Yonsei Medical Journal
Vol .4, 1963

Effect of Serotonin on Gastric Secretion in the Dog*

Kyu Chul Whang,† Sa Suk Hong, Tai Soon Cho and Woo Choo Lee

Department of Pharmacology
Yonsei University College of Medicine, Seoul, Korea

(Received for publication: December 10, 1963)

ABSTRACT

Heidenhain pouch secretion in response to small dose of serotonin was studied in conscious dogs. A single subcutaneous injection of 0.5 to 2.0 mg of serotonin produced no changes in spontaneous fasting secretion; however, the milk-induced secretion was greatly inhibited by the same dose. This inhibition was abolished by treatment of dibenzyline or LSD(d-lysergic acid diethylamide). LSD alone enhanced the response of gastric secretion to milk. Constant intravenous infusion of serotonin, at levels of 3 to 10 μg/kg/min was associated with a significant increase in the volume of gastric juice aspirated from three anesthetized dogs, but the acidity of juice varied very slightly. However, when histamine is given as much as 0.8 to 3 μg/kg/min, a marked increase in both the volume and acidity was observed.

A significant elevation of mucin content in the juice obtained from the Heidenhain pouch was seen in dogs receiving a single subcutaneous injection of 1.0 mg of serotonin. In case of histamine, the mucin content of pouch juice was not relatively increased and merely an increase in the total amount of mucin secondary to the volume increase was seen. The observed increase in mucin by serotonin was inhibited by LSD, BOL (2-bromo-d-lysergic acid diethylamide) or dibenzyline, and mildly by morphine. Atropine or hexamethonium did not block the response of mucin production to serotonin. The gastrointestinal motility elicited by serotonin was not affected by these agents. It is felt that the receptor(s) responsible for the mucin production in the dog belongs to the D-receptor types postulated by Gaddum and Picarelli.

* This study was partly supported by the China Medical Board of New York. Inc., N.Y., U.S.A.
† Present address, Department of Surgery, Severance Hospital, Yonsei University, Seoul, Korea.

INTRODUCTION

White and Magee (1958) have reported that the continuous intravenous infusion of serotonin increased the secretion of mucin from the pyloric mucosa. Furthermore, they demonstrated that the serotonin effect on mucin secretion was not dependent on an increased motility of the pylorus, since the effect was present also in the everted gastric pouch, and was not abolished by hexamethonium which decreases gastric motility. Gaddum and Picarelli (1957) reported that there are two types of serotonin receptors, namely the M-receptor(nervous) and D-receptor (smooth muscle) in the guinea pig ileum. The nervous receptor is blocked by morphine or atropine, while the smooth muscle receptor is blocked by dibenzyline or d-lysergic acid diethylamide(LSD).

The present study attempts first to clearify the relationship between these receptors and gastric secretion and motility, and secondarily, to confirm the effect or role of serotonin on dietary induced gastric secretion in dogs.

METHODS

Ten healthy mongrel dogs, weighing 10 to 15 kg, were employed in these experiments. According to the technique described by Devito and Harkins (1959) we prepared denervated (Heidenhain) pouches in six dogs. In four animals we made innervated (Pavlov) pouches using the method of Hollander and Jemerin (1938) or Gregory et al (1942).

The dogs were maintained on a semi-fluid rice diet made of 90% starch and 10% protein. They were fasted for 15 hours bofore each experiment. Powdered whole milk was used as the standard food for the stimulation of gastric juice production. The dogs were fed portions containing 100 calories in a soluiton of milk powder diluted with distilled water to a volume of 200 ml. Two grams of sodium chloride were added to each 200 ml. In order that the effects of calories and volume might be eliminated in these studies we used other foods in an equi-caloric and equi-volumetric basis in some of the animals. The effects of the subcutaneous injection of serotonin creatinine sulfate, histamine (base), and other agents on gastric secretion induced by the standard milk preparation were examined. The secretion volume and degree of acidity were determined at thirty minute intervals. The free and total acidity of the gastric juice were measured in 1.0 ml aliquots by titration of the sample with N/20 NaOH, using Töpfer's reagent and Phenolphthalein as indicators. Total acidity was considered to be a more accurate reflection of the parietal cell secretion than free acidity(shay et al. 1950). The pro-tein content of the gastric juice(gastric mucin)was also determined by the biuret reaction.

After the dogs were anesthetized using pentobarbital sodium, they were prepared for an acute series of testing of the effect of serotonin on the volume and acidity of the gastric secretion by inserting and fixing a Levine tube in the stomach and by ligating the pylorus.

In five dogs gastric and duodenal motility and intraluminal water pressures were determined after tubes with attached balloons were passed through a gastrostomy opening into both the stomach and the duodenum. Kymographic recording were made over periods of several hours. Also, simultaneously,

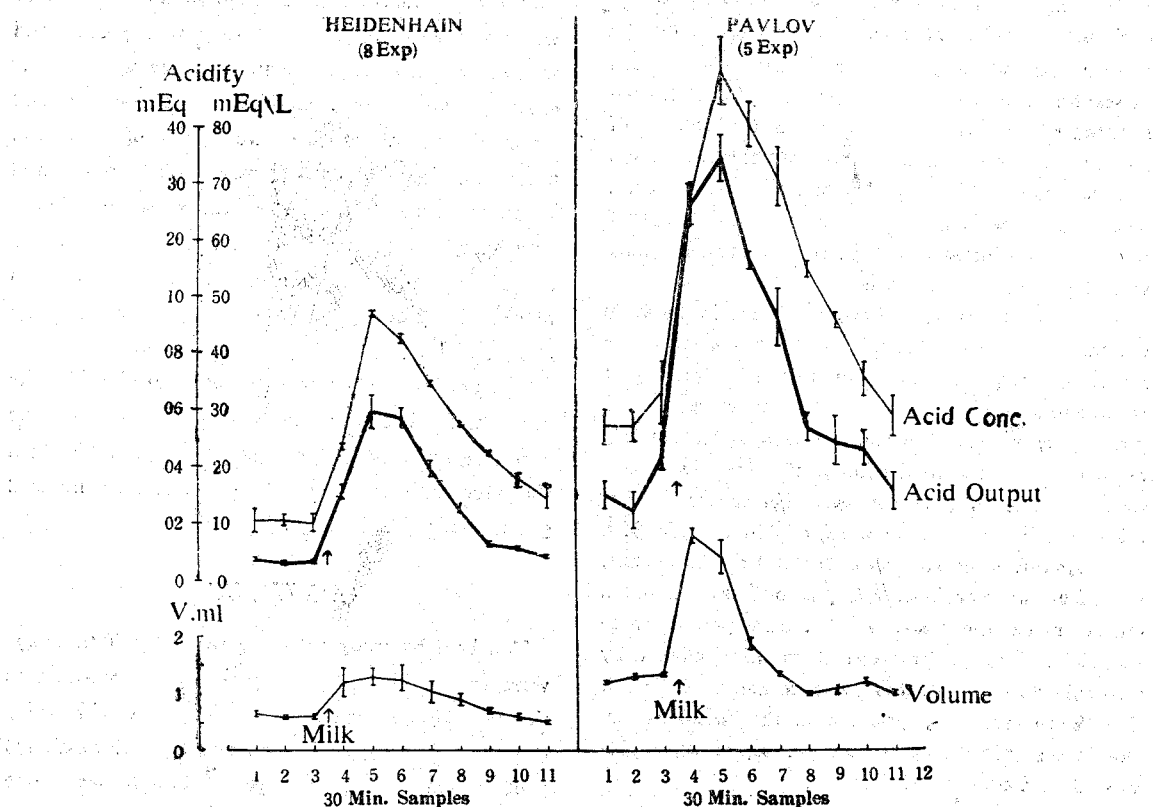


Fig. 1. Effect of milk on gastric secretion of Heidenhain and Pavlov pouches.
The volume and acid secretion is moderately increased after oral administration of milk containing 100 calories in Heidenhain pouch. The increases of volume and acid secretion due to same quantity of milk are high in Pavlov pouch and the patterns of gastric secretion due to milk and histamine in this pouch are somewhat similar.

changes in blood pressure and in respiration were recorded.

RESULTS

Gastric Secretion:

In most experiments the Heidenhain pouch dogs showed a spontaneous fasting secretion of 0.5 to 1.0 ml per 30 minutes of a clear, viscous fluid which contained practically no free acid, and 0.01 to 0.03 mEq of total acid. Milk stimulated the production of gastric juice(Fig. 1). In dogs having the denervated pouch the pattern of response to milk feeding was quite consistent. Secretion lasted about 4 hours with the peak of secretion being reached in the second half hour after feeding. After four hours there was a negligible output of secretion.

Following the subcutaneous administration of histamine, the peak of the gastric secretion was observed in the first half hour, and the output of secretion lasted about two hours (Fig. 2)·The pattern

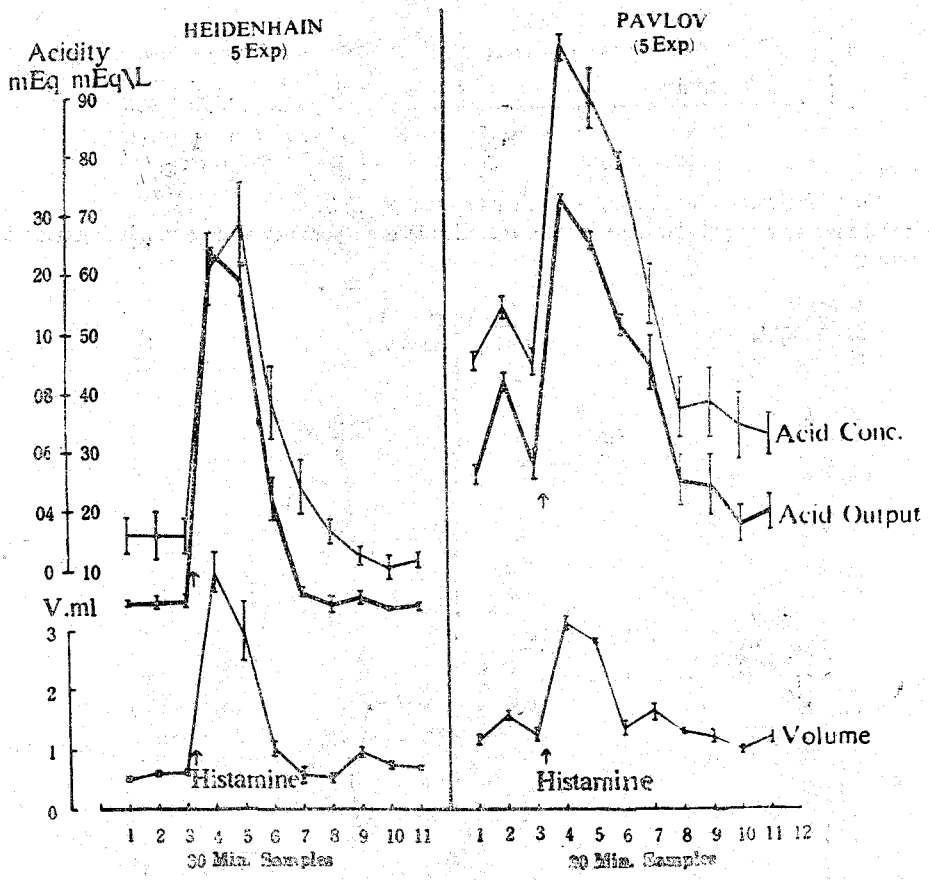


Fig. 2. Effect of histamine on gastric secretion of both pouches.
Note a significant increase in acid secretion in both Heidenhain and Pavlov pouches after single injection of 0.2 mg of histamine. It can be seen that the response of acid secretion to histamine is greater in innervated Pavlov pouch.

of response of secretion to the stimulation of milk in the Pavlov pouch dogs was quite similar to that seen in the histamine stimulation of both Heidenhain and Pavlov pouch dogs. However, the pattern was more uniform in the Heidenhain pouch dogs.

In 15 experiments using Heidenhain dogs and 5 experiments using Pavlov dogs the single subcutaneous injection of 0.5~2.0 mg of serotonin produced little changes, or even a decrease, in both the volume and degree of acid output(Fig. 3). Furthermore, serotonin greatly inhibited the milk-induced secretion in the Heidenhain pouch dogs(Fig. 4). This inhibition was absent when histamine was used to stimulate the gastric secretions in the same animals.

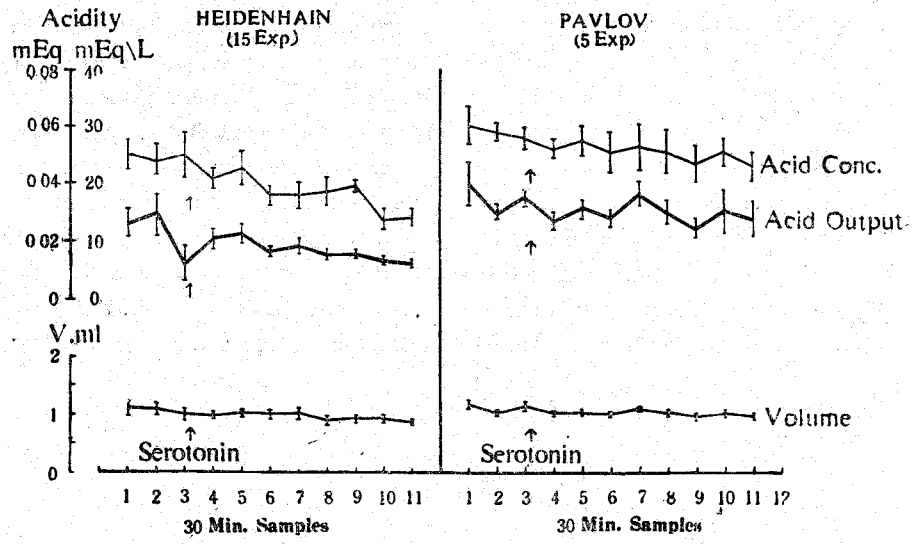


Fig. 3. Effect of serotonin on fasting secretion of both pouches.
Note no change or a slight decrease in acid secretion in both pouches after a single injection of 0.5 to 2.0 mg of serotonin.

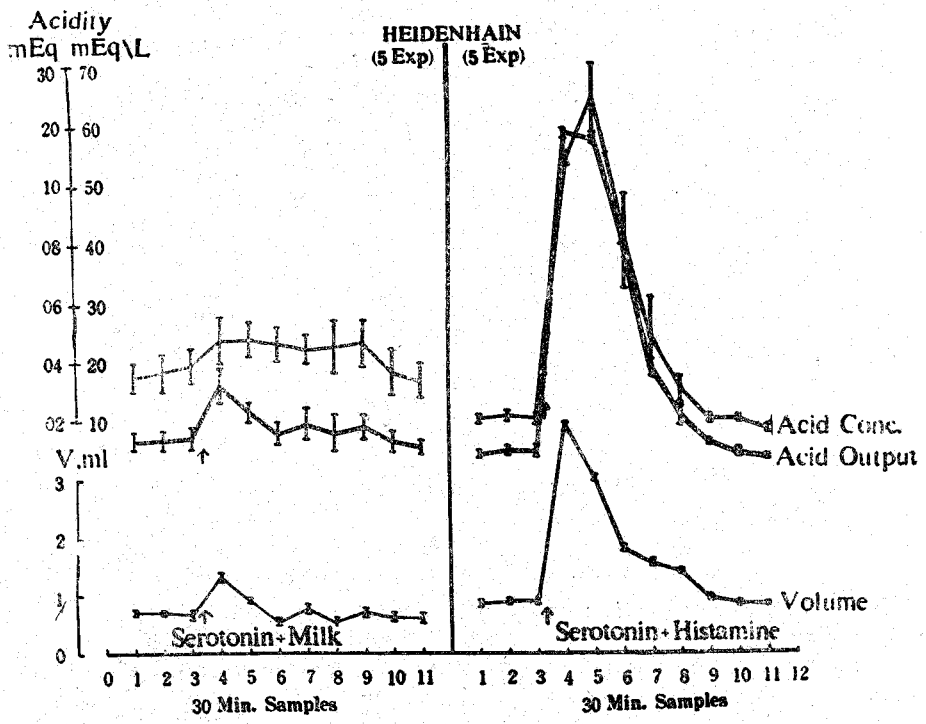


Fig. 4. Effect of serotonin on milk or histamine induced gastric secretion of Heidenhain pouches.
Note a significant inhibition in volume and acid secretion in Heidenhain pouch after single injection of 1.0 mg of serotonin when milk was used to stimulate the gastric secretion, however, the inhibition was absent when histamine was used in place of milk.

The milk stimulated gastric secretion was blocked by the administration of 1.0 mg of atropine, 10 mg of hexamethonium or either plus 1.0 mg of serotonin and partly by the administration of 20 mg of morphine alone or plus serotonin. It was not altered by the administration of 50 mg of dibenzyline and

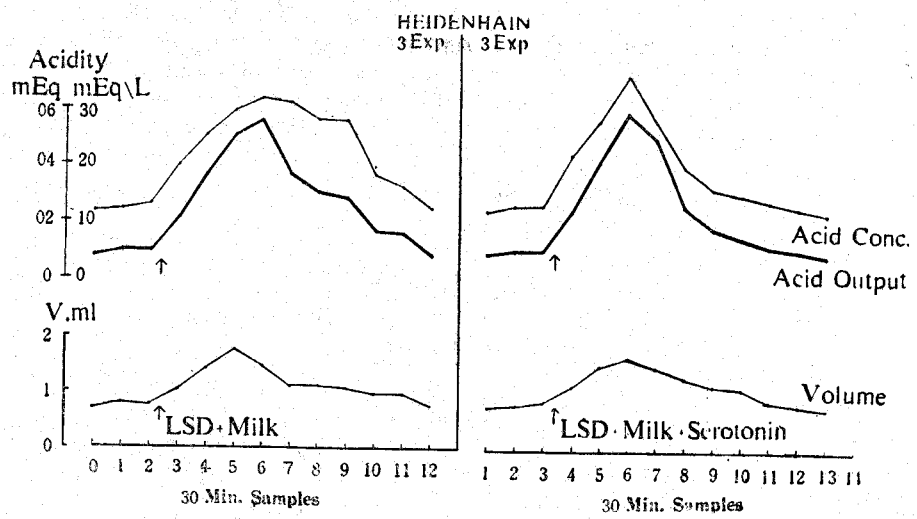


Fig. 5. Effect of LSD on milk or milk plus serotonin induced gastric secretion in Heidenhain pouches. Milk response is enhanced following subcutaneous injection of 1.0 mg of LSD. Inhibition of milk response by serotonin is dismissed following administration of LSD.

it either was not altered or was enhanced by LSD, 10 mg subcutaneously. Following administration of dibenzyline or LSD the gastric secretory response to milk was not influenced by serotonin, which alone was an inhibitor of the milk induced gastric secretion in this experiment(Fig. 4, 5). The milk induced gastric secretion was enhanced by the administration of 1.0 mg of pilocarpine and reduced by 0.3 mg of epinephrine, respectively. Dietary beef in an equi-caloric and equi-volumetric basis produced rapid increase of gastric secretion in both volume and acidity. Rice diet produced smaller

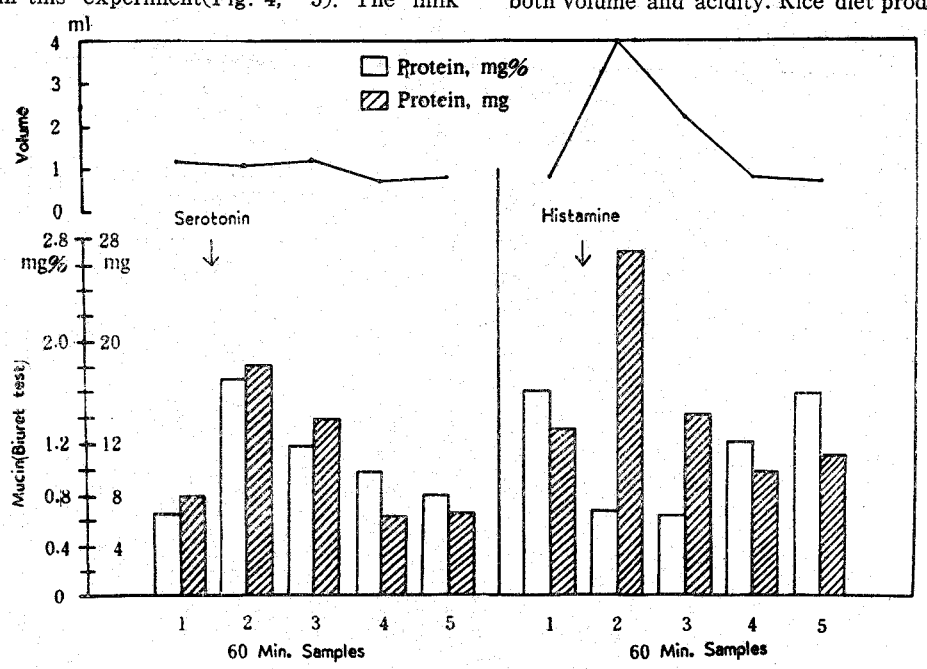


Fig. 6. Effect of serotonin and histamine on mucin production in Heidenhain pouches. Note a significant increase in mucin production (with biuret reaction) in Heidenhain pouches after subcutaneous injection of 1.0 mg of serotonin. Mucin content is decreased following injection of 0.2 mg of histamine. The rise in total mucin after histamine is due to increased gastric volume in water and acid

increase of gastric secretion.

The continuous intravenous administration of serotonin, at levels of 3-10 μg per kg per minute was associated with a significant increase in the volume of gastric juice aspirated from three dogs which were anesthetized with pentobarbital. The degree of acidity varied only a little. On the contrary to the serotonin effect, histamine given at dose levels of 0.8 to 3 μg per kg per minute caused a marked increase both in the volume and in the degree of aci-

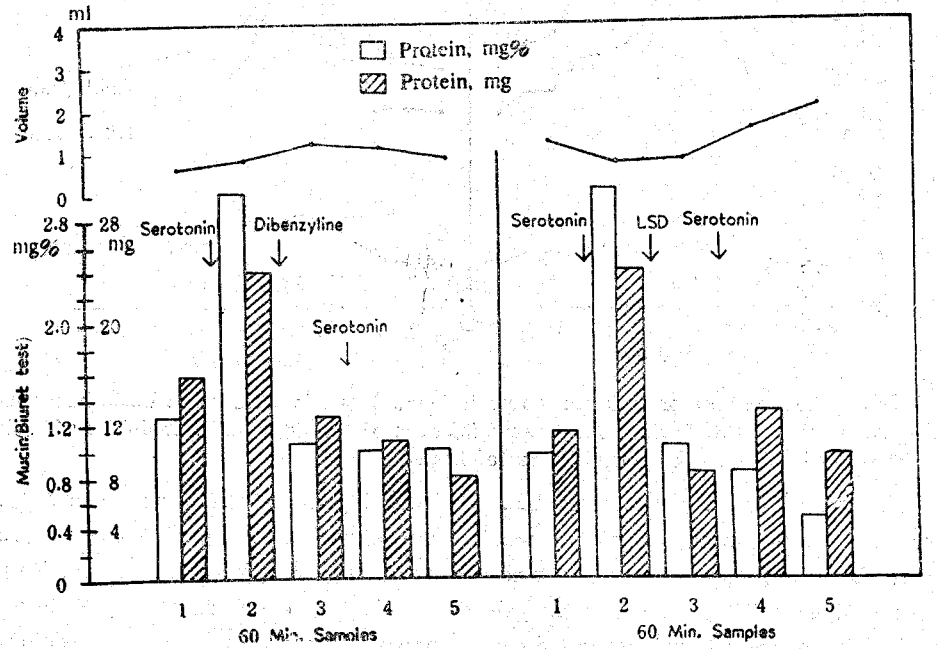


Fig. 7. Effect of dibenzyline and LSD on serotonin induced mucin production in Heidenhain pouches. Mucin production following serotonin was completely blocked by the subcutaneous injection of 50.0 mg of dibenzyline or 1.0 mg of LSD.

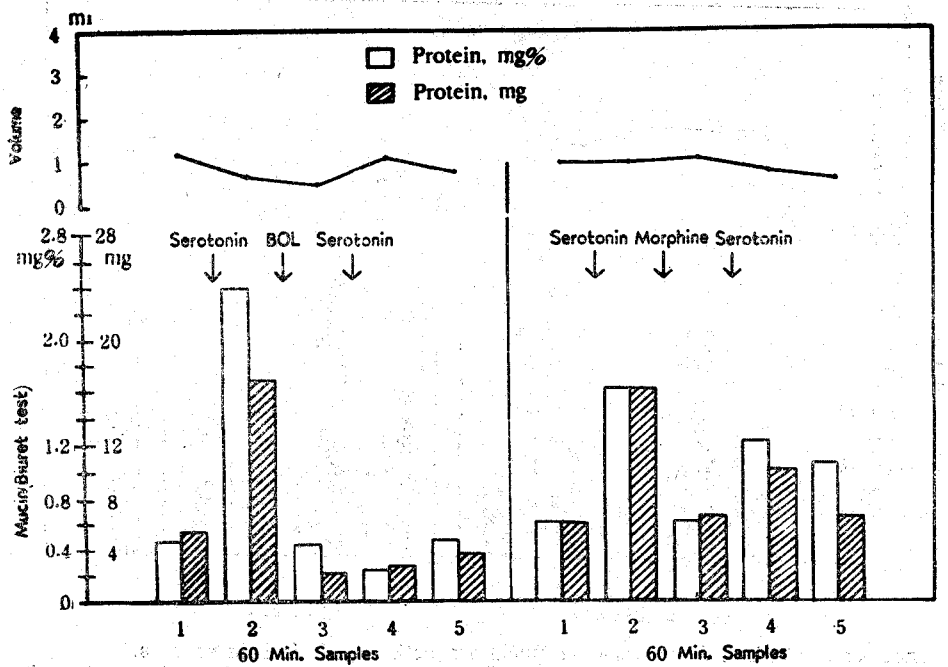


Fig. 8. Effect of BOL and morphine on serotonin induced mucin production in Heidenhain pouches. 20.0 mg of BOL completely blocked mucin production due to serotonin. Serotonin induced mucin production is not fully blocked by 25.0 mg of morphine.

dity of the gastric juice in these same three animals.

2) Gastric Mucin Secretion :

There was a significant increase in the mucin content of gastric juice obtained the Heidenhain pouch following a single subcutaneous injection of 1.0 mg of serotonin(Fig. 6). However, following the administration of 0.2 mg histamine or of histamine plus 1.0 mg of serotonin, the mucin content was not relatively increased. There was an increase in the total amount of mucin secondary to the increased total volume of the gastric juice. This increase inthetotal mucin production and in the degree of acid output paralleled the increase in the total gastric secre

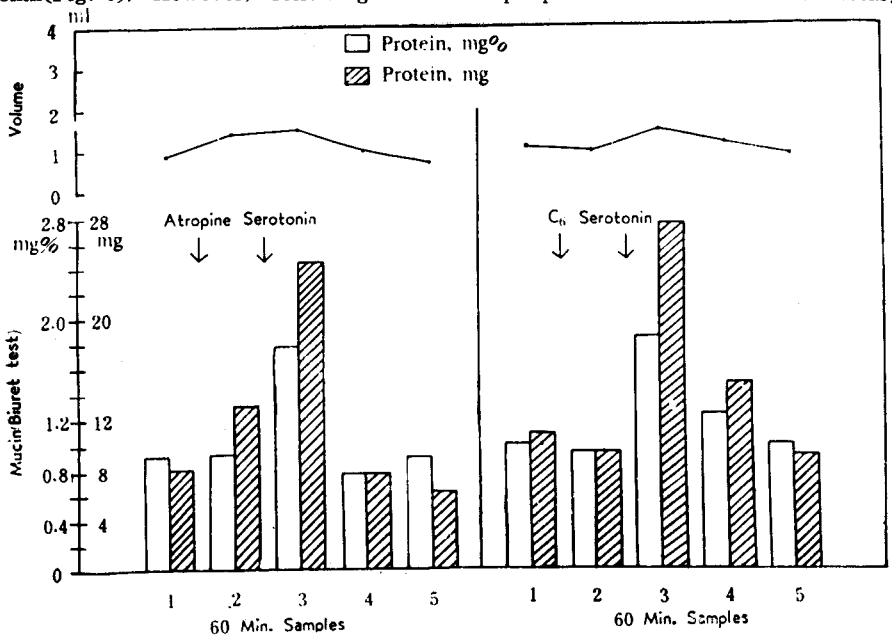


Fig. 9. Effect of atropine and hexamethonium on serotonin induced mucin production in Heidenhain pouches. Serotonin effect on mucin production was not influenced following 1.0 mg of atropine or 10.0 mg of hexamethonium.

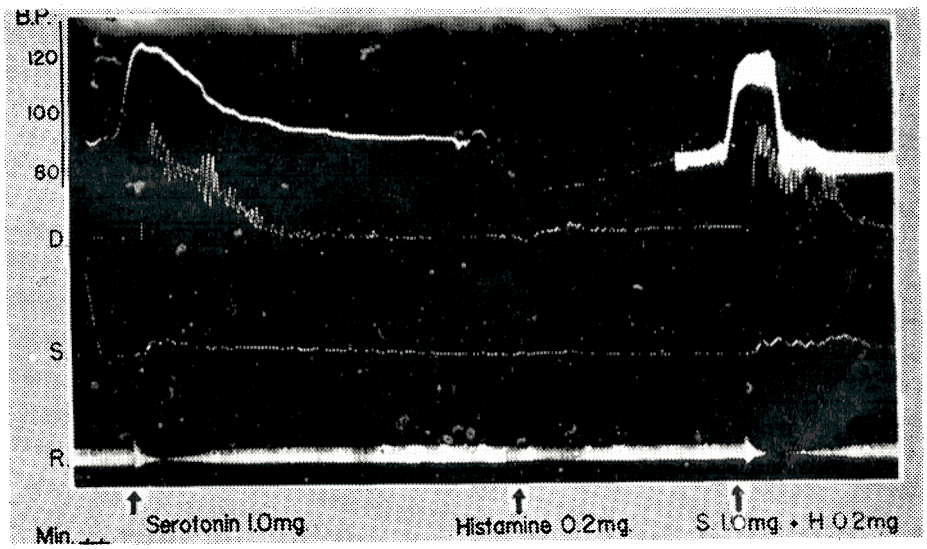


Fig. 10. Kymographic tracing of duodenal(D) and gastric(S) motility using balloons in anesthetized dogs. Blood pressure(B.P.) and respiration(R) were also recorded.

Single intravenous injection of serotonin produced an immediate increase in gastric and duodenal tonus and motility. Blood pressure increased and hyperpnea after the apnea were appeared following injection of serotonin. Histamine did not affect the serotonin response and histamine alone decreased the blood pressure.

tion volume secondary to the histamine stimulation.

In the Heidenhain pouch dogs the stimulation of mucin production following the administration of serotonin was strikingly inhibited by the subcutaneous injection of 1.0 mg of LSD, of 20 mg of 2-bromo-d- lysergic acid diethylamide (BOL) or of 50 mg of dibenzyline(Fig. 7, 8). The subcutaneous injection of 25 mg of morphine produced a mild inhibition of the serotonin effect of stimulation of mucin production in the gastric juice. 1.0 mg of atropine or 10 mg of hexamethonium did not block the increased production of mucin following serotonin injection (Fig. 9). Nevertheless, dibenzyline, LSD, BOL, morphine, atropine or hexamethonium alone, did not affect on gastric mucin production.

3) Gastric Motility:

The single administration of 0.5 mg of serotonin

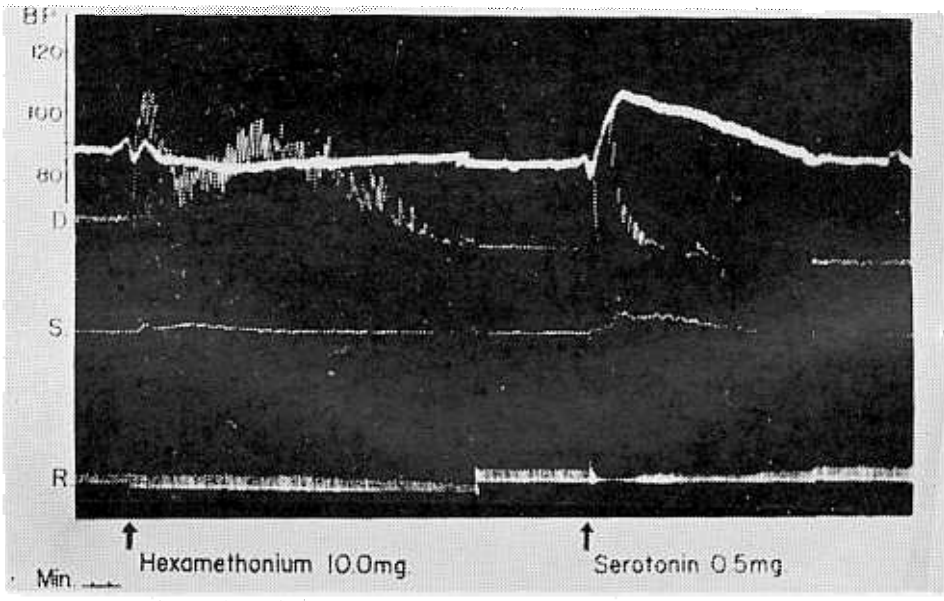
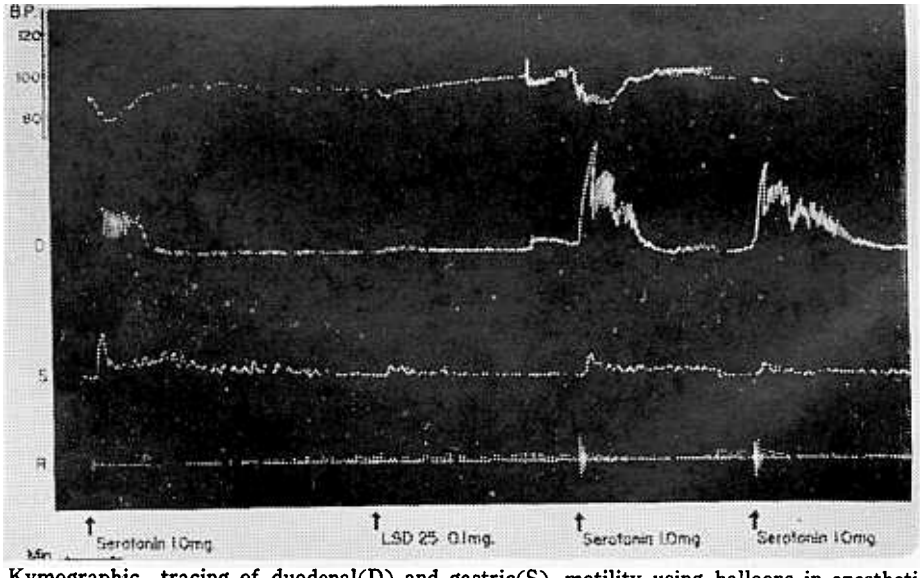


Fig. 11. Kymographic tracing of duodenal(D) and gastric(S) motility using balloons in anesthetized dogs. Blood pressure(B.P.) and respiration(R) ware also recorded.
Hexamethonium did not inhibit serotonin response. Blood pressure was decreased after serotonin in this animal.



Eig. 12. Kymographic tracing of duodenal(D) and gastric(S) motility using balloons in anesthetized dogs. Blood pressure(B.P.) and respiration(R) were also recorded.
Injection of LSD did not inhibit the serotonin response.

produced an immediate increase in gastric and duodenal tonus and motility in the anesthetized dogs (Fig. 10). The arterial blood pressure also rapidly increased. A period of apnea was followed by a transient hyperpnea. The increased motility, elicited by the serotonin, usually ceased within 10 minutes, and gastrointestinal motility returned to normal.

The effect of several pharmacologic agents in modifying the gastrointestinal response to serotonin was examined. The intravenous administration of 1.0 mg of atropine did not inhibit the serotonin response. Intravenous administration of 10 mg of hexamethonium(Fig. 11), or 20 mg of morphine stimulated duodenal motility but had no effect on gastric motility. However, the response of duodenal motility to serotonin was not inhibited by hexamethonium or morphine. A single intravenous injection of 1.0 mg of LSD caused no response in gastroduodenal motility. Furthermore, there was no inhibitory action to serotonin induced motility(Fig. 12). The intravenous administration of 0.2 mg of histamine did not affect on increased duodenal motility caused by serotonin. However, administration of histamine plus serotonin, raised arterial blood pressure.

DISCUSSION

The effect of serotonin on gastic secretion is still controversial. Smith(1957) or Black et al (1958)has mentioned that serotonin inhibited the secretion of acid in response to histamine stimulation using anesthetized dogs after total gastric fistula and pyloric ligation. However, White et al. (1959) could not find any effect of serotonin on histamine stimulated volume and acid production in either of the Heidenhain or Pavlov pouches, but increased pepsin in Pavlov pouches. Cali and Cordova (1956) noticed that serotonin sharply stimulated acid gastric secretion but had no action on water secretion. Recently Sosin et al (1962) noticed that serotonin given concomitantly with histamine by constant intravenous infusion enhanced acid secretion from canine Heidenhain pouches.

In the present experiment serotonin with a single subcutaneous injection greatly inhibited the milk induced pouch secretion in dogs and this inhibition was absent when histamine was used to stimulate the gastric secretion in the same animals. Furthermore, a single dose of serotonin produced little changes, or even a decrease in spontaneous fasting secretion in either of the pouches. These indicate that serotonin with even a single small dose appears to have an inhibitory mechanism on the gastric mucosa resulting in the spontaneous or food induced gastric secretion, however, when once full parietal secretion takes place, the mechanism seems to be no more effective.

LSD, dibenzyline and BOL which are known as serotonin inhibitors in some tissues(1961)did not influence the gastric secretory response to milk. However, the pretreatment of these agents abolished the inhibitory effect of milk response elicited by serotonin. In the case of LSD the milk response of gastric secretion was even enhanced. Atropine and hexamethonium alone, or either plus serotonin blocked the response to milk induced gastric response, and morphine also blocked but partially. This effect of an anticholinergic or a ganglionic blocking agent on gastric secretion is well recognized.

In the serotonin inhibitors Haverback et al. (1957) with their provisional observation stated that LSD stimulated gastric secretion in dog. Resnick et al. (1962) with their clinical observation reported that 1-methyl-d-lysergic acid butanolamide bimaleate (UML-491), which is another chemically related inhibitor of serotonin, also stimulated gastric secretory function in man. From these, together with our findings, it is obvious that the efficacy of serotonin blocking agents to gastric function is variable.

In their continuous infusion experiment, White and Magee(1958) have shown that serotonin stimulated the production of pyloric mucin through a direct action on the mucosa,while Black et al.(1958) have shown that this is a diffuse effect on the stomach. However, these results are only obtained under the special occasions, using extraordinarily a large amount of serotonin with continuous intravenous administration. Not only continuous infusion, but a single subcutaneous injection induced a significant increase in the mucin content of gastric juice in our experiment. The mucin content was not relatively incre-

ased as volume following the administration of histamine or of histamine plus serotonin, namely an increase in the total amount of mucin only secondary to the increased total volume of the gastric juice. The increase in the total mucin production and in the degree of acid output paralleled the increase in the total gastric secretion volume secondary to the histamine stimulation. This fact, together with the abundant presence of the amine in gastrointesinal mucosa of many species (1954) raise the interesting speculation that it may exert as the specific stimulator of the mucus-producing cells as like histamine being of the acid-producing cells in digestive function.

The increase in mucin by serotonin was inhibited by LSD, BOL or dibenzyline and mildly by morphine. Atropine or hexamethonium did not block the response of mucin production to serotonin.The gastrointestinal motility elicited by serotonin was of independence to these agents. Comparing the finding of mucin production to the response of gastric secretion in volume and acidity by serotonin one can think of a certain differenciated sensitivity of the amine to mucosal cells, e. g., mucus-producing cells that respond to serotonin-action are stimulated by serotonin; acid-producing cells are inhibited. Nevertheless, serotonin action of above types in gastric secretion was completely abolished by LSD, BOL or dibenzyline. Gaddum and Picarelli (1957) demonstrated that there are two types of receptors sensitive to serotonin, namely the M-receptor (nervous) and the D-receptor (smooth muscle) in the guinea pig ileum. The nervous receptor is blocked by morphine or atropine, and the smooth muscle receptor is blocked by dibenzyline or LSD. According to the serotonin receptor concept it is felt that the receptor(s) responsible for gastric secretion particularly the mucin production in the dog belongs to the D-receptor types.

Acknowledgments: We wish to express our thanks to Dr. Roberta G. Rice, for her help in preparing the manuscript; and to Dr. K.S. Min, for his encouragement in performing this experiment.

REFERENCES

Black, J. W., E. W. Fisher and A. N. Smith: *J. Physiol., Lond. 141 : 27, 1958.*

Cali, G. and C. Cordova: *Progr. med., Paris, 12 : 752, 1956. Cited by I.H. Page; Serotonin (5-hydroxytryptamine). Physiol. Rev. 38 : 277, 1958.*

DeVito, R. V. and H. N. Harkins: *J. Appl. Physiol. 14 : 138, 1959.*

Erspamer, V.: *Pharmacology of indolealkylamines. Pharmacol. Rev. 6 : 425, 1954.*

Gaddum, J. H. and Z. P. Picarelli: *Brit. J. Pharmocol. 12 : 323,1957.*

Gregory, R.A., G.A. Hallenbeck and C. F. Code: *Proc. Soc. Exper. Biol. & Med. 49 : 400, 1942.*

Gyermek, L.: 5-hydroxytryptamine antagonists. Pharmacol. Rev. *13 : 399, 1961.*

Haverback, B. J., C. A. M. Hogben, N. C. Moran and L. L. Terry: *Gastroenterology 32 : 1058, 1957.*

Hollander, F. and E. E. Jemerin: *Proc. Soc. Exper. Biol. & Med. 39 : 87, 1938.*

Resnick, R. H., C. F. Adelardi. and S. J. Gray: *Gastroenterology 42 : 22, 1962.*

Shay, H., S. A. Komarov and J. E. Berk: *Gastroenterology 15 : 110, 1950.*

Smith, A.N.: *The effect of* 5-*hydroxytryptamine on gastric secretion. p. 183-190. In G.P. Lewis(Editor), 5-Hydroxytryptamine; Proc. of a symposium held in London on Ist-2nd April, 1957, Pergamon Press, London, 1958.*

Sosin, H., D.M. Nicoloff, E. T. Peter, A. I. Walder. and O. H. Wangensteen: *Fed. Proc. 21(2) : 264, 1962.*

White, T. T. and D. F. Magee: *Gastroenterology 35 : 289, 1958.*

White, T. T., R. A. MacAlexander and D. F. Magee: *Surg., Gynec. & Obst. 109 : 168, 1959.*