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Possible Central Antisecretory Action of Exogenous Serotonin in Rats

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The effect of exogenous serotonin (10 mg/kg i. p.) in rats pretreated and unpretreated with 6-hydroxydopamine, propranolol or with α-methyltyrosine on intragastric pH was studied. It was observed that after serotonin administration, the intragastric pH increased by approximately five units. The chemical sympathectomy by administration of 6-hydroxydopamine did not alter significantly either basal intragastric pH or the serotonin-induced increase of intragastric pH. The administration of propranolol did not alter significantly the basal intragastric pH, whilst the pretreatment with propranolol abolished the antisecretory effect of serotonin. Repeated dosages with α-methyl tyrosine did not alter the basal intragastric pH, but inhibited the effect of serotonin on intragastric pH. These results seem to indicate that the antisecretory effect of exogenous serotonin on gastric acid output, is caused by the inhibition of the vegetative brain centres responsible for the secretory activity of the parietal cells. Furthermore, it is suggested that the antisecretory effect of serotonin is mediated by a release of noradrenaline from the brain adrenergic neurones.

Serotonin has been shown to be widely distributed in various parts of the gastrointestinal tract in man and animals (8-10, 15, 25, 28, 32) and it has been described as a strong inhibitor of basal gastric secretion in experimental animals (2, 3, 16, 20, 27). However, the mechanism responsible for this antisecretory action is still unknown. It seemed definite that the antisecretory effect of serotonin was not related to its vascular properties (7) or to a direct effect on gastric parietal cells (17). Recently, BUGAJSKI *et al.* (4) and MISHER and BROOKS (22) have postulated that this action may be exerted by centrally inhibiting the ventromedial hypothalamic structures responsible for gastric volume and acid output, as this amine, has been shown at least in part, to cross the blood-

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brain barrier (4-6). It has also been shown that after administration of higher doses serotonin accumulates into catecholaminergic neurones, it competes with catecholamine for the same uptake sites (26) and causes a dose-dependent release of labelled noradrenaline (12-14). Furthermore, the catecholamines are described as inhibitors of gastric secretion in experimental animals (1, 18, 23). These studies seem to support the previously reported hypothesis that, in rats, the antisecretory effect of serotonin depends on a balance between adrenergic and serotoninergic mechanisms (11).

The purpose of this study was to examine if the serotonin-induced increase of the intragastric pH depends on the displacement of noradrenaline in the peripheral or central adrenergic neurones. Subsequently, the intragastric pH after administration of exogenous serotonin separately or in combination with substances blocking the noradrenaline action, was investigated in rats.

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 the experiments. Serotonin creatinine sulfate, 6-hydroxydopamine hydrobromide, *dl*-propranolol-HCl, α-methyltyrosine methyl-ester-HCl and carboxy methyl cellulose were purchased from the Sigma Chemical Company. All drugs were dissolved in a 2 % aqueous suspension of carboxy methyl cellulose to the desired concentration and injected intraperitoneally. The volumes used were always 2 ml.

The rats were divided into 5 groups according to the experimental programme. In all animals the intragastric pH was determined after administration of serotonin in normal rats or in rats pretreated with other substances. *Group A:* 10 mg/kg of serotonin. *Group B:* an identical dose of serotonin was administered in rats pretreated with 6-hydroxydopamine (200 mg/kg, one week before the test). *Group C:* the same dose of serotonin was administered in rats pretreated with propranolol (8 mg/kg, 150 min before the pH lecture). *Group D:* an identical dose of serotonin was injected in rats previously treated with repeated dosages of α-methyltyrosine (50 + 100 + 50 mg/kg, 25, 18 and 2 h before the pH lecture). *Group E:* the control rats received the solvent of drugs.

At 30, 60, 90 and 120 minutes after serotonin administration 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 the intraluminal gastric pH was obtained by introducing a sealed glass electrode (type 406 M3, Dr. W. Ingold Ltd., Switzerland) into the stomach through a small incision in the rumen. The pH lecture was taken with a pH meter (Orion Res. Co., England).

Results

The intragastric pH after the administration of serotonin separately or in rats pretreated with 6-hydroxydopamine, propranolol or α-methyltyrosine is shown in figure 1. It was observed that after the administration of 10 mg/kg i.p. of serotonin the intragastric pH increased by approximately 5 units, indicating a strong decrease in gastric acidity. The maximum increase appeared from 60 to 90 minutes. An increase in the intragastric pH was also observed at 30 min after the solvent administration in the control rats, but intragastric pH remained at baseline after this time.

The chemical sympathectomy by administration of 6-hydroxydopamine (200 mg/kg i.p., one week before the test) did not alter significantly either the basal intra-

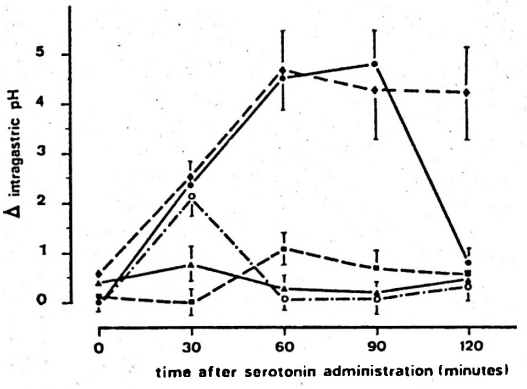

Fig. 1. *Influence of exogenous serotonin alone or combinated with 6-hydroxydopamine, propranolol or α-methyltyrosine in intragastric pH in rats, expressed as Δ of the basal value.* Serotonin (●——●), serotonin + 6-hydroxydopamine (◆– – –◆), serotonin + propranolol (▲———▲) and serotonin + α-methyltyrosine (■– – –■). Control rats (O—·—·—O). Each value represent the mean ± S.D. from 10 rats.

gastric pH or the serotonin-induced increase of the intragastric pH until 90 minutes after the serotonin administration, but at 120 min the intragastric pH remained at high values in sympathectomized rats whilst in the normal rats it returned to basal values.

The administration of propranolol (8 mg/kg i.p., 150 min before the pH lecture) did not alter significantly the basal intragastric pH, whilst the pretreatment with propranolol abolished the serotonin-induced increase of the intragastric pH during the 120 minutes of the experiment.

Repeated dosages with α-methyltyrosine (50 + 100 + 50 mg/kg i.p., 25, 18 and 2 hours the pH lecture) did not alter the basal intragastric pH but inhibited the effect of serotonin on the gastric acid output throughout the study.

Discussion

The basal gastric secretion in rats is inhibited after administration of exogenous serotonin. This effect does not seem to be either related to its vascular actions since serotonin may dilate the gastric mucosal vessels (7) or to a direct effect on gastric secretion as it has been reported that the serotonin containing cells in the stomach are not localized close to the parietal cells (17). It is thus possible that the regulation of gastric secretion in these animals is the reflection of a peripheral balance between adrenergic and serotoninergic mechanisms. In this study it is shown that serotonin-induced increase of the intragastric pH is unaffected by the pretreatment with 6-hydroxydopamine, a drug known to produce a selective long lasting depletion of peripheral noradrenaline from various sympathetically adrenergic innervated tissues (24, 31), without altering peripheral serotonin concentration (33). These results do not agree with the previously reported by FJALLAND (11) who observed that a 6-hydroxydopamine pretreatment diminished the antisecretory effect of exogenous serotonin. This disagreement may be due to the different experimental model used by this author. Our results seem to indicate that the increase of the intragastric pH observed after the administration of 10 mg/kg of exogenous serotonin is not dependent on noradrenaline concentration in peripheral adrenergic neurones, and that exogenous serotonin may rather exert its antisecretory effects acting on the hypothalamic centres controlling the gastric secretory activity, as was proposed by BUGAJSKI *et al.* (4) who observed that serotonin administered into the lateral cerebral ventricle caused a stronger antisecretory action than after intraperitoneal administration.

In this study it has also been shown that the pretreatment with propranolol, a beta blocker which easily crosses the blood-brain barrier (34), abolished the serotonin-induced increase of the intragastric pH. The results quoted above suggest that the action of serotonin on gastric acid output is exerted on the hypothalam-

ic centres and that this action is blocked by propranolol. But it is not yet clear if this effect is the result of a direct inhibition on brain centres responsible for gastric acid output or if it is due to displacement of noradrenaline in the central adrenergic neurones, since it has been shown that propranolol presents a stereospecific affinity for the serotonin receptor isolated from the rat brain (21), and that serotonin causes a dose-dependent release of labelled noradrenaline from adrenergic neurones (12-14). For this reason, and in order to throw some light on the function of serotonin *per se* in control of gastric secretion in rats without the interference of noradrenaline, we examined the intragastric pH after serotonin administration in rats pretreated with α-methyltyrosine, a drug that selectively reduces the central and peripheral noradrenaline concentration (19, 29, 30). In this study it has been shown that serotonin-induced increase of the intragastric pH was antagonized by pretreatment with α-methyltyrosine, indicating that in presence of diminished concentration of brain noradrenaline, serotonin looses its gastric antisecretory properties. Based on these results it is proposed that the antisecretory effect of exogenous serotonin on gastric acid output is mediated by a release of noradrenaline from the brain adrenergic neurones, and that this noradrenaline could be responsible for the inhibition of ventromedial hypothalamic and vagal structures responsible for gastric acid output.

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Resumen

Se estudia en ratas el efecto de la administración intraperitoneal de serotonina (10 mg/kg) sola y en ratas pretratadas con 6-hidroxidopamina, propranolol o α-metiltirosina sobre el pH intragástrico. Se observa que después de la administración de serotonina el pH intragástrico se eleva aproximadamente cinco unidades. La simpatectomía química, obtenida por la administración de 6-hidroxidopamina, no afecta significativamente ni al pH basal ni al ascenso del pH intragástrico inducido por la serotonina. La administración de propranolol no altera el pH basal, pero el pretratamiento con propranolol bloquea el ascenso del pH intragástrico inducido por la serotonina. Dosis repetidas de α-metil tirosina tampoco alteran el pH basal, pero inhiben el efecto de la serotonina sobre el pH intragástrico. Estos resultados parecen indicar que el efecto antisecretor de la serotonina exógena es debido a una inhibición de los centros cerebrales responsables de la actividad secretora de las células parietales. Además, se sugiere que el efecto antisecretor de la serotonina es mediado por la liberación de noradrenalina desde las neuronas adrenérgicas cerebrales.

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