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Alimentary tract and pancreas

Stimulation of mucosal prostaglandin synthesis in human stomach and duodenum by antacid treatment

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SUMMARY **The effect of a low dose antacid treatment on mucosal prostaglandin metabolism was studied in 15 healthy volunteers. A daily dose of 46 mmol (=138 mval) $Al(OH)_3$ and 42 mmol (=84 mval) $Mg(OH)_2$ with a titrated *in vitro* neutralising capacity of 272 mval of H^+ was given for three weeks. Total prostaglandin formation and the prostaglandin profile as well as the degradation of PGE_2 were assayed by incubating homogenates of endoscopic biopsies from antral and duodenal mucosa with the precursor (^{14}C)arachidonic acid. Total prostaglandin synthesis in antrum (623 (110) pmol/mg protein) and duodenum (432 (72) pmol/mg) was stimulated after three weeks administration of low dose antacids by 176% ($p<0·05$) and 154% ($p<0·05$), respectively. An untreated control group exhibited no significant changes. In contrast, the prostaglandin profile showed only a small increase of the prostacyclin metabolite 6-keto PGF_{1a} ($p<0·05$) at the expense PGD_2. PGE_2 catabolism was unaffected. This enhanced activity of mucosal prostaglandin cyclooxygenase might represent one possible mechanism of action of a low dose antacid treatment.**

Antacids heal peptic ulcers at doses[1,2] too low to significantly affect gastric acidity.[3] Antacids may therefore have cytoprotective effects and this is supported by some animal experiments.[4-6] Antacids release mucosal prostaglandins,[5] which could mediate this protective effect.[7] In this study prostaglandin synthesis in homogenates of endoscopic biopsies was measured in response to antacid administration.

Methods

STUDY DESIGN

Fifteen healthy volunteers were treated for three weeks with an antacid (Maalox 70, 4×10 ml), containing 46 mmol (=138 mval) $Al(OH)_3$ and 42 mmol (=84 mval) $Mg(OH)_2$ per day. The *in vitro* neutralising capacity amounted to 272 mval/day. A separate group of eight volunteers remained untreated and served as controls. Three mucosal biopsies were taken endoscopically from both the prepyloric antrum and duodenal bulb at the start and end of the study period. The last antacid was taken at 10 00 pm and the volunteers were fasted overnight before endoscopy at 9 00 am. None had a history of peptic ulcer disease and the endoscopy findings were completely normal. Histological examination revealed normal mucosa in all volunteers except for three with minimal surface gastritis. No smoking and no other medication was allowed and the volunteers maintained a normal diet without specific standardisation during the study.

DETERMINATION OF ENDOGENOUS PROSTAGLANDIN SYNTHESIS

For each assay three biopsies (1·5 (0·5) mg protein) were added to 600 μl buffer and were immediately homogenised with a Potter-Elvehjem grinder at 4°C. The prostaglandin synthesis was determined as described previously for rabbit mucosa.[8] Protein content was measured according to Lowry *et al.*[9]

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(1-^{14}C)-arachidonic acid (1 mCi/mmol) and (^{3}H)-PGE_2 were purchased from New England Nuclear Chemicals GmbH (Dreieich, West Germany). Unlabelled arachidonic acid, adrenaline and the standard prostaglandins were supplied by Sigma Chemical Co (Deisenhofen, West Germany).

In brief, 50 mM Tris buffer (pH 8·0) containing 1 mM epinephrine as a cofactor was used for homogenisation and assay. The assay was started immediately after homogenisation by adding 0·5 ml tissue homogenate to the same volume of a substrate buffer solution, containing 160 nmol (^{14}C)-labelled arachidonic acid (0·25 μCi). After 20 minutes of incubation at 37°C the reaction was stopped with 0·5 ml 1·0 N acetic acid.

After extraction into 7·5 ml of a chloroform-methanol solution (2:1, by vol) the primary prostaglandins D_2, E_2, F_{2a}, and the stable degradation products of thromboxane A_2 and prostacyclin, thromboxane B_2 and 6-keto prostaglandin F_{1a}, respectively, were separated according to Goswami *et al*,[10] using chloroform-isopropanol-ethanol-formic acid (45:5:0·5:0·3, by vol) as the solvent system with repeat development. The prostaglandins A_2 and B_2 (comigrating) and the prostaglandin E_2 metabolites 15-keto E_2 and 13,14-dihydro-15-keto E_2 (EM) were isolated from the same sample by a parallel chromatography according to Korte *et al*[11] with chloroform-methanol-acetic acid-water (95:5:1:0·2, by vol) as the solvent system using a single development. After visualisation with iodine vapour the bands were scraped and the newly synthesised, (^{14}C)-labelled prostanoids were counted with a liquid scintillation counter, using Lumagel as scintillation fluid.

After subtraction of blanks the amount of each single prostaglandin formed during the incubation was calculated from the counts measured in the corresponding band and the specific radioactivity of the labelled arachidonic acid. Values were normalised to the protein content. Total prostaglandin synthesis was calculated from the sum of all the primary prostanoids isolated. Statistical calculations were performed using the Wilcoxon's test for paired samples.

The kinetic properties of the endogenous prostaglandin synthesis in human mucosa were similar to the rabbit.[8] The reaction was linear with respect to protein concentration and curvilinear with respect to time up to 20 minutes. Substrate saturation was achieved at an arachidonic acid concentration of 80 μM.

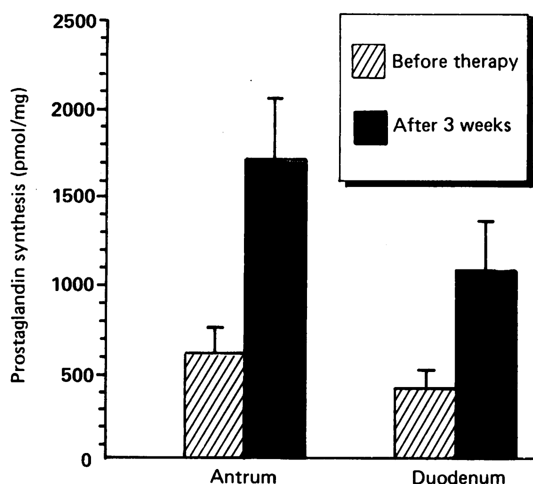

Figure *Prostaglandin synthesis from (^{14}C)arachidonic acid by antral and duodenal mucosal homogenate. Measurements were made in 15 volunteers, before and after administration of a low dose antacid regimen for three weeks. The results represent means (SE).*

Results

Total prostaglandin synthesis by antral mucosal biopsies was slightly higher than that by duodenal biopsies ($p<0·05$, Figure). Prostaglandin formation by mucosal homogenates significantly increased after the three weeks antacid regimen; total prostaglandin synthesis was stimulated by 176% in the antrum and by 154% in the duodenum ($p<0·05$). In contrast, prostaglandin synthesis in the untreated control group (n=8) was not changed significantly in antrum (853 (123) *v* 1263 (111) pmol/mg, mean (SE)) or duodenum (500 (79) *v* 650 (47) pmol/mg).

As shown in the Table, the prostaglandin profile was only marginally affected by antacid treatment. The only significant change was the increased proportion of 6-keto F_{1a} ($p<0·05$), the metabolite of prostacyclin, at the expense of PGD_2. In the controls the prostaglandin profile was constant.

Both major metabolites of PGE_2, 15-keto PGE_2 and 13,14-dihydro-15-keto PGE_2 accounted for only 2·6 to 6·3% and 0·5 to 4·5%, respectively, of total prostaglandins synthesised in both the antral and duodenal homogenates. There was no significant difference between pre and post-treatment values.

Discussion

The effects of an antacid treatment on the endogenous prostaglandin metabolism in human antral and duodenal mucosa was investigated, using *in vitro* incubation of mucosal homogenate with exogenous, (^{14}C)-labelled arachidonic acid as precursor. The method determines the mucosal capacity to synthe-

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Table *Effects of antacid treatment on prostaglandin profile in human antral and duodenal mucosa*

		% of total					
		A2/B2	*D2*	*E2*	*F2a*	*6-keto Fla*	*TxB2*
Antrum/	before	21·4 (3·4)	9·6 (1·8)	25·9 (2·1)	30·2 (3·2)	4·8 (0·7)	8·1 (1·0)
	after	25·7 (2·3)	7·9 (0·7)*	22·7 (1·5)	27·1 (2·0)	7·5 (0·8)*	10·0 (0·8)
Duodenum/	before	17·9 (3·1)	15·1 (3·0)	27·2 (3·4)	29·1 (4·3)	4·3 (1·1)	6·4 (1·0)
	after	24·3 (3·0)	6·6 (1·2)	25·8 (2·4)	27·7 (2·2)	7·2 (1·0)	8·3 (1·1)

Proportion of various prostaglandins formed from (^{14}C)arachidonic acid by mucosal homogenate before and after therapy, as detailed in Figure 1. The results shown are the means (SE) of the percentage distribution in 15 volunteers.
*$p<0·05$ *v* respective control before treatment.

sise prostanoids and the complete prostaglandin profile. In addition, the catabolism of newly synthesised PGE_2 was also measured. As discussed in a previous review article,[12] this technique is probably less subject to experimental artefacts than other methods based on content or release of mucosal prostaglandins. The method has shown a specific defect of prostaglandin synthesis in duodenal ulcer patients.[13]

After three weeks of low dose antacid administration the capacity of the mucosa to synthesise prostaglandins in the antrum and duodenum was significantly raised, whereas only minor differences in the prostaglandin profile were detectable. This rise of the prostaglandin synthesising capacity is in accordance with the enhanced PGE_2 content of or release by the mucosa in rat and human stomach after antacid treatment.[4 5 14] This study shows that increased PGE_2 secretion is not only the result of a short lived prostaglandin release but is also related to an enhanced synthetic capacity of the mucosa. Measurable effects probably are independent from endogenous substrate and dietary intake of polyunsaturated fatty acids because exogenous arachidonic acid is added to the assay at saturating concentrations. Changes of the endogenous cofactor supply of the cyclooxygenase also are unlikely to be responsible for this finding because adrenaline was added to the assay buffer as a cofactor at an optimal effective concentration.[12] Similarly, reduced degradation of the newly synthesised prostaglandins was excluded at least for PGE_2. The increased synthetic capacity appears to be related to an elevated activity of prostaglandin cyclooxygenase,[5] rather than subsequent enzymatic steps, because the complete prostaglandin profile, including the proportion of thromboxane B_2, was essentially unchanged. It remains unclear whether this effect is indirectly caused by a regulatory response to antacid induced alterations in mucosal integrity including low grade superficial damage by antacid crystals and leucocyte accumulation[16] or by a more direct effect of antacid compounds on the enzymatic complement of the epithelial cells.

The observed increase in mucosal prostaglandin synthesising capacity was a prolonged effect of antacids, because there was a 12 hours interval between the last antacid intake and the endoscopy.

Low dose antacids therefore resemble bismuth compounds and sucralfate, whose cytoprotective action is independent of acid binding or secretion and is related to an increase of mucosal PG E_2 generation.[17]

Whether this antacid effect is of any therapeutic significance for patients with erosive gastritis or peptic ulcer disease is unclear because the role of the endogenous prostaglandin synthesis in these diseases is still unknown.

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