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Pathophysiology of Parkinson: An Updated Review

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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.

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INVOLVEMENT OF NO IN THE PATHOGENESIS OF PD

Excessive NO synthesis and parkinsonism authenticate the statistical implications of *NOS1* and *NOS2A* in PD [1]. Also there is a significant increase in the CSF nitrite content in the PD patients. Raised levels of 3-NT formed by the NO attack on free tyrosine and tyrosine has been found in proteins in PD [2]. Pharmacological inhibition of iNOS has been shown to prevent dopaminergic neurodegeneration as a consequence of microglial activation and transgenic mice lacking iNOS are more resistant to MPTP-mediated dopaminergic neurotoxicity [3]. Activated microglia secretes various pro-inflammatory mediators including cytokines such as IL-6 and TNF-α, reactive oxygen species, and reactive nitrative species such as NO. These factors are believed to contribute to microglia-mediated neurotoxicity [3]. Selective inhibition of NF-κB activation suppressed microglial activation and prevented DA neuronal loss against MPTP-injured PD mouse model. Fluoxetine significantly inhibited LPS-induced NF-κB activation, which might be responsible for the decreased production of pro-inflammatory factors and consequent neuroprotection [4]. A common feature observed in the neuronal cells of AD and PD victims in this sporadic variant was the attachment of nitric oxide (NO) to the redox-active cysteines of protein-disulfide isomerase (PDI) to form S-Nitroso PDI. The formation of S-nitroso-PDI coupled with the making the oxidoreductase a chief target for the prevention of these two neurodegenerative disorders in the nitrosative-stress-linked variant of the diseases. PDI is severely compromised by the addition of nitric oxide resulting from elevated levels of nitrosative stress [5].

Brain appears to be particularly susceptible to oxidative stress due to its heavy oxygen demands but the nigra seems to be highly susceptible to oxidative stress presumably due to its large population of dopaminergic neurons, which produce abundant quantities of ROS. There is a necessary fine-tuned balance between the extent of the production of and the removal of oxidants, and it is this balance that keep ROS and RNS constantly at low, non-toxic levels. Thus PD is associated with a higher production of or a lower detoxification of oxidants [6]. The presence of oxidative stress in PD has been associated with increased oxidation of lipids, DNA and proteins and the generation of ROS. Furthermore, oxidative stress has been demonstrated in PD sufferers and evidence also clearly supports the involvement of impaired mitochondrial function in PD [7]. The total of 1% of all oxygen consumption might be reduced to superoxide or hydrogen peroxide. However, neither superoxide nor hydrogen peroxide is particularly toxic. Cells can greatly increase the toxicity of superoxide by producing nitric oxide [7].

The death of the dopaminergic neurons in the SN results in the accumulation of extracellular NM and NM activate microglia, suggesting a proinflammatory role for NM. NM activates microglia by triggering NK-κB activation [8]. Upon activation, microglia proliferate, undergo morphogenesis, and increase cell volume with extension of their processes. Activated microglia are well adapted for the induction of inflammation, cytokine-mediated and antibody-dependent cell cytotoxicity. These toxic substances include reactive oxygen species (ROS), reactive nitrogen species (RNS), proinflammatory cytokines, and prostaglandins. Uncontrolled microglial activation is toxic to neurons, due in part to release of pro-inflammatory factors including, but not limited to interleukin one beta (IL-1β), tumor necrosis factor alpha (TNF-α), IL-6, nitric oxide (NO), prostaglandin E2 (PGE2), and superoxide radical [9].

TNF-Alpha, a pro-inflammatory cytokine, is produced by many cell types, including macrophages, lymphocytes, fibroblasts and keratinocytes, in response to inflammation, infection, and other environmental stresses. TNF-Alpha acts by binding to its receptors, TNFR1 (p55) and TNFR2 (p75), on the cell surface. Most cells express TNFR1, which is believed to be the major mediator of the cytotoxicity of TNF-Alpha [10, 11]. Binding of TNF-Alpha to its two receptors, TNFR1 and TNFR2, results in recruitment of signal transducers that activate at least three distinct effectors. Through complex signaling cascades and networks, these effectors lead to the activation of Caspases and two transcription factors, Activation Protein-1 and NF-KappaB (Nuclear Factor-KappaB). Initially, TRADD (TNFR-Associated Death Domain) protein, binds to TNFR1, then, TRADD recruits FADD (Fas-Associated Death Domain). Binding of TRADD and FADD to TNFR1 leads to the recruitment, oligomerization, and activation of Caspase8. Activated Caspase8 subsequently initiates a proteolytic cascade that includes other Caspases (Caspases3,6,7) and ultimately induces apoptosis. Caspase8 also cleaves BID (BH3 Interacting Death Domain). tBID (Truncated BID) disrupts the outer mitochondrial membrane to cause release of the pro-apoptotic factors CytoC (Cytochrome-C). CytoC that is released from the intermembrane space binds to APAF1 (Apoptotic Protease Activating Factor-1), which recruits Caspase9 and in turn can proteolytically activate Caspase3. A novel 61-kDa protein kinase RIP2 is related to RIP that is a component of TNFR1 which mediates the recruitment of Caspase death proteases. TRAF2 (TNF Receptor-Associated Factor-2) has been implicated in the activation of two distinct pathways that leads to the activation of Activation Protein-1 via the JNK (Jun NH2-terminal Kinase), MEKK (MEK Kinase), p38 and, together with RIP, NF-KappaB activation, via the NIK (NF-KappaB-Inducing Kinase). Overexpression of SODD (Silencer Of Death Domains), a 60 kDa protein, associated with the DD of TNFRI suppresses TNF-induced cell death and NF-KappaB activation demonstrating its role as a negative regulatory protein for these signaling pathways [12]. Expression of NOS2 in diverse cell types is highly dependent on the NF-κB signaling pathway and we demonstrated previously a requirement for NF-κB in the expression of NOS2 in activated astrocytes after stimulation with inflammatory cytokines and manganese. TNF-α induced activation of NFkB and thus is responsible for NFκB mediated iNOS induction [13].

Astrogliosis results in increased production of various neurotoxic inflammatory mediators, including nitric oxide (NO) that contributes to progressive loss of nigrostriatal neurons. Supporting a deleterious role for excessive NO production in PD are postmortem observations of increased NOS2 expression in patients diagnosed with PD, as well as reports that deletion of the *Nos2* gene in mice confers protection against MPTP-mediated neurotoxicity. Microglial cells expresses high levels of iNOS in the SN of PD patients compared with control patients. iNOS is known to mediate NO production, which causes neuronal toxicity. Thus, it is suggested that toxic NO levels may occur in close proximity to dopaminergic neurons [14]. The important target of mitochondrial superoxide is NO. The spontaneous reaction of superoxide with NO occurs at a rate comparable to that with SOD2 and generates peroxynitrite, a powerful oxidizing species. Cellular damage induced by peroxynitrite includes

depletion of thiol-dependent antioxidants, DNA strand breakage, lipid oxidation, and protein nitration [15].

Prx family proteins are important antioxidant enzymes that limit accumulation of intracellular peroxides. Active Prx2 reduces H_2O_2 and other peroxides by using normal redox cycle and detoxifies intracellular peroxides. Prx2 activity is regulated by NO. S-nitrosylation targets the redox-active Cys-51 and Cys-172 residues and forms SNO-Prx2 which results in the generation of nonfunctional Prx2, which furthers results in accumulation of cellular peroxides that further oxidize SNO-Prx2 to Prx2-$SO_{2/3}$H. Interfering with the normal antioxidant system by the generation of SNO-Prx2 may contribute to neuronal cell death. NO-mediated pathway leading to neuronal cell death involving Prx2 dysfunction may lead to the development of new therapeutic approaches for sporadic PD and other neurodegenerative disorders associated with nitrosative stress [16]. XIAP is an antiapoptotic protein that is known to be crucial for cell survival. The mechanism by which S-nitrosylation of parkin impairs its protective function appears to occur through inhibition of its E3 ubiquitin ligase activity. This idea contrasts with the mechanism of impairment of XIAP antiapoptotic function by S-nitrosylation. XIAP antiapoptotic function is inhibited by S-nitrosylation through preventing XIAP's binding to caspase-3. Neuroprotective proteins such as peroxiredoxin and protein-disulphide isomerase are modified by S-nitrosylation, and this modification compromises their normal protective functions. Thus nitrosative stress is an important contributor in the pathogenesis of PD [17].

Lewy bodies are the neuropathological hallmark of the diagnosis and pathophysiology of the neurodegenerative process [18]. *α*-Syn is the main protein component of Lewy bodies, but, importantly, the *α*-syn found in Lewy bodies is misfolded and phosphorylated, indicating that a pathogenic variety of *α*-syn accumulates in diseased or damaged cells. The native *α*-syn monomer is an unfolded, soluble protein, and *in vitro* studies have shown that monomeric, oligomeric, and fibrillar species of *α*-syn exist in equilibrium [19]. Oligomerization of αsyn initiates with the dimerization of partially folded monomers, followed by the formation of β-sheet rich nonfibrillar, oligomeric intermediates, also known as protofibrils. Protofibrils are transient β-sheet-containing oligomers that are formed during aggregation. Studies have shown that the presence of the disease-associated mutations in αsyn increase rates of self-assembly and fibrillization [19, 20]. Its aggregation is involved in Lewy body formation and subsequent neuronal cell death. Oxidized glutathione (GSSG) is known to accelerate this aggregation and neuronal death [21]. The importance of extracellular aSyn is further supported by the role of aSyn in triggering neuroinflammatory glial responses. Extracellular aggregated aSyn added to neuron-glia culture lead to microglia activation and enhanced dopaminergic neurodegeneration [22]. *α*-synuclein act as a negative regulator of dopamine release, perhaps by modulating vesicle fusion and distribution. Thus the overexpression of *α*-synuclein decrease the rate of dopamine release [23]. Nitrated α-synuclein has also been detected in the SN and ventral midbrain of mice treated with MPTP Recombinant α-synuclein treated with nitrating agents (peroxynitrite/CO_2 myeloperoxidase/H_2O_2/nitrite) generates highly stable nitrated α-synuclein oligomers as a consequence of oxidation resulting in the formation of crosslinked o-o'-ditryrosine. This form of aggregated α-synuclein is resistant to proteolysis, perhaps due to its structural stabilization. Nitrated α-synuclein activated T cells enhances microglial activation and degeneration of dopaminergic neurons. This suggests that oxidative/nitrative PTMs may cause an adaptive immune response that augments the neuropathology in PD [24].

NO MEDIATED NEURODEGENERATION IN PD

NO plays key role in neurotransmission but at higher concentrations, it is implicated in the pathogenesis of stroke, demyelination, and other neurodegenerative diseases. NO derived from activated glial cells is assumed to contribute to oligodendrocyte degeneration in demyelinating diseases and neuronal death during ischemia, trauma and neurodegenerative diseases [25]. Microglia are the major resident immune cells in the brain and under physiological conditions, microglia exhibit a deactivated phenotype that is associated with the production of anti-inflammatory and neurotrophic factors. Microglia switch to an activated phenotype in response to pathogen invasion or tissue damage and thereby promote an inflammatory response that serves to further engage the immune system and initiate tissue repair [26]. Mechanisms by which activated microglia kill neurons include the increased expression of iNOS in glia [27].

NOS induction is predominantly regulated by the two pro-inflammatory transcription factors NF-κB [28]. Single-nucleotide genetic polymorphisms in the TNF promoter that increase transcriptional activity and TNF production are associated with earlier onset of disease in patients with idiopathic PD. Also TNF mRNA and protein levels are elevated in postmortem brain and cerebrospinal fluid. Soluble TNF (solTNF) is the ligand species mediating the cytotoxic effects on DA neurons [29]. TNF-α, is rapidly produced in the brain in response to tissue injury. TNF-α induced activation of

NF-kB and thus is responsible for NF-κB mediated iNOS induction [13]. CD23-dependent activation of iNOS in microglial cells may be involved in the cascade of events leading to DA cell death. However, the principal ligand for CD23-IgE has not been detected in the SN of PD patients and it is thought that other likely ligands such as the α chain CD11b and CD11c of the adhesion molecules CD11b/CD18 and CD11c/CD18 may trigger CD23 activation in PD [14].

Increased expression of iNOS results in the increased production of NO. It is believed that NO can react with superoxide radicals forming the highly toxic peroxynitrite, which causes nitration of tyrosine residues (3-nitrotyrosine) on cellular proteins resulting in both structural and functional alterations. PN can also cause protein damage by modifying tyrosine (3-nitrotyrosine formation, 3NT), cysteine (*S*-nitrosylation or SNO formation), or tryptophan (via formation of *N*-formylkynurenine) residues. The significance of this neurotoxic mechanism is supported by studies that demonstrate increased 3-nitrotyrosine immunostaining in Lewy bodies in PD patients and also the presence of increased 3-nitrotyrosine in MPTP-lesioned mice [14, 30]. Levels of 3-nitrotyrosine, a biomarker of attack by $ONOO^-$ and other reactive nitrogen species upon protein-bound tyrosine residues, were also significantly increased in the mutant Parkin transfectants, again independent of Parkin enzyme activity. The mutant proteins could elevate levels of NO /NO_3^- , for which increased expression of nNOS (but not iNOS) was presumably responsible.

Proteasomal dysfunction may be a significant contributor to neuronal cell death in the major neurodegenerative diseases [31]. NO is known to inhibit several enzymes including complexes I and IV of the mitochondrial electron transport chain and aconitase [30]. NO can exacerbate neuronal injury resulting from excitotoxicity. Increased intracellular Ca^{2+} levels, resulting from activation of glutamate receptors such as NMDA receptors, stimulate nNOS to produce more NO. The continual influx of Ca^{2+} through the open NMDA receptors compounds the stress on mitochondria, which attempt to sequester and buffer Ca^{2+}. As mitochondrial membrane potential decreases because of the overflow of Ca^{2+}, mitochondria reverse their ATP synthase in an attempt to restore it. Eventually, the excess Ca^{2+} uptake causes mitochondrial membrane potential loss, mitochondrial swelling, opening of the mitochondrial permeability transition pore, outer membrane rupture, and spill of Ca^{2+} and apoptogenic factors into the cytoplasm [32]. Ca^{2+} loads in the matrix sensitize the mPTP to apoptotic stimuli [33].

Mitochondria have been identified as critical for the apoptotic process. Mitochondrion integrates death signals engaged by proteins in the Bcl-2 family and releases pro-apoptotic molecules residing in the mitochondrial intermembrane space to activate caspases leading to internucleosomal cleavage of DNA. Apoptotic stimuli produce conformational changes and oligomerization of pro-apoptotic proteins (Bax, Bak, etc.) and destabilizes lipid bilayer, creating pores which results into the release of cytochrome *c* into the cytoplasm, which induces the formation of the Apaf1-containing macromolecular complex called the apoptosome. Released cytochrome *c* then triggers the assembly of the cytoplasmic apoptosome a protein complex of apoptotic protease activating factor 1 (Apaf1), cytochrome *c*, and procaspase-9. This is the engine that drives caspase-3 activation. [34]. Caspases contain a single cysteine at the catalytic site, which is susceptible to redox modification and can be effectively modified by *S*-nitrosylation in the presence of NO. *S*-nitrosylated caspases can be a source to transfer of NO to XIAP via transnitrosylation and contribute to an additional mechanism to produce SNO-XIAP, inhibit its E3 ubiquitin ligase activity, leading to neuronal death. Also the Caspase activation during NO stimulation also occurs as a result of down-regulation of X-linked inhibitor of apoptosis protein (XIAP) which interacts with active caspases-3/-7/-9 in the cytosol and inhibit the catalytic activity of apoptotic caspases [35].

NO MEDIATED NEURONAL PROTECTION IN PD

An unbalanced generation of RNS as a feature of PD pathology. Glial cells within the *SN* exhibit increased NO levels, possibly due to the accumulation of interferon-γ (IFN-γ), a cytokine which was shown to promote induction of RNS in brain [36]. The highly abundant mitochondria in brain cells are a major site of generation and action of ROS/RNS. Specific forms of ROS and RNS include hydrogen peroxide (H_2O_2), superoxide (O_2^-), nitric oxide (NO), peroxynitrite ($ONOO^-$). Oxidative stress occurs in cells and tissues because of overproduction of superoxide (O_2^-) and its secondary oxidants that are formed from several sources, including NADPH oxidase, xanthine oxidase, and the mitochondrial electron transport chain [37].

NO reacts with O_2^- and generates $ONOO^-$, which is capable of initiating further protein oxidation and nitration. The addition of NO to thiol groups on proteins, S-nitrosation (also referred to as S-nitrosylation), has also been reported in neurodegenerative diseases [38]. GSNO, a modulator of cellular redox, is a physiological metabolite produced by the reaction of nitric oxide (NO) with glutathione (GSH). It is an

efficient nitrosylating agent, and the mechanism of nitrosylation modulates protein functioning in health and disease. Pharmacologically, GSNO has been shown to protect the central nervous system (CNS) against excitotoxicity, inflammation, and reactive oxygen species (ROS) in a variety of injury conditions mainly through the down regulation of the expression of NF-κB, adhesion molecules, cytokines and inducible NOS (iNOS) and neuroprotective effects via reducing the neuronal apoptotic cell death and inhibiting the activity of caspase-3 [39]. MPTP toxicity could not be induced in nNOS knocked out mice and thus 7-Nitroindazole (7-NI), a specific NOS inhibitor, also dose dependently inhibited the MPTP induced dopamine depletionand prevented the increase in peroxynitrite induced 3-NT formation in mice [2].

However the production of the NO exerts the beneficial effects initially when produces in the lower concentrations. Ca^{2+} influx after NMDA-receptor activation results in increased NOS activity- hence increased NO production and loss of membrane potential in mitochondria. Loss of membrane potential decreases Ca^{2+} uptake by mitochondria, which decreases mitochondrial NO production, salvages mitochondrial function, and protects neurons from NMDA toxicity. However, in mature hippocampal neurons, NO production after NMDA activation does not depend on mitochondrial membrane potential because the active NOS is localized to the cytosol rather than the mitochondria. Thus, the feedback effect of NO on mtNOS is not relevant and cannot protect the neurons from Ca^{2+} [32].

NO produced in mitochondria and is an important modulator of O_2^- production, as the ETC contains several NO reactive-redox metal centers. At physiological concentrations, NO modulates mitochondrial oxygen consumption by inhibiting cytochrome *c* oxidase in a reversible process. Also, $NO^{\bullet}$ undergoes radical–radical reaction with O_2^- at near diffusion-limited rates forming peroxynitrite ($ONOO_2^-$), an oxidant capable of irreversible nitration of proteins, inactivation of enzymes, DNA damage, and disruption of mitochondrial integrity [40]. Nitrite-dependent S-nitrosation of mitochondrial complex I may play a role in this phenomenon, the mechanism by which nitrite mediates cytoprotection. Complex I is particularly susceptible to ischemic damage and is a major target for NO and its metabolites. Several studies demonstrate that S-nitrosation of critical thiols on the complex can inhibit the enzyme, resulting in cytoprotection Inhibition of complex I activity appears to be cytoprotective due to its inhibitory effect on ROS generation, particularly at the time of reperfusion when rapid entrance of oxygen into the electron chain results in a burst of ROS formation [41]. The ATP synthase plays a vital role in cellular energetics as it is the predominant site of ATP formation in the cell. increased ATP hydrolysis by the ATP synthase during ischemia contributes to the depletion of the ATP pool. Thus, downregulation of the enzymatic activity of the ATP synthase may be beneficial through the preservation of cellular ATP. ATP synthase alpha subunit shows increased nitration after IR. GSNO-dependent preconditioning induced a concentration dependent S-nitrosation of the F1-ATP synthase alpha subunit, which inhibited the activity of the complex. The NO or nitrite dependent preservation of ATP in the ischemic tissue may contribute to the cytoprotective mechanism of IPC [42]. S-nitrosation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) inhibits its dehydrogenase activity and induces an acyl phosphatase activity in the enzyme, resulting in the uncoupling of glycolytic flux from ATP synthesis. Nitrosated GAPDH can also translocate to the nucleus, enabling it to degrade selected target proteins and affect apoptosis [43].

Mitochondria served as critical for the apoptotic process and integrates death signals engaged by proteins in the Bcl-2 family and releases pro-apoptotic molecules residing in the mitochondrial intermembrane space to activate caspases leading to internucleosomal cleavage of DNA. Apoptotic stimuli produce conformational changes and oligomerization of pro-apoptotic proteins (Bax, Bak, etc.) and they cause destabilizing of lipid bilayer, creating pores or interacting with channels which results into the release of cytochrome *c* into the cytoplasm, which (in the presence of dATP) induces the formation of the Apaf1-containing macromolecular complex called the apoptosome. Released cytochrome *c* then triggers the assembly of the cytoplasmic apoptosome a protein complex of apoptotic protease activating factor 1 (Apaf1), cytochrome *c*, and procaspase-9 and activates caspase-3 [34]. NO abrogates cytochrome c release is through its nitrosylation of the heme in cytochrome *c*, resulting in the inhibition of its peroxidase activity and subsequent oxidation of CL. Therefore, nitrosylation of CL-bound cytochrome *c* represents a mechanism through which NO prevents the initiation of the intrinsic apoptotic pathway. NO-mediated gradual wake-up of the electron transport chain could indirectly prevent mPTP formation by attenuating mitochondrial Ca^{2+} overload and ROS overproduction [44]. Bcl-2 is a key apoptosis-regulatory protein of the mitochondrial death pathway. NO, through its ability to *S*-nitrosylate Bcl-2, may interfere with the ubiquitination process and inhibit proteasomal degradation of the protein [45].

NO at low doses may have antiapoptotic characteristics by blocking caspase activity via *S*-nitrotyrosylation [46]. Most of the caspases contain a single cysteine at the catalytic site, which is susceptible to redox modification and can be

effectively modified by *S*-nitrosylation in the presence of NO with the subsequent inhibition of enzyme activity. NO reportedly inhibits the enzymatic activity of caspase-3 and -8 via *S*-nitrosylation of active-site cysteine residues and suppresses apoptosis [35].

In the light of above findings it is suggested that the NO is implicated in the pathogenesis of PD.

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