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Influence of Donor Age on the Survival of Human Embryonic Dopaminergic Neural Grafts

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There is substantial variability worldwide in the donor ages utilized in nigral transplantation programs for the treatment of Parkinson's disease. In multiple non-human species, it has been repeatedly demonstrated that optimal graft survival occurs when embryonic nigral neurons are harvested before the period of axonal extension, most likely due to axotomy and cell death of older neurons /1; see 2,3/.

Neurons which form the human substantia nigra develop within the ventricular zone primarily between post-ovulatory (PO) day 33 and 63 /2,5/. The nigrostriatal bundle begins to develop at approximately PO day 56 /2/. From this data it could be predicted that the optimal period for suspension graft survival would occur before PO day 56 /2,3/. Solid grafts in non-human species have been found to have a slightly longer donor age "window" for graft harvesting than suspension grafts /see 3/.

We compared the ability of solid and suspension grafts of human embryonic dopaminergic neurons at different embryonic ages to survive grafting into 6-OHDA lesioned immunosuppressed rats. Donor age was determined using the atlas of O'Rahilly and Müller /4, also see 2/. Suspension grafts survived best from PO day 37 to 56 with diminishing success through PO day 65. These implants displayed numerous healthy tyrosine-hydroxylase-immunoreactive (TH-ir) neurons which sent extensive neuritic processes into the host striatum. Conversely, suspension grafts of human embryonic dopaminergic neurons survived poorly when the donor age was greater than PO 65 days.

In contrast to suspension grafts, solid implants of human ventral mesencephalic tissue displayed only modest survival of TH-ir neurons derived from younger donors. These grafts also

displayed a limited host innervation. Good/excellent survival of TH-ir neurons was observed in solid grafts employing embryonic donors between PO day 45 and 65. Only trace numbers of TH-ir neurons were present within grafts derived from PO 72 tissue.

In conclusion, the upper age limit for survival of human embryonic dopaminergic suspension grafts correlates well with the period of development of the human nigrostriatal pathway. Optimal donor ages for human nigral suspension grafts range from PO day 37 to 56 days. The donor age "window" for transplantation of solid human embryonic dopaminergic grafts appears to be extended by about nine days in comparison with suspension grafts. In younger age ranges (less than or equal to 41 days), intraparenchymal suspension nigral grafts survive better than solid grafts. The optimal donor age for intraparenchymal solid grafts ranges from PO day 45-65. There appears to be a sharp fall-off in the

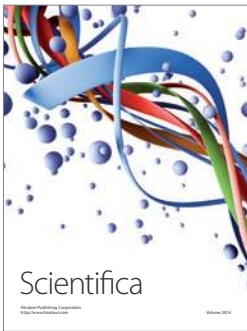
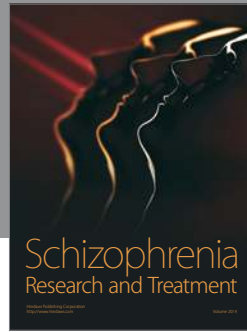
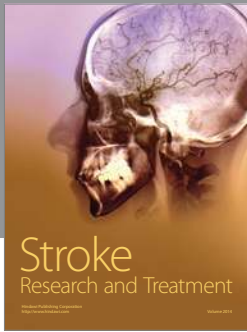
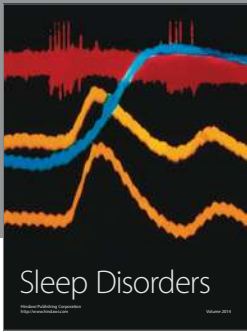
SURVIVAL OF INTRAPARENCHYMAL HUMAN EMBRYONIC NEURAL XENOGRAFTS BY AGE

Post Ovulatory Age (days)	Donor stage	Foot Length (mm)	Graft Survival (Best)	
			Suspension	Solid
33	15	--	***	--
37	16	--	****	**
41	17	--	*****	***
45-56d	18-23	--	*****	*****
57	--	5.5	***	--
65	--	7.5	0-**	****
72	--	8.5	0	trace cells

number of surviving dopaminergic neurons in both solid and suspension grafts derived from older donors. We suggest that clinical nigral transplant programs for the treatment of Parkinson's disease limit donor age to these dates.

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