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Brain Grafts and Parkinson's Disease

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Abstract In animal models, grafts derived from several different tissues, principally fetal substantia nigra and adrenal medulla from young adults, have been found to be effective in alleviating some of the manifestations of lesions of the substantia nigra. It has been suggested that these grafts function by diffusely secreting dopamine, by exerting trophic effects on the host brain, or by producing a new innervation of the host corpus striatum. Evidence for each of these modes of action is briefly reviewed. Several brain tissue transplantation techniques have been described. Each of these techniques has significant limitations in animal models. The significance of these limitations for human application is described, and possibilities for improving the efficacy of brain tissue transplantation in animal models and for human application are discussed.

Key words: tissue transplantation, catecholamines, dopamine, L-DOPA, genetic engineering

Parkinson's disease is undoubtedly the functional central nervous system (CNS) disorder for which the goals of transplantation are most clearly defined. It is generally accepted that many of the manifestations of this disorder are related to a single missing circuit link: the dopaminergic innervation of the corpus striatum. There is no other major CNS functional disorder which has been so definitively linked to dysfunction of a single, defined system. Thus the goal of most therapeutic approaches to Parkinson's disease, including transplantation, has been replacement of the striatal dopaminergic innervation.

Early studies of tissue transplantation into the brain in animal models of Parkinson's disease were exclusively focused on tissues known to contain and secrete catecholamines. Some types of tissue transplants do appear to exert their effects via catecholamine release or secretion; however, recent data also suggest that, at least in some cases, brain grafts may produce indirect "trophic" effects in host brain or, at least, exert effects other than direct secretion of neurotransmitter substances. The purpose of the present paper is to briefly review the possible mechanisms of action of brain grafts in animal models of Parkinson's disease, and to explore various transplantation techniques and potential for human application.

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POSSIBLE MECHANISMS OF ACTION OF BRAIN GRAFTS

Diffuse Release of Catecholamines

Infusions of dopamine into the striatum of rats with substantia nigra (SN) lesions decrease apomorphine-induced rotational behavior [1,2]. Other studies have shown that alleviation of most of the effects of SN lesions, including aphagia, adipsia, and sensorimotor neglect, can be obtained by systemic injections of apomorphine or other dopamine agonists [3,4]. These data suggest that at least some of the behavioral deficits following SN lesions in animals can be reversed by diffuse, non-synaptic delivery of catecholamines.

The only cell type, other than SN neurons, that has been extensively studied as graft material in animal models of Parkinson's disease is the adrenal chromaffin cell. Under certain conditions, transplanted adrenal chromaffin cells may survive and produce functional effects in animal models. These conditions include transplantation of tissue from young donors into the ventricle [5,6] and transplantation of tissue into the striatal parenchyma in combination with nerve growth factor (NGF) infusions [7]. Other transplantation conditions, including intraparenchy-

mal grafts, in most cases result in relatively poor long-term cell survival and minimal functional effects [8–11]. Thus it appears that cell survival at least contributes to the efficacy of adrenal medulla grafts. On the other hand, it has also been suggested that NGF exerts its effects of adrenal medulla grafts through mechanisms other than by increasing chromaffin cell survival [12].

For intraventricular adrenal medulla grafts, which survive relatively well, it was initially suggested that functional effects were produced through secretion of catecholamines, which then reach receptor sites in the denervated striatum by diffusion [5]. Whether diffuse "paracrine" secretion of catecholamines from adrenal medulla grafts actually occurs is somewhat in doubt, as catecholamines have not been found in the cerebrospinal fluid (CSF) of animals with intraventricular adrenal medulla grafts [13].

A modified version of this hypothesis was that dopamine is secreted from adrenal medulla grafts into local blood vessels, and reaches the striatum via the circulatory system and compromised blood-brain-barrier function [13]. The finding that dopamine concentrations in peripheral blood were correlated with the functional effects of adrenal medulla grafts initially supported this hypothesis. Our most recent data, however, suggest that decreases in rotational behavior are seen specifically in animals that receive adrenal medulla grafts, as compared to controls. In addition, the transplantation surgery non-specifically increased blood dopamine concentrations, and these increases were associated with small decreases in rotational behavior. These non-specific increases in blood dopamine may have been mediated by the host adrenal medulla, in that increases in blood dopamine were not seen in adrenalectomized animals, and decreases in rotational behavior in adrenalectomized animals were smaller than those seen in animals with intact adrenal glands (H. Takashima, M. Poltorak, J.B. Becker, and W.J. Freed, unpublished). This suggests that the functional effects produced by adrenal medulla grafts may be due to a combination of two smaller effects: a specific effect of surviving grafts and a non-specific response to surgery mediated by the host adrenal gland. It is not clear, however, whether the specific effect of adrenal medulla grafts is due to release of catecholamines.

Trophic Effects on Host Brain

It has been suggested that trophic effects underlie the functional changes which are seen after adrenal medulla grafts [8]. Some studies suggest that adrenal medulla grafts produce alterations in host dopaminergic systems even if the grafts do not survive. For example, Bohn and coworkers [8] found that adrenal medulla grafts enhance tyrosine hydroxylase (TH) immunoreactivity in the striatum of mice following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment. Fiandaca and coworkers [10] reported similar findings in sub-human primates. These studies employed MPTP models, and did not examine functional effects of the grafts. In another study, a localized increase in TH-immunoreactive neurites was reported following implantation of adrenal medulla, control tissues such as adipose tissue and sciatic nerve, and even cavitation without tissue implantation [14]. These increased TH-immunoreactive neurites were interpreted as sprouting. Behavioral changes were seen after this surgery; however, similar sprouting was seen in the cavitation-only group at a time when the behavioral changes had disappeared.

Most of the studies which have reported sprouting-like phenomena following adrenal medulla grafts have used animals with MPTP-induced damage of the nigrostriatal system, and in this model spontaneous recovery of dopaminergic systems may occur. One study, by Pezzoli and coworkers [12] using rats with 6-hydroxydopamine-induced damage of the nigrostriatal system, however, reported functional changes following adrenal medulla, sciatic nerve, and adipose tissue grafts when the grafts were combined with NGF infusions. Increased growth of dopaminergic neurites from transplanted embryonic SN has also been reported following cortical injury [15]. Possible mechanisms through which adrenal medulla grafts may produce trophic effects include production of basic fibroblast growth factor [16], cell adhesion molecules [17], or effects mediated by macrophages or inflammatory events [8,10,12]. These trophic effects or sprouting phenomena may contribute to functional effects of adrenal medulla grafts.

Reinnervation of Host Brain

Neurons obtained from the SN of fetal animals have been transplanted into the brains of animals in numerous studies, and under appro-

priate conditions can alleviate functional manifestations of SN damage [6,18–22]. Transplanted dopaminergic neurons show spontaneous electrical activity at a rate approximating that of normal nigral neurons [23]. Grafted SN neurons develop neurites which enter the host brain [18,20], and form synaptic contacts with host neurons [24,25]. In addition to the normal synaptic contacts with spiny nigral projection neurons, transplanted nigral neurons also appear to form contacts with giant neurons, which are thought to be cholinergic interneurons [24].

The primary methods used for intracerebral transplantation of SN include intraventricular grafts of solid tissue fragments [6], solid tissue grafts into pre-prepared cortical cavities [20], and intrastriatal grafts of dissociated cells [21]. Tissue from earlier developmental stages is required for dissociated cell grafts, as the tissue disruption concommittant with dissociation is damaging to more differentiated tissue. For dissociated cell grafts from rat donors, the optimal age for rat donors is 14–16 days of gestation [21], while the optimal age for solid tissue grafts is 15–17 days [26]. Optimal donor ages for obtaining functional effects appear to roughly correspond to the optimal ages for obtaining survival of transplanted dopaminergic neurons [21,26]. The functional effects of SN grafts in individual animals also is correlated with the amount of reinnervation of the host brain [20,26].

Using the intraventricular transplantation model, we have conducted a series of experiments aimed at elucidating the factors which control the efficacy of intraventricular SN grafts. When transplanted into adult hosts, intraventricular SN grafts usually reinnervate only a part of the host striatum. When intraventricular embryonic SN grafts are combined with grafts of embryonic corpus striatum, however, the striatal grafts are completely innervated by the SN grafts, to the exclusion of host brain [27; also cf. 28]. This suggests that the efficacy of SN grafts is limited in mature hosts because the target tissue (e.g., the host striatum) is mature. When SN grafts were made into immature, neonatal hosts, a substantial prevention of the consequences of subsequent bilateral SN lesions were obtained. This included partial protection from the aphagia and adipsia, as well as the akinesia and rigidity produced by complete bilateral SN lesions [22]. It appears, therefore, that age of the host or target tissue is an important factor which influences the efficacy of SN grafts.

PROPERTIES AND LIMITATIONS OF BRAIN GRAFTS

Fetal SN Grafts

The advantage of fetal neurons, as compared to other substitute cells, is primarily that these cells have the potential to express all of the properties—such as the ability to make appropriate neurotransmitters, co-transmitter, and trophic substances, extend neurites, form synapses, and exhibit regulated neuronal activity—which are required for functional activity. Nonetheless, there are some limitations. First, there are the practical problems in obtaining human tissue, legal and ethical issues, and immunological obstacles. Second, there is almost certainly a limitation in the degree of integration of these grafts into the host brain, in that transplanted neurons do not become fully afferented and the complete nigro-striatal-nigral circuitry cannot be re-established. Accordingly, there may be a limitation on the amount of behavioral effect that can be obtained.

The two major techniques that have been used to assess the efficacy of brain grafts involve measurements of rotational behavior induced by amphetamine and apomorphine. Amphetamine stimulates dopamine release, and thus acts on the terminals of transplanted dopaminergic neurons. Changes in amphetamine-induced rotation are therefore a measure of properties of the graft. Apomorphine, in contrast, acts post-synaptically upon striatal dopaminergic receptors; these are a part of the host brain. Changes in apomorphine-induced rotation, therefore, constitute measurements of the effects of the graft upon the host.

Amphetamine-induced rotation is readily decreased, and even entirely eliminated, by SN grafts implanted by a variety of techniques, even though these grafts may be only partially effective when assessed by other methods. In one experiment, for example, intraventricular SN grafts were found to, on the average, produce complete elimination and reversal of amphetamine-induced rotation. These same grafts only partially reinnervated the host striatum, decreased apomorphine-induced rotation by about 50%, and produced a partial decrease in dopaminergic receptor supersensitivity [29]. Several other studies, using a variety of methods, have found very large decreases in amphetamine-

induced rotation [20,30,31]. It has been suggested that transplanted SN neurons are very sensitive to amphetamine [32] and also that transplanted SN neurons may not release dopamine normally, thus building up excess stores of dopamine which are susceptible to amphetamine-stimulated release. Thus large decreases in amphetamine-induced rotation are not conclusive evidence of large functional effects of SN grafts.

Apomorphine-induced rotation, in contrast, is usually decreased only moderately by SN grafts implanted by a variety of methods. Decreases in apomorphine-induced rotation of about 50% were reported in early experiments (18–20). Similarly limited decreases in apomorphine-induced rotation have also been reported in studies involving transplantation of fetal rat SN into multiple sites [30] and transplantation of human fetal SN into rat striatum [31], even though both methods result in very substantial reinnervation of the striatum. Thus, measurements of apomorphine-induced rotation suggest that there are limitations on the restoration of function that can be achieved by transplantation of SN into adult hosts, which are similar for all known transplantation methods. The significance of this limitation is striking in view of the fact that apomorphine-induced rotation does not appear at all except in animals with nearly complete denervations of the striatum. This limitation in the efficacy of embryonic SN grafts is not limited only to apomorphine-induced rotation; the aphagia and adipsia caused by bilateral SN lesions cannot be reversed by SN grafts [33] except in neonatal host animals [22].

It is not clear whether the limited efficacy of SN grafts represents a limitation in the maximum possible effects of SN grafts, or in the amount of effect that has been obtained using the techniques which have so far been developed. These limitations might be based on either pre- or post-synaptic events. It might be, for example, that SN lesions induce essentially permanent changes in striatal circuitry, including perhaps degenerative events [34] or gliosis, which cannot be reversed by changes in the dopaminergic afferentation. Alternatively, it is possible that the growth of SN grafts, in terms of the ability of transplanted neurons to extend neurites or produce synapses, is limited because of properties of the grafts or the methods that are used, so that as-yet-undiscovered methods could still enhance their effects.

Adrenal Chromaffin Cells

Many of the effects that have been produced by SN grafts in animal models have been duplicated by grafts of adrenal chromaffin cells, although there have been few direct comparisons. Comparisons of SN and adrenal chromaffin cell grafts are greatly complicated by the fact that adrenal chromaffin cells do not always survive transplantation. Thus experiments which have shown greater effects of SN than adrenal chromaffin cells grafts when few of the chromaffin cells survive [35] would not necessarily have reached the same conclusions if the transplanted chromaffin cells had survived.

Notwithstanding, it seems that the effects of chromaffin cell grafts may be somewhat less than those of SN grafts. Reductions in apomorphine-induced rotational behavior produced by (surviving) chromaffin cell grafts seem to be on the order of 30–50%, as compared to 50–80% for SN grafts. Adrenal chromaffin cell grafts produce a modest alleviation of aphagia and adipsia, but no effect on impaired locomotor activity when transplanted into neonatal animals [36], while SN grafts cause marked alleviation of the effects of bilateral SN lesions by all three measures [22].

Adrenal chromaffin cell grafts have been employed in a large number of patients with Parkinson's disease. As it is possible to employ autografts, tissue procurement problems and immunological difficulties are not an obstacle. Significant mortality and morbidity have, however, been associated with these procedures. Whether these grafts have produced clinically significant improvement is very controversial. Initial studies using intraparenchymal transplantation [37], which is not effective in animals, found only transient clinical improvement. Some subsequent experiments using peri-ventricular transplantation, similar to the methods that have been found to produce effects in animals, have reported large clinical changes [38]. Some of these early trials used relatively informal assessment methods and small numbers of patients. Subsequent trials of the periventricular transplantation method using larger groups of patients and objective assessment methods indeed found some lasting improvements [39]. The clinical significance of these improvements, and possible physiological reasons for the improvements, are discussed elsewhere [40]. It is, however, important to note

that large changes should not be expected in view of the relatively small functional effects of adrenal medulla grafts in animals.

Genetically Modified Cells

Recent experiments have examined the possibility that genetically altered cells could be used for intracerebral transplantation in animal models of Parkinson's disease. There are two fundamentally different approaches to this problem. One possibility is to alter embryonic dopaminergic neurons, so that they can be grown in tissue culture, and then employed for transplantation. This might be accomplished, for example, by the introduction of stably-integrated immortalizing oncogenes, such as SV-40 large T antigen, using viral- or retroviral-mediated gene transfer methods [41]. This approach is discussed in another paper in this volume (Geller et al., this volume).

A second approach involves the introduction of DNA coding desirable cell properties into a readily available cell type, either cell lines or primary cells. Because L-dihydroxyphenylalanine (L-DOPA) is pharmacologically effective in treating Parkinson's disease, and in view of the benefits of continuous L-DOPA infusions [42], cells which contain TH and produce L-DOPA might be useful for transplantation.

One approach is the use of primary cells, such as fibroblasts, from the same subject, modified by the introduction of DNA encoding TH. Fibroblasts could be obtained by biopsy, altered by gene transfer of human tyrosine hydroxylase cDNA, and reintroduced into the brain of the host. Such an approach would virtually eliminate immunological complications, because cells would be derived from the same individual and human proteins could be produced. This methodology could be applicable to modification of primary astrocytes, macrophages, or other transplantable cells such as a recently described cortical cell line [43].

Full length cDNA encoding enzymatically active TH has been isolated from rat [44,45] and human [46,47] libraries. The human gene, in contrast to that of the rat, produces multiple mRNA species encoding active TH [47]. Recently, Cottingham and coworkers [48] have introduced the cDNA for human tyrosine hydroxylase form 2 in pDOLMP10 retroviral vector into murine NIH-3T3 fibroblasts. These recombinant TH-3T3 fibroblasts contain TH mRNA as well as TH immunoreactivity by in vitro staining and western analysis. The TH produced by these recombinant TH-3T3 cells was catalytically active, requiring the tetrahydropterin cofactor [48]. When the cells were grown in culture for 24 to 48 hr with tyrosine and cofactor, substantial concentrations of L-DOPA were found in the medium.

To test for possible behavioral effects of the TH-3T3 cell grafts, a reserpine treatment model was used. Reserpine acts by depleting monoamine storage granules, and induces an L-DOPA responsive state of inactivity. Animals with intrastriatal grafts of TH-3T3 cells or control grafts (normal 3T3 cells or recombinant 3T3 cells containing the DOLMP10 vector, without the TH cDNA) received reserpine 10 mg/kg I.P. Between one and seven days later, these animals were treated with L-tyrosine, with or without D,L-6-methyl-5,6,7,8 tetrahydropterine cofactor I.P. Behavioral activity of these animals was then tested over the following 2 to 6 hours in Omnitech photocell-activated activity monitors. In some experiments, L-tyrosine, with or without cofactor, was found to produce activation of the reserpine-treated mice to a greater degree than the controls for approximately 2 to 3 hours after administration. This activation was greatest when the animals were tested three days after reserpine injection [49]. These data suggest that recombinant fibroblasts which express TH activity can produce functional and behaviorally-significant alterations in host animals. The transplanted cells were readily identified in hematoxylin and eosin stained sections, by immunostaining with an antibody to fibronectin, or by in situ hybridization histochemistry for TH.

Wolff and coworkers [50] have reported that TH-infected fibroblasts transplanted into the brains of animals with unilateral lesions of the SN decreased rotational behavior induced by apomorphine or amphetamine (data were not reported separately). It is not clear why amphetamine-induced rotation would be decreased by TH-infected fibroblasts, as these cells would not be expected to be sensitive to amphetamine. Confirmation that these grafts continued to express TH activity following transplantation was not obtained. Subsequent studies by Horellou and coworkers [51] obtained expression of human TH, by retroviral-mediated gene transfer, in three cell lines, a fibroblast (NIH-3T3), a neuroblastoma (NS20 Y), and a neuroendocrine (AtT-20) line. The AtT-20 line contained dopamine and showed depolarization-dependent dopamine release [51]. Two of these cell lines,

the NS20Y and the AtT-20 cells, were transplanted into rats with unilateral SN lesions and were found to decrease apomorphine-induced rotation on a short-term basis [52]. Tumor formation occurred rapidly, within two weeks for both of these latter cell types, which precluded longer-term experiments. Uchida and coworkers [53] have also obtained expression of TH in C6 glioma cells, and have shown TH immunostaining after intracerebral transplantation. These cells also rapidly formed large tumor-like masses.

At the present time, therefore, there are indications that cells which have been modified to express TH can produce functional effects in animal models. Methods for consistently introducing TH into primary cells, or for introducing TH into cells which are stable and do not form tumors following transplantation, still need further development.

CONCLUSIONS

The three cell types which have received the greatest amount of attention to date for transplantation in animal models of Parkinson's disease are fetal neurons, adrenal chromaffin cells, and cells which have been recombinantly modified to contain the TH enzyme. Each cell type has potential advantages and disadvantages.

Fetal neurons, at least in principle, have the greatest potential. The major disadvantages of these cells, in terms of potential human application, are practical: Tissue is difficult to obtain, there are legal and ethical problems associated with the use of fetal tissue, there are potential immunological problems, and it is also conceivable that transplanted fetal neurons would be subject to destruction through the same process that led to loss of the host SN neurons. In addition, as discussed above, there appear to be limitations to the efficacy of fetal SN grafts in animal models. There have been several human studies of transplantation of fetal dopaminergic neurons in Parkinson's disease. Some have reported minor improvement, although the results have generally been disappointing [54,55]. One recent study reported substantial improvement in a single human patient [56], but the time course of the changes was not entirely consistent with what would have been expected from animal studies using similar methods.

Adrenal medulla grafts produce effects in animals which are generally somewhat smaller than those produced by embryonic SN grafts. As it is possible to use autografts for clinical studies, tissue is readily available and immunological obstacles are minimal or nonexistent. This advantage of ready availability of tissue may, however, turn out to be somewhat paradoxical. Even under optimal conditions, the functional effects of adrenal medulla grafts are relatively small. Adrenal medulla grafts appear to be most effective, however, when both the donors and hosts are relatively immature, and little or no functional effect is found when aging hosts or donors are employed [6,11,57]. In fact, studies that have obtained positive behavioral effects of adrenal medulla grafts have usually employed transplantation of tissue from very immature animals (i.e., rats less than two months old) into rat hosts which are less than one year old [5,11,36, H. Takashima, M. Poltorak, and W.J. Freed, unpublished]. Thus the most effective methodologies might not be practical to employ in human subjects.

A promising approach to future transplantation strategies is the use of genetically altered cells. The approaches that have so far been reported have used only cell lines, some of which can form tumors following transplantation. Grafts which are stable on a long-term basis are not yet possible; however, it is probably possible to develop genetically altered cells which are capable of long-term stability following transplantation using current technology.

To be considered for human application, however, additional improvements will be needed, possibly including increases in the levels of gene expression, incorporation of mechanisms to allow for regulation of some biochemical properties of the altered cells, or techniques which allow for consistent and predictable introduction of genes into primary cells. Studies which have so far been reported suggest that mere expression of TH may be sufficient for functional effects in animal models; however, only minimal data on this point is so far available on very small numbers of animals, and there is certainly a possibility that TH production alone can influence only a limited spectrum of the manifestations of SN lesions. A great deal of additional data will be required before the potential of TH-containing cells for therapy in humans can reasonably be assessed.

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