A proposed role for PGE_2 in the genesis of stress-induced gastric ulcers

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Prostaglandins are potent inhibitors of gastric secretion in rats (Robert, Nezamis & Phillips, 1968), dogs (Robert, Phillips & Nezamis, 1968) and humans and they are able to prevent ulcer formation in rats after pylorus legation, administration of steroids or infusion of secretogogues (Robert, Nezamis & Phillips, 1968).

In our experiments the effect of PGE_2 administration has been evaluated on stress induced gastric ulcers in rats. PGE_2 (50-200-800 μg/kg s.c.) and $PGF_{2\alpha}$ (100-400-1600 μg/kg s.c.) inhibit ulcer formation in dose-dependent fashion, PGE_2 being 10 times more potent than $PGF_{2\alpha}$. Indomethacin, a drug known to inhibit the synthesis of prostaglandins (Vane, 1971), when administered at doses scarcely ulcerogenic at room temperature (1.25, 2.5, 50 mg/kg orally) increases the severity of gastric ulcers induced by stress, but this effect is completely antagonized by PGE_2 administration.

A possible role for prostaglandins on gastric homeostasis was discussed.

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The effect of mucosal damage on gastric glycoprotein synthesis in the rat

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Recently great interest has been shown in the role that gastric mucus plays in the protection of the mucosa against acid-pepsin digestion (Waldron-Edward, 1970). As glycoproteins are important constituents of gastric mucus, the effects of ulcerogenic procedures on gastric mucosal glycoprotein synthesis were investigated by measurement of the rate of incorporation of a radioactively labelled sugar.

Female Wistar rats, Biorex strain, 140-150 g, were used. Phenylbutazone (200 mg/kg), suspended in 1 ml of 0.1% aqueous Tween 80, was given to rats as a single oral dose. Stress erosions

Table 1 The effect of various experimental procedures on the rate of incorporation of *N*-acetyl-0[1-^{3}H]-glucosamine into gastric mucosal glycoproteins

Treatment	*No. of animals (n)*	*Percentage of rats with erosions*	*Rate of incorporation of [^{3}H]-GlcNAc (d/min/mg protein)*	*Percentage reduction in rate of incorporation*
Control	17	0	5430 ± 720	–
Starved 24 h	6	0	2500 ± 610 ($P < 0.01$)	54
Starved + cold 6 h	6	0	4050 ± 790 ($P > 0.2$)	25
Restrained + cold 6 h	11	55	2940 ± 510 ($P < 0.02$)	46
* Phenylbutazone (200 mg/kg orally)	6	33	3150 ± 560 ($P < 0.025$)	42

* Rats were killed 6 h after single administration.

Portions of fundal tissue of rats were incubated with 1.0 μCi [^{3}H]-*N*-acetylglucosamine for 2.5 hours. The values shown are means for the numbers of rats (*n*) ± s.e. mean. Probability values (*P*) for the differences from controls (Student's *t* test) are also given.

were produced by restraining rats in wire mesh for 6 h at 16 ± 1.5°C (Brodie & Hanson, 1960; Senay & Levine, 1967). After the restraint or starvation period, or 6 h after drug administration, the rats were killed and their stomachs examined for mucosal damage. The rate of incorporation of *N*-acetyl-0[1-^{3}H] glucosamine was measured in a circular portion of fundus, 14 mm diameter, by modifications of the method of Lukie & Forstner (1972).

From the results shown in Table 1 it may be seen that significant decreases in the rate of [^{3}H]-*N*-acetylglucosamine incorporation occur after 24 h starvation, restraint, or administration of phenylbutazone, but only the latter two treatments result also in the formation of gastric erosions. However, a relationship between erosion formation and the rate of [^{3}H]-*N*-acetyl-glucosamine incorporation does exist since in the restrained group of rats those with erosions showed a much greater reduction in the rate of incorporation (59%, $n = 6$, $P < 0.01$) than those showing no mucosal damage (31%, $n = 5$, $0.2 > P > 0.1$).

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Effects of bombesin and bombesin-like peptides on gastrointestinal myo-electric activity

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Bombesin produces an inhibitory effect *in vivo* on human upper intestinal motility and a stimulating effect *in vitro* on intestinal muscle strips both in human and in various animal species. Studies on smooth muscle electric activity however are lacking. The present investigation was carried out on the effect of bombesin on the electric activity of gastrointestinal tract *in vivo*. Three synthetic peptides, C-terminal fragments of the bombesin molecule, were also investigated in order to identify the shortest active amino acid sequence in the bombesin molecule.

Thirty-seven experiments were performed in three healthy, conscious dogs with bipolar silver electrodes chronically implanted at different levels between the stomach and the rectum. After a 20 min control period each compound was infused i.v. for 20 minutes. A 20 min recovery period followed. Bombesin was infused at 5, 10, 15, 30 ng kg^{-1} min^{-1}; C-terminal heptapeptide at 20, 80 ng kg^{-1} min^{-1}; C-terminal nonapeptide at 10, 15, 30 ng kg^{-1} min^{-1}. The effects of the drugs on frequency, amplitude, rhythm and propagation velocity of pacesetter potentials (PP) and on incidence of spikes were evaluated.

Bombesin significantly increased the frequency of PP in the antrum ($P = 0.01$), duodenum ($P = 0.01$), jejunum ($P = 0.01$) and ileum ($P = 0.05$). In the duodenum and jejunum the increase of PP frequency showed linear correlation with the reduction of PP amplitude. The propagation velocity was reduced from 8.0 ± s.e. mean 0.41 to 4.1 ± 0.60 cm/second. Spikes were not affected in the antrum and ileum, whereas they were abolished in the duodenum and jejunum. In the duodenum and jejunum the increase of PP frequency and the slowing down of propagation velocity was followed by the loss of PP phase lock and appearance of a characteristic electric pattern, consisting of an irregular sequence of slow and small potentials ('electric disorganization'). The mechanical counterpart, controlled by means of an intraluminal microballoon, was the disappearance of motility. In the colon the effect of bombesin on electric activity was not consistent.

Neither the C-terminal heptapeptide nor the octapeptide showed a significant effect on myo-electric activity, whereas the effect of nonapeptide was similar to that of bombesin showing, however, an activity which was 75% of that of bombesin.

These experiments show that bombesin induces characteristic gastrointestinal myo-electric changes