

17.04

## Human and Rat Monoaminergic Neuroblasts Grafted to Rats with Unilateral Dopamine Depletions

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Fetal monoaminergic tissue was examined for its capacity to reinnervate rat striatum and to study the function of the graft. When grafting human fetal mesencephalic tissue to dopamine depleted striatum, a reduction in apomorphine rotational behavior was well correlated with the time outgrowing fibers were detected with tyrosine hydroxylase (TH) immunohistochemistry. Cell migration from graft to host was seen at 1.5 months postgrafting. Spontaneously firing dopaminergic neurons were found within the graft. Local application of the dopaminergic antagonist *cis*-flupenthixol resulted in excitation of the dopaminergic neurons, indicating that they had developed dopamine autoreceptors by the time of recording. The dopamine antagonist also excited striatal neurons on the graft-reinnervated side, which indicated that dopaminergic activity existed and could be blocked. The spontaneous discharge rate of striatal neurons in the reinnervated side was normalized, while the firing rate of neurons in dopamine depleted striata was increased.

We also examined the specificity of the target of the outgrowing fibers from dopaminergic grafts. Human fetal mesencephalic tissue was grafted to cingulate cortex of unilateral dopamine denervated rats. Outgrowing fibers, visualized with TH- and human specific Thy-1-immunohistochemistry, penetrated corpus callosum and reinnervated the host brain, but grew only into the denervated side. Furthermore, the human-derived nerve fibers grew from cortex to the ventral limbic parts of striatum. The reduction in apomorphine-induced rotational behavior was as good in these animals as in rats with grafts placed in the lateral ventricle.

Human fetal mesencephalic tissue, grafted to the lateral ventricle, was also tested for its sensi-

tivity to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Rotational behavior was tested monthly and when apomorphine-induced rotations were reduced, subcutaneous injections of MPTP were performed. In some rats, the rotational pattern reappeared after the MPTP-treatment. Histological evaluations revealed surviving grafts using antibodies against human specific Thy-1. Few TH-positive neurons were seen within the graft area, but no TH-positive nerve terminals could be detected in dorsal striatum. However, in ventral limbic parts, a TH-positive nerve plexus was still found. These results indicate that there is a subdivision of dopaminergic neurons within the graft that are less sensitive to MPTP and that reinnervate the ventral limbic parts while the dopaminergic neurons that reinnervate the dorsal striatum are sensitive and degenerate after MPTP-treatment.

Grafted dopaminergic neurons appear to reinnervate the host in a target-specific manner. We tested the specificity of the neurons that are able to reinnervate the denervated host. Outgrowth from grafted catecholamine-rich tissue from locus coeruleus and nucleus arcuatus was compared with outgrowth from grafted tissue from the nigral area. Histological evaluations showed surviving grafts in all cases. Outgrowth of a dense nerve fiber network into the host was seen in rats grafted with nigral tissue, but very few outgrowing nerve fibers were detected in rats grafted with locus coeruleus. Those were both TH- and DBH-positive, indicating that they still produced noradrenaline. Surviving TH-immunoreactive neurons were found within the graft derived from nucleus arcuatus. A relatively dense nerve fiber network was found within the graft area, but no fibers penetrated into host striatum. Functionally, a reduction of rotational

behavior was only detected in rats grafted with substantia nigra neurons. Furthermore, a normalized firing rate was found in the striata of rats with implanted mesencephalic tissue only. The firing rates of striatal neurons in rats grafted with locus coeruleus or nucleus arcuatus were

increased as in dopamine depleted animals. In conclusion, there is a high degree of specificity in the outgrowth from fetal catecholaminergic tissue grafted to dopamine depleted rats and a precise matching of rotational behavior, electrophysiological results and graft outgrowth.