THE INCREASE IN CYCLIC AMP CONTENT IN THE ISOLATED GUINEA PIG GASTRIC MUCOSA DURING HISTAMINE-STIMULATED ACID SECRETION

Toshio SHIRAKAWA, M.D., Haruki MATSUMOTO, M.D., Keiji OHE, M.D. and Akira MIYOSHI, M.D.
First Department of Internal Medicine, Hiroshima University School of Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima, 734 Japan

Summary
Using the isolated guinea pig gastric mucosa perfused in vitro with a constant acid secretion and potential difference, the cyclic AMP (cAMP) contents in the gastric mucosa and in the serosal solution were measured during the course of acid secretion stimulated by histamine or dibutyryl cyclic AMP (db-cAMP). (1) The acid-secreting response of the gastric mucosa to histamine was reproduced by addition of db-cAMP. (2) The acid secretion stimulated by db-cAMP was not inhibited by cimetidine whereas the histamine-stimulated acid secretion was inhibited. (3) The increase in mucosal cAMP content was accompanied by histamine-stimulated acid secretion. (4) The increase in the mucosal cAMP content preceded the increase in acid secretion stimulated by histamine. From these findings, it has been concluded that cAMP plays an important role in the mechanism of histamine-stimulated acid secretion, including the morphological transformation of parietal cells, although its role as the intracellular mediator of the stimuli for the hydrogen ion pump itself requires further investigation.

Key Words: cyclic AMP, gastric mucosa, in vitro perfusion, acid secretion, histamine.

Introduction
Cyclic AMP (cAMP) has been proposed to be the intracellular mediator of theophylline-stimulated acid secretion\(^1\). However, for other stimuli which are important in physiological regulation of gastric acid secretion, the role of this cyclic nucleotide is not firmly established. The theophylline-stimulated acid secretion is conceivably transmitted by increasing the cAMP content, because theophylline is an inhibitor of phosphodiesterase which metabolizes the cAMP to 5'-AMP. However, with histamine and gastrointestinal hormones such as gastrin, no evidence has been presented to indicate that the stimuli to secrete acid is transmitted by this cyclic nucleotide.

With the above background, it is important to study the time course of the increase in mucosal cAMP content in comparison with the acid-secreting response to histamine, because a definite sequence between these two
phenomena should be found if the former is required for the latter. By using the isolated guinea pig gastric mucosa, which survived with a constant acid secretion for more than 3 hours\(^2,5\)}, the content of cAMP in the gastric mucosa was studied comparatively with acid secretion stimulated by histamine or dibutyryl cyclic AMP (db-cAMP). Evidence to show that the cAMP increase is taking place in the gastric mucosa preceding the acid secretion by histamine is presented in this report.

**Materials and Methods**

**Animals**

Female guinea pigs, 300 to 500 g of body weight, were used.

**In vitro perfusion of the isolated gastric mucosa**

After overnight fast, the stomach was excised from the animals killed by decapitation, and its serosa and the outer muscular layer were removed with its mucosal surface being immersed in the mucosal solution gassed with 100% oxygen. The gastric mucosa thus prepared was mounted between two Luicite chambers with 2 cm\(^2\) opening, connected to the top reservoirs with gas-lift circulation system kept at 38°C, and its mucosal and serosal sides were perfused separately in an apparatus similar to that reported by Ussing and Zerahn\(^4\), as shown in Fig. 1. The composition of the serosal and mucosal solution was as shown in Table 1, which is derived from the reports by other investigators\(^5,6\). The serosal solution was saturated with 95% O\(_2\)-5% CO\(_2\) whereas the mucosal solution was bubbled with 100% oxygen. The mucosal solution was continuously titrated to pH 4.5 using a pH-stat with the electrodes placed as shown in Fig. 1. The pH of the serosal solution was kept at 7.4 by CO\(_2\)-HCO\(_3^-\) buffer and continuously recorded. The potential difference between serosal and mucosal sides of the gastric mucosa was measured using 610 C solid state electrometer from Keithley Instruments Co. with two calomel electrodes in top reservoirs, and continuously recorded with MN 641 multirecorder from Watanabe Instruments Co.

**Stimulation of acid secretion by histamine or db-cAMP and its inhibition by an H\(_2\)-receptor antagonist, cimetidine**

Histamine, db-cAMP or cimetidine was added to the desired final concentration in the presence of 50 μM 3-isobutyl-1-methylxanthine (IBMX) in the serosal solution.