Elevated Cholecystokinin-Like Activity in the Duodenal Mucosa in Patients with Cholecystolithiasis

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Cholecystokinin (CCK) is one of the most important hormones in digestive tracts along with gastrin and secretin (Mutt 1980). It is extensively used in clinical practice for testing extra-pancreatic secretion functions (Takebe et al. 1976) and contractile functions of the gall bladder (Griffen et al. 1980).

However, it should also be admitted that the pathological physiological role of CCK in cholelithiasis and pancreatitis has scarcely been clarified to date. This would be attributable to the fact that most of the antibodies to CCK are overlapping with gastrin and thus radio-immunoassay specific for CCK can scarcely be developed. On the other hand, the bioassay of CCK has difficulties in its sensitivity. We, however, paid attention to the bioassay using the in situ gall bladder of the guinea pig, and reported that it is fully practical in the determina-

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tion of activities of CCK in the duodenal mucosa (Kataoka 1982).

The present paper described the results of the study intended for bioassay of CCK-like activities in the duodenal mucosa of the patients in whom contrast radiography of the gall bladder is feasible with an i.v. contrast medium of the gall bladder and also intended for clarification of the pathophysiological role of CCK in cholecystolithiasis through comparative evaluation of contractions of the gall bladder following oral administration of egg yolk or following i.m. administration of caerulein.

**Materials and Methods**

**Patients**

The determination of the CCK-like activities in the duodenal mucosa was conducted in 8 patients suffering from cholecystolithiasis in whom contrast radiography of the gall bladder was feasible with an i.v. contrast medium. The 8 patients comprised 4 males and 4 females, with a mean age of 59 years (37–77 years). All of them were interviewed, had a complete physical examination including serological tests, a series of upper gastrointestinal tests, pentagastrin-stimulated gastric analysis, upper gastrointestinal endoscopy, and were proved to have no complication. Some had a caerulein-secretin-stimulated pancreatic exocrine test and glucose tolerance test.

Nine subjects, aged 41–60 years (median 49 years), comprising 6 males and 3 females, were selected as control from outpatients in our hospital. All of them were interviewed, had the same complete examination as patients with cholecystolithiasis had, and were proved to have no diseases, much less cholecystolithiasis. The controls tended to be in lower age than patients with cholecystolithiasis, but there was no statistically significant difference.

Thirty patients with cholecystolithiasis in whom contrast radiography of the gall bladder was feasible with an i.v. contrast medium were involved in the test on the contractile test of the gall bladder. Following the contrast radiography, two egg yolks were orally given to 10 patients, whereas 12 μg of caerulein were administrated i.m. to the other 20 patients. The conditions of the contractions of the gall bladder were grossly observed and photographed. The group which received egg yolk included 4 males and 6 females with a mean age of 50 years (28–65 years). The group which received caerulein included 4 males and 16 females with a mean age of 53 years (34–73 years). There was no statistically significant difference in age composition between the two groups. For the control, 57 subjects with no abnormality in the results of health check at Tsukidate Hospital were involved. All the 57 subjects underwent contrast radiography of the gall bladder, of whom 26 received oral administration of two egg yolks and the remaining 31 received i.m. administration of caerulein so as to photograph the conditions of the contraction of the gall bladder. The group which received egg yolk comprised 13 males and 13 females with a mean age of 47 years (18–67 years). The group which received caerulein comprised 22 males and 9 females with a mean age of 47 years (23–75 years). There was no statistically significant difference in the age composition between the two groups. Nor was there any significant difference between these groups and the groups of patients with cholecystolithiasis. Those whose body weights exceeded ±20% of the standard body weight were excluded, which was calculated from \((\text{height in cm}-100)\times0.9\) kg according to modified Broca's method, so that the influence of variations in body weight could be excluded.

**Methods**

The duodenal mucosa was collected under endoscopic observation. A duodenofiberscope (JFB type, Olympus) was inserted into the vicinity of papillae of the
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The CCK-like activities were determined with the procedure earlier reported (Kataoka 1982). Briefly, male Hartley guinea pigs weighing 230-450 g were laparotomized under anesthesia with urethane. The gall bladder was carefully picked up and its bottom was pinned by a clip tied up with a thread. The other end of the thread was connected with liver. The movements of the gall bladder were recorded on a kymograph with 7 times larger amplification. The right jugular vein was cannulated with a thin polyethylene tube, via which standard CCK or test sample was infused. The unitage of CCK-like activities was expressed in Ivy Dog Unit per dry weight of duodenal mucosa collected (IDU/mg, dry weight) (Kataoka 1982).

The contrast radiography of the gall bladder was performed by use of the generally adopted method. Briefly, on the previous day of the radiography, evening meal with limited content of fats was given earlier than regular time. On the following morning, the patients were fasted, and 250 ml of Biligrafin® (meglumine adipiodone, Schering AG, Berlin/Bergkamen) was dripped i.v. for 60 min. After an interval of 60 min, the first radiography of the gall bladder was made. Then, two egg yolks were orally administrated to 10 patients with cholecystolithiasis and 26 normal control subjects. On the other hand, caerulein in a dose of 12 μg was i.m. administrated to the other 20 patients with cholecystolithiasis and 31 normal control subjects (Bertaccini 1980), and radiography of the gall bladder was made at 15 and 30 min. The space between the X-ray tube and film was firmly designated as 70 cm. The photographing was invariably made in a supine position with the left lateral side of body lifted up in an angle of 30°.

Areas of the gall bladder at 15 and 30 min expressed as percentages those on the X-ray film before the administration of stimulants of the gall bladder were taken to represent its rates of contraction. The measurement of the area of the gall bladder on the X-ray film was conducted by use of the image treatment system “Digigram” (Muto Kogyo, Model G series).

Values are given in terms of mean±S.D. All the statistical treatment was conducted according to Student’s t-test.

RESULTS

(1) The CCK-like activities in the duodenal mucosa of 8 patients with cholecystolithiasis was 0.978±0.328 IDU/mg dry weight, whereas those of the 9 normal control subjects were 0.520±0.202 IDU/mg dry weight. Thus, a significant rise in CCK-like activities was noted in the group of cholecystolithiasis (t=3.45, p<0.01) (Table 1).

(2) The areas of the gall bladder on the X-ray film of 26 normal control subjects after oral administration of egg yolk were 68.5±21.2 per cent at 15 min and 39.8±15.9 per cent at 30 min. Likewise, those after i.m. administration of caerulein to 31 control subjects were 51.8±25.5 per cent at 15 min and 42.8±22.2 per cent at 30 min. When compared in the values at 15 min, the rate of contraction of the gall bladder in the caerulein group was higher than that of the egg-yolk group. However, no significant difference was found in the values at 30 min between the two groups (Table 2).
The areas of the gall bladder at 15 and 30 min after oral administration of egg yolk to 10 patients with cholecystolithiasis were 63.2±15.7 per cent and 42.6±27.8 per cent, respectively. The values thus noted at 30 min were comparable to those in the group of egg yolk or caerulein in the control group of normal subjects. However, the contraction of the gall bladder in 20 patients with cholecystolithiasis who received caerulein was obviously poorer than that of 10 patients with cholecystolithiasis receiving egg yolk (p<0.02 at 15 min and p<0.05 at 30 min) (Table 2).

(3) Finally, the influence of aging upon per cent area of the gall bladder at
30 min after administration of either egg yolk or caerulein in 57 normal subjects was investigated. The rate of contraction of the gall bladder in 31 normal subjects following administration of caerulein in a designated dose was significantly lowered as aging (Fig. 1). However, as illustrated in Fig. 2, it was found that there was no influence of advancing in age upon the contraction of the gall bladder following administration of egg yolk to 26 normal subjects.

**DISCUSSION**

The CCK-like activities in the duodenal mucosa of the patients with cholecystolithiasis were significantly higher than those of normal subjects (Table 1). This result can be interpreted in two ways. The one will attribute the
difference to the abnormalities on the CCK side such as the disturbance of release of CCK or its promoted dissimilation. In this case, the blood level of CCK would be lower and, in order to maintain it on the normal level, the production of CCK will be accelerated, whereby the sensitivity of the gall bladder to CCK would be normal. The other will attribute the difference to the lowered sensitivity of the gall bladder to CCK. In this case, it should be interpreted that the CCK levels in blood would be high due to the accelerated production of CCK so as to replenish the lowered sensitivity of the gall bladder to CCK and to maintain the normal contraction of the gall bladder.

In order to identify which of the two concepts is correct, the difference of the sensitivities of exogenous CCK (caerulein) and endogenous CCK of the gall bladders of the 30 patients with cholecystolithiasis was evaluated in 57 normal subjects as the controls. The reason why 15 and 30 min were selected as the intervals after the administration of stimulants of the gall bladder was that the contraction of the gall bladder in normal subjects via the endogenous CCK following the administration of egg yolk exceeded 50% at 30 min (Table 2), i.e., that the change whereby the favorable or poor contractility could be judged was noted at 30 min (Sosman 1944). Externally, in the case of administration of caerulein, sufficient contraction could be noted in an even shorter period of time (Adlercreuts et al. 1960; Vagne 1968) (Table 2). The reason why the statistical treatment was made regardless of sexes was, as explained above, that there was no statistically significant difference between the two sexes in the patients or normal subjects covered by the present study in terms of contractility of the gall bladder (Spellman et al. 1979). The results revealed that the contraction rate of the gall bladder of the patients with cholecystolithiasis was significantly lower in the group with caerulein used as the contractor than that of any other three groups (Table 2). Additionary, closer investigation revealed that, in the group of patients with cholecystolithiasis receiving caerulein, contraction of the gall bladder was maintained in a linear way up until 30 min (Table 2). This finding denies the first hypothesis that the dissimilation of CCK is promoted in the patients with cholecystolithiasis. On the other hand, the rate of contraction of gall bladder in the cases of egg yolk administration with intermediation of the endogenic CCK showed no difference between the group with cholecystolithiasis and the control group of normal subjects (Table 2). Therefore, the insufficiency of release of CCK also can be denied in the patients with cholecystolithiasis. Consequently, it can be interpreted that the rise in the CCK-like bioactivities in the duodenal mucosa in the patients with cholecystolithiasis may be attributable to the lowered sensitivity of the gall bladder to CCK.

This conclusion described above would mean that the sensitivity of the gall bladder to CCK is exerting important influences upon the production of CCK in the duodenal mucosa. In the other words, there must be a feed-back mechanism between the gall bladder and CCK. This mechanism was identified also from the
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correlation of the changes in the contractility of the gall bladder in aging and the CCK-like bioactivities in the duodenal mucosa. As illustrated in Fig. 1, 12 μg of caerulein should be sufficient to induce contraction of the gall bladder in younger subjects, whereas it would be insufficient in the aged subjects. However, as illustrated in Fig. 2, it was found that there was no influence of advancing in age upon the contraction of the gall bladder via the endogenic CCK following administration of egg yolk to normal human subjects. The results revealed that endogenic CCK is produced and released in amount sufficient to replenish the sensitivity of gall bladder to CCK which is gradually reduced as aging. In fact, we earlier reported that the CCK in the duodenal mucosa increase as aging (Kataoka et al. 1978). From these findings, it may be concluded that there is doubtlessly a feed-back mechanism between the sensitivity of the gall bladder to CCK and the output of CCK in the duodenal mucosa irrespective of the cases of physiological changes such as aging or of the pathological cases such as cholecystolithiasis. This mechanism would possibly exist also between the function of extrapancreatic secretion (Harvey et al. 1973) and the function of intra-pancreatic secretion (Kataoka et al. 1980).

References