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Novel therapies in the treatment of Parkinson's disease

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Abstract

Although various effective treatments for Parkinson's disease are available, novel therapies targeting the different pathways that lead to cell dysfunction and death are still required. Some of these pathways that have been implicated so far include mitochondrial dysfunction, oxidative stress, kinase pathways, calcium dysregulation, inflammation, protein handling and prion-like processes. Safinamide, currently in phase III clinical trials for the treatment of PD, is a unique molecule with multiple mechanisms of action and a very high therapeutic index. It combines potent, selective, and reversible inhibition of MAO-B with blockade of voltage-dependent Na^+ and Ca^{2+} channels and inhibition of glutamate release. Several of these proposed newer agents have innovative mechanisms of action (increase mitochondrial biogenesis; reduce apoptosis, upregulation of heat shock proteins, increase endosomal release and uptake of α synuclein by recipient cells.) Finally, surgical-based approaches such as deep brain stimulation, neuroablative procedures such as thalamotomy and pallidotomy and neural transplantation are other potential treatments. However, technical improvements in these procedures are required to address procedural safety concerns.

Keywords: Parkinson's disease, mitochondrial biogenesis, apoptosis, heat shock proteins

1. Introduction

In 1817 James Parkinson first published and described the clinical features of Parkinson's disease. (PD) [1] He provided a visual and detailed description of symptoms and discussed progressive worsening of the disorder. PD is a leading cause of neurological disability and it is the second most common progressive neurodegenerative disorder with an age adjusted incidence of 13.5-13.9 per 1,00,000 person years and an age related prevalence of roughly 115 per 1,00,000 population. The frequency of the disorder is about 1.3 cases per 1,00,000 people younger than 45 years of age, 3100 per 1,00,000 in those aged 75-85 years and 4300 per 1,00,000 in those older than 85 years.[2] It has no gender preference and has a worldwide distribution. [3]

2. Patho physiology [4]

The main cause of the PD is unknown, but it is well characterized. The degeneration of brain cell occurs primarily in the midbrain region area called as substantia nigra. Normally, substantia nigra brain cells communicate with another region of the brain called as the striatum via chemical messenger called dopamine. The loss of cells in the substantia nigra results in decrease in the levels of available dopamine. The pathological changes seen are:

1) Degeneration of darkly pigmented dopaminergic neurons in the substantia nigra
2) Loss of dopamine in the neostriatum
3) Presence of intracellular inclusion bodies known as Lewy bodies.

A small subset of patients has familial form of PD with an autosomal dominant pattern of inheritance. Genetic mutations in at least 3 proteins have been identified so far. These genes encode for alpha synuclein and carboxy terminal hydroxylase of parkin and ubiquitin.

Several important advances have been made in our understanding of the pathways that lead to cell dysfunction and death in PD. Some of these pathways that have been implicated so far include mitochondrial dysfunction, oxidative stress, kinase pathways, calcium dysregulation, inflammation, protein handling and prion-like processes. [2]

Mitochondrial dysfunction and oxidative stress: Evidence suggests that defects of the respiratory chain (complex I), increased accumulation of mitochondrial DNA mutations, abnormal mitochondrial calcium homeostasis, defective autophagic removal of mitochondria (mitophagy) and increased oxidative stress are all involved in the pathogenesis of

Parkinson's disease. [5] Mutations in parkin and PINK1 genes reduce turnover of mitochondria and of respiratory chain proteins. The accumulation of damaged respiratory chain proteins or mitochondria may contribute to the bioenergetics defects in neurodegenerative diseases. [6] Treatments that enhance the removal of defective mitochondria could potentially improve or restore neuronal function. [7]

Calcium handling: Calcium homeostasis, receptor activity, and calcium evoked oxidative stress are recognized as potential contributors to the pathogenesis of Parkinson's disease and potential targets for therapeutic intervention.[8] L type Ca channels (Ca(v)1.3) generate mitochondrial mediated oxidative stress during autonomous activity which in turn induces mitochondrial uncoupling as a protective mechanism.[9]

Changes in protein handling: Unwanted proteins are usually cleared from the cell by the ubiquitin proteosome or autophagy lysosomal systems and defects in these pathways are identified in patients of Parkinson's disease. [10]

Alpha synuclein is the primary protein that accumulates in Parkinson's disease and mutations in this protein are associated with the familial forms of the disease.

α synuclein toxicity is thought to be related to protein accumulation with misfolding and formation of toxic oligomers.[11]

A vicious cycle could exist consisting of formation of toxic oligomers, fibrils and aggregates; secondary inhibition of ubiquitin proteosome and lysosomal systems by α synuclein aggregates, further protein accumulation and ultimately cell death.

Clinical overview: Parkinsonism is a clinical syndrome consisting of four cardinal features:

- Bradykinesia (slowness and poverty of movement),
- Rigidity,
- Pill rolling tremors (which usually abates during voluntary movement),
- An impairment of postural balance leading to disturbances of gait (shuffling gait) and falling.[12]

Others features of the disease being akathisia, sialorrhea, masked facies etc. [3] Cognitive decline occurs in many patients as the disease advances.

2.Pharmacotherapy:

3.1: Existing therapies for treatment of Parkinson's disease include

i) **Dopamine enhancing drugs**:

1. Dopamine precursor: Levodopa
2. Peripheral decarboxylase inhibitors: Carbidopa, Benserazide;
3. MAOI: Selegiline, Rasagiline;
4. COMT Inhibitors: Entcapone, Tolcapone ;
5. Dopaminergic agonists: Bromocriptine, Ropinirole, Pramipexole;
6. Dopamine facilitator: Amantadine.

ii) **Anticholinergics**: Trihexyphenidyl, Procyclidine, Biperiden

After thirty years of use, levodopa still remains the mainstay of treatment for PD. Unfortunately it doesn't slow disease progression and long term complications. All the above existing therapies provide benefit for dopaminergic features of the disease. [3]

3.2 Novel therapeutic targets:

1. Adenosine receptor antagonists: Istradefylline, Preladenant, Tozedelant

Adenosine A2A receptors are selectively located in GABAergic cell bodies and terminals of indirect striatopallidial pathway. Adenosine is functionally linked to D2 receptors & enhances GABA release in external globus pallidus which contributes to over activity of indirect pathway; which is the underlying mechanism of PD. Adenosine antagonist improve symptoms by acting on indirect pathway ;allowing D 1 mediated direct pathway.

Istradefylline (KW-6002), an analogue of caffeine and a selective antagonist at he A_{2A} receptor has been investigated in clinical trials for about a decade. It reduces dyskinesia resulting from long-term treatment with classical antiparkinsonian drugs such as levodopa. Levodopa works by boosting levels of dopamine, a key chemical messenger, in the brain. But for many people, PD symptoms return in between doses, when levodopa's effects wear off. This fluctuation in the drug's effectiveness is known as "off" time.

Several clinical trials have tested whether adding istradefylline to dopamine therapy can even out motor fluctuations and lessen "off" time. One such being a study conducted in Japan, which adds new evidence to istradefylline, stating that this drug that has been investigated but not approved in the US due to mixed results on its effectiveness, can reduce "off" time in people with PD who are taking levodopa therapy. In 2008, the US Food and Drug Administration issued a "not approvable" letter to the drug's Japanese developer. [13,14]

Glutamate release inhibitors (Safinamide, Zonisamide): Safinamide, currently in phase III clinical trials for the treatment of PD, is a unique molecule with multiple mechanisms of action and a very high therapeutic index. It combines potent, selective, and reversible inhibition of MAO-B with blockade of voltage-dependent Na+ and Ca2+ channels and inhibition of glutamate release. Safinamide potentiates levodopa-mediated increase of DA levels in DA-depleted mice and reverses the waning motor response after prolonged levodopa treatment in 6-OHDA-lesioned rats. Safinamide has excellent bioavailability, linear kinetics, and is suitable for once-a-day administration. Therefore, it may be used in PD to reduce l-dopa dosage and it also represents a valuable therapeutic drug to test disease modifying potential. [15]

Recent studies have provided data suggesting that **Zonisamide** has an efficacy in treating motor and nonmotor symptoms in patients with PD. The pharmacological mechanisms underlying the beneficial effects of zonisamide in PD are unclear and both dopaminergic and nondopaminergic mechanisms seem to be involved. The potential mechanisms are:

Enhancement of dopamine release: Therapeutic doses increase intracellular and extracellular dopamine in the rat striatum while supratherapeutic doses reduce intracellular dopamine. This effect is not observed in rats with 6-hydroxydopamine-induced denervation of dopaminergic fibers except when zonisamide is administered with L-DOPA and a dopa decarboxylase inhibitor.

Blockade of T-type calcium channels: The pattern of neuronal activity in basal nuclei neurons in PD patients and MPTP (1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine) monkeys changes to a bursting discharge pattern. This activity could be reduced by the blockage of T-type calcium channels and inhibition of glutamate release, one of the mechanisms of action of zonisamide. However, the effects of modulating T-type calcium channels on PD symptoms are unknown and more studies are warranted.

Inhibition of MAO-B: MAO-B inhibitors such as rasagiline and selegiline are well known treatments in PD and zonisamide does inhibit MAO-B. However the potency of this activity is unknown. In the study conducted by Murata *et al*. [2007], it was effective even in the group of patients who were on a sufficient dose of selegiline, suggesting that the inhibition of MAO-B is not the principal mechanism of action to improve parkinsonian symptoms.

Neuroprotection: There has been a growing interest in the use of antiepileptic drugs for neuroprotection. Established antiepileptic drugs such as phenytoin, phenobarbital and carbamazepine, have shown neuroprotective activity in an ischemic/ hypoxic model of neuronal injury. Animal model studies also have suggested that newer antiepileptic drugs such as levetiracetam, topiramate and zonisamide, may have not only antiepileptigenic but also neuroprotective properties. Since neurodegeneration seems to be present in PD, zonisamide neuroprotective properties could have a role in the progression of the disease. [16]

3. Other drugs targeting the potential defective pathways

3.1. Mitochondrial dysfunction and oxidative stress:

Increase in neuronal mitochondrial content could compensate for bioenergetics defects in neurodegeneration. Peroxisome proliferator – activated receptor gamma (PPAR-γ) coactivator 1α (PGC-1α) is an important regulator of mitochondrial function and acts with SIRT1 to upregulate mitochondrial biogenesis.[5] PPAR-γ activators including resveratrol and drugs already used in the treatment of diabetes (e.g. Rosiglitazone, pioglitazone, and troglitazone) substantially increase mitochondrial biogenesis. [17] Resveratrol and bezafibrate , another PGC-1α agonist, have been protective against 6-hydroxydopamine in animal models of dopamine depletion.[18] Another target of interest in this area is the glucagon like peptide 1 (GLP-1) which originates in the L cells of the intestine and the longer half life GLP-1 peptide exenatide (EX-4) which are used in the treatment of type II Diabetes.GLP-1 and EX-4 promote cellular growth, increase mitochondrial biogenesis, reduce apoptosis and might be anti-inflammatory although the precise mode(s) of action remain uncertain. [19]

Thus treatments that enhance the removal of defective mitochondria could potentially improve or restore neuronal function.

2.2. Calcium handling:

As mentioned earlier, L type Ca channels (Ca (v) 1.3) generate mitochondrial mediated oxidative stress during autonomous activity which in turn induces mitochondrial uncoupling as a protective mechanism. Thus selective L type Ca channel (Ca (v) 1.3) inhibitors have recently been developed and offer a new approach to disease modification in Parkinson's disease. [20]

3.3 Changes in protein handling

Since defective ubiquitin proteosome pathway or autophagy lysosomal systems are identified in patients of Parkinson's disease, gene delivery of defective or missing ubiquitin proteosome or lysosomal components and drugs such as glucocorticoids that help the clearance of abnormal proteins and prevent the cascade of continuing protein accumulation and cell death are other approaches that are currently being tried.

α synuclein toxicity is thought to be related to protein accumulation with misfolding and formation of toxic oligomers. Heat shock proteins promote refolding of misfolded proteins and act as chaperones to transfer unwanted proteins to the ubiquitin proteasome and autophagy- lysosome system for clearance. Experimental upregulation of heat shock proteins with drugs such as geldanamycin, a naturally occurring benzoquinone ansamycin that promotes upregulation of heat shock protein 70, has been shown to inhibit alpha synuclein aggregation and reduce neurodegeneration caused by over expression of α synuclein. [21] However unfortunately this drug class is associated with hepatic toxicity. α synuclein toxicity develops in a sequential and predictable manner and involves transfer from affected to unaffected neurons. [22] Although the precise mechanism by which transfer occurs is not known, agents that inhibit lysosomal function increase endosomal release and uptake of α synuclein by recipient cells, [23] and agents that block endocytosis reduce α synuclein mediated damage in experimental models. [24]

3.4 Immunotherapy:

Immunotherapies with monoclonal antibodies have been shown to reduce oligomer levels [25] and vaccination with human α synuclein reduces aggregate formation in transgenic animals. [26]

Most recent evidence shows that antibodies directed against α synuclein specifically target and promote the clearance of extracellular α synuclein by microglia and not neuronal cells or astrocytes [27]. Therefore these antibodies might be of greatest value in preventing spread to neighbouring cells.

3.5 Others:

N-2 (adamantyl) hexamethyleneimine hydrochloride (himantane) is a new potential antiparkinsonian drug targeted at several neurochemical systems. The drug exhibits the properties of a low-affinity noncompetitive blocker of the ion channels of glutamate NMDA receptors. Hemantane increases the content of dopamine in the striatum, while decreasing the level of dopamine metabolite dioxyphenylacetic acid (DOPAC). [28]

4. Other approaches

Gene therapy: The treatment, called ProSavin, uses a modified virus to deliver three genes: Genes for the synthesis of: Tyrosine hydroxylase, Glutamate acid decarboxylase and Aromatic Acid Decarboxylase into the striatum, the part of the brain that controls movement.[29]

Neurotrophic factors (NTFs) are a class of molecules that influence a number of neuronal functions, including cell survival and axonal growth. Experimental studies in animal models suggest that members of neurotrophin family and GDNF family of ligands (GFLs) have the potent ability to protect degenerating dopamine neurons and to promote regeneration of the nigrostriatal dopamine system.

Stem cell therapy: A breakthrough study from Lund University in Sweden showed it is possible to get human embryonic stem cells to produce a new generation of dopamine cells that behave like native dopamine cells when transplanted into the brains of rats. The new cells show all the properties and functions of the dopamine neurons that are lost in PD. [30] This is a new area of interest in the treatment of PD.

Surgical procedures: [31]

Deep brain stimulation: Deep brain stimulation uses electrical impulses to stimulate a target area in the brain. It is the preferred surgery for treating most cases of advanced PD. The observation that high-frequency electrostimulation in the ventral lateral nucleus (VL) of the thalamus eliminates tremors in patients undergoing thalamotomy led to investigation of long-term deep brain stimulation (DBS) as a reversible alternative to neuroablation. DBS has become the surgical procedure of choice for Parkinson disease (PD) because it does not involve destruction of brain tissue; it is reversible; it can be adjusted as the disease progresses or adverse events occur; and it allows the performance of bilateral procedures without a significant increase in adverse events.

Neuroablative lesion surgeries involve the destruction of targeted areas of the brain to control the symptoms of PD; they have largely been replaced by DBS. During neuroablation, a specific deep brain target is destroyed by means of thermocoagulation. A radiofrequency generator is used most commonly to heat the lesioning electrode tip to the prescribed temperature in a controlled fashion.

The 2 most commonly performed neuroablative procedures are thalamotomy and pallidotomy, in which lesions are created in the ventral lateral thalamic nucleus (VL) and the internal segment of the globus pallidus (GPi; also known as the globus pallidus medialis), respectively.

Pallidotomy: Pallidotomy involves the precise destruction of a very small area in a deep part of globus pallidus that causes symptoms. Pallidotomy studies have demonstrated significant improvements in each of the cardinal symptoms of PD (tremor, rigidity, bradykinesia), as well as a significant reduction in dyskinesia. However, the tremor improvement is less consistent than that seen with thalamotomy. The most serious and frequent (3.6%) adverse effect of pallidotomy is a scotoma in the contralateral lower-central visual field. This complication occurs when the internal segment of the globus

pallidus (GPi) lesion extends into the optic tract, which lies immediately below the GPi. The risk of visual-field deficit is reduced greatly by accurate delineation of the ventral GPi border by microelectrode recording. Less frequent complications (< 5%) include injury to the internal capsule, facial paresis, and intracerebral hemorrhage (1-2%). Abnormalities of speech, swallowing, and cognition may also be observed. Bilateral pallidotomy is not recommended, because complications, including speech difficulties, dysphagia, and cognitive impairment, are relatively common.

Ventrolateral Thalamotomy: VL thalamotomy was the most frequently performed procedure for movement disorders in the prelevodopa era because tremor responds best to thalamotomy and can be monitored more easily in the operating room than gait abnormalities, rigidity, and akinesia. In this procedure, a part of the thalamus, generally the ventral intermediate (VIM) , is destroyed to relieve tremor. The VIM is almost unanimously considered the best target for tremor suppression; with excellent short- and long-term results in 80-90% of patients with PD. Thalamotomy have little effect on bradykinesia, rigidity, motor fluctuations, or dyskinesia. When rigidity and akinesia are prominent, other targets, including the GPi and the subthalamic nucleus (STN), are preferred. Thalamotomy is indicated in patients with PD who are disabled by medically refractory tremor. The anticipated benefit of tremor reduction or elimination must be considered carefully. Rest tremor alone is rarely disabling, and bradykinesia and rigidity can reduce dexterity irrespective of tremor. Most patients with PD who undergo thalamotomy have significant improvement in tremor of the limbs contralateral to the side of the lesion. Bilateral thalamotomy is generally avoided, because complications, especially speech and cognitive impairment, are common.

Neurotransplantation: Neural transplantation is a potential treatment for Parkinson disease (PD) for the following reasons:

-The neuronal degeneration is site- and type-specific (i.e., dopaminergic)

-The target area is well defined (ie, striatum)

-Postsynaptic receptors are relatively intact

-The neurons provide tonic stimulation of the receptors and appear to serve a modulatory function

Neurotransplantation is an experimental procedure being studied in monkeys for the treatment of Parkinson's disease. It involves implanting cells that produce dopamine into the brain Information about how well neurotransplantation works is limited.

The cells used are:-Autologous Adrenal medullary cells ,Fetal porcine dopaminergic cell transplant and Human retinal pigment epithelial cell(RPE)transplant.

5. Conclusion

Thus, pharmacological treatment of PD should be tailored to the individual patient. Drug therapy is not obligatory in early PD; many patients can be managed for a time with lifestyle interventions and exercise. In most patients levodopa with carbidopa still forms the mainstay therapy. But with the association of multiple newer targets and pathways in the pathology of PD, many novel agents acting via non dopaminergic pathways are under various stages of clinical trials and showing good results which could be further exploited.

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