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Locomotor Behavior Changes Induced by E-17 Striatal Transplants in Normal Rats

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HAGENMEYER-HOUSER, S H AND P R SANBERG *Locomotor behavior changes induced by E-17 striatal transplants in normal rats* PHARMACOL BIOCHEM BEHAV 27(3) 583–586, 1987 —It is well established that embryonic tissue transplantation into an abnormal or lesioned brain can ameliorate some of the accompanying symptomotology Specifically, transplants placed into kainic acid (KA) or ibotenic acid lesioned striatal rats promote behavioral recovery in various ambulatory measures In the KA animal model, when the transplant encroached on normal host tissue, the behavioral recovery was diminished However, little has been done to reveal what effect tissue transplants have on normal host brain The present study placed E-17 striatal tissue into a normal adult striatum Digiscan locomotor testing revealed that ten weeks after surgery, the implanted animals demonstrated pervasive nocturnal hyperactivity Ambulatory, vertical and stereotypic measures were significantly increased when compared to controls Rats with ten week implants showed lower increases in body gain yet increased food consumption when compared to controls The transplants survived and contained normal looking AChE positively stained neurons Evidence for fiber passage through the host-graft interface was also seen When comparing three and ten week implants, there was a decrease in transplant size in the latter group accompanied by enlarged ventricles giving the brain a lesioned-like appearance From these results, it is suggested that the placement of E-17 striatal tissue into adult striatum results in lesion-like behavior which may be attributed to the physical disruption of striatal systems

Neural transplantation Huntington's disease Digiscan Locomotor behavior Striatum

WITHIN the last decade, tissue transplants have been used as a potential method of treatment for many CNS disorders ranging from neurodegenerative and behavioral abnormalities to genetically based enzymatic deficiencies [4] Most investigations have placed fetal tissue into transplantation cavities, lesioned sites, or the ventricle Recently, several investigators have demonstrated that fetal striatal transplants injected into the lesioned striatum of a rodent model of Huntington's disease (HD) can reverse the pervasive hyperactivity exhibited by these animals [2, 3, 6, 14] Furthermore, the transplants grow robustly within the degenerated striatum and dilated ventricles [14] Transplants which encroached on the normal brain parenchyma in the lesioned animals failed to promote behavioral recovery [15] In envisioning the potential use of neural transplants in treating HD, one possible strategy might entail placing neural grafts into the CNS of those diagnosed as carrying the autosomal dominant gene for HD Theoretically, the implanted cells, lacking the deleterious chromosome, may assume normal striatal function and ameliorate the multiple behavioral abnormalities seen in patients with HD However, very little is known about what effects transplants have on normal host tissue The present study investigated the issue by examining the effects of striatal transplants on adult normal striatal tissue

METHOD

Fifty-six male Sprague-Dawley rats, weighing 325–375 grams were randomly assigned to one of four test groups transplant (N=20), sham (N=20), unilateral transplant (N=8), and unilateral sham (N=8) All the procedures remained the same with the exception that the sham groups received the vehicle solution Fetal striatal tissue from 17 day embryos was dissected out of the embryonic brain and placed into lactated Ringers solution Striatal ridge tissue (graft volume was about 8 μl) was drawn into glass capillary tubing (0 6 mm i d , 0 8 o d) and placed into the adult striatum by stereotaxic surgery A more detailed explanation of transplant methodology is presented elsewhere [3]

Bilaterally transplanted animals were tested for behavioral differences one week before surgery and 3 or 10 weeks

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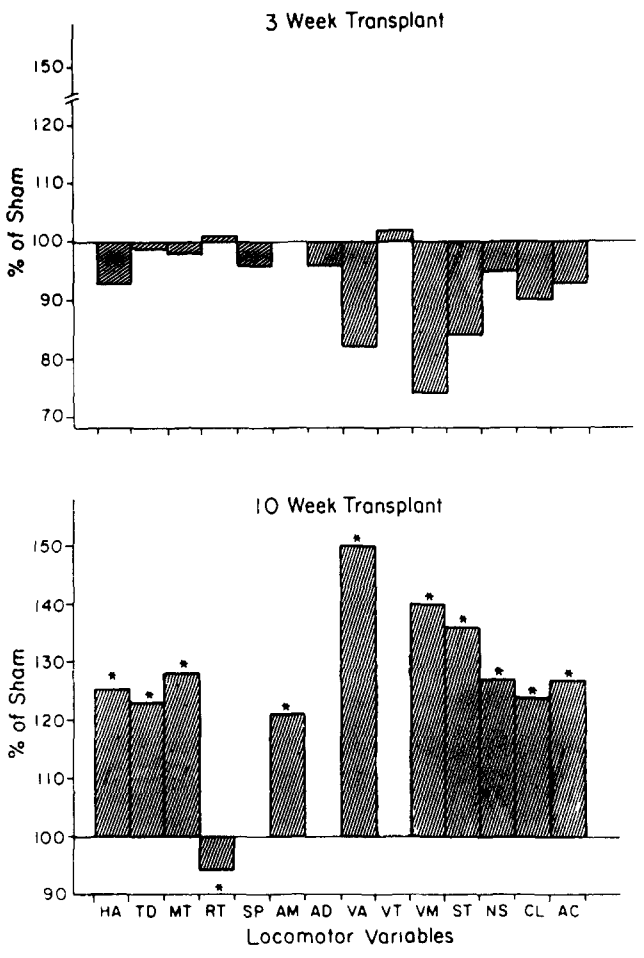

FIG 1 Nocturnal locomotor activity as measured in Digiscan Animal Activity Monitors Three week animals demonstrated a slight hypoactive trend while ten week animals exhibited locomotor hyperactivity Asterisks indicate behavioral measures were significantly different from controls ($p<0$ 05)

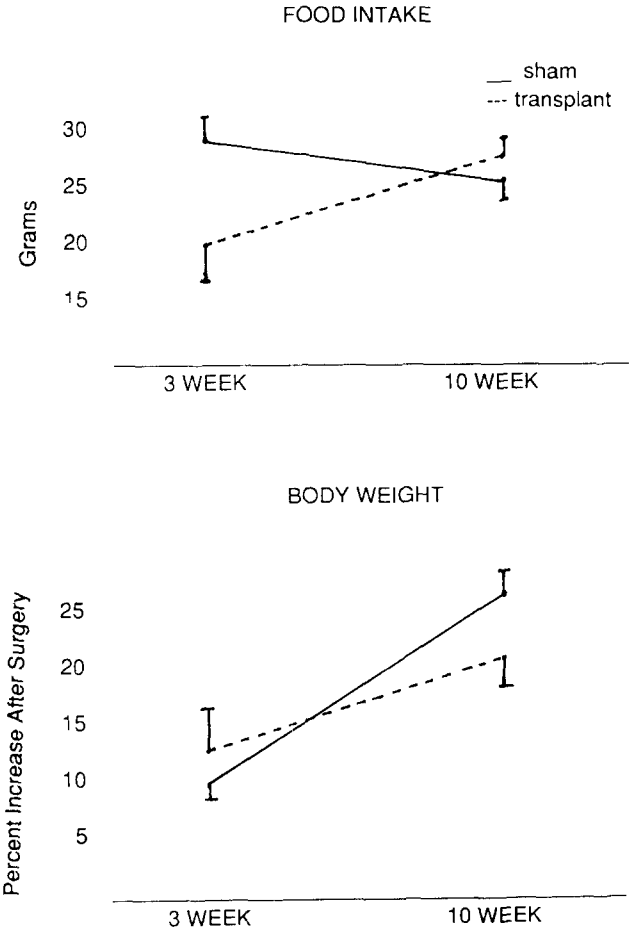

FIG 2 Animals transplanted with 17 day fetal striatal ridge demonstrated an increase in food consumption and less body weight gain as compared to controls Both food consumption and body weight measures showed significant interactions with time post-transplantation ($p<0$ 05)

after surgery Animals were run in the computerized Digiscan Animal Activity Monitors (Omnitech Electronics, Version 2 7) from 7 30 p m to 8 30 a m [13] Individual behavioral variables included ambulatory measures (horizontal activity–HA, total distance–TD, rest time–RT, movement time–MT, average number of movements–AM, speed–SP, average distance–AD), rearing behaviors (vertical activity–VA, number of vertical movements–VM, vertical time,–VT) stereotypic activities (stereotypy time–ST, number of stereotypic behaviors–NS) and rotational behaviors (clockwise–CL and anticlockwise–AC) Nocturnal food intake and weekly body weight measures were also collected during the experiment Due to the variability in the original body weights, the animal's increase in mass was divided by their original body weight taken the day of implant, thereby providing each subject with a percent increase value which could be quantitatively compared between groups

At the conclusion of the 3 and 10 week locomotor tests, animals were perfused with 0 9% saline followed by 10 0% formalin solution Brains were placed in a 40 0% sucrose/formalin fixative for one day and 20 μ coronal sections were cut on the cryostat and stained with cresyl violet and for acetylcholinesterase (AChE) as described elsewhere [9] Locomotor and regulatory changes were measured using a between groups ANOVA ($p<0$ 05), and Tukey's HSD was applied where necessary

RESULTS

Locomotor Behavior

Of the 14 locomotor measures collected before surgery, the average number of movements was the only variable which showed a significant difference among groups, $F(3,33)=4$ 5, $p<0$ 05 Three weeks after transplantation, host animals demonstrated an insignificant decrease in nocturnal behavior when compared to controls However, when tested ten weeks after surgery, these animals demonstrated pronounced hyperactivity (Fig 1) Ambulatory measures showed an average of 25% increase in horizontal activity, total distance, and movement time No difference was found in speed or average distance A 48% increase in vertical activity was noted, and stereotypic and rotational measures increased an average of 35% and 25% respectively Overall, the

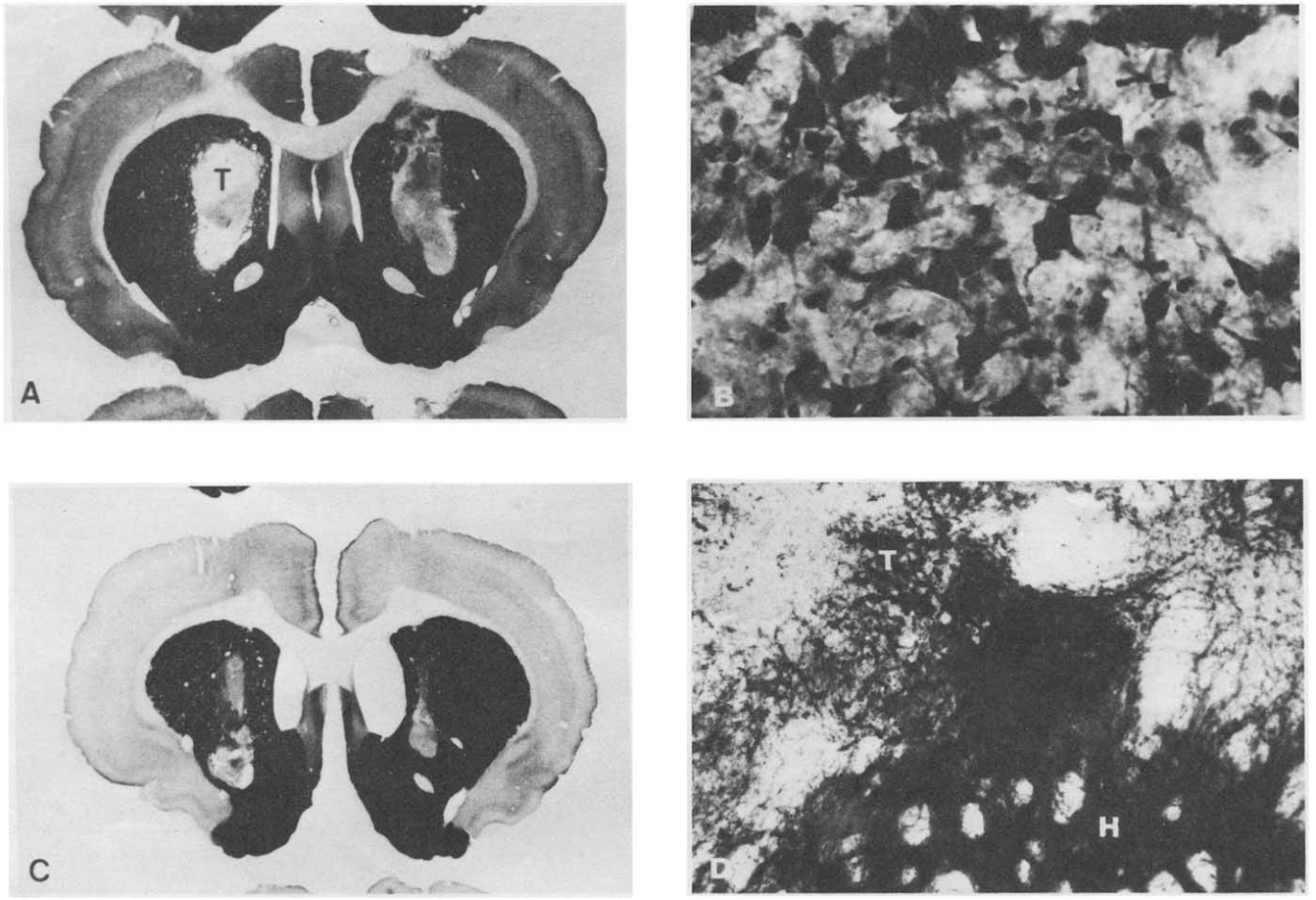

FIG 3 Histological results (A) Three week striatal transplant (T) showing patchy AChE, normal ventricles and lack of corticofugal fiber bundle tracks (×7) (B) Three week old transplant neurons stained with cresyl violet (×444) (C) Ten week striatal transplant stained for AChE When compared to three week animals, the transplants appeared smaller in size and ventricular dilation was increased (×7) (D) Higher magnification of the host-graft interface ten weeks after implantation (×118, H=host)

animals demonstrated a pronounced nocturnal hyperactivity two months after tissue implant

Regulatory Behaviors

Body weight changes were not significantly different among the groups tested, however, a significant interaction was noted between the animals' body weight and the post-transplantation interval, $F(1,38)=4\ 4$, $p<0\ 05$ Perhaps of equal interest was the fact that there was also a significant interaction in the food intake measures and the time post-transplantation, $F(1,39)=5\ 3$, $p<0\ 05$, as seen in Fig 2

Histology

The brains of the sham subjects which were injected with the vehicle solution showed glial infiltration along the cannula tract Three week sham animals showed virtually no ventricular dilation, while ten week animals exhibited slightly larger ventricles

Transplants were easily identified by their patchy AChE staining and their lack of corticofugal fiber bundles (Fig 3A, C) As seen under the light microscope, transplants of the ten week group were smaller in size than the three week test group The host-transplant interface was also more difficult to distinguish in the older grafts (Fig 3A, C, D) Ventricular dilation was visible in both bilaterally and unilaterally implanted animals, however, the unilateral animals showed increased dilation on the side of the implant Neurons were found in both three week and ten week transplants, as seen in Fig 3B, while the density of glial cells appeared to decrease with the age of the transplant

DISCUSSION

Perhaps the most robust finding in this study was that transplantation of fetal striatal tissue into the striatum of normal adult rats caused a pervasive nocturnal hyperactivity This change in behavior appeared to be time-dependent, with increasing effects during the first 2–3 months following implantation The behavioral profile exhibited by the 10 week transplant group resembled that of other striatally lesioned animals As previously demonstrated, KA lesioned animals exhibited decreased stance time, and rest time, but increased horizontal activity, total distance, movement time, average distance, stereotypic, and rotational measures [3, 5, 8, 14] Furthermore, average speed is not affected in striatally lesioned rats [13] and the same result was also found in the present study The similarity in the topography of hyperactivity exhibited by the transplanted animals and striatally lesioned animals suggests that common neuronal mechanisms may be involved

Animals lesioned with KA show decreased body weight gain when compared to controls in addition to food intake changes following periods of food deprivation [12] Normal animals with transplants show a 30% increase in food consumption yet less body weight gain than controls One explanation of these findings may be that the transplanted animals undergo some type of metabolic hyperactivity causing an increase in the amount of calories used The locomotor hyperactivity could possibly account for the increase in food intake These results further suggest that normal animals with transplants demonstrated lesion-like regulatory changes when compared to controls Both the regulatory and locomotor data appear to contradict previous findings that normal animals which received cortical, midbrain and cerebellar transplants into the parenchyma of the brain preserved their usual social, regulatory and locomotor behaviors [1]

The decrease in transplant size suggests that the transplants degenerate over time [10] Animals in the ten week transplant group demonstrated ventricular dilation resembling that of striatally lesioned animals [11] Furthermore, it has been found that following some types of brain lesions there is an immediate increase in gliosis which decreases over time [16] The present study found similar results when looking at the glial densities within the transplant

The hyperactivity found in the ten week transplant group appeared to mimic locomotor abnormalities found in striatally lesioned animals, thereby suggesting that the locomotor behavioral effects resulted from a loss of intrinsic striatal neurons or disruption of striatal efferent pathways Further studies need to look closely at the cholinergic and GABAergic activity of the striatum before definite conclusions can be made concerning the role that these systems play in modulating transplant-induced hyperactivity

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