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• BRIEF REPORTS •

Expression of growth hormone and its receptor in chronic atrophic gastritis and its clinical significance

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Abstract

AIM: To investigate the growth hormone (GH) and growth hormone receptor (GHR) expression of and its clinical significance in patients with chronic atrophic gastritis (CAG).

METHODS: A total of 90 cases were enrolled in the study. Thirty were healthy controls, the other 60 patients were divided into two groups according to the endoscopical and histological diagnosis. Blood samples were drawn in the morning (menarche did not occur during the blood extraction in female patients), gastric mucosa was obtained by endoscopy. Serum GH and gastrice mucosal GHR levels were measured using radioimmunoassay (RIA) and En Vinsion technique.

RESULTS: The average GH level was 1.021±0.132 μg/L in CAG patients, in controls it was 2.869±0.512 μg/L. There was a significant difference between these two groups (P<0.01). The positive rate of GHR in CAG patients was 10%, in controls the rate was 100%. There was a significant difference (P<0.01). There was no significant change of GH level (3.176±0.421 μg/L) in patients with gastric carcinoma compared with controls (P>0.05).

CONCLUSION: The study shows that levels of GH and GHR expression are low in CAG patients. CAG pathogenesis has a correlation with mucosal nutrient deficiency, decreased levels of GH and GHR have an adverse effect on the repair and regeneration of CAG. There is no significant change of GH in gastric carcinorma patients, GH dose not play a role in the pathogenesis of gastric cancer.

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INTRODUCTION

Growth factor family is a group of protein hormones discovered during the 20th century. This family includes growth hormone (GH), insulin-like growth factor (ILGF), epidermal growth factor (EGF), transfer growth factor (TGF), and vascular endothelial growth factor (VEGF), *etc*. These factors can stimulate cell DNA, RNA and protein synthesis, control cell growth and differentiation, and promote regeneration of injured epithelia[1-7]. Studies in recent years have shown that there is an intimate relationship between growth factor and gastric mucosal disease[6]. Growth hormone (GH) is a type of monopeptide strain hormone released from anterior pituitary eosinophilic cells. In the gastrointestinal (GI) tract, GH is known to promote water and electrolyte transport and calcium absorption. The proliferative functions of GH have been reported as well. Administration of GH restores the intestinal and gastric mucosal weight after hypophysectomy in rats, it is regarded as an important nutrient factor[8].

Chronic atrophic gastritis (CAG) is a gastric precancerous lesion and has a high morbidity in China[9]. Gastric mucosal malnutrient is considered as an important factor in the pathogenesis of CAG[10-13].

Since CAG was recognized as a precancerous condition of the stomach by the World Health Organization in the early 1980 s, a number of methods have been tested for their ability to reverse and prevent the development of cancer. Most gastric mucosa protectors promote the growth and repair of gastric mucosa by promoting the aggregation and secretion of growth factors such as EGF, TGF. In a previous animal study, GH/GHR expression was measured on atrophic gastritis rats. The levels of GH and GHR expression in rats with CAG were low[14]. However, the effect and safety of GH in clinical use are uncertain in CAG. The purpose of the present study was to investigate the expression of GH/GHR in patients with CAG and gastric cancers.

MATERIALS AND METHODS

Research subjects

Ethical approval for this study was given by the Sir Run Run Shaw Hospital in May 1999. Clinical data were obtained by review of case records for all patients. Patients were selected at random from adult out-patients attending the gastroenterology clinics. Diagnosis was made on the basis of clinical, endoscopical and histological data according to standard criteria. We excluded the patients who had abnormal findings in other vital organs (such as the heart, liver, lung, pancreas and pituitary). Patients were divided in two groups. Thirty patients in group B were diagnosed as moderate-severe gastritis and 30 patients in group C were diagnosed as gastric cancer, 30 unrelated individuals served as controls. Characteristics of the research subjects are shown in Table 1.

Sample collection and processing

After an overnight fast, 3 mL of blood was taken from cubital vein. Blood samples were set for two hours, then centrifuged at 3 500 rpm for 15 min. Supernatant was saved and stored at -20 ℃. Two samples were taken from gastric antrum tissue and two from gastric body tissue, or four from the primary focus, and immediately immersed in 10% buffered formalin and embedded in paraffin wax using standard techniques. Five μm thick sections were cut and stained with hematoxylin and eosin for histopathological analysis. Each slide was assessed.

Analytical methods

The level of serum GH was measured by radioimmunoassay

(RIA) (Reagents were from DPC Company in Tianjing). The detection of gastric mucosal GHR expression was carried out by immunohistochemistry and En Vinsion assay (reagents from Biogenesis Company).

Table 1 Base-line characteristics of the patients

Characteristic	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)
Age (yr)	48±7	50±6	52±9
Male	19	17	20
Female	11	13	10
Endoscopical finding	normal gastric mucosa	chronic atrophic gastritis(CAG)	gastric cancer
Pathologic finding	mild superficial gastritis(non-active)	moderate-severe CAG with or without intestinal malplasia	gastric cancer

Statistical analysis

Concentrations of serum GH were expressed as mean±SD. Differences between the two groups were evaluated by *t*-test. Significance was shown as $P<0.05$. The expression of GHR was expressed as positive rate. Differences between groups were evaluated by χ^2 test. Significance was shown as $P<0.05$. All experimental data were analyzed with Spss-pc+ software.

RESULTS

The average level of serum GH was lower in group B than in groups A and C. There were significant differences between them, but there was no significant difference between groups A and C.

Table 2 Serum GH Level (ng/mL) in the studied groups (mean±SD)

Group	A group (n = 30)	B group (n = 30)	C group (n = 30)
GH level	$2.869\pm0.512^{1,2}$	1.021 ± 0.132^{1}	3.176 ± 0.421^{2}

$^{1}t_{AB} = 3.135$ $P<0.01$ $^{1}t_{BC} = 3.537$ $P<0.01$ $^{2}t_{AC} = 1.893$ $P>0.05$.

Table 3 Positive rate of gastric mucosal GHR expression in the studied groups (%)

Group	A group (n = 30)	B group (n = 30)	C group (n = 30)
GHR expression	100 (30/30)[1]	10 (3/30)[2]	13 (4/30)[1,2]

$^{1}\chi^2_{AB}=49$ $P<0.01$ $^{1}\chi^2_{AC}=45$ $P<0.01$ $^{2}\chi^2_{BC} = 0.16$ $P>0.05$.

The positive rate of gastric mucosal GHR expression in groups B and C was lower than that in group A. There were significant differences between them, but there was no difference between groups B and C.

DISCUSSION

Growth hormone (GH) is a type of monopeptide strain hormones released from anterior pituitary eosinophilic cells. Growth hormone receptor (GHR) is widely distributed in the gastrointestinal tracts. GH takes its effect on target tissues by combining with GHR. In the stomach, GHR is mainly distributed among parietal and chief cells. In 1995, Nagano *etc* by using reverse transcription PCR technology and Southern blot analysis, found the wide distribution of GHR in the gastrointestinal tract especially in epidermal cells, suggesting that GH and GHR could play an important role in the regulation of metabolism, growth, and differentiation of gastric mucosal cells. GH and GHR could improve protein synthesis, promote wound healing, stimulate gastrointestinal tract proliferation and repair, regulate immunological responses, and improve absorption of nutrients[8]. Presently, clinical applications of recombinant human growth hormone (rhGH) in various gastrointestinal ailments such as malabsorption and short bowel syndrome were reported[15-19].

Chronic atrophic gastritis (CAG) is a gastric precancerous lesion and listed as the first of cancer prevention by WTO. CAG pathogenesis has a correlation with mucosal nutrient deficiency. CAG patients had a decreased serum level of trace elements and beta-carotene with malnutrition[20-21].

During the last several years, we have focused on exploring the correlation between CAG and GH. In a previous animal study, we measured the GH/GHR expression in atrophic gastritis rats, and found the levels of GH and GHR expression in rats with CAG were rather low. After removing the pituitary glands from rats, Crean GP discovered that there were gastric mucosal atrophy, shrinkage and decreased expression of parietal and chief cells. Increased secretion of gastric acid and pepsin, and exogenous GH have been shown to promote protein synthesis and increase gastrointestinal absorption of nutrients. We have considered using GH to treat CAG[14].

Our present study showed the same results as before[14]. The levels of GH/GHR expression in patients with CAG were significantly lower than normal. GH and GHR could regulate the metabolism, growth and differentiation of gastrointestinal epidermal cells, therefore, a decreased GH/GHR level would hinder the repair and recovery of CAG. Decreased levels of GH and GHR had an adverse effect on the progression of CAG. This study suggests that when CAG is treated, GH or GH-like drugs may be considered in the treatment regimen to promote mucosal repair and stop the progression of CAG.

Exogenous GH has been shown to significantly increase the expression of c-myc oncogene[22]. Watanabe *et al*.[23] showed that by using N-methyl-N-nitrosourea solution to induce gastric cancer in F344 rats, GH levels were elevated, suggesting that high concentrations of GH play a role in the pathogenesis of gastric cancer. Studies have shown that acromegalic patients, had an increased risk of developing gastrointestinal tumor and carcinoma[24-28]. Therefore, cautions should be taken to monitor the possibilities of gastrointestinal cancers. Whether clinical usage of growth hormone and medicine which stimulates the release of growth hormone causes the carcinogenesis of atrophic gastritis is concerned. Our study showed that the serum GH level in gastric cancer patients and normal individuals was similar, the positivity rate of GHR expression was not high, suggesting that GH dose not play a role in the development of gastric cancer. Lobie *et al*.[29] investigated the effect of GH on gastric structure and function in GH-deficient Lewis (dwarf) rats, Bovine GH (65 micrograms/100 g body wt), was administered twice daily to adult male dwarf rats for 6 d (DW+) while control animals received vehicle only (DW-). Administration of GH produced a significant increase in body ,stomach wt and stomach to body wt ratio. GH administration also resulted in an increase of total gastric DNA, RNA, and protein. The density of differentiated (parietal and chief) cell types was not significantly different in DW- and DW+ animals. They demonstrated that GH could stimulate proliferation and enlargement of the gastric mucosae without significant alterations in cellular composition. So we recommend using GH as a treatment agent for CAG, but a definite conclusion needs further clinical observations.

REFERENCES

1 **Arzt E**, Pereda MP, Castro CP, Pagotto U, Renner U, Stalla GK. Pathophysiological role of the cytokine network in the an-

terior pituitary gland. *Front Neuroendocrinol* 1999; **20**: 71-95
2 **Li HW**, Wang JB. Study on TGFβ_1, TGFβ_2, TGFβ_3 expression in the chick basilar papilla following gentamicin toxicity. *Lingchuang Erbiyanhouke Zazhi* 1998; **12**: 463-465
3 **Shirakata Y**, Komurasaki T, Toyoda H, Hanakawa Y, Yamasaki K, Tokumaru S, Sayama K, Hashimoto K. Epiregulin, a novel member of the epidermal growth factor family, is an autocrine growth factor in normal human keratinocytes. *J Biol Chem* 2000; **275**: 5748-5753
4 **Kobayashi T**, Hashimoto K, Okumura H, Asada H, Yoshikawa K. Endogenous EGF-family growth factors are necessary for the progression from the G1 to S phase in human keratinocytes. *J Invest Dermatol* 1998; **111**: 616-620
5 **Zushi S**, Shinomura Y, Kiyohara T, Miyazaki Y, Tsutsui S, Sugimachi M, Higashimoto Y, Kanayama S, Matsuzawa Y. Role of heparin-binding EGF-related peptides in proliferation and apoptosis of activated ras-stimulated intestinal epithelial cells. *Int J Cancer* 1997; **73**: 917-923
6 **Abe S,** Sasano H, Katoh K, Ohara S, Arikawa T, Noguchi T, Asaki S, Yasui W, Tahara E, Nagura H, Toyota T. Immunohistochemical studies on EGF family growth factors in normal and ulcerated human gastric mucosa. *Dig Dis Sci* 1997; **42**: 1199-1209
7 **Ono I**, Gunji H, Zhang JZ, Maruyama K, Kaneko F. Studies on cytokines related to wound healing in donor site wound fluid. *J Dermatol Sci* 1995; **10**: 241-245
8 **Nagano M**, Chastre E, Choquet A, Bara J, Gespach C, Kelly PA. Expression of prolactin and growth hormone receptor genes and their isoforms in the gastrointestinal tract. *Am J Physiol* 1995; **268**(3 Pt 1): G431-G442
9 **Pan GZ**, Chao SZ, Liu TH, Lu XH, Chen YF, Chen SP. Contemporary Gastroenterology. 1st ed. Beijing: *Science Pub* 1998: 991
10 **You WC**, Blot WJ, Li JY, Chang YS, Jin ML, Kneller R, Zhang L, Han ZX, Zeng XR, Liu WD. Precancerous gastric lesions in a population at high risk of stomach cancer. *Cancer Res* 1993; **53**: 1317-1321
11 **Fukao A**, Hisamichi S, Ohsato N, Fujino N, Endo N, Iha M. Correlation between the prevalence of gastritis and gastric cancer in Japan. *Cancer Causes Control* 1993; **4**: 17-20
12 **Jin GQ**, Yao JS, Jiang YN, Zhu HW, Ye YG, He MJ, Xiao SD. Observasion on gastric mucosa of the healthy elderly. *Zhonghua Xiaohua Zazhi* 1984; **4**: 18-19
13 **Krasinski SD**, Russell RM, Samloff IM, Jacob RA, Dallal GE, McGandy RB, Hartz SC. Fundic atrophic gastritis in an elderly population. Effect on hemoglobin and several serum nutritional indicators. *J Am Geriatr Soc* 1986; **34**: 800-806
14 **Cao Q**, Si JM, Li XL. GH/GHR expression on atrophic gastritis in rats. *Zhonghua Xiaohua Zazhi* 2001; **21**: 627-628
15 **Jeppesen PB**, Mortensen PB. Enhancing bowel adaptation in short bowel syndrome. *Curr Gastroenterol Rep* 2002; **4**: 338-347
16 **Zhu WM**, Li N, Ren JA, Gu J, Jiang J, Li JS. Rehabilitation therapy for short bowel syndrome. *Chin Med J* 2002; **115**: 776-778
17 **Scolapio JS**. Treatment of short-bowel syndrome. *Curr Opin Clin Nutr Metab Care* 2001; **4**: 557-560
18 **Gu Y**, Wu ZH, Xie JX, Jin DY, Zhou HC. Effects of growth hormone (rhGH) and glutamine supplemented parenteral nutrition on intestinal adaptation in short bowel rats. *Clin Nutr* 2001; **20**: 159-166
19 **Ukleja A**, Tammela LJ, Lankisch MR, Scolapio JS. Nutritional support for the patient with short-bowel syndrome. *Curr Gastroenterol Rep* 1999; **1**: 331-334
20 **Bukin YV**, Zaridze DG, Draudin-Krylenko VA, Orlov EN, Sigacheva NA, Dawei F, Kurtzman MYA, Schlenskaya IN, Gorbacheva ON, Nechipai AM. Effect of beta-carotene supplementation on the activity of ornithine decarboxylase (ODC) in stomach mucosa of patients with chronic atrophic gastritis. *Eur J Cancer Prev* 1993; **2**: 61-68
21 **Palli D**, Decarli A, Cipriani F, Forman D, Amadori D, Avellini C, Giacosa A, Manca P, Russo A, Salkeld RM. Plasma pepsinogens, nutrients, and diet in areas of Italy at varying gastric cancer risk. *Cancer Epidemiol Biomarkers Prev* 1991; **1**: 45-50
22 **Murphy J**, Bell GI, Friesen HG. Growth hormone stimulates sequential induction of c-myc and insulin-like growth factor I expression *in vivo*. *Endocrinology* 1987; **120**: 1806-1812
23 **Watanabe H**, Fujimoto N, Kawamoto K, Ando Y, Yamada K, Okamoto T, Kanin GN, Ito A. Elevated serum growth hormone accelerates gastric tumorigenesis in F344 rats after treatment with N-methyl-N-nitrosourea in their drinking water. *Jpn J Cancer Res* 1995; **86**: 631-637
24 **Ezzat S**, Strom C, Melmed S. Colon polyps in acromegaly. *Ann Intern Med* 1991; **114:** 754-755
25 **Pines A**, Rozen P, Ron E, Gilat T. Gastrointestinal tumors in acromegalic patients. *Am J Gastroenterol* 1985; **80**: 266-269
26 **Asai K**, Shimoyama S, Sanno N, Kaminishi M, Oohara T. A rare case of gastric cancer in an acromegalic patient. *J Gastroenterol* 1997; **32**: 528-532
27 **Kojima K**, Miyake M, Nakagawa H, Yunoki Y, Ogurusu K, Saino S, Wani T, Kawaguchi Y. Multiple gastric carcinoids and pituitary adenoma in type A gastritis. *Intern Med* 1997; **36**: 787-789
28 **Papotti M**, Cassoni P, Volante M, Deghenghi R, Muccioli G, Ghigo E. Ghrelin-producing endocrine tumors of the stomach and intestine. *J Clini Endocrinol Metab* 2001; **86**: 5052-5059
29 **Lobie PE**, Garcia-Aragon J, Waters MJ. Growth hormone (GH) regulation of gastric structure and function in the GH-deficient rat: up-regulation of intrinsic factor. *Endocrinology* 1992; **130**: 3015-3024

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