Effects of a Novel Cholecystokinin (CCK) Receptor Antagonist, MK-329, on Gallbladder Contraction and Gastric Emptying in Humans

Implications for the Physiology of CCK

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Abstract

To explore the physiology of cholecystokinin (CCK) in humans, we investigated the effect on gallbladder contraction and gastric emptying of a recently developed CCK receptor antagonist, MK-329. In a double-blind, four-period crossover study eight subjects received single doses of 0.5, 2, or 10 mg MK-329, or placebo, followed by an intravenous infusion of CCK-8 (30 pmol/kg·h). In placebo-treated subjects gallbladder volumes decreased on average to 43% of initial volumes after 2 h of CCK infusion. MK-329 caused a dose-dependent inhibition of CCK-stimulated gallbladder contraction with 10 mg producing complete blockade (P < 0.01, cf. placebo).

Gallbladder contraction and gastric emptying rates after a mixed meal were then measured in a two-period crossover study. Subjects received placebo or 10 mg of MK-329 2 h before eating. Gastric emptying of both solids and liquids was measured simultaneously by gamma scintigraphy. In placebo-treated subjects plasma CCK levels increased postprandially to 2.3 pM, gallbladder volumes decreased 68.4±3.8% (SE), and the times for 50% emptying of liquids and solids from the stomach were 58±10 and 128±8 min, respectively. In MK-329-treated subjects there was a marked elevation in peak CCK levels to 13.8 pM (P < 0.01, cf. placebo), and gallbladder contraction was completely inhibited. Solid and liquid emptying rates were unaffected.

These findings demonstrate that (a) MK-329 is a potent, orally active antagonist of CCK in humans, and (b) CCK is the major regulator of postprandial gallbladder contraction. These data also support the concept of negative feedback regulation of CCK secretion and suggest that mechanisms other than CCK play a dominant role in the regulation of postprandial gastric emptying rates.

Introduction

Cholecystokinin (CCK) has been proposed to be a major hormonal regulator of gallbladder contraction and gastric emptying in humans (1, 2). Studies measuring the effects of CCK-8 infusion reproducing postprandial bioactive plasma concentrations of the hormone have demonstrated that physiologic concentrations of CCK stimulate gallbladder contraction and delay gastric emptying of liquids (3–5). However, prior difficulties in measuring circulating concentrations of CCK and the existence of multiple molecular forms of CCK in plasma have limited the interpretation of these experiments. It has not previously been possible in humans to selectively inhibit CCK secretion or block the action of CCK by inhibiting binding of CCK to its receptor on target tissues. Either of these two mechanisms would be useful ways to examine the physiologic actions of the hormone.

Recently, a nonpeptide CCK receptor antagonist, MK-329 (3S(−)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4 benzodiazepine-3-yl)-1H-indole-2-carboxamide, previously designated L-364,718), specific for peripheral (type A) CCK receptors has been developed (6, 7). In vitro studies have shown MK-329 to be an effective inhibitor of CCK binding to pancreas and gallbladder tissues (IC50 = 81 and 45 pM, respectively), with a ~1,000-fold lower affinity for binding to cerebrocortical CCK (type B) receptors (6, 7). In addition, little affinity can be demonstrated for numerous other types of receptors (e.g., adrenergic, dopaminergic, benzodiazepine, and gastrin) (7). In animals, MK-329 inhibited CCK-stimulated pancreatic exocrine secretion and colonic contraction (8). MK-329 has also been demonstrated to inhibit CCK-stimulated gallbladder contraction in cats and antagonize CCK-induced inhibition of gastric emptying in mice (8). These data (6–8), taken as a whole, show that MK-329 is a specific peripheral CCK antagonist in animals.

The present investigation consisted of two separate studies. First, subjects received placebo or three dose levels of MK-329 followed by an infusion of CCK-8 in a four-period crossover fashion. The objectives of this study were to demonstrate that MK-329 given orally is an effective CCK antagonist in man, and to establish the dose range of antagonist activity based on inhibition of CCK-stimulated gallbladder contraction. Second, subjects received a single dose of MK-329 or placebo followed by ingestion of a meal. The objectives of this second study were to use MK-329 as a probe of the physiologic actions of endogenous CCK by assessing the effect of CCK receptor blockade on (a) meal-induced gallbladder contraction, (b) meal-stimulated plasma CCK concentrations, and (c) gastric emptying of both the liquid and solid components of a mixed meal.

Methods

Experimental subjects

15 healthy male volunteers 23–44 y of age were selected for study. One subject participated in both studies. Volunteers were taking no medications before the study and each subject was within 15% of ideal body

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Each subject had a normal screening physical examination and laboratory tests, including urinalysis, complete blood count, serum chemistries, and electrocardiogram. Subjects had no history of significant illness or surgery. The study was approved by the Committee on Protection of Human Subjects of Mount Zion Hospital and Medical Center and the Committee on Human Research of the University of California, San Francisco. Written informed consent was obtained from each subject.

Study protocols

All studies were conducted the morning after an overnight (12 h) fast.

Effect of MK-329 on CCK-stimulated gallbladder contraction. Eight subjects participated in a four-period, double-blind, placebo-controlled, balanced crossover study (Latin square design). On 4 d, separated by at least 1 wk, subjects received either placebo or one of three single doses of MK-329 (0.5, 2, or 10 mg). Before drug administration, subjects had an indwelling butterfly catheter placed in an arm vein for drawing blood, and gallbladder volume was determined by abdominal ultrasound (3). Subjects took placebo or drug orally with 150 ml of water, followed 2 h later by a 2-h intravenous infusion of CCK-8 administered at a rate of 30 pmol/kg·h (3). Blood was drawn and gallbladder sonograms were performed at various times over the study period.

Effect of MK-329 on meal-stimulated gallbladder contraction and gastric emptying. Eight subjects participated in a double-blind, placebo-controlled, balanced, two-period crossover study in which MK-329 was given before ingestion of a standardized mixed meal. At least 10 d elapsed between study periods. On each day, before dosing, subjects had an indwelling butterfly catheter placed in an arm vein for drawing blood, and gallbladder size was determined by abdominal ultrasound. Subjects took placebo or 10 mg MK-329 orally with 150 ml of water. 2 h later subjects ate a 614-kcal breakfast within a 5-min period: two scrambled eggs, two slices of white toasted bread, 8.2 g butter, 75 ml of half-and-half (one-half milk and one-half cream), and 300 ml clear apple juice. This meal contained 66.8 g carbohydrate, 29.4 g fat, and 20 g protein. 500 µCi 99mTc-technetium sulfur colloid was cooked into the eggs and served as a marker of solid gastric emptying. 100 µCi 111In-dual-thiodylenetriamidine pentacetic acid was added to the apple juice and served as a marker of liquid gastric emptying. Blood was collected and gallbladder volumes and fractional retention of the radiolabels in the stomach were measured at various times.

Measurement of plasma CCK concentration

Blood for measurement of plasma CCK was collected on ice into tubes containing EDTA (1.2 mg/ml blood). Blood was centrifuged at 2,000 g for 10 min and plasma was extracted onto Sep-Pak C-18 cartridges (Waters Associates, Milford, MA) previously washed with 3 ml methanol and 20 ml water. 2 ml of plasma was applied to each cartridge, which was then rinsed with 20 ml of water, dried with air, and stored at −20°C. At the time of assay Sep-Paks were eluted with 80% ethanol, 0.1% trifluoroacetic acid, and eluants dried under nitrogen at 45°C. Plasma extracts were resuspended in assay buffer (0.05 M sodium phosphate buffer, pH 7.4, containing 10 mM EDTA, 0.02% sodium azide, and 0.5% egg albumin) such that 0.8 ml of original plasma was assayed in duplicate.

Plasma CCK concentrations were measured by a sensitive RIA as previously described (10, 11). This assay used antibody OAL 656, which is specific for the amino terminus of CCK-8 and thus recognizes the biologically active forms of CCK (12). Recoveries of CCK-8 and -33 added to CCK-free human plasma were 86.2±5.3 and 82.6±3.9%, respectively. Using 125I-Bolton-Hunter-labeled CCK-8 as tracer the relative potencies of CCK-8, -14, -33, and -39 were 100, 88.0, 67.8, and 58.9%, respectively. Crossreactivity with sulfated gastrin-17 was 0.18%. The antibody did not bind to CCK-4, nonsulfated CCK-8, or nonsulfated gastrin-17. The smallest amount of CCK that could be differentiated from zero hormone concentration with 95% confidence was 0.25 fmol/tube using CCK-8 as standard. The intra- and interassay coefficients of variation were 6.0 and 10.2%, respectively. Addition of MK-329 directly to the RIA buffer (500 µg/ml, n = 3) or to plasma before extraction (5 µg/ml, n = 3), did not significantly interfere with CCK immunoreactivity.

Measurement of gallbladder volume

Determinations of gallbladder volumes were made by abdominal ultrasonography as described by Everson et al. (13). Longitudinal sonograms of the gallbladder were recorded on film with a commercially available real-time scanner (Advanced Technological Laboratories, Bellvue, WA) using a 3.5-MHz transducer. Scans were obtained by manipulating the transducer so that it followed the appropriate long axis of the gallbladder, and the largest gallbladder dimensions at each time were recorded. No gallstones, wall thickening, or other pathology were identified in any subject. Gallbladder volumes were calculated by the sum of cylinders method (13) without knowledge of the subject's treatment status (i.e., drug vs. placebo).

Measurement of gastric emptying

Determinations of gastric emptying were made by gamma scintigraphy of the abdomen (4, 14, 15). A gamma camera with a medium energy collimator, interfaced to an ADAC 3350 computer (Analytical Development Corp., San Jose, CA) was used for imaging. 99mTc and 111In were surveyed through 140- and 247-keV windows, respectively. Images were obtained for 60 s for 99mTc and 120 s for 111In. Subjects remained seated between counts but stood in front of the camera for counts taken every 10 min for the first 30 min of the test, and every 15 min thereafter. Data were collected in the anterior view for calculating the gastric emptying, since we had previously found that the geometric means of the anterior and posterior projections were very similar to those of the anterior views alone (4). Data were stored on computer disks for subsequent analysis. Using the computer display, the gastric regions were outlined, excluding the small intestine. For each time point the total radioactivity in the region of interest was summated. Corrections for radionuclide decay were calculated to yield final values for residual radioactivity remaining in the stomach. Background counts were small with respect to the total counts. Counts in the gastric region were expressed as a percentage of the total counts in the whole field in the first 5 postcibal min. The colon (the organ with greatest radiation exposure) and whole body radiation doses were calculated to be 1.0 and 0.03 rad, respectively, for each study (calculations by Mr. Phillip Purser, Mount Zion Hospital and Medical Center, San Francisco, CA). Subjects were given 60 ml milk of magnesia upon conclusion of each treatment period to aid in evacuation of radioactivity from the colon.

Statistical analysis

The data were analyzed with an analysis of variance model for either a four- or two-period (16) crossover design as appropriate. The four-period crossover model included factors for subject, period, treatment, and carryover. The two-period crossover model included factors for subject, period, and treatment, and a test for carryover was performed. No evidence for carryover or period effects was found, and the carryover factor was dropped from the four-period crossover model. The normality and homogeneity of variance assumptions of the analysis of variance model were tested with the Shapiro-Wilk statistic and Hartley's maximum F test on variance of residuals, respectively. Due to a violation of the variance homogeneity assumption in the two-period crossover model, a nonparametric analysis for the plasma CCK data was performed on the ranks of the data. Data are presented in the text as the mean±the between-subject SE or as the median, as appropriate. The number of subjects included in each analysis was eight, except for the 10-mg treatment in study I, where only seven subjects received this dose. Differences between treatment groups were considered significant for P < 0.05 (two-tailed test).

Results

Effect of MK-329 on CCK-stimulated gallbladder contraction. To determine whether MK-329 was an effective antagonist of
exogenous CCK, subjects ingested placebo, 0.5, 2, or 10 mg of MK-329 2 h before receiving a 2-h infusion of CCK-8 at a rate of 30 pmol/kg·h (Fig. 1). Mean basal (predose) plasma levels of CCK ranged between 0.6 and 0.8 pM in all treatment periods (P = NS). With either 2.0 or 10.0 mg MK-329, mean preinfusion plasma CCK levels were generally higher than those observed after placebo; however, these differences were not statistically significant (P > 0.1) except at 105 min after 10 mg MK-329 (P = 0.02, cf. placebo).

Infusion of CCK-8 produced steady-state plasma CCK levels between 7.7 and 10.4 pM within 15 min of initiating the infusion. There were no statistically significant differences in plasma CCK concentrations achieved during CCK infusion between any of the drug or placebo treatments (overall treatment effect, P > 0.1).

Baseline (average of −15- and 0-min timepoints) and preinfusion (average of 105- and 120-min postdose timepoints) gallbladder volumes ranged between 21.1 and 25.1 ml and between 21.8 and 25.0 ml, respectively, and were not different between the four treatments (P > 0.1). The changes in gallbladder volumes in response to CCK infusion and the ability of MK-329 to affect this change are shown in Fig. 2. In placebo-treated subjects, infusion of CCK-8 promptly decreased gallbladder volume 26±7.1% (P < 0.05, within-treatment comparison) within 20 min and 57±9.4% within 2 h (P < 0.05) of beginning the infusion. MK-329 inhibited CCK-induced gallbladder contraction in a dose-dependent manner. Although 0.5 mg of MK-329 did not modify the response to CCK, the 2-mg dose reduced the decrease in gallbladder volumes to 36±6.1% at the end of the 2-h CCK infusion (P < 0.05) and 10 mg MK-329 completely inhibited CCK-stimulated gallbladder contraction (P < 0.01 as compared with placebo).

Effect of MK-329 on meal-stimulated gallbladder contraction and gastric emptying. To determine the effect of MK-329 on meal-stimulated gallbladder contraction and gastric emptying rates, subjects received placebo and 10 mg of MK-329 2 h before eating a mixed meal. The 10-mg dose was chosen because it was the maximally effective dose observed in the previous study.

Supporting initial suggestions, MK-329 treatment resulted in a significant increase in fasting plasma CCK concentrations from median predose values of 0.7–1.0 pM (P < 0.01, cf. placebo) just before the meal. Median plasma CCK concentrations at the same times on placebo treatment were 0.6 and 0.5 pM. Plasma CCK concentrations gradually increased in both placebo- and MK-329-treated subjects beginning 15 min after ingestion of the mixed meal (Fig. 3). However, in subjects receiving MK-329 there was an accentuation of the postprandial increase in plasma CCK concentrations with median peak values of 13.8 pM compared with 2.3 pM after placebo (P < 0.01). Peak CCK concentrations occurred 124±10 and 126±19 min after the meal, following placebo and MK-329 treatments, respectively (P > 0.1).

2 h after dosing, just before meal ingestion, gallbladder volumes were similar after placebo and MK-329 treatment (27.1±2.0 and 27.4±2.3 ml, respectively). In placebo-treated subjects gallbladder volumes decreased 68.4±3.8% 2 h after eating (Fig. 4). However, in subjects receiving MK-329, despite much higher circulating CCK concentrations, gallbladder contraction was not evident after the meal (P > 0.1, within-treatment comparison).

The effects of MK-329 on gastric emptying of both the solid and liquid components of the meal were measured simultaneously. Gastric emptying of the solid component of the meal was based on the rate at which the 99mTc-labeled marker disappeared from the area of the stomach (Fig. 5 A). After placebo treatment the solid marker emptied slowly so that 37±3.1% of the label remained in the stomach at the end of 2.5 h and the time for 50% emptying was 128±8 min. There was no difference (P > 0.1) between placebo and MK-329 treatment groups in these parameters. After placebo, liquids emptied more rapidly with only 16±4% of the 111In-labeled marker remaining in the stomach after 2.5 h (Fig. 5 B). The time for 50% emptying of the liquid marker in the placebo treatment period was 58±10 min. The rate of emptying of liquids from the stomach was also unaffected by MK-329.

Adverse effects. No serious adverse effects were observed after the administration of MK-329. In the study of exogenous CCK infusion, diarrhea and/or abdominal cramping developed in eight treatment periods (four subjects at 10 mg, two at 2.0 mg, one at 0.5 mg, and one on placebo) starting 8–16 h after dosing. Symptoms were self-limited and resolved within 24 h. In the meal study, adverse effects were again gastrointestinal in nature, but the relation to drug was more difficult to decipher because all subjects were given milk of magnesia 4 h after the meal. This was done to decrease radiation exposure of the bowel from the radiolabeled meal. Seven subjects after both placebo and drug treatments complained of loose stools or diarrhea, though abdominal cramping 8–12 h after treatment was slightly more common after MK-329 (three subjects vs. two after placebo). Headache, heartburn, and flatus, resolving within 12 h, were reported by one subject after
MK-329 and were probably drug related. All adverse effects were considered mild in intensity. No significant changes in serial blood chemistries, urinalyses, or electrocardiograms were seen in any subject.

**Discussion**

In the present investigation MK-329 was shown to be a potent, orally active CCK antagonist in humans. MK-329 inhibited CCK-8-stimulated gallbladder contraction in a dose-dependent manner. Using MK-329 as a tool to assess the consequences of CCK receptor blockade after a mixed meal, 10 mg of the antagonist was shown to (a) completely inhibit meal-stimulated gallbladder contraction, (b) dramatically increase postprandial plasma CCK concentrations, and (c) have no effect on gastric emptying rates of either the liquid or solid components of the meal.

The dose-dependent inhibition of CCK-8-induced gallbladder contraction demonstrated the CCK antagonist activity of MK-329 in man, which had previously been shown in animals (8). The ability of MK-329 to completely inhibit meal-induced gallbladder contraction indicates that CCK is the major regulator of physiologic gallbladder contraction. Although other factors such as cholinergic innervation of the gallbladder may be necessary to maintain gallbladder tone and/or CCK responsiveness, interference with CCK action is sufficient to abolish gallbladder contraction.

MK-329 administration markedly increased meal-stimulated plasma CCK concentrations. Three possibilities could account for this effect. First, the rate of CCK clearance could be reduced by MK-329, indicating that a receptor-mediated mechanism participates in removal of CCK from the circulation, as has been suggested by higher CCK levels in patients with cirrhosis (11). However, in the study involving CCK-8 the

**Figure 3.** Effect of MK-329 on plasma CCK concentrations with ingestion of a mixed meal. Eight subjects orally received placebo (○) or 10 (●) mg of MK-329 2 h before ingestion of a 614-kcal mixed meal. Plasma CCK results are expressed as the median values and the interquartile range (numbers in parenthesis at the 185-, 215-, and 245-min timepoints signify the 75th percentile). Premeal plasma CCK concentrations were significantly greater after MK-329 treatment (P < 0.05 of placebo) despite basal (predose) values similar to placebo. All CCK values after ingestion of the meal were significantly greater than premeal values for both treatment groups (P < 0.05 within-treatment comparison). Postprandial CCK levels in subjects receiving MK-329 were significantly greater than those observed in placebo-treated subjects (*P < 0.05, **P < 0.01).

**Figure 4.** Effect of MK-329 on gallbladder volumes after ingestion of a mixed meal. Gallbladder volumes were measured in the subjects described in Fig. 3. Results are expressed as the percent of initial (premeal) gallbladder volume (mean of the 105- and 120-min determinations). Values given are the mean±SEM. Asterisks, values statistically different from placebo (**P < 0.01). †P < 0.05 within-treatment comparison to premeal baseline.

**Figure 5.** Effect of MK-329 on gastric emptying. Gastric emptying of solids (A) and liquids (B) was measured in the subjects described in Figs. 3 and 4. The solid component of the meal was labeled with 99mTc sulfur colloid. The liquid component of the meal was labeled with 111In-diethylene triamine pentaacetic acid. Results are expressed as the mean±SEM.
peptide was infused at 30 pmol/kg·h, resulting in steady-state plasma CCK levels in the range of 7.7–10.4 pmol. There were no significant differences in steady-state plasma levels of CCK between any dose of MK-329 or placebo. Furthermore, the achievement of steady-state concentrations was rapid, occurring within 15 min of initiation of the infusion in all treatment periods. These findings indicate that the receptor antagonist does not influence CCK clearance, and therefore it is unlikely that receptor-mediated mechanisms are necessary for CCK catabolism.

A second possible reason for higher CCK levels after MK-329 administration would be increased delivery of nutrients to the duodenum secondary to accelerated gastric emptying. However, no statistically significant differences in the gastric emptying of solids or liquids were demonstrable in the present study (Fig. 5). Furthermore, the time of peak median CCK concentration after the meal was nearly identical after placebo and MK-329 treatment, consistent with similar rates of delivery of nutrients to the duodenum. One cannot, therefore, ascribe the higher CCK response to the meal after treatment with MK-329 to an acceleration of gastric emptying.

The third possibility that could account for the accentuated postprandial levels of CCK after MK-329 is a negative feedback mechanism regulating CCK secretion. In the rat it has been well demonstrated that diversion of pancreatico-biliary juice from the duodenum, or inhibition of duodenal pancreatic enzyme activity with trypsin inhibitors, causes a prompt increase in pancreatic exocrine secretion (17). It has recently been confirmed that CCK is stimulated both by pancreatic diversion and trypsin inhibitor ingestion, and CCK appears to mediate the negative feedback regulation of pancreatic secretion (18, 19). In other species such as the dog it has been extremely difficult to demonstrate feedback regulation, and in humans the existence of similar negative feedback regulation has been debated (20–22). However, recent studies in humans measuring plasma CCK levels suggest that feedback regulation of CCK secretion does exist (22). In the present study the observation that peak plasma CCK levels were sixfold higher in subjects who received MK-329 suggests that MK-329 may have inhibited meal-induced pancreatic secretion in addition to gallbladder contraction. The absence or diminution of active pancreatic juice and bile in the duodenum could have been the cause of the greater increase in CCK secretion. Moreover, there was a small but significant increase in plasma CCK concentrations during the 2-h period immediately after administration of the drug, suggesting that basal CCK secretion may also be dependent on a feedback mechanism. Together, these data support the concept of negative feedback regulation of CCK secretion in humans.

The role of CCK in the regulation of gastric emptying of a mixed meal was also evaluated in the current study. The traditional way to establish whether a candidate hormone functions in physiologic concentrations has been to measure the circulating hormone concentration simultaneous with its target tissue response, then to reproduce those blood concentrations by infusion of exogenous hormone and quantitating the effect on the target tissue. With this approach it has been demonstrated that CCK has several hormonal actions including delaying the gastric emptying of liquids (4). However, since other hormones may also affect gastric emptying, the importance of CCK alone may not be fully appreciated by this technique (23, 24).

At the dose level investigated in the present study, MK-329 had no effect on gastric emptying of solids or liquids, although postprandial gallbladder contraction was completely inhibited. This finding alone cannot be interpreted to mean that CCK has no physiologic effect on gastric emptying. Since physiologic levels of CCK can affect gastric emptying rates it appears likely that other factors compensate for, or obscure, the effects of CCK in the milieu of ingestion of a mixed meal. Alternatively, it is possible that higher doses of MK-329 might demonstrate an acceleration of gastric emptying if the CCK receptors involved were different in some way from those mediating gallbladder contraction. This is unlikely, however, as animal studies have revealed MK-329 to be a potent antagonist of CCK-induced inhibition of gastric emptying (8, 25, 26). Since gastric emptying and CCK release are regulated by various properties of a meal, including nutrient composition, it is also possible that an alteration of gastric emptying with MK-329 may be demonstrable with other diets.

The numerous postulated physiologic effects of CCK suggest several possible therapeutic applications for a CCK antagonist (27), although these remain to be evaluated. Because MK-329 is selective for peripheral-type CCK receptors it should also be possible to use this agent to distinguish between receptor subtypes responsible for specific actions of CCK.

In conclusion, the present study has demonstrated that MK-329 is an effective, orally active antagonist of CCK based on the inhibition of CCK-8-induced gallbladder contraction. Furthermore, these studies have demonstrated the usefulness of MK-329 as a probe of the physiologic activity of endogenous CCK, revealing (a) the central role of this hormone in postprandial gallbladder contraction, (b) the significant effect of CCK antagonism on the plasma concentrations of the hormone supporting earlier suggestions of feedback regulation, and (c) a possibly limited role of CCK in regulating gastric emptying rates after a mixed meal.

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