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Effect of Exogenous Serotonin on Intragastric pH and its Influence on Serum Gastrin Levels in Rats

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The effect of various doses of serotonin on the serun gastrin levels and intragastric pH in rats, was studied. After serotonin administration of 10 mg/kg i.p., a significant increase in serum gastrin levels was noted, as well as a strong increase in the intragastric pH. It was also observed that a lower dose, 5 mg/kg i.p., significantly increased serum gastrin levels, while intragastric pH was not affected, remaining at baseline values throughout the study. These results suggest that the increase observed in serum gastrin levels after administration of exogenous serotonin is not mediated by increase in intragastric pH.

The digestive system of the rat has been noted to contain at least 60 per cent of total body serotonin (4). It was originally found in the gastric mucosa of the rabbit (25), but subsequently it has been identified throughout the gastrointestinal tract in many diverse species (5, 7, 11, 19, 24). In mammals, serotonin is localized primarily in the enterochromaffin cells of the gastrointestinal mucosa (6, 22).

In a previous report, we showed that exogenous serotonin enhances the serum gastrin levels in rats (13). The mechanism of this action is unknown, but is questionable whether serotonin possesses a direct effect on the *G* cells, or whether this effect is secondary to other factors. It is known that serotonin and its precursor 5-hydroxytryptophane administered in very high doses inhibit gastric acid output of several animal species (1, 2, 12, 15, 21), and it has also been reported that gastric alkalinization increases antral gastrin release (3, 14, 17). These results give support to the possibility that the increase observed in the gastrin serum levels after serotonin administration is secondary to the decrease observed in the gastric acid output.

The purpose of this work was to examine if the enhancement observed in the serum gastrin levels depends on the increase observed in the intragastric pH after serotonin administration.

Materials and Methods

Male Charles River rats, 200-250 g, were caged (5 per cage) under controlled temperature conditions (22 ± 2° C) on a standard light-dark cycle (14 h light and 10 h dark). The rats were starved 24 h before use, but allowed free access to water until 2 h before the experiments. The serotonin creatinine sulfate (Sigma) was dissolved in a 2 % aqueous suspension of carboxy methyl cellulose (Sigma) to the desired concentration and injected intraperitoneally. The volume used was always 2 ml.

At various time periods after administration of 0.05, 0.1, 1, 5 or 10 mg/kg of serotonin in the experimental groups and carboxy methyl cellulose in the control group, the rats were anesthetized with dyethyl ether (Merck). The abdominal cavity was opened and each animal was exsanguinated by withdrawing blood from the abdominal aorta; immediately after, the intraluminal gastric pH was obtained by introduction of a sealed glass electrode (type 406 M3, Dr. W. Ingold Ltd., Switzerland) into the stomach through a small incision in the gastric fundus. The pH lecture was taken by pH meter (Orion Res. Co., England).

The sera were divided in aliquots and stored at —20° C until assayed. Serum gastrin concentration was measured in duplicate by a specific and sensitive radioimmunoassay, as described by YALOW and BERSON (26) and purchased from *Cea Ire Sorin* (Gastrin radioimmunoassay kit). Antibodies of gastrin were obtained by immunizing rabbits with synthetic human gastrin I (G-2-17, Imperial Chemical Industries, Macclesfield, England) and used in a final dilution of 1 : 53,000. The within assay variation determined by repeated measurements of two pools of sera ranged from 3.0 to 6.2 %, and was 6.1 to 10.1 % between assay variations. The immunoassay system was sufficiently sensitive to detect 10 pg/ml of serum gastrin.

The significance of the mean values for serum gastrin was evaluated by Kruskal Wallis test. P values less than 0.05 were considered significant.

Results

The effect of various doses of serotonin on the serum gastrin levels and intragastric pH in normal rats was investigated. A serotonin dose of 10 mg/kg i.p., caused a significant increase in the serum gastrin ($p < 0.001$) as compared with the basal values. The maximum increase appeared at 105 min after the treatment (fig. 1a). It was also observed that intragastric pH increased by approximately 5 units, indicating a strong decrease in gastric acidity.

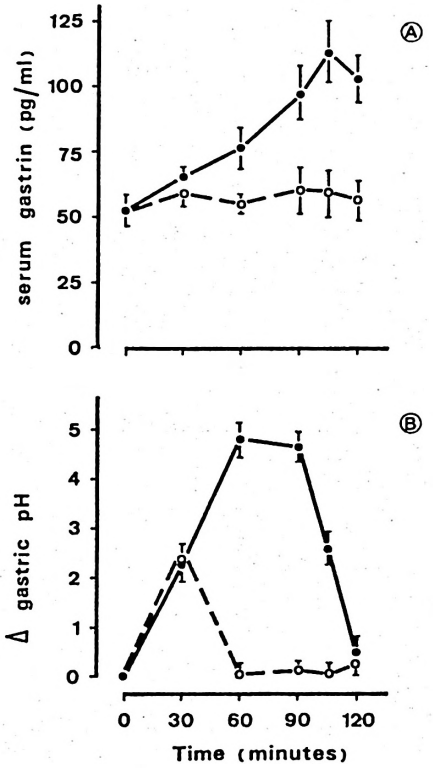

Fig. 1. *Serum gastrin levels (A) and Δ intragastric pH (B), in rats after 10 mg/kg of serotonin (●—●) and serotonin solvent administration (○— —○).*
Each value is the mean ± S.D. from 10 rats.

The maximum increase appeared from 60 to 90 minutes (fig. 1b).

A lower dose, 5 mg/kg i.p., also enhanced the serum gastrin levels. The peak increase ($p < 0.001$) above the baseline, appeared 105 min after the treatment (fig. 2a). Whilst, a slight variation in the intragastric pH from baseline was observed, throughout the study (fig. 2b).

Small doses of serotonin (0.05, 0.1 or 1.0 mg/kg i.p.) do not alter significantly either the serum gastrin levels or the intragastric pH at 90 and 105 minutes after serotonin administration (table I).

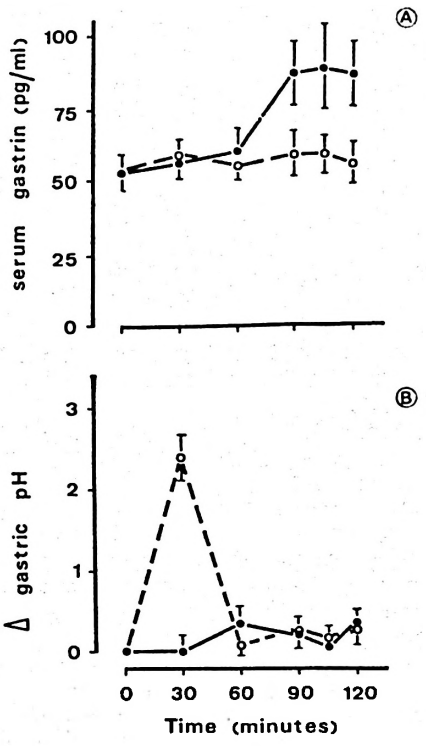

Fig. 2. *Serum gastrin levels (A) and △ intragastric pH (B), in rats after 5.0 mg/kg (●—●) and serotonin solvent administration (○– –○).* Each value is the mean ± S.D. from 10 rats.

Discussion

The increase of the intragastric pH observed after administration of 10 mg/kg of exogenous serotonin do not seem to be responsible for the increase observed in the serum gastrin levels, since the gastrin levels also enhance significantly after administration of 5 mg/kg of exogenous serotonin without altering the basal intragastric pH and, moreover, an increase of the intragastric pH in control rats without affecting the serum gastric was also observed. These observations are in agreement with LEVINE *et al.* (18) who observed that the alkalinity of the antral pH does not significantly stimulate the basal gastrin level. According to the results of this study it would appear that increase in the serum gastrin levels after serotonin administration are not related to the intragastric pH. On the other hand. SHASKAN and SNYDER (20) have shown that after the administration of serotonin in higher

Table I. *Serum gastrin (pg/ml) and gastric pH after various doses of serotonin.* The values are means ± S.D. N = 10. Basal serum gastrin: 53.41 ± 5.81 pg/ml. Basal intragastric pH: 1.78 ± 0.16.

Serotonin administration:	90 minutes		105 minutes	
Dose of serotonin (mg/kg I.p.)	Serum gastrin	Intragastric pH	Serum gastrin	Intragastric pH
0 *	60.86 ± 9.00	2.04 ± 0.19	60.10 ± 8.42	1.97 ± 0.16
0.05	59.10 ± 6.01	1.78 ± 0.15	56.32 ± 7.67	1.81 ± 0.17
0.1	54.06 ± 8.81	1.87 ± 0.17	63.13 ± 11.33	1.86 ± 0.15
1.0	56.61 ± 11.15	1.90 ± 0.13	57.32 ± 7.29	1.94 ± 0.14

* Control rats.

doses, it accumulates into catecholaminergic neurones, and serotonin and catecholamines compete for the same uptake sites. Furthermore, it was shown that serotonin caused a dose-dependent release of labelled noradrenaline from the adrenergic neurones (8-10) and that gastrin secretion is regulated by the adrenergic receptor mechanism; stimulation of beta adrenergic enhances its secretion, while stimulation of alpha receptors inhibits it (16, 23). In agreement with these studies it is possible that the effect of exogenous serotonin on serum gastrin levels is due to displacement of noradrenaline in the gastric adrenergic neurones. To clarify this problem further studies are necessary.

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Resumen

Se estudian los niveles séricos de gastrina y el pH intragástrico en ratas después de la administración intraperitoneal de diversas dosis de serotonina. Se observa que, a la dosis de 10 mg/kg, tanto los niveles séricos de gastrina como el pH intragástrico ascienden significativamente en estos animales. Mientras que, cuando la dosis de serotonina administrada es menor, 5 mg/kg, los niveles séricos de gastrina ascienden significativamente, pero los valores del pH intragástrico no se modifican respecto de los valores basales. Todo ello parece indicar que el aumento observado en las concentraciones séricas de gastrina, después de la administración de serotonina, no es mediatizado por el ascenso observado en el pH intragástrico.

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