# Gastric Mucosal Erosion in the Rat Following Administration of the Serotonin Precursor, 5-Hydroxytryptophan. (23232)

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The presence of serotonin (5-hydroxytryptamine) in the gastrointestinal mucosa of the mammalian species has stimulated investigation concerning its role in the normal function and in disease of the gastrointestinal tract(1). It therefore became of interest to determine what effect administration of 5-hydroxytryptophan (5HTP), the metabolic precursor of serotonin, has on the gastrointestinal tract of the experimental animal. Previous studies have demonstrated that 5HTP is converted to serotonin *in vivo*, and measurable increases of serotonin in blood and tissue have been demonstrated within 15 minutes, reaching a maximum in about 60 minutes, and persisting for several hours after administration of 5HTP(2,3).

*Methods.* Seventy-five Sprague-Dawley rats weighing between 200 and 300 g were used. All substances were administered intraperitoneally except as indicated in Table I. The stomachs of the rats were examined 3 hours after administration of 5HTP.

*Results.* As is shown in Table I, almost all animals that received 5HTP in a dose of 300 mg/kg developed hemorrhagic gastric erosions which occurred almost exclusively in the corpus and antrum, which constitute the glandular portion of the stomach (Fig. 1). Occasionally a lesion was noted in the mucosa of the proximal duodenum. The lesions varied from 1 to 3 mm in diameter, and on microscopic examination showed necrosis of one-third of the thickness of the mucosa. Evidence of hemorrhage surrounding the necrotic material and a mild polymorphonuclear leukocytic infiltration were present.

As large doses of reserpine have been demonstrated to liberate stored serotonin from the gastrointestinal tract(4), reserpine alone was administered in an attempt to produce the gastric erosions. No erosions were found 3 hours after administration of 1 and 5 mg/kg. However, 18 hours after administration of 5 mg of reserpine per kg, hemorrhagic erosions were noted. Benditt(5) also has reported the presence of hemorrhagic erosions in the gastric mucosa of the rat following reserpine administration.

Atropine sulfate administered one hour before 5HTP was effective in preventing the erosions. As atropine had this effect, the action of 5HTP on gastric acid secretion in the rat was determined. Studies have indicated that 5HTP decreases gastric acid secretion in a Shay-rat preparation. After ligation of the pylorus, 6 rats were given 300 mg/kg of 5HTP and 5 rats were given 5 ml of isotonic saline intraperitoneally. Three hours later the mean gastric volume and acidity were 2.1 ml and 5 meq per liter in those receiving 5 HTP and 3.8 ml and 55 meq per liter in those receiving saline.

*Discussion.* These findings take on added significance in view of the apparent increased incidence of peptic ulceration in the malignant carcinoid syndrome where a hyperserotonemia exists. MacDonald reported an incidence of stomach and duodenal ulceration of 38% in 21 cases(6), and Manion found peptic ulceration in 4 of 6 autopsied cases.* Gastric analysis in 3 patients with malignant carcinoid syndrome did not reveal hypersecretion of acid juice. The average volume and free acidity of six 15-minute collections of basal gastric secretion in these patients were 14 ml and 9 meq per liter, respectively. Furthermore, studies in dogs have shown that when 5HTP is administered intravenously, the major effect on gastric secretion is inhibition(7). In 3 similar experiments on a dog with a simple gastric fistula and intact vagal innervation, the mean volume and free acidity of the spontaneous secretion were 20 ml and 93 meq per liter during a 40 minute period. In the interval 20 to 60 minutes after admin-

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TABLE I. Gastric Mucosal Erosions Following Administration of 5-Hydroxytryptophan and Related Compounds.

| Test substance | Time of autopsy after drug admin. (hr) | No. of rats | No. with erosions | Avg No. of erosions per rat |
|---|---|---|---|---|
| Saline | 3 | 10 | 0 | 0 |
| 5-Hydroxytryptophan 300 mg/kg | | | | |
| Intraper. | 3 | 16 | 14 | 4 |
| Subcut. | 3 | 5 | 5 | 5 |
| Reserpine | | | | |
| 1 mg/kg | 3 | 4 | 0 | 0 |
| 5 | 3 | 9 | 0 | 0 |
| 3 | 18 | 6 | 2 | <1 |
| 5 | 18 | 4 | 4 | 3 |
| Atropine sulfate 5 mg/kg | | | | |
| 5-Hydroxytryptophan 300 mg/kg | 3 | 10 | 2 | <1 |

istration of 20 mg per kg of 5HTP these values declined to 2 ml and 0 meq per liter, respectively. Although reserpine produces gastric erosions, it is not necessary to attribute these to the demonstrated stimulation of gastric secretion in dog and man(8,9).

Selye and others have demonstrated that similar erosions may be produced in the rat by a variety of drugs, traumatic injuries, burns, excessive muscular exercise, cold and other alarming stimuli(10). As serotonin occurs naturally in the stomach mucosa, it is logical to inquire whether this substance may be involved in the production of the erosions by the various stimuli.

*Summary.* 5-Hydroxytryptophan administered to rats in a dose of 300 mg/kg produced hemorrhagic mucosal erosions in the glandular portion of the stomach. When atropine sulfate was injected prior to 5-hydroxytryptophan administration, the lesions were decreased in number or their occurrence prevented. Administration of reserpine also produced similar lesions which were delayed in appearance.

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FIG. 1. Hemorrhagic gastric erosions occurring in glandular portion of the stomach of the rat 3 hr after administration of 5-Hydroxytryptophan in a dose of 300 mg/kg.

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