Comparison of Gastrin and Histamine on Gastric Mucosal Blood Flow (33585)

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Agents which increase gastric secretory rate also increase gastric mucosal blood flow (1, 2). Increased perfusion under these circumstances probably arises from the production of local dilator metabolites during secretion, although secretory stimulants may also induce direct dilator responses. Sorting these 2 dilator mechanisms (indirect metabolic versus direct pharmacological) becomes especially difficult if the gastric secretory stimulant is an established dilator drug, such as histamine.

It follows from the preceding considerations that of 2 agents capable of stimulating secretion equally, the drug which possesses more pronounced dilator action should induce a greater mucosal blood flow. Thus, one would expect that at comparable secretory rates histamine would stimulate a greater flow of blood than gastrin, the difference in flows reflecting the more potent dilator properties of the amine.

In conscious dogs with denervated gastric pouches there was suggestive evidence that mucosal perfusion was greater with histamine than with gastrin, although comparisons were not made in the same animals (1). In anesthetized cats with denervated stomachs, however, no difference in mucosal blood flows was found when secretion was stimulated by histamine versus a crude gastrin preparation (3). The present investigation was initiated to compare mucosal clearances in the innervated stomach of conscious dogs during stimulation of secretion with histamine and with natural and synthetic gastrins.

Methods. Studies were conducted on 10 dogs, each previously prepared with a gastric fistula. Animals were adjusted to the laboratory for at least 1 month after surgery before our experiments were performed.

In 5 dogs gastric secretory rates of 1–4 ml min^{-1} were established over a period of several hours using histamine (0.25–1.0 mg hr^{-1}) or extracted porcine gastrin (5–20 g hr^{-1}) carried through the first propanol stage (4). Separate experiments were performed on different days in the same animal. Each dog in this group was tested once with each stimulant. The ratio (R) of gastric mucosal blood flow to secretory rate with each drug could be compared in each animal when secretory rates were the same with each drug.

In 5 other dogs gastric secretory rates approximating 50% of maximal were established for 2-hr periods with either histamine or a synthetic gastrin-like peptide (5–10 μg hr^{-1} of the beta alanine pentapeptide, I.C.I.). On any one day either histamine or synthetic gastrin-like peptide was the only secretory stimulant employed. Each dog was tested twice with each stimulant. Again, the ratio of gastric mucosal blood flow to secretory rate (R) with histamine was contrasted with R during administration of synthetic gastrin at similar secretory rates.

Prior to each experiment a loading dose of aminopyrine (20 mg kg^{-1} hr^{-1}) was injected intravenously, after which a maintenance dose (10 mg $kg^{-1}hr^{-1}$) was infused throughout the experiment. Histamine and the gastrins were also administered continuously with aminopyrine by means of a constant flow infusion pump (Harvard Apparatus Co.).

Gastric juice samples were collected at 15-min intervals during experiments. These samples were analyzed for acid concentration using an autoburette (radiometer) to a pH of 7.0. The volume of each sample and the acid output per 15-min period were also determined. Aminopyrine concentrations were measured in each gastric juice sample and in

TABLE I. Comparison of Acid Output and R Values in 2 Series (5 dogs each) during Submaximal Stimulation with Either Histamine and Extracted Gastrin (Series I, 5 determinations/dog) or with Histamine and Synthetic Gastrin-Like Peptide (Series II, 16 determinations/dog).[a]

	Histamine	Extracted gastrin	Difference
Series I			
Acid output (meq/15 min)	4.7 ± 0.4	4.6 ± 0.4	NS
R	42 ± 4	27 ± 2	p <.01
		Synthetic gastrin-like peptide	
Series II			
Acid output (meq/15 min)	2.8 ± 0.3	3.0 ± 0.4	NS
R	48 ± 2	42 ± 2	p <.01

[a] Each set of values represents mean ± SE.

plasma samples drawn at hourly intervals by the method of Brodie and Axelrod (5).

The ratio (R) of gastric mucosal blood flow to secretory rate is identical with the ratio of gastric juice aminopyrine concentration to plasma concentration of aminopyrine (1).

Statistical comparisons in both series (histamine vs extracted gastrin and histamine vs synthetic gastrin-like peptide) were made using the Student t test.

Results. In the first series of 5 dogs in which histamine and extracted gastrin were contrasted, R was significantly ($p<.01$) greater with histamine at comparable secretory rates (Table I). In the second series of 5 dogs R was also significantly ($p<.01$) greater with histamine than with synthetic gastrin-like peptide.

An incidental comparison can be made between R values in the 2 series of animals during histamine stimulation. These values are also significantly different (42 ± 4 versus 48 ± 2, $p<.05$); however, the secretory rates in the 2 series are not comparable (4.7 ± 0.4 versus 2.8 ± 0.3 meq/15 min, $p<.01$), and previous studies have shown that there is a decline in measured R as secretory rates increase (1).

Discussion. The R values rather than calculated gastric mucosal blood flow values were employed in these experiments for 3 reasons: (i) calculated gastric mucosal blood flow is the product of secretory rate and R, (ii) R values are determined independently of the volume rate of secretion, and (iii) R is also the ratio of mucosal blood flow to secretory rate. We asked the question whether mucosal perfusion was greater in the stomach stimulated with histamine than in the stomach stimulated with gastrin when secretory rates were the same with either drug. The first reason cited above would greatly obscure a comparison of calculated mucosal blood flows at similar secretory rates, since secretory rate enters into the calculation.

Our results indicate that at comparable secretory rates, gastric mucosal blood flow is greater with histamine as the secretory stimulant than with either extracted or synthetic gastrin. This finding in the innervated stomach of conscious dogs conforms to what had been suggested by a previous study in conscious dogs with vagally denervated gastric pouches (1) and also by a study of total gastric perfusion in anesthetized dogs (6). In addition, preliminary investigations in our laboratory indicate that neither form of gastrin has any consistent depressor action on systemic arterial pressure in conscious dogs. Histamine is a well-known depressor drug and potent arteriolar dilator.

The discrepancy between our findings and those of Harper *et al.* (3) may be due to species differences or differences in preparations. These latter authors compared mucosal blood flows with the 2 secretory stimulants using anesthetized cats with vagally denervated stomachs stimulated by histamine and by a crude gastrin extract.

Summary. Studies were conducted to determine whether the gastric mucosal circulation responds more to histamine than to extracted porcine gastrin or to a synthetic gastrin-like peptide. In conscious dogs provided with a gastric fistula, the stomach was stimulated to secrete at submaximal rates with each agent. At comparable secretory rates gastric mucosal blood flow was greater with histamine than with either form of gastrin.

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One-State "Factor V" Bioassays: Specific and Other Determinants in Blood-Clotting Test Systems* (33586)

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Recent studies with blood-clotting assay systems, using three types of activator, namely, (1) tissue thromboplastin, (2) Stypven (Russell's viper venom), (3) thrombokinase, convincingly show that 2-stage thrombin-generation systems (4) fail to yield more than a simple and immediate summation of factor V (V) and thrombin (T) effects, whereas all three types of 1-stage factor V assay systems indicate large apparent potentiations of the (T + V) mixtures. Since the first of these seemingly incompatible data renders untenable the current popular idea of a V → Va activation, it is necessary to find some new explanations for the potentiations in the 1-stage systems. Because many possible reactions and interactions could be proceeding simultaneously or successively in so complicated a mixture as is provided by the deceptively simple 1-stage tests, reinterpretations may not be easy but could require a very sophisticated analysis. An important new step in this direction is offered in the present study, which attempts to assess the specific and the combined (or derived) effects of the five basic components (II, TK, V, PL, Ca^{2+}) in a thrombokinase (TK)-activated thrombin-generation mixture when added to the above test systems. This communication will deal chiefly with the extrinsic (PT) and intrinsic (TK) 1-stage factor V assay methods.

Materials and Methods. Reagents are fully described in recent publications[1] (1) and may be briefly identified as follows: *V-deficient substrate* (—V sub) is factor V-poor aged normal human oxalated plasma. *Tissue thromboplastin* (Tpln, factor III?) is commercial Simplastin (Warner-Chilcott). This contains an adequate amount of *calcium* (Ca^{2+}), of which an equivalent, in the form of 0.1 ml of 25 mM $CaCl_2$, is supplied in all other 1-stage tests, unless otherwise specified. The *additive* (incubate) mixtures, described under "Results," contain 0.2 vol of 0.1 M $CaCl_2$ whenever Ca^{2+} is indicated. *Buffer* (IBS) is 0.9 vol of saline (0.85% NaCl) with 0.1 vol of imidazole, buffered at pH 7.35. *Phospholipid* (PL) is commercial Thrombofax (Ortho Lab.). *Thrombokinase* (TK, factor Xa?), courtesy of Dr. J. H. Milstone, is from "step 7" in the current method of purification (5). The TK_5, TK_{10} indicate, by the subscript, actual protein concentrations as $\mu g/ml$, by which the enzyme test solutions are quantitated. *Factor V* (V) is purified from $BaSO_4$-adsorbed bovine oxalated plasma and assayed as recently described (1, 6). *Prothrombin* (factor II) is a barium citrate–citrate eluate (El) of bovine citrated plasma, which is a very potent II and low in factors V, VII, X[1] (7).

Assays. These are by the routine 1-stage

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[1] Methodologies, which are not considered in this paper, will be published elsewhere: Thromb. Diath. Haemorrhag., in press.