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Lack of Caffeine Stimulation of Gastrin Release in Man (39712)[1]

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In 1944 Roth and Ivy (1) reported that caffeine given orally stimulates gastric secretion in man and the cat but not in the dog. They also reported that patients with duodenal ulcer had greater and longer responses to caffeine than did nonulcer subjects (2). With the introduction of histamine and other stimuli for gastric secretion, the caffeine test fell into disuse.

Recent physiologic studies by Debas and his colleagues have shown that the acid response to caffeine is linearly related to plasma caffeine levels (3). The earlier report of Roth and Ivy studying the combination of caffeine and histamine appears inconclusive (4). Furthermore, it has been shown that caffeine is not synergistic to pentagastrin stimulation (5).

Review of these data led us to inquire whether an aberration in gastrin release might be responsible for the apparently greater responsiveness of duodenal ulcer patients to caffeine and whether, in fact, the stimulation of gastric secretion by caffeine was mediated by the release of gastrin. Results indicated that it is not through gastrin release that caffeine stimulates gastric secretion.

Methods. In two patients with duodenal ulcer and in two normal controls, caffeine benzoate was given intravenously at the dose of 80 mg/hr for 2 hr and for 1 hr at 320 mg/hr. Gastric juice was collected by a radiologically placed nasogastric tube for 1 hr before and the 3 hr during the caffeine infusion. Samples were collected in 15-min periods and aliquots were titrated electrometrically to pH 7.0 for H^+. Pepsin was measured by a hemoglobin digestion method, in which 1 μg of Sigma pepsinogen measures 4 units. Blood was drawn before the tube was passed, after 1 hr, and then at the end of 2 and 3 hr. All sera were separated and frozen for later assay in duplicate at one time by a radioimmunoassay, using rabbit antibody to human gastrin (G17-1)[5] and an ^{125}I-labeled tracer, 15 nor-leucine synthetic human gastrin standard. Separation of bound from free labeled hormone was done using Amberlite/IRP 58M resin at a concentration of 100 g/liter.

Results. Figure 1 shows the combined results of the four subjects (two duodenal ulcer, two nonulcer normals) with a two- to threefold dose-responsive increase in both H^+ and pepsin. All four subjects had a similar increase in gastric secretion, but none had a rise in serum gastrin concentration above fasting levels. The mean serum gastrin value remained between 50 and 65 pg/ml.

In 11 (6 controls and 5 duodenal ulcer), 250 mg of caffeine in 250 ml of water were taken by mouth, and blood was drawn at 0, 15, 30, 60, and 90 min. Small but significant increases of the same magnitude in serum gastrin were seen in both groups. No change was seen with 250 ml of water in 3 of 11 subjects (Table I).

Discussion. Unlike the findings by Berkowitz *et al.* (6), we report that intragastric caffeine, but not an equivalent volume of water, increased serum gastrin concentration by a mean of 22 pg/ml within 30 min of

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[5] Antibody 1296 kindly supplied by Dr. John Walsh, Division of Gastroenterology, U.C.L.A. School of Medicine, Los Angeles, California.

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TABLE I. SERUM GASTRIN CONCENTRATIONS BEFORE AND AT INTERVALS AFTER 250 mg OF CAFFEINE IN 250 ml OF WATER IN SIX HEALTHY CONTROLS AND IN FIVE PATIENTS WITH DUODENAL ULCER (DU).[a]

	Mean (years)	Age (range)	Sex (M/F)	N	Fasting value	Mean change from fasting (pg/ml ± SE) 15 min	30 min	60 min	90 min
Caffeine control	34	25-63	4/2	6	83 ± 31	+11 ± 2.3*	+22 ± 6*	+14 ± 8	+33 ± 16
Caffeine DU	46	32-62	2/3	5	72 ± 8	+16 ± 6*	+12 ± 13	+5 ± 7	+23 ± 16
Water control	38	32-44	0/3	3	31 ± 9	+1.3 ± 10	−1 ± 2	−11 ± 8	−9 ± 6

[a] The equivalent volume of water in two of the DU and one of the control subjects produced no significant change in serum gastrin.
* $P < 0.05$.

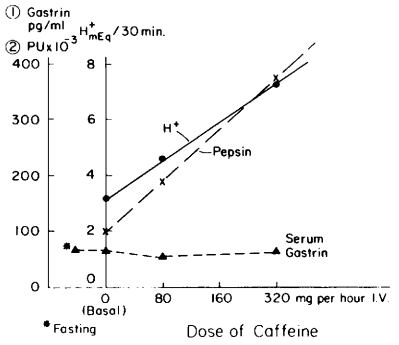

FIG. 1. Dose responsive (H^+) and pepsin output in four subjects (two normal, two DU). Basal secretion was collected for 60 min and serum gastrin was measured at 0 and 60 min in the basal state. The 80-mg dose of caffeine was given for 2 hr and the 320-mg dose was given for 1 hr.

intake. The increase in duodenal ulcer subjects was of the same order of magnitude. In the four subjects showing a substantial rise in gastric H^+ and pepsin with caffeine given intravenously, there was no change in serum gastrin. Cohen *et al.* (5) have shown that caffeine does not act synergistically with pentagastrin and also (3) that the degree of gastric response was proportional to the concentration of caffeine in the blood. It is thus unlikely that caffeine acts primarily by releasing small quantities of gastrin and then magnifying its effect through synergism as the vagus does. It is more likely that the effect is direct. The mechanism that immediately comes to mind is that of inhibition of phosphodiesterase, thereby increasing the effective cellular concentration of cAMP (7, 8). Even this explanation must be questioned in view of the nonresponse of dogs to caffeine (1). This has been confirmed in dogs by Cooke *et al.* (9) and by us (unpublished observation) by showing that neither caffeine nor aminophyllin directly stimulated nor acted synergistically with histamine or pentagastrin.

It remains to be shown by more direct means whether caffeine stimulates gastric secretion in man by a cAMP mechanism and, if so, whether it could act in the absence of another stimulus as in the amphibian (7, 8).

Summary and conclusions. Caffeine benzoate given intravenously to four subjects (two with duodenal ulcer and two normals) in dose-responsive tests at 80 and 320 mg/hr stimulated gastric H^+ and pepsin secretion two- and threefold, respectively, but did not change serum gastrin levels. In five patients with duodenal ulcer and six normals, 250 mg of caffeine benzoate intragastrically, but not an equivalent volume of water, raised serum gastrin concentrations by 16 to 22 pg/ml ($P < 0.05$). There was no difference in caffeine-stimulated gastrin release between the duodenal ulcer group and normals.

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