

Short communication

Ultrastructural changes in the duodenal mucosa induced by ingested histamine in patients with chronic urticaria

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Histamine in food may be responsible for some cases of food intolerance. We previously demonstrated disturbances in the metabolism of ingested histamine in patients with chronic urticaria (CU) and proposed that this could be related to increased intestinal permeability to histamine. The present study was undertaken to look for ultrastructural changes in the intestinal tract that might explain this abnormality. We examined duodenal biopsies from seven patients with CU before and after intraduodenal administration of histamine (120 mg). Five subjects had clinical symptoms (diarrhea, urticaria, headache, accelerated heart rate, and drop in blood pressure) within 1 h of duodenal histamine challenge (DHC). Ultrastructural changes, including edema of the interstitial tissue, enlargement of the basal intercellular spaces, slight congestion of the endothelial cells, and pericapillary edema, were observed in six subjects 45 min after DHC. In all the biopsies, the epithelium was normal, and the tight junctions were not modified by DHC. This morphologic study demonstrates that histamine can induce edema in the basal intercellular spaces of the duodenal mucosa and in the submucosa without evident change in the integrity of intercellular junctions. The most plausible route for histamine to have taken would appear to be an intracellular one.

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Many foods contain histamine (1, 2). Numerous reports have emphasized that histamine ingested in food may be responsible for some cases of food intolerance, which may include systemic symptoms such as headache, urticaria, or anaphylactoid shock (3–5). This phenomenon is especially common in patients with chronic urticaria. Healthy subjects apparently tolerate fairly large doses of intestinally administered histamine, but this is not the case in patients with chronic urticaria. The intraduodenal administration of 120 mg of histamine is well tolerated by healthy subjects but induced an attack of urticaria in 64% of a group of patients with CU (6). In our previous study, 72%

of patients with CU had an abnormal increase in their plasma histamine levels after this histamine challenge.

Little is known about the direct effects of ingested histamine on the intestinal mucosa. Studies in animals have demonstrated that histamine administered by infusion into mesenteric blood vessels damages the duodenal epithelium (7, 8). We have observed the effects of histamine administered via a more physiologic route, that is, intraluminally through an endoscope, on the duodenal epithelium (9). The purpose of the present study was to see whether the direct application of histamine on the duodenal mucosa of patients

with CU might lead to ultrastructural changes that could explain the increased transepithelial transport of this substance which occurs in these patients.

Material and methods

Patients

Five women and two men, their ages ranging from 26 to 52 years (mean age 35 ± 9 years), suffering from CU for 6–36 months (mean duration 17.9 ± 10.6 months), volunteered to participate in this study. Each had a history of at least one spontaneous attack per week in the weeks before the study, and none had a history of physically induced hives. Their treatment, consisting of antihistamines and corticosteroids, was stopped at least 8 days before they were studied. Patients served as their own controls.

Digestive histamine challenge (DHC)

A duodenal-jejunal endoscopic tube was inserted under gastroscopic control. A macroscopic photograph and a mucosal biopsy were obtained. Immediately thereafter, 200 mg of histamine bihydrochloride (equivalent to 120 mg of histamine base) was instilled through the tube into the duodenum. This dose did not induce symptoms in healthy subjects. After 45 min, the site of histamine instillation was photographed, and a second biopsy was obtained. Throughout the endoscopy, the blood pressure was monitored, and the onset of any clinical symptoms and signs, including facial flushing, pruritus, urticaria, headache, and gastrointestinal or respiratory disturbances, was noted. For ethical reasons, we did not perform DHC in healthy subjects.

Electron microscopy of the biopsy specimens

The mucosal biopsies were fixed immediately in 2.5% glutaraldehyde for 2 h at room temperature and then washed in 0.1 M cacodylate buffer at pH 7.4. The specimens were then postfixed in osmium tetroxide, dehydrated in ethyl alcohol, and embedded in epon.

Ultrathin sections were stained with uranyl acetate and lead citrate (Reynolds' method) before being mounted on grids. Four grids from each patient, two from before and two after the DHC, were examined in a Phillips CM10 electron microscope, going from left to right and from top to bottom of each grid. The biopsies were examined blindly by the pathologist.

Results

Clinical manifestations after DHC

Four patients developed clinical manifestations within 1 h after instillation of histamine intraduodenally: urticaria, headache, acceleration of heart rate greater than 8 beats/min, and a fall in both systolic and diastolic blood pressure of at least 10 mmHg. One patient developed diarrhea 4 h later.

Macroscopic observations

Before the instillation of histamine, the duodenal mucosa appeared normal in all seven subjects. At the time of the second biopsy, erythema and edema were visible in the duodenal mucosa of two of the seven patients, while it had a normal appearance in all the others.

Microscopic observations

On light microscopy, the duodenal mucosa appeared normal in all the biopsy specimens before DHC. After DHC, there was mucosal and submucosal edema in one case, whereas all the others were normal.

When examined by electron microscopy, the sections obtained before DHC revealed normal duodenal architecture in all cases. Enterocytes with a well-defined apical microvillous border were the principal epithelial cells. They contained a moderately large number of mitochondria, mostly in the supranuclear cytoplasm. Adjacent cells were held together by junctional complexes, desmosomes, and lateral interdigitations, which ensure the mechanical stability of the epithelium. Goblet cells were interspersed between the enterocytes and characteristically shaped simple unicellular glands. A few lymphocytes were seen in the basal half of the epithelium. The submucosa appeared to be normal, without evidence of edema. Mast cells, some of which were degranulated, were scattered throughout the submucosa.

After DHC, ultrastructural changes were found in biopsies from six of the seven patients, including five who had experienced clinical symptoms after DHC; the biopsy of the patient who did not react clinically presented no structural changes. In all positive cases, the main change was edema in the interstitial tissue. Enlargement of the basal intercellular spaces (Grünhagen spaces) was seen in four cases (Figs. 1 and 2), and the endothelial cells were slightly congested. Pericapillary edema was also observed (Figs. 3 and 4). Otherwise, the epithelium, including the enterocytes and goblet cells, appeared to be normal. The tight junctions

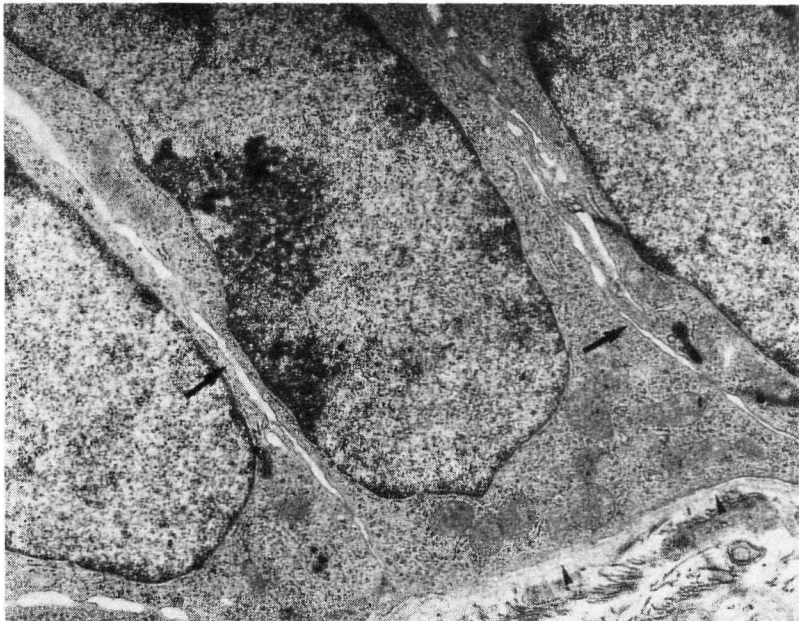


Fig. 1. Basal intercellular spaces before DHC ($\times 3900$). Note narrowness of basal intercellular spaces ($\rightarrow$), and basement membrane ($\blacktriangleright$).

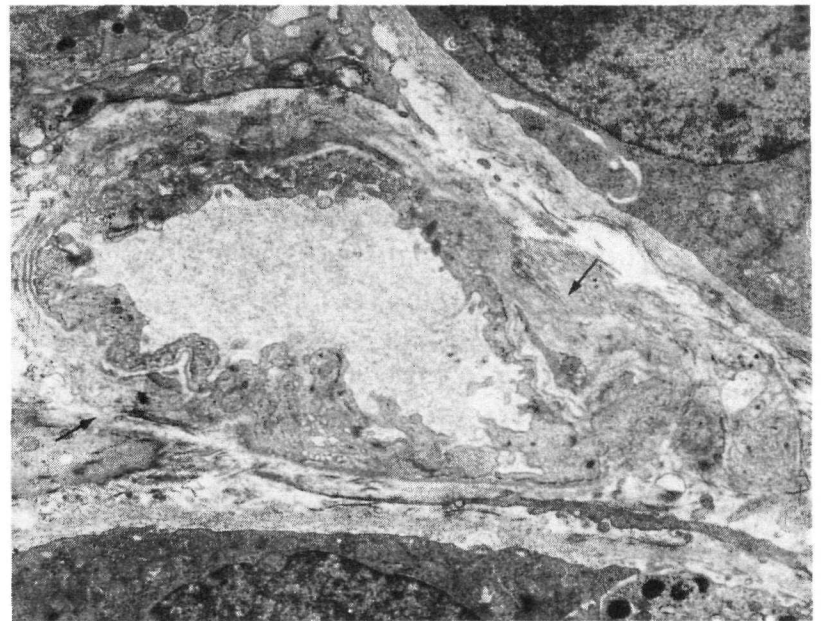


Fig. 3. Capillary before DHC ($\times 5200$). Note well-organized perivascular conjunctival tissue ($\rightarrow$).

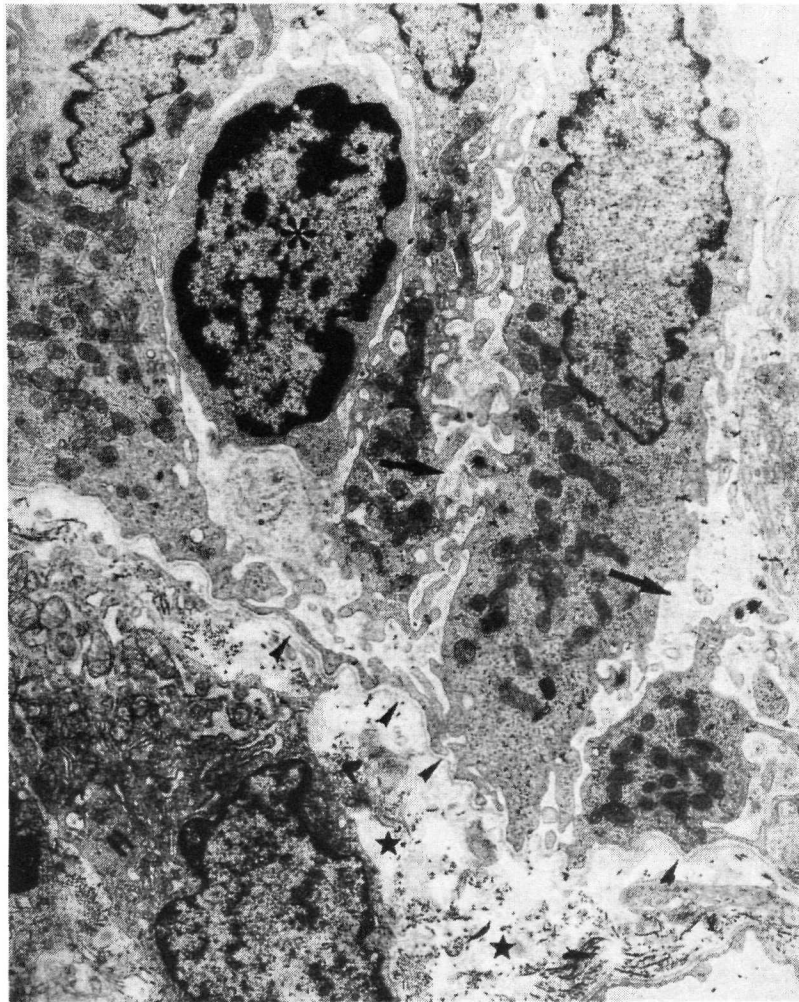


Fig. 2. Enlargement of basal intercellular spaces after DHC ($\times 3900$). Note enlargement of basal intercellular spaces ($\rightarrow$). Lymphocyte (*) is migrating across basal lamina, pushing between enterocytes. Under basement membrane ($\blacktriangleright$), there is pericapillary edema in submucosa ($\star$).

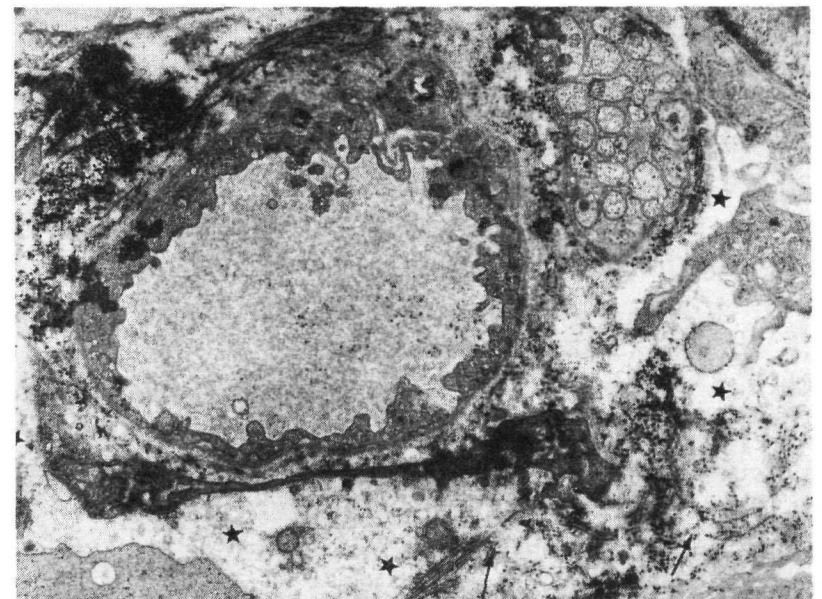


Fig. 4. Capillary after DHC ($\times 5200$). Note pericapillary and interstitial edema ($\star$). Interstitial tissue shows disorganization ($\rightarrow$).

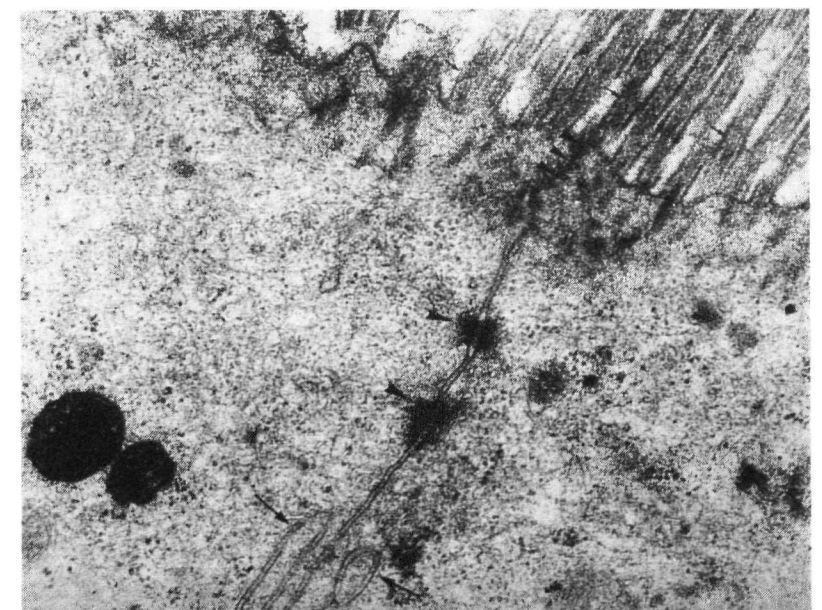


Fig. 5. Tight junction after DHC ($\times 21\,000$). Note integrity of epithelial cell junctional complexes ($\blacktriangleright$), desmosomes ($\blacktriangleright$), lateral interdigitations ($\rightarrow$), and well-defined apical microvillous border ($\rightarrow$).

were not modified in any of the specimens (Fig. 5), and there was no increase in the number of degranulated mast cells. The enterocyte cytoplasm retained the same appearance. We did not note goblet cell intercellular disruption.

Discussion

Man is very sensitive to the intravascular infusion of histamine; the blood pressure falls when the plasma concentration is at 6–8 ng/ml (10). In contrast, large quantities of biogenic amines are generally innocuous when introduced via the digestive route, because of the important physiologic barriers noted above. Thus, 120 mg of histamine instilled into the gut is well tolerated in healthy subjects, whereas 7 µg intravenously induces undesirable effects (11).

There are few published reports on the action of histamine on the digestive tract. This is surprising since the gut is frequently in contact with this amine, owing to the fact that it is present in many foods (1, 2). The few studies on the effects of histamine on intestinal mucosa were done in animals (7, 8), and the route of administration used in those studies did not correspond to the physiologic conditions of histamine ingestion. Nevertheless, the results demonstrate that histamine can modify intestinal architecture. Tanaka et al. demonstrated that a single subcutaneous dose of histamine (20 mg/kg) in rats induced villous changes in the duodenum, consisting of severe exfoliation of epithelial cells and exposure of the lamina propria (8). These changes were reversed within 8 h, indicating rapid mucosal repair. In another study, Porvaznik et al. infused histamine (at 1 mg/kg) into the mesenteric artery of rabbits and analyzed the results by freeze fractures on electron microscopy (7). No abnormalities were found in the tight junctions between enterocytes. But, within the first hour, goblet cells appeared to bulge at their apical ends. The junctional complexes of goblet cells were disorganized, creating a breach in the permeability barrier. By 2–3 h later, the tight junctions were repaired.

In both of those studies, histamine went from the vascular bed in the direction of the basal portions of the enterocytes. Thus, it did not encounter the mechanical and enzymatic barriers on the luminal side of the intestinal epithelium. In our study, no alterations of the epithelium or of the tight junctions were observed. It seems reasonable to believe, therefore, that the existence of these barriers could explain why epithelial damage was not observed, since histamine administered intraluminally encounters the apical rather than the basal portion of the epithelium.

Another reason for the lack of similar damage after DHC, in addition to possible species differences in sensitivity to histamine, could be that the dose of histamine administered to the animals in those studies was much larger than that tolerated by man.

Nevertheless, there were ultrastructural changes in the duodenum after DHC, including interstitial edema and enlargement of the intercellular basal spaces. The interstitial edema might have been the indirect result of the vasopermeability induced by histamine. Histamine has a dilating effect on most vascular tissues, and it clearly increases vascular permeability in mesenteric tissue (12). It induces the formation of capillary pores and also causes pericytes to contract (13, 14), and these microvascular effects are dose dependent.

The ultrastructural changes, together with the occurrence of clinical symptoms, suggest that histamine must have passed from the intestinal lumen into the digestive mucosa. The transport of histamine through the intestinal paracellular pathway is normally limited by the tight intercellular junctions. Since the tight junctions appeared to have remained intact after DHC in our patients, the most plausible route for histamine to have taken would appear to be an intracellular one; that is, through the enterocytes.

The passage of histamine into enterocytes in CU patients might be explained by a deficiency in the local barrier to histamine transport. Diamine oxidase, an important component of this barrier, is located in the cytoplasm of enterocytes (15), implying that histamine must be able to enter these cells. A previous study has demonstrated reduced diamine oxidase activity in patients with CU (16), and the susceptibility of CU patients to DHC is probably related to this defect (6).

In conclusion, ultrastructural examination of duodenal mucosa both before and after DHC revealed no evidence of a defect in the integrity of the digestive epithelium. Histamine appeared not to have altered intercellular junctions. On the other hand, there was evidence of histamine-induced interstitial and capillary lesions, indicating that the histamine administered into the duodenum probably passed through the intestinal wall by an intracellular route. These observations support the hypothesis of an enzymatic deficiency, mainly in diamine oxidase, in patients with CU.

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