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Review Article

NITRIC OXIDE MEDIATED NEURODEGENERATION IN PARKINSON'S DISEASE

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ABSTRACT

Nitric oxide (NO) is an endogenous molecule which functions as a neurotransmitter, hormone, free radical, etc. NO has been found to regulate the release of neurotransmitters, synaptic transmission, cell death, etc. NO is involved in the pathogenesis of various neuropsychiatric and neurodegenerative disorders. NO plays a key role in cellular apoptosis and neuronal degeneration. Parkinson' disease (PD) is a neurodegenerative disorder characterized by motor dysfunction that can be seen in the patients suffering from PD. The motor dysfunction is due to the progressive degeneration of dopaminergic neurons in mid brain. Dopamine (DA) is highly reactive molecule and is prone to the oxidation very much. The oxidation of DA is accompanied by the production of the reactive oxygen species that activates microglia cells. Upon activation, microglia cells cause the upregulation of inducible NO synthase, the enzyme involved in the production of NO. NO thus plays a key role in the neurodegeneration process implicated in PD. Thus, the aim of the present manuscript is to describe the possible role of NO in PD.

Keywords: Dopamine, Neuromelanin, Nitric oxide, Parkinson.

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INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in substantia nigra (SN) region of the brain. This degeneration of dopaminergic neurons in nigro striatal region contributes to the motor dysfunction in the patients of PD [1]. Therefore, the patients suffering from PD exhibits the symptoms such as rigidity, tremor, and bradykinesia. [2]. Excessive oxidation of proteins, and lipids, mitochondrial defects, low glutathione (GSH) levels, excessive dopamine (DA) o-quinone synthesis, and excessive levels of 5-cysteinyldopamine in the cerebrospinal fluid has been implicated in the patients of PD [3,4]. The death of dopaminergic neurons in the brain results in the release of neuromelanin, a pigment composed of a complex polymer of 5, 6-dihydroxyindole, and possibly 5-cysteinyldopamine, on a glycoprotein matrix [5]. Normally, neuromelanin is neuroprotective because it is a potent antioxidant, mops up toxic catecholamine o-quinones, and chelates large amounts of toxic heavy metals [6]. However, in excess, it becomes neurotoxic, largely by the disruption of cells [7]. Neuromelanin is known to activate the microglia cells that contain inducible nitric oxide synthase (iNOS), which when expressed produces greater quantity of NO. Thus, NO plays a key role in the pathogenesis of PD [8].

NO is one of the simplest biologically active molecules of unique chemical nature which plays a very important role in neurotransmission, acts in many tissues to regulate a wide range of physiological, pathological, and cellular processes [9]. NO plays a key role in several process such as the regulation of cell death, neurotransmission, and immune defense [10]. NO functions as a hormone, reactive oxygen species (ROS), neurotransmitter, constitutive mediator, inducible mediator, cytoprotective, and cytotoxic molecule [11]. Abnormal regulation or control of NO synthesis by impaired expression of NOS is capable of affecting a number of important biological processes and has been implicated in a variety of diseases [12]. NO diffuse rapidly across cell membranes and exerts its biological effects through the reaction of NO with a number of targets such as cysteine residues, hem groups, and iron and zinc clusters [13]. NO also enhances catecholamine release and to inhibit reuptake, possibly by reversing the transporter [14]. The above facts suggested the role of NO in PD [15].

NOS AND THEIR FUNCTIONS

NO is a highly reactive, short-lived molecule produced from a group of enzymes known as NOS [16]. NO is produced from enzymes NOS which exists in three isoforms, from the amino acid L-arginine in the presence of many cofactors NADPH using flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), heme, thiol and tetrahydrobiopterin, and oxygen [17]. There are three types of NOS - endothelial NOS (eNOS), iNOS and neuronal NOS (nNOS) [18]. In each NOS, there are three distinct domains: Reductase domain, calmodulin (CaM)-binding domain, and oxygenase domain [19]. (1) Reductase domain contains the FAD and FMN moieties, and it transfer electrons from NADPH to oxygenase domain [20]. (2) CaM binding domain detects the changes in intracellular calcium levels, and therefore, the binding of CaM is required for the activity of all NOS isoforms [21]. (3) Oxygenase domain catalyzes the conversion of arginine into citrulline and NO [22]. This domain contains the binding sites for tetrahydrobiopterin, hem (heme), and arginine. iNOS is found in microglia cells and the expression of this isoform has been known to produces the high concentrations of NO [23]. iNOS mediated production of NO is preceded by increased intracellular Ca^{2+} concentration because is a CaM -dependent isoform [24]. The specific actions of NO on the neurotransmission are attributed primarily by NO produced by nNOS after the activation of N-methyl-d-aspartate (NMDA) receptors [25]. nNOS is linked with NMDA receptors via postsynaptic density protein [26]. Thus, the NMDA receptors activation exposes the enzyme directly to the flux of Ca^{2+} entering the ion channel. NO produced by the nNOS around the NMDA receptor reflects the activity of glutamate mediated neurotransmission [27]. NO synthesized intracellularly diffuses out through the neuronal membrane to induce the depolarization of the neuronal membrane and evoked the neurotransmitter release [28,29]. e-NOS produces NO results in the activation of soluble guanylyl cyclase, followed by the accumulation of cyclic guanosine monophosphate (cGMP), in vascular smooth muscle cells, which further results in the relaxation and vasodilatation [30]. The production of cGMP leads to the activation of cGMP-dependent protein kinases possibly to increase the expression of anti-apoptotic proteins [31].

NO AND CELLULAR APOPTOSIS

NO is a potential bioregulator of apoptosis [32]. NO may prevent or induce apoptosis and can also increase or decrease the Bcl-2 levels. NO may act as an antiapoptotic signal by suppression of mitochondrial cytochrome c release, ceramide generation, and caspase activation [33]. NO donors elevate Bcl-2 expression and prevent apoptotic cell death. NO can inhibit apoptosis in some cells, whereas it promotes apoptosis in others cells [34]. Antiapoptotic signaling has been generally correlated with low or physiological NO levels [35]. NO shortage - induced decrease in CREB activity that interferes with the cGMP-dependent protein kinase, the most important intracellular signaling pathway activated by NO [36]. CREB and its associated proteins act as survival factors for human melanoma cells [37]. High physiological concentrations of NO-induced apoptosis in cells by the formation of transition metal complexes [32]. Thus, the activation of iNOS facilitates cell death [38]. NO also results in the activation of neutral SMase and increase the ceramide generation, main cell death mechanisms [39]. The mechanism of death action for ceramide may also involve, at least in part, a p53-dependent suppression of Bcl-2 expression [40]. It has also been showed that p53 promotes permeabilization of the outer mitochondrial membrane by forming complexes with the protective Bcl-xL and Bcl-2 proteins [41]. Moreover, the tumor suppressor p53 may also transactivate the expression of pro-apoptotic genes such as bax and cyclin-dependent kinase inhibitor p21 [42].

NO AND NEURODEGENATION

NO plays a key role in the neurodegeneration. It has been suggested that the levels of the GSH reduces in the patients of various neurodegenerative disorders PD and AD [43]. GSH levels were found to be lower in SN of PD. GSH is low molecular weight cellular non-enzymatic antioxidant which is synthesized in two steps: The enzyme g-glutamyl-cysteine synthetase (g-GCS) that catalyzes the synthesis of g-glutamyl-cysteine from glutamate and cysteine; and GSH synthetase (GS), which catalyzes the formation of GSH from glycine and g-glutamylcysteine [44]. It is present as a reduced form and two oxidized species: GSH disulfide and GSH mixed disulfide with protein thiols [45]. GSH acts as a cofactor of GSH peroxidase and participates in the detoxification of lipid and organic peroxides [46]. GSH modulates several proteins, including receptors, molecules involved in signaling and nuclear transcription factors [47]. It has been reported that in neurodegenerative diseases, the activity of both g-GCS and GS progressively decreases through the downregulation of gene expression and GSH decrease could be a consequence of the formation of protein mixed disulfides [48]. NO reacts with oxygen, superoxide anion (O_2^-), and reducing agents to give products such as nitroxyl, oxides (NO_2, N_2O_4, and N_2O_3), peroxynitrite ($ONOO^-$), and S-nitrosothiols (RSNO) that produces the toxic effects and nitrosative stress [49]. In anaerobic conditions, direct reaction between NO and biological thiols can occur by a very slow oxidation reaction that yields thiol disulfide and nitroxyl anion [50]. The presence of oxygen is essential for the formation of S-nitrosoglutathione (GSNO) and protein RSNO [51]. NO toxicity in neuronal cells, indicate the disruption of cellular buffering mediated by GSH and the reaction of GSH with NO makes the neuronal cells more susceptible to damage [52]. The formation of GSNO is plausible, because it has a longer lifetime than NO and protein RSNO and is considered as a pool of NO that can be released when or where it is required for signaling [53]. Upon the depletion of GSH and upon inhibition of GSH synthesis, endogenous NO is the primary factor affecting cell proliferation and viability through the NO-cGMP pathway and NO-mediated DNA damage and protein oxidation [54]. This suggests that GSH could be an essential buffer of NO under physiological conditions and its imbalance is linked with the harmful effects of NO [55]. GSH decrease causes protein nitration, S-nitrosylation, and DNA strand breaks [56]. Such alterations results in the inhibition of cytochrome-c oxidase activity and microtubule network disassembly, which are considered hallmarks of NO toxicity [57]. Also it has been suggested that the treatment with physiological amounts of NO donors, an increase in GSH levels has been also reported [58]. Therefore, NO exerts neurodegenerative and neuroprotective effects in the concentration dependent manner.

NO AND PD

PD is characterized by the death of dopaminergic neurons in the SN region of brain. The main reason behind the death of the dopaminergic neurons is not known clearly but it is suggested that the oxidative stress plays a key role in the pathogenesis of PD. Brain is susceptible to oxidative stress, due to its high oxygen demands, higher rate of oxidative metabolism, lower level of protective antioxidant system, higher membrane to surface area to cytoplasm volume, abundant neuronal network, etc., [59]. However, SN of midbrain is highly susceptible to oxidative stress because of its large population of dopaminergic neurons that produce abundant quantities of ROS species [60]. The higher level of oxidative stress in SN is marked by increased lipid peroxidation, decreased levels of GSH, increased iron concentrations, mitochondrial dysfunction, and DNA and protein oxidation [61].

The oxidation of DA initiates the neurodegeneration possibly due to the depletion of GSH and oxidation of ascorbate [62]. In SN, the increased metabolism of DA has been found to be associated with increased levels of ROS [63]. Increased production of ROS results in the disruption of mitochondrial enzymes participating in respiration and electron transport chain [64]. Oxidative stress in SN occurs due to the autoxidation of DA into semiquinones, which further generates ROS and ROS makes the dopaminergic neurons vulnerable to death [65]. The loss of DAergic neurons is due to the failure of glucose metabolism due to aberration in mitochondrial respiration which is further responsible for the failure of DA neurotransmission [66]. Oxidation of DA results in the DA quinone, which directly modifies the proteins and causes the irreversible inhibition of complex I activity, lead to impaired energy metabolism and cell death [67]. Mitochondrial-related energy failure disrupts the vesicular storage of DA and leads to increased auto-oxidation of DA neurotransmitter [68].

DA in SN is deaminated by the action of monoamine oxidase, which results in the production of dihydroxyphenylacetic acid and H_2O_2 [66]. H_2O_2 produced is converted into highly destructive hydroxyl radicals by the fenton reaction, with Fe^{2+} being liberated and these hydroxyl radicals then lead to widespread cellular damage [69]. Oxidation of DA produces DA-quinones, which cyclizes to form aminochrome, and aminochrome form adducts with proteins and is the precursor of neuromelanin that contribute to neurodegeneration by triggering neuroinflammation [70-73]. NM is natural protective and sequesters iron, free radicals, and toxic quinines. In PD, the loss of NM occurs gradually due to massive dopaminergic neuronal death [74,75]. NM can also binds with the heavy metals such as iron and the loss of these neurons in PD is correlated with an abundance of nonheme iron (Fe^{3+}). Moreover, it has been suggested that the infusion of ferric iron into SN produces a dose-dependent reduction in dopaminergic activity. Iron released from neuromelanin increases oxidative stress in mitochondria and disrupts the mitochondrial function. The presence of iron together with a diminished supply of antioxidants leads to an increased generation of hydroxyl radicals through various reactions in the microglia, producing a cascade of destructive events including oxidative stress, lipid peroxidation, and eventually apoptosis. Moreover, the unbound iron initiate a range of cytotoxic and inflammatory effects, such as the activation of redox-sensitive transcriptional factor nuclear factor-κB and cytokine release from activated microglia [65]. The neuromelanin pathway can produce deleterious DA-quinone, which are potent inhibitors of mitochondrial complex I and promotes the α-synuclein fibrillization [76-79].

Neuromelanin, released by dying DA neurons, has been reported to activate microglia cells [80]. Activated microglial cells contribute to an inflammatory reaction seen in PD [81]. Increased density of microglial cells expressing iNOS in SN of PD patients compared with control has been observed in the previous studies [82]. Activation of microglia is associated with an upregulation of iNOS resulting

in increased production of NO, suggesting that reactive nitrogen species plays a critical role in the disease [83]. Activated glial cells expresses the higher level of cytokines such as tumor necrosis factor-α, interleukin--1β and interferon-γ as well as iNOS, which have been reported in SN in PD [84]. These inflammatory cytokines, along with factors released from the dying dopaminergic cells, seem to amplify, and sustain the neuroinflammation as well as further consequent immune responses leading to a potentially lethal descent into irreversible destruction of dopaminergic neurons in SN [85]. The cytotoxic mechanism thus involves the upregulation of iNOS. Increased expression of iNOS is known to mediate the increased production of NO, which has been shown to cause neuronal toxicity [86]. Therefore, the toxicity mediated by the increased NO levels may contribute to the death of the dopaminergic neurons. It has been suggested that the NO interact with oxygen-free radicals such as superoxide (O^{2-}) to produce $ONOO^-$ and which further contribute to cellular injury, including lipid peroxidation, nitrosylation of some molecules, inactivation of sodium channels, and interactions with metals, which have redox potential such as iron and copper [87]. NO also increase the glutamate release, leading to inappropriately high NMDA receptor activity [88]. $ONOO^-$ oxidize DA, deplete available reduced GSH/ascorbate, incur a substantial loss of endogenous GSH-peroxidase, and destroy the natural ability of GSH to act as an antioxidant [76,89]. $ONOO^-$ is potent oxidizing agent than NO, induces DNA fragmentation and lipid peroxidation. $ONOO^-$ also induces a dose-dependent impairment in DA synthesis independent of DA oxidation or cell death [13,90]. Exposure to $ONOO^-$ disrupts the catalytic activity of tyrosine hydroxylase, the rate-limiting enzyme involved in the DA synthesis [91,92]. $ONOO^-$ produced by high NMDA receptor activity depletes the adenosine triphosphate (ATP) pools by two major mechanisms [93]. It attacks mitochondrial proteins and lead to lowered production of ATP generation. It also nicks DNA, followed by the activation of poly (ADP-ribose) polymerase, leading to the depletion of NAD pool and finally ATP depletion, because NAD/NADH have essential roles in oxidative ATP generation [94]. It is well known that when ATP levels get lowered, NMDA receptors become hypersensitive due to lowering of the plasma membrane potential [95]. Thus, the stimulation of NMDA receptors results in the ATP depletion [96]. Excessive activation of NMDA receptors, results in excessive Ca^{2+} influx through a receptor's associated ion channel [97]. Increased Ca^{2+} levels in conjunction with the CaM, trigger the activation of nNOS, and subsequent generation of NO, a damaging free radicals, contributing to cell injury and death [98]. NO inhibits several enzymes including complexes I and IV of the mitochondrial electron transport chain, leading to ROS generation [99]. Therefore, overstimulation of NMDA receptors mediates neuronal damage. The intense hyperstimulation of NMDA receptors leads to necrotic cell death, but milder or chronic overstimulation results in apoptotic or other forms of cell death implicated in many neurological disorders [100]. Therefore, either the NO or NOS can be the targets for the treatment of PD and the modulators of NO can be the effective treatment of PD.

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