Transplantation of Fetal Dopamine Neurons in Parkinson's Disease: One-year Clinical and Neurophysiological Observations in Two Patients with Putaminal Implants

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Ventral mesencephalic tissue from aborted human fetuses (age, 6–7 weeks' postconception) was implanted unilaterally into the putamen using stereotactic surgery in 2 immuno suppressed patients (Patients 3 and 4 in our series) with advanced idiopathic Parkinson's disease. Tissue from 4 fetuses was grafted to each patient. Compared with our previous 2 patients, the following changes in the grafting procedure were introduced: the implantation instrument was thinner, more tissue was placed in the operated structure, and the time between abortion and grafting was shorter. There were no postoperative complications. Both patients showed a gradual and significant amelioration of parkinsonian symptoms (most marked in Patient 3) starting at 6 and 12 weeks after grafting, respectively, reaching maximum stability at approximately 4 to 5 months; patients remained relatively stable thereafter during the 1-year follow-up period. Clinical improvement was observed as a reduction of the time spent in the “off” phase and the number of daily “off” periods; a lessening of bradykinesia and rigidity during the “off” phase, mainly but not solely on the side contralateral to the graft; and a prolongation and change in the pattern of the effect of a single dose of L-dopa. Neurophysiological measurements revealed a more rapid performance of simple and complex arm and hand movements bilaterally, but primarily contralateral to the graft. The results indicate that patients with Parkinson's disease can show significant and sustained improvement of motor function after intrastral implantation of fetal dopamine-rich mesencephalic tissue. The accompanying paper by Sawle and colleagues describes the results of repeated positron emission tomography scans in these patients.


The introduction of grafting of fetal dopamine (DA)-rich mesencephalic tissue as a possible treatment for Parkinson's disease (PD) has been prompted by the problems encountered in long-term medical therapy and the severity of symptoms in this disorder. Although the animal experimental basis for clinical trials is promising [1–4], it should be remembered that it has not been possible to reverse all functional deficits even in rat-to-rat grafting experiments [5–8] (e.g., those impairments observed in more complex motor tasks [5, 8]). Furthermore, it has been reported that for those deficits in parkinsonian monkeys that are improved by fetal mesencephalic grafts, the "degree of functional change in each animal still falls far short of optimal recovery" [4]. Successful neural grafting with present procedures in patients with PD would thus be expected to effect only a partial improvement of their parkinsonian symptoms. In a patient with advanced PD, however, even a partial restoration of function (e.g., a prolongation of the L-dopa effect and less motor

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fluctuations) would be beneficial. Apart from these therapeutic considerations, the major scientific objective with the first clinical trials using neural grafting in PD has been to test whether the basic principles of cell replacement established in animal experiments are also valid in the diseased human brain. For this purpose it is of critical importance to be able to correlate any clinical improvement with the demonstration of a surviving dopaminergic graft. A majority of patients with PD subjected to fetal mesencephalic grafting have been reported to exhibit improved motor function [9–14], but few attempts to show graft survival have been undertaken. Autopsy studies in 2 patients who died 1 and 4 months, respectively, after implantation of fetal mesencephalic tissue have been reported to show surviving central nervous system (CNS) tissue; however, no surviving DA neurons could be identified in the grafts (J. Dynecki, personal communication, 1990) [15].

In the first 2 patients in our series of patients with idiopathic PD [16, 17], followed for 2 years, we observed a modest reduction of parkinsonian symptoms after transplantation, which agreed well with the minor changes of 6-[(18F)]fluorodopa uptake measured in the grafted striatum using positron emission tomography (PET). With an improved transplantation procedure in our third patient, we observed both a clearly more marked functional effect as well as a significant increase of striatal fluorodopa uptake on PET 5 months postoperatively [18]. These findings provided the first evidence that fetal mesencephalic grafts can restore DA synthesis and storage in the denervated human striatum and that this restoration can lead to a significant and sustained improvement of motor function in patients with idiopathic PD. We report the clinical and neurophysiological observations up to approximately 1 year after transplantation in our third patient as well as another patient with PD (Patient 4) subjected to neural grafting with the same procedure.

Methods

Study Design

The patients entered the study program approximately 1 year before transplantation. They were followed clinically both preoperatively and postoperatively at 1- to 2-week intervals for a day during which they stayed for approximately 8 hours in the neurological ward. Clinical evaluation of the symptoms of PD was carried out to 6 times each test day, randomly during “off” period, with the patients receiving full antiparkinsonian medication. Some observations were also made during “on” phases. Due to the reduction of the time spent in “off” phases postoperatively, the majority of tests from 3 months (Patient 3) and 4 months (Patient 4) after grafting had to be carried out before the first morning dose of l-dopa to obtain data from an “off” period. Diurnal variations (“on/off” phenomena) were assessed continuously by the patients themselves, who kept daily logs and scored their motor symptoms every 30 minutes. The test battery also included a single-dose l-dopa test, neurophysiological measurement of simple and complex arm and hand movements, and a PET scan using 6-[(18F)]fluorodopa as a tracer. During one preoperative and three postoperative 1-week periods, in connection with the PET scans, Patient 3 discontinued bromocriptine therapy. Otherwise, they were maintained on the same doses of antiparkinsonian drugs during 11 months (Patient 3) and 6 months (Patient 4) preoperatively and during the entire 12 to 14 months of the postoperative follow-up period.

Immunosuppression and Grafting Procedure

Immunosuppressive treatment was begun 2 days before transplantation and has continued since then, using a combination of low-dose cyclosporine, azathioprine, and low-dose prednisolone [16]. The daily maintenance doses are 2 to 4 mg/kg of cyclosporine, according to whole blood concentration; 1 to 2 mg/kg of azathioprine, according to blood cell counts; and 10 mg of prednisolone.

Dissected ventral mesencephalic tissue was implanted stereotaxically in the anterior, middle, and posterior part of the putamen on the side contralateral to the most affected limbs (i.e., in the left putamen in Patient 3 and in the right putamen in Patient 4). The tissue grafted to each patient was procured from 4 fetuses obtained at routine suction abortions, with informed consent from the women and with approval by the Research Ethical Committee of the Medical Faculty at the University of Lund, Sweden. The women were negative for human immunodeficiency virus and hepatitis B. The fetuses were 6 to 7 weeks’ postconception (crown-rump lengths measured with ultrasound were 20 to 25 mm, corresponding to Carnegie stages 20–22). The fetal tissue fragments were rinsed and stored in buffered Hanks’ balanced salt solution (HBSS; pH 7.4) for 1 to 3 hours at room temperature. The ventral mesencephalon was dissected from each fetus, cut into 5 to 10 pieces, and pooled with pieces from other fetuses. The pieces were incubated in trypsin at 37°C for 20 minutes and then rinsed repeatedly with HBSS. They were partially dissociated in HBSS just before the first implantation in a final volume of approximately 80 μL. The time between abortion and initiation of implantation surgery was 2.5 to 4 hours. Implantation was performed under local anesthesia at three sites in either the left or the right putamen with a stereotaxic technique. For each site, 20 μL of the dissociated tissue were drawn into the instrument (outer diameter, 1.0 mm). The graft tissue was injected along 10-, 12-, and 14-mm linear tracts in Patient 3, and along 8-, 12-, and 12-mm linear tracts in Patient 4, in eight 2.5-μL portions for 15 to 20 seconds each. Between each injection there was a 2-minute delay, and the cannula was then retracted 1.5 to 1.7 mm. After the final injection, the cannula was left in situ for 8 minutes before being slowly withdrawn from the brain. At the end of the surgery, the remaining cell suspension was relatively free of tissue pieces, and the viability was assessed to be 70% [19]. The remaining cell suspension was taken for bacteriological analyses and found to be sterile. Compared to the transplantation procedure used in our first 2 patients [16], the following potentially important changes were introduced in Patients 3 and 4 [18]. The implantation cannula was
considerably thinner (1.0 mm versus 2.5 mm outer diameter in Patients 1 and 2); the medium used for storage and dissociation of the tissue was a buffered, pH-stable salt solution rather than saline; the technique of loading the cannula was improved so that virtually all the tissue could be used; the time of tissue storage before transplantation was shorter (2.5-4 hr compared with 4-6 hr); and the same amount of tissue (from 4 fociuses in all patients) was implanted only in one striatal structure (putamen) instead of both caudate and putamen.

Method of Assessment

CLINICAL EVALUATION

1. Rigidity was evaluated by using a scoring system based on passive joint movements with the patient relaxed in the supine position: 0 = absent, 1 = slight, 2 = moderate, and 3 = severe. Large joints in all four extremities and the neck were examined.

2. Tremor was recorded as present or absent.

3. Succession movements (pronation-supination) were evaluated by noting the time needed for tapping the knee alternately with the palm and dorsum of the hand 20 times.

4. Fist clenching were repeated 20 times with each hand, and the time was noted.

5. Finger dexterity was evaluated by recording the time needed for tapping the thumb with the forefinger and then with each finger in rapid succession and back to the forefinger 10 times.

6. Foot lifting was assessed as the time patients needed to lift their foot approximately 2 cm from the floor 20 times.

7. Gait was evaluated as the number of steps and time needed to walk 7 meters and then return.

SINGLE-DOSE L-DOPA TEST. The response to a single dose of l-dopa was tested four to five times preoperatively and at monthly intervals postoperatively. The patients fasted overnight and took their last l-dopa and bromocriptine dose 14 hours before the start of the test. At 9 AM, the patients were given 100 or 200 mg of l-dopa with decarboxylase inhibitor by mouth. Blood sampling for plasma l-dopa determination and clinical testing were then carried out every 15 minutes until approximately 90 minutes after the l-dopa-induced improvement of mobility had disappeared [16].

SIMPLE AND COMPLEX ARM AND HAND MOVEMENTS. Performance of self-paced simple and complex arm and hand movements in the “off” state was measured one year before and 5, 8, and 13 months (Patient 3) and 7 and 12 months (Patient 4) after surgery, according to Lindvall and associates and Bennecke and colleagues [16, 20]. The following tests were performed: time taken to flex the elbow through 13 degrees; time taken to flex the elbow at the same time as an isometric squeeze of the hand; time taken to flex the elbow after a preceding squeeze; and interval between onset of squeeze and flexion movement in a sequential task (interonset latency).

MAGNETIC RESONANCE IMAGING. Magnetic resonance imaging (MRI) was carried out in Patient 3 10 months after grafting on a FONAR 3-3000 M scanner (FONAR, Melville, NY) using T1- and T2-weighted images before and after contrast injection (0.1 mmol/kg body weight of gadolinium dihydrogenenpentacetic acid [Gd-DTPA]).

Results

Patient 3

This patient is a 50-year-old man with PD, which began with unilateral resting tremor and rigidity in the right arm in 1977. Initial treatment with l-dopa was successful, but in 1984 he developed progressively worsening “on-off” phenomena. At the beginning of the study (April 1988) he was rated stage III on the scale of Hoehn and Yahr [21]. During “off” periods he had severe rigidity, hypokinesia, and a moderate tremor in the right arm; less marked symptoms were evident in the left arm and legs. During “on” periods he displayed only very minor symptoms. The patient was taking daily doses of 700 mg of l-dopa (combined with benserazide), 10 mg of bromocriptine, and 6 mg of benzhexol chloride.

After an initial worsening of parkinsonian symptoms lasting for approximately 2 weeks, during the second month after transplantation there was a marked reduction of both the time spent in “off” periods (from approximately 50 to 20% of the day) and the number of daily “off” periods (from 4-5 to 2; Fig 1). The patient noted a progressive reduction of rigidity, particularly in his right arm, and improvement of mobility during the night and in the morning before the first l-dopa dose. He was now able to sleep through the night without additional intake of l-dopa, which had been impossible during the preoperative assessment period. After the first l-dopa dose, he often spent the rest of the day “on,” with no or only a single brief “off” period, during which he had clearly less severe parkinsonian symptoms than preoperatively. In addition, he sometimes had very brief periods (up to 2-3 min) with tremor during “on” phases, but without any accompanying signs of rigidity or hypokinesia. From 4 to 5 months postoperatively he experienced no further improvement and regarded his condition as relatively stable up to the end of the 14-month observation period except that he sometimes noted more difficulties in initiating walking than preoperatively.

Beginning during the second postoperative month, there was a gradual reduction of muscle tone in all joints examined during “off” periods (Fig 2A). Although the change was bilateral, it was most pronounced in the right arm, which had been severely rigid preoperatively. The rigidity almost completely disappeared between 2 and 3 months postoperatively. From the 12th postoperative month (see Fig 2A), a slight bilateral increase of muscle tone could be noted in the arms.

Of the different timed neurological tests, carried out
randomly during "off" periods with the patient on medication, the performance of 20 pronations and supinations showed the most marked differences between "on" and "off" phases preoperatively (9 sec for both arms in "on" phase and 14 and 24 sec for the left and right arm, respectively, during "off" phases; Fig 2B). From 2 to 3 months after surgery, the patient exhibited a marked improvement of movement speed during "off" periods in the right arm and a similar change (although of lesser magnitude) in the left arm (see Fig 2B). The big difference in performance time (10 sec) between the arms before surgery disappeared almost entirely. The movement speed was then stable for the rest of the study period, but from 11 months after grafting and onward the amplitude of the pronation-supination movement seemed to be slightly reduced (not shown in Fig 2B), although it was still clearly better than preoperative amplitude. Similar postoperative changes were observed in the fist clenches test, the performance of which improved bilaterally, particularly on the right side. The improvements in the finger dexterity test were less pronounced (Fig 2C), were observed consistently only in the right arm, and were no longer significant 1 year postoperatively. The preoperative difference in the time taken to perform the foot lifting and walking tests (as well as the number of steps needed) during "on" and "off" phases, respectively, was too small to allow for any analysis of postoperative improvements. There was no change in the localization and severity of tremor after surgery.

The speed of a series of self-paced arm and hand movements was measured, using the computerized test...
procedure of Benecke and colleagues [20], before the first morning dose of L-dopa 12 months before surgery, and 3, 8, and 15 months after surgery (Fig 3). There was a significant bilateral improvement of the speed of all elbow flexion movements. In addition, the interval between the onset of the hand squeeze and the elbow flexion movement in the sequential task decreased after surgery on the right side. With the left arm, this interonset latency was longer 5 and 8 months after transplantation as compared with preoperative results, but there was a minor improvement also on the left side 13 months after grafting.

The effects on motor performance of a single dose of L-dopa were tested in the morning after a drug-free period of 14 hours. In the tests before transplantation, the patient was severely rigid and hypokinetic before L-dopa administration, and when the effect of L-dopa disappeared (after 90 to 120 min; mean, 105 min) he rapidly returned to the same condition (Fig 4A). This pattern showed a gradual change after transplantation (Fig 4B, C). After the fifth postoperative week, his motor performance before L-dopa intake progressively improved, and the duration of the drug-induced “on” phase was longer in all postoperative tests (mean, 160 min; range, 135–195 min). Indeed, after the ninth week the movement speed in the pronation-supination test during the morning “off” period was close to that recorded during the subsequent L-dopa–induced “on” period. Furthermore, there was no immediate major worsening of motor symptoms at the end of the “on”
periods in the tests performed from 14 weeks after transplantation: few parkinsonian symptoms were evident, even 4 hours after l-dopa intake. The analysis of plasma l-dopa levels in the preoperative tests showed that the peak value \( [11.7 \pm 1.1 \text{ ng/5 mL of plasma; mean} \pm \text{ standard error of the mean (SEM)}] \) occurred after 60 ± 6 minutes in Patient 3. No significant change \( (p > 0.05) \); Student’s unpaired t-test) of these parameters was observed in the tests performed after transplantation (peak value, 10.6 ± 0.9 ng/5 mL of plasma at 55 ± 3 min).

Ten months postoperatively, MRI showed increased signal on T2-weighted images corresponding to the injection tracts, which ended as intended in the anterior, middle, and posterior part of the left putamen. There was no enhancement after Gd-DTPA injection.

**Patient 4**

This patient is a 60-year-old man with PD since 1980, at which time he started to exhibit rigidity and tremor in his left arm. l-dopa treatment was initiated in 1982 and the patient did well until 1986 when he began to develop “on-off” symptoms. He was rated stage III on the scale of Hoehn and Yahr [21] at the beginning of the study (April 1988). During “off” periods he had moderate resting tremor and severe rigidity in the arms, particularly on the left side; marked hypokinetism movements in the left arm; and moderate tremor and hypokinetism movements in the legs. During “on” periods he had only minor parkinsonian symptoms. The patient was taking 450 mg of l-dopa (combined with benzerazide).

There was a transient postoperative worsening of parkinsonian symptoms in Patient 4 (similar to Patient 3, but even more pronounced) (Figs 5, 6). During the fourth month after transplantation the patient noted a marked reduction of both the number and duration of daily “off” periods (see Fig 5). Before grafting he spent approximately 60% of the day in the “off” phase and had 3 to 4 daily “off” periods. From the fourth postoperative month he improved, and since then he has spent approximately 30% in the “off” phase and has had 2 to 3 daily “off” periods. He also reported better performance with the left than with the right arm during “off” phases, including improved movement speed and less subjective rigidity.

No major change in rigidity (see Fig 6A) or tremor during “off” phases could be detected, but from the fourth postoperative month increased speed of arm and hand movement was observed on the side contralateral to the graft. Thus, the time to perform 20 pronations and supinations (see Fig 6B) with the left arm was significantly reduced from approximately 28 seconds preoperatively to between 13 and 22 seconds postoperatively. There was no improvement on the right side, and, in fact, during many tests the patient performed better with his left arm, which did not occur preoperatively. Also, the fist clench test demonstrated clearly better performance with the left arm during “off” periods. In contrast, the time to perform the finger dexterity test (see Fig 6C) with the left hand showed no positive changes after grafting. On the right side the speed was, in fact, significantly slower than preoperative speed (see Fig 6C). The differences between performance of the foot lifting and walking tests in “on” and “off” phases were small, and no significant postoperative changes could be demonstrated.

In the computerized tests of simple and complex arm and hand movements, performed at 7 months, there was a marked improvement on both sides (Fig 7). The speed of all elbow flexion movements had increased at this time, but at 12 months, no significant improvements remained except in the interval between the onset of the squeeze and the flexion movements in the sequential task. It should be pointed out, however, that at the time of this latter test the clinical test battery showed a transient worsening (over a few days) of parkinsonian symptoms.

The effects on motor performance of a single dose of l-dopa are shown in Fig 8. In the preoperative tests, he performed the pronation-supination test with the left arm in approximately 30 seconds before onset of the effect of l-dopa; the duration of the l-dopa-induced “on” phase was 90 to 120 minutes (mean, 110 min); the patient then directly returned to a severe “off” phase (see Fig 8A). After grafting (see Fig 8B, C), from the ninth postoperative week, he performed the tests more rapidly in the morning (approximately 20 sec); the duration of “on” phases was longer (range, 135–180 min; mean, 155 min); and, particularly in the
later tests, he did not return to the same preoperative severe “off” state. In the preoperative tests, the peak value of plasma l-dopa levels (8.1 ± 1.0 ng/5 µL of plasma; mean ± SEM) occurred after 63 ± 10 minutes. No significant change (p > 0.05; Student’s unpaired t-test) of these parameters was observed in the tests performed after transplantation (peak value, 6.2 ± 0.3 ng/5 µL of plasma at 64 ± 8 min).

Discussion
This study demonstrates improved motor function in 2 patients with idiopathic PD after intrastratal transplantation of fetal DA-rich mesencephalic tissue. Improvement was observed in both patients (although more marked in Patient 3) as a significant reduction of the time spent in the “off” phase and the number of daily “off” periods, a prolongation and change in the pattern of the effect of a single dose of l-dopa, and a lessening of parkinsonian symptoms in the “off” phase, mainly contralateral to the graft. As described in the accompanying paper [22], PET showed increased uptake of fluorodopa in the grafted striatum in the 2 patients, whereas nongrafted striatal areas exhibited unchanged or reduced fluorodopa uptake.

The interpretation that the functional changes in these patients are graft-derived is based on the following observations. (1) Spontaneous fluctuations seem unlikely because the symptomatology was relatively stable in both patients over the 11- and 6-month preoperative assessment periods. Furthermore, the patients continued to receive the same doses of medication throughout the study to minimize the risk that clinical improvement could be due to transient changes in medication. (2) Nonspecific effects of the stereotactic surgery and placebo effects can probably be ruled out because in our previous 4 patients given deep implants into the striatum and subjected to the same assessment protocol, much less improvement was observed. These patients included 2 who received adrenal medulla grafts into the putamen [25] and 2 who were subjected to neural grafting in both the caudate nucleus and the putamen [16]. These previous transplantations were carried out with instruments of a larger outer diameter, which probably caused more tissue damage at the implantation site. Furthermore, it seems unlikely that a placebo response would appear gradually (predominantly on the side contralateral to the graft) after a time lag of 2 to 4 months and then remain relatively stable up to approximately 1 year after transplantation.

(3) The clinical data give no support for the possibility that the improvement observed in these patients would be due to a deficient blood-brain barrier (BBB) at the transplantation site, which could hypothetically lead to a more efficient, focal entry of systemically administered l-dopa or bromocriptine to the brain parenchyma adjacent to the graft. The patients showed improve-
ment of motor performance when tested before the first morning dose (i.e., when plasma l-dopa levels are very low). There were no signs of a more efficient entry of catecholamines into the brain after l-dopa administration as compared with preoperative testing (which would probably be revealed by peak-dose dyskinesias). Furthermore, MRI performed before and after Gd-DTPA injection 10 months after grafting in Patient 3 showed no signal enhancement, supporting the concept of a patent BBB. It has been shown in animal experiments that intracerebral neural grafts establish a well-developed physical BBB within 1 to 2 weeks after implantation [24], and in patients with stereotactic implants of fetal neural tissue the BBB seems to be intact to parenterally administered DA 5 days after surgery [25].

During the early postoperative period, no symptomatic improvement was observed in either patient. In fact, both patients showed an initial worsening of their parkinsonian symptoms. Furthermore, it has been demonstrated that brain tissue from rat fetuses placed in the anterior chamber of the eye in the rat is completely revascularized from the host 3 days after transplantation [26] and that the newly formed vessels exhibit a barrier toward l-dopa (i.e., an enzymatic barrier soon after they have been formed) [26]. Even if the endothelial cells in the graft vessels were donor-derived in these patients, it seems likely that the enzymatic BBB had developed at the time of the PET scans. Thus, the enzymatic barrier for l-dopa has been demonstrated as early as 20 to 22 weeks' post gestation in human fetal cortical tissue [27].

Clinical improvement appeared after approximately 6 and 12 weeks after transplantation. This delayed effect is most likely explained by the functional action of the dopaminergic graft, the survival of which is evidenced by PET [22]. The first signs of synapse formation have been observed after 8 to 11 weeks and improvement of amphetamine-induced rotarional asymmetry after 13 to 15 weeks in previous human-to-rat grafting experiments [28, 29]. This finding is in contrast to studies of rodent donor tissue, in which functional compensation of deficits in rotational behavior can be demonstrated after approximately 3 weeks [24]. It has been proposed [30] that this slower time
course of development for human fetal DA neurons might reflect an "internal clock." More recent studies indicate, however, that there is significant fiber outgrowth from grafted human mesencephalic cells after 3 weeks [31] and that apomorphine-induced rotational asymmetry can be reduced in 2 months [32]. One difference between transplantation into the rat and into these patients with PD is that the latter have been continuously treated with L-dopa. The observed early improvement might thus also be explained by a combined L-dopa-plus-graft effect in these patients.

The clinical improvement after transplantation was most pronounced in the contralateral limbs, which agrees well with what could be expected for a functioning dopaminergic graft (e.g., on the basis of previous data obtained in patients with hemiparkinsonism [33, 34]). Could the ipsilateral amelioration of parkinsonian symptoms (observed in Patient 3) and the reduction of the duration and number of "off" periods (when the patients have bilateral symptoms) also be graft-induced? It seems highly unlikely that a unilateral graft would be able to influence motor function bilaterally through diffusion of DA to the contralateral striatum. Several lines of evidence indicate, however, that manipulations of striatal function on one side can have bilateral effects. (1) A major output from the striatum is directed to the supplementary motor area, which controls both sides of the body [35]. (2) It is well established that the two nigrostriatal DA systems are not functionally independent, but that any modification in the activity of one pathway influences the activity of the contralateral pathway [36]. Unilateral lesions of the DA input to the striatum lead to a more than 100% increase of DA release in the contralateral striatum [37]. In animals with such lesions, there is also a marked reduction of both basal and potassium-stimulated gamma-amino butyric acid (GABA) release in the contralateral globus pallidus [38]. (3) Electrical stimulation of the striatum has been reported to increase GABA release in both the ipsilateral and contralateral globus pallidus [39]. (4) Unilateral DA-rich grafts placed in the ventral striatum (nucleus accumbens) can reinstate and drive amphetamine-induced locomotor activity [40], which is severely impaired after bilateral lesions of the DA input to this structure [41]. From these data it seems likely that unilateral DA-rich striatal implants could have the ability to influence brain function on both sides, which might underlie the observed bilateral improvements in these patients.

An interesting selectivity in the degree of improvement of different parkinsonian symptoms was observed. During the "off" phase, hypokinesia was reduced in both patients; there was also a substantial improvement of rigidity in Patient 3. The severity of tremor, however, seemed to be virtually unchanged, which agrees well with the relatively poor response of tremor to L-dopa treatment. Furthermore, the minimal changes after transplantation in the performance of the finger dexterity task as compared with the pronation-supination and fist clenches tests could indicate that more skilled limb movements, as has been shown in rats [8], are not improved by dopaminergic neural grafts. It has been proposed that this failure is due to poor integration of the graft with host neuronal circuitries in its ectopic site; however, this hypothesis is not supported by the finding that most parkinsonian symptoms in patients can be reversed by subcutaneous infusion of the DA receptor agonist apomorphine [42]. This finding makes it more likely that lack of graft-induced recovery is due to other factors, such as when certain graft placements are suboptimal for a given symptom or when the total volume or degree of reinnervation are insufficient.

In conclusion, the present and the accompanying PET study [22] provide further evidence that fetal mesencephalic grafts can survive transplantation into diseased parkinsonian brains and exert significant and sustained functional effects. The findings support the idea that neural grafting can be developed into a useful treatment for patients with PD. The symptomatic relief in our 2 patients, or in any other reported cases, however, is not of the magnitude that would justify the procedure in a large number of patients. One approach to increase the therapeutic efficacy of neural grafts would be to implant fetal nigral tissue bilaterally and probably in both the caudate and the putamen. It may be necessary, based on the symptomatology in the patient, to place grafts also in the nucleus accumbens, which in animal experiments are important for the amplitude of locomotion [40]. Transplantation of DA-producing cells will only be clinically useful if it can be performed with minimal risks and if it provides symptomatic relief comparable to or better than that obtained with conventional drug treatments and infusion of DA agonists, such as apomorphine [42]. This approach is still at an experimental stage, and PD neural grafting should only be performed in a few well-monitored patients and within the framework of carefully designed research programs involving animal experiments to improve long-term survival and action of the grafts.

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