

REVIEW

The Past, Present and Future of Parkinson's Disease Treatment

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Abstract:

Parkinson's Disease was first introduced by James Parkinson in 1817. Since then, major strides have been made in the development of its treatment. Early treatments were dominated by traditional and complementary therapies, which were largely serendipitous and observation-based. Current drug-based therapies manifest in the form of levodopa accompanied by dopamine agonist, COMT inhibitor, or MAO-B inhibitor, for the purpose of reducing the levodopa-induced symptom fluctuation. In terms of surgical treatment, while ablative surgeries in the brain have been abandoned due to high mortality rate in the late 1900s, Deep Brain Stimulation in the subthalamic nucleus or internal globus pallidus has mostly replaced ablative surgeries since its introduction in 1987. Current research topics include non-dopaminergic agents for motor fluctuation reduction, transplantation of dopaminergic neurons, gene therapies using viral vectors, reduction of alpha-synuclein neurotoxicity, and neuroprotective therapies. Especially, due to the fact that the etiology of the disease is yet to be elucidated, neuroprotective therapies aimed at slowing or stopping disease progression are of particular interest. It is suggested that future research should aim towards clarifying the cause of the disease, for the development of a treatment that can permanently halt or reverse Parkinson's Disease-related neurodegeneration.

Keywords: Parkinson's Disease, Treatment, Anticholinergics, Levodopa, Deep Brain Stimulation, Alpha-synuclein

Introduction

Parkinson's Disease (PD) is a neurodegenerative disease characterized by distinct triad cardinal motor symptoms of bradykinesia, rigidity, and resting tremor. It is caused by dopamine deficiency following the loss of dopaminergic neurons primarily in the substantia nigra pars compacta (SNc), but the reason for the neuronal death is unknown to date. However, it is strongly suggested that, in cases of idiopathic PD, the combination of genetic factors and environmental factors leads to various mechanisms that trigger neuronal death [1]. It is often accompanied by the pathological hallmark of Lewy Bodies - aggregated alpha-synuclein proteins - in the nigrostriatal pathway.

Since its first medical introduction by James Parkinson in 1817 [2], there have been major strides in the development of treatments for PD, from anticholinergics and ablative surgeries to levodopa to Deep Brain Stimulation. Current research revolves around developing therapies that can stop or reverse the progression of the disease. A number of agents are being tested for their neuroprotective abilities, but none of them have been proven adequate for clinical use to date [3]. Although all current therapies are symptomatic in nature and no single cure for the disease exists, the development of new molecular targets, biomarkers, and toxin animal models are providing a deeper understanding of the causes and mechanisms of PD. This article is a narrative of the major advances in the treatment for Parkinson's Disease since its first description, as well as its future prospects.

Early treatments

Early treatments of PD were largely serendipitous and observation-based in nature, with traditional and complementary therapies prevailing.

Although Parkinson acknowledged in his "An Essay on the Shaking Palsy" that a "countervailing remedy" is yet to be discovered, he hoped to find an intervention that would stop the progression of the disease [2]. Assuming that the disease originates from the medulla, he recommended venesection in the upper part of the neck, followed by the insertion of vesicatories to induce inflammation on the skin; this was intended to divert blood away from the medulla and depressurize it [2].

Early pharmacological treatments were dominated by anticholinergics, which reduce the acetylcholine levels in the central nervous system to restore the acetylcholine-dopamine balance in PD patients. The first widely-recognized groups of drugs were belladonna alkaloids, first introduced by Charcot's student Ordenstein [4]. Out of multiple belladonna-based anticholinergic agents, Charcot especially advocated the use of hyoscyamine, along with rye-based ergot products from which today's dopamine agonists are derived [5]. However, despite the widespread use of belladonna alkaloids, it was recognized by contemporary medical practitioners that they had moderate yet limited palliative effect on Parkinsonism [6].

Ablative surgeries in the brain were introduced in the early 1900s, with the development of a stereotaxic equipment by Horsley and Clarke [7]. In the 1940s, the basal ganglia was first targeted by Meyers for the reduction of Parkinsonian tremor, and noticed an improvement in rigidity as well as tremor; however, it was abandoned due to high mortality rates [8]. After Cooper's serendipitous

discovery of the effect of thalamotomy on tremor in the 1950s [9], the procedure was used intermittently, but was also soon replaced by medication with the emergence of levodopa in 1960.

Current treatments

Drug-based therapies

Levodopa

Following the discovery of dopamine deficiency in the striatum and the SNc of PD patients in 1960 by Ehringer and Hornykiewicz, levodopa, also known as l-dopa, was proven effective as an anti-parkinsonian agent in 1961 [10]. Since then, levodopa still remains as the most effective therapy for controlling the motor symptoms of PD [11].

As a precursor of dopamine, levodopa can cross the BBB, which in turn gets converted into dopamine in the brain, binds to D1 and D2 receptors, and restores dopamine deficit. However, most of the drug undergoes peripheral metabolism by amino acid-decarboxylase (AADC) and catechol-o-methyltransferase (COMT) before reaching the CNS, increasing the concentration of plasma dopamine and causing complications including nausea, vomiting, and orthostatic hypotension [8]. It is thus often taken together with AADC inhibitors such as carbidopa and benserazide, with the first combination of carbidopa-levodopa becoming commercially available in 1975 [12].

In addition to the side-effects, long-term use of levodopa inevitably leads to levodopa-induced fluctuation between the 'on' and 'off' periods: during 'on' periods, PD patients show a good response to the drug; during 'off' periods, motor complications, most often dyskinesia, predominate [13]. For this reason, levodopa treatment has often been delayed until significant impairment of function; however, increasing evidence suggests that delaying levodopa treatment has little impact in long-term motor symptoms, but only prevents patients from receiving therapeutic relief in the initial stages [14].

As an alternative to oral administration of levodopa - which results in a discontinuous supply of levodopa to the brain and thus causes motor complications [15] - continuous levodopa-carbidopa intestinal gel infusion (LCIG) has been developed. In LCIG, levodopa-carbidopa can be infused through a percutaneous gastrojejunostomy tube by a battery-powered pump. Typical indications of LCIG are advanced PD complicated by "Off" periods that cannot be satisfactorily controlled with "optimized" medical therapy, where "optimized" is defined as a combination of levodopa-carbidopa, a dopamine agonist, and at least one other anti-parkinsonian agents (COMT inhibitor, MAO-B inhibitor) [16]. It is reported that LCIG results in a significant reduction of daily mean 'off' time and an increase of mean 'on' time without dyskinesia in advanced PD patients [16]; however, it is commonly accompanied by complications such as abdominal pain, skin infection, peritonitis, gastric reflux, and aspiration [17].

Dopamine agonists

Dopamine agonists (DA) are agents that bind to dopamine receptors to mimic the effects of dopamine. They have advantages over levodopa, in that they do not generate toxic metabolites, are independent of neuronal capacities, have longer half-lives than levodopa, and can target specific subtypes of dopamine receptors [18]. However, they are relatively less effective in terms of controlling motor symptoms than levodopa; for this reason, they are typically used in managing early stages or young onsets of PD, or as an adjunct to levodopa to reduce its “off” periods as well as dyskinesia [11].

Although they have less motor complications, DAs are associated with other side effects such as somnolence, edema, and hallucination [19]; moreover, the long-term perceived quality of life for PD patients treated with either DA or levodopa did not significantly differ [20]. Today, whether the monotherapy of DA followed by levodopa or the use of low initial dose of levodopa along with DAs is more effective in the long-term is yet to be concluded [11]. Common DAs in use include bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), ropinirole (Requip), piribedil, cabergoline, apomorphine, and lisuride.

In the 1980s, a novel way of apomorphine administration - continuous subcutaneous apomorphine infusion (CSAI) - was introduced, which injected the drug through a portable pump around the waist or the neck. The main indication for CASI is severe PD with pronounced motor fluctuations, dyskinesias, and nocturnal akinesia [21]. It was found to be more effective in reducing ‘off’ periods and dyskinesia than its oral counterpart [22]. However, one of the most common complications of CSAI, affecting approximately 50% of CSAI-treated PD patients, is the development of skin nodules at the injection sites; they can be reduced by good skin hygiene and the use of Teflon cannula needle technology [23].

COMT inhibitors

In addition to inhibitors of AADC, inhibitors of COMT - an enzyme responsible for the peripheral metabolism of levodopa - have been used as a complement to levodopa to increase its elimination half-life and thus the duration of ‘on’ periods in PD patients [24].

COMT inhibitors have been associated with side effects such as nausea, vomiting, and mild dyskinesia due to increased dopaminergic stimulation, but most complications are mild [25]; nevertheless, tolcapone - a type of COMT inhibitor - has been associated with the risk of fulminant liver failure, while its counterpart entacapone does not show hepatotoxicity [26]. For this reason, tolcapone has been removed from European and Canadian market [27].

Recently, it has been suggested that the combined use of COMT inhibitors with levodopa does not have benefits over using levodopa alone: in a double-blind trial of 747 PD patients, those who received entacapone with levodopa in fact displayed shorter time to onset and frequency of dyskinesia [28].

MAO-B inhibitors

In 1983, Langston identified 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-derived Parkinsonism; MPTP, as a neurotoxin, is oxidized by monoamine oxidase-B (MAO-B) into MPP⁺, which is a toxic metabolite that kills dopaminergic neurons in the SNc [29]. MAO-B inhibitors - namely

selegiline(deprenyl) and rasagiline - were one of the first agents tested for their neuroprotective effects. In the 1989 clinical trial 'Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism' (DATATOP), selegiline was found to be able to significantly delay the time at which disease progression reached the stage that requires levodopa therapy; nonetheless, it was reported that whether the effects of selegiline were symptomatic or truly neuroprotective is unclear [30].

Similarly, in a 2005 clinical trial, rasagiline was demonstrated to be effective as a supplementary treatment to levodopa; it increased the duration of "on" time without dyskinesic side effects and the overall perceived quality of life, with dopaminergic side effects similar to those of the placebo group [31]. The potential neuroprotective function of rasagiline has been largely attributed to its ability to reduce the release of cytochrome C by closing the mitochondrial transition pore, modify pro-antiapoptotic genes and proteins, and inhibit the nuclear translocation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [32]. Nonetheless, the US Food and Drug Administration (FDA) concluded in 2011 that there is insufficient evidence that supports the potential neuroprotective effects of rasagiline in PD [33].

Revival of surgeries

In the late 1980s, ablative therapies, which were largely abandoned since the advent of levodopa in 1960, began to receive renewed attention. This was largely due to the limited efficacy of levodopa stemming from its motor complications and fluctuations, new understanding that the hyperactivity of subthalamic nucleus (STN) and internal globus pallidus (GPi) in PD could be controlled by STN lesions from MPTP primate models [34], and the development of novel neuroimaging techniques such as CT and MR [11].

After the report that the GPi is hyperactive in non-human primate models of PD [35], pallidotomy creating lesions in the GPi has received attention as an option for treating advanced PD patients. Unilateral pallidotomy was found to improve tremor, rigidity, bradykinesia, gait, and balance in 36 PD patients compared to those treated with medical therapy, and the effect was sustained 2 years after the intervention [36]. A review article reported that the risk of adverse events following unilateral pallidotomy was about 30% with the most frequent being speech problem and facial paresis, and the mortality rate was 1.2% [37].

Alternatively, subthalamotomy - which targets the STN - was found to improve parkinsonism in MPTP primate models [38]; however, in another study, unilateral subthalamotomy resulted in 16% of the subjects developing permanent dyskinesia as well as hemiballism and hemichorea [39].

Due to high risks of developing surgical complications following invasive ablative surgeries, thalamotomy, pallidotomy, and subthalamotomy have been mostly replaced by Deep Brain Stimulation in most countries.

Deep brain stimulation

DBS was first introduced by Benabid and colleagues as a less destructive alternative to lesioning procedures in 1987 [40]. It is the implantation of a continuous electrical stimulation device, which sends impulses to the STN or GPi to mitigate PD-related motor symptoms and dyskinesia [41]. Neuronal

degeneration in the substantia nigra and the following dopamine deficiency lead to an excessive excitation of GPi by the STN; the resulting inhibition of the thalamus reduces thalamocortical activity, which mediates various motor symptoms of PD. DBS is said to interfere with this pathophysiologic pathway, but the exact mechanism of action is unknown to date. Proposed mechanisms of DBS include the inhibition of neurons near the electrode to manage the output pathway, effect on the neurochemical state of the CNS, the disruption of PD-related pathological oscillations, and the induction of synaptic plasticity [42].

DBS has advantages over ablative therapies as it is reversible without destroying the brain tissue, and over continuous infusions as no lines, needles, or portable pumps are necessary. The effectiveness of DBS has been demonstrated in a study in which advanced PD patients experienced an increase of 4.6 hours a day of 'on' period, 71% rise in motor improvement, and increased quality of life [43]. Its beneficial effect is known to persist for at least 3 to 5 years after DBS [44].

No significant difference between DBS in the STN and GPi has been reported in both the motor function and quality of life; although patients treated with STN DBS required less dopaminergic medications and had a greater decrease in visuomotor speed, there was no significant disparity in the occurrence of long-term adverse events between patients treated with STN DBS and those treated with GPi stimulation [45].

Despite the absence of major lesions, DBS has been associated with significant surgical complications including infection, hemorrhage, seizure, pulmonary embolism, cerebrospinal fluid (CSF) leak, confusion or disorientation, and death [46]. DBS requires chronic implantation of electrodes and pulse generators, from which hardware complications frequently occur. In a review of 360 PD patients who received DBS therapy, complications of lead replacement or repositioning (due to fracture, malfunction, or dislocation), extension wire replacement, pulse generator replacement, and allergic reactions have been identified [46]. Although cognitive or behavioral complications related to electric stimulation have been relatively mild, it is suggested that DBS in the STN may be associated with the development of apathy [47]. Such condition is hypothesized to be triggered by a sudden postsurgical decrease in dopaminergic medication, and may be mitigated by an increased dosing of drugs [48]. Other potential complications include an increase in suicidal rate [49] and exacerbation of restless legs syndrome [50].

Current studies focus on increasing the precision and efficacy of DBS; for instance, there is mounting interest in the development of a closed-loop DBS, where stimulation can be turned on and off based on the presence of an increased oscillatory activity in PD patients [51]. The notion of increasing the anatomical specificity and adaptability of non-invasive DBS, such as transcranial magnetic stimulation and focused ultrasound, is also gaining interest [52].

It is believed that a better understanding of the mechanisms involved in the reduction of PD motor symptoms via DBS will open up new applications and target sites for DBS.

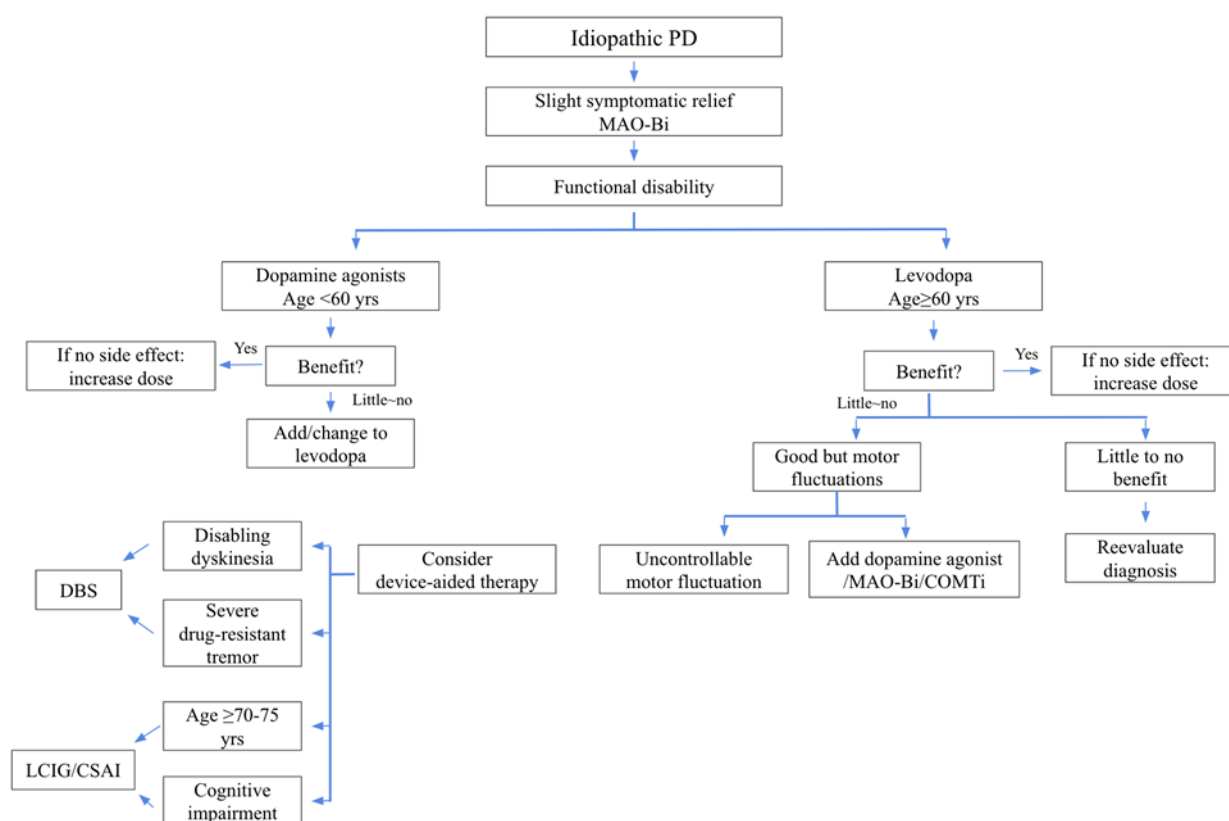


Figure 1: Algorithm for the choice of medical and device-assisted treatment for PD. Originally based on the study of Dietrichs and Odin [53], with modifications made by the author. (PD: Parkinson's Disease; MAO-Bi: MAO-B inhibitors; COMTi: COMT inhibitors; DBS: Deep Brain Stimulation; LCIG: Continuous levodopa-carbidopa intestinal gel infusion; CSAI: continuous subcutaneous apomorphine infusion)

Rehabilitation

Rehabilitation is considered an adjunct to pharmacological and surgical therapies, in order to maximize functional ability. Although exercise cannot slow the progression of motor dysfunctions, it can improve functions in certain motor tasks[54] and alleviate a few nonmotor symptoms[55]. Regular physical exercise programs and physiotherapy may improve rigidity, hypokinesia, flexibility, gait, strength, and quality of life[56]. Lee Silverman Voice Treatment (LSVT), which aims to maximize vocal loudness, has been found to be effective for patients with dysarthria and hypophonia[57]. Occupational therapy often accompanies physiotherapy, and is found to improve self-perceived performance of daily activities and the quality of life[58].

Future prospects

Non-dopaminergic agents

Despite the remarkable effect of medicinal therapies, PD patients experience severe motor complications and fluctuations that significantly harm their quality of life. Thus, the use of non-dopaminergic agents for symptomatic relief has been extensively investigated.

Glutamate antagonists

N-Methyl-d-aspartate (NMDA) glutamate receptors can be inhibited by glutamate antagonists such as amantadine and memantine, which can theoretically reduce the GABAergic inhibition of the thalamus and thus reduce motor symptoms. Amantadine has been shown to have antidyskinetic effects in PD patients [59], sustained for at least a year following the intervention [60]. Nonetheless, the development of psychiatric side effects has limited the use of glutamate antagonists in clinical settings [61].

Riluzole has also been shown to reduce dyskinesia with better patient toleration [62] and have neuroprotective effects on dopaminergic neuron in MPTP primate models [63], but in a 2002 clinical trial no significant change in Unified Parkinson Disease Rating Scale (UPDRS) motor score was observed [64].

Adenosine A2A antagonist

Antagonists that target adenosine A2A receptors in striatal cholinergic interneurons, namely istradefylline, have been reported to significantly reduce the “off” time in PD patients [65]. Further investigation of adenosine A2A antagonists is being delayed, with the absence of approval from the US FDA [66].

Other non-dopaminergic agents under investigation include: opioid antagonists, serotonergic 5-HT_{2C} agonists, cannabinoid CB1 agonists, α 2-antagonists, dopamine uptake inhibitors, selective muscarinic antagonists, and nicotinic agonists [8]. However, most drugs have failed to be translated from preclinical to clinical trials due to inconsistent results [11].

Restorative therapies

Neural transplantations

For more than 2 decades, there has been a continuous effort to develop a therapy based on the restoration of dopaminergic neurons. The transplantation of fetal-derived mesencephalic dopaminergic cells showed some promising results with motor symptoms improving in younger patients; however, the majority of the patients developed “off” period dyskinesia that persisted even after medication withdrawal [67].

Alternatively, replacement therapies using human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) have shown potential with derived neurons surviving in vivo in animal trials [68], but are in the process of clinical application.

Such stem-cell based therapies face inevitable safety concerns, as there is a danger of tumor formation due to an overgrowth or genetic abnormalities in the graft [69]. Moreover, creating patient-specific iPSCs by reprogramming somatic cells is highly cost-consuming [69]; thus, sufficient trials and investigations to ensure safety and affordability would be required.

Recent research interests have been directed to the direct lineage reprogramming of glial cells to dopaminergic neurons, as it has benefits of no ethical concerns, no risk of tumor formation, and no requirement of transplantation [70].

Gene therapies

Viral vector gene delivery

Restoration of dopamine has been attempted with gene therapies, by using adeno-associated virus vectors (AAV) to deliver genes coding for dopamine biosynthetic enzymes - aromatic amine decarboxylase (AADC), tyrosine hydroxylase, and cyclohydrolase-1 - into the striatum [69]. Several phase I trials for the delivery of AADC via AAV into the putamen showed increased “on” time for PD patients and thus the safety of the intervention [71,72,73]. Moreover, the delivery of AADC, tyrosine hydroxylase, and cyclohydrolase-1 into the putamen using lentivirus vectors - which have a larger potential genetic cargo compared to AAV - resulted in a significant increase in Unified Parkinson Disease Rating Scale (UPDRS) motor scores [74].

Alternatively, gene encoding glutamic acid decarboxylase (GAD), an enzyme responsible for the synthesis of gamma-aminobutyric acid (GABA), has been delivered to the STN using AAV in the hope of reducing STN hyperactivity [75]. The AAV-GAD group showed significant improvement in the UPDRS motor scores compared to the sham group, with mild adverse events.

Restorative gene therapies

AAV has also been used in restorative gene therapies; glial cell line derived neurotrophic factor (GDNF), which is responsible for the differentiation and maintenance of dopaminergic neurons, has been delivered to the putamen using AAV under MRI-guided administration, resulting in an increased GDNF expression without clinical or radiographic toxicity [76]. However, phase II trial of AAV delivery of neurturin, a natural analogue of GDNF, has shown insignificant increase in UPDRS motor score compared to that of the sham group [77].

Alpha-synuclein based therapies

After the first identification of mutations in the SNCA gene coding for alpha-synuclein as the first genetic cause of PD in 1997 [78], it was found that alpha-synuclein was the main composition of Lewy bodies and Lewy neurites in PD [79]. Since then, various experimental approaches have been tested to reduce the neurotoxicity of alpha-synuclein aggregates.

Reducing alpha-synuclein production

One approach to the alpha-synuclein therapy is reducing the translation of the protein through RNA interference, where exogenous synthetic RNA molecules trigger the knockdown of the alpha-synuclein mRNA [80]. For instance, the introduction of a small-interfering RNA (siRNA) directed against alpha-synuclein in a mouse model led to the reduction of alpha-synuclein expression [80]; moreover, a similar study conducted in non-human primate models resulted in a 40-50% reduction in alpha-synuclein expression.

In an alternative perspective, the alpha-synuclein gene can be silenced to reduce the transcription of the mRNA. β 2-adrenergic receptor agonist - namely clenbuterol - has been reported to reduce alpha-synuclein gene expression by

35%, and a potential association with a reduction of developing PD has been identified [81].

A point of consideration in these methods is that the inhibition of alpha-synuclein expression may lead to a loss of the protein's normal physiological function, which is hypothesized to be related to a number of roles including the suppression of apoptosis [82], regulation of glucose levels [83] and dopamine production [84], chaperone activity [85], and antioxidation [86]. This is supported by studies that observed neurotoxicity and neurodegeneration in the SNc of alpha-synuclein silenced models [87].

Increasing alpha-synuclein clearance

Immunotherapies aimed at degrading extracellular alpha-synuclein aggregates are currently being actively investigated in preclinical as well as clinical trials. In a phase I clinical trial of an immunotherapy vaccine containing alpha-synuclein-mimicking peptides, the vaccine was found to trigger immune response against the peptide as well as extracellular alpha-synuclein without significant complication [88]. Moreover, anti-alpha-synuclein monoclonal antibodies were shown to reduce alpha-synuclein levels in healthy human subjects without adverse events and neurotoxicity [89], and are currently being tested against early PD patients in a phase II trial.

In terms of intracellular alpha-synuclein, the lysosome-autophagy system that can clear alpha-synuclein aggregates via autophagy can be enhanced to reduce alpha-synuclein accumulation. This idea has been supported by the study showing that rapamycin, an agent that induces macroautophagy, is able to reverse alpha-synuclein accumulation [90]. Other autophagy enhancers such as trehalose and nortriptyline are currently being studied as potential subjects for clinical trials [69].

Neuroprotective therapies

Neuroprotective therapies are aimed at slowing or stopping disease progression. Of particular interest is exenatide, which is a glucagon-like peptide-1 (GLP-1) receptor agonist typically used in the improvement of glycemic control in type 2 diabetes mellitus patients. Its ability to protect neurons from metabolic and oxidative stress has been demonstrated in rodent models of PD, created by 6-hydroxydopamine (6-OHDA), lipopolysaccharide (LPS) [91], and MPTP [92]. Moreover, in a phase 2 clinical trial, PD patients that received subcutaneous administration of exenatide showed a slight improvement of symptoms during the "off" period; however, a relatively small sample size and short trial duration limit the study's implications and thus would need further investigation [93].

In addition to the MAO-B inhibitors, NMDA glutamate receptors, neurotrophic factors, and exenatide, several agents are being investigated for their potential neuroprotective effects on PD. They include iron chelators (i.e. deferiprone) [94], calcium channel blockers (i.e. isradipine) [95], coenzyme Q10 with antioxidative effects, antiapoptotic agents (i.e. inosine) [96], and nicotine. However, none of them are found to be truly neuroprotective to date.

Conclusion

Since the 1817 introduction of PD by James Parkinson, significant strides have been made not only in the development of effective treatments, but also in the understanding of the potential mechanisms of the disease and the creation of models to test them. However, the exact etiology of the disease and a therapy that can reverse disease progression are yet to be determined.

Existing treatments for PD are palliative in nature, focusing on the relief of dopaminergic motor symptoms and the simultaneous reduction of drug related complications such as dyskinesia and motor fluctuations. Such debilitating side effects and the resulting reduction of the efficacy of medicinal therapy in advanced PD indicate the pressing need for the development of a treatment of which the therapeutic effect can be persisted continuously. In this context, it is suggested that active research is required in the direction of elucidating the fundamental factors responsible for the pathogenesis of the disease, such as the dynamics of alpha-synuclein fibrillation and mitochondrial defects. This will ultimately lead to the creation of curative treatments addressing the cause of PD to permanently halt or reverse neurodegeneration.

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