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Acetylcholine and Gastric Secretion[1] (39558)

T. KONDO[2] AND D. F. MAGEE

Creighton University, Department of Physiology, Omaha, Nebraska 68178

Recently morphine was found to abolish the dose-response relationships between pentagastrin and gastric acid and pepsin but not those for histamine and cholinergic stimulants of gastric secretion (1). It was suggested that this was a consequence of the well-known morphine interference with acetylcholine release (2). The explanation advanced was that acetylcholine is an intermediate in the stimulation of pepsin and gastric acid by gastrin. If this hypothesis is correct, hemicholinium (H3) which depresses acetylcholine synthesis should interfere with the action of gastrin and pentagastrin (PG) (3).

Methods. Four dogs, weighing approximately 20 kg and bearing gastric fistulae and Heidenhain pouches, were used in these experiments. Juice was collected and measured at 10-min intervals by a wash-out technique from the pouch and by simple drainage from the fistula.

Graded dose-response relationships to ascending doses of PG,[3] histamine, and pilocarpine were compared with those achieved 30 min after 200 μg of hemicholinium.[4] These experiments were conducted on different days. H3 was given as a single iv bolus; all the other drugs were given by continuous iv infusion.

Since generalized symptoms of Ach lack were expected of H3, in the first few experiments doses were increased by 50-μg increments to 200 μg without apparent toxicity during or at any time after the experiments. No attempt was made to determine the H3 tolerance.

Vagal stimulation was effected with iv 2-deoxy-D-glucose (2DG), 50 mg/kg in 30 min. After 30 min, H3 was given. The subsequent course of secretion was compared with controls without H3.

Acid was titrated using a Radiometer machine and pepsin was estimated by Anson's method (4).

Doses in the dose-response experiments were given for at least three collection periods. Calculations were based on the last two collections of each period. Paired Student's t was used for differences. Dose-response curves were analyzed for variance between slopes and maximal responses with an Olivetti 602 and its statistical manual. Maximal responses were calculated from reciprocal plots.

Results. 2-Deoxy-D-Glucose. The stimulatory effect of 2DG on acid and pepsin secretion from pouch and fistula was diminished significantly by H3 (Fig. 1). Depression in the pouch means either depressed gastrin release from the pylorus or impeded action of gastrin on secretory elements in the pouch or both. This holds also for the fistula with the addition of possible impairment of the direct action of the vagi on fundic secretory cells.

Pentagastrin (Figs. 2 and 3). After H3, PG no longer produced progressively increasing acid secretion with dose (nonsignificant correlation coefficients from either fistula or pouch). Fistula pepsin actually showed a decline in secretion with increasing PG dose. In Fig. 2, significant lag behind control can be seen at the higher PG doses in the H3 experiments.

Histamine. H3 either significantly augmented or left unchanged histamine-stimulated acid secretion (Figs. 4 and 5). Pepsin secretion remained unchanged from both parts of the stomach. The histamine V_{max}'s before and with H3 were not significantly different in either pouch or fistula (Table I).

Pilocarpine. When pilocarpine was used as gastric stimulant, pouch acid secretion was augmented by prior treatment with H3 (Fig. 6) and pouch pepsin secretion was un-

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[2] Visiting Instructor from Nagoya University, Japan.

[3] Kindly supplied by Ayerst.

[4] Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

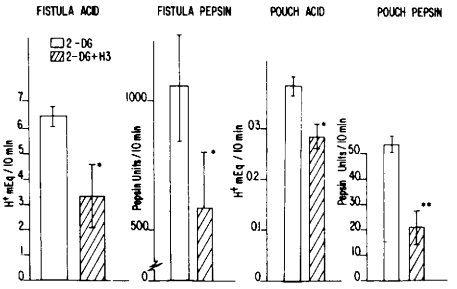

FIG. 1. The effect ± SE of hemicholinium (H3) on 2-deoxy-D-glucose-stimulated acid and pepsin secretion from gastric fistula and Heidenhain pouch. $*P < 0.05$ for paired difference in four dogs; $**P < 0.01$ for paired difference in four dogs.

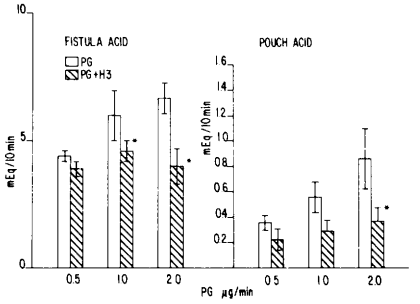

FIG. 2. The effect ± SE of hemicholinium (H3) on pentagastrin-stimulated acid from gastric fistula and Heidenhain pouch. $*P < 0.05$ for paired difference in four dogs.

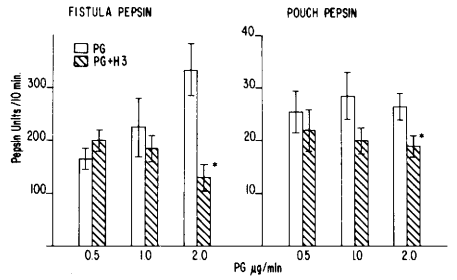

FIG. 3. The effect ± SE of hemicholinium (H3) on pentagastrin-stimulated pepsin secretion from gastric fistula and Heidenhain pouch. $*P < 0.05$ for paired difference in four dogs.

changed. Fistula secretion after pilocarpine was too contaminated with saliva and duodenal juice to be of value.

Discussion. The depression of 2DG stimulation of gastric secretion and the failure to depress pilocarpine stimulation establish that release rather than action of the cholinergic transmitter is blocked by H3. In view of the established pharmacological action of H3, this is expected (3).

The finding of H3 depression of PG-stimulated acid and pepsin secretion, but not of histamine-produced secretion or its V_{max}, implies acetylcholine release as an intermediate step in PG but not in histamine action. In fact, H3 often produced augmentation of histamine- and pilocarpine-stimulated acid output. This was the case with morphine also and the fact that morphine is a histamine liberator was advanced to explain it since morphine augmented even resting secretion. This interpretation cannot be used in the present experiments. Alternatively, we propose the existence of a competitive tonic cholinergic suppressor mechanism. In the work of Walsh *et al.* (5), there is suggestion of such. They invoked such a mechanism to explain augmented PG-stimulated acid secretion from Heidenhain pouches after bilateral vagotomy. We invoke it to

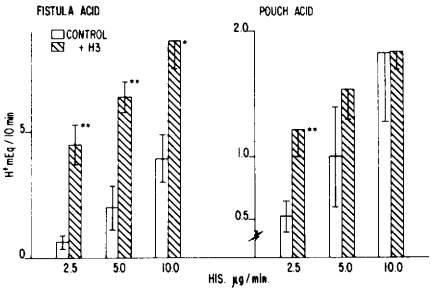

FIG. 4. The effect ± SE of hemicholinium (H3) on histamine-stimulated acid secretion from gastric fistula and Heidenhain pouch. $*P < 0.05$ for paired difference in four dogs; $**P < 0.01$ for paired difference in four dogs.

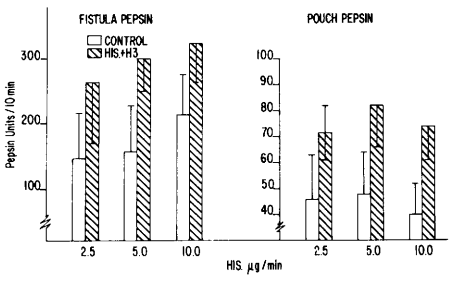

FIG. 5. The effect ± SE of hemicholinium (H3) on histamine-stimulated pepsin secretion from gastric fistula and Heidenhain pouch. $*P < 0.05$ for paired difference in four dogs; $**P < 0.01$ for paired difference in four dogs.

TABLE I.

	Fistula		Pouch	
	$1/V_{max}$	b	$1/V_{max}$	b
Acid				
Histamine	−0.9	0.414	0.070	0.170
Histamine + H3[a]	+0.07	0.545	0.430	0.086
Pilocarpine			0.768	0.008
Pilocarpine + H3			0.684	0.014
PG	0.116	1.522	1.080	0.320
PG + H3	–	NS[b]	–	NS
Pepsin				
Histamine	–	NS	–	NS
Histamine + H3	–	NS	–	NS
Pilocarpine	–	NS	0.0063	1.551
Pilocarpine + H3	–	NS	0.0069	0.802
PG	0.0031	115.18	–	NS
PG + H3	0.0088*	−47.35*	–	NS

[a] H3 did not produce any other alteration in either slopes or V_{max}, except that after H3 the PG dose–response relationship was abolished. V_{max} was, therefore, uncalculable.

[b] NS, Nonsignificant correlation coefficients.

* Significant difference from control; $P < 0.05$.

explain a parallel shift of the histamine dose–response curve to the left of control and an unaltered histamine acid V_{max} after H3. There is a serious discrepancy, however, in that Walsh *et al.* (5) could not show postvagotomy augmentation of the histamine response.

Since H3, like morphine, produces a suppression of PG-stimulated gastric secretion, the hypothesis advanced in the previous paper (1), that acetylcholine is an obligatory intermediate between PG and acid and pepsin secretion, the latter in innervated mucosa only, is supported.

A characteristic of H3 action is that it is delayed. This is held to be due to the existence of acetylcholine stores which must be used up before the H3-blocking action becomes evident. This is consistent with the finding that only the highest doses of gastrin, which were, of course, the last, showed greatest depression and with the significant negative steps in the PG pepsin dose–response curve after H3.

Summary. Hemicholinium in conscious dogs with gastric fistulae and Heidenhain pouches depressed PG and 2 deoxy-D-glucose stimulation of acid and pepsin secretion. On the other hand, it either augmented or did not significantly change histamine- and pilocarpine-promoted secretion. These results support the view that acetylcholine is an obligatory mediator of the action of PG at secretory effector sites.

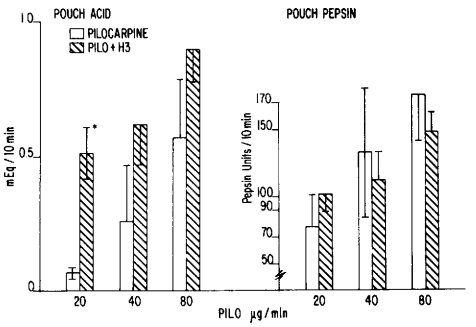

FIG. 6. The effect ± SE of hemicholinium (H3) on pilocarpine-stimulated acid and pepsin secretion from Heidenhain pouches. *$P < 0.05$ for paired difference in four dogs.

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