Neuronal cell replacement in Parkinson’s disease

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Transplantation of foetal dopamine neurons into the striatum of Parkinson’s disease patients can provide restoration of the dopamine system and alleviate motor deficits. However, cellular replacement is associated with several problems. As with pharmacological treatments, cell therapy can lead to disabling abnormal involuntary movements (dyskinesias). The exclusion of serotonin and GABA neurons, and enrichment of substantia nigra (A9) dopamine neurons, may circumvent this problem. Furthermore, although grafted foetal dopamine neurons can survive in Parkinson’s patients for more than a decade, the occurrence of Lewy bodies within such transplanted cells and reduced dopamine transporter and tyrosine hydroxylase expression levels indicate that grafted cells are associated with pathology. It will be important to understand if such abnormalities are host- or graft induced and to develop methods to ensure survival of functional dopamine neurons. Careful preparation of cellular suspensions to minimize graft-induced inflammatory responses might influence the longevity of transplanted cells. Finally, a number of practical and ethical issues are associated with the use of foetal tissue sources. Thus, future cell therapy is aiming towards the use of embryonic stem cell or induced pluripotent stem cell derived dopamine neurons.

Keywords: dopamine, neurobiology, neurology, neuroscience, stem cell transplantation.

Affected neuronal systems and current treatments

Parkinson’s disease is characterized by cellular loss of substantia nigra pars compacta (SNpc) dopamine neurons that project to the striatum. Dopamine neurons of the ventral tegmental area (VTA) also degenerate, but to a lesser extent [1]. The SN, VTA and subthalamic nucleus (STN) together with the striatum (putamen, caudate and accumbens nuclei) and the globus pallidus (GP) external and internal segments constitute the basal ganglia, a group of subcortical nuclei involved in motor control, cognition, emotions, and learning through interconnections with the cerebral cortex, thalamus and brainstem. Dopamine from the SNpc modulates cortical and thalamic activity through dopamine receptors that facilitate or gate glutamate input. Loss of dopamine neurons in the SN results in motor dysfunction, including tremor, rigidity, bradykinesia and postural instability.

Parkinson’s patients also display disturbances in sleep, cognition and mood, with anxiety and depression occurring in a large group of affected individuals, reviewed in [2]. Many of these nonmotor symptoms are likely influenced by the loss of both dopamine- as well as nondopamine neurons in different disease-affected brain regions. For example, the degeneration of noradrenergic neurons of the locus ceruleus could in part explain symptoms such as depression, anxiety and sleep disturbances [3, 4] and the loss of cholinergic neurons of the pedunculopontine nucleus pars compacta (PPNc) could contribute to motor symptoms and disturbances in sleep and cognition [5, 6]. Furthermore, it has been reported that serotonin neurons of the dorsal raphe nucleus are lost in Parkinson’s
disease and that parkinsonian patients displaying depression show a more severe loss of serotonin neurons [7] and reduced levels of the serotonin metabolite 5-hydroxyindoleacetic acid in the cerebrospinal fluid [8]. Of note, however, also the loss of dopamine neurons likely contributes to depression in Parkinson’s disease [4, 9]. In fact, animal studies have shown that lesioning of both the substantia nigra and the ventral tegmental area can increase depressive-like behaviour in rats [10]. Additional neuronal groups that are affected in Parkinson’s disease include, but are not limited to: (i) neurons of the dorsal nucleus of the vagus nerve, which provide parasympathetic innervation of the heart, gastrointestinal tract, lungs and muscles around the mouth, including the larynx, thereby affecting speech [11], (ii) neurons of the Edinger–Westphal nucleus [12], which influence pupil contraction [13], and (iii) cholinergic neurons of the nucleus basalis of Meynert, which project to the neocortex, and have been correlated with the development of dementia in some Parkinson’s disease patients [14]. Thus, loss of nondopamine neurons in Parkinson’s disease emphasizes that an optimized treatment strategy for parkinsonian patients may necessitate therapy beyond the dopamine system. However, the dopamine system, with its vast projections to areas of the cortex and limbic systems, could likely be responsible for, or contribute to, many of the nonmotor symptoms as well.

The main treatment for Parkinson’s disease is directed at improving the motor symptoms, which are a major burden for patients. Alleviation of motor symptoms is achieved by the administration of the precursor L-DOPA, which is transformed into dopamine within cells (including dopamine neurons) that express the L-aromatic amino acid decarboxylase (AADC). However, only 1–5% of L-DOPA enters the dopamine neurons, whilst the remaining L-DOPA is metabolized to dopamine elsewhere causing a wide variety of side effects. More than 50% of Parkinson’s disease patients develop L-DOPA-induced dyskinesias (abnormal involuntary movements) long term. Furthermore, as the disease progresses, patients develop axial symptoms; i.e. disturbances in gait, posture and speech. In time these symptoms, which respond poorly to L-DOPA, become the main contributors to the motor handicap of the patient. In addition to L-DOPA, dopamine agonists (e.g. pramipexole and ropinirole) are also used to treat motor symptoms of Parkinson’s disease. So called ‘direct’ dopamine receptor agonists can function in the absence of host dopamine neurons, as they act directly on post synaptic dopamine receptors. In contrast ‘indirect agonists’ (e.g. amphetamine) increase dopamine neurotransmission e.g. by increasing dopamine release and therefore require the presence of dopamine neurons. Dopamine agonists are associated with a reduced risk of developing dyskinesias. However, these drugs are less effective and are associated with side effects such as hallucinations, excessive sleepiness and addictive behaviour, reviewed in [15].

In addition to pharmacological regimens, nonpharmacological methods to improve motor function in Parkinson’s disease include surgical methods of which deep brain stimulation (DBS) is currently the most commonly used. In DBS the GP internal segment (GPI), the subthalamic nucleus or more recently the pedunculopontine nucleus (PPN) is stimulated using high frequency electrical pulses (130–185 Hz). Treatment often results in substantial improvements in motor and daily living scores as well as significant reduction in patients’ medications, reviewed in [16]. The precise mechanism of action remains uncertain, but DBS is likely to either inhibit or stimulate brain activity in the targeted brain area. Patients who have undergone DBS generally need to be maintained on L-DOPA.

In contrast to the above described symptomatic treatment methods, transplantation of foetal dopamine neurons into the striatum of affected individuals aims to reconstitute a normal dopamine network capable of restoring feedback-controlled release of dopamine in the nigrostriatal system (Fig. 1). Such cell therapy can alleviate motor deficits in Parkinson’s disease patients [17–33], and in some cases enable patients to discontinue L-DOPA treatment completely [25, 26]. However, as with pharmacological treatment, DBS and gene therapies [34], cellular replacement is associated
with several complications. Below, we review critical experiences from foetal cell grafting in humans and animals. These previous studies emphasize a number of important problems and point out key directions for future work utilizing stem cells as a source for transplantable dopamine neurons.
Survival and innervation of grafted dopamine neurons

The recovery of motor function by grafted dopamine neurons appears dependent upon several crucial parameters. Initially, it is vital that the cells survive the grafting procedure. Survival of cells can be improved by preincubation/hibernation of the cells prior to transplantation with growth factors such as glial cell line-derived neurotrophic factor (GDNF) and substances that inhibit apoptosis [35–37]. However, despite the addition of such factors, cell survival is relatively modest and additional improvements in methodology could substantially improve the feasibility of transplantation. A complementary approach to promoting survival of the cells after grafting would be to increase the number of dopamine neurons in vitro prior to transplantation. For example, incubation of ventral mesencephalic cell suspensions with Wnt1 and/or Wnt5a can augment the number of dopamine neurons by increasing proliferation and/or terminal differentiation of dopamine neuron precursors into mature dopamine neurons [38–40] (Fig. 1).

As initially shown in a rat model of Parkinson’s disease [where 6-hydroxydopamine (6-OHDA) is used to unilaterally lesion the mesostriatal dopamine system], improvement in motor function is correlated to the extent of reinnervation of the denervated striatum by grafted dopamine neurons [41, 42]. Furthermore, for optimal recovery it is important that specific subregions of the striatum are innervated [43, 44], with re-establishment of synaptic connections. The distribution of dopamine neurons throughout the striatum using multiple injection sites can ensure that axonal coverage of the denervated area is optimized [31, 45].

It is important to determine whether grafted cells are able to relieve l-DOPA-induced dyskinesias without causing off-medication effects or exacerbating l-DOPA-induced dyskinesias. Although some transplanted patients have shown substantial recovery of motor function, the clinical benefits of foetal ventral mesencephalic grafts have been highly variable, with some patients displaying no improvement and/or a worsening of l-DOPA-induced and/or off-medication dyskinesias [30, 46, 47]. An increased understanding of the parameters that induce such variability in clinical outcome is crucial for transplantation to develop into a standard treatment strategy for Parkinson’s disease patients.

Cellular composition of ventral mesencephalic grafts and clinical implications

The developing ventral mesencephalon contains dopamine neurons of the SNpc (A9 dopamine neurons) and the VTA (A10 dopamine neurons), which are distinct in morphology, expression of G-protein-gated inwardly rectifying K+ channel 2 (Girk2) [48, 49], calbindin [50–52] and Raldh1 [53–55]. Moreover, they differ in their axonal projections and vulnerability to degeneration in Parkinson’s disease [1, 50]. After transplantation of mesencephalic tissue, innervation of the host dorsal striatum is mainly derived from transplanted A9 dopamine neurons [56–58], whereas A10 dopamine neurons project to the frontal cortex [58]. Differences in donor tissue dissection and the age at which embryonic tissue is retrieved could greatly influence the proportion of A9 dopamine neurons present in the transplant and thereby the resulting striatal reinnervation and functional outcome.

The foetal ventral mesencephalon typically contains approximately 5% dopamine neurons, demonstrated through specific transgenic labelling of Pitx3-positive midbrain dopamine cells [59]. Consequently, grafts will have a mixed composition containing a majority of glial cells, but also serotonin, GABA, enkephalin, and substance P-containing neurons [60, 61] (Fig. 1). Transplanted glial cells spread throughout the striatum, but do not extend projections. In contrast, non-dopamine neurons within mesencephalic suspension grafts extend widespread and distinct projections into the host tissue [62, 63]. Specifically, serotonin [61] and GABA neurons [64] form extensive projections into the host tissue. Dependent on the method of dissection, foetal ventral mesencephalic grafts will contain different proportions of mesencephalic raphe serotonergic neurons. Furthermore, the formulation of the graft (e.g. suspension, solid tissue pieces or strands) could also influence the proportion of dopamine cells [28, 30, 31] (Fig. 1, Table 1).
It has been speculated that excessive release of dopamine from transplants containing a higher percentage of dopamine neurons could be the cause of graft-induced dyskinesias seen in some transplantation trials [30, 47]. However, recent data implies that the cellular composition of the graft is a more important parameter [65]. Accordingly, a positron emission tomography analysis of human mesencephalic suspension grafts showed that dopamine release from grafted neurons in the putamen was not excessive [66]. Furthermore, transplantation of mouse mesencephalic foetal tissue lacking the dopamine transporter (DAT) resulted in high and diffuse levels of dopamine in the striatum but nonetheless improved l-DOPA induced dyskinesias without causing off-medication dyskinesias [67]. It is therefore possible that the proportion of dopamine neurons relative to other neuronal cell types and their respective innervation patterns determine successful

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<td>Optimization of in vitro differentiation protocols for ESCs and iPS cells Increasing the proportion of A9 dopamine neurons (the main dopamine neuron subpopulation innervating the striatum [56–58]) e.g. by over expression of Pitx3 [54] Increase the distribution of dopamine neurons throughout the striatum using multiple injection sites to ensure that axonal coverage of the denervated area is optimized [31, 45] Implantation of growth factor-containing capsules to increase outgrowth and attract axons [148]</td>
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versus detrimental clinical outcome. Indeed, experiments in 6-OHDA lesioned rats have shown that grafts containing a small proportion of dopamine relative to serotonin neurons develop a progressive worsening of L-DOPA-induced dyskinesias. In contrast, dopamine-rich grafts alleviate dyskinesias independent of the proportion of serotonin neurons present [65].

Serotonin neurons have the capacity to store and release dopamine after administration of L-DOPA [68–70] due to the presence of AADC and the vesicular monoamine transporter-2 (VMAT2) within these neurons. However, in contrast to dopamine neurons, serotonin neurons are not able to regulate dopamine release in a normal way, due to their lack of DAT and auto-regulatory dopamine D2 receptors, which eliminate excess dopamine from the synaptic clefts and fine-tune release from dopamine terminals, respectively. Interestingly, selective agonists of 5-HT1A and 5-HT1B autoreceptors, which inhibit transmitter release from serotonin terminals can reduce L-DOPA induced dyskinesias in rodent and primate animal models of Parkinson’s disease, further supporting a role for serotonin neurons in graft-induced dyskinesias [71, 72]. Thus, careful assessment of graft composition will clearly be critical, a conclusion that was further emphasized by a thorough analysis of transplanted Parkinson’s disease patients, which revealed the presence of serotonin neurons in foetal ventral mesencephalic grafts [73]. These patients did not display graft-induced dyskinesias [73], but the finding demonstrates the importance of controlling for cellular composition before grafting and warrants a more careful phenotypic analysis of grafts derived from patients suffering from dyskinesias post transplantation (Table 1).

The existing level of host dopamine innervation also appears important for the induction of dyskinesias through serotonin neurons. At advanced stages of disease when dopamine innervation of the striatum is reduced below 10–20%, as modelled in 6-OHDA lesioned rats, grafted serotonin neurons are more likely to aggravate L-DOPA-induced dyskinesias [74]. Consequently, if severely affected Parkinson’s disease patients are grafted with cellular suspensions that contain a large number of serotonin neurons it is possible that dyskinesias progressively worsen until the grafted dopamine neurons have extended a large network in the denervated striatum. Furthermore, it is possible that even a relatively small proportion of serotonin neurons could cause dyskinesias if grafted dopamine neurons are only inefficiently innervating the host tissue. Such imbalance can develop as a consequence of the intrinsic dopamine fibres’ ability to inhibit reinnervation from grafted dopamine neurons [58, 75], whilst serotonin neurons appear unaffected by the presence of an intact serotonergic innervation [65]. Moreover, imbalance could also result from a high proportion of grafted A10 relative to A9 dopamine neurons. In such cases the host striatum would not be properly innervated as A10 neurons preferentially target cortical areas. Thus, co-grafted serotonin neurons would presumably have a greater dyskinetic effect.

Whilst serotonin neurons can provide an extensive innervation of striatal tissue, they do not appear to extend any significant projections outside of this region [64, 65]. However, GABAergic neuronal precursors present within ventral mesencephalic grafts appear to have an ability to send out long distance projections towards their normal targets in the superior colliculus, thalamus and cortex [64]. Thus, as with serotonin neurons it is possible that grafted GABA neurons could also have an impact on behavioural outcome.

**Induction of disease-related events in grafted dopamine neurons**

One of the hallmarks of Parkinson’s disease is the presence of inclusion bodies, rich in ubiquitin and α-synuclein, termed Lewy bodies, residing within nigral dopamine neurons and other cell types. α-synuclein exists naturally in many neuronal populations, mainly in presynaptic terminals in neocortex, hippocampus, substantia nigra, thalamus and cerebellum. However, modifications of α-synuclein either through point mutations [76] or increased gene dosage [77] can cause familial Parkinson’s disease. Furthermore, over expression of wildtype or mutant α-synuclein results in Parkinson’s disease-like development in
primates [78, 79], rats [80–83], mice [84–86], flies (Drosophila melanogaster) [87] and nematodes (Caenorhabditis elegans) [88, 89]. One suggested mechanism by which high levels of α-synuclein could lead to neuronal death is through disruption of complexes formed between the neuronal survival factor MEF2D and Hsc70, leading to dysregulation of MEF2D activity [90]. Furthermore, α-synuclein can be modified by phosphorylation [91], nitration and glycosylation [92, 93]. Extensive phosphorylation of α-synuclein at Ser129 is detected in brains of Parkinson’s disease patients [91], but the significance of this modification remains unclear. Whilst, analysis in the Drosophila Parkinson’s model has showed that the phosphorylation of Ser129 can mediate the neurotoxicity of this protein [94], findings in a rat model have instead suggested that this specific phosphorylation could decrease α-synuclein toxicity [82].

Foetal dopamine grafts can survive long-term in Parkinson’s disease patients [73, 95–97]. However, recent studies have shown that some dopamine neurons present in transplants older than 10 years of age show the presence of Lewy bodies [95–97] and phosphorylated α-synuclein [96]. It is currently unclear if Lewy bodies result in a functional impairment of grafted cells. In fact, inclusion bodies may function to sequester toxic proteins, as an increased number of inclusion bodies correlates with reduced toxicity from (i) α-synuclein in models of Parkinson’s disease [94], (ii) mutant huntingtin in Huntington’s disease models [98, 99] and (iii) mutant ataxin-1 in models of spinocerebellar ataxia type 1 [100]. Therefore, the presence of Lewy bodies does not necessarily indicate that these neurons are degenerating, although their presence appears to be a sign of pathological processes within the grafted tissue. Furthermore, it appears that the transplanted cells undergo a disease process similar to the endogenous nigral dopamine neurons, with a subsequent downregulation of the dopamine transporter (DAT) [95, 97, 101] and tyrosine hydroxylase (TH) [97, 102, 103]. Decrease in TH immunoreactivity might represent a protective mechanism, considering that both age-matched controls and Parkinson’s disease patients display the highest proportion of TH-negative neurons in the ventrolateral (VL) part of the substantia nigra, which is relatively spared in brain ageing [103].

It is currently unknown if dopamine cells implanted into an adult parkinsonian brain age faster than they would if implanted into a healthy age-matched individual. Implantation of foetal dopamine neurons into newborn as well as aged wildtype and aged α-synuclein over expressing mice could perhaps shed some light on this issue. However, the shorter life-span of the mouse may complicate the interpretations of such experiments and more long-term analysis in primate α-synuclein models might be necessary. If we assume that the accumulation of α-synuclein and other proteins within the grafted cells is related to the disease and not a natural ageing process, what factors are then contributing to the formation of inclusions within relatively young grafted neurons? Ventral mesencephalic grafts are commonly closely surrounded by resting and activated microglia [31, 47, 73, 96, 97, 104]. It is possible that inclusions are the result of cellular stress associated with the transplantation process itself and not specifically from the disease. Solid grafts that contain blood vessels may induce strong immunoreactivity, and would probably generate a higher level of neuroinflammation with a larger proportion of ramified microglia than grafts lacking blood vessels [31, 47, 73, 96, 97, 104] (Table 1). On the other hand, as Parkinson’s disease patients display reactive microglia within the substantia nigra [105, 106], graft-associated inflammation in the striatum could indicate an active pathological disease process [105, 106] spreading to the implanted tissue independent of the graft composition. In fact, neuroinflammation appears to be a common denominator which present independent of the initial cause of Parkinson’s disease, exemplified by that humans exposed to the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), who display Parkinsonism, also exhibit gliosis and clustering of microglia in the nigra [107]. Furthermore, analysis of the primate MPTP model of Parkinson’s disease, that displays dysfunctions similar to Parkinson’s disease patients (without the formation of Lewy bodies) [108–112], confirmed that the neuroinflammation in the substantia nigra [113, 114] is correlated with the disease itself and not the
treatment, as these animals never received L-DOPA. In this animal model the striatum appeared spared from excessive inflammatory events [114]. It seems that neuroinflammation participates in the slow degeneration of dopamine neurons [115, 116], as decreased activation of microglia after administration of cyclooxygenase 2 (COX-2) inhibitors [115, 116] can prevent progressive degeneration of dopamine neurons in rodent models of Parkinson’s disease [115–117]. In fact, a recent study using viral (adenovirus 2)-mediated delivery of mutant human α-synuclein into the substantia nigra of rats demonstrated an increase of activated microglia in the striatum prior to protracted midbrain dopamine neuron cell death, indicating that neuroinflammation could be involved in the early disease progression [83]. If inflammation is a main contributor to endogenous midbrain dopamine cell loss and these events are mainly localized to the nigra in the later stages of disease, it would appear that the striatum is a safer target for cellular placement. Indeed, ventral mesencephalic dopamine neurons seemed to have a lower survival rate in a Parkinson patient after placement into the midbrain compared with the striatum [31], although this specific question needs to be further investigated. A larger analysis performed in different progressive animal models of Parkinson’s disease (toxin- as well as α-synuclein induced) could shed more light on a possible correlation between target placement, the stage of disease that the cells were grafted and cell death of grafted neurons as well as accumulation of Lewy bodies. In addition, the specific correlation between disease-induced versus graft-induced neuroinflammation and their respective contributions to degeneration of transplanted cells could be further analysed.

**Alternative cellular sources for transplantation**

In addition to the complications associated with the mixed cellular composition, transplantation of primary mesencephalic tissue requires multiple embryos for each patient to be grafted, resulting in technical, logistic as well as ethical complications. Thus, future cell replacement therapy in Parkinson’s disease probably needs to rely on alternative tissue sources. Self-renewable stem cells, which can be propagated indefinitely in culture, can provide a more realistic way forward. However, this requires that stem cells can be induced to differentiate into midbrain dopamine neurons with the correct SNpc phenotype. Developmental studies have provided important information regarding the molecular mechanisms underlying the generation of dopamine neurons and have greatly facilitated the development of protocols for *in vitro* differentiation of dopamine neurons from stem cells. The use of embryonic stem cells (ESCs) for the derivation of midbrain dopamine neurons offers the most promising possibility to derive large quantities of correctly differentiated dopamine neurons for transplantation. Over expression of specific transcription factors that are important during development, such as NurR1, Pitx3 and Lmx1a can increase the efficiency of midbrain dopamine neuron generation [54, 118–122] (Fig. 1). Inhibition of bone morphogenetic protein (BMP) signalling by using the soluble factor Noggin or the Nodal receptor antagonist SB431542 can increase the generation of neuroepithelial progenitors generated from human ESCs in culture [123–125], especially if used in combination [126]. These neuroepithelial cells can further develop into midbrain dopamine neurons [124, 126] at a high efficiency if the density of the cells in culture is well controlled [126] (Table 1). It is possible that the combination of noggin, chordin and follistatin could additionally promote neuronal fate *in vitro*, but this remains to be investigated.

Co-culture with astrocytes has also proven successful in improving the proportion of midbrain dopamine neurons generated in culture [127]. Enrichment of cells of interest and/or exclusion of unwanted cell types can be achieved by using fluorescence-activated cell sorting (FACS) [128–132] (Table 1). The recent development of methods for the generation of ES-like induced pluripotent stem (iPS) cells by cellular reprogramming of adult somatic cells by the introduction of defined factors such as Oct3/4, Sox2, C-myc and Klf4 [133, 134] offers new possibilities to treat patients with autologous cell grafts (Fig. 1). iPS cells can also circumvent ethical problems associated with the use of human ES cells. Initially, iPS cells were generated by the introduction of the defined factors through viral integration into the
host genome [133, 134]. However, iPS cells can now be generated without viral integration [135–137] and with removal of the reprogramming factors [137–139], increasing the utility of such cells in future clinical settings. iPS cells could then be derived from e.g. skin cells isolated from the patient to be transplanted [138, 140, 141] or from a healthy individual with an appropriate human leukocyte antigen type. Interestingly, iPS cells derived from mouse fibroblasts have been successfully differentiated into midbrain dopamine neurons, which could alleviate motor asymmetry in 6-OHDA lesioned rats [142].

Concluding remarks

Transplantation of dopamine neurons can restore motor function in Parkinson’s disease patients over a long time period. A refinement of the cellular composition, placement and distribution of grafted cells within the host tissue could optimize treatment efficacy whilst reducing side effects such as dyskinesias (Table 1). Although Lewy bodies have been detected within grafted neurons, it still remains unclear if this sign of pathology significantly affects the clinical outcome. However, in the combination with the downregulation of TH and DAT, the presence of Lewy bodies indicates that transplanted dopamine neurons are subjected to pathological stress. Future experiments could clarify if modulation of host inflammatory processes might protect transplanted cells better and could also elucidate if autologous dopamine cells derived from iPS cells show a different response than regular allografts. Finally, despite hurdles that need to be overcome we believe that optimized neuronal cell transplantation can offer a successful and feasible future treatment strategy for Parkinson’s disease.

Conflict of interest statement

No conflict of interest was declared.

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