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Bridging between transplantation therapy and neurotrophic factors in parkinson's disease

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Abstract

Parkinson's disease (PD) represents a challenging condition where different therapeutic options have evolved over the last 50 years. The potential use of cell transplantation for cell replacement or gene delivery of neurotrophic factors has received a great deal of attention. Currently, all available treatment options are directed towards the amelioration of symptoms. A greater understanding of the distinctive pathology underlying PD might offer some novel therapeutic approaches. Transplantation of embryonic ventral mesencephalon (VM) dopaminergic neurons has shown promise in animal studies, but similar transplant procedures have shown limited success in clinical trials. One important issue may be the site of transplantation. Previous studies have transplanted VM into the striatum, which is the target of these neurons. With increased understanding of growth and guidance molecule effecting dopaminergic neurons, it may be feasible to place transplants in the damaged substantia nigra and direct the growth of axons into target regions to reconstruction midbrain dopamine circuitry. In this review, we discuss transplantation therapy and how selective guidance molecules could be used to reconstruction of nigrostriatal circuit.

Keywords

Neurotrophins; Parkinson's disease; dopamine; transplants; netrin

2. INTRODUCTION

PD is typically characterized as a disease of the basal ganglia, with a progressive degeneration of dopaminergic neurons located in the substantia nigra (SN) and projecting to the striatum with subsequently loss of the nigrostriatal circuit. The loss of dopamine in striatum results in motor dysfunction, including resting tremor, muscular rigidity, bradykinesia and postural instability. Many strategies have attempted to reconstruct this circuit but failed to satisfy clinical trials. No complete therapies are yet available that

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reverses or slows down the progression of this illness. The inhibitory environment of the adult brain and the long distance between the SN and the striatum make the reconstruction of nigrostriatal circuits difficult. The concept of restoring or repairing damaged neural pathways can be broadly divided into techniques that involve neurotrophic factors for dopaminergic neurons survival and the transplantation of dopaminergic cells for cell replacement. Transplantation mechanisms for repair in PD have utilized human fetal graft techniques in which embryonic dopaminergic cells are harvested from the developing midbrain. The clinical outcomes of these studies have been mixed but show very good transplant survival in the striatum and integration of grafted dopaminergic neurons (1, 2, 3, 4). Some trials evaluating human fetal grafting raised significant concerns about this technique with a number of patients developing 'off'-medication dyskinesia (5, 6). The other exciting novel therapy that has gained interest in recent decades is the use of neurotrophic factors (NFTs) to enhance neuronal survival. NTFs are secreted proteins that regulate multiple aspects of neuronal development including neuronal maintenance, survival, axonal growth, axonal guidance and synaptic plasticity. These properties of NTFs make them likely candidates for preventing neurodegeneration and promoting neuroregeneration. Thus fine tuning of transplantation therapy with neurotrophins may lead to novel therapeutic strategies for Parkinson's disease.

3. BRIEF BACKGROUND ABOUT PD

The symptoms of PD were first described in the year 1817 by James Parkinson. He named the disease Paralysis agitans (shaking palsy). The French neurologist Jean-Martin Charcot in 1886 renamed this disorder to PD after James Parkinson. The cardinal motor symptoms of PD are resting tremor (tremors while at rest), rigidity (resistance to passive movement), bradykinesia (slowness of movement) and postural instability (poor balance).

The pathology of the disease is characterized by the accumulation of a protein called alpha-synuclein into inclusions called Lewy bodies in neurons, and the selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc). The selective loss of dopaminergic neurons in SNpc subsequently causes a profound reduction of dopamine in the striatum. When 50–60% of the DA neurons degenerated and 70–80% of DA terminals in the brain have been depleted, the motor symptoms become evident (7). Overtime the level of dopamine will continue to decrease and the motor symptoms will continue to worsen.

Approximately 1% of the population at age 65 has PD and the incidence increases with age, reaching 5% at age 85 (8). Young-onset PD (below 40 years old) affects 5–10% of patients. The ratio of men to women is about 2:1. Ethnicity does not affect the risk of PD (9).

Several factors are involved including aging, genetic mutation and environmental factors (10). Aging is one of the major factors in the development of PD. After age 50, normally up to 6% of DA neurons in the substantia nigra are lost (11) and this number increases with age. Another important factor for PD development is genetic mutation. There are two major types of PD. One is the heritable PD, which accounts for about 10% of PD cases. Heritable PD is associated with mutations in a number of specific genes, including alpha-synuclein, LRRK2, Parkin, PINK1, DJ1, ATP13A2 and FBXO7. Mutations in these genes potentially

lead to autosomal dominant or autosomal recessive forms of PD (12, 13, 14, 15, 16, 17, 18, 19, 20). Another type of PD is sporadic, which accounts for 90% of all PD cases. The sporadic PD is related to environmental factors. Exposure to pesticides, industrial wastes and neurotoxins are thought to be involved in disease progression (21). Interactions of all these factors likely drive the progressive loss of DA neurons within the SN. Studies have shown that some common factors causing DA cell death are impaired energy metabolism produced by mitochondrial dysfunction, selective oxidative stress in the SN and accumulation of toxic proteins due to inefficiency of the ubiquitin-proteasome pathway (22, 23, 24, 25, 26).

4. PHARMA THERAPY

With advances in the understanding of the etiology and molecular pathophysiology of PD, a variety of pharmacologic therapies have been developed, aiming to replace lost dopamine to alleviate motor symptoms. The most widely used type of medication is the dopamine precursor called L-3, 4-dihydroxyphenylalanine (levodopa, L-dopa). Levodopa helps to alleviate the tremors and muscle stiffness that come with the disease. However, long-term treatment with levodopa eventually leads to reduced clinical benefits and troubling motor complications known as “levodopa–induced dyskinesia”. Long-term use can also cause hallucinations (27, 28, 29, 30, 31). Other medications have also been used to treat Parkinsonian symptoms as alternative or complementary medications, such as DA agonists, monoamine oxidase (MAO) inhibitors cathecol-O-methyltransferase (COMT) inhibitors, 5-HT1A agonist sarotizan, adenosine A2A antagonists, anticholinergics, amantadine and opioids. These medications act through different mechanisms (25, 32, 33, 34). These pharmacologic treatments, although having benefits at early stage of PD, are not always effective in treating PD over time.

5. NEUROTROPHIN THERAPY

GDNF and neurturin (NTN) are the two main members of the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs) widely tested in animal models of PD and clinically tested in PD patients. GDNF has neuroprotective and neurorestorative effects on dopaminergic neurons demonstrated using adeno associated virus (AAV) in rodents (35, 36, 37, 38), AAV in non-human primates (39, 40, 41, 42), Lentivirus (LV) in rodents (43, 44, 45, 46), LV in non-human primates (38, 47), Adeno virus in rodents (48, 49, 50, 51) and Herpes Simplex Virus in rodents (52, 53). A recent study using gene delivery of GDNF in an aged rhesus monkey model of PD suggests that the degree of neuroprotection depends on GDNF levels (54). Likewise, Neurturin (NTN), the homolog of GDNF has recently also show effectiveness in promoting neuronal survival. NTN shares 42% protein homology with GDNF, uses similar signaling pathways (55), and promotes survival of dopaminergic neurons (56). AAV-mediated delivery of NTN in a rodent model of PD shows bioactive NTN is stably expressed, is neuroprotective, and shows no adverse effects (57, 58). Injections directly into the striatum have growth-promoting effects on dopaminergic neurons within the substantia nigra (59). Studies using AAV-NTN in a primate model show long-term expression and neuroprotection with no adverse side effects with a wide safety margin of dosages (59, 60, 61, 62).

6. CLINICAL TRIALS: BENEFITS AND TRIBULATIONS

Based on the encouraging results from animal studies, the first clinical trial using GDNF in PD patients was initiated in 1996. Direct bolus injections of GDNF into the lateral ventricles were initiated for trophic factor delivery. The study was unblinded after the first 8 months and the results were disappointing. Patients showed no statistically significant recovery and several adverse events including nausea, vomiting and anorexia occurred for several days after GDNF administration. Patients who received higher doses of GDNF also experienced weight loss and symptoms of depression. Postmortem analysis of one patient from this study indicated that GDNF did not efficiently diffuse out of the lateral ventricles and, thus, was unable to elicit any effect in the striatum or the substantia nigra (63). The trial initiated by AMGEN was halted in September 2004 (64).

Amgen optimistically again conducted an initial Phase I open-labeled trial for intra-putamen injection of GDNF in five patients (65). No adverse side effects were reported after 1 year of treatment, and in fact significant decreases were reported in both “on” and “off” Unified Parkinson’s Disease Rating Scale (UPDRS) scores. Postmortem analyses of one of the patient’s brain tissue indicated that there was a more than five-fold increase in tyrosine hydroxylase immunoreactivity in the right putamen (infused side) compared to left putamen (66). Patients received these unilateral infusions also showed increased growth-associated protein 43 (GAP43) staining in the right putamen. The increased TH staining in the putamen might either be a result of sprouting of fibers or an upregulation of the enzyme in spared fibers.

The intra-putamen delivery of AAV-NTN (CERE-120) was also performed in humans for dosing, tolerability and safety (67, 68). Phase II testing failed because there was no change in the primary UPDRS motor off score at 12 months (Ceregene, Press Release 11/26/2008). Unfortunately, Phase II clinical trials have failed for both GDNF and neurturin (CERE-120) in PD patients (69). Briefly, initial results of intra-putamen GDNF administration in PD patients were promising but a Phase II double-blinded study was halted prematurely, mainly because of two safety issues (64). One concern was the detection of antibodies to GDNF in blood samples of some patients. The other safety concern was the formation of lesions in the cerebellum of rhesus monkeys receiving high doses of GDNF within the putamen for a 6 month-period.

7.1. Transplantation therapy

Transplantation therapy for PD can be divided into two types i.e intrastriatal transplantation and nigral transplantation. Transplantation of neuronal tissue has been extensively studied both in animal models and in clinical trials, in an effort to regain lost function in PD. The most commonly transplanted cell type in the rodent models of PD is dopaminergic neurons from the ventral mesencephalon (VM) of developing embryos (70, 71, 72, 73). Rodent striatal transplantation was done by direct injection of these cells into the striatum (5, 74, 75, 76). In an open clinical trial, 40 patients between 34 to 75 years of age having severe Parkinson’s disease (mean duration, 14 years) received striatal transplants of these cells (5). In transplant recipients, cultured mesencephalic tissue from four embryos was implanted into the putamen bilaterally. In summary, human embryonic dopamine-neuron transplants

survive well in patients with severe Parkinson's disease resulting in some clinical benefit for younger but not for older patients. The occurrence of late dystonia and dyskinesia in five of the patients with transplants indicates that the surgical technique needs further refinement. Another double blind, placebo-controlled clinical trial also failed to show significant clinical benefit after fetal nigral transplantation (77). In this study, transplantation was associated with modest improvement in more traditional motor outcomes, particularly in patients younger than 60 years, but approximately 15% developed a disabling form of dyskinesia. Thus, fetal nigral transplantation failed to provide significant clinical benefits despite having evidence of survival of high numbers of implanted cells. The role of nigral transplantation as a treatment for PD thus has not been established.

The use of human fetal tissue as a source for transplantation has always posed a number of ethical and practical concerns and it is possible that these could be avoided by the use of human embryonic stem (ES) cells or induced pluripotent stem (iPS) cells. ES cells could potentially provide an unlimited source of human midbrain dopaminergic neurons with appropriate neural precursor cell selection and culture techniques (78). Transplantation of these cells into animal models of PD induced partial functional recovery, although evidence of striatal reinnervation or in vivo dopamine release was not demonstrated. One major concern regarding ES cells is their underlying potential to produce tumors (79). Unlike ES cells, iPS cells are a potential autologous source of dopaminergic cells with reduced concerns for both ethical and immunological difficulties. They are derived by exposing a patient's own somatic cells, such as fibroblasts (80) to genetic manipulation. The functionality has only been demonstrated using mouse fibroblasts in a rat model of PD (81). Evaluation of the potentiality of stem cell therapy has been gained through a number of clinical trials (82, 83, 84). The long-term success of these grafted cells is difficult to predict. Although they have the ability to form synaptic connections within the host, it remains unclear if grafted stem cells will be able to match similar levels of refinement as observed with fetal VM transplants. It may be possible to improve treatment efficacy by generating stem cells with dopaminergic characteristics that also release trophic factors like GDNF for therapeutic value of PD patients.

7.2. Axonal targeting in transplantation therapy of Parkinson's disease

A few studies have attempted to reconstruct the nigrostriatal pathway by placing the transplants into the substantia nigra (85, 86, 87). Several studies have been done using "bridging" techniques to create a growth supportive conduit extending from the substantia nigra to the target striatum. Bridges have been created by injecting GDNF (88), dissociated striatal tissue (89), fibroblast growth factor (FGF)-4-secreting schwannoma cells (90), GDNF-secreting Schwann cells (91) and kidney tissue (92). Although these techniques increased the growth of tyrosine hydroxylase (TH^+) fibers from the SN to the striatum and resulted in some improvement in motor recovery, the amount of striatal reinnervation was still too low to reach clinical relevant behavioral improvement such as spontaneous motor behavior changes.

Further improvements are still needed to reconstruct of nigrostriatal circuit after placing the transplant into the substantia nigra. We have established long distance directional growth

of dopaminergic axons from VM transplant along pathways of netrin-1 and GDNF in the rat brain (93). The goal of this research is to reconstruct nigrostriatal circuit by targeting dopaminergic axons to the striatum along the nigrostriatal pathway prepared by lentiviral expression of axon growth supporting molecules (GDNF, GFRα1, Netrin-1) in a 6-hydroxy dopamine (6-OHDA) induced rat model (Figure 1). Identifying guidance molecules involved in directing the growth of grafted neurons could be useful for cellular therapy in Parkinson's patients, as these molecules may help direct axon growth over the long distance they have to travel from the substantia nigra to the striatum. We are presently using this method to identify dopaminergic axons growth and guidance factors for improving transplantation therapy.

7.3. Factors affecting growth and targeting of dopaminergic axon

Previous studies show GDNF increases survival of dopamine neurons, but was not known to act as a guidance factor for these neurons. It has been widely used in animal models and in clinical trials for Parkinson's disease (94, 95, 96, 97). It has also been shown to increase differentiation, fiber outgrowth and dopamine release of fetal midbrain dopaminergic neurons both in vitro and in vivo (98, 99). GDNF has been used successfully to increase the survival of fetal dopaminergic cell transplants in the 6-OHDA-lesioned rat striatum (100,101). Viral mediated over-expression of GDNF within the striatum establishes a gradient that induces axon growth into the striatum from dopaminergic neurons within nigral transplant in both mouse and non-human primate models, thus acting to guide axon towards their target. Both studies were performed in partially lesioned animals. Complete lesions in the mouse model failed to show growth of transplanted axons toward the striatum, indicating surviving endogenous dopaminergic might act as a growth supportive scaffold. Although, there is little evidence supporting the role of GDNF as a chemo attractant for dopaminergic axons, when combined with the GPI-linked glial cell line-derived neurotrophic factor receptor α1 (GFRα1) there is an attractive guidance effect on other populations of GDNF-responsive neurons (sensory and sympathetic) (102). The signaling of GDNF has been shown to be dependent of binding to its co-receptor GFRα1. This dimer complex binds to the transmembrane receptor tyrosine kinase RET, causing auto phosphorylation and activation of downstream signaling events (103). In another signaling pathway independent of cRET, NCAM acts an alternative receptor for GDNF/GFRα1. Signaling through this pathway activates the cytoplasmic protein tyrosine kinases Fyn and FAK in cells, thus stimulates axonal growth (104, 105). GDNF signaling can occur by forming dimmers with GFR-α1 on neurons themselves (cis mechanism), or between the neurons and substrate or target cells (trans) (106). In the trans configuration GFRα1 has been shown to bind and increase the local concentration of GDNF to enhance short or long range directional guidance of axons even when in a uniform concentration (102).

Another molecule which acts as a chemo attractant guidance cue is netrin-1, which has recently been shown to have positive directional effects on neurite outgrowth from cultured dopaminergic neurons (107). Netrin-1 is well-characterized member of the netrin family of guidance cues. It has been identified as a bi-functional guidance factor, either attracting or repelling extending axons during the development of the central nervous system (108, 109, 110, 111). The attractive or repulsion actions of netrin-1 are known to depend on the

activation of specific receptors or receptor complexes on the cell surface: the deleted in colorectal cancer (DCC) or the UNC5 homologues (UNC5H, A-D), respectively (112, 113). Down syndrome cell adhesion molecule (DSCAM) has been identified as a novel netrin-1 receptor involved in signaling axon guidance but the signal transduction has not been well understood (114, 115). Netrin-1 binds to DCC receptor and signals through downstream proteins that regulate cytoskeletal reorganization, thus causes growth cone extension and neurite growth (107, 116, 117). Netrin-1 directs the assembly and disassembly of actin filaments by activation of the Rho family of small GTPases (118, 119) and promotes actin polymerization in lamellipodia and filopodia by activation of Rac and Cdc42 (120, 121). Deleted in colorectal cancer (DCC) receptor is widely expressed in developing brain. However, in adult brain DCC is only expressed in limited populations of neurons, the majority of them being ventral A9 dopamine neurons in the substantia nigra (122). In addition, there is a dramatically decrease in the ratio of DCC: UNC5H receptors expression in the DA neurons after puberty with UNC5H receptors predominance (123). When UNC5H receptors signaling predominate in the dopaminergic neurons in our adult animals, no endogenous dopaminergic axons growth were seen.

8. SUMMARY AND PERSPECTIVE

The original restoration of nigrostriatal dopaminergic system in PD focused predominantly on the transplantation therapy. Most strategies graft embryonic dopaminergic neurons into the striatum, with only a few studies attempt to reconstruct the entire nigrostriatal pathway by grafting into the substantia nigra (124, 125, 126, 127). In this review, we discussed transplantation studies performed over the past 10 years and summarize the current knowledge of cellular and molecular signals involved in mediating survival, growth and guidance of dopaminergic neurons. A major challenge in transplant therapies in the SN is to identify potential dopaminergic growth factors and assay their ability to direct axon growth along an appropriate pathway to reach their targets.

A definitive therapy for PD is reliant upon a complete understanding of the underlying neurodegenerative process, and future strategies need to be developed that are able to stop or reverse progression of the disease. Clarification of the molecular mechanisms of interaction between transplants and neurotropic factors will provide the optimal therapeutic target for PD and perhaps represents the only real hope for a potential cure for the disease in its entirety. It might be worthwhile in future studies to introduce combined manipulation of both the intrinsic growth properties of neurons while providing extrinsic factors to create a favorable local environment for axonal growth and connection. For example, a recent study induced denervating lesions to the striatum and used AAV encoding Akt/Rheb to transduce surviving dopaminergic neurons in the SN to promote recovery (128). They demonstrate that expression of Rheb expression promoted axons growth and reinnervation of the striatum. It will be easier for transplanted neurons with a higher intrinsic growth capacity to extend axons within the inhibitory environment of the adult brain and reinnvervate the denervated striatum, especially with the help of growth factors.

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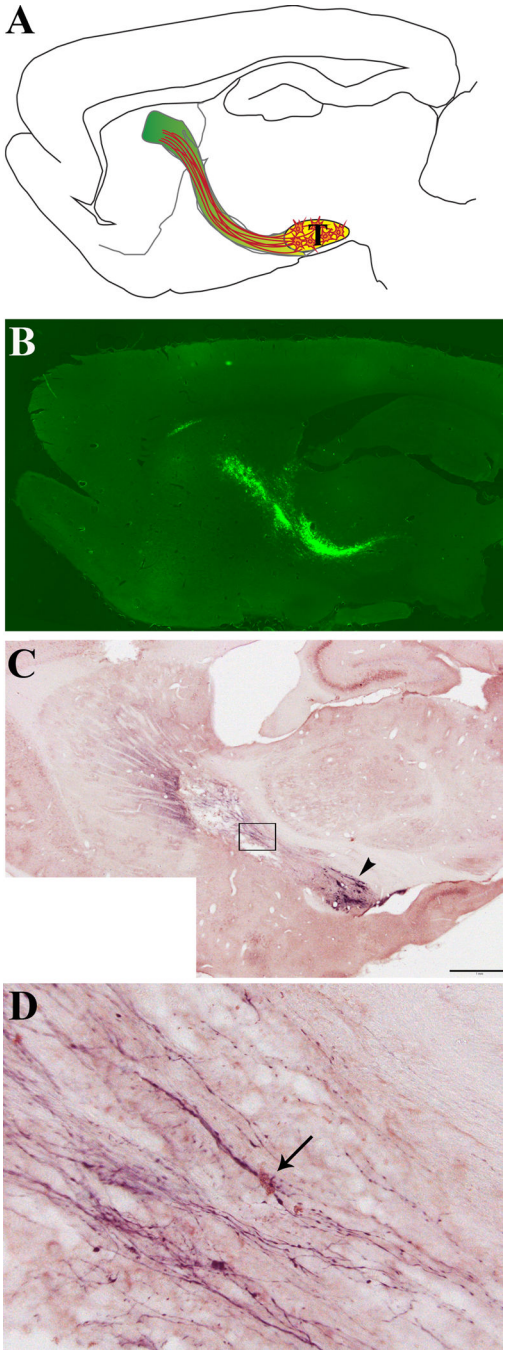

Figure 1.

Reconstruction of the nigrostriatal pathway in adult rats: A) Schematic diagram showing the location of transplant (T), the preformed growth supportive pathway (green), and axons growing along the pathway (orange lines). B) A sample sagittal section from a brain injected with lenti-GFP, showing GFP expression (fluorescence) all along the pathway between the midbrain (lower right) and the striatum (upper left), with some spread of expression within the corpus callosum (top). C & D) Double immunostaining showing TH^+ fibers and netrin-1 expression along the nigrostriatal pathway. Eight weeks after transplantation, brains

were harvested, sliced in parasagittal sections and stained with antibodies to both tyrosine hydroxylase (TH) and netrin-1, then developed with DAB + Nickel enhancement (purple color, TH) and NovaRed (pink color, netrin-1). C) Low magnification image showing TH^+ axon outgrowth along the preformed growth pathway extending from transplant (arrowhead) to striatum, scale bar = 1mm. D) Higher magnification of boxed area in A, arrow points to a cell with high expression of netrin-1 with a thick bundle of TH^+ axons growing over it.