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Effect of polaprezinc on impaired healing of chronic gastric ulcers in adjuvant-induced arthritic rats – role of insulin-like growth factors (IGF)-1

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SUMMARY

Polaprezinc, N-(3-aminopropionyl)-L-histidinatozinc, has been shown to stimulate the prodution of insulin-like growth factor-1 (IGF-1) in mesenchymal cells, the polypeptide playing a role in the gastric epithelial wound repair. The present study was performed to examine the effect of polaprezinc on the impaired healing of chronic gastric ulcers in adjuvant-induced arthritic rats, in relation to IGF-1. Arthritis was induced in male Dark Agouti (DA) rats by a single injection of Freund's complete adjuvant (FCA), and the gastric ulcers were induced by thermal cauterization (70°C for 30 sec) 7 days after FCA injection. Omeprazole (30 mg/kg) was administered p.o. once daily, while recombinant human IGF-1 (rhIGF-1) (30 μg/kg, s.c.) or polaprezinc (3∼10 mg/kg, p.o.) was administered twice daily, starting from 3 days after ulceration for 14 days. The healing of gastric ulcers was significantly delayed in arthritic rats as compared to normal rats on day 10 and 17 following ulceration. The expression of IGF-1 mRNA was markedly increased in the ulcerated mucosa, but this response was apparently attenuated in arthritic rats. Repeated administration of polaprezinc accelerated the healing of gastric ulcers in both normal and arthritic rats, in a dose-dependent manner, and this effect was more pronounced in arthritic rats. Likewise, treatment with omeprazole also significantly promoted the healing of gastric ulcers in both normal and arthritic rats. On the other hand, rhIGF-1 significantly promoted the gastric ulcer healing in arthritic rats without any effect on that in normal rats. These results suggest that the impaired healing of chronic gastric ulcers in arthritic rats is, at least partly, accounted for by less expression of IGF-1, and the polaprezinc improves the delayed healing of gastric ulcers in arthritic rats, probably through an increase in IGF-1 production.

BACKGROUND

Rheumatoid arthritis (RA) is a systemic and chronic autoimmune disease characterized by joint swelling, synovial inflammation and cartilage destruction. It has been reported that the patients with RA are more susceptible to non-steroidal anti-inflammatory drugs (NSAIDs)-related gastropathy than other NSAID users [1]. Indeed, several investigators reported that gastric lesions induced by various ulcerogenic stimuli, such as pyloric ligation, stress or NSAIDs, were markedly worsened in experimentally-induced arthritic animals [2–4]. We have recently found that the healing of chronic ulcers was also significantly delayed in arthritic rat stomachs, with a decreased expression of basic fibroblast growth factor (bFGF) and suggested the involvement of dysregulation of bFGF in the impaired healing of gastric ulcers observed in arthritic conditions [5]. However, there is no report

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concerning the relation of other growth factors, such an insulin-like growth factor-1 (IGF-1), to the delayed healing of gastric ulcers in arthritic rats.

Polaprezinc [N-(3-aminopropionyl)-L-histidinatozinc] is a chelate compound consisting of zinc and L-carnosine [6]. This agent not only prevents gastric mucosal lesions in various experimental models but also shows the healing promoting effect on gastric ulcers [6,7]. This action of polaprezinc may be accounted for by stimulation of mucus secretion and antioxidant action, although the exact mechanism remains unknown [8–10]. It has been recently demonstrated that polaprezinc stimulates the IGF-1 production in mesenchymal cells, the polypeptide playing an important role in the gastric epithelial wound healing [11]. We also found that polaprezinc promoted the delayed healing of acute gastric lesions in diabetic rats, through up-regulation of the IGF-1 expression [12]. Thus, it is possible that polaprezinc might improve the impaired ulcer healing in arthritic rats, which might occur in association with a decreased production of IGF-1.

In the present study, we investigated the possible involvement of IGF-1 in the impaired healing of chronic gastric ulcers in arthritic rats, and examined the effect of the polaprezinc, a stimulator of IGF-1 expression, on the healing of gastric ulcers in these animals.

MATERIAL AND METHODS

Animals

Male Dark Agouti (DA) rats (140–160 g, SLC, Shizuoka, Japan) were used. The animals were fed standard rat chow and tap water ad libitum. All experimental procedures described were approved by the Experimental Animal Research Committee of the Kyoto Pharmaceutical University. Studies were carried out using four to six animals per group under unanesthetized conditions.

Induction of arthritis

Arthritis was induced by a single injection of 50 μl Freund's complete adjuvant (FCA; 10 mg/ml heat-killed Mycobacterium tuberculosis H37Ra suspended in paraffin oil) into the plantar region of the right hindfoot. Normal rats were housed in the same manner for the same period, so that we used age- and batch-matched normal and arthritic rats in all of the following experiments. The severity of arthritis was assessed by measuring paw volume.

Induction of chronic gastric ulcers

Chronic gastric ulcers were induced by thermal cauterization on day 7 after the FCA injection, according to the method described previously [13]. Under ether anesthesia, the stomach was exposed through a midline incision, the electric probe (Fuchigami, Kyoto, Japan, diameter 9 mm) was attached to the serosa of the mid-corpus, and a gastric ulcer was induced by heating the tip at 70°C for 20 sec. The animals were killed on various days (3, 10 and 17 days) after ulceration. Then, the stomachs were removed, inflated by injection of 7 ml of 2% formalin, and immersed in 2% formalin to fix the tissue wall, and opened along the greater curvature. The area (square millimeter) of each ulcer crater was measured under a dissecting microscope (x10). Omeprazole (30 mg/kg, p.o.) was administered once daily for 14 days, starting 3 days after ulceration, while polaprezinc (3, 10 and 30 mg/kg) or rhIGF-1 (30 μg/kg, s.c.) was administered twice daily for the same period.

Analysis of IGF-1 gene expression

The expression of the IGF-1 mRNA was analyzed in both the intact and ulcerated gastric mucosa on day 10 following ulceration, according to the method described by Watanabe et al. [11]. Briefly, rats were killed by deep ether anesthesia, and both intact and ulcerated portions were excised from the same animal. Total cellular RNA was isolated from cells using an ISOGEN RNA extraction kit (Wako Pure Chemical Inc, Osaka, Japan). RT-PCR and southern blot analysis assessed IGF-1 mRNA contents. First-stand cDNA synthesis was performed by a reverse transcription of 0.08 μg of total RNA using Moloney murine leukemia virus (M-MLV) reverse transcriptase (TOYOBO, Tokyo, Japan). For IGF-1.2 μl of the cDNA was amplified by Taq DNA polymerase in conditions programmed as follows: 32 cycles of PCR (30 sec at 94°C, 30 sec at 57°C, 45 sec at 72°C), following by a final 7 min extension at 72°C. The primers for IGF-1 had the following sequences: sense 5′-GTACTTCAGAAGCAA-TGGGA-3′, antisense 5′-GGTGCGCAATACATCTCCAG3′. A portion of the PCR products was loaded on 3% agarose gel for electrophoresis, and the products were transferred onto nylon membranes after the gels were stained by ethidium bromide (Hybond N^+; Amersham, Little Chalfont, Bucks, UK). After prehybridization, the nylon membranes were hybridized with cDNA-labeled FI (fluorescein) using PCR. Hybridization

Table 1. Effects of various drugs on changes in paw volume and body weight in adjuvant-induced arthritic ratse.

Treatment	Dose	No. ofrats	Paw Edema (△ml)	Body Weight (g)
Normal	-	5	0.02±0.05	190±5
Control	-	6	1.28±0.08#	129±1#
Omeprazole	30 mg/kg	6	1.03±0.13#	131±4#
rhIGF-1	30 ug/kg	5	1.29±0.26#	140±3#
Polaprezinc	3 mg/kg	6	1.28±0.17#	132±3#
	10 mg/kg	6	1.34±0.10#	139±3#
	30 mg/kg	5	1.35±0.13#	128±3#

Values are presented as the mean±SE from 5 or 6 rats per group. Arthritis was induced by injection of Freund's complete adjuvant (FCA) into the planter region of the right hindfoot, and the measurements were done 24 after FCA injection (day 17 following ulceration). Omeprazole (30 mg/kg, p.o.) was administered once daily, while rhIGF-1 (30μg/kg, s.c.) or polaprezinc (3, 10 and 30 mg/kg, p.o.) was administered twice daily, starting from day 3 following ulceration for 14 days. # Statistically significant difference using a one-way analysis of variance followed by the Dunnett's multiple comparison test from normal rats at $P<0.05$, No statistically significant difference was found between the control and any other treated groups.

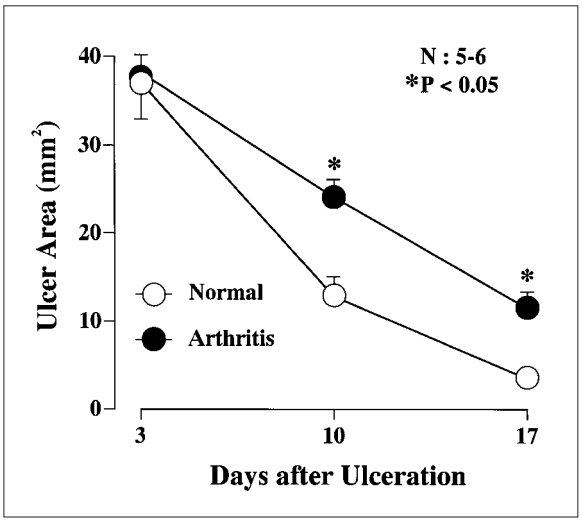

Figure 1. Changes of ulcer area in normal and arthritic rats after ulceration. Arthritis was induced by injection of Freund's complete adjuvant (FCA) into the planter region of the right hindfoot, and the ulcer was induced by thermal cauterization (70°, 30 sec) 7 days after the FCA injection. The animals were killed on day 3, 10 and 17 following ulceration. Data are presented as the mean±SEM from 5 or 6 rats. *Statistically significant difference using a t-test from normal rats.

was performed for two days at 42°C in the presence of 50% formamide. The cDNA probes were prepared from rat stomach cDNA libraries and the probes covered a region of amplified fragment. Detection of signals on x-ray film was performed using ECL detection kit (Amersham) with anti-FI antibody-labeled horseradish peroxidase. X-ray film analysis was performed by an image analyzer V10 (TOYOBO).

Preparation of drugs

Drugs used in this study were heat-killed Mycobacterium tuberculosis (H37Ra: Difco, Detroit, MI, USA), paraffin oil (Wako, Osaka, Japan), omeprazole (Hassel, Mondale, Sweden), recombinant human IGF-1 (Fujisawa Pharmaceutical Co, Ltd, Osaka, Japan) and polaprezinc (Zeria Pharmaceutical Co, Ltd, Saitama, Japan). Omeprazole and polaprezinc were in 0.5% carboxymethylcellulose (CMC) solution, while the other drugs were dissolved in saline. All drugs were prepared immediately before use and given in a volume of 0.5 ml per 100 g body weight.

Statistical analysis

Data are presented as the means±SE from 5~6 rats per group. Statistical analyses were performed using a t-test or a one-way analysis of variance followed by the Dunnett's multiple comparison test, and values of $P<0.05$ were considered as significant.

RESULTS

Occurrence of adjuvant-induced arthritis

Single injection of FCA into the right hindfoot induced severe arthritis in all animals. The volume of the left hind paw (the uninjected paw) did not change for the first 7 days, but apparent increases in paw volume were observed from day 10, reaching a maximum 24 days after FCA injection. The increases in uninjected paw (left) volume of arthritic rats was 1.28±0.01 ml on day 24 following FCA injection (17 days after ulceration)(table 1). In contrast, the repeated administration of neither omeprazole (30 mg/kg, p.o.), rhIGF-1 (30 μg/kg, s.c.) nor polaprezinc (3–30 mg/kg, p.o.) has any effect on the paw edema in these animals. On the other hand, arthritic rats also showed less body weight gain after the FCA injection as compared to normal rats. This body weight response in arthritic rats was not affected by daily treatment with any of these drugs.

Healing of gastric ulcers in normal and arthritic rats

Three days after subjecting the stomach to thermal cauterization, well-defined ulcers developed in the corpus mucosa of both normal and arthritic rats.

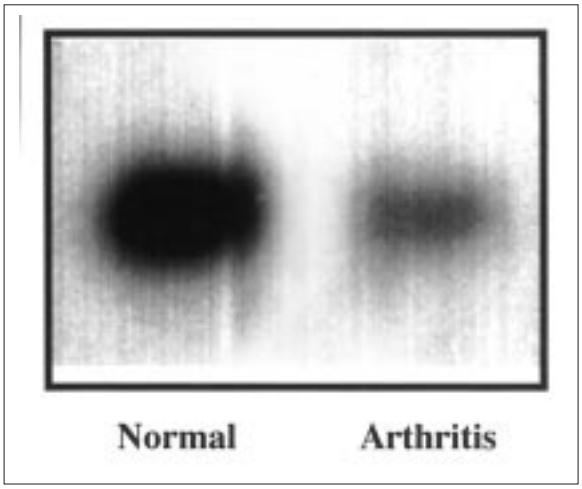

Figure 2. Expression of IGF-1 mRNA in the intact and ulcerated gastric mucosa of normal and arthritic rats on day 10 following ulceration). Note that the mucosal expression of IGF-1 mRNA was detected slightly in the intact mucosa of both rats, while the expression in the ulcerated mucosa was markedly enhanced in the ulcerated mucosa of the former but not the latter. N: normal rats; A: arthritic rats.

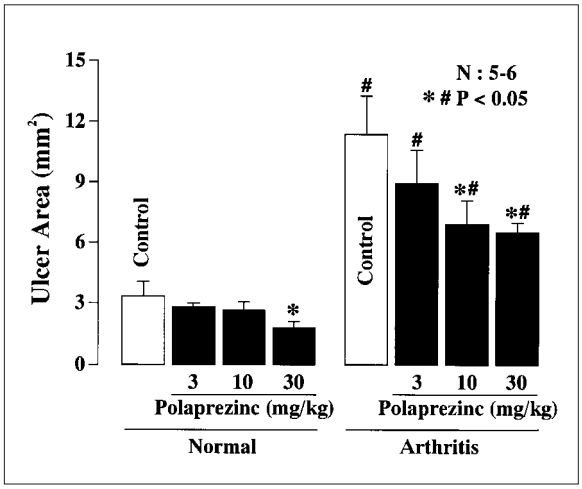

Figure 3. Effects of omeprazole and recombinant human insulin-like growth factor (rhIGF)-1 on the healing of gastric ulcers in normal and arthritic rats. The animals were administered omeprazole (30 mg/kg, p.o.) once daily, and rhIGF-1 (30 {mikro - symbol}g/kg, s.c.) twice daily for 14 days, starting from 3 days after ulceration, and they were killed 17 days later. Data are presented as the mean ± SEM from 5 or 6 rats. Statistically significant differences using a one-way analysis of variance followed by the Dunnett's multiple comparison test at P<0.05; *from the respective control; #from the normal rats.

The area of the ulcers did not significantly differ between these two groups, the ulcer areas on day 3 after ulceration being 37.0±4.1 mm^2 and 38.0±2.1 mm^2, respectively (figure 1). In normal rats, these ulcers healed gradually, and the ulcer areas on day 10 and 17 following ulceration were 12.8±2.2 mm^2 and 3.4±0.7 mm^2, respectively. In contrast to normal rats, the healing of gastric ulcers was significantly delayed in arthritic rats on day 10 and 17 following ulceration, the ulcer areas on day 10 and 17 being 24.0±2.0 mm^2 and 11.4±1.9 mm^2, respectively, which were significantly greater than that in normal rats.

Expression of IGF-1 mRNA in the gastric mucosa

The expression of IGF-1 mRNA was markedly up-regulated in the normal rat stomachs on day 17 after ulceration, although the IGF-1 mRNA was slightly observed even in the intact mucosa of both normal and arthritic rats (Figure 2). However, in the ulcerated mucosa of arthritic rats, this increased expression of IGF-1 mRNA was apparently decreased when compared to that in the ulcerated mucosa of normal rats.

Effect of omeprazole, rhIGF-1 and polaprezinc on healing of gastric ulcers

Daily administration of omeprazole (30 mg/kg, p.o.) for 14 days promoted the gastric ulcer healing

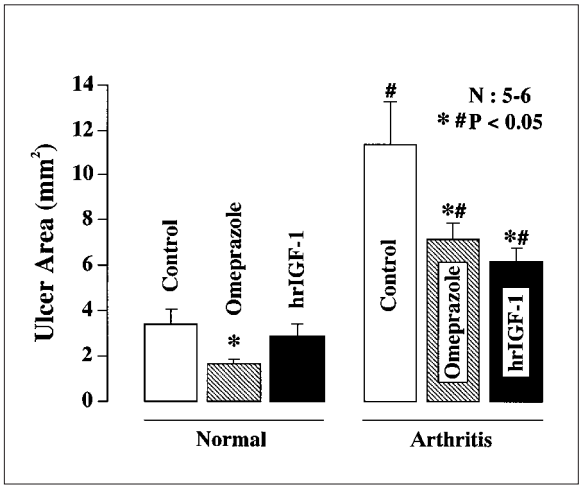

Figure 4. Effects of polaprezinc on the healing of gastric ulcers in normal and arthritic rats. The animals were administered p. o. polaprezinc (3, 10 and 30 mg/kg) twice daily for 14 days, starting from 3 days after ulceration, and they were killed 17 days later. Data are presented as the mean ± SEM from 5 or 6 rats. Statistically significant differences using a one-way analysis of variance followed by the Dunnett's multiple comparison test at P<0.05; *from the respective control; #from the normal rats.

in both normal and arthritic rats, the ulcer scores being 1.7±0.2 mm^2 and 7.2±0.7 mm^2, respectively, both of which were significantly smaller as compared to those (3.4±0.7 mm^2 and 11.4±1.9 mm^2) in control rats received the vehicle alone. In contrast, rhIGF-1 (30 μg/kg, s. c.) accelerated the gastric ulcer healing in arthritic rats, without affecting the ulcer healing in normal rats. The ulcer score on day 17 in arthritic rats was 6.2±0.6 mm^2, which was significantly different from that in the control group (Figure 3). On the other hand, the repeated treatment with polaprezinc (3, 10 and 30 mg/kg, p.o.) given twice daily for 14 days promoted the healing of gastric ulcers in both normal and arthritic rats, in a dose-dependent manner, the ulcer areas at 30 mg/kg being 1.9±0.3 mm^2 and 6.2±0.6 mm^2, respectively (Figure 4). Of interest, the healing promoting effect of polaprezinc was more pronounced in the arthritic rats; the significant effect was observed at over 10 mg/kg, while that in normal rats was obtained only at 30 mg/kg.

DISCUSSION

We confirmed in the present study that healing of gastric ulcers was markedly delayed in adjuvant-induced arthritic rats [5] and further found that these rats showed a decreased expression of IGF-1 in the gastric mucosa. We also found that polaprezinc, a stimulator of IGF-1 synthesis, as well as rhIGF-1 significantly improved the delayed ulcer healing in arthritic rats. It is therefore assumed that the impaired ulcer healing observed in arthritic conditions is attributable, in part, to a decreased production of IGF-1, in addition to other growth factors such as bFGF [5].

We have recently reported that the healing of chronic gastric ulcers induced by thermal cauterization was significantly delayed in adjuvant-induced arthritic rats, with a decreased expression of bFGF [5]. Since exogenous bFGF improved the delayed healing response in these animals, we suggested that the impaired ulcer healing observed in arthritic rats was, at least partly, due to the bFGF deficiency. However, the involvement of other growth factors such as IGF-1 in this phenomenon remains unknown. IGF-1, one of the key mediators regulating soft tissue repair, is released from platelet granules immediately after injury and plays an important role in angiogenesis and epithelialization in injured tissues [11,14–16]. Indeed, we observed in the present study that IGF-1 mRNA was markedly up-regulated in the gastric mucosa after ulceration in normal rats, similar to bFGF [5]. In arthritic rat stomachs, however, the expression of IGF-1 was apparently decreased after ulceration, although there was no difference in the intact mucosa between normal and arthritic rats. These results suggest that the impaired IGF-1 synthesis in arthritic rat stomachs following ulceration may occur at the pretraslational level, involving transcription or RNA turnover. Since the delayed healing of gastric ulcers observed in arthritic rats was significantly improved by daily supplementation with rhIGF-1, it is likely that the decreased IGF-1 production may be involved in the mechanism for the delayed ulcer healing in arthritic conditions. We previously reported that diabetic animals also showed a delayed healing of gastric ulcers and also exhibited a decreased expression of IGF-1 mRNA in the stomach [17]. Thus, it may be assumed that dysregulation of IGF-1 production, in general, results in delayed healing of gastric ulcers.

As expected, polaprezinc, a complex chelating agent consisting of doubly deprotonate L-carnosine (β-alanyl-L-histidine) [6], significantly promoted the healing of chronic gastric ulcers in both normal and arthritic rats, and this effect was more pronounced in the latter group, suggesting an improvement of delayed ulcer healing in IGF-1 deficient conditions. Zinc is an essential trace element for the activities of many metalloenzymes, among them the DNA and RNA polymerases being crucial for tissue repair. Indeed, zinc deficiency delayed porcine skin and connective tissue wound repair [18]. Watanabe et al [11] reported that polaprezinc stimulated IGF-1 production in mesenchymal cells and expedited the gastric epithelial wound healing. Recently, we also observed that polaprezinc enhanced the gene expression of IGF-1 in the gastric mucosa of diabetic animals [12]. Therefore, it is possible that the salutary effect of polaprezinc on the impaired healing of gastric ulcers in arthritic rats may be, in part, attributable to an increased IGF-1 production through a concerted effect on different cell types at various stages in the healing process.

It should be noted in the present study that polaprezinc accelerated the ulcer healing in both normal and arthritic rats, whereas rhIGF-1 promoted the healing in arthritic rats but not in normal rats. This phenomenon remains unexplained at present, yet these different effects may be explained by some actions of polaprezinc other than stimulation of IGF-1. Indeed, polaprezinc has been demonstrated to show a prostaglandin-independent cytoprotection and membrane stabilization as

well as antioxidant activity [10,19,20]. Thus, it is possible that the potent healing promoting action of polaprezinc appears through those combined effects at various stages in the healing process, although the events associated with IGF-1 should play a major role in the healing promoting action. On the other hand, we also observed that omeprazole exhibited a significant healing promoting effect in both normal and arthritic rats, similar to polaprezinc. However, the latter compound has been shown to devoid of the antisecretory effect [6], the mechanism should be different between these two drugs; the omeprazole action is mainly due to inhibition of acid secretion, while the polaprezinc effect, as shown in this study, may be ascribed mainly to stimulation of IGF-1.

CONCLUSION

The present results taken together suggest that arthritic rat stomachs decreased IGF-1 production, and this may account at least partly for the impaired healing of gastric ulcers in these animals. Polaprezinc may improve the impaired ulcer healing in arthritic rats, probably through an increase of IGF-1 production. Thus, it is assumed that polaprezinc may be useful for treatment of peptic ulcers in arthritic patients, that frequently occur as an adverse reaction of NSAIDs.

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