EFFECTS OF METIAMIDE AND PROPRANOLOL ON GASTRIC SECRETION IN ANESTHETIZED DOGS

Susumu OKABE, Chen R. HUNG, Koji TAKEUCHI
Yoshinobu TAKATA and Keijiro TAKAGI

Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences,
University of Tokyo, Bunkyo, Tokyo 113, Japan

Accepted September 6, 1976

Abstract—The effects of metiamide, a histamine H2-receptor antagonist, and propranolol, a beta-adrenergic blocking agent, on gastric secretion were studied in anesthetized dogs. Metiamide, 1.45 mg/kg i.v., markedly inhibited the gastric secretion induced by a continuous i.v. infusion of tetragastrin (8 µg/kg-hr), histamine dihydrochloride (160 µg/kg-hr), or methacholine bromide (100 µg/kg-hr). Propranolol 0.5 or 1.0 mg/kg i.v. produced a significant potentiation of tetragastrin-induced gastric secretion but no influence on the secretion induced by methacholine. Propranolol at 5 or 10 mg/kg i.v. produced a slight reduction of the tetragastrin-induced secretion and a significant reduction of methacholine-induced secretion. Histamine-induced gastric secretion was not affected by propranolol at either 1 and 10 mg/kg i.v. These findings lend support to the hypothesis that interactions among histamine, gastrin and acetylcholine receptors do occur though the degree would not be the same in all directions.

Grossman and Konturek (1) have reported a new hypothesis from the effect of metiamide, a histamine H2-receptor antagonist (2), and atropine on gastric secretion in Heidenhain pouch dogs. According to this hypothesis, the parietal cell has separate receptors for histamine, gastrin and acetylcholine and these receptors interact. Blockade of the histamine receptors by metiamide changes the properties of the gastrin or acetylcholine receptors to the extent that there is a reduction in the stimulation by gastrin or acetylcholine. However, blockade of the acetylcholine and gastrin receptors by atropine only weakly suppresses histamine receptors, indicating that the degree of interaction would be directionally unequal. Since the beta-adrenergic blocking agent, propranolol, is known to exert various effects on basal or stimulated gastric secretion in rats (3–6), dogs (7, 8) and man (9, 10), it was used herein as a pharmacological tool together with metiamide.

MATERIALS AND METHODS

Thirty-eight male mongrel dogs, weighing 8–15 kg, were deprived of food for 24 hr and then anesthetized with pentobarbital Na (30 mg/kg, i.v.). The abdomen was incised and the stomach exposed. The pylorus was ligated and a stainless steel cannula was introduced into the stomach through the anterior wall and secured tightly around the inserted part with two purse-string sutures. The cannula was brought out through a stab wound in the abdominal wall and the incision was closed. The esophagus was also tied off at the neck region. In order to continuously infuse gastric stimulants and physiological saline
solution, a fine polyethylene tube was introduced into a vein in the right or left fore-leg. The gastric lumen was washed with 30 ml of saline solution more than 4 times until the recovered solution was clean. Thirty min after washing the gastric lumen, the gastric stimulants tetragastrin (8 μg/kg-hr), histamine dihydrochloride (160 μg/kg-hr) or methacholine bromide (100 μg/kg-hr) were continuously infused by a peristaltic pump (Harvard Apparatus Co.). Doses of these stimulants were those shown in a preliminary study to give submaximal responses in anesthetized dogs. Saline solution was concomitantly and continuously drop infused at a rate of about 80 ml per hr throughout the entire experiment. Gastric samples were collected from the gastric cannula by gravity drainage at 15 min intervals, and measurements were made for volume and acidity. All samples were titrated to pH 7.0 with 0.1 N NaOH. Ninety min after start of the infusion of stimulants or after reaching the plateau level, either metiamide (Smith Kline & French Lab) 1.45 mg/kg, or propranolol HCl (Sumitomo Co.) 0.5, 1.0, 5.0 or 10 mg/kg, was given by a single i.v. injection. Metiamide was first dissolved in 0.3 N HCl, adjusted to pH 7.0 with 0.3 N NaOH and then an appropriate amount of saline solution was added to the metiamide solution to make a proper concentration while propranolol was dissolved in saline solution. Two hr after administration of these drugs, the experiment was terminated. The next experiment was not begun until the gastric secretion had returned to almost the preinjection level and was being maintained at a steady state in the presence of stimulants. Every experiment was done with the dogs under deep pentobarbital Na anesthesia and levels of anesthesia were maintained by i.m. injections as required. After the completion of two experiments, the dog was sacrificed by an overdose of saturated KCl solution given i.v. Inhibitory activity was expressed as a percentage of the preinjection output of gastric secretion. The pre-injection value was determined by taking the mean output of two 15 min preinjection outputs of gastric secretion immediately before the injection of the test material. The significance of these changes was calculated according to Student's paired t-test.

RESULTS

Effects of metiamide on tetragastrin-, histamine-, or methacholine-stimulated gastric secretion
As shown in Fig. 1, metiamide at the dose of 1.45 mg/kg produced a marked inhibition of the gastric secretion induced by each of the three stimulants. The beginning of inhibition of gastric secretion induced by either tetragastrin or methacholine appeared 15 min after the injection of metiamide and was sustained for more than 2 hr. The inhibition of histamine stimulated gastric secretion was observed 30 min after the injection of metiamide and was sustained only for 1 hr; i.e., at 105 min after the injection, the levels of gastric secretion had returned to those prior to injection.

Effects of propranolol on tetragastrin-, histamine- or methacholine-stimulated gastric secretion
It can be seen in Fig. 2 that a single injection of propranolol (1.0 mg/kg, i.v.) produced a marked augmentation of tetragastrin-stimulated gastric secretion in all of 7 experiments in 5 dogs. The maximum response was observed 45 min after propranolol administration and then a gradual decline followed. Even 1.5 hr later, the stimulating effect was
FIG. 1. Effects of metiamide on the gastric secretion induced by a continuous i.v. infusion of tetragastrin, histamine, or methacholine in anesthetized dogs. Mean value ± S.E. of gastric acid output before injection of metiamide was 1.7 ± 0.4 (N=8), 4.2 ± 0.5 (N=12), or 1.9 ± 0.5 (N=6) mEq/15 min for tetragastrin, histamine or methacholine stimulated groups, respectively. Vertical bars indicate the standard error of the mean. Asterisks indicate significant difference from the preinjection level (P<0.05).

FIG. 2. Effects of propranolol on the gastric secretion induced by a continuous i.v. infusion of tetragastrin, histamine or methacholine in anesthetized dogs. Mean value ± S.E. of gastric acid output before injection of propranolol was 1.5 ± 0.1 (N=14), 3.2 ± 0.4 (N=14), or 3.9 ± 0.7 (N=12) mEq/15 min for tetragastrin, histamine or methacholine stimulated groups, respectively. Vertical bars indicate standard error of the mean. Asterisks indicate significant difference from the preinjection level (P<0.05).
FiG. 3. Effects of propranolol on the gastric secretion induced by a continuous i.v. infusion of tetragastrin, histamine or methacholine in anesthetized dogs. Mean value ± S.E. of gastric acid output before injection of propranolol was 2.2 ± 0.2 (N = 26), 3.5 ± 0.5 (N = 16) or 3.6 ± 0.2 (N = 10) mEq/15 min for tetragastrin, histamine or methacholine stimulated groups. Vertical bars indicate standard error of the mean. Asterisks indicate significant difference from the preinjection level (P < 0.05).

significant (P < 0.05) as compared with that of preinjection level. In one experiment, 0.5 mg/kg of propranolol produced almost the same increment of gastric secretion as that in 1 mg/kg treated groups. However, the duration of effect was shorter than that of 1 mg/kg. Histamine- or methacholine-stimulated gastric secretion, however, was not appreciably affected at the dose of 1 mg/kg of propranolol. In contrast to the results with 1 mg/kg of propranolol, 10 mg/kg of the agent produced a slight reduction of tetragastrin-stimulated gastric secretion (Fig. 3). Propranolol 5 mg/kg, in one experiment, induced no changes in gastric secretion in response to tetragastrin. It was found that propranolol, 10 mg/kg, significantly inhibited the methacholine-stimulated gastric secretion in all cases; the inhibition being sustained about 45 min. It should be noted that histamine-stimulated secretion was not affected by 10 mg/kg of propranolol.

DISCUSSION

These studies show that a histamine H2-receptor antagonist, metiamide, produced a strong inhibition on the gastric secretion stimulated by histamine, tetragastrin or methacholine in anesthetized dogs, as has been found in conscious dogs (1, 11, 12). The effect of metiamide had a faster onset and longer duration vs. tetragastrin- or methacholine-induced secretion than vs. that induced by histamine. It is possible that metiamide cannot quickly and adequately occupy histamine receptors in order to prevent gastric acid secretion as a result of histamine administration. However, even such an inadequate occupation of histamine receptors by metiamide may be sufficient to affect immediately and markedly the tetragastrin and methacholine receptors with the suppression of gastric secretion due to
these agonists.

In contrast to metiamide, propranolol produced different responses at different doses on tetragastrin-, methacholine- or histamine-stimulated gastric secretion. It was found that although a small dose of propranolol (0.5 to 1.0 mg/kg) potentiated tetragastrin-induced gastric secretion in anesthetized dogs, the drug produced a slight reduction of the secretion at a higher dose (10 mg/kg). This potentiating activity of a small dose of propranolol on gastric secretion is consistent with the results reported by Lin and Evans (7) and Curwain et al. (8) who used pentagastrin as a stimulant in conscious Heidenhain pouch dogs. As the mechanism of the gastric stimulation, Lin and Evans (7) speculated that the blocking of the beta-adrenergic effect to the pouch by propranolol resulted in a release of the parietal cells from the inhibitory action which existed as a physiological tonus. If such is indeed the mechanism, propranolol should also augment the gastric secretion induced by histamine or methacholine. However, there was no potentiation of these responses. Propranolol per se has no stimulating effect on basal gastric secretion in anesthetized dogs (unpublished data). It thus seems that a small dose of propranolol specifically increases the sensitivity of penta- or tetra-gastrin receptors on the parietal cell, but at a larger dose, the potentiating action is masked or reversed. It should be noted that a large dose of propranolol produced a considerable inhibition of methacholine-stimulated gastric secretion but no change in the histamine-induced secretion. The basal gastric secretion in rats which is inhibited by anticholinergic agents or vagotomy was strongly inhibited by a large dose of propranolol (3, 5, 6). Therefore, the inhibitory effect of propranolol on methacholine-stimulated secretion may be interpreted in the same way as results obtained in rats. There is also the possibility that such a high dose of propranolol might inhibit the methacholine-stimulated gastric secretion through its local anesthetic activity (13). If so, histamine or tetragastrin induced secretion should be also inhibited by the drug, but such was not the case. Geumei et al (10) reported that in man, histamine-induced gastric secretion was inhibited with 10 mg of propranolol. At present we have no explanation for these species differences.

In addition to the data obtained with metiamide and propranolol, it is well known that both secretin and glucagon markedly inhibit the gastric secretion induced by gastrin but not that induced by histamine (14-16). We have already reported that atropine sulfate markedly inhibited the methacholine or tetragastrin stimulated gastric secretion but exerted less influence on histamine stimulated secretion in anesthetized dogs (17). These findings clearly support the hypothesis of Grossman and Konturek (1) and suggest the rather exclusive character of histamine receptors in contrast to those of gastrin and acetylcholine.

The influence of anesthesia on the sensitivity of the parietal cell to gastric stimulants or antagonists and limitation of interpretation of receptor mechanisms in whole animals are now being investigated together with detailed properties of each receptor.

Acknowledgements: Thanks are due to Dr. David A. Brodie for pertinent comments. Metiamide and propranolol were provided by SKF Laboratory and Sumitomo Kagaku Co., respectively.
REFERENCES

1) Grossman, M.I. and Konturek, S.J.: Gastroenterology 66, 517 (1974)
2) Black, J.W., Duncan, A.M., Emmett, J.C., Ganellin, C.R., Hesselbo, T., Parsons, M.E. and Wyllie, J.H.: Agents and Actions 3, 133 (1973)
3) Takagi, K., Okabe, S., Yano, S., Kawashima, K. and Saziki, R.: Japan. J. Pharmacol. 19, 327 (1969)
4) Okabe, S., Saziki, R. and Takagi, K.: Japan. J. Pharmacol. 20, 10 (1970)
5) Danhof, I.E., and Geumeti, A.: Brit. J. Pharmacol. 46, 170 (1972)
6) Debnath, P.K., Gode, K.D., Govinda Das, D. and Sanyal, A. K.: Brit. J. Pharmacol. 51, 213 (1974)
7) Lin, T.M. and Evans, D.C.: Gastroenterology 64, 1126 (1973)
8) Curwain, B.P., Holton, P., McIsaac, R.L. and Spencer, J.: Brit. J. Pharmacol. 51, 217 (1974)
9) Konturek, S.J. and Oleksy, J.: Scand. J. Gastroen. 4, 13 (1969)
10) Geumeti, A., Issa, I., El-Gendi, M. and Abd-El-Samie, Y.: Am. J. dig. Dis. 17, 55 (1972)
11) Gibson, R., Hirschowitz, B.I. and Hutchison, G.: Gastroenterology 67, 93 (1974)
12) Konturek, S.J., Demitrescu, T. and Radecki, T.: Am. J. dig. Dis. 19, 999 (1974)
13) Hermansen, K.: Brit. J. Pharmacol. 35, 476 (1961)
14) Gillespie, I. and Grossman, M.J.: Gut 5, 342 (1964)
15) Lin, T. M. and Warrick, M.W.: Gastroenterology 61, 328 (1971)
16) Wilson, D.E., Ginsberg, B., Levine, R.A. and Washington, A.: Gastroenterology 63, 45 (1972)
17) Okabe, S., Hung, C.R., Takluchi, K., Naganuma, T. and Takagi, K.: Pharmacometrics 10, 157 (1975) (in Japanese)