Effects of Cimetidine on Prostanoid Production in the Gastric Corpus Specimens from Rats

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Accepted September 24, 1988

Abstract—In order to examine the effect of cimetidine on the production of prostanoids in the stomach mucosa, the amounts of prostaglandin (PG) E₂, F₁α and thromboxane (TX) B₂ were determined after the specimens from the rat stomach corpus were incubated in the presence of cimetidine. Cimetidine significantly stimulated the production of PGE₂ in the specimens at a concentration of 10 µM, but did not significantly affect the production of PGF₁α and TXB₂ at concentrations of 1 to 100 µM.

Cimetidine, a well-known H₂-antagonist, has been widely used clinically for treating peptic ulcer. There is no doubt that the major antiulcer effect of cimetidine is the inhibition of gastric acid secretion. Recently however, in addition to the inhibition of gastric acid, the possibility that cimetidine has a cytoprotective action has also been suggested. For example, cimetidine prevented the gastric lesion of rats induced by aspirin plus 0.15 N HCl (1). On the other hand, prostaglandin (PG) E and A and prostacyclin have been shown to be strong inhibitors of gastric acid secretion (2-4). On the basis of these findings, the effects of cimetidine on the prostanoid synthesis in the gastric mucosa have been examined (5-7), but the results so far reported are contradictory.

In this paper, the authors examined whether cimetidine enhances prostanoid synthesis in the cultured rat stomach corpus.

Male Wistar rats weighing 152–167 g were used. The animals that had been fasted for 12 hr before the experiments were killed by exsanguination from the carotid artery, and their stomachs were excised and washed in Ca²⁺/Mg²⁺-free phosphate-buffered saline. The stomach corpus was cut in approximately 4 mm² specimens under a microscope.

The culture method of Eastwood and Trier (8) slightly modified according to Ohara et al. (9) was used. Four tissue specimens of the corpus were placed, with the mucosal surface facing upward, on a stainless steel grid which was hung over a small well placed in a plastic culture dish (Falcon Plastics, Los Angeles, CA, U.S.A.). The well was filled with 0.75 ml of a culture medium consisting of 90% Eagle’s minimum essential medium, 10% dialyzed fetal calf serum and 6 mg/100 ml medium of tobramycin and maintained at 37°C for 3 hr in 5% CO₂ and 95% humid air.

Cimetidine was dissolved in dimethyl sulfoxide and added to the culture medium in the well at concentrations of 1, 10 and 100 µM. The final concentration of dimethyl sulfoxide was 0.01% in the culture medium. The culture medium contained 0.01% of dimethyl sulfoxide. At the end of the culture period, the culture medium was aspirated for the determination of prostanoids.

To determine PGE₂, PGF₁α and thromboxane (TX) B₂ in the culture medium, Du Pont PG [¹²⁵I]-radioimmunoassay kits (E.I. du Pont de Nemours & Co., Inc., NEN Products) were used. The radioactivity was measured by an Aloka ARC-300 auto-well r-system.

The results were expressed as the mean± S.E. of 6 experiments, and significant differ-
ences of the means were assessed by Student’s t-test.

The accumulation of PGE2 in the culture medium was dose-dependently increased by cimetidine in the range from 1 to 10 μM. Ten μM of cimetidine significantly increased the accumulation of PGE2 as compared with that of the control, but 100 μM of cimetidine tended to decrease the PGE2 as compared with that by 10 μM of cimetidine.

On the other hand, cimetidine exerted no significant effect on the accumulation of PGF1α and TXB2 in all concentrations used.

According to Arakawa et al. (6), cimetidine administered to rats twice a day for 7 days at a daily dose of 40 mg/kg decreased PGE2 and PGF1α in the gastric mucosal tissue. By contrast, Branski et al. (5) reported that the accumulation of PGE2 and PGF1α in the biopsy specimens from the stomach of ulcer patients was significantly increased after 4 weeks of cimetidine treatment at a daily dose of 1 g. Okada et al. (10) also showed that the PGE2 level in the gastric mucosa of rats exposed to restraint and water-immersion stress was elevated by 25 mg/kg of oral cimetidine.

In the present work, we used the stomach corpus specimens which included mucosa and muscle layers. The specimens were cultured for 3 hr at 37°C in the absence or the presence of cimetidine, and the prostanoids secreted in the culture medium were determined. Under these conditions, cimetidine significantly increased the concentration of PGE2 in the medium at 10 μM, although both the higher (100 μM) and the lower (1 μM) concentrations of cimetidine failed to increase PGE2 production. The reason for the bell-shaped dose-effect relation of cimetidine is not clear at present. The production of PGF1α and TXB2 was not significantly affected by cimetidine under the present conditions. It should be noted that the amount of PGE2 was much lower than those of PGF1α and TXB2 as shown in Table 1. We measured the amounts of these prostanoids in the incubation medium. According to Branski et al. (5), the accumulation of PGF1α and TXB2 in the medium by cultured biopsy specimens obtained from the stomach of ulcer patients was similar to that of PGE2. The discrepancy seems to come from the differences in animal species and experimental conditions. However, their results that only the PGE2 production was increased by cimetidine are compatible with those obtained by the present work. Whether the increase in PGE2 by cimetidine is due to the blockade of H2 receptors is an interesting problem. Since ranitidine, another strong H2 blocker, does not significantly affect the gastric mucosal PGE2 in rats (11), the effect of cimetidine on PGE2 production seems to be exerted by some actions other than its H2 blocking action. In the present experiments, specimens were incubated in a culture medium, suggesting that the acid produced by the mucosa will have little effect on the prostanoid production.

### Table 1. Effect of cimetidine on prostanoid synthesis in cultured corpus

| Cimetidine | PGE2 (ng/l) | PGF1α (ng/l) | TXB2 (ng/l) |
|------------|------------|-------------|-------------|
| 0 μM       | 369.1±24.12| 4352.0±268.80| 2588.8±126.65|
| 1 μM       | 425.9±23.05| 3978.5±172.17| 2438.9±64.65 |
| 10 μM      | 472.8±18.63*| 3918.9±219.45 | 2367.8±116.44 |
| 100 μM     | 422.4±34.27| 4153.8±278.47 | 2495.3±121.17 |

The amounts of prostanoids accumulated in each culture medium in which four corpus specimens were incubated were determined by radioimmunoassay as described in Materials and Methods. Figures in the table denote the mean±S.E. of 6 experiments. *: P<0.05 significant difference from the control (cimetidine, 0 μM) by Student’s t-test.

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