Neurobiology of Disease 77 (2015) 191–203

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Interrogating the aged striatum: Robust survival of grafted dopamine neurons in aging rats produces inferior behavioral recovery and evidence of impaired integration

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ARTICLE INFO

Article history:
Received 17 January 2015
Revised 28 February 2015
Accepted 3 March 2015
Available online 11 March 2015

Keywords:
Parkinson's disease
Aging
Rodent
Grafting
Dyskinesias
Levodopa
Synaptopodin

ABSTRACT

Advanced age is the primary risk factor for Parkinson's disease (PD). In PD patients and rodent models of PD, advanced age is associated with inferior symptomatic benefit following intrastriatal grafting of embryonic dopamine (DA) neurons, a pattern believed to result from decreased survival and reinnervation provided by grafted neurons in the aged host. To help understand the capacity of the aged, parkinsonian striatum to be remodeled with new DA terminals, we used a grafting model and examined whether increasing the number of grafted DA neurons in aged rats would translate to enhanced behavioral recovery. Young (3 months), middle-aged (15 months), and aged (22 months) parkinsonian rats were grafted with proportionately increasing numbers of embryonic ventral mesencephalic (VM) cells to evaluate whether the limitations of the graft environment in subjects of advancing age can be offset by increased numbers of transplanted neurons. Despite robust survival of grafted neurons in aged rats, reinnervation of striatal neurons remained inferior and amelioration of levodopa-induced dyskinesias (LID) was delayed or absent. This study demonstrates that: 1) counter to previous evidence, under certain conditions the aged striatum can support robust survival of grafted DA neurons; and 2) unknown factors associated with the aged striatum result in inferior integration of graft and host, and continue to present obstacles to full therapeutic efficacy of DA cell-based therapy in this model of aging.
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Introduction

The therapeutic potential of dopamine (DA) neuron grafts in patients with Parkinson's disease (PD) has been variable and remains controversial and incompletely understood. Despite a moratorium on clinical grafting in PD over the previous decade, a critical reappraisal of preclinical and clinical transplantation data has lead to a limited renewal of clinical trials (Evans et al., 2012; Barker et al., 2013; ClinicalTrials.gov NCT01898390). This, together with continuing interest in stem cell-based replacement strategies (Ambasudhan et al., 2014; Buttery and Barker, 2014; Sundberg and Isacson, 2014) and trophic factor-induction of nigral DA terminal re-growth (Kordower and Bjorklund, 2013; Hickey and Stacy, 2013), highlights the importance of understanding the capacity and limitations of repairing the parkinsonian striatum. In addition to implications for clinical application of DA neuron grafting, cell transplantation is a valuable approach for interrogating the nature of the environment of the aged brain as it permits or discourages integration of new elements intended to facilitate restoration and repair. The presence of grafted cells, in effect, reveals characteristics of the environment through their attempts to survive, grow, and integrate with the host brain.

While clinical and preclinical data support the idea that DA neuron transplantation into the striatum is most effective in younger individuals (Collier et al., 1999; Freed et al., 2001; Sortwell et al., 2001) with less severe DA-depletion (Breysse et al., 2007; Piccini et al., 2005), clinical grafting trials to date have enrolled primarily patients with advanced PD that were not benefiting from standard medical therapy (Evans et al., 2012; Kefalopoulou et al., 2011; Ma et al., 2011). The rationale for choosing this population of patients is valid in that these individuals represent the population most in need of alternative therapeutics; nevertheless, the impact of factors associated with the

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Available online on ScienceDirect (www.sciencedirect.com).

http://dx.doi.org/10.1016/j.nbd.2015.03.005
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environment of the severely DA-depleted, aged striatum on the overall success of previous cell transplantation trials in PD remains incompletely understood.

There have been painstaking efforts both in the clinic and the laboratory to characterize optimal donor cells used for cell transplantation therapy in PD, addressing issues including the source material for grafted cells, donor cell age, density of cell grafts, immune factors, and growth factors (e.g.: Steece-Collier et al., 1990; Annett et al., 1997; Freeman et al., 1995; Sladek et al., 1998; Collier et al., 1999; Freed et al., 2001; Winkler et al., 2006; Torres et al., 2007; Matarredona et al., 2003; Terpstra et al., 2007; Soderstrom et al., 2008; Bjorklund and Kordower, 2013). However, comparatively little has been done to determine the impact of the host environment on transplant success, with most of the attention given to defining the optimal transplant location (Strömberg et al., 1986; Goren et al., 2005; Breysse et al., 2007). In humans (Freed et al., 2001) and in rats (Collier et al., 1999; Breysse et al., 2007) grafting into aged parkinsonian subjects is significantly less effective in providing behavioral benefit than grafting in their younger counterparts. It has long been known that the aged brain lacks many support factors found in younger brains (Collier et al., 1999, 2005; Ling et al., 2000), and is generally considered to be an impoverished or hostile environment for grafted embryonic neurons. Many researchers continue to explore methods of increasing survival of grafted DA neurons for PD (e.g.: Büchele et al., 2014; Chermenina et al., 2014; Battista et al., 2014), irrespective of host age. However, the purpose here was to determine if cell replacement therapy in the aged parkinsonian rat is equally therapeutic as in a younger cohort when the challenge of limited survival of grafted cells is overcome.

Previous data from our laboratories (Collier et al., 1999[1]; Sortwell et al., 2001[2]) has indicated that when the same number (i.e.: 200,000[1] or 300,000[2]) of embryonic rat ventral mesencephalic (VM) cells is grafted into the striatum of parkinsonian rats of varying ages, there is a proportional decrease in survival of engrafted DA neurons with increasing host age. This reduced survival of grafted DA neurons is associated with diminished reinnervation of the striatum, and blunted recovery of asymmetric rotational behavior (Collier et al., 1999). In an attempt to achieve an equivalent number of surviving grafted neurons across host ages, we extrapolated cell survival data from our previous study (Collier et al., 1999) and grafted two-fold or five-fold the number of VM cells into 15- or 22-month-old parkinsonian rats, respectively, compared to their 3 month-old counterparts. Numbers of surviving grafted neurons and their pattern of reinnervation were evaluated. The behavioral efficacy of embryonic VM grafts was evaluated using amphetamine-induced rotational behavior and amelioration of levodopa-induced dyskinesias (LID). The results from this study suggest that even when increased survival of grafted neurons and increased neurite outgrowth are achieved for all aging parkinsonian subjects, yet-to-be-identified factors in the aged, parkinsonian brain continue to limit the behavioral efficacy of graft integration and function. While significant recovery of rotational behavior is achieved, improvements in the more complex repertoire of levodopa-induced dyskinetic behaviors are delayed or absent in the aged host.

Materials and methods

Animals

Fischer-344 (F344) rats (Harlan, Indianapolis, IN, USA) were housed in groups of three with ad libitum access to food and water in their home cages. Three age groups of rats were studied: (1) young adult rats (3 months old at time of the lesion, N = 8, sham or DA graft), (2) middle-aged rats (15 months old at time of the lesion, N = 15, sham or DA graft), and (3) aged rats (22 months old at time of the lesion, N = 15, sham or DA graft). Rats were maintained on a 12 h light:dark cycle with lights on at 0700. All studies were carried out in accordance with the Declaration of Helsinki and with the Institute for Laboratory Animal Research of the National Academy of Science *Guide for the Care and Use of Laboratory Animals* and were approved by The Institutional Animal Care and Use Committee at University of Cincinnati, where the studies were carried out. All efforts were made to minimize the number of animals used and to avoid pain or discomfort.

Experimental design overview

The experimental timeline is shown in Fig. 1. Briefly, rats were rendered parkinsonian via unilateral stereotaxic injection of 6-hydroxydopamine (6-OHDA) into the substantia nigra and medial forebrain bundle. Two weeks after 6-OHDA surgery, rats were evaluated for lesion success with amphetamine-induced rotational behavior. One week later (3 weeks post-surgery), rats were primed with levodopa for 4 weeks prior to grafting. Seven weeks after lesioning, and four weeks into levodopa treatment, parkinsonian rats from each age group received an intrastriatal embryonic day 14 (E14) ventral mesencephalic (VM) or a sham (cell-free media) graft. Rats were withdrawn from levodopa for one week following graft surgery (Lee et al., 2000; Steece-Collier et al., 2003; Maries et al., 2006) and reinitiated thereafter. All parkinsonian rats were evaluated for levodopa-induced dyskinesias (LID) behaviors prior to and following grafting (Fig. 1). Eleven weeks after graft surgery, functional benefit was assessed with amphetamine-induced rotational behavior, with levodopa withdrawn for 48 h prior to amphetamine. Rats were sacrificed 24 h after this final amphetamine behavioral assessment. Details of surgical procedures, behavioral evaluations and drug treatments are provided in the following paragraphs.

6-OHDA lesion surgery

F344 rats received unilateral stereotaxic injections of 6-OHDA into both the left medial forebrain bundle (MFB) and left substantia nigra (SN). The SN coordinates were 4.8 mm posterior to bregma, 1.7 mm lateral to mid-sagittal suture, and 8.0 mm below the skull surface (Paxinos and Watson, 1998). MFB coordinates were 4.3 mm posterior to bregma, 1.2 mm lateral to mid-sagittal suture, and 8.0 mm below the skull surface. Animals were anesthetized prior to surgery with an intraperitoneal (i.p.) injection of chloropent (3.0 ml/kg body weight; chloral hydrate, 42.5 mg/ml + sodium pentobarbital, 8.9 mg/ml) and placed in a stereotaxic frame. The neurotoxin solution (5 μg 6-OHDA hydrobromide/μl 0.9% sterile saline containing 0.2 mg/ml ascorbic acid) was injected at a rate of 0.5 μl/min (2.0 μl total at each site) using a 5 μl Hamilton syringe with a 26-gauge needle.

Amphetamine-induced rotational behavior

Amphetamine-induced rotational asymmetry was examined at 2 weeks after the 6-OHDA surgery to confirm the presence of an adequate lesion, and 11 weeks after graft surgery to assess behavioral efficacy of neural grafts (Fig. 1). Rats were injected with amphetamine sulfate (5.0 mg/kg, i.p.) and rotational behavior was monitored for 90 min using automated rotometers (TSE Systems, Germany). Rats rotating, prior to transplantation, at a rate of ≥7 ipsilateral turns per minute over 90 min were included in this study. Our lab has previously confirmed that rats with this rotational rate have >95% SN DA neuron loss and striatal DA depletion and readily develop LID (Maries et al., 2006; Steece-Collier et al., 2003).

Levodopa administration

Three weeks after a 6-OHDA lesion, but prior to grafting, animals were injected once daily with levodopa to induce abnormal involuntary dyskinetic behaviors, or LID. Subjects were first primed with once daily (Monday thru Friday) levodopa at a dose of 25 mg/kg levodopa plus 25 mg/kg benserazide (intraperitoneal (i.p.)) for one week.

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