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Letter to the Editor

Effects of non-steroidal anti-inflammatory drugs (NSAIDs) on serum allergen levels after wheat ingestion

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To the Editor

Absorption of food allergens from the intestinal tract is thought to be important in the development of food allergies. A recent report showed that intestinal permeability to macromolecules was increased in patients with adverse reactions to food [1]. Passage of intact dietary allergens, such as β -lactoglobulin and ovalbumin in meal, into the blood has been documented [2]. In our previous study, we demonstrated that the circulating levels of gliadin, which is recognized as an allergen for a variety of wheat allergies, were correlated with the clinical symptoms in patients with wheat-dependent exercise-induced anaphylaxis (WDEIA) [3,4]. Interestingly, increased serum gliadin levels induced by exercise and aspirin were also observed in healthy subjects. In addition, a recent case report described a patient with WDEIA induced by low-dose aspirin therapy for secondary prevention of cardiovascular events [5]. Intake of aspirin enhances intestinal permeability, which is associated with gastrointestinal disorders [6]. Thus, it is hypothesized that aspirin facilitates the absorption of intact gliadin due to an increase in gastrointestinal permeability. However, the dose effects of aspirin and administration of other non-steroidal anti-inflammatory drugs (NSAIDs) on the absorption of wheat gliadin remain unclear. The purpose of the present study was to evaluate the effects of administration of low-dose aspirin and conventional-dose of diclofenac, loxoprofen and meloxicam on serum gliadin levels after wheat ingestion in healthy subjects.

Seven healthy volunteers (5 males, 2 females; mean age: 39.1 years; range: 25–48 years) abstained from food for at least 6 h before eating udon, a type of Japanese noodle, made from 120 g of wheat flour. Since common bread wheat includes approximately 6% gliadin, the amount of gliadin ingestion in this study was estimated to be 7.2 g. Each dose of aspirin was administered 30 min before wheat ingestion. Blood samples were taken serially and the serum concentrations of gliadin were determined as described previously [3].

The serum concentrations of gliadin increased very little after wheat ingestion without administration of aspirin. However, various amounts of serum gliadin (17.7–297 pg/mL) were detected in all subjects after administration of 1000 mg of aspirin (Fig. 1). Slight increases in the serum gliadin level (16.9–39.0 pg/mL) were observed in 5 of 7 subjects (subjects 1, 2, 3, 5 and 6) by administration of low-dose aspirin (100 mg). The maximum concentrations of serum gliadin increased in an aspirin dose-dependent manner.

Next, we studied the effects of loxoprofen sodium, diclofenac and meloxicam on the serum gliadin levels after wheat ingestion in 5 subjects (subjects 1–5). Increases in the serum gliadin level were observed in 3 subjects (subjects 1, 2 and 3) after administration of 120 mg of loxoprofen and in 4 subjects (subjects 1, 2, 3 and 5) after administration of 50 mg of diclofenac (Fig. 2). The maximum concentrations of serum gliadin were lower than those when 1000 mg of aspirin was administered. On the other hand, no or only marginal elevation of serum gliadin was induced by administration of 15 mg of meloxicam. In subject 4, the three tested NSAIDs did not increase the serum gliadin levels after wheat ingestion.

To assess the allergenicity of the gliadin detected in sera, the histamine release activities of serum samples containing the maximum concentrations of gliadin from subjects 1, 6 and 7 before and after wheat challenge with 1000 mg of aspirin were examined. Peripheral blood leukocytes containing about 1% basophils were obtained from a WDEIA patient with specific IgE antibodies against recombinant ω 5-gliadin (1.57 kUA/L) as described previously [7,8]. When the sera collected from the three subjects after wheat and aspirin challenge were incubated with the basophils, the histamine releases were 7.3, 14 and 9.6%, respectively. In contrast, the sera collected before wheat challenge did not induce histamine release. This result indicates that the gliadin with allergenic activity is absorbed from the intestine.

NSAIDs have the common property of inhibiting cyclooxygenase (COX) activity, which is essential for prostaglandin production. COX exists in two forms, COX-1 and COX-2, and NSAIDs are targeted against COX-2 to reduce inflammation and lower fever. Traditional NSAIDs generally inhibit both isoforms of COX, and inhibition of COX-1 in the gastrointestinal mucosa causes small intestinal damage related to alterations in intestinal permeability. It has been reported that NSAIDs such as aspirin, diclofenac and meloxicam increase intestinal permeability [6,9]. Thus, passage of gliadin into the blood was suggested to be enhanced under the condition of increased intestinal permeability by NSAIDs.

Increased serum gliadin levels induced by 1000 mg of aspirin, 50 mg of diclofenac or 120 mg of loxoprofen, which represent the clinical doses, were observed in almost all the tested subjects. Low-dose aspirin (100 mg) also slightly increased the serum gliadin level. In contrast, an increased serum gliadin level was

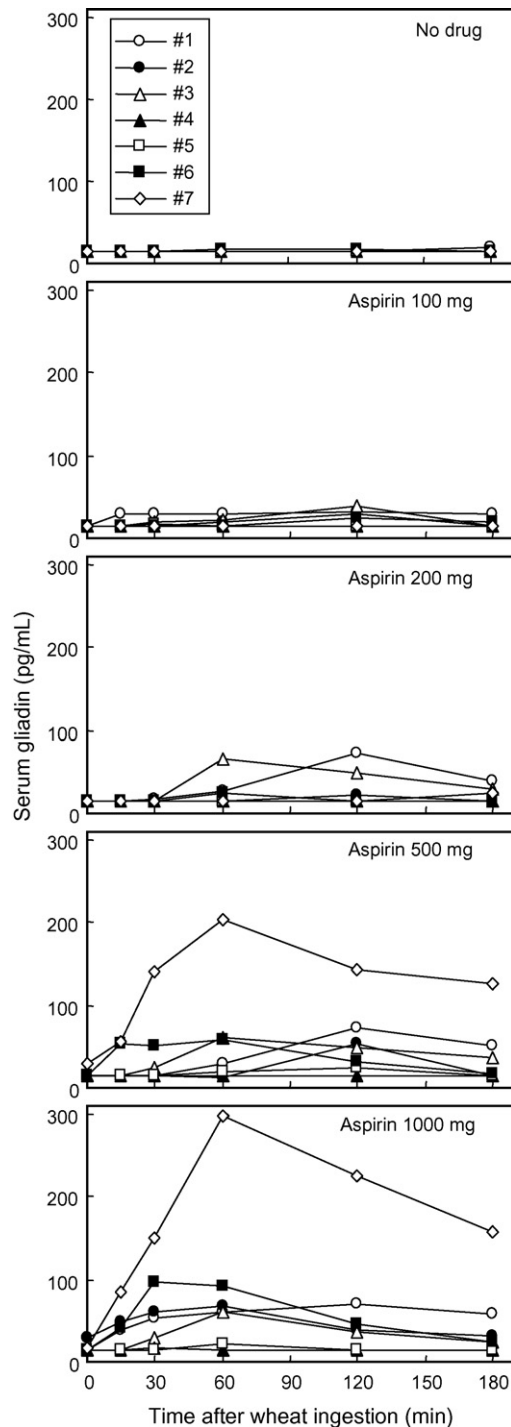


Fig. 1. Individual serum gliadin concentration versus time plots after ingestion of a wheat product and aspirin. Aspirin was administered 30 min before ingesting 120 g of the wheat product. Gliadin levels were measured by ELISA and values under the detection limit are depicted as 15 pg/mL.

only observed in 1 of 5 subjects administered 15 mg of meloxicam. Meloxicam, a preferential COX-2 inhibitor, produce fewer gastrointestinal side effects than older non-selective NSAIDs [10]. It has been suggested that meloxicam has less effect on intestinal gliadin permeability. Loxoprofen is a preferential COX-1 inhibitor, similar to aspirin, but did not increase the serum gliadin levels in 2 of 5 subjects. This may be attributed to the weak

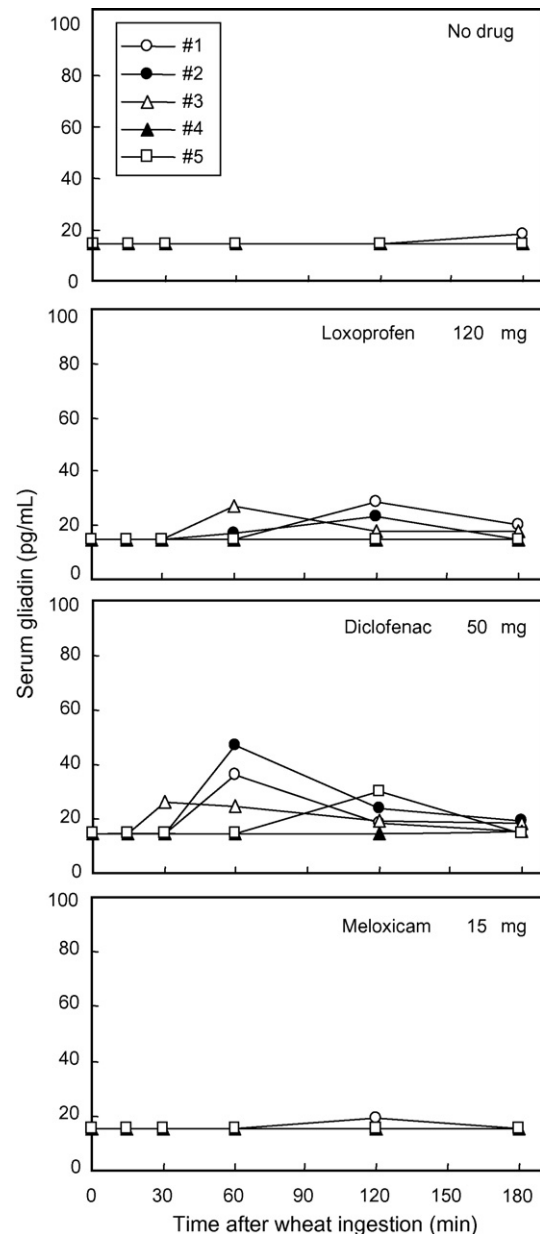


Fig. 2. Individual serum gliadin concentration versus time plots after ingestion of a wheat product and individual NSAIDs. Each NSAID (loxoprofen at 120 mg; diclofenac at 50 mg; meloxicam at 15 mg) was administered 30 min before ingesting 120 g of the wheat product. The gliadin levels were measured by ELISA and values under the detection limit are depicted as 15 pg/mL.

gastrointestinal ulcerogenicity of loxoprofen due to its prodrug form. Our present results, together with those of previously published studies regarding intestinal alterations, suggest that NSAIDs that cause mucosal injury in the gastrointestinal tract as a side effect facilitate gliadin absorption from the gastrointestinal tract in humans.

In conclusion, the present study clearly demonstrates that aspirin, diclofenac and loxoprofen facilitate the absorption of wheat gliadin with allergenic activity from the gastrointestinal tract into the circulation. Our results suggest that, even for low-dose aspirin, NSAIDs that can cause gastrointestinal hyperpermeability may accelerate symptom development in gliadin-sensitized patients with wheat allergy.

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