Dyskinesias and Neural Grafting in Parkinson’s Disease

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1. Introduction

In the past 20 years, intracerebral transplantation of embryonic ventral mesencephalic (VM) tissue has been looked upon as a particularly promising approach for the treatment of Parkinson’s disease (PD). Among the many possible treatment options for the future, transplantation bore the promise of a truly curative approach: endogeneous, degenerating dopamine (DA) neurons would be substituted for by healthy DA-producing cells, restoring the damaged nigrostriatal circuit once and for all (Nikkhah and Brandis, 1995; Barker, 2000; Fricker-Gates et al., 2001). Hopes were fostered by the encouraging results produced by intrastriatal VM transplants both in animal models of PD (Björklund, 1992; Björklund and Stenevi, 1979; Herman and Abrous, 1994; Perlow et al., 1979) and in early open-label clinical trials (Lindvall, 1994; Lindvall and Hagell, 2000 and Chapter 5). The latter showed that embryonic VM tissue can engraft in the parkinsonian striatum and provide a local source of DA storage and release. In a majority of transplanted patients the grafts were found to ameliorate many of the symptoms of PD and to reduce the need for L-DOPA pharmacotherapy (Lindvall and Hagell, 2000). In addition to their immediate implications for PD, these results also suggested that neural cell replacement could develop into a radically new treatment approach for a wide range of neurological disorders (Gage et al., 1988; Lindvall and Björklund, 1992; Aichner et al., 2002; Turner and Shetty, 2003; Grisolia, 2002; Peschansky and Dunnett, 2002; Studer et al., 1998). This early enthusiasm was dampened by alarming reports from the first NIH-sponsored clinical
trial of neural transplantation, where a subgroup of patients had manifested a severe and persistent form of dyskinesia at late postoperative periods (Freed et al., 2001; Greene et al., 1999; Kolata, 2001 and Chapter 6). Other reports were soon to follow indicating that dyskinesias indeed can develop as a complication of intrastriatal VM grafting (Hagell et al., 2002; Ma et al., 2002; Olanow et al., 2003). These dyskinesias are a puzzling phenomenon that had not been foreseen by experimental studies of VM transplantation in animal models. This phenomenon does not presently lend itself to any simple explanation. In fact, current pathophysiological models are inadequate to explain the emergence of dyskinesia after interventions that can provide a source of continuous DA release in the striatum. Yet, understanding this issue appears essential in order to be able to plan further application of cell-replacement therapy in PD.

In this chapter, we shall first provide a general review of the clinical spectrum and pathophysiology of the dyskinesias that complicate the treatment of PD. We shall then discuss the effects of VM grafts on L-DOPA-induced dyskinesias that are present prior to transplantation surgery. Thereafter, we will specifically address the issue of graft-induced dyskinesia, viz., an apparently novel clinical entity that is caused by the intrastriatal grafts themselves. Finally, we shall provide a speculative review of possible mechanisms underlying the development of dyskinesia following intrastriatal VM transplantation.

2. Dyskinesias in Parkinson’s Disease

2.1. Clinical Spectrum

The main motor symptoms of PD are caused by the loss of striatal DA that results from nigral neuron degeneration. Pharmacological DA replacement by L-DOPA typically results in an excellent initial symptomatic response. However, within some years of treatment a significant proportion of patients develop motor complications, i.e., motor fluctuations and dyskinesias (Marsden et al., 1981; Quinn, 1998). Estimates based on published data indicate that both of these complications appear in about 40% of patients after 5–6 years of treatment (Ahlskog and Munter, 2001). With time, especially in patients with young-onset PD, motor complications often increase in severity and to the point that drug therapy is no longer optimal (Marsden et al., 1981; Nutt, 1992; Quinn, 1998; Quinn et al., 1987).

Motor fluctuations appear as oscillations between good response to medication with no or minimal PD-related disability (“on” phases), and episodes of poor drug response with increased PD-related disability (“off” phases) (Quinn, 1998). Dyskinesias appear as hyperkinetic and dystonic abnormal involuntary movements and postures. Chorea (randomly “flowing,” purposeless, dance-like movements) is the most common type of hyperkinesia, but other types (e.g., ballism, stereotypies) also occur (Marsden