

Dopamine Toxicity in Parkinson's Disease: Impact of Altered Protein-Protein Interactions

Tapasi Roy^{1*}, Snehasikta Swarnakar²

¹Acharya Jagadish Chandra Bose College, Kolkata, West Bengal, India

²CSIR-Indian Institute of Chemical Biology, Infectious Diseases and Immunology Division, Kolkata, West Bengal, India

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*Correspondence:

*Dr. Tapasi Roy, Acharya Jagadish Chandra Bose College, Kolkata, West Bengal, India; Email: dr.tapasi.roy@gmail.com

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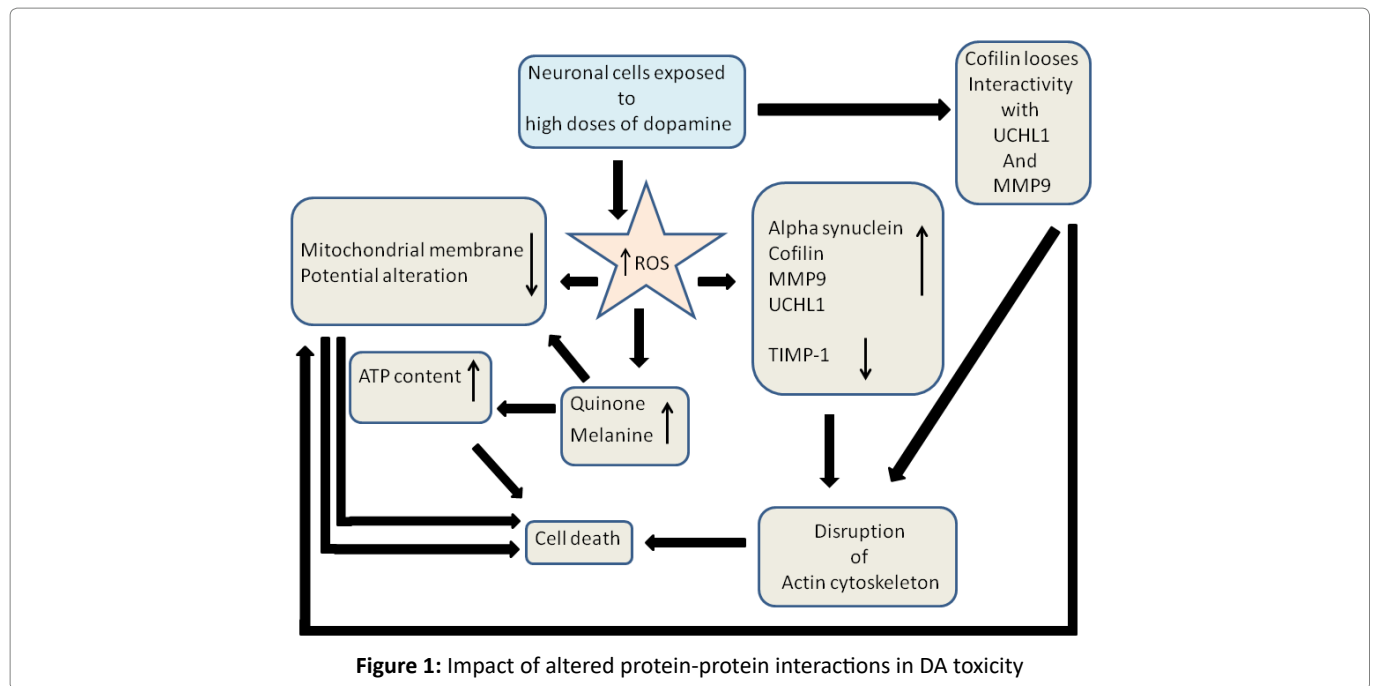
ABSTRACT

Parkinson's disease (PD) is a frequently occurring neurodegenerative condition. The onset of the disease is due to selective loss of dopaminergic neurons, causing increased dopamine (DA) in the neuronal microenvironment. Neurotoxicity due to such increased DA is the outcome of reactive oxygen species (ROS) and oxidative products of DA. Proteins like alpha-synuclein, ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), Cofilin and matrix metalloproteinases 9 (MMP9) are few known key regulators in PD. The impact of elevated DA on these protein-protein interactions plays a crucial role in disease progression. Further, DA toxicity leads to alteration of protein-protein interactions and degrades neuronal cytoskeleton, leading to cell death. This review suggests a novel arena in PD treatment by targeting DA altered protein-protein interactions.

Introduction

Dopamine (DA), a precursor of norepinephrine and epinephrine and belongs to the catecholamine family. This neurotransmitter is endogenous to substantia nigra¹. At physiological concentrations, DA activates the gene expressions related to cell survival. Higher DA concentrations lead to neurotoxicity via the generation of reactive oxygen species (ROS), toxic quinones and semiquinones which are the oxidative products of DA². DA toxicity also leads to proteasomal inactivity, nuclear factor κ B (NF κ B) activation, or activation of mitogen-activated protein kinase (MAPK) pathways and finally cell death³. Such dysregulation of DA is responsible for the pathophysiology of Parkinson's disease (PD)⁴. In PD, dysregulation of the dopaminergic system is a multifaceted interaction⁵. Genes such as alpha-synuclein and ubiquitin carboxyl-terminal hydrolase L1 (UCHL1) are among the key regulators in PD. Current reports have shown that UCHL1 is responsible for membrane-proximal events⁶. It was also reported to control the reorganization of the actin cytoskeleton⁷. On the other hand, alpha-synuclein is shown to activate cofilin-1 by phosphorylation. Phosphorylated cofilin-1 impairs actin dynamics upon binding with F-actin⁸. Another protein, matrix metalloproteinases (MMPs) are Zn⁺²-containing Ca⁺²-dependent endopeptidases, which are activated upon excess ROS production due to DA dysregulation. Reports suggested that, proteolytic cleavage of MMPs gives rise to the catalytically active proteases which leads to extracellular matrix (ECM) remodeling⁹. Specific MMPs are known to be involved in the PD pathogenesis¹⁰. MPTP treatment may enhance MMP9 in the substantia nigra and striatum of mice¹⁰. A recent report has shown that DA alters the interaction patterns among the above mentioned proteins.

In this mini review, we precisely discuss the effects of higher DA



concentrations on protein – protein interactions in the context of PD. (Figure 1)

PD: The Second Most Frequently Occurring Neurodegenerative Disorder

PD affects 1 in every 100 individual above the age of 60 years and accounts for about 15% of all dementia cases¹¹. It is the second most common neurodegenerative disorder¹². Although the reason behind PD pathogenesis remains unclear, a wide range of environmental¹³ and genetic risk factors¹⁴ are involved in the PD pathogenesis. Death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and Lewy body formation in the affected regions of the brain¹⁵ are the hallmarks of PD. This part of the human brain is engaged in movement coordination and muscle contraction through signals transmitted to the spinal cord. Damage to this region may cause bradykinesia, difficulty in walking, postural instability, tremors at rest, freezing, shuffling gait and hypomimia¹². At the later stages of the disease, slowness, disrupted sleep, and sensory disturbances will occur¹².

Current therapeutic approaches for PD treatment aim to compensate for dopamine deficiency by boosting the concentration of intracellular DA within dopaminergic neurons by using L-DOPA, dopamine antagonists, and agents that inhibit dopamine breakdown. These treatments are mostly symptomatic and do not inhibit the progression of neurodegeneration¹⁶. Following an initial phase of apparent benefit; extended use of these drugs lead to the development of dystonia and dyskinesia, which in turn exacerbates disease progression¹⁷. This has given rise to the general hypothesis that elevated

dopamine levels could potentially be detrimental to brain function. Indeed, previous studies have established the fact that high localized DA concentration in dopaminergic neurons induces high oxidative burden triggering multiple signaling pathways and thus causes gradual loss of those dopaminergic neurons¹⁸.

DA: The Inducer of PD Pathology

DA is synthesized by substantia nigra (SN)¹⁹ and is secreted by the presynaptic neuron to the synaptic cleft. It then binds to the DA receptors located on the postsynaptic neuron¹⁹. Dopaminergic neurodegeneration lowers DA content in the SN and striatum and initiates the onset of PD clinical symptoms²⁰. However, evidence shows that spontaneous or enzyme mediated DA oxidation can trigger specific oxidative stress in dopaminergic neurons²¹ producing ROS, DA quinones (DAQs) and 3,4-dihydroxyphenylacetaldehyde (DOPAL)¹⁶. ROS mediated oxidative stress leads to the formation of covalent conjugate between DOPAL and DAQs with lysine, cysteine, and tyrosine residues of proteins, causing cross-linking, misfolding, aggregation and functional inactivation^{21,22}. DA affects mitochondrial functions, ubiquitin–proteasome system (UPS), lysosome and autophagy, leading to the vulnerability of dopaminergic neurons^{21,22}.

DA Mediated Neurodegeneration: Impact on Protein-Protein Interactions

Several proteins are associated with DA toxicity mediated neurodegeneration; some are discussed below.

Alpha-synuclein

Alpha-synuclein is a 14 kDa protein expressed in neurons

located within the central and peripheral nervous system along with blood cells and other tissues²³. Although alpha-synuclein is known for its 'natively unfolded' monomeric forms, endogenous alpha-synuclein naturally occurs in a folded tetrameric form of ~58 kDa²⁴. The intricate balance in the monomer-tetramer ratio, when disrupted may give rise to pro-aggregating forms. Alpha-synuclein in its native form is found in the nucleus, mitochondria, endoplasmic reticulum (ER), Golgi apparatus (GA) and endolysosomal system of neuronal cells as well as in the synaptic terminals^{25,26}. In physiological conditions, alpha-synuclein regulates DA storage in synaptic vesicles upon interaction with vesicular monoamine transporter 2 (VMAT2) in nigral neurons. In pathological conditions, alpha-synuclein mediates functional mitochondrial failure by disrupting mitochondrial morphology, impairing complex I function, and decreasing basal mitochondrial oxygen consumption rate²⁶. Missense mutations in alpha-synuclein gene (SNCA) lead to alpha-synuclein accumulation, microglia activation, neuroinflammation, and degeneration of the striatal neurons²⁷. Alpha-synuclein aggregates impair the molecular machinery related to DA secretion from the presynaptic neurons²⁸.

Cofilin

Cofilin, a member of eukaryotic actin-binding proteins, is crucial in the progression of disease pathogenesis²⁹. Cofilin 1 is a small conserved protein with 166 amino acids and plays a pivotal role in the progression of neurodegenerative diseases. It remodels actin and help prion-like aggregates to penetrate the cell membrane³⁰. Cofilin also binds alpha-synuclein, promotes the aggregation of the latter and generates neurotoxic fibres²⁹. Additionally, mitochondrial dysfunction in PD activates cofilin, as a result fragmentation of mitochondria and neuronal damage will occur. It also contributes to neuroinflammation, cytoskeletal disruption and apoptosis³¹. These suggest that cofilin is associated with the onset of PD. Cofilin therefore is a preferred therapeutic target for neurodegenerative diseases.

Ubiquitin carboxyl-terminal hydrolase L1 (UCHL-1)

UCHL1 is highly expressed in neurons, and constituting up to 2% of the total soluble proteins. It is important in normal synaptic functions. It regulates both glycolysis and energy-dependent mitophagy pathway³². Structurally UCHL-1 composed of a central β -sheet and two flanking α -helices. Crystal structure revealed that the protein is an asymmetric dimer; although equilibrium sedimentation analysis revealed that UCHL-1 in solution remains in a monomeric form³³. UCHL1 regulates the actin cytoskeleton in the Parkinsonian brain, primarily by influencing protein ubiquitination and degradation³².

Matrix metallo-proteinases (MMPs)

Matrix metallo-proteinases (MMPs) belonging to a superfamily of metzincin are calcium (Ca^{2+}) and zinc (Zn^{2+})-dependent endopeptidases. They are crucial for several physiological and pathological processes³⁴. MMPs are produced as pro-MMPs (zymogens) through a cysteine switch mechanism which in turn is activated by enzymes and free radicals¹⁰. MMP activity is regulated via proteolytic activation of pro-MMP and its natural inhibitor, TIMPs. TIMPs (tissue inhibitors of metalloproteinases) having 21–28 kDa molecular weight binds to the active site of MMPs' in 1:1 ratio³⁵. Tissue remodelling may be dysregulated due to insufficient TIMP control and metalloproteinase over-expression, resulting in various neurodegenerative diseases³⁶. Moreover, high ROS levels can also leads to the activation of MMPs¹⁰. Although the early endeavours of targeting matrix metalloproteinases were not successful in clinical trials, metalloproteinases are still preferred as one of a potential therapeutic target, considering their importance in disease progression³⁷.

Role of ROS in Altered Protein-Protein Interaction

DA toxicity alters mitochondrial function and leads to noticeable increase in intracellular ROS level. The toxic oxidative products of DA also disrupt the outer and inner mitochondrial membranes; alter mitochondrial permeability transition, state IV respiration and mitochondrial trans-membrane potential³⁸. Reports have shown that, ROS mediated toxic condition of DA is also responsible to select negatively charged amino acids for the interaction between alpha-synuclein and UCHL1. As a result salt bridges are formed between alpha-synuclein and UCHL1, stabilizing the 3D conformation of the protein complex. Another outcome of DA oxidation is the loss of interaction between UCHL1 and cofilin, suggesting conformational change of the protein complex between alpha-synuclein, cofilin and UCHL1. ROS mediated DA oxidation enhances the activity and expression of MMP9 in the medium, expressing the importance of MMP9 in DA mediated neuroinflammation. Additionally, the TIMP-1 expression becomes markedly reduced after DA exposure.

Altered Protein-Protein Interactions in DA Toxicity

Recent study on murine neuroblastoma cell line shows that, alpha-synuclein, UCHL1, and MMP9 interact directly with DA. The binding site of DA resides at the core of the proteins. Alpha-synuclein binds with DA via polar amino acid threonine while MMP9 and UCHL1 bind through non-polar, aliphatic amino acids with DA. Further, MMP9 interacts with alpha-synuclein and UCHL1 through electrostatic bonds. Interactions between MMP9 and cofilin have shown to be lost after DA exposure; implying that DA destabilizes the 3D conformation of intracellular protein complexes, a probable reason of disease progression³⁹. Cofilin 1 on the

other hand binds with alpha-synuclein and promotes its aggregation as well as its uptake. Presence of cofilin 1 also leads alpha-synuclein aggregates to form harmful mixed fibrils. These mixed aggregates subsequently induced further neuronal injury. Cofilin also modulates MMP9 activity upon regulating actin cytoskeleton⁴⁰. Alternatively, MMP9 degrades the extracellular matrix which in turn affects the activity of cofilin activity by altering the actin cytoskeleton³⁹. Certain MMPs also regulated by Alpha-synuclein genes⁴¹. The increased activity and expression of MMP9 DA exposure, suggests a pivotal role of MMP9 in the onset of neuroinflammation in DA toxicity.

Conclusion

In recent past, efforts have been made targeting different proteins to develop disease-modifying therapies for PD. This review raises the concern of targeting protein complexes for drug development by inhibiting their complex formation, rather than targeting individual protein for developing better therapeutics. Further research on gene therapy procedures to prevent intracellular protein interactions could be a new avenue for therapeutic development.

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