Effect of prostaglandins on the adult rat stomach and intestine

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Robert was the first to put forward the hypothesis that prostaglandins may act as trophic hormones^{1,2} in much the same way as gastrin has shown to be trophic to the gastric corpus. Cell kinetic studies performed by Johnson and Guthrie³ suggested that this trophic effect was very feeble and restricted to the duodenum. Histomorphometric studies carried out in our laboratories, however, revealed that in adult rats topical application of 5-100 µg/kg 16,16-dimethyl prostaglandin E₂ (PGE₂) every eight hours produces an impressive dose dependent increase in the height of the mucosa of the stomach as well as of the small intestine and to a lesser degree of the colon.⁴ Treatment with the high dose resulted in a thickening of the gastric mucosa macroscopically visible from the aspect of the mucosal ridge at the border between

the forestomach and the corpus (Figure). The increase in height and width of the ridge was the result of the combined increase of the volume of stratified epithelium as well as of that of the lamina propria. Morphometric analysis of the glandular parts of the stomach revealed both cell hypertrophy and hyperplasia. The cells particularly affected both in the gastric corpus and the antrum were the surface and foveolar mucous cells. The numbers were increased by approximately 30 % even with the low dose, while this amounted to almost 100 % with the high dose. Neither the number nor the size of the parietal cells were significantly increased, however, an insignificant increase in both the cell numbers and cell size additively contributed to a significant increase of the total parietal cell volume. In the upper small bowel

Table Cell proliferation: comparison of various studies

Author	Model	Treatment	Methods	Proliferation
Johnson ³ 1976	rat	16,16-dm PGE ₂ 200 µg/kg tds 3 days	3H-T incub in vitro DPM/µg DNA	no effect in corpus duodenum
Reinhart ⁴ 1983	rat	16,16-dm PGE ₂ 100 µg/kg tds ig 3 weeks	mitotic index	antrum
Halter ⁵ 1984	rat	16,16-dm PGE ₂ 25 µg/kg tds ig, ip 3 weeks	3H-T ip, labelling index	ip: antrum ig: corpus
Uribe ⁶ 1986	rat	15,15-me PGE ₂ ig dose? 5 days	3H-T ip labelling index	antrum
Dembinski ⁷ 1985	rat	PGE ₂ (1mg/kg) 15,15-dm PGF _{2a} (1 mg/kg) tds 2 days	3H-T incub in vitro DPM/µgDNA	corpus duodenum
Fich ⁸ 1985	man	misoprostol 4 weeks	3H-T incub in vitro labelling index	antrum fundus
Baumgartner ⁹ 1986	rat	16,16-dm PGE ₂ 100 µg/kg ig 8 h after single dose	3H-T ip, labelling index and DPM/µgDNA	antrum
Tytgat ¹⁰ 1986	man	15,15-me PGE ₂ 400 mg ig 3 months	3H-T incub in vitro labelling index	no effects in corpus + antrum

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Figure Macroscopic and microscopic view of the stomach and the forestomach-corpus border of rats after 14 days treatment with placebo (left panel) and 16,16-dm PGE2 100 µg/kg tds for 3 weeks (right panel). FS = forestomach, C = corpus

both the height of the villi and the depth of the crypts were significantly increased.

These results were confirmed subsequently by other authors using both natural prostaglandins E_2 as well as various analogues of prostaglandin E_1 and E_2 in experimental animals and man.^{6-8 10}

Studies undertaken to evaluate the mechanisms of this trophic effect have yielded conflicting results (Table). Several reports show the slight increase in cell proliferation induced in the early treatment phase whereas cell renewal seems to be delayed during prolonged prostaglandin application. Of particular interest is the study of Uribe *et al*⁶ who found evidence that prostaglandins delay the clearance of labelled DNA from the corpus, antral, duodenal and jejunal mucosa suggesting an increase in the survival of glandular cells. A slight decrease in cell proliferation was observed also by Fich⁸ in duodenal ulcer patients treated for four weeks with the PGE analogue misoprostil, while a similar study with R15 methyl PGE₂¹⁰ revealed no difference in cell proliferation despite hyperplasia of the mucous cells of the gastric antrum. Differences in dosage and duration of treatment and the timing of cell proliferative studies may be responsible for these discrepancies. One may speculate that prostaglandin treatment initially stimulates production of new cells which then have a longer life cycle. This would result in a decrease in cell shedding and may as suggested by Uribe *et al*⁶ in turn exert a negative feedback on cell reproduction. It is thus likely that both the initial increase in cell proliferation and the prolonged cell survival contribute to the increase in epithelial cell mass.

References

- 1 Robert A. An intestinal disease produced experimentally by a prostaglandin deficiency. *Gastroenterology* 1975; **69**: 1045-7.
- 2 Robert A. Antisecretory, antiulcer, cytoprotective and diarrheogenic properties of prostaglandins. *Adv Prostaglandin Thromboxane Res* 1976; **2**: 507-20.
- 3 Johnson LR, Guthrie B. Effect of cholecystokinin and 16,16-dimethyl prostaglandin E_2 on RNA and DNA of gastric duodenal mucosa. *Gastroenterology* 1976; **70**: 59-65.
- 4 Reinhart, WH, Müller O, Halter F. Influence of long-term 16,16-dimethyl prostaglandin E_2 treatment on the rat gastrointestinal mucosa. *Gastroenterology* 1983; **85**: 1003-10.
- 5 Halter F, Meyrat P, Fritsche R, Müller O, Lentze MJ, Koelz HR. Both topical and systemic treatments with 16,16-dimethyl prostaglandin E_2 are trophic to rat gastric mucosa. *Scand J Gastroenterol* 1984; **19**: Suppl 101: 47-54.
- 6 Uribe A, Rubio C, Johannsson C. Cell kinetics of rat gastrointestinal mucosa. Autoradiographic study after treatment with 15(R)-15-methyl-prostaglandin E_2 . *Scand J Gastroenterol* 1986; **21**: 246-52.
- 7 Dembinski A, Konturek SJ. Effects of E, F and I series prostaglandins and analogues on growth of gastroduodenal mucosa and pancreas. *Am J Physiol* 1985; **248**: G170-5.
- 8 Fich A, Arber N, Sestieri M, Zajicek G, Rachmilewitz D. Effect of misoprostol and cimetidine on gastric cell labeling index. *Gastroenterology* 1985; **89**: 57-61.
- 9 Baumgartner A, Weber D, Varga L, Halter F. Comparison of autoradiographic (AR) and Radiochemical (RC) estimation of DNA synthesis in gastric mucosa. *Gastroenterology* 1986; **90**: 1341.
- 10 Tytgat GNJ, Offerhaus GJA, van Minnen AJ, Everts V, Hensen-Logmans SC, Samson G. Influence of oral 15(R)-15-methyl prostaglandin E_2 on human gastric mucosa. *Gastroenterology* 1986; **90**: 1111-20.