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REVIEW ARTICLE

Role of Nitric Oxide in Neurodegeneration: Function, Regulation, and Inhibition

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Abstract: Reactive nitrogen species (RNS) and reactive oxygen species (ROS), collectively known as reactive oxygen and nitrogen species (RONS), are the products of normal cellular metabolism and interact with several vital biomolecules including nucleic acid, proteins, and membrane lipids and alter their function in an irreversible manner which can lead to cell death. There is an imperative role for oxidative stress in the pathogenesis of cognitive impairments and the development and progression of neural injury. Elevated production of higher amounts of nitric oxide (NO) takes place in numerous pathological conditions, such as neurodegenerative diseases, inflammation, and ischemia, which occur concurrently with elevated nitrosative/oxidative stress. The enzyme nitric oxide synthase (NOS) is responsible for the generation of NO in different cells by conversion of L-arginine (Arg) to L-citrulline. Therefore, the NO signaling pathway represents a viable therapeutic target. Naturally occurring polyphenols targeting the NO signaling pathway can be of major importance in the field of neurodegeneration and related complications. Here, we comprehensively review the importance of NO and its production in the human body and afterwards highlight the importance of various natural products along with their mechanisms against various neurodegenerative diseases involving their effect on NO production.

Keywords: Alzheimer's, NO, iNOS, neuroinflammation, neurotransmission, neurotoxicity.

1. INTRODUCTION

Neurodegenerative diseases are a heterogeneous group of disorders, which are portrayed by gradually progressive and selective loss of neuronal systems, and are considered as a major threat to human health [1, 2]. A characteristic feature of several neurodegenerative diseases, such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and Parkinson's disease (PD), is abnormal protein aggregation. Other specific characteristics, such as fibrillar deposits, are also observed in different disease conditions. These include extracellular amyloid plaques and neurofibrillary tangles in AD, nuclear inclusions in HD, and Lewy bodies in PD [3, 4].

An important role is played by abnormal protein assemblies in the triggering of ferocious cycles of anomalous neuronal activity, changes in neurotransmitter receptors, and associated signaling pathways, which lead to failure of neurological functioning by synaptic deficits and disintegration of neural networks [5]. Even though the incidence of neurodegenerative diseases is rapidly increasing in the last few decades [6], the results of clinical trials are not satisfactory to get an efficient therapeutic approach to cure these debili-

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tating disorders [5]. The reason behind failure of various drugs, targeting neurotransmitter receptors, might be the disruption of related signaling pathways due to the assemblies of abnormal proteins [5].

A common feature of neurodegenerative disorders includes the alteration of brain mitochondrial functions and dynamics with a drop of cell energy, mitophagy, and triggering of neural cell death [7-10]. Alterations of mitochondrial function, due to the accumulation of mitochondrial DNA (mtDNA) mutation and overproduction of reactive oxygen species (ROS) by dysfunctional mitochondria, have also been associated with the aging process, a major risk factor for neurodegenerative diseases [1]. Triggering of programmed cell death (PCD) by different factors, including reactive oxygen and nitrogen species (RONS), excitotoxicity, mitochondrial-complex inhibition, calcium ion entry, trophic-factor withdrawal, misfolded proteins, are also associated with neurodegenerative diseases [9]. Different signaling pathways are of particular interest in neurodegeneration and related diseases as they are involved in almost all of the major clinical ailments [11]. Apart from these, tauopathies (Tau proteins are members of microtubule-associated protein (MAP) family), characterized by the accumulation of copious filamentous tau inclusions [12], are also involved in the pathophysiology of neurodegenerative disorders [13]. These tauopathies are present in AD, progressive supranuclear palsy, Pick's disease, corticobasal degeneration, and argyrophilic grain disease [14].

Nitric oxide (NO) is a small, unstable, and highly lipophilic gas, endogenously synthesized by several cell types and involved in various processes, including immune response, neurotransmission, and platelet aggregation [15-21]. NO has also been shown to mediate several physiological processes, including neuromodulation and the action of neurotransmitters [20]. NO was originally identified as an endothelium-derived relaxing factor, acting as a mediator of blood vessel dilation [22-25]. Production of a higher amount of NO takes place in numerous pathological conditions, including neurodegeneration and neuroinflammation, and usually is accompanied by elevated nitrosative/oxidative stress [26].

In this review, starting with a brief description of NO biochemistry and function, the role of NO and the oxidative/nitrosative stress in mediating neuroprotection and/or neurotoxicity is discussed. Cellular insult occurs as a consequence of hypoxia during ischemia. This is further exacerbated upon reperfusion of the ischemic tissue due to reoxygenation because, along with the surplus restoration of the oxygen supply in the ischemic tissue, reactive oxygen species are also generated. Therefore, hypoxic conditions during ischemia and extensive superoxide generation during reperfusion, result in diminished NO production. This further results in aberrations in endothelial function. As consequence, tetrahydrobiopterin (BH4), an eNOS co-factor, stimulates the uncoupling of eNOS so that eNOS then begins to generate superoxide radicals instead of synthesizing NO. Simultaneously, ischemia-reperfusion injury in neurons also triggers metabotropic glutamate receptor-mediated stimulation of nNOS and synthesis of NO, which combines with the superoxide radicals to form nitric oxide radicals (ONOO-). An inflammatory cascade also accompanies ischemia-reperfusion mediated neuronal insult that triggers NO synthesis by iNOS in microglia, neutrophils, and glial cells. NO, thus generated, combines with the superoxide radicals to form ONOO- that interacts with several vital biomolecules, including nucleic acid, proteins, and membrane lipids, and alter their function irreversibly leading to protein tyrosine nitration, mitochondrial dysfunction, DNA damage and poly-(ADP-ribose)-polymerase (PARP) activation resulting in neurotoxicity (Fig. **1**). Afterwards, a comprehensive insight is presented focused on inhibition of NO production followed by targeting NO signaling pathway by natural compounds as a possible therapeutic strategy in neurodegenerative diseases.

2. NITRIC OXIDE AND THE CELLULAR REDOX STATUS

NO, with an unpaired electron, is a short-living free radical gas that can be generated rapidly in the human body. Specific NO features, such as free diffusion across various cell membranes and high reactivity, involve this molecule in several biological processes in various body systems, for instance, in the immune, cardiovascular, and nervous systems [27-29]. The influence of NO on different cellular process is highly concentration-dependent. Physiological NO levels act as neuromodulators or neurotransmitters in response to different brain stimuli within the central nervous system (CNS) and it plays an important role in long term potentiation of the hippocampus and synaptic plasticity by controlling appetite, sleep, neurosecretion, and body temperature [27, 30-32].

Diet and the L-arginine–NO synthase pathway are two major sources of nitrite and nitrate in the body [33]. NO is oxidized in blood and tissues for the formation of nitrite and nitrate [19, 34]. The key enzyme NOS is responsible for the synthesis of NO and L-citrulline through a two-step process of conversion, which involves nicotinamide adenine dinucleotide phosphate (NADPH), molecular oxygen, and L-arginine as co-substrate. Flavin mononucleotide (FMN), tetrahydrobiopterin (BH4), and flavin adenine dinucleotide (FAD) are essential co-factors, and haem and calmodulin are important prosthetic groups in this process [35, 36]. In response to pathological and physiological events, the inducible nitric oxide synthase (iNOS), one of the three key enzymes generating NO from the amino acid L-arginine (the others being the neuronal nitric oxide synthase (nNOS) and the endothelial nitric oxide synthase (eNOS)), may play a key role as a sensitive regulator in neurogenesis. Even though nNOS-derived NO negatively regulates the neurogenesis *in vivo*, it was also demonstrated that nNOS-mediated suppressing effect was due to NO generated by neurons [37].

According to the study conducted by Droge [38], the redox signaling is defined as ''a regulatory process in which the signal is delivered through redox chemistry''. In this process, post-translational modification of certain precise amino acid residues of signaling proteins occurred by RONS [38, 39]. Redox cell signaling is accepted as a major cellular

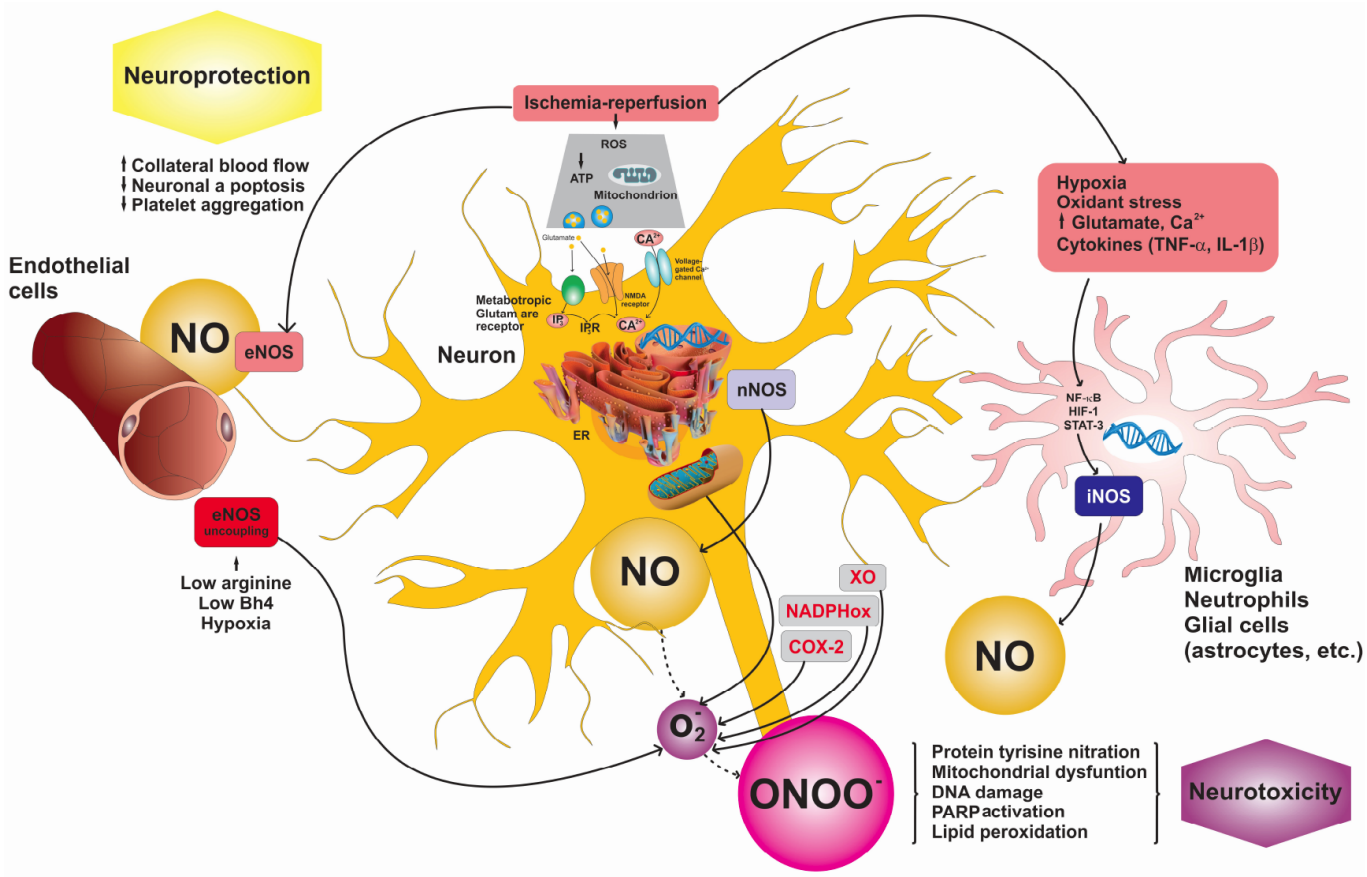

Fig. (1). Scheme of NO signaling pathways involved in neuroprotection and/or neurotoxicity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

process and dysfunction in redox cell signaling has been associated with the pathogenesis of several diseases, including cancer, ischemia-reperfusion injury, atherosclerosis, and diabetes [38, 40-42]. In some studies, both neuroprotective, as well as neurotoxic effects, have been reported at different concentrations. However, NO is supposed to be neuroprotective but considered to be neurotoxic when its cellular level increases [32, 43, 44]. Moreover, the production of several redox signaling mediators occurs in a highly controlled fashion by enzymatic or oxidative processes. The enzymes included in these processes are NOS, cyclooxygenase (COX), NADPH oxidase (NOX), lipoxygenase (LOX), heme oxygenase (HO), and cystathionine-β-synthase (CBS) [31]. NOX2, which is involved in pathogen control, is correlated with the generation of high superoxide ($O_2^{\bullet-}$) levels. NOX1, 3, 4, 5, and 6 are associated with additional regulatory roles and generate lesser fluxes of $O_2^{\bullet-}$ [31, 45-47].

The enzyme NOS is responsible for the generation of NO, which is substantially increased by elevated NOS expression and is associated with reduced neurogenesis in mice with Niemann-Pick type C disease. On the other hand, L-NAME, a NOS inhibitor, restored the ability of neural stem cell (NSCs) differentiation partially, and thus, reducing the amount of Fluoro-Jade C-positive degenerating neurons [48]. Additionally, Chen and colleagues [49] showed the mechanism of eNOS regulation in neurogenesis in a stroke model. It is assumed that stroke damage can cause the induction of NSC proliferation and migration in impaired brain parts, swapping the neurons that are damaged [49]. NSCs neurogenesis and proliferation are promoted by the repair stimuli through nNOS activation and neuron-derived increase of exogenous NO, which has, on the other hand, the ability to suppress these effects. Alternatively, inhibitors of iNOS can simultaneously reduce pathological NO, which is produced from reactive microglia and NSCs. Hence, NO suppression produced by iNOS may possess neuroprotective effects [50, 51]. Vasodilation can also be promoted by NO through various pathways [52, 53]. It generally involves the soluble guanylate cyclase (sGC) in smooth muscle cells with consequent cGMP-dependent protein kinase (PKG) activation. Myosin light chain dephosphorylation is promoted by PKG, finally resulting in vasorelaxation [54, 55].

NO is a signaling intermediate while glutamatergic neurotransmission in the CNS [56]. NO is believed as a crucial retrograde messenger at glutamatergic synapses, and also possess an important role at GABAergic synapses [57]. There is a close association of NO signaling with the glutaminergic transmission. NO synthesis is closely associated with the activation of glutamate receptors [55, 58] and also have an important role in the establishment of the neurovascular-neuroenergetic coupling axis [55]. Still, several shreds of evidence are present that advocate the importance of NO in the neurovascular coupling. When NO was identified as an intercellular diffusible messenger, an important role in the

regulation of cerebral blood flow (CBF) associated neuronal activity was proposed [55, 59]. It has also been reported that retrograde NO-signaling system is much more suitable for the general presynaptic controlling role and might also have the potential to fine-tune network activity in the course of early postnatal progression, while the GABAergic transmission is depolarizing [57].

2.1. NO Interaction with ROS Metabolism and Thiol Reaction

Oxygen is vital in aerobes for metabolism and formation of normal free radicals, which results in the maintenance of redox homeostasis crucial for the survival of brain cell due to their high need of metabolic energy to sustain neurotransmitter release, electrochemical gradients, and membrane lipid stability [60]. Various free radicals are the products of normal metabolism, which are utilized in many cellular processes like vasomotor tone, immune response, and signaling and later on, neutralized by antioxidant machinery of the cell. Free radicals may be superoxide ($O_2^{\bullet-}$), peroxyl radicals (ROO●), nitric oxide ($^{\bullet}NO$), and hydroxyl radicals ($^{\bullet}OH$), and some non-radical molecules like peroxynitrite ($ONOO^-$) and hydrogen peroxide (H_2O_2) are produced as well [61]. These are further divided into RONS, which may have $O_2^{\bullet-}$, $^{\bullet}OH$, ROH, H_2O_2, and RNS like $^{\bullet}NO$ and $ONOO^-$ [60]. RONS formation can also be catalyzed by various peroxidases, for instance, myeloperoxidase, which can oxidize nitrite to nitrogen dioxide by utilizing hydrogen peroxide [62].

Many proteins containing thiol are of prime importance to various cellular processes, functions of which can be modified through thiol oxidation or nitrosation. It was reported that the thiol nitrosation and oxidation by NO and superoxide, respectively, can be estimated by relative fluxes and could be of high physiological importance [63]. NO-induced nitrosative stress is responsible for the S-nitrosylation of antioxidant neuroprotective protein, peroxiredoxin 2, which leads to impairment of vital defensive cell mechanisms crucial for maintaining functionality, survival, and structure of the neuron [64]. Therefore, higher levels of NO trigger redox reactions, which is associated with protein misfolding (a hallmark of neurodegenerative disorders). Moreover, parkin S-nitrosylation also disrupts the activity of E3 ubiquitin ligase activity, and thus influence the formation of Lewy body and induce cell death of neurons [65]. The redox mechanism of NO is reviewed in detail by many authors [66-69].

3. OXIDATIVE/NITROSATIVE STRESS IN NEURODEGENERATION

Various redox-active species along with free radical species give rise to the modifications in numerous biomolecules, which are considered as an integral part of several pathological mechanisms. In redox reactions, electron exchange with RONS is crucial. It is mainly based upon two major mechanisms that include the classical receptor-mediated signaling pathway where binding of RNS and ROS at a precise target takes place, for instance, post-translational alteration of thiols and interaction with heame and non-heame iron targets [31]. The second mechanism is "redox tone", where control of the overall activity of the signaling pathway is dependent upon redox reactions and amino acid residues, which are responsible for the modulation of protein function [70]. The conversion of molecular nitrogen into ammonia and nitrate occurs during the nitrogen cycle, in which facilitation of assimilation of nitrogen takes place, together with the production of intermediate species, which are more reduced and more oxidized than N_2 in general [31]. Different facets of metabolism in prokaryotic and eukaryotic cells are governed through redox biology.

A large number of sources are responsible for oxidative stress, including unhealthy lifestyle, disease state, sleep restriction, excessive caloric intake, malnutrition, excessive alcohol consumption, and sleep apnoea [71-75]. The oxidative/nitrosative stress pathway has been implicated in several cardiovascular, neurodegenerative, and systemic disorders [26, 76], and plays an imperative role in cognitive impairments and neural injury [74, 77, 78]. In neurodegenerative diseases, such as AD, damage by oxidative stress is an early and common feature. Neurotoxic RONS levels increase during the neuroinflammation process, which is associated with cognitive decline [75].

As mentioned in section 2, the three major NOS involved in NO metabolism are the iNOS, eNOS, and nNOS [26, 79]. These enzymes can be found in the central as well as the peripheral nervous systems. These isoforms are encoded with different genes. Two are known as constitutive enzymes (cNOS), encompassing eNOS, encoded by NOS3, and nNOS, encoded by NOS1 genes [36]. RONS interact with several vital biomolecules, including nucleic acid, proteins, and membrane lipids, and alter their function in an irreversible manner, which sometimes leads to cell death [80].

4. NITRIC OXIDE IN NEURODEGENERATION AND MECHANISM

There are several important roles of NO in the peripheral and central nervous systems. It has a role in both neuroprotection and neurotoxicity, the presence of eNOS is found in the vascular endothelium, which is involved in the regulation of blood flow, decrease neuronal apoptosis, and platelet aggregation. The involvement of NO and other free radicals in neuroprotection and neurotoxicity is depicted in detail in Fig. **1**. It was also reported that neuronal relaxation is mimicked by agents producing NO [81, 82], supported by the data that nerve mediated gut relaxation is prevented by NOS inhibitors [81-83]. Numerous studies, few on autopsied human brains, have demonstrated a significant involvement of NO in neurodegenerative disorders. Decreased levels of endothelial NO play a key role in the upregulation of Aβ expression and modulation of amyloid precursor protein (APP) in the cerebrovasculature [84]. Utilizing anti-3-nitrotyrosine polyclonal antibody-mediated immunolabelling, Duda and coworkers [85] demonstrated a widespread nitration of Lewy bodies and Lewy nitrites in the autopsied cortex of patients with Lewy bodies and Alzheimer's disease. Furthermore, nitration of α-synucleins in glial cells of the autopsied cerebellar white matter, in patients of multiple system atrophy, and nitration of Lewy body-like inclusions and neuroaxonal spheroids in the autopsied globus pallidus was found in patients with neurodegeneration with brain iron accumulation type 1 [85]. Similarly, by utilizing n847 monoclonal anti-

body-mediated immunoreactivity, Horiguchi *et al*. [86] demonstrated widespread nitrated tau proteins in autopsied brains of AD, frontotemporal dementia with Parkinsonism linked to chromosome-17, Pick's disease, corticobasal degeneration, progressive supranuclear palsy, and Down syndrome afflicted individuals [86]. Another study showed that sodium nitroprusside (SNP), an NO donor, significantly elevated Aβ accumulation in HSV-1 infected as well as non-infected primary neuronal culture cells and mixed glial culture cells, while aminoguanidine, an iNOS inhibitor, inhibited the same [87].

The involvement of NO and its reaction product (with superoxide radicals), peroxynitrite, in AD pathology has also been reported from post-mortem studies on AD afflicted human brains as exceptionally raised levels of nitration of neurofibrillary tangles were evident in the hippocampus of AD patients as compared to the age-matched controls [88]. Some studies, based on animal models of 1-methyl 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (neurotoxin responsible for inhibition of mitochondrial respiratory chain complex I and imitates PD symptoms through degeneration of substantia nigra neurons)-induced neurotoxicity, showed that NOS inhibition delayed the progression of disease pathology. The involvement of NO and peroxynitrite was also reported from post-mortem studies of PD afflicted brains wherein elevated nitration of tyrosine residues in the degenerating neurons of substantia nigra pars compacta was reported [89]. Additionally, nitration of tyrosine residues of proteins has emerged as a crucial factor in the pathogenesis of a wide array of neurodegenerative disorders [90]. It is also interesting to note here that a majority of neurodegenerative pathogenicities, mediated by NO, are through nitration.

4.1. Pathways for Nitration of Tyrosine Residues of Proteins

The reaction of NO radicals with superoxide radicals results in the formation of peroxynitrite. Upon reacting with carbon dioxide, peroxynitrite forms nitrosoperoxocarboxylate that further generates NO and carbonate radicals. NO and carbonate radicals ultimately result in the nitration of tyrosine residues [90, 91]. The reaction of peroxynitrite with a proton results in the formation of peroxynitrous acid that decomposes to hydroxyl radical and nitrogen dioxide radical. Nitric dioxide and hydroxyl radicals result in the formation of tyrosyl radicals by extracting a proton from tyrosine and then further results in the formation of 3-nitrotyrosine, due to the recombination of tyrosyl and NO radicals [90, 91].

Alternatively, peroxynitrite reacts with a transition metal species that results in the generation of nitronium ions. These nitronium ions are involved in the nitration of tyrosine residues in proteins [90]. NO induces necrosis of neurons in neurodegeneration through glutamate-mediated excitotoxicity that surfaces due to NO-mediated inhibition of mitochondrial respiration. This was shown in lipopolysaccharide activated astrocytes and microglial cell cultures by Bal-Price and Brown [92].

The production of NO from isoforms of NOS varies wih the respective isoform. Nanomolar concentrations of NO are generated by nNOS, with a physiological neuroprotective function, while NO concentrations, in the range of micromolar concentrations, are synthesized by iNOS. Micromolar concentrations proinflammatory stimuli are neurotoxic [93, 94]. Free radical properties by the abnormal overproduction of NO plays a crucial role in neuroinflammation. This results in the dysfunction of mitochondria by mitochondrial fission through compromised viability and cellular integrity [94].

Initially, NOS was identified in different parts of the brain including the dentate gyrus and CA1 region of the hippocampus, cerebral cortex, paraventricular and supraoptic nuclei of the hypothalamus, olfactory bulb, ventral endopiriform nucleus, nucleus accumbens, olfactory nuclei, pedunculopontine tegmental and lateral dorsal nuclei, thalamus, cerebellum amygdale, and striatum [43]. Its expression was further found in parts of the peripheral nervous system, such as NANC neurons at the GI tract and skeletal muscles [93, 94]. The presence of nNOS in the CNS was reported in cerebral blood vessels and astrocytes. Alpha, beta, gamma. and mu are the four splice variants of nNOS [94]. In the peripheral system, the presence of eNOS is found in the vascular endothelium, which is involved in the regulation of blood flow. Deficiency of iNOS and eNOS can be well endured, whereas, the deficiency of nNOS can lead to apoptotic cell death of neurons of the spinal cord [93, 94].

4.2. Neuronal Nitric Oxide Synthase in Neurodegeneration

Several toxic effects of nNOS were reported in different models of PD, including rotenone, MPTP, and 6-hydroxy dopamine (6-OHDA) [95-97]. Parathath and colleagues [98] reported significant role of NO in facilitating neurodegeneration following tissue plasminogen activator mediated excitotoxicity [99] and an indispensable role of nNOS in neurodegeneration induced by kainic acid-mediated excitotoxicity in hippocampal regions of the brain in C57B16 mice [98]. Increased cerebral expression of NOS3 in Long Evans rats has been reported to induce neurodegeneration similar to that encountered in AD accompanied by elevated levels of Aβ, APP, Tau proteins, glial fibrillary acidic proteins, and reduction in expression of choline acetyltransferase [100]. Protection from nigrostriatal dopaminergic neurodegeneration induced by zinc was shown to be mediated by NO/nNOS. This effect was due to the reduction of NO by Zn through the inhibition of nNOS, leading to intrinsic apoptosis-mediated neuronal cell death caused by an increased oxidative stress. Additionally, nNOS showed negative regulation against Zn induced Parkinsonism [101].

nNOS is responsible for the generation of NO in the CNS, which is attributed to the regulation of different pathological and physiological functions, including neurodegeneration and neurogenesis [102, 103]. In some cases, endogenous nNOS was shown to play a positive role in neurogenesis [104]. nNOS is mainly expressed in the neuronal cytoplasm, but it is also found in astrocytes and neuronal stem cells (NSCs) [105-107]. Negative regulation of neurogenesis by nNOS was revealed by several studies [108-110]. One study reported that nNOS-derived and iNOS -derived NO exhibited opposite role in neurogenesis regulation in the dentate gyrus after cerebral ischemia and revealed that there is an involvement of reduced nNOS in hippocampal neuro-

genesis induced by ischemia *via* upregulation of iNOS expression, along with phosphorylation of cAMP response element-binding protein [110]. Furthermore, nNOS products have a decisive role in the loss of neurons, sometimes followed by neurotrauma [111]. In traumatic brain injury (TBI), nNOS plays a deleterious role and inhibition of nNOS exhibited a neuroprotective role in TBI [112, 113]. Studies revealed that S-nitrosylation of nNOS, besides phosphorylation or dephosphorylation, reversibly regulates the activity of nNOS [113-116]. This undoubtedly clears the role of nNOS S-nitrosylation in the regulation of nNOS activity and its' modulation can be of potential importance in the development of therapeutic intervention for neurodegereative disease.

4.3. Inducible Nitric Oxide Synthase in Neurodegeneration

The response to agents like lipopolysaccharide and cytokines leads to the production of NO in inflammatory cells, which is, in general, arbitrated mainly by iNOS [117]. Hence, inhibiting NO generation *via* iNOS suppression is an important aspect of the treatment of inflammatory diseases [118]. Destruction of normal functional tissues takes place during acute and chronic inflammation by overproduction of NO *via* iNOS [119]. The expression of iNOS is relatively low and highly upregulated in microglia and astrocytes, which leads to traumatic, neurotoxic inflammatory, and ischemic damage [43, 120-122]. In response to tumour necrosis factor-α (TNF- α), interleukin-1 (IL-1), and interferon-γ, LPS, and other cytokines, NO is generated by iNOS of microglia and astrocyte origin [123-126].

The enhancement of iNOS in neural precursor cells by poly-L-ornithine has also been reported [107]. Furthermore, blocking of the ERK signaling pathway was reported in iNOS+/+ microglia [127]. Elevated expression of iNOS in NSCs obtained from Niemann-Pick type C disease mice was demonstrated [48]. Moreover, higher concentrations of NO were reported in isolated NSCs, followed by a significant reduction in the growth and induction of an apoptotic cascade through the enrichment of caspase 3 and GSK 3 activation in cultured neurospheres [48, 122]. Although the levels of NO are low in the NSCs, its levels significantly increased in Niemann-Pick type C disease [48], and following the exposure to poly-L-ornithine [107], corticosterone [128], and leukaemia inhibitory factor [122, 129].

Inflammation is the main factor in most of the brain pathologies, in which NO generation takes place [130-135]. Several researchers identified the different mechanisms of action leading to neuronal death by activated glia in cultures [131, 132]. It was found that high levels of NO, which are mainly produced by iNOS expression in glia, cause induction of neuronal death through inhibition of neuronal mitochondrial cytochrome oxidase [92, 136]. Depolarization of neurons, the release of glutamate, and subsequent excitotoxicity following activation of the N-methyl-D-aspartate (NMDA) receptor is caused by the inhibition of neuronal respiration by NO [92, 137-139]. The potentiation of excitotoxicity also occurs by a different mode of action as iNOS generated NO leads to the release of glutamate from astrocytes due to increased calcium ion mobilization from stores present intracellularly, which stimulates vesicular glutamate exocytosis [140]. This mechanism only takes place when the generation of NO is very high from elevated iNOS expression [130]. iNOS generated NO may have protective effects by blocking cellular death in the brain [141, 142]. Conversely, iNOS expression at low levels may serve in synergy with certain other conditions, such as hypoxia, to persuade cell death [143, 144]. NO can also induce oxidative stress [145] and in the absence of oxidative phosphorylation, NO produced from iNOS along with oxidants from various sources may kill cells [130, 145].

5. INHIBITION OF NITRIC OXIDE PRODUCTION

Several synthetic, as well as natural inhibitors, have the potential to inhibit NO production. Previous reviews on the inhibition of NO production focused on synthetic inhibitors of NO or arginine based inhibitors [35, 146]. Another review summarizes NO-hybrid derivatives [147]. Herein, we focus on natural products that have potential effects on NO production. Two xanthones, α-mangostin and γ-mangostin, obtained from *Garcinia mangostana* L.*,* exhibited significant NO production inhibitory activity in LPS-stimulated RAW264.7 cells which were mediated by suppression of iNOS expression [118, 148]. Xia *et al*. experimented with some isolated phytoconstituents from *Curcuma phaeocaulis* concerning their inhibitory effect on NO production and found that several compounds had moderate inhibitory effects on NO synthesis with the range of IC50 values of 17.34 to 30.02 μM. However, the mechanisms of action of these compounds remained unexplored [149]. The NO inhibitory effects of phacadinanes A–D, which are four cadinane-type sesquiterpenes isolated from *C. phaeocaulis,* were examined in LPS-activated macrophages and it was found that two of these compounds possessed strong inhibitory activities with IC50 values of 3.88±0.58 and 2.25±0.71 μM [150]. Moreover,1-feruloyl glycerol and 1-feruloyl diglycerol, which are two hydrophilic derivatives of ferulic acid, were investigated against NO production and iNOS expression in primary astrocytes of rats resulting in a concentration-dependent inhibition of iNOS expression and NO production. The mechanism for this effect was thought to be the suppression of the nuclear factor-κB pathway [151].

Stemona javanica root extract, composed of stemofoline and stemanthrene C, also exhibited inhibitory activity against NO production in LPS stimulated murine macrophage-like cell line J774.1. The proposed mechanism of action of stemofoline was the suppression of iNOS expression in J774.1 cells, while stemanthrene C showed higher radical scavenging activity, which leads to NO inhibition [152]. Leaf extracts of *Sarcocephalus pobeguinii* showed significant NO inhibitory activity in LPS-activated RAW 264.7 macrophages [153]. In a recent study, new gedunin-type limonoid, carapansin C, phragmalin-type limonoids, carapanosins A and B, and five known limonoids compounds were isolated from the *Carapa guianensis* seeds and studied in LPS-activated mouse peritoneal macrophages. The results revealed that carapansin C and two known limonoids showed potent inhibitory effects on macrophage activation through the inhibition of NO synthesis [154]. Prevention of morphine dependence and tolerance by inhibition of NO overproduction was reported using *Nepeta menthoides* and methadone

[155]. Significant NO inhibitory activity was found from 80% methanolic extract of roots of *Pteris multifida* in LPS-activated BV-2 microglia cells. Some of the isolated constituents from this extract also exhibited potent inhibition of NO production in LPS-stimulated BV-2 cells and reduced COX-2 protein expression and also inhibited the level of TNF-α, prostaglandin E2 (PGE2), IL-1β, and IL-6 levels [156]. In primary microglia, the sesquiterpene lactone parthenolide, naturally occurring in the plant feverfew (*Tanacetum parthenium*), was demonstrated as an inhibitor of iNOS/NO synthesis. The molecular mechanisms by which parthenolide prevents iNOS/NO synthesis were suggested to be the inhibition of p42/44 mitogen-activated protein kinase (MAPK), but not IκB alpha degradation or NF-kB p65 activation (Fiebich *et al*., 2002).

A traditional Chinese medicine, Da Chuanxiong formula [dried rhizomes of *Ligusticum chuanxiong* and *Gastrodia elata* at 4:1 (w/w)], was reported to possess the ability to suppress NO productions by iNOS and COX-2 expression in LPS-stimulated RAW 264.7 cells [157]. Terpenoids from *Salvia plebeian* comprised of two new diterpenoids, two new meroditerpenoids, two sesquiterpenoids, and one known meroditerpenoid, which inhibited NO production induced by LPS in BV-2 cells. Furthermore, possible mechanisms revealed interactions with the iNOS protein of some of these natural compounds when examined by molecular docking [158]. Significant inhibition of mRNA expressions of iNOS, IL-6, and IL-1β in LPS-stimulated RAW 264.7 macrophages was reported from a macrolactin derivative identified as 7,13-epoxyl-macrolactin A from *Bacillus subtilis* B5, which is derived from 3000-meter deep-sea sediment [159]. An extract of *Bridelia ferruginea* revealed anti-neuroinflammatory activity by preventing iNOS and NO synthesis through the inhibition of NF-kB and p38 MAPK signaling in BV2 microglia (Olajiide *et al*., 2012).

CONCLUSION AND FUTURE PROSPECTS

NO plays a tremendous role in various pathological conditions and neurodegeneration in particular. As a neurotransmitter, it functions through different mechanisms. Therefore, targeting NO production and different NOS enzymatic pathways might be an important strategy to combat neurodegenerative diseases. Natural products targeting NO can be of great importance. Clinical evidence is mainly present in the area of vasodilation and not much is available for neurodegeneration. Therefore, further research in the area of the efficacy of different natural products targeting inhibition of NO can serve as a potential mechanism for neurodegeneration and related complications.

LIST OF ABBREVIATIONS

6-OHDA	=	6-Hydroxy Dopamine
AD	=	Alzheimer's Disease
ALS	=	Amyotrophic Lateral Sclerosis
APP	=	Amyloid Precursor Protein
CBF	=	Cerebral Blood Flow
CBS	=	Cystathionine-β-Synthase
CGMP	=	Cyclic Guanosine Monophosphate
CNS	=	Central Nervous System
COX	=	Cyclooxygenase
eNOS	=	Endothelial NOS
FAD	=	Flavin Adenine Dinucleotide
FMN	=	Flavin Mononucleotide
HD	=	Huntington's Disease
HO	=	Heme Oxygenase
iNOS	=	Inducible NOS
L-NAMA	=	NG monomethyl-L-arginine
L-NAME	=	N omega-Nitro-L-Arginine Methyl ester
LOX	=	Lipoxygenase
MAP	=	Microtubule Associated Protein
MPTP	=	1-methyl 4-phenyl-1,2,3,6-tetrahydropyridine
mtDNA	=	Mitochondrial DNA
NADPH	=	Nicotinamide Adenine Dinucleotide Phosphate
nNOS	=	Neuronal NOS
NO	=	Nitric Oxide
NOS	=	Nitric Oxide Synthase
NOX	=	NADPH Oxidase
NSC	=	Neuronal Stem Cells
$O_2^{\bullet-}$	=	Superoxide
PCD	=	Programmed Cell Death
PD	=	Parkinson's Disease
RNS	=	Nitrogen Species
ROS	=	Reactive Oxygen Species
sGC	=	Soluble Guanylate Cyclase

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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