STUDIES ON THE HORMONAL CONTROL OF GASTRIC SECRETION*

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The effects of serotonin lack and replacement on Histamine-stimulated gastric secretion from Heidenhain pouches of dogs were studied. Serotonin lack was produced either by reserpine-depletion or l-methyl-d-lysergic acid butanolamide (UML 491)-antagonism. Serotonin lack significantly increased gastric acid secretion (P 0.02) and significantly reduced gastric pepsin secretion (P 0.05). Serotonin replacement by injecting 5-hydroxytryptophan significantly reduced gastric acid secretion (P 0.02) and significantly increased gastric pepsin secretion (P 0.05). These results indicate that serotonin is an inhibitor of gastric acid secretion and stimulator of pepsin secretion, and the mechanism of serotonin action must be, at least partyly, hormonal.

The duodenal mucosa contains several hormones that are capable of inhibiting gastric secretion and accordingly, each hormone was given the general name "**Entrogastrone**."[8, 13-15] Cholecystokinin,[6, 8, 10] gastric polypeptide,[10, 12, 14] secretin[6, 14] and serotonin[13] are some of the hormones that have been isolated in purified forms from the duodenal mucosa. Cholecystokinin[6, 8, 10] and gastric inhibitory polypeptide[10, 12] inhibit both acid and pepsin secretion; secretin[6, 8, 9] and serotonin[3, 7, 24] also inhibit acid secretion but stimulate pepsin secretion. White et al[24] demonstrated that serotonin inhibited gastric acid secretion but stimulated gastric pepsin secretion from the innervated gastric pouches. In our studies, we used Heidenhain pouches which had their vagal innervation divided during their surgical construction.

Well over seventy-five percent of total body serotonin is located in the alimentary canal.[4, 5] In fact, serotonin is synthesized from its percursor 5-hydroxytryptophan by the Entrochromaffin cells[4, 5, 13, 22] that are located at the bases of the gastric and intestinal tubular glands. Serotonin is then stored in these Entrochromaffin cells in the form of granules.[4, 5, 13, 22] The parenteral administration of serotonin[3, 7, 24] or its precursor 5-hydroxytryptophan[24] was shown repeatedly to inhibit gastric acid secretion. Moreover, the release of duodenal serotonin during duodenal acidification was also demonstrated[7, 16, 21, 25, 26] and was found to be associated with the inhibition of gastric acidity.

MATERIALS AND METHODS

Fifteen mongrel dogs were provided with Heidenhain pouches and gastric cannulae. The gastric cannulae were kept open during the studies to prevent the gastric acid secreted by the stomach from entering the duodenum and inhibiting gastric secretion. In all the studies, histamine phosphate was infused intravenously at a rate of 0.04 mg/kg/hr to produce maximal gastric secretion. Collections were made from Heidenhain pouches every fifteen minutes. H^+ output in mEq/15 minutes was calculated and pepsin output as pepsin units/15 minutes ($PU^{Hb} \times 10^3$/15 min.) were also calculated according to Anson and Mirsky.[1]

Two types of studies were performed. In the first study, reserpine was injected intramuscularly 0.1 mg/kg 24 hours before commencing histamine infusion to deplete serotonin stores. When gastric secretion became maximal, the depleted serotonin stores were replenished by an intravenous injection of the serotonin precursor, 5-hydroxytryptophan, at a dose of 20 mg/kg. In

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the second type of studies, body serotonin was reduced by the administration of a potent serotonin antagonist, 1-methyl-d-lysergic acid butanolamide (UML 491), which was infused intravenously at a rate of 2 mg/hr, 30 minutes before maximal gastric secretion was established.

RESULTS

A. **Studies on gastric acid secretion** (Figures 1 and 2)

Histamine infusion alone increased gastric acid secretion to a peak (1.00 ± 1.15 mEq/15 min.) and then maintained acid output at this peak level as a plateau. When serotonin was depleted by the prior administration of reserpine to the same dogs, histamine-stimulated gastric acid secretion became significantly increased (1.71 ± 0.50 mEq/15 min.; P 0.02). Figure 1.

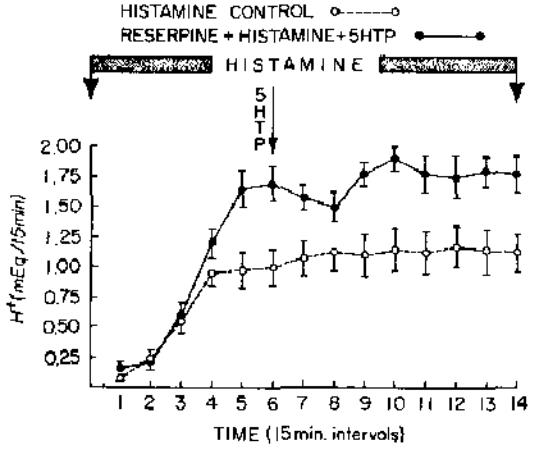

FIGURE 1 Effect of serotonin depletion and replacement by 5-HTP on histamine-stimulated gastric acid output.

When the depleted serotonin stores were replenished by the single intravenous injection of 5-hydroxytryptophan, gastric acid secretion was significantly reduced (1.50 ± 0.12 mEq/15 min.; P 0.02). Figure 1.

When body serotonin was antagonized by the intravenous infusion of 1-methyl-d-lysergic acid butanolamide (UML 491), again gastric acid secretion was significantly elevated (1.69 ± 0.12 mEq/15 min.) compared to only 1.10 mEq/15 min. when histamine was infused alone into the same dogs (P 0.03). Figure 2.

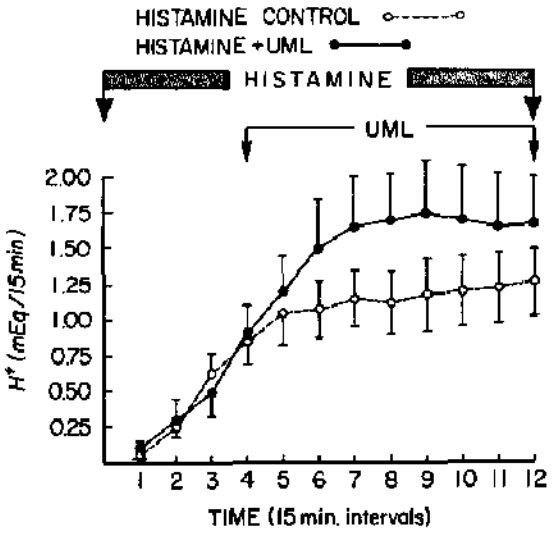

FIGURE 2 Effect of a serotonin antagonist (UML 491) on histamine-stimulated gastric acid output.

B. **Studies on gastric pepsin secretion** (Figures 3 and 4)

Histamine infusion alone produced an initial peak in pepsin secretion (169 ± 41 PU^{Hb} x 10^3/15 min.). Serotonin depletion abolished this initial peak (26 ± 7 PU^{Hb} x 10^3/15 min.; P 0.05). Figure 3.

But when serotonin depletion was corrected by the single intravenous injection of the serotonin precursor 5-hydroxytryptophan, gastric pepsin

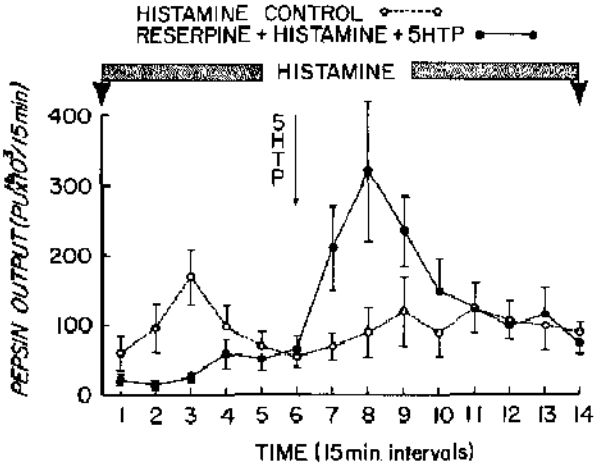

FIGURE 3 Effect of serotonin depletion and replacement by 5-HTP on histamine-stimulated gastric pepsin output.

secretion was significantly increased (318 ± 117 PU^{Hb} x 10^3/15 min.; P 0.05). Figure 3.

Serotonin antagonism by the intravenous infusion of UML 491 significantly decreased gastric pepsin secretion and abolished the secondary increase in pepsin secretion (20 ± 8 PU^{Hb} x 10^3/15 min.); when histamine was infused alone into the same dogs, pepsin secretion was very much higher (81 ± 16 PU^{Hb} x 10^3/15 min.; P 0.01). Figure 4.

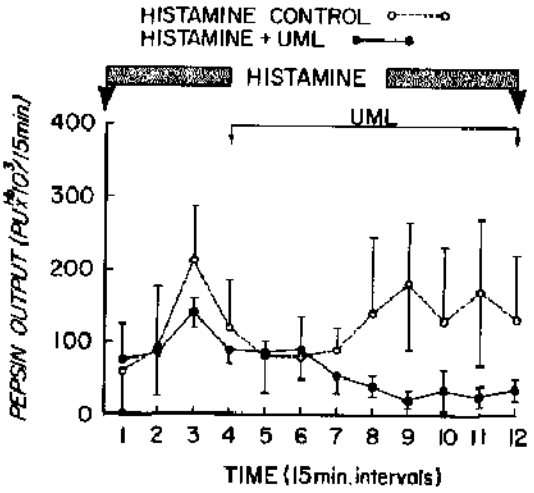

FIGURE 4 Effect of a serotonin antagonist (UML 491) on histamine-stimulated gastric pepsin output.

DISCUSSION

Duodenal ulceration is usually associated with gastric hyperacidity and it was suggested that duodenal mucosa must have a self regulatory mechanism to prevent such ulceration by simply inhibiting acid secretion from the stomach.(19, 20) And it was documented that the entrance of gastric acid into the duodenum liberates some hormones (ENTROGASTRONE) from the duodenal mucosa which inhibit the prietal cells and reduce acid secretion.(7, 16, 20, 21, 25, 26)

Serotonin (5-hydroxytryptamine), the predominant intestinal monoamine,(4, 5) is subject to the release from the duodenal mucosa by such self-perpetuated mechanisms as was documented experimentally.(7, 16, 21, 25, 26) Serotonin is synthesized mainly by the gastro-intestinal entrochromaffin cells and then stored in these cells as granules that constitute over 75% of body serotonin.(4, 5, 13) The localization of the site of synthesis and storage of serotonin was demonstrated by radiautography(4, 5) and histochemical method.(13) Exogenous serotonin(3, 7, 24) was found to inhibit acid secretion. Endogenous serotonin, whether released by duodenal acidification(7, 16, 21, 25, 26) or synthesized following parenteral administration of 5-hydroxytryptophan,(24) also inhibit gastric acid secretion. Portal vein serotonin was also found to increase during these experiments.(7)

The results of the present studies brought further evidence in favor of the inhibitory effect of serotonin on acid secretion. Reserpine was shown previously to degranulate the entrochromaffin cells(2, 4, 5, 16) and reduce intestinal serotonin.(2, 16, 25, 26) UML 491 was also shown to reduce duodenal serotonin(21, 25, 26) In the present studies, the prior administration of reserpine or UML 491 caused a significant increase in gastric acid secretion. The increase of gastric acidity could be related to the lack of serotonin that was created by reserpine or UML 491. Although the regulation of gastric acid secretion has been very well established, the mechanism of gastric pepsin secretion has never been clearly understood. Previously we have demonstrated that the intravenous infusion of histamine phosphate is a stimulator of pepsin output and that histamine stimulatory effect is biphasic.(23) In the present studies, histamine infusion alone also produced a biphasic stimulatory effect on pepsin secretion (Figures 3 and 4). But serotonin lack by reserpine depletion abolished the initial stimulatory phase by histamine infusion, while serotonin replacement by injecting 5-hydroxtryptophan increased pepsin secretion (Figure 3). Also, serotonin antagonism by UML 491 abolished the secondary stimulatory phase of histamine infusion (Figure 4). White et al(24) demonstrated that serotonin was a stimulator of pepsin secretion from the innervated gastric pouches. Our studies were performed on denervated gastric pouches, which brings additional evidence for the hormonal nature of serotonin action.

CONCLUSIONS

1. Serotonin must be an inhibitor of gastric acid secretion since serotonin lack, whether produced by depletion or antagonism, increased gastric acid secretion, while serotonin resynthesis by injecting 5-hydroxytryptophan de-

creased gastric acid secretion.

2. Serotonin is a stimulator of gastric pepsin since serotonin lack diminished gastric pepsin secretion and serotonin replenishment increased gastric pepsin secretion.
3. The mechanism of serotonin action must be hormonal because denervated gastric pouches were used in the present studies.

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