elevation of plasma gastrin (*11*). Several pieces of evidence indicate that CRF acts through modulation of the autonomic nervous system. Vagal tone has a critical role in gastric acid secretion elicited by pylorus ligation, intracisternal injection of TRH, or intravenous infusion of pentagastrin (*2*, *12*) (Fig. 2). We demonstrated that CRF markedly suppressed acid secretion produced under these conditions (Table 1 and Fig. 1) and that vagotomy reversed the inhibitory action of CRF (Fig. 2).

Corticotropin-releasing factor acts within the brain to cause an increase in sympathetic outflow leading to hyperglycemia (*13*). Adrenalectomy just before the injection of CRF completely reversed both the gastric (Table 1) and the hyperglycemic (data not shown) response to CRF in pylorus-ligated rats. These results show that intracisternal injection of CRF, unlike intravenous administration (*8*), decreases gastric acid secretion through vagal and adrenal-dependent mechanisms. This contrasts with the inhibition of gastric acid secretion induced by intracisternally administered bombesin, which is unmodified by vagotomy or by adrenalectomy just before treatment (*6*). In that respect, some specific neuropeptides may be used as new chemical probes to further elucidate the various neurohumoral mechanisms involved in brain-gut interaction.

Although the physiological role of CRF has yet to be elucidated, the findings that CRF mimics the autonomic and endocrine response to stress (*3*, *13*) and that it alters gastric secretion in a manner similar to that of various stressors (*14*) suggest that CRF may have a role in the pathophysiologic gastric response to stress.

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5. Coordinates used for microinjections into the dorsolateral hypothalamic area were anterior posterior, −2.4; lateral, ±1.9; and dorsoventral, −7.8. Coordinates for microinjections into the dorsomedial frontal cortex were anterior posterior, +4.0; lateral, ±2.0; and dorsoventral, −0.7. The cannulas (28 g, stainless steel) were lowered into position bilaterally and simultaneously, and 1 μl of saline or 0.20 to 0.90 nmole of CRF was expelled over 2.0 minutes; after another 2 minutes the cannulas were slowly withdrawn. Pentagastrin (16 μg/kg per hour) was then infused into the femoral vein, and gastric acid secretion was monitored every 10 minutes. At the end of the experiment, the brains were removed and fixed in 10 percent Formalin. Frozen sections at 50 μm were mounted and stained with thionine for microscopic examination (five to seven animals per treatment).
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Normalization of Spiroperidol Binding in the Denervated Rat Striatum by Homologous Grafts of Substantia Nigra

Abstract. *Transplantation of embryonic substantia nigra into the adult rat brain decreases the motor asymmetry that is produced by dopamine receptor supersensitivity after a unilateral lesion of the substantia nigra. The authors report that this effect of transplantation is specific to grafts of substantia nigra. They also report that, in conjunction with the decrease in motor asymmetry, these grafts cause postsynaptic dopaminergic binding sites to return to normal density as measured by tritiated spiroperidol autoradiography. Thus, in animals with brain lesions, grafts of substantia nigra produce a long-term alteration in the functional status of host brain cell receptors that is associated with a reduction in the behavioral deficit.*

Brain tissue transplantation has been used in several central nervous system areas to correct genetically produced hormone deficiencies or to reverse the effects of lesions (*1–5*). For example, unilateral lesions of the rat substantia nigra eliminate the ipsilateral dopaminergic innervation to the striatum, causing supersensitivity of dopaminergic receptors (*6–8*). It is believed that this supersensitivity is brought about by an increase in receptor density rather than by an increase in receptor affinity. When animals with these lesions are given apomorphine, a dopamine receptor agonist, they rotate away from the lesioned side, presumably because apomorphine stimulates the supersensitive striatum more than the intact side (*8*). Grafting fetal substantia nigra (*2–4*) or adult adrenal medulla (*5*) to the denervated striatum decreases this rotation effect and increases the concentrations of dopamine in parts of the striatum adjacent to the graft (*4*). We now report that grafts of other brain areas do not reduce apomorphine-induced turning. Furthermore, in adjacent areas of the striatum, grafts of fetal substantia nigra restore dopamine receptor density to normal levels, as measured by light microscopic autoradiography with [^{3}H]spiroperidol.

We lesioned the right sustantia nigra of 41 Sprague-Dawley albino rats with stereotaxic injections of the neurotoxin 6-hydroxydopamine. We then screened

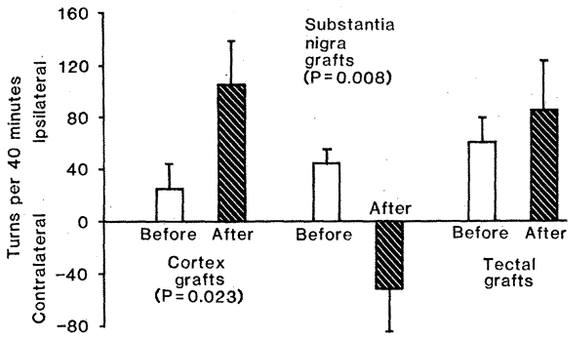

Fig. 1. Effects of fetal brain grafts on lesion-induced rotational behavior. Rotation induced by *d*-amphetamine sulfate (1.5 mg/kg) is shown before and after grafting. A two-way analysis of variance showed a significant main effect of treatment groups [$F(2, 38) = 3.95$, $P = 0.027$] and a significant interaction between treatment groups and measures [$F(2, 38) = 8.15$, $P = 0.0015$]. Levels of probability for the change in each group after transplantation were determined by Scheffé's test. Amphetamine-induced turning was reduced only in the rats that received substantia nigra grafts.

the animals for a marked depletion of striatal dopamine by observing rotations induced by apomorphine (0.1 or 0.25 mg/kg, subcutaneously), and subsequently tested them with the smallest dose that elicited at least two turns per minute (*4*). Apomorphine-induced rotation was measured as an index of the degree of sensitivity of postsynaptic dopamine receptor sites in the denervated host striatum; it shows little spontaneous compensation as a function of time after the lesion (*2, 8*). After seven trials with the assigned dose, the animals were further tested with apomorphine at 0.05, 0.1, and 0.25 mg/kg for one session with each dose in counterbalanced order. Finally, each animal was tested for one session with *d*-amphetamine sulfate (1.5 mg/kg) to provide an indication of the release of dopamine. Substantia nigra from 17-day fetuses was then transplanted to the right lateral ventricle of 20 rats (*2*). Because in our earlier studies we used only peripheral nervous tissues (for example, sciatic nerve) as controls, it was decided to employ as controls other types of fetal brain grafts. Therefore, the remaining animals received grafts of similarly sized pieces of frontal cortex ($N = 11$) or tectum ($N = 10$). These tissues were chosen because the frontal cortex normally innervates the striatum, and the tectum is physically close to the substantia nigra but does not project to the striatum. Lesioned animals were randomly assigned to each group. Beginning 7 weeks after transplantation, the rats were tested in the same sequence as before.

Apomorphine-induced rotation was significantly reduced (at least 20 percent in most cases) only in the group that received grafts of fetal substantia nigra (*9*). No significant reductions were found in the group that received grafts of frontal cortex. In the group that received tectal grafts, some animals had reductions in turning. The overall reduction in this group, however, was not significant (*9*).

Amphetamine-induced rotation also was decreased only by the substantia nigra grafts ($P < 0.005$) (Fig. 1). Amphetamine-induced turning was increased after grafting in the group that received cortex grafts, probably because of sensitization to the drug (*10*), and there was no significant change in the tectal graft group. In the animals that received substantia nigra grafts, however, amphetamine-induced turning was not only decreased but actually reversed, so that most of the animals began to rotate away from the lesioned side. This suggests that the amount of dopamine released by amphetamine on the grafted side exceeded that in the normal side. In fact, we previously found fetal substantia nigra grafts and parts of the adjacent reinnervated striatum to contain high concentrations of dopamine and dense networks of fibers and terminals (*4*).

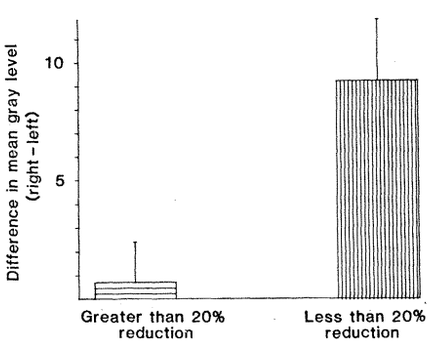

Fig. 2. Spiroperidol binding in the striatum of substantia nigra–lesioned rats with fetal brain grafts that reduced rotational behavior, compared with controls. Differences in film density (gray levels) are shown between the dorsomedial quadrant of the lesioned (right) and normal (left) striatum in rats with reductions in rotations of 20 percent or more ($N = 6$, 15 sections) and in animals without significant reductions ($N = 4$, nine sections). The ordinate represents the absolute difference in mean gray level per pixel (± standard error) over 512 by 512 pixels. The difference between groups is statistically significant at $P < 0.01$ (two-tailed *t*-test).

Histological analysis showed that all three types of grafts survived and appeared to contain viable neurons. Measurements of the graft volumes 12.5 months after implantation showed that the substantia nigra and tectal grafts were similar in size, while the cortical grafts were significantly larger. In the group with substantia nigra transplants, reductions in apomorphine or amphetamine-induced turning were not correlated with graft size (Pearson's $r = 0.26$, $P = 0.45$).

Substantia nigra grafts placed in the ventricle usually reinnervate only the dorsomedial quadrant of the striatum, as determined from concentrations of dopamine in punch samples (*4*) or from histochemical fluorescence studies (*2, 4*). Thus, any effect of ventricular grafts on dopamine receptor density could be detected only by quantitative measurements of regional binding in small brain areas. For this purpose we used in vitro light microscopic autoradiography with [^{3}H]spiroperidol (*11*). Mounted brain sections were incubated in buffer containing [^{3}H]spiroperidol, which is a dopamine receptor antagonist that binds primarily to sites in the striatum postsynaptic to the nigrostriatal terminals (*12*). The sections were then apposed to tritium-sensitive film (^{3}H-Ultrafilm, LKB, Rockville, Maryland) for 3 months (*11, 13, 14*). Spiroperidol binding could then be quantified in terms of film density. We digitized sections from several rostral-caudal levels of each of four control animals (that is, animals with no reductions in apomorphine-induced turning, irrespective of graft type) and six experimental animals with reductions in turning of 20 percent or more. All but one of the nigral animals that were examined had reductions in turning of more than 20 percent. Data were analyzed by computerized densitometry and image enhancement (*14*).

The regions of the dorsomedial striatum on both sides of each coded section were divided into 512 by 512 pixels. A frequency distribution histogram of pixel gray levels (grain density) for each side was constructed, and a mean density per pixel obtained. For the control animals, the mean gray level, reflecting the mean grain density and thus spiroperidol binding, was higher in the dorsomedial quadrant of the striatum on the lesioned side by a mean difference of 9.2 ± 2.6 gray

level units, corresponding to 5.5 fmole of spiroperidol per milligram of protein. In contrast, the mean difference between lesioned and nonlesioned sides in the animals with grafts that reduced rotation was only 0.7 ± 1.7 gray level units (0.42 fmole per milligram). The difference between reduced and nonreduced rotation groups was statistically significant [$T(22) = 2.88$, $P < 0.01$] (Fig. 2).

The degree of denervation supersensitivity measured here by [^{3}H]spiroperidol autoradiography in slices was fairly well correlated with the results of previous studies in vitro. Several investigators (*15*) have found a 15 to 45 percent increase in receptor density in whole striatal homogenates after dopamine denervations. Further research is necessary to determine whether the characteristics of in vitro radioligand binding differ for dorsomedial and lateral striatal dopamine receptors.

In conclusion, the ameliorating effect of grafts of fetal substantia nigra on lesions of the nigrostriatal dopamine system is specific and is not produced by grafts of other parts of the fetal brain. The reductions in drug-induced rotation are associated with reductions in receptor sensitivity in graft recipients. Thus, grafts of fetal substantia nigra may release dopamine not only when stimulated by amphetamine but also spontaneously on a tonic basis. This produces an adjustment of the functional status of dopaminergic receptors in nearby areas, causing them to return to a more normal level and diminishing the apomorphine-induced behavioral response.

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9. Turning was significantly reduced after grafting with substantia nigra [$T(19) = 3.61$, $P < 0.001$, Scheffé's test]. Turning was not significantly decreased in either the tectal graft group [$T(9) = 1.80$, $P = 0.075$] or the cortex graft group [$T(10) = 0.38$, $P = 0.705$]. Apomorphine-induced rotation in the 20 rats with substantia nigra grafts was studied for 6 months after transplantation. There was no further change in rotation rates 7 to 25 weeks after grafting.
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13. Dopamine receptor binding was performed in 8-μm coronal sections of rat brain as previously described (*11*). Serial sections were incubated in 0.17*M* tris-HCl (*p*H 7.4) containing 120 m*M* NaCl, 5 m*M* KCl, 2 m*M* $CaCl_2$, 1 m*M* $MgCl_2$, and 0.001 percent ascorbic acid for 1 hour at room temperature in the presence of 0.4 n*M* [^{3}H]spiroperidol and various other drugs. 2-Amino-6,7,dihydroxy-1,2,3,4-tetrahydronaphthalene (ADTN) (1.0 μ*M*) was added to some sections to block binding to dopamine receptors, 0.3 μ*M* cinanserin was added to the incubation medium to block binding to serotonin receptors, and 0.4 μ*M* haloperidol was added to generate blank values. Sections incubated with cinanserin were used in obtaining all the data reported here. After incubation, the sections were washed twice for 5-minute intervals in ice-cold buffer, rapidly dried in a cold airstream, and exposed to ^{3}H-Ultrafilm for 3 months. Quantitative analysis of ligand-binding density in the autoradiograms depended on comparison with a standard curve derived from brain tissue standards containing known amounts of radioactivity (*11*). These standards were coexposed with the experimental sections.
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15. In vitro binding of various tritiated ligands, such as haloperidol (*6*), apomorphine, and spiroperidol [D. Staunton, B. Wolfe, P. Groves, P. Molinoff, *Brain Res.* **211**, 315 (1981); I. Creese and S. Snyder, *Eur. J. Pharmacol.* **56**, 277 (1979)] has been studied in homogenates of intact and dopamine-denervated striatal homogenates. Depending on the ligand used, increases in maximum binding of 15 to 45 percent have been reported on the lesion side, with little change in dissociation constant values.
16. We thank E. Krauthamer for preparing the histological materials, I. Strömberg for performing the densimetric measurements, and the secretarial and support staff of the Adult Psychiatry Branch and D. Rogers for their invaluable assistance. We also thank S. Hsiao, W. Rasband, and C. Goochee for constructing the rotometers and for other assistance. Supported in part by grants NS-09199, MH-00289, MH-25951, and MH-00053 from the Public Health Service and by Swedish Medical Research Council grants 14P-5867 and 14X-03185.

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Early Auditory Experience Aligns the Auditory Map of Space in the Optic Tectum of the Barn Owl

Abstract. *Auditory and visual space are mapped in the optic tectum of the barn owl. Normally, these maps of space are in close mutual alignment. Ear plugs inserted unilaterally in young barn owls disrupted the binaural cues that constitute the basis of the auditory map. Yet when recordings were made from the tecta of these birds as adults, the auditory and visual maps were in register. When the ear plugs were removed from these adult birds and binaural balance was restored, the auditory maps were shifted substantially relative to the visual maps and relative to the physical borders of the tecta. These results demonstrate that the neural connectivity that gives rise to the auditory map of space in the optic tectum can be modified by experience in such a way that spatial alignment between sensory modalities is maintained.*

The locations of auditory and visual stimuli in space are represented topographically by multimodal neurons in the optic tectum (superior colliculus). The left-right location (azimuth) of a stimulus is represented along the rostrocaudal axis of the tectum, and the up-down location (elevation) along a mediolateral or dorsoventral axis (*1*, *2*). These physiological maps of auditory and visual space are mutually aligned, particularly in the tectum of the barn owl where they correspond, both in azimuth and elevation, to within a few degrees (*1*). This alignment of sensory maps is manifested as a spatial coincidence of the optimal locations of auditory and visual stimuli for exciting single units (*1–3*).

How does the alignment of spatial maps from different sensory modalities come about? The visual and auditory maps are constructed differently. The visual map results from point-to-point projections from the retinas to the tec-