Effects of Insulin-like growth factor-I (IGF-I) peptides on the growth and function of the gastrointestinal tract in adult and suckling rats

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ABSTRACT

Growth and development of the gastrointestinal tract in mammals is regulated by the complex interaction of dietary, hormonal, neural and luminal factors. To investigate the effects of insulin-like-growth factor-I (IGF-I) peptide infusion on the growth and function of the gastrointestinal tract, adult and suckling rats (6 and 12 days old) have been treated with increasing doses of IGF-I or LongR^3 IGF-I (LR^3IGF-I), an IGF-I analog that shows greatly reduced binding affinity to several of the IGF binding proteins. Peptides were delivered via subcutaneously implanted mini-osmotic pumps. Control animals received vehicle carrier (0.1M acetic acid). Adult rats were maintained in metabolism cages throughout the treatment period for assessment of body weight gain, food and water intake and faecal and urinary output. Suckling rats were returned to their mother following pump implantation (9 pups/dam). At sacrifice, internal organs and the gastrointestinal tract were rapidly excised for subsequent histological, biochemical and autoradiographic analyses. Biological activities of Lactase-Phlorizin Hydrolase (LPH) and the alpha glucosidase sucrase-isomaltase were measured in tissue homogenates of suckling animals to assess IGF-I peptide effects on the maturation of GIT function. Distribution patterns of enzyme expression along the villus axis were determined in cryostat sectioned tissue samples.

In the adult rats, a dose-dependent increase in gut tissue weight and intestinal length was observed following peptide treatment for 14 days. Both mucosal and non-mucosal tissue components increased with proportional increments in proliferative cells within the crypt epithelium as indicated by proliferative cell nuclear antigen labelling (PCNA). Administration of IGF-I peptides rapidly induced proliferative activity as indicted by an increase in tritiated thymidine labelling following a 3 day peptide administration protocol to adult rats.
In 6-day old pups, treated for 6.5 days with LR³IGF-I but not IGF-I, increased body weight gain. However, both peptides increased the relative weights of organs, including the spleen and kidney. A selective action of IGF-I and the LR³IGF-I was indicated by the marked increase in gastrointestinal tissue components, so that total gut weight increased by up to 59% above control values following treatment with the highest dose of LR³IGF-I. Responses were particularly apparent in the small intestine and the stomach, and histological and biochemical analyses suggested that growth occurred through proportional increases of the mucosal and non-mucosal tissue mass. The thymidine labelling index increased in proportion to crypt population.

In the 12 day old pups, lactase activity, as measured in jejunal tissue homogenates, was significantly reduced following treatment with LR³IGF-I. Histocytochemical detection showed a significant reduction in surface staining for lactase along the entire length of duodenal villi. Conversely, in these animals, sucrase activity measured in either jejunal tissue homogenates or in cryostat sectioned tissue, was precociously induced.

The results of this study suggest that IGF-I peptides, in particular LR³IGF-I, significantly influence gastrointestinal growth in normal adult and suckling rats. IGF-I peptides stimulate intestinal proliferation and furthermore, influence the maturation and cytodifferentiation of enterocytes in the immature intestine. These findings indicate that IGF-I peptides may have therapeutic implications both in conditions of impaired gut function in the adult gastrointestinal tract and in the treatment of gut disease in the immature intestine.
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