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Glutamate, Calcium, NMDA Receptor: Their Contribution to Parkinson's disease

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder of the extrapyramidal motor system characterized by loss of dopaminergic neurons in substantia nigra pars compacta of basal ganglia. Enhanced level of glutamate levels causes excessive stimulation of NMDA receptor which initiates various pathways that leads to neuronal death. NMDA hyperactivation leads to a pathological process called excitotoxicity and protein aggregation and misfolding. Excitotoxicity is due to an increase in Ca2+levels. When levels of Ca2+are beyond control it results in loss of ATP production, finally emerging in cell death in different pathological conditions. NMDA overstimulation further causes the generation of NO, ultimately disrupting functions of parkin and PDI and producing protein aggregates, and stimulation of the UPR pathway. Prolonged UPR pathway activation and ER stress further lead to cell death. Both the mechanism contributes to the progression of Parkinson's disease. We summarize this review by considering various approaches for neuroprotection and different targets like glutamate, calcium, parkin.

INTRODUCTION:

Parkinson's disease is a neurodegenerative disorder characterized by loss of dopaminergic neurons in the substantia nigra pars compacta.[1]It is a multifactorial disorder dependent on several factors such as aging, genetics, and environmental factors.[2]Various mechanisms such as excitotoxicity, mitochondrial dysfunction oxidative stress, protein aggregation, and inflammation contribute to the pathogenesis of Parkinson's disease. It is characterized by motor symptoms like resting tremor, bradykinesia, hypokinesia, and rigidity along with nonmotor symptoms like mood, cognitive, sleep, sensation, autonomic disturbances.

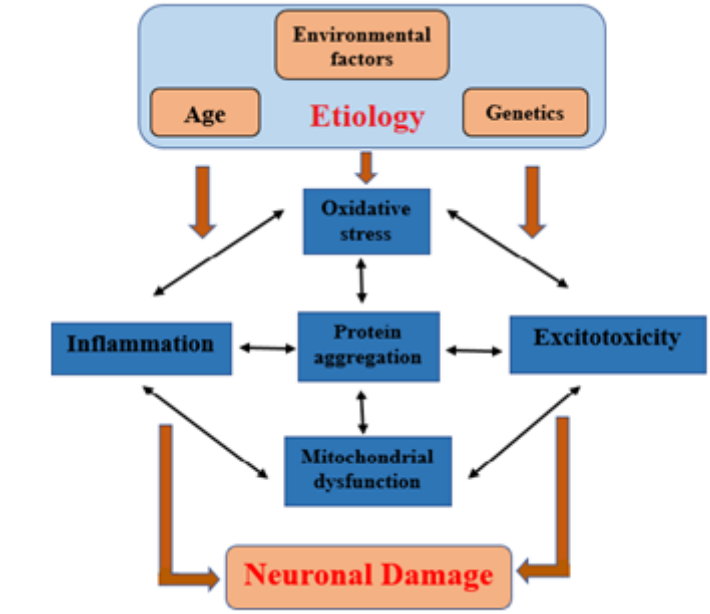

Figure No. 1: Etiology and pathogenesis of Parkinson's disease

Pathophysiology

Parkinson's disease is caused due to changes in the nigrostriatal system which is one of the four major dopamine pathways in the brain. The nigrostriatal pathway regulates two other pathways, the direct and the indirect pathways. The direct pathway operates directly from the putamen to Globus Pallidus internus (GPi) and Substantia Nigra reticulate (SNr) whereas the indirect pathway connects the putamen with the GPi/SNr via synaptic projections in the globus pallidus pars externa (GPe) and subthalamic nucleus (STN). Signals from putamen to GPe and from GPe to STN are GABAergic and inhibitory, leading to inhibition of the GPe,

disinhibition of the STN, and excitation of the GPi/SNr. Neurons in the STN activate neurons in the GPi/SNr by glutamate.[3]

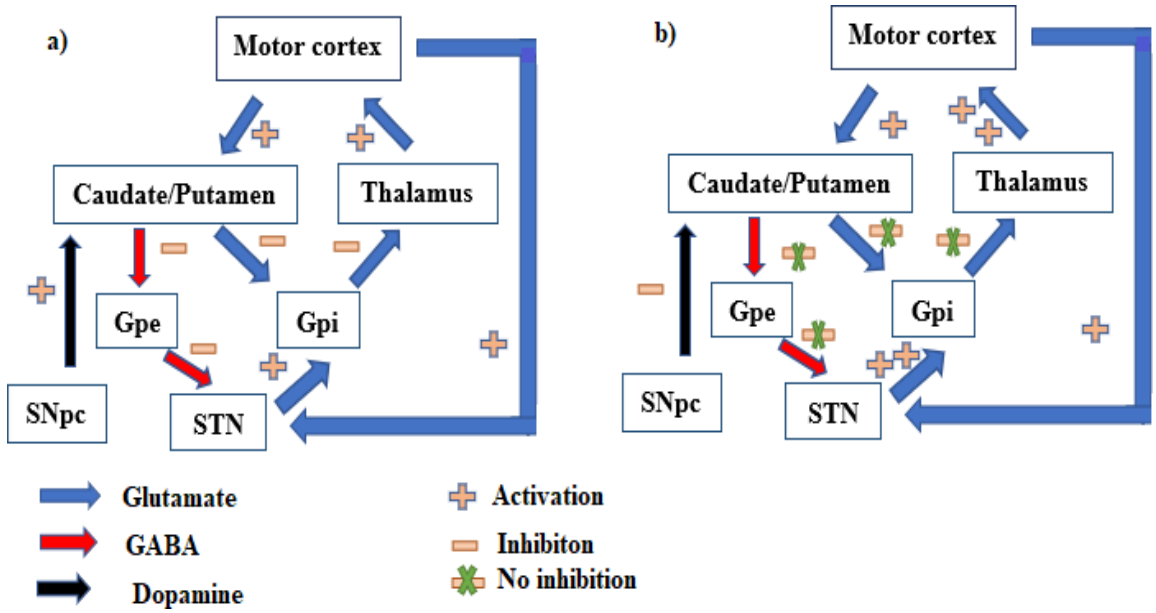

Figure No. 2: Pathophysiology

a) Basal ganglia circuit in normal brain. b) Basal ganglia circuit in PD brain.

Excitotoxicity Glutamate

Glutamate is one of the important excitatory neurotransmitters in the central nervous system. It plays an important role in synaptic plasticity (important for learning and memory), the formation of neural networks during the development and repair of the CNS.[5,6,7]Under certain conditions, however, glutamate can damage nerve tissue and is implicated in several brain disorders, including PD.[7] At excitatory synapses, glutamate is stored in vesicles and can be found in pre-and post-synaptic neurons, as well as in glial cells, and astrocytes. Astrocytes contribute to buffer most of the extracellular glutamate by stimulating its uptake through high-affinity protein carriers named Excitatory Amino Acid Transporters (EAATs). Astrocytes also take part in the conversion of glutamate into the inactive metabolite glutamine. Glutamate per se is not toxic but can exert toxic effects by persistently and excessively stimulating glutamatergic receptors.[8]

Glutamate receptors

They are of two types:

1. Ligand-gated ion channels (Ionotropic receptors). Three groups (AMPA, NMDA & Kinate receptors).

2. G-protein coupled (Metabotropic receptors).

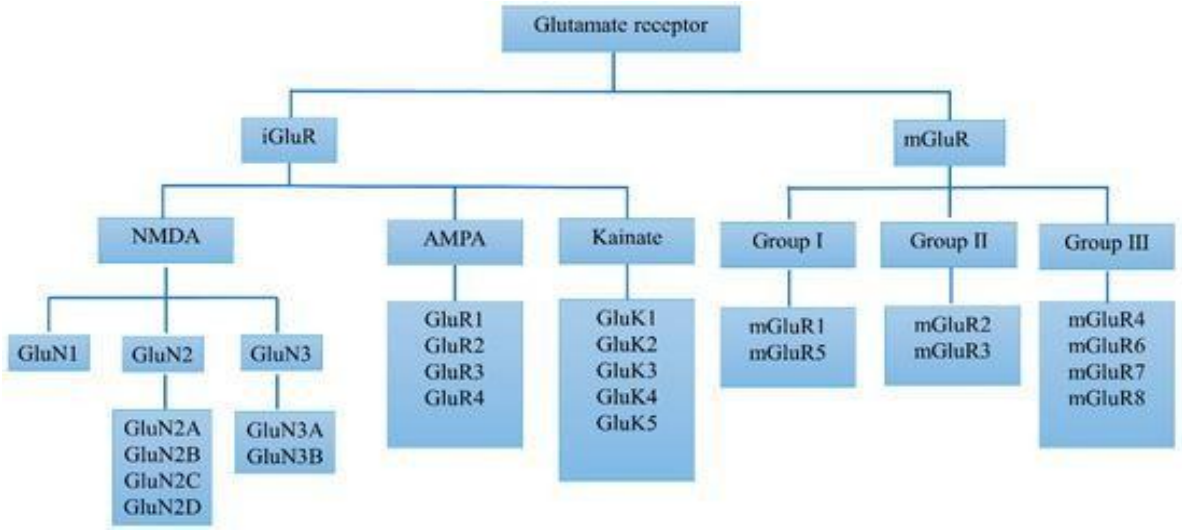

Figure No. 3 Classification of glutamate receptors[9]

Calcium

Calcium is a universal second messenger that plays a vital role in the functioning of the nervous system.[10,11]Calcium homeostasis is crucial for the survival and functioning of neurons. Neurons use both extracellular and intracellular sources of Calcium.[1]Intracellular $Ca^{2+}$is a key for neurotransmitter release and contributes to the electrical activity of neurons by controlling the membrane permeability to K ions.[11]Extracellular Ca^{2+} is also responsible for the release of the nervous transmitter.

Neuronal Voltage-Gated Calcium Channels and their Types

Voltage-Gated Calcium Channels play a role in the generation and propagation of the nerve impulse and cell homeostasis.[10]Opening of Voltage-Gated Calcium Channels results in Cain flux which triggers the release of neurotransmitter and other calcium-dependent processes.

Voltage-gated calcium channels that activate in response to large membrane depolarizations are grouped as high voltage-activated (HVA) and those that are activated by smaller voltage changes are called low voltage-activated (LVA).[12,13]Calcium channels are defined by 5 distinguished subunits (α1, α2, β, γ, δ) which are encoded by different genes. Depending on the type of α1 pore-forming subunit, they are divided into three subfamilies, namely, Cav1,Cav2, and Cav3, and into six further classes, termed L, N, P, Q, R,(high voltage-activated) and T (low voltage-activated), based on the physiological and pharmacological properties of the type of current they carry. The Cav1 subfamily mediates the L-type currents and encodes three different neuronal channels termed Cav1.2, Cav1.3, and Cav1.4 plus a skeletal muscle-specific isoform, Cav1.1. Cav2 channels generate P/Q- type (CaV2.1), N-type (CaV2.2), and R-type (CaV2.3), the Cav3 subfamily is responsible for the T-type current and is molecularly classified into three types; CaV3.1, CaV3.2, and CaV3.3.[10,12,14]

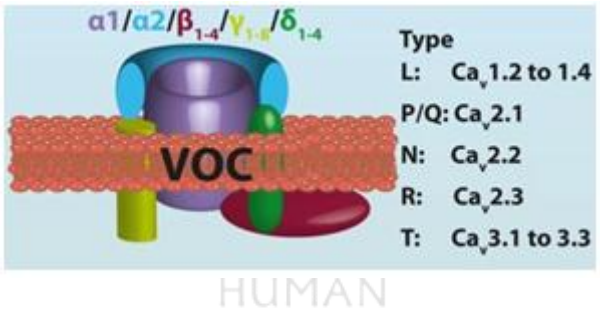

Figure No. 4: Voltage-Gated Calcium Channels and their Types[10]

Glutamate excitotoxicity and disturbance in Ca^{2+} homeostasis

Excitotoxicity is due to glutamatergic receptor overstimulation which is triggered by the excitatory neurotransmitter glutamate.[8] N-Methyl-D-aspartate (NMDA) receptors are a major subtype of ionotropic excitatory glutamate receptors that mediate synaptic transmission in the central nervous system. Persistent and excessive glutamate causes overstimulation of NMDA receptors, due to high calcium permeability of NMDA receptors, their over-activation is also accompanied by an accumulation of excessive amounts of intracellular calcium. Glutamate also activates AMPAR leading to the opening of voltage-activated calcium channels, releasing more glutamate. An increase in intracellular calcium further initiates other intracellular cascades, leading to slow (delayed) apoptotic neuronal loss.[15]

Mitochondria and endoplasmic reticulum (ER) have an enormous capacity to accumulate and store calcium but when calcium levels increase to a certain limit, $Ca^{2+}$is released from ER and mitochondria. This phenomenon is modulated also by mGluRs and is responsible for activating secondary cascades involving calpains and activation of pathways leading to either necrotic or apoptotic cell death. Furthermore, Ca^{2+}overload induces the activity of nitric oxide synthases (NOS) and affecting mitochondrial integrity and functions. Ca^{2+}enhances reactive oxygen and nitrogen species (ROS and RNS) production. Increased levels of ROS inhibit mitochondrial complex I activity, pyruvate dehydrogenase, and critical enzymes involved in the tricarboxylic acid cycle, thereby leading to impaired ATP production and energy failure. Ca^{2+}overload also triggers the opening of the mitochondrial permeability transition (MPT) pore and cytochrome c release, caspase 3 further causing damage of cellular macromolecules and the activation of apoptogenic pathways (Fig. 5).

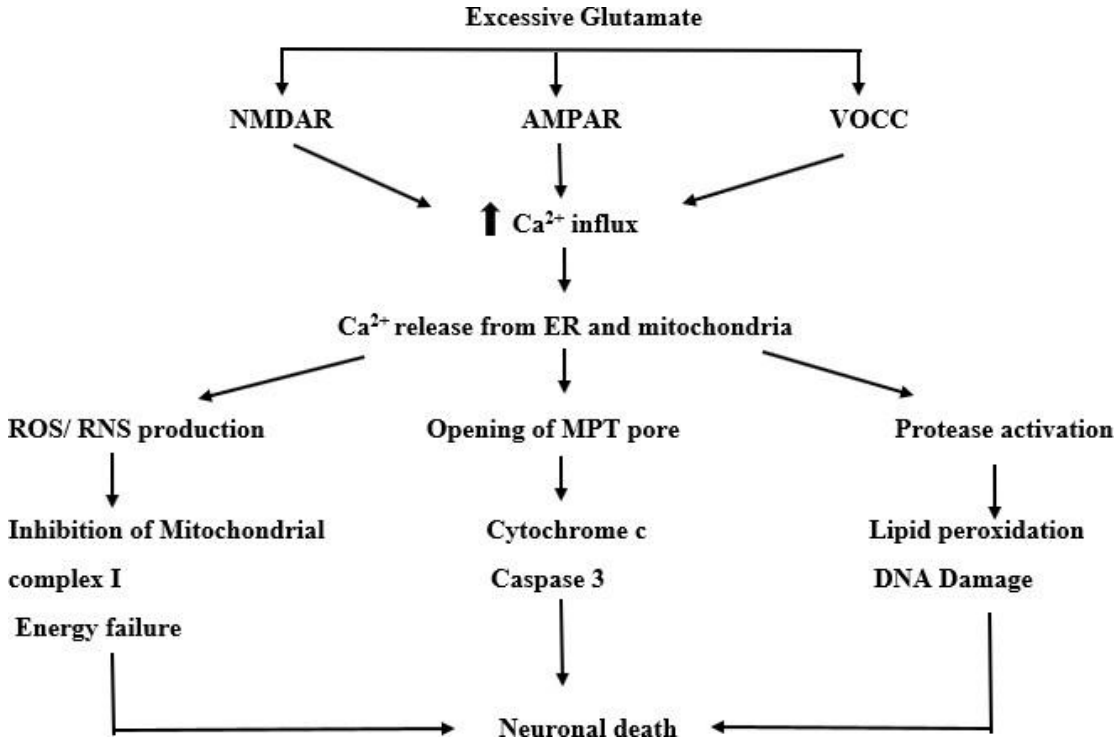

Figure No. 5: Molecular mechanisms of glutamate-mediated excitotoxicity

Glutamate mediated NMDAR hyperactivation and protein aggregation and misfolding

NMDAR hyperactivation generates NO/ROS and cytochrome C release fro**m** mitochondria leading to activation of caspases, and other apoptotic pathways, causing neuronal death. NO produced by hyperactivation of NMDAR participates in cellular signaling pathways, which

controls brain function, like synaptic plasticity, normal development, and neuronal cell death.[16]In general, NO exerts physiological and pathophysiological action via stimulation of guanylate cyclase to form cyclic guanosine-30,50-monophosphate (cGMP) or through S-nitros(yl)ation of regulatory protein thiol groups,[16,17]S-Nitrosylation is a process of addition of an NO group covalently to acystein ethiol/sulfhydryl (RSH or, more properly, thiolate anion, RS-) to produce an S-nitrosothiol derivative (R-SNO). Whereas, denitrosylating enzymes and pathways mediated by thioredoxin/thioredoxin reductase, PDI, and intracellular glutathione, can restrict the lifespan of protein SNOs.[16,18,19,20] NO is neuroprotective via-nitrosylation of NMDA receptors but can also be neurodestructive by the formation of peroxynitrite. NO produced causes S-nitrosylation of various neuronal proteins such as parkin (forming SNO-PARK) and PDI (forming SNO-PDI) and causes neuronal cell injury by triggering the accumulation of misfolded proteins.[16]Increased nitrosative/oxidative stress have been linked to chaperone and UPS dysfunction, facilitating protein misfolding and triggering neurodegenerative disease such as Parkinson's disease.[16,21]

S-Nitrosylation of Parkin

Parkin is an E3 ubiquitin ligase that takes part in the ubiquitin-proteasome system (UPS). The ubiquitin-proteasome system (UPS) is known to participate in the clearance of abnormal or aberrant proteins. Parkin also has a role in protein degradation during ER stress. Disruption of parkin activity causes dysfunction in protein degradation, leading to accumulation/aggregation of proteins and resulting ER. S-nitrosylation, parkin's E3 ligase activity initially increases followed by a decrease in activity may be because of autoubiquitination. Degradation of substrate proteins, potentially contributing to Lewy body and dysfunction of UPS formation resulting in neuronal cell injury or death.[21,22]In Parkinson, intracellular or extracellular protein aggregates are known to accumulate in the brain as a result of a decrease in molecular chaperone activities or dysfunction in UPS. [21]

S-Nitrosylation of PDI

PDI is a cellular defense protein that works when there is the accumulation of unfolded or misfolded proteins.

It is known to increase the activity of chaperones and isomerases. S-nitrosylation of PDI may hamper its capacity to act as a defense protein. It may, therefore, contribute to the progression of Parkinson's disease and cause ER stress.[22] SNO-PDI may transport NO to the extracellular space, where it could exert additional adverse effects.[21]

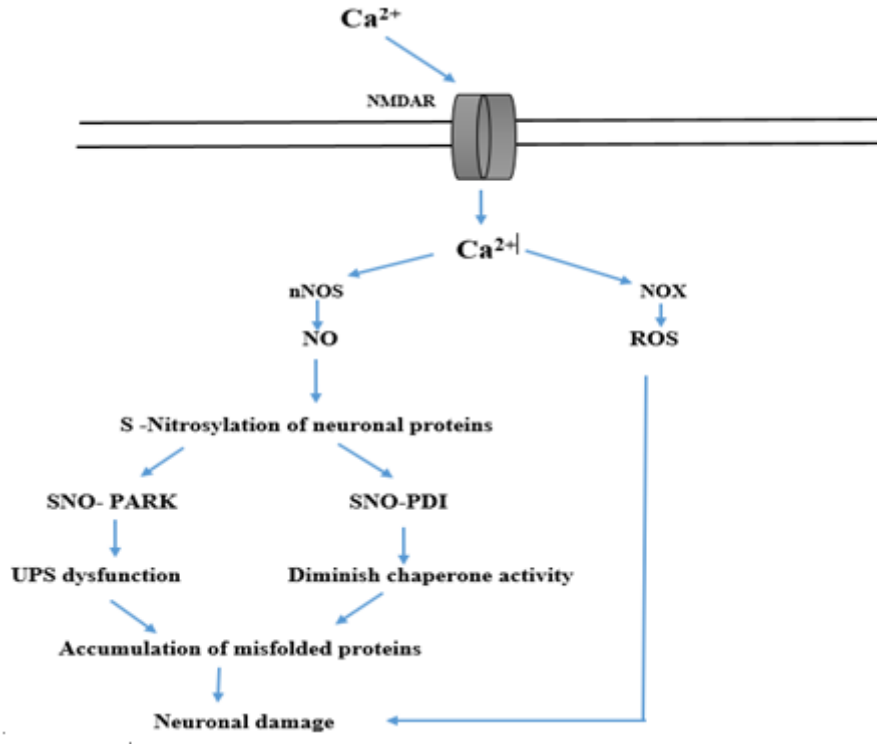

Figure No. 6: S-nitrosylation leading to accumulation of aberrant proteins and neuronal damage.

UPR pathways in ER stress

Disturbance of $Ca2^{+}$ homeostasis within the ER plays a pivotal role in ER stress and accumulation of misfolded proteins and aggregates. Excessive generation of NO can contribute to activation of the ER stress pathway, due to diminished chaperone activity[26] Firstly the activation of the UPR in PD pathogenesis might have a neuroprotective effect, to remove the neurotoxic unfolded proteins. However, prolonged ER stress and UPR activation can trigger cell death[24]. The UPR is a network mediated by the activation of three main stress sensors located at the ER membrane, including inositol requiring kinase 1α (IRE1α), activating transcription factor 6 (ATF6), and protein kinase RNA-like ER kinase (PERK) (Figure7).

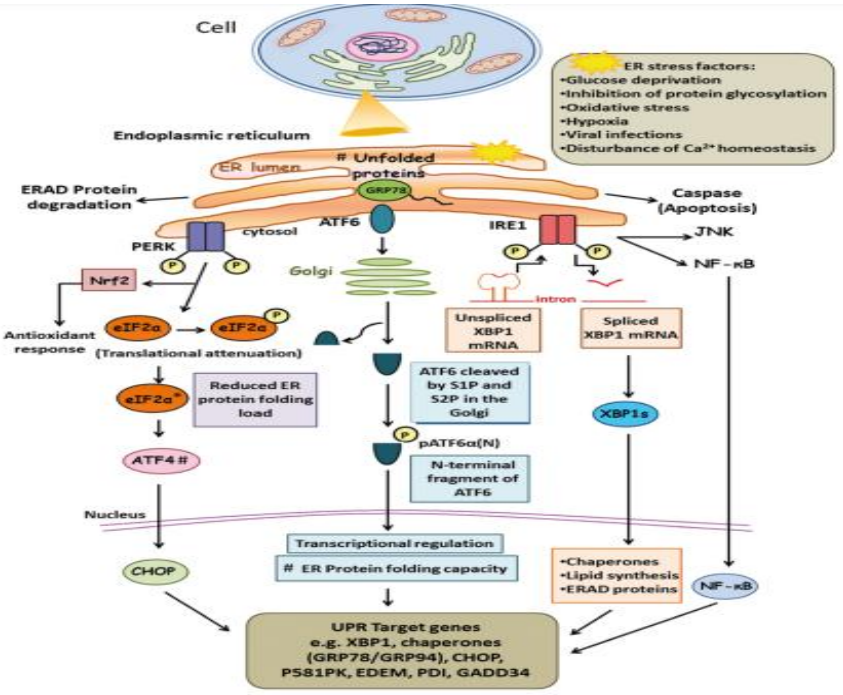

Figure No. 7: UPR PATHWAYS IN ER STRESS[23]

Activation of the UPR enhances the efficiency of protein folding and quality control mechanisms, besides; to amplify ER and Golgi biogenesis, protein secretion, and the clearance of abnormally folded proteins through the autophagy and ERAD pathways. In conditions like prolonged ER stress, UPR sensors shift their signaling towards cell death by apoptosis through distinct complementary mechanisms, demolishing damaged cells. The ER chaperone Glucose regulated protein 78 (Grp78/BiP) is a key adjustor of the UPR since its association to the three stress sensors maintains the UPR on an inactive state which upon the accumulation of misfolded proteins within the ER, it dissociates from UPR sensors leading to their activation. IRE1α is a serine-threonine kinase and endoribonuclease which when activated commences the processing of the mRNA encoding the transcription factor Xbox binding protein-1 (XBP1) which regulates the expression of UPR-target genes related to folding, ER/Golgi biogenesis, and ERAD.[25]IRE1 signaling also involves JNK signaling (Jun-N-terminal kinase) linking and NF-κB signaling pathways.[23] In the Golgi, ATF6 undergoes regulated intramembrane proteolysis (RIP) and is cleaved by the Golgi-resident serine proteases site 1 proteases (S1P) and site 2 proteases (S2P). The Cleaved ATF6 (N-terminal fragment of ATF6) acts as a transcription factor, which travels to the nucleus and induces transcription of UPR target genes including X-box binding protein 1 (XBP1), CHOP

(enhancer-binding protein homologous protein) along with molecular chaperones GRP78 and GRP94. [23]PERK is an ER-located kinase when activated phosphorylates the eukaryotic initiation factor 2α (eIF2α) and regulates transcription factors like Nrf2 for the antioxidant response. eIF2α phosphorylated further cause translation of activating transcription factor 4 (ATF4), which upregulates many important genes functioning in redox control, amino acid metabolism, and protein folding. Under chronic stress, ATF4 regulates the expression of pro-apoptotic transcription factor CHOP (CEBP homologous protein).[25] Expression of CHOP, affects the expression of genes favoring apoptosis in response to ER stress. That ER stress and UPR activation play a critical role in neuronal cell death in PD pathogenesis.[24]

Neuroprotection

The main aim of neuroprotection is to hamper or decrease the progression of disease ultimately aiming protection of neurons. Neuroprotection means safeguarding neuronal structure and function.[27]Most patients develop motor complications that are difficult to control with currently available treatments along with non-motor symptoms, including anosmia, sleep disorders, autonomic impairment, and cognitive impairment. The complexity of these symptoms urges to development of new strategies that could be able to showcase neuroprotective action and may be used in the earlier stage of the disease to halt or delay the later complications of the disorder. Common mechanisms include increased levels in oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammatory changes, iron accumulation, and protein aggregation.[27,28,29] Of these mechanisms, neuroprotective treatments often target protein aggregation and excitotoxicity—both of which are highly associated with CNS disorders.

Neuroprotective approaches

A) Drugs acting against Excitotoxicity

Glutamate antagonist

Glutamate antagonists obstruct glutamate from binding to glutamate receptors. Glutamate antagonists, therefore, work by hindering the activity of glutamate receptors in the brain. Glutamate antagonists are known to lessen the progression of Parkinson's disease by restricting glutamate release preventing loss of dopaminergic neurons. Riluzole-

neuroprotective effects are generally regarded to be caused by its effects on reducing glutamate release in neurons.[30]

NMDA receptor antagonist

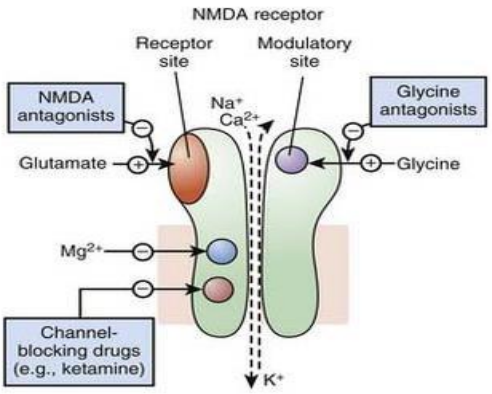

Figure No. 8: NMDA receptor and drugs acting on it[33]

NMDA receptor antagonists inhibit NMDA receptor activity, thereby decreasing NMDA receptor overstimulation by glutamate, and preventing excitotoxicity. Amantadine-is an selective NMDA antagonist currently in clinical use to treat LID.[31] Competitive and non-competitive are the two kinds of NMDA antagonists. The competitive antagonist acts directly against the glutamate; may not easily cross the hemato-encephalic barrier, but have high specificity and potency. The non-competitive ones act in the membrane of specific NMDA places and prevent the Ca^{2+} influx. They easily cross the blood-brain barrier. The main examples of these drugs are dizocilpine (MK 801), selfotel, celestas, dextromethorphan. Low doses are associated with altered sensory perception, dysphoria, and hypotension, while higher doses may cause psychological adverse events such as excitement, paranoia, and hallucinations. [32]

Calcium channel antagonist

By blocking the influx of calcium, a calcium channel antagonist can help in halting the progression of PD. L- type voltage-gated calcium channels 1.3 are present in neurons which

can be targeted in PD. Dihydropyridine calcium channel blockers (DiCCB) and non-DiCCB can be used in PD.[34]

Polyphenols

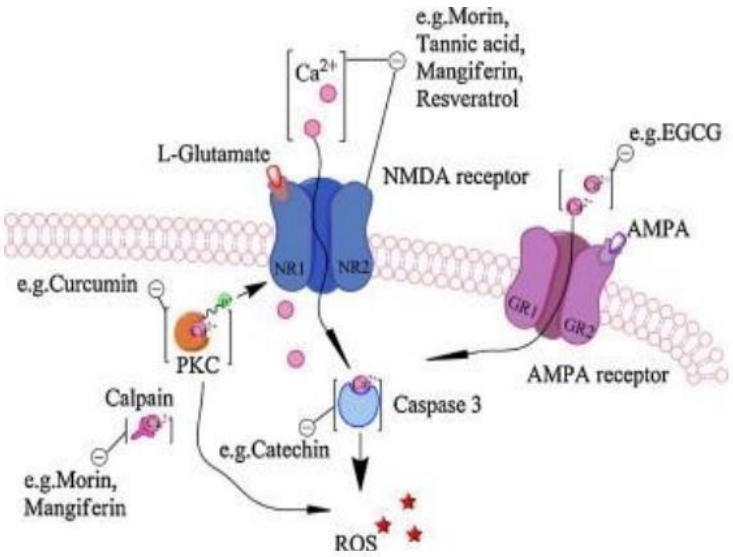

Figure No. 9: A schematic illustration of NMDA pathway and polyphenol targets within pathway[35.36]

Polyphenols have been known to have a neuroprotective effect against NMDA excitotoxicity. Polyphenols interact with the NMDA pathway through inhibitory activity on various steps. Catechin act as an inhibitor of caspase 3. Polyphenols, such as morin, tannic acid, mangiferin, and resveratrol inhibit glutamate-mediated Ca2+ influx. Catechin can inhibit PKC activity and reduce ROS generation and further neural degeneration. Curcumin and tannic acid inhibit PKC activity and phosphorylation of NR1 of the NMDA receptor, reducing glutamate-induced excitotoxicity. EGCG interacts with the NMDA pathway by antagonizing the AMPA receptor. Morin and mangiferin are able to inhibit calpain activity and further celldegeneration.[36,37]

GABA agonists

GABA is the most important inhibitory amino-acid and has an opposite action to that of glutamate, hence may reverse the toxic effects of glutamate through hyper-polarization of the neuronal membrane. A GABA agonist clomethiazole can beuseful.[32]

B) Drugs acting against Protein aggregation and misfolding

Drugs that can target impaired UPS

Pramipexole, a dopamine receptor D3 preferring agonist, has been used to treat Parkinson's disease (PD) for many years. It has shown to have neuroprotection activity in a model of PD induced by the ubiquitin-proteasome system (UPS) impairment.[38]

Parkin Activators

Parkin is involved in the ubiquitin-proteasome system (UPS) for the clearance of abnormal or aberrant proteins. Interference in parkin activity disrupts protein degradation. Hence activators of Parkin can help to treat PD. Studies are being done on developing small molecule activators, such as an UbFluor probe has been developed to precisely compute variations in the activity of Parkin due to phosphorylation, protein substrates, and activating structural mutations.[39]

CONCLUSION:

Excessive glutamate results in NMDA hyperactivation causing accumulation of calcium leading to excitotoxicity and protein aggregation and misfolding further resulting in the progression of death of the dopaminergic neuron. Depletion in dopaminergic neurons results in Parkinson's disease. Though this disease is incurably targeting glutamate receptors, NMDA receptors, calcium channel, parkin can help in preventing further progression of the disease. With this review we can conclude increased glutamate levels is one of the main reasons behind the pathogenesis of Parkinson's disease, hence a neuroprotection strategy should be implemented that could help in halting the progression of Parkinson's disease.

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