A Hypothesis of the Possible Immunological Mechanisms Behind the Chronic Gastritis and Peptic Ulcerations Associated with the Campylobacter pylori Infection

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A short review of the data regarding the presence of *Campylobacter pylori* in the peptic ulcer patients and those with chronic gastritis has been presented together with the data regarding the presence and functions of the gastric mucosal mast cells and IgE molecules at their surface.

A speculation is made that the physiological role of the IgE/mast cell system in the gastric mucosa, beside bringing the immunocompetent cells to the place of infection, consists also in producing a local tide in the gastric acid secretion that would facilitate pathogen elimination. Chronic infection with *C. pylori* and other pathogens could lead to the permanent activation of this system resulting in the chronic gastritis or spots of hyperacidity that might turn into ulcers.

Findings of the humoral response to *C. pylori* in ulcer patients support the presented hypothesis. Further studies of the total and specific IgE content in the gastric mucosa of ulcer patients and experimental animals are required to test its validity.

Key words: Campylobacter pylori, gastritis, IgE, infection, peptic ulcer

Since the first papers by Marshall and Warren[9] on finding *Campylobacter*-like organism in the gastric mucosa of the patients with gastritis and peptic ulcerations, numerous studies have confirmed that there is a more or less significant association between the presence of *Campylobacter pylori* and the conditions of the type B chronic gastritis or gastric and duodenal ulcerations.[3] Possible pathological mechanisms behind this association are often left uncleared. The source of infection and its transmission routes still remain undefined.[4]

This association can help us to speculate about the physiological role of histamine in the regulation of the gastric acid secretion.[11] Since the idea of histamine as a final gastric parietal cell stimulator has been abandoned, no other hypothesis has been replaced it. Therapeutical use of H_2 blockers has proved that histamine liberation occurs continuously in the normal gastric mucosa.

Mast cells have been recognised as the main source of histamine in the gastric mucosa[11] and it is believed that they are of the same kind as elsewhere. IgE molecules have been detected on their surface,[1] which allows us to presume that the specific IgE mediated mast cell degranulation could be the main mode of histamine liberation in the gastric mucosa. Some histamine can also be liberated after some other nonspecific stimulations, as it has been observed on mast cells elsewhere in the body.

The real importance of IgE — mast cell system in the body is often left uncleared. It seems very unlikely that a whole class of Ig molecules and the cells with receptors for it have been developed in numerous species just to be used in parasyte infestations and potentially harmful atopic reactions. Each organ or system has to improve the survival chances of the individual organism continously, or it has to be modified or even lost during evolution. This basic principle of evolution emphasizes the suggested importance of IgE as a gatekeeper.[5]

IgE and mast cells might have developed as a specific changeable and tuneable alarm system of the extravasal tissue space that cannot be fully and permanently controlled by the immunocompetent cells. In this case the system of IgE and mast cells is being used to gather immunocytes where necessary. Under normal conditions, only a few of the mast cells would recognise the specific antigen and degranulate simultaneously, affecting only the neighbouring vessels.

This kind of allarm system can be temporarily sensitized and tuned up by the idiotypes of circulating IgE covering the mast cell surface. Since the half-life of IgE attached to the surface of mast cells ranges from one to two weeks, changes in the available IgE idiotypes can cause very slow changes and modifications in the sensitivity of the whole system.

Gastric acid and pepsin play an important role in our defense against mycrobes. Still better efficacy would be achieved if the gastric acid secretion could be deliberately increased in the presence of pathogens. The parietal cells would have to be able to recognise the mast cell degranulation, caused by the encountering the specific antigen.

It is possible to speculate that under physiological conditions pathogens are being closely followed on their stomach route by a local tide in the gastric acid secretion. The tide is promoted by the specific, IgE mediated, histamine liberation from the mucosal mast cells (as shown in Fig. 1).

This histamine action on the parietal cells is mediated through the H_2 receptors. The same type I reaction in the lower parts of the digestive tube might be responsible for the changes in the gut motility and secretion, often provoked by parasytes.

C. pylori, as a specific pathogen able to survive in stomach, can easily produce chronic infections of the gastric mucosa and submucosa. Numerous mast cell degranulation would lead to the chronic inflammatory response, as seen in the chronic gastritis, probably mediated by the vasal H_2 receptors. On the other hand, liberated histamine would strongly stimulate the neighbouring parietal cells producing the spots of chronic focal hyperacidity with good chances of turning into ulcers.

Arguments in favour of the presented hypothesis are as follows. *C. pylori* is able to survive in stomach and even pe-

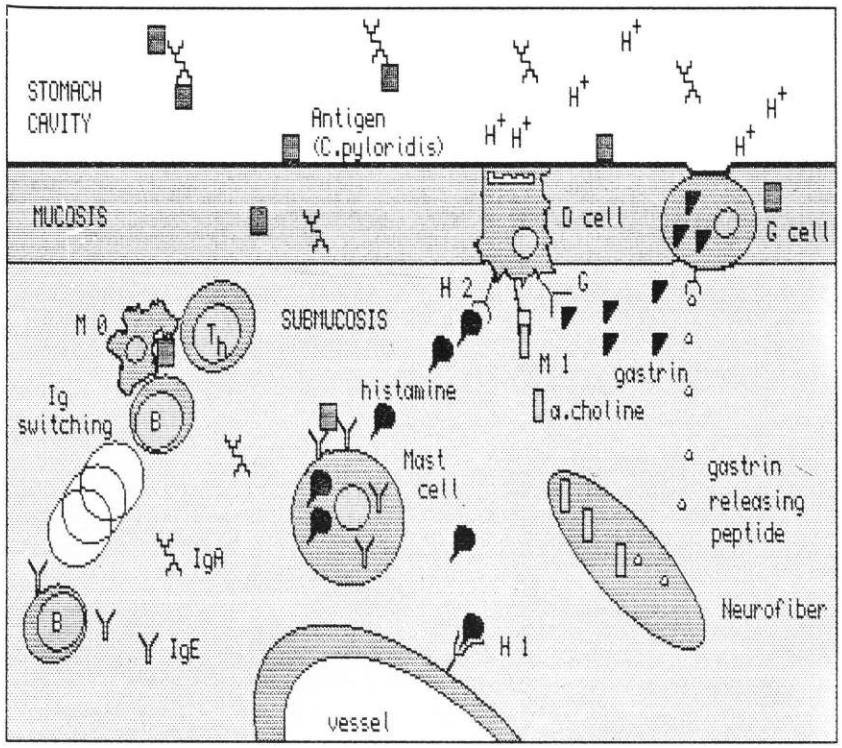

Fig. 1

The suggested concept of the IgE mediated stimulation of gastric acid secretion in the chronic *Campylobacter pylory* infection.

Left side: *C. pylori*, able to penetrate mucosa, is presented by the macrophage (MO) to the T helper and B cell. – The Ig gene switching from IgM, through the IgG subclasses, ending with IgA and IgE, allows production of the whole humoral response. IgA is released at the mucosal surface.

In the middle: The mucosal mast cell is being temporarily sensitized by the IgE and it degranulates after encountering the specific antigen. Liberated histamine affects the neighbouring vessel through H_2 receptor and stimulates the parietal cell (D) through H_2 receptor. The latter can be blocked by the H_2 blockers.

Right side: The M_1 receptor of the D cell is stimulated by acetylcholine from the vagal fibres and it can be blocked by anticholinergics. The third, gastrin receptor (G), is stimulated by gastrin liberation from G cells in mucosa. The activity of G cells is in the negative feedback with the luminal concentration of hydrogen ions (H^+), produced by D cells. It can be influenced by gastrin releasing peptide, or bombesin, released from the vagal fibers.

netrate gastric mucosa.[8, 10] Specific IgG serum antibodies against *C. pylori* have been significantly ($p < 0.001$) more common in the group of 37 ulcer patients compared to the control group of 50 laboratory staff and 31 children under the age of 10.[7] Distribution of these specific IgG antibodies varies among different populations, which is probably connected with the sources of infection and other factors. High incidence of IgG positive sera againts *C. pylori* in the Ethiopean ethnic group in Australia has been associated with the high incidence of duodenal ulcer in Ethiopia.[4] Finding of the specific humoral antibodies in the blood strongly suggests that *C. pylori*, similarly as the *C. jejuni* (another member of the Campylobacter family), is able to promote the complete humoral response, renging from IgM, through IgG subclasses to IgE and IgA. This sequence, controlled by the switching of the genes responsible for the Ig heavy chain, includes the secretory and atopic antibodies. Specific serum Ig antibodies to *C. pylori* have been studied in a group of 347 persons.[12] It showed that the levels of specific IgG and IgA detected in the sera of the gastritis and ulcer patients are higher than among healthy individuals. Low titers among healthy controls correlated well with age. *C. jejuni*, a well known ethiological agent of the early childhood bacterial diarrhea, is capable of producing the complete humoral response. It has been found that rabbits fed with these bacteria develop systemic antibodies in serum and secretory antibodies in enteric mucosa. In humans, 45 out of 46 patients have developed IgG antibodies against *C. jejuni*.[6] Specific IgG persisted over 50 days. Also, specific IgA and IgM were present in blood.

Since the systemic humoral response to *C. pylori* does not necessarily reflect the local humoral status of the gastric mucosa further more specific studies are needed to test the presented hypothesis. It would be important to measure the total IgE and specific IgE content in the gastric mucosa of ulcer patients and infected experimental animals. The next step would be to study specific mast cell degranulation in the presence of *C. pylori*.

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Sažetak

HIPOTEZA O MOGUĆIM IMUNOLOŠKIM MEHANIZMIMA NASTANKA KRONIČNOG GASTRITISA I PEPTIČKOG ULKUSA POVEZANIH S INFEKCIJOM CAMPYLOBACTER PYLORIDIS

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Učinjen je kratki pregled podataka o povezanosti prisustva *Campylobacter pylori* u bolesnika s kroničnim gastritisom i peptičkim ulceracijama, zajedno s podacima o prisustvu i funkciji mastocita i IgE u sluznici želuca.

Ukratko je objašnjeno shvaćanje da se IgE/mastocit sustav razvio tijekom evolucije kao sustav za uzbunjivanje i dovođenje imunokompetentnih stanica u dijelove tijela koji su nedostupniji cirkulirajućim stanicama imunog sustava. Tu spadaju sva rubna tkiva, u što spada i probavna cijev, te interstanični tkivni prostori. Specifičnost i osjetljivost takvog sustava za uzbunjivanje je u direktnoj vezi sa spektrom idiotipova IgE antitijela u cirkulaciji.

U želučanoj sluznici je dokazano postojanje mastocita prekrivenih antitijelima klase IgE, te se smatra da su oni glavni izvori oslobađanja histamina unutar sluznice. Uz mogućnost liberalizacije histamina iz mastocita na nespecifične podražaje, ne može biti isključena mogućnost da je specifična imunološka reakcija IgE/mastocit sistema, nakon susreta sa specifičnim antigenom, glavni izvor oslobođenog histamina u želučanoj sluznici.

Učinjena je hipoteza da je posebna fiziološka uloga IgE/ /mastocit sistema u želučanoj mukozi, uz pozivanje imunokompetentnih stanica na mjesto infekcije, također i stvaranje lokalne plime u lučenju želučane kiseline koja olakšava eliminaciju patogena. Kronična infekcija sluznice s *C. pylori* i sličnim patogenim mogla bi dovesti do permanentne aktivacije ovog sistema, što bi moglo doprinijeti razvoju kroničnog gastritisa ili nastanku točaka stalne hiperacidnosti pogodnih za nastanak ulkusa.

U prilog hipotezi govore nalazi specifičnog humoralnog odgovora na *C. pylori* u bolesnika s ulkusnom bolešću. Pravu provjeru bi pružile studije sveukupnog i specifičnog IgE u želučanoj sluznici duodenalnih bolesnika i inficiranih eksperimentalnih životinja.

Ključne riječi: Campylobacter pylori, gastritis, IgE, infekcija, peptički ulkus

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