Intraparenchymal Striatal Transplants Required For Maintenance of Behavioral Recovery in an Animal Model of Huntington's Disease

Paul R. Sanberg, Magda Giòrdano, Mark A. Henault,
David R. Nash, Michael E. Ragozzino
and Starr H. Hagenmeyer-Houser*

*Division of Neuroscience
Departments of Psychiatry, Neurosurgery,
Psychology, and Physiology
University of Cincinnati College of Medicine
Cincinnati, Ohio 45267-0559
*Department of Neurobiology and Anatomy
University of Rochester Medical School
Rochester, New York 14642*

ABSTRACT

Rats which receive injections of kainic acid (KA) into the striatum show many of the anatomical, biochemical and behavioral abnormalities seen in patients with Huntington's disease. Recently, it has been reported that fetal striatal transplants into the lesioned striatum could normalize the neurological and behavioral abnormalities produced by the KA lesion. The present study examined the issue of transplant integration in producing behavioral recovery. In one experiment, lesioned animals with transplants located within the lateral ventricle were compared against parenchymally transplanted rats. It was found that unless the ventricular transplant grew into the lesioned striatum there was no recovery. The second experiment demonstrated that electrolytic destruction of a successful fetal striatal transplant could reverse the transplant-induced behavioral recovery. These results suggest that the integrity of the transplant is important in maintaining behavioral recovery. A continuing functional interaction between the host brain and transplanted tissue may be a vital element in the success of the fetal striatal transplant.

Reprint address:
Dr. Paul R. Sanberg
Department of Psychiatry
University of Cincinnati College of Medicine
231 Bethesda Avenue
Cincinnati, OH 45267-0559

INTRODUCTION

Neural tissue transplants represent a potential approach to treating brain injury and neurodegenerative disorders. It has been reported that neural tissue transplants can reverse the behavioral deficits observed in several animal models of neurodegenerative diseases /10-17,19,27,31,37,40/. At present there are no effective methods available to treat progressive neurodegenerative diseases such as Huntington's disease /23,34/. Hence, it is of great interest to determine if the deficits produced by the disease may be reversed by using neural transplantation techniques. It has been reported that transplants of fetal striatal ridge tissue into the striatum of adult host rats that have received excitotoxin lesions of the striatum, survive, grow and produce behavioral recovery /10,11,18,19,25,27,31,37/.

Although fetal striatal tissue transplants reverse the behavioral deficits induced by excitotoxin lesions of the striatum, it is unclear at present how this is achieved. Pritzel et al. /30/ demonstrated that neuronal connections between host brain and the transplanted tissue can be observed 6 to 11 months following the transplant. The fact that behavioral recovery is seen in transplanted animals as early as three weeks post-transplant has

suggested that synaptic connections may not underlie the behavioral recovery /36,37/. It is possible also that the transplanted tissue releases trophic factor(s) which may induce functional reorganization within the host brain /5,12/. This induced reorganization might underlie the observed functional recovery. Interestingly, Cotman and his colleagues /20/ reported that glial cells or even gelfoam previously exposed to fetal tissue produced behavioral recovery in a model of Alzheimer's disease. Furthermore, Stein et al. /41,42/ reported that following cortical lesions and subsequent transplant the fetal transplant could be removed weeks later without affecting the observed transplant-induced behavioral recovery. In this view, neuroanatomical connections between the host and donor tissue would not be a necessary prerequisite for behavioral recovery. The present studies were conducted to help determine the role of the transplanted fetal material in producing the behavioral recovery observed in an animal model of Huntington's disease /7,32/.

The first study compared behavioral recovery in excitotoxin lesioned rats receiving fetal striatal transplants located solely within the dilated lateral ventricles with those having transplants that were placed within the remaining host striatum. Presumably, if recovery is based on the release of some trophic factor or section of transmitters into the host brain, then both transplant conditions might be expected to produce behavioral recovery. In the second study, a small electrolytic lesion was made into the transplant of rats which had previously demonstrated behavioral recovery, to find out whether the transplant is required to maintain the behavioral recovery once established.

MATERIALS AND METHODS

Animals and Housing

Adult male Sprague-Dawley rats (Zivic-Miller), weighing 280-300 g, were housed individually in stainless steel cages (24 x 11 x 20 cm) and were given free access to food and water. Twelve-hour light/dark cycles were held constant, starting at 8:00 and 20:00, respectively. The time-pregnant female rats were housed individually in the same conditions until used. The antibiotic oxytetracycline was administered prophylactically to the water of all rats.

Apparatus

Locomotor behavior was analyzed using Digiscan Activity Monitors (Onmnitech Electronics, Inc., Colum-

bus, OH), which have been described in detail elsewhere /33,35,38/. Each monitor consists of an acrylic box (40 x 40 x 35.5 cm) surrounded by two levels of infrared beams. Each monitor had cedar chips on the floor, and animals had access to food and water.

Surgery

Striatal Kainic Acid (KA) Lesion: Animals were initially administered 0.4 mg/kg of atropine sulfate (Sigma Chemical Co.) in physiological saline, i.p. The animals were anesthetized five minutes later with sodium pentobarbital (50 mg/kg) i.p. and then stereotaxically positioned and injected with 2 nmol of KA in 0.4 ul phosphate-buffered saline (pH = 7.4) into each striatum. The stereotaxic coordinates were AP = 1.5, ML = +/- 2.4, DV = 4.5, according to Paxinos and Watson /29/. The KA was injected via a 26 gauge needle over a five minute period. After injection the needle was left in place for 5 minutes to allow diffusion of the drug solution. Control rats underwent similar operations but received microinjections of the vehicle alone (sham lesions). After surgery the animals received 0.1 ml of penicillin i.m. (Procane Penicillin G, Pfizer) to prevent the onset of any infection, and 3 ml of dextrose (5%) i.p. in order to enhance post-surgical recovery. Postoperatively, all animals were housed separately and given free access to food mash (powdered food pellets with Similac added) and water, and their body weights were recorded daily. All animals with lesions were tube-fed intragastrically with 10 ml Soyalac once daily until they started to feed themselves. Only animals with aphagia, adipsia and a loss of body weight of at least 20%, which are characteristic of the lesion, were included in the studies /31/. In the present studies approximately 90% of the lesioned animals meet this criterion. Normal rat chow was reinstated once the animals began to gain weight at the same rate as controls, which usually was within 4 days after surgery.

Transplant Operations: The transplanted rats received bilateral implants of day 17 fetal rat striatum into the KA-lesioned striatum. The donor embryos were obtained from a stock of laboratory-bred Sprague-Dawley rats. The female animals providing donor embryos were bred overnight, and vaginal smears were obtained the following morning. The day when vaginal smears were sperm positive was considered Day 1 of gestation. The staged pregnant female rat was anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/kg) and prepared for laparotomy. The mother was kept anesthetized until all fetuses had been dissected /8/. The

dissection began by cutting the uterus with microscissors and gently pulling out the embryo with forceps. The umbilical cord was sectioned and the fetus was placed in lactated Ringer's solution. The extraction of the tissue did not last more than 20 min. The dissection was performed under an operating microscope using Dumont No. 5 dissecting forceps. The embryonic brain was removed by peeling the skin and cranial cartilage away from the brain surface, and ensuring the complete removal of all attached meninges /8/. The cortex was removed and peeled laterally in order to expose the half moon shaped striatal tissue. This tissue was aspirated into a capillary needle (25 5/8 G) and lowered into the host striatum.

The fetal tissue was then lowered stereotaxically by means of a glass syringe (Hamilton syringe, 50 ul) fitted with the glass needle into the host striatum. Coordinates were AP = 1.5 mm, ML = +/− 2.2 mm (for ventricular transplants) or +/− 2.6 mm (for parenchymal transplants), and DV = 6.0 mm. Tissue was injected at a rate of one microliter per minute, the needle was left in place for one additional minute and then it was raised 0.8 mm. The procedure was repeated until 4 microliters per side were delivered (1 - 1.5 cubic mm). The final stereotaxic coordinates, for the DV dimension were 2.8 mm. The needle was left in place for five additional minutes to allow diffusion, prior to slow retraction of the needle /8/. Sham transplants consisted of the identical operation; however, sciatic nerve was used instead of fetal striatal tissue.

Electrolytic Lesion: The electrolytic lesions were performed using a similar procedure to that used for the KA injections except that a monopolar platinum electrode was placed at the same AP and ML coordinates as the intraparenchymal transplants, with DV set midway between the second and third injections. A 0.5 milliamp current was delivered through the uninsulated 1 mm tip of the electrode for a period of 20 sec. The electrode was removed slowly two minutes later and the animal sutured and allowed to recover.

Histology: At the conclusion of the locomotor testing for each group, the animals were anesthetized using 50 mg/kg sodium pentobarbital. Intracardial perfusions were performed with 0.9% saline for two minutes followed by a 10.0% formalin solution. Brains were removed and placed in 40% sucrose/formalin solution for one day.

In preparation for sectioning, animal brains were frozen in liquid 2-methyl butane (Fisher) at −20°C and quickly mounted on an International-Harris Cryostat (−200°C). Twenty micron sections were taken beginning

at the rostral caudate, and were directly mounted onto gelatinized slides, dried, and prepared for staining with cresyl violet as described by Paxinos and Watson /29/.

PROCEDURE

Ventricular vs. Parenchymal Transplant Study

Four groups were used: 1) sham lesion with sham transplant, 2) KA lesion with sham transplant, 3) KA lesion with striatal transplant located in ventricles, and 4) KA lesion with striatal transplant located in the striatal parenchyma. Each group consisted of seven rats. All rats were tested for locomotor activity prior to any surgery. At approximately four weeks following the striatal lesion all animals were again tested for locomotor activity. The day after testing, the rats underwent their appropriate transplant operation. Extra rats were operated on to replace any animals that died during the surgical techniques. Nine weeks post-transplant, the animals were again tested for locomotor behavior. During the locomotor testing the animals were individually placed into the Digiscan Monitors at approximately 7:00 pm. In pilot studies of spotaneous nocturnal behavior the peak nocturnal activity period was found to be between 9:00 and 11:00 pm. Therefore, the peak activity period (9:30 − 10:30 pm) was used as the measure of spontaneous activity.

Electrolytic Lesion Study

One month after receiving bilateral KA lesions animals were randomly divided into two groups: fetal transplant group (n = 9); sham transplant group (n = 10). Each group was initially tested for locomotor activity prior to any surgery. Twenty-one days after the striatal lesions, locomotor activity was reassessed. The animals then received the appropriate transplants and 9 weeks later were once again assessed for spontaneous nocturnal activity. After the behavioral assessment, all animals received electrolytic lesions into the striatum. Locomotor activity was then assessed 4-6 weeks later.

Statistical Analyses

In the ventricular transplant study and the electrolytic lesion study, a repeated measures ANOVA was utilized to compare differences across trials for each group. Post-hoc t-tests were performed to compare trials within each group and are reported in the results. All statistics were computer with Stats-Soft statistical software package for the IMB PC XT (Statsoft, Inc., Tulsa, OK).
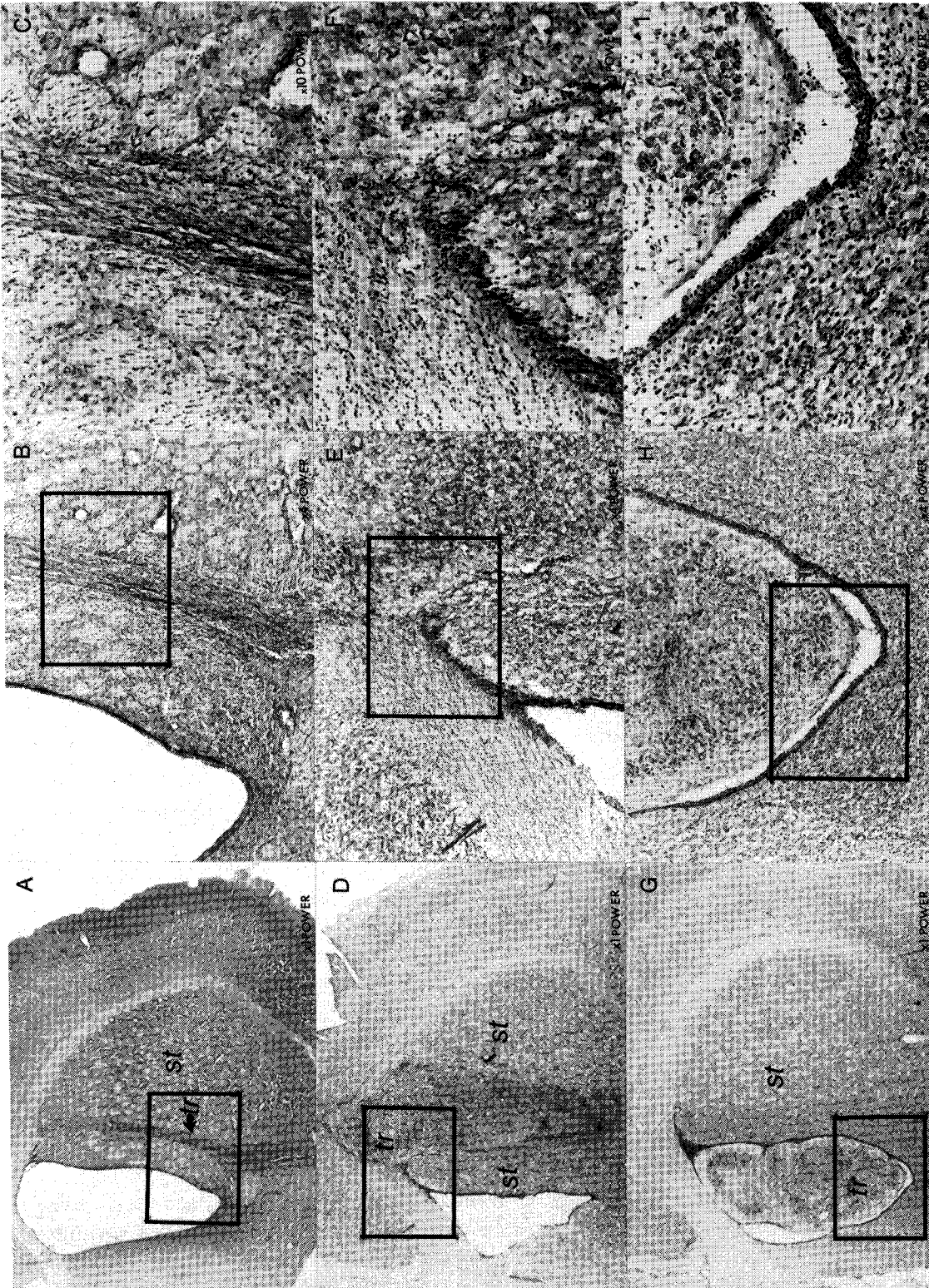
Fig. 1: Representative photomicrographs of coronal sections through the striatum (st) and area of the transplant (tr) stained with cresyl violet. Bilateral KA lesion of striatum and transplant of sciatic nerve are seen in A (x1 power), B (x4 power) and C (x10 power). An intraparenchymally located fetal striatal transplant is seen in D (x1 power), E (x4 power) and F (x10 power), and a fetal striatal transplant located within the ventricular space is seen in G (x1 power), H (x4 power) and I (x10 power). Only behavioral data of animals whose grafts were solely contained within the ventricle was utilized. Cell bodies are present within the graft tissue. Sections correspond to AP 1.7 according to Paxinos and Watson /29/. Boxes correspond to area of magnification for next photomicrograph.

RESULTS

Ventricular vs. Parenchymal Transplant Study

As shown in Figs. 1A — 1C, bilateral lesions of striatum produced loss of cells and shrinkage of the striatum with a concomitant enlargement of the lateral ventricles. The transplanted sciatic nerve (sham transplant) can be seen in this section A as a small dark vertical band. As shown in the representative photomicrographs in Figs. 1D — 1I, histological analysis revealed that the fetal striatal transplants survived and grew robustly within the host brain; in many cases growing to a maximum extent possible when transplanted within the dilated ventricles (Fig. 1G). However, behavioral recovery was only apparent in animals where the fetal striatum was transplanted and grew into the host striatum (e.g., Fig. 1D). Animal behavior was assessed by Digiscan Activity Monitors in terms of total distance traveled, number of stereotypic movements, and number of vertical movements (Fig. 2).

There were no differences between the groups in spontaneous nocturnal activity prior to surgery (data not shown). As demonstrated in previous studies, all rats displayed significant increases in spontaneous nocturnal activity following intrastriatal injections of KA (data not shown, see references 18,36,37,39). Animals that received fetal striatal transplants directly into the remaining host striatum showed recovery back to control levels by nine weeks in all behavioral variables studied. However, animals that received ventricular transplants maintained increased nocturnal activity compared to controls. Fig. 2 demonstrates these differences for three locomotor indices of ambulation, stereotypy and rearing behavior. This increased activity in the ventricular transplant group was similar to that found in animals that received sciatic nerve transplants (sham transplants) into the lesioned striatum. Both the sham transplant and the ventricular transplant animals showed a significant increase in distance traveled (t's = 3.4 and 3.7, respectively, df = 13, p's < .01) and stereotyped movements (t's = 3.6 and 4.2, respectively, df = 13, p's < .01) compared to controls, whereas only the ventricular transplant animals demonstrated increased rearing behavior (t = 2.5, df = 13, p < 05). There were no differences between the sham and ventricular transplant groups (t's < 1), except in rearing behavior (t = 2.3, df = 13, p < .05).
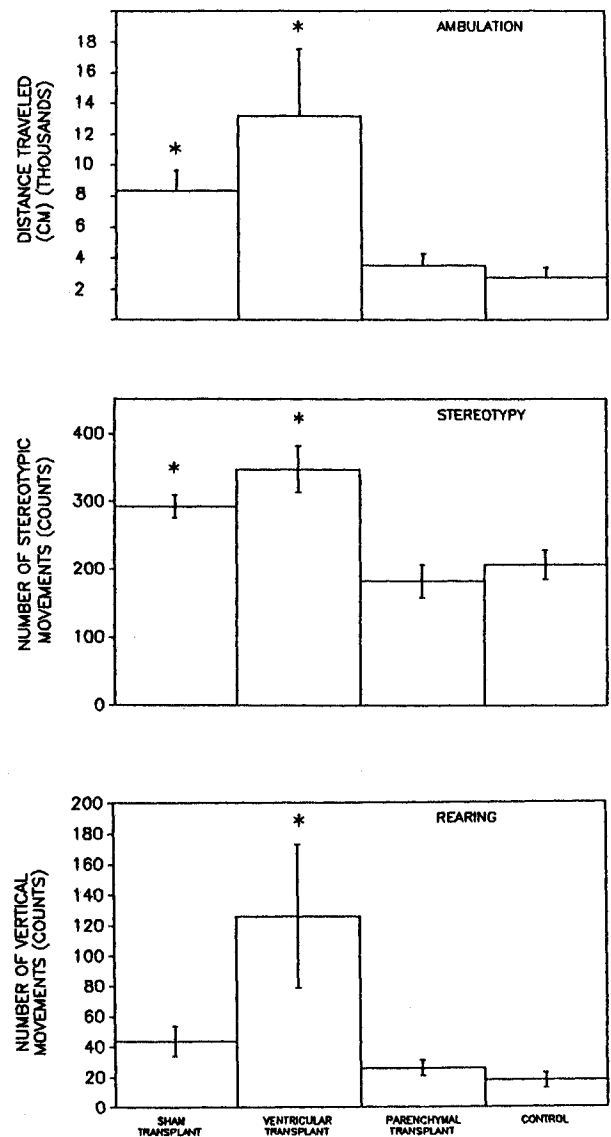

Fig. 2: The effect of transplant placement into the ventricular space or into the host parenchyma or locomotor activity in rats with KA lesions of striatum. Animals from each group were tested for spontaneous nocturnal behavior in Digiscan Activity Monitors using three different variables: ambulation, stereotypic movements, and rearing behavior. The testing period was a one hour.peak activity period during the dark phase of a 12 hour cycle. In all three variables studies, animals that received ventricular transplants showed a significance increase in activity compared to controls. Additionally, animals receiving sciatic nerve transplants (sham transplants) instead of parenchymal transplants also showed a significant increase in activity compared to controls in both the stereotypy and ambulation variables. In contrast, animals that receive parenchymal transplants demonstrated spontaneous nocturnal behavior nearly identical to that of controls. * p < .05.
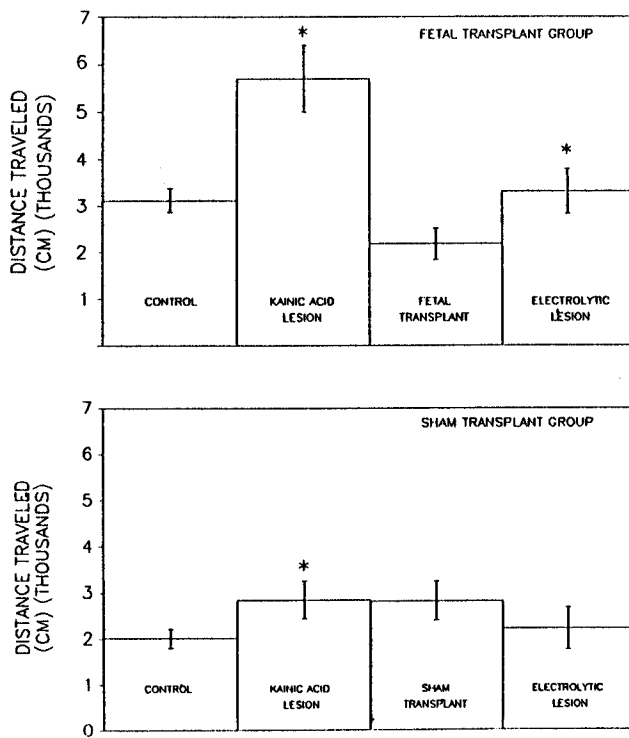
Fig. 3: The effect of electrolytic lesion of striatal transplants on the normalization of locomotor activity produced by striatal transplants into KA lesioned striatum. Animals were divided into two groups. One group received fetal transplants into the lesioned striatum, and the other group received injections of vehicle into the lesioned striatum. Animal behavior was evaluated with Digiscan monitors in all four trials: before lesions, after lesions, after fetal transplants/vehicle injections, and after electrolytic lesions. The testing period was a one hour peak activity period during the dark phase of a 12 hour cycle. The fetal transplant group showed a significant difference across all four trials while the sham group showed no difference across all four trials. Both groups showed a significant increase in activity following KA lesions of the striatum. The fetal transplant group following electrolytic lesions showed a significant increase in activity from levels attained with fetal transplants. The change in activity in the sham group following electrolytic lesions was not significant * p < .05.

Electrolytic Lesion Study

A baseline level of activity in terms of the total distance traveled was established for each group. There was a significant increase in activity in both groups following KA lesions (sham group t = 5.7, df = 9, p < .04; transplant group t = 17.3, df = 8, p < .004).

Animals that received fetal striatal transplants showed a significant reduction in spontaneous nocturnal activity from the increased levels observed after KA lesions (t =

36.4, df = 8, p < .0006). The animals that received fetal striatal transplants displayed spontaneous nocturnal activity which was not significantly different from control levels. Animals that received sham transplants showed no change in spontaneous nocturnal activity from levels following KA lesions of the striatum.

Electrolytic lesions of the transplant region were then performed on each group, and the animals were once again assessed for spontaneous nocturnal activity (see Fig. 3). All electrolytic lesions except one, were within the area of transplant. This one animal was not used in the analysis although its activity was within the distribution of the group. Under the present conditions, the electrolytic lesions appeared to be relatively small. Interestingly, electrolytic lesions of the transplanted striatal tissue partially abolished the locomotor changes induced by the transplant. The electrolytic lesion of the fetal transplant produced a significant increase (t = 3.25, df = 7, p < .02) in the total distance traveled (see Fig. 4). The electrolytic lesion in the sham transplant group did not cause any significant change in the hyperlocomotion. After all behavioral testing was completed histological examination was performed. An example is shown in Fig. 4.
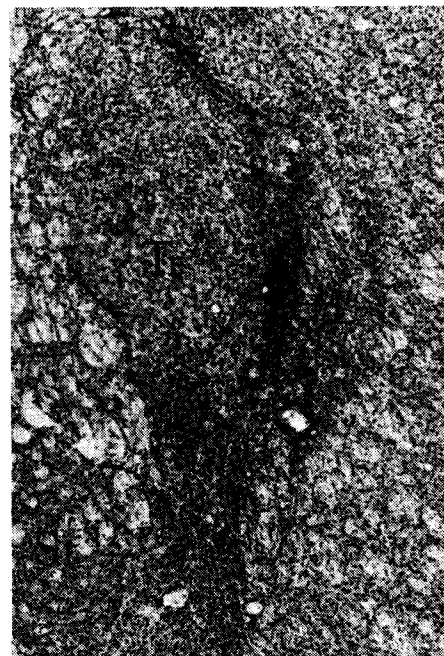

Fig. 4: Photomicrograph of a coronal section through the striatum and area of the transplant stained with cresyl violet. The transplant (tr) is present within the striatum (st). Only the behavioral data of animals where the electrolytic lesion was solely within the borders of the transplant was utilized. The area of electrolytic lesion (I) is noticeable as the dark black area through the transplant.

DISCUSSION

Kainic acid lesions of the striatum caused an increase in spontaneous nocturnal activity, and transplants of fetal striatal tissue reversed these behavioral deficits supporting earlier studies /10, 11, 18, 19, 27, 36, 37/. The first experiment examined whether ventricular grafts might be capable of promoting behavioral recovery. The ventricular placement of the graft could test the possible effects of trophic factors independently of graft integration with the host in the area of the lesion. If, in fact, trophic factors released from the fetal transplant were the mechanism of behavioral recovery, then the ventricular grafts should promote some recovery. Trophic factors released into the CSF should bath the site of the lesion, promote neurogenesis, and reestablish host-host neuronal connections leading to behavioral recovery. Although the ventricular grafts grew robustly, animals receiving these grafts failed to display a significant decrease in nocturnal activity from the lesion-induced level of hyperactivity. Interestingly, animals whose ventricular grafts grew into the lesioned striatum did show some recovery of behavior (data not shown). The results suggest that if the ventricular grafts do, indeed, release trophic factors, that these factors acting alone may be insufficient to promote either synaptogenesis in the area of the lesion or the switching on of 'silent pathways' and subsequent behavioral recovery. On the other hand, it is also possible that when the graft is in the ventricle the dilution of any factor in the ventricular CSF may account for the lack of effect, whereas the localized diffusion of the trophic factor in the striatum by parenchymal transplants is acting directly, in high enough titers to produce recovery.

The second preliminary experiment examined whether the behavioral recovery following a successful fetal transplant into lesioned striatum could be reversed by an electrolytic lesion of the transplant. It was felt that lesioning the transplant with KA was not suitable in the present study, since this excitotoxin could have diffused into surrounding host tissue following intrastiatal injection, thereby complicating any interpretation. Furthermore, since KA's neurotoxic action is dependent on cortico-striatal afferents /3/ any failure of these fibers to innervate and grow throughout the transplant may have limited its lesioning effects. An electrolytic lesion, although possibly damaging fibers of passage, would localize its effects to the transplant without causing injury to surrounding host tissue. If the transplants were only functioning to provide trophic factors, then the integrity of the transplant would no longer be important

after the appropriate neuronal pathways were turned on or neural connections reestablished. In this scenario, the behavioral recovery should continue to persist if the transplanted tissue was destroyed. However, when the transplant was destroyed the animals displayed a significant increase in nocturnal activity thereby reversing the effects of the transplant. These results although preliminary indicated that the integrity of the transplant is of primary importance in promoting and maintaining behavioral recovery. Trophic factors alone do not appear to be the only mechanism of recovery. A continuing functional interaction between the host brain and transplanted tissue may be a vital element in maintaining behavioral recovery.

Although it appeared that the integrity of the transplant is necessary for behavioral recovery, it does not necessarily follow that the host and graft become integrated by developing neuronal connections. An alternative possibility is that the graft might function as a neuronal bridge /1,2,9,21/. The possibility exists that the transplant provides the appropriate substratum for neuronal growth and thereby allowing host-host neuronal connections to restructure and bypass the lesioned area. The transplant tissue would serve as a conduit for the passage of neurons over the lesion. Histological examination of the neuronal connections within the transplant would serve to further elucidate the mechanism of transplant-induced recovery.

Attempts to show anatomical connections between transplanted striatal tissue and host dopaminergic neurons have been controversial. McAllister and his colleagues /24,43/ used horseradish peroxidase (HRP) injections in the ventral midbrain region of the host four to eight weeks after transplanation to examine connections between host and graft. They reported many anterogradely labelled and a few retrogradely labelled neurons in the graft-host interface. The study also used HRP injections into the graft and demonstrated the presence of neuronal connections strictly within the boundaries of the transplant. In contrast, Pritzel /30/ found afferent and efferent connections between graft and host at 6 to 11 months following transplant. It is conceivable that the neuronal connections found in the graft-host interface /44/ may explain the behavioral recovery found 3-9 weeks after transplant /37/. At least initially, the graft-host interface may be functioning as a bridge for the neuronal reconnections that restore behavior. It is also possible that as the graft matures, the neurons travelling through the interface may form synapses with the neurons McAllister found to be located strictly within the graft. These graft-host connections in mature

grafts would serve to further restore the original graft-host circuitry, and possibly rectify the findings of McAllister and Pritzel.

If the transplants were functioning as a bridge, then the important aspect of the transplant would be its ability to function as an effective substratum rather than its neuronal content. The cells constituting the substratum would most likely be the glia which is known to have a positive effect on neuronal growth /2/. Kesslak et al. /20/ have done interesting work using rats with aspiration lesions of the frontal cortex followed by implantation of gelfoam cultured either with astrocytes or soaked in a brain cavity lesion. The gelfoam soaked in the lesion contained three cell types: astrocytes, erythrocytes, and macrophages. These two transplant techniques were as effective in promoting behavioral recovery as fetal frontal cortex transplants. It is possible that the glial environment at the graft-host interface, as in the studies of Kesslak et al. /20/, provided an approrpiate substrate for neuronal growth. Additionally, glial cells may possibly support the process of synaptogenesis by releasing trophic factors, removing excitotoxins and/or restoring ionic balance /6,20,22,26,28/.

In conclusion, the present results indicate that the continuous presence of the transplanted tissue within the lesioned parenchyma may be necessary to maintain the behavioral recovery produced by the transplant. What remains to be determined is to what degree the transplants become functionally integrated with the host or function as a substrate allowing the reestablishment of host-host neuronal connections.

ACKNOWLEDGEMENTS

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