PARKINSON’S DISEASE, ITS IMPLICATION AND TREATMENT WITH SPECIAL REFERENCE TO LIVER X RECEPTOR: A REVIEW

Rajnish Srivastava*, Deepa, Amit Kumar Srivastava, Piush Khare, Hemant Nagar,
Truba Institute of Pharmacy, Affiliated to Rajiv Gandhi Prodyogiki Vishwavidhyalaya,
Karond Gandhinagar Bypass - Bhopal (Madhya Pradesh) – 462038

ABSTRACT
Parkinson's disease is a chronic, degenerative neurological disorder that affects more than five million peoples worldwide. The risk of developing the disease increases with age. Sustained microglia over activation and resulting neuroinflammation is believed to play important role in the mechanism of chronic dopaminergic neuronal loss in Parkinson’s disease. The disease is characterized by skeletal muscle hypertonic and hyperkinetic impairment. The main objective for the effective treatment of Parkinson’s disease is to increase and replenish the dopaminergic activity of the brain. So, therapy consist use of drugs that either increase synaptic concentration of dopamine and dopamine release or inhibit its degradation. A new therapeutic target for the treatment of Parkinson’s disease has been identified.

Liver X receptors (LXR-α, LXR-β) are ligand-dependent nuclear receptors which are targeted for ventral midbrain neurogenesis in vivo. Cholic acid and 24 (S), 25-epoxycholestrol (24-25 EC) are the two types where the latter was found to be the mostpotent in the developing mouse midbrain whereas both ligands promoted neural development in an LXR dependent manner in Zebrafish in vivo. Notably, each ligand selectively regulated the development of distinct midbrain neuronal populations. Whereas cholic acid has increases survival and neurogenesis of Brn3a positive red nucleus neurons, while 24-25 EC promoted dopaminergic neurogenesis. Moreover, 24-25 EC promoted dopaminergic differentiation of embryonic stem cells, suggesting that LXR ligands may contribute to the development of cell replacement and regenerative therapies for Parkinson's. Administration of the LXR agonist GW3965 to MPTP-treated wild type, mice protected against dopaminergic loss in neurons along with the fibers projecting to the striatum. Hence a novel strategy can be designedwherein the drug viz.
dopamine can be loaded in brain targeted carrier system which is loaded or coupled to LXr ligand which will act in dual way for management of Parkinsonism.

**KEY WORDS:** Parkinson’s disease, Neuroinflammation, Neurogenesis, Microglia, LXr-α, LXr-β, Cholic acid and 24(S), 25-epoxycholestrol (24-25 EC)

**INTRODUCTION**

Parkinson’s disease is an extra pyramidal, slowly progressive, motor neurodegenerative disorder. It is a consequence due to the degeneration of neurons especially in the region of the brain that controls movement. This result in imbalancement of a neurotransmitter called dopamine, therefore causing impaired motor response. If untreated the symptoms progress over several years to end-stage disease in which the patient is unable to move, unable to breath properly and succumbs mostly to chest infections and embolism. In most of the cases it is generally seen as first symptoms later in life, i.e. 40 years or older. Parkinson’s disease is sometimes called primary Parkinsonism or idiopathic Parkinson's disease so that to differentiate it from other forms of Parkinsonism. It is a common accelerative bradykinetic disorder that can be easily diagnosed. It is characterized by the presence of severe loss in the motor region of pars-compacta cell and aggravation of α-synuclein in specific brain stem, spinal cord, and cortical regions.

**Historical background**

James Parkinson entitled this disease as "Shaking Palsy", and characterizes the patient as involuntary tremors and weak muscles even in resting condition or when supported. The patient is even unable to walk in a normal pace and nosologist does not recognize the disorder. The father of neurology ‘Jean Martin Charcot’ proposed the syndrome as *maladie de Parkinson* (Parkinson’s disease). The cause remains as mysterious as when it was first described in 1817, but important genetic and pathological clues have recently been found.

**Fig.1. Substantia nigra region of mid brain**
Symptoms
The symptoms of Parkinson’s disease possess a range and severity between different individuals and that can progress at different rates throughout the disease process. In most of the cases, the first symptom seen is a one sided tremor, shaking, in a limb although the body is in resting posture/condition. Early symptoms are typically mild but progress gradually.

Major symptoms
There are four symptoms that the majority of patients experience.

Rigidity
Stiffness or freezing in case when a patient is tried to move an arm, neck, or the leg is moved. The muscles remains extensively tensed and contracted, meanwhile the person feels weak and lacking grace or pace.

Resting tremor
A condition when the person is at resting condition and muscles are relax for example when the hands are placed on the laps or hanging next to trunk. This mostly affects fingers or hand and is also provoke under stressful condition. In about 60-70% of cases, the effect of tremor affects only one body part or half of the body initially, but becomes more severe over time.

Bradykinesia
It is characterize by inability or slowness in initiating a movement. The contributory faults include decreased facial movement, shuffling gait, change in speech and problems with fine-fingered movements. Many patients feel drastic frustration which is the most challenging aspect of the disease. The patient is even feels difficulty and unable to carry out basic functions of everyday life, such as writing, getting dressed, using utensils for eating and serving, and leaving from chairs or bed.

Postural reflexes impairment
or posture instability consists of inability to balance the whole body with conditional coordination. Patients sometimes take a backward or forward lean to balance and fall easily which is characterize by the stooped appearance with mild hip and knee flexion, bowed head and rounding of the shoulders.
Secondary symptoms
Anxiety, stress, tension, constipation, difficulty in swallowing, insomnia, slow blinking, low blood pressure when getting up, sweating and lack of body temperature control.

Fig.2. Illustration of the slightly anxious frozen face and characteristic flexed posture of a Parkinson’s disease patient

Etiology
Idiopathic Parkinsonism
In 70-80% of cases the physician is unable to diagnose the exact cause of PD, often known as idiopathic Parkinsonism. It have been found that about 15% of cases were have a relation with the occurrence of disease, involvement of single gene mutations in genes like Alpha-synuclein non A4 component of amyloid precursor (SNCA), Leucine-rich repeat kinase
2 (LRRK2), Parkin RBR E3 ubiquitin protein ligase (PARKIN), Parkinson protein 7 (DJ-1), PTEN induced putative kinase 1 (PINK1) and Htra serine peptidase 2 (HTRA2) genes etc. have been linked to mitochondrial dysfunction, which results in impaired function of the electron transport chain (ETC), oxidative stress with increased susceptibility of excitotoxicity in substantia nigra and frontal cortex cells. Accumulation of damaged synuclein proteins and apoptosis is also triggered.

SCNA

Mutations in the SNCA gene have been linked to one of the way of familial inheritance that involved autosomal dominancy with the presence of lewy bodies, as primary pathological mechanism/symptoms of the disease. The SCNA gene expresses as alpha-synuclein, which is a constituent of lewy bodies. However there is an associative relationship exist between over expression of alpha-synuclein and mitochondrial dysfunction, which associates with abnormal mitochondria, damaged mitochondrial DNA, increased cytochrome c release, and increased free radical production.

LRRK2

LRRK2 gene damage serves 5-7% of cases with a familial history and is the most common known cause for idiopathic Parkinsonism; autosomal dominant is the one of the most common mutation of this gene and results in impaired activity of kinase and results in altered function of the outermost membrane of mitochondria. LRRK2 autosomal dominancy positive patient experiences middle to late disease onset.

PARKIN and DJ-1

Parkin gene expresses as mitochondrial biogenesis and mitochondrial DNA replication; so mutations in such cases become consequences for abnormal mitochondria, elevated oxidative stress, and more prone to oxidative stress. The DJ-1 gene is primarily responsible for protecting cells from death related to oxidative-stress. DJ-1 gene mutations in mice have showed increase susceptibility to oxidative stress in cortical neurons at embryonic stage with degeneration of dopaminergic neurons. However DJ-1 gene absence has been related with a down-regulation (decreased cellular genetic material) of the particular receptor for glial cell line-derived neurotrophic factor (GDNF), which provides survival, development and functional support to the developing dopaminergic neurons.
PINK 1
As compared to parkin and DJ-1 genes the PINK1 gene has also been correlated with an autosomal recessive form of PD but is much rarer. The gene encodes for a protein called kinase and functions to reduced the release of chromosome c and counteract the apoptosis. The impaired genetic consequences due to this gene are same as in case of parkin gene with respect to mitochondria.

HTRA2
A mutation of the HTRA2 gene in individuals with PD is very rare but in case of homozygous knockout mice via striatal degeneration, the mutation in HTRA2 is associated with the increase in risk for development of the disease. The consequences of mutations of this gene include increased mitochondrial volume with impaired electrochemical changes in the mitochondrial membrane, with augmented probability of risk of cell death related to an ATP kinase inhibitor staurosporine. It is also thought that mutations to the PINK1 gene is associated with negative influence HTRA2 function.

Table 1. Genes associated to L-dopa responsive Parkinsonism

<table>
<thead>
<tr>
<th>Pathological aggregates</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td>Parkin</td>
<td>Substantia nigra degeneration but usually no lewy bodies</td>
</tr>
<tr>
<td>Pink 1</td>
<td>No pathology report</td>
</tr>
<tr>
<td>DJ-1</td>
<td>No pathology report</td>
</tr>
<tr>
<td>ATP13A2</td>
<td>No pathology report</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td>α-Syneuclin</td>
<td>Lewy bodies</td>
</tr>
<tr>
<td>LRRK-2</td>
<td>Usually lewy bodies</td>
</tr>
<tr>
<td>GBA</td>
<td>Lewy bodies</td>
</tr>
</tbody>
</table>

GBA- Glucocerebrosidase, LRRK2- Leucine rich repeat kinase 2, PINK1- PTEN induced putative kinase1

Secondary Parkinsonism
Secondary Parkinsonism is defined as “A group of disorders with identifiable causes that are associated with basal ganglia functional abnormalities along with symptoms similar to Parkinson’s. Underlying causes like metabolic causes (hypothyroidism, hyperparathyroidism,
Wilson’s disease) viruses, drugs, toxins, tumours in basal ganglia, hydrocephalus, and vascular disease etc. are some predisposition factors associated with secondary Parkinsonism.

**Environmental Factors**

Epidemiological studies have demonstrated that the following environmental factors are positively correlated with the risk of developing PD.

**Exposure to pesticide (Rotenone and Paraquat)**

According to the report of NIEHS (National Institute of Environmental Health Sciences) it have been reported that rotenone and paraquat directly inhibits the mitochondrial function. People who get expose with these pesticide likely to develop disease 2.5 times more than the non exposed population. Another study suggested that the patient with Paraquat exposure lacking a certain metabolic enzyme called GSTT1. Contact with certain industrial chemicals Trichloroethylene, manganese, carbon disulphide, carbon monoxide, cyanide, methanol, exposure to wood preservatives and exposure to MPTP. It was thought that most of these environmental factors are associated with the mitochondrial dysfunction.

**Hemeoxygenase**

Hemeoxygenase 1 (HO-1) and hemeoxygenase 2 (HO-2) are normally occurring enzymes that can be induced by oxidative stress and other noxious stimuli. Although present in many tissues, HO-1 is normally present in the brain at very low levels compared to HO-2. These enzymes facilitate the degradation of heme proteins (responsible for oxygen transport in red blood cells, among other functions), producing biliverdin, bilirubin, and low levels of carbon monoxide (CO).

At low levels, CO is neuroprotective*, and biliverdin and bilirubin have strong antioxidant properties. But free iron, which is also generated, combines with naturally occurring hydrogen peroxide to generate the highly reactive hydroxyl radical and is therefore a source of oxidative stress.

This system is generally thought to have protective effects by increasing the antioxidant capacity of cells. Recent data suggest, however, that chronic overproduction of HO-1 may actually increase rather than decrease oxidative stress by generating excessive iron. HO-1 and iron are present in the substantia nigra at higher levels in people with Parkinson’s disease than in controls. HO-1 is also present at higher levels in the hippocampus of people with Alzheimer’s disease compared to controls.
*High levels of CO exposure as may be caused by CO poisoning from an outside source may cause brain damage and symptoms of Parkinsonism. Brain imaging studies after CO poisoning show widespread damage of white matter and the basal ganglia.

Fig.3. Hemeoxygenase system

Some neuroscientists propose that the hemeoxygenase system, which normally has a neuroprotective function, may under certain circumstances, actually increase oxidative stress and cell death by generating excessive amounts of free iron, a powerful oxidant (Greater Boston Physicians for Social Responsibility and Science and Environmental Health Network).

Drug-induced Parkinsonism (DIP)

The drug-induced Parkinsonism (DIP) is the subsequent most common type of Parkinsonism in the elderly and is mostly misdiagnosed as PD. The drugs which are the most common involved as predisposition include:

Table 2. Examples of drugs typically induced PD

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Category/Classification</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Typical antipsychotic agents</td>
<td>Flupentixol, Chlorpromazine, Sulpiride, Promazine, Benperidol, Trifluoperazine, Pimozide, Haloperidol, Fluphenazine</td>
</tr>
<tr>
<td>2</td>
<td>Calcium channel blockers</td>
<td>Flunarizine, Cinnarizine</td>
</tr>
<tr>
<td>3</td>
<td>Antiemetic agents</td>
<td>Prochlorperazine, Metoclopramide</td>
</tr>
<tr>
<td>4</td>
<td>*Atypical antipsychotic agents</td>
<td>Risperidone, Olanzapine</td>
</tr>
<tr>
<td>5</td>
<td>Antihypertensive agents</td>
<td>Reserpine, α-methyldopa</td>
</tr>
<tr>
<td>6</td>
<td>Central Monoamine-Depleting Agents</td>
<td>Tetrabenazine</td>
</tr>
</tbody>
</table>

*At higher dose*

These drugs interfere with either pre or postsynaptic dopaminergic mechanisms which may include its selective presynaptic reuptake, its premature degradation and receptor
desensitization. Nearly 80% of patients develop extra pyramidal symptoms when exposed to typical antipsychotic agents (neuroleptics) and nearly 25% develop exact DIP and its symptoms can most often reversed within a month on termination of the responsible underlying medication. The efficacy and tolerability of antipsychotic drugs has been linked to their binding to dopamine D2 receptors. Positron emission tomography (PET) studies have indicated that the therapeutic effects of antipsychotics are achieved at a blockade of 60-70% of dopamine receptors and that DIP appears when blockade of dopamine receptors is more than 80%. A greater affinity of conventional antipsychotics for dopamine D2 receptors may account for their increased risk of DIP. Elderly people are prone to antipsychotic induced Parkinsonism. Guidelines recommend the use of low doses of antipsychotics in elderly patients and physicians follow these recommendations in daily practice. However, potential mechanisms underlying the influence of age on antipsychotic (adverse) effects are not clear.

![Fig.4. Principle underlying drug induced Parkinson’s Disease Progression](image)

**Disease Progression**

Parkinsons progresses at a different rate although everyone is different in their signs and symptoms and patient may experience the motor impairment symptoms with varying
intensity at each stage. The progression of the disease symptoms may take 20 years or more but the rate of progression varies from patient to patient. The *Hoehn and Yahr Stage scale* is the most commonly used scale/scoring system by the doctors which gives an idea to the patients and physician about how far the disease has progressed so as to decide the implementation of the optimised individualised therapy.

**Fig.5. The Hoehn and Yahr Stage scale**

**Pathophysiology**

**Genetics**

Until last few decades no. of research scientists believed that environmental factors was the only whole and sole cause for PD, but investigations like gene mutations in familial, or inherited or autosomal forms of PD has led to a global exposure in the research of neurobiology and the impaired function of the altered proteins that are encoded by these genes. Most people do not inherit PD, but the genes that are responsible for the sporadic form
of PD can help investigators to understand both inherited and non-hereditary cases of the disease. It has been found that the genes and proteins that are responsible to cause inherited form of PD is same as in case of non-inherited form but environmental toxins or other factors are also act as supporting risk factors for this.

**Alpha-synuclein**
Alpha-synuclein was the first gene exposed to have a concrete relationship to Parkinson’s disease. Various studies about the genetic profiles of sporadic and non-sporadic cases was done and found that the neuro histopathology of the disease was somewhat correlated to impaired protein disposal system of cells due to mutation in alpha-synuclein. These studies favour the role of alpha synuclein, which is responsible in the formation of Lewy bodies (clumps of alpha-synuclein proteins). These finding revealed a potential link between non sporadic and sporadic forms of the disease so that investigator could understand about the bio-molecular and histopathological differences between the typical functioning of alpha-synuclein and its debilitated effects due to mutations in alpha-synuclein during normal course of cellular activity. It was later found that during normal course of cellular activity interior in cell body, all the individual molecules of alpha-synuclein protein gets converted into spiral and coiled structure together and forms small protein fibers called fibrils; by the process is called fibrillization. But the mutated alpha-synuclein gene impairs this fibrillization process and leads to the accumulation as protofibrils, a transitional process during alpha-synuclein fibrillization. The structure of Proto fibrils resembles as bacterial and insect toxins and makes membranes leaky and causes cell death. The normal housekeeping functioning of the cells are being damaged by the mutated alpha synuclein induced impaired fibrillization .The consequences of this type of impairment results in amassment of proteins up to toxicity levels.

![Image](image.png)

**Fig.6.** Light microscopy surviving neuron in the substantia nigra of a patient, the neuron consist of Lewy bodies
In normal protein disposal system the alpha-synuclein is battered by lysosomal activity. However, mutant alpha-synuclein, blocks the lysosomal battering of alpha synuclein as well as other proteins and ‘garbage’ due to toxic buildup of protein takes place. In postmortem report of brain tissue of diffuse Lewy body disease patient the presence of alpha-synuclein in a close vicinity of cell membrane was reported  it have been concluded that it may due to the clogging up the protein disposal system of neurons and cause to die.

**Fig.7. Summary of Pathophysiological processes believed to be central to PD**

**Pathways to Parkinson’s disease**

No. of research have been going on to understand the complexities at cellular level as well as protein interactions leading to PD. Cellular factors that have been implicated which include immune factors, mitochondrial interactions, oxidative stress, apoptosis (programmed cell death), excitotoxicity, ubiquitin-proteasome protein degradation system (UPDS) and protein aggregation. These factors represent many different implications of research in the field of neuroscience, to understand how these implications may collectively link together to form clear picture of how the disease progression takes place.

**Mitochondria, Oxidative Stress, and Programmed Cell Death**

For many years, mitochondria, the powerhouse of the cell, have been strongly implicated in the development of disease. Mitochondria have their own DNA called mtDNA. This DNA is different from the genes that are found in the nucleus of cell. Most of the researchers found
that abnormalities in complex I (group of proteins), the largest and most efficient energy processing component of mitochondria manifested in PD. Mitochondria are major source of free radicals for the cell itself that damage their own components such as damage to biomolecules e.g. DNA protein and fats due to free radical via the process referred as oxidative stress.

Mitochondria also play a key role in protein battering, Lewy body construction, neuron cell toxicity and death. Toxins, including MPTP and rotenone, dysfunction the mitochondrial complex I and it produce increased number of free radicals that can tweak alpha synuclein such that it aggregate or forms clump together to form microfibers, called fibrils. Studies suggested that mitochondria specifically straitial neurons are more susceptible to complex I impairment due to the specific genetic polymorphisms in mtDNA which increases the risk of getting Parkinson, while other type of mtDNA variations favors lower risk. An another implication suggested that in response to oxidative stress and mitochondrial toxins, mitochondria also trigger apoptosis by the activation of caspases viz. releasing a substance called cytochrome c that activates these caspases and other cell death factors. Collectively, oxidative stress and mitochondrial induced apoptosis are the governing and definitive factors to the neuronal loss which provides possible targets to develop treatment strategy.

**Fig.8. Common pathways underlying PD pathogenesis**
Protein Degradation (Ubiquitin Proteasome System - UPS)

Ubiquitin Proteasome System (UPS) is a cell’s natural protein disposal system. Researchers believe that in case of failure of this disposal system tends to increase the probability of toxins build up and other substances up to harmful toxic levels inside the cells, leading to cell cytotoxicity. In the UPS, ubiquitin which acts as regulatory protein as a tagging component targets certain proteins for degradation by the one of the major intracellular device called proteasomes, as well as recycling of unnecessary proteins. Proteasomes action primarily deals with endogenous proteins like cyclins, proteins encoded by viruses and other pathogens. Several proteins including parkin and UCH-L1 interact between each other in the UPS. The interruption in the UPS pathway may supports the underlying mechanism through which mutations in these genes occurs and causes Parkinson.

Studies have suggested that UCH-L1 gene is involved in the production of ubiquitin and the normal proteosomal function gets affected due to mutation in the parkin gene. Exposure to certain toxin that inhibits the UPS causes mutation in alpha-synuclein which is susceptible to apoptosis and is proceeds by activation of death domains called caspases accompanied by mitochondrial damage. The releases of factors that activate caspases are prevented by Cyclosporine- A thus inhibits apoptosis. The consequences of Proteasome inhibition result in accumulation of molecules such as Bax, NFKB and p53, which are the contributing factors and help to promote apoptosis.

Excitotoxicity

Excitotoxicity is the hyperdepolarization of neuron that leads to cell death. In excitotoxicity, the brain becomes over sensitized for specially glutamate, which causes hyper activity of brain. However dopamine acts as both excitatory and inhibitory type neurotransmitter depending upon the type of receptor present. In this case the deficiency of DA causes hyperactivity of sub-thalamic neurons, which may lead to excitotoxic damage there. Studies have shown that the in case of excitotoxicity in Parkinson, parkin may play defensive role. In the histopathology of DA neurons in PD patients, it have been found that a degradative protein called cyclin E gets accumulated in those neurons that are get exposed to excitotoxicity and causes the degradation of neurons. But as defensive role, the cyclin E is effectively tagged by parkin which effectively degraded it and thus prevents the neurons from being degradation by cyclin E. In contrast, the mutated form of parkin was unable to trigger the degradation of cyclin E thus neuron cells are getting dying.
In a particular research it have been found that in case of kainite induced over stimulated dopaminergic neuron, the increased amount of parkin abate the cyclin E function and thus prevent the neuronal cells from dying.

**CMA: Chaperone Mediated Autophagy**

Fig.9. Summary of Scheme illustrating genetic and environmental factors involved in alpha-synuclein (α-SYN) toxicity and possible therapeutic targets

**Neuroinflammation**

The neuroinflammation in PD patients involves over activation of specialized immune supportive cells microglia in the brain that produce signaling non antibody proteins called cytokines. In spite of inflammation, that can be damage, but studies have shown that activating immune cells can protect nerve cells in vivo. In the PD patients the level of inflammatory enzyme COX-2 is higher in dopaminergic neurons as compared to non PD patients. The scientists also found an elevated level of COX-2 in a mouse model with PD. Administration of Rofecoxib (COX-2 inhibitors) inhibits COX-2, and also increases the number of neurons that survived. However the drug does not reduced neuroinflammation but instead, may protect neurons by preventing oxidative stress.
Current Treatments
Medicinal therapy
Dopamine replacement therapy:
L-dopa was discovered 50 years ago in 1960, after James Parkinson in 1817 when describe about the disease and still considered to be a milestone as replacement therapy as ‘Old is Gold’. Due to its effective lipophilicity it crosses BBB and gets converted into dopamine and replenishes the deficiency locally to improve motor disability. L-dopa is generally administered or prescribed in combination with carbidopa, as carbidopa (Atamet) delays the peripheral conversion of L-dopa into dopamine and reaches the brain in L-dopa form as it is. Thus prevents some of the peripheral side effects of L-dopa and thus improves the midbrain deficiency of dopamine.

Dopamine Agonist:
The drugs of this class do not convert into dopamine instead these drugs mimic the effect of dopamine by binding to the same receptor. Bromocriptine, pergolide, pramipexole, and ropinirole etc. closely resembles the role as of dopamine in the midbrain. Dopamine agonists directly stimulate the DA receptor that normally being stimulated by dopamine. Overall, dopamine agonists can improve motor functioning when used alone in early PD and also have a benefit in postponing the L-dopa therapy. Pramiprexole and ropinirole are considered to be the newer agonist of this class and are better tolerated. The rotigotine transdermal system (Neupro Patch) uses a different delivery system to get the dopamine agonist into the body.

MAO-B inhibitors
Monoamine oxidase is a class of enzyme that breaks down certain neurotransmitters including dopamine. Monoamine oxidase inhibitors are the class of drug that blocks the enzyme and prevents the dopamine degradation so the dopamine is well available in the brain thus leading to fewer motor symptoms. Selegiline (Eldepryl, Zelapar) and rasagiline are few examples when given with L-dopa, seems to potentiate the action by enhancing and prolonging the response of L-dopa.

Other drugs
COMT inhibitors would never be given alone as does not plays any direct role in treatment of PD but is preferred in combination with L-dopa thus preventing breaking down of L-dopa and directs more and more of the dopamine to reach directly to the brain. It has been found that in PD the level of cholinergic neurotransmitter increases and cause extrapyramidal
symptoms (EPS) so anticholinergics also play an important role in effective management of symptoms by controlling tremor and rigidity.

Table 3. Medications that induced PD

<table>
<thead>
<tr>
<th>Sl no.</th>
<th>Drugs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antidepressants</td>
<td>Mood disorders</td>
</tr>
<tr>
<td>2</td>
<td>Gabapentin, Duloxetine</td>
<td>Pain relief</td>
</tr>
<tr>
<td>3</td>
<td>Fludrocortisone, Midodrine, Botox, Sildenafil</td>
<td>Autonomic dysfunction</td>
</tr>
<tr>
<td>4</td>
<td>Armodafinil, Clonazepam, Zolpidem</td>
<td>Sleep disorders</td>
</tr>
</tbody>
</table>

Surgery

Surgery is not performed since the discovery of L-dopa. These surgeries do not cure Parkinson's, but may help ease symptoms.

Cryothalamotomy

This method includes insertion of a super cooled metal probe to destroy the thalamus area of the forebrain that is responsible in producing tremors.

Pallidotomy

As the name suggest the destruction of the globus pallidus, thus may relief tremor, rigidity, and bradykinesia, by interrupting the neuronal pathway that relays impulses between the globus pallidus and the corpus striatum or thalamus.

Deep brain stimulation (DBS)

Surgical treatments for PD were used to selectively destroy small portions of the brain that are associated to produce tremor and rigidity. But these procedures often led to irreversible side effects.
One surgical treatment for PD is called deep brain stimulation (DBS). DBS can be performed on either one side (unilateral) or both sides of the body (bilateral). In bilateral DBS, electrodes are implanted in the sub-thalamic nucleus or the globus pallidus of the brain. Insulated wires are then passed under the skin of the head, neck, and shoulder to connect the electrodes to battery-operated neuro-stimulators that are implanted under the skin, usually near the collar bones. Impulses from the neuro-stimulators interfere with and block the brain signals that cause PD symptoms.

**Drawbacks**

Costly and sophisticated these surgeries do not cure Parkinson's, but may cause irreversible neurological complications.

**Research Approaches to Parkinson’s treatment**

**Stem Cell Transplantation**

Stem cell transplantation is one of the recent therapeutic approaches for the effecting replacement and repairing of the damaged neurons that cause PD. Stem cells are considered to be renewable source of tissue that can be transformed to become cell types of different types of the body. Researchers believed that stem cell research has a great potential scope to develop a disease modifying approaches for the treatment of PD. The major barrier of this approach is the current lack of effective and progressive pharmacological screening model for screening of any proposed design of stem cell treatment for PD. Pharmacological cell models for PD generated from stem cells could help the investigators to screen out the best approach more efficiently than the currently used animal models.

**Fetal stem cells**

During clinical trials for, globally hundreds of patients transplanted with fetal cells and it have been found in Positron emission technology (PET) scans that the transplanted fetal stem cell (neurons) shows some grow and functional changes that somewhat reduced the severity of symptoms. But, for ethical use it is not the best long-term source for this purpose. So the investigators are transforming the fetal stem cells to adult neural stem cells and embryonic stem cells as iPSCs (Induced Pluripotent Stem Cells).

**Endogenous stem cells**

Endogenous stem cell transplantation involves the transplantation of the patients own (endogenous) adult neural stem cells that are located in the patient’s own brain specially in
white matter that can multiply and differentiated to form all the major brain cells including DA neurons. In vivo preclinical studies in rodents shows that although adult neural stem cells have a great capacity to multiply at its home site in brain but still shows limitation in their ability to differentiate into DA neurons. So genetic reprogramming may be essential to overcome this limitation.

**Embryonic stem cells**

Embryonic stem cells possess a capacity to grow and differentiated into all other cells types in the body. So embryonic stem cell transplants are very promising to promote its transplantation, but fail due to two main challenges that interferes the translation in results of clinical trials. The first is that, embryonic stem cells may carry the risk of developing tumors. The second is that after many years, some of the transplanted dopamine neurons may fail in the disease and thus end up its contribution to the disease for making it better.

**Neural stem cells**

As the use of embryonic stem cells may inherent genetic consequences so to avoid this best way is to replace its use by neural stem cells. However the regeneration of the neural stem cell is GDNF (Glial cell line-derived neurotrophic factor) dependent manner that helps the cells survival and growth. So the right combination of growth factors and other signaling molecules are to be available to favors the stem cells cultivation to a point at which it could then be implanted in the brain where they are have to becoming dopamine neurons.

**Induced pluripotent stem cells**

Induces pluripotent stem cells (iPCs) was discovered in 2007 and was the recent milestone in the field of stem cell research to treat PD. The main objective of this approach is to create subject specific cells lines in which the adult cells have been genetically reprogrammed to embryonic stem cell like state and force to express genes and factors in a target and functional specific manner to maintaining the targeted properties. This technology has also been implemented in a same manner to construct induced motor neurons (iMNs), creating induced DA neurons in treating patients with PD.

**Gene Therapy**

It has been great to design such an engineered virus that is able to deliver enzymes important for the production of levodopa. Scientists do hard to perform experiments to deliver the gene for 1-amino acid decarboxylase (AADC) that converts levodopa into dopamine. Researchers
also are experimenting to deliver the glial cell derived neurotrophic factor (GDNF) gene to the brain which prevented dopamine neurons from dying, and the primates also regained some of their lost motor ability and skills.

**Trans cranial Magnetic Stimulation**

Trans cranial magnetic stimulation (TMS) is a technique which involves a course of low frequency of magnetic stimulation in repeated form. An insulated wire coil placed on the scalp to create a magnetic pulse that stimulates the supplementary motor area of the brain which improves motor symptoms and also able to produce promising effects on gait and freezing postural defects. The effects of the repeated TMS last for about 3 months after treatment. Clinical studies on rTMS might have beneficial effects for people with PD and improves the patient’s condition.

**Receptor targeting based strategies:**

**Liver x receptor β (LXrβ)**

**Location and Function:**

The liver X receptor β (Nuclear receptor subfamily 1, group H, member 2) was first discovered in 1995 and was found near the surrounding microglia that function as an active immune defense and plays essential role in the survival of DA neurons. Recently, investigators reported that this receptor shows promising role as a potential therapeutic target to treat Parkinson’s disease, as well as other neurological disorders. LXr β is not expressed in the dopamine-producing DA neurons, but only in the microglia which surrounds the neurons. Microglia is the immune cells of the brain, that keeping things in order to maintain homeostasis for the dopaminergic neurons. In Parkinson’s disease, sustained microglial over activation and resulting neuroinflammation is believed to play an important role in the mechanism of chronic dopaminergic neuronal loss in Parkinson’s disease. LXr β prevents and calm down the microglia and prevents neuronal damage.

**Potential link between LXr β and Parkinson’s disease**

In evidence to, LXr β promotes the survival of dopaminergic neurons in brain tissues. The investigators used a genetically engineered mouse lacking the gene responsible for the expression for this receptor. The engineered mice (LXr negative) and wild type mice (LXr positive) were then subjected to the neurotoxic drug MPTP (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) that damages the brain in such a manner that closely mimic the damage in PD. Results revealed that the dopamine-producing neurons of the substantia nigra of the LXr
negative mice were much more severely damaged by MPTP as compared to those of the LXr positive controls. The activated Microglia and astrocytes cells were also found in excess population in the substantia nigra of the LXr negative than in the controls.

**Agonists**

**Cholic acid and 24 (S), 25-epoxycholestrol (24-25 EC)** are the two potent LXr agonists recently design and was found to be the most potent LXr β ligand in the midbrain of developing mouse whereas in case of zebrafish both ligands supported the neural development in an LXr dependent manner. Each ligand selectively regulated the development of the neurons of distinct midbrain region. However cholic acid increased survival chances and neurogenesis in red nucleus area of Brn3a (POU domain containing transcription factor for the development of sensory nervous system) positive neurons and 24-25 EC promoted neurogenesis of stratal regions. Moreover, 24-25 EC synergize dopaminergic differentiation of embryonic stem cells, revels that LXr ligands may thus commit to the development of cell replacement and regenerative therapies for PD. Another LXr agonist GW3965 when administration to MPTP-treated WT mice found to be protective against loss of dopaminergic neurons. The possibility generated from the above findings suggested that LXr could be the effective targets to deliver L-dopa in a carrier mediated system.

**Table 4. Brain targeting strategies**

<table>
<thead>
<tr>
<th>NEUROSURGICAL</th>
<th>PHARMACOLOGIC</th>
<th>PHYSIOLOGIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BBB destruction</td>
<td>1. Liposomes</td>
<td>1. Pseudonutrients</td>
</tr>
<tr>
<td>2. Intraventricular infusion</td>
<td>2. Chemical delivery</td>
<td>2. Chimeric peptides</td>
</tr>
</tbody>
</table>

**Fig. 10. Proposed design for the effective treatment and management of the PD**
CONCLUSION
Parkinsonism has been a dreaded disease and causes responsible for the same have been unclear. Different treatment strategies have been proposed but these suffer due to one or other owes advantages. Moreover these have been directed towards management of the disease rather than complete cure. Lots of research have is being focused on the development of newer treatment /therapeutic options against the disease. LXr β receptors are newer addition to the enormous research being applied for the same delivery of LXr- β agonists along with the dopamine to brain holds great potential in this regard strategies viz. carrier mediated delivery of both entities hold great promise against Parkinsonism.

REFERENCES


