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-hydroxy tryptophan 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 partly, 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 precursor 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 x 10³/15 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 \(1.00 \pm 1.15 \text{ mEq/15 min.}\) 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 \(1.71 \pm 0.50 \text{ mEq/15 min.}; P < 0.02\). Figure 1.

![Figure 1](image)

**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 \(1.50 \pm 0.12 \text{ mEq/15 min.}; P < 0.02\). 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 \(1.69 \pm 0.12 \text{ mEq/15 min.}\) compared to only \(1.10 \text{ mEq/15 min.}\) when histamine was infused alone into the same dogs \(P < 0.03\). Figure 2.

![Figure 2](image)

**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 \((169 \pm 41) \text{ PU Hb x } 10^3/15 \text{ min.}\). Serotonin depletion abolished this initial peak \((26 \pm 7 \text{ PU Hb x } 10^3/15 \text{ min.}; P < 0.05\). Figure 3.

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

![Figure 3](image)

**FIGURE 3** Effect of serotonin depletion and replacement by 5-HTP on histamine-stimulated gastric pepsin output.
Serotonin was demonstrated by autoradiography (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 inhibits 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 enterochromaffin 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-hydroxytryptophan increased pepsin secretion (Figure 3). Also, serotonin antagonism by UML 491 abolished the secondary stimulatory phase of histamine infusion (Figure 4). While 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 did-
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.

REFERENCES


Synovial fluid was 20,720/cmm, mostly polymorphonuclear cells. The cell count ranged from as low as 200 to as high as 96,800 cells/cmm. Synovial fluid mucin clot was fair to good, protein and glucose contents were within normal limits and cultures for microorganisms were sterile.

On radiological examination, joint chondrocalcinosis was present in 70 of 72 patients and was most commonly seen in knees. The other joints commonly showing chondrocalcinosis were wrists, pubic symphysis, hips, elbows, shoulders, metacarpophalangeal joints, ankles and rarely even intervertebral discs.

Radiological changes in patients with chondrocalcinosis resembled mostly those seen in patients with primary osteoarthritis (unassociated with any underlying associated disease), but there are certain differentiating points:

1. Involvement of joints (e.g. wrists, shoulders and metacarpophalangeal joints) which are rarely affected by OA.
2. More prominent and more numerous subchondral cyst formation.
3. Joint degeneration more severe and more progressive, with subchondral bony collapse and fragmentation.
4. Isolated narrowing of patello-femoral joint space in knees and radiocarpal joint space in wrists more common.

Associated diseases: Three patients had associated hyperparathyroidism and one had hemochromatosis. Although one finds these associated diseases in only a minority of patients with chondrocalcinosis, it is important to exclude them in every patient. Chondrocalcinosis can be the first clinical manifestation of these associated diseases, as was seen in this patient with hemochromatosis who had no other clinical manifestation of hemochromatosis, e.g. hepatic dysfunction, diabetes or bronzed skin.

Three patients had associated gout. Both the urate and the CPPD crystals were identified in synovial fluids of these patients. Two patients had associated rheumatoid arthritis. Some of the knee joint symptoms in these two patients were due to CPPD crystal deposition because such crystals were identified in the synovial fluid aspirated from these swollen knees.

Treatment: Acute or subacute attacks of pseudogout are readily recognized by identification of CPPD crystals in synovial fluid leukocytes by compensated polarized light microscopy. Such attacks usually respond to aspiration of the swollen joints. Sometimes intra-articular injection of hydrocortisone may be needed to treat most severe attacks. When needle aspiration of the swollen joint is not feasible or when many joints are involved, short course of treatment with aspirin or preferably other non-steroidal anti-inflammatory drugs like indomethacin and butazolidine is quite effective. Effect of colchicine in pseudogout is not as predictable as in gout. For chronic arthritis, long term treatment with non-steroidal anti-inflammatory drugs is needed. Occasionally, arthroplasty is needed for severely damaged joints.

GASTRIC SECRETION . . . (Continued from page 8)