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Anatomy of graft-induced dyskinesias: Circuit remodeling in the parkinsonian striatum

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ABSTRACT

The goal of researchers and clinicians interested in re-instituting cell based therapies for PD is to develop an effective and safe surgical approach to replace dopamine (DA) in individuals suffering from Parkinson's disease (PD). Worldwide clinical trials involving transplantation of embryonic DA neurons into individuals with PD have been discontinued because of the often devastating post-surgical side-effect known as graft-induced dyskinesia (GID). There have been many review articles published in recent years on this subject. There has been a tendency to promote single factors in the cause of GID. In this review, we contrast the pros and cons of multiple factors that have been suggested from clinical and/or preclinical observations, as well as novel factors not yet studied that may be involved with GID. It is our intention to provide a platform that might be instrumental in examining how individual factors that correlate with GID and/or striatal pathology might interact to give rise to dysfunctional circuit remodeling and aberrant motor output.

Contents

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Grafting offers unrealized hope to those with PD

"*It's not that I'm so smart, it's just that I stay with problems longer*".

Albert Einstein

There has long been interest in whether cells of the nervous system that die due to trauma or disease could be replaced by new ones. While very early attempts at brain cell grafting were unsuccessful, Dr. Elizabeth Dunn [1], at the turn of the 20th century, showed that brain tissue grafted from one newborn rat to another newborn rat could survive transplantation. Despite this landmark discovery, little progress was made in the area of neural transplantation over the next 50 years. However, resurgent interest in the 1970s, particularly in the field of Parkinson's disease, led to an explosion of preclinical research. Promise from animal studies in the field led to the initiation of clinical grafting trials. A number of small open-labeled clinical trials took place throughout the 1980s and 1990s. There was a lack of consensus over the optimal grafting paradigm to employ and, accordingly, these studies were quite variables in their outcomes. However, a significant number of studies were able to show unequivocal evidence of grafted cell survival, graft-derived neurite outgrowth and behavioral recovery (e.g., [2–8]). These encouraging findings culminated in two large double-blind placebo controlled studies preformed in the late 1990s with the aim of confirming the efficacy of fetal tissue grafting for PD.

Unfortunately, both double-blind placebo control trials reported failure to find statistical significance in their primary behavioral endpoints at the end of the blinded phase of each study [9,10]. However, a recent follow-up report from the Denver/Columbia trial [9] showed that at 2 and 4 years post-transplantation there was continued and significant symptomatic improvement [11]. Despite the generalized disappointment from these double-blind studies, clinical trials involving transplantation of embryonic mesencephalic DA neurons have demonstrated that grafted neurons can survive long-term [11], innervate the denervated striatum [12–14], release DA [15], and become functionally integrated into host neural circuits [16]. Further, it is important to appreciate that clinical data indicate that a favorable therapeutic response to transplantation appears to be dependent on specific variables including the extent of loss of nigrostriatal dopaminergic terminals at pre-graft baseline and age of the recipient (e.g., [9,11,51]). Thus, the *clinical efficacy is perhaps best viewed as variable rather than a failure*, and a primary challenge to the employment of graft therapy for PD is in understanding how to develop strategies to allow all patients to respond favorably to engraftment of replacement DA neurons.

The unexpected side effect: graft-induced dyskinesias

More disconcerting than a lack of consistent therapeutic efficacy of grafting is an ethical challenge related to a bothersome side-effect that was noted in a subpopulation of grafted patients in both placebo control trials, and one retrospective study. The side-effect has come to be known as graft-induced dyskinesias (GID), the cause is not known, and in contrast to levodopa-induced dyskinesias (LID), these behaviors cannot be ameliorated by lowering the dose of antiparkinsonian medications like levodopa. In the remainder of this manuscript, we detail the phenomenology that is GID, contrast it to LID, and examine possible mechanisms that may underlie GID etiology. The ethical dilemma of this unforeseen challenge relates to the Latin phrase, often attributed to the Hippocratic oath, "primum non nocere" ("above all else, do no harm").

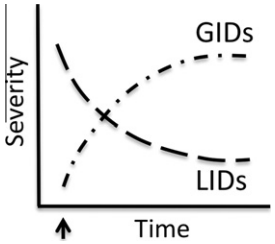

Fig. 1. Differential time course of expression of levodopa-induced dyskinesias (LIDs) versus graft-induced dyskinesias (GID). The arrow demarks the time of graft surgery. As the graft matures, the incidence of LID lessens and there is an emergence of GID behaviors (e.g., [9,10,17,20,21]).

Indeed, it was the intermittent expression of the sometimes devastating GID side-effect that was the principal reason for the discontinuation of clinical trials worldwide, although a lack of a consistent beneficial effect was a contributing factor.

The post-surgical side effect of GID was first described in the Denver/Columbia placebo control, double-blind trial [9] with an additional incidence subsequently reported in a retrospective clinical report out of Sweden [17] and the second placebo control, double blind trial in the United States [10]. In these trials, 15–50% of trial participants developed abnormal dyskinesia with characteristics largely unique from the common drug-induced dyskinesias. Indeed, information available suggests that GID may represent a distinct neurological entity from the common drug-induced, LID [18,19].

The idea that GID and LID may represent distinct neurological phenomena comes from several lines of evidence. First, the temporal expression of these two behaviors is disparate (Fig. 1). In both humans [9,10,17] and animal models [19–21] the specific post-graft dyskinetic profile develops as the graft matures, and as the typical pre-graft profile of LID disappear, thus giving an inverse time-course of expression of these two behavioral phenotypes. Second, in contrast to the more widespread (e.g., involving both upper and lower extremities), primarily dystonic and choreic appearance of drug-induced dyskinesias [22], GID bear some resemblance to biphasic drug-induced dyskinesias [18], often involving stereotypy and hyperkinesia, and localized to the upper or lower extremities [10,17,20]. Unlike LID, lowering the dose of levodopa does not provide relief from this troublesome side effect. In fact, GID in humans occurs primarily when plasma levodopa is low or absent. Interestingly, in both humans [9,10,17] and animal models [21], GID appear to be dopamine (DA) mediated despite the above mentioned paradox in patients. The pharmacology of GID will be detailed later in this review.

Modeling graft-induced dyskinesias

In order to delineate the mechanisms responsible for the expression of aberrant behaviors following fetal tissue grafting in PD, research laboratories have created a rodent model of experimental GID. By utilizing rats rendered unilaterally parkinsonian via 6-hydroxydopamine (6-OHDA) delivery to the nigrostriatal pathway, researchers have found that aberrant behaviors similar to those seen in the clinic can be elicited in experimental animals following the delivery of a fetal mesencephalic tissue grafted to the parkinsonian striatum.

The post-graft dyskinetic profiles expressed by animals are phenotypically similar to the GID observed in human patients. Specifically, similar to grafted patients (see [18], for review), in one of the rodent models (e.g., the model where levodopa rather than amphetamine is used to induce the expression of experimental GID [19,20]), experimental GID is expressed as focal, stereotypic,