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Selective serotonin reuptake inhibitor fluvoxamine ameliorates stress- and NSAID-induced peptic ulcer possibly by involving Hsp70

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) have recently become potential candidates for a new therapeutic approach to ulcer and gastric bleeding. Heat shock protein 70 (Hsp70) plays an important role in cellular resistance to nonsteroidal anti-inflammatory drugs (NSAIDs). However, there is lack of evidence that fluvoxamine recruits Hsp70 to affect stress-induced gastric ulcer. Therefore, we investigated the effect of fluvoxamine on NSAID- and stress-induced gastric ulcer and the possible involvement of Hsp70.

Methods: ICR mice were used in the study. Stress induction was made by the water-immersion-plus-restraint method. NSAID-induced gastric ulcer was produced by oral administration of indomethacin. Fluvoxamine was given orally 30 min before stress induction and indomethacin treatment.

Results: Stress and indomethacin treatment significantly increased the ulcer index and intraluminal bleeding score. Stress and indomethacin treatment also significantly increased the expression of Hsp70. Fluvoxamine significantly decreased the ulcer index and intraluminal bleeding in both ulcer models. Moreover, fluvoxamine further increased the expression of Hsp70 in the gastric tissue of stress- and indomethacin-treated mice.

Conclusions: Our results indicate that fluvoxamine may have a protective effect against stress- as well as NSAID-induced gastric ulcer. In addition, the present study suggests the possible involvement of Hsp70 in the amelioration of gastric ulcer by fluvoxamine.

Keywords: fluvoxamine; gastric ulcer; Hsp70; SSRI; stress.

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Introduction

Stress affects many people in the world and induces numerous psychiatric disorders such as depression, post-traumatic stress disorder (PTSD), anxiety, and schizophrenia [1]. Stress has been widely reported as one of the causes of gastric ulcer [2]. Gastric ulcer affects 4 million people around the world per year. The life-threatening perforation occurs in about 2–14% of ulcers [3, 4]. In critically ill patients, the prevalence of stress-related gastric ulcer followed by bleeding ranges between 15% and 50%. Stress-induced mucosal bleeding is considered a severe complication with high mortality [5, 6]. It is challenging to provide an ideal management to completely treat gastric ulcer, particularly stress-induced gastric ulcer. The use of antacids and H2 blockers has become inadequate in the management of gastric ulcer. Long-term proton pump inhibition may lead to several serious adverse events [7, 8]. Therefore, the development of new approaches in treating stress-induced ulcer is still needed.

The extensive reports on the protective effect of several antidepressants on gastric ulcer have raised a new challenge to explore a new therapeutic approach for ulcer and the underlying mechanism. Selective serotonin reuptake inhibitors (SSRIs) belong to one of the drug classes effectively used for the treatment of depression, a psychiatric disorder induced mainly by stressful life events. Studies show that SSRIs may be potential candidates for a new therapeutic approach for ulcer and gastric bleeding. Fluoxetine was found to dose-dependently decrease intraluminal bleeding in rats with indomethacin-induced gastric ulcer [9]. In the stress model, fluoxetine suppresses acute cold-restrain-stress-induced gastric ulcer possibly by decreasing malondialdehyde and increasing gastric

catalase and nitric oxide [10]. Repeated administration of paroxetine suppresses water-immersion-stress-induced gastric ulcer. Similarly, paroxetine treatment attenuates the corticosterone level increase during stress and demonstrates anxiolytic and antidepressive effects [11]. Previous studies have shown that serotonin-noradrenaline reuptake inhibitors (SNRIs) have more potent antiulcerogenic effect than fluoxetin. However, another report showed that SNRIs such as duloxetine and amitriptyline have lower efficacy compared to SSRIs (fluoxetine) in indomethacin-induced gastric ulcer, suggesting that the antiulcerogenic effect of antidepressants may depend on their affinity to the receptor or transporter as well as the type of gastric ulcer [9].

Even though studies have demonstrated a detrimental effect of SSRIs on gastric mucosal tissue, they have also suggested that fluvoxamine effectively reduces the ulceration. Among the antidepressants, fluvoxamine binds to the serotonin transporter and demonstrates the lowest affinity for binding to muscarinic receptors, histaminergic receptors, and noradrenaline transporter [12]. Fluvoxamine suppresses NSAID (nonsteroidal anti-inflammatory drug)-induced gastric ulcer by increasing the total glutathione and nitric oxide levels. Moreover, fluvoxamine reduces the increase of oxidant parameter level in indomethacin-induced gastric ulcer [13]. However, to date, there is no study that directly compares the effect of fluvoxamine on stress- and NSAID-induced gastric ulcer. Moreover, there is lack of evidence in the gastroprotective mechanism of fluvoxamine. Therefore, further studies on the exact mechanism how fluvoxamine affects NSAID- and stress-induced ulcer are still needed.

Heat shock proteins (HSPs) are a family of molecular chaperones that play a vital role in protein folding and protein transport to the subcellular compartment. Hsp70 is widely known to have protective effect against gastric lesion and inflammation. It is known that various stressors, including NSAIDs, induce HSP expressions [14–17]. Induction of Hsp70 expression provides cellular resistance to NSAIDs. Studies using transgenic mice have shown that the absence of HSF-1, a transcription factor of HSP genes, increases indomethacin-induced gastric lesion. Moreover, an *in vitro* study has demonstrated that Hsp70 silencing promotes higher indomethacin-induced apoptosis [18]. These evidences suggest the important protective role of Hsp70 in gastric ulcer. However, the role of Hsp70 in the effect of fluvoxamine on stress- and NSAID-induced ulcer still remains to be determined. Therefore, in the present study, we investigated the effect of fluvoxamine on NSAID- and stress-induced gastric ulcer and the possible involvement of Hsp70 in the fluvoxamine action.

Materials and methods

Drugs

The materials used were fluvoxamine (Wako Pure Chemical Industries, Kyoto, Japan), Tween 80 (Wako Pure Chemical Industries), normal saline (PT. Otsuka Indonesia, Malang, Indonesia), and the antibody for Hsp70 (Santa Cruz Biotech, CA, USA). All true solutions and drug suspensions in 1% Tween were freshly prepared.

Experimental animals and treatments

Male 6–8-week-old ICR mice were used in the experiments. All mice were cared with equal treatment, given standard chow diet ad libitum, and subjected to a 12-h light–dark cycle. All experiments were performed in accordance with "The Guiding Principles for the Care and Use of Animal Research of Universitas Airlangga No. 683-KE". All efforts were made to minimize suffering of the animals and to reduce the number of animals used. Each animal was used only once.

After an acclimatization period of 14 days, 48 mice were randomly divided into the saline group, the non-stress group, the stress group, the stress group treated with vehicle or fluvoxamine, the indomethacin group, and the indomethacin group treated with vehicle or fluvoxamine. Fluvoxamine was administered at the dose of 50 and 100 mg/kg.

Gastric ulcer induction

Stress-induced gastric ulcer was produced following the method of Ji et al. [9]. Animals were deprived of food overnight. Thirty minutes after fluvoxamine or saline injection, stress induction was started. The animal was restrained in a polypropylene tube with sufficient holes for air circulation. The tube was vertically immersed in a water bath at 25 °C for 6 h.

NSAID-induced gastric ulcer was produced by treating the animal with indomethacin. The animals were deprived of food overnight. Thirty minutes after the administration of fluvoxamine or vehicle, indomethacin (25 mg/kg) was administered orally [19].

Assessment of gastric mucosal injury

After water immersions for 6 h, or 6 h after ulcer induction with indomethacin, the animals were sacrificed. The stomach tissue was rapidly removed, opened along the greater curvature, and gently washed by normal saline. Scoring of the ulcer was performed toward the macroscopic mucosal lesions to calculate the ulcer index and intraluminal bleeding [9, 19]. Briefly, the stomach was pinned out flat and observed for the presence of blood or mucus. The severity of intraluminal bleeding was evaluated according to an arbitrary scale [20] as follows: 0, no blood detectable; 1, thin blood follows the rugae; 2, thick blood follows the rugae; 3, thick blood follows the rugae with blood clots in certain areas; 4, extensive covering of the whole mucosal surface with thick blood. Then the stomachs were gently rinsed with saline to remove the gastric contents, and after the blood was wiped off, spread and pinned flat for subsequent examination of the ulcer index. Color photographs

of the mucosal surface were taken. Each lesion area was measured in square millimeters, and the cumulative area of all lesions served as the measure of erosion damage [9]. The tissue was fixated and stained with hematoxylin–eosin and Hsp70 antibody.

Statistical analysis

All data are presented as means ± SEM (standard error of the mean). One-way analysis of variance (ANOVA) followed by a *post hoc* Bonferroni test was used to compare the groups. Student's *t*-test was used to compare two groups, where appropriate. Differences were considered statistically significant when p was <0.05.

Results

Effect of fluvoxamine on NSAID-induced gastric ulcer

The photograph of gastric lumen showed that oral administration of indomethacin @ 25 mg/kg increased the gastric lesion (Figure 1A, B). A dark spot in the gastric lumen represents the lesion. Fluvoxamine @ 50 mg/kg decreased the appearance of the dark spots in the lumen. Fluvoxamine @ 100 mg/kg decreased the dark spots' appearance more in the indomethacin-treated and fluvoxamine (50 mg/kg) groups (Figure 1C, D).

The calculation of the ulcer index showed that indomethacin treatment significantly increased the ulcer index. Fluvoxamine @ 50 mg/kg markedly decreased the ulcer index. Furthermore, fluvoxamine @ 100 mg/kg notably reduced the ulcer index (Figure 2A). Indomethacin treatment significantly increased the intraluminal bleeding score. Fluvoxamine @ 100 mg/kg, but not @ 50 mg/kg, suppressed the indomethacin-induced rise in the intraluminal bleeding score (Figure 2B).

Histological measurements using hematoxylin–eosin staining showed the damage to the epithelial tissue after treatment with indomethacin. It showed that fluvoxamine decreased the damage induced by indomethacin (Figure 3A–D).

Effect of fluvoxamine on stress-induced gastric ulcer

Photograph of the gastric lumen showed that stress using the water immersion and restraining method increased

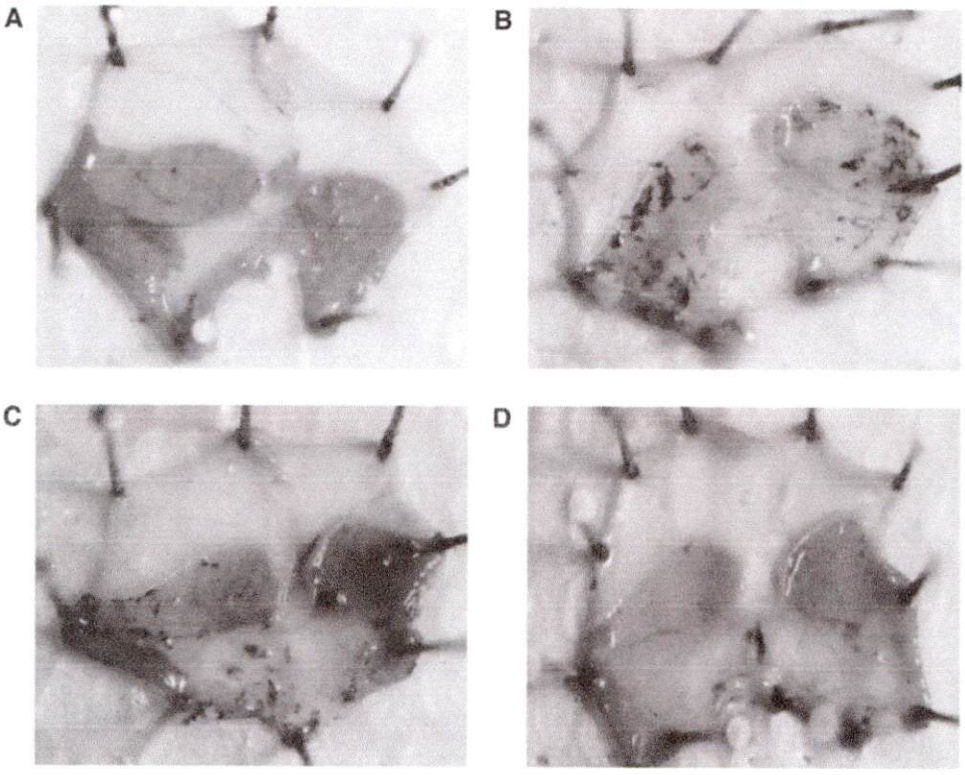

Figure 1: Representative photograph of the gastric lumen of mice.
Treated with vehicle (A), indomethacin–Tween-80 (B), indomethacin–fluvoxamine @ 50 mg/kg (C), and indomethacin–fluvoxamine @ 100 mg/kg (D). Tween-80 and fluvoxamine were injected 30 min prior to indomethacin administration. Tissues were sampled 6 h after indomethacin administration.

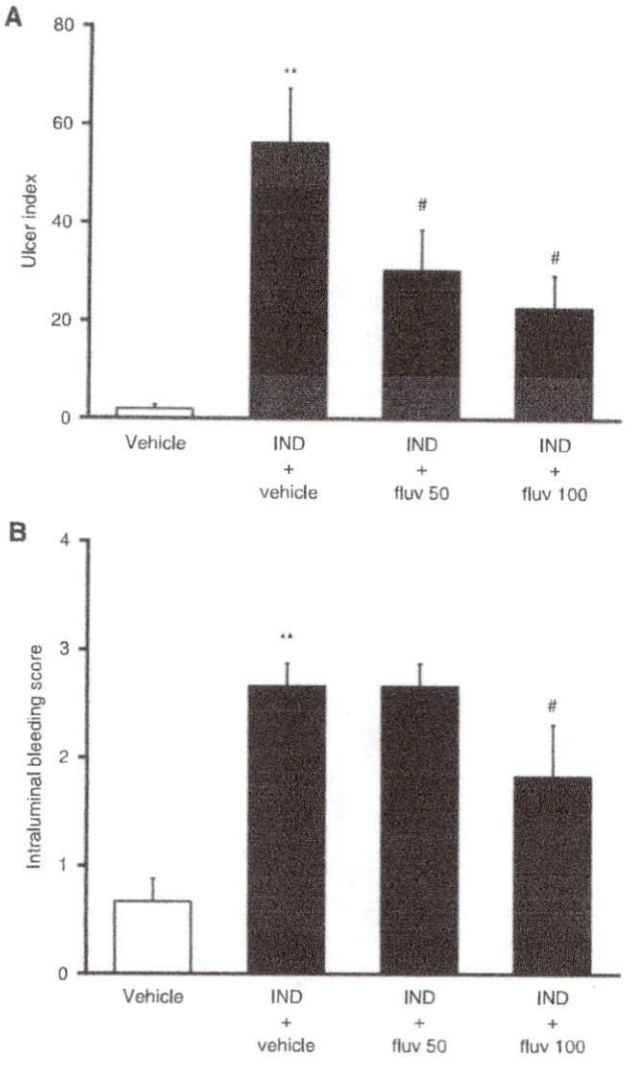

Figure 2: Effects of fluvoxamine.
Effects of fluvoxamine on indomethacin-induced increase in ulcer index (A) and intraluminal bleeding score (B). Each column represents the mean ± SEM of six mice. $^{**}p < 0.01$ vs. the vehicle group. $^{\#}p < 0.05$ vs. IND + vehicle group.

the gastric lesion (Figure 4A–B). Fluvoxamine @ 50 mg/kg decreased the gastric lesion in the lumen. Fluvoxamine @ 100 mg/kg decreased the gastric lesion in the lumen as compared to the stress group and the fluvoxamine (50 mg/kg) group (Figure 4C, D).

Pretreatment with stress significantly increased the ulcer index as compared to the non-stress group. However, fluvoxamine @ 50 mg/kg markedly decreased the ulcer index compared to saline-treated stress group. Furthermore, fluvoxamine @ 100 mg/kg notably reduced the ulcer index (Figure 5A). Accordingly, stress induction significantly increased the intraluminal bleeding score. Fluvoxamine @ 50 and 100 mg/kg suppressed the stress-induced increase in the intraluminal bleeding score (Figure 5B).

Histological measurements using hematoxylin–eosin staining showed the damage of the epithelial tissue after 6 h of stress induction. The result showed that fluvoxamine decreased the gastric ulcer induced by stress (Figure 6A–D).

Effect of fluvoxamine on Hsp70 expression in gastric ulcer

Immunohistochemistry was conducted using anti-Hsp70. Indomethacin treatment increased the expression of Hsp70 (Figure 7A, B). Injection of fluvoxamine @ 50 and 100 mg/kg prior to indomethacin treatment further increased the expression of Hsp70 compared to the indomethacin-treated group (Figure 7B–D). Accordingly, water-immersion-restraint stress increased the expression of Hsp70 (Figure 7E, F). Injection of fluvoxamine @ 50 and 100 mg/kg prior to stress induction further increased the expression of Hsp70 compared to the stress group (Figure 7F–H).

Discussion

The gastric ulcer models induced by NSAID administration and stress induction have been commonly used to evaluate the efficacy of gastroprotective agents. In the present study, we clarified that NSAID-induced gastric ulcer can be successfully produced by the oral administration of indomethacin @ 25 mg/kg. This result is in agreement with the previous study by Ji et al. [9], showing that a single administration of indomethacin successfully induces ulceration. Furthermore, our result showed that fluvoxamine dose-dependently decreased the ulcer index induced by indomethacin. Moreover, fluvoxamine @ 100 mg/kg suppressed the intraluminal bleeding induced by indomethacin. This is in agreement with the previous study by Dursun et al. [13] showing that fluvoxamine affects the antioxidant and oxidant parameters in the gastric tissue to inhibit ulcer formation [13].

The inhibitory effect of fluvoxamine on indomethacin-induced gastric ulcer has raised the potential gastroprotective effect of fluvoxamine on stress-induced ulcer. Reports show that some SSRIs have a protective effect against stress-induced ulcer. For example, fluoxetine suppresses acute cold-restrain-stress-induced gastric ulcer [10]. Moreover, repeated administration of paroxetine decreases water-immersion-stress-induced ulcer possibly by modulating the corticosterone level increase during stress [11]. The present study demonstrates that

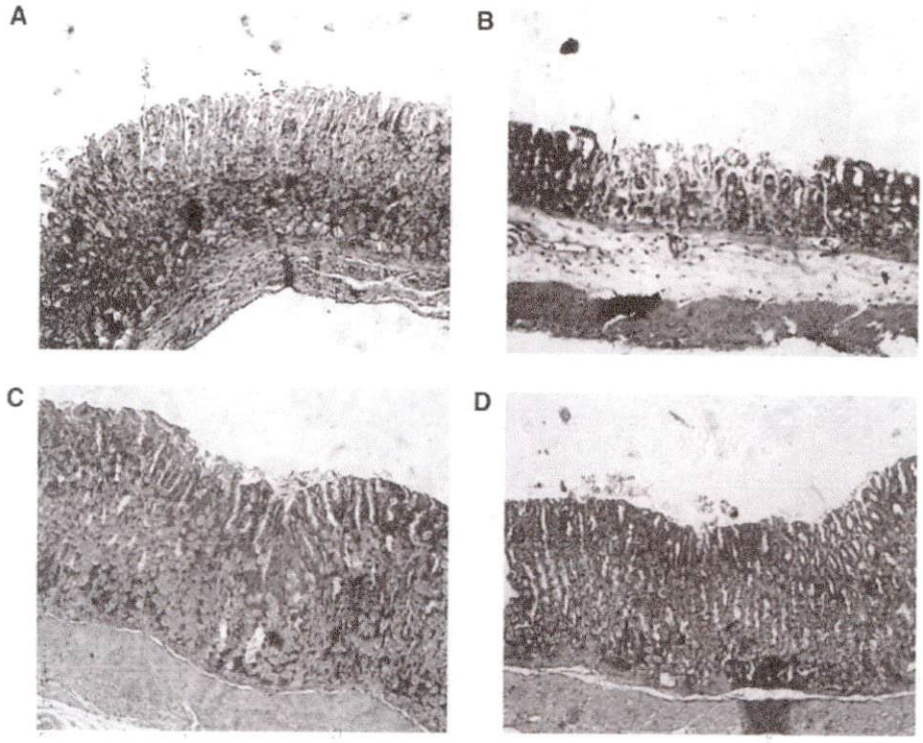

Figure 3: Representative microphotograph of the gastric epithelial tissue of mice.
Treated with vehicle (A), indomethacin–Tween-80 (B), indomethacin–fluvoxamine @ 50 mg/kg (C), and indomethacin–fluvoxamine @ 100 mg/kg (D). The transverse sections were stained with hematoxylin–eosin to identify epithelial tissue damage.

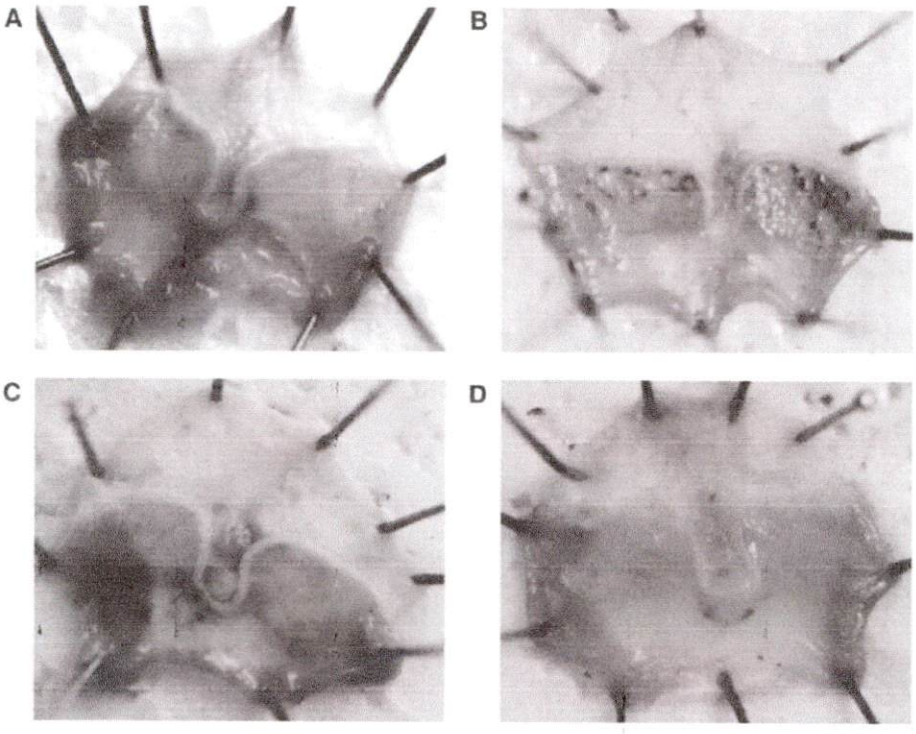

Figure 4: Representative photograph of gastric lumen of mice.
Treated with no stress (A), stress followed with Tween-80 (B), stress followed with fluvoxamine @ 50 mg/kg (C), and stress followed with fluvoxamine @ 100 mg/kg (D).Tween-80 and fluvoxamine were injected 30 min prior to stress induction. Tissues were sampled soon after the termination of 6-h stress induction.

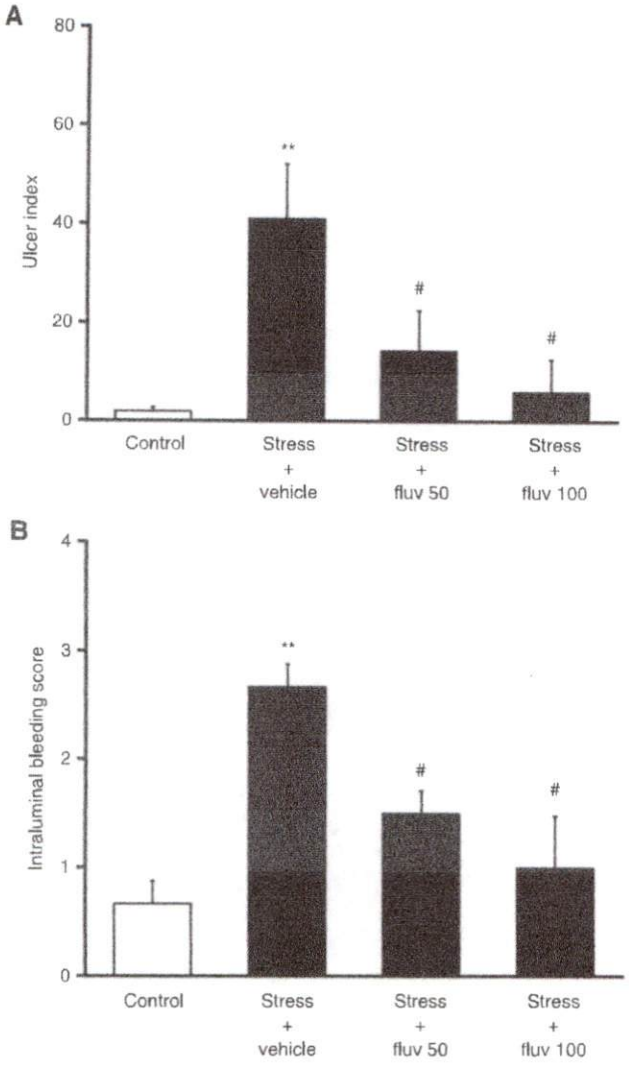

Figure 5: Effects of fluvoxamine.
Effects of fluvoxamine on stress-induced increase in ulcer index (A) and intraluminal bleeding score (B). Each column represents the mean ± SEM of six mice. $^{**}p < 0.01$ vs. control group. $^{\#}p < 0.05$ vs. the stress + vehicle group.

the 6-h stress induction produced by water immersion and restrain procedure in mice generates gastric ulcer and intraluminal bleeding. This result is in agreement with a previous study showing that 6 h water immersion in a restraining cage effectively induced ulcer formation and intraluminal bleeding [9].

Furthermore, the present study demonstrates that fluvoxamine dose-dependently and significantly decreases the rise in ulcer index induced by stress. Moreover, fluvoxamine dose-dependently and significantly attenuates the stress-induced increase in intraluminal bleeding score. A different result with another SSRI, fluoxetine, has been previously reported. Fluoxetine attenuates the ulcer index and gastric intraluminal bleeding in NSAID-induced gastric ulcer, but not those induced by stress [9, 10]. The difference in effects between fluvoxamine and fluoxetine may be caused by their different affinity to the target receptors or transporters. Fluvoxamine has been reported to have much lower potency for binding to muscarinic receptors, histaminergic receptors, and noradrenaline transporter as compared to fluoxetine. Moreover, a previous report has indicated that fluvoxamine exhibits the highest affinity to sigma-1 receptors as compared to fluoxetine. Recent evidence shows that sigma-1 receptor signaling plays a protective role against cell damage [21]. Another possibility is that fluvoxamine may be exhibiting higher efficacy to overcome stress during water immersion and restraining. A double-blinded, randomized study has shown that fluvoxamine is more effective in treating depression and sleep disturbance when compared to fluoxetine [22]. Since there is no evidence showing the mechanism underlying the protective effect of fluvoxamine on stress-induced gastric ulcer, we further investigated the possible molecule related to cell damage in the gastric tissue.

Hsp70 is known to be a gastroprotective molecule in an ulceration event. In the present study, we found that the expression of Hsp70 increases in gastric ulcer induced by indomethacin. This is in agreement with the study by Suemasu et al. [18] showing that downregulation of Hsp70 expression increases cell damage induced by indomethacin. Moreover, deleting the transcription factor of Hsp70, HSF, increases the lesion index induced by indomethacin. Subsequently, our results showed that fluvoxamine administration before ulcer induction by indomethacin further increases the expression of Hsp70 in the gastric tissue. Together with the result showing an ameliorative effect of fluvoxamine on gastric ulcer, this result suggests that fluvoxamine decreases indomethacin-induced gastric ulcer possibly by upregulating Hsp70 expression in the gastric tissue.

Previous studies have shown that the high expression of Hsp70 is associated with the protective effect of moxibustion on stress-induced ulcer [23]. Similarly, our results show that the expression of Hsp70 increases in stress-induced gastric ulcer condition. These suggest that Hsp70 may play a protective response to stress-induced ulcer. Furthermore, the present study shows that treatment with fluvoxamine further increases the Hsp70 expression in the gastric tissue. This suggests that fluvoxamine ameliorates gastric ulcer possibly by upregulating the expression of Hsp70 in the gastric tissue. Our study lacks in direct evidence that connects fluvoxamine treatment, Hsp70 expression elevation, and ulcer recovery. Further studies are therefore needed to clarify the role of Hsp70 as a key molecule in the antiulcerogenic effect of fluvoxamine, for example, by examining the effect

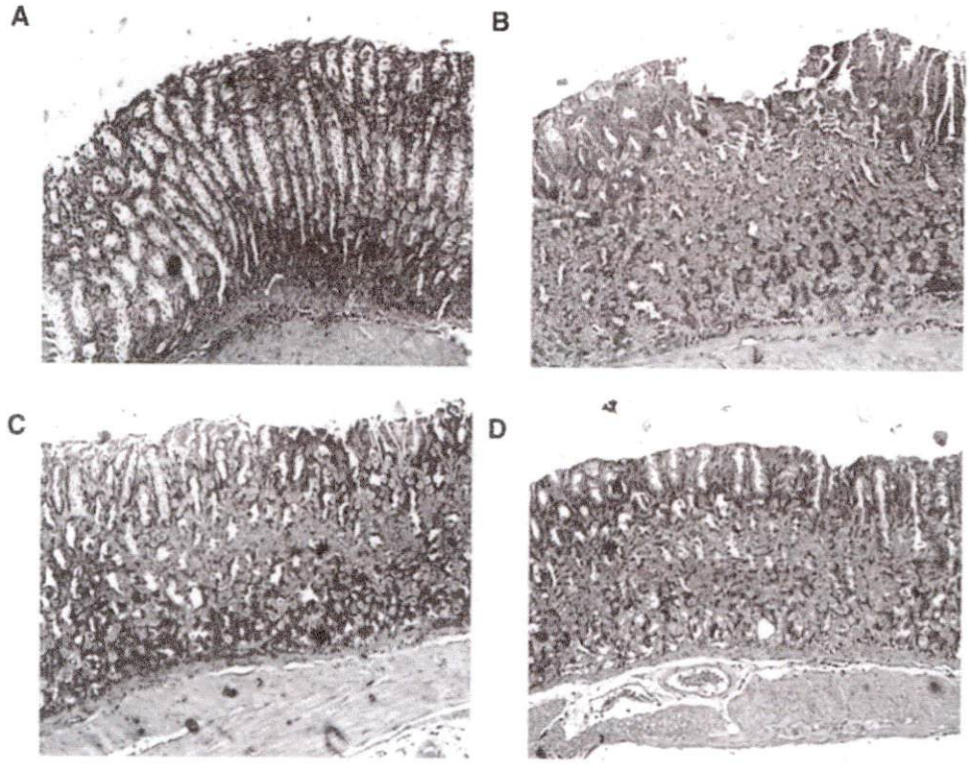

Figure 6: Representative microphotograph of gastric epithelial tissues of mice.
Treated with no stress (A), stress followed with Tween-80 (B), stress followed with fluvoxamine @ 50 mg/kg (C), and stress followed with fluvoxamine @ 100 mg/kg (D). The transverse sections were stained with hematoxylin–eosin to identify epithelial tissue damage.

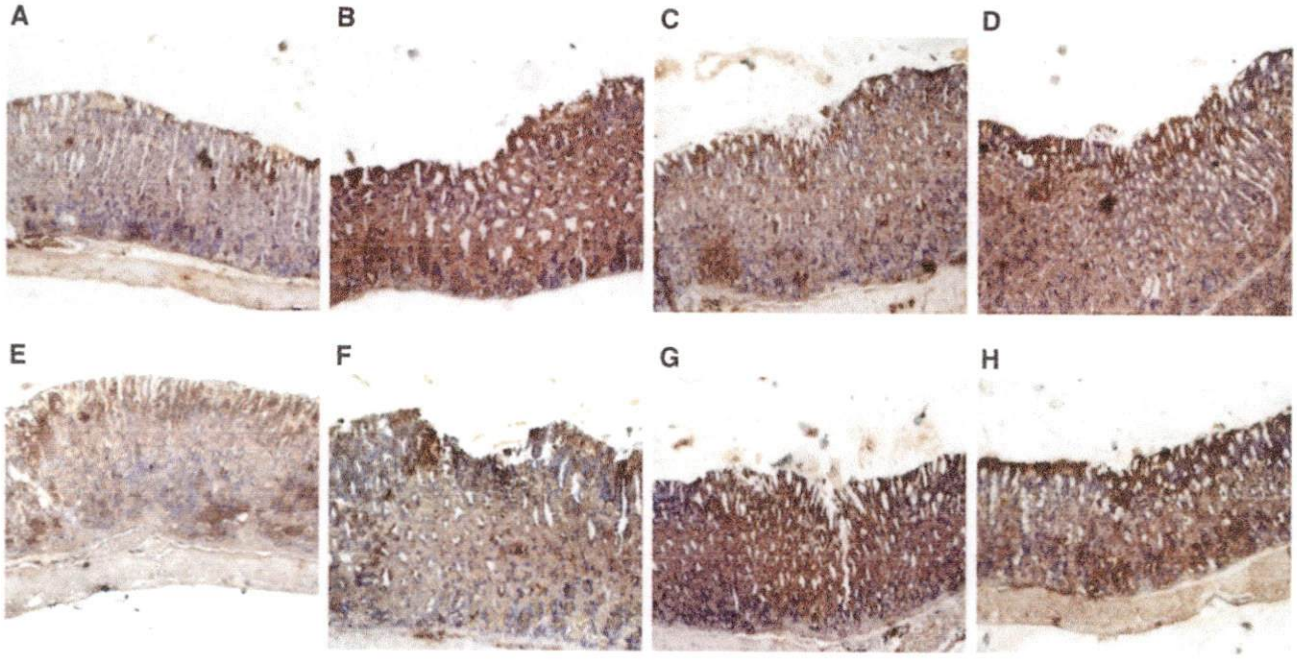

Figure 7: Representative microphotograph showing Hsp70 expression in gastric tissues.
After treatment with oral administration of normal saline (A, E), indomethacin–Tween-80 (B), indomethacin–fluvoxamine @ 50 mg/kg (C), indomethacin-fluvoxamine @ 100 mg/kg (D), stress followed with Tween-80 (F), stress followed with fluvoxamine @ 50 mg/kg (G), and stress followed with fluvoxamine @ 100 mg/kg (H). The transverse sections were stained with anti-Hsp70.

of fluvoxamine on Hsp70 expression in normal gastric tissue.

The mechanism of how fluvoxamine upregulates Hsp70 expression remains unknown. The sigma-1 receptor, the receptor for fluvoxamine, has been reported to bind Hsp70 in the endoplasmic reticulum. Binding by fluvoxamine on the sigma-1 receptor may break the sigma-1 receptor–Hsp70 binding and activate the chaperoning activity of each component [24]. Further research is needed to clarify this issue.

Conclusions

The present study has shown that fluvoxamine ameliorates the gastric ulcer induced by stress as well as by NSAIDs in mice. Moreover, fluvoxamine further increases the upregulation of Hsp70 expression in the gastric epithelial tissue. Further studies on the detailed mechanism of fluvoxamine's antiulcer activity may lead to the prospective development of effective treatment modalities to stress-induced gastric ulcer.

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Author contributions: Study conception and design: JK, MR, CA, KN, DWS, TA, S; acquisition of data: JK, MR, KN, RO, AR, YD; analysis and interpretation of data: JK, MR, CA, KN; drafting of the manuscript: MR, CA, KN, RO, AR, YD; critical revision: JK, MR, CA, RO, AR, YD, DWS, TA, S.

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