● THE INFLUENCE OF OMEPRAZOLE (OMP) AND FAMOTIDINE (FAM) ON MUCIN SYNTHESIS AND PGE2 RELEASE IN THE RAT STOMACH. K. Yoshimura, S.G. Delbarre, E.R. Kraus, S. Shimakura, and C.R. Boland. VAMC and Univ. of Michigan, Ann Arbor, MI.

H2-receptor antagonists and proton pump inhibitors are widely used for gastric acid suppression. However, little is known about the influence of these drugs on the defensive factors in the stomach such as mucin production. We tested the hypothesis that the proton pump inhibitor and the H2-receptor antagonist FAM may affect mucin synthesis and PGE2 release in the stomach. METHODS: 30 mg/kg OMP, 4 mg/kg FAM, or buffer control was administered by gavage to rats once daily. After 2 or 4 weeks of treatment, and 5 days after the end of 4 weeks of treatment, the fundus was removed, cut into small pieces and incubated in tissue culture medium. After 3 hours, PGE2 released into media was measured by RIA. Mucin synthesis was measured by $^{3}H$-glucosamine and $^{35}SO_4$ incorporation. RESULTS: The results of each assay are expressed as a percentage of control wells. PGE2 release was maximally inhibited after 2 weeks of OMP and 4 weeks of FAM. Total glycoprotein synthesis (i.e., $^{3}H$-incorporation) was inhibited at all time points by OMP, but only after cessation of treatment with FAM. PGE2 release and sulfated glycoprotein synthesis were restored to control values or more by the fifth day after the end of treatment, whereas total glycoprotein synthesis was still suppressed, in both groups.

| | | 2 weeks | 4 weeks | 5 days after treatment |
|---|---|---|---|---|
| OMP | PGE2 | 43 ± 4 *** | 67 ± 11* | 119 ± 26 |
| | $^{3}H$ | 84 ± 1*** | 94 ± 1* | 92 ± 3* |
| | $^{35}S$ | 85 ± 7* | 97 ± 9 | 113 ± 8 |
| FAM | PGE2 | 80 ± 10 | 69 ± 8** | 110 ± 7 |
| | $^{3}H$ | 95 ± 4 | 104 ± 3 | 84 ± 2*** |
| | $^{35}S$ | 85 ± 6* | 93 ± 3 | 96 ± 4 |

(*P<0.05, **P<0.01, ***P<0.001, vs control; n=5)

SUMMARY: 1) OMP treatment significantly inhibits PGE2 generation and total glycoprotein synthesis; PGE2 generation recovers within 5 days of therapy, whereas glycoprotein synthesis does not. 2) FAM inhibits PGE2 generation only at the 4 week time period, and full recovery occurs within 5 days of cessation of therapy; glycoprotein synthesis was not affected until after withdrawal of the drug. 3) Sulfated glycoprotein synthesis was inhibited by both OMP and FAM at 2 weeks, but recovered by 4 weeks, and after treatment. CONCLUSIONS: Antisecretory therapy also inhibits the production of factors involved in gastric mucosal defense, which should be considered in the assessment of response to treatments.

● THE EFFECT OF HISTAMINE AND RECEPTOR ANTAGONISTS ON PGE2 RELEASE BY EXPLANTS AND ISOLATED CELLS FROM RABBIT STOMACH. K. Yoshimura, S.G. Delbarre, E.R. Kraus, S. Shimakura, J.M. Scheiman, and C.R. Boland. VAMC and University of Michigan School of Medicine, Ann Arbor, MI.

The stimulation of gastric mucosal PGE2 release by histamine may have important implications for epithelial defense. We used mucosal explants and isolated gastric cells to test the hypothesis that a gastric mucosal cell population with histamine receptors plays an important role in PGE2 release. METHODS: Rabbit fundic and antral mucosa were cut into small pieces and studied as explants. Dispersed gastric cells were prepared using tissue digestion and enriched by counterflow elutriation. The tissues or cells were incubated with $10^{-5}$M histamine (Hist) + $10^{-5}$M IMX; Hist + IMX + $10^{-5}$M pyrilamine (Anti-H1); Hist + IMX + $10^{-5}$M cimetidine (Anti-H2); and IMX as a control. After 16 hours, PGE2 released into the the media was measured by radioimmunoassay (RIA). RESULTS: The results of each assay are expressed as a percentage of control wells. Hist significantly increased PGE2 release in both fundic and antral explants. The increase in PGE2 release was not blocked by the addition of anti-H1, but was significantly suppressed by anti-H2. Antral tissue release of PGE2 was 142% of that released by fundic tissue explants. All treatments failed to stimulate PGE2 release above control values in isolated mucous, chief, and parietal cells.

| | PGE2 release (% of control) | | |
|---|---|---|---|
| (explants; n=6) | Hist | +Anti-H1 | +Anti-H2 |
| fundus | 152 ± 12 * | 149 ± 27 | 103 ± 14 + |
| antrum | 174 ± 23 * | 180 ± 58 | 80 ± 12 ++ |
| (isolated cells; n=4) | | | |
| mucous & chief | 111 ± 13 | 104 ± 19 | 112 ± 13 |
| parietal | 125 ± 12 | 114 ± 10 | 89 ± 10 |

(*P<0.01, vs control; + P<0.05, ++ P<0.01, vs Hist)

SUMMARY: 1) Hist stimulates the release of PGE2 in both fundic and antral explants. 2) The increase in PGE2 is not blocked by anti-H1 but is by anti-H2. 3) This effect is not seen in the isolated mucous, chief, or parietal cells. CONCLUSIONS: The effects of histamine and the anti-H2 agent cimetidine on PGE2 release are significantly greater in tissue explants than in dispersed, isolated populations of mucous, chief, or parietal cells. Although these isolated epithelial cell populations release PGE2, these results suggest that a non-mucous, non-chief, non-parietal cell population may be of greater importance in the defensive response to histamine in intact gastric mucosa.

● COLONIZATION OF GASTRODUODENAL MUCOSA WITH HELICOBACTER PYLORI IN PATIENTS WITH RHEUMATOID ARTHRITIS DURING TREATMENT WITH GOLD COMPOUNDS. Z.J. Yu, J. Sarosiek, T. Feng, B.J. Marshall, P. Kaplan, J.S. Davis, R.W. McCallum. University of Virginia Health Sciences Center, Charlottesville, Virginia.

The strong microbicidal activity of gold compounds towards Helicobacter pylori (HP) has been recently demonstrated in vitro (Gastroenterology 98:A25,90) raising its potential clinical therapeutic application. We have studied, therefore, the incidence of HP in patients with rheumatoid arthritis (RA) before and during treatment with intramuscular gold (Myochrysine) or oral compound (Auranofin).

The study was conducted in 13 patients (9 females and 4 males) with definite RA treated with gold for a period of 5 months to 3 years. The confirmation of HP colonization was performed by the measurement of serum HP-IgG by ELISA and by the [$^{14}$C]urea breath test. Serum total IgG was simultaneously measured.

The incidence of HP in patients with RA before gold therapy was 66% (over twice the incidence of this microorganism in age-matched population of the Charlottesville area(30%)). After therapy with gold compounds serum HP-antibodies significantly decreased from 0.517 to 0.301 (p<0.001). The total serum IgG decreased only 5%. The [$^{14}$C]urea breath test confirmed data obtained in an ELISA assay.

This study confirms a therapeutic potential of gold compounds in the treatment of HP colonization in patients with RA. Oral gold might be particularly worthy of consideration in the treatment of refractory HP-related gastric and duodenal ulcer. The observation of a high incidence of HP in RA patients raises the question as to a relationship between HP and the development of NSAID-induced gastroduodenal pathology.

● SYMPTOMS AND MOTOR ABNORMALITIES INDUCED BY ESOPHAGEAL EXPOSURE TO ACID AND ALKALI. G. Zaninotto and T.R. DeMeester. Department of Surgery, University of Southern California Med. Ctr., Los Angeles, California.

The symptomatic and motor response to stimulation of esophageal nociceptors by luminal contents is poorly understood. We evaluated symptoms, esophageal motor activity, and intraesophageal pH in ten normal volunteers while infusing the esophagus 2 cm below the crico with saline, 0.1 N HCl, 0.05 N NaOH, and gastric juice on separate days at 5 ml/minute for 30 minutes. No symptoms or motility changes were recorded during saline infusion (pH 6.2). HCl infusion after 18±4 minutes caused heartburn in 8/10 associated with chest pain in two (pH 1.2±0.3). Motility abnormalities were observed in all who developed symptoms and in one who was asymptomatic. Gastric juice infusion caused symptoms in 3/10 (pH 2.5±1.6) after a mean of 18.1±2.7 minutes. Motility abnormalities were observed in only two of the three subjects and none of the others. NaOH infusion caused heartburn in 8/10 associated with chest pain and dyspnea in four (pH 10±0.2) after a mean of 8.0±4 minutes. Motility abnormalities were observed in 110/10. Motility abnormalities induced by acid or gastric juice ceased within 5.2±3.3 minutes of stopping the infusions, but persisted to the end of the test after stopping alkaline infusion. The motility characteristics (Table) show that symptoms are associated with increased frequency of contractions which have a longer duration, slower propagation, and a higher incidence of abnormal morphology.

| | Saline | HCl | HCl+Sympt | GJ | GJ+Sympt | NaOH+Sympt |
|---|---|---|---|---|---|---|
| Swallows/min. | 1.3±0.3 | 1.8±0.7 | 2.8±0.3^ | 1.3±0.5 | 3±1.3 | 4.3±1.6^ |
| Amplitude | 107±16 | 99±9.3 | 130±18^ | 104±16 | 104±17 | 124±13 |
| Duration | 5.8±0.6 | 5.5±0.2 | 7.8±1.1^ | 4.7±0.3 | 6.8±0.4 | 7.5±0.5^ |
| Propagation | 5.5±1 | 7.0±0.4* | 9.2±1.1^ | 6.6±0.2 | 9.8±2.6 | 10.2±0.7^ |
| % Abn. Morph. | 3±2 | 14±4* | 34±6.5^ | 3.4±1.8 | 23±8.6* | 35.7±6.3^ |

^ = p<0.05 compared to HCl infusion * = p<0.05 compared to saline infusion

Conclusion: The esophagus in normal subjects is insensitive to short periods of gastric juice, acid, or alkaline exposure. Symptoms of heartburn, chest pain, and dyspnea occur with prolonged exposure, and are associated with induced motility abnormalities.