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Oxidative Stress: An Important Target in Parkinson Disease

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ABSTRACT

Parkinson's disease (PD) is a chronic and progressive neurological disorder associated with the loss of dopamine-producing neurons in the substantia nigra pars compacta of the brain. Oxidative stress plays a vital role in the degeneration of dopaminergic neurons in Parkinson's disease (PD). Oxidative stress intervenes when there is disequilibrium between ROS production and cellular antioxidant activity. Several sources and mechanisms for the generation of reactive oxygen species (ROS) are recognized including the metabolism of dopamine itself, neuroinflammation, and mitochondrial dysfunction. These ROS attack all macromolecules, including lipids, proteins, and nucleic acids, resulting in cellular damage. The reduction of oxidative stress could be achieved by lowering the generation of oxidative stress by prevention of ROS formation or by quenching of ROS with antioxidant which may provide targeted new approaches towards neuroprotection.

INTRODUCTION

Parkinson's disease (PD)is an age-related neurological disorder that negatively affects the dopamine-producing neurons in a specific area of the brain called substantia nigra. This loss of dopamine creates deregulation in the basal ganglia circuitries leading to the appearance of motor symptoms such as rigidity, bradykinesia, postural instability, and resting tremor, and non-motor symptoms such as sleep disturbances, depression, and cognitive deficits3. Accumulation of Lewy bodies, increasing age, genetics factors, environmental factors such as neurotoxins, pesticides like rotenone, paraquat, etc causes Parkinson's disease. Although the mechanisms underlying the pathogenesis of PD have not been fully understood, increasing evidence suggests that oxidative stress plays an important role the degeneration of dopamine-producing neurons.[2]

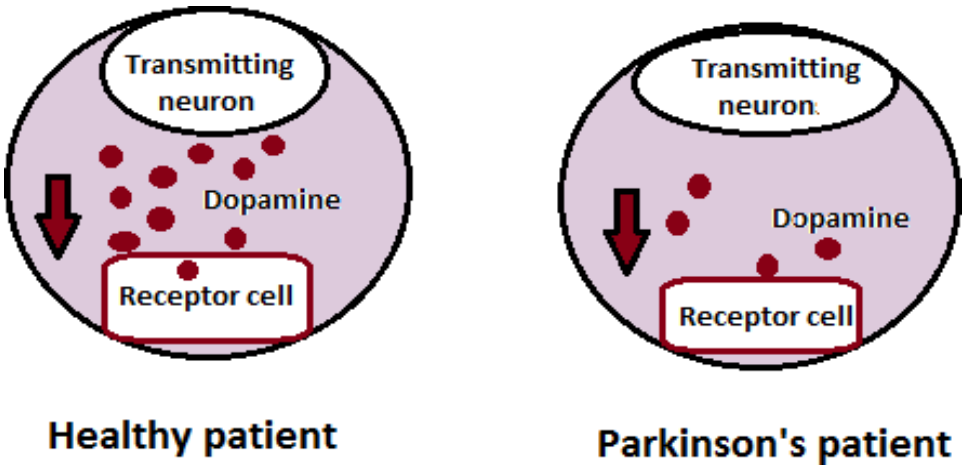

Figure No 1: Dopamine level in Parkinson's disease

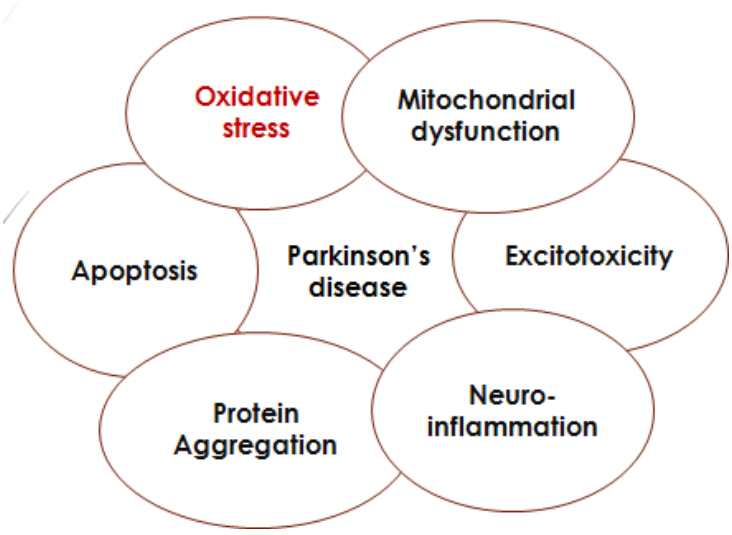

Figure no 2: Pathogenesis of Parkinson's disease

Oxidative stress

Progressively Oxidative stress is recognized as a central event contributing to the degeneration of dopaminergic neurons in the pathogenesis of Parkinson's disease (PD). Oxidative stress is defined as the imbalance between the levels of reactive oxygen species (ROS) produced and the ability of the biological system to detoxify the reactive intermediates, creating cellular damage.2 ROS that mostly damage to cells includes hydrogen peroxide, the hydroxyl radical, nitric oxide (NO), and the superoxide radical, whereas the vital antioxidants in the human body are superoxide dismutase (SOD), catalase, and glutathione1. The conversion of superoxide radicals is catalyzed by SOD to hydrogen peroxide, and then hydrogen peroxide is converted to water and oxygen by catalase and glutathione peroxidase. Glutathione peroxidase also converts nitrate to nitrite, which indicates the NO activity1.ROS which is produced due to Disturbances in the normal redox state of cells can cause toxic effects that damage the macromolecules, including proteins, lipids and DNA1.The defects in these macromolecules result in neuroinflammation and mitochondrial dysfunction, which consequently increase the generation of ROS and ultimately neuronal damage. Besides ROS, RNS is also involved in neuronal damage by producing nitrosative stress.

Mechanism of oxidative stress

Improper functioning in various pathways resulting from genetic modifications in PD-related genes and lead to an increase in oxidative stress. Mutations in the expression of the neuronal protein can lead to impaired mitochondrial function, oxidative stress, and protein misfolding and aggregation. Also, dopamine metabolism may be oxidized to reactive dopamine quinines leading to an increase in the levels of ROS. Alfa-synucle in becomes modified and accelerates sits aggregation. Increased oxidative stress causes impairment in the functions of UPS that degrades misfolded or damaged proteins and thereby further affecting cell survival. Environmental toxins affect mitochondrial function and increase the generation of ROS. Complex I inhibition leads to bioenergetics disturbance, causing damage to neurons. Also, neuroinflammatory mechanisms may contribute to a cascade of consequences leading to cell death. In summary, all these mechanisms contribute to oxidative stress which causes selective degeneration of dopaminergicneurons.[3]

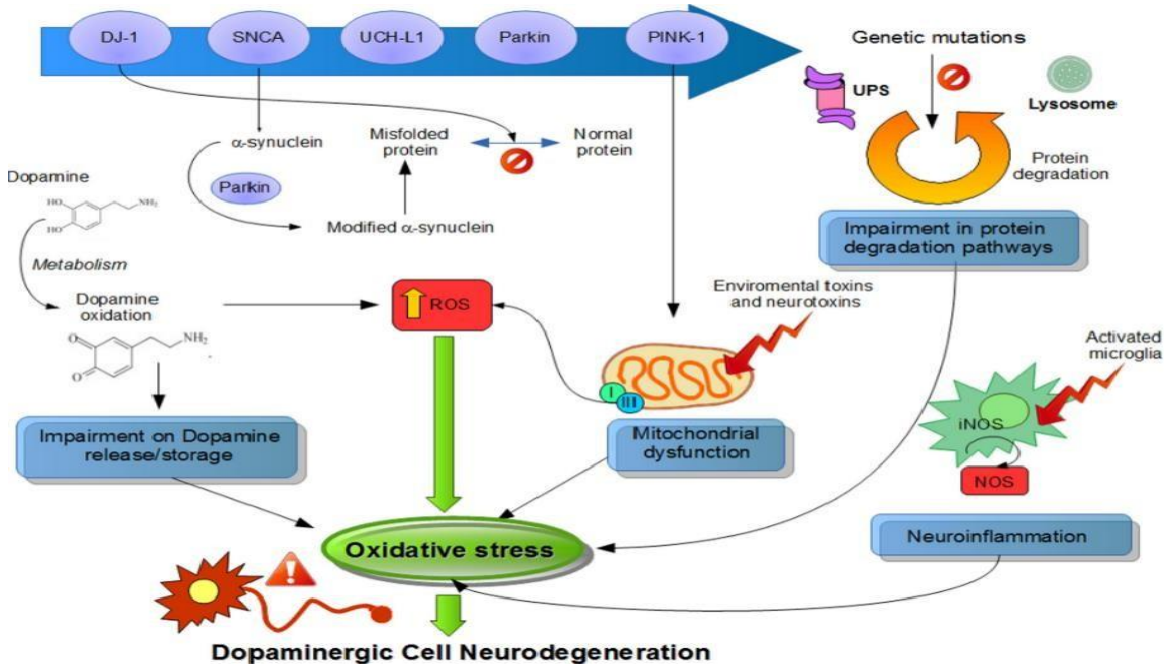

Figure no 3: Mechanism of oxidative stress[3]

Generation of ROS and RNS

The generation of ROS is an outcome of oxygen-dependent (aerobic) respiration. In eukaryotes, mitochondria produce energy in the form of ATP from macromolecules via Krebs cycle and electron transport chain (ETC) 7. Leaking of electrons from the electron transport chain, leads to the partial reduction of molecular oxygen to superoxide (O2−) which is converted into hydrogen peroxide (H2O2) by superoxide dismutase's (SOD). H2O2usingcatalase (CAT) and peroxiredoxin (Prx) get converted into H2O and oxygen.H2O2can also be converted to highly reactive hydroxyl radical (OH)with Fe2+ as a catalyst via Fenton reaction. Overstimulation of N-methyl-Daspartatereceptor (NMDAR) will lead to activation of neuronal nitric oxide synthase (nNOS) which generates an excess amount of nitric oxide (NO). NO reacts with O2− to form the more reactive species called peroxynitrite (ONOO−).ONOO− can convert to nitrogen dioxide (NO2) and the highly reactive OH or carbonate radical (CO3−) when reacted with H+orCO2. Catabolism of dopamine by monoamine oxidase (MAO) generates H2O2. Oxidation of DA also produces ROSand DA quinone radical (DAQ) that can modify protein directly. In neuroinflammatory conditions, glial cells are activated. Inducible nitric oxide synthase (iNOS)produces NO and NADPH oxidase (NOX) produces ROI in activated microglial cells. Which then diffuses to SNc Dopamine neurons and causes both oxidative and nitrosative stress. SNcDA neurons

express cyclooxygenase (COX). COX produces (PG) prostaglandin and generates H2O2 as an end product

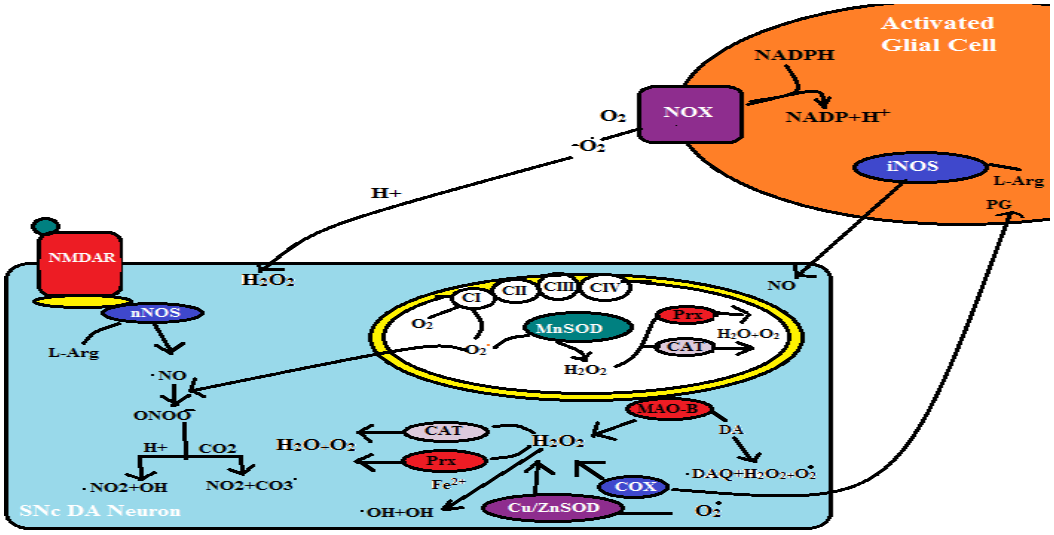

Figure no 4: Generation of ROS and RNS

Major Sources of Oxidative stress

Dopamine metabolism

Dopamine (DA), is the neurotransmitter produced from DA neurons and is responsible for the regulation of inhibitory and excitatory synaptic transmission for ensuring smooth coordinated movement14. The movement disorder in PD patients is basically because of the deficiency of DA. Dopamine is an unstable molecule that may be auto-oxidized to form quinones and H2O2.15,16H2O2 could react with oxygen or iron to form more reactive˙OH17. DA quinones could react with the sulfhydryl groups of the cysteine in proteins, specifically glutathione (GSH), a ROSs cavenger, resulting in lower GSH levels, and higher ROS level18. Also, H2O2 has generated as by a product in the process of dopamine oxidative metabolism by MAO B19,20. Apart from the synthesis and degradation, the transport and storage of dopamine also contribute to an increase in the production of ROS. Dopamine is produced in cytosol and then stored into synaptic vesicles to provide a favourable environment for DA. Dopamine reuptake, occurred with the help of dopamine active transporter (DAT), is essential for maintaining the dopamine level in the synaptic cleft. Any disturbance in the storage and reuptake of dopamine would raise cytoplasmic dopamine, which will enhance the sensibility to oxidation. Besides this mutation in the α-synuclein causes enhanced dopamine reuptake and down-regulates VMAT2. Accumulation

of dopamine by reuptake of dopamine from extracellular space to cytosol DAT causes dopamine neurotoxicity. Conclusively, dopamine is an unstable molecule and is prone to auto-oxidation.

Any disturbance in elevating the cytoplasmic dopamine can increase dopamine auto-oxidization and subsequently will increase ROS production and eventually will cause oxidative stress.[10]

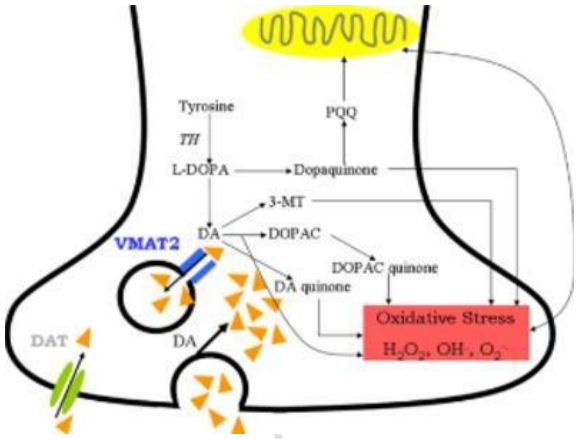

Figure no. 5: Dopamine Metabolism[12]

Mitochondrial dysfunction

Mitochondria play a dual role as source and target of ROS. Mitochondria are known as the "powerhouse" of cells, the cells which generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS). During ATP production, ROS also generate from the electron transport chain [ETC]. The reactive oxygen species (ROS) from mitochondrial complex I am transported to the mitochondrial matrix, while the ROS from complex III is transported to the mitochondrial matrix as well as the inner membrane space. Mitochondrial dysfunction leads to increase in the ROS production which is harmful to ETC itself, leading to even excess production of ROS. It was suggested that overproduction of ROS by mitochondria was a key factor responsible for cell death and the progression of neurodegenerative diseases, particularly in idiopathic PD. Mitochondrial dysfunction leads to the shortage of ATP, which is important especially to dopaminergic neurons to maintain ionic gradients, propagate electrical signals, and secrete dopamine. Compared with age-matched controls, the activity of the mitochondrial electron transport chain was decreased in the substantia nigra of PD patients, further supported the role of mitochondrial dysfunction

in PD. In summary, mitochondrial dysfunction can cause oxidative stress through the over production of ROS, which causes dopaminergic neuron death in PD.[10]

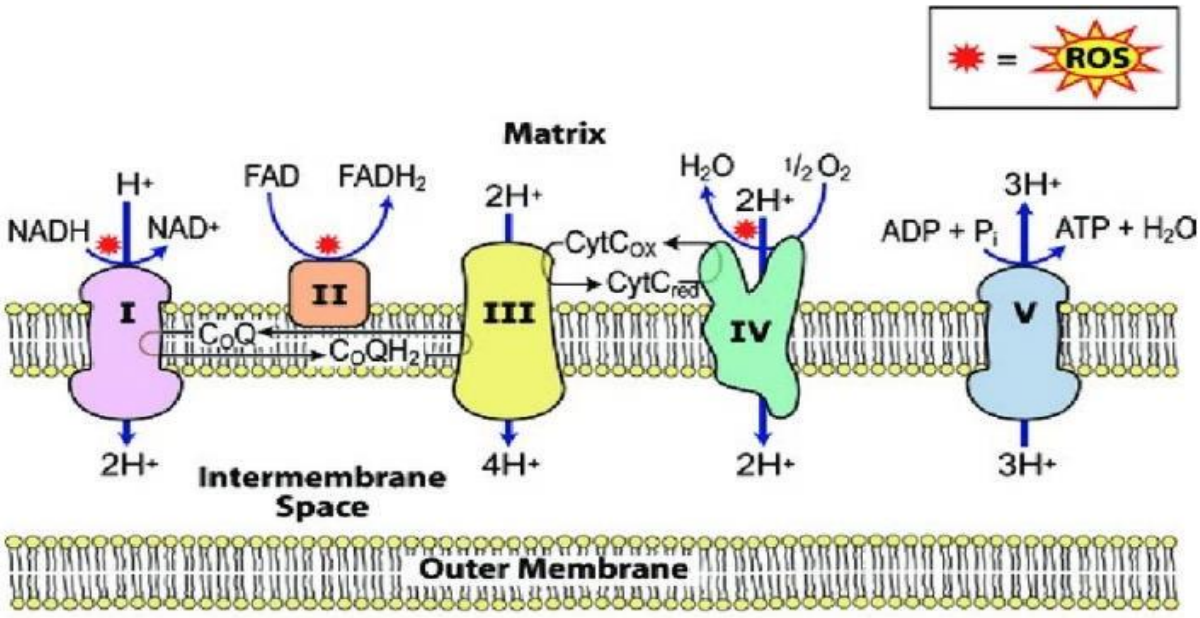

Figure no 6: Generation of ROS via ETC[22]

Neuroinflammation

Neuroinflammation is the cellular and biochemical responses of the nervous system to infection and injury. It induces the release of trophic factors and ROS to protect against stimulus to facilitate regeneration and repair. Once inflammation is overwhelmed, it would cause accumulation of ROS and eventually cell death. Chronic inflammation is involving in neurodegenerative diseases, particularly the pathogenesis of PD. Microglial cells are main participants of the inflammatory response. Activated microglia cells release various cytokines and chemokines to begin corresponding processes to augment additional microglia and leukocytes to the site of injury. Cytokines such as IL-1β, TNF-α, and IFN-γ, are pro-inflammatory, which will activate NADPH oxidases (Nox). Nox2 is an isoform of Nox, which is present in the nervous system and involved in the generation of ROS as a result of catalyzing the electron transfer from NADPH to oxygen. TNF-α could cause the depletion of endogenous antioxidants such as GSH, which will cause neurons more susceptible to ROS.IL-1β causes aberrant mitochondrial membrane potential and the depletion of ATP by the formation of peroxynitrite, ultimately leading to mitochondria dysfunction and ultimately increased ROS formation. Beside chemokines and cytokines, microgliac anal so activated by endogenous proteins such as α-synuclein. α-Synuclein directly promotes

activation of Nox2 in microglia leading to a generation of ROS. Cytokines and chemokines released by microglia can activate NADPH oxidase activity, which further enhances the level of ROS ultimately leading to PD. [10]

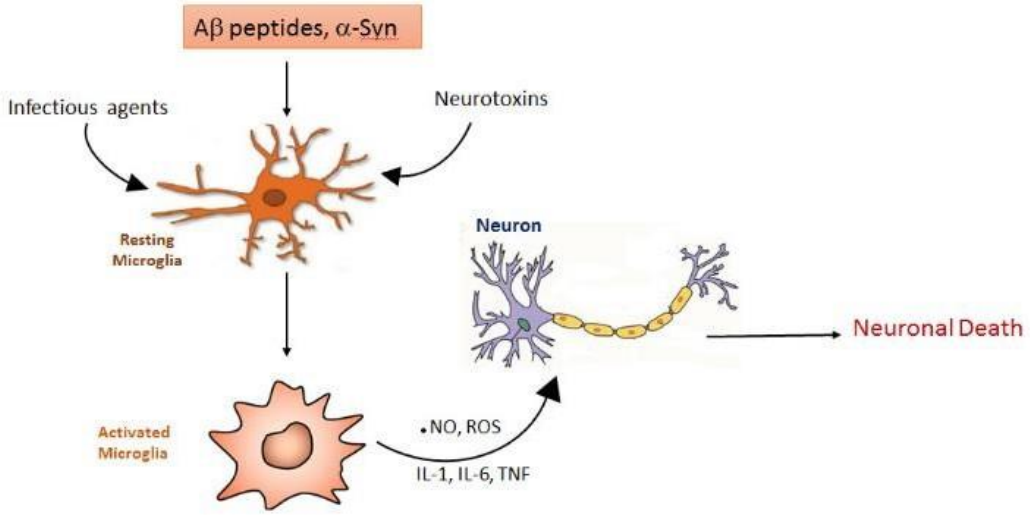

Figure no 7: Microglia-mediated neuron inflammation[13]

Neuroprotection

Neuroprotection is the capability for therapy to prevent neuronal cell death by intervening in and inhibiting the pathogenetic cascade that results in cell dysfunction and eventual death.[21] Neuroprotection aims to prevent or slow disease progression and injuries by stopping or at least slowing the loss of neurons. Common mechanisms include increased levels of oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregation. Out of these mechanisms, neuroprotective therapies often target oxidative stress and neuroinflammation—both of which are highly related to CNS disorders. Common neuroprotective therapies are antioxidants, nutraceuticals, anti-inflammatory agents which intend to decrease oxidative stress and neuroinflammation individually.

Neuroprotective approaches against oxidative stress

Antioxidants and mitochondrial targeting

Antioxidants such as vitamin E, vitamin C, and glutathione (GSH) have been tested in several clinical trials for neuroprotection. Recently, it has been focused on novel ways to target antioxidants to particular organelles (e.g., mitochondria) that are known to generate

high levels of ROS. For instance, mitochondrial-targeted antioxidant peptides, vitamin E, and ubiquinone (MitoQ) are all being actively studied for their neuroprotective properties.[11]

Catalytic antioxidants

Chemical compounds that mimic the catalytic activities of either superoxide dismutase or catalase is currently being evaluated in vitro and in vivo animal models of neurodegeneration. These compounds act catalytically to detoxify free radicals. Several chemical classes of catalytic antioxidants are under development, and their promising effects in animal models suggest that they may produce tangible benefits to patients in clinical trials ofneurodegeneration.[11]

Natural products ("nutraceuticals")

Natural products in the diet recently gained significant attention as possible therapeutic candidates for neurodegeneration. These nutraceuticals are found in a variety of spices and foods and are chemically known as flavonoids, polyphenols, catechins, curcuminoids, etc. Some of these compounds provide neuroprotection directly by free radical scavenging, whereas others, such as the polyphenols, resveratrol, and the organosulfur compound sulforaphane, activate Nrf2-dependent transcription of endogenous antioxidant genes. In addition, some natural polyphenols, such as the green tea catechin, epigallocatechin 3-gallate (EGCG), show an innate capacity to accumulate in mitochondria and protect neurons from mitochondrial oxidative stress. Also, polyphenols like curcumin have been chemically modified to produce derivatives that display enhanced antioxidant, anti-inflammatory, and neuroprotective properties. These observations of nutraceuticals provide an abundant source of potential therapeutic agents that could be used to mitigate oxidative stress and inflammation in neurodegenerative diseases.[11]

Inhibitors of NO pathway–

Selective inhibition of nNOS inhibiting the specific production of toxic NO can lead to protection to neuronal tissues. The NO produced from nNOS plays an important role in the production of free radicals and its selective inhibition can lead to neuroprotection. 7-nitroimidazole is under clinical studies; it inhibits then NOS. Lubeluzole inhibits the production of the NO pathways.[9]

Free radical scavengers–

Free radical scavengers like, selenium, tocopherol, b-carotene, have little action on neuronal tissue. Tirilazad is a new free radicalscavengerunderclinicalstudy.[9]

Glutathione promoters:

Glutathione (GSH) protects from oxidative stress-induced damage by the reduction of reactive oxygen species (ROS). The reduction of GSH activity has been shown to increase cell sensitivity to free radicals. So promoters of glutathione such as selenium combined with other antioxidant can be used to reduce ROS.

SUMMARY

Parkinson's disease pathogenesis seems to be closely related to oxidative stress due to ROS generation. The mechanisms that potentially cause oxidative stress in PD are still unknown. Dopamine metabolism, mitochondrial dysfunction, and neuroinflammation all play crucial roles in the generation of ROS. Once ROS overcome antioxidant defense systems, excessive ROS can induce protein oxidation, lipid peroxidation, and DNA oxidation to initiate PD-related cell loss in the SN. Protective role of antioxidant therapies on inhibition of the ROS generation and correcting the antioxidant imbalance in patients with neurodegenerative diseases are an important area of further research.

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