ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Aug; 20 (8): 763 - 768
http://www.simm.ac.cn; www.chinainfo.gov.cn/periodical


# Effect of recombinant human basic fibroblast growth factor on stomach ulcers in rats and mice

WANG Jun-Zhi[1], WU Yong-Jie[2], RAO Chun-Ming, GAO Ming-Tang[2], LI Wen-Guang[2]
(*Department of Biochemistry, National Institute for the Control of Pharmaceutical and Biological Products, Beijing 100050*; [2]*Department of Pharmacology, Lanzhou Medical College, Lanzhou 730000, China*)

**KEY WORDS** basic fibroblast growth factor; peptic ulcer; granulation tissue; famotidine; reserpine

## ABSTRACT

**AIM**: To study the curative effects of recombinant human basic fibroblast growth factor (rh-bFGF) on gastric ulcer healing. **METHODS**: Pylorus ligated, water immersion stress-induced, reserpine-induced, and acetic acid-induced gastric ulcers in rats or mice were prepared. Morphometric analyses on ulcer were performed using microscope and true color image analysis system. The DNA and RNA contents were measured by diphenylamine method and orcinol method, respectively. **RESULTS**: In acetic acid-induced gastric ulcers in rats, rh-bFGF 2.5 - 40 kU·kg$^{-1}$ ig accelerated the chronic ulcer healing with a bell-shaped dose-effect curve and the best dosage was 10 kU·kg$^{-1}$. The regenerated gland epithelium width, density of capillaries in granulation tissue, and collagen content in scar tissues obviously increased in rh-bFGF-treated groups. Simultaneously, rh-bFGF promoted the differentiation and maturation of regenerated glands around ulcers. rh-bFGF 2 - 4 kU·kg$^{-1}$ sc also increased the synthesis of RNA in ulcer tissues. In acute gastric ulcers, rh-bFGF ig was only effective on pylorus ligated ulcers, but showed no effect on total acid output and pepsin activity in gastric juice of rats. **CONCLUSION**: rh-bFGF promoted the gastric ulcer healing and improved the quality of gastric ulcer healing.

[1] Correspondence to Dr WANG Jun-Zhi.
Phn 86-10-6701-7755, ext 380. Fax 86-10-6701-7683.
Received 1998-02-23 Accepted 1998-12-06

## INTRODUCTION

Basic fibroblast growth factor (bFGF) showed potent ulcer healing activity on experimental peptic ulcers[1-2]. However, there was an acid degradation during oral administration of wild bFGF. This problem could be overcome either by recombining an acid-resistant bFGF or by adding a protective agent like heparin. In this study, we used heparin to protect the recombinant human bFGF (rh bFGF) in testing its antiulcer action.

## MATERIALS AND METHODS

rh-bFGF and vehicle (Torita Bio-Pharma Co, Zhuhai, China) with a special activity 1 mg = 2.5 MU (arbitrary units), purity > 95 %, were stored under -20 ℃, and diluted with normal saline (NS) just before use. Famotidine (Industry and Commerce Company of Changzhou Xing-Hua), purity > 99.8 %, was dissolved in NS. Wistar rats (Clean grade, Certificate № 14-006; Animal Feeding Room № 14-008) were purchased from Animal Breeding Center of Lanzhou Medical College. Kunming mice (Clean grade, Certificate № 14-001; Animal Feeding Room № 14-010) were purchased from Animal Breeding Center of Lanzhou Institute of Biological Products, Ministry of Public Health. CIMAS8-type true color image analysis system was produced by Image Analyzing Center of Beijing Aviation and Space University. Color video camera (WV-CP410) was from Sony Company of Japan.

### 1 Induction of acute gastric ulcer

Rats (♂, ♀) were randomly divided into control group, famotidine 40 mg·kg$^{-1}$ group, rh-bFGF 2.5, 5, and 10 kU·kg$^{-1}$ group. Control was treated with NS. The rats were fasted but watered for 24 - 54 h

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Aug; 20 (8)
E-mail aps@server.shcnc.ac.cn Phn/Fax 86-21-6474-2629

before induction of ulcers. Drugs were given ig 30 min before induction of ulcers. The stomach was fixed with 10 % formaline and photographed by video camera. The image was transferred to a computer and the ulcer area was determined with true color image analysis system.

**1.1 Pylorus-ligated gastric ulcer** Rats ($n$ = 40, weighing 130 – 150 g, fasted for 54 h), gastric ulcer was induced according to Shay method[3]. The Ulcer index was calculated according to Okabe mehtod[4].

**1.2 Water immersion stress-induced gastric ulcers in mice** Mice ($n$ = 55, weighing 19 – 21 g, ♂ 6 ♀ 5 in each group, fasted for 24 h) were immersed in a water bath (4 cm × 4 cm × 40 cm) at (23 ± 0.5) ℃ for 24 h to the xyphoid level (water depth: 5.5 cm). Immediately after the stress, the stomach was filled with 10 % formaline. The gastric lesions were counted though image analysis system.

**1.3 Reserpine-induced gastric ulcers in rats** Rats ($n$ = 50, weighing 180 – 220 g, ♂ ♀, fasted for 24 h) were injected ip with reserpine 5 mg·kg$^{-1}$. After 18 h, the stomach ulcer area was determined by image analysis system.

**1.4 Measurement of hydrochloric acid and pepsin secretion** Rats ($n$ = 40, weighing 180 – 220 g, fasted for 48 h) were divided into 5 groups. Six hours after pylorus ligation, the gastric juice was collected. The pH of gastric juice was measured by pH meter. Gastric juice acidity was titrated with NaOH 100 μmol·L$^{-1}$ using phenolphalein as indicator. The pepsin activity was determined as Anson's method[5] by using albumin as a substrate, and was expressed as tyrosine μmol·h$^{-1}$.

**2 Induction of chronic acetic acid gastric ulcers in rats**

**2.1 Preparation of rats** Wistar rats ($n$ = 96, weight 150 – 180 g, ♂ ♀) were fasted for 24 h. A 20 % acetic acid 50 μL was injected under the anterior serosal surface of the rat stomach at the border of the fundic and antrial regions. On the next day, the rats were divided into control, famotidine 40 mg·kg$^{-1}$, rh-bFGF 2.5, 5, 10, 20, 40, and 80 kU·kg$^{-1}$ groups randomly. The tested agents were given ig bid (8:00 and 17:00) for 14 d. The abdomen was incised under pentobarbital 60 mg·kg$^{-1}$ ip anesthesia. The stomach was fixed and the ulcer area was examined.

**2.2 Histopathological examination** After further fixation in 10 % formaline for 72 h, ulcers were longitudinally cut along the long-axis of ulcers, embedded in paraffin, cut into 5 μm thick sections, and stained with HE, PAS (periodic acid-Schiff), or Masson's method[6]. Four indices were selected to reflect the velocity and quality of ulcer healing:

Regenerated glandular epithelium width was determined by micrometer under microscope. The origin of regenerated glands could be easily judged by: (a) regenerated glands usually showed cystic dilation; (b) PAS stain showed potent positive reaction in whole layer of regenerated glands in contrast to that weak positive reaction limited in the superficial normal glands; (c) lack of muscular layer of mucosa, and (d) there existed large number of collagen fibers in ulcer tissues. Regenerated glandular epithelium width was defined as the average distance from the origin part of regenerated glands to ulcer edge on two sides of the ulcer.

Capillary density within granulation tissues of ulcers was counted with reticular micrometer under microscope (× 400 magnification) on HE stain sections in the ulcer center. Each field was 145 μm × 145 μm. At least 4 fields were examined on each section. Capillary density within granulation tissues of ulcers was expressed as the average capillary numbers in the fields.

Collagen content within scar tissues of ulcers Collagen fibers in scar tissue specially displayed green color in sections stained by Masson's method and were determined with image analysis system. Each field was 145 μm × 145 μm. At least 4 fields were examined on each section. Collagen content within scar tissues of ulcers was an average percentage of the surface area.

Heterotypic extent of gastric glands around ulcer craters Two indices were used to reflect the heterotypic extent of gastric glands.

A: Cystic dilatation of glands Gade 0: glands were close to normal morphologically. Grade 1, 2, or 3: diameter of dilated glands was over than 1, 2, and 3 times of normal; or/and dilated glands were about 1/3, 2/3, or almost all of the regenerated glands, respectively.

B: Co-wall of glands It is the phenomena of adjacent glands sharing the same well during the

proliferation of glands, reflecting the extent of proliferation and immaturation of regenerated glands. Co-wall glands were divided into 4 grades according to proportion of regenerated glands sharing a wall. Grade 0: co-wall glands were rarely seen. Grade 1, 2, or 3: co-wall glands were about 1/3, 2/3, or almost all of regenerated glands, respectively.

**2.3 Biochemical analysis of ulcerated mucosa** Rats ($n = 60$, weighing 190 – 220 g), were divided into 6 groups (Tab 3). Acetic acid gastric ulcers in rats were induced. The rh-bFGF sc, sulcralfate ig, or NS ig in control group and normal rats or sc in each group were given from d 2 to d 11 after operation. The rats were decapitated on d 12 after operation. The portion of tissues was excised from the ulcer margin and weighed. The DNA and RNA contents were measured by diphenylamine method and orcinol (5-methylresorcinol) method[7], respectively.

## RESULTS

**1 Effect on acute gastric ulcers** In pylorus-ligated gastric ulcers of rats, rh-bFGF 2.5 kU·kg$^{-1}$ decreased slightly the ulcer index, ($P > 0.05$). Famotidine 40 mg·kg$^{-1}$, rh-bFGF 5 and 10 kU·kg$^{-1}$ evidently decreased the ulcer indices as compared with control ($P < 0.01$). The ulcer index in rh-bFGF 5 kU·kg$^{-1}$ group was evidently lower than that of other groups. (Tab 1)

rh-bFGF 2.5 – 10 kU·kg$^{-1}$ had no effect on water immersion stress-induced gastric ulceration in mice or on reserpine-induced gastric ulceration in rats. (Tab 1)

**2 Effect on gastric secretion in rats** As compared with control (Tab 1), pepsin output, total acid output of gastric juice in rh-bFGF 2.5 – 10 kU·kg$^{-1}$ did not show evident change. On the contrary, famotidine 40 mg·kg$^{-1}$ decreased the acidity and pepsin activity of gastric juice ($P < 0.01$).

**3 Curative effect on chronic gastric ulcers**

**3.1 Effect on ulcer index** rh-bFGF 2.5 kU·kg$^{-1}$ obviously promoted the ulcer healing in acetic acid-induced gastric ulcers of rats. The best dosage was 10 kU·kg$^{-1}$ with a bell-shaped dose-response curve. The ulcer healing action of rh-bFGF was more potent than that of famotidine. (Tab 2)

**3.2 Effect on maturation of gastric glands around ulcer craters** In control group, the marginal glands were obviously heterotypic, expressing as that there were a large number of cystic dilatation of glands, PAS-positive neutral mucopolysaccharide appeared in glandular cavity, and the regenerated glands shared co-wall. rh-bFGF 5 – 20 kU·kg$^{-1}$ decreased the numbers of co-wall glands and reduced the heterotypic extent of the glands. But famotidine did not reduce the extent of cystic dilation of glands, but slightly decreased the numbers of co-wall glands ($P < 0.05$) as compared with control. (Tab 2)

**3.3 Effect on collagen formation within scar tissues** Image analysis on Masson's staining sections demonstrated that rh-bFGF 5 – 20 kU·kg$^{-1}$ obviously increased collagen content as compared with control, indicating that rh-bFGF promoted the collagen formation in ulcer tissues. Nevertheless, the collagen content of ulcer tissues in famotidine group showed only a slight rise ($P > 0.05$). (Tab 2)

**3.4 Effect on capillary proliferation in granulation tissues of ulcers** rh-bFGF 5 – 20 kU·kg$^{-1}$ increased the capillary numbers within granulation tissues of ulcer craters. However, famotidine showed no such effect. (Tab 2)

**Tab 1. Effect of rh-bFGF on water immersion stress-induced (11 mice), reserpine-induced (10 rats), and pylorus ligated (8 rats) gastric ulcers.** $\bar{x} \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

| Drugs | Stress ulcers/ points | Reserpine ulcer area/mm$^2$ | Pylorus ligated gastric ulcer | | |
|---|---|---|---|---|---|
| | | | Ulcer index | Pepsin output/ tyrosine μmol·h$^{-1}$ | Output of total acid/mmol·h$^{-1}$ |
| Control | 23 ± 12 | 6.1 ± 2.3 | 4.0 ± 1.9 | 44 ± 7 | 79 ± 10 |
| Famotidine 40 mg·kg$^{-1}$ | 6 ± 4$^c$ | 0.6 ± 0.8$^c$ | 1.5 ± 1.4$^c$ | 16 ± 7$^c$ | 16 ± 6$^c$ |
| rh-bFGF 2.5 kU·kg$^{-1}$ | 23 ± 15$^a$ | 6.6 ± 1.6$^a$ | 3.0 ± 2.1$^a$ | 44 ± 5$^a$ | 88 ± 12$^a$ |
| rh-bFGF 5 kU·kg$^{-1}$ | 26 ± 10$^a$ | 6.4 ± 1.6$^a$ | 0.25 ± 0.46$^b$ | 44.7 ± 1.7$^a$ | 74 ± 8$^a$ |
| rh-bFGF 10 kU·kg$^{-1}$ | 23 ± 10$^a$ | 6.1 ± 1.7$^a$ | 1.1 ± 1.0$^c$ | 38 ± 5$^a$ | 72 ± 7$^a$ |

ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Aug; 20 (8)
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**Tab 2. Effect of rh-bFGF on acetic acid-induced gastric ulcers in rats.** $n = 8-11$. $x \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control.

| Drugs | Ulcer area/mm² | Cystically dilated glands/rats | | | Glands of co-wall/rats | | | Regenerated epithelium width/μm | Capillary density in granulation tissues/ numbers in 21600 μm² | Collagen content in scar tissues/% |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Grade 0 | Grade 1 | Grade 2 | Grade 0 | Grade 1 | Grade 2 | | | |
| Control | 20 ± 7 | 0 | 5 | 6 | 0 | 4 | 7 | 1034 ± 136 | 2.9 ± 0.8 | 36 ± 5 |
| Famotidine 40 mg·kg$^{-1}$ | 10 ± 6$^c$ | 0 | 5 | 3$^a$ | 3 | 5 | 2$^b$ | 1266 ± 34$^c$ | 3.1 ± 1.1$^a$ | 41 ± 12$^a$ |
| rh-bFGF 2.5 kU·kg$^{-1}$ | 13 ± 6$^b$ | | | | | | | | | |
| rh-bFGF 5 kU·kg$^{-1}$ | 8.1 ± 2.1$^c$ | 0 | 7 | 2$^a$ | 0 | 9 | 0$^b$ | 1248 ± 59$^c$ | 5.3 ± 1.1$^c$ | 44 ± 8$^b$ |
| rh-bFGF 10 kU·kg$^{-1}$ | 6 ± 5$^c$ | 2 | 4 | 4$^a$ | 6 | 4 | 0$^c$ | 1356 ± 107$^c$ | 7.1 ± 1.5$^c$ | 54 ± 10$^c$ |
| rh-bFGF 20 kU·kg$^{-1}$ | 7 ± 4$^c$ | 5 | 3 | 0$^c$ | 5 | 2 | 1$^c$ | 1388 ± 93$^c$ | 6.2 ± 1.5$^c$ | 53 ± 9$^c$ |
| rh-bFGF 40 kU·kg$^{-1}$ | 9 ± 8$^c$ | | | | | | | | | |
| rh-bFGF 80 kU·kg$^{-1}$ | 19 ± 9$^a$ | | | | | | | | | |

**3.5 Effect on regeneration of glandular epithelium of ulcer margin** Famotidine 40 mg·kg$^{-1}$, or rh-bFGF 5 – 20 kU·kg$^{-1}$ increased the regenerated glandular epithelium width around ulcer craters as compared with control. Simultaneously, the effects of rh-bFGF groups showed an evident dose-dependent manner. (Tab 2)

**3.6 Effect on RNA and DNA synthesis in acetic acid-induced gastric ulcer tissues** rh-bFGF 4 and 8 kU·kg$^{-1}$ sc or sulcralfate 400 mg·kg$^{-1}$ alone all slightly increased the DNA content in ulcer tissues, but showed no significant difference as compared with control. DNA content in ulcer tissues was increased by rh-bFGF plus sulcralfate group as compared with control ($P < 0.05$, Tab 3). RNA content in ulcer tissues was obviously increased in all drug treated groups. In the meantime, the ulcer indices in rh-bFGF plus sulcralfate group were lower than those of control, rh-bFGF or sulcralfate group alone, indicating that there is a synergistic action between rh-bFGF and sulcralfate. (Tab 3)

**Tab 3. Effect of rh-bFGF im on RNA, and DNA synthesis in ulcer tissues and its synergsim with sulcralfate (Sulc, 400 mg·kg$^{-1}$, ig) in rats with acetic acid induced-gastric ulcers.** $x \pm s$. $^aP > 0.05$, $^bP < 0.05$, $^cP < 0.01$ *vs* control. $^dP > 0.05$, $^eP < 0.05$, $^fP < 0.01$ *vs* sulc 400 mg·kg$^{-1}$ ig group. $^gP > 0.05$, $^hP < 0.05$, $^iP < 0.01$ *vs* rh-bFGF 8 kU·kg$^{-1}$ sc group.

| Drugs | Rats | DNA/mg·g$^{-1}$(tissues) | RNA/mg·g$^{-1}$(tissues) | Ulcer indices/mm² |
|---|---|---|---|---|
| Normal | 9 | 2.83 ± 0.18$^a$ | 50 ± 5$^b$ | |
| Control | 10 | 2.98 ± 0.67 | 37 ± 7 | 26.4 ± 2.5 |
| Sulc 400 mg·kg$^{-1}$ | 8 | 3.54 ± 0.81$^a$ | 63 ± 11$^c$ | 15.5 ± 2.7$^c$ |
| rh-bFGF 4 kU·kg$^{-1}$ | 9 | 3.19 ± 0.70$^a$ | 48 ± 11$^c$ | 16.9 ± 4.2$^c$ |
| rh-bFGF 8 kU·kg$^{-1}$ | 8 | 2.88 ± 0.37$^a$ | 58 ± 11$^c$ | 12.5 ± 2.9$^c$ |
| rh-bFGF 8 kU·kg$^{-1}$ + sulc 400 mg·kg$^{-1}$ | 10 | 3.70 ± 0.88$^{bdi}$ | 63 ± 13$^{edg}$ | 4.8 ± 3.3$^{cf}$ |

## DISCUSSION

The regular therapy for gastric ulcers includes anti-hydrochloric acid, anti-helicobacter pylori, and protecting the gastric mucosa barrier, and et cetera. The traditional therapy is helpless on the active repair of ulcers. The discovery of polypeptide growth factors provides a new way and a new theory for treatment of peptic ulcers. The growth factors mainly promote the active repair process of ulcers like angiogenesis, re-epithelialization and collagen proliferation. Therefore, the therapy with rh-bFGF is an epoch-making advance in treatment for peptic ulcer.

A lot of investigations[8-9] revealed that rh-bFGF strongly stimulated proliferation and differentiation of epithelial cells, stimulated the angiogenesis and collagen formation, further promoting the active repair process of peptic ulcer. Konturek SJ[10] reported that rh-bFGF also increased the blood flow in ulcer tissues. rh-bFGF also promoted the cellular proliferation by

increasing synthesis of RNA, DNA. rh-bFGF cured gastric ulcers which was not related to gastric acid or pepsin activity. Simultaneously, it did not affect the acute experimental ulcers like reserpine-induced or water-immersion stress-induced, which mainly caused by excessive secretion of gastric acid.

The induction cause of pylorus ligated ulcers are more complicated than those of other acute ulcer models. It was brought about not only by excessive secretion of gastric juice, but also by gastric ischemia caused by a rise of pressure within stomach and a decrease of gastric mucosa blood flow[10]. rh-bFGF was able to increase the blood flow of gastric tissue[2], and it also possesses anti-ischemia activity in cardinal or cerebral tissues. Thus, this protective action against pylorus ligated ulcers might be related to its anti-ischemia activity, which remains to be clarified in gastric ischemic model.

This study demonstrated that rh-bFGF possessed an obvious curative effect on chronic gastric ulcer. It could promote the ulcer healing, by promoting angiogenesis, re-epithelialization. Its activity was shown to be dose-dependent in certain dosage range, but was lost over high dosage, suggesting that there is a selection problem for most adequate dosage in clinic.

Traditionally, assessment of ulcer healing is usually based on visual endoscopic examination of patients or on gross measurements of ulcer size in experimental studies. Using quantitative histology and ultrastructure assessment of subepithelial mucosa reconstruction, Tarnawski A *et al* demonstrated that re-epithelialized mucosa of grossly 'healed' experimental gastric ulcers had prominent abnormalities: reduced height, marked dilation of gastric glands, poor differentiation and/or degenerative changes in glandular cells[11]. Indeed, clinical studies have demonstrated that gastric ulcers tend to recur at the same location[12]. Therefore, the quality of mucosal structure restoration may be crucial factor in determining future ulcer recurrence and should be paid more attention in evaluation of action of antiulcer agents. This experiment demonstrated that rh-bFGF attenuated the heterotypic extent of the regenerated glands around ulcer healing area, suggesting that rh-bFGF is capable of promoting the maturaion of regenerated glands. This effect of bFGF providing balanced regeneration of ulcerated mucosa may be crucial for reconstructing epithelial structures, and may be the basis for the improved quality of mucosal reconstruction.

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763-768


ISSN 0253-9756 Acta Pharmacol Sin 中国药理学报 1999 Aug; 20 (8)
E-mail aps@server.shcnc.ac.cn Phn·Fax 86-21-6474-2629

## 重组人碱性成纤维细胞生长因子对大、小鼠胃溃疡的影响

R 775.6

王军志[1]，吴勇杰[2]，饶春明，高明堂[2]，李文广[2]

（中国药品生物制品检定所生化室，北京 100050；[2]兰州医学院药理学教研室，兰州 730000，中国）

rh bFGF

**关键词** 碱性成纤维细胞生长因子；消化性溃疡；肉芽组织；法莫替丁；利血平

**目的**：研究重组人碱性成纤维细胞生长因子（rh-bFGF）对实验性溃疡病的治疗作用。**方法**：采用大鼠和小鼠溃疡病模型，用图象分析仪进行形态计量，用显微镜观察病理组织学变化、用二苯胺法测 DNA 含量，用地衣酚法测 RNA 含量。**结果**：对大鼠醋酸性溃疡，rh-bFGF 2.5－40 kU·kg$^{-1}$ ig bid 缩小溃疡指数；最佳剂量为 10 kU·kg$^{-1}$；量-效曲线呈钟型。rh-bFGF 使溃疡边缘再生腺上皮宽度、肉芽组织内毛细血管密度及瘢痕组织内胶原含量提高；并促进再生腺体成熟与溃疡边缘组织 RNA 合成。对急性溃疡模型，rh-bFGF 5，10 kU·kg$^{-1}$仅对大鼠幽门结扎型有效，但不影响胃液酸度及胃蛋白酶活性。**结论**：rh-bFGF ig 或 sc 加速大鼠慢性胃溃疡愈合，并提高愈合质量。

（责任编辑　朱倩蓉）