Adrenal Medullary Grafts Restore Olfactory Deficits and Catecholamine Levels of 6-OHDA Amygdala Lesioned Animals

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SUMMARY

Aside from motor and cognitive deficits, Parkinson patients also manifest a little-studied olfactory deficit. Since in Parkinson's disease there is a dopamine depletion of the amygdala due to mesocorticolimbic system degeneration, we decided to test olfactory and taste performance of 6-OHDA amygdala lesioned rats, as well as the possible restoration of either function with adrenal medullary transplants.

Two 6-OHDA lesioned groups and one control group were tested in the potentiation of odor by taste aversion paradigm. On taste aversion none of the groups showed any impairment. In contrast, the 6-OHDA lesioned rats showed a marked impairment in olfactory aversion. At this point, one of the lesioned groups received a bilateral adrenal medullary graft within the lesioned area. After two months, all groups were submitted again to the behavioral paradigm. Taste remained unaffected, but the lesioned only group did not recover either olfactory aversion or normal catecholamine levels. The grafted group, on the other hand, restored olfactory aversion and catecholamine levels. It can be concluded from this study that catecholamine depletion of the amygdala is sufficient to produce a selective olfactory deficit, not accompanied by taste impairments, and that such a deficit can be reversed by adrenal medullary transplants, which in turn restore catecholamine levels.

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INTRODUCTION

The main dopamine (DA) innervation to the telencephalon is provided by the mesencephalic DAergic system which is divided into two main subsystems, the mesostriatal cell group (MS) projecting to the striatum /7,11,48/, and the mesocorticolimbic cell group (MCL), projecting to the limbic system and the cortex /7,15,23/.

The mesencephalic projections to the striatum have been widely studied in rodents and have provided a useful model for the study of motor impairments in Parkinson's disease (PD) /66,67,70/. As such, the unilateral DA depletion of the rat striatum, which produces motor deficits characterized by circling behavior /5,6,20,53/, has been shown to be alleviated by transplantation of DA-rich cells /6,7,20,51/. Based on the animal studies mentioned above, alleviation of the symptoms of PD have been observed in some patients subjected to transplantation of dopamine producing cells from the adrenal medulla or from embryonic substantia nigra /19,29,30,33,43,45,62/.

In addition to motor deficits, PD patients also have cognitive deficits /10,12,42/. These symptoms have been ascribed partially to the second main DAergic subsystem /36,57,58,69/. The cognitive deficits seen in PD patients are similar to those seen in frontal lobe patients when these deficits are measured with the Wisconsin Card Sorting Test /41/, which is the critical probe for prefrontal subjects /46,47,65/. Since these cognitive deficits

have also been alleviated in transplanted PD patients /50/, the role of DA in these deficits may be critical.

Additional support for DA involvement in the cognitive deficits comes from post-mortem studies of PD patients which demonstrate severe degeneration of the MCL dopaminergic system /38,59/ and from studies showing that DA disruption of the prefrontal cortex of monkeys impairs a delayed non-matching to sample task /9,56/, while depletion of the MCL DA-system in the rat produces impairments in alternation tasks /60/.

A little studied non-motor disturbance of PD patients is reflected in a deficit in olfactory discrimination or recognition tasks /1,13,16,17,39, 68/. Although the neuronal basis of this olfactory deficit has not been established, a candidate structure could be the amygdala, since DAergic innervation from the MCL system to the amygdala /22,24,49/ is severely affected in PD subjects /37,59/. Moreover, aside from receiving DAergic innervation, the amygdala, which in addition receives an olfactory input from the pyriform cortex /63/, has been shown to be involved in different olfactory learning tasks /2,31/.

Therefore, the purpose of the present experiments was to determine whether adrenal medullary grafts could restore catecholamine levels and olfactory deficits in 6-OHDA amygdala lesioned rats, in order to have an animal model for the study of the olfactory dysfunction seen in Parkinson's disease.

MATERIALS AND METHODS

Subjects

Subjects were 24 male Wistar rats, weighing 250 g at the beginning of the experiment. The rats were housed under standard laboratory conditions with food and water *ad libitum,* unless otherwise indicated. The lights were automatically turned on at 8:00 and turned off at 20:00 h.

The subjects were randomly assigned to one of three groups of eight rats each: 1. Control group (NON-LESIONED GROUP) (n=8) which received sham lesions only; 2. amygdala lesioned group (LESIONED + SHAM GRAFT) (n=8), which two months after receiving 6-OHDA bilateral lesions in the amygdala, received sham transplants; 3. adrenal medullary transplant group (LESIONED + AM GRAFT) (n=8) which, after the first behavioral test (to be described), received bilateral adrenal medullary transplants into the previously 6-OHDA lesioned amygdala.

Surgery

Animals were deeply anesthetized with halothane for stereotaxic surgery. Two of the groups received bilateral injections of 4 μg of 6-OHDA dissolved in 0.5 μl of saline solution 0.9%. The following coordinates according to Paxinos' and Watson's stereotaxic atlas of the rat /52/ were used for the amygdala lesion (n=8): A-P: -2.2; L: 4.5; H: -7.5; Control animals (n=8) were given vehicle injections in the same coordinates. The injections were administered with a 1 μl Hamilton syringe at a rate of 0.5 μl in five minutes. Injector needles were left in place at each injection site for five additional minutes. Subjects were allowed to recover for 7 days with food and water *ad libitum.*

Behavioral paradigm

To evaluate olfactory learning, we used the potentiation of odor aversion by taste paradigm (POAT) /51/. We chose this paradigm because it is sensitive to amygdaloid lesions, it only requires one single session of acquisition of the learning task and enables us to compare the olfactory versus the taste learning in the same animal in order to discard a general learning deficit /2,35,51/. All the POAT procedures were carried out in 30x45x20 cm clear plastic cages. The tops of the cages were fitted with holes which provided access to two 50 ml test tubes with stainless steel drinking spouts fitted with a filter paper disk around the drinking spout. The filter paper disk consisted of a 1 cm^2 piece of filter paper scented with 0.1 ml of the odor scent only when indicated. The test tubes which were alternated every day from side to side contained water except in the acquisition and taste trials. The total volume of liquid consumed from the taste tubes was recorded daily as a baseline consumption measure.

Pre-transplant tests

After the recovery period the subjects were habituated during 30 minutes to the experimental apparatus. Then, the animals were restricted to a drinking schedule in which water was available in two bottles twice a day, once for ten min each morning (10:00) and again for ten min each afternoon (17:00). After the animals reached a stable base-line of water consumption (5 days), all rats received in the morning a presentation of a neutral odor (peach) in the odor disk, while drinking water in a single test tube. After two more days of base-line water consumption, all rats received in the morning period a single acquisition trial, which consisted of the presentation of an odor (almond) paired with sodium saccharin dissolved in distilled water (0.1%) instead of water alone. Thirty min after the presentation of the compound, a 0.4 M LiCl intraperitoneal injection (1 ml/100 g) was given to all subjects. After the conditioning trial, subjects received both periods of water consumption on 3 consecutive days to reestablish base-line drinking. Then, the animals were tested for each of the components of the flavor. The odor and taste were tested alternately, taste and odor being counterbalanced within groups.

Odor behavioral test

The odor test consisted of water in both test tubes with almond in one odor disk versus peach in the other one. The odor test procedures were given until three extinction tests were completed.

Taste behavioral test

The taste test consisted of saccharin solution in one test tube and water alone in the other test tube. The taste test procedures were given until three extinction tests were completed.

Transplant procedure

After the first behavioral testing was completed, eight of the previously lesioned rats (LESIONED + AM GRAFT group) were submitted to the transplant procedure, which consisted of placing two solid adrenal medullas, taken from newborn rats, into the site of each of the previously lesioned amygdala. The transplants were made using a 100 μl Hamilton (gas-tight) syringe. The injection of each solid medullary fragment was aided by adding a 0.9% saline solution whose volume varied between 3 and 10 μl. Half of the LESIONED + SHAM GRAFT animals received sham transplants, which consisted of the injection of 10 μl of vehicle alone in each of the previously lesioned amygdala. After completion of all surgical procedures the rats were allowed to recover for two months.

Post-transplant tests

After the recovery period, all groups were submitted to the same behavioral procedure as described above, i.e., acquisition of POAT and three extinction trials for odor and taste counterbalanced.

Tissue monoamine level measurements

After all the behavioral tests were finished, the rats were decapitated and the brains were rapidly removed and dissected on ice as follows. With the help of a chopper the brains were cut into 2 mm wide slices. The amygdala nuclei were obtained from the slices with the help of a punch 1.8 mm in diameter. After the dissection procedure the amygdala nuclei of both hemispheres were weighed and homogenized together on ice in 100-200 μl of 0.4 M perchloric acid containing known amounts of dihydroxybenzylamine (DHBA). All the samples were centrifuged at 12,000 rpm for 15 min. Supernatants from the samples were filtered through Millipore 5JHV 0.45 μm. Aliquots of 20 μl of the filtered samples were injected into the HPLC system.

Chromatograph measurements were carried out using a Beckman System Gold chromatograph and a reversed-phase Ultrasphere Ion Pair C18 column (200 x 4.6 mm I.D.). The column eluent was monitored with an electrochemical detector Model LC-4 and a glassy carbon electrode from Bioanalytical Systems LC4. The detector potential was +0.75 V vs an Ag/AgCl reference electrode. The flow-rate was maintained at 1.7 ml/min. The mobile phase was 32% acetonitrile and 68% 10 mM potassium phosphate (NaH_2PO_4), 40 mM sodium

lauryl sulfonate, and 0.5 mM EDTA. Water was deionized and, like the buffer and acetonitrile, was filtered through Millipore GS 0.22 μm. The column was used at room temperature. All catecholamine values were calculated on the basis of an external standard and expressed as ng/g wet weight tissue /32/.

Behavioral analysis

All data analyses were performed using the Aversion Index (AI) using the following formula: A/(A+B). In the taste test 'A' was the consumption of saccharin and 'B' the consumption of water. In the odor test 'A' was water consumption in the presence of almond, and 'B' was water consumption in the presence of peach. With this formula, therefore, an AI of 0.1 would indicate a strong aversion, while an AI of 0.9 would suggest a strong preference for that compound.

Data from the odor and taste tests were evaluated using a simple analysis of variance (ANOVA) with post hoc comparisons (Sheffé) to evaluate the main effects and interactions among groups. F and p values are given only when significant, i.e. $p \leq 0.05$.

RESULTS

Taste behavior

In the first behavioral procedure the control group showed strong taste aversions (AI = 0.12, 0.13 and 0.09) (see Figure 1). Both 6-OHDA amygdala lesioned groups also showed strong taste aversions (AI = 0.9, 0.10 and 0.14, and AI = 0.05, 0.07 and 0.09, respectively).

Two months after the graft procedure, in the second behavioral test (see Figure 1), the control and both LESIONED + SHAM GRAFT and LESIONED + AM GRAFT groups still maintained strong taste aversions (AI = 0.16, 0.19 and 0.24; AI = 0.12, 0.15, 0.16; and AI = 0.15, 0.14 and 0.18, respectively).

Odor behavior

In the post-lesion tests there were significant differences among groups ($F(2,21) = 19.1$, 7.6, and 6.8 for the three test trials, respectively) ($p<0.01$). The control group showed a strong odor aversion (AI = 0.17, 0.23 and 0.27), while both 6-OHDA amygdala lesioned groups showed significantly disrupted POAT (AI = 0.46, 0.47 and 0.49, and AI = 0.61, 0.48 and 0.50, respectively) ($p<0.01$ as compared with the control group) (Figure 2).

In the behavioral test, after fetal brain grafts, the control group still showed strong odor aversion (AI = 0.07, 0.19 and 0.25). The LESIONED + SHAM GRAFT group had disrupted odor aversion even with two acquisition sessions (AI = 0.47, 0.5 and 0.52) ($p<0.01$). The LESIONED + AM GRAFT group showed a strong odor aversion (AI = 0.09, 0.13 and 0.24) to the almond scented test tubes and was no different from the control group.

Tissue monoamine level measurements

The HPLC results showed a significant difference between groups for DA [$F(2,21) = 70.0$] and NE [$F(2,21) = 4.6$] measurements ($p<0.05$). The LESIONED + SHAM GRAFT group showed a significant decrease of DA (91.7%) and NE (79.8%) with respect to control ($p<0.05$) (Table 1). The LESIONED + AM GRAFT showed a complete recovery of DA levels, which were even slightly higher (110.5%). The NE content of this group, though not significantly different from controls, was only 48.3% of the control level. The 5-HT levels were not significantly different among the three groups.

DISCUSSION

The main conclusion obtained from these experiments is that catecholamine depletion of the amygdala is sufficient to produce a selective olfactory deficit, not accompanied by taste impairment, and that such a deficit can be reversed by adrenal medullary transplants, which in turn restore catecholamine levels. Although the specific mechanism by which the adrenal medulla transplants induced the behavioral restoration is not known, it seems that it is not due to the surgical procedure,

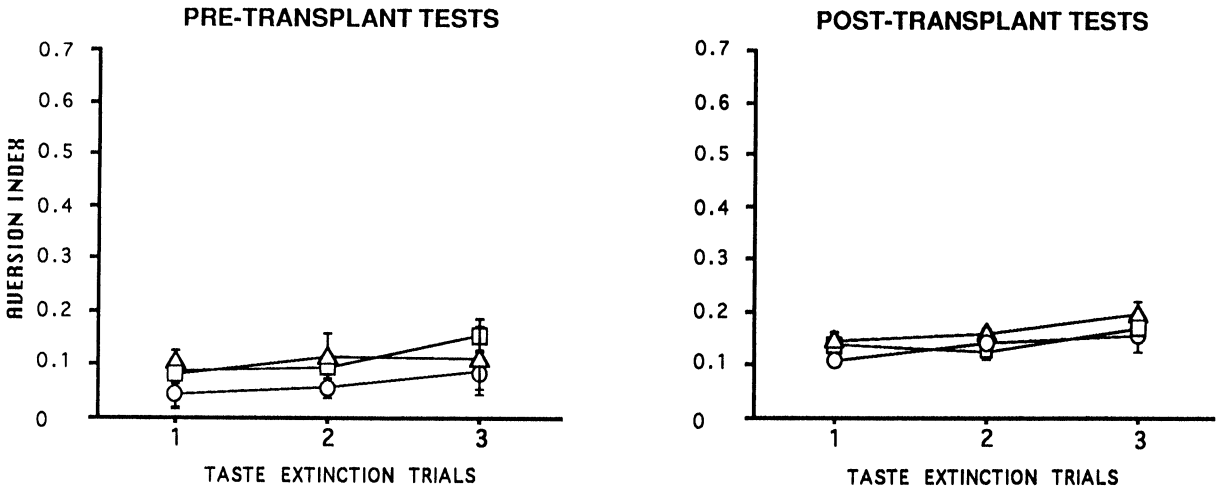

Fig. 1: Taste tests. Left side: Taste aversion effect of 6-OHDA injections in the amygdala of two groups (LESIONED + AM GRAFT and LESIONED + SHAM GRAFT). Right side: Behavioral effect of adrenal medullary transplant in one of the previously lesioned groups (LESIONED + AM GRAFT). NON-LESIONED GROUP = -Δ-, Control; LESIONED + SHAM GRAFT = -□-, amygdala lesioned group; LESIONED + AM GRAFT = -O-, amygdala lesioned group with adrenal medullary transplant after the first behavioral test. Aversion Index = water consumption of saccharine containing test tube / total water consumption. *=p<0.05. Note the performance similarity of the three groups both pre- and post-transplant.

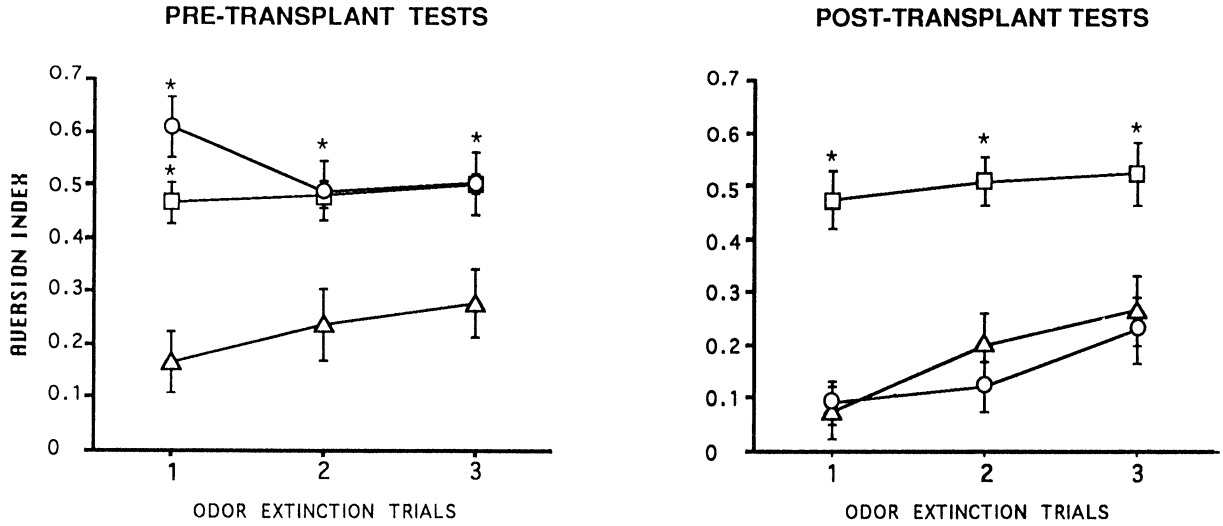

Fig. 2: Odor tests. Left side: POAT effect of 6-OHDA injections in the amygdala of two groups (LESIONED + SHAM GRAFT and LESIONED + AM GRAFT). Right side: Behavioral effect of adrenal medullary transplant in one of the previously lesioned groups (LESIONED + AM GRAFT). NON-LESIONED GROUP = -Δ-, control; LESIONED + SHAM GRAFT = -□-, amygdala lesioned group; LESIONED + AM GRAFT = -O-, amygdala lesioned group with adrenal medullary transplant after the first behavioral test. Aversion Index = water consumption of almond scented test tube / total water consumption. *=p<0.05. Note the reduction of Aversion Index in the LESIONED + AM GRAFT group after the adrenal medullary transplant.

TABLE 1
Monoamine levels in amygdala of non-lesioned, LESIONED + SHAM GRAFT and LESIONED + AM GRAFT groups (n=8 per group)

	NE	DA	5-HT
NON-LESIONED GROUP	462.7 ± 132.5	151.8 ± 46.0	216.0 ± 55.9
LESIONED + SHAM GRAFT	93.6 ± 31.3*	12.6 ± 8.6*	364.5 ± 78.1
LESIONED + AM GRAFT	223.8 ± 32.0	167.8 ± 22.6	302.0 ± 38.5

Results are given as ng/g tissue (wet weight), mean ± SEM.
*$p<0.05$, comparison of the values found in the amygdala lesioned, adrenal medullary transplanted and control groups by an ANOVA simple analysis of variance, and a post hoc comparison (Sheffé) to evaluate the effects and interactions.

since the sham transplant procedure did not restore the behavior. It is also unlikely that tissue implantation alone produced the behavioral effect, since it has been shown that there is no behavioral difference between sham and sciatic nerve control subjects /64/. In addition, it could be suggested that this animal model may be an appropriate one for studying the olfactory deficits seen in PD patients. Interestingly, the deficiency in olfactory discrimination or recognition seen in idiopathic PD is not shared by 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) or by supranuclear palsy patients (SPN), even though they have similar motor disturbances. One of the differences between PD and MPTP or SPN patients is that in the last two, there is no significant lesion of the MCL system, while there is significant damage to that pathway in PD /14,18,55/. Should the olfactory deficit in PD be specifically related to MCL damage, the reason the other two groups of patients do not have the olfactory dysfunction can be easily understood /18/.

The nature of the olfactory deficit in 6-OHDA lesioned amygdala rats is not related to a general learning deficit, since the taste aversion was well acquired by both groups of lesioned rats; therefore, the alteration seems to be related to a specific deficit in the acquisition of the olfactory modality of the POAT. Although in rodents it is difficult to differentiate among the various components of this behavior, it can be argued that the deficit is not related to an olfactory sensory disruption, since there is evidence suggesting that amygdala lesioned rats are not anosmic /2,31/. The same can be argued in relation to the cognitive aspects of the deficit produced by amygdala lesions, since they do not produce a general non-specific effect; i.e., the taste aversion remained unaltered. Moreover, this specific effect can be reversed by adrenal medulla transplants, results that are compatible with previous reports on the effects of brain transplants on different cognitive tasks /3,26,40,61/. One of these tasks is the conditioned taste aversion paradigm, in which fetal insular cortex transplants to lesioned rats can restore taste aversion /3,21,25,44/. Previous findings in the study of conditioned taste aversion and POAT suggest that different structures are involved in the acquisition process of taste and odor aversions. While it is clear that the insular cortex is highly involved in the acquisition of taste aversion, the odor aversion acquisition seems to depend on structures like the amygdala or the hippocampus, and not on the insular cortex or the dorsal striatum /4/. It thus appears clear that olfactory and taste functions depend on different brain structures.

The present results suggest that the 6-OHDA lesion of the amygdala affects olfactory but not taste aversion, a deficit which was reversed by adrenal medullary transplants. It remains to be determined whether the olfactory deficits of this animal model are linked to the olfactory incapacity seen in Parkinson's disease patients.

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