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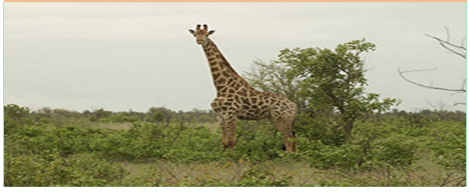

Vol. 10 (3), pp. 1, December, 2022

Studies in animal models of parkinson's disease

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Received: 02-Dec-2022, Manuscript No. GJAEB-22-84783; **Editor assigned:** 05-Dec-2022-PreQC No. GJAEB-22-84783 (PQ); **Reviewed:** 20-Dec-2022, QC No. GJAEB-22-84783; **Revised:** 26-Dec-2022, Manuscript No. GJAEB-22-84783 (R); **Published:** 03-Jan-2023, DOI: 10.15651/GJAEB.23.10.013

DESCRIPTION

Parkinson's Disease (PD) is characterised by loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) region of the brain. PD symptoms, majority being motor incoordination, result from severe loss of Dopamine (DA) levels in nucleus caudate-putamen, commonly referred to as the striatum. Supplementation of DA by the administration of its precursor L-3,4-dihydroxyphenylalanine, direct activation of dopamine receptor by agonists, or augmentation of the remaining dopaminergic neurotransmission through inhibition of dopamine degrading enzymes are the most popular choices of therapies for the disease. However, with time these treatments lose their efficacy and patients develop fluctuations in motor functions, on-off phenomena and dyskinesias. These limitations have encouraged a search for unconventional treatment paradigms, especially cell transplantation strategies, with an idea to restore or replace dopaminergic neurons in the brain.

In animal experiments it is well documented that cells transplanted into the brain regions can survive to establish connections with the host cells, however the advancement in research in the area is clearly too preliminary to take it towards clinical practice. The approach requires further standardization of neuronal differentiation protocols and a lot more information on recovery following transplant of pure differentiated or differentiating neurons or a mixed population of neural cells, the graft survivability, chemical environment within and around the graft, cell-to-cell interaction within the graft, and so on. Major problems envisaged are poor availability of pure, DA rich autologous cultures, lack of standardized cell culture techniques that refrain from cross species contamination, consistency in the quality of cells generated, and above all unavailability of a rich source of cells that can be differentiated into DA-rgic neurons. Moreover, the transplantation outcome and the the degree of symptomatic relief in clinical trials have been controversial.

Studies, including clinical trials, performed using embryonic Ventral Mesencephalic (VM) tissue, showed considerable symptomatic recovery and survival of grafted cells and extensive re-innervation into the host tissue. But ethical concerns of using aborted foetus and the limited supply of tissue are certain problems associated with the use of VM tissue. Embryonic Stem Cells (ESC), neural stem cells and human umbilical cord blood derived mesenchymal stem cells are other sources that can generate DA neurons, and their easy availability makes them a good resource for transplantation therapy. There are several studies that show the generation of neurons from ESC.

CONCLUSION

These are grown and maintained on a feeder layer of mouse embryonic fibroblasts in a medium containing foetal bovine/calf serum, which may lead to unexpected viral infection and cross-species contamination. Thus, for human therapeutic applications, ESC must be grown in a safe synthetic medium without factors or cells from other animals. Owing to the above mentioned reasons we have used ESC as the donor cells and differentiated them under serum free condition, in a synthetic medium and without any exogenous factors by the process of default neurogenesis. These were characterized for their neural progenitor status, ability to differentiate into midbrain DA-rgic neurons and the mixed population of cells transplanted into the striatum of a rotenone-induced hemiparkinsonian rat model. The present study describes the characteristics of the differentiated neurons and the host response to achieve transplantation recovery and the molecular biomarkers that help in the process. Animals were intracranially infused with rotenone (MP Biomedicals) to create hemiparkinsonian rat models.