ROLE OF PROSTAGLANDINS IN THE MECHANISM OF ACTION OF CHOLECYSTOKININ ON THE GALL BLADDER

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One of the principal manifestations of the action of the classical intestinal hormone cholecystokinin (CCK) is contraction of the gall bladder [12], through its direct action on this organ, which is physiological and is effected with the aid of receptors located in the muscle of the gall bladder and on Oddi's sphincter [4]. Meanwhile, the mechanism of the action of CCK has not yet been adequately studied. Furthermore, the discovery in recent years that endogenous biosynthesis of prostaglandins (PG) takes place in the liver [5, 9, 11], the appearance of these substances and their active metabolites in the mucosa and muscle tissue of the gall bladder and in the bile [15], and also the therapeutic effect of PG, shown by clinical and experimental studies [3], served as the basis for the hypothesis that PG are involved in the hormonal regulation of the contractile function of the gall bladder. We also know that chronic diseases of the liver are often accompanied by dyskinesias of the biliary system, whose pathogenesis is not yet clear.

We studied the role of PG in the mechanism of action of CCK on the human gall bladder and the development of dyskinesias of the biliary system in chronic liver disease as well as the possible effect of this pathology on the above-mentioned regulatory mechanisms.

EXPERIMENTAL METHOD

Bile was obtained by duodenal catheterization from patients with fatty degeneration of the liver with normal (15 patients) and disturbed (hypokinetic dyskinesia, 20 patients) contractile function of the gall bladder, confirmed by cholecystography. Concentrations of PG of the E and $F_{2\alpha}$ groups were determined by radioimmunoassay in 10-min portions of duodenal contents for 1.5 h, under basal conditions (1-3 portions obtained without stimulation) and after intravenous stimulation by CCK ("Boots," England, IU/kg body weight, 4-9 portions), using standard kits of reagents ("Clinical Assays," USA); cholesterol and cholic acid levels were determined by the usual methods. The experimental results were subjected to statistical analysis by Student's *t* test.

EXPERIMENTAL RESULTS

Both under basal conditions and after intravenous stimulation by CCK, the bile was shown to contain PGE and $PGF_{2\alpha}$ (Fig. 1). Their basal levels in subjects with normal gall bladder function were 2.43 ± 0.22 ng/ml for PGE and 1.15 ± 0.16 ng/ml for $PGF_{2\alpha}$; the $PGE/PGF_{2\alpha}$ ratio was 2.11 ± 0.16. This is in agreement with results of the few investigations of the PG level in human bile to be found in the literature [6].

Analysis of the data showed definite relationships in the character of PG excretion with the bile into the duodenum under the influence of CCK. The results in Fig. 1, obtained on patients with fatty degeneration of the liver but with normal gall bladder function, indicate the significant role of $PGF_{2\alpha}$ in the hormonal regulation of bile excretion and, in particular, their role in the mechanism of action of CCK on the gall bladder. This was demonstrated, first, by the parallel increase in volume of the duodenal contents and the increase in the concentration of the main components of bile (cholesterol, cholic acid) and $PGF_{2\alpha}$ in

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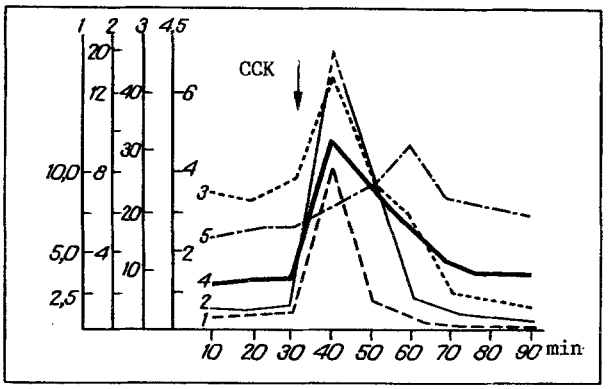

Fig. 1. Excretion of PG and main components of bile into duodenum under the influence of intravenous injection of CCK (1U/kg body weight) with normal bile secretory function. 1) Cholesterol (nmoles/liter), 2) cholic acid (g/liter), 3) volume of bile (ml), 4) $PGF_{2\alpha}$ (ng/ml), 5) PGE (ng/ml).

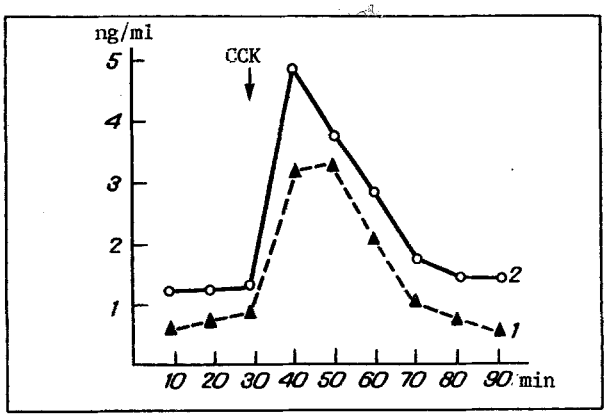

Fig. 2. Excretion of $PGF_{2\alpha}$ with bile into duodenum under the influence of CCK in patients with gall bladder hypofunction (1) and with normal gall bladder function (2).

them after stimulation by CCK, and second, the fact that the period of maximal excretion of bile, which was observed 10 min after intravenous injection of CCK and corresponded to contraction of the gall bladder, also was characterized by the maximal increase in the concentration of $PGF_{2\alpha}$ in the bile (from 1.1 to 4.8 ng/ml). Meanwhile, as Fig. 1 shows, the highest PGE level (4.6 ng/ml) in the bile did not coincide with the period of its greatest excretion into the duodenum, despite the increase in the output of PGE, the maximal rise of its concentration was observed, unlike with $PGF_{2\alpha}$, not until 20 min after hormonal stimulation.

Thus, the choleretic effect of CCK is mediated by PG, more especially by $PGF_{2\alpha}$, in agreement with modern views on the role of these biologically active substances in the realization of hormonal actions.

It is stated in the literature that $PGF_{2\alpha}$ has a regulatory role in the kinetics of the bile ducts and in the mechanism of cholecystokinetic effects [7], that the action of CCK is induced by stimulation of biosynthesis of endogenous PG and this action is inhibited by inhibitors of prostaglandin synthetase [13], and also that $PGF_{2\alpha}$ plays a role in the development of inflammatory processes during cholecystitis [8]. Taking these data and our own results showing PG deficiency in chronic liver disease [1] into account, we decided to study PG excretion with the bile during hormonal stimulation in patients with fatty degeneration of the liver accompanied by disturbances of gall bladder function (dyskinesias).

The results in Fig. 2 show that in patients with disturbed gall bladder function (hypofunction) a characteristic finding was significant fall both in the concentration of $PGF_{2\alpha}$ in all portions of bile and in its output (the latter was depressed on average by 29% compared with patients with normal gall bladder function), and also an increase in the time (from 10 to 20 min)

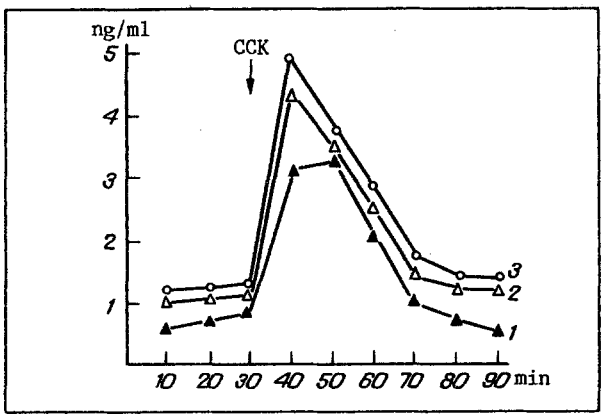

Fig. 3. Effect of linoleic acid preparation on $PGF_{2\alpha}$ excretion with the bile into duodenum in patients with fatty degeneration of the liver accompanied by gall bladder hypofunction. Before (1) and after (2) treatment, with gall bladder hypofunction, 3) with normal gall bladder function.

of maximal increase of the $PGF_{2\alpha}$ level after stimulation by CCK. Incidentally, these factors may be among the mechanisms of disturbance of hormonal regulation of bile excretion in the realization of the action of CCK may play an important role in the pathogenesis of dyskinesias of the biliary tract and changes in their functional state.

This hypothesis is convincingly confirmed by the results of the study of patients with fatty degeneration of the liver and gall bladder hypofunction, receiving intravenous and peroral therapy with "Essentiale" (Natterman, Yugoslavia), a preparation of linoleic acid, which is one of the main precursors for endogenous PG biosynthesis. The $PGF_{2\alpha}$ level in the bile, previously depressed, rose significantly in these patients, both under basal conditions on average from 0.69 ± 0.05 ng/ml (before treatment) to 1.0 ± 0.08 ng/ml (after treatment, $p > 0.05$), and under the influence of CCK: in cystic bile from 3.15 ± 0.12 to 4.05 ± 0.22 ng/ml ($p < 0.05$) and in hepatic bile — from 0.15 ± 0.05 to 2.13 ± 0.15 ng/ml ($p < 0.05$) respectively (Fig. 3). These data correlated with a definite restoration of the normal functional state of the gall bladder, revealed roentgenologically, after administration of the linoleic acid preparation to patients with fatty degeneration of the liver, and also by the improvement of liver function in these patients, as reported by the present writers previously [2].

Further confirmation of the active involvement of $PGF_{2\alpha}$ in the mechanism of the cholecystokinetic effect of CCK also is given by: the mediator function characteristic of PG (activation of endogenous PG biosynthesis is essential for the onset and realization of several physiological reactions), modulation by $PGF_{2\alpha}$ of the contractile function of the gall bladder and intensification of the action of CCK by them, as revealed in experimental studies on guinea pigs [10], and stimulation of bile excretion from the liver in dogs by $PGF_{2\alpha}$ [7].

The facts described in this paper thus indicate a mediator role of PG, especially $PGF_{2\alpha}$, in the mechanism of action of CCK on the human gall bladder and their possible participation in the pathogenesis of dyskinesias of the biliary tract in chronic liver diseases.

These results correlate not only with the protective and therapeutic effects of PG in the gastroduodenal mucous membrane known at the present time, but also with facts relating to cytoprotection by PG and their synthetic analogs in the liver, discovered in recent years [14].

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ACTH FRAGMENTS IN MECHANISMS OF COMPENSATION OF SELF-STIMULATION BEHAVIOR AFTER SEPTAL DESTRUCTION IN RABBITS

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The septal region of the brain, connecting phylogenetically older and newer brain formations by means of numerous afferent and efferent connections passing through it, plays a leading role in the organization of self-stimulation (SS) behavior [4, 9]. The role of the septum in mechanisms of SS is particularly interesting because, by virtue of 2-way functional connections with the paraventricular and supraoptic nuclei of the hypothalamus [8], it participates in regulation of the hypothalamo-hypophyseo-adrenocortical system. Many ACTH-sensitive neurons are found in the septal region [11]. Injections of ACTH 4-10 lowered the threshold for evocation of SS behavior from the medial septum in rats and increased the number of times the animals pressed the lever in response to low-intensity stimulation [10]. In experiments on rats [6] fragments ACTH 4-9 and 5-8 potentiated SS behavior evoked from the medial forebrain bundle, whereas intraperitoneal injection of ACTH 5-10 [1] reduced the intensity of SS from the lateral hypothalamus in rabbits. In our previous investigations cyclic analogs of ACTH/MSH fragments, depending on the dose, increased or reduced the frequency of SS of the lateral hypothalamus [2], whereas fragment ACTH 4-10 restored SS in rabbits in which protein synthesis was blocked by cycloheximide and actinomycin [3].

The aim of this investigation was to study the effects of fragments ACTH 1-24 and ACTH 4-10 in the mechanisms of SS behavior in rabbits after destruction of the septal region of the brain.

EXPERIMENTAL METHOD

Experiments were carried out on 32 male chinchilla rabbits weighing 3-3.5 kg. Bipolar nichrome stimulating electrodes were implanted 24 h after the animals were scalped into the region of the lateral hypothalamus (P = 2, L = 2, H = 15-16 mm). Electrodes also were implanted unilaterally into the rabbits in the region of the septum (A = 3, L = 1, H = 9-10 mm). To inject the ACTH fragments into the animals, steel cannulas 14 mm long and 0.8 mm in diameter were implanted into the lateral ventricles. During the experiments the rabbits were kept in a chamber with a fixed metal ring, and had free access to water and food. By touching the metal ring with their nose and lips, the unrestrained animals quickly learned to close the electric circuit in

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