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Gastroprotective Effects of Betahistine Against an Indomethacin-Induced Gastric Mucosal Ulcer in Rats: The Role of CINC-2α Gene

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Abstract

Background: The role of histamine H3 receptors (H3Rs) in gastric protection and anti-inflammatory function is controversial. In this study, we investigated the gastroprotective effect of a histamine H3 receptor antagonist drug, betahistine, on cytokine-induced neutrophil chemoattractant (CINC) gene expression in a rat model of indomethacin-induced gastric mucosal injury.

Methods: In this experiment, rats were divided into four groups; the control group received no treatment, group 2 was treated with indomethacin at a dose of 25 mg/kg, group 3 pre-treated with famotidine at a dose of 50 mg/kg, and group 4 pre-treated with betahistine (as a reference drug) at a dose of 50 mg/kg. The last two groups were followed by indomethacin administration (25 mg/kg), three days later. The obtained values were expressed as the mean and standard error of the mean (mean ± SEM). The level of statistical significance was set at $\alpha = 0.05$

Results: Indomethacin treatment resulted in large ulcerative lesions with a mean ulcer index of 29± 13.63 mm. However, ulcerative indices were significantly improved in groups pre-treated with famotidine (15.5 ± 8.68 mm; $P < 0.05$) and betahistine (11±5.66 mm, $P < 0.01$), compared to the indomethacin-treated group. The expression levels of gastric CINC-2α were significantly elevated in indomethacin-induced groups by 0.028±0.05 in the indomethacin group, 0.005±0.01 in indomethacin + famotidine, and 0.012±0.03 in indomethacin + betahistine groups, compared to the control group ($P < 0.05$). Besides, pre-treatment with betahistine significantly reduced the expression of CINC-2α induced by indomethacin administration ($P < 0.05$).

Conclusion: Betahistine for five days before administrating indomethacin reduced the ulcer index and downregulated the expression of CINC-2α significantly. Overall, pre-treatment with betahistine protects against the gastric damage induced by indomethacin by lowering the expression of CINC-2α.

Keywords: Betahistine, H3 receptor antagonist, Cytokine-induced neutrophil chemoattractant, Non-steroidal anti-inflammatory drugs, Gastric ulcer

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↑What is "already known" in this topic:
A peptic ulcer is a prevalent health issue that impacts approximately 10% of the global population. Various medications, such as proton pump inhibitors, histamine H2 receptor antagonists, anticholinergics, antacids, antibacterial medicines, sucralfate, and bismuth, have been shown to be ineffective and can have adverse effects. Previous experimental models of gastric injury have produced conflicting results regarding the influence of the histamine H3 receptor (H3R) on gastric acid secretion.

→What this article adds:
This finding suggests that betahistine (an H3R antagonist) may have a potential therapeutic role in preventing indomethacin-induced gastric damage through its modulation of CINC-2α levels.

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Introduction

A stomach ulcer, also called a peptic ulcer, is a common health problem that affects up to 10% of the world's population. A peptic ulcer is histologically a rupture in the inner layer of the stomach that can have negative effects on the quality of life (1, 2). Peptic ulcers were originally considered to be caused mostly by Helicobacter pylori infection, stress, poor nutrition, alcohol use, and nonsteroidal anti-inflammatory medications (NSAIDs) (2). One of the current issues in stomach ulcer therapy is antibiotic resistance against Helicobacter pylori infection in conjunction with NSAIDs (2). Several medications, including proton pump inhibitors, histamine H_2 receptor antagonists, anticholinergics, antacids, antibacterial medicines, sucralfate, and bismuth, are ineffective and have a variety of negative effects (1). In light of the increased frequency of stomach ulcers in the community, it seems that novel medicines with fewer side effects should be studied for the treatment of this condition (1).

Previous experimental in-vitro and in-vivo models of gastric injury have revealed conflicting evidence on the impact of the histamine H_3 receptor (H_3R) on gastric acid secretion; however, the mechanism of action of this phenomenon is unclear (1). The role of this receptor seems to be different in different species and experimental techniques (3, 4).

Immune cells produce many immune cell derivatives during inflammation, including histamine, nitric oxide, TNF-α, IL-1β, IL-6, and IL-8 (5). Histamine is one of the inflammatory agents inducing vascular permeability and edema. Many studies have shown that H_3 receptor activation causes pro-inflammatory activity; hence, the use of H_3 receptor antagonists might play an essential role in reducing the generation of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. H_3R antagonists have been shown to reduce the production of pro-inflammatory cytokines induced by the H_3R. Therefore, the use of H_3R antagonists can play an important role in preventing inflammation in many diseases (6, 7). Also, pro-inflammatory cytokines, such as IL-1β and TNF-a, have been shown to stimulate cytokine-induced neutrophil chemoattractant (CINC) production (8). In research conducted both in vitro and in vivo settings, it was revealed that CINC is a chemokine produced by rats that particularly stimulates neutrophil infiltration (8, 9).

Betahistine (N-methyl-2-pyridylethylamine) is commonly indicated for the decrease of recurrent vertigo episodes associated with Meniere's disease in many patients. Betahistine, which acts as a powerful affinity antagonist for histamine H_3R and a weak affinity as an agonist for histamine H_1R, is commonly indicated to reduce recurrent vertigo episodes associated with Meniere's disease in many patients. This is because betahistine acts as an agonist for histamine H_1R (10).

In the current study, we postulated the hypothesis that betahistine has gastroprotective and wound-healing properties due to its action on H_3R. The present research seeks to determine whether betahistine pre-treatment might minimize the incidence of indomethacin-induced acute gastric ulcer in rats, as well as the functions of CINC-2 in neutrophil infiltration of ulcerated gastric tissue in male Wistar rats.

Methods

Animals

In this study, 24 adult male Wistar rats weighing 200-250 g were purchased from the Research Institute of Medicinal Plants, affiliated with Academic Jihad of Alborz province, and then divided into four groups (n=6 rats per each group). The experiment was conducted under controlled laboratory conditions (ambient temperature 20-25°C, relative humidity 60-65%, and light: dark cycles of 12h/12h) in which the animals had free access to food and water (11). This study was carried out in accordance with the guidelines provided by the Care and Use of Laboratory Animals established by the National Egyptian Community (12). All efforts were made to minimize animal suffering and reduce the number of animals used.

Chemicals and drugs

Betahistine was purchased from Abbott Laboratories Inc. (North Chicago, Illinois, USA). Indomethacin and famotidine were procured from Hakim Company (Tehran, Iran). Other drugs and chemicals were purchased from Histogenotech Laboratory (Tehran, Iran). All drug solutions were freshly prepared and applied.

Experimental design

Rats were randomly assigned into four experimental groups (n=6 rats per each group). Group 1 comprised normal rats receiving no treatments. Group 2 received carboxymethyl cellulose solution (CMC) by gavage (13). Group 3 orally received famotidine at a dose of 50 mg/kg for 3 days before indomethacin administration (used as a standard reference drug). Group 4 was treated with betahistine at a dose of 50 mg/kg for 5 days before the administration of indomethacin (25mg/Kg). (14). All drug solutions were administered to animals by intragastric gavage. All animals were fasted for 24 hours before indomethacin administration, except for water to eliminate the exogenous food effect.

Gastric ulcer induction

Previous reports have shown that indomethacin caused gastric ulceration (15). On the sixth day, mice were deprived of food for 24 hours with free access to water. On the seventh day, 25 mg/kg indomethacin was administered via intragastric gavage to all groups except the control group.

Collection of samples

Rats were anesthetized by placing them in a carbon dioxide chamber for four hours after indomethacin administration. Parallel to the spinal cord of the rats, their stomachs were cut in a way the incision was made along the greater curvature according to a method established by (1). The stomach was rinsed with cold normal saline to remove

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Table 1. The sequences of the designed primers

Gene	Primer
r-GAPDH	F: AGGTCGGTGTGAACGGATTTG
	R: TGTAGACCATGTAGTTGAGGTCA
r-CINC2a	F: CTGCTTCTGCTGCTTCTGCT
	R: GGCTATGACTTCTGTCTGGGTG

any adherent food particles and mucus. The stomach was then placed on a corkboard to provide a clear macroscopic image of the gastric mucosa, and bleeding lesions were evaluated. Lesions were ranked according to the length and severity using a 3-point scoring system. Severity factor 1 denotes lesions less than 1 mm in length, severity factor 2 denotes lesions 1-2 mm in length, and severity factor 3 implies lesions more than 2 mm in length (16). Then, a portion of stomach tissue was removed for quantitative reverse transcriptase PCR (qRT-PCR) analysis (including ulcerative lesions wherever they occurred).

Gene expression analysis using real-time PCR

The total RNA was isolated from gastric tissue using a commercial RNA extraction kit (QIAGENE). PCR was performed using the TaqMan One-Step RT-PCR kit. The sequences of the designed primers are listed in Table 1.

Analysis of relative gene expression data was performed by normalizing the corresponding gene with the housekeeping gene using the $2^{-\Delta\Delta CT}$ method (13). All experiments were carried out in duplicates, and all specimens were collected in three biological replicates.

Statistical analysis

The obtained values were expressed as the mean and standard error of the mean (mean ± SEM). The difference between the groups was analyzed using a one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. The level of statistical significance was set at $P < 0.05$. The analysis of the data was conducted by the SPSS software version 20.

Results

Effect of betahistine pre-treatment on the ulcer index

In the control group, no obvious abnormalities were detected (Figure 1, a). Nonetheless, indomethacin treatment resulted in large ulcerative lesions dispersed over the mucosal surface of the stomach (Figure 1 b). There were improvements in ulcerative lesions in Famotidine + Indomethacin (Figure 1 c) and Betahistine + Indomethacin groups (Figure 1 d). The mean ulcer index in the Indomethacin group was 29± 13.63 mm (Figure 2). However, ulcerative indices were significantly improved in groups pre-

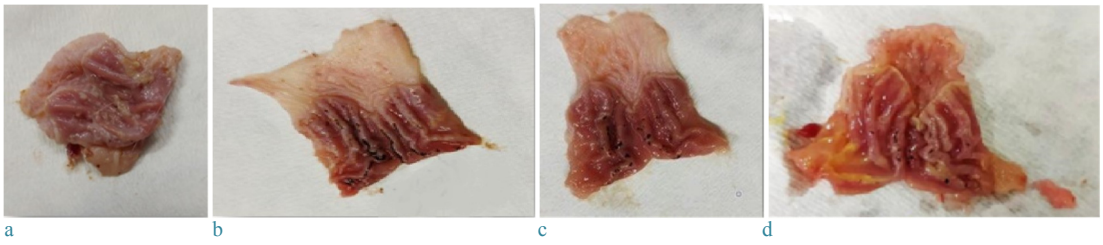

Figure 1. Macroscopic evaluation of gastric ulcers in the studied groups.
The maximum amount of stomach damage caused in each group is given for comparison.
a: Control group
b: Indomethacin group
c: Famotidine + Indomethacin group
d: Betahistine + Indomethacin group

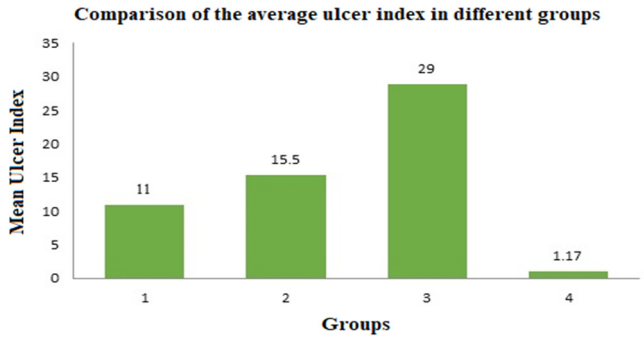

Figure 2. Comparison of the average gastric ulcer index obtained in the studied groups, ulcerative indices were significantly improved in groups pre-treated with famotidine (15.5 ± 8.68 mm; $P < 0.05$) and betahistine (11 ± 5.657 mm $P < 0.01$) compared with the indomethacin-treated.
group-1: control group.
group-2: Indomethacin
group-3: Famotidine + Indomethacin;
group-4: Betahistine + Indomethacin;

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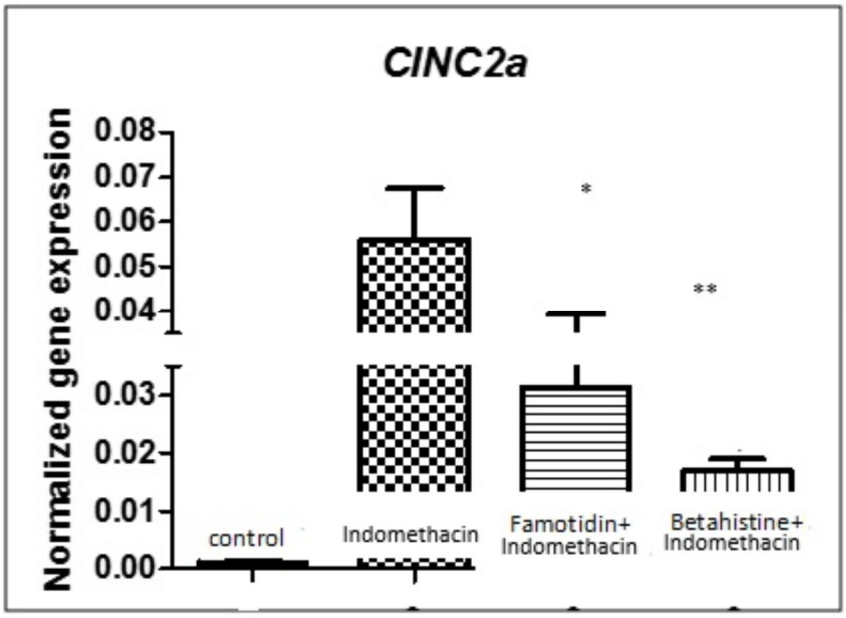

Figure 3. Comparison of the CINC-2α gene expression in gastric mucosa in the studied groups. P <0.01**; P < 0.05*. CINC-2a expression was significantly improved in groups pre-treated with famotidine (P < 0.05) and betahistine (P < 0.01) compared with the indomethacin-treated group

treated with famotidine (15.5 ± 8.68 mm; P < 0.05) and betahistine (11 ± 5.66 mm, P < 0.01) compared with the indomethacin-treated group.

Effect of betahistine on gene expressions of CINC-2a levels

The expression analysis of the CINC-2α gene in gastric mucosa indicated that the expression of this gene was increased in all experimental groups except for the control group (Figure 3).

Compared with the control group, the expression levels of gastric CINC-2α were significantly elevated in indomethacin-induced groups by 0.028 ± 0.05 in the indomethacin group, 0.005 ± 0.01 in indomethacin + famotidine group, and 0.012 ± 0.03 in indomethacin + betahistine group, compared to the control group.

Besides, pre-treatment with betahistine significantly reduced the increased expression of CINC-2α induced by indomethacin administration, compared to the control group. On the other hand, gastric CINC-2α levels were significantly decreased in the betahistine-treated group by 69.7% compared with the indomethacin-induced group. Surprisingly, the CINC-2α level was upregulated in the famotidine-treated group when compared with the betahistine-treated group.

Discussion

The present study demonstrated the gastrointestinal protective effect of betahistine measured through its anti-inflammatory effects using macroscopic evaluation (Figure 1 a). The ulcer index was comparable with gastric ulcer caused by indomethacin (Figure 2). Although peptic ulcer is a common disease whose cause, diagnostic methods, and treatment are well known, its complications are still one of the main causes of death in humans worldwide (17). Many pathogenic mechanisms can cause peptic ulcers, such as NSAIDs, psychological stress, and Helicobacter pylori infection (15, 17). To date, one of the methods to induce ulcers in the stomach of animals is the use of indomethacin, a representative of NSAIDs causing the generation of ROS, initiation of lipid peroxidation, infiltration of leukocytes, and inhibition of prostaglandin synthesis (17). Many conventional medicines are already available to treat stomach ulcers, but their prolonged usage has been linked to adverse effects, including impotence, arrhythmia, hematopoietic alterations, hypersensitivity, and gynecomastia (1, 17).

Histamine exerts biological activities, such as mediating inflammation and regulating innate and adaptive immunity through interacting with four distinct histamine receptors (H_1, H_2, H_3, and H_4) belonging to the G-protein coupled receptor (GPCR) family. It has been reported that these types of receptors are differentially expressed throughout the body (1, 18). H_3R is expressed pre-synaptically as an autoreceptor through Gi/o-proteins to regulate histamine release and as hetero-receptors on non-histaminergic neurons, and blocking the neurotransmitter release, such as acetylcholine, dopamine, serotonin, norepinephrine, and GABA (19). Thus, histamine controls the release of neurotransmitters in the central and peripheral nervous system through presynaptic H_3R (20).

Although the role of H_3R antagonists in the treatment of many disorders, such as COPD, asthma, ADHD, cognitive disorders, obesity, and allergic rhinitis, has been identified (21), the functionality of H_3 receptors in the release of histamine and gastric acid secretion is not fully known in in-vivo studies (1). H_3R appeared to be present exclusively in endocrine cells scattered in the gastrointestinal mucosa and gastric fundus, whereas they are rarely found in other regions (1, 22). Some research has shown that stimulation of H_3 receptors increases gastric acid secretion, while other

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studies have found the opposite. In 1920, Popielski et al. exhibited that histamine stimulated gastric acid secretion (23); however, another study indicated that histamine had a gastric protective effect against stress-induced gastric ulcer through stimulation of histamine H_1 and H_3 receptors, and sensory nerve transection resulted in the loss of this effect, which appeared to be mainly dependent on inactivation of histamine H3 receptors (24).

Betahistine is an active oral drug that improves labyrinth microcirculation by acting on the inner ear stria-vascularis pre-capillary sphincters and, therefore, lowering the pressure in the endolymphatic space (10, 25). Betahistine acts as a presynaptic H_3 receptor antagonist in rats, regulates histamine release in-vitro, and has no effect on postsynaptic H_2 receptors. It seems that the mechanism of action of betahistine mainly depends on its effect on H_3 receptors (25, 26). However, research published in 2010 by (25) showed that the therapeutic effects of betahistine in the brains of mice after acute intraperitoneal and acute oral administration are caused by an increase in histamine neuron activity caused by inverse agonism at H_3 autoreceptors, which is a moderate antagonist and a weak agonist. Due to these contradictory findings, the impact of betahistine on stomach acid secretion is not completely understood. The objective of the current research was to determine if interactions with H_3Rs mediate gastric protection in-vivo utilizing an indomethacin-induced gastric ulcer model in Wistar rats followed by intragastric injection of betahistine.

In this in-vivo stomach ulcer model, the gastroprotective impact of betahistine was compared to that of famotidine, a reference medicine with established anti-ulcer potential, to explain the underlying processes. We demonstrated that indomethacin caused a significant increase in the gastric index of wound mucosa, and betahistine was effective in inhibiting indomethacin-induced gastric index (Figure 2). However, the functional role of the H_3R is still opaque. These results contrast with previous studies in which H_3R antagonist stimulation resulted in significant gastric acid secretion (1, 27), suggesting that the mechanisms responsible for the protective action observed for betahistine appear to be unrelated to their effects on gastric acid secretion or may be due to its effect as an H_3R inverse agonist. Among many chemoattractants, interleukin (IL-8) and CINCs are known to have potent chemoattraction for neutrophils in vitro and in vivo (28). Since IL-8 has not yet been identified in rats, CINCs can play an important role as a predominant chemokine in rats (29). The role of CINCs in murine inflammation, such as gastric ulcers, has been fully characterized (30, 31). Many studies have shown that gastric ulcers caused by NSAIDs can continuously increase the chemotactic activity and marked infiltration of neutrophils into the ulcerated tissue (17, 28). CINC-2α is one of the C-X-C chemokines that play an important role in neutrophil infiltration and damage to the site of inflammation in an in-vivo study. It has been reported that the level and duration of its expression were higher and longer than other CINCs, suggesting that CINC-2α serves as a major chemoattractant in gastric ulcers (32). The present study was conducted to investigate the role of CINC-2α in the infiltration of neutrophils associated with ulceration in rats.

Similar to famotidine, pre-treatment with betahistine in rats resulted in the reduction of indomethacin-induced CINC-2α expression and thus reduced gastric tissue inflammatory cytokine levels (Figure 3). These markers were significantly decreased in the control group compared to the indomethacin-treated group. Our findings were consistent with previous studies reporting an association between indomethacin use and increased CINC-2α expression.

Conclusion

The findings show that the gastroprotective effect of betahistine (an H_3R antagonist) is partially attributed to the anti-inflammatory effect, suggesting that the protective effects may be due to mechanisms other than histaminergic neurotransmission. Betahistine, hence, has significant anti-ulcer potential. The gastroprotective action of betahistine is, at least in part, a result of CINC-2 expression being modulated, which prevents inflammation in stomach ulcers.

Authors' Contributions

B.T and R.J contributed to study design and methodology. G.V and R.J supervised the whole process and modified it. Sh.T contributed to manuscript provision, data analysis, and submission process. Sh.T, H.F and A.Kh contributed to writing and editing draft. All authors have read and approved the manuscript.

Ethical Considerations

The experimental procedures were approved by the Institutional Research Ethics Committee of Alborz University of Medical Sciences (Approval No: IR.ABZUMS.REC.1400.051). All efforts were made to minimize animal suffering and reduce the number of animals used.

Acknowledgment

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Conflict of Interests

The authors declare that they have no competing interests.

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