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• BASIC RESEARCH •

# Gastrin, somatostatin, G and D cells of gastric ulcer in rats

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## Abstract

AIM: **To investigate the relationship among gastrin, somatostatin, G and D cells in gastric ulcer and in its healing process in rats.**

METHODS: **Fourty-nine Wistar rats were divided into 7 groups. The gastric ulcer model was induced by acetic acid successfully. The gastrin and the somatostatin in rat plasma, gastric fluid and antral tissue were measured by radioimmunoassay(RIA). G and D cells in antral mucosa were analyzed with polyclonal antibody of gastrin and somatostatin by immunohistochemical method and Quantimet 500 image analysis system.**

RESULTS: **In gastric ulcer, the level of gastrin in plasma, gastric fluid, and antral tissue increased, that of somatostatin declined, and the disorder gradually recovered to the normal level in the healing process. Immunohistochemical technique of G and D cells in antral mucosa demonstrated that the number of G cells increased and that of D cells decreased, both areas of G and D cells declined, the ratio of number and area of G/D increased in gastric ulcer, and the disorder gradually recovered in the healing process.**

CONCLUSION: **In gastric ulcer, the increased gastrin secreted by G cells, the declined somatostatin secreted by D cells, and the disordered G/D cell ratio can lead to gastrointestinal dysfunction.**

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## INTRODUCTION

Gastrin is secreted in G cells, while somatostatin is secreted in D cells. Gastrin, somatostatin and other gastrointestinal hormones regulate the function of gastrointestinal tract such as secretion, movement, absorption, circulation and nutrition of cells[1-12]. The nerve system and the endocrine system participate in the healing process of gastric ulcer and regulate the absorption of inflammantory filtration, hyperplasia of granulation tissues, and regeneration of epithelial tissues. Obvious regular change takes place in many endocrine tissues[13-24]. In order to investigate the relationship between gastrin, somatostatin, G and D cells in the period of gastric ulcer and its healing process in rats, the gastrin and somatostatin in plasma, gastric juice and antral tissue were tested in rats. At the same time, the number of G and D cells was measured in the antral mucosa.

## MATERIALS AND METHODS

### *Animal*

Forty-nine healthy male Wistar rats weighing from 200g to 260g were obtained from the Experimental Animal Center of Sun Yat-Sen University of Medical Sciences. The rats were divided into seven experiment groups: 4, 7, 10, 14, 21, 28d groups, and a control group. The rats of six experimental groups were anesthetized with 30g·L$^{-1}$ sodium pentobarbital intraperitoneally at a dose of 30mg·kg$^{1}$. The abdomen was opened and its stomach was found, 0.05mL acetic acid was injected into rat's antral tissues. Omentum majus and antral tissue of the injection site were stitched. The peritoneum, parietal abdomen and ventral muscle, and skin were stitched continually. After operation, the rats were raised separately, and fasted overnight with free access to water one day before sacrifice. No treatment was given to normal control group.

### *Plasma sampling*

The rats' abdomen and chest chambers were opened and 4mL blood was directly withdrawn from the heart ventricle. Fourty μL(500u) aprotinin (Livzon Libao Biochemical & Pharmacertical Co. Ltd) and 60μL of 100g·L$^{-1}$ EDTA was added to each blood sample. The samples were centrifuged at 3500r.min$^{-1}$ for 15min to obtain plasma. The plasma samples were then stored at -70℃ until assay.

### *Gastric juice*

After the rats' abdomen was opened, a plastic catheter was inserted into the stomach through pylorus and another catheter was inserted through oral cavitas and esophagus into stomach. Two mL saline(pH7.0, 35℃) was infused into the stomach at a flow velocity of 12mL/h. The gastric fluid was collected and 40μL(500u) aprotinin was added. The samples were centrifuged at 3500r.min$^{-1}$ for 15 minutes to obtain gastric fluid. The gastric fluid samples were then stored at -70℃ until assay.

### *Antral mucosa*

The rats' stomach was separated and was split from the greater curvature of stomach. The antral tissues in the ulcer area and non-ulcer area were separately taken with ophthalmic scissors. The tissue was quickly weighed by an electric analytical balance and was boiled in a microwave stove. The boiled tissue was homogenized into homogenate in a homogenizer with 1mL of 1mol.L$^{-1}$ acetic acid. Then 1mL of 1mol.L$^{-1}$ NaOH was added to neutralize it. The homogenate was centrifuged at 3500r.min$^{-1}$ for 15 minutes and the supernatant was collected. The samples were then stored at -70℃ until assay. The stomach was separated and was split from the greater curvature of stomach. About 1.0×0.5cm antral tissues in the ulcer area and non-ulcer area was separately taken with ophthalmic scissors. The specimen was fixed in 100mL·L$^{-1}$ neutrally buffered formalin. It was embedded with paraffin 24h later and was serially sectioned at 4μm. The sections were mounted onto histostick-coated slides. Adjacent ribbons were collected for immunohistochemical staining.

### *Measurement of gastrin and somatostatin*

Gastrin and somatostatin were detected by using RIA method. The gastrin kits were purchased from Tianjin Qianye Biotech Co. Ltd, and the somatostatin kits were bought from the Department of Neurobiology of the Second Military Medical University. Measurement procedures were performed according to the instruction attached to the kits. The unit of result of plasma and gastric fluid was transformed to $ng \cdot L^{-1}$, while the unit of result of antral mucosa tissue to $ng \cdot g^{1}$.

### *Immunohistochemical staining for G and D cells*

The anti-gastrin antibody(Sigma Co. USA) and anti-somatostatin antibody(GYMED Co. USA) were used and immunohistochemical staining for G and D cells was performed with the strept-avidin-biotin-peroxidase complex(SABC)(Wuhan Boster Biological Technology Co. Ltd), negative control sections were normal serum blocking and PBS instead of the primary antibody. Images of 5 views randomly selected under microscope(10×40) from each anti-gastrin immunohistochemical staining section were input into the Quantimet 500 image analysis system(Leica Co, Germany). The number and area of G cells were calculated by the computer. The mean number and area of G cells in 5 views of the section served as the number and area of G cells of a section. That of D cells was calculated in the same way as the G cells. The ratio of G/D number and G/D area was acquired by separately dividing the number of G cells and the area of G cells by the number of D cells and the area of D cells in adjacent sections.

### *Statistical analysis*

The result of quantitative data was expressed as mean±SE. Data was analyzed using the variance analysis(ANOVA). Post hoc analysis between factors was performed using least significant difference test. Unpaired data was compared using the Wilcoxon ranksum test and correlated using Pearson's correlation.

## RESULTS

The concentration of gastrin and somatostatin in the plasma, gastric juice, antral mucosa is shown in Tables 1 and 2. The number and area of G and D cells in the rat antral mucosa, and the ratio of G/D number and G/D area is shown in Table 3. The relationship between rat G and D cells, and the relationship between G or D cells with gastrin or somatostatin are shown in Table 4.

**Table 1** Gastrin concentration in rat plasma, gastric juice, and antral mucosa ($\bar{x}\pm s$, $n$=7)

| Group | Plasma($ng \cdot L^{-1}$) | Gastric juice($ng \cdot L^{-1}$) | Ulcer mucosa($ng \cdot g^{-1}$) | Non-ulcer mucosa($ng \cdot g^{-1}$) |
|---|---|---|---|---|
| Control | 147±41 | 44±15 | - | 3.7±1.1 |
| 4d | 397±130[a] | 56±16 | 2.0±0.7 | 6.7±2.3[a] |
| 7d | 364±91[a] | 114±34[a] | 1.3±0.4[b] | 6.1±1.8[a] |
| 10d | 255±87[a] | 60±20 | 2.3±0.8 | 1.9±0.7[a] |
| 14d | 238±88 | 45±21 | 1.9±0.7 | 1.1±0.4[a] |
| 21d | 211±65 | 44±17 | 1.3±0.4[b] | 1.1±0.7[a] |
| 28d | 216±95 | 60±18 | 1.5±0.5 | 1.5±0.3[a] |

[a]$P$<0.05, *vs* control group. [b]$P$<0.05, *vs* 4d group.

**Table 2** Somatostatin concentration in rat plasma, gastric juice, and antral mucosa ($\bar{x}\pm s$, $n$=7)

| Group | Plasma($ng \cdot L^{-1}$) | Gastric juice($ng \cdot L^{-1}$) | Ulcer mucosa($ng \cdot g^{-1}$) | Non-ulcer mucosa($ng \cdot g^{-1}$) |
|---|---|---|---|---|
| Control | 45±12 | 64±16 | - | 1.4±0.4 |
| 4d | 13±5[a] | 46±15[a] | 0.3±0.1 | 0.4±0.1[a] |
| 7d | 22±8[a] | 42±15[a] | 0.3±0.1 | 0.4±0.2[a] |
| 10d | 41±9 | 54±17 | 0.2±0.1 | 0.8±0.2[a] |
| 14d | 33±8[a] | 54±12 | 0.9±0.4[b] | 1.3±0.4 |
| 21d | 32±9[a] | 49±12 | 1.1±0.2[b] | 1.1±0.4 |
| 28d | 35±10[a] | 51±20 | 1.1±0.3[b] | 1.1±0.3 |

[a]$P$<0.05, *vs* control group. [b]$P$<0.05, *vs* 4d group.

**Table 3** Number and area of G and D cells, and the ratio of G/D number and G/D area ($\bar{x}\pm s$, $n$=7)

| Group | No.(G cells) | Area of G cells ($\times 10^{-6} m^2$) | No.(D cells) | Area of G cells ($\times 10^{-6} m^2$) | Number ratio of G/D | Area ratio of G/D |
|---|---|---|---|---|---|---|
| Control | 33±6 | 99±7 | 15±2 | 70±11 | 2.3±0.1 | 1.4±0.1 |
| 4d | 50±7[a] | 87±7[a] | 10±2[a] | 56±8[a] | 4.9±0.3[a] | 1.6±0.1[a] |
| 7d | 69±8[a] | 91±7[a] | 9±2[a] | 60±9[a] | 7.6±0.5[a] | 1.5±0.2 |
| 10d | 73±13[a] | 94±7 | 10±1[a] | 63±7 | 7.4±0.4[a] | 1.5±0.1 |
| 14d | 62±11[a] | 95±9 | 11±2[a] | 66±11 | 5.8±0.5[a] | 1.5±0.1 |
| 21d | 46±8[a] | 95±8 | 14±2 | 68±11 | 3.4±0.2[a] | 1.4±0.1 |
| 28d | 43±6[a] | 95±7 | 14±2 | 66±8 | 3.1±0.1[a] | 1.4±0.1 |

[a]$P$<0.05, *vs* control group.

**Table 4** Relationship between rat G and D cells, and between G or D cells and gastrin or somatostatin

| Group | No. of G cells *vs* No. of D cells | Area of G cells *vs* area of D cells | No.of G cells *vs* gastrin in non-ulcer mucosa | No.of D cells *vs* somatostatin in non-ulcer mucosa | Area of G cells *vs* gastrin in non-ulcer mucosa | Area of D cells *vs* somatostatin in non-ulcer mucosa |
|---|---|---|---|---|---|---|
| Control | 0.97[b] | 0.95[b] | 0.95[b] | 0.93[b] | 0.94[b] | 0.93[b] |
| 4d | 0.92[b] | 0.93[b] | 0.87[a] | 0.90[b] | 0.98[b] | 0.86[a] |
| 7d | 0.97[b] | 0.93[b] | 0.98[b] | 0.98[b] | 0.93[b] | 0.94[b] |
| 10d | 0.97[b] | 0.96[b] | 0.93[a] | 0.88[b] | 0.93[b] | 0.95[b] |
| 14d | 0.91[b] | 0.99[b] | 0.87[a] | 0.89[b] | 0.78[a] | 0.99[b] |
| 21d | 0.97[b] | 0.88[b] | 0.90[b] | 0.68 | 0.98[b] | 0.99[b] |
| 28d | 0.99[b] | 0.94[b] | 0.95[b] | 0.89[b] | 0.92[b] | 0.96[b] |

[a]$P$<0.05, [b]$P$<0.01, *vs* control group.

## DISCUSSION

Both gastrin and somatostatin are gastrointestinal hormones closely related to the function of gastrointestinal system. Gastrin is mainly secreted in G cells in antral and upper small intestines. It has several kinds of molecules and distributes in plasma, tissues, gastric juice, and intestinal juice. Somatostatin is a 14 amino peptide. It also has several kinds of molecules and distributes vastly in the body. The somatostatin in gastrointestinal system is secreted in D cells. It is mainly in intestinal nerve plexus, stomach and pancreas, and it is also in gastric and intestinal fluid. In the antrum there are many G and D cells, most of which belong to the open type endocrine cells that can directly secrete gastrin or somatostatin into gastric fluid. Elevated gastrin level can increase the secretion of basal and peak gastric acid, pepsin and inner factor, increase the amount of circulating blood in the mucosa of upper gastrointestinal tract, improve the nutrition of gastric mucosa cells. Somatostatin can obstruct the secretion of basal gastric acid and pepsin and inhibit the invoking function of gastrin to the secretion of gastric acid[25-38]. Our experiment is to reveal the change of gastrin and somatostatin in gastric ulcer rats. The result shows that when the rat had gastric ulcer, the gastrin in plasma, gastric juice and antral mucosa tissue increased, and the somatostatin declined. With the healing of ulcer, gastrin and somatostatin gradually recovered to the normal level.

G and D cells have interactive relation in the function[39-49]. In order to study their morphology we used the immunohistochemical method to identify the G and D cells and to measure the number and area of G and D cells by the medical image analysis system. We found that with ulcer the number of G cells increased as compared with the normal control group, the D cells decreased, and both areas of G and D cells declined. And with the healing of the ulcer, the number and area of G and D cells gradually recovered to the normal level. This suggests that in the ulcer stage, the function of synthesis and secretion of G cells increased, while that of D cells declined. This inclined us that the increased secretion of gastrin in ulcer rat might be related to the increased number of G cells. The declined area of G cells may be related to the increased secretion of gastrin. The decline of somatostatin secretion in gastric ulcer is likely related to both the decreased number of D cells and the reduced area of D cells. It is known that somatostatin can inhibit G cells to secrete gastrin. Because in the gastric ulcer, the somatostatin secretion of D cells in rats lowered its inhibitory effect to G cells, gastrin secretion of G cells increased.

G and D cells are interrelated in morphology. In normal gastrointestinal mucosa, the ratio of G/D number and G/D area is stable. This is useful for keeping the normal gastrointestinal function. The ratio of G/D cells can be an important index for knowing the change of the two kinds of cells and its effect on focal endocrine function[50-58]. Our result showed that in gastric ulcer, the ratio of G/D number and the ratio of G/D area increased than that in normal control group. In the healing process, the disorder recovered gradually to the normal level. This proves that the number of G cells increased and the number of D cells declined in gastric ulcer. It also shows that in gastric ulcer rat, the decrease of the D cell area is more obvious than that of G cells. The statistical analysis indicates that there is a relationship between the number of G and D cells, and between the area of G and D cells. There is also a relationship between the number and area of G cells and gastrin in antral mucosa, and between the number and area of D cells and somatostatin in antral mucosa. In summary, our result further proves histologically that in gastric ulcer rat, the G cell secreted gastrin increased, and the D cell secreted somatostatin reduced, the ratio and function of G/D cells were imbalanced.

## REFERENCES


1 Schmitz F, Schrader H, Otte J, Schmitz H, Stuber E, Herzig K, Schmidt WE. Identification of CCK-B/gastrin receptor splice variants in human peripheral blood mononuclear cells. *Egul Pept* 2001; 101:25-33
2 Caplin M, Khan K, Grimes S, Michaeli D, Savage K, Pounder R, Dhillon A. Effect of gastrin and anti-gastrin antibodies on proliferation of hepatocyte cell lines. *Dig Dis Sci* 2001; 46:1356-1366
3 Janecka A, Zubrzycka M, Janecki T. Somatostatin analogs. *J Pept Res* 2001; 58:91-107
4 Klisovic DD, O'Dorisio MS, Katz SE, Sall JW, Balster D, O'Dorisio TM, Craig E, Lubow M. Somatostatin Receptor Gene Expression in Human Ocular Tissues: RT-PCR and Immunohistochemical Study. *Invest Ophthalmol Vis Sci* 2001; 42:2193-2201
5 Hocker M, Cramer T, O'Connor DT, Rosewicz S, Wiedenmann B, Wang TC. Neuroendocrine-specific and gastrin-dependent expression of a chromogranin A-luciferase fusion gene in transgenic mice. *Gastroenterology* 2001; 121:43-55
6 Monstein HJ, Ohlsson B, Axelson J. Differential expression of gastrin, cholecystokinin-A and cholecystokinin-B receptor mRNA in human pancreatic cancer cell lines. *Scand J Gastroenterol* 2001; 36:738-743
7 McWilliams DF, Grimes S, Watson SA. Antibodies raised against the extracellular tail of the CCKB/gastrin receptor inhibit gastrin-stimulated signalling. *Regul Pept* 2001; 99:157-161
8 Yamamoto S, Kaneko H, Konagaya T, Mori S, Kotera H, Hayakawa T, Yamaguchi C, Uruma M, Kusugami K, Mitsuma T. Interactions among gastric somatostatin, interleukin-8 and mucosal inflammation in Helicobacter pylori-positive peptic ulcer patients. *Helicobacter* 2001; 6:136-145
9 Morisset J, Wong H, Walsh JH, Laine J, Bourassa J. Pancreatic CCK(B) receptors: their potential roles in somatostatin release and delta-cell proliferation. *Am J Physiol Gastrointest Liver Physiol* 2000; 279:G148-G156
10 Cui RT, Cai G, Yin ZB, Cheng Y, Yang QH, Tian T. Transretinoic acid inhibits rats gastric epithelial dysplasia induced by N-methyl-N-nitro-N-nitrosoguanidine: influences on cell apoptosis and expression of its regulatory genes. *World J Gastroenterol* 2001; 7:394-398
11 Takeuchi K,Kawauchi S,Araki H,Ueki S, Furukawa O. Stimulation by nizatidine, a histamine H2-receptor antagonist, of duodenal $HCO_3$-secretion in rats:relation to anti cholinesterase activity. *World J Gastroenterol* 2000; 6:651-658
12 Li W, Zheng TZ, Qu SY. Effect of cholecystokinin and secretin on contractile activity of isolated gastric muscle strips in guinea pigs. *World J Gastroenterol* 2000; 6:93-95
13 Kermorgant S, Lehy T. Glycine-extended gastrin promotes the invasiveness of human colon cancer cells. *Biochem Biophys Res Commun* 2001; 285:136-141
14 Berger AC, Gibril F, Venzon DJ, Doppman JL, Norton JA, Bartlett DL, Libutti SK, Jensen RT, Alexander HR. Prognostic value of initial fasting serum gastrin levels in patients with Zollinger-Ellison syndrome. *J Clin Oncol* 2001; 19:3051-3057
15 Waldum HL, Aase S, Kvetnoi I, Brenna E, Sandvik AK, Syversen U, Johnsen G, Vatten L, Polak JM. Neuroendocrine differentiation in human gastric carcinoma. *Cancer* 1998; 83:435-444
16 Sun FP, Song YG, Zhu XS, Tang SN, Du J, Qiu QL, Zhao T. The establishment of acetic-acid-induced rat's gastric ulcer model and the observation of ulcer antral mucosa through microscope and electromicroscope. *Shijie Huaren Xiaohua Zazhi* 2001; 9:135-138
17 Annibale B, Aprile MR, Ferraro G, Marignani M, Angeletti S, D'Ambra G, Caruana P, Bordi C, Delle Fave G. Relationship between fundic endocrine cells and gastric acid secretion in hypersecretory duodenal ulcer diseases. *Aliment Pharmacol Ther* 1998; 12:779-788
18 Wright NA. Aspects of the biology of regeneration and repair in the human gastrointestinal tract. *Philos Trans R Soc Lond B Biol Sci* 1998; 353:925-933
19 Solcia E, Rindi G, Buffa R, Fiocca R, Capella C. Gastric endocrine cells: types, function and growth. *Egul Pept* 2000; 93:31-35
20 Ling YL, Meng AH, Zhao XY, Shan BE, Zhang JL, Zhang XP. Effect of cholecystokinin on cytokines during endotoxic shock in rats. *World J Gastroenterol* 2001; 7:667-671
21 Zhang LH, Yao CB, Li HQ. Effects of extract F of red-rooted Salvia on mucosal lesions of gastric corpus and antrum induced by hemorrhagic shock-reperfusion in rats. *World J Gastroenterol* 2001; 7:672-677
22 Zhang H, Jiang SL, Yao XX. Study of T-lymphocyte subsets, nitric oxide, hexosamine and *Helicobacter pylori* infection in patients with chronic gastric diseases. *World J Gastroenterol* 2000; 6:601-604
23 Zhu L, Yang ZC, Li A, Cheng DC. Reduced gastric acid production in burn shock period and its significance in the prevention and treatment of acute gastric mucosal lesions. *World J Gastroenterol* 2000; 6:84-88
24 Huang Y,Lu SJ,Dong JX,Li F.The new proof of neuro-endocrine-immune network-expression of islet amyloid polypeptide in plasma cells in gastric mucosa of peptic ulcer patients.*World J Gastroenterol* 2000;6:417-418
25 Zavros Y, Fleming WR, Hardy KJ, Shulkes A. Regulation of fundic and antral somatostatin secretion by CCK and gastrin. *Am J Physiol* 1998; 274:G742-G750
26 Ray JM, Squires PE, Meloche RM, Nelson DW, Snutch TP, Buchan AM. L-type calcium channels regulate gastrin release from human antral G cells. *Am J Physiol* 1997; 273:G281-G288
27 Kamada T, Haruma K, Kawaguchi H, Yoshihara M, Sumii K, Kajiyama G. The association between antral G and D cells and mucosal inflammation,

atrophy, and Helicobacter pylori infection in subjects with normal mucosa, chronic gastritis, and duodenal ulcer. *Am J Gastroenterol* 1998; 93:748-752
28 Nagano T, Itoh H, Takeyama M. Effect of Dai-kenchu-to on levels of 3 brain-gut peptides (motilin, gastrin and somatostatin) in human plasma. *Biol Pharm Bull* 1999; 22:1131-1133
29 Naito T, Itoh H, Yasunaga F, Takeyama M. Rikkunshi-to raises levels of somatostatin and gastrin in human plasma. *Biol Pharm Bull* 2001; 24:841-843
30 Johansson B, Uvnas-Moberg K, Knight CH, Svennersten-Sjaunja K. Effect of feeding before, during and after milking on milk production and the hormones oxytocin, prolactin, gastrin and somatostatin. *J Dairy Res* 1999; 66:151-163
31 Park SM, Lee HR, Kim JG, Park JW, Jung G, Han SH, Cho JH, Kim MK. Effect of Helicobacter pylori infection on antral gastrin and somatostatin cells and on serum gastrin concentrations. *Korean J Intern Med* 1999; 14:15-20
32 Fung LC, Greenberg GR. Somatostatin-14 modulates acid-dependent inhibition of meal-stimulated gastrin via muscarinic pathways in dogs. *Regul Pept* 1998; 74:159-166
33 Hiraoka S, Miyazaki Y, Kitamura S, Toyota M, Kiyohara T, Shinomura Y, Mukaida N, Matsuzawa Y. Gastrin induces CXC chemokine expression in gastric epithelial cells through activation of NF-kappaB. *Am J Physiol Gastrointest Liver Physiol* 2001; 281:G735-G742
34 Vantus T, Keri G, Krivickiene Z, Valius M, Stetak A, Keppens S, Csermely P, Bauer PI, Bokonyi G, Declercq W, Vandenabeele P, Merlevede W, Vandenheede JR. The somatostatin analogue TT-232 induces apoptosis in A431 cells. Sustained activation of stress-activated kinases and inhibition of signalling to extracellular signal-regulated kinases. *Cell Signal* 2001; 13:717-725
35 Zavros Y, Paterson A, Lambert J, Shulkes A. Expression of progastrin-derived peptides and somatostatin in fundus and antrum of nonulcer dyspepsia subjects with and without *Helicobacter pylori* infection. *Dig Dis Sci* 2000; 45:2058-2064
36 Gromada J, Hoy M, Buschard K, Salehi A, Rorsman P. Somatostatin inhibits exocytosis in rat pancreatic alpha-cells by G(i2)-dependent activation of calcineurin and depriming of secretory granules. *J Physiol* 2001; 535:519-532
37 Peng X, Feng JB, Yan H, Zhao Y, Wang SL. Distribution of nitric oxide synthase in stomach myenteric plexus of rats. *World J Gastroenterol* 2001; 7:852-854
38 Tuo BG, Yan YH, Ge ZL, Ou GW, Zhao K. Ascorbic acid secretion in the human stomach and the effect of gastrin. *World J Gastroenterol* 2000; 6:704-708
39 Pesce C, Rossi R, Lenti E, Tanzi R. G-cell density in the antral mucosa: a feasibility study. *Histopathology* 1997; 30:315-318
40 Sun FP, Song YG, Zhu XS, Tang SN, Du J, Qiu QL, Liang QM, Zhao T. Establishment of acetic-acid-induced rat's gastric ulcer model and the histological observation of ulcer antral mucosa in healing stage. *Diyi Junyi Daxue Xuebao* 2001; 21:578-581
41 Larsson LI. Developmental biology of gastrin and somatostatin cells in the antropyloric mucosa of the stomach. *Microsc Res Tech* 2000;48:272-281
42 Mihaljevic S, Katicic M, Karner I, Vuksic-Mihaljevic Z, Dmitrovic B, Ivandic A. The influence of Helicobacter pylori infection on gastrin and somatostatin values present in serum. *Hepatogastroenterology* 2000; 47: 1482-1484
43 Zavros Y, Fleming WR, Shulkes A. Concurrent elevation of fundic somatostatin prevents gastrin stimulation by GRP. *Am J Physiol* 1999; 276:G21-G27
44 Westbrook SL, McDowell GH, Hardy KJ, Shulkes A. Active immunization against somatostatin alters regulation of gastrin in response to gastric acid secretagogues. *Am J Physiol* 1998; 274:G751-G756
45 Ren J, Dunn ST, Tang Y, Wang Y, Gao J, Brewer K, Harty RF. Effects of calcitonin gene-related peptide on somatostatin and gastrin gene expression in rat antrum. *Egul Pept* 1998; 73:75-82
46 Weigert N, Schepp W, Haller A, Schusdziarra V. Regulation of gastrin, somatostatin and bombesin release from the isolated rat stomach by exogenous and endogenous gamma-aminobutyric acid. *Digestion* 1998; 59:16-25
47 Squires PE, Meloche RM, Buchan AM. Bombesin-evoked gastrin release and calcium signaling in human antral G cells in culture. *Am J Physiol* 1999; 276:G227-G237
48 Cappelli E, Degan P, Thompson LH, Frosina G. Efficient repair of 8-oxo-7,8-dihydrodeoxyguanosine in human and hamster xeroderma pigmentosum D cells. *Biochemistry* 2000; 39:10408-10412
49 Chen YQ, Guo WH, Chen ZM, Shi L, Chen YX. Effect of gastrectomy on G-cell density and functional activity in dogs. *World J Gastroenterol* 2000; 6:419-420
50 Chamouard P, Walter P, Wittersheim C, Demuynck P, Meunier O, Baumann R. Antral and fundic D-cell numbers in *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol* 1997; 9:361-365
51 Iyo T, Kaneko H, Konagaya T, Mori S, Kotera H, Uruma M, Rhue N, Shimizu T, Imada A, Kusugami K, Mitsuma T. Effect of intragastric ammonia on gastrin-, somatostatin-and somatostatin receptor subtype 2 positive-cells in rat antral mucosa. *Life Sci* 1999; 64:2497-2504
52 Lloyd KC, Amirmoazzami S, Friedik F, Chew P, Walsh JH. Somatostatin inhibits gastrin release and acid secretion by activating sst2 in dogs. *Am J Physiol* 1997; 272:G1481-G1488
53 Kamada T, Haruma K, Kawaguchi H, Yoshihara M, Sumii K, Kajiyama G. The association between antral G and D cells and mucosal inflammation, atrophy, and Helicobacter pylori infection in subjects with normal mucosa, chronic gastritis, and duodenal ulcer. *Am J Gastroenterol* 1998; 93:748-752
54 Tzaneva M. Light and electron microscopic immunohistochemical investigation on G and D cells in antral mucosa in *Helicobacter pylori*-related gastritis. *Exp Toxicol Pathol* 2001; 52:523-528
55 Magert HJ, Reinecke M, David I, Raab HR, Adermann K, Zucht HD, Hill O, Hess R, Forssmann WG. Uroguanylin: gene structure, expression, processing as a peptide hormone, and co-storage with somatostatin in gastrointestinal D-cells. *Regul Pept* 1998; 73:165-176
56 Beales IL. Effect of platelet-activating factor on gastrin release from cultured rabbit G-cells. *Dig Dis Sci* 2001; 46:301-306
57 Ford MG, Valle JD, Soroka CJ, Merchant JL. EGF receptor activation stimulates endogenous gastrin gene expression in canine G cells and human gastric cell cultures. *J Clin Invest* 1997; 99:2762-2771
58 Yao YL, Xu B, Zhang WD, Song YG. Gastrin, somatostatin, and experimental disturbance of the gastrointestinal tract in rats. *World J Gastroenterol* 2001; 7:399-402

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