Exploring the Potential of Glial Cell Derived Neurotrophic Factor (GDNF) in Parkinson's Disease Treatment

Brandon Pang

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Parkinson's disease (PD) is one of most common neurodegenerative diseases. Currently, there are no treatments that can stop the progression of PD or cure it, so current treatments are focused on reducing PD symptoms. Glial cell-derived neurotrophic factor (GDNF) is a neurotrophic protein that protects and regenerates dopamine neurons in the brain and has recently been considered as a treatment option for PD symptoms with the potential to reverse or slow the progression of the disease. In this article, we reviewed past and current studies in animal and clinical trials on GDNF in the treatment of PD. Studies using PD animal models have shown positive results of GDNF infusions into the brain that protect dopamine neurons, increase dopamine levels, and improve motor scores. However, in clinical trials, the results have not shown similar outcomes. This review will look at the potential use of GDNF as a disease modifying treatment in PD and discuss some of the challenges and possible future directions as a potential treatment.

Key words: Glial cell-derived neurotrophic factor, GDNF, Parkinson's disease.

introduction

Parkinson's Disease is the second most common neurodegenerative disease affecting 1-2% of the population over 50 years of age. Furthermore, as the population ages, the number of new PD cases are expected to double within the next two decades [1]. In most PD cases, the cause is due to a number of environmental and genetic factors. Currently, there are 8 known monogenic genes thought to be associated with the cause of PD (LRRK2, CHCHD2, VPS35, SNCA, PARKIN, DJ1, PINK1, and GBA). The SNCA and GBA genes are of particular importance. SNCA is the gene that codes for the neuro protein alpha-synuclein that is thought to be responsible for Parkinson's Disease and other neurodegenerative diseases like Alzheimer's disease. Variance in the GBA gene has up to a 30% penetrance [2].

Some environmental factors that are thought to be associated with PD include pesticides (paraquat, rotenone, maneb, organochlorines), air pollution, and head injury. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), a neurotoxin found in the herbicide cyperquat and illicit drugs like heroin, was found to cause parkinson symptoms. MPTP is no longer used in herbicides, but is now mainly used in research to induce parkinson's-like symptoms in animals.

PD is defined by the loss of dopaminergic neurons in the substantia nigra (SN). The SN is a structure of the basal ganglia in the midbrain that is thought to control motor function. The clinical symptoms of PD include resting tremor, bradykinesia, postural instability, and rigidity, accompanied by non-motor symptoms including autonomic, cognitive, and psychiatric problems [2].

Current treatments for PD focus primarily on treating symptoms rather than the disease itself. The most common treatment is replacement of dopamine (DA) in the brain via the combination drug Carbidopa/Levodopa. Although effective at controlling motor symptoms, these medications lose their effectiveness over time leading to "off and on time" symptoms–off time being a period when medication wears off and symptoms re-emerge, and on time when the medication is working [3]. Currently, no treatment can slow down or reverse Parkinson's disease. However, ongoing studies have been looking at new intervention to target disease progression.

One potential method involves delivering neurotrophic factors to the basal ganglia to provide protection for DA neurons. Specifically, glial cell line-derived neurotrophic factor (GDNF) is one that shows promise for future disease modifying treatments in PD. GDNF belongs to the transforming growth factor-β family which plays a crucial role in the survival, maintenance, and regeneration of dopaminergic neurons during development [4]. Early studies have shown improvement in motor functions with GDNF infusions in animal models of PD [5]. However, recent studies have not reproduced similar clinical results, but have shown increased dopamine production and neuroprotection in human trials [6].

This paper therefore aims to provide a review of some of the past and current studies on GDNF in the treatment of PD, and discuss some of the challenges and possible future directions as a potential treatment.

Pathophysiology of Parkinson's Disease

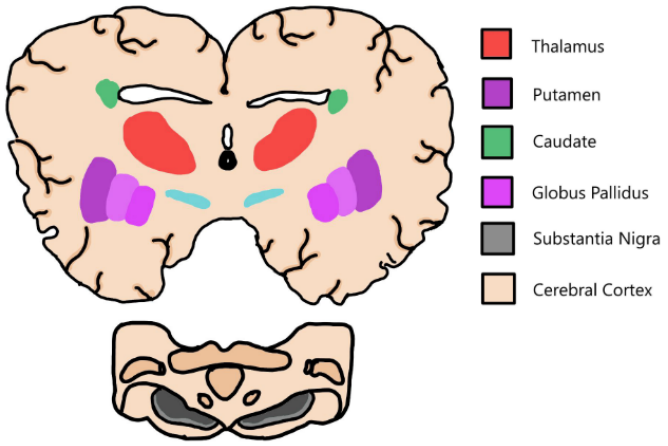

Figure 1. Coronal section of the brain showing structures of the basal ganglia.

The main defect in PD is neurodegeneration of DA producing neurons in the substantia nigra that result in decreased DA levels in the basal ganglia. This leads to the motor symptoms seen in PD. The basal ganglia is made up of a collection of nuclei located in the midbrain, where its function is to control movement. The parts of the basal ganglia include the caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra[7]. (Figure 1) There are two pathways of the basal ganglia, the direct and indirect pathways. Both pathways help control movement. The direct pathway stimulates wanted motor movement by exciting thalamic neurons which communicate with the cerebral cortex to stimulate movement. The indirect pathway has the opposite effect by inhibiting activity of thalamic neurons that project to the motor cortex to prevent unwanted movement. The communication from the substantia nigra pars compacta (SNc) to the striatum is called the nigrostriatal pathway, where the SNc provides the major dopamine input to the striatum and causes both excitatory and inhibitory influences on the striatum[7]. In PD, neurodegeneration of the DA producing neurons in the SNc results in the decrease of DA. When DA levels drop below 60%, motor symptoms of PD traditionally appear, including decreased motor activity in the direct and indirect pathways. This explains the hallmark PD symptoms, rigidity, tremors, and bradykinesia[8].

The cause of PD is complicated and is due to a combination of genetic and environmental factors. Known gene mutations including SNCA, LRRK2, GBA, PINK1, PARKIN are linked to PD. However, only about 5-10% of PD patients carry one of these mutated genes[1]. Environmental factors include chemical exposure to pesticides, head trauma, and lifestyle factors like smoking, alcohol, and diet. Another barrier to understanding PD is its heterogeneity. Patients have different clinical presentations and progression of the disease. Some PD patients present more with motor dysfunction like tremors and rigidity, while others show more cognitive decline and automatic dysfunction[1]. Also, the rate of progression of the disease ranges from slow to rapidly progressive. The multiple causes, the heterogeneity of PD symptoms, and different progression rates make finding a single treatment very difficult.

Current Advancements for PD Treatment

Treatment of PD can be divided into symptomatic treatments (ST) and disease modifying treatments (DMTs)[9]. DMTs can make the most impact for PD patients because it prevents or slows the progression of PD so patients can live longer with less symptoms. Current research on DMTs are looking at neurotrophic factors, alpha-synuclean targets, glucocerebrosidase (GBA) gene modulators, iPSC cell replacement, neuroinflammation reducers, kinase inhibitors, and mitochondrial modulators[9]. (table 1) Each of these treatments come with its own challenges.

Gene therapy has shown promise, however, there are challenges including finding a delivery vector, immunity, and risk of mutations. Delivery methods include viruses like adeno-associated virus (AAV), lentivirus, adenovirus, and retrovirus. Non-viral biomaterial-aided growth factor vectors include nanoparticles, peptides, and liposomes. These vehicles used in gene therapy each have their benefits and risks including size, accuracy, and safety. Recombinant engineered AAVs have shown promise as a vector due to its low immunogenicity and long lasting expression[10]. These vectors are currently being looked at to deliver possible gene treatments like GDNF that can not cross the blood-barrier directly to the basal ganglia dopamine neurons. Both animal and clinical trials using AAV vectors for gene therapy injected directly in the putamen have shown promise for a safe, long-term, and accurate treatment of PD[11].

Another delivery system for PD treatment is the use of encapsulated cell biodelivery (ECB). ECB is the use of genetically modified cells that are enclosed in a semipermeable capsule that are directly implanted into the brain. This allows the cell to be protected from immune reactions while being able to distribute proteins like GDNF to the surrounding brain[12]. Benefits of ECB include protection of the cells from immune destruction, increase in direct diffusion of factors such as GDNF, and sustainability.

Finally, the use of iPSCs has also shown promise for PD treatment. Researchers have looked at implanting iPSCs to develop into dopamine producing neurons. iPSCs can be autologous, from the patient stem cell line, or allogenic, from a donor. Autologous iPSCs have the advantage of less immunogenicity but take longer and much more expensive. Early studies have shown safe use of autologous iPSCs in animal PD models with increased dopamine production, decreased symptoms. Several

Table 1 Potential disease modifying treatments (DMTs) for PD and their developmental phases[9].

Treatment	Mechanism of Action	Category	Development Phase
Ambroxol	GCase chaperone; enhances lysosomal clearance of α-synuclein	DMT (GBA modulator)	Phase 2
Prasinezumab	Monoclonal antibody against aggregated α-synuclein	DMT (antibody)	Phase 3
NLRP3 Inhibitors	Inhibit microglial inflammasome-mediated neuroinflammation	DMT (immunomodulator)	Phase 1/2
LRRK2 Inhibitors	Block LRRK2 kinase overactivity to reduce neuronal toxicity	DMT (genetic target)	Phase 2
Tau-targeting agents	Reduce tau protein pathology in synuclein-associated disease	DMT (proteinopathy)	Phase 2
GLP-1 Agonists	Enhance neuroprotection via metabolic and anti-inflammatory	DMT	Phase 2/3
Gene Therapy (AAV-GDNF/GBA)	Deliver GDNF or functional GBA via viral vector	DMT	Phase 1/2
Cell Therapy – iPSC dopamine progenitors	Replace degenerated dopaminergic neurons via cell transplantation	DMT	Phase 1/2
CDNF/MANF based therapies	Modulate ER stress & proteostasis; support dopaminergic neurons	DMT	Preclinical / Phase 1

studies are currently underway in human trials and may be a possible disease modifying treatment in PD[13].

Of these DMTs, this review focuses on the potential of the neurotrophic factor, GDNF. GDNF has shown significant promise in animal studies, has the potential to benefit early PD patients to prevent disease, and with new biomarkers for identifying PD early and better delivery systems directly to the basal ganglia, GDNF has a lot of potential in clinical trials.

Neurotrophic Factors and PD

Neurotrophic factors (NTF) are small proteins that protect and promote neuron growth. They help with proliferation, differentiation, and maturation of neurons[14]. Examples of NTFs include GDNF, brain derived neurotrophic factor (BDNF), mesencephalic astrocyte derived neurotrophic factor (MANF), and cerebral dopamine neurotrophic factor (CDNF). Because of these properties, they can be a major factor in the treatment of PD. Of these NTFs, GDNF is the most well studied, showing promise in animal models and mixed results in human clinic trials. While GDNF works primarily on protection of dopamine neurons, CDNF and MANF was found in cells in the endoplasmic reticulum (ER) where it reduces intracellular stress response in the ER. An increase in the ER stress response was seen in degenerating dopamine neurons[14]. BDNF has also shown benefits in animal models as a possible factor to protect against neuron degeneration. Unlike GDNF that targets mainly dopamine producing neurons, BDNF has a broader neuroprotective role that can possibly improve cognitive decline in PD patients but may be less helpful for motor symptoms[15]. More clinical trials are needed to assess BDNF's role in PD treatment.

Glial Cell-Derived Neurotrophic Factor (GDNF)

GDNF is a glycosylated, disulfide-bonded homodimer that belongs to the transforming growth factor-beta family and was discovered in 1993. In rat models, it was found that GDNF protects and promotes growth of dopaminergic neurons in the midbrain. Additionally, after brain injury, glial cells were found to produce more GDNF[16]. GDNF functions by binding to a receptor called GDNF family receptor alpha1 (GFRα1). This GDNF/GFRα1 bond is then able to tightly connect with another receptor called rearranged during transfection (RET) receptor, a tyrosine kinase receptor. The connection between the two receptors activates 2 intracellular cascades, the Ras-Erk and P13K-AKT. These cascades are essential to neuronal survival as a response to GDNF[17]. Therefore, GDNF was found to benefit growth and survival of dopaminergic neurons. This was especially evident in the SNc[18]. With this data, GDNF was considered a possible treatment for PD patients by protecting dopamine neurons in the basal ganglia.

GDNF in Early Animal Models

In 1993, GDNF was found to specifically protect DA producing neurons in cultured brain tissue[19]. Since then, many stud-

ies have looked at GDNF in both rodent and primate models. During one, GDNF was delivered to the SNc and striatum within the basal ganglia, where DA producing neurons are found. This was done in animal models using neurotoxins 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) to cause DA neuron degeneration and PD symptoms. Early studies have shown that when GDNF was injected into the SNc or striatum of mice before and after MPTP administration, GDNF protected and restored DA levels. It also showed that these mice had improved motor functions compared to untreated mice[5].

Another study examined whether GDNF-transfected macrophages injected into the blood could alter loss of DA neurons in mice. These mice were also injected with 6-OHDA to cause DA neuron degeneration. The study found that the GDNF macrophages specifically targeted inflamed brain cells, showing protection of DA neurons and reducing inflammation in the area. Motor function in the mice also showed improvement[20]. Alternate delivery of the GDNF macrophages intranasally also found the same benefits as blood injection[21]. These findings support the potential of GDNF treatment for PD through DA neuron protection and regeneration.

Additional studies were then performed on non-human primates, as their brains are more similar to humans. Researchers injected GDNF directly into the SNc of monkeys every four weeks. Parkinsonian symptoms and neurodegeneration were induced by using MPTP. In the monkeys treated with GDNF, they found a higher density of nigrostriatal DA neurons and increased levels of DA in the midbrain. They also found improvement in PD symptoms including bradykinesia and postural instability[22]. Another study in primates looked at lentiviral delivery of GDNF (lenti-GDNF) into the SNc and striatum in aged and MPTP injected monkeys. They found that in aged monkeys, GDNF increased DA levels and function. In the MPTP treated monkeys, they found that GDNF prevented DA cell degeneration and improved motor functions[23]. These findings once again supported the hypothesis that GDNF is a possible treatment for PD.

GDNF in Clinical Trials

Given the positive results in both mice and non-human primate models, researchers looked into clinical trials of GDNF for treatment of PD patients. In 2003 a randomized, double-blind trial was done where GDNF was delivered to the ventricles of the brain through an implanted catheter. Patients received infusions once a month for 8 months. Results showed no improvement in patients receiving GDNF compared to the control group using the Unified Parkinson's Disease Rating Scale (UPDRS, a scale to measure symptom response to medications in PD. Patients also developed effects like nausea, vomiting, paresthesia (Lhermitte sign), and weight loss[24]. The study was extended another 8 months to see if a longer duration would be beneficial. However, there were no changes in the UPDRS in the additional 8 months. One reason why there was no benefit from these GDNF infusions may have been due to where it was delivered. In the study, GDNF was infused into the ventricles and not directly to the basal ganglia, resulting in smaller amounts of GDNF reaching the target area of the basal ganglia. Another study in 2003 that was not randomized controlled looked at continuous delivery of GDNF directly into the putamen of patients with PD. Although this was a low power study with a small sample size (Table 2), the study showed this method resulted in minimal side effects and was generally well tolerated in the subjects. It also showed an improvement in motor symptoms based on UPDRS scores, with patients also reporting fewer dyskinesias. Also, they found that continuous infusion of GDNF showed increased [18F]dopa uptake around the catheter tip after 18 months. [18F]dopa is a radioactive form of levodopa that is used to visualize DA in the brain. This proved that GDNF affects DA production around the area of infusion[25].

To confirm the results of the 2003 study, researchers conducted a randomized controlled trial to study weekly infusions of GDNF directly into the putamen of PD patients. The patients were studied for over 6 months, and PET scans confirmed increased [18F]dopa in the area of infusion, which means GDNF infusions increased DA levels in the putamen. In addition, GDNF was well tolerated in these patients with low side effects[26]. However, the study did not show significant changes in UPDRS scores compared to control patients. Some reasons why this study failed may have been due to a different catheter delivery system of GDNF to the putamen, the dose may have been lower, or the duration of the study was too short to produce significant results.

The most recent randomized controlled trial of GDNF infusion treatment into the putamen of PD patients was done in 2019. This study used a convection-enhanced delivery system to increase delivery of GDNF to the putamen. Patients received infusions of GDNF every 4 weeks for 40 weeks. Once again, [18F]dopa PET imaging did show increased DA levels in the putamen in the treatment with no improvement of clinical symptoms or change in UPDRS scores between the control groups and the GDNF treated group[6]. The study was extended for another 40 weeks for all patients who wanted to continue GDNF infusions, which showed similar results. This confirms the results of previous randomized controlled trials of GDNF infusion in PD patients. Reasons for this study's failure may be due to the dose of GDNF being too low to produce a high enough increase in DA levels to show benefit. Also, the selection of patients with more advanced disease could have affected the results as these patients had more advanced neurodegeneration with less neurons to protect. Although GDNF treatment in animal models showed promise for future PD treatments, clinical randomized controlled trials failed to produce similar positive results.

Table 2 Summary of clinic studies of GDNF treatment. Hoehn & Yahr scale measures progression of PD on 1-5 scale. PET [18F]dopa measures uptake of tracer by active dopamine neurons.

Study	Sample Size	Study Design	Inclusion Criteria	Outcome Measures	Results	Delivery Method	Post-hoc Analyses
Gill et al. (2003)	5	Low power, small N, not blinded, no placebo control	Severe PD, failed medical therapy	UPDRS, PET [18F]dopa, safety	[18F]dopa ↑ 28%, improvement of UPDRS of 39%	Direct intraputamenal delivery vial infusion pump, no biomarker validation	Not reported
Nutt et al. (2003)	34	Randomized, double-blind, placebo-controlled trial and cohort study	PD diagnosis >5 years, age 35–75, Hoehn & Yahr 2–4	UPDRS, safety, no PET	No significant benefit, some non-specific placebo response possible	ICV infusion, poor target coverage	No subgroup benefits identified
Lang et al. (2006)	34	Randomized, double-blind, placebo-controlled trial	Age 35–75 Moderate PD severity, Hoehn & Yahr 2–4	UPDRS OFF, PET [18F]dopa, ADL	[18F]dopa ↑28%, no significant UPDRS improvement	Implanted catheter with port, infusion verified	Subgroup with moderate baseline severity may have trended better
Whone et al. (2019)	41	Good sample size. Randomized, double-blind, placebo-controlled trial	Age 35–75 Moderate PD severity, Hoehn & Yahr 2–3	UPDRS OFF, PET [18F]dopa, diary time	[18F]dopa ↑ ∼100% at 9 months; no significant UPDRS improvement	Intermittent CED via implantable pump; accurate coverage validated with gadolinium	PET responders had some symptom benefit

Discussion

Translational Barriers of GDNF from Animal Models to Clinical Benefits

GDNF has been shown to increase DA production and improve motor symptoms in animal studies. However, human clinical trials have not shown the same improvement. Randomized controlled trials in PD patients have failed to show clinical improvement in symptoms even with evidence of increased DA production. (Table 2). This lack of clinical benefit shows that there may be multiple translational barriers. These may include limitations in GDNF distribution in the basal ganglia, decrease relative DA production compared to animal models, poor delivery systems, differences in disease models between animals and humans, and advanced patient stage of PD.

GDNF Distribution in the Basal Ganglia

One barrier may be the distribution of GDNF in the smaller primate brain versus human brains. The clinical effect size of GDNF therapy largely depends on the availability and distribution of GDNF protein in the basal ganglia[4]. With lower GDNF distribution in the basal ganglia in humans compared to animal models, DA produced in the human models may not be enough to reverse any of the PD symptoms.

Studies have shown that PD symptoms occur when about 60% of DA levels are lost. Given the smaller brain size in animal models, the increase in DA levels and activity produced from GDNF may have been enough to treat PD symptoms compared to that in the larger human brain. Also, dose limitations of GDNF in clinical trials due to patient safety may also affect the clinical response. Because GDNF does not cross the blood brain barrier, direct infusion to the brain is required which can limit dosing with higher doses. Improved delivery models including the use of AAV2, nanoparticles, and encapsulated cell biodelivery may improve delivery of higher doses of GDNF with less side effects. Also, identifying biomarkers to measure the distribution of GDNF in the brain and to measure its activity can help to understand how GDNF activity, DA levels, and clinical response are related.

Poor Primary Outcome Clinical Measures

In clinical trials, the primary outcome measure was usually clinical improvement of symptoms. The studies relied on the

Unified Parkinson's Disease Rating Scale (UPDRS). This scale is less sensitive to early-stage disease and relies on patient and observer reporting[4]. This may have affected the lack of positive results in clinical trials. Future clinical trials using a more sensitive, standardized end point measure or possibly use of digital tools like wearables or smartphones may help to get a more reliable measure of clinical improvement in GDNF treated patients.

Fundamental Differences in Disease Models in animals vs humans

Another possible explanation as to why GDNF treatments in animal models differ from clinical trials may be due to the different causes for neurodegeneration. In animal models, they use the neurotoxins 6-OHDA and MPTP to cause breakdown of DA neurons. In humans, PD symptoms are usually caused by aggregation of the protein α-synuclein. In a study done in 2011, researchers looked at the effect of GDNF on the rat α-synuclein model of PD. They found that GDNF did not protect DA neurons from degeneration, did not improve behavioral functions, and had no effect on α-synuclein aggregation[27]. The study shows that there was no neuroprotection by GDNF in α-synuclein models of PD. In this case, α-synuclein in human brains could be an additional factor preventing GDNF protection of DA neurons in the brain, and would need further studies.

Moderate to Advanced Stage of PD in Human Trials

Another possible explanation of the failure of clinical trials to show benefits from GDNF infusions could be due to patient selection. Patients in these trials had moderately advanced PD with around 5 years or more of symptoms (Table 2). These patients likely had more degeneration of DA neurons. More than 60% of DA neurons are lost when patients start having symptoms. For moderate to advanced cases, even more DA neurons are lost. In a study from 2019, researchers looked at GDNF treatment in early versus advanced PD mice models. They used lentivirus with GDNF to turn on GDNF production and found that in the mice with early degeneration, DA neurons were rescued and motor symptoms improved. In mice with advanced DA neuron injury, there was no DA neuron rescue and no change in motor functions. This supports the possibility that GDNF treatment may have a greater beneficial effect on reversing DA neuron degeneration when given early in the course of PD.

A promising new cohort study identified a biomarker, called α-synuclein seeding amplification assay (SAAs) that may be used to diagnose PD early on. The study looked at the use of SAAs in identifying PD in different groups of patients by looking at their cerebral spinal fluid. They looked at sporadic patients with PD, healthy patients, patients with possible genetic cause, and patients with prodromal symptoms like REM behavior disorder and hyposmia. The study showed that SAAs biomarker was present in healthy patients who later developed PD[28]. In prodromal and at risk groups, SAAs demonstrated promising results which can lead to early diagnosis of PD in patients with minimal symptoms. This would allow for earlier identification of PD in patients and earlier use of GDNF where it can be most effective. These patients will still have intact DA neurons in which GDNF has been shown to protect, and could therefore be a useful treatment option.

Potential for Gene Therapy

Finally, recent studies have looked at using gene therapy with GDNF in the treatment of PD. The benefits of gene therapy over continuous or repeated infusions of GDNF into a patient's midbrain include a decrease in side effects like weight loss, frequent visits to infusion centers, and a single dose versus continuous infusions to initiate treatment. A recent study in 2020 looked at the safety of gene therapy using adeno-associated virus, serotype-2 vector carrying GDNF(AAV2-GDNF) that was delivered into the putamen of advanced PD patients. Researchers found that the AAV2-GDNF treatment was well tolerated with no adverse effects when given in different doses. The study also showed an increase in activity of DA neurons by looking at [18F]dopa uptake in the basal ganglia. However, it did not show any improvement in UPDRS scores in treated patients[29]. This can be explained because only 26% of the putamen was covered from the AAV2-GDNF infusion. Future studies may improve possible clinical benefits using gene therapy by finding a better delivery system through using better positioned catheters, a systemic delivery system through the blood or intranasally, or using newer nanoparticle technology for delivery. Also, future studies can now look at gene therapy treatments in patients with early PD who may find greater benefits with GDNF treatment as a prevention for further neurodegeneration.

Understanding GDNF Pharmacokinetics and Pharmacodynamics

The pharmacokinetics and pharmacodynamics of GDNF is still not well understood. Some of these areas include the inability to quantify the distribution of GDNF in the target tissue, unknown half-life and clearance, and effect of immune response and antibodies to GDNF[6]. Also, the lack of biomarkers to assess GDNF activation affects our understanding of GDNF in human clinical trials. Future studies will benefit from development of biomarkers to assess GDNF activation and distribution in the tissue, evaluation of different doses and response, and dividing patients based on stage of disease, type of symptoms, and possible physiologic cause will help us to better understand GDNF's potential as a disease-modifying treatment for PD[4].

Conclusion

GDNF is a neurotrophic factor that has been shown to protect and regenerate DA producing neurons. Early animal studies have shown promise with results of neuroprotection and regeneration of DA neurons and improvement in symptoms. However, clinical trials have not replicated the same results in human patients. Factors that may contribute to this disparity include insufficient dopamine production in humans compared to animal models, differences in the causes of neurodegeneration, and insufficient doses of GDNF. Recent developments in using biomarkers to diagnose PD early before significant DA neuron degeneration may offer opportunities for more effective GDNF intervention. Also, gene therapy approaches using viral vectors and nano particles are being explored. While GDNF's potential as a PD treatment remains, further research is needed to fully understand its role in PD treatment.

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