EFFECT OF α-SYNUCLEIN AGGREGATION AND DISRUPTED Ca2+ SIGNALLING PATHWAY IN PARKINSON’S DISEASE

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INTRODUCTION

Parkinson’s disease (PD), is the second most common, neurodegenerative disorder (in group of synucleinopathies), in humans after Alzheimer’s disease, affecting about 6.3 million people worldwide. Main theme of PD is α-synuclein aggregation into Lewy-bodies, formed in oligodendrocytes, dopaminergic (DA) neurons in brain region [substantia-nigra-pars-compacta (SNc)] other than genetics. An important key pathological feature caused α-synuclein aggregation, is the disruption of Ca²⁺ second messenger homeostasis. L-type voltage-gated Ca²⁺ channels have been implicated in PD in neurons. Calcineurin (Ca²⁺-CaM dependent serine phosphatase) is an essential enzyme in adult brain playing important role in neurite extension, memory, learning and key mediator of α-synuclein toxicity. On the other hand, Monosialotetrahexosylganglioside (GM1), a member of the sialic acid-containing glycosphingolipids group, that is highly expressed in PM of neural cells, can modulate Ca²⁺-ATPase (PMCA). Most of the organelles affected in PD are the major Ca²⁺ reservoirs. Thus, here we study how novel therapeutic ways of PD can be derived from molecular dysregulated targets.

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their as a time-compensation for the loss of naturally produced dopamine and alleviate symptoms.

**AIMS AND OBJECTIVES**

The primary objective of this paper is to accumulate the available data from various relevant published resources and to establish a simpler way to find out actual molecular dysregulation of PD to highlight what the novel therapeutic ways of PD can be developed from achieving organelle-network-operated cellular plasticity by Ca\(^{2+}\) second messenger.

**Function of Ca\(^{2+}\) in Neuronal Signalling and Abnormalities in its Functioning in Parkinson’s Disease**

Ca\(^{2+}\) ion shows notable effect on the neuronal membrane potential through both voltage-gated channel movement and membrane interactions. An abnormal decrease in extracellular Ca\(^{2+}\) concentration increases nerve excitability and increased extracellular Ca\(^{2+}\) concentration stabilize the membrane by reducing excitability.

But, in case of PD, the increased influx of Ca\(^{2+}\) is one of the molecular symptom of the disease disturbing neuronal signaling (chemical) leading to misfolding of neurotransmitter dopamine and affecting action potential as well as neuro-muscular transmission and finally leading to one of the main problems of PD, impairment in body movement.

**Primary key Problems of Parkinson’s Disease and its Mediators**

One of the main characterized problems of PD is the loss of Dopaminergic neurons of the midbrain [substantia-nigra-pars-compacta (SNc)], the source of Dopamine (a neurotransmitter) production in the central nervous system. They play critical roles in voluntary movement, a broad array of emotional-behavioral processes (mood, stress, addiction etc.). As the number of these DA neurons are few, thus their loss due to PD is quite problematic. The increased levels of cytoplasmic dopamine in PD patients might result in dopamine oxidation and in generation of reactive oxygen species that can kill these neurons (Brundin Pratik et al, 2002). On the other hand, presence of Lewy-body is another distinguished molecular symptom of PD. Formation of Lewy-bodies keep the brain away from making acetylcholine and dopamine (in case of PD). Building up of Lewy-bodies can lead to the problems of movement, memory (happens in later stage) as well as behavior and thus leading mainly to PD.

\(\alpha\)-syn aggregation is the key mediator of PD and Calcineurin is the mediator of \(\alpha\)-synuclein aggregation in case of PD. Calcineurin (Ca\(^{2+}\)-CaM dependent serine phosphatase) is an essential enzyme in adult brain playing important role in neurite extension, memory, learning and key mediator of \(\alpha\)-synuclein toxicity. On the other hand, Monosialotetrahexosylganglioside (GM1), a member of the sialic acid-containing glycosphingolipids group, that is highly expressed in PM of neural cells, can modulate Ca\(^{2+}\)-ATPase (PMCA), to reduce excitotoxicity and oxidative stress by acting as a neuroprotective in PD.

**Potent Inhibitor and Control of \(\alpha\)-Synuclein Aggregation in Brain**

DJ-1 is a deglycase enzyme which exhibits a redox-sensitive chaperone-like activity. The partially oxidized state of DJ-1 is active in inhibiting the aggregation of \(\alpha\)-synuclein, the highly performing protein associated with Parkinson’s disease. The partially oxidized DJ-1 possesses an adhesive surface which isolates \(\alpha\)-synuclein monomers and blocks the early stages of \(\alpha\)-synuclein aggregation and also restricts the elongation of \(\alpha\)-synuclein fibrils leading to a control of PD. DJ-1 reframes mature \(\alpha\)-synuclein fibrils into heterogeneous toxic oligomeric species, which has loose surface topology due to a decrease in elastic modulus and disrupt membrane architecture, internalize easily and induce aberrant nitric oxide release (Kumar Roshan et al, 2019).

**Pathogenesis and Medication of Parkinson’s Disease**

The most common motor symptoms of PD are rigidity, loss of balance, hypokinesia, tremor, impairment of walking or slow movement and loss of memory, thinking or skills in advanced stages or rare cases. By DAT scan, MRI, CT or USG of Brain for conformation of PD, Carbidiopa-levodopa (a natural chemical passes into the brain and is converted into dopamine), Pramipexole or Ropinirole (mimic dopamine effect in brain after injecting), Xadago or Zelapar (MAO B inhibitor), Talcapon (COMP inhibitor) etc. are generally used. Another way is the surgical way, where electrodes are implanted into a specific part of brain by the process of Deep brain stimulation.

**DISCUSSION AND CONCLUSION**

Parkinson’s disease is one of the most harmful brain disorders, second most common and progressive neurodegenerative disease affecting millions of people. Here, in this study we discussed about the role of \(\alpha\)-synuclein aggregation, loss of dopaminergic neurons, impaired Ca\(^{2+}\) metastasis leading to development of the central nervous system disease, PD. Most of the organelles affected in PD are the major Ca\(^{2+}\) reservoirs. Thus, Ca\(^{2+}\) signaling contributes to the progression of PD, vitally important for highlighting how novel therapeutic ways of PD can be derived from achieving cellular plasticity by Ca\(^{2+}\) signalling. The treatments available are eventually failed, but can be useful as a primary one. The molecular mechanism of Ca\(^{2+}\) signal transduction in PD should be focused on to prevent dopamine breakdown and the potent inhibitor of \(\alpha\)-syn should be used to check its aggregation and formation of Lewy bodies. A campaign has to be established by the Government to conduct a periodic checkup of senior citizens (60+), as PD is more common in elderly persons with all ethical and controlled conditions to ensure optimal success of early diagnosis of PD.
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Data Availability Statement

The datasets collected for the study are available to the corresponding authors.

Author Contributions

DM wrote the first draft. SA completed the manuscript, organized, designed the study and DM provided critical revision thoroughly. All authors read and approved the submitted version.

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Conflict of Interest

The authors declare that this study was completed without any interference of commercial or financial relationships.

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