ROLE OF HISTAMINE AND CYCLIC NUCLEOTIDES IN THE REGULATION OF GASTRIC SECRETION IN EXPERIMENTAL THYROTOXICOSIS

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UDC 616.441-008.61-07:616.33-008.8-02:615.218.1

KEY WORDS: thyroxine; cyclic nucleotides; histamine; gastric secretion.

There is considerable experimental evidence [1, 2, 4, 10] that cyclic nucleotides participate in the mechanism of hydrochloric acid (HCl) secretion. However, different workers have reached highly contradictory conclusions on these matters. Some workers [2, 4, 5] found correlation between the level of HCl secretion and the concentration of cyclic nucleotides in the stomach, whereas others were unable to confirm this dependence. According to data in the literature [1, 5, 8, 14] histamine is the chief pharmacologic stimulus which increases HCl secretion. According to the model suggested in [9], histamine is an essential link in the stimulation of HCl production by the stomach. Cyclic nucleotides act as mediators in this chain. Meanwhile other workers found no connection between histamine and cyclic nucleotides [11].

The aim of this investigation was to study the role of histamine and cyclic nucleotides in the gastric mucosa in the disturbance of HCl secretion arising in experimental thyrotoxicosis.

EXPERIMENTAL METHOD

Experiments were carried out on 48 male Wistar rats weighing initially 160-180 g. The animals were kept under ordinary vivarium conditions. L-thyroxine (from Reanal, Hungary) was injected intraperitoneally in a dose of 2.5 mg/kg body weight for 10 days (series I) and for 30 days (series II). When thyrotoxicosis was produced by this scheme the animals lost weight (on average by 25-30%). Gastric juice was collected from the rats 10 days after fistula formation. Before the experiment the animals were deprived of food for 18 h. The true rate of HCl secretion was calculated. At each stage of the experiment 16 animals were used. Each of the experimental groups included eight control animals kept under similar conditions, and receiving the corresponding volume of physiological saline at the same times. Homogenates of gastric mucosa were studied by a radioisotope method, using standard kits (from Amersham Corporation, England) for cyclic nucleotide assay. Radioactivity was counted by means of a Mark II liquid scintillation counter (from Nuclear Chicago, USA). The histamine concentration in the mucosa of the gastric fundus was determined by the method in [12]. The numerical results were subjected to correlation analysis. From the total number of correlations, moderately strong ($r = \pm 0.51$-0.69), strong ($r = \pm 0.70$-0.89), and strongest, or "functional" ($r = \pm 0.9$-1.0) were selected.

EXPERIMENTAL RESULTS

After injection of thyroxine in a dose of 2.5 mg/kg for 10 days HCl secretion was increased (by 60%), but after thyroxine administration for 30 days HCl secretion was reduced by 47% (Fig. 1).

The rising true rate of HCl production corresponded to the high histamine and cAMP concentrations in the gastric mucosa (Fig. 1). The study of correlation between the true rate of HCl production and the histamine and cAMP concentrations in the gastric mucosa showed strong positive correlation ($r = +0.84$, $r = +0.79$ respectively) in the early stages of thyrotoxicosis and negative correlation ($r = -0.96$, $r = -0.91$) after administration of the

Central Research Laboratory, Grodno Medical Institute. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Kupriyanov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 2, pp. 29-30, February, 1983. Original article submitted April 22, 1982.

0007-4888/83/9502-0195$07.50

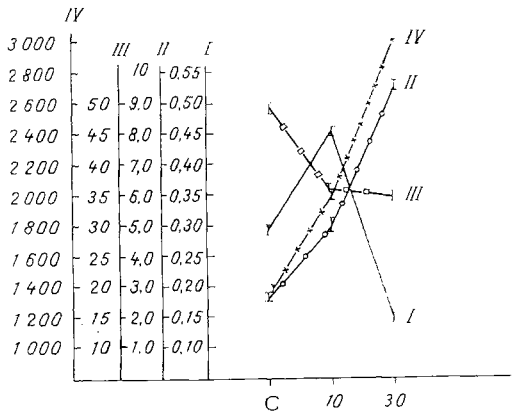

Fig. 1. Changes in HCl secretion and histamine and cyclic nucleotide concentrations in gastric mucosa of rats at different stages of thyroxine administration. Abscissa, duration of injection of thyroxine (in days). I) True rate of HCl secretion, II) histamine concentration in gastric mucosa, III) cyclic GMP, and IV) cyclic AMP levels. C) Control.

hormone for 30 days. No correlation was found between the cGMP concentration in the gastric mucosa and the true rate of HCl production ($r = +0.32$ for thyroxine administration for 10 days and $r = +0.18$ for 30 days).

It can be concluded from these results that correlation between HCl secretion and the cAMP level in the gastric mucosa is not stable, and that correlation between the cGMP level and true rate of HCl secretion does not exist at all. It has to be stated that we would not be right to ignore those few investigations [4, 10] in which a leading role in the mechanism of disturbance of HCl secretion is ascribed to cyclic nucleotides, but this investigation did not lead to that conclusion. To clarify the precise points of application of thyroxine in its action on HCl secretion correlation was analyzed between the cAMP and histamine concentrations in the gastric mucosa. Strong positive correlation ($r = +0.95$ for thyroxine administration for 10 days, $r = +0.86$ for 30 days) was found between these parameters. Changes in the histamine and cAMP concentrations in the stomach were synchronized at the different stages of thyroxine administration.

It was shown previously that thyroxine, irrespective of its dose and duration of administration, stimulates the adenylate cyclase system of the parietal cells [3] and, as a result, raises the cAMP level in the gastric mucosa.

Consequently, in the early stages of thyrotoxicosis increased HCl secretion correlated with the raised histamine and cAMP levels. The discovery of strong correlation is evidence that the parameters studied are undoubtedly interconnected by a relationship of cause and effect. In the late stages of thyrotoxicosis correlation between the histamine and cAMP levels in the gastric mucosa is still present, but these parameters no longer correlate with those of the parietal cells. These cells are apparently refractory to histamine and to cyclic nucleotides.

Evidence has thus been obtained of an indirect (through histamine and cAMP) action of thyroxine on the parietal cells in the early stages of hyperthyroidization and of a direct action of the parietal cells (which are refractory to endogenous histamine and cAMP) during prolonged hyperthyroidization.

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