Proximal enterectomy provides a stronger systemic stimulus to intestinal adaptation than distal enterectomy

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SUMMARY Enteroglucagon has been implicated as a tropic hormone in the control of intestinal adaptation. Because cells producing enteroglucagon are located mainly in the distal small bowel (and colon), ileal resection might be expected to produce less adaptive change than a jejunal resection of equivalent length. This hypothesis was tested in male Sprague-Dawley rats ($n = 40$) weighing 184.0 ± 7.3 g and receiving a Thiry-Vella fistula (TVF) of the mid-60% of the small intestine. One group had concomitant resection of the jejunum proximal to the TVF ($n = 12$), another had resection of the ileum distal to the TVF ($n = 13$), while controls had a TVF alone ($n = 15$). When killed 10 days postoperatively rats with ileal resection weighed only 81% of controls ($p < 0.001$) and 85% of those with jejunal resection ($p < 0.01$). Jejunal resection produced an 81% increase in crypt cell production rate (measured by a stathmokinetic technique) over control values (28.5 ± 4.2 vs 15.8 ± 2.3 cells/crypt/h; $p = 0.025$), whereas ileal resection had no demonstrable effect (17.5 ± 2.3 cells/crypt/h). Adaptive hyperplasia in isolated small bowel is modulated by factors localised to the distal small intestine, enteroglucagon being a plausible candidate.

Although the phenomenon of intestinal adaptation has been recognised for a century, it was not until the 1960's that serious consideration was given to the mechanisms governing compensatory hyperplasia. Loran and Crocker proposed the existence of an 'intestinal epithelial growth hormone', whereas Dowling and Booth underlined the paramount importance of luminal nutrition. There now seems little doubt that humoral agents are involved, being secreted in response to luminal chyme. We have previously summarised the data that implicate systemic agents, including the detection of a modest compensatory response in isolated loops of bowel or parabiotic partners of rats with resection.

On present knowledge the most plausible single candidate for the role of an 'enterotropin' is enteroglucagon. Certainly plasma concentrations of enteroglucagon closely parallel ileal crypt cell production rate in several models of adaptation including small bowel resection, hypothermia, lactation and intravenous feeding. Moreover one patient with an enteroglucagonoma had dramatic intestinal hyperplasia that disappeared after resection of the tumour.

As enteroglucagon is found in greatest concentration in the distal ileum (and colon), we have compared the adaptive potential of jejunal and ileal resections in loops of mid-small bowel isolated as a Thiry-Vella fistula.

**Methods**

**Animals**

Fifty male Sprague-Dawley rats (Olac Ltd, Bicester) weighing 180 ± 7.3 g were submitted to laparotomy under light ether anaesthesia. In each animal a Thiry-Vella fistula (TVF) was created by isolating the mid-60% of the jejunum and exteriorising each end as a mucous fistula. This length of fistula was chosen after a pilot study had shown that shorter TVFs were often associated with atrophy or necrosis of the loop.

Rats were randomly allocated to one of three groups. Controls had no further operative procedure, intestinal continuity being directly restored by end-to-end jejunooileal anastomosis (Fig. 1). The other groups...
Fig. 1  Creation of a Thiry-Vella fistula from the mid 60% of the jejunileum.

Fig. 2  Creation of a Thiry-Vella fistula plus 20% proximal small bowel resection.
Proximal enterectomy provides a stronger systemic stimulus

had a 20% small bowel resection in addition to TVF. Rats with jejunal resection had all jejenum proximal to the TVF excised, with anastomosis between the duodenojejunal flexure and distal ileum (Fig. 2). Rats with ileal resection had all ileum distal to the TVF resected, with anastomosis between the proximal jejunum and ileocecal junction (Fig. 3). All intestinal anastomoses were created using a continuous 6/0 silk suture. The two stomas were sutured to the skin with interrupted 6/0 catgut on either side of the midline laparotomy incision. Each rat received an im injection of vitamin K 0.25 mg/kg at the end of the operation to prevent postoperative bleeding.

Ten days postoperatively rats were weighed and then were killed at intervals 40–180 minutes after ip injection of vincristine sulphate (Oncovin, Eli Lilly, Basingstoke) 1 mg/kg which was given to bring about metaphase arrest within the intestinal crypts.\(^\text{11}\) A small segment of bowel obtained from the centre of the TVF was fixed in Carnoy's fluid for four hours, then stored in 70% alcohol. Bowel samples were stained by the Feulgen reaction for DNA, the mucosa was stripped off the muscle coat and metaphase figures were counted in 10 individually micro-dissected crypts per specimen.\(^\text{12}\) The mean number of metaphase arrests was plotted against time after vincristine administration, and crypt cell production rate (CCPR) was calculated by linear regression analysis.\(^\text{11}\)

Ten animals were lost to analysis because of premature death (n = 6) or because the TVF was unusable.

Statistical significance was assessed using Student's t test for unpaired data.

Results

**BODY WEIGHT** (Table 1)

Controls with TVF alone gained 20% in weight over the 10 days of the experiment. Rats with jejunal resection also gained weight (by 14% overall), but rats with ileal resection remained at a similar weight to the preoperative value.

<table>
<thead>
<tr>
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<th>Weight 10 days postoperatively (g)</th>
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<tbody>
<tr>
<td>Ileal resection</td>
<td>178.4±12.3*</td>
</tr>
<tr>
<td>Controls</td>
<td>221.4±14.6</td>
</tr>
<tr>
<td>Jejunal resection</td>
<td>209.2±13.9</td>
</tr>
</tbody>
</table>

\(^* p = 0.0001 \text{ v controls}; p = 0.008 \text{ v jejunal resection}\)
Table 2 Crypt cell production rate (cells/crypt/h)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileal resection</td>
<td>17.5 ± 2.3</td>
</tr>
<tr>
<td>Controls</td>
<td>15.8 ± 2.3</td>
</tr>
<tr>
<td>Jejunal resection</td>
<td>28.5 ± 4.2*</td>
</tr>
</tbody>
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*p = 0.025

Crypt cell production rate (Table 2)
Compared with control values, jejunal resection produced an 81% increase in CCPR in the centre of the TVF (p = 0.025). Ileal resection produced a non-significant 17% increase, and CCPR was only 62% of that in rats with jejunal resection.

Discussion

This study further supports the involvement of humoral agents in the control of adaptation. Because the intestine in a TVF is completely isolated from the luminal stream, the 81% increase in CCPR seen after jejunal resection must surely be mediated systemically. We have also confirmed that an enhanced adaptive response follows jejunal as opposed to ileal resection, and it seems that the explanation for this is at least in part hormonal. Hyperaemia might conceivably cause compensatory hyperplasia, but would seem unlikely to explain the marked response in CCPR to a limited (20%) resection of the small bowel.

Enteroglucagon is produced mainly in the distal ileum (and colon). Tissue levels are much higher at this site than in the jejunum and rise still further after partial resection. A tropic role for enteroglucagon has been postulated in both man and animals. It is thus possible that increased release of enteroglucagon from the remaining ileum of rats with jejunal resection stimulates hyperplasia within the TVF. This stimulus would have been much lower after ileal resection, as this removes the major source of enteroglucagon. Alternatively an antitrophic substance present in the proximal bowel is removed by jejunal resection but still present after ileal resection. Somatostatin is found in decreasing amounts from jejunum to ileum and infusions of this peptide prevent postresectional ileal hyperplasia. Doubtless the situation is complex, as somatostatin inhibits various gastrointestinal functions including enteroglucagon release, and other potentially tropic hormones such as neurotensin and bombesin could also be involved. It is entirely logical that any substance controlling adaptation of the small intestine should reside distally. At that site alterations in chyme are maximal after resection and it is presumably these alterations that initiate the release of humoral agents.

References

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