ROLE OF CYCLIC GMP IN THE MECHANISM OF THE EFFECT OF CHOLECYSTOKININ-PANCREOZYMIN ON HEPATOBILIARY FUNCTION IN MAN

A. S. Loginov and T. V. Goryacheva

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The role of cyclic nucleotides in the mechanism of the functional response of target cells to hormones has recently been demonstrated for many hormones including those of gastrointestinal nature. Some workers, for instance, consider that the adenylate cyclase—cAMP system participates in the mechanism of the secretagogue action of gastrin on the gastric mucosa [10, 11]. Investigations have shown that the choleretic action of secretin, glucagon, and other hormones on the ductular mechanisms of bile secretion is evidently effected through the participation of a system of cyclic nucleotides [6, 7]. A role for cAMP in bicarbonate secretion by the pancreas under the influence of secretin and of vasoactive intestinal peptide has been demonstrated [3, 4, 8].

The intestinal hormone cholecystokinin-pancreozymin (CCK) is known to exert its main influence on the digestive system by stimulating enzyme secretion by the acinar cells of the pancreas and causing contraction of the gall bladder and expulsion of bile into the duodenum. Stimulation of enzyme synthesis in pancreatic cells by CCK has been shown to take place with the participation of Ca^{++} and cyclic nucleotides (cAMP and cGMP), whose role in this process is not entirely clear [12, 13].

The cholecystokinetic action of CCK is probably aimed directly at the gall bladder muscle, but this also has not been finally studied. All that is known is that contraction of the gall bladder muscle tissue *in vitro* was accompanied by an increase in its cGMP content [1] and that cholecystokinin caused an increase in intracellular phosphodiesterase activity and a decrease in the cAMP content in gall bladder muscle tissue [2].

The aim of the present investigation was therefore to study the role of cyclic nucleotides (cAMP and cGMP) in regulation of bile secretion in man by CCK.

EXPERIMENTAL METHOD

Eleven patients with fatty degeneration of the liver combined with normal contractile function of the gall bladder (six patients) or with hyperkinetic (two patients) and hypokinetic (three patients) dyskinesias of the gall bladder were investigated.

Cyclic nucleotides (cAMP and cGMP) in the duodenal contents were determined radioimmunologically and cholic acid and cholesterol in the duodenal contents were determined by the usual methods. For radioimmunologic assay of cyclic nucleotides, kits from Amersham Corporation (England) were used and the activity of the samples was measured on a Mark 3 liquid scintillation counter (USA). The duodenal contents were collected and analyzed in portions obtained in the course of 10 min; three such portions were obtained before and six portions after stimulation by intravenous injection of CCK (from Boots, England) in a dose of 1 Unit/kg body weight.

EXPERIMENTAL RESULTS

In the patients with normal gall bladder function, expulsion of bile from the gall bladder into the duodenum was observed 10 min after intravenous injection of CCK, as shown by an increase in the volume of duodenal secretion during this period and an increase in its concentration of cholic acid and cholesterol (Fig. 1).

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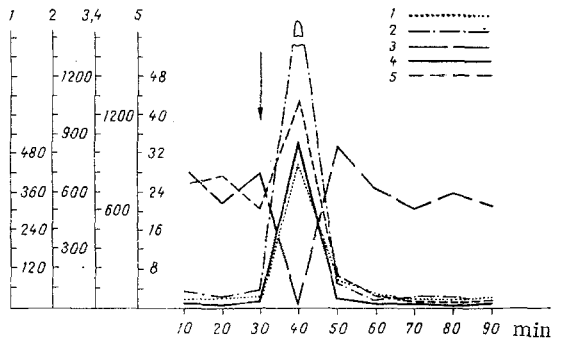

Fig. 1

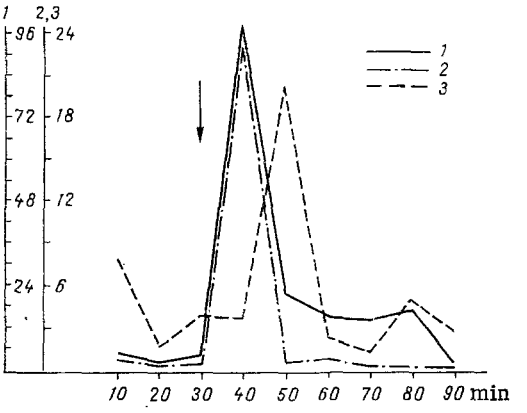

Fig. 2

Fig. 1. Changes produced by CCK in concentration of cyclic nucleotides and principal components of bile in duodenal contents from patient K. with normal gall bladder function. 1) Cholesterol concentration (in mg %); 2) cholic acid concentration (in mg %); 3) cAMP concentration (in pmoles/ml); 4) cGMP concentration (in pmoles/ml); 5) volume of duodenal contents (in ml). Here and in Fig. 2: ordinate, concentration of components of bile; abscissa, time (in min). Arrow indicates time of injection of CCK.

Fig. 2. Changes in absolute output of cyclic nucleotides in duodenal contents of patient D. with normal gall bladder function under the influence of CCK. 1) Volume of duodenal contents (in ml); 2) absolute cGMP output (in μmoles); 3) absolute cAMP output (in μmoles).

The investigation showed that the arrival of bile in the duodenum under the influence of CCK was combined with a sharp rise in the cGMP concentration in the duodenal contents (Fig. 1), whereas the cAMP concentration fell sharply. Later, 10-20 min after the "peak," the cGMP concentration returned gradually to its initial level whereas the cAMP concentration rose above the background values. The same time course of changes in the bile components and cyclic nucleotides also was observed in patients with hyperkinetic dyskinesia of the gall bladder.

The cGMP concentration, which averaged 47 ± 10 pmoles/ml before stimulation, underwent a sevenfold increase 10 min after injection of CCK to a mean value of 370 ± 140 pmoles/ml, and in some patients the cGMP concentration in the duodenal contents was increased by 25-40 times after hormonal stimulation.

The mean cGMP content, expressed relative to the total quantity of secretion liberated at a given moment of time, was 630 ± 120 pmoles before stimulation, but after injection of the hormone it was increased on average by 42 times to 26,700 ± 50 pmoles, and in some patients the increase in the cGMP output during hormonal stimulation was by as much as 50-90 times.

The fall in the cAMP concentration, which before injection of the hormone averaged 440 ± 60 pmoles/ml whereas during the first 10 min after injection of the hormone it was only 85-20 pmoles/ml, was evidently due to dilution of cAMP by digestive secretions liberated in response to injection of CCK.

This conclusion is confirmed by the fact that the absolute output of this nucleotide, which before stimulation averaged 6460 ± 1310 pmoles, remained virtually unchanged during the first 10 min and averaged 5830 ± 1680 pmoles. However, 20-30 min after stimulation the absolute cAMP output was increased by 5-10 times (Fig. 2).

The increase in both the concentration and the absolute output of cAMP observed 20-30 min after bile expulsion was evidently connected with processes involving the arrival of gall-bladder bile in the duodenum. It is stated in the literature that the expulsion of bile from the gall bladder into the duodenum is accompanied by a rise in the blood secretin concentration [5, 9], and if it is recalled that the action of this hormone on secretion of the liquid part of the bile and pancreatic juice causes an increase in output of cAMP with the corresponding secretions [3, 7], it can be postulated that the observed increase in the cAMP concentration is in fact connected with the effect of the liberated secretin on these processes.

Another interesting fact is evidently that in patients with hypokinetic dyskinesia of the gall bladder who took part in the investigation, the expulsion of bile into the duodenum was delayed by CCK. The largest volume of secretion and an increase in its concentration of bile components were observed 20 min and not 10 min after injection of the hormone. Correspondingly, the absolute cGMP output also was increased along with expulsion of gall-bladder bile after 20 min. The fact that an increase in the concentration of bile components and an increase in the concentration and absolute output of cGMP coincided irrespective of the time when gall-bladder bile was expelled into the duodenum suggests that this phenomenon is associated with the cholecystokinetic action of CCK.

It can thus be concluded that the action of CCK on the human hepatobiliary system is evidently mediated through cGMP, and that cAMP evidently does not participate in this process. The results also suggest that a role of considerable importance in the pathogenesis of hypokinesias of the gall bladder may be played by a disturbance of the hormonal regulation of its activity, possibly connected with an insufficiency of the hormone in the mediator systems transmitting its action.

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