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Changes in Blood–Brain Barrier Permeability Are Associated with Behavioral and Neurochemical Indices of Recovery following Intraventricular Adrenal Medulla Grafts in an Animal Model of Parkinson's Disease

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Intraventricular adrenal medulla grafts were found to produce dissociable effects on rotational behavior induced by amphetamine and apomorphine in rats with unilateral striatal dopamine depletions. Some animals showed a decrease in the behavioral response to apomorphine, some showed a decrease to amphetamine, and some showed a decrease to both amphetamine and apomorphine. Using *in vivo* microdialysis, the experiments reported demonstrate that in animals with decreased rotational behavior, assessed with either amphetamine or apomorphine, there was an increase in the permeability of the blood–brain barrier to dopamine. The increased blood–brain barrier permeability was visually confirmed with horseradish peroxidase. The extent of the blood–brain barrier disruption, however, was greater in animals with a decreased response to amphetamine. Animals that exhibited decreased amphetamine-induced turning after adrenal medulla grafts also had a greater amphetamine-stimulated increase in striatal dopamine and greater extracellular striatal dihydroxyphenylacetic acid concentrations compared to controls and animals with a graft-induced decrease in the response to apomorphine. We conclude that more than one mechanism is involved in mediating the behavioral effects of adrenal medulla grafts.

INTRODUCTION

Autografts of adrenal medulla tissue have been used as a treatment for patients with intractable Parkinson's disease (PD). The first reports of successful adrenal medulla grafts in patients with PD received considerable attention but subsequent studies have been less optimistic about the usefulness of the procedure (for review see Refs. (3, 14)). In general, the latest reports suggest that intracerebral autografts of adrenal medulla tissue produce modest improvement, at best, in patients with PD (1, 15). These findings suggest that further experimentation is needed to determine the factors that influence the behavioral effectiveness of adrenal medulla grafts.

Clinically, PD is characterized by resting tremor, muscular rigidity, and akinesia (26). Bilateral striatal dopamine (DA) denervation in rats produces a syndrome that is akin to PD in humans. The symptoms of this syndrome include akinesia, rigidity, and abnormal posture (26, 27). Unilateral striatal DA denervation in rats produces a movement disorder that has been used extensively as an animal model of PD since the deficits are relatively easy to quantify. These deficits include contralateral sensorimotor neglect, contralateral resting tremor, and drug-induced rotational behavior (10, 19, 28, 29). It is the drug-induced rotational behavior, however, that has been primarily used for evaluating graft effectiveness in this animal model of PD.

Drugs that stimulate DA activity produce rotational behavior in the unilateral DA-denervated rat. Amphetamine (AMPH), for example, induces DA release and decreases DA uptake at presynaptic terminals. This results in ipsiversive rotational behavior due to the asymmetry in DA release between the intact and the denervated striatum (21, 22, 29). In contrast, apomorphine (APO), a DA agonist, induces rotational behavior in the direction contralateral to the striatal DA denervation. This contraversive turning has been attributed to the postsynaptic DA receptor supersensitivity that occurs following DA denervation of the striatum (11, 28). Intraventricular adrenal medulla grafts decrease the rotational behavior induced by AMPH or APO in rats with unilateral striatal DA denervation (5, 13). The decrease in the turning behavior is interpreted as decreased asymmetry or normalization of function and is used as an index of behavioral recovery of function.

The implicit assumption, to date, has been that AMPH- and APO-induced rotational behaviors are interchangeable measures of the asymmetry in striatal

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DA function. In a recent study from our laboratory, however, we found that there are differential changes in the behaviors induced by these two drugs following adrenal medulla grafts (2). In other words, some animals showed a decreased behavioral response to both AMPH and APO, but other animals with adrenal medulla grafts exhibited a decreased response exclusively to AMPH or APO. This suggests that there are distinct mechanisms involved in mediating the graft-induced behavioral changes in response to AMPH and APO. Since the primary mechanisms by which AMPH and APO induce rotational behavior are quite different, it is possible that adrenal medulla grafts can affect these two behaviors via independent processes.

It was originally hypothesized that adrenal medulla grafts promote recovery via the diffuse release of catecholamines into the surrounding cerebrospinal fluid (CSF) and the paraventricular brain tissue. DA is not detectable within the CSF following behaviorally effective adrenal medulla grafts in rats, however, suggesting that some other mechanism(s) is involved (5). A study by Becker and Freed (5) has found that there are changes in striatal DA metabolism and AMPH-induced DA release associated with adrenal medulla grafts that result in decreased AMPH-induced turning. It seems, therefore, that some behaviorally effective adrenal medulla grafts supply and/or facilitate striatal DA function. One possible mechanism that could be responsible for this is a compromised blood–brain barrier (BBB) that allows catecholamines from the graft and/or the periphery to gain access to the denervated striatum. This idea is supported by experiments that show the blood vessels from surviving adrenal medulla grafts anastomos with the host blood vessels while retaining the permeability of peripheral tissue (25). Furthermore, there is an increase in serum DA in rats with adrenal medulla grafts that is correlated with decreased APO-induced turning (5). Therefore, DA released by the grafted chromaffin cells may enter the vascular system and gain access to the adjacent host brain through a compromised BBB. What remains to be determined is the relationship between the disruption of the BBB following adrenal medulla grafts and behavioral recovery.

The present study uses behavioral, neurochemical, and histological techniques to examine the underlying neurological processes associated with specific behavioral profiles following intraventricular adrenal medulla grafts. Extracellular striatal DA concentrations were assessed using *in vivo* microdialysis within the denervated striatum of rats with adrenal medulla grafts that resulted in decreased rotational behavior induced by AMPH or APO. The integrity of the BBB was analyzed in these animals to determine if a compromised BBB was associated with graft-induced changes in behavior and/or striatal DA activity. We report that behavioral recovery is associated with increased permeability of the BBB to DA.

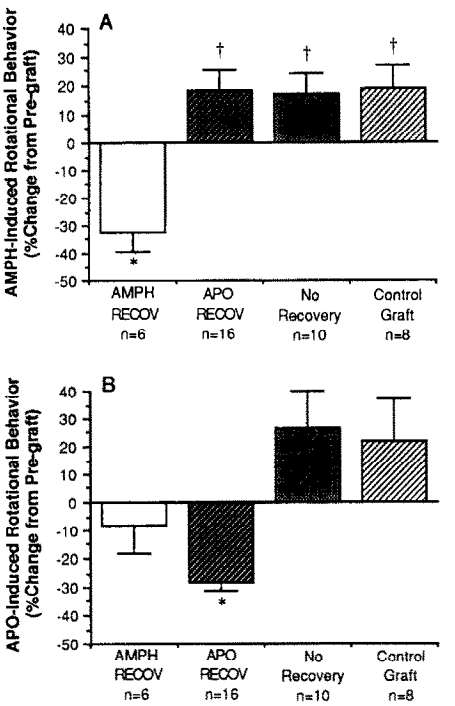


FIG. 1. The effect of adrenal medulla or control grafts on (A) AMPH- and (B) APO- induced rotational behavior expressed as % change from pregraft (mean ± SEM). All animals that showed at least a 10% decrease in a drug-induced behavior were considered to express recovery in response to that drug. *Following intraventricular adrenal medulla grafts there was a significant decrease from pregraft rotational behavior ($P < 0.009$). †Following intraventricular adrenal medulla grafts or control grafts there was a significant increase in AMPH-induced rotational behavior compared to pregraft ($P < 0.05$).

MATERIALS AND METHODS

Experimental Animals, Surgery, and Rotational Tests

Adult female Long–Evans rats (180–200 g) were maintained on a 14:10 [light:dark] cycle with food and water continuously available. One group ($n = 16$) of rats was ovariectomized (OVX) to minimize the variation in drug-induced rotational behavior that is seen over the estrous cycle (7). A second group of rats ($n = 24$) was not OVX due to the excessive weight gain that occurred in the first group that lead to difficulty in handling. Intact and OVX rats were equally represented in all treatment groups and there was no effect of OVX on the results. The results from these two groups were, therefore, combined for all analyses reported here. All procedures were carried out according to an approved University Committee on Use and Care of Animals protocol.

Animals were tested for rotational bias during two 1-h tests in automated rotometers with 0.85 mg/kg AMPH (ip). The animals then received an injection of 6-hy-

TABLE 1

Pregraft Rotational Behavior

Group	3.0 mg/kg AMPH[a] mean ± SEM	0.1 mg/kg APO[b] mean ± SEM
AMPH RECOV (n = 6)	2214.89 ± 456.58	382.00 ± 125.58
APO RECOV (n = 16)	1945.00 ± 216.12	515.91 ± 70.40
No recovery (n = 10)	2104.68 ± 197.62	309.15 ± 35.74
Control (n = 8)	1577.26 ± 292.68	374.23 ± 71.31

[a] Total number of rotations (360° turns) made in a 2-h test session.
[b] Total number of rotations made in a 1-h test session.

droxydopamine-HBr (8 μg/4 μl at 0.5 μl/min) into the substantia nigra (SN) contralateral to the preferred direction of rotation during the two AMPH tests (i.e., a lesion of the dominant nigrostriatal pathway) as described previously (22). Two weeks following the unilateral SN lesion, rats underwent two 1-h rotational tests with 0.25 mg/kg apomorphine (sc) and two 1-h tests with 0.85 mg/kg AMPH (ip). Those rats that rotated greater than 100 contraversive 360 degree turns following APO and greater than 50 ipsiversive turns following AMPH were used in this study. Previous studies have demonstrated that animals meeting these criteria have greater than 90–95% DA depletions (18, 22). To prevent confounding behavioral effects due to the sensitization to AMPH (23), the 40 rats that met criteria were given injections of 5.0 mg/kg AMPH each weekday for 2 weeks and then withdrawn from the drug for 3 weeks. Following the sensitization to AMPH, the rats underwent pregraft rotational behavior testing with 0.1 mg/kg APO (sc). At least three and no more than six 1-h APO tests separated by 48 h were conducted until the rotational behavior stabilized. The same schedule was then used to test with 3.0 mg/kg AMPH (ip; 2-h tests). The number of turns induced during the last three test sessions with each drug was used to calculate the mean baseline rate for APO- and AMPH-induced rotational behavior for each animal.

Graft Procedure

Following pregraft rotational testing, animals received intraventricular grafts of adrenal medulla tissue (n = 32), adrenal cortex tissue (n = 6), or a sham graft (cannula was lowered but no tissue ejected; n = 2). Adrenal medulla and adrenal cortex tissue was obtained from female Long–Evans rats. The donors received an overdose of sodium pentobarbital and the adrenals were removed under aseptic conditions. Prior to transplantation the hosts were anesthetized with 30 mg/kg sodium pentobarbital and supplemented with methoxyflurane. Using standard stereotaxic techniques and under aseptic/sterile conditions, a small burr hole was drilled in the skull over the lateral ventricle adjacent to the denervated striatum (4). Pieces of adrenal medulla or adrenal cortex tissue were aspirated into a 21-gauge injection cannula. The cannula was lowered (from skull flat) 5.3 mm to punch through the wall of the ventricle and was then raised 0.5 mm. A Teflon plunger was used to push the tissue out of the cannula. Thirty animals received either adrenal medulla tissue (n = 24) or adrenal cortex tissue (n = 6) from two to four adrenals obtained from 2-month-old female donors. Eight rats received adrenal medulla tissue from donors less than 1-month-old (these grafts were equally effective and are treated the same as the older donor tissue in subsequent analyses).

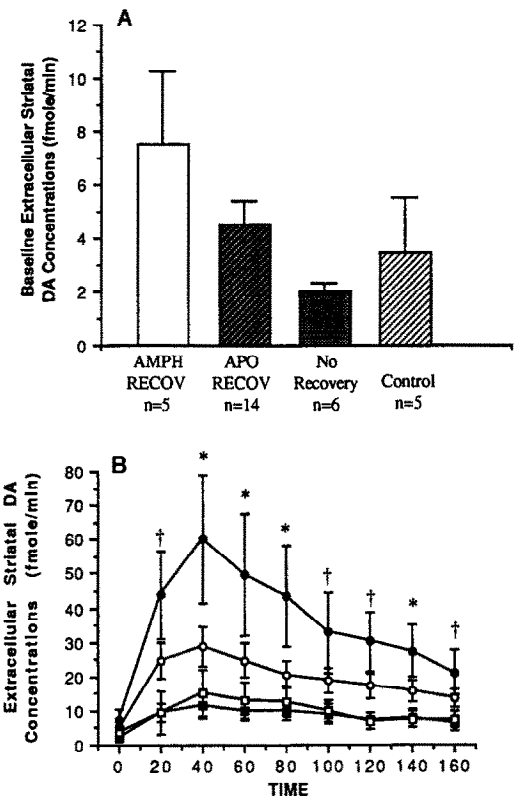


FIG. 2. Baseline and AMPH-stimulated extracellular striatal DA concentrations (fmol/min) in AMPH RECOV (filled circles), APO RECOV (open circles), no recovery (filled squares), and control animals (open squares). (A) AMPH RECOV animals tended to have higher basal extracellular DA concentrations within the denervated striatum than animals in the other three groups, but this difference did not reach statistical significance. (B) Extracellular striatal DA concentrations during baseline (0 min) and eight 20-min dialysate samples following 3.0 mg/kg AMPH. There was a significant difference in AMPH-stimulated DA release among the four groups. This was indicated by a significant main effect of group ($F(3, 26) = 3.924$, $P = 0.0195$), an effect of time ($F(3, 8) = 27.846$, $P = 0.0001$), and a group by time interaction ($F(8, 24) = 3.634$, $P = 0.0001$). *AMPH RECOV rats had significantly ($P < 0.05$) greater extracellular striatal DA concentrations than APO RECOV, no recovery, and controls. †AMPH RECOV rats had significantly greater extracellular striatal DA concentrations than controls and animals with no recovery ($P < 0.05$).

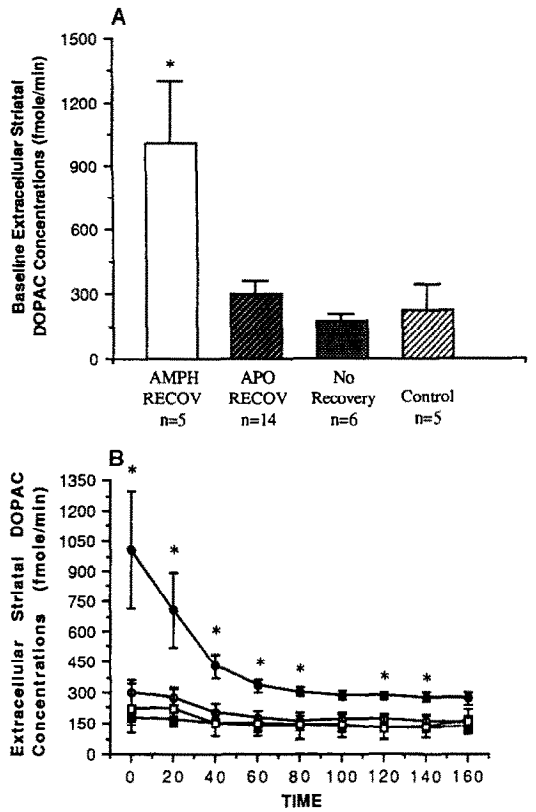


FIG. 3. Baseline and AMPH-induced extracellular DOPAC concentrations (fmol/min) within the denervated striatum of AMPH RECOV (filled circles), APO RECOV (open circles), no recovery (filled squares), and control animals (open squares). (A) There was a significant effect of group on baseline extracellular DOPAC ($F(3, 26) = 7.689$, $P = 0.0008$). *DOPAC concentrations within the denervated striatum of AMPH RECOV rats were significantly greater than the other three groups ($P < 0.01$). (B) Extracellular striatal DOPAC concentrations were significantly different among groups during baseline (0 min) and following AMPH treatment. This difference was indicated by a significant main effect of group ($F(3, 26) = 5.586$, $P = 0.004$) as well as an effect of time ($F(3, 8) = 17.782$, $P = 0.0001$) and a group by time interaction ($F(8, 24) = 6.663$, $P = 0.0001$). *AMPH RECOV animals had significantly higher extracellular DOPAC concentrations within the denervated striatum compared to the other three groups ($P < 0.05$).

Beginning 6 weeks postgraft, animals were tested once a week with 0.1 mg/kg APO (1-hour test) and 48 h later with 3.0 mg/kg AMPH (2-h test). Sixteen of the rats were tested every 2 weeks until 22 weeks postgraft. This extended test period allowed us to examine the stability of behavioral changes observed following intraventricular adrenal medulla grafts. The changes in rotational behavior stabilized by 10 weeks postgraft. The remaining 26 rats were, therefore, tested weekly with each drug until 10 weeks postgraft. The mean of the number of turns induced in the last three behavioral tests postgraft was compared with the pregraft mean to calculate the percentage change in rotational behavior ([postgraft − pregraft/pregraft] × 100%).

In vivo Microdialysis

Thirty of the forty experimental animals used in the behavioral experiments described above underwent *in vivo* microdialysis (some animals died during surgery and others had malfunctioning dialysis probes on the day of dialysis). Following the last postgraft rotational test, 13 animals received implants of a unilateral guide cannula aimed at the denervated striatum and 17 animals received bilateral guide cannulae aimed at both the intact and the denervated striatum. At least 1 week later, the rats were anesthetized with sodium pentobarbital, received a jugular catheter, and the dialysis probe(s) was lowered through the guide cannula(e) into the striatum. The dialysis probe was of a concentric design and consisted of a 4-mm long dialysis membrane with a 250-μm outer diameter (MW cutoff = 6000) as previously described (24). Sixteen to eighteen hours following implantation, the dialysis experiments began (flow rate = 1.5 μl/min). Samples were collected at 20-min intervals throughout the experiment. Baseline samples were taken until stable extracellular striatal DA concentrations were obtained. All samples were analyzed for DA, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) using HPLC-EC as described elsewhere (4). Animals then received an injection of 3.0 mg/kg AMPH (ip) and dialysate samples were collected for an additional 160 min.

Dopamine Penetration into Striatum

Twenty-five of the 30 rats above (5 rats lost their jugular catheters) plus 19 rats from a previous study (3) that

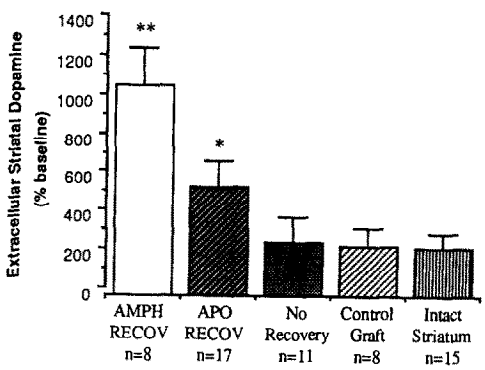


FIG. 4. Extracellular DA concentrations within the denervated striatum adjacent to behaviorally effective and ineffective adrenal medulla grafts, control grafts, or within the intact striatum of animals with bilateral dialysis probes, following a peripheral bolus of 200 μg DA. There was a 1078% ± 193% (mean ± SEM) increase in extracellular DA compared to baseline within the denervated striatum of rats with AMPH RECOV. APO RECOV rats had a 561% ± 130% increase in extracellular striatal DA compared to baseline. **Following a peripheral bolus of DA, the increase in extracellular striatal DA concentration was significantly higher than in all other groups ($P < 0.01$). *Following a peripheral bolus of DA, the increase in extracellular striatal DA concentration was significantly greater than that in the intact striatum ($P < 0.05$).

were treated similarly, were involved in a second dialysis experiment that followed the administration of AMPH to stimulate DA release. Within 2 h after the last AMPH sample, rats received an injection of 30 mg/kg sodium pentobarbital and 0.2 mg haloperidol through the jugular catheter. Two 10-min dialysate samples were collected and used as baseline samples. The animals then received an intrajugular injection of 200 μg DA in 100 μl Ringer's to determine if the BBB had become permeable to DA. Samples were collected 5, 10, 20, and 30 min after the DA injection and analyzed for DA in animals with behaviorally effective (n = 25) or ineffective (n = 11) adrenal medulla grafts or control grafts (n = 8). In addition, extracellular DA concentrations were monitored in the contralateral intact striatum of 15 rats.

HRP Penetration into Striatum

Six animals, four with adrenal medulla grafts, one with an adrenal cortex graft, and one with a unilateral SN lesion but no graft, were analyzed for BBB permeability to a systemic injection of horseradish peroxidase (HRP). One of the animals with an adrenal medulla graft expressed a graft-induced decrease in AMPH-induced turning, two expressed a decrease in APO-induced turning, and one expressed no behavioral recovery. The six animals were anesthetized, the femoral vein was exposed, and a bolus of horseradish peroxidase (Sigma type VI; 1 mg/5 g body wt dissolved in 0.7 ml Ringer's) was injected. Thirty minutes later, 0.9% saline was perfused transcardially, followed by 3% glutaraldehyde (500 ml over 30 min), and then 10% sucrose-buffer (500 ml over 30 min at 4°C). The brains were removed immediately and stored in sucrose-buffer (4°C) for no more than 2 days. Twenty-micrometer sections were cut on a cryostat at −14°C and thaw mounted onto chrom-alum-subbed slides. The sections were incubated for HRP reaction product with 3,3′-diaminobenzidine (DAB) and/or tetramethylbenzidine (TMB) (16, 20).

RESULTS

Rotational Behavior

As we have shown previously, adrenal medulla grafts induced differential changes in the behavioral response to AMPH and APO. Some animals showed adrenal medulla graft-induced recovery as indicated by a decrease in the behavioral response to AMPH and APO (n = 3). However, some animals expressed decreased AMPH-induced turning exclusively (n = 3), some expressed decreased APO-induced turning exclusively (APO RECOV; n = 16), while others showed no recovery (n = 10). The effect of adrenal medulla or control grafts on AMPH- and APO-induced rotational behavior is illustrated in Fig. 1. Animals that showed at least a 10% decrease in either drug-induced turning behavior were considered to have behavioral recovery. The six animals that showed a decrease in the response to AMPH are considered to be one group throughout the remainder of this paper (AMPH RECOV; n = 6). As shown in Table 1, the behavioral response to AMPH and APO prior to the grafts was not significantly different among the four groups.

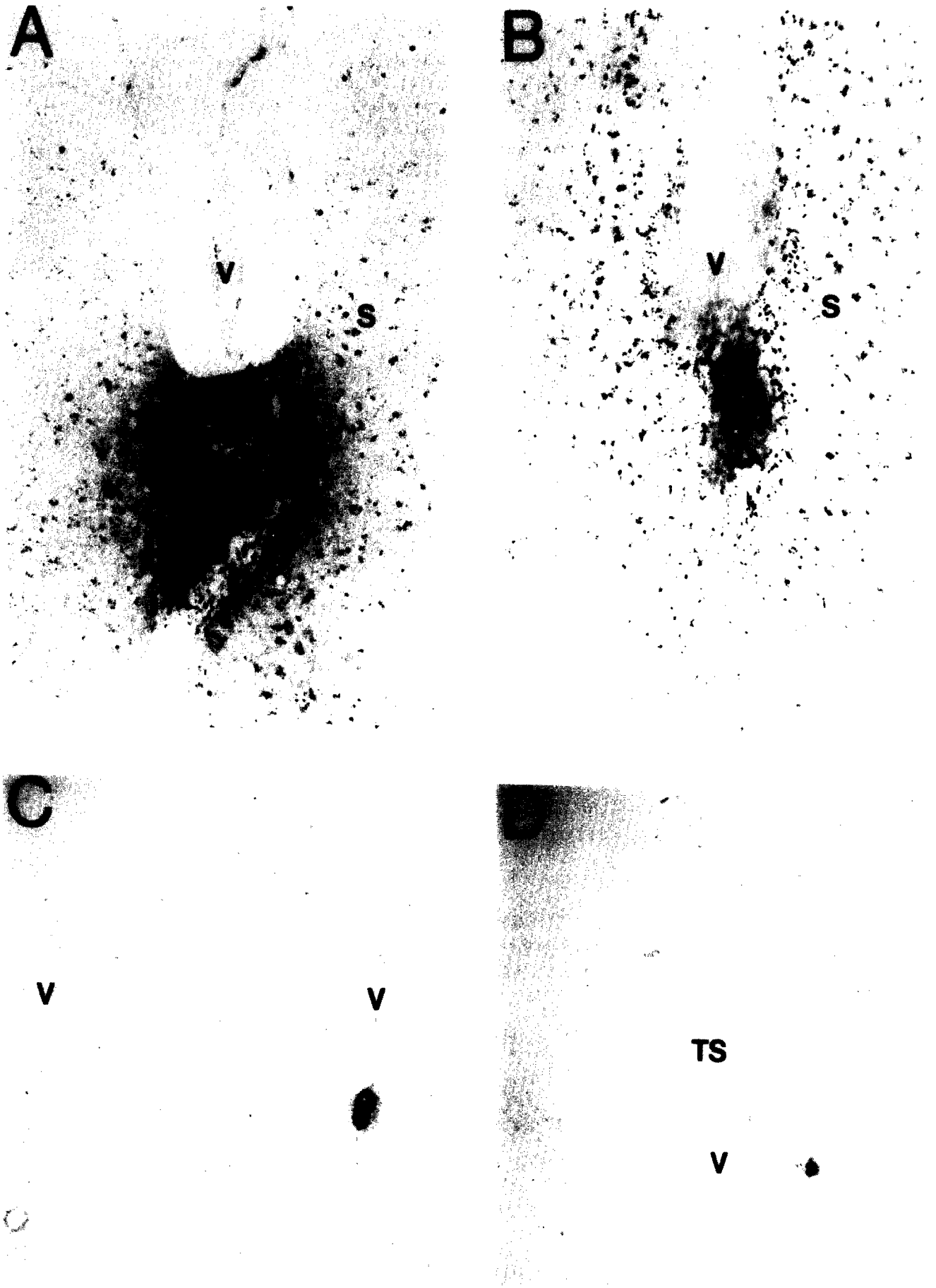
In vivo Microdialysis

As determined by *in vivo* microdialysis, the AMPH-stimulated increase in extracellular DA within the denervated striatum was significantly potentiated in AMPH RECOV rats versus APO RECOV, no recovery, or control animals (Fig. 2B). The baseline extracellular striatal DA concentrations also tended to be higher in the striatum of AMPH RECOV rats compared with the other three groups although this was not a statistically significant effect (Fig. 2A). By contrast, baseline concentrations of extracellular striatal DOPAC were significantly greater in AMPH RECOV rats than in APO RECOV, no recovery, or control groups ($P < 0.01$; Fig. 3A). This difference was maintained even after AMPH treatment which produced a steady decline in extracellular DOPAC concentrations in all groups (Fig. 3B).

Dopamine Penetration into Striatum

The average striatal extracellular DA concentrations following a peripheral bolus of DA (200 μg) were increased 10-fold in AMPH RECOV rats within the first two 5-min dialysate samples (Fig. 4). This increase was significantly higher than baseline (P = 0.005) and was greater than the increase found in any other group, or the contralateral intact striatum ($P < 0.01$). A peripheral bolus of DA also resulted in a large increase in striatal extracellular DA concentrations in APO RECOV animals (560% ± 130%). This increase was significantly greater than baseline (P = 0.008) or the increase seen in the intact striatum ($P < 0.05$). There was a slight

FIG. 5. HRP (DAB reaction) penetration into intraventricular adrenal medulla grafts and the adjacent denervated striatum in an APO RECOV animal (A; ×200 original negative magnification) and an AMPH RECOV animal (B; ×200). No reaction product is visible in the left ventricle or the intact striatum in an APO RECOV animal although it is visible in the graft and denervated striatum (C; ×40). HRP reaction product is visible within the adrenal medulla graft and surrounding host tissue of an animal with no recovery, but the graft is located caudal to the intended graft site and is not adjacent to the denervated striatum (D; ×40). Abbreviations: striatum (S), lateral ventricle (V), and triangular septal nucleus (TS).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but significant increase in extracellular DA concentrations within the denervated striatum of rats with no recovery when compared to baseline ($P = 0.03$). Therefore, while the BBB was apparantly compromised in all groups that had received adrenal medulla tissue implants, animals with grafts that were behaviorally effective showed the greatest permeability of DA into striatum.

HRP Penetration into Striatum

The disruption of the BBB following peripheral tissue grafts, demonstrated by the DA infusion data, was visually confirmed with HRP. Animals with behaviorally effective grafts (AMPH RECOV and APO RECOV) that showed an increase in striatal extracellular DA following the peripheral bolus also showed HRP reaction product within the graft that extended into the adjacent denervated striatum (Figs. 5A and 5B). The contralateral intact striatum of these animals was devoid of reaction product (Fig. 5C). In the lesion-only and cortex-grafted control rats (data not shown), there was no HRP reaction product visible within either striatum, while in the animal with no recovery the adrenal medulla graft was found caudal to the intended graft site (Fig. 5D).

DISCUSSION

Permeability of the BBB to DA and HRP was found to be associated with behaviorally effective adrenal medulla grafts. Beneficial effects of adrenal medulla grafts, as indicated by decreased turning induced by either AMPH or APO, were also found to be associated with specific neurochemical changes in the DA-denervated striatum adjacent to the grafts. Animals that had an improvement in the behavioral response to AMPH had an enhanced AMPH-induced increase in extracellular striatal DA and increased baseline concentrations of DOPAC indicating that the functional activity of DA in the striatum of these animals was increased. These neurochemical changes were not seen in animals with decreased APO-induced rotational behavior. We suggest that further analysis of the neurological changes associated with specific behavioral profiles induced by intracerebral transplantation procedures will contribute to our understanding of the mechanisms mediating recovery of function.

The increase in extracellular striatal DA adjacent to the graft following peripheral DA administration in AMPH RECOV animals was significantly greater than the increase seen in all other groups. AMPH RECOV animals also had enhanced functional DA activity in the striatum. Whether this is due to the compromised BBB has not been determined. Additional graft-induced changes may be necessary to produce the increase in striatal DA activity. A feasible explanation, however, is that DA and DOPAC from the graft gain access to the striatum via the compromised BBB. AMPH could then induce DA release from the grafted chromaffin cells which would have access to the denervated striatum to decrease the asymmetry in striatal DA release. While we do not know that the DA detected in striatum was produced by the graft, previous reports have shown that adrenal medulla grafts contain DA (4). These results suggest that a dopaminergic mechanism mediates the behavioral results reported for AMPH RECOV.

Studies using intrastriatal fetal mesencephalic tissue grafts have also found a correlation between an increase in striatal DA activity and a decrease in the behavioral response to AMPH (9, 30). These findings lend strong support for a dopaminergic mechanism involved in decreased AMPH-induced turning following fetal mesencephalic grafts and this corresponds with the present results as well as previous findings with adrenal medulla grafts (5). The mechanism(s) by which the two graft paradigms produce an increase in striatal DA activity, however, may be different. The reinnervation of the host striatum by fetal mesencephalic grafts has been associated with the increase in striatal DA activity and a decrease in AMPH-induced rotational behavior (9). In contrast, the present findings suggest that adrenal medulla graft-induced changes in the BBB are associated with the increase in striatal DA activity and AMPH RECOV.

The decrease in the behavioral response to APO following adrenal medulla grafts suggests that there is a decrease in the postsynaptic DA receptor supersensitivity that occurs following striatal DA denervation. It is still unclear whether the decrease in APO-induced rotational behavior following adrenal medulla grafts is associated with a decrease in postsynaptic DA receptor supersensitivity, although a decrease in the receptor supersensitivity has been found to occur following fetal mesencephalic grafts (12). Experiments that provided exogenous DA to the denervated striatum have demonstrated that increasing striatal DA can decrease APO-induced rotational behavior (6, 17). The present findings, however, do not support a theory involving a purely dopaminergic mechanism underlying adrenal medulla graft-induced APO RECOV.

Despite the fact that striatal DA activity was enhanced in AMPH RECOV animals, and that extracellular DA tended to be increased, the response to APO was not affected in all of these animals. This suggests that an increase in extracellular DA is not sufficient to decrease DA receptor supersensitivity. A further dissociation of the postsynaptic supersensitivity from extracellular DA concentrations is seen in the APO RECOV animals. These animals had decreased APO-induced turning, but extracellular DA concentrations were not enhanced. Furthermore, since the grafts were located in

the ventricle, nonspecific damage to the striatum that results in the destruction of striatal cells with DA receptors is an unlikely mechanism underlying the decrease in APO-induced turning.

The apparent lack of DA involvement in adrenal medulla graft-induced APO RECOV indicates that this type of recovery may actually be detrimental. For example, previous work by Marshall and colleagues (19) suggests that the postsynaptic DA receptor supersensitivity is important for producing spontaneous recovery of sensorimotor deficits following unilateral striatal DA denervation. A decrease in the postsynaptic supersensitivity could, therefore, result in an increase in sensorimotor deficits in the absence of an increase in striatal DA activity. In a clinical setting, a decrease in the postsynaptic DA receptor supersensitivity without an increase in striatal DA activity could lead to a decrease in a patients response to therapeutic drugs such as levodopa and DA agonists.

APO RECOV animals did express a graft-induced increase in the permeability of the BBB to DA. This suggests that the BBB may also play a role in the decrease in APO-induced rotational behavior following adrenal medulla grafts. The increase in striatal DA after peripheral DA administration that was seen in APO RECOV rats, however, was significantly lower than the increase seen in AMPH RECOV rats. The difference in the extent of BBB disruption and/or the location of the graft relative to the striatum may dissociate AMPH RECOV and APO RECOV by influencing the access of DA and/or other peripheral agents to the denervated striatum. Future research will examine these possibilities.

The integrity of the BBB in the three control groups reinforces the link between BBB disruption and recovery of function following adrenal medulla grafts. The increase in BBB permeability to DA in animals with no recovery following adrenal medulla grafts was significantly less than that seen in animals with behaviorally effective grafts. The lack of a behavioral effect in the no recovery group may be due to poor graft survival and/or placement so that there was only marginal BBB permeability. It should be noted that no significant increase in extracellular DA was found within the intact striatum following peripheral DA administration. Similarly, no visible HRP reaction product was seen in the intact striatum, indicating that the insertion of the microdialysis probe did not disrupt the BBB. This is in agreement with a previous study that has demonstrated that the BBB is intact within 30 min following probe insertion (8). Animals that received intraventricular adrenal cortex grafts would also be expected to have a disrupted BBB. In fact, one animal with an adrenal cortex graft did show a large increase in extracellular striatal DA concentrations following the peripheral bolus of DA. This same animal also expressed a greater than 10% decrease in APO-induced rotational behavior. Most animals with cortex grafts, however, did not show this effect, perhaps because the graft location and/or survival tended to be more variable in these animals. This finding further supports the theory that BBB disruption is associated with APO RECOV and that there may be nondopaminergic mechanisms involved.

In conclusion, intraventricular adrenal medulla grafts produce dissociable effects on AMPH- and APO-induced rotational behavior that are associated with differences in the permeability of the BBB to DA. The ability of peripheral DA to gain access to the denervated striatum is greater in AMPH RECOV animals than in APO RECOV animals. In addition, this more extensive permeability to DA is associated with an increase in striatal DA activity in the AMPH RECOV group. The adrenal medulla graft-induced APO RECOV, however, appears to involve a distinct mechanism(s) that may not involve DA. Trophic mechanisms and/or the involvement of other graft derived substances that were not measured in the present study could be responsible for APO RECOV. Future studies need to explore possible avenues for increasing the percentage of animals that express AMPH RECOV since the dopaminergic mechanism involved in this type of recovery may be more beneficial when extrapolated to a clinical setting.

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