Minireview

L-DOPA and graft-induced dyskinesia: Different treatment, same story?

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Abstract

One of the well-recognized problems of long-term L-3,4-dihydroxyphenylalanine (L-DOPA) therapy in the treatment of Parkinson's disease is the development of L-DOPA induced dyskinesia. These abnormal movements cause significant disability and narrow the therapeutic window of L-DOPA. Cell transplantation is one of the most promising upcoming therapies for the treatment of Parkinson's disease, and may help alleviate or avoid L-DOPA-induced dyskinesia. However, the more recently acknowledged phenomenon of graft-induced dyskinesia is posing a major obstacle to the success of this treatment. This motor side-effect closely resembles abnormal movements induced by chronic L-DOPA treatment, yet they remain after withdrawal of the medication indicating their origins lie in the transplant. In this review, we compare these two therapy-induced adverse effects, from the way they manifest in patients to the possible mechanisms underlying their development.

Keywords: Parkinson's disease, animal model, transplantation, 5-HT

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Introduction

Parkinson's disease is one of the most common neurodegenerative conditions with an incidence of 6.3 million people worldwide, presenting with a developing tremor, rigidity, bradykinesia and postural instability.[1,2] Although the associated cell dysfunction is now considered to be fairly widespread throughout the nervous system, the critical site of neuronal loss for many of the motor symptoms has long been known to be the pigmented dopaminergic neurons of the nigrostriatal pathway. The resulting loss of dopamine (DA) in the caudate nucleus and the putamen[3] is ameliorated by treatment with the DA precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), which effectively alleviates many of the motor symptoms. This pharmacological approach has been used for over 50 years and remains the gold standard treatment.[4,5] However, years of chronic L-DOPA treatment invariably led to significant motor consequences, including motor fluctuations and the appearance of disabling involuntary movements, known as L-DOPA-induced dyskinesia (LID). The first description of LID dates from the end of the 1960s, only five years after the drug became widely available[6,7] and it is now established that on average, LID affects 40% of patients treated for more than five years, with the incidence increasing by 10% for each subsequent year of treatment.[8] This may be changing with new practices (i.e. the use of D2 receptor agonists) but remains a significant problem, and patients may resist the transition to L-DOPA medication due to their perceptions of the LID.[9,10] This incidence and the lack of good pharmacological alternatives to L-DOPA has driven the search for other approaches that might alleviate the motor symptoms but without the generation of abnormal movements.

Since the late 1970s there has been significant progress towards the installation of a 'dopamine factory' directly into the caudate and putamen to replace the degenerating nerve terminals. This is mediated by the intrastriatal transplantation of foetal dopaminergic neuron precursors; with the first clinical trial starting in 1980.[11] Since then, more than 100 patients worldwide have received intra-striatal fVM transplants. Several small open-label clinical trials performed in the 1980s and early 1990s illustrated the potential of the technique, showing significant improvement in various parameters, notably in the Unified Parkinson's Disease Rating Scale (UPDRS) and Activities of Daily Living scale (ADL) scores. In some cases, the improvement in motor symptoms was extensive enough to allow a reduction in daily L-DOPA medication.[12–15] Positron emission tomography (PET) scans revealed an increase in ^{18}Fluorodopa uptake in grafted patients, revealing surviving

reinnervating grafts, supported by the postmortem analyses of patients who died from unrelated events at different intervals posttransplantation showing good fVM survival associated with partial host tissue reinnervation.[12,15,16] The open-label trials provided robust proof of concept that fVM can survive, innervate the host's putamen, produce DA and alleviate symptoms. However, two double-blind US-based studies showed some, but limited functional improvement in the transplanted groups versus placebo treated cohorts. Moreover, The Freed *et al*. study was the first to report the development of adverse effects abnormal movements had developed in some patients which were comparable in severity to mild LID, but which endured even after withdrawal of L-DOPA treatment. A retrospective video analysis of the patients transplanted in the London-Lund-Marburg open-label clinical trial also revealed a similar type of 'off' medication dyskinesia in half of the patients enrolled in that trial.[17] In general, these 'graft-induced dyskinesia' were mild and required significant clinical expertise to identify, but a couple of patients from each study were severely affected with the need for additional interventions to resolve them. These reports have led to a period of relative quiescence in the clinic, which has allowed greater investigation into the variability of functional improvement in the transplanted patients, in addition to significant progress in understanding the side-effects.

Superficially, these two dyskinetic conditions present with similarities in phenomenology, and it is therefore easy to assume that L-DOPA-induced dyskinesia and graft-induced motor dysfunction follow the same mechanisms. However, this is not proving so simple, and while 40 years of research on LID has provided a great insight into the mechanisms underlying their development; our knowledge regarding abnormal movements driven by a dopaminergic graft is fairly limited. This review aims to put into perspective our understanding of LID and GID, and discusses the similarities and differences in the way they manifest in PD patients, the available tools that we have to study them and our current knowledge about their mechanisms.

Manifestation in patients

L-DOPA-induced dyskinesia

Of the many side-effects that L-DOPA treatment can have, the most striking and disabling is dyskinesia. Patients typically respond well to treatment during the first few years and a significant improvement in drug management has reduced the incidence of LID.[18] DA agonist monotherapy can be used to delay the onset of L-DOPA therapy, and thus delays the development of LID for a few years.[19] Unfortunately, after this 'honeymoon period', patients start to experience fluctuations in their response to the drug and the symptoms of LID gradually appear. Most of the time, the symptoms of LID correlate with the drug's optimal therapeutic window, and correspond to the maximal plasma and brain level of L-DOPA. These 'peak-dose LID' are mainly choreiform and become more dystonic as the disease progresses. LID can also be observed during the rise and fall of L-DOPA plasma levels, with these 'diphasic dyskinesia' usually being more dystonic. Other forms of pure dystonia, in one foot for example, have also been reported in the absence of abnormal movement, in both 'on phase' and 'off phase' (high or low plasma level of L-DOPA respectively).[7,20,21] Patients do not always notice early LID as they tend to affect facial muscles, usually manifesting as jaw movements and tongue protrusion,[20] but they are very heterogeneous and vary from patient to patient. However, they rapidly spread to the head and neck, usually in a wave-nodding movement, before affecting the limbs in a more dystonic and disabling manner. LID is also associated with weakening of the tendon reflexes and, more sporadically, toe flexion or panting respiration has also been described. LID also has a tendency to affect the side of the body that was first affected by the disease, which typically remains the worst side in terms of function. The main cited risk factors for LID are the extent of DA denervation and the dose and duration of L-DOPA treatment; although early onset of the disease also significantly increases the risk of developing premature dyskinesia.[22]

Graft-induced dyskinesia

These movements, appearing in direct response to the transplantation of PD patients with fVM within two years of the surgery, are not linked to acute L-DOPA administration and present with a differing pattern from the classical choreiform peak-dose LID. They were firstly reported in the Denver-Columbia double-blind clinical trial as dystonia and hyperkinesia, mainly affecting the arm, head and neck of five of the 33 transplanted patients.[23] Later, reports from the Tampa-Mount Sinai trial also described 'off-drug' side-effects in 13 out of the 23 grafted patients. These abnormal movements were described as stereotypic and dystonic and mainly affected the lower parts of the body, and thus were similar to diphasic LID.[24] Finally, the video-based reassessment of the 14 Lund-London's patients transplanted in the 1990s found six patients exhibiting choreiform and dystonic movements in various parts of the body, sometimes associated with repetitive and ballistic movements.[17] In general, GID is described as being more dystonic, stereotypic and rhythmic than peak-dose LID and is therefore more comparable to diphasic LID.[24] They are generally mild but may increase in severity over time, reaching their peak at 2–4 years after the transplantation procedure.[17,24] However, as for LID, reports of GID suggest that they can be very different from one patient to another in their manifestation, as well as the time frame over which they develop. Interestingly, one study reported an increase in [^{18}F]-fluorodopa (F-DOPA) uptake on PET scans in discrete locations they termed 'hot spots', in patients who exhibited severe GID, but not in non-GID grafted patients. These results were not replicated in similar analyses from other studies.[17,24] Although not all grafted patients show GID, GID has only been observed in patients who show improvements in their PD symptoms, suggesting that side-effects are associated with a functional graft.[25]

Animal models

L-DOPA-induced dyskinesia

The main postmortem characteristic of the PD brain is the absence of pigmented cells in the SN. Neurotoxin-induced models of dopaminergic depletion have been used for decades to reproduce this selective neuronal loss in primates and rodents as models of PD (reviewed by Lane and Dunnett).[26] Non-human primates treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) display motor dysfunction similar to that experienced in PD and exhibit choreiform and dystonic movements when exposed repeatedly to L-DOPA treatment.[27–31] They represent a reliable model for the study of LID as they exhibit peak-dose dyskinesia that can be easily scored using a modified version of the human dyskinesia rating scale.[32,33] Moreover, they display other features experienced by patients after long-term treatment with L-DOPA, such as fluctuations in the response to the treatment inducing 'wearing off' phases or diphasic dyskinesia.[34] For these reasons, non-human primates have been used to study the mechanisms underlying the development of LID, as well as to test new potential anti-dykinetic drugs.

However, a more cost-effective alternative, and now widely used and accepted model of LID, is the induction of L-DOPA-induced dystonic and hyperkinetic movements in unilateral 6-OHDA-lesioned rats, with new models now also using mice.[35–37] 6-OHDA is a neurotoxin delivered surgically into the rodent brain, where it enters the catecholamine neurons via the DA transporter and induces cell death through oxidative stress.[38] Unilateral motor deficits are evident under test conditions and rodents will rotate when challenged with agents which influence dopaminergic drive.[39–41] L-DOPA induces a contralateral rotational response as the resulting DA stimulates the supersensitive DA receptors in the lesioned hemisphere. Following several days of L-DOPA treatment, abnormal movements also develop which are distinct from the acutely driven stereotypic behaviors and are scored using rodent abnormal involuntary movements (AIM) rating scales.[35,42–44] When challenged with compounds with proven anti-dyskinetic effects, these experiments reflect similar findings to those in MPTP-treated primates and/or in clinical trials.[36,45,46]

While neurotoxin-based models of LID exhibit AIM akin to those observed in patients chronically treated with L-DOPA, they constitute an incomplete model of the disease as a whole. Indeed, they only mimic the main degenerative feature of PD; depletion of the dopaminergic pathway. However, it is well established that other neurotransmitters are affected in PD, such as serotonin, noradrenaline, acetylcholine, glutamate and GABA.[47–49] Moreover, PD is associated with another major pathological hallmark, α-synuclein positive protein inclusions called Lewy bodies. The lack of these other features of the disease in toxin-based animal models of PD may contribute to the lack of predictive validity of anti-dyskinetic drugs when translated to the clinic. Indeed, a lot of medications proven effective in the reduction of LID in animals have failed to show any benefit to patients. Among them, 5-HT_{1A} agonists and adrenergic α_{2A} antagonists were found to be very effective in rodents and non-human primates but failed to alleviate LID significantly in patients without worsening PD symptoms,[50–52] although this problem may be also ascribed to the selectivity of the agents. Most recently, Levetiracetam, an anti-epileptic able to reduce dyskinesia in monkeys,[53,54] showed no or very little effect in alleviating dyskinesia in patients.[55–59] The creation of animal models which carry more of the pathophysiological features of PD has been a major research focus.[60,61] Whilst now widely available in a variety of forms, genetically modified rodents often develop mild and inconsistent nigrostriatal dopaminergic cell loss and do not develop AIMs when exposed to L-DOPA; likely due to the lack of severe dopaminergic depletion.[60,62] For these reasons, neurotoxin-based models currently remain the most reliable way to study LID in rodents. It is, however, reasonable to think that the combination of genetic models and using toxin to create specific lesions could offer new models for the study of LID that would better reproduce the major hallmarks of PD.

Graft-induced dyskinesia

After the development of transplantation side-effects in patients, transplantation studies in lesioned rats and monkeys explored whether this had been 'missed' in animal models through lack of monitored observations in the absence of anti-Parkinsonian drugs. Despite the efforts made to reproduce conditions as close to the clinical experience as possible (i.e. extremely severe DA depletion mimicking late stage patients and long-term, high dose L-DOPA to induce severe LID prior to grafting), only infrequent, spontaneous GID was observed in a large-scale MPTP-treated primate study.[63] Similarly, in reports of spontaneous GID in 6-OHDA lesioned rats observed in the absence of medication, these movements were considered inconsistent and an unreliable measure of GID.[64] Prior to the advent of GID, it had been established that dopaminergic grafts were capable of reducing AIMs induced by L-DOPA and, furthermore, were able to prevent their occurrence if given prior to the initiation of L-DOPA treatment.[65] However, closer examination revealed that single site 'hot-spot' fVM transplanted animals displayed a novel, more stereotypic behavioural phenotype.[43] These facial and forelimb stereotypies described were not observed in rats receiving multiple sites deposition of the same number of foetal cells producing a more evenly innervating graft and was consistent with the proposal from the Denver-Columbia clinical trial which identified 'hot spots' of DA in their GID patients.[25,43] However, this movement is hard to evaluate as it can be easily masked by mild LID and besides is only present during L-DOPA administration, unlike true GID, which remains present after prolonged L-DOPA withdrawal.

An alternative approach, which still relies upon exogenous drug administration, is that of amphetamine-induced abnormal movements. The amphetamine-induced rotation test is commonly used to assess the severity of DA depletion following 6-OHDA unilateral lesions as a crude estimate of the success of fVM transplantation. Prior to recognition of

clinical GID, it was observed that amphetamine induced stereotypies and an over-expression of c-fos in the lateral striatum post-transplantation, were prevented by severance of the corticostriatal pathway.[66] Closer observation in the knowledge of GID suggested that dyskinetic movements were also evoked, generally resembling mild to moderate LID.[64,67] Typically, although not universally, the movements reach their peak severity at 12–16 weeks post-transplantation and disappear if the graft is completely rejected.[68] Described as hyperkinetic limb movements usually associated with orofacial dyskinetic and stereotypies, they demonstrate a strong similarity with patients GID.[64,67] Nevertheless, a selection of transplanted patients received amphetamine for ^{13}C raclopride PET imaging scans and did not show the appearance or worsening of GID.[69]

We therefore have two quantifiable models of changes in the profile of abnormal movement, which are elicited primarily in the presence of a dopaminergic graft, in a formerly DA depleted striatum. These behaviors are more prominent after L-DOPA priming but both have to be evoked by the exogenous administration of either L-DOPA or amphetamine. Valuable data have been gathered from these models but it is pertinent to consider that in neither the rodent nor the primate are we able to establish true GID.

Mechanisms

It is well established that the severity of dyskinesia increases as the disease progresses. Indeed, a late stage of PD at the onset of treatment, high dose, and long-term L-DOPA therapy constitute the main risk factors of developing LID.[70,71] However, the exact mechanisms underlying the development of LID remain unclear. This has been extensively reviewed elsewhere[72–74] but involves long-term changes in synaptic function within the basal ganglia and at the corticostriatal pathway. There is much less certainty when considering the generation of post-graft dyskinesia. Despite the correlation observed between the severity of LID prior to grafting and AIM post-grafting in rodents, the question of the existence of a shared mechanism remains unresolved.[75] However, aberrant processing of DA is believed to play a key role in the development of both LID and GID.

Serotonergic neurons have been shown to play a role in aberrant release of DA associated with LID, and this has led to questions about their role in GID. 5-HT neurons contain the enzymatic machinery, namely the aromatic L-amino acid decarboxylase (AADC), required for the conversion of L-DOPA to DA. They can also store the neurotransmitter in vesicles at the synapse, and have been proved very effective in releasing DA converted from L-DOPA.[76,77] However, being serotonergic neurons, they lack the DA auto-receptors that allow normal negative feedback, altering the control of DA release and potentially flooding the striatum with DA. This intrastriatal infusion of DA is sufficient to induce LID in 6-OHDA lesioned rats, regardless of any pre-treatment[78] and pulsatile discharge of DA in the striatum is thought to be a major protagonist in the development of LID.[77,79] Furthermore, PET scans performed on dyskinetic PD patients revealed a correlation between the severity of LID and the amplitude of changes observed in striatal DA levels.[80] The potential role of the serotonergic system in DA dysregulation is further evidenced by the sprouting of 5-HT terminals in the striatum of dyskinetic animals correlating with AIM severity, a phenomenon which may further exacerbate aberrant DA release.[77,81]

An increased understanding of the role played by striatal 5-HT innervation in LID has led to the hypothesis that GID may be caused by excessive serotonergic innervation of the striatum. This idea has been reinforced by the difficulty in distinguishing between the developing raphe, rich in serotonergic precursor cells, and the developing substantia nigra containing dopaminergic precursors while dissecting the fVM for transplantation. It first emerged from the clinical evaluation of three patients exhibiting severe GID, which revealed increased ^{11}C-DASB signal in PET scans indicating the increased binding of serotonin transporters in the graft area compared to both age-matched PD patients and healthy controls.[82] Importantly, these clinical studies have not examined transplanted patients that did not have GID, so an important group is missing in this analysis. Postmortem evaluations have been inconclusive with regard to 5-HT; the only study able to detect 5-HT neurons found high levels of tryptophan hydroxylase positive neurons within the graft in patients that did not show GID.[83] This has become an increasingly complex story as rodent studies were inconsistent with this hypothesis, showing that 5-HT enriched grafts can worsen post-graft LID in rodent models of PD but does not influence the severity of the effects of amphetamine.[84] Furthermore, studies depleting host 5-HT neurons did not find any improvement in amphetamine-induced dyskinesia in grafted rats.[84,85] More recent evidence from both rodent and patient evaluations suggests that it may be the ratio of 5-HT/DA transporters available in the striatum rather than the increased serotoninergic innervation that is important in GID.[86–88] Pharmacological data is also similarly open to interpretation. Administration of the 5-HT$_{1A}$ agonist buspirone successfully alleviated GID in three patients, but it is important to note that buspirone is also a weak D_2-like receptor antagonist, therefore the reduction of GID observed could be due to the inactivation of D_2 receptors more than a normalization of the activity of 5-HT terminals.[82,87] Indeed, animal studies showed that 5-HT$_{1A}$, even when co-administered with 5-HT$_{1B}$ agonist, can only partially reduce dyskinesia induced by amphetamine whilst D_2 receptor antagonism completely abolishes them.[86] Finally, in the case of GID, which occurs in the absence of L-DOPA, striatal DA does not result from the conversion of L-DOPA in 5-HT neurons (which appears to be the case in LID)[89] but is directly produced by the transplanted dopaminergic cells. Therefore, the role of 5-HT neurons in GID is still questionable. The ability of transplanted DA neurons to control DA reuptake and therefore manage DA levels effectively has also been brought into question.[90] Rather than the relative extent of 5-HT versus DA innervation, the availability of dopaminergic terminals controlling the level of DA at the synaptic cleft and their location and dispersion throughout the striatum, along with other striatal modifications probably plays a bigger role in the development of GID.[90]

Chronic L-DOPA treatment is known to generate important post-synaptic modifications that correlate with the severity of LID; and these modifications predominantly occur in the subregions of the striatum most closely linked with the motor phenotypes observed. Among them, an increased striatal level of ΔFosB-like proteins has been reported in both human and animal models.[37,91–94] Chronic L-DOPA treatment is also associated with an increased level of prodynorphin mRNA, along with hyper-sensitization of striatal DA receptors.[95] Rodent models demonstrate that these changes are normalized by a dopaminergic transplant, but that the effect is restricted to the engrafted region, leaving areas of remaining hypersensitivity, which may respond to the low levels of diffused DA released by the graft.[96] Moreover, animals still exhibit amphetamine-induced dyskinesia even with a normalized level of ΔFosB.[43,75,88] In LID, up-regulation of these immediate early genes, particularly in the caudal-lateral part of the rat striatum, correspond to the generation of abnormal movements. fVM transplants into this particular area are also more likely to induce amphetamine-induced dyskinesia when compared to a more rostral location,[67] data which correlates with the location of increased uptake of [^{18}F]-DOPA observed on the PET scans of the dyskinetic patients.[97] All together, these results suggest that the location of the graft, as well as the pattern of reinnervation within the striatum, is likely to be a critical factor in the development of GID development. Indeed, a patchy graft, firing DA unevenly into an adjacent region partially normalized for FosB-family and prodynorphin genes expression and full of DA hypersensitive DA receptors would generate conditions similar to those associated with LID. In that situation, the aberrant release of DA stimulates hyper-sensitive receptors leading to the inhibition of the internal globus pallidus (GPi).[98,99] This hypothesis is supported by the fact that high frequency stimulation of the GPi is effective in the treatment of LID, however, the results in patients suffering from GID have been more variable, highlighting once again the important differences between LID and GID.[99,100]

Conclusion

Despite 50 years of extensive research, the mechanism underlying LID is still not fully understood. The appearance of comparable side-effects following fVM transplantation has raised new questions regarding the safety of transplants but also research into how the mechanisms could overlap. A major problem facing researchers of GID is the lack of a truly comparable animal model, which has proved to be a significant advantage in the understanding of LID. The time course of GID development (six months–two years post-transplantation) does not, by and large, fit with the more prolonged period required for plateau of symptom improvement and graft development as observed by ^{18}FDOPA PET scans. Significant pieces of the puzzle are still missing, in particular regarding the possible role of the immune system, and importantly there is still work to be done to maximize the functional improvements possible with transplantation and consistency with which this can be achieved. The correlation observed between the severity of LID and GID would argue in favor of an association between the two conditions, and highly dyskinetic patients are currently not considered good candidates for fVM transplantation. Finally, as we develop our knowledge of GID evoked by fVM, we must be conscious of the new developments in the stem cell arena, and evaluate whether the same risk exists with other transplants, or if this may also influence what we transplant when we have greater control of the cellular constituents within the grafted material.

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