[Frontiers in Bioscience, Landmark, 22, 824-834, January 1, 2017]

Nitric oxide-mediated pathways and its role in the degenerative diseases

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1. ABSTRACT

Nitric oxide (NO) is a relatively short-lived inorganic free radical, which can be produced by different types of cells in multi-cellular organisms. This diffusible messenger functions as either an effector or a second messenger in many intercellular communications or intracellular signaling pathways. NO becomes noxious if it is produced in excess. These effects are mainly mediated by the reactivity of NO with various reactive oxygen species, which can be countered by antioxidant enzymes. In addition, NO can directly modify biological molecules via S-nitrosylation and lead to altered signaling responses. Accumulating evidence suggests that NO has a double-edged role in a dose-dependent, cell-type specific, and biological milieu-dependent way. In the present review, we summarized the synthesis and signaling pathway of NO, and especially focused on its involvement in biological processes, such as endoplasmic reticulum stress, apoptosis and autophagy. Besides, we discussed the functions of NO in the nervous system and its potential role in neurodegenerative diseases. We proposed the target on NO may shed light on the treatment of the related diseases.

2. INTRODUCTION

Nitric oxide (NO) is a gaseous molecule with a simple structure, which was first described as an endothelium-derived relaxing factor (EDRF). In 1980, Furchgott and Zawadzki found that acetylcholine (Ach) influenced the vascular smooth muscle and caused the relaxation of blood vessels with the presence of endothelial cells. It has been demonstrated that Ach acts on muscarinic receptors of endothelial cells, and then they can release a substance, which is named as EDRF, and contributes to relaxed vascular smooth muscle or vasodilation (1). In 1987, Pamler *et al* confirmed that EDRF was actually NO, which exists naturally in mammalian cells (2). Thereafter, emerging functions of NO have been identified, including anti-thrombotic and anti-inflammatory, which represents its multifunctional roles in cardiovascular system, nervous system, immune system, and so on (3). In 1998, the importance of NO in life sciences was finally underscored as a multifunctional molecule involved in a variety of physiological and pathological processes when the Nobel Prize for Physiology and Medicine was awarded. NO is a relatively short-lived inorganic free radical, which can be produced by different types of cells in multi-cellular organisms. This diffusible messenger functions as either an effector or second messenger in many forms of intercellular communication or intracellular signaling. NO becomes noxious if produced in excess. These effects are mainly mediated by the reactivity of NO with various reactive oxygen species, which can be countered by antioxidant enzymes. In addition, NO can directly modify biological molecules via S-nitrosylation and lead to altered signaling responses. Accumulating evidence suggests that NO has a double-edged effect, which is dose-dependent, cell-type specific, and largely depending on the biological milieu. In the present review, we summarized the production and signaling pathway of NO, especially focusing on its involvement in biological processes, such as endoplasmic

reticulum stress, apoptosis and autophagy. Besides, we also discussed the function of NO in the nervous system and its potential role in neurodegenerative diseases. We proposed the target on the production of NO may be a promising treatment against the related diseases.

2.1. The synthesis and functions of nitric oxide in the physiological conditions

Under physiological conditions, NO is generated by three isoforms of nitric oxide synthase (NOS) including endothelial (eNOS), neuronal (nNOS) and inducible NOS (iNOS). These NOSs have distinct structures and functions, and mostly exist in different cells. eNOS exists in endothelial cells while nNOS is from neurons. These two isoforms have similar regulating mechanism, which are activated by the increase of intracellular calcium concentration. Meanwhile, iNOS is calcium-independent, mainly acting in immune system (4). After produced by NOS, NO will diffuse to other tissues or organs to mediate different kinds of activities although NO is not stable and its half-life is only 1-5 seconds *in vivo* (5). NO is firstly produced from the L-arginine. When the intracellular concentration of calcium has risen, Ca^{2+} will enter the cells and soon complex with calmodulin and transform into calcium-calmodulin-complex, which activates NOS to decompose L-arginine into NO and L-citrulline.

After NO has been synthesized by eNOS, it would be released into intercellular space and finally traverse the cell membrane of vascular smooth muscle cells (6). In physiological conditions, when NO enters the vascular smooth muscle cells, it will bind to soluble guanylyl cyclase (sGC) that is the only intracellular definitive receptor for NO. And, when heme-containing NO receptor sGC receives NO, sGC (>) is activated to convert from guanosine 5'-triphosphate (GTP) to cyclic guanosine 3',5'-monophosphate (cGMP) so that the intracellular concentration of cGMP will increase.

sGC is not always activated by NO. Under some pathological conditions, there is another signaling pathway, which is NO-independent and heme-dependent action or a NO- and heme-independent process. Johannes-Peter Stasch *et al* found that BAY 58-2667 could activate sGC by an NO- and heme-independent mechanism. At the same time, vasodilatation will be caused under oxidative stress (7-9). The change of sGC and the elevation of cGMP lead to the transmission from an NO signal to the downstream elements, including the signaling cascade-cGMP-dependent protein kinase, cGMP-gated cation channels and cGMP-regulated phosphodiesterase, which are three target proteins of cGMP (8). Meanwhile, there is still a cGMP-independent mode of NO, where cGMP is not available. NO will have its role via the interaction with transition metal, and be involved in posttranslational modification of proteins, such as S-nitrosothiol (5).

2.2. Effects of NO on major disease-related biological processes

According to the current report, NO mainly takes actions in three ways to attend the disease mediation.

2.2.1. Endoplasmic reticulum (ER) stress (ERS)

Endoplasmic reticulum (ER) stress (ERS) was first identified as a cellular response pathway induced by the accumulation of unfolded proteins in ER to preserve ER functions. Later, it is found that ERS is also activated by various cellular stresses to protect cells. However, when stresses are severe, apoptosis is induced to remove damaged cells (10). Although some researchers have associated excessive NO production with the induction of ERS, only a few of them concerning the mechanism on how NO activates ERS pathway.

First, NO could directly induce S-nitrosylation of the endoplasmic reticulum chaperones and sensors. Protein disulfide isomerase (PDI) can provide neuroprotection from misfolded proteins or ERS through its molecular chaperone and thiol-disulfide oxidoreductase activities. The S-nitrosylation of PDI by NO inhibits its enzymatic activity, leads to the accumulation of polyubiquitinated proteins, and activates the unfolded protein response. S-nitrosylation also abrogates PDI-mediated attenuation of neuronal cell death triggered by ERS (11). In addition to PDI, S-nitrosylation is also likely to affect critical thiol groups on other ERS sensors, such as IRE1 and PERK (12). While S-nitrosylation of IRE1 inhibited its ribonuclease activity, S-nitrosylation of PERK activated its kinase activity and downstream phosphorylation/inactivation of eIF2.

Second, NO might disrupt Ca^{2+} homeostasis in the ER. Sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) is a Ca^{2+}-ATPase that transfers Ca^{2+} from the cytosol of the cell to the lumen of the sarcoplasmic reticulum (SR). NO was reported to inhibit Ca^{2+}-ATPase activity of SERCA by tyrosine nitration within the channel-like domain. Ryanodine receptors (RyR) mediate the Ca^{2+} release from the endoplasmic reticulum. It is reported that the activities of RyR are increased by NO through S-nitrosylation (13). Thus, it is speculated that NO depletes ER Ca^{2+} either by inhibiting Ca^{2+} uptake from cytosol through SERCA or by activating Ca^{2+} release to cytosol through RyR.

At last, NO could interrupt mitochondria-ER crosstalk by inhibiting the mitochondrial enzyme cytochrome c oxidase (complex IV) in competition with oxygen. Increased concentration of NO can prevent cytochrome c oxidase from using any available oxygen and then disrupt the respiratory chain (14). It is speculated that disrupted electron transfer at cytochrome c oxidase may result in ionic readjustment and modulation of the Ca^{2+} flux between the mitochondria and the ER. Xu and his colleagues found that NO-mediated change in

Ca^{2+} flux was sufficient to activate the Ca^{2+}-dependent protease (site-1 protease, S1P) involved in a regulated intermembrane proteolysis (RIP) pathway (15). S1P, in association with the site-2 protease locating in the Golgi apparatus, cleaves the ERS-regulated transmembrane transcription factor p90 ATF6. The resulting soluble transcription factor p50 ATF6 is then free to translocate to the nucleus where it subsequently activates ERS-responsive genes, such as glucose regulated protein 78 (Grp78). Therefore, excess NO will definitely cause injuries by directly disturbing ER function and activating ERS pathway, indicating NO may be the origination of ERS. Based on that ERS involved in many diseases, maintenance of NO homeostasis deserves a thorough exploration in the future researches.

2.2.2. Apoptosis

NO has both pro- or anti-apoptotic effects determined by its concentration, source of production and biological milieu. NO induces apoptosis via modulating multiple receptors along the signaling pathways, including both the death receptor and mitochondrial pathways. Fas (APO-1/CD95) belongs to the tumor necrosis factor-receptor superfamily. Binding of Fas ligand (FasL) to this receptor by NO initiates the assembly of death-inducing signaling complex (DISC), activates caspase-8 proteolytic cascades, and finally triggers apoptosis. Researchers have found that NO can modify the cytoplasmic domain of Fas by S-nitrosylation of cysteine residues 199 and 304. This post-translational modification promotes redistribution of Fas to lipid rafts, formation of DISC, and induction of apoptosis (16).

Bax/Bcl-2 ratio was also shown to be increased by the NO donor, sodium nitroprusside (SNP), in human gingival fibroblast (HGF) cells (17). Increased Bax/Bcl-2 ratio in turn leads to increased mitochondrial permeability and cytochrome c release. However, the effects of NO on the opening of mitochondrial permeability pore and cytochrome c release depend on its concentrations. Low levels of NO reversibly decreased mitochondrial permeability, while higher than physiological concentrations accelerated mitochondrial transition pore opening and cytochrome c release (18).

Besides the role of NO on complex IV mentioned above, NO or peroxynitrite can also inhibit the electron transport chain complex I-III to reduce energy production and induce DNA damage (19, 20). Apoptotic cell death initiated by death receptor or mitochondrial pathway activates upstream caspase-8 and -9, respectively. The executioner caspases (caspase-3, -6 and -7) in turn process substrates and eventually lead to the cellular changes associated with apoptosis. NO-mediated initiation of caspase activation has been found in vascular smooth muscle cells and retinal ganglion cells, the mechanisms of which are associated with X-linked inhibitor of apoptosis (XIAP) inactivation (21-23). XIAP is the most widely expressed inhibitor of apoptosis (IAPs), which regulate cell survival through binding to caspases. Researchers have demonstrated that S-nitrosylation of XIAP impairs its ability to inhibit caspase-3 activity.

The anti-apoptotic actions of NO also involve both death receptor and mitochondrial pathways of apoptosis. Caspase-3 activity is inhibited by posttranslational S-nitrosylation. The maintenance of inactive caspase-3 in low level by S-nitrosylation is associated with apoptosis inhibition (24). Chouchani *et al* use a mitochondria-selective S-nitrosylating agent, MitoSNO, to determine the mechanism of S-nitrosylation induced cardioprotection. They found that MitoSNO can induce S-nitrosylation of mitochondrial complex I, whose rapid reactivation is a central pathological feature of ischemia-reperfusion injury. Reversible S-nitrosylation of complex I slows the reactivation of mitochondria, thereby decreasing ROS production, oxidative damage and tissue necrosis (25). Bcl-2 is a key apoptosis regulatory protein of the mitochondrial pathway whose expression is largely controlled by post-translational modifications. Bcl-2 undergoes S-nitrosylation by endogenous NO in response to multiple apoptotic mediators and this modification inhibits ubiquitin-proteasomal degradation of Bcl-2. Inhibition of NO production by the NO scavenger and NO synthase inhibitor effectively inhibited S-nitrosylation of Bcl-2, increased its ubiquitination, and promoted apoptotic cell death (26).

To sum, NO exhibits contradictory effects in the regulation of apoptosis. Part of the reason is that the actions of NO are mediated by different pathways, and are activated by different concentrations of NO. The proapoptotic effects seem to be linked to pathophysiological conditions, where high amount of NO is produced by the iNOS. In contrast, transient production of NO by eNOS and nNOS inhibits apoptosis and attributes to physiological NO effects.

2.2.3. Autophagy

Autophagy is a highly conserved cellular process that is important for the removal of damaged organelles, protein aggregates, and infecting organisms. Physiologically, it serves to preserve the balance between organelle biogenesis, protein synthesis, and their clearance (27). The autophagy pathway culminates in the formation of a double membrane structure, the autophagosome. This envelops intracellular material and ultimately fuses with lysosomes allowing degradation of the enveloped materials. The autophagy pathway is a tightly regulated pathway that can be stimulated by multiple forms of cellular stress, including nutrient or growth factor deprivation, hypoxia, reactive oxygen species, DNA damage, protein aggregates, damaged organelles, or intracellular pathogens. These stressors signal through a number of upstream regulators (e.g., JNK1, AKT, IKK,

AMPK, and SIRT1)-often by way of either mTOR or Beclin 1-to trigger autophagosome biogenesis (28). Effects of NO and other RNS on autophagy have been investigated in recent years. Lipopolysaccharides (LPS)-induced autophagy in murine cardiac HL-1 cells is dependent on endogenous NO, as its effect on autophagy is attenuated by NOS inhibitor L-NMMA (29). Increased protein tyrosine nitration by ONOO-treatment is associated with autophagy-lysosome activation in a concentration-dependent manner in cultured endothelial cells, as determined by LC3II/I conversion, GFP-LC3 puncta accumulation, lamp2 and cathepsin B activation. OGD-induced autophagy-lysosome cascades were attenuated by siRNA-mediated knockdown of eNOS (30).

Although evidences pointed out the connection between NO production and autophagic pathways, none of them mentioned the possible mechanisms. Sarkar *et al*. provided the first evidence for involvement of NO bioactivity in autophagy and proposed the underlying mechanisms (31). They demonstrated that exposure of cells to high levels of NO (using NO donors or NOS over-expression) impaired autophagosome formation in primary cortical neurons, HeLa cells, and HEK cells. Inhibition of endogenous NO production by pan-NOS inhibitors had a net effect of promoting autophagy. NO inhibited autophagy via S-nitrosylation of proteins that were components of two independent pro-autophagic pathways: JNK1/Bcl-2/Beclin 1 and IKK/AMPK/mTORC1. In the first pathway, NO S-nitrosylates and inactivates JNK1, which in turn decreases Bcl-2 phosphorylation, reduces its inhibitory interaction with Beclin 1, and finally inhibits autophagic signaling.

In the second pathway, S-nitrosylation of IKK inhibits its phosphorylation of AMPK, thereby unleashes mTORC1 activity and decreases autophagic flux (31). Consistent with this study, other researchers also found that NO donors inhibited autophagy in meniscal cells via inactivation of JNK (32). And vice versa, there are also some reports showing that autophagy status can regulate NO signaling. Impairment of autophagy with Atg3 siRNA in endothelial cells prevented shear-stress-induced NO production (33). Autophagy markers decreased in freshly isolated endothelial cells from diabetic subjects, in parallel with decreased eNOS activity. Disruption of autophagosome-lysosome fusion by bafilomycin A inhibited eNOS activation, suggesting that autophagy plays a critical role in maintaining NO bioavailability (34). It seems that there exists a complicated interplay between NO and autophagy, which should be explored further.

NO is able to interact with many intracellular targets to trigger an array of signal transduction pathways. Although discussed separately, the above three ways of disease mediation are not isolated from each other, so does the function of NO in these pathways. Excessive ERS can either induce apoptosis or autophagy. There are also crosstalk between apoptosis and autophagy. We cannot simplify the function of NO to be protective or noxious. The multifaceted role of this molecule presents both challenges and opportunities to intervene in these biological processes.

3. THE ACTIONS OF NITRIC OXIDE IN NERVOUS SYSTEM

Emerging evidences show NO plays an important role in nervous system. NO was found to be a vital transmitter generated in response to neuronal NMDA receptor activation and caused cGMP generation (35). Since cGMP is an important second-massager in nervous system, NO can build impressive influences on nervous system via the action with cGMP as the summary in Table 1.

In nervous system, NO is synthesized by nNOS, which is activated by Ca^{2+}. The nNOS includes 5 isoforms: nNOS-alpha, nNOS-beta, nNOS-Mu, nNOS-gamma and nNOS-2. Monomer of nNOS is incompetent, and only the dimer can catalyze the reaction. Dimerization of NO needs to bind to tetrahydrobiopterin (BH4), heme and L-arginine (36). When NO diffuses from the cellular membrane, it can act as an inhibitory neurotransmitter to mediate the efferent autonomic nervous system. In the vertebrate peripheral nervous system (PNS), there are many different NO-involved actions. The innervations of anococcygeus muscle, retractor penis, artery, gut, and trachea are all associated with NO. These NO-mediated nerves were named “nitrergic”or “nitroxidergic” (37).In the past years, it has been accepted that NO is involved in neurogenesis, neuronal differentiation and development, memory, and some protection process of nervous system.

Diverse roles of NO in CNS and PNS are presented in Table 1, which are caused by its interaction with cGMP, NOS or other members in L-Arg---NO---cGMP pathways. To days, it is commonly accepted that NO is mainly an inhibitory neurotransmitter in both CNS and PNS. In addition, NO is also confirmed to be involved in some neurodegenerative diseases such as neurodegenerative diseases. So it is important to elucidate the functions of NO in nervous system both under physiological and pathological conditions.

In the cerebral cortex, NO can be generated by neuronal nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d), which has been identified as a kind of NOS. In this condition, nNOS will localize in a subpopulation of calbindin-containing or GABAergic interneurons (38). In CNS, nNOS activation is regulated by Ca^{2+} via N-methyl-D-aspartate -type glutamate receptors (NMDARs). NO biosynthesis is influenced by postsynaptic density protein 95 (PSD-95), which together with nNOS and NMDA receptors constitutes a

Table 1. Functions of NO in CNS and PNS

Actions	References
Central nervous system	
Visual system development	(66)
Neuroprotection and neurotoxicity	(67) (66)
Neurogenesis	(68)
Circadian rhythms	(69)
Neurotransmission	(70, 71)
Sleep, appetite, and body temperature	(72, 73)
Neurosecretion	(74)
Peripheral nervous system	
Penile erection	(75)
Stimulation of vasodilator nerves	(76, 77)
Peristalsis of gastrointestinal tract	(78)

postsynaptic protein complex. PSD-95 has an important domain named PDZ domains. When NO biosynthesis is required, PDZ domain will bind to the COOH termini of specific NMDA receptor subunits. In the meanwhile, nNOS will bind to the complex under the interaction of a novel PDZ-PDZ, and then PSD-95 recognizes an internal motif adjacent to the consensus nNOS PDZ domain. After the complex protein has been formed, nNOS is activated, and NO will be produced via the NO-cGMP pathway with the mediation of the calcium/calmodulin complex (39).

NO plays an important role in learning and memory. Nowadays, scientists find that both of the immediate and the prolonged phase of mitogen-activated protein kinase (MAPK) activation, a necessary signaling pathway for memory formation, depends on NO signaling. NO also plays a vital role in auditory fear conditioning and fear memory formation. In some behavioral experiments, the role of PKG signaling in auditory fear conditioning and in the lateral amygdala (LA) was examined. It was found that intra-LA infusion of the PKG inhibitor Rp-8-Br-PET-cGMPS had an inhibitory effect on fear memory formation, and long-term memory impairment. In contrast, the infusion of the PKG activator 8-Br-cGMP enhanced LTM. So it is concluded that fear acquisition and STM formation have been kept after manipulation of PKG signaling. These findings provide evidence that the NO-cGMP-PKG signaling pathway is critical for fear memory formation (40).

As a second messenger in the central nervous system, NO can activate many protein kinases through signal transduction. Long-term learning will start after the activation of PKA and PKC (41). And, after the activation of MAPK, short-term LFI memory formation will be initiated (42).While, PKG is reported to be involved in MAPK activation and then influence the long-term memory (43).

4. THE ROLE OF NITRIC OXIDE IN NEURODEGENERATIVE DISEASES

As an important member in the signaling pathway, NO plays a role in many diseases of nervous system, including neurodegenerative diseases. Neurodegenerative diseases are detrimental and can cause disorders in the behaviors, memories and so on, such as Parkinson's and Alzheimer's diseases. Recent evidence has accumulated that this kind of disease is also linked to the activation of NOS and the concentration of NO.

Parkinson's disease (PD) is a common neurodegenerative disease which can lead to slow movement, tremors, rigidity and gait impairment, with the average age of about 60 years old. It is generally accepted that the over-expression of iNOS in astrocytes, macrophages, and microglial cells contributes to the occurrence of PD (44). So, different from Alzheimer's disease (AD), inhibition of iNOS in PD models represents a protective influence against MPTP-induced neurotoxicity, which results in an alleviation of PD symptoms (45). Excessive production of NO may lead to aberrant protein S-nitrosylation, which results in protein misfolding, mitochondrial damage, transcription factor abnormality, and synaptic dysfunction (46). The modulation of NO in both extrinsic and intrinsic apoptotic cell death signaling pathways will result in the death of dopaminergic neurons (47). Researches also showed the involvement of NO in other biological processes of PD, such as ERS and autophagy. NO can *S*-nitrosylate sensors of ERS via the unfolded protein response, which contributes to the etiology of PD (48). During the pathogenesis of PD, the accumulation of immature and denatured proteins results in ER dysfunction, but the upregulation of PDI represents an adaptive response to protect neurons. NO-induced S-nitrosylation of PDI inhibits its enzymatic activity, leads to the accumulation of polyubiquitinated proteins, and activates the unfolded protein response (49). Parkin is an E3 ubiquitin ligase, whose activity can be inhibited by NO so that abnormal protein aggregates appear because of the reduction of ubiquitin proteasomal degradation to damaged or misfolded proteins (50). Proteasome activities seem to be involved in parkin-induced mitophagy, the selective engulfment of mitochondria by autophagosomes with subsequent lysosomal fusion and degradation (51). *α*-Synuclein can be modified by nitrative stress, which increases its propensity to aggregate. *α*-Synuclein also targets to mitochondria, where it causes a decrease in complex I activity and/or mitochondrial damage. This mitochondrial damage causes an increase in mitophagy, presumably as an attempt to clear damaged mitochondria (52). In addition, *S*-nitrosylation of other

proteins such as caspase-3, MEF2, and so on, is also the vital cause to the occurrence of PD (53-55). This series of *S*-nitrosylation phenomenon in PD model provides both an effective biomarker and a therapeutic target against PD, which may be responsible for the modest therapeutic effect and deserves a thorough exploration.

AD is considered as the main cause of dementia among elderly people, and is characterized as a multifactorial and fatal neurodegenerative disorder. By now, the pathogenesis of AD is still obscure and the nature of human brain tissue is inaccessible, which impeded the identification and treatment strategy against AD. The role of NO in the etiology of AD is complicated in the human body, which is either protective or toxic involved in each physiological system (56). Previous researches of postmortem materials and animal models have indicated the modification of NOS expression and different NO signaling pathway in AD (57). The increase of NO production in AD, which may be derived from over-activation of NMDA receptors in neurons, microglial activation, or retrograde messenger activity, is reported to contribute to Abeta-induced cytotoxicity (58). In addition, the increase of NO production leads to S-nitrosylation of dynamin-related protein 1 after Abeta exposure, thus resulting in the dysfunction of mitochondrial fission machinery (59). Interactions between Abeta and surface neuronal cell receptors may induce ROS production and expression of caspases and proapototic genes, and determine an increase in mitochondrial membrane permeability (60). Abeta may also stimulate the extrinsic apoptotic pathway through its proinflammatory action, able to activate astrocytes and microglia, and trigger the release of proinflammatory mediators such as TNF-alpha (61). Neurodegenerative disorders may produce mutant proteins that can be removed with autophagy through degradation and the dysfunction of autophagy pathway will cause accumulated toxicity of these proteins. A recent study shows that the protective concentrations of L-NAME, a NOS inhibitor, can enhance autophagy pathway. Conceivably, autophagy activation in rats treated by effective concentrations of L-NAME, increased cell survival and improved memory in Abeta-pretreated rats. So, they suggest that function of autophagy can be protective in their study (62). Another dependent study showed that after intra-hippocampal infusion of Abeta, autophagy process became active, whereas the autophagic markers increased till the 7th day after Abeta injection and afterwards, the autophagy markers decreased in a temperate manner (63). Researchers also found that PDI was S-nitrosylated in the brains of patients suffering from AD, but not in normal brains. NO-mediated S-nitrosylation of the redox enzyme PDI leads to dysregulated protein folding within the ER, and consequently results in ERS that promotes neuronal cell death (49). However, other paradoxical results suggest that NO may be protective to neurons (64). As evidence indicates that the constitutive activation of NOS results in the uncoupling of the enzyme, and the formation of peroxynitrite blocks the protective effect of NO (65). To our knowledge, due to the physiological effect of NO, the destruction of NO homeostasis may contribute to the divergent function of NO, and the maintenance of NO homeostasis may alleviate the neuronal injuries in AD.

NO can influence the process of neurodegenerative disease via a lot of pathways, especially the protein S-Nitrosylation mediated by NO. The S-Nitrosylation of many proteins is involved in mitochondrial fission, synaptic cytoxicity and apoptosis, which may contribute to neuronal death in AD, PD and HD. Moreover, the quantity of NO is vital in the degenerative diseases. Low concentration of NO can protect against mutant huntington fragment toxicity. While, excessive NO production has been considered as one of the mediators of excitotoxicity. Similar with many disease-related mechanisms, such as apoptosis, autophagy, or ERS, NO represents as a two-edged sword in the process of degenerative diseases. Although target on NO will support a promising treatment, it is difficult to keep NO in the specific regions and the quantity of NO is hard to maintain, which should be fully considered in the future researches (79). Taken together, NO homeostasis is vital for the maintenance of normal functions, which sheds light on a novel therapeutic target against neurodegenerative diseases.

5. ACKNOWLEDGEMENTS

This work is supported by the following grants: National Natural Science Foundation of China (31571162, 31200895), Beijing Municipal Talents Project (2013D005018000010). Beijing outstanding talent training program for youth backbone individuals (2015000020124G110); Natural Science Foundation of Capital Medical University (2016ZR11).

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Key Words: Nitric Oxide (NO), Autophagy, Apoptosis, Endoplasmic Reticulum Stress (ERS), Neurodegenerative Diseases, Review

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