

RESEARCH LETTER

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Cofactors of wheat-dependent exercise-induced anaphylaxis increase gastrointestinal gliadin absorption by an inhibition of prostaglandin production

To the Editor,

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is distinguished from common immediate-type wheat allergies by the clinical feature that ingestion of the wheat alone does not induce allergic symptoms and co-factors, such as exercise and non-steroidal anti-inflammatory drugs (NSAIDs), are required to induce the symptoms. Several hypotheses have been proposed to explain the induction of allergic symptoms by cofactors, including increase in gastrointestinal permeability, tissue transglutaminase activation in the gut mucosa, blood flow redistribution, and mast cell heterogeneity, increases in plasma osmolarity inducing basophil histamine release, and acidosis and mast cell degranulation.¹ Among these potential hypotheses, the hypothesis of increase in gastrointestinal permeability is very attractive for understanding the cofactor-inducing mechanism of WDEIA.

We measured the blood gliadin levels in patients with WDEIA during a challenge test, using a highly sensitive enzyme-linked immunosorbent assay (ELISA) that can specifically detect wheat gliadin.^{2,3} As a result, the blood gliadin level increased preceding the allergic symptoms when induced by the combination of wheat ingestion and exercise, while serum gliadin was not detected or remained at a very low level in the case of the wheat ingestion alone. Increased absorption of gliadin by exercise after ingestion of wheat or preadministration of aspirin was seen not only in patients with WDEIA but also in healthy individuals without a history of wheat allergy.²

Recently, Scherf et al. have reported a study of blood gliadin monitoring after gluten ingestion in healthy volunteers.⁴ Blood gliadin levels were measured for up to 120 min in 12 subjects who had ingested 32 g of gluten. Blood gliadin levels were elevated for 15–120 min after gluten ingestion; however, no enhancing effects were found for aspirin, alcohol, or exercise on blood gliadin levels. In their study, the peak average value of gliadin levels after ingestion of 32 g of gluten was as high as 1014 pg/mL. It is likely that the absorption of gliadin had already reached a plateau after the intake of the 32 g of gluten, and the cofactors had no additional effect. Yokooji et al. detected plasma gliadin after ingestion of 50 mg of gluten or 100 mg/kg of gliadin combined with aspirin intake in rats by using ELISA specific for ω 5-gliadin.⁵ They estimated that a 50 mg gluten dose in rats corresponds to 1.3 g in humans. Considering these results, we

conducted a challenge test with a lower amount of gluten in combination with exercise or aspirin intake to determine the effects of these cofactors on the gastrointestinal gliadin absorption. All subjects provided written informed consent. In this study, two slices of bread (mean weight, 142 g) containing 12.6 g of protein (approximately 1.2 g of gluten), 6.4 g of lipid, 69.2 g of carbohydrate, and 2.0 g of salt was taken by 10 healthy subjects without a history of food allergy. Exercise or aspirin intake was added right after or before the wheat ingestion, respectively, and blood gliadin levels were measured according to the method of Matsuo et al.²

As a result, the blood gliadin level did not significantly increase after the ingestion of bread from 30 min to 120 min (blue in Figure 1), but the level significantly increased from 30 min to 120 min by adding exercise (yellow in Figure 1). Gliadin levels also significantly increased with 500 mg of aspirin intake before bread ingestion (red in Figure 1). Peak gliadin level was observed at 30 min in the exercise challenge, whereas at 60 min in the aspirin challenge. This is supported by the fact that time to maximum blood concentration of salicylate in aspirin ingestion is approximately 60 min (Interview form, a summary of product characteristics in Japan).

There are several case reports claiming that simultaneous oral administration of a prostaglandin (PG) E₁ analogue (misoprostol), a protective agent against NSAID-induced gastrointestinal epithelial damage, suppressed allergic symptoms induced by aspirin and wheat ingestion, and decreased blood gliadin levels.⁶ These observations suggest that the inhibitory effect of aspirin on cyclooxygenase-mediated PG production is involved in the enhancement of gastrointestinal allergen absorption. To investigate the involvement of PG metabolism in the increase in blood gliadin levels in healthy subjects, the effects of misoprostol were examined. When misoprostol ingestion was added to the bread + exercise challenge, blood gliadin remained at non-significant levels (green in Figure 1), in contrast to that of bread + exercise (yellow in Figure 1). Misoprostol pretreatment also suppressed the aspirin-induced increase in the gliadin levels (grey in Figure 1). These results suggest that cyclooxygenase inhibition is involved in the increase in blood gliadin levels induced by exercise as well as the increase induced by aspirin.

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To observe individual differences and reproducibility in the increase in blood gliadin levels, a challenge test combining bread and aspirin was performed twice at 2 weeks intervals in the 10 healthy subjects. The results for each subject are shown in Figure 2. After ingestion of bread and aspirin, the mean blood gliadin level at 30 min was 406 ± 247 pg/mL (distribution range 90–898 pg/mL) in the first test (blue line in Figure 2) and 513 ± 390 pg/mL (distribution range 102–1479 pg/mL) in the second test (red line in Figure 2). The mean blood gliadin level at 60 min was 458 ± 288 pg/mL (distribution range 141–1090 pg/mL) in the first test and 641 ± 437 pg/mL (distribution range 161–1636 pg/mL) in the second test. Lastly, the mean blood

Key messages

- Bread ingestion combined with exercise or aspirin increased the serum level of wheat gliadins.
- Prostaglandin E_1 analogue (Misoprostol) co-ingestion suppressed the exercise- or aspirin-induced increase in the gliadin levels.
- Impaired tight junction sealing may be caused by an inhibition of prostaglandin production in enterocytes.

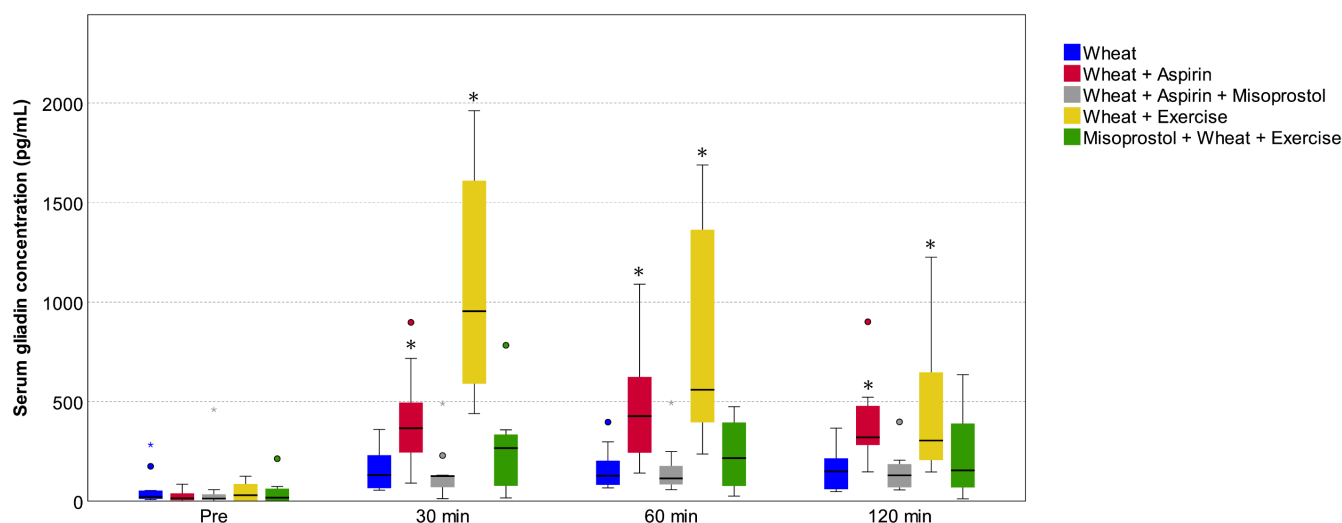


FIGURE 1 Challenge tests involved 142 g bread ingestion (blue box), 500 mg aspirin administration followed by 142 g bread ingestion (red box), 200 mg misoprostol and 500 mg aspirin administration followed by 142 g bread ingestion (grey box), 142 g bread ingestion followed by 15 min-treadmill exercise (yellow box), and 200 mg misoprostol and 142 g bread ingestion followed by 15 min-treadmill exercise (green box). Serum gliadin level was determined by a sensitive ELISA previously described.² *: Values were significantly high compared with those of pre-challenge ($p < .05$). Changes in the serum gliadin concentration at each time point were tested for significance using Steel-Dwass method considering the non-nominal distribution and multiplicity. The statistical analysis was conducted using Bell Curve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan)

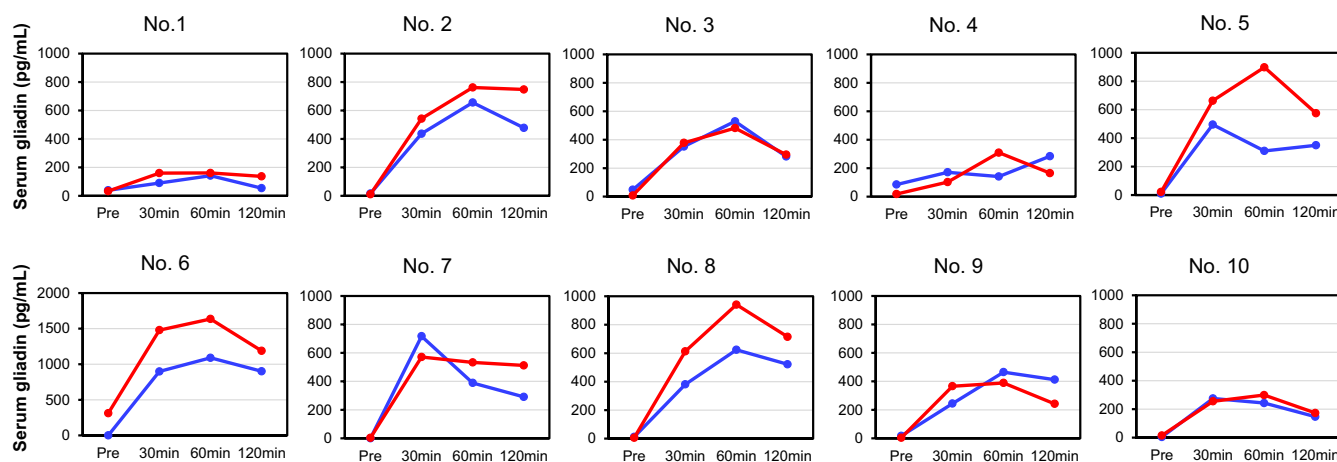


FIGURE 2 Reproducibility of blood gliadin level change in a challenge test in 10 healthy subjects (No. 1–10). The challenge test involved 500 mg aspirin administration followed by 142 g bread ingestion and serum gliadin level was determined by a sensitive ELISA previously described.² The same challenge was performed after 2 week-interval. Blue line; first challenge, and red line; second challenge

gliadin level at 120min was 372 ± 233 pg/mL (distribution range 54–901 pg/mL) in the first test and 475 ± 340 pg/mL (distribution range 137–1188 pg/mL) in the second test. These results indicate that an increase in gliadin levels is reproducible in each subject, although the range of increased gliadin levels varies largely among individuals.

It is noteworthy that the present study (Figure 1), together with those of Matsuo, et al.,^{2,7} showed an increase in gliadin levels by both exercise and NSAIDs, even in the healthy subjects who were not sensitized with gliadins. This suggests that an increase in gastrointestinal permeability occurs independently of mast cell activation. Animal models of intestinal ischaemia have demonstrated that intestinal ischaemia increases permeability owing to the loss of tight junction proteins, resulting in the absorption of large molecules.⁸ The disruption of tight junctions by ischaemia is rapidly reversed by the administration of PGE₂, and the repair is mediated by the activation of the ClC-2 chloride channel, a type 2 chloride channel expressed in the intestinal epithelium.⁸ The repairing role of the PGE₂ analogue misoprostol has also been demonstrated in an aspirin-induced gastrointestinal lysozyme absorption model in rats.⁹

In conclusion, the present study suggests that both exercise and aspirin enhance gliadin absorption from the gastrointestinal tract, and the mechanism may be due to impaired tight junction sealing caused by the inhibition of PG production in enterocytes.

AUTHOR CONTRIBUTIONS

Eishin Morita: conducted the study. **Yuko Chinuki:** data collection and analysis. **Kunie Kohno:** data analysis. **Hiroaki Matsuo and Eishin Morita:** writing of the text. All authors reviewed and provided critical feedback on all version of the text.

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KEYWORDS

exercise, gliadin, non-steroidal anti-inflammatory drugs, prostaglandin, wheat-dependent exercise-induced anaphylaxis

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of the Shimane University Faculty of Medicine (approval number: 121).

CONCENT OF PARTICIPATE

All subjects provided written informed consent.

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