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Effect of caloric vestibular stimulation on brain neurotransmitters in an MPTP-induced mouse model of Parkinson's disease

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ABSTRACT

The Parkinson disease is a slowly progressive, degenerative disease of the nervous system associated with damage of dopaminergic neurons in the brain. Though PD was mainly due to damage of damage of dopaminergic system, other neurotransmitters also effected during PD and contribute to non-motor symptoms of PD. The current study was undertaken to observe the effect of caloric vestibular stimulation on brain neurotransmitters in an MPTP-induced mouse model of Parkinson's disease. 24 healthy, adult male Swiss albino mice with body weight ranging between 25 - 40g were used in the study. The middle ear cavity of the mice was irrigated with hot (40°C) water. 0.5 ml of water was taken in 5 ml syringe with the needle removed. The ear was irrigated with water drop by drop, using the syringe. After 30 days of the experimental period, the animals were fasted overnight and sacrificed by cervical decapitation and neurotransmitter levels were estimated. The present study provides evidence for beneficial effects of caloric vestibular stimulation in limiting the changes in neurotransmitter levels in Parkinson's disease. We recommend further detailed studies in this area to understand the mechanism of action and to recommend vestibular stimulation as adjunctive therapy in the management of Parkinson's disease.

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INTRODUCTION

The Parkinson disease is a slowly progressive, degenerative disease of the nervous system associated with damage of dopaminergic neurons in the brain. It was reported that in PD there would be an increase in the formation of Lewy's bodies which contributes to the damage of the nerve fibres (Shibeshi W *et al.,* 2006). It was reported that the prevalence of PD is 1-2 in every thousand people (Tysnes OB *et al.,* 2017). Though Levodopa was a well-accepted drug for the management of PD, still it has several side effects like an increase in the balance problems and also impairing cognitive functions (Hely MA *et al.,* 2004). These side effects have a strong negative impact on the overall quality of life of these PD subjects. Hence, there is a need for developing alternative therapies with minimum or no side effects. The vestibular system comprises of tiny receptors located in the inner ear mainly for the maintenance of equilibrium. In recent years multiple beneficial effects of vestibular stimulation have been explored and several studies and clinical trials are in progress. Vestibular system has wide connections throughout the brain and its stimulation was reported to affect multiple systems of the body and its stimulation was recommended throughout the life. It was reported that Disrupted interhemispheric connectivity is the major cause for most of the neurodegenerative disease including PD and followed by vestibular stimulation,

there was a significant increase in the interhemispheric connectivity in PD subjects (Soojin Lee, Kim D, McKeown MJ, 2017). Studies reported that there was a significant improvement in motor performance in PD subjects followed by vestibular stimulation (Soojin Lee *et al.,* 2015). Animal studies reported that the rotarod performance was improved followed by vestibular stimulation and this effect may be due to an increase in the release of Gamma Amino Butyric Acid in the brain. (Ghazaleh Samoudi *et al.,* 2012). Though PD was mainly due to damage of damage of dopaminergic system, other neurotransmitters also effected during PD and contribute to non-motor symptoms of PD. It was reported that the decline in the cognitive functions in the PD subjects is due to the loss of cholinergic neurons (Giorgio Rizzi and Kelly R, 2017). Interestingly, it was reported that cold water vestibular stimulation improved the release of acetylcholine from hippocampus in rats (Horii A *et al.,* 1994). Depression, fatigue and weight changes in PD are due to dysfunction of the serotonergic system (Marios Politisand Clare Loane, 2011). It was reported that there was an increase in the release of serotonin followed by vestibular stimulation in guinea pigs (Ma FR *et al.,* 2007). Abnormalities in the glutaminergic transmission also reported as a major contributor to the pathophysiology of PD (Blandini F *et al.,* 1996). As all these neurotransmitters have a pivot role in the PD, vestibular stimulation may have a beneficial effect in PD through altering these neurotransmitter levels. Hence, it is essential to observe the effect of stimulating the vestibular system on the brain neurotransmitters. The current study was undertaken to observe the effect of caloric vestibular stimulation on brain neurotransmitters in an MPTP-induced mouse model of Parkinson's disease.

MATERIALS AND METHODS

Animals: 24 healthy, adult male Swiss albino mice with body weight ranging between 25 - 40g were used in the study. Mice were housed under standard laboratory conditions with food and water provided ad libitum. All studies were conducted in accordance with the Indian National Science Academy guidelines as well as for data management and interpretation and all efforts were made to minimize the number of animals used and their suffering.

Mice were randomly assigned to four groups.

Group 1 (n=6): Control mice - no drug or intervention was given

Group 2 (n=6): PD mice - Parkinsonism was induced by administration of MPTP and no vestibular stimulation was given.

Group 3 (n=6): - PD induced + hot water vestibular stimulation for 30 days.

Group 4 (n=6): - PD induced + cold water vestibular stimulation for 30 days.

MATERIALS

MPTP administration: 15 mg/kg of MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) was dissolved in 0.9 % saline and administered i.p. Intraperitoneal injection. MPTP hydrochloride was purchased from Sigma Chemical Co (J.V Lewis *et al.,* 1995).

Estimation of brain neurotransmitters: After 30 days of the experimental period, the animals were fasted overnight and sacrificed by cervical decapitation. The brains were excised immediately and the brain tissue was homogenized in ice-cold butanol solution and used for estimation of biochemical parameters. All the test protocols were carried out between 10:00 am to 12:00 pm. Acetylcholine, dopamine, serotonin and GABA were estimated by using kits and purchased from Sigma Chemical Co.

Caloric vestibular stimulation: The middle ear cavity of the mice was irrigated with hot (40^{o}C) water. 0.5 ml of water was taken in 5 ml syringe with the needle removed. The ear was irrigated with water drop by drop, using the syringe. Gently the earlobe of mice was shaken. The procedure was continued with the other ear (Seth S. Horowitz *et al.,* 2004).

Study setting: The present study was conducted at Little Flower Medical Research Centre, Angamaly, Kerala, India.

Ethical consideration: The study was approved by the institutional animal ethical committee of Little Flower Hospital and Research Centre, Angamaly, Kerala, India.

Data analysis: Data was analyzed by using SPSS 20.0 version. One-way ANOVA followed by Tukey HSD post hoc test was applied to observe the significance of the difference between the groups. A p-value less than 0.05 was considered as significant.

Results: Table 1 presents the estimation of the brain neurotransmitters in the experimental animals followed by hot and cold-water vestibular stimulation**.** There was a significant decrease($P<0.001$) in the acetylcholine levels in only MPTP group. This decrease was limited effectively by cold water vestibular stimulation. There was a significant decrease in the dopamine levels in only MPTP group. This decrease was limited significantly ($P<0.001$) by both hot and cold-water vestibular stimulation. There was a significant decrease in serotonin levels in only MPTP group ($P<0.01$). This decrease in the serotonin levels was

Table 1: Estimation of brain neurotransmitters

Groups	Control group	Only MPTP group	MPTP+hot water stimulation group	MPTP + cold water stimulation group	F value
ACH (mole/minute/mg tissue)	0.192± 0.0014	0.16±0.0052	0.125±0.0020	0.144±0.0031	453.36
Dopamine (ng/g tissue)	0.187±0.0018	0.108±0.0024	0.131±0.0019	0.136±0.0040	930.86
Serotonin (ng/g tissue)	0.141±0.0014	0.117±0.0007	0.124±0.0058	0.129±0.0021	60.59
GABA (ng/g tissue)	0.193±0.0013	0.129±0.0010	0.146±0.0035	0.143±0.0024	898.45

(ACH- Acetylcholine, GABA-Gamma Amino Butyric Acid) (Data presented are in Mean± SEM)

limited by both hot and cold-water vestibular stimulation. However, it was not statistically significant. A significant decrease in the glutamate levels was observed in only the MPTP group. Both hot and cold-water vestibular stimulation significantly ($P<0.05$) limited the surplus of glutamate. A significant decrease in the GABA levels was observed in only the MPTP group. Both hot ($P<0.001$) and cold water ($P<0.05$) vestibular stimulation significantly limited the surplus of glutamate.

DISCUSSION

Although Parkinson's disease was considered as a progressive neurodegenerative disease due to damage of the dopaminergic system, the non-motor symptoms of the PD subjects are also important to be considered. These symptoms include depression, fatigue, hallucinations, cognitive disorders like dementia, olfactory dysfunction, pain and disorders of the gastrointestinal tract like constipation. These non-motor functions together with motor symptoms will decrease the overall quality of life (Barone P, 2010). Hence, the therapeutic targets should concentrate not only alleviating the motor but also the non-motor symptoms with minimum or no side effects. One such adjunctive therapy is vestibular stimulation. Though this system was primarily considered for maintenance of posture and equilibrium, it affects almost all systems of the body through its wide connectivity with all the brain structures. Due to this wide variety of functions, the vestibular system was accepted as sixth sense (Alexandra Reichenbach *et al.,* 2016). Degeneration of dopaminergic system is the major cause for the motor symptoms of PD (Vernier P *et al.,* 2004). There was a decrease in the GABA levels in the cerebrospinal fluid in PD subjects (RJ Abbott *et al.,* 1982). Stochastic vestibular stimulation was reported to increase GABA levels without altering the dopamine levels in substantial nigra and striatum (Ghazaleh Samoudi *et al.,* 2012). In the present study, we have observed that vestibular stimulation effectively limited changes in the dopamine and GABA levels.

Several studies reported a loss of the cholinergic neurons in PD and this loss is as prominent as observed in Alzheimer's disease (Nakano I and Hirano A, 1984; Rogers JD *et al.,* 1985; Tagliavini F *et al.,* 1984). Hot water caloric vestibular stimulation with 45 degrees centigrade and with ice water caloric vestibular stimulation was reported to increase the release of acetylcholine release from the hippocampus. This increase in the release of acetylcholine was independent of the histaminergic system (Aratahorii *et al.,* 1994). This increase in the acetylcholine levels from the spot hippocampal cells facilitate the long-term potentiation and helps to enhance memory (Siew Kian Tai and L.Stan Leung, 2012). Further vestibular stimulation also increases the acetylcholine concentration by decreasing the levels of acetylcholine esterase enzyme (Devi N P, Mukkadan J K, 2016). Our study results are in accordance with earlier studies as we have observed that vestibular stimulation effectively limited the decrease in acetylcholine levels. Recent studies reported that serotonin also has a role in PD (Fox SH *et al.,* 2009). The decrease in the serotonin release in PD reported causing visual hallucinations (Benedicte Ballanger *et al.,* 2010). Vestibular stimulation was reported to increase the release of serotonin from the dorsal raphe nucleus (Mickle *et al.,* 1953). In the present study, we have observed that vestibular stimulation effectively limited the changes in serotonin levels.

CONCLUSION

The present study provides evidence for beneficial effects of caloric vestibular stimulation in limiting the changes in neurotransmitter levels in Parkinson's disease. We recommend further detailed studies in this area to understand the mechanism of action and to recommend vestibular stimulation as adjunctive therapy in the management of Parkinson's disease.

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