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Emerging restorative treatments for Parkinson's disease

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ABSTRACT

Several exciting approaches for restorative therapy in Parkinson's disease have emerged over the past two decades. This review initially describes experimental and clinical data regarding growth factor administration. We focus on glial cell line-derived neurotrophic factor (GDNF), particularly its role in neuroprotection and in regeneration in Parkinson's disease. Thereafter, we discuss the challenges currently facing cell transplantation in Parkinson's disease and briefly consider the possibility to continue testing intrastriatal transplantation of fetal dopaminergic progenitors clinically. We also give a more detailed overview of the developmental biology of dopaminergic neurons and the potential of certain stem cells, i.e. neural and embryonic stem cells, to differentiate into dopaminergic neurons. Finally, we discuss adult neurogenesis as a potential tool for restoring lost dopamine neurons in patients suffering from Parkinson's disease.

Contents

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Abbreviations: Ad, adenovirus; AAV, adeno-associated virus; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; CD45, cluster of differentiation 45; CNTF, ciliary neurotrophic factor; CSF, cerebrospinal fluid; DAT, dopamine transporter; E, embryonic day; EB, embryoid bodies; EGF, epidermal growth factor; ELISA, enzyme-linked immunosorbent assay; En, engrailed; ESC, embryonic stem cell; F-DOPA, fluorodopamine; FGF, fibroblast growth factor; Foxa, forkhead/winged helix transcription factors; Gbx2, gastrulation brain homeobox 2; GDNF, glial cell line-derived neurotrophic factor; Girk2, G-protein-coupled inwardly rectifying K^+ channel; h, human; IGF, insulin-like growth factor; L-dopa, levodopa; LIF, leukemia inhibitory factor; Lmx1a, LIM homeobox transcription factor 1; LV, lentivirus; m, mouse; Mash1, mammalian achaete scute homolog 1; MPTP, methylphenyltetrahydropyridine; Msx1, muscle segment homeobox transcription factor 1; NCS, neural stem cell; NeuroD, neurospecific basis helix–loop–helix transcription factor; NGF, nerve growth factor; Ngn2, neurogenin 2; NTN, neurturin; NT4/5, neurotrophin-4/5; Nurr1, nuclear receptor 1; Otx2, orthodenticle homolog 2; PET, positron emission tomography; Pitx3, paired-like homeobox transcription factor 3; PD, Parksinon's disease; PSA-NCAM, polysialylated neuronal cell adhesion molecule; SDIA, stromal-derived inducing activity; SGZ, subgranular zone; SHH, sonic hedgehog; SVZ, subventricular zone; TAT, the protein transduction domain of transactivating transcription polypeptide; TGF, transforming growth factor; TH, tyrosine hydroxylase; VMAT2, vesicular monoamine transporter 2; Wnt1, wingless-related 1; 6-OHDA, 6-hydroxydopamine.

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1. Introduction

Almost 20 years ago, the first successful cell transplantation trials in Parkinson's disease (PD) patients promoted the view that the damaged brain can be repaired by replacing lost neurons (Lindvall et al., 1990). Over the last decade, new discoveries have indicated that the adult human brain has the potential to generate its own new neurons, and that therefore the adult brain is much more plastic than was initially believed (Curtis et al., 2007; Eriksson et al., 1998). Furthermore, the concomitant exploration of several growth factors with neurotrophic capacity, and demonstration that they can promote regrowth of damaged neural connections, have reinforced the view that the adult brain may be amenable to restorative therapies. The idea that adult neurogenesis can be controlled and manipulated to restore lost dopaminergic neurons in the brains of PD patients has attracted recent attention. Meanwhile, another aspect of stem cell research has focused on regenerative medicine, based on attempting to restore lost cells and tissues in the human body by grafting stem cells or their progeny.

The future outlook for existing PD therapies has been reviewed by Singh et al. (2007). Current therapies for PD are primarily based on pharmacological replacement of lost striatal dopamine. Dopamine replacement can be achieved through administration of the dopamine precursor L-dopa, direct activation of the dopamine receptor by agonists, or by augmentation of the remaining dopaminergic neurotransmission through inhibition of dopamine-degrading enzymes. These approaches have achieved remarkable relief of PD symptoms. However, none lead to complete dopamine restoration or marked neuroprotection of the remaining dopaminergic neurons, and long-term drug administration can result in side effects related to disease progression. In advanced disease, the vast majority of patients experience fluctuations in response to medication, a phenomenon known as the "on–off" effect. Patients are able to move during the "on" period, whereas they are immobile during the "off" period. After a few years of drug treatment, most patients exhibit multiple "off" periods every day. In addition, patients may suffer from L-dopa-induced dyskinesias, typically during "on" periods or when they transition from "on" to "off". Patients with this complication can be successfully treated with deep brain stimulation, mainly targeting the subthalamic nucleus. These operations can partially normalize abnormal neural activity in the subthalamic-pallidum connections, which drives some of the symptoms.

Regardless of the known side effects, pharmacological dopamine replacement remains an important therapy, which illustrates the fundamental centrality of the nigrostriatal dopamine system to the symptomatology of PD. Indeed, much would be gained if these neurons could be restored or replaced in the brains of PD patients. The successful transplantation of embryonic mesencephalic cells into the striatum of patients with PD in the late 1980s raised hopes that it may be possible not only to halt progression, but also to actually reverse the disease. The shortage of suitable embryonic donor tissue is a major limiting factor that precludes use of this cell therapy as a general therapy for PD. In addition, results from animal studies indicate that only roughly 10% of these cells survive transplantation (Brundin et al., 2000a). Based on this considerable cell death, and the fact that only few dopaminergic precursors are present in the donor tissue to begin with, enrichment of dopaminergic neurons prior to transplantation would be valuable. Thus, there is an unmet need for a means of generating a large pool of dopaminergic precursors or neurons for use in transplantation procedures.

In this review, we discuss various approaches to restorative therapy in PD (Fig. 1). Some, such as the viral vector-mediated delivery of dopamine-synthesizing enzymes, are based on restoring the neurochemistry of the striatum (Carlsson et al., 2007; Singh et al., 2007). However, in this review we do not discuss attempts to directly restore neurotransmitter-synthesizing enzymes further. Instead we focus on therapies that promote structural and cellular restoration of the basal ganglia in PD patients. These therapies are primarily applicable to patients in which conventional pharmacotherapy has begun to fail. We describe them in order of the PD stages to which they are relevant, as the disease progresses from moderate to severe. Hence, we will first discuss neuroprotection/restoration of the diseased nigrostriatal dopamine system by growth factor delivery, particularly delivery of glial cell line-derived neurotrophic factor (GDNF). When the diseased nigral dopaminergic neurons in the PD brain are beyond rescue, cell transplantation is an option to restore lost neurons. In the next section, we will therefore cover cell transplantation and briefly describe key animal experiments, as well as available clinical data regarding fetal cell transplantation. In the subsequent section, we will describe the developmental biology of dopaminergic neurons, and the characteristics of different stem cells