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Gastrointestinal Effects of Growth Hormone

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GH receptor immunoreactivity is found throughout the gastrointestinal tract. GH has proliferative effects upon intestinal epithelium, and influences enteroendocrine cell secretion, calcium absorption, and intestinal amino acid and ion transport. The proliferative effects of GH may be reflected in the increased incidence of neoplastic colonic polyps in individuals with long-term GH excess reported by some investigators. GH also increases hepatic cytochrome P450 expression, potentially altering drug and steroid hormone metabolism.

Current clinical research efforts include the use of exogenous GH as a stimulant of gut growth and adaptation in patients who have undergone massive intestinal resection. Exogenous GH is also being studied in animal models of critical illness where it appears to increase intestinal glutamine uptake, which may prevent deterioration of the intestinal mucosal barrier.

Key words: Growth hormone; gastrointestinal tract; acromegaly; short gut syndrome; enteroendocrine cell.

Introduction

Growth hormone (GH) appears to have diverse actions in the gastrointestinal tract. GH receptor immunoreactivity is present not only in the liver, where it stimulates production of the major source of circulating insulin-like growth factor-1 (IGF-1) concentrations, but also throughout the intestine, pancreas, and salivary glands *(1–3)*. Early studies of hypophysectomized rats revealed hypotrophy of the gastrointestinal tract, which could be reversed with GH therapy *(4–8)*. Subsequent physiologic studies in animals and humans have suggested an effect of GH on calcium, sodium chloride, and amino acid transport in the intestine *(9–12)*. A proliferative effect of GH on gut epithelium was confirmed in transgenic mice that overproduced GH *(13)*. Since recombinant DNA hGH became available in an unlimited supply in 1985, the effects of exogenous GH have been studied in the short gut syndrome *(14,15)* as a potential aid to intestinal adaptation, and in models of critical illness where it augments intestinal glutamine uptake, which may protect the gut mucosal barrier *(16,17)*. Clinical data supporting an increased risk of intestinal tumor formation in patients with GH excess are also accumulating *(18–20)*.

In this article, current knowledge of GH actions in the gastrointestinal tract will be reviewed with attention to its relevance to clinical medicine.

Localization of GH Receptors in the Gastrointestinal Tract

In 1990, Lobie et al. *(1)* used immunohistochemical techniques to explore GH receptor immunoreactivity in the gastrointestinal tract of adult rats. Heterogeneous distribution of GH receptor was found throughout the intestine, salivary glands, liver, and endocrine and exocrine pancreas, primarily in cells of epithelial origin, and to a lesser extent, in mesenchymal cells. Specific [^{125}I]hGH binding was demonstrated in crude fractions of stomach and intestine. IGF-1 immunoreactivity had previously been observed in the majority of these tissues *(21)*, consistent with the hypothesis that the proliferative effects of GH were likely mediated through local IGF-1 production. In the stomach, GH receptors were more plentiful on enteroendocrine cells, chief, and parietal cells, than in the gastric isthmus. It was postulated that GH may affect gastric mucosal growth through stimulation of IGF-1 plus an additional factor such as gastrin *(1,22,23)*. Immunoreactivity for GH receptors but not IGF-1 was demonstrated in pancreatic acinar cells suggesting an independent role for GH in pancreatic exocrine function.

Transcripts for GH receptor have been detected in small intestinal mucosa and gastric glands of the rat fetus *(3)*. GH was reported to be critical to the growth and histogenesis of rat fetal intestinal transplants *(24)*. GH, its binding protein, and IGF-1 are present in rat and human milk *(25)*. A physiologic role for these ingested peptides in the function of the newborn gastrointestinal tract has not been confirmed.

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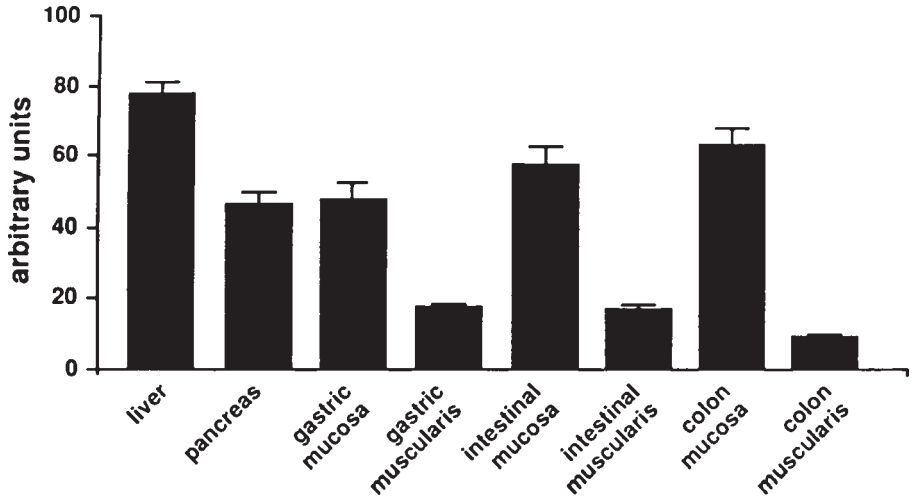

Fig. 1. GH receptor mRNA in tissues of the human gastrointestinal tract. Quantification of *in situ* hybridization signal using complimentary DNA probes encoding part of the intracellular and extracellular domains of the GH receptor. Figure reproduced with permission from The Endocrine Society. Original figure appeared in Delehaye-Zervas et al. *(2)*.

Recently, Delehaye-Zervas et al. *(2)* demonstrated expression of the GH receptor gene throughout the human digestive tract. Using tissue samples from patients of varying ages undergoing a variety of surgical procedures, a 4.5 kb mRNA transcript encoding the full-length membrane GH receptor, was found in human liver, pancreas, stomach, small intestine, and colon (**Fig. 1**). In the liver, the signal was primarily in the cytoplasm of hepatocytes. In the stomach, the signal was prevalent in the gastric mucosa, and in chief and parietal cells. In the small intestine and colon, the signal was primarily in the deep area of the crypts corresponding to the zone of proliferation and differentiation. In the pancreas, the signal was detected in both exocrine and endocrine cells.

Nagano et al. *(3)* also identified GH receptor transcripts in human surgical specimens of intestine. In addition to the full-length GH receptor, GH receptor d3 (lacking exon 3 of the human GH receptor) was broadly expressed. Expression of this isoform appeared slightly increased in a small number of samples from colon and gastric adenocarcinoma patients, even in adjacent normal tissue. The d3 receptor is capable of binding GH as well as the wild-type *(26)*. No relationship between its expression and pathological characteristics has yet been observed *(27)*.

Decreased GH receptor has been documented in human cirrhotic liver consistent with the GH resistance that is clinically apparent in this condition *(28)*. Affected patients may still respond to supraphysiologic doses (10x the usual adult replacement dose) of GH with a 2.5-fold rise in serum IGF-1 levels and improved nitrogen balance after 7 d of therapy *(29)*.

Proliferative Effects of GH

There has been evidence of an effect of pituitary hormones upon growth of the gastrointestinal tract for decades. Hypophysectomy results in hypotrophy of the stomach, small intestine, and pancreas *(4–8)*. In 1955, Leblond and Carriere described a proliferative effect of GH in the crypts of Lieberkühn of the duodenum in hypophysectomized rats *(4)*. Subsequently, it was shown that hypertrophy of the GI tract of hypophysectomized rats to supra-normal levels was achieved by administration of GH alone *(5)*. Dubreuil and Morisett reported that rats treated 14 d with GH-releasing hormone with or without somatostatin antisera had increased GH levels and increased dry weight of the liver, pancreas, and small intestine *(30)*. Transgenic mice over-expressing bovine GH had increased small bowel weight and length, and 50–100% greater mucosal mass. Increased villus height and crypt depth were most notable in the proximal bowel *(13)*. Transgenic animals were compared to a pair-fed wild-type control group and thus, the findings were independent of food intake, a factor known to stimulate mucosal growth *(31)*. Villus content of IGF-1 mRNA in bowel was greater in GH transgenics than in wild-type mice, consistent with the theory of local IGF-1 production stimulated by GH. In rats undergoing 75–80% small intestinal resection, hGH and IGF-1 have been shown to augment postoperative hyperplasia that occurs in the ileal remnant *(14,32)*. hGH-treated animals had greater body weight, villous height, DNA, and protein content compared to saline-treated animals. GH administration to rats increases mass, collagenous proteins, and biomechanical strength of the colon *(33)*.

An increased prevalence of colonic polyps in the clinical syndrome of GH excess has been reported by several investigators *(18–20)*. In a recent prospective study *(18)* of 129 biochemically proven acromegalic patients, colonoscopy revealed a 5% incidence of adenocarcinoma (many of which were asymptomatic), 13.5 times higher than the incidence reported for the general population *(34)*. Tubulovillous aden-

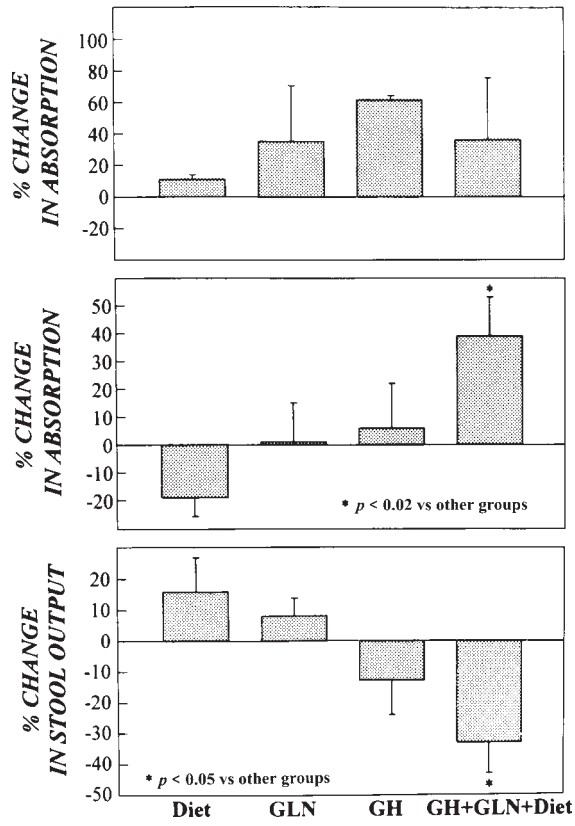

Fig. 2. The effect of high carbohydrate, low fat diet, glutamine (GLN), growth hormone (GH), and all three in combination on absorption of sodium (top panel), protein (middle panel), and stool output (bottom panel) in 15 patients with short-bowel syndrome initially dependent upon intravenous hyperalimentation. An increase in absorption above baseline represents enhanced absorption. A negative change in stool output indicates decreased stool volume. Figure reproduced with permission from Lippencott-Raven Publishers. Original figure appeared in Byrne et al. *(15)*.

oma (a premalignant lesion) was found in 26%, the majority occurring in patients over 70 yr old. In patients over 49 yr there was a fourfold increase in the incidence of adenomas compared to the normal population *(35)*. The mechanisms for development of neoplasms are unclear. GH, independently of IGF-1, stimulates induction of c-myc expression *(36)*, a proto-oncogene that induces dysplastic changes in colonic mucosa *(37)*. IGF-1 is a mitogen that can stimulate growth of several colon cancer cell lines, and expression of IGF-1 mRNA is enhanced in colon cancers *(38)*. IGF-1 receptors are present on the surfaces of colon cancer cells as well as normal gastrointestinal mucosa *(39,40)*. Jenkins et al. recommended that patients with acromegaly be offered colonoscopy beginning at age 40 yr to be repeated at three yearly intervals *(18)*.

Clinical efforts are ongoing to examine the effectiveness of exogenous GH upon adaptation of the small bowel after massive intestinal resection. Patients with only 50–70 cm of small bowel remaining with the colon, or 110–150 cm in the face of colectomy are usually dependent upon chronic intravenous nutrition due to lack of adequate gut absorptive surface. Such patients are prone to intravenous catheter infections, progressive kidney failure, liver dysfunction, and nutrient deficiencies *(41)*. Byrne et al. are currently advocating the use of GH therapy in addition to the amino acid glutamine in patients with short bowel syndrome *(15)*. Glutamine is an essential precursor for nucleotide biosynthesis *(42)*. Glutamine-supplemented nutrition administered in combination with IGF-1 to rats enhances protein deposition in the residual mucosa after small bowel resection compared with trophic effects of glutamine or IGF-1 alone *(43)*. Byrne et al. have reported a 39% increase in protein absorption and 33% decrease in stool volume in patients initially dependent on parenteral nutrition following 4 wk of therapy with subcutaneous GH (0.14 mg/kg/d), enteral and parenteral glutamine, and a high fiber, high carbohydrate, low fat diet *(15)*. Analysis of the effect of each component of the treatment program is shown in **Fig. 2** for 17 patients. **Figure 3** shows the relative dependency of 47 patients upon parenteral nutrition at 28 d after initiation of the combined treatment and approx 1 yr later. In this protocol GH therapy was stopped at 28 d and enteral glutamine and the modified diet were continued. The data are encouraging but need to be confirmed by other investigators. Vanderhoof et al. could not demonstrate effectiveness of GH and glutamine therapy in a rat short gut model *(44)*.

GH therapy has been studied in patients with gastric ulcer. In 1975, Winawer et al. reported improved survival in a small group of patients with severe hemorrhage from gastric stress ulcers *(45)*. Six of eight control patients died compared to two of eight GH-treated patients (10 mg/d for 4 to 18 d). The authors speculated there may have been a favorable effect of GH therapy on protein synthesis or fibroblast proliferation.

Other Effects of GH on Gastrointestinal Tract Physiology

Wa and Mineral Transport

GH appears to have actions in the gastrointestinal tract that are independent of its proliferative effects. GH increases water and sodium chloride absorption in the rat small intestine and colon *(11)*. A specific dose-dependent effect of GH on vitamin D-dependent calcium-binding protein in the hypophysectomized rat intestine has been reported *(46)*. Chipman et al. studied seven GH-deficient children before and after 5–14 mo of GH therapy *(10)*. Fractional intestinal absorption of calcium increased, serum 1,25 hydroxyvitamin D concentrations decreased, and serum parathyroid hormone, 24,25-hydroxyvitamin D, and 25-hydroxyvitamin D levels did not change. The authors suggested that GH therapy increased intestinal sensitivity to 1,25-hydroxyvitamin D. Increased intestinal calcium absorption has been described in patients with GH excess, which decreased with treatment of the acromegaly *(47)*.

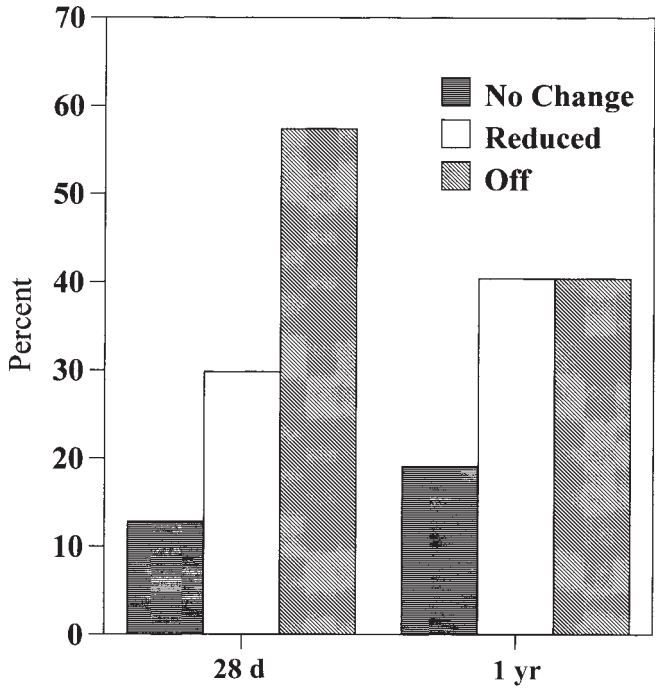

Fig. 3. The total parenteral nutrition (TPN) status of 47 patients with short bowel syndrome, initially dependent upon TPN, after 28 d of therapy with growth hormone, glutamine, and a high carbohydrate, low fat diet. The growth hormone was then discontinued and oral glutamine and the diet were continued. TPN status at approx 1 yr is shown. Figure modified from data originally presented by Byrne et al. *(15)*.

Amino Acid Transport

Exogenous GH given daily for 3 d prior to surgical resection, resulted in global increases in amino acid transport activity in human small intestinal brush border membrane vesicle preparations *(12)*. GH and IGF-1 have been shown to promote intestinal uptake of the amino acid glutamine in animal trauma/sepsis models. Glutamine is the preferred metabolic fuel for the small intestine *(48)*, essential for nucleic acid synthesis. Glutamine deficiency results in intestinal mucosal atrophy, which may cause loss of barrier function, increased permeability, and translocation of bacteria or bacterial products *(49,50)*. In the critically ill patient loss of mucosal barrier may lead to multiorgan failure *(51)*. Despite demonstration of increased glutamine uptake by the intestine in septic piglets treated with GH *(17)*, there has not been significant benefit of exogenous GH on outcome of moderately ill septic humans *(52,53)*.

Enteroendocrine Cell Function

GH has been demonstrated to increase enteroendocrine cell secretion in animals. GH stimulates both the gastrin and somatostatin contents of rat stomach *(21,22)*. Both serum and antral gastrin levels are reduced in hypophysectomized rats *(21)*, and growth of the gastric mucosa is partially restored by GH, but by no other pituitary hormone. Pentagastrin and GH cause similar increases in nucleic acid content of the pancreas and weight of the duodenum in hypophysectomized rats *(21,54)* The trophic effect of GH on the upper GI tract is thought to be at least partially mediated by gastrin in addition to IGF-1. The finding of GH receptors on chief and parietal cells of the stomach suggests that GH might have a regulatory role in the secretory products of these cells *(1)*. The chief cell secretes pepsinogen and intrinsic factor; the parietal cell secretes hydrochloric acid. Although GH deficiency results in decreased peptic activity in the rat, GH treatment did not restore peptic activity in this model *(55,56)*. In the dog, peptic activity was reported to increase with GH treatment *(57)*. Intrinsic factor is responsible for the binding and intestinal transport of cyanocobalamin (vitamin B12) before the complex attaches to the ileal intrinsic factor receptor. Mucosal intrinsic factor increased proportionately with the epithelial component of the mucosa in GH-deficient rats treated with GH *(56)*. GH-induced vitamin B12 availability might be necessary for ATP and thymidine production required for DNA synthesis and growth. While GH has been reported to increase gastric acid secretion in rats *(55)*, Nagano et al. could not demonstrate an effect of GH on basal or stimulated acid secretion in rabbit parietal cells *(3)*.

Hypophysectomy lowers basal plasma secretin levels but increases duodenal secretin stores in rats *(57)*. As GH reverses these effects, it has been suggested that GH may play a role in the release and metabolism of secretin *(58)*.

Hypophysectomy results in a decrease in RNA content, enzyme activity, and number of zymogen granules in salivary glands *(6)*. Localization of GH receptors on salivary glands and pancreatic acinar groups may reflect a specific role for GH in salivary gland secretion and pancreatic exocrine function. GH receptors have been identified on all cell types of the pancreatic islets, though predominantly on alpha and delta cells *(1)*. GH induces mitogenesis and has long-term effects on proliferation and insulin biosynthesis of pancreatic beta cells in culture *(59,60)*.

Cytochrome P450

GH increases expression of hepatic cytochrome P450 (specifically CYHP3A4) in human hepatocytes in cell culture *(61)*. This enzyme is important in the metabolism of many drugs (cyclosporin, midazolam, erythromycin, lidocaine, nifedipine) and steroid hormones. GH therapy increases clearance of theophylline and decreases clearance of amobarbitol in GH-deficient children, possibly reflecting alteration of specific P450 enzymes *(62)*. A potential effect of GH therapy on concurrent medical therapy, such as immunosuppressive agents, should be considered.

Conclusions

GH clearly has proliferative effects in the gastrointestinal tract, mediated primarily through stimulation of local

IGF-1 production. GH also appears to increase sodium chloride, water, calcium, and amino acid absorption in the gut. An effect of GH on enteroendocrine secretion is suggested by animal studies; however, physiologic significance is yet to be determined. GH may affect metabolism of other drugs through alteration of cytochrome P450 expression and, therefore, monitoring for such an effect seems prudent. The usefulness of exogenous GH therapy in augmentation of gut adaptation after massive intestinal resection is of great interest, but is preliminary and requires confirmation by other investigators. GH therapy to improve outcome in critical illness continues to be studied; however, at present no consistent improvement has been demonstrated.

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