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Prostaglandin Cytoprotection Does Not Involve Interference with Aspirin Absorption (40631)

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In 1976 Robert (1) demonstrated that prostaglandins in nonantisecretory doses protect the gastric mucosa against lesions produced by a variety of agents. He referred to this as the cytoprotective effect of prostaglandins. This finding has been confirmed by other laboratories (2–5), but the mechanism by which prostaglandins provide cytoprotection remains an enigma. Miller and Jacobson (6) recently reviewed the evidence for and against various postulated mechanisms. A number of investigators have shown that prostaglandins inhibit disruption of the gastric mucosal barrier to acid back diffusion by topical barrier breakers (7–9). Bommelaer and Guth (9) suggested that this protection might be due to interference with absorption of the barrier breaker. However, they found that although prostaglandin protected against barrier disruption by topical aspirin, the salicylate content of the gastric mucosa, 1 hr after aspirin administration was the same in prostaglandin-treated and control animals. Nevertheless, the question of a possible effect of prostaglandin on aspirin absorption at a shorter time after aspirin instillation remained. This study was designed to answer that question.

Materials and Methods. Male Sprague–Dawley rats weighing between 150 and 200 g were fasted for 48 hr but allowed water *ad libitum.* Under ether anesthesia the abdomen was opened and the pylorus ligated. Groups of six rats were then injected with either 20 μg/kg 16,16-dimethylprostaglandin E_2 ($dmPGE_2$) s.c. or NaCl (control) s.c. One-half hour after the injection, 40 m*M* acetylsalicylic acid (ASA) in 150 m*M* HCl, 1 ml per 100 g body wt, was instilled into the stomach via orogastric intubation.

Ten, thirty, and sixty minutes after the ASA instillation, the stomach of rats in one $dmPGE_2$ group and one NaCl group were removed. In addition, 1 cm of small bowel 1.5 cm distal to the pylorus, diaphragm, and aortic blood were obtained before killing the rats. The stomachs were opened along the greater curvature, washed in saline, and lesions scored according to size and number: petechiae were given a score of 1, erosions less than 1 mm 2, 1–2 mm 3, 2–4 mm 4, and over 4 mm 5. The stomachs were then surgically divided into forestomach, corpus, and antrum and the corpus and antral mucosa scraped off. The forestomach, corpus mucosa, antral mucosa, small bowel, and diaphragm were weighed, placed in 1 ml perchloric acid, and frozen for salicylate content determination. The blood was placed in oxalate, centrifuged, and the plasma removed for salicylate determination. Salicylate determinations were performed by the Saltzman method (10) using an Aminco–Bowman spectrofluorometer set at 310 n*M* for excitation and 400 n*M* for emission. Histologic sections of corpus and antral tissue remaining after mucosal scraping revealed mucosa down to the muscularis mucosae had been removed.

Results. Mucosal lesions were present primarily in the corpus of the stomach. Some animals also had antral lesions but none had forestomach lesions. Lesion scores and the salicylate concentration of corpus mucosa, antral mucosa, and forestomach at the time intervals studied are presented in Table I. Lesions were present as early as 10 min after the instillation of ASA and the mean lesion score was lower in the $dmPGE_2$-treated rats. This difference was not significant. With increase in duration of exposure to ASA, there was an increase in mucosal damage. Lesion scores continued to be lower in the $dmPGE_2$-treated rats and the difference was statistically significant at both 30 and 60 min ($P < 0.05$, unpaired t test).

Gastric salicylate concentration was highest in the forestomach and slightly higher in the antral mucosa than the corpus mucosa

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(Table I). The concentrations were in the same range at 30 min as at 10 min in all areas, but fell slightly at 60 min in the corpus and antral mucosa. In all areas at all times there were no significant differences between $dmPGE_2$-treated and control rats. This was true also in the corpus mucosa in spite of the statistically significant difference in lesion scores at 30 and 60 min.

Salicylate concentrations in small bowel, diaphragm, and plasma are presented in Table II. The concentrations were in the same range in these three groups, were much lower than in the stomach, and, except for a slight rise in plasma concentration, did not change with time. Again there was no significant difference between $dmPGE_2$-treated and control animals in any group at any time.

Discussion. The significant difference in ASA-induced lesions between rats receiving $dmPGE_2$ and saline supports the previously demonstrated cytoprotective effect of this prostaglandin analog (1–5). Although an antisecretory dose of $dmPGE_2$ was administered, the ASA was instilled in 0.15 *M* HCl so the protective effect could not be due to lack of acid (4). In spite of this protective effect, the salicylate concentration in both corpus and antral mucosa was not affected by $dmPGE_2$, thus disproving the hypothesis being tested. The cytoprotective effect of prostaglandin does not involve inhibition of entry of aspirin into the gastric mucosal cells.

Although one would expect a decline in gastric tissue salicylate concentration with time after the intragastric instillation of aspirin, this did not occur as the pylorus was ligated. The stomach mucosa was continuously bathed in an aspirin–acid solution of high concentration throughout the time periods studied. The salicylate concentrations in small bowel and diaphragm were significantly lower than that in the stomach as they reflected blood-borne absorbed aspirin. The concentration in these latter two tissues was approximately the same as in plasma.

Cytoprotection by prostaglandin is a real phenomenon. Robert has demonstrated that local synthesis and release of prostaglandin is an important, natural, gastric cytoprotective mechanism (11). The elucidation of the manner by which prostaglandins exert this effect remains a challenge to investigators in this field.

Summary. Acute gastric mucosal lesions were produced in pylorus-ligated rats by the intragastric instillation of an aspirin–acid solution. Prior administration of 16,16-dimethyl

TABLE I. LESION SCORES AND GASTRIC SALICYLATE CONCENTRATION (MEAN ± SE) AFTER DIFFERENT TIMES OF EXPOSURE TO INTRAGASTRIC ACETYLSALICYLIC ACID IN PYLORUS-LIGATED RATS[a]

	10 min	30 min	60 min
Lesion score			
NaCl	6.2	19.3	33.2
	±2.2	±2.0	±8.3
$dmPGE_2$	2.6	7.3*	11.2*
	±1.5	±3.6	±5.3
Salicylate concentration (nmol/g)			
Corpus mucosa			
NaCl	2.43	2.45	1.97
	±0.48	±0.43	±0.28
$dmPGE_2$	2.35	2.62	1.82
	±0.16	±0.41	±0.19
Antral mucosa			
NaCl	2.43	3.79	1.69
	±0.47	±0.60	±0.33
$dmPGE_2$	3.24	3.55	3.05
	±0.42	±0.55	±0.83
Forestomach			
NaCl	4.91	5.52	4.85
	±0.94	±1.02	±0.67
$dmPGE_2$	5.05	5.98	5.03
	±1.16	±1.33	±0.69

[a] There were six rats in each group. An asterisk indicates results were significantly different from control (NaCl) at $P < 0.05$ (unpaired t test).

TABLE II. SALICYLATE CONCENTRATION (NMOLE/G, MEAN ± SE) IN VARIOUS TISSUES AT DIFFERENT TIMES AFTER INTRAGASTRIC ACETYLSALICYLIC ACID ADMINISTRATION IN PYLORUS-LIGATED RATS[a]

	10 min	30 min	60 min
Small bowel			
NaCl	0.44	0.46	0.30
	±0.13	±0.13	±0.4
$dmPGE_2$	0.28	0.41	0.50
	±0.12	±0.10	±0.15
Diaphragm			
NaCl	0.63	0.48	0.37
	±0.16	±0.07	±0.09
$dmPGE_2$	0.40	0.63	0.62
	±0.09	±0.06	±0.17
Plasma			
NaCl	0.25	0.30	0.43
	±0.03	±0.05	±0.09
$dmPGE_2$	0.31	0.38	0.40
	±0.05	±0.07	±0.06

[a] There were six rats in each group. None of the values in the $dmPGE_2$-treated rats were significantly different from their control (NaCl) values.

prostaglandin E_2 s.c. decreased lesion formation but did not affect gastric mucosal salicylate concentration. The cytoprotective effect of prostaglandin does not involve inhibition of entry of aspirin into the gastric mucosal cells.

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