species (ROS)/RNS [59]. Therefore, it is concluded that NO has toxic effects on mitochondria of OLs.

Monocarboxylate transporter (MCT) is an extracellular membrane channel for transmembrane transport of lactate, pyruvate and ketone bodies and protons. In CNS, MCT1 is almost completely present in OLs [60], and its down-regulation can lead to axonal injury and/or neuronal cell loss [61].

The MCT1 in OLs is the key transporter of axon energy metabolites to axons. The attenuation of MCT1 is a reason for axon pathological changes caused by local energy failure in axons [33]. MCT1 has been proved to be a novel target for S-nitrosation [62]. NO also has a regulatory effect on energy metabolism. In our previous studies, it has been assumed that NO may influence the expression of MCT1 in OLs [63]. Although there is still a lack of conclusive evidence to show that NO has an exact impact on MCT1, it has been inferred that the possibility is likely to exist, and a great deal of studies are in need to prove this point [63].

4.2. Lactate is an important energy metabolite in central nervous system

OLs nutritionally support neurons through MCT1 [32]. It has been found that OLs provide energy directly to axons through MCT1 and also have an impact on human diseases like AD, in which axonal energy loss, such as mitochondrial failure, has become possible. All these adult neurodegenerative diseases showed “degenerative” neuropathy, indicating early axonal failure [28,29].

Lactate is necessary in the energy supply of neurons in vivo [27], and it is essential for neuronal ATP homeostasis, whether it is provided by astrocytes or OLs. Neurodegeneration or neuronal dysfunction is produced by interfering with this pathway and may even be related to the function of memory [28,29]. The importance of lactate as an energy metabolite of neurons has been determined. In a study, the long-term memory in rats was significantly impaired by hippocampal specific inhibition of the expression of MCT1, MCT2 or MCT4, and the injection of L-lactate rather than equivalent glucose alleviated MCT1 or MCT 4 deficiency [27].

The cellular sources of lactate providing long-term memory were initially considered as astrocytes; however, subsequent identification of MCT1 expression in OLs suggested that OLs may also mediate these effects. Lactate has neuroprotective effects in brain injury models. It can be used as a metabolite of neurons and a signal molecule that binds to lactate receptor of neurons. The findings highlighted the underlying

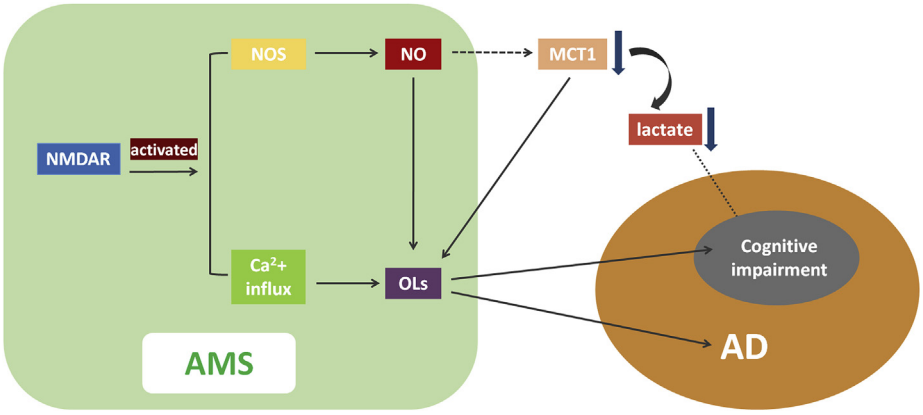

Fig. 3. Nitric oxide (NO) serves as an inducing factor contributing to cognitive impairment in Alzheimer's disease (AD). Based on existing experiments and evidences, it is concluded that endogenous NO may act on oligodendrocytes (OLs) by interfering with their energy metabolism. OLs also plays an indispensable role in the cognitive functions and neuropathology of AD. In other words, NO may be involved in the progression of cognitive impairment of AD. It is explored whether there are some key substances that make NO play a potential role in the development of AD, especially cognitive impairment. Therefore, it is focused on the monocarboxylate transporter 1 (MCT1). Lactate, the energy substrate that MCT1 transports, is thought to be related to cognition and memory. A new possible mechanism, that is, axo-myelinic synapses (AMS), is tried to explain it in terms of energy supply. The production of NO in OLs is caused by the activation of glutamate N-methyl-D-aspartic acid receptor (NMDAR) in OLs, which leads to the influx of calcium ion and the activation of nitric oxide synthase (NOS). In the context of AMS, on one hand, the activation of NMDAR causes the activation of NOS, which leads to the production of NO. On the other hand, the influx of Ca^{2+} may regulate the structure of myelin sheath or signal transduction to OLs. MCT1 is located on the inner surface of myelin sheath opposite to the axon membrane and is used to transport lactate and provide nutritional/metabolic support to axons. At the same time, it is speculated that the production of NO may influence the expression of MCT1, which is likely to result in the down-regulation of MCT1. Therefore, it is assumed that the expression of MCT1 may be down-regulated by NO in glial cells, resulting in insufficient energy supply of axons and neurons, impaired myelin structure and functions, and affecting the advanced functions of brain, which eventually leads to cognitive impairment in AD patients. If the hypothesis turns out to be true, then MCT1 serves as an intermediate of energy transport, and NO acts as a possible influencing factor. Inhibiting the production of NO and maintaining the energy transport of MCT1 may be targeted in the treatment of AD.

role of lactate in neurodegenerative models with nervous neuronal metabolism [27,59].

Since the transport mediated by MCT1 is bidirectional, lactate is also thought to be a potential source of ATP homeostasis in OLs, which is important to the production and maintenance of myelin integrity. In cortical slices cultured under low glucose conditions, myelin formation and the formation of OLs were seriously damaged, but lactate supplementation could rescue it, indicating that lactate plays an important part in the maturation and myelination of OLs [27].

4.3. Nitric oxide may serve as a potential factor contributing to cognitive impairment in Alzheimer's disease for the deficiency of lactate

AD is believed to be a gray matter disorder caused by the accumulation of neurotoxicity of Aβ and tau proteins. Nevertheless, there is increasing evidence that white matter lesions take effects in the pathogenesis of AD. Disorders of AMS lead to mental disorders involving white matter. Myelin determines the speed and timing of signals, which is known to be crucial for higher-level brain functions [44,45].

Interestingly, AD-related Aβ peptides increase the activity of NMDAR and, as discussed above, NMDAR is also associated with AMS [45]. In a word, it has been recognized as an important part of AD pathology in the known pathological features of Aβ and the new molecular structure of AMS. Although the dysfunction of glutamate is just a hypothesis, it is speculated that defective signals create a “chronic excitotoxicity” environment due to persistent inflammation, that is a potentially degenerative process. AMS is likely to be a potential target. Chronic hyperstimulation of axo-myelin complexes may be detrimental to myelin sheath [44,45].

As mentioned above, NO can affect the energy metabolism of OLs. Lactate plays an indispensable role in the energy supply of neurons and glial cells. MCT1 is an important transporter of lactate from OLs to neurons. OLs play an inevitable role in AD cognitive impairment. Apart from this, in terms of AMS, this new model of cell signaling is also challenged by axonal energy metabolism. Timely supply of lactate can solve the problem of axonal energy failure. From the point of view of energy supply, it is hypothesized that MCT1 expression may be down-regulated by NO in neurons and glial cells, resulting in insufficient energy supply of axons and neurons, impairing myelin structure and functions, and influencing the advanced functions of brain, which eventually leads to cognitive impairment in AD patients. If the hypothesis turns out to be true, then MCT1 serves as an intermediate of energy transport, and NO acts as a possible influencing factor. Inhibiting the production of NO and maintaining the energy transport of MCT1 may be targeted in the treatment of AD [44,45] (Fig. 3).

5. Perspectives

This study proposes that NO-induced down-regulation of MCT1 in OLs may play a vital role in cognitive impairment in AD, which offers promising application. Particularly, NO and MCT1 in OLs may be of great value in clinical treatment of neurodegenerative diseases. Moreover, AMS, as a novel model of cell signaling, this kind of basic intercellular signal interferences may support many important diseases in CNS, in which myelin sheath and white matter lesions are considerable pathophysiological events. In turn, drugs targeting AMS may represent a new direction in the current treatment of drug-resistant diseases in CNS. Future studies may lay emphasis on further exploring the proposed mechanism and new therapeutic strategies. The hypothesis is just the beginning, with more evidence to be explored and discovered.

Conflicts of interest

The authors have no conflict of interest to disclosure.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.niox.2019.07.006.

References

[1] Y. Zhao, P.M. Vanhoutte, S.W. Leung, Vascular nitric oxide: Beyond eNOS, J. Pharmacol. Sci. 129 (2) (2015) 83–94.
[2] .S. Panthi, S. Manandhar, K. Gautam, Hydrogen sulfide, nitric oxide, and neurodegenerative disorders, Transl. Neurodegener. 7 (2018) 3.
[3] J. Garthwaite, Nitric oxide as a multimodal transmitter in the brain: discovery and current status, Br. J. Pharmacol. 176 (2) (2019) 197–211.
[4] S. Nadjafi, S.A. Ebrahimi, N. Rahbar-Roshandel, Noscapine protects OLN-93 oligodendrocytes from ischemia-reperfusion damage: Calcium and nitric oxide involvement, Acta Physiol. Hung. 102 (4) (2015) 351-62.
[5] B. Waldau, A.K. Shetty, Behavior of neural stem cells in the Alzheimer brain, Cell. Mol. Life Sci. 65 (15) (2008) 2372-84.
[6] B.C.M. Stephan, et al., Cardiovascular disease, the nitric oxide Pathway and Risk of cognitive Impairment and dementia, Curr. Cardiol. Rep. 19 (9) (2017) 87.
[7] J.K.Y. Tse, Gut microbiota, nitric oxide, and Microglia as Prerequisites for neurodegenerative disorders, ACS Chem. Neurosci. 8 (7) (2017) 1438–1447.
[8] K. Gzielo, et al., Long-term Consumption of high-fat Diet in rats: Effects on Microglial and astrocytic Morphology and neuronal nitric oxide synthase expression, Cell. Mol. Neurobiol. 37 (5) (2017) 783–789.
[9] F. Jagla, O. Pechanova, Age-related cognitive Impairment as a Sign of geriatric neurocardiovascular interactions: may polyphenols Play a protective role? Oxid. Med. Cell Longev. 2015 (2015) 721514.
[10] M. Venturelli, et al., Impact of nitric oxide Bioavailability on the progressive Cerebral and peripheral circulatory impairments during Aging and Alzheimer's disease, Front. Physiol. 9 (2018).
[11] R. Balez, L. Ooi, Getting to NO alzheimer's disease: Neuroprotection versus neurotoxicity Mediated by nitric oxide, Oxid. Med. Cell Longev. (2016) 1–8 2016.
[12] F. Zhu, C. Qian, Berberine chloride can ameliorate the spatial memory impairment and increase the expression of interleukin-1beta and inducible nitric oxide synthase in the rat model of Alzheimer's disease, BMC Neurosci. 7 (2006) 78.
[13] A.N. Tran, et al., NOS Expression and NO Function in Glioma and Implications for patient therapies, Antioxidants Redox Signal. 26 (17) (2017) 986–999.
[14] S.Y. Yao, C. Natarajan, S. Sriram, nNOS mediated mitochondrial injury in LPS stimulated oligodendrocytes, Mitochondrion 12 (2) (2012) 336-44.
[15] N. Asiimwe, et al., Nitric oxide: Exploring the contextual Link with Alzheimer's disease, Oxid. Med. Cell Longev. (2016) 7205747 2016.
[16] N. Asiimwe, et al., Nitric oxide: Exploring the contextual Link with alzheimer's disease, Oxid. Med. Cell Longev. (2016) 1–10 2016.
[17] S. Kennard, et al., TNFalpha reduces eNOS activity in endothelial cells through serine 116 phosphorylation and Pin1 binding: Confirmation of a direct, inhibitory interaction of Pin1 with eNOS, Vasc. Pharmacol. 81 (2016) 61-8.
[18] S.A. Austin, et al., Endothelial nitric oxide deficiency promotes Alzheimer's disease pathology, J. Neurochem. 127 (5) (2013) 691–700.
[19] S.A. Austin, Z.S. Katusic, Loss of endothelial nitric oxide synthase Promotes p25 Generation and tau Phosphorylation in a murine Model of alzheimer's diseaseNovelty and significance, Circ. Res. 119 (10) (2016) 1128–1134.
[20] Y. Ma, et al., Activated cyclin-dependent kinase 5 promotes microglial phagocytosis of fibrillar beta-amyloid by up-regulating lipoprotein lipase expression, Mol. Cell. Proteom. 12 (10) (2013) 2833-44.
[21] J. Seo, et al., Activity-dependent p25 generation regulates synaptic plasticity and Abeta-induced cognitive impairment, Cell 157 (2) (2014) 486–498.
[22] R. Pannu, I. Singh, Pharmacological strategies for the regulation of inducible nitric oxide synthase: neurodegenerative versus neuroprotective mechanisms, Neurochem. Int. 49 (2) (2006) 170-82.
[23] S. Chakroborty, et al., Nitric oxide signaling is recruited as a compensatory mechanism for sustaining synaptic plasticity in Alzheimer's disease mice, J. Neurosci. 35 (17) (2015) 6893-902.
[24] M. Simons, K.A. Nave, Oligodendrocytes: Myelination and axonal support, Cold Spring Harb Perspect Biol 8 (1) (2015) a020479.
[25] S.E. Nasrabady, et al., White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes, Acta Neuropathol Commun 6 (1) (2018) 22.
[26] X.Q. Zhu, et al., Effects of propofol on myelin basic protein expression in oligodendrocytes of SD rats at different developmental stages, Nan Fang Yi Ke Da Xue Xue Bao 37 (12) (2017) 1615–1619.
[27] M.H. Ou-Yang, W.E. Van Nostrand, The absence of myelin basic protein promotes neuroinflammation and reduces amyloid beta-protein accumulation in Tg-5xFAD mice, J. Neuroinflammation 10 (2013) 134.
[28] X. Zhan, et al., Myelin injury and degraded myelin vesicles in Alzheimer's disease, Curr. Alzheimer Res. 11 (3) (2014) 232-8.
[29] A. Roy, K. Pahan, Myelin basic protein-primed T helper 2 cells suppress microglial Activation via AlphaVBeta3 integrin: Implications for multiple sclerosis, J. Clin.

Cell. Immunol. 7 (2013) 158.
[30] A. Chiarini, et al., Calcium-sensing Receptors of human neural cells play crucial Roles in Alzheimer's disease, Front. Physiol. 7 (2016) 134.
[31] R.D. Terry, N.K. Gonatas, M. Weiss, Ultrastructural studies in alzheimer's presenile dementia, Am. J. Pathol. 44 (1964) 269-97.
[32] Y.X. Dong, et al., Association between Alzheimer's disease pathogenesis and early demyelination and oligodendrocyte dysfunction, Neural Regen. Res. 13 (5) (2018) 908–914.
[33] B.M. Morrison, Y. Lee, J.D. Rothstein, Oligodendroglia: metabolic supporters of axons, Trends Cell Biol. 23 (12) (2013) 644–651.
[34] X. Zhan, B. Stamova, F.R. Sharp, Lipopolysaccharide Associates with amyloid plaques, Neurons and Oligodendrocytes in Alzheimer's disease brain: a review, Front. Aging Neurosci. 10 (2018) 42.
[35] M.K. Desai, et al., Early oligodendrocyte/myelin pathology in Alzheimer's disease mice constitutes a novel therapeutic target, Am. J. Pathol. 177 (3) (2010) 1422-35.
[36] O. Imamura, et al., Nicotinic acetylcholine receptors mediate donepezil-induced oligodendrocyte differentiation, J. Neurochem. 135 (6) (2015) 1086-98.
[37] N. Zhang, M.L. Gordon, Clinical efficacy and safety of donepezil in the treatment of Alzheimer's disease in Chinese patients, Clin. Interv. Aging 13 (2018) 1963–1970.
[38] J. Cummings, et al., Role of Donepezil in the Management of neuropsychiatric Symptoms in Alzheimer's Disease and Dementia with lewy bodies, CNS Neurosci. Ther. 22 (3) (2016) 159-66.
[39] F. Agosta, et al., Myeloid microvesicles in cerebrospinal fluid are associated with myelin damage and neuronal loss in mild cognitive impairment and Alzheimer disease, Ann. Neurol. 76 (6) (2014) 813-25.
[40] Y. Yang, et al., Chronic stress regulates NG2(+) cell maturation and myelination in the prefrontal cortex through induction of death receptor 6, Exp. Neurol. 277 (2016) 202–214.
[41] L. Holleran, et al., Altered interhemispheric and temporal lobe white matter microstructural organization in severe chronic schizophrenia, 39 (4) (2014) 944-54.
[42] Y. Yang, et al., Neonatal maternal separation impairs prefrontal cortical Myelination and cognitive Functions in rats through Activation of wnt signaling, Cerebr. Cortex 27 (5) (2017) 2871–2884.
[43] E.M. Gibson, et al., Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain, Science 344 (6183) (2014) 1252304.
[44] I. Micu, et al., The molecular physiology of the axo-myelinic synapse, Exp. Neurol. 276 (2016) 41–50.
[45] I. Micu, et al., Axo-myelinic neurotransmission: a novel mode of cell signalling in the central nervous system, Nat. Rev. Neurosci. 19 (1) (2018) 49–58.
[46] I. Micu, et al., Axo-myelinic neurotransmission: a novel mode of cell signalling in the central nervous system, Nat. Rev. Neurosci. 19 (1) (2017) 58.
[47] P.K. Stys, The axo-myelinic synapse, Trends Neurosci. 34 (8) (2011) 393–400.
[48] A.N. Murphy, G. Fiskum, M.F. Beal, Mitochondria in neurodegeneration: bioenergetic function in cell life and death, J. Cereb. Blood Flow Metab. 19 (3) (1999) 231-45.
[49] G. Aliev, et al., Oxidative stress induced mitochondrial DNA deletion as a hallmark for the drug development in the context of the cerebrovascular diseases, Recent Pat. Cardiovasc. Drug Discov. 6 (3) (2011) 222-41.
[50] V.C. Stewart, et al., Astrocyte-derived nitric oxide causes both reversible and irreversible damage to the neuronal mitochondrial respiratory chain, J. Neurochem. 75 (2) (2000) 694–700.
[51] J.P. Bolanos, et al., Effect of peroxynitrite on the mitochondrial respiratory chain: differential susceptibility of neurones and astrocytes in primary culture, J. Neurochem. 64 (5) (1995) 1965-72.
[52] J.P. Bolanos, et al., Nitric oxide-mediated inhibition of the mitochondrial respiratory chain in cultured astrocytes, J. Neurochem. 63 (3) (1994) 910-6.
[53] N.J. Solenski, et al., Nitric-oxide-induced depolarization of neuronal mitochondria: implications for neuronal cell death, Mol. Cell. Neurosci. 24 (4) (2003) 1151-69.
[54] D.R. Green, F. Llambi, Cell death signaling, Cold Spring Harb. Perspect. Biol. 7 (12) (2015).
[55] M. Singer, The role of mitochondrial dysfunction in sepsis-induced multi-organ failure, Virulence 5 (1) (2014) 66–72.
[56] D.E. Christofferson, J. Yuan, Necroptosis as an alternative form of programmed cell death, Curr. Opin. Cell Biol. 22 (2) (2010) 263-8.
[57] K.D. Marshall, C.P. Baines, Necroptosis: is there a role for mitochondria? Front. Physiol. 5 (2014) 323.
[58] C. Natarajan, et al., Activation of NOD2/RIPK2 pathway induces mitochondrial injury to oligodendrocyte precursor cells in vitro and CNS demyelination in vivo, J. Neuroimmunol. 265 (1–2) (2013) 51–60.
[59] B.K. Bitanihirwe, T.U. Woo, Oxidative stress in schizophrenia: an integrated approach, Neurosci. Biobehav. Rev. 35 (3) (2011) 878-93.
[60] Y. Lee, et al., Oligodendroglia metabolically support axons and contribute to neurodegeneration, Nature 487 (7408) (2012) 443-8.
[61] N. Snaidero, et al., Antagonistic Functions of MBP and CNP establish cytosolic Channels in CNS myelin, Cell Rep. 18 (2) (2017) 314–323.
[62] A.R. Diers, et al., S-Nitrosation of monocarboxylate transporter 1: inhibition of pyruvate-fueled respiration and proliferation of breast cancer cells, Free Radic. Biol. Med. 69 (2014) 229-38.
[63] X. Tang, et al., Effect of nitric oxide to axonal degeneration in multiple sclerosis via downregulating monocarboxylate transporter 1 in oligodendrocytes, Nitric Oxide 67 (2017) 75–80.