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A Review on Neuroprotective Mechanisms and Disease Modifying Effects of Lipid-Lowering Drugs and Oral Anti-Hyperglycemic Agents in Parkinson's Disease

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ABSTRACT

Parkinson's disease (PD) is a chronic progressive age-related neurodegenerative disorder characterized by rest tremor, bradykinesia, muscle rigidity, shuffling gait and flexed posture which is due to extensive loss of dopaminergic neurons in substantia nigra pars compacta of the brain. Management of the disease is effective initially with levodopa, but as the disease progresses there is a gradual loss of dopaminergic cells, thus the level of dopamine in the brain will get increasingly depend on the availability of levodopa in blood. Further long-term treatment with levodopa results in motor fluctuations or dyskinesias and its effectiveness inexorably diminishes over time. Statins are 3-hydroxy 3-methylglutaryl coenzyme A (HMG- CoA) reductase inhibitors, the antihyperlipidemic agents are found to possess multiple cholesterol independent biochemical mechanisms of action like suppression of proinflammatory molecules, microglial activation, inhibition of oxidative stress, attenuation of alpha-synuclein aggregation, *etc*. many of which offer neuroprotective potential. Metformin is a widely prescribed oral antihyperglycemic drug for the clinical treatment of diabetes mellitus. Metformin exerts its protective antidiabetic effects in part by activating AMP-activated protein kinase (AMPK).AMPK has a crucial role in neuroprotection, anti-inflammation, and alteration of oxidative stress. Metformin administration has also been found to increase levels of GLP-1 and it was shown that GLP-1 agonists had positive effects on motor symptoms in Parkinson disease, generating a new potential mechanism for metformin action in neurodegeneration. Since statins and metformin are commonly prescribed drugs in the older age the neuroprotective effects of these drugs may provide a disease-modifying effect and delay the progression of disease which will be beneficial for long term PD.

INTRODUCTION

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder that belongs to a group of conditions called movement disorders or motor system disorders. It is caused by the progressive loss of dopaminergic neurons in a part of the brain called substantia nigra, which produces the chemical dopamine. PD was originally described in 1817 by James Parkinson, a British physician. The disease in which there is no known cause is known as Idiopathic Parkinson disease. Loss of nigrostriatal neurons results in a reduction of cortical activation; virtually all the motor deficits of IPD are attributable to the marked loss in dopaminergic neurons projecting to putamen. There is a positive correlation between the degree of nigrostriatal dopamine loss and disease severity. Although the etiology of Parkinson's disease is not completely understood, factors such as genetic factors, environmental exposures, and family history also may increase a person's risk of developing the disease. [1]

PD often presents with four cardinal motor manifestations: tremor at rest, limb muscle rigidity, bradykinesia, and postural instability. Not all patients initially presented with all of the classical signs of the disorder; there may be only one or two. The diagnosis of Parkinson disease is based mainly these manifestations on clinical examination, which includes the exclusion of other conditions (medication induced eg: - antipsychotics, antiemetics, or metoclopramide) and response to levodopa or a dopamine agonist. At present, pharmacological treatment is the mainstay for the management of Parkinson disease patients. The commonly used medications for the treatment of Parkinson disease are levodopa/carbidopa, catechol-O-methyltransferase (COMT) inhibitors - entacapone and tolcapone, dopamine receptor (DA) agonists - bromocriptine, pramipexole and ropinirole, monoamine oxidase type B (MAO-B) inhibitors - selegiline and rasagiline, anticholinergics - trihexyphenidyl and NMDA receptor antagonist - amantadine. Although management of the disease is mainly with levodopa, the dopamine precursor which is the cornerstone in symptomatic treatment and is very effective initially and along with other adjunct drugs, but as the disease progresses there is a gradual loss of dopaminergic cells, thus level of dopamine in the brain will get increasingly depend on availability of levodopa in blood. Further long-term treatment with levodopa results in motor fluctuations or dyskinesias, on-off phenomenon, wearing off effect, dementia, falling, freezing of gait and its effectiveness inexorably diminishes over time.[2]

Motor fluctuations and dyskinesias are the most common motor complications that manifest within the first few years from the initiation of levodopa therapy in patients with Parkinson disease. Motor fluctuations are alterations between periods of being "on," during which the patient experiences a positive response to medication and being "off," during which the patient experiences a re-emergence of the Parkinson symptoms suppressed during the "on" state. It includes wearing off which means symptom re-emergence, sudden on-off fluctuation and sudden off periods. Dyskinesia consists of levodopa-related abnormal, involuntary movements, which is a result of treatment with excessive amounts of levodopa.[3]

Statins are 3-hydroxy 3-methylglutaryl coenzyme A (HMG- CoA) reductase inhibitors, interrupting the conversion of HMG-CoA to mevalonate, the rate-limiting step in de novo cholesterol biosynthesis. Reduced synthesis of LDL and enhanced catabolism of LDL mediated through LDL receptors appear to be the principal mechanisms for lipid-lowering effects. These agents include atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin. Statins may also help to stabilize plaques in the arteries. That makes heart attacks less likely.[4]

Statins are found to possess multiple cholesterol independent biochemical mechanisms of action many of which offer neuroprotective potential which include suppression of proinflammatory molecules and microglial activation stimulation of endothelial nitric oxide synthase, inhibition of oxidative stress, attenuation of alpha-synuclein aggregation, modulation of adaptive immunity and increased expression of neurotrophic factors.[5] Statins are found to exert the neuroprotective effects on striatal dopaminergic neurons by blocking the mevalonate pathway.[6] Statins also up-regulate the dopamine D1, D2 receptors in the brain. These effects are found to alleviate neuroinflammation and reduce Parkinson disease risk.[7]

Metformin is a widely prescribed oral antihyperglycemic drug for the clinical treatment of diabetes mellitus. Metformin exerts its protective antidiabetic effects in part by activating AMP-activated protein kinase (AMPK) and also inhibits glycation reactions. AMPK plays a role in regulating glucose and lipid metabolism, senses metabolic stress and integrates diverse physiological signals to restore energy balance. AMPK also serves as a regulator of cell survival or death in response to pathologic hypoxia, osmotic and oxidative stress. AMPK has a crucial role in hyperglycemia associated with Type 2 DM, neuroprotection, anti-inflammation and alteration of oxidative stress. Dysregulation of AMPK is associated with

insulin resistance and neuroinflammation. Both acute and chronic metformin administration has been found to increase levels of GLP-1, an incretin known to induce insulin secretion and it was shown that GLP-1 agonist had positive effects on motor symptoms in Parkinson disease, generating a new potential mechanism for metformin action in neurodegeneration.[8]

REVIEW OF LITERATURES

1. Mutez E *et al* (2009)[9] conducted a study on 'Lipid-lowering drugs are associated with delayed onset and slower course of Parkinson's disease'. It was a retrospective cohort study in 419 patients which found that, in PD patients receiving either a statin or a fibrate, the average age of disease onset was detained by almost 9 years when compared with control PD patients who were not taking lipid-lowering treatment. Fibrates and statins are found to activate Peroxisome Proliferator-Activated Receptor alpha (PPAR-alpha) which is a nuclear receptor that controls the genes governing inflammation, apoptosis and oxidative stress, the key mechanisms for neuronal death in PD. The mixed linear model of the study revealed that the increase in levodopa-equivalent daily dose over 2 years was remarkably smaller in the group taking a statin (+24 mg) than in the control group (+212 mg) where p=0.004. The Unified Parkinson's Disease Rating Scale motor score progression was found to be similar in both groups. No difference was found in the course of disease in patients taking a fibrate from the controls.

2. Kun-Der Lin *et al* (2016)[10] conducted a study on 'Statin therapy prevents the onset of Parkinson's disease in patients with diabetes'. It was a population-based cohort study conducted on 50432 patients followed from 2001 to 2008 which found that the incidence of Parkinson's disease was lower in statin users with a strong dose-dependent trend in diabetic patients. The relative risk of PD was lowered by simvastatin, atorvastatin but not by lovastatin and the beneficial protective effect was observed in both male and female diabetic patients after the adjustment of clinical variates. In statin users, the hazard ratio of PD incidence was 0.63 when compared to users. The relative risk (RR) of PD incidence was 0.70 on Cox regression analysis with dose-dependent trends (p for trends <0.001). In patients with hyperlipidemia and statin use, the RR of PD incidence was lower whereas it was higher in patients with stroke events and older age. This study also analyzed previous animal studies which showed that chronic simvastatin treatment can affect dopamine levels in the prefrontal cortex and striatum of the brain. Also, statin treatment had anti-inflammatory effects on pathways like upregulation of cyclooxygenase-2 and iNOS which are a neuroinflammatory

process that can lead to PD. The study concluded that its findings warrant additional studies on statins in PD of its neuroprotective mechanisms among diabetic patients. Since statins are found to be safe and easily available its application can be extended beyond cardiovascular protective and lipid-lowering effects.

3. Angelika D. Wahner *et al* (2008)[11] conducted a study on 'Statin use and risk of Parkinson's disease'. It was a population-based study that recruited 312 incident Idiopathic Parkinson's disease cases and 342 controls between January 2001 and January 2007. The study categorized the participants as ever or never users of statins and Odds ratio (OR) was calculated using unconditional logistic regression method. The study stratified statin use by duration in years, age at diagnosis, a gender that made the heterogeneity in the effects to be estimated using Breslow-Day Test for homogeneity. The study results showed a high frequency of statin use among controls as compared to cases with a 55% PD risk reduction among ever statin users. In long-term users (> 5years) strong dose-response relationship was noted with OR 0.50; 95% CI 0.23 to1.10, which supported a strong protective association. No difference in protective effect estimates was noted between men and women. A slightly stronger protective effect was evident in the younger age group (<60) and among never smokers versus ever smokers with OR 0.35; 95% CI 0.17, 0.70 and OR 0.57; 95% CI 0.32, 1.02 respectively. On evaluation of each individual statin the study noted a 60- 70% risk reduction for all statins except pravastatin (atorvastatin OR 0.39; 95% CI 0.21to 0.71, simvastatin OR 0.38; 95% CI 0.16 to 0.91, lovastatin OR 0.27; 95% CI 0.09 to 0.87, pravastatin OR 1.78; 95% CI 0.43 to 7.42). The study discussed the least lipophilic property of pravastatin and its difficulty in crossing the blood-brain barrier as the reason for the inverse relation between PD and pravastatin. The study supported the possibility of a causal relationship of statins with PD protection via strong dose-response relation and biologic evidence of neuroprotective mechanisms of statins that include nitric oxide (NO) and nitric oxide synthase (NOS) regulation, anti-oxidant effects, reducing the induction of pro-inflammatory mediators such as cytokines.

4. Ming Lu *et al* (2016) [12] conducted a study on 'Metformin prevents dopaminergic neuron death in MPTP/P induced mouse model of Parkinson's disease via autophagy and mitochondrial ROS clearance'. The study explored the neuroprotective effect of metformin in 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine plus probenecid-induced mouse model of Parkinson's disease and cultured SH-SY5Y cells to investigate the mechanism. Mice were

randomly divided into 4 groups viz. saline-treated, MPTP/P treated, MPTP/P + metformin-treated and metformin alone treated groups. Mice received 20mg/kg MPTP, 250 mg/kg probenecid and metformin 5mg/ml in drinking water. The analytical studies revealed that metformin improved motor impairment and increased dopamine levels in the striatum of MPTP/P induced PD mice. Metformin increased sustained rotarod time and HPLC analysis showed increased DA and dihydroxyphenylaceticacid levels by 115.5 %. The number of TH-positive neurons in SNc of MPTP/P PD mice was significantly increased by metformin by 25% and metformin had no influence on monoamine oxidase B activity which indicated that metformin prevents DA neuron degeneration. A 47.3% decrease in alpha-synuclein positive cells was exhibited by immunohistochemistry staining. Microglial activation plays a critical role in DA neuron death while metformin administration dramatically suppressed it. Metformin administration for 5 weeks inhibited the expressions of TNF- alpha, IL-6 mRNA, significantly increased IL-10 production contributing to inhibition of neuroinflammation. Mitochondrial dysfunction is believed to be involved in PD. Metformin pre-treatment significantly recovered mitochondrial membrane potential which was evident from the proportion of dysfunctional mitochondria (19.4% in MPP^+ treated cells reversed to 8.5% in MPP^+/ MET co-treated cells). The study findings supported the potential of metformin to be used as a new therapeutic avenue in Parkinson's disease.

5. Ming-Chang Chiang *et al* (2014)[13] conducted a study on 'The neuroprotective role of metformin in advanced glycation end product treated human neural stem cells is AMPK-dependent'. The study showed a potential relationship between AMPK (AMP-activated protein kinase) and AGEs (advanced glycosylation end products) in diabetic neuropathy. Autophagic dysfunction is involved in DA neuron dysfunction. Activation of AMPK is an effect of metformin and autophagy is an important function of AMPK activation. Metformin could also increase the phosphorylation level of AMPK. Human neural stem cells were cultured being with or without exposed to AGEs and then to metformin and evaluated the cell growth, conducted western blot assays, measured cytochrome c release, RNA isolation Q-PCR, intracellular ATP concentration, mitochondrial mass, and its functional parameters, cell transfection and statistical analysis. The results showed that treatment with AMPK agonist (metformin) significantly normalized cell viability and prevented cytochrome c from mitochondria to the cytosol where cytochrome c is needed in AGE-induced cell death in hNSCs. Metformin significantly enhanced the protein phosphorylation levels of PGC1-alpha, indeed stimulation of AMPK also directly phosphorylates it, which in turn induced genes

associated with mitochondrial function and biogenesis. Metformin increased neuroprotective gene expression levels in AGE-treated hNSCs. All these findings clarified AMPK in hNSCs as a critical target of AGE-mediated neurodegenerative pathological effects which can be rescued by metformin via upregulation of AMPK expression and activity. This study revealed neuroprotective potentials of metformin supporting its emergence for application in neurodegenerative diseases like Parkinson's disease.

6. Mark L. Wahlqvist *et al* (2012)[14] conducted a study in the Taiwanese population on 'Metformin-inclusive sulfonylurea therapy reduces Parkinson's disease occurring with Type 2 diabetes'. The representive cohort of 800,000 was classified based on the presence or absence of Type 2 diabetes and whether any oral anti-hyperglycemic agents (OAA) were used or not. Out of 800,000 cohorts, those with and without Type 2 diabetes was 64,166 and 698,587 respectively. 41,003 patients administered OAA whereas 23,163 patients didn't use it. PD incidence densities (PID, per 10,000 person-years) and hazard ratios (HR) were calculated and data were analyzed. The results showed that for sulfonylurea therapy alone PID increased from 58.3 to 83.2. The HR for metformin-alone therapy was 0.95, sulfonylurea-alone 1.57 and for combined therapy 0.78. The study results concluded that there may be a causal relationship between the incidence of Parkinson's disease and Type 2 diabetes since the incident risk of PD in T2DM was 2.2 fold. Upon usage of sulfonylureas, as a therapeutic regimen for T2DM, this risk was further increased by 57%. But the key finding of the study was that the risk of PD incidence was avoided by the combination therapy with metformin in patients with T2DM.

CONCLUSION

This review on various research studies related to the neuroprotective effects of statins and metformin in Parkinson's disease concluded that these drugs will provide additional therapeutic potential in Parkinson's disease. Parkinson's disease usually occurs above the age of 50 and by the time lipid-lowering drugs, anti-hyperglycemic agents, *etc* will be a common prescription as evidenced by our lifestyle and diet changes. These research studies prove that statins and metformin may provide a disease-modifying effect like neuroprotection and thereby a better health status, improved quality of life in Parkinson's disease when compared to non-users of these drugs. This review points out the need for further research works on this field supporting these drugs to be a novel therapeutic avenue in Parkinson's disease.

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