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Review Article

# Stem Cell Therapy in Parkinson's disease

**Vivek Sharma*[1], Arcahna Kashyap[1], Sapna Sharma[1], Dheeraj Kaushik[2]**

[1]Govt. College of Pharmacy, Rohru Distt. Shimla -171207 Himachal Pradesh, India

[2]Govt. Polytechnic Rohru Distt Shimla -171207 Himachal Pradesh, India

*Corresponding author: viveksharma_pharma@yahoo.co.in

**ABSTRACT**

Stem cells are undeveloped cells without mature, tissue-specific characteristics that are able to proliferate, to reproduce themselves and to produce generations of progenitor cells, which can differentiate into one or more specialized cell types. India is an emerging player in the stem cell arena. The research and therapeutic applications of stem cell has been growing rapidly in recent years and scientists have for years looked for ways to use stem cells to replace cells and tissues that are damaged or diseased. Stem cells have shown great promise in treatment of debilitating diseases like heart diseases, liver diseases, stroke, spinal injuries, Parkinson's disease, Alzheimer's disease, retinal degeneration, muscular dystrophy, diabetes mellitus, osteoarthritis and rheumatoid arthritis. Parkinson's disease (PD) is a chronic neurodegenerative disorder characterized by tremors, rigidity, and hypokinesia. The main pathology underlying disease symptoms in PD is a rather selective degeneration of nigrostriatal neurons leading to severe loss of dopamine (DA) in the striatum. At present, drug treatments and surgery cannot fundamentally solve the problem. With the development of cell replacement therapy, medical professionals are exploring treatment by restoration of dopamine neurotransmitters in the neural circuitry of patients with PD by getting dopaminergic neurons and cell transplantation. The clinical studies with intrastriatal transplants of fetal mesencephalic tissue in PD patients have provided proof-of-principle for the cell replacement strategy in this disorder. The grafted dopaminergic neurons can reinnervate the denervated striatum, restore regulated dopamine (DA) release and movement-related frontal cortical activation, and give rise to significant symptomatic relief.

**Keywords:** Parkinson's disease, Dopamine, Stem cell

## 1. INTRODUCTION

Parkinson's disease is the second most common neurodegenerative disorder affecting more than 1% of all individuals over the age of fifty years with a lifetime risk of 2% for men and 1.3% for women.

Due to increasing life expectancy and a higher prevalence of neurodegenerative and neurovascular pathologies in the elderly population, these disorders are of great concern for our society in the future and there is need for the development of new, adequate treatment options.

Parkinson's disease is a degenerative disorder of the central nervous system [1] that affects movement, muscle control and balance. The disease was named after James Parkinson, the English physician who first described it in 1817. This disease is associated with the reduced production of dopamine (an important neurotransmitter) by the brain [2].

Parkinson's disease is referred in the ancient Indian medical system of ayurveda under name kampavata and in western medical literature it was described by the physician Galen as shaking palsy in AD [3]. In the 1940s and 1950s, neurosurgeons began to perform surgery on the basal ganglia of the brain that resulted in improvements in Parkinson's disease symptoms. While this surgery was effective, it was risky, with about 12 percent of patients dying as a result of the operation. The biggest advancement in Parkinson's treatment came in the 1960s, when researchers identified differences in the brains of people with Parkinson's disease that were associated with low levels of dopamine, a brain chemical that allows for smooth, coordinated movement [4].

Parkinson (1755-1824) observed the classic symptoms of Parkinson's disease in three of his patients and in his essay; he gave a clear descriptions of some of the main symptoms of Parkinson's disease: tremors, rigidity, and postural instability. He theorized that the disease developed because of a problem in the medulla of the brain. Charcot and his colleagues distinguished the disease from other neurological conditions and termed it "Parkinson's disease"[4] Public awareness campaigns include Parkinson's disease day (on the birthday of James Parkinson, April 11) and the use of a red tulip as the symbol of the disease. People with Parkinsonism who have enhanced the public's awareness include Michael J. Fox and Muhammad Ali [5].

Tremor (4 and 6 hertz), Rigidity (increased muscle tone), Bradykinesia, akinesia, Posture disturbances, camptocormia, dystonia, speech, sialloroea, seborrhea, swallowing disturbances, hypophonia, Drooling, Hypomimia, Micrographia, Akathisia are the common problems associated with PD [6].

Parkinson's disease is associated with a gradual loss of cells in the substantia nigra, which produces dopamine. Dopamine is a chemical messenger that transmits a signal between two regions of the brain, the substantia nigra (a black substance) and the corpus striatum to regulate muscle activity. Etiology of this degeneration is endogenous radicals generated by hydrogen peroxide [7]. Toxic α,β-unsaturated aldehydes which could react with reduced glutathione (GSH) or metabolic compounds of the catecholamine metabolism such as 5-S-cysteinyldopamine and 6-hydroxydopamine could all potentially trigger Parkinson's disease [8].This disease is mainly idiopathic (having no specific known cause) but a small proportion of cases can be attributed to genetic factors [9].

## 2. EXISTING THERAPY

While these are some effective treatments for patients with PD but treatment strategies are mainly symptomatic and aimed at increasing dopamine levels in the degenerating nigrostriatal system. Existing drugs are limited in their relief and decrease in effectiveness as PD progresses. Nevertheless, these treatments do not halt the progressive nature of PD and are ineffective against gait freezing and postural instability, which are more disabling than tremors and rigidity. Further, as PD progresses, drug-induced motor complications, such as "wearing off" and dyskinesia appear and notes that PD dementia is not responsive to dopaminergic therapy and is considered the most important factor influencing the daily activities and survival of Parkinson's patients.

The main families of drugs useful for treating motor symptoms are levodopa (usually combined with a dopa decarboxylase inhibitor or COMT inhibitor), dopamine agonists and MAO-B inhibitors [10]. The most logical approach to correcting this problem is to replace the dopamine (DA). It cannot be taken orally as it does not cross the blood brain barrier (BBB). L-dopa therapy is the gold standard treatment for Parkinson's disease. L-dopa is a naturally occurring substance. It is in the chemical family of compounds known as amino acids. Amino acids are the building blocks of proteins. Its absorption can be reduced if taken with a high protein meal. Once absorbed, L-dopa is converted to DA in the blood, liver and kidneys. A compound called carbidopa is given with L-dopa. Carbidopa inhibits the enzyme in the liver, kidneys, and blood that converts L-dopa to DA. This allows more L-dopa to pass into the brain [11]. Carbidopa and benserazide are peripheral dopa decarboxylase inhibitors, which help to prevent the metabolism of L-DOPA before it reaches the dopaminergic neurons, therefore reducing side effects and increasing bioavailability. Levodopa has been related to dopamine dysregulation syndrome, which is a compulsive overuse of the medication, and punding [12].

Tolcapone inhibits the COMT enzyme, which degrades dopamine, thereby prolonging the effects of levodopa. It has been used to complement levodopa; however, its usefulness is limited due to its side effects such as liver damage [13].

Dopamine agonists were first introduced in the 1970s. Dopamine agonists have the capacity to directly stimulate brain dopamine receptors. The first generation of dopamine agonists were all ergot derivatives, including bromocryptine, cabergoline, dihydroergocriptine, lisuride,and pergolide., Also the non ergot agonist is apomorphine which is a potent mixed D1-type and D2- type dopamine agonist receptor agonist with L-dopa-like antiparkinsonian effects [14]. Most of the currently used nonergot dopamine agonists include pramipexole, ropinirole, rotigotine, and piribedil. Rotigotine is available as a once-daily transdermal patch formulation [15] while apomorphine is used as subcutaneous infusion treatment for patients with refractory response oscillations or as rescue medication for sudden unpredictable off periods [16].

Selegiline and rasagiline are both irreversible inhibitors of MAO-B producing dopaminergic effects. They inhibit monoamine oxidase-B (MAO-B) which breaks down dopamine secreted by the dopaminergic neurons. The reduction in MAO-B activity results in increased L-DOPA in the striatum. Selegiline is metabolized to methamphetamine and to a lesser extent, to amphetamine [17] which blocks dopamine reuptake and releases dopamine and may account for some of the dopaminergic effects. Rasagiline even highly potent and does not give rise to amphetamine like metabolites, but degrades to aminoindan and selegeline, rasagiline and aminoindan have neuroprotective properties [18].

Other drugs such as amantadine and anticholinergics may be useful as treatment of motor symptoms. Amantadine's exact mechanism of action remains uncertain, its NMDA receptor–blocking activity is generally believed to play a major role in producing its anti parkinsonian effects [19].

In the 1860s Ordenstein and Charcot were the first to treat (PD) by using extracts from Hyscyamus niger, Atropa belladonna, and Datura stramonium. With the development of synthetic anticholinergic drugs, they were the gold standard for treating PD in the 1940s [20].

## 3. DRAWBACKS OF THERAPIES

Dopamine precursor: Sedation and daytime sleepiness is common and occasionally dose limiting side effect of L-dopa. In addition, L-dopa is known to trigger a variety of psychiatric symptoms, including illusions, hallucinations, and paranoid

psychosis [21]. Rarely, high-dose L-dopa treatment particularly in patients with young-onset PD may cause behavioral changes (dopamine dysregulation syndrome) [22]. Affected patients may perform continuous, purposeless, non-goal-oriented repetitive behaviors, frequently related to a patients' habits or interests and hobbies, gambling, hypersexuality, or binge eating are rare with L-dopa monotherapy [23].

Dopamine agonist: The use of dopamine agonists has increased due to their effectiveness in treating symptoms of Parkinson disease (PD) but serious adverse effects have been linked to DA agonists, including sudden somnolence, cardiac valvulopathy and repetitive behaviors [24].

In 1999, Frucht and colleagues reported "sleep attacks" in eight patients taking pramipexole and one taking ropinorole. All nine patients fell asleep while driving, resulting in accidents. These episodes of sleep were sudden, irresistible and occurred without warning. All occurred after patients began taking a DA agonist and ceased once the medication [25] Ergot DA agonists causing fibrotic degeneration of cardiac valves. [26].

Other Side effects of these dopamine agonists include gastrointestinal upset, nausea, vomiting, light-headedness when standing, and nasal congestion.

MAO B inhibitors**:** Transient hypertensive episodes within 2 hours after ingestion of MAO inhibitors, which were independent of dietary or drug interactions, have been reported. Dose-related orthostatic hypotension was reported (occurring in 9.8% vs 6.7% with placebo) and was most likely to occur in elderly patients [27].

Serotonin syndrome has been reported with MAO inhibitor monotherapy in rare cases. Serotonin syndrome is characterized by mental status changes, restlessness, myoclonus, hyperreflexia and diaphoresis [28]. The most common adverse events with the selegiline patch include application-site reaction, headache, insomnia, diarrhea, dry mouth, and dyspepsia.

Anticholinergics: Side effects are tachycardia, prostate hypertrophy, gastrointestinal obstruction, and megacolon. They may cause blurred vision, urinary retention, nausea, constipation, and reduced sweating may interfere with temperature regulation and central anticholinergic activity impairs short-term memory and may interfere with mental function so that the use of anticholinergics is contraindicated in patients with cognitive decline and dementia impairs short-term memory and may interfere with mental function [29].

## 4. STEM CELL THERAPY IN PARKINSON'S DISEASE

Stem cells are defined as immature cells with a capacity of self-renewal and, depending on their origin, can differentiate into specialized cell types or retain the potential to differentiate into any somatic cell, including DA-ergic neurons [30]. The use of cell-based therapy is based on two different strategies; exogenous and endogenous.

The former approach involves the introduction of a population of cells (i.e. *via* transplantation) into the diseased brain in order to replace lost cells and to support the remaining cells (cell replacement). The latter approach, triggers brain repair through enhancing the proliferation, differentiation and migration of host endogenous stem cells (endogenous regeneration). There are a large variety of stem cells including embryonic stem cells (ESC), fetal neural stem cells (fetal NSC), adult stem cells (ASC) and induced pluripotent stem cells which have shown promise in the treatment of PD.

Cell replacement in the treatment of PD is a viable option for the following reasons: 1) PD is a disease that mainly involves the selective destruction of a specific cell population, 2) nigrostriatal DAergic neurons primarily modulate striatal function and provide tonic stimulation of target receptors, (3) downstream basal ganglia neurons are relatively preserved [31].

Hence, the application of stem cells in PD has the potential for the replacement of lost DA-ergic neurons within the SNc, the reversal of DA deficit in the striatum and the subsequent restoration of brain function [32]. The presence of proliferating stem cells in the adult brain has raised suggestions that the generation of new neurons (neurogenesis) may occur postnatally and thus can potentially be targeted to induce endogenous brain repair.

## 5. STEM CELLS AS A SOURCE OF DOPAMINERGIC NEURONS FOR CELL-REPLACEMENT

There are two key properties that define a stem cell: self-renewal, which is the ability to undergo numerous cycles of cell division while maintaining the undifferentiated state; and potency, its differentiation potential. On this basis, stem cells can be broadly classified as being totipotent, pluripotent or multipotent. Totipotent stem cells can only be isolated from the early developing embryo (i.e. the morula) and can differentiate into any cell type within the body, including extra-embryonic tissue. Similarly to totipotent stem cells, pluripotent stem cells are also capable of differentiating into any cell type so they are able to give rise to cells from any of the three major tissue lineages: the ectoderm, mesoderm and endoderm. Pluripotent stem cells are found in the blastocyst of the embryo, but unlike totipotent cells, these have already begun the differentiation process. Multipotent stem cells are typically lineage restricted meaning they can only differentiate into the 140 select cell types from which they are derived and can be isolated from numerous tissue sources within the adult human body [33].

## 6. FIBROBLASTS USE IN PD

Fibroblast growth factor (bFGF) enhances the survival and growth of dopaminergic neurons in vitro whether cells genetically modified to produce bFGF would improve the functional efficacy of dopaminergic neurons implanted into rats with experimental Parkinson's disease [34]. Moreover, rats implanted with such co-grafts display the most pronounced behavioral improvements post-grafting, and also enhancing the survival and function of dopamine neurons grafted into the damaged brain [35].

Fibroblast growth factor-20 (FGF-20) has been shown to protect dopaminergic neurons against a range of toxic insults in vitro, through activation of fibroblast growth factor receptor 1 (FGFR1 FGF-20 also displayed protective efficacy in the unilateral, 6-hydroxydopamine (6-OHDA) lesion rat model of Parkinson's disease. infusion of FGF-20 (2.5 μg/day) for 6 days post-lesion gave significant protection (~40%) against the loss of TH-positive cells in the SNpc and the loss of striatal TH immunoreactivity [36].

## 7. EMBROYNIC STEM CELL

Embryonic stem (ES) cells are clonal cell lines derived from the inner cell mass of developing blastocysts [37]. The distinguishing features of these cells are their capacities to renew themselves and to differentiate into a broad spectrum of derivatives of all three embryonic germ layers: ectoderm, mesoderm, and endoderm [38]. The differentiation of mouse ES cells into dopaminergic neurons and its [39] ability to develop into dopaminergic neurons is therapeutic strategies in the treatment of PD, such as cell transplantation and tissue regeneration [40]. ESCs are pluripotent and are highly proliferative, having the greatest potential to be used in the clinical setting in PD as they can give rise to any type of cell in the body including DA-ergic neurons [41] therapeutic potential of ESCs by transplanting undifferentiated mouse ESCs into the striatum of experimentally 6-hydroxydopamine (6-OHDA)-induced parkinsonian rats. The ESCs were able to give rise to DA-ergic neurons that were able to fully integrate into the lesioned brain and mediate hemodynamic changes in the striatum and associated brain circuitry [42].

### 7.1. Fetal Neural stem cell

NSCs that can be harvested from the embryo around embryonic day (E) 14 – E15 in rodents [43] or 13 weeks post-fertilization in humans [44] are multipotent cells that have the ability to regenerate and also to give rise to neurons, oligodendrocytes and astrocytes that represent the three major cell lineages of the CNS. Undifferentiated human fetal NSCs transplanted into the SNc of a MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine)-induced primate model of PD were able to survive, integrate and subsequently reduce some behavioral deficits [45]. Fetal NSCs can readily differentiate into DA-ergic neurons, having the low yield (1-5%) of generated DA-ergic neurons [46], Hence, it seems that when compared to ESCs, fetal NSCs are not advantageous when it comes to production of DAergic neurons due to a much-reduced proliferative potential. This reduced proliferative capacity means that fetal NSCs are associated with a lower risk of tumor formation [47]. The first in vitro assessments of mouse fetal NSCs has revealed that NSC proliferation can be induced using fibroblast growth factor-2 (FGF-2) [48], and epidermal growth factor (EGF) [49], while retaining the ability to differentiate into CNS progeny. This has led to successful transplantation studies in PD rat models as demonstrated by a greater yield of rat fetal NSC-derived DA-ergic neurons and significant recovery from motor deficits [50, 51] Other substances such as cytokines (i.e. interleukin-1β and interleukin-11) [52], and glial neurotrophic factors (GDNF) (i.e. neurturin; NTN) [53] may also be able to modulate and increase NSC differentiation towards a DA-ergic phenotype.

### 7.2. Mesenchymal stem cell

Mesenchymal stem cells are a great therapeutic cell source. Transplantation of embryonic mesencephalic cells into the striatum of PD patients was initiated in the 1980s [54]. MSCs are adult stem cells that belong to the mesodermal lineage and are traditionally found in the bone marrow as bone marrow mesenchymal stem cells (BMSCs) [55]. MSCs can also be isolated from other mesenchymal tissues, such as umbilical cord, dermis, adipose tissue, and peripheral blood, [56]. MSCs have long thin cell bodies with a large nucleus similar to fibroblasts. MSCs have a high capacity for self-renewal while maintaining multipotency [57]. MSCs can be obtained from patients (for auto cell transplantation) as well as from healthy donors (for allo-transplantation).

MSCs are multipotent stem cells that are known to differentiate into osteocytes, chondrocytes, and adipocytes. These differentiations are within the same mesodermal lineage, but recent reports demonstrated that MSCs show unorthodox differentiation into ectodermal and endodermal cells [58]. Cells genetically modified to produce L-DOPA or neurotrophic factors such as neurotrophins and glial cell line-derived neurotrophic factor (GDNF) are effective for the amelioration of PD symptoms [59], MSCs induced into immature neurons using basic fibroblast growth factor (bFGF), epidermal growth factor, platelet-derived growth factor, sonic hedgehog, FGF-8, GDNF, or the reagents butylated hydroxyanisole and dibutyryl cAMP were transplanted into a PD model, but these immature neurons did not effectively ameliorate the PD symptoms [60]**.** The umbilical cord and adipose tissues are other realistic sources of MSCs. Mesenchymal tissues of the umbilical cord, so-called Wharton's jelly, as well as fat tissues, contain an abundance of

MSCs. Adipose tissue, which is easily obtained from liposuction, also contains large amounts of MSCs called adipose-derived stem cells (ADSCs) [61].

## 8. CONCLUSION

The present article reviews current therapies used in treatment of Parkinson's disease with a special emphasis on their contraindicative manifestations and possibility of stem cells as a potential therapeutic target in treatment of the same. Although the work reviewed so far presents a positive picture of stem cell use in PD however they are associated with several adverse effects (tumor formation etc). This warrants further extensive research efforts to make their use safe and free of life threatening complications.

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