SEROTONIN SECRETION BY THE INTESTINE IN RESPONSE TO HYPERTONIC SOLUTIONS

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Experiments on isolated segments of rat intestine showed that introduction of hypertonic solutions of glucose or dextran into the small intestine leads to the appearance of a substance in the intestinal contents increasing the tone of the test segment. This effect is blocked by preliminary treatment of the intestinal segments with tipindol, cocaine, atropine, nicotine, and procaine. Physostigmine potentiates the tonic effect of the filtrate. It is concluded from these results that the substance secreted into the filtrate is serotonin.

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Several investigators have demonstrated that the motor and evacuatory functions of the stomach are dependent on the osmotic properties of food constituents present in it [1, 3, 11, 12]. Stimulation of the duodenal osmoreceptors by hypertonic solutions slows gastric evacuation by reflex closure of the pylorus [9, 10]. The pylorus thus plays the main role in protecting the small intestine from the excessive entry of osmotically active food. After resection of the stomach osmotically active food enters the small intestine more rapidly (dumping).

The object of this investigation was to study the character of substances secreted in the small intestine when hypertonic solutions enter it.

EXPERIMENTAL METHOD

Two glass vessels containing Gaddum's solution (9 g NaCl, 0.4 g KCl, 0.03 g $CaCl_2$, 0.15 g $NaHCO_3$, and 1 g glucose per liter distilled water) were placed in the bath of an ultrathermostat at 24°. A segment of the terminal ileum or initial portion of the transverse colon of a rat, 1.5 cm in length (the test segment), was immersed in the contents of one vessel. The bottom end of this segment was fixed by a thread to the glass tube through which the Gaddum's solution was aerated constantly from a type MK-1 microcompressor. The top end of the test segment of intestine was connected to a pen recording its tone and peristalsis on a smoked kymograph drum. A segment of small intestine, 20 cm in length, excised from the proximal portion of the duodenum (experimental segments of intestine), preliminarily washed with Gaddum's solution, was immersed in the contents of the second vessel. Its proximal end was occluded by a ligature, while its distal end was fixed to the glass tube through which the segment was filled with 3-5 ml of glucose solutions of different concentrations (10, 20, 40%) or with 6% dextran solution.

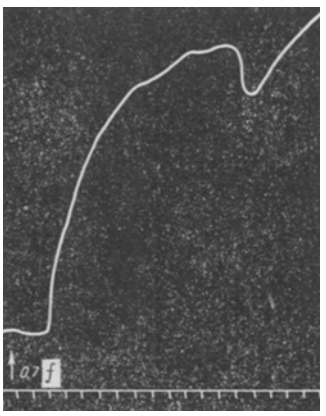

Fig. 1. Effect of filtrate of 40% glucose solution on test segment. 0.7 *f* Denotes injection of 0.7 ml filtrate.

These solutions were withdrawn from the experimental segment 30 min after their introduction, filtered, and added to the vessel containing the test segment. Changes in tone and motor activity thereby arising in the test segments gave evidence of the presence of active substances in the filtrates secreted by the experimental segments of intestine in response to stimulation by the hypertonic solution.

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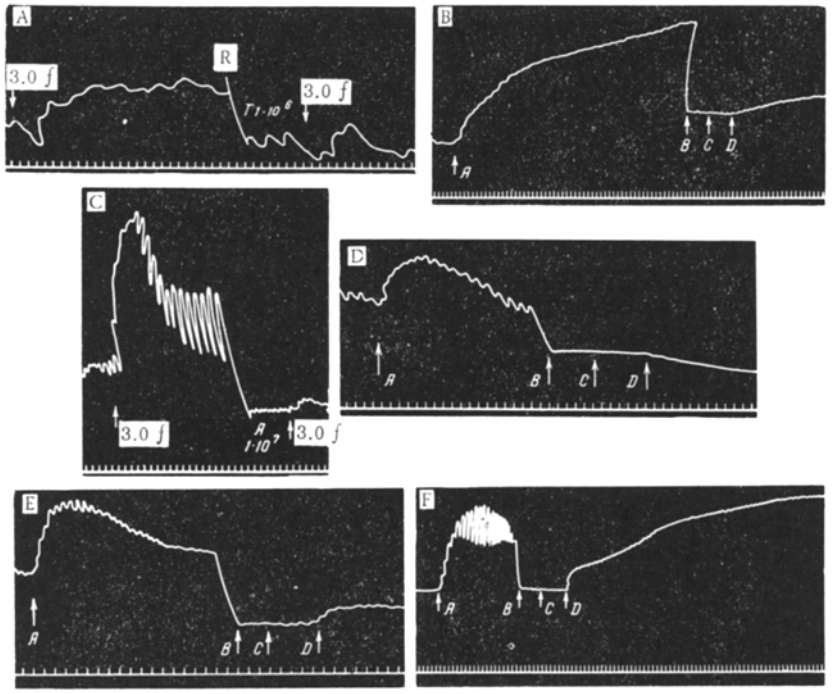

Fig. 2. Effect of tipindol (A), cocaine (B), atropine (C), nicotine (D), procaine (E), and physostigmine (F) on tonic effect of filtrate of contents of experimental intestinal segment. A: 3.0 f) injection of 3 ml filtrate; R) rinsing of test segment; T) injection of tipindol ($1 \cdot 10^{-6}$); B: A) injection of 3 ml filtrate; B) rinsing of test segment; C) injection of cocaine ($1 \cdot 10^{-6}$); D) repeated injection of 3 ml filtrate; C: 3.0 f) injection of 3 ml filtrate; R) rinsing of test segment; A) injection of atropine ($1 \cdot 10^{-7}$); D: A) injection of 3 ml filtrate; B) rinsing of test segment; C) injection of nicotine ($1.25 \cdot 10^{-7}$); D) 2nd injection of 3 ml filtrate; E: A) injection of 3 ml filtrate; B) rinsing of test segment; C) injection of procaine ($1 \cdot 10^{-8}$); D) 2nd injection of 3 ml filtrate; F: A) injection of 3 ml filtrate; B) rinsing of test segment; C) injection of physostigmine ($1 \cdot 10^{-7}$); D) 2nd injection of 3 ml filtrate.

Preliminary experiments showed that 10% glucose solution and 6% dextran solution had no effect on the contractile activity of the test segment, whereas higher concentration of glucose lowered its tone.

EXPERIMENTAL RESULTS

The Gaddum's solution withdrawn from the experimental segment after 30 sec did not change the character of contraction of the test segment. However, if this solution was introduced under pressure into the experimental segment, it caused the intestine to secrete a substance (or substances) increasing the tone of the test segment. The tonic response of the test segment bore a direct relationship to the degree of stretching of the walls of the experimental segment, i.e., on the pressure created within it. The relationship between this effect and liberation of serotonin by the stretched intestine was demonstrated previously [6, 7].

Filtrates of hypertonic solutions in contact with the experimental segment, when introduced into the vessel containing the test segment, increased its tone (Fig. 1) and contractions. The tonic action of the filtrates increased parallel to the increase in concentration of the solutions introduced into the experimental segment. Injection of hypertonic solutions into the experimental segment under pressure caused it to secrete a larger quantity of substances increasing the tone of the test segment.

Since the character of the response of the test segment resembled its response to administration of serotonin solutions, it was concluded that serotonin may be present in the tested filtrates. Further evidence

in support of this hypothesis was given by the tachyphylactic properties of the filtrate which were demonstrated, characteristic of serotonin also.

To determine the nature of the substance present in the filtrate we first used a method based on the specific serotonin-liberating effect of reserpine on the enterochromaffin cells of the intestine. These cells are known to be a reservoir of serotonin [4, 5, 8].

Experiments were carried out on 29 rats weighing 180-200 g which received intraperitoneal injections of reserpine in doses of from 1 to 5 mg/kg daily for 1-6 days. These experiments showed that exhaustion of the serotonin reserves leads to a sharp decrease in the effect of the filtrate on the intestinal contents on the tone of the test segment. This property of the experimental segment was gradually restored after reserpine administration ended.

We next analyzed the mechanism of action of the tonic factor contained in the filtrate of the experimental segments on serotonin-sensitive receptors of M and D types in the test segment. Atropine ($1 \cdot 10^{-7}$-$1 \cdot 10^{-8}$), procaine ($1 \cdot 10^{-8}$), cocaine ($1 \cdot 10^{-6}$), nicotine ($1.25 \cdot 10^{-5}$), blocking mainly the M-receptors, and physostigmine ($1 \cdot 10^{-7}$), increasing sensitivity of the M-receptors to serotonin [13], were used for the analysis. Simultaneous blocking of M- and D-types of serotonin-sensitive structures was produced by the action of a new specific antiserotonin preparation—tipindol [2].

The experiment showed that atropine, procaine, nicotine, cocaine, and tipindol definitely block the action of the filtrate of content of the experimental segment of intestine to produce spasm of the test segment, while physostigmine potentiated this action (Fig. 2). Analogous experiments with serotonin yield the same results.

It can be concluded from these findings that the substance appearing in the filtrate of hypertonic solutions introduced into the small intestine of rats and increasing the tone of the test segment of intestine is serotonin and that the formation of an excess of serotonin liberated from the enterochromaffin cells of Kulchitsky probably plays an important role in the pathogenesis of the dumping syndrome, during which the rapid entry of hypertonic food substances into the duodenum, accompanied by stretching of its walls, takes place.

LITERATURE CITED

1. V. G. Kassil', in: Motor Function of the Gastro-Intestinal Tract [in Russian], Kiev (1965), p. 83.
2. I. N. Pidevich, Uchen. Zapiski Inst. Farmakol. i Khimoter. Akad. Med. Nauk SSSR, 3, 258 (1963).
3. B. M. Sosina-Izraitel', The Motor-Evacuatory Function of the Human Stomach [in Russian], Doctorate Dissertation, Minsk (1950).
4. E. P. Benditt and K. L. Wong, Am. J. Path., 32, 638 (1956).
5. E. P. Benditt and K. L. Wong, J. Exp. Med., 105, 509 (1957).
6. E. Bülbring et al., J. Physiol. (Lond.), 140, 381 (1958).
7. E. Bülbring and A. Crema, J. Physiol. (Lond.), 146, 18 (1959).
8. V. Erspamer, Experientia, 10, 471 (1954).
9. J. Gershon-Cohen and H. Shay, Am. J. Dig. Dis., 4, 637 (1937).
10. J. N. Hunt, Gastroenterology, 41, 49 (1961).
11. W. G. Karr, W. O. Abbott, O. D. Koffman, et al., Am. J. Med. Sci., 200, 524 (1940).
12. B. A. McSwiney and W. R. Spurrell, J. Physiol. (Lond.), 79, 437 (1933).
13. E. C. Savini, Actualités Pharmacol., Ser. 17, 117 (1964).