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ORIGINAL ARTICLE

Effect of growth hormone on small intestinal homeostasis relation to cellular mediators IGF-I and IGFBP-3

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Abstract

AIM: To evaluate the effects of growth hormone (GH) on the histology of small intestines which might be related to the role of insulin like growth factor (IGF)-I, IGF-binding protein 3 (IGFBP-3) and its receptors.

METHODS: Twelve week-old adult male Wistar albino rats were divided into two groups. The study group (n = 10), received recombinant human growth hormone (rGH) at a dose of 2 mg/kg per day subcutaneously for 14 d and the control group (n = 10) received physiologic serum. Paraffin sections of jejunum were stained with periodic acid shift (PAS) and hematoxylin and eosin (HE) for light microscopy. They were also examined for IGF-I, IGFBP-3 and IGF-receptor immunoreactivities. Staining intensity was graded semi-quantitatively using the HSCORE.

RESULTS: Goblet cells and the cells in crypt epithelia were significantly increased in the study group compared to that of the control group. We have demonstrated an increase of IGF-I and IGFBP-3 immunoreactivities in surface epithelium of the small intestine by GH application. IGF-I receptor immunoreactivities of crypt, villous columnar cells, enteroendocrine cells and muscularis mucosae were also more strongly positive in the study group compared to those of in the control group.

CONCLUSION: These findings confirm the important trophic and protective role of GH in the homeostasis of the small intestine. The trophic effect is mediated by an increase in IGF-I synthesis in the small intestine, but the protective effect is not related to IGF-I.

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Key words: Growth hormone; Small intestine; Like growth factor-1; Insulin like growth factor binding protein 3

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INTRODUCTION

Growth hormone (GH) is a pituitary-derived polypeptide hormone that has diverse physiologic effects including the regulation of growth in long bones, carbohydrate, lipid metabolism, and metabolic functions of the liver[1]. The mitogenic effect of GH in the crypts of Lieberkuhn of the duodenum in hypophysectomized rats was first described by Leblond and Carriere in 1955[2]. Small intestine that is lined by epithelial cells with a rapid turnover rate has been considered as a potential target of GH[3,4]. Systemic administration of GH markedly increases trophic action in the small intestine and enhances the remnant bowel morphological and proliferative adaptation[3].

Circulating GH binds to the GH receptor (GHR) in

target cells and stimulates the production of insulin like growth factor (IGF)-I in the liver and other target tissues including the intestine. The GHR is expressed throughout the epithelium and in the lamina propria, muscularis mucosa, submucosa, and muscularis propria. The presence of GH receptors in crypt and villus epithelial cells of rats suggests a direct cellular effect of GH on small intestinal growth[5]. GH action has traditionally been believed to be mediated by GH dependent hepatic production of IGF-I. However, with the discovery of various extrahepatic IGF-I synthesis sites, some of which are GH dependent, a paracrine/autocrine mechanism of action has been proposed[6]. IGF-I receptors have also been immunolocalized in the gastrointestinal tract of rats[7,8]. Locally expressed IGF binding proteins (IGFBPs) are known to modulate IGF-I action. Of six known high-affinity IGFBPs, IGFBP-3 has been of interest with respect to a role in regulating intestinal growth. Systemically administered IGF-I is known to increase the expression of IGFBP-3 in rat small intestine[9] and colon[10], although there are segmental differences in the effects of circulating IGF-I on locally expressed IGFBPs, which correlate with segment-specific growth effects[9,10].

GH action is primarily mediated by IGF-I, although both growth factors show tissue-selective effects. Specific binding sites for IGF-I, and GH are present in the small intestine and evidence suggests that circulating IGF-I and GH can interact with their respective functional intestinal receptors[2,11,12]. GH administration stimulates mucosal growth in normal rats[2]. GH action has been attributed to be the result of both a direct effect of GH, and an indirect stimulating effect on the target cells *via* IGF-I released locally or from the liver[3]. Specific GH receptors (GHR), IGF-I receptors, and local production of IGF-I have been shown throughout the epithelial and mesenchymal derived elements of the gastrointestinal tract[4,5], implicating a complex interaction between direct and indirect effects of GH[12-14]. It has not yet been shown whether GH affects the small intestine directly or *via* IGF-I. Therefore, the objective of this study was to evaluate the morphological effects of GH on normal small intestines due to changes occuring in IGF-Rs and IGFBP-3 by administration of GH.

MATERIALS AND METHODS

The animal facilities and protocols used in the present study were approved by the Animal Research Ethics Committee of the University of Celal Bayar. This study was performed in the Department of Histology and Embryology and Department of Pediatrics, between 2001 and 2002. Twelve week-old adult male Wistar albino rats (250-300 g) were included in the study. All animals were kept under standard conditions on a 12 h light/dark cycle and maintained at optimal temperature. The animals were fed with a standard diet and given free access to water. They were randomized into two groups. The study group (n = 10) received recombinant human GH (Norditropin-Novo Nordisk, Denmark) at a dose of 2 mg/kg per day subcutaneously for 14 d and the control group (n = 10) received the same volume of serum physiologic intracutaneously. Anesthesia was achieved by intraperitoneal injection of pentobarbitone. Animals were perfused intracardiacally with phosphate buffered saline (PBS) and subsequently with 10% formalin solution. The antrum of the jejenum was dissected and postfixed in 10% formalin solution for 24 h at room temperature. The samples were washed overnight with tap water and were dehydrated through a graded series of ethanol. They were incubated in xylene and then embedded in paraffin. Serial sections (5 μm) were taken from both groups and collected onto gelatin-coated slides. Sections were deparaffinized at 60℃ overnight, immersed in xylene and rehydrated through a graded series of ethanol. They were then washed in tap water and stained using either histochemical (H-E or PAS) or immunohistochemical (IGF-I, IGF-R, IGFBP-3) methods according to their routine protocols. H-E or PAS stained slides were mounted using entellan covered with glass cover slips prior to viewing and photographed under the Olympus BX-40 (Olympus, Tokyo, Japan) light microscope. Morphometric parameters were measured by three blinded observers using the Olympus BX-40 microscope with a video camera (JVC-TK-C 601, Tokyo, Japan) for digital imaging. Villus height as a distance from the tip of the villus to the villus-crypt junction, total epithelial thickness, villus/crypt ratio, and the size and the number of goblet cell were measured at 15 sites of the jejunum[15,16].

An indirect immunofluorescence method was used to determine the immunoreactivities of IGF-I and IGFBP-3. Prior to preincubation in non-immune serum for 1 h, all slides were washed in PBS three times. Sections were then incubated with the primary antibody (Goat-anti-human IGF-I: DSL-2800 IRMA and anti-IGFBP-3; DSL-6600 IRMA, Diagnostic system Laboratories-Texas, USA) in a humid, sealed chamber at 4℃ for overnight. Slides were then washed three times in PBS and the site of antigen-antibody reaction was revealed by incubation with fluorescence isothiocyanate (FITC)-conjugated anti-goat diluted 1:100, for 2 h at 4℃. After incubation, sections were rinsed and mounted. Control staining included omission of the primary antibody and replacement with rabbit nonimmune serum. Sections were examined in a fluorescence microscope (Olympus, Tokyo, Japan) equipped with filter setting for viewing FITC fluorescence.

An indirect immunoperoxidase method was used to determine the immunoreactivity of IGF-I Receptor. Deparaffinized sections were washed with PBS and treated with 0.1% trypsin solution. After that, they were washed with PBS and treated with 0.3% hydrogen peroxide for 10 min at room temperature to inactivate endogenous peroxidase activity. These sections were then washed in PBS and they were incubated with the primary antibody mouse monoclonal anti-IGF-I Receptor diluted 1:100 (Calbiochem, CA, USA) in a humid chamber overnight at 4℃. They were then incubated with avidin-biotin-horseradish peroxidase complex (anti-mouse immunoperoxidase antibody: Universal DAKO LSAB2 Kit, CA, USA) for 1 h. The colour reaction was developed using AEC Substrate System-containing 3-amino-9-ethylcar-

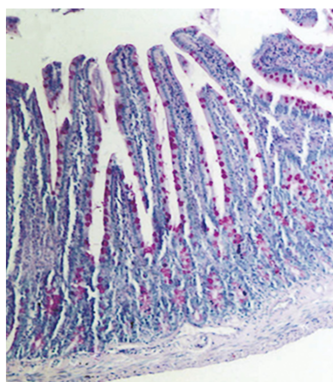

Figure 1 Photomicrograph of the tunica mucosa (M) and muscularis mucosa (MM) of the small intestine in the GH-administered group. Villous hypertrophy and increased goblet cells were seen in the small intestine. PAS, × 100 (Original magnification).

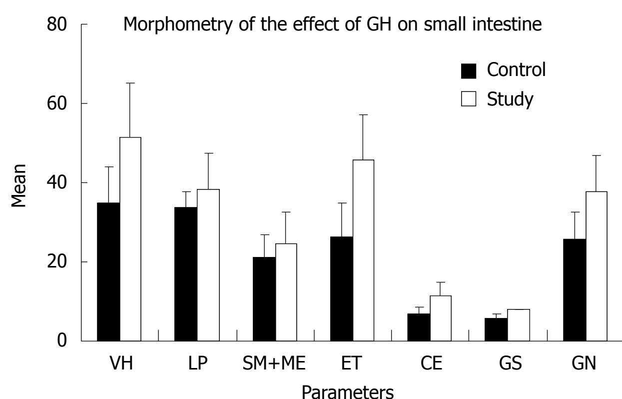

Figure 2 Morphometric criteria to determine the effects of growth hormone on small intestine. VH: The height of villus; LP: Lamina Propria; SM: Submucosa; ME: Muscularis externa; ET: Thickness of epithelium; CE: Crypt epithelial cell; GS: The size of goblet cell; GN: The number of goblet cells per villus. Height of the villi, epithelial thickness, and crypt epithelial cell number rats given GH were significantly increased (P < 0.01). The size and the number of goblet cells were also significantly increased (P < 0.05).

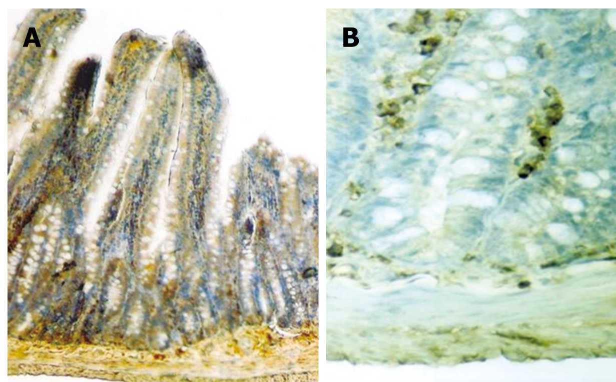

Figure 3 Like growth factor (IGF)-R immunoreactivity pattern in small intestines of the rats in the study group given growth hormone (A) and control group (B) by using the immuno-peroxidase technique. While weak to moderate IGF-R immunostaining was observed in the epithelial cells of the small intestines in the control group, an increase in the immunostaining was seen in the study group. Note the strong immunoreactivity in the epithelial component and the moderately immunostained smooth muscle of the muscularis mucosa. Goblet cells display little or no immunoreactivity, in contrast to the dense immunoreaction in columnar cells of the study group. × 100 (Original magnifications).

bazole (Dako, Glostrup, Denmark). Between each step, sections were washed three times in PBS. Sections were counterstained with Mayer's hematoxylin, dehydrated, and covered with mounting medium. Normal mouse serum was used as a negative control.

Three observers blinded to clinical information evaluated the immunohistochemical staining scores independently. Staining intensity was graded semi-quantitatively using the H-SCORE[17] which was calculated with the following equation: H-SCORE = $\sum$Pi (i + 1), where i = intensity of staining with a value of 1, 2 or 3 (mild, moderate, or strong, respectively) and Pi is the percentage of epithelial cells stained with different intensity, varying between 0%-100%. Results were expressed as mean ± SE. Differences between groups were statistically analyzed with one-way ANOVA. P value of < 0.05 was considered significant.

RESULTS

Histological examination

Rats that were given GH displayed hypertrophy in the small intestine (Figure 1). Height of the villi (34.9 ± 9.2 *vs* 51.6 ± 13.8), epithelial thickness (26.3 ± 8.3 *vs* 45.7 ± 11.7), and crypt epithelial cell number (6.7 ± 2.1 *vs* 11.4 ± 3.7) of these rats were significantly increased (P < 0.01). The size (5.7 ± 1.2 *vs* 7.8 ± 1) and the number (25.6 ± 6.8 *vs* 37.9 ± 9) of goblet cells were also significantly increased (P < 0.05). The morphometric results of the groups according to histologic criteria are shown in Figure 2.

Localization of IGF-R immunoreactivity

Immunohistochemical staining for the IGF-R showed specific staining in the crypts as well as the apical and basolateral membranes of villus epithelial cells of the control group. Immunoreactivity was primarily observed in the cytoplasm. All staining was similar to each other and they were considered to be of moderate intensity (++) staining. Crypt and villous columnar cells of the small intestine displayed moderate immunoreactivity, whereas goblet cells were weakly immunostained. No immunostaining was evident in occasional large goblet cells of the small intestine. Enteroendocrine cells of the intestinal mucosa were positively immunostained. Muscularis mucosae, muscularis externa and medial smooth muscle cells of vessels exhibited moderate immunoreactivity. Macrophages in the lamina propria and submucosa exhibited positive immunoreactivity in the control group (Figure 3).

There appeared to be a greater intensity of staining for the IGF-R in the study group compared with the control group, as shown in Figure 3 (intensity +++). Crypt epithelial cells and enteroendocrine cells of the intestinal mucosa were strongly positive immunostained (intensity +++). Weak or no immunostaining was evident in large goblet cells of the small intestine. Muscularis mucosae, muscularis externa and medial smooth muscle cells of vessels exhibited moderate immunoreactivity. Scattered macrophages in the lamina propria and submucosa exhibited intense immunoreactivity in the study group. There was also an increase in the intensity of IGF-R immunoreactivity as well as the number of

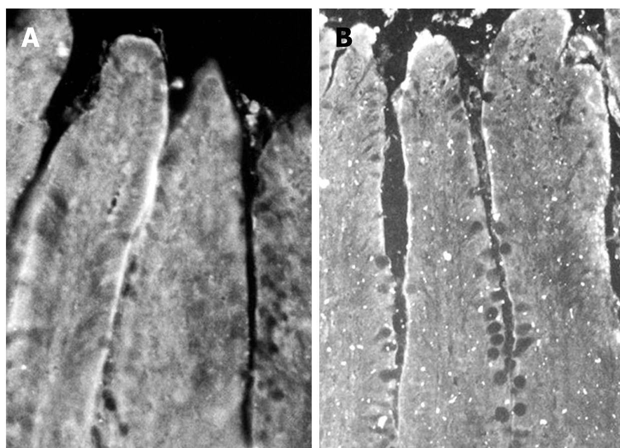

Figure 4 Immunoreactivity of IGF-I was seen in the small intestine of the control group (A) and the study group (B) by using an immunofluorescence technique. Increased immunoreactivity was seen in the study group. × 200 (Original magnifications).

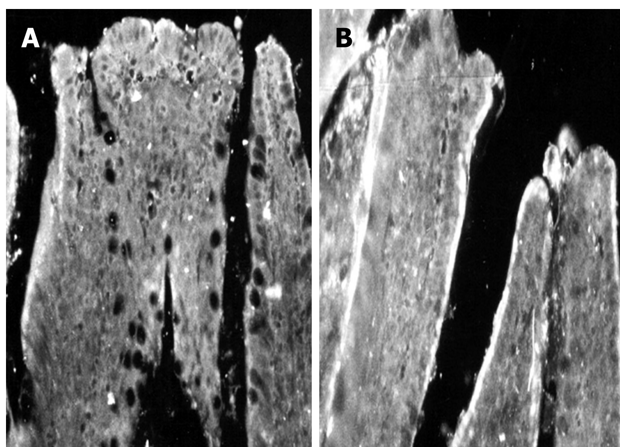

Figure 5 Immunoreactivity of IGF-binding protein 3 (IGFBP-3) was seen in the small intestines by using an immunofluorescence technique in the control group (A) and the study group (B). Increased immunoreactivity was seen in the study group. × 200 (Original magnifications).

immunoreactive cells in general. The morphometry of immunoreactivities is shown in Table 1.

Localizations of IGF-I and IGFBP-3 Immunoreactivity

In the control group, both the immunoreactivities of IGF-I (Figure 4A) and IGFBP-3 (Figure 5A) were considered moderate in the small intestine (intensity +/++, respectively). Immunoreactivity was mainly localized on the surface epithelium. Rats that were given GH showed a statistically significant ($P < 0.001$) increase in the immunoreactivities of IGF-I (Figure 4B, 85.33 ± 11.06 *vs* 195.00 ± 9.00) and IGFBP-3 (Figure 5B, 91.00 ± 16.82 *vs* 201.33 ± 18.04) which were determined by H-SCORE (Figure 6).

DISCUSSION

In our study, histological examination revealed an increase in the wall thickness, villus height and crypt cell proliferation of the small intestine after GH administration. Our findings have shown that systemic administration of GH increases intestinal growth by stimulating crypt cell production as has been reported by previous studies[10,17]. Trophic and promoting effects of GH on the small intestine as shown in human and animal studies have suggested that this peptide could be used in the treatment of patients with malabsorption and malnutrition caused by extensive disease or resection of the small bowel, as is the case in patients with the short bowel syndrome[10,17-19]. Exogenous GH has been particularly useful in gastrointestinal rehabilitation of patients with short bowel syndrome in some series[20-22], although not all[23].

In our study, a significant increase in the number of goblet cells was observed in the study group compared to that in the control group. Gastrointestinal epithelium is covered by a protective mucus gel composed predominantly of mucin glycoproteins which are synthesized and secreted by goblet cells[24]. This epithelium provides a barrier against potential injury threats of luminal acids, enzymes, bacteria and toxins[25]. This result suggests that GH could play a protective role on intestinal mucosa by increasing mucus-producing cells. A previous study has shown the protective effects of GH in rats receiving abdominal radiotherapy[26]. However, its functional role had not been clearly assessed *in vivo*.

Effects of GH could be mediated *via* the regulation of intermediate factors like IGF-I, the best known and most intensively studied among the factors. IGF-I is pro-

Table 1 Intensity of cellular localization of IGF-receptor in small intestines of the rats in the control and study groups

Cells	Control group	Study group
Crypt and villous columnar cells	+/++	+++
Enteroendocrine cells	++	+++
Goblet cells	-/+	-/+
Occasional large Goblet cells	-	-/+
Paneth cells	-	-
Muscularis mucosae and muscularis externa	++	+++

Weak immunostaining: +; Moderate immunostaining: ++; Strong immunostaining: +++. IGF: Like growth factor.

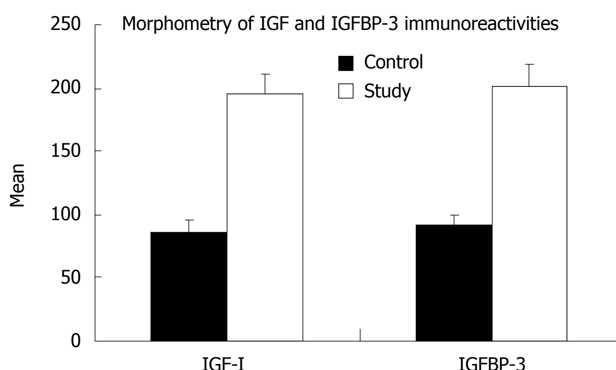

Figure 6 IGFBP-3 and IGF-I immunoreactivities in rat small intestine epithelium in the control and the study groups using the indirect immunofluorescence method. (Weak immunostaining: +; Moderate immunostaining: ++; Strong immunostaining: +++). In rats that were given growth hormone, there was a statistically significant increase in the immunoreactivities of IGF-I.

duced in the liver and other tissues in response to GH stimulation[27]. As expected, this had led the investigators to conclude that the local production and function of IGF-I were dependent on GH. However, it is now clear that IGF-I could have functions independent from GH. The results of our study have shown that IGF-I receptor immunoreactivity in crypt and villous columnar cells, enteroendocrine cells and muscularis mucosae was stronger in the study group compared to the control group. Immunoreactivity of Paneth cells was found negative and goblet cells displayed faint to moderate immunoreactivity. These results suggest that the effects of GH on crypt, villous columnar cell, enteroendocrine cells and muscularis mucosae can be mediated *via* IGF-I. In transgenic mouse studies, overexpression of the gene encoding IGF-I has been found to be associated with increased small bowel length, mucosal mass and crypt cell proliferation[28,29]. Wheeler *et al*[5] have shown that the effects of GH/IGF-I on crypt epithelial cell proliferation in human duodenal mucosa *in vitro*, were similiar to the effects of IGF-I alone and were greater than GH alone, suggesting an action mediated solely by IGF-I. Sigalet *et al*[30] had demonstrated significant alteration in intestinal morphology of the rat by IGF-I treatment. It has been shown that systemic administration of GH increases trophic activity of the small intestinal mucosa and enhances morphologic and proliferative adaptation of the remnant bowel after surgical resection, both through a direct effect *via* GH receptor present in the gastrointestinal tract and through augmentation of IGF-I synthesis and activity[31,32].

We found that goblet cells were weakly immunostained for IGF-I receptor both in the study and the control group. In another study that detected GH receptor, goblet cells showed faint to moderate immounoreactivity or were immunonegative[2]. These results suggested that GH could have direct effects on goblet cell proliferation of the rat small intestine. In the present study, enteroendocrine cells were positive for IGF-I receptor immunostaining in small intestines of rats given GH which may stimulate local or systemic IGF-I production. In addition to its trophic action, IGF-I receptor appears to be extremely important not only for IGF-I but also for modulation of the effects of other growth factors[33,34]. Overexpression of IGF-I receptor may promote trophic actions of other growth factors on small intestinal mucosa. Moreover, IGF-I, due to its trophic action, may increase the secretion of gastrointestinal hormones from enteroendocrine cells.

GH increases circulating levels of IGF-I and seems to enhance IGF-I expression locally in the intestinal mucosa[35]. A characteristical feature of IGF-I is its ability to bind high affinity IGFBPs which are thought to modulate its actions[9,36]. One of the major functions of IGFBPs is to control access to the receptors and consequently to modulate biologic responses of cells to IGF-I. IGFBP-3 has the highest affinity for IGF and is the most abundant IGFBP in plasma[6]. In this study, an increase in the immunoreactivities of IGF-I and IGFBP-3 were observed in small intestines of GH-administered rats. This result suggested that GH causes an increase in both IGF-I and IGFBP-3 production in the small intestine. The plasma concentration of IGFBP-3 is regulated by GH. IGFBP-3 concentration that is low in GH deficient patients increases with GH treatment[6,36]. This increase is attributed to a direct effect of GH on IGFBP-3 synthesis as well as the prolongation of the half-life of IGFBP-3 by binding to other proteins[7]. Systemic administration of GH may cause binding of IGF-I and IGFBP-3 to microvilli on the small intestinal epithelium of rats and may increase their synthesis directly. Thus, IGFBP3 may regulate tissue localization, distribution and access to IGF-I receptor that modulates the cell response to IGF-I.

Indeed, even in GH transgenic animals, only transient effects of GH excess on crypt proliferation were observed at weaning and were not sustained in adult animals despite maintained increases in mucosal mass through adulthood. This contrasts with IGF-I, in which a majority of studies in IGF-I transgenic mice and multiple in vivo models of IGF-I induction, including TPN and resection models, have demonstrated potent trophic actions of IGF-I accompanied by proliferative and anti-apoptotic actions. While these trophic actions of IGF-I may be beneficial to increase the mass of functional intestinal mucosa, they may also increase the risk of intestinal tumors. Despite the long-held view that GH is a trophic hormone and the proliferative effects of which are mediated by IGF-I, evidence in the healthy intestine suggests that IGF-I is a more potent enterotrophic factor than GH. This is found even when GH elevates plasma IGF-I to levels similar to those found in models of IGF-I infusion. Available evidence has suggested that the local expression of IGF-I occurs primarily in mesenchymal cells of the lamina propria of the normal intestine. IGF-I also has autocrine actions that increase the proliferation and growth of mesenchymal cells. Collectively, these results suggest that IGF-I derived from intestinal mesenchymal cells regulates the growth and function of neighboring epithelial cells, as well as mesenchymal cells themselves. Further support for this hypothesis comes from observations that levels of local IGF-I mRNA expression correlate with bowel growth during periods of altered nutrient status, resection, and disease[3,4,37].

In summary, systemic administration of GH has caused proliferation of crypt epithelial cells, goblet cells and enteroendorine cells in the small intestinal mucosa of rats. The number of IGF-I receptors in small intestinal mucosa, particularly in crypt epithelial and enteroendocrine cells, was increased. However, there was not an increase in the number of IGF-I receptors in goblet cells. Increases observed in mucosal height may be mediated through local rather than systemic IGF-I production, as IGF-I and IGFBP-3 were found to increase in rats' small intestine particularly in the surface epithelium. Increased IGF-I expression has been observed after GH administration and GH exerts some of its effects through stimulation of IGF-I and IGFBP-3 expression. GH improved villous morphology and small intestine homeostasis by affecting the cells through mediators. These

findings provide a basis for further studies on the role of GH in the regulation of gastrointestinal function and growth, in health and in colorectal diseases.

In conclusion, GH exerts trophic and protective effects on small intestinal mucosa by increasing IGF-I synthesis. It seems to exert its trophic actions *via* IGF-I by increasing number of IGF-I receptors on crypt and epithelial cells. IGF-I by itself does not have a role in protective action. Further research into the mechanism of action of GH and IGF-I is also needed to fully define the clinical appropriateness of these growth factors in particular settings.

COMMENTS

Background

Growth hormone (GH) has a lot of diverse physiologic effects. Systemic administration of GH markedly increases trophic action in the small intestine. The peripheral effects of GH are mediated by IGF-1. IGFBP-3 is a GH-dependent molecule and can be an important indicator of conditions associated with altered GH secretion and action. It is not known whether effects of GH on small intestine are direct or mediated *via* IGF-1.

Research frontiers

To demonstrate histologic changes induced by GH in the small intestine and to define mechanisms of trophic and protective effects of GH on small intestine.

Innovations and breakthroughs

This is the first study reporting the importance of IGF-1 as a mediator for protective and trophic effects of GH on small intestines. The authors' study demonstrated that trophic effects are related to IGF-1 while protective effects are not.

Applications

Better understanding of trophic and protective effects of GH on small intestines provide researchers with an opportunity to observe the effectiveness of treatment of intestinal diseases like small bowel syndrome. Also IGF-1 treatment may be considered as a therapeutic option in such diseases.

Peer review

The authors evaluate the effects of growth hormone on the histology of small intestines which might be related to the role of IGF-I, IGF-bindingprotein 3 (IGFBP-3) and its receptors. They find trophic effect is mediated by an increase in IGF-I synthesis in small intestine, but the protective effect is not related to IGF-I.

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