Effect of vestibular stimulation on lipid profile in MPTP induced Parkinsonian mouse model

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Abstract

The changes in blood lipid levels in Parkinson's disease (PD) patients and their clinical significance remains unclear till date. Many studies have found that lipid metabolic abnormalities may be a major cause of Parkinson’s disease (PD). The present study was undertaken to study the effect of vestibular stimulation on body weight and lipid profile in MPTP induced mice. Total of 24 male mice are divided into 4 groups with 6 mice in each group by simple random sampling. Mice were given intraperitoneal injection of MPTP at a dose of 30mg/kg body weight once daily for 5 consecutive days to induce PD. Caloric vestibular stimulation was applied by instilling warm (40°C) water into external ear of the mice. At the end of the intervention mice were sacrificed and blood was collected by cardiac puncture. Total cholesterol, triglycerides, HDL, and LDL were analysed in all the groups. Our study shows that caloric vestibular stimulation has a positive effect on the levels of total cholesterol, triglycerides, high density lipoprotein, and low-density lipoprotein. Further studies with a large sample size are needed to establish vestibular stimulation as a new therapeutic agent in treatment of PD.

Keywords: Lipid profile, body weight, MPTP, Parkinson’s

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Introduction

Parkinson disease (PD) is a prevalent neurological disorder and has a prevalence of roughly 2% in adults aged 65 and older. Clinical signs of Parkinson’s disease include motor symptoms, such as motor delay, resting tremor, and muscle rigidity, cognitive dysfunction is the most prevalent nonmotor symptom, which includes mild cognitive impairment and dementia. Patients and their...
family are adversely affected by the onset and progression of PD dyskinesia and cognitive dysfunction; therefore, it is of utmost importance to prevent and delay these conditions in aged patients (Xue Hong). Recent research indicates that lipids and uric acid levels in the blood may be associated with the incidence of PD (M. X. Dong). It has been hypothesised that cholesterol and/or its oxidised metabolites (oxysterols) may have a possible endogenous responsibility in the development of Parkinson disease. Clinical investigations point to a direct relationship between increased levels of cholesterol in plasma and the prevalence of PD. Additionally, a high-fat diet worsens Parkinsonian pathologies in animal models of the disease, including the loss of dopamine neurons (Paul R). In some recent animal studies, it was discovered that vestibular stimulation can successfully control TG and total cholesterol, assisting in the maintenance of a healthy body weight (Saritha S). Vestibular stimulation promotes sleep and regulates food intake via the vagus nerve, insulin, arcuate nucleus, thyroid hormones, and PA-axis. (Sadanandan NN).

In the present study Caloric, vestibular stimulation (CVS) is used to stimulate the vestibular apparatus. It is a simple and non-invasive procedure that is shown to improve the motor and non-motor symptoms of PD in pre-clinical experiments (Jagadeesan T). The primary goal of this research is to determine the impact of bilateral CVS on lipid profile in MPTP induced Swiss albino mice.

**Materials and Methods**

**Experimental animals**

After receiving ethical approval from the AIMST University Animal Ethics Committee (AUAEC/FOM/2020/04), 24 healthy male Swiss albino mice weighing 25-30 gm were used for the study. Following the minimal number of animals used in previous studies and to obtain statistically significant results, the sample size of 6 animals per group was chosen. The animals were kept under a 12-hour light/dark cycle with temperature and humidity control in spacious polyacrylic cages. Food and water were available to the animals’ ad libitum.

**MPTP animal model**

MPTP was purchased from Sigma Aldrich, USA, and dissolved in sterile saline. Mice were given intraperitoneal injection of MPTP at a dose of 30mg/kg body weight once daily for 5 consecutive days to induce dopaminergic neuron death in the substantia nigra. (Zhu YL et al, 2019, Schober, 2004)

**Caloric vestibular stimulation**

Hot water at a temperature of 42°C, was used to irrigate the middle ear canals of the mice. 2 ml of hot water was delivered into each ear with a polyethylene tube. The flow rate was kept at 0.2mL/s to ensure continual stimulation of the vestibular system. (Sadanandan S).

**Experimental design**

Swiss albino mice were divided into four groups at random. Each group had 6 animals.

Group 1: Normal control
Group 2: MPTP control
Group 3: Only CVS for 30 days
Group 4: MPTP + CVS for 30 days

Body weight of all the mice was estimated on 1st, 7th, 14th, 21st and 28th day.

**Blood Collection**

Mice were anaesthetized with chloral hydrate (350 mg/kg; i.p.) at the end of the experiment, and blood was collected via cardiac puncture. The serum was separated by centrifugation at 3000 x g for 4 minutes and used for analysis (Paul R).

**Lipid Profile Analysis**

The serum total cholesterol was estimated by in vitro enzymatic technique using a colorimetric kit CHOD-PAP method(Allain CC) as per the manufacturer’s instructions. The GPO-PAP method was used to calculate triglycerides (Henkel). The precipitation method was used to estimate HDL and LDL. (Demacker, Kerscher).

**Data analysis**

The findings were tabulated as Mean ±SEM. For statistical analysis, the one-way ANOVA was used, followed by Tukey's post hoc test. Statistical analyses were performed by GraphPad prism 8.0 software.

**Results**
Body weight
Although there was a slight decrease in the weight of mice treated with MPTP when compared to that of the normal control, it was not statistically significant as given in Table 1. There was no difference between the control and CVS groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>27.40 ± 0.71</td>
<td>27.72 ± 0.64</td>
<td>28.02 ± 0.70</td>
<td>28.17 ± 0.59</td>
<td>28.23 ± 0.68</td>
</tr>
<tr>
<td>MPTP control</td>
<td>26.68 ± 1.27</td>
<td>26.37 ± 1.26</td>
<td>25.68 ± 1.32</td>
<td>25.60 ± 1.28</td>
<td>25.25 ± 1.32</td>
</tr>
<tr>
<td>CVS 30 days</td>
<td>27.05 ± 0.70</td>
<td>27.38 ± 0.65</td>
<td>27.48 ± 0.65</td>
<td>27.82 ± 0.65</td>
<td>27.83 ± 0.68</td>
</tr>
<tr>
<td>MPTP + CVS 30 days</td>
<td>28.08 ± 0.59</td>
<td>28.17 ± 0.53</td>
<td>28.23 ± 0.51</td>
<td>28.42 ± 0.54</td>
<td>28.52 ± 0.56</td>
</tr>
</tbody>
</table>

Table 1: Effect of caloric vestibular stimulation on MPTP treated mice in various Results are tabulated as mean ± SEM and P<0.05 was considered statistically significant. There is no statistical difference in the weight of the mice.

Effect of vestibular stimulation on Lipid Profile
Mice that were treated with MPTP showed an increase in the Total Cholesterol (TC), but the difference was not statistically significant as shown in Table 2. However, administering CVS has decreased the values as seen in the treatment group. No difference was seen in the group of mice that received only vestibular stimulation.

As shown in Table 2, there was a noticeable increase in the values of Triglycerides (TG) in the MPTP treated group when compared to the normal mice. CVS has reduced the values of TG in the treatment group, but the difference is not statistically significant. There was no significant effect of CVS on TGs in the CVS alone group.

The study suggested that HDL level in the MPTP treated mice was markedly lower than that of healthy controls. CVS has significantly increased the values of HDL in both the MPTP treated mice and CVS alone groups (Table 2). Both LDL and vLDL levels were significantly increased in the MPTP treated mice in the current study. CVS has significantly increased the values of both LDL and vLDL in mice administered with MPTP and in CVS alone group (Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>Total Cholesterol (mg/dL)</th>
<th>Triglyceride (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>LDL (mg/dL)</th>
<th>vLDL (mg/dL)</th>
<th>Atherogenic Index (AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal control</td>
<td>117.50 ± 3.85</td>
<td>80.83 ± 2.30</td>
<td>43.83 ± 1.92</td>
<td>20.17 ± 1.45</td>
<td>4.03 ± 0.29</td>
<td>0.27 ± 0.03</td>
</tr>
<tr>
<td>MPTP control</td>
<td>143.00 ± 10.40</td>
<td>113.33 ± 10.03**</td>
<td>24.17 ± 1.62***</td>
<td>30.50 ± 0.99**</td>
<td>6.10 ± 0.20**</td>
<td>0.67 ± 0.04***</td>
</tr>
<tr>
<td>CVS 30 days</td>
<td>115.83 ± 6.02</td>
<td>95.00 ± 5.03</td>
<td>42.00 ± 2.90##</td>
<td>22.67 ± 2.12#</td>
<td>4.53 ± 0.42#</td>
<td>0.36 ± 0.04###</td>
</tr>
<tr>
<td>MPTP + CVS 30 days</td>
<td>121.33 ± 6.04</td>
<td>95.17 ± 5.49</td>
<td>36.50 ± 2.17##</td>
<td>23.67 ± 1.93#</td>
<td>4.73 ± 0.39#</td>
<td>0.42 ± 0.04###</td>
</tr>
</tbody>
</table>

All the values are mean ± SEM (n = 6). **P<0.01 and ***P<0.001 compared with that of control; #P<0.05, ##P<0.01 and ###P<0.001 compared with that of PD control (One-way ANOVA followed by Tukey’s post-hoc test).

Discussion
In the present study MPTP was administered to the mice to induce Parkinson disease (PD). The serum total cholesterol level in the animal’s post MPTP administration was slightly decreased and the values improved...
post CVS intervention, however this change was not statistically significant. HDL was lowered and TG, LDL and vLDL values were increased in the animals that were given MPTP. The incidence of PD is second only to that of Alzheimer’s disease among middle-aged and older individuals (Z song). Blood lipids have emerged as a biochemical blood index in recent years, that may be associated with Parkinson’s disease in numerous clinical trials, but the results of these research are inconsistent (Garcia Sanz). Lipids can protect the nervous system. According to research HDL-C in lipids can actively contribute to the anti-inflammatory and antioxidant effects. The increased risk of neuronal degeneration is correlated with the decline in HDL-C levels (Hong X). The association of TC with PD is still controversial and inconclusive as some studies have shown that there is lower risk of PD with higher serum TC (Miyake Y) and some studies have shown otherwise (Hu). Lipid-lowering drugs are thought to offer therapeutic potential in PD because of their anti-inflammatory, antioxidant, and antiplatelet actions in animal or cell studies (Bar-On P). Numerous studies have also revealed that lipid-lowering medication use was somewhat beneficial in PD patients (Fu X). In our study, vestibular stimulation deceased the levels of serum TC, TG, LDL and vLDL and increased the levels of HDL. Neha et al in their study have showed that vestibular stimulation has significantly reduced the levels of serum TC, TG and LDL in pre-menstrual women (Sara MN). Antihyperlipidemic effect of vestibular stimulation was also proven by Neethu et al in their animal study (Sadanandan).

Conclusion
Vestibular stimulation was found to be effective in reducing the levels of serum cholesterol, Triglycerides and LDL and increased the levels of HDL. To investigate the relationship between lipid levels and PD severity or clinical progression, larger sample size studies are required. Effective intervention measures for cholesterol and its metabolites will have a significant clinical impact in delaying the onset of Parkinson’s disease, and vestibular stimulation may become a new therapeutic agent.

References


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