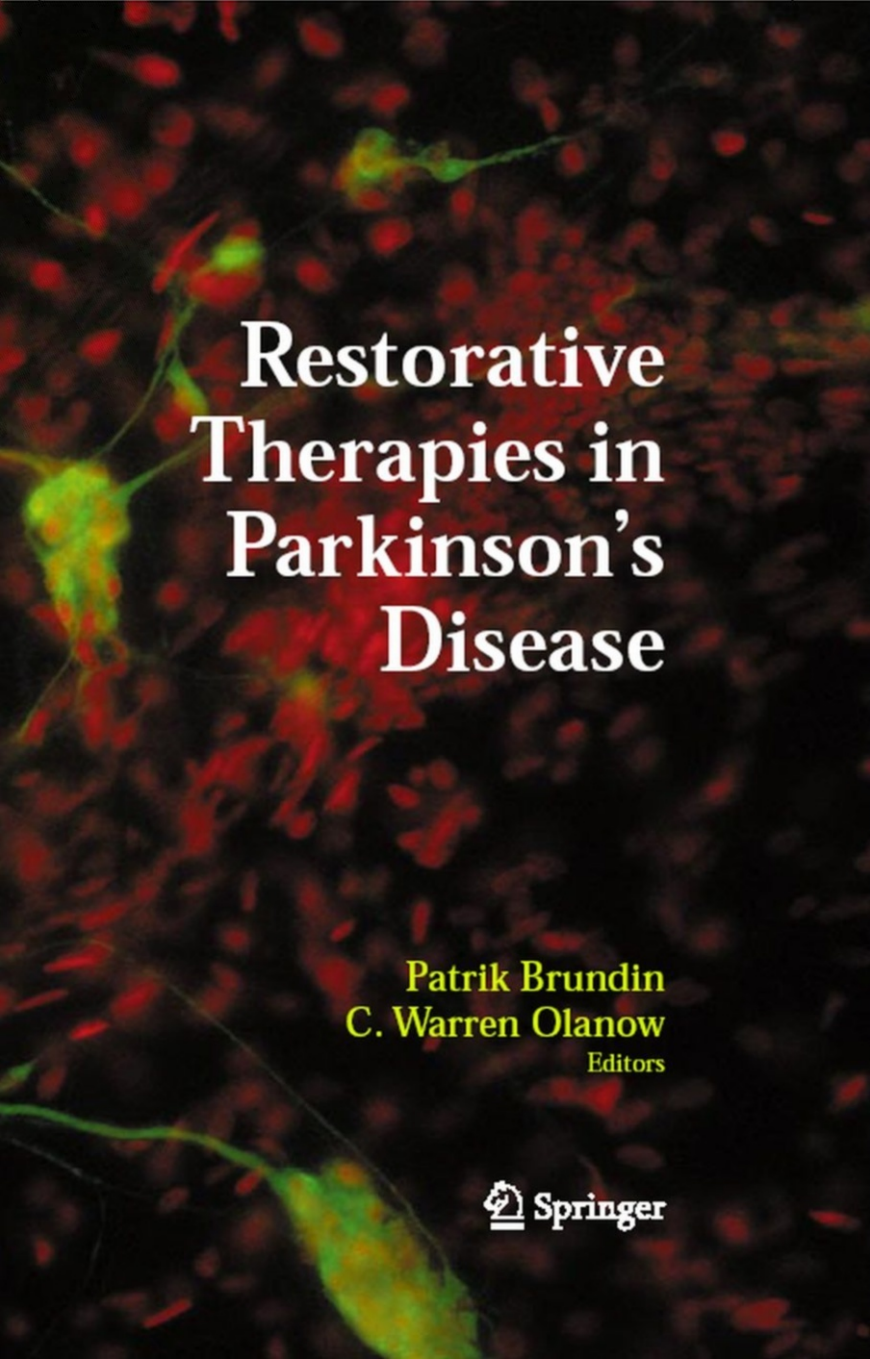

Restorative Therapies in Parkinson's Disease

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Cover Illustration: Photomicrograph demonstrating dopaminergic neurons (stained green using an antibody against tyrosine hydroxylase) derived from human embryonic stem cells. The red label shows that the cells are human (stained using an antibody against human nuclear antigen). This type of stem cell-derived neuron is used for transplantation. Kindly provided by Ana Sofia Correia and Sergey V. Anisimov, Lund University.

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To our families.

Preface

Existing pharmacological treatments for Parkinson's disease (PD) are largely focused on a dopamine replacement strategy. However, despite dramatic motor benefits with levodopa and other anti-parkinsonian agents, particularly in early disease, patients continue to suffer disability with chronic treatment and advancing disease. The majority of patients treated with levodopa for more than 5 years experience motor complications in the form of wearing off and dyskinesia. Further, disease progression is associated with the emergence of features that are not adequately controlled with dopaminergic therapies. These include freezing phenomena, gait dysfunction with postural instability, sleep disorders, autonomic dysfunction, psychiatric problems, and dementia. Further, current therapy does not prevent disease progression – indeed, there is concern that reactive oxygen species associated with the oxidative metabolism of levodopa may accelerate neuronal degeneration. Clearly a therapeutic approach for PD that slows, stops or reverses disease progression is an urgent unmet medical need.

Only three decades ago, a volume on restorative therapies in Parkinson's disease would have been better suited for the science fiction section of book stores. However, over recent years this field of investigation has matured into an area with an impressive array of scientific investigations, and several different approaches to restorative therapy have already been tested in clinical trials.

Restorative Therapies in Parkinson's Disease critically reviews these scientific and clinical studies, and considers whether replacing only the dopamine system is sufficient. It presents two main approaches to improving brain function in the patients: cell replacement and growth factor administration. The concept of neural transplantation entails replacing degenerated dopaminergic neurons with new dopamine cells that can integrate into the host brain circuitry and restore normal dopaminergic anatomy and physiology. Initial laboratory studies demonstrated that transplanted dopamine neurons derived from fetal mesencephalon had the capacity to survive, manufacture

dopamine, and restore motor function in models of PD. Open label clinical studies testing fetal nigral grafts implanted into the striatum reported modest to important therapeutic benefits with excellent restoration of striatal dopaminergic function based on PET and pathology studies. However, the results of these open label trials were not confirmed in double-blind, placebo-controlled trials. This volume discusses in detail these trials, and how transplant protocols might be improved in the future so as to enhance therapeutic benefits and avoid undesirable side effects. It also raises issues concerning research ethics, clinical trial design, and how the grafts best can be assessed using modern brain imaging methods.

The source of transplanted dopaminergic neurons has been an area of intense ongoing research. Of particular interest are stem cells which offer the potential to provide an unlimited supply of dopaminergic neurons for transplantation. These cells can be expanded in cell culture, and induced to differentiate into optimized dopamine neurons that can be tailored to avoid immune rejection. In this volume, experts describe the different forms of stem cells that have the capacity to differentiate into dopamine neurons, and discuss how these multipotent cells might contribute to future cell therapies of PD. Other approaches that have been or may be examined in the future are considered such as porcine xenografts.

A second approach to restoration of brain function described in this volume is the administration of growth factors in an attempt to restore function to host neurons. Similar to the case of neural transplantation, the initial enthusiasm spawned by small open label trials using infusions of glial cell line-derived neurotrophic factor (GDNF) into the brains of PD patients has not been matched by results obtained in a controlled study. Also safety issues with this procedure have been raised. Here too, however, there is still considerable hope for the future. Current studies utilized catheter delivery of trophic factors which may have limited diffusion of the protein and its potential to influence behavioral responses. Novel ways of delivering the growth factor, using genetically modified cells or viral vectors, may resolve both the current efficacy and safety issues.

These approaches to restore brain function in PD represent a pioneering form of translational research. *Restorative Therapies in Parkinson's disease* integrates the viewpoint of physicians and scientists with expertise in neuroscience, neurology, neurosurgery, brain imaging, viral vector biology, neurotrophic factors, developmental and stem cell biology. This research has provided insight into the organization of the normal and PD brain, offered great promise for those who suffer from this disabling disorder, and opened up the playing field for those interested in brain repair in acute and slowly progressing neurological disease. We are very grateful to all the contributors to this volume who have shared their expertise and thereby helped the research community more rapidly bring effective cures to the many patients in need.

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December 11, 2005

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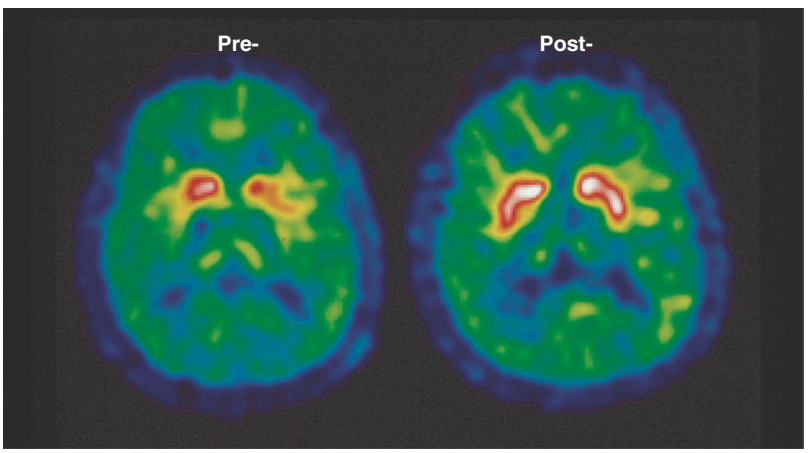

FIGURE 6.1. Flurodopa PET studies in a representative PD patient performed at baseline (**left panel**) and 6 months following bilateral fetal nigral transplantation into the posterior putamen. Note the classical picture of PD at baseline, with reduced striatal uptake particularly in the posterior putamen and the dramatic increase on each side following transplantation.

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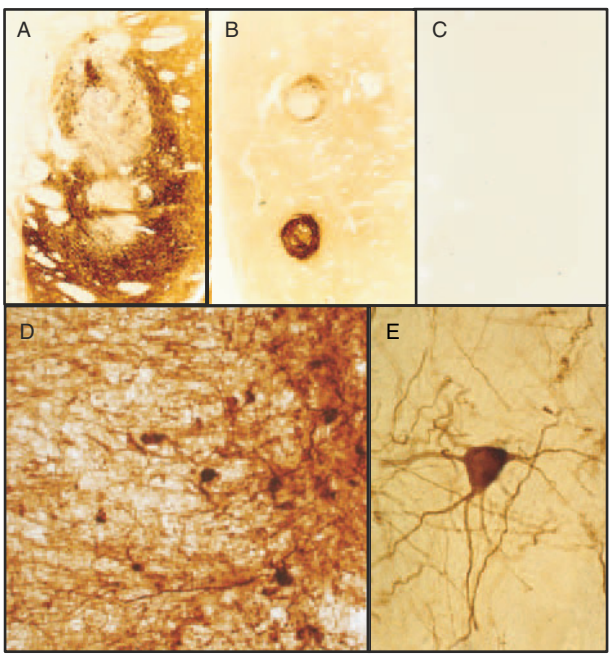

FIGURE 6.2. Tyrosine-hydroxylase immunoreactive staining of the striatum in PD patient receiving transplantation with 4 donors per side (**A**), 1 donor per side (**B**), or a sham procedure (**C**). Note that in the four-donor group, graft deposits have a cylindrical appearance with survival of more than 100,000 dopamine neurons per side. Grafts in the one-donor group have a more dense and circular appearance, with survival of approximately 30,000 TH-positive cells per side, although there still appeared to be continuous TH staining of striatum between graft deposits. High-power images show fibers extending from the graft deposit to provide innervation of striatum (**D**). Higher-power magnification shows normal-appearing implanted dopamine neuron (**E**).

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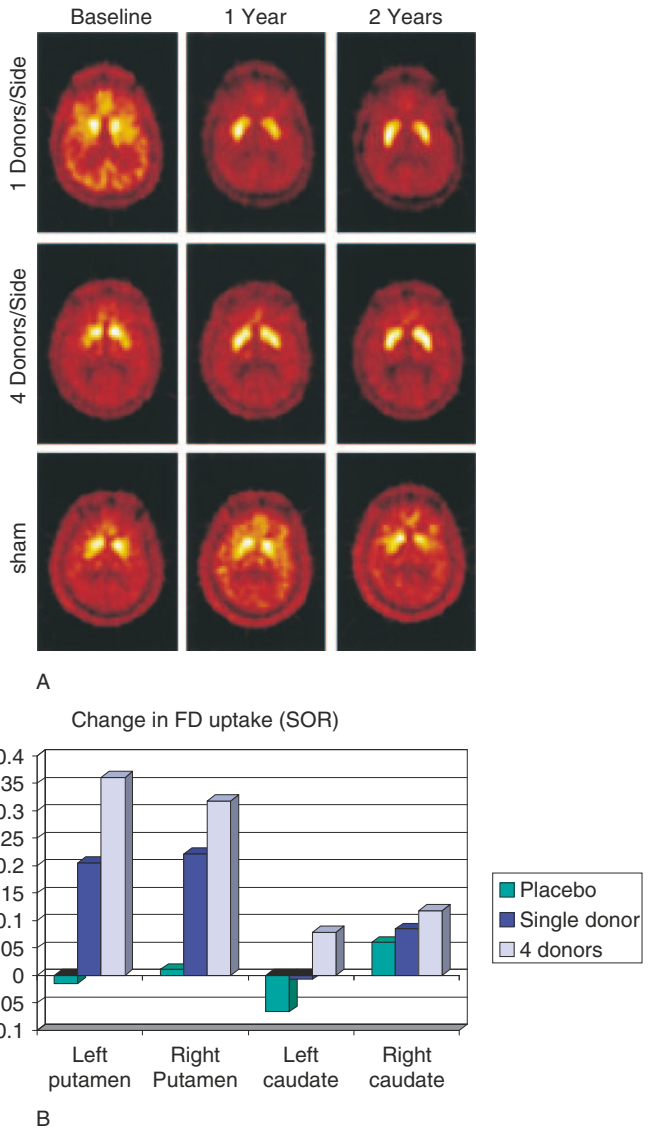

FIGURE 7.1. **A**. Axial PET images of 6-[^{18}F]-fluoro-L-dopa uptake in representative subjects following sham (bottom panel), one (top panel), or four (middle panel) donors per striatum. In the one- and four-donor subjects, there is an increase in tracer uptake seen at one year (middle column), with a further increase at two years (right column). In the sham-operated subject, fluorodopa uptake continues to decline (from Olanow et al., Ann. Neurol. 2003[40]). **B**. Mean change in striatal:occipital ratio of fluorodopa from baseline to two years following transplant. Note that changes are seen in both left and right putamen, but not in the caudate nuclei, which were not implanted (from Olanow et al., Ann. Neurol. 2003[40]).

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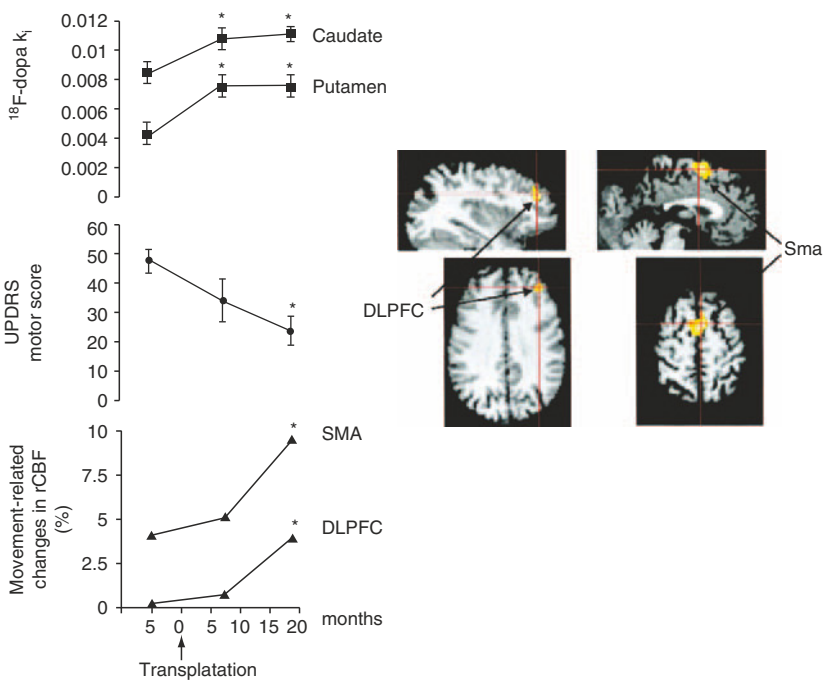

FIGURE 7.2. Increases in fluorodopa uptake following transplantation precede improvement in activation-induced increases in cerebral blood flow in supplementary motor area (SMA) and dorsolateral prefrontal cortex (DLPFC). Increases in the latter are associated with further clinical improvement (from Piccini et al., Ann. Neurol. 2000[1]).

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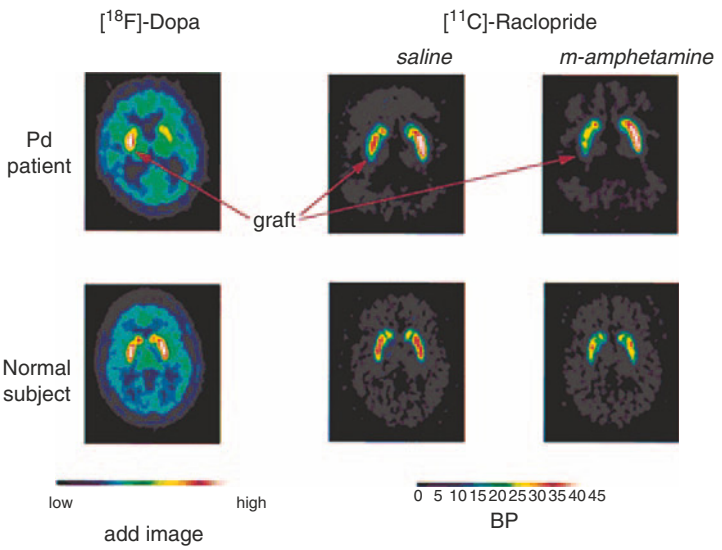

FIGURE 7.3. Fluorodopa uptake (**left panel**) and [^{11}C]raclopride binding (**middle** and **right panels**) in a Parkinson patient with a unilateral transplant in the right striatum (shown on the left side of the image). In the grafted striatum, fluorodopa uptake improves to near normal levels. Following saline injection (middle panel), raclopride binding is increased compared to control levels in the *non-grafted* striatum, with no response to intravenous methamphetamine (right panel). In contrast, raclopride binding is normal in the grafted striatum, with a further reduction following methamphetamine (as seen in controls). This reduction represents occupancy of dopamine receptors by dopamine released in response to the pharmacological stimulus (from Piccini et al., Nat. Neurosci. 1999[31]).

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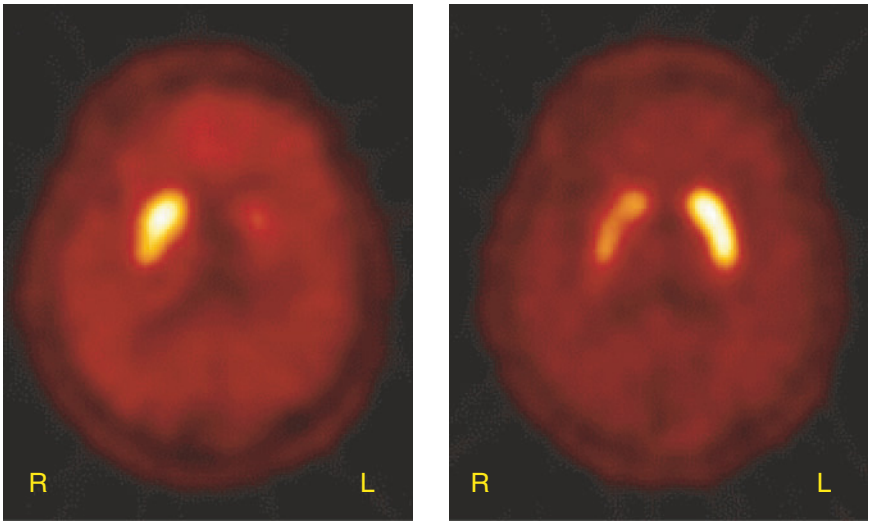

[^{18}F]Fluorodopa [^{11}C]Raclopride

FIGURE 7.4. Fluorodopa and raclopride PET scans in a patient with left hemibody dyskinesias 8 years following transplant. Note that there is a marked increase in fluorodopa uptake in the right caudate nucleus, while raclopride binding is reduced below control levels throughout the right striatum. The findings suggest aberrantly increased dopamine synthesis and release in the striatum contralateral to dyskinesias (UBC-TRIUMF PET team).

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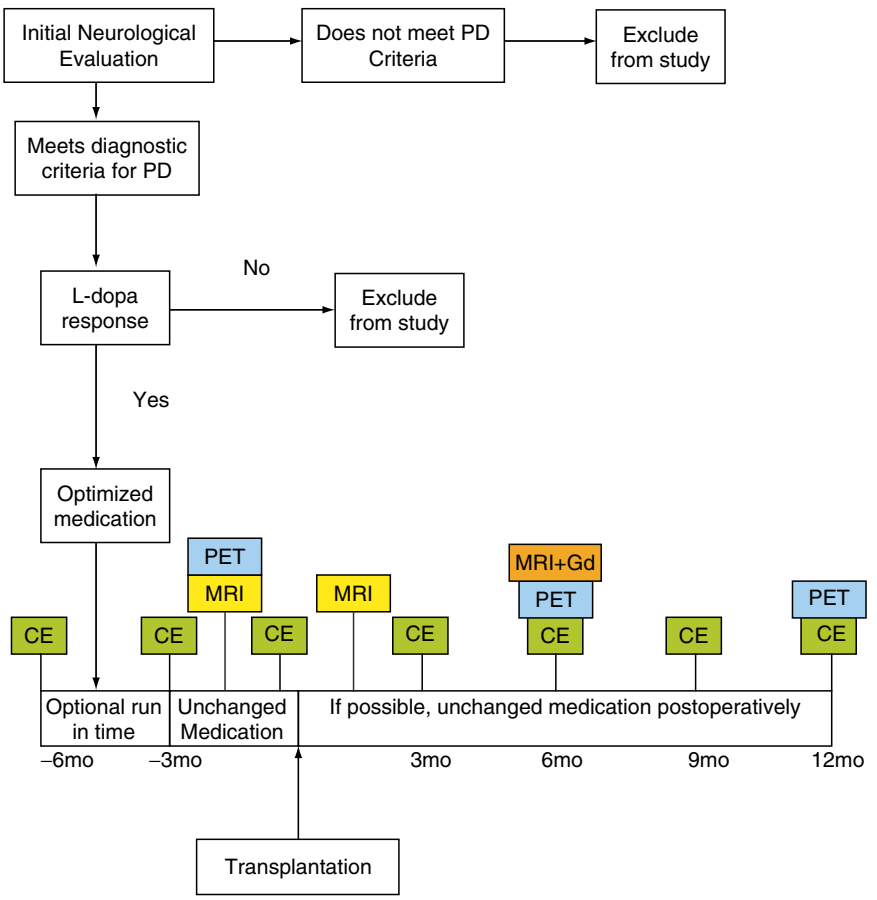

FIGURE 9.1. Schematic of the CAPIT protocol (modified from Langston et al., 1992).

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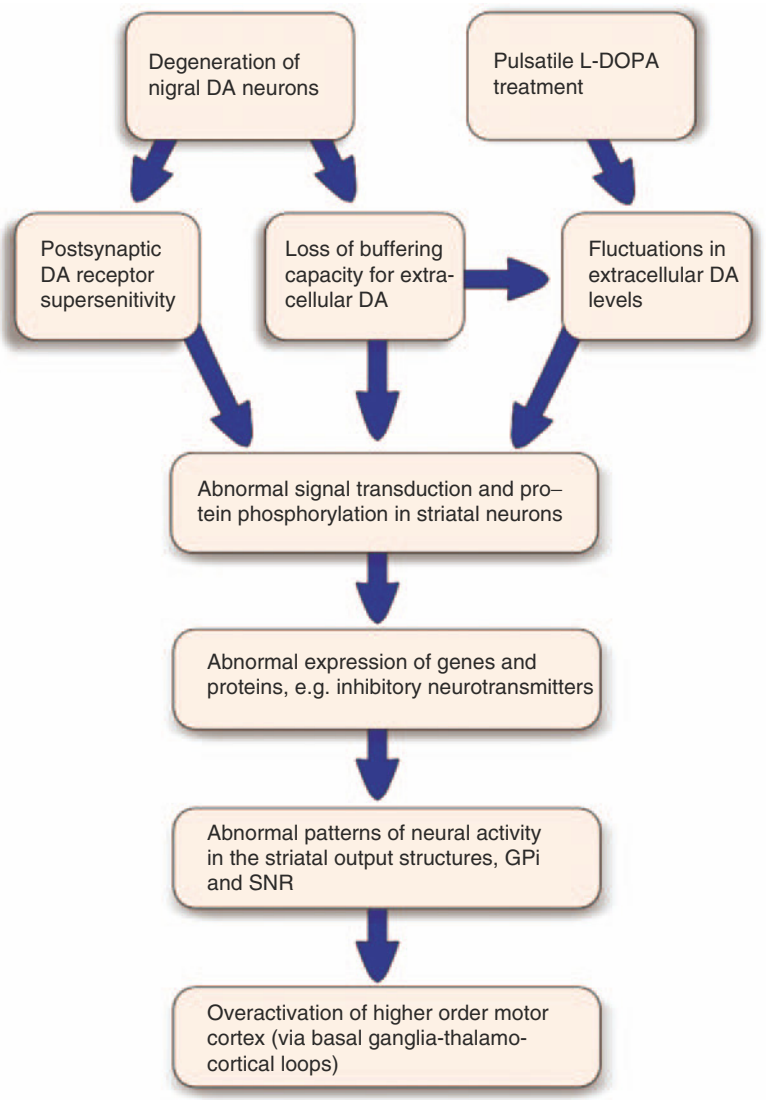

FIGURE 10.1. Flow chart illustrating the sequence of events at the basis of L-DOPA-induced dyskinesia according to commonly accepted notions. GPi, globus pallidus pars interna; SNR, substantia nigra pars reticulata.

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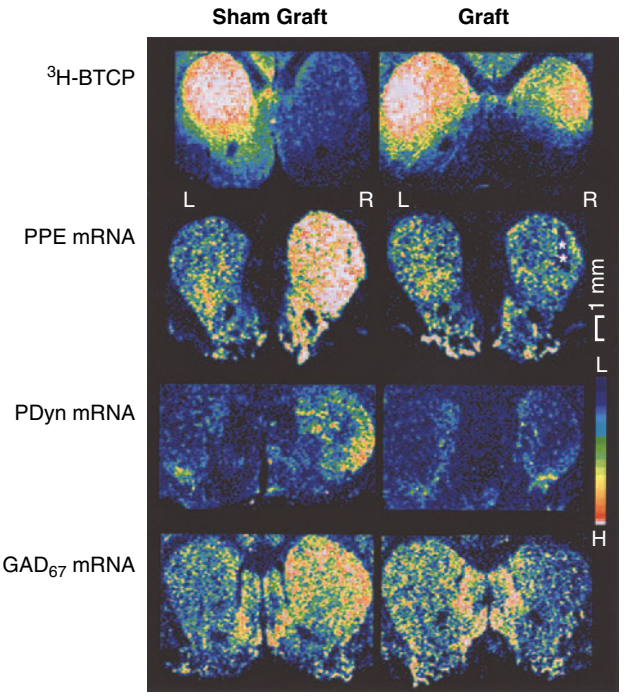

FIGURE 10.3. Pre- and post-synaptic effects of intrastriatal VM grafts in rats with unilateral 6-OHDA lesions that were treated with L-DOPA. In this study VM grafts were found to improve L-DOPA-induced "on" dyskinesia (see Fig. 2). Autoradiographic pictures of striatal sections from VM-grafted rats ("graft") are represented in the right-hand column, whereas pictures from sham-grafted controls ("sham graft") are shown in the left column. In all pictures, the DA-denervated and grafted side of the striatum is shown to the right (**R**), and the contralateral intact side is shown to the left (**L**). [^{3}H]BTCP binding autoradiography (which labels DA uptake sites in the striatum) showed a nearly complete restoration of striatal DA fiber density in the grafted animals. In situ hybridization histochemistry was used to measure the expression of mRNAs encoding for preproenkephalin (PPE), prodynorphin (PDyn), and glutamic acid decarboxylase (GAD$_{67}$). These transcripts are expressed in striatal medium-sized spiny neurons, and are known to exhibit a marked up-regulation following DA-denervating lesions and/or pulsatile L-DOPA treatment (compare lesioned side and contralateral intact side in the sham-grafted animals). The levels of all these transcripts were restored to normal values by the VM grafts (from Lee et al., 2000).

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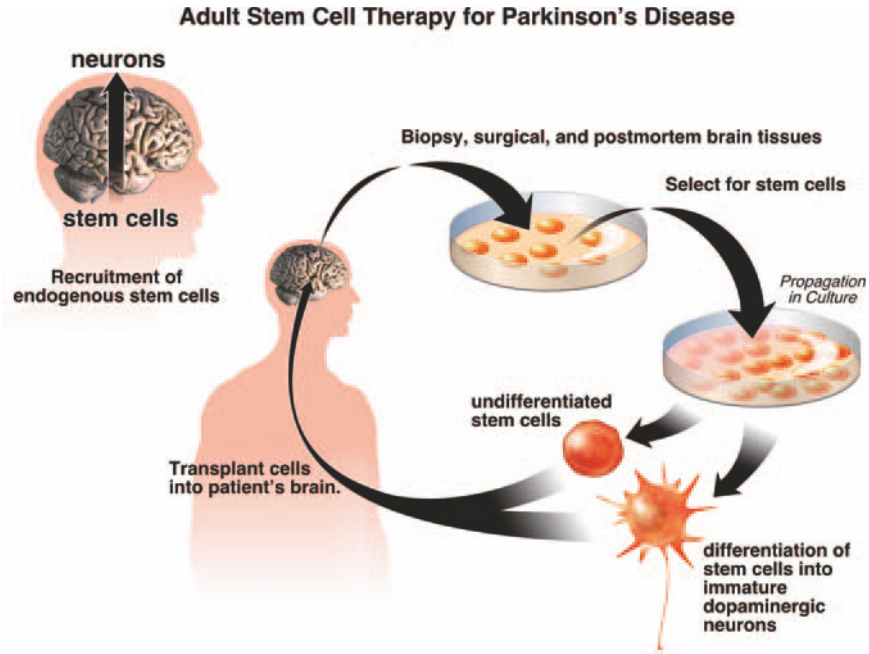

FIGURE 12.1. Schematic diagram showing strategies for using adult stem cells for treating PD. For transplantation therapy, stem cells can be isolated from surgical and post-mortem adult brain tissues, propagated in vitro, manipulated in vitro (e.g., genetically modified, differentiated, etc.) and transplanted into the brain of a patient with PD.

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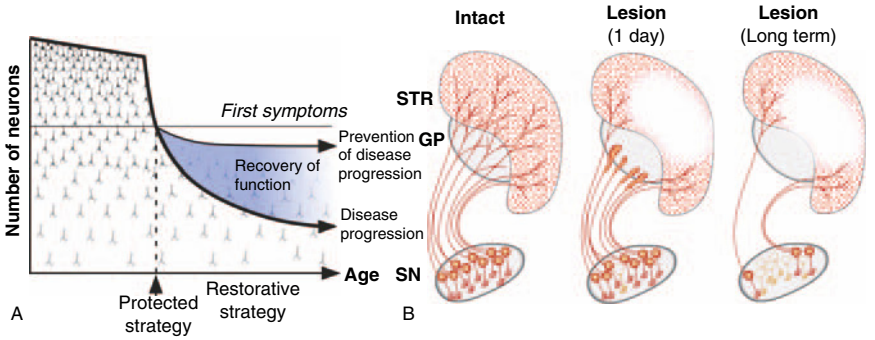

FIGURE 15.1. Protective treatment strategy for Parkinson's disease. **A**: The slow and protracted loss of nigral DA neurons in PD presents opportunities to intervene in the degenerative process and prevent the further progression of the disease. A protective "disease-modifying" treatment strategy would be relevant in the early phases of the disease, when a substantial portion of the nigral DA neurons remain and may involve treatment with neurotrophic factors, such as GDNF. **B**: The intrastriatal 6-OHDA lesion provides us with a progressive nigral cell degeneration model. Injection of 6-OHDA into the striatum induces an acute lesion of the DA axon terminals, followed by a slow retrograde degeneration of the nigral DA neurons.

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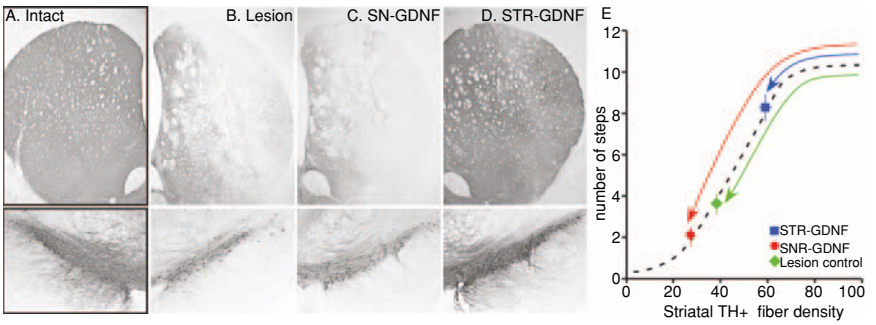

FIGURE 15.2. Protection of the nigrostriatal DA pathway after recombinant GDNF protein treatment. The photomicrographs show cross-sections from the central striatum and corresponding SN immunostained for TH representing four different conditions: (**A**) intact nigrostriatal system, (**B**) vehicle-treated lesion controls, (**C**) nigral GDNF injection group, (**D**) striatal GDNF injection group. Delivery of recombinant GDNF protein into the SN or striatum prior to an intrastriatal 6-OHDA lesion provides a significant protection of the nigral cell bodies as compared with the vehicle-treated controls. Protection of the DA terminals, on the other hand, can only be obtained following delivery of GDNF into the striatum. Note that the performance of the animals in the stepping test can best be explained by preservation of the striatal TH-positive fibers (**E**). The intrastriatal 6-OHDA lesion induces depletion of DA terminals accompanied with a reduction in the number of steps the animals can perform (green arrow in E). While administration of GDNF into the striatum preserves the TH-positive fibers and thus the normal motor function (blue arrow), the nigral GDNF group fails to be beneficial (red arrow). (Figure modified from data published in Kirik et al., 2000a).

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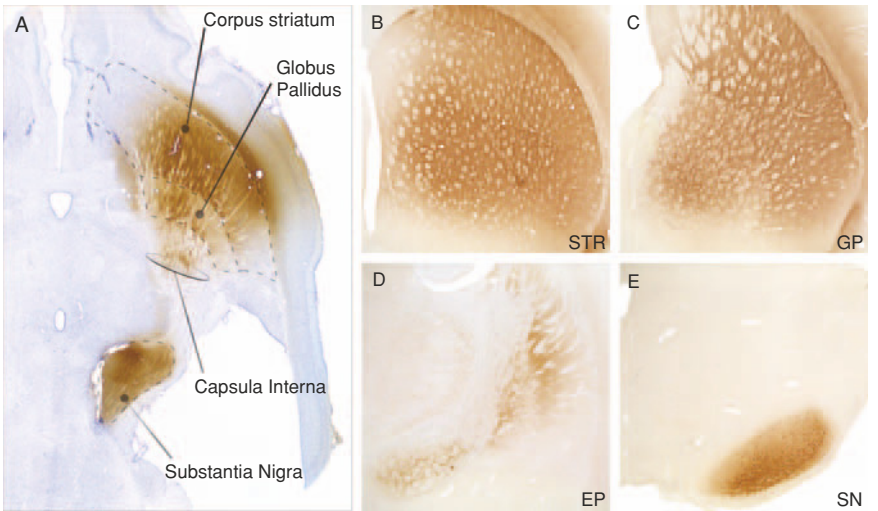

FIGURE 15.3. Expression and distribution of GDNF following rLV-GDNF injection into the striatum. **A**: A horizontal section immunostained for GDNF demonstrates the extensive diffusion of GDNF protein in the striatum, as well as transport and release of GDNF along the striatopallidal and striatonigral projections. In this particular animal, rLV-GDNF was injected into the striatum after a complete 6-OHDA lesion, demonstrating that the transport of GDNF to the GP and SN pars reticulata was in the anterograde direction. Coronal sections from the striatum (**B**) and the different striatal output nuclei (**C–E**) further illustrate the distribution of GDNF. (Figure modified from data published in Georgievska et al., 2002a).

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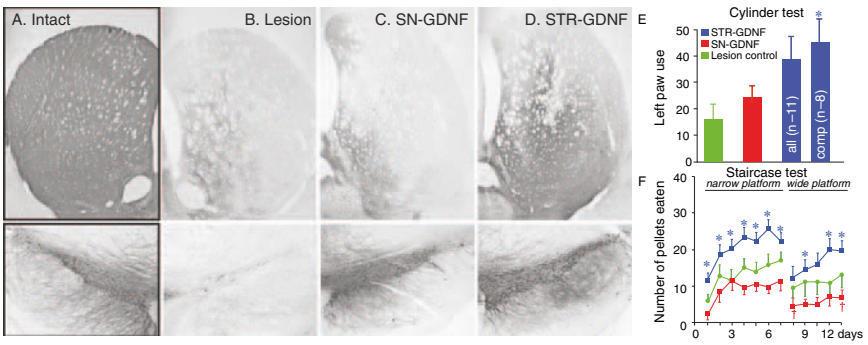

FIGURE 15.4. Protection of the nigrostriatal DA pathway after rAAV-mediated GDNF delivery. The photomicrographs show cross-sections from the central striatum and corresponding SN immunostained for TH representing four different conditions: (**A**) intact nigrostriatal system, (**B**) GFP vector-treated lesion controls, (**C**) nigral rAAV-GDNF injection group, (**D**) striatal rAAV-GDNF injection group. Expression of GDNF protein in the SN or striatum prior to an intrastriatal 6-OHDA lesion provides a significant protection of the nigral cell bodies, as compared with the lesion controls. Protection of the DA terminals, on the other hand, can only be obtained following delivery of rAAV-GDNF into the striatum. The results from the cylinder test (**E**) and the staircase test (**F**) indicate that functional improvements were seen only after delivery of rAAV-GDNF into the striatum (coded by blue colors in E and F), while nigral rAAV-GDNF delivery appeared to be ineffective (compare red to green color). (Figure modified from data published in Kirik et al., 2000b).