Cholinergic components in the gastrin pathway of gastric acid stimulation

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Summary. In the isolated whole stomach of the mouse, cimetidine and atropine appear to be specific antagonists of histamine- and acetylcholine-induced stimulation of parietal cells. Interactions were demonstrated between cimetidine and gastrin, atropine and gastrin, respectively. In addition to a histaminergic pathway of gastrin stimulation, a cholinergic part, probably postganglionic, can be taken into consideration.

The details of the gastrin pathway of gastric acid stimulation are still obscure. One possibility was proposed by Code[2] who suggested that histamine is the final common mediator of all kinds of gastric stimulation, gastrin included. Recently, Soumarmon et al.[3] demonstrated that parietal cells probably possess separate gastrin receptors. It could be that gastrin stimulates acid secretion by acting on its separate receptors. On the other hand, it is known that atropine inhibits pentagastrin-induced acid secretion in the dog[4], indicating that a cholinergic pathway is also involved in gastrin-induced acid secretion. The isolated stomach preparation, in which hormonal, vascular and neural effects are minimized, seems to be a suitable model for studying the direct actions of secretagogues. In the present work, the possible cholinergic pathway of gastrin stimulation is investigated in the isolated whole stomach of the mouse.

Method. Fed mice of either sex, weighing between 20 and 23 g, were anaesthetized with ether. The isolated whole stomach preparation was made according to Angus and Black[5]. A detailed description has been given elsewhere[6]. The lumen of the stomach was perfused at a constant rate of 1 ml/min. Changes in pH of the effluent perfusate were continuously recorded (Watanabe, Type MC 6601). The rate of acid secretion was expressed as H^+nmole/min. All drugs were added in a volume not exceeding 0.4 ml, to the buffered serosal solution bathing the serosal surface of the stomach. The basal acid output was allowed to stabilize for 20 min before the secretory response to an agonist was investigated. When an antagonist was added to the bath 20 min after setting up the preparation, the agonist was administered a further 40 min later. The response to a single dose of an agonist was calculated as the amount of acid secreted at peak response minus the preceding basal level. Fresh solutions of drugs were made up each day in physiological saline. The following drugs were used: pentagastrin (Gastrodiagnost, Merck AG), atropine sulphate (Merck AG), histamine acid phosphate (Sigma), acetylcholine chloride (Sigma), hexamethonium bromide (Sigma), cimetidine (Smith, Kline & French). The effect of antagonists on acid secretion was evaluated by using Student's t-test for unpaired groups of results[7]. A p-value less than 0.05 was considered to be significant.

Results. The effect of hexamethonium, atropine and cimetidine on gastric acid secretion induced by pentagastrin, histamine and acetylcholine has been summarized in the table. Hexamethonium did not inhibit pentagastrin-induced acid secretion in the mouse isolated stomach. Relatively high concentrations of atropine (10^{-5} M) strongly inhibited acid output stimulated by pentagastrin. In the presence of cimetidine, acid secretory response to pentagastrin was significantly reduced. In the presence of both atropine and cimetidine, acid secretory response to pentagastrin was more strongly inhibited than in the presence of a single antagonist. It seems likely that inhibition in the presence of both antagonists is additive. Hexamethonium and atropine did not influence histamine-induced acid secretion. As expected, only cimetidine, a specific H_2-antagonist, significantly inhibited acid secretory responses to histamine in the isolated whole stomach of the mouse. When acid secretion was stimulated by acetylcholine, only atropine inhibited acid response to the parasympathomimetic agent. Both hexamethonium and cimetidine failed to inhibit cholinergically-stimulated acid secretion in the isolated mouse stomach.

Discussion. Acid secretion from the mouse isolated stomach induced by pentagastrin was inhibited by cimetidine and by

The effect of hexamethonium, atropine, and cimetidine on acid secretory response to pentagastrin, histamine, and acetylcholine in the isolated whole stomach of the mouse (*$p < 0.05$). Results represent mean ± SEM with number of experiments in brackets

Agonist	Antagonist	Acid output (nmoles/min)	Inhibition in % of control value
Pentagastrin (2.5 µg/ml)	None	128 ± 11 (25)	0
	Hexamethonium (10^{-5} M)	118 ± 10 (8)	9
	Atropine (10^{-6} M)	117 ± 22 (6)	9
	Atropine (10^{-5} M)	84 ± 6+ (6)	34
	Cimetidine (10^{-5} M)	62 ± 18+ (9)	52
	Cimetidine (10^{-4} M)	22 ± 8+ (8)	83
	Atropine (10^{-5} M) + Cimetidine (10^{-5} M)	29 ± 5+ (11)	77
Histamine (10^{-5} M)	None	214 ± 12 (22)	0
	Hexamethonium (10^{-5} M)	208 ± 34 (6)	3
	Atropine (10^{-5} M)	190 ± 28 (9)	11
	Cimetidine (10^{-5} M)	115 ± 16+ (6)	46
Acetylcholine (10^{-3} M)	None	162 ± 18 (26)	0
	Hexamethonium (10^{-5} M)	169 ± 12 (4)	+4
	Atropine (3×10^{-7} M)	47 ± 13+ (8)	71
	Atropine (10^{-5} M)	4 ± 1+ (6)	98
	Cimetidine (10^{-5} M)	159 ± 17 (10)	2

atropine. A part of the stimulatory action of gastrin appears to be of a histaminergic nature, since acid responses to pentagastrin were antagonized by a histamine H_2-antagonist, cimetidine, as shown in this and previous studies[8]. A further possibility for the gastrin-induced stimulation consists of a cholinergic pathway. Goto and Watanabe[9] reported that the tetragastrin-induced acid secretion was inhibited by atropine in the isolated amphibian gastric mucosa preparation. Similar results were found in our study. Direct evidence of the release of acetylcholine by gastrin in the stomach is still absent; however, the possibility should not be considered to be completely excluded. Benneth[10] found that in the guinea-pig ileum the contraction produced by gastrin is caused by the release of acetylcholine and that it could be abolished by hyoscine. Gregory and Tracy[11] demonstrated that atropine reduced the motor effect of gastrin on the stomach and jejunum of the dog. Vizi et al.[12,13] showed that gastrin released acetylcholine from the myenteric plexus in the guinea-pig ileum. The structure of the parasympathetic autonomic innervation (Auerbach's and Meissner's plexi) is almost uniform in the alimentary tract. As shown in in vivo and in vitro studies, atropine inhibits pentagastrin-stimulated acid secretion[14,15]. In the isolated whole stomach of the mouse, gastrin-induced acid secretion was also inhibited by atropine but not by hexamethonium, suggesting that the acid stimulatory effect of gastrin on the stomach is partly mediated via acetylcholine which is released from the postganglionic parasympathetic nerves.

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Coronary perfusion pressure as a determinant of ventricular performance[1]

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Summary. The results observed in this work support the view that coronary perfusion pressure affects ventricular performance independently of metabolic effects; a mechanism operating in beat-to-beat regulation is proposed.

The depressant effect on contractile force produced by myocardial undernourishment secondary to ischemia or hypoxia is well known. Effects of coronary perfusion pressure on ventricular performance apart from those due to unfulfilled myocardial metabolic requirements are not as well established. Therefore, we investigated the influence of perfusion pressure on ventricular performance and our results seem to confirm that coronary perfusion pressure by itself does affect ventricular contractile function.

Methods. Studies were performed in the isolated metabolically supported canine heart preparation described by others[2]. The heart was perfused with blood derived from the femoral artery of a support dog to a reservoir whose height was adjusted to maintain a perfusion pressure of 100 mm Hg. Coronary venous outflow returned from pulmonary artery to the support dog and a catheter was inserted through the apex of left ventricle to drain thebesian flow. Through a small right atrial incision a total atrioventricular blockade was induced by injecting 0.3–0.5 ml of formalin 10% in the region of the A-V node and ventricular pacing was maintained at the lowest frequency attainable (mean $\pm$ SD = 65 ± 11 beats/min). The mitral apparatus was excized and a soft distensible latex balloon attached to a coupling cannula was maintained in the left ventricle. The cannula was connected to a P23Db pressure transducer and the balloon was filled with saline until a systolic pressure of 70–80 mm Hg was obtained. To test the influence of perfusion pressure on myocardial performance, the line of coronary perfusion was occluded during 10–30 sec and, thereafter, suddenly released. The sole influence of perfusion pressure on cardiac performance was analyzed by comparing pressure developed (DP) by 2 successive beats: the last one that occurred during underperfusion and the first one following the release of the coronary line.

Results and discussion. In order to prevent misinterpretation of the results strict attention was paid to the possible

Effect of coronary perfusion pressure on ventricular performance

Experiment	Δt (sec)	A (mm Hg)	B (mm Hg)	Percent*
1	0.5	34	46	+35
2	0.4	54	67	+24
3	0.5	42	58	+38
4	0.5	46	53	+15
5	0.9	49	62	+26
6	0.7	30	37	+23
7	0.8	39	51	+31
Mean $\pm$ SD	0.61 ± 0.18	42.0 ± 8.4	53.4 ± 10.0	$+27.4 \pm 7.8$

Δt: time elapsed from the relief of coronary perfusion line to the onset of the next ventricular contraction; A: developed pressure of the last contraction occurred during occlusion of coronary line; B: developed pressure of the 1st beat occurred after relief of coronary perfusion; * percentual difference between B and A.