Restoration of synaptic plasticity in the host striatum: can transplants make it?
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Intrastriatal transplantation of dopamine (DA) neurons can restore DA levels in the striatum and improve parkinsonian deficits in experimental studies. However, the mechanisms underlying these effects are poorly understood. Corticostriatal synaptic plasticity represents an important cellular mechanism for information storage and behavioural learning in the brain. This mechanism is defective in Parkinson’s disease (PD). Indeed, the lack of endogenous DA innervation to the striatum causes morphological and functional rearrangements that are associated with altered synaptic plasticity in the corticostriatal pathway. In turn, malfunctioning synaptic plasticity is associated with motor deficits that resemble features of PD. It is yet unknown whether or not transplanted dopaminergic neurons can restore these striatal deficits in PD. Could this be the mechanism underlying the therapeutic effects of transplants? Recent studies have begun to shed light on this matter using different approaches. NeuroReport 24:1016–1018 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Functional organization in the striatum of importance for synaptic plasticity?
The striatum composes a complex mosaic organization that can be divided into several functional compartments on the basis of different cortical afferents; for example, the ventromedial versus the dorsolateral striatal subregion, the patch and the matrix compartments or the direct or the indirect pathway of the striatal output neurons, that is, the medium-sized spiny neurons (MSNs) [1,2]. Whether or not this mosaic organization is reflected in the striatal synaptic plasticity has not yet been properly addressed.

Long-lasting changes in synaptic plasticity, that is, long-term potentiation (LTP) and long-term depression (LTD) are mechanisms that modulate the glutamatergic signal from the cortex to the striatum. This modulation is necessary for information storage and behavioural learning [3–5]. Corticostriatal plasticity is dependent on synaptic interactions from both glutamatergic and dopaminergic inputs onto the dendritic spines and shafts of the MSNs, and requires the activity of several receptor signalling pathways, such as that of N-methyl-D-aspartate (NMDA), 2-amino-3-(5-methyl-3-oxo-1,2-oxazol-4-yl) propanoic acid (AMPA) as well as dopamine (DA) receptors and metabotropic glutamate receptors [6,7]. As these receptors might have different expression levels in the different compartments of striatum, distinct synaptic plasticity pattern could be evident in the different subregions of the striatum.

Region-specific and age-specific heterogeneity in synaptic plasticity has been detected in the intact striatum of the rat [8]. Whereas dorsomedial anterior striatum exhibits a propensity to express NMDA-dependent LTP across the entire developmental time period, neurons in the dorsolateral subregion express LTD at postnatal days 15–34 and LTP at postnatal days 12–14 [8]. Hence, activity-dependent changes vary as a function of postnatal age distinctly in the dorsolateral subregion of striatum.

Regional differences in synaptic plasticity in Parkinson’s disease (PD) are thus far unknown. The most common animal model of PD, the 6-OHDA lesion model, attempts to mimic the state of profound DA depletion in the dorsal striatum (caudate putamen nucleus). The loss of DA is uniform throughout the striatum and therefore there have been no extensive efforts to distinguish subregional differences in synaptic plasticity after PD. Gene studies have, however, evidenced pronounced differences in the expression levels of opioid precursors and plasticity-related molecules between the medial and the lateral caudate putamen, the ventral and the dorsal regions and between striosomal and matrix compartment [2,9,10]. These differences may be blunted following DA denervation but are usually exacerbated following DA replacement.

Synaptic plasticity in Parkinson’s disease models and its significance to behaviour and dyskinesia
PD pathology involves, in addition to the loss of midbrain DA neurons, also morphological alterations of MSNs, including shrinkage and loss of dendritic small protrusions, the spines. These structural changes can lead to a loss or reorganization of the synapses and alter the
corticostratial synaptic plasticity. Accordingly, PD is associated with deficits in synaptic plasticity.

Synaptic plasticity measurements in the PD rat model have thus far been exclusively measured from dorsolateral striatum. Ventrolateral striatum has not yet been studied in this purpose, although this region is of importance for orofacial and forelimb movement [11]. Experimental studies in rat have shown severe alteration or loss of synaptic plasticity in dorsolateral striatum after a parkinsonian lesion. A complete DA denervation causes a loss of both LTP and LTD [3,12], whereas a partial DA denervation spares the LTD [12]. In line with animal models, clinical studies from PD patients have revealed an impairment of LTP-like plasticity in the corticostriatal pathway [13]. The PD-induced synaptic abnormalities can be ameliorated by L-DOPA pharmacotherapy [13]. However, L-DOPA-induced dyskinesia is associated with an inability of MSNs to reverse the strength of LTP (a phenomenon called depotentiation), and with persistent deficits in LTD [3,14]. On the basis of these data, L-DOPA-induced dyskinesia has been proposed to depend on a loss of corticostratial synaptic plasticity toward LTP, which would render MSNs unable to gate cortically driven motor commands [7].

**Dopamine transplants for Parkinson’s disease – can they functionally integrate into the host striatum?**

Transplantation of foetal ventral mesencephalic DA neurons can restore the lost endogenous DA levels in the parkinsonian striatum. Intracerebral transplantation has shown promising results both in experimental models and in some patients using foetal DA neurons [15,16]. Grafted nigral DA neurons are able to innervate the host striatum, release DA and reverse alterations in neuropeptide expression after a parkinsonian lesion [17]. Is this sufficient for optimal therapeutic effect or does this require synaptic and functional innervation to the host neurons? Thus far, little has been done to examine how transplanted neurons integrate into the altered signalling system in the parkinsonian striatum.

Grafted neurons can be implanted into several sites in the striatum from where axonal fibres innervate the host striatum. Grafted DA fibres are able to form new functional connections with the MSNs [18] and receive innervation from host neurons. In vivo electrophysiological recordings in rats with embryonic mesencephalic transplants have revealed established physiologically functional connections between grafts and host neurons [19]. More importantly, DA transplants fully or partially recover motor function after a few months [20]. The fact that the grafts restore DA storage and reuptake capacity in the host striatum within a few weeks, whereas a complete functional restoration may require months, indicates that the latter requires that the transplants modulate network functions and synaptic plasticity in the host brain.

The altered neuronal morphology of the dendrites and spines of the MSNs can complicate the innervation of the transplanted neurons into the PD striatum. Indeed, although sometimes inducing good functional recovery, DA-grafted neurons can form aberrant synaptic connections to the host MSNs that have been correlated to aberrant behaviour with the occurrence of dyskinesia post-transplantation, that is, graft-induced dyskinesia [21]. The host morphological aberrations can be prevented, and dyskinesia reduced, by the in vivo administration of an L-type calcium channel antagonist [4,5], suggesting that improved synaptic connection between the transplants and host neurons more effectively relieves PD symptoms through restoration of synaptic plasticity.

**The implication of other neural cell types in the transplants**

In addition to DA neurons, ventral mesencephalic transplants often contain serotonin (5-HT) neurons (as the raphe nuclei develop close to the substantia nigra). Post-mortem analyses from transplanted PD patients have shown large numbers of 5-HT neurons in the grafts [22], and a recent PET imaging study links graft-derived 5-HT innervation in transplanted PD patients with graft-induced dyskinesia [22]. It is possible to yield grafts rich in either DA or 5-HT neurons by applying different dissection protocols to the embryonic donor tissue [23]. Using this approach, a previous study has compared the functional effects of transplants obtained from DA versus 5-HT-donor tissue in a rat PD model. Results showed that grafts containing mainly DA neurons induced good functional recovery, whereas transplants enriched in 5-HT neurons caused a dramatic worsening of L-DOPA-induced dyskinesia and no improvement of physiological motor tasks [23]. Furthermore, a high density of endogenous serotonin fibres in the striatum has been associated with L-DOPA or graft-induced dyskinesia [22,24].

Taken together, it can be hypothesized that dyskinesia post-transplantation is linked to an aberrant synaptic plasticity of the host MSNs innervated by DA transplants or 5-HT transplants. Yet, the influence of 5-HT neurons on synaptic plasticity in PD has never been evaluated.

**Concluding remarks**

Further progress of neural transplantation as a treatment for PD has been halted because of the inter-individual variability in clinical improvement and because of the occurrence of dyskinesia post-transplantation [16]. Another major obstacle is the limited amount of foetal donor tissue. In an attempt to overcome the latter obstacle, large efforts have been focused on the development of alternative sources of donor tissue (e.g. stem cells). Thus far, little effort has been made on evaluating the potential
for functional integration and connectivity of the graft into the host brain. Yet, this aspect needs to be investigated to fully appreciate the therapeutic potential of neural transplants for PD. To this end, measuring corticostriatal plasticity in animal models of PD is a useful approach that allows one to probe different compartments of the striatum as well as the impact of different types of donor tissue. Optimally, studies of synaptic plasticity could be combined with morphological analyses to determine how and where grafted neurons make synaptic contacts with host neurons. A possible restoration in synaptic plasticity that is linked with recovery in motor function could illustrate a proper functional integration of the transplants, whereas aberrant synaptic rewiring could be linked to the occurrence of dyskinesia. Therefore, to study the plasticity of a graft-innervated striatum would be a crucial step toward the understanding of postgrafting dyskinesias and to establish ways to prevent them.

Grafted neural cells can survive for more than 20 years in the brain with therapeutic benefits in PD patients [16]. Because the main clinical features of PD are so clearly linked to striatal DA depletion, this disease represents an ideal model to develop cell-based therapies for neurological disorders. With the progression of PD, pharmacological DA replacement therapy becomes less and less effective, and severe motor complications appear. Under these conditions, people with PD can currently choose between two options: deep brain stimulation or continuous delivery of dopaminergic compounds. Both options are very expensive, very invasive and associated with significant adverse events [25]. In this scenario, implanting DA neurons in the DA-denervated striatum may restore the lost dopaminergic input once and for all.

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Conflicts of interest

There are no conflicts of interest.

References