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Extrinsic Reinnervation of the Intestine After Small Bowel Autotransplantation in Dogs

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IMMUNOHISTOCHEMICAL examination of two failed human small intestinal grafts showed no evidence of extrinsic reinnervation for up to 22 or 8 months whereas intrinsic neural innervation showed only a slight decrease from normal intestine. The mechanisms responsible for this lack of neural input are not known. The purpose of this study was to examine extrinsic reinnervation in canine small bowel autotransplantation (SBT). This model eliminates potential aggravating factors such as rejection and immunosuppressant medications.

MATERIALS AND METHODS

The entire small intestine of adult mongrel dogs was isolated on a vascular pedicle of the superior mesenteric artery (SMA) and vein (SMV). After flushing the SMA and irrigating the lumen, the graft was immediately reimplanted into the same dog. Arterial reconstruction was done by either end-to-end SMA to SMA (E-E) or end-to-side SMA to aorta with an iliac arterial interpositional graft (E-S). Venous reconstruction was done by E-E SMV to SMV anastomoses. Intestinal continuity was restored by E-E anastomoses of the jejunum and ileum. The animals were killed to obtain specimens at four intervals; 1, 3, 6, and 12 months following transplantation. High performance liquid chromatography was used to measure the concentration of norepinephrine (NE) on full thickness specimens of jejunum and ileum from sham control dogs as well as those of host/graft jejunum (Table 1) and host/graft ileum (Table 2) from autotransplanted dogs at each time period. Indirect immunohistochemistry was applied to jejunal and ileal specimens from six controls and autotransplanted dogs to examine immunelike reaction to extrinsic (tyrosine hydroxylase [TH]), mixed intrinsic and extrinsic (neuropeptide Y, substance P, calcitonin, gene-related peptide), and intrinsic neurotransmitters (vasoactive intestinal peptide, galanin, gastrin releasing peptide, L-enkephalin, and somatostatin).

Table 1. Tissue NE Concentration

Group	No.	Host Jejunum (ng/g)	Graft Jejunum (ng/g)
Control	10	108.12 ± 31.50	
1 mo	6	54.42 ± 50.46	0.60 ± 0.46
3 mo	5	46.58 ± 40.17	0.50 ± 0.30
6 mo (E to E)	2	85.96 ± 82.87	1.23 ± 0.02
6 mo (E to S)	2	63.44 ± 2.40	0.70 ± 0.99
12 mo (E to E)	3	64.00 ± 27.74	29.24 ± 8.14*
12 mo (E to S)	3	111.36 ± 27.94	10.57 ± 4.82

Abbreviations: E to E, end-to-end arterial anastomosis; E to S, end-to-side arterial anastomosis with arterial graft interposed.

*P < .05 vs the other graft jejunum by analysis of variance. 27% value of control jejunum.

Table 2. Tissue NE Concentration

Group	No.	Host Ileum (ng/g)	Graft Ileum (ng/g)
Control	8	136.46 ± 48.54	
1 mo	2	71.89 ± 40.13	0.13 ± 0.18
3 mo	3	77.53 ± 36.13	1.31 ± 0.11
6 mo (E to E)	2	191.81 ± 0.48	1.22 ± 0.46
6 mo (E to S)	2	137.87 ± 67.22	0.46 ± 0.21
12 mo (E to E)	3	168.96 ± 15.54	60.14 ± 30.00*
12 mo (E to S)	3	201.12 ± 70.82	5.12 ± 3.10

Abbreviations: E to E, end-to-end arterial anastomosis; E to S, end-to-side arterial anastomosis with arterial graft interposed.

*P < .05 vs the other graft ileum by analysis of variance, 44% value of control ileum.

RESULTS

The concentration of NE in the host jejunum (Table 1) and in the host ileum (Table 2) of autotransplanted dogs was the same as respective controls. No measurable levels of NE were detected in any graft from 1, 3, and 6 months nor in the 12-month E-S graft. In contrast, NE in the 12-month E-E graft jejunum and graft ileum was significantly increased compared with the other grafts. Immunoreactivity to intrinsic neuropeptides was similar to controls for all grafts. However, there was no evidence of immunoreactivity to extrinsic neuropeptides or TH in any experimental animal up to 3 months after transplantation. At 6 months, one of six E-E dogs showed scant perivascular staining for all four extrinsic peptides. At 12 months, sparse extrinsic peptide immunoreactivity was seen in all three dogs that underwent E-E anastomosis. In dogs undergoing E-S anastomosis, extrinsic innervation was absent in one and very sparse in the other two. In the dogs that had positive fibers, the graft ileum had more positive fibers than the graft jejunum with the exception of one 12-month-old E-S dog.

DISCUSSION

A previous report showed no reappearance of TH immunoreactive extrinsic nerves 100 days after SBT in rats,¹ and an extrinsically denervated in situ canine model

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showed no measurable values of tissue catecholamine up to 12 weeks postoperatively.² Contrary to these findings, a recent report showed extrinsic adrenergic nerve regrowing along the mesenteric artery starting 3 weeks after SBT, followed by reappearance in the intramural area 15 weeks after SBT using an E-S vascular anastomosis model in rats.³ From the present study we conclude: (1) Extrinsic reinnervation of autotransplanted canine small intestine is first detected 1 year after SBT, as evidenced by the presence of NE in tissues, and the presence of fibers

immunoreactive to TH and extrinsic neuropeptides; (2) extrinsic reinnervation occurs more readily in E-E arterial anastomosis than in E-S arterial anastomosis; and (3) extrinsic reinnervation is more prominent in the graft ileum than in the graft jejunum.

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