Protective effects of pentadecapeptide BPC 157 on gastric ulcer in rats

Xiao-Chang Xue, Yong-Jie Wu, Ming-Tang Gao, Wen-Guang Li, Ning Zhao, Zeng-Lu Wang, Chun-Jie Bao, Zhen Yan, Ying-Qi Zhang

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.

Xue XC, Wu YJ, Gao MT, Li WG, Zhao N, Wang ZL, Bao CJ, Yan Z, Zhang YQ. Protective effects of pentadecapeptide BPC 157 on gastric ulcer in rats. World J Gastroenterol 2004; 10(7): 1032-1036

http://www.wjgnet.com/1007-9327/10/1032.asp
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 mm²) was better than that of famotidine (the ulcer area 8.20 mm²). 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.

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, Figure 1).

| Administration | Agents          | Dosage (ng/kg) | Ulcer (mm²) | Inhibition ratio (%) |
|----------------|-----------------|----------------|-------------|---------------------|
| im             | Saline control  | -              | 19.22±2.95  | -                   |
|                | Excipient control| -              | 20.99±5.55  | -                   |
|                | Famotidine      | 40 000         | 8.20±4.68   | 60.8!               |
|                | BPC 157         | 200            | 9.71±5.00   | 53.5!               |
|                | BPC 157         | 400            | 7.22±4.01   | 65.5!               |
|                | BPC 157         | 800            | 7.22±4.64   | 65.5!               |
| ig             | Saline control  | -              | 20.18±8.50  | -                   |
|                | Famotidine      | 40 000         | 8.28±3.45   | 58.9!               |
|                | BPC 157         | 200            | 13.56±6.79  | 32.8                |
|                | BPC 157         | 400            | 9.92±2.62   | 50.8                |
|                | BPC 157         | 800            | 9.75±5.25   | 51.7!               |

Effects of BPC 157 on pylorus ligation induced gastric ulcer formation (n=10)

| Administration | Agents          | Dosage (ng/kg) | Ulcer (mm²) | Inhibition ratio (%) |
|----------------|-----------------|----------------|-------------|---------------------|
| im             | Saline control  | -              | 131.2±58.1  | -                   |
|                | Excipient control| -              | 130.2±68.2  | -                   |
|                | Famotidine      | 40 000         | 55.7±46.7   | 57.2!               |
|                | BPC 157         | 200            | 80.9±22.8   | 37.8!               |
|                | BPC 157         | 400            | 47.6±27.8   | 63.5!               |
|                | BPC 157         | 800            | 44.8±19.4   | 65.6!               |

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).

Effects of BPC 157 on pylorus ligation induced gastric ulcer formation (n=10)

| Administration | Agents          | Dosage (ng/kg) | Ulcer (mm²) | Inhibition ratio (%) |
|----------------|-----------------|----------------|-------------|---------------------|
| im             | Saline control  | -              | 13.66±4.10  | -                   |
|                | Excipient control| -              | 13.98±4.00  | -                   |
|                | Famotidine      | 40 000         | 9.18±3.04   | 34.3!               |
|                | BPC 157         | 200            | 9.75±3.62   | 30.2!               |
|                | BPC 157         | 400            | 6.81±3.67   | 51.3!               |
|                | BPC 157         | 800            | 5.60±1.91   | 59.9!               |
| ig             | Saline control  | -              | 14.96±6.21  | -                   |
|                | Famotidine      | 40 000         | 3.20±1.54   | 78.6!               |
|                | BPC 157         | 200            | 9.78±4.28   | 34.6!               |
|                | BPC 157         | 400            | 8.13±2.84   | 45.7!               |
|                | BPC 157         | 800            | 7.80±2.63   | 47.8!               |

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

P<0.05, P<0.01 vs excipient control (im) or saline control (ig).
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, cinmetidin and ranitidine) were not as effective[21]. 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, apomorphine 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[10], 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 GABergic 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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Edited by Wang XL and Xu FM Proofread by Zhu LH