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Inhibition of gastric acid secretion by sodium cromoglycate and FPL 52694

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Histamine is present in the gastrointestinal tract of nearly all vertebrates in concentrations ranging from 1 μg to over 100 μg per gram of tissue (Vugman & Rocha e Silva 1966; Lorenz et al 1973). The highest concentrations are those in the stomach, particularly in the acid secreting fundus and body of the stomach. For many years histamine has been believed to play a part in the regulation of gastric acid secretion and Code (1965) has proposed histamine as a final common mediator which stimulates the parietal cell in response to other secretagogues. More recently, belief in the importance of histamine in regulating gastric acid secretion has been reinforced by the introduction of specific histamine H_2 receptor antagonists (Black et al 1972). In the experiments reported below, the effects of two mast-cell stabilizing agents have been studied on gastric acid secretion; sodium cromoglycate and FPL 52694 (5{2-hydroxypropoxy}-4-oxo-8-propyl-4H-1-benzopyran-2-carboxylic acid, sodium salt). Sodium cromoglycate has been shown to inhibit the release of histamine from mast cells in response to a number of stimuli (Cox et al 1970). FPL 52694 is approximately equiactive to sodium cromoglycate in both passive cutaneous anaphylaxis induced in the rat by IgE antibody and mast cell degranulation induced in rat skin by compound 48/80 (P. A. Riley, unpublished observations).

Stomachs were perfused in anaesthetized rats using a method similar to that described by Ghosh & Schild (1958). Male rats, 200–300 g, were fasted for 18 h before being anaesthetized with urethane (7·7 g kg^{-1} intraperitoneally). The stomach was perfused via a cannula in the oesophagus with 5% dextrose solution at 37°C, at a rate of 2 ml min^{-1}, and the effluent perfusate collected from a cannula in the pylorus. The perfusate was then passed over a pH electrode to provide a continuous record of pH and, by means of an anti-log unit, H^+ concentration. In some experiments the left cervical vagus was dissected, sectioned high in the neck and placed over bipolar platinum stimulating electrodes. The nerve was stimulated at supramaximal voltage using 2 ms pulses at a frequency of 6 Hz. Experiments were also carried out in rats in which both cervical vagi were cut during the preliminary dissection. In the experiments on dogs, beagles of either sex, 12–15 kg, were anaesthetized with thiopentone sodium (25 mg kg^{-1} i.v.), a cuffed endotracheal tube inserted and anaesthesia maintained with 1–1·5% halothane in a 2:1 N_2O/O_2 mixture. An Andersen's tube was passed into the stomach via the oesophagus and the optimal position determined by means of a water recovery test in which at least 18 ml of a 20 ml bolus of water given through the tube could subsequently be recovered. Gastric juice was then continuously aspirated and collected for 15 min periods. The volume of fluid collected in each 15 min period was measured and acid concentration was determined by titrating an aliquot to pH 7·0 with 0·1 M sodium hydroxide using a Radiometer Auto-burette.

In perfused rat stomachs, both sodium cromoglycate (0·1–10 mg kg^{-1} i.v.) and FPL 52694 (1·25–20 mg $kg^{-1}h^{-1}$ i.v.) significantly inhibited gastric acid secretion in response to pentagastrin (3·8 μg $kg^{-1}h^{-1}$ i.v.). The inhibition developed gradually, reaching a peak in 20–40 min with either sodium cromoglycate or FPL 52694 and the maximum inhibition produced by both drugs was about 40% (Fig. 1). The effects of FPL 52694 (5 mg $kg^{-1}h^{-1}$ i.v.) were also studied on gastric acid secretion evoked by stimulation of the cervical vagus and by infusing histamine (3 mg $kg^{-1}h^{-1}$ i.v.); the results are shown in Table 1. The response to vagal stimulation was inhibited by 40%, but there was no significant reduction in the response to histamine. After vagotomy, the response to pentagastrin in the rat was reduced by over 30%. However, FPL 52694 still produced a significant reduction in the remaining response.

In the anaesthetized dog, gastric acid secretion in response to pentagastrin was reduced by FPL 52694 in doses of 2·5–10 mg $kg^{-1}h^{-1}$. The maximum reduction in acid output with an infusion of 10 mg $kg^{-1}h^{-1}$ of FPL 52694 was

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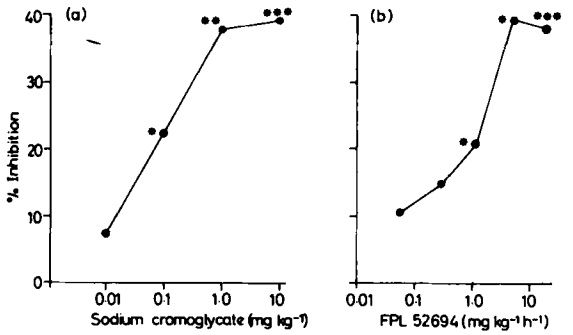

FIG. 1. Inhibition of acid secretion in the perfused rat stomach in response to pentagastrin (3·8 μg $kg^{-1}h^{-1}$) by (a) sodium cromoglycate and (b) FPL 52694. Each point is the mean of 5–7 experiments.
Paired *t*-test: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.002$.

65–70% and this response was achieved between 15 to 30 min after starting the infusion. As shown in Fig. 2, the effect of FPL 52694 on H^+ output was due to a reduction both in the volume of gastric juice secreted and in the H^+ concentration of the gastric juice. Sodium cromoglycate was not tested in the dog on account of the very marked cardiovascular effects produced in this species (Cox et al 1970).

We have therefore demonstrated that two compounds which stabilize mast-cells inhibit the secretion of gastric acid in response to pentagastrin. Initial results in two subjects from a human volunteer study in which FPL 52694 (5 mg $kg^{-1}h^{-1}$) was given by intravenous infusion also showed an inhibition in the volume of gastric juice secreted in response to pentagastrin (0·3 μg $kg^{-1}h^{-1}$) of 33 and 48% (M. Thomas and L. Hicks, personal communication). In the rat, FPL 52694 reduced the secretory responses to pentagastrin and vagal stimulation as do metiamide (Grossman & Konturek 1974) and cimetidine (Brimblecombe et al

Table 1. The effects of sodium cromoglycate and FPL 52694 on H^+ output in the perfused rat stomach in the presence of various secretory stimuli. H^+ output is in μM min^{-1} (mean ± s.e.) and all figures are the means of 4–5 experiments.

Secretagogue	Drug treatment	H^+ Output during control period	H^+ Output during drug treatment
Pentagastrin (3·8 μg $kg^{-1}h^{-1}$)	Sodium cromoglycate (1 mg kg^{-1})	3·62 ± 0·98	2·46 ± 0·86*
Pentagastrin (3·8 μg $kg^{-1}h^{-1}$)	FPL 52694 (5 mg $kg^{-1}h^{-1}$)	3·70 ± 0·82	2·24 ± 0·50*
Pentagastrin (3·8 μg $kg^{-1}h^{-1}$) after vagotomy	FPL 52694 (5 mg $kg^{-1}h^{-1}$)	2·40 ± 0·68	1·86 ± 0·68*
Vagal stimulation at 6 H6	FPL 52694 (5 mg $kg^{-1}h^{-1}$)	3·80 ± 0·88	2·30 ± 0·48*
Histamine (3 mg $kg^{-1}h^{-1}$)	FPL 52694 (5 mg $kg^{-1}h^{-1}$)	3·94 ± 0·70	3·58 ± 0·68 N.S.

* Paired *t*-test, $P < 0.05$.

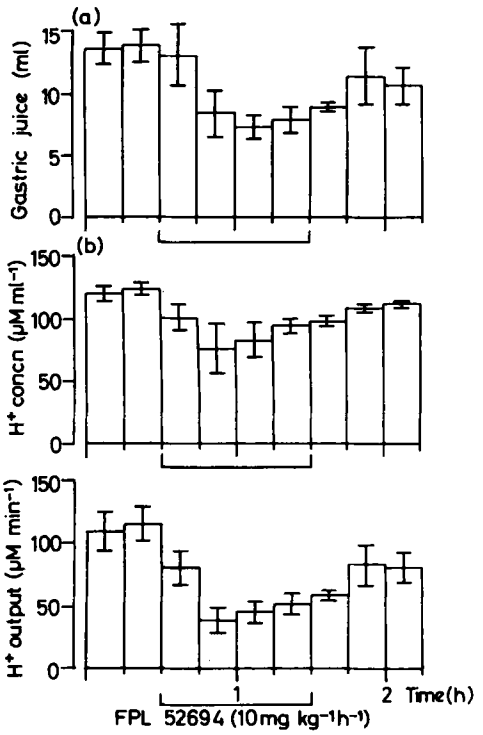

FIG. 2. Effect of FPL 52694 (10 mg $kg^{-1}h^{-1}$) on gastric acid secretion in the anaesthetized dog. Mean of 4 experiments; standard errors are indicated by vertical bars.

1978), but the response to histamine was unaffected. The action of the compound cannot therefore be mediated by histamine H_2 receptor blockade. It is tempting to speculate that the inhibition of secretion by sodium cromoglycate and FPL 52694 may be due to an inhibitory effect on the release of histamine in the stomach. Johansson et al (1972) reported that gastrin increases the histamine-forming capacity of the stomach and the urinary excretion of histamine. More recently the release of histamine from frog gastric mucosa has been demonstrated directly in response to pentagastrin (Rangachari 1975). There is therefore evidence that gastrins influence both storage and release of histamine in the stomach. The inhibition of pentagastrin-induced secretion by FPL 52694 and sodium cromoglycate in the experiments described above is consistent with interference with the release of histamine, which subsequently stimulates the parietal cell to release H^+. However whereas in the dog and man, histamine in the stomach is stored almost exclusively in mast cells, in the rat stomach histamine storage is in enterochromaffin-like cells (Aures et al 1970). The available evidence suggests that sodium cromoglycate is specific in blocking histamine release from mast cells (Assem & Mongar 1970; Lichtenstein & Adkinson 1969). It was therefore unexpected that mast cell stabilizers should inhibit histamine release from the rat stomach.

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LETTER TO THE EDITOR

Photolytic destruction of adriamycin

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A recent communication in this Journal (Tavoloni et al 1980) reported on the destruction of adriamycin by irradiation with fluorescent lights. In reference to anthracycline antibiotics, the authors stated, 'no photolytic studies on this group of compounds have been published'. However, the susceptibility of three anthracycline antibiotics (adriamycin, daunomycin and rubidazone) to irradiation by daylight fluorescent lights has been reported (Daugherty et al 1979).

The protective effect of fresh rat bile on adriamycin photodestruction was postulated to possibly be due to an effect of filtration of radiation by the yellow-green colour of the bile or to an interaction with the solvent or components of the solvent (Tavoloni et al 1980). Since we have observed the photodestruction of the drug to be prevented by the addition of the free radical scavenger, butylated hydroxytoluene (BHT), and most commercial animal chow to contain BHT, which is involved in enterohepatic circulation in rats (Ladomery et al 1967), it is possible that the protective effect may have been partially due to the presence of BHT or its metabolites or some other free radical scavenging agent.

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