PARTICIPATION OF THE NERVOUS SYSTEM IN HISTAMINE SECRETION OF THE GASTRIC GLANDS

N. V. Maevskaya

UDC 612.323:612.822.2]-08

There is abundant information in the literature on the relationship between the secretory effect of histamine on the stomach and nervous influences. It has been established most clearly that anatomical and pharmacological disturbance of the vagus innervation leads to a decrease in secretion in response to injection of histamine [2, 3, 5, 12, 14, 21, 23, 25, etc], although data have also been obtained indicating the absence of changes in secretion of juice in these conditions [4, 10, 18, 23]. Reports have been published both of a decrease in the histamine secretion under the influence of ganglion-blocking agents [17] and of the absence of any such changes [6, 20, 23, 24]. The data relating to the participation of the sympathetic nervous system and of adrenalin in the histamine secretion are few in number and particularly contradictory. According to the results of some investigations, a disturbance of the sympathetic innervation leads to an increase in secretion, while sympathomimetic drugs and stimulation of the sympathetic nerve depress it [9, 11, 16, 26-28]; in other investigations no direct effect of the sympathetic system was found [13, 15, 21, 22]. The problem of whether nervous and, in particular, sympathetic stimuli act directly on histamine secretion, or whether they act indirectly through changes in the state of the blood vessels, is unsolved.

In the present investigation methods of pharmacological and anatomical denervation were used to analyze the role of the nervous system in the reaction of the gastric glands to histamine.

EXPERIMENTAL METHOD

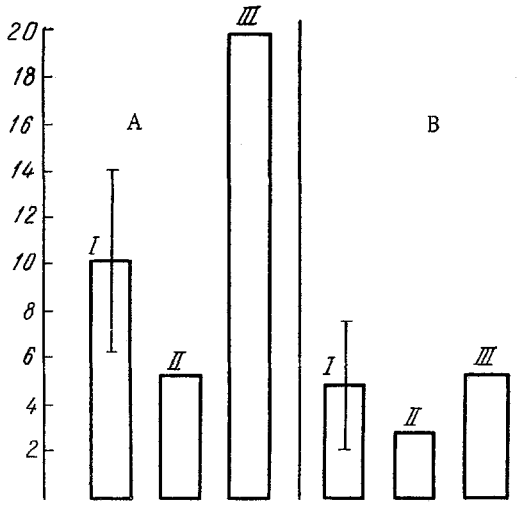
The investigation was conducted on 11 dogs with fundal gastric pouches formed by Pavlov's method (5 animals) and by Heidenhain's method (6 animals). In 4 dogs undergoing the Heidenhain procedure, the isolated gastric pouch was transplanted subcutaneously, and after an interval of not less than 5 months, it was denervated by Ivy's method by division of the mesentery. Secretion was evoked by the subcutaneous injection of 0.5 mg of histamine. The volume of juice was recorded every 15 min for 2 h. The acidity of the gastric juice was determined by titration with 0.1 N NaOH and its digestive activity by N. P. Pyatnitskii's method [7]. The content of free hydrochloric acid in milligrams, and of pepsin in conventional units, secreted during the experiment, was determined. In some of the experiments 5-30 min before the injection of histamine, the dogs received an injection of hexamethonium in a dose of 6-10 mg/kg subcutaneously or 2 mg/kg intravenously. In the other experiments the animals received a subcutaneous injection of bretylium [1] in a dose of 9-10 mg/kg 30 min before the histamine was given.

EXPERIMENTAL RESULTS

In the experiments on the dogs undergoing the Pavlov operation (5 animals) and the Heidenhain operation (5 animals also), after the preliminary injection of hexamethonium the secretion during the 2 h of the experiment fell on the average by $43.9 \pm 9.1\%$ ($P < 0.001$), as is clear from the figure, A. Analysis of the results of the experiments on the individual animals showed that the secretion was unchanged after blocking of the autonomic ganglia in only one of the 10 dogs, one with a Heidenhain pouch. Under the influence of hexamethonium the latent period of the histamine secretion was lengthened, the acidity of the juice was reduced, and the amount of hydrochloric acid secreted during the experiment was diminished, all by a statistically significant margin. In the dog Dik, for example, the latent period rose from 10.7 ± 0.35 min ($M \pm m$) to 13.0 ± 0.15 min ($P < 0.001$). The acidity fell from 119.0 ± 1.70 ml to 99.1 ± 3.13 ml ($P < 0.001$). The amount of hydrochloric acid secreted during the experiment fell from 41.5 ± 4.45 to 19.1 ± 0.75 mg ($P < 0.001$). The content of proteolytic enzyme secreted decreased parallel to the volume of juice.

The negative results of the investigation of the effect of hexamethonium on the histamine secretion [20, 24] were evidently attributable to the fact that in these cases in clinical practice the dose of hexamethonium used was

Department of Physiology, Donetsk Medical Institute (Presented by Academician V. V. Parin). Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 62, No. 11, pp. 13-17, November, 1966. Original article submitted March 30, 1965.



Effect of hexamethonium and bretylium on gastric secretion in response to injection of 0.5 mg histamine in the dog Adol'f before and after denervation of the transplanted gastric pouch. Along the axis of ordinates—volume of gastric juice (in ml). Columns—secretion during 2 h of the experiment: I) Control, 95% confidence interval $M \pm \sigma t$; II) experiment with hexamethonium (7 mg/kg 30 min before injection of histamine); III) experiment with bretylium (10 mg/kg 30 min before injection of histamine); A) experiments before denervation; B) after denervation.

insufficient to cause a complete block of the autonomic ganglia.

To investigate the role of the sympathetic nervous system in the mechanism of histamine secretion, in experiments on three dogs with a Heidenhain pouch the sympatholytic drug bretylium was used. This agent disturbs the transmission of nervous impulses from the postganglionic nerve fiber to the effector.

The preliminary administration of bretylium considerably increased the secretion of the gastric glands in response to injection of histamine. In the dog Adol'f (see figure, A), for example, the standard deviation of the volume of juice in the experiment with bretylium was 6.75 σ when the limit of the 95% confidence interval in the control experiments was $M \pm 2.36\,\sigma$. The acidity of the juice rose. The total amount of hydrochloric acid secreted during the experiment rose from 33.20 ± 17.51 mg ($M \pm \sigma t$) to 68.2 mg, and the amount of proteolytic enzyme from 99.25 ± 65.89 to 600 conventional units.

To continue the analysis of the role of the nervous system in histamine secretion, the secretion was studied in 4 dogs before and after division of the mesentery of the pouch transplanted subcutaneously. Denervation gave rise to a statistically significant decrease in secretion in 3 of the 4 dogs. In the dog Dinka, for example, the volume of juice fell during 2 h from 8.39 ± 0.63 ml ($M \pm m$) in the 10 experiments preceding denervation to 3.05 ± 0.22 ml after denervation.

The character of the secretory curve remained unchanged. The increase in the latent period to 1 h and the need for an increase in the dose of histamine in order to produce secretion [19] were evidently associated with the disturbance of the function of the glandular elements after the too early denervation of the transplanted pouch.

According to the author's findings, the acidity of the juice after denervation was lowered by more than half. After denervation of the dog on which injection of hexamethonium had no action, the secretion was unchanged.

Investigation of the secretion of the denervated gastric pouch is not only interesting on its own account for confirming the role of the nervous system in histamine secretion, but it also gives grounds for concluding that the action of hexamethonium and of bretylium on secretion takes place as a result of their blocking of nervous impulses.

After denervation, bretylium and hexamethonium had no effect on secretion (see figure, B), ruling out the possibility of their direct action on the gastric glands. Abolition of the action of bretylium and hexamethonium as a result of denervation likewise provides no evidence for attributing their effect on secretion to changes in the circulation, because these changes persisted after division of the mesentery, for besides the blood vessels of the anterior abdominal wall, nerve fibers also invaded the transplanted gastric pouch. Finally, the changes in histamine secretion following administration of bretylium show that the sympathetic nervous system influences the stomach directly, and not through changes in the secretion of adrenalin by the adrenals [15], because bretylium is known not to depress the secretion of adrenalin or the sensitivity of the tissues to it.

The changes in histamine secretion after anatomical and pharmacological denervation of the stomach confirm the participation of the nervous system in the reaction of the gastric glands to histamine.

It may be assumed that histamine acts on the glands directly, and not through the intramural nervous system, as shown by the abolition of the effect of the ganglion-blocking agent on secretion after division of the mesentery. During histamine secretion, in contrast to secretion evoked by a food stimulus, the content of acetylcholine in the gastric juice is not increased [8], confirming the absence of a cholinergic link in the mechanism of the stimulant action of histamine on the stomach. Nervous stimuli evidently participate in histamine secretion, determining the functional state of the glandular cells in relation to histamine.

It may be concluded from the increase in secretion after the pharmacological exclusion of the sympathetic innervation that negative tonic influences are exerted by the sympathetic nerves on the fundal glands. Impulses from the vagus nerve, on the other hand, evidently increase the excitability of the secretory cells relative to histamine. After the simultaneous exclusion of both parasympathetic and sympathetic influences by means of a ganglion-blocking agent or by division of the mesentery, the secretion in response to histamine was reduced, and it may, therefore, be assumed that in normal conditions the tonic influences of the vagus nerves are stronger than those of the sympathetic nerves.

The author is inclined to attribute the similarity, in the majority of cases, between the results of the experiments on the Pavlov and the Heidenhain pouches, and the absence of changes after injection of hexamethonium and surgical denervation in only one dog undergoing the Heidenhain operation, to the usually incomplete division of the parasympathetic fibers during isolation of a fundal pouch by the Heidenhain method. A special study of this problem is required.

It may be concluded from the results of these experiments that the reactivity of the gastric glands in relation to histamine is determined by interaction between the parasympathetic influences on the secretory apparatus.

LITERATURE CITED

1. V. P. Vvedenskii, E. S. Rozovskaya, and I. B. Simon, Problems in the Physiology and Pathology of the Endocrine Glands [in Russian], Khar'kov (1961), p. 20.
2. S. G. Genes, N. G. Lesnoi, and M. Z. Yurchenko, Fiziol. Zh. SSSR, No. 4, 426 (1956).
3. I. T. Kurtsin, Hormones of the Digestive System [in Russian], Leningrad (1962).
4. V. F. Lysov, Fiziol. Zh. SSSR, No. 9, 758 (1956).
5. I. V. Malkiman and E. I. Zlotnik, Byull. éksp. Biol., No. 1, 44 (1949).
6. T. A. Mel'nikova, Effect of Some New Cholinolytic Substances (Anicain, Difacil, and Tetramon) on the Secretory Function of the Alimentary Tract. Doctorate dissertation, Leningrad (1954).
7. N. P. Pyatnitskii, Klin. Med., No. 4, 74 (1955).
8. Ya. P. Sklyarov, Gastric Secretion [in Russian], Kiev (1954), p. 32.
9. D. K. Skulov, Fiziol. Zh. SSSR, 25, Nos. 1-2, 83 (1938).
10. A. V. Solov'ev, New Data on the Secretory Function of the Stomach and the Pancreas [in Russian], Leningrad (1959), p. 61.
11. Yu. N. Uspenskii, Fiziol. Zh. SSSR, No. 4, 458 (1960).
12. F. Antia, C. Rosier, and C. R. Robertson et al., Am. J. Physiol., V. 166 (1951), p. 470.
13. M. R. Brown, Ibid., V. 105 (1933), p. 399.
14. S. Emås, Acta physiol. scand., V. 61 (1964), p. 255.
15. A. P. Forrest and C. F. Code, Am. J. Physiol., V. 177 (1954), p. 425.
16. Idem, J. Pharmacol. exp. ther., V. 110 (1954), p. 447.
17. M. I. Grossman and C. R. Robertson, Proc. Soc. exp. Biol., New York, V. 79 (1952), p. 226.
18. A. P. Ingegno and L. Kertzner, New York St. J. Med., V. 54 (1954), p. 1185.
19. A. L. Ivy and J. Farrell, Am. J. Physiol., V. 74 (1925), p. 639.
20. A. W. Kay and A. N. Smith, Brit. med. J., V. 1 (1950), p. 460.
21. F. J. Lewis, Surgery, V. 30 (1951), p. 478.
22. S. Linde, Acta physiol. scand., V. 21, Suppl. 74, 1 (1950).
23. P. Mantegazza and F. Piccinini, Boll. Soc. ital. biol. Sper., V. 39 (1963), p. 479.
24. R. Merten and W. Fetscher, Klin. Wschr., 34, 45 (1956).
25. H. A. Oberhelman and L. R. Dragstedt, Proc. Soc. exp. Biol. Med., V. 67 (1948), p. 336.
26. H. A. Oberhelman, E. R. Woodward, C. A. Smith, and L. R. Dragstedt, Am. J. Physiol., V. 166 (1951), p. 679.
27. S. N. Pradhan and H. W. Wingate, Arch. intern. pharmacodyn., V. 140 (1962), p. 339.
28. C. R. Robertson and M. I. Grossman, Ibid., V. 91 (1952), p. 1.