EFFECT OF SEROTONIN (5-HYDROXYTRYPTAMINE) AND RELATED COMPOUNDS ON GASTRIC SECRETION AND INTESTINAL MOTILITY IN THE DOG

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In 1937 Vialli and Erspamer found that extracts of the rabbit's gastric mucosa contain a pharmacologically active amine which has since been identified as 5-hydroxytryptamine or serotonin and has been recognized in extracts of gastrointestinal mucosa of many species.[1, 2] In mammals serotonin is found primarily in the blood platelets, brain, and gastrointestinal tract. Of the three depots, the gastrointestinal mucosa has the largest amount. It is believed that gastrointestinal serotonin is localized primarily in the enterochromaffin cells which have been considered to constitute a diffuse system designed for the production and storage of serotonin.[2] Masson[3] demonstrated that the enterochromaffin cells in mammals extend from the cardia to the anus and are found principally in the basilar portions of the gastric glands, Brunner's glands, and the glands of Lieberkühn.

Although serotonin is a potent pharmacologic stimulus to smooth muscle contraction, its physiologic role in the gastrointestinal tract is unknown. Because of the predominant localization of serotonin in the gastrointestinal mucosa, this study was undertaken to determine the effect of serotonin on gastric secretion and on intestinal motility in the dog.

METHODS AND MATERIALS

After a 12-hr. fast, four dogs with Heidenhain pouches received intravenously isotonic saline, serotonin creatinine sulfate, histamine dihydrochloride, or reserpine. The first three agents were infused continuously over periods of 1 to 2 hr. and the last drug was given in single injections. The volume and pH of the gastric juice were recorded at 20-min. intervals. With the exception of histamine, each agent was given on a different day.

The effect of serotonin on gastric secretion was also determined in dogs anesthetized with pentobarbital and prepared for acute observation by fixing a Levin tube in the stomach through a duodenostomy and ligating the pylorus around the tube. After aspirating gastric contents for three 15-min. periods

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which served as controls, serotonin creatinine sulfate was administered subcutaneously, 0.03 mg. per kg. every 15 min. for three doses to 2 dogs, by continuous intravenous infusion 0.03 mg. per kg. per min. for 45 min. to 1 dog, and another dog received a single intravenous dose of 0.06 mg. per kg. Gastric juice was then aspirated for at least 60 min. and its volume and free acidity determined at 15-min. intervals.

The effect of serotonin and other drugs on jejunal motility and intraluminal pressure was determined in 17 dogs by passing an open-end tube through a gastrostomy into the upper jejunum. The recordings were made over several hours while the animals were under pentobarbital anesthesia. The measuring apparatus consisted of a P 23 B Statham electrical transducer, a bleeder system, and a Sanborn Polyviso amplifying and recording unit as described by Lorber and Shay.[4] The recording sensitivity was such that a 10-mm. pen deflection was equivalent to 5 cm. of water pressure. The paper speed was 0.5 mm. per second. Serotonin was always administered as the creatinine sulfate and all doses are expressed as the salt.

RESULTS

Gastric Secretion

Serotonin in doses of 0.001 to 0.04 mg. per kg. per min. intravenously had no marked transient or sustained effect on the volume and pH of gastric secretion from the denervated Heidenhain pouch. The mean volume was slightly greater and the mean pH lower during administration of 0.01 mg. per kg. per min. of serotonin than that obtained when saline was given alone (table 1). While a

TABLE 1

Comparison of the effects of isotonic saline, serotonin creatinine sulfate, reserpine, and histamine dihydrochloride on gastric secretion in the Heidenhain pouch dog

	Dog 1		Dog 2		Dog 3		Dog 4	
	Vol.	pH	Vol.	pH	Vol.	pH	Vol.	pH
Isotonic saline	0.37	4.2	0.15	3.7	0.05	3.7	0.05	3.7
Serotonin creatinine sulfate (mg./kg./min.)								
0.001			0.04	1.6			0.46	2.2
0.01	0.48	2.4	0.62	1.9	0.16	2.9	0.75	2.1
0.04			0.10	2.4	0.2	7.0	0.05	4.1
Reserpine (0.2 mg./kg.)			3.7	1.0	1.1	1.0	5.1	1.0
Histamine dihydrochloride (0.005 mg./kg./min.)	15.7	1.0	8.8	1.0	2.6	1.0	14.8	1.0

Each figure for saline and serotonin represents the average value of six 20 min. periods, those for reserpine and histamine three to six 20 min. periods. The volume is expressed in ml. per 20 min. period.

larger number of observations might serve to establish the statistical significance of such a small difference, the physiologic significance of such a slight increase would remain doubtful. In only one 20-min. period in 8 experiments during serotonin infusion did the pH fall below 1.5, and in this instance the free acidity was 20 mEq. per l. When 0.04 mg. per kg. per min. of serotonin was infused, the pH of the resultant small volume of gastric juice rose. This dose of serotonin produced profuse salivation and irritability in the animal.

The secretory response to serotonin is contrasted with the response to reserpine because of a possible relationship which is discussed subsequently. Reserpine evoked an appreciable secretion of highly acid juice, although the volume

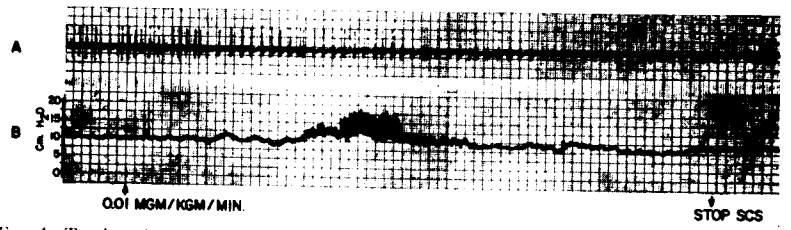

FIG. 1. Tracing *A* represents respiration and tracing *B* intestinal motility. Five min. after the continuous infusion of serotonin was started, increased intestinal motility is apparent. Two min. later tachyphylaxis is noted.

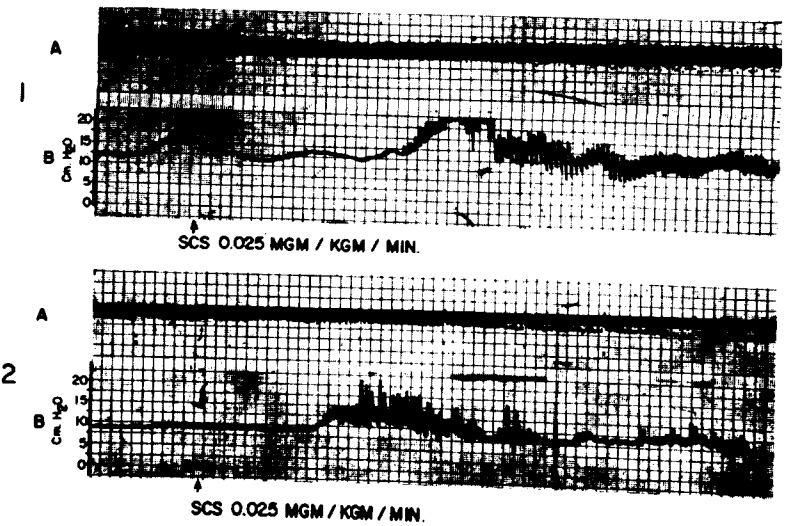

FIG. 2. Tracing *A* represents respiration and tracing *B* intestinal motility. In graph *1* 0.25 mg. per kg. of atropine sulfate intravenously, given 49 min. previously, did not inhibit the serotonin response. In graph *2* 4 mg. per kg. of hexamethonium ion intravenously, given 20 min. previously, did not inhibit the serotonin response.

was generally less than that following histamine (table 1). In single experiments, 0.01 mg. per kg. per min. of either sodium acetate or 5-hydroxyindoleacetic acid (serotonin catabolite) did not stimulate gastric secretion in the Heidenhain pouch, while the so-called serotonin antagonist lysergic acid diethylamide in the dose of 50 μg. per kg. produced a secretory response comparable to that of reserpine.

Serotonin given subcutaneously or intravenously in amounts comparable to those given to the Heidenhain pouch dogs did not stimulate secretion from the innervated stomachs of the anesthetized dogs. The method employed to collect gastric juice would preclude confident detection of such small changes as were observed with the denervated pouch.

Intestinal Motility

Serotonin stimulated jejunal motility in a dose as low as 0.01 mg. per kg. per min. in many of the dogs and the response was not modified by bilateral cervical vagotomy. In all instances increasing doses of serotonin (0.01 to 0.08 mg. per kg. per min.) evoked increasingly greater responses in jejunal motility (fig. 4). Tachyphylaxis developed during the continuous intravenous infusion of serotonin irrespective of dose, and the increased motility elicited by a given

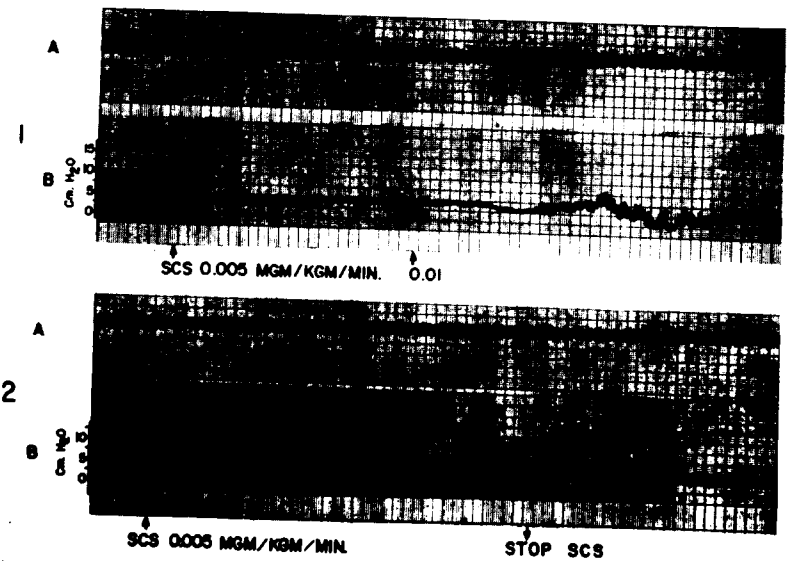

FIG. 3. Tracing *A* represents respiration and tracing *B* intestinal motility. Graph *1* illustrates the absence of a serotonin response when serotonin is infused at a rate of 0.005 mg. per kg. per min. Graph *2* illustrates the intestinal response 17 min. after the intravenous administration of 50 μg. per kg. of lysergic acid diethylamide when the same dose of serotonin is administered.

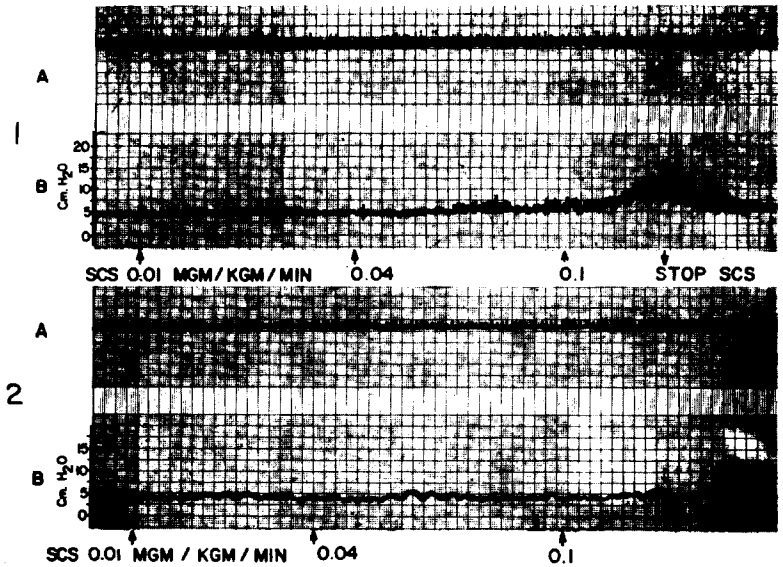

FIG. 4. Tracing *A* represents respiration and tracing *B* intestinal motility. Graph *1* shows the increasingly greater intestinal responses with increasing doses of serotonin. Graph *2* shows the absence of an intestinal response to the same doses of serotonin following 0.5 mg. per kg. of the histamine-releasing Compound 48/80 administered 15 min. previous to the serotonin infusion.

dose usually ceased within 5 min. (fig. 1). Within 10 min. after cessation of the serotonin infusion the bowel regained its former sensitivity.

The ability of several pharmacologic agents to modify the intestinal response to serotonin was examined. In 3 dogs, the intravenous administration of up to 0.75 mg. per kg. of atropine did not inhibit the serotonin response (fig. 2). Administration of 4 mg. per kg. of hexamethonium ion intravenously in 2 other dogs stimulated gut motility slightly but did not inhibit the serotonin response (fig. 2). In 4 dogs a single intravenous injection of 50 μg. per kg. of lysergic acid diethylamide caused marked potentiation of the serotonin response and tachyphylaxis was not observed (fig. 3). The potentiation of the serotonin response by lysergic acid diethylamide persisted following bilateral cervical vagotomy. After intravenous administration of 0.5 mg. per kg. of the potent histamine releasing agent, Compound 48/80,* the response of the intestine to serotonin was variable. In three of five instances, prior administration of Compound 48/80 inhibited the response to serotonin (fig. 4). In two instances no inhibition was noted. Prior administration of Compound 48/80 more consistently blocked tachypnea and hyperpnea induced by serotonin than the

* Compound 48/80 was generously supplied by Dr. Edwin De Beer of the Wellcome Research Laboratories.

increased gut motility. Administration of the antihistamine agent, mepyramine, in 1 dog in a dose of 5 mg. per kg. intravenously caused a slight stimulation of the intestine but did not alter the serotonin response. The administration of reserpine in a dose of 0.5 mg. per kg. in 2 dogs did not stimulate jejunal motility observed over a period of 2 hr.

DISCUSSION

The results of this study indicate that, although systemically administered serotonin stimulates intestinal motility, it does not evoke a significant secretion from either the denervated pouch or the innervated stomach. Although not demonstrated, it is possible that serotonin might be a physiologic stimulus to secretion if either (a) systemically administered serotonin causes inhibition which overcomes the secretory response or (b) exogenous serotonin does not reach the effector site in sufficient concentration. The latter possibility is not likely because the administration of the serotonin precursor, 5-hydroxytryptophan, which is decarboxylated in the body to yield high levels of serotonin, inhibits gastric secretion.[5]

The gastric response to serotonin is also of interest in considering the mode of action of reserpine on gastric secretion. Recently, Brodie and co-workers have demonstrated in animals that large doses of reserpine (1 to 5 mg. per kg.) cause the release of serotonin from the blood platelets, brain, and gastrointestinal tract[6-8] and it has been postulated that the serotonin which continues to be formed is in a free or physiologically active form.[9] Since reserpine increases both the volume and acidity of gastric secretion,[10, 11] it was logical to consider the possibility that the stimulus of reserpine to gastric secretion is mediated by serotonin. Although the failure of systemically administered serotonin to stimulate secretion does not unequivocally exclude the possibility that serotonin might be a physiologic stimulus, it would appear that reserpine stimulates gastric secretion by a mechanism other than serotonin release. In fact, the serotonin precursor, 5-hydroxytryptophan, inhibits spontaneous secretion, but does not block the gastric response to reserpine or histamine.[5]

If the enterochromaffin cells normally influence intestinal motility, it is probable that they do so by releasing a humoral agent which acts on neural elements of the intestine. Because of the location of the enterochromaffin cells, it is unlikely that serotonin could reach the smooth muscle cells except via the general circulation. While the present experiments do not establish a physiologic role for serotonin in intestinal motility, they indicate that this amine is a potent stimulus to gut motility. This can be demonstrated equally well using open-end catheters or distended intraluminal balloons. While the hyperactivity induced by serotonin as reflected by pressure waves is striking, the mean intra-

luminal pressure seldom increases by more than 1 to 2 cm. of water relative to the intra-abdominal pressure measured by an intra-abdominal catheter.

In our experience, atropine, hexamethonium, and mepyramine did not inhibit the serotonin stimulus to intestinal motility. The lack of effect of these agents *in vivo* is thus similar to the experience *in vitro*.[2, 12, 13] The partial inhibition of serotonin-induced intestinal motility by the potent histamine releasing agent, Compound 48/80, is an interesting incidental finding but not sufficiently consistent to warrant a conclusion.

It is of interest that lysergic acid diethylamide which has been shown to antagonize the central actions of serotonin in mice[14] and the stimulatory effect of serotonin on uterine muscle *in vitro*,[13] in contrast, potentiates the intestinal motility induced by serotonin. This finding is in keeping with the apparent potentiation by lysergic acid diethylamide of the peripheral effects of serotonin in patients with the malignant carcinoid syndrome. In this syndrome blood serotonin levels are markedly elevated and the administration of lysergic acid diethylamide produced bronchospasm, facial edema, and aggravation of flushing reactions.[15] *In vitro*, lysergic acid is a feeble and questionably specific antagonist to the stimulus of serotonin to the guinea pig ileum.[16] Our provisional observations indicate that lysergic acid diethylamide stimulates gastric secretion, while serotonin in large doses inhibits secretion.

SUMMARY

1. Exogenous serotonin in a dose up to 0.01 mg. per kg. per min. has no significant effect on gastric secretion of acid, but with a dose of 0.04 mg. per kg. per min. the Heidenhain pouch secretion becomes less acid.

2. The stimulus of reserpine to gastric acid secretion does not appear to be mediated by serotonin release.

3. Serotonin in a dose as low as 0.01 mg. per kg. per min. is a potent stimulus to intestinal motility in the dog. This response is characterized by tachyphylaxis and is not blocked by atropine, hexamethonium, or mepyramine.

4. Lysergic acid diethylamide potentiates the intestinal response to serotonin in contrast to an apparent central antagonism.

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