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Review on Parkinson's Disease, a Neurodegenerative Disorder and The Role of Ceruloplasmin Protein in It

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ABSTRACT

Parkinson's disease (PD), a neurodegenerative disease is becoming major health concern mainly for elder people of age over 60 years. The main cause of PD is permanent loss/death of dopaminergic nerve cells present in brain part called *substantia nigra,* which is responsible for dopamine synthesis. MAO-B, monoamine oxidase B, regulates dopamine metabolism and increased activity of MAO-B causes dopamine degradation which in turn promotes the accumulation of glutamate and oxidative stress with free radical liberation. Several factors like oxidative stress, free radical formation, increased cholesterol, mitochondrial dysfunction, nitric oxide toxicity, signal-mediated apoptosis, head trauma, and environmental toxins and gene mutations like VPS35, SNCA, EIF4G1, GBA, CHCHD, LRRK2, PINK1, DNAJC13 and SOD2 are associated with PD. Symptoms of PD include bradykinesia, muscle rigidity, resting tremors, postural instability and shuffling gait, constipation, sleep problems, fatigue, apathy, loss of smell and taste, excessive sweating, frequent nightmares, dream enacting behaviour, anxiety, depression, daytime drowsiness. In PD, low levels of ceruloplasmin were observed in people with early onset of PD. Ceruloplasmin, a ferroxidase enzyme which is synthesized in liver parenchymal cell, regulates iron metabolism and lower level of which causes iron accumulation in brain which is responsible for the early onset of PD. Levodopa-based preparations, Dopamine agonists, Catechol-o-methyltransferase (COMT) inhibitors, MOA-B inhibitors, Adjunctive therapy, Antiglutamatergics drugs are currently used for the treatment of PD.

Keywords- Parkinson's disease, Quercetin, Ceruloplasmin, Monoamine oxidase B (MAO-B)

I. INTRODUCTION

Neurodegenerative disease, a permanent loss/death of nerve cells is becoming a major concern for human health, mostly for elderly people. Huntington's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Spinocerebellar ataxias, Alzheimer's disease and frontotemporal dementia are all the examples of neurodegenerative disease [Gitler et al., 2017]. Increasing Age is the one of the most common risk factor associated with neurodegenerative disease, especially in case of Alzheimer's and Parkinson's disease [Przedborski et al., 2003]. In this study, main focus will be the cause of PD and ceruloplasmin role in it.

Parkinson's disease

Parkinson's disease (PD) is the second most occurring disease after Alzheimer's disease in elder people over the age of 60 years and was first explained as "shaky palsy" in 1817 by James Parkinson. The main cause of PD is the loss of dopaminergic nerve cells present in brain part called *substantia nigra* where neurotransmitter dopamine is synthesized [DeMaagd and Philip, 2015; Marino et al., 2020]. Monoamine oxidases (MAO) discovered by Mary L.C. in 1928, regulates monoamine neurotransmitters levels and two isoforms: MAO-A and MAO-B. MAO-B metabolizes dopamine (DA) in *substantia nigra* and increased activity of MAO-B causes DA degradation which in turn promotes the accumulation of glutamate and oxidative stress with free radical liberation [Yeung et al., 2019; Marino et al., 2020].

Risk factors and Genetic Mutations

Risk factors and genetic mutations both are associated with PD. Some risk factors associated with PD are free radical formation, oxidative stress, elevated cholesterol, mitochondrial dysfunction, nitric oxide toxicity, signal-mediated apoptosis, head trauma, and environmental toxins like Cyanide, Carbon disulphide, Methanol and organic solvents, Pesticides and Herbicides [DeMaagd and Philip, 2015].

Gene mutations associated with PD are VPS35, SNCA, EIF4G1, GBA, CHCHD, LRRK2, PINK1, DNAJC13 and SOD2 [DeMaagd and Philip, 2015; Marino et al., 2020].

***SNCA*:** A 14.5 kDa protein of 140 amino acids expressed mainly in brain and also in heart, pancreas and skeletal muscle is thought to be involved in regulation of release and transport of DA. In nondopaminergic neurons, it inhibits the expression of p53 and transactivation of proapoptotic genes and provides a neuroprotective

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phenotype but this neuroprotective effect is eliminated by missense mutations in SNCA which causes apoptosis by reversing the p53 expression [Siddiqui et al., 2016].

***GBA*:** The gene, GBA encoding a lysosomal enzyme, glucocerebrosidase (GCase) which is involved in glucosylceramide metabolism, is present in a gene rich region on chromosome 1 (1q21). A mutation in GCase makes it unable to fold properly causing its accumulation in dopaminergic neurons cellular compartments. Accumulation of alpha synuclein (SNCA) is observed due to impaired GCase activity [Riboldi et al., 2019; Sidransky and Lopez, 2014].

Symptoms of PD

PD symptoms can be classified in two categories: Motor symptoms and Non-motor symptoms.

***Motor Symptoms*:** Lag in movement initiation (bradykinesia), muscle rigidity, resting tremors, postural instability, speech disturbances, dystonia (sustained muscular contraction) and shuffling gait are some motor symptoms [Fritsch et al., 2012; Sveinbjornsdottir 2016].

***Non-Motor Symptoms*:** Constipation, sleep problems, fatigue, apathy, loss of smell and taste, excessive sweating, frequent nightmares, dream enacting behaviour, anxiety, depression, daytime drowsiness are some non-motor symptoms of PD [Fritsch et al., 2012; Sveinbjornsdottir 2016].

II. ROLE OF CERULOPLASMIN IN PARKINSON'S DISEASE

Ceruloplasmin, encoded by CP gene in humans is a ferroxidase enzyme which is synthesized in liver parenchymal cell and member of multicopper oxidase family. It is a major carrier of copper in blood (90-95% of copper) which is added by the P-type ATPase after its synthesis. Copper is required by ceruloplasmin for its proper folding. The molecular weight of ceruloplasmin is 132 kDa and it is composed of three asparagine-linked oligosachharides and a polypeptide chain of size 1046 amino acids [Lopez et al., 2021, Gaware et al., 2010, Hellman et al., 2002]

Ceruloplasmin is a redox reaction catalyst and it regulates iron metabolism i. e. the oxidation of iron from ferrous (fe^{2+}) to ferric iron (fe^{3+}) which helps in iron binding to transferrin [Lopez et al., 2021]. Transferrin is a glycoprotein found in blood plasma that has high affinity to ferric iron. It carries iron to various tissue such as spleen, liver and bone marrow [Ogun et al., 2020].

In Parkinson's disease lower level of ceruloplasmin has been observed in people with early onset of PD. Mutation in ceruloplasmin gene causes the absence or low level of ceruloplasmin. Accumulation of iron occurs in the liver, brain and pancreas due to the absence of ferroxidase activity which causes damage to the tissues by the formation of free radicals [Bharucha et al., 2008, McNeill et al., 2008]

III. CURRENT TREATMENT METHODS FOR PD

No permanent cure for PD has been found yet but a great deal of progress has been made for the treatment of PD. Some of the treatment [Stoker et al., 2018, Jankovic et al., 2008] currently used for PD are:

1. Levodopa-based preparations
2. Dopamine agonists
3. Catechol-o-methyltransferase (COMT) inhibitors
4. MOA-B inhibitors
5. Adjunctive therapy
6. Antiglutamatergics drugs

Deep brain stimulation (DBS), a safe treatment method for PD which could be efficacious in improving the movement disorder [Stoker et al., 2018].

IV. CONCLUSION

Even though PD is the second most common neurodegenerative disease after Alzheimer's disease, still it poses a major health concern for elder people and no cure has yet been found for it. Several treatments are proved to be very efficient for PD among which Levodopa being a better option than others but long time treatment with levodopa is not recommended because of its side effects. Several factors and mutations are associated with PD but main cause is the iron accumulation and oxidative stress due to free radical formation in nerve cells. This study mainly focussed the cause and current treatments used for PD.

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