The Role of Cellular Defense Systems of Mitochondrial Proteostasis and Ferroptosis in Parkinson's Disease

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Abstract

Despite small size and proportion brain has immense significance with only 2% of human body weight. Brain or CNS has neurodegenerative disorders marked by behavioral and cognitive impairment that arise from gradual decline and loss of functional neurons. Because of expansion of aging population the scale on the graph of the effectiveness of neurodegeneration the number of patients increases day by day. Urgent focused and significant efforts required for the treatment of the root causes of neurodegenerative disorders. Modifications in structure and functional cognition of brain tend to become prominent at the late stage of the disorder.

Keywords: Neurodegenerative disorders • Parkinson's disease • Alzheimer's disease

Introduction

Neurodegenerative disorders like Parkinson's disease and Alzheimer's disease impose a considerable burden to society. Most prominent neurodegenerative disorder that rapidly progressing is Parkinson's disease causes a burden to serious health and socio-economic state of people. Therapeutic expressions of PD comparises both motor and non-motor signs and symptoms and primary diagnosis is specify by the aggregation of alpha-synuclein and decline of dopaminergic neurons in the part of brain called substantia nigra. Primary therapeutic hallmark of this disease relates to the decline of dopaminergic neurons and restore of these dopamine enhance the treatment of PD, dopaminergic decline also linked to the significant aggregation of iron and mitochondrial dysfunction. PD shows irregular accumulation of iron cause imbalance equilibrium of iron as a hallmark that becomes the reason of the development of ROS.

Description

Various components involve in the development of ROS in PD including, inflammation, mitochondrial dysfunction and Alpha-synuclein. The primary emphasis in this discourse will center on mitochondrial dysfunction and iron accumulation in substantia nigra by disturb equilibrium of iron that initiated by iron regulatory protein in PD. Advance observations indicate the disturbance of mitochondrial proteostasis that cause mitochondrial dysfunction resulted in the form of mitochondrial Oxidative Stress (OS), mitochondrial Unfolded Protein Response (UPRmt) and mitophagy. The progression of PD is frequently related to imbalance in mitochondrial proteostasis that enhance the severity of PD. Sustaining of mitochondrial proteostasis including four major aspects like mitochondrial OS, mitochondrial-associated protein transport, mitophagy and UPRmt. Different factors interconnected with ferroptosis including disturb iron homeostasis, influence lipid metabolism and disturbance in various organelles gives a way to enhanced progression of Reactive Oxygen Species (ROS). There is a mechanism between disruptions of membrane to ferroptosis including harmful buildup of lipid peroxides in cell membrane gives a way to impairment and rupture of membrane that leads to organelles severity. Different factors interconnected with ferroptosis including disturb iron homeostasis, influence lipid metabolism and disturbance in various organelles gives a way to enhanced progression of Reactive Oxygen Species (ROS). There is a mechanism between disruptions of membrane to ferroptosis including harmful buildup of lipid peroxides in cell membrane gives a way to impairment and rupture of membrane that leads to organelles severity. In PD brain imaging investigations shows an interaction between inclination of dopaminergic neurons and accumulation of iron in brain's substantia nigra leads to neuronal death. Various mechanism aimed at neutralize ROS being observed as a potential therapeutic strategies approach to enhance alleviate aggregation of iron and oxidative stress in PD. Ferroptosis is a type of non-apoptotic cellular death that occasion of regulated necrosis that depends on iron by uncontrolled lipid peroxidation-mediated oxidative harm to the cell membrane. Processes of cytologic transformation caused by ferroptosis different from other type of cellular death and presents modification in morphology like necrosis that include mitochondrial dysfunction because of the phagocytosis of ferritin (iron storage protein). Narration of different studies shows that the use of ferroptosis suppressors and diminishing level of ROS in the effective therapy of PD enhances the rescue of dopaminergic neuronal death in PD. Growing abundance of analysis emphasizes an interaction between PD and ferroptosis. For neuroprotection in PD cells now progress new and more advance three defensive systems to oppose the harmfulness of ferroptosis enhanced by lipid peroxidation. The defensive mechanisms against to ferroptosis facilitated by GPX4 that reduces the rate of lipid peroxidation and PD and protect dopaminergic neurons and its initiation and expression is strategically a form of protection against neurodegenerative disorders. Another defensive system for PD relevant to ferroptosis enhance by FSP-1 that progressively cease

the activity of ferroptosis. GTP Cyclohydrolase 1 (GCH) alteration also included in defense systems of neuroprotection against neurodegeneration that reduce the PD by affecting its phenotype also facilitate the productions of BH4/BH2 (tetrahydrobiopterin/ dihydrobiopterin) an important endogenous antioxidant work with same mechanism of independent of GPX4.

Conclusion

From this study we can estimate that maintained mitochondrial proteostasis and homeostasis of iron accumulation mitigate the rate of PD because these interrelated forms cause the neurodegenerative disorders like PD. Different ways of living can protect from PD like exercise regulate the mitochondrial proteostasis and mitochondrial dysfunction caused by ferritin. Future analysis and investigations must be able to enhance the function of mitochondrial proteostasis in reduction and enhancement of PD by exercise that leads to a new and advance way to gives a hypothetical base for the neuroprotection against PD. This observation also becomes helpful for clinical point of view to recommend practical activity to mitigate the rate of these diseases. According to this study there is another effective defense system of neuroprotection in the therapy of PD is the reduction of ferroptosis toxicity caused lipid peroxidation. This will be a more effective as a potential therapeutic approach for treating Parkinson's disease. This will provide new strategies to diagnose and treat PD. However, there has been a great deal of research on the prevention and therapy of Parkinson’s disease and all other neurodegenration diseases.

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