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• BASIC RESEARCH •

Protective effects of pentadecapeptide BPC 157 on gastric ulcer in rats

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Abstract

AIM: To investigate the protective effects of gastric pentadecapeptide BPC 157 on acute and chronic gastric ulcers in rats and to compare the results in therapy of human gastric ulcers by different administration methods.

METHODS: Gastric pentadecapeptide BPC 157 was administered (initial single or continuous administration) into rats either intragastrically or intramuscularly before (induced acute gastric ulcer) or after (induced chronic gastric ulcer) the applications of inducing agents, and each animal was sacrificed to observe the protective effects of BPC 157 on gastric ulcers.

RESULTS: Both intramuscular (im) and intragastric (ig) administration of BPC 157 could apparently reduce the ulcer area and accelerate the healing of induced ulcer in different models and the effect of im administered BPC 157 was better than that of ig. The rats treated with higher dosages (400 ng/kg, 800 ng/kg) of BPC 157 (im and ig) showed significantly less lesion ($P<0.01$ *vs* excipient or saline control), the inhibition ratio of ulcer formation varied between 45.7% and 65.6%, from all measurements except 400 ng/kg BPC 157 in pylorus ligation induced model ($P<0.05$), in which the inhibition rate was 54.2%. When im administered (800 ng/kg BPC 157) in three models, the inhibition ratio of ulcer formation was 65.5%, 65.6% and 59.9%, respectively, which was better than that of famotidine (its inhibition rate was 60.8%, 57.2% and 34.3%, respectively). Continuous application of BPC 157 (in chronic acetate induced gastric ulcer) could accelerate rebuilding of glandular epithelium and formation of granulation tissue ($P<0.05$ at 200 ng/kg and $P<0.01$ at 400 ng/kg and 800 ng/kg *vs* excipient or saline control).

CONCLUSION: Both im and ig administered gastric pentadecapeptide BPC 157 can apparently ameliorate acute gastric ulcer in rats and antagonize the protracted effect of acetate challenge on chronic ulcer. The effect of im administration of BPC 157 is better than that of ig, and the effective dosage of the former is lower than that of the latter.

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INTRODUCTION

Pentadecapeptide BPC 157 (M_r 1 419), with the sequence Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val, a 15-amino acid fragment of body protection compound (BPC) peptide in gastric juice[1,2], is thought to be essential for BPC's activity and has been fully characterized and investigated. Although the detailed mechanism is poorly understood, BPC 157 appears to be beneficial to almost all organ systems in many species when very low dosages (mostly mg/kg and ng/kg) are used. It has many functions such as attenuating liver, lung, colon and gastric lesions[3-13], displaying anti-anxiety and antidepressant effects[14,15], improving angiogenesis and wound healing[8,16,17], reversing MPTP-motor abnormalities in Parkinson's disease models[11], having mucosal protective and anti-inflammatory effects[10,18,19], particularly affecting dopamine systems[20], and persistent activity[6,21]. All these findings showed that BPC 157 could be a useful prototype of a new class of drugs and organ protective agents.

In this present we studied the protective effects of synthesized BPC 157 on acute and chronic gastric ulcers and also discussed the differences resulted from different administration methods.

MATERIALS AND METHODS

Materials

BPC 157 was synthesized and purified in our laboratory. Famotidine (Lot No. 970422) was provided by Changzhou Xinhua Industry General Company. Indomethacin was purchased from Lanzhou Pharmaceutical Factory. CIMAS8 true color image analyzer was from Beijing University of Aeronautics & Astronautics. WV-CP410 color camera was produced by Panasonic Electrical Company Limited.

Animals

A total of 330 male Wistar rats, weighing 200-240 g, were used for 3 different gastric ulcer models, namely indomethacin induced model, pylorus ligation induced model and acetate induced model. In each model, rats were randomly divided into 11 groups, of which 6 for intramuscular (im) administration and 5 for intragastric (ig) administration, 10 rats for each group.

Methods

Gastric pentadecapeptide BPC 157 was ig or im administered (1 mL/kg) at three different dosages (200, 400 and 800 ng/kg) in each model. Saline, excipient (mannitol) and famotidine were used as saline control, excipient control and positive control, respectively.

In model 1, the rats were fasted but with free access to water for 24 h, and then BPC 157 was given. Sixty minutes later

ulcer was induced by injection of indomethacin (33 mg/kg body mass). The rats were sacrificed 12 h later and both pylorus and cardia were ligated, followed by injection of 10 mL formaldehyde (40 g/L) into the stomach. Thirty minutes later, the stomach was cut and spread out and the area of the ulcer was measured.

In model 2, the rats were fasted for 54 h with free access to water before administrations of BPC 157. Famotidine and saline were given and pylorus ligation was performed by surgical procedure 60 min later. The rats were fasted for an additional period of 18 h and sacrificed and treated as in model 1.

In model 3 (chronic gastric ulcer model), the stomach was exposed under anesthesia followed by injection of 50 μL acetate (300 mL/L) under the chorion after the rats were fasted with free access to water for 24 h. After injection of acetate, the rats were immediately treated with BPC 157 twice daily for 12 d. Twelve hours following the last treatment, the rats were sacrificed and the ulcer area, glandular epithelium rebuilding and granulation tissue thickness were investigated. The reepithelialization was reflected by the diameter of remnant ulcer and the thickness of granulation tissue was measured every 500 μm.

RESULTS

Effects of BPC 157 on indomethacin induced gastric ulcer

BPC 157 could apparently inhibit the progression of indomethacin induced gastric ulcer. When im administered (400 ng/kg and 800 ng/kg), the protective effect of BPC 157 (the gastric ulcer area was 7.22 mm^2) was better than that of famotidine (the ulcer area 8.20 mm^2). While im and ig application had different effects, the former was better than the latter. The effective (P<0.01 *vs* excipient control or saline control) dosage was different; im administration of 200 ng/kg BPC 157 was as effective as ig administration of 400 ng/kg of BPC 157 (Table 1, Figure 1).

Table 1 Effect of BPC 157 on indomethacin induced gastric ulcer formation (n=10)

Administration	Agents	Dosage (ng/kg)	Ulcer (mm^2)	Inhibition ratio(%)
im	Saline control	-	19.22±2.95	-
	Excipient control	-	20.90±7.55	-
	Famotidine	40 000	8.20±4.68	60.8[b]
	BPC 157	200	9.71±5.00	53.5[b]
	BPC 157	400	7.22±4.01	65.5[b]
	BPC 157	800	7.22±4.64	65.5[b]
ig	Saline control	-	20.18±8.50	-
	Famotidine	40 000	8.28±3.45	58.9[b]
	BPC 157	200	13.56±6.79	32.8
	BPC 157	400	9.92±2.62	50.8[b]
	BPC 157	800	9.75±5.25	51.7[b]

[b]P<0.01 *vs* excipient control or saline control.

Effects of BPC 157 on pylorus ligation induced gastric ulcer

The effect of BPC 157 on pylorus ligation induced gastric ulcer was similar to that on indomethacin induced ulcer. When BPC 157 was im administered, it was effective (P<0.01 *vs* excipient control) even at dosage of 200 ng/kg and the effects at dosages of 400 ng/kg and 800 ng/kg were better than that of famotidine. When BPC 157 was ig administered, the higher dosages showed significant effect compared with saline control (P<0.05) and the lower dosage did not (P>0.05) (Table 2, Figure 1).

Effects of BPC 157 on acetate induced gastric ulcer

In chronic acetate induced animal model, the lower dosage was effective (P<0.05), and the higher dosages showed significant effects (P<0.01) when compared with excipient control (im) or saline control (ig) (Table 3, Figure1).

Table 2 Effect of BPC 157 on pylorus ligation induced gastric ulcer formation (n=10)

Administration	Agents	Dosage (ng/kg)	Ulcer (mm^2)	Inhibition ratio(%)
im	Saline control	-	131.2±58.1	-
	Excipient control	-	130.2±68.2	-
	Famotidine	40 000	55.7±46.7	57.2[b]
	BPC 157	200	80.9±22.8	37.8[b]
	BPC 157	400	47.6±27.8	63.5[b]
	BPC 157	800	44.8±19.4	65.6[b]
ig	Saline control	-	140.1±78.1	-
	Famotidine	40 000	34.1±33.1	75.7[b]
	BPC 157	200	110.5±41.5	21.1
	BPC 157	400	64.1±35.4	54.2[a]
	BPC 157	800	58.6±37.6	58.2[b]

[a]P<0.05, [b]P<0.01 *vs* excipient control (im) or saline control (ig).

Table 3 Effect of BPC 157 on acetate induced gastric ulcer area (n=10)

Administration	Agents	Dosage (ng/kg)	Ulcer (mm^2)	Inhibition ratio(%)
im	Saline control	-	13.66±4.10	-
	Excipient control	-	13.98±4.00	-
	Famotidine	40 000	9.18±3.04	34.3[a]
	BPC 157	200	9.75±3.62	30.2[a]
	BPC 157	400	6.81±3.67	51.3[b]
	BPC 157	800	5.60±1.91	59.9[b]
ig	Saline control	-	14.96±6.21	-
	Famotidine	40 000	3.20±1.54	78.6[b]
	BPC 157	200	9.78±4.28	34.6[a]
	BPC 157	400	8.13±2.84	45.7[b]
	BPC 157	800	7.80±2.83	47.8[b]

[a]P<0.05, [b]P<0.01 *vs* excipient control (im) or saline control (ig).

BPC 157's effect on rebuilding of glandular epithelium and granulation tissue formation in chronic acetate induced gastric ulcer was also investigated. Table 4 shows that BPC 157, im and ig administered, had significant protective effects compared with controls (P<0.05), and the effect of BPC 157 on the thickness of granulation tissue was more significant than that of famotidine (P<0.01). The ulcer in rats treated at 800 ng/kg dosage of BPC 157 was almost healed and the granulation tissue became thick. In the control, putrescence and exudation were apparent, the ulcerous gap was large and the granulation tissue was very thin (Figure 2).

Table 4 Effects of BPC 157 on rebuilding of glandular epithelium and formation of granulation tissue in acetate induced chronic gastric ulcer (n=10)

Administration	Agent	Dosage (ng/kg)	Diameter of remnant ulcer (μm)	Thickness of granulation tissue (μm)
im	Saline control	-	3 928±636	718±165
	Excipient control	-	3 981±594	652±169
	Famotidine	40 000	3 175±577[b]	768±268
	BPC 157	200	3 266±671[a]	992±295[b]
	BPC 157	400	2 658±744[b]	1 018±202[b]
	BPC 157	800	2 426±511[b]	1 012±306[b]
ig	Saline control	-	4 098±795	673±112
	Famotidine	40 000	1 772±458[b]	805±100[a]
	BPC 157	200	3 260±728[a]	797±110[a]
	BPC 157	400	2 972±564[b]	837±114[b]
	BPC 157	800	2 904±577[b]	862±171[b]

[a]P<0.05, [b]P<0.01 *vs* excipient control (im) or saline control (ig).

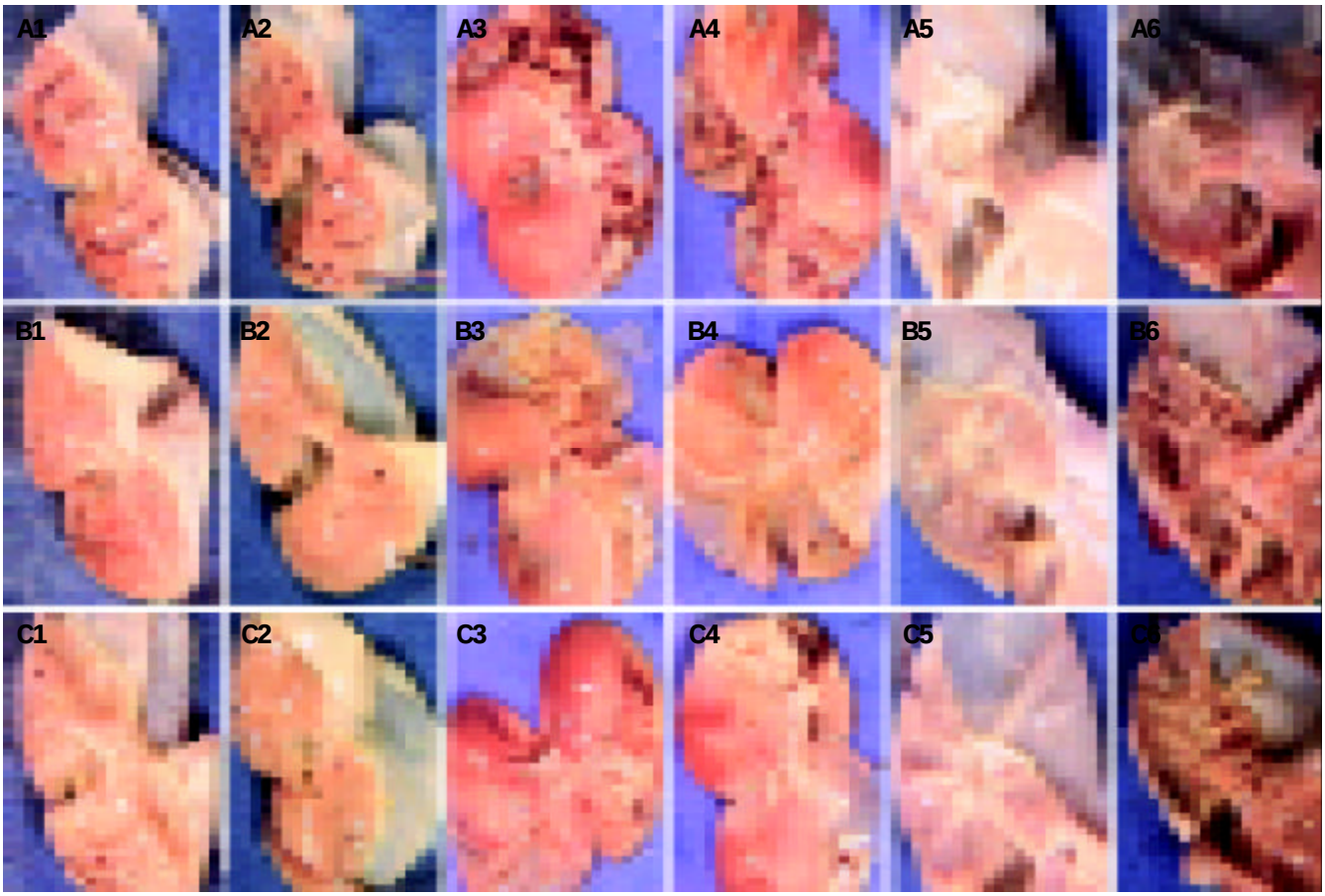

Figure 1 Effects of BPC 157 on gastric ulcers. A*n* (*n*=1-6), B*n* and C*n* represent the excipient control (im) or saline control (ig) group, famotidine group and BPC 157 (800 ng/kg) group, respectively. Numbers 1-6 represent indomethacin induced model (im, ig), pylorus ligation model (im, ig) and acetate induced model (im, ig), respectively.

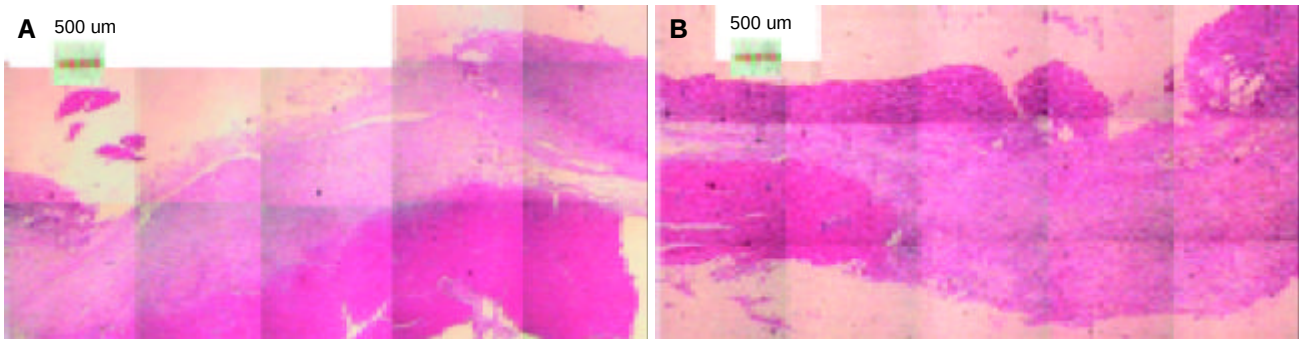

Figure 2 Effects of BPC 157 on regeneration of glandular epithelium and formation of granulation tissue in acetate induced chronic gastric ulcer. A, Saline control; B, BPC 157 (800 ng/kg) treated group.

DISCUSSION

Gastric pentadecapeptide BPC 157 is a widely studied molecule bearing cyto/organo- protective effects in many organs and can be administered in various ways. In the present study, we investigated the protective effects of chemically synthesized and purified BPC 157 on acute and chronic gastric ulcers in rats. The application way of the agent was also considered.

Generally, in acute and chronic induced gastric ulcers, im and ig administered gastric pentadecapeptide BPC 157 can prominently attenuate the syndrome in rats. When BPC 157 was im administered, the protective effect reached a statistical significance at a low dose (200 ng/kg) and the effect was better than that of famotidine, the positive control, at a higher dose (400 ng/kg or 800 ng/kg). When BPC 157 was ig administered, the effect was less than that when it was im administered, but better than that of saline controls. In the control, the ulcer area was larger. What was more, the synthesized BPC 157 had a high bioactivity especially in pylorus ligation induced animal model. The effective dosage of famotidine (40 mg/kg) was 50 times that (800 ng/kg) of BPC 157. In acetate induced chronic gastric ulcer model, both famotidine and BPC 157 could apparently antagonize protracted acetate challenge by accelerating rebuilding of glandular epithelium and formation of granulation tissue. Although the protective effect of famotidine was as good as certain dosages of BPC 157, granulation tissue formation was far less than that of BPC 157, so BPC 157 may act at least to some extent in a different way from famotidine.

Although the function of BPC 157 has been fully elucidated, the detailed mechanism of BPC 157 is still poorly understood. Sikiric *et al*. found that gastric pentadecapeptide BPC 157 attenuated chronic amphetamine disturbances and the effect was present throughout the observation period at a statistically

significant level. So they believed that BPC 157 had a modulatory effect on dopamine system[20]. In a haloperidol-induced gastric lesion model, both dopamine agonists (*i.e*., bromocriptine, amantadine) and gastric pentadecapeptide BPC 157 could antagonize these lesions, but other antiulcer agents (atropine, pirenzepine, misoprostol, pantoprazole, lansoprazole, cimetidine and ranitidine) were not as effective[10]. Besides, a particular interaction of BPC 157 with central dopamine system was also shown in other experimental models (*i.e*., protection of stress ulcers). Likewise, a considerable number of evidence for interaction of gastric peptides with dopamine system has been found in gastric mucosal protection studies.

However, Sikiric *et al*. found that although the dopaminomimetics (bromocriptine, apomophine and amphetamine) could apparently attenuate the otherwise consistent haloperidol or reserpine-gastric lesions when they were co-administered, their beneficial effects were absent in rats injured by haloperidol in combination with reserpine. On the other hand, BPC 157 was also effective. This result showed that BPC 157 might not act directly through dopamine system, but through a corresponding system parallel to dopamine system, and it might still function despite the extensive inhibition of endogenous dopamine system activity[22]. Considering the indicated GABA (gamma-amino butyric acid)/ dopamine system interactions, besides an anti-anxiety effect[14], BPC 157 might act through GABA. Jelovac[23] found that BPC 157 acted in favor of the natural homeostasis of the GABA receptor complex and of the GABAergic transmission, thus having a mechanism at least partly different from those involving diazepam tolerance/withdrawal.

With respect to the prolonged activity of BPC 157 and its surprisingly high activity (at ng level), it can be reasonably speculated that pentadecapeptide BPC 157 was most likely to act through the regulation of central nervous system (CNS) or some beneficial factors[24-28], and then might activate a cascade network, but not directly act on the target tissue or cells. It was reported that the disordered ratio of G/D cells, which can secrete gastrointestinal hormones gastrin and somatostatin, could lead to gastrointestinal dysfunction in acetic acid induced gastric ulcer model[29]. Maybe BPC 157 can antagonize the agents induced damage by modulating the number of G and D cells and maintaining the stable circumstances of stomach.

Although the mechanism of gastric ulcer has been studied for many years, the therapy of human gastric ulcer is still a hard nut to crack. Many substances have been investigated for the therapy of gastric ulcer, but few of them were found to be effective, some were bi-directional[30]. It is well known that human gastric ulcer is characterized by relapse and difficulty in prevention. So, emphasis of treatment of peptic ulcer should be put on preventing relapse. Wang *et al*.[31] found that traditional Chinese medicine Danshen (*Salvia miltiorrhiza*) was effective in promoting ulcer healing and preventing recurrence by strengthening gastric mucosal barrier and promoting gastric mucosal cell proliferation along the edge of the ulcer. The effect of BPC 157 on preventing gastric ulcer recurrence is under investigation.

In conclusion, BPC 157 is a potentially useful peptide and can be used in the treatment of human gastric ulcer. It may have other uses because of its multiple activity. Further studies on its mechanism are needed before we can benefit from this pentadecapeptide.

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