Effect of Secretin on Histamine-Stimulated Secretion in the Gastric Fistula Rat (34422)

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In the dog, secretin is a potent inhibitor of gastrin-stimulated acid secretion but has no effect on histamine-induced secretion (1). This enterogastrone-like effect of secretin is, however, species dependent, for secretin produced little if any inhibition in the cat (2). In the rat, the effect of secretin on gastric secretion is similar to the dog, as it was recently shown that a physiological dose of secretin completely abolished gastric secretion in response to a maximal dose of pentagastrin (3).

In dog (1) and cat (2) histamine-stimulated acid secretion was refractory to inhibition by secretin. One would, therefore, presume that in the rat the same pattern would be followed. However, the question of whether or not secretin inhibits histamine-stimulated secretion in the rat is of considerable theoretical importance. Based mainly on studies in rats, Kahlson *et al.* (4) proposed that gastrin stimulates secretion by releasing intramuscosal histamine which then activates the parietal cells. The depletion of histamine in turn activates mucosal histidine decarboxylase to replenish histamine stores. We have found, however, that while secretin completely inhibited gastrin-stimulated acid secretion (3) there was no inhibition of the activation of histidine decarboxylase (5). In accordance with the Kahlson hypothesis, this suggests that in the presence of secretin, gastrin releases histamine and inhibition of the secretory process takes place after that release.

Methods. Four male Sprague-Dawley rats, weighing 275–310 g, were prepared with gastric fistulas using the cannula and surgical procedure described by Lane *et al.* (6). Experiments were started 2 weeks after surgery and were run on alternate days no more than 3 times a week.

Before each experiment, animals were fasted from 20 to 24 hr in cages with wide mesh wire floors. During an experiment the animals were restrained in Bollman cages (7). The cannulas were opened and the stomachs were washed out with saline and allowed to drain 90 min before collecting samples. After collecting basal secretion for 1 hr, histamine dihydrochloride in doses doubling from 5 to 40 mg/kg or 20 mg/kg of histamine–2 HCl in combination with 75 units of secretin/kg was injected subcutaneously. Secretion was then collected for an additional 2.5 hr.

Secretion was collected in 1-ml disposable syringes sealed at one end. A short length of PE 50 polyethylene tubing was used to lead the fluid from the cannula to the collecting tube. The volume of secretion was read to the nearest 0.01 ml every 15 min and the acid content was determined by titration of 0.1 ml of sample to pH 7.0 with 0.2 *N* NaOH using an Autoburette and pH meter (Radiometer, Copenhagen).

Only one dose of histamine was given to a rat during a day's test. On days in which secretin was injected, 2 rats received histamine alone and 2 received the combination of secretin and histamine. Experiments were repeated so that each rat received each dose of histamine twice and the combination of 20 mg of histamine/kg with secretin twice. Secretin was obtained from G.I.H. Laboratory, Karolinska Institute, Stockholm, Sweden.

All results are expressed as μeq H^+/15 min. Means and standard errors of the means were calculated for 2 observations in each of 4 animals.

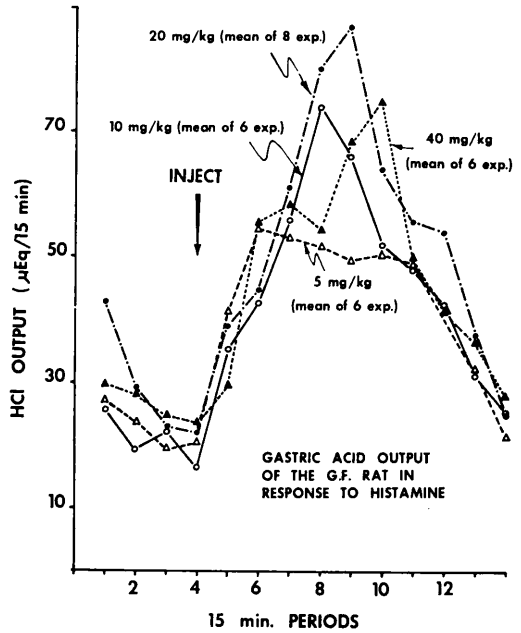

FIG. 1. Gastric acid response to 5, 10, 20, and 40 mg of histamine-2HCl/kg; first four points are basal secretory levels.

Results. Acid secretory responses to 4 doses of histamine–2 HCl are shown in Fig. 1. Increasing outputs were seen with 5, 10, and 20 mg of histamine–2 HCl/kg. Maximal secretion occurred with a dose of 20 mg/kg; doubling the dose to 40 produced a decrease in acid production.

Secretin (75 units/kg) failed to inhibit gastric secretion evoked by a maximal dose of histamine (Fig. 2). The response to 20 mg of histamine–2 HCl/kg plus secretin was essentially identical to the response to that dose of histamine alone.

Discussion. In the rat as in the dog (1) and cat (2), secretin had no effect on histamine-stimulated acid secretion. The dose of secretin used in the present experiments, 75 units/kg, completely inhibited acid secretion in the rat stimulated by maximal and supermaximal doses of pentagastrin (3). There can be no doubt, therefore, about the adequacy of the dose of secretin employed.

The hypothesis proffered by MacIntosh (8) in 1938 that gastric mucosal histamine might be a local common mediator for other stimulants of gastric acid secretion is still being debated today. In most species evidence that the hypothesis is correct is, at best, unconvincing (9). The argument, in the case of the rat, is bolstered by the finding that after feeding or gastrin injection, mucosal histamine content decreased, acid secretion began, and histidine decarboxylase activity increased (4). Most attempts to demonstrate parallel changes in other species have been unsuccessful (9, 10).

In accordance with their results Kahlson and his co-workers (4) constructed a model which accounted for acid secretion in terms of histamine release and formation. This model has received wide publicity and assumes that (i) depletion of histamine resulting from the release of histamine by gastric secretagogues stimulates an increase in the activity of the histamine forming enzyme, histidine decarboxylase, and (ii) histamine,

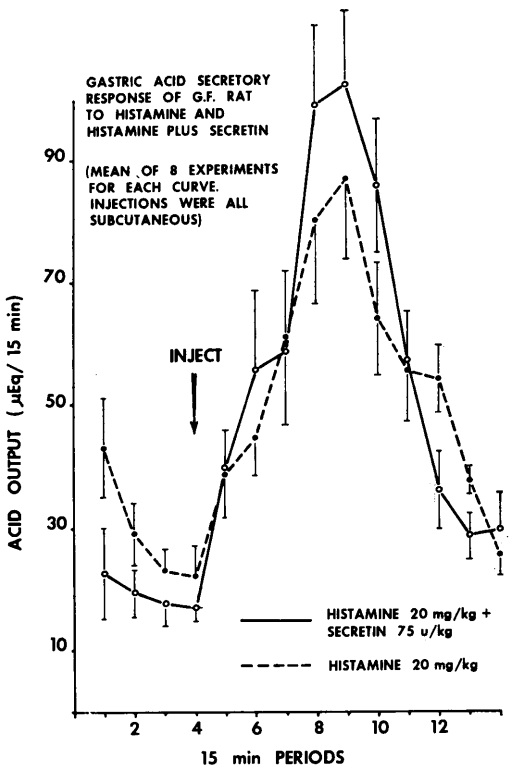

FIG. 2. Gastric acid response to 20 mg of histamine-2HCl/kg alone and in combination with 75 units of secretin/kg; means and standard errors of the means for two observations in each of four rats.

after being released, stimulates acid secretion. Previous data from our laboratory when coupled with the current results are incompatible with these assumptions. That is, secretin inhibits gastrin-stimulated acid secretion in the rat (3), while not affecting the increase in activity of histidine decarboxylase (5). These results could be explained in terms of Kahlson's hypothesis by assuming that secretin inhibited secretion by acting on histamine after it had been released, thereby allowing the proposed feedback mechanism between depletion of mucosal histamine stores and stimulation of histidine decarboxylase activity to remain intact. The current finding that secretin does not inhibit histamine in the rat makes this explanation untenable.

We are, therefore, left with the conclusion that one or both of the assumptions in Kahlson's hypothesis are incorrect. In the antrectomized rat the only effective stimulant of histidine decarboxylase activity was gastrin itself or the structurally related hormone, cholecystokinin (11, 12). Basal histidine decarboxylase activity was also absent from the antrectomized rat oxyntic gland mucosa. This means that the increased activity of histidine decarboxylase produced by urecholine, insulin, and 2-deoxy-D-glucose in the normal rat may be due to direct stimulation by gastrin itself, for it is now common knowledge that vagal activity releases gastrin. This is indirect evidence that gastrin may directly stimulate an increase in the activity of histidine decarboxylase, thus excluding the necessity of histamine release for triggering the increase in enzyme activity. Perhaps, however, the assumption that histamine stimulates secretion after being released is wrong. Thunberg (13) has shown that in the rat gastric histamine is localized in structures at the base of the gastric gland which are unrelated to the parietal cells. This was confirmed by Häkanson *et al.* (14). It is, therefore, possible that after being released, histamine could be destroyed or removed from the mucosa without stimulating secretion.

Summary. In rats with chronic gastric fistulas, secretin had no effect on histamine-stimulated acid secretion. This finding, together with our earlier studies showing that secretin inhibited pentagastrin-stimulated acid secretion but not the increase in histidine decarboxylase activity, cannot be reconciled with the hypothesis that gastrin stimulates acid secretion by releasing histamine.

We are grateful to Dr. Morton I. Grossman for advice and support and to Dr. Lawrence W. Way for help with surgery. This study was supported by Veterans Administration Research Funds. Dr. Johnson was supported by NIH Training Grant No. 5 TO1 AM05470-05. Dr. Johnson's current address is the Department of Physiology and Biophysics, University of Oklahoma Medical Center, Oklahoma City, Oklahoma 73104.

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Received Sept. 9, 1969. P.S.E.B.M., 1970, Vol. 133.