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Effect of glycopyrronium bromide on basal, and histamine- or gastrin-induced gastric secretion

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Acid secretory responses were obtained in rats given either intravenous histamine as dihydrochloride or gastrin subjected to partial purification. A continuous recording method for measuring gastric acid secretion was used. When the rat stomach was perfused with weak sodium hydroxide solution, glycopyrronium bromide (a powerful anticholinergic drug) blocked the acid gastric secretory effects of both histamine and gastrin. Glycopyrronium bromide in doses of 2 μg/100 g body weight of rat is well tolerated. Doses higher than 2 mg/100 g caused respiratory disturbances. The action of glycopyrronium bromide in blocking the gastric secretory effects of gastrin supports the hypothesis that gastrin acts partly by stimulating the vagus nerve.

Recent advances in the physiology of gastric secretions have shown that the vagus nerve and gastrin are the two most important factors controlling the secretion of acid gastric juice (Hollander, 1962). The secretion can be divided into basal secretion due to vagal activity and the histamine- and gastrin-induced acid secretion. The basal secretion due to vagal activity can be controlled by atropine and anticholinergic drugs. Atropine also inhibits the histamine- and gastrin-induced secretion (Gregory & Tracy, 1961; Makhlouf, McManus & Card, 1965). Atropine inhibits endogenous or exogenous gastrin in gastric pouch dogs and the secretion of acid in response to pentagastrin (Hirschowitz & Sachs, 1968).

Franco & Lunsford (1960) reported that a series of n-substituted-3-pyrrolidyl-substituted phenylacetates possessed high anticholinergic activity. In particular, glycopyrronium bromide (3-cyclopentyl mandeloyloxy-1,1-dimethylpyrrolidinium bromide) was exceptionally active in suppressing smooth muscle motility and the volume and acidity of gastric secretion. The present experiments were made to demonstrate the effects of glycopyrronium bromide on acid secretory responses to histamine and gastrin. Amure & Ginsburg (1964) showed that inhibitors of histamine metabolism also enhanced gastric acid secretory responses to exogenous gastrin. The object of the present work was to evaluate acid secretory responses to histamine and gastrin in rats pre-treated with glycopyrronium bromide.

The vagal release of gastrin is now an established mechanism (Woodward, Robertson & others, 1957), by which gastrin stimulates the gastric acid secreting glands during the phase of basal secretion due to vagal activity and functions in addition to the direct vagal action on the glands. The results show that glycopyrronium bromide inhibits this basal phase as well as exogenous histamine and gastrin-induced acid secretion; provided the present concept of the hormonal role of histamine remains valid.

EXPERIMENTAL

Male albino rats, 150 to 350 g, were anaesthetized with urethane (0·6 ml/100 g of a 25%, v/v solution, intramuscularly), and the stomach was prepared for perfusion (Ghosh & Schild, 1958) with 0·001–0·00025 N sodium hydroxide solution. The rat was chosen because it tolerates large doses of histamine without untoward effects. Another advantage is that, as the acid secretion from the stomach of the anaesthetized rat is recorded continuously in the Ghosh & Schild method, the activity of both histamine and gastrin can be measured accurately. Amure & Ginsburg (1964) described a bioassay of gastrin in rats. All drugs were given intravenously through a cannulated external jugular vein. When histamine or gastrin was being tested, glycopyrronium bromide was injected 2 min before their injection. The pH was allowed to return to normal base line before the next injection. Doses are expressed as μg of the salts, except for histamine which was expressed in μmol of histamine base. Gastrin activity was measured in units of the partially purified extract of crude gastrin powder. The response metameter chosen was the maximum fall in pH after the injection and the response metameters are plotted against log dose of gastrin.

Materials

These were histamine dihydrochloride (Light and Co.); glycopyrronium bromide (A. H. Robins Co., Inc.); hog gastrin powder was prepared according to Blair, Harper & others (1961). Fresh hog antra were collected from the abattoir and transported in ice to the laboratory. The crude gastrin powder was further subjected to partial purification by gel-filtration and acid fractionation as described by Amure & Ginsburg (1964).

RESULTS

The assay of histamine and gastrin depends on changes of pH in the effluent fluid from the lumen of the perfused rat stomach after intravenous injections of histamine or gastrin. When histamine is given, changes in the pH of the gastric effluent occur 5–7 min later and gastrin, 2–3 min later (Amure & Ginsburg, 1964).

Responses to histamine and gastrin

In all experiments, histamine and gastrin had noticeable effects on gastric acid secretions. The results showed that animals varied in their sensitivity to either of the two secretagogues. Some animals responded appreciably to low doses of either agent while other animals required large doses before any appreciable changes occurred in the pH of the gastric effluent. Table 1 shows results of typical responses to histamine (0·5 and 0·25 μmol) and to gastrin (0·4 and 0·2 units).

Table 1. *Typical effects on the gastric effluent pH of rats of histamine, gastrin and glycopyrronium bromide*

Animal I		Animal II		Animal III			
Histamine dose μmol	pH change in units	Gastrin dose in units	pH change in units	Histamine dose μmol	pH change units	Glyco-pyrronium dose μg	pH change units
0·5	−2·4	0·4	−1·5	0·5	−1·5	5	+0·2
0·5	−2·3	0·2	−0·8	0·5	−1·5	5	+0·2
0·25	−1·0	0·2	−0·8	0·2	−0·4	2	no change
0·25	−1·0	0·2	−0·8	0·1	no change	1	no change

Responses to glycopyrronium bromide

Glycopyrronium bromide in small doses (2–5 μg) given intravenously to rats of not less than 150 g, caused complete inhibition of basal acid gastric secretion and acid secretions induced by either histamine or gastrin. In some animals, glycopyrronium bromide caused an initial rise in the pH of gastric effluent. Higher doses (1–2 mg/100 g) were tolerated but above this the drug gave rise to respiratory disturbances. For these experiments, small doses (2 or 6 μg/100 g) adequately controlled acid secretory responses to histamine or gastrin. Table 1 shows the results of typical responses of acid gastric secretion to 1, 2 and 5 μg of glycopyrronium bromide.

Effect of glycopyrronium bromide and histamine

The effect on the effluent pH after histamine given before and after the intravenous injection of glycopyrronium bromide shown in Table 2, in which the typical responses are shown by results from four rats. In all experiments, gastric acid secretory responses to histamine in animals pre-treated with glycopyrronium bromide (2 μg/100 g) were less than before glycopyrronium bromide was given.

Effect of glycopyrronium bromide and gastrin

These experiments were similar to those with glycopyrronium and histamine. Partially purified gastrin was given intravenously. In each experiment, gastrin was given until at least 4 similar responses were obtained. This was followed by glycopyrronium bromide (2 μg/100 g), after the pH of the effluent had returned to control level. Two min after glycopyrronium bromide had been injected, gastrin was given in the same dose as that given before the glycopyrronium bromide. In all experiments, the results showed that glycopyrronium bromide reduced responses to gastrin. Typical results in four such experiments are in Table 2.

Table 2. *Effects of histamine (μmol) or gastrin (units) on the pH of gastric secretion in anaesthetized rats before and after intravenous injection of glycopyrronium bromide (in μg) in rats*

Substance	Dose given	pH change units	Dose given	pH change units	Dose given	pH change units	Dose given	pH change units
	Animal 1		Animal 2		Animal 3		Animal 4	
Histamine	3·0	−1·9	0·25	−0·5	0·5	−1·5	0·25	−0·8
Histamine	2·5	−1·7	0·25	−0·5	0·5	−1·5	0·5	−0·8
Histamine	2·5	−1·7	0·25	−0·5	0·2	−0·8	0·5	−0·8
Histamine	2·5	−1·7	0·25	−0·6				
Glycopyrronium ..	6		3		6		4	
Histamine	2·5	−0·9	0·25	−0·1	0·5	−0·8	0·5	−0·3
Glycopyrronium ..	6		3	No	6		4	
Histamine	2·5	−0·7	0·25	change in pH	0·5	−0·8	0·5	−0·1
	Animal 5		Animal 6		Animal 7		Animal 8	
Gastrin	0·1	−0·8	0·5	−1·2	0·4	−1·5	0·4	−0·5
Gastrin	0·1	−0·7	0·5	−1·2	0·2	−0·8	0·6	−1·2
Gastrin	0·1	−0·8	0·5	−1·2	0·2	−0·8	0·6	−1·4
Gastrin	0·1	−0·8	0·5	−1·1	0·2	−0·8	0·6	−1·4
Glycopyrronium ..	5		5		4		5	
Gastrin	0·1	−0·2	0·5	−0·8	0·2	−0·4	0·6	−0·8
Glycopyrronium ..	5		5		4		5	
Gastrin	0·1	−0·3	0·5	−0·6	0·2	−0·5	0·6	−0·9

DISCUSSION

Acid secretory responses to stimulation by histamine and gastrin as reported previously by Ghosh & Schild (1958) and Amure & Ginsburg (1964) were confirmed in all respects. The animals tolerated gastrin better than either histamine or glycopyrronium bromide. In all experiments, glycopyrronium bromide had an inhibitory effect on basal acid secretions as shown in Table 2 where the pH of the gastric effluent rose by 0·2 pH units immediately after the administration of glycopyrronium bromide, and was sustained for about 5–6 min. This effect is analogous to the inhibition of gastric acid secretion by chlorpromazine which was demonstrated in dogs (Sun & Shay, 1959) and in rats (Konturek & Radecki, 1963). The effect is probably of nervous origin and mediated by the vagus.

Glycopyrronium bromide also reduced acid secretions induced either by intravenous histamine or gastrin. This was evident in all experiments in which the animals were pre-treated with glycopyrronium bromide. The evidence adduced shows that glycopyrronium bromide is capable of reducing acid secretory responses to both exogenous histamine and gastrin.

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