

Coffee stimulation of cholecystokinin release and gallbladder contraction in humans¹⁻³

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ABSTRACT We studied the effect of the ingestion of 400 mL regular coffee on plasma cholecystokinin (CCK) concentrations and of 165 mL regular and decaffeinated coffee on plasma CCK and gallbladder contraction in six healthy regular coffee drinkers. Plasma CCK concentrations rose 3.3 ± 0.4 pmol/L after 400 mL and 2.8 ± 0.9 pmol/L after 165 mL regular coffee compared with 1.8 ± 0.6 pmol/L after 165 mL decaffeinated coffee. These plasma CCK increments were greater than those after 400 and 165 mL of an isosmotic and isothermic sodium chloride solution (0.6 ± 0.2 and 0.4 ± 0.1 pmol/L, respectively). An average gallbladder contraction of $33 \pm 7\%$ was observed after 165 mL regular coffee and of $29 \pm 10\%$ after 165 mL decaffeinated coffee, whereas after 165 mL sodium chloride the contraction was only $10 \pm 12\%$. We conclude that both regular coffee and decaffeinated coffee give rise to increments in plasma CCK and contractions of the gallbladder. *Am J Clin Nutr* 1990;52:553-6.

KEY WORDS Coffee, gallbladder, cholecystokinin

Introduction

Coffee is one of the most widely consumed beverages in Western society and therefore any disease state related to its consumption has great implications for public health. In several epidemiologic studies (1-7) the association between coffee consumption and adenocarcinoma of the pancreas was investigated. The results of these studies were contradictory and they still are the subject of some controversy. If or how the consumption of coffee is related to human pancreatic carcinogenesis is still unknown. Chronic stimulation of secretion and growth of the exocrine pancreas may render this organ more susceptible to carcinogenesis. In rats it was demonstrated that substances that chronically stimulate the pancreas by release of cholecystokinin (CCK), such as soy bean trypsin inhibitor, promote pancreatic carcinogenesis (8, 9). It was demonstrated that coffee with or without caffeine stimulates pancreatic secretion in normal persons (10). Although plasma CCK was not measured in that study, it is possible that this effect was mediated by the release of CCK. Besides the effects on the pancreas, coffee is also capable of causing several symptoms in the digestive tract such as heartburn and disordered bowel function (11). Coffee is also generally believed to cause pain in gallstone patients, and physicians often forbid its use for these patients. There is, though, no proof that it causes gallbladder contrac-

tions and this symptom could be caused by other foodstuffs consumed simultaneously, eg, cream.

CCK, a polypeptide hormone produced by I cells in the proximal small intestine and released after the ingestion of a meal, is not only a major stimulus for both pancreatic secretion and gallbladder contraction, but it also possesses powerful trophic effects on the pancreas. In fact, this hormone was shown to cause hyperplasia and tumor development of the pancreas in experimental animals (12-14). Furthermore, CCK may promote pancreatic carcinogenesis by carcinogens in hamsters (15). We therefore decided to investigate the effects of the ingestion of coffee on CCK release and gallbladder contraction in healthy volunteers.

Methods

This study was performed on six healthy volunteers (four male, two female, aged 27-38 y) all of whom were regular coffee drinkers (> 500 mL/d for ≥ 5 y). This study was performed in accord with the Helsinki Declaration of 1975 as revised in 1983 and was approved by the University Hospital ethics committee.

Coffee was obtained from commercially available sources (Douwe Egberts, Utrecht, The Netherlands) and brewed according to Dutch customs with an equivalent of 50 g roasted and ground coffee beans/1000 mL water. The coffee was prepared in a separate part of the building, transported to the study room in a closed container, and drunk immediately after it was poured into a cup.

The control solutions consisted of equal amounts (by volume) of a sodium chloride solution with an osmolality (113 mmol/L) and a temperature (60 °C) equal to the coffee's. The test solutions (400 and 165 mL regular coffee, 165 mL decaffeinated coffee, and 400 and 165 mL NaCl solution) were consumed in 10 min, after an overnight fast.

Blood samples were obtained at -5, 0, 10, 20, 30, 40, 50, and 60 min and plasma CCK concentrations were measured by a

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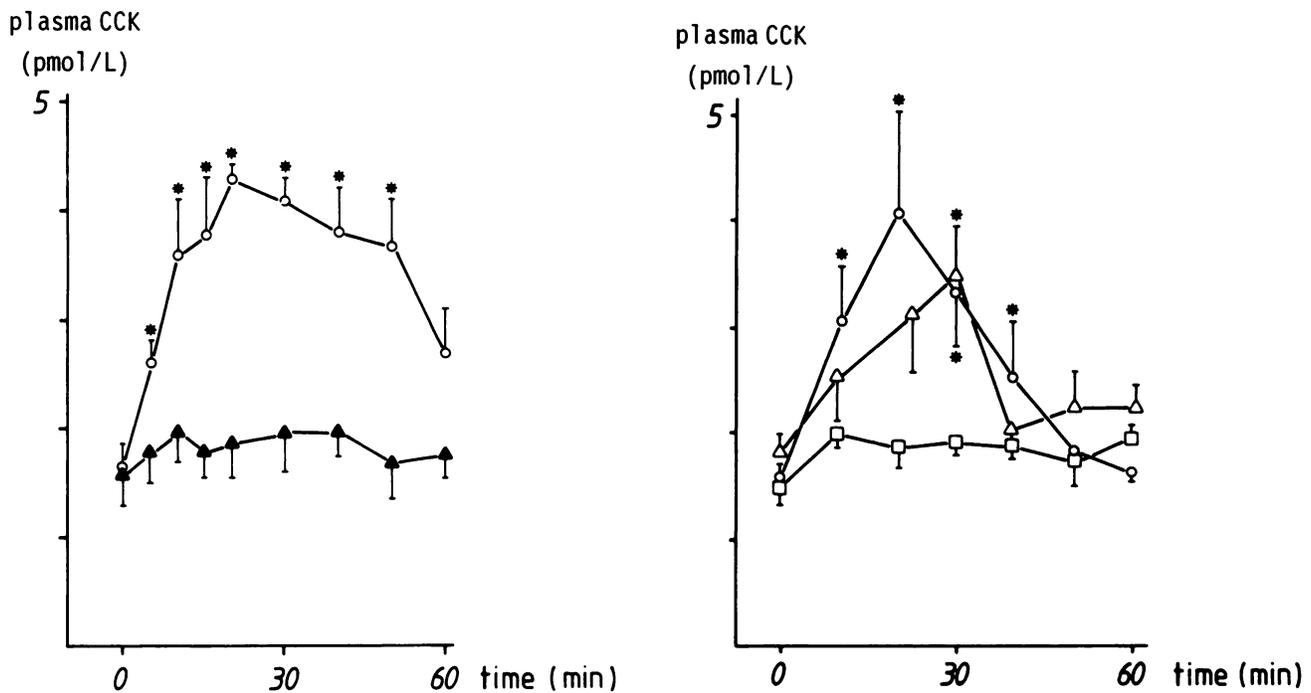


FIG 1. Left panel: plasma CCK concentrations in response to ingestion of 400 mL regular coffee (open circles) and 400 mL NaCl control solution (filled triangles). Right panel: plasma CCK concentrations in response to ingestion of 165 mL regular coffee (open circles), 165 mL decaffeinated coffee (open triangles), and 165 mL NaCl control solution (open squares). Asterisks denote significant increases above basal concentrations ($p < 0.05$).

sensitive and specific radioimmunoassay by use of an antiserum directed against the biologically active forms of CCK (16, 17). In the studies of the 165-mL solutions, ultrasonography of the gallbladder was performed with a real-time scanner (Auto Sector III, series A021-864, Technicare, Denver). Ultrasonograms were obtained at 0, 10, 20, 30, 40, 50, and 60 min. Volumes were calculated by the method of Everson et al (18).

Results were expressed as the $\bar{x} \pm \text{SEM}$. Student's t test for paired observations was used for the statistical analysis of the results. A value of $p < 0.05$ was considered significant.

Results

Ingestion of both regular coffee and decaffeinated coffee induced significant increases in plasma CCK over basal concentrations, whereas the sodium chloride solution did not (Figs 1 and 2). The maximum CCK increments (ΔCCK) were $3.3 \pm 0.4 \text{ pmol/L}$ after 400 mL and $2.8 \pm 0.9 \text{ pmol/L}$ after 165 mL regular coffee, $1.8 \pm 0.6 \text{ pmol/L}$ after 165 mL decaffeinated coffee, and $0.6 \pm 0.2 \text{ pmol/L}$ after 400 mL and $0.4 \pm 0.1 \text{ pmol/L}$ after 165 mL NaCl solutions. The increments after both volumes of regular coffee and after decaffeinated coffee were significantly greater than after sodium chloride solutions ($p < 0.005$, $p < 0.01$, and $p < 0.05$, respectively). The response to 165 mL regular coffee, however, was not significantly higher than that to the decaffeinated coffee. The integrated CCK responses to 400 and 165 mL regular coffee and to 165 mL decaffeinated coffee were $130 \pm 14 \text{ pmol} \cdot \text{L}^{-1} \cdot 60 \text{ min}^{-1}$, $109 \pm 35 \text{ pmol} \cdot \text{L}^{-1} \cdot 60 \text{ min}^{-1}$, and $45 \pm 26 \text{ pmol} \cdot \text{L}^{-1} \cdot 60 \text{ min}^{-1}$, respectively, whereas that to the 400- and 165-mL NaCl solutions were 10 ± 3 and $7 \pm 13 \text{ pmol} \cdot \text{L}^{-1} \cdot 60 \text{ min}^{-1}$, respectively (Fig

2). All values after ingestion of coffee were significantly greater than after the control solutions ($p < 0.01$, $p < 0.01$, and $p < 0.05$ for 400 and 165 mL regular coffee and 165 mL decaffeinated coffee, respectively), whereas the response to 165 mL regular coffee was not significantly greater than that to 165 mL decaffeinated coffee. The differences in the plasma CCK

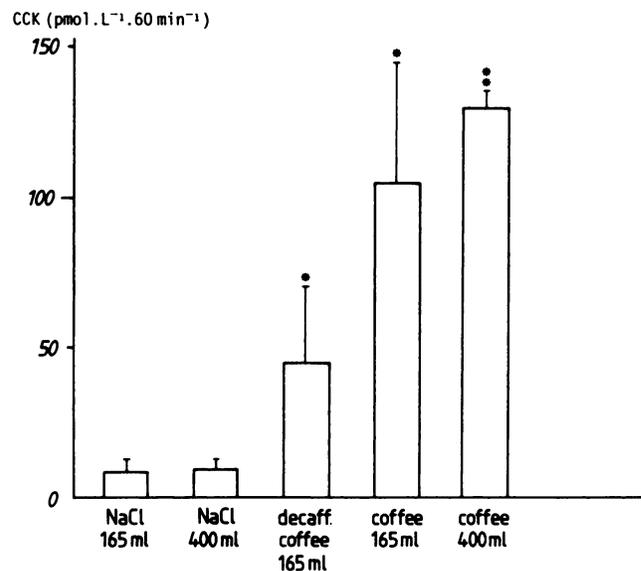


FIG 2. Integrated plasma CCK response after ingestion of 165 and 400 mL NaCl control solution, 165 mL decaffeinated coffee, and 165 and 400 mL regular coffee. * $p < 0.05$, compared with control. ** $p < 0.01$, compared with control.

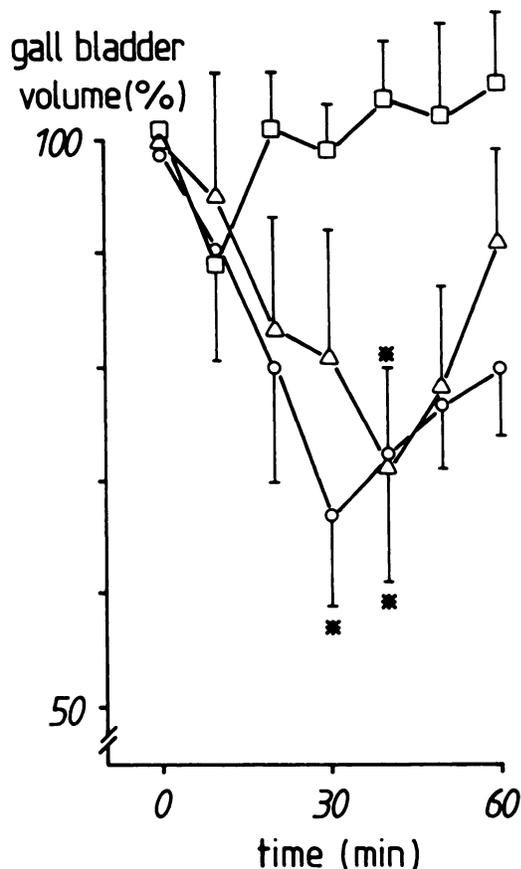


FIG 3. Gallbladder contraction in response to ingestion of regular coffee (open circles), decaffeinated coffee (open triangles), and NaCl control solution (open squares). Asterisks denote significant decreases from the fasting value.

results after 400 and 165 mL regular coffee were not statistically significant.

The maximum decreases in gallbladder volume in response to 165 mL regular coffee, decaffeinated coffee, and sodium chloride were $33 \pm 7\%$, $29 \pm 10\%$, and $10 \pm 12\%$, respectively. The decreases in gallbladder volume after both regular and decaffeinated coffee were statistically significant ($p < 0.01$ and $p < 0.05$) when compared with the gallbladder response to the control solution (Fig 3).

Discussion

In coffee drinkers we demonstrated significant increases of plasma CCK concentrations after ingestion of both 400 and 165 mL regular coffee and of 165 mL decaffeinated coffee. This was not due to distention of the stomach or to temperature and osmolality of the solution because the control sodium chloride solutions showed no significant increase. The increase in plasma CCK concentrations could also not be ascribed to caffeine alone because decaffeinated coffee still had a significant effect. The increases in plasma CCK after 165 mL regular and 165 mL decaffeinated coffee were accompanied by significant contractions of the gallbladder. Because great care was taken to prevent the subjects from smelling and seeing the coffee before

ingestion, it was unlikely that this gallbladder contraction was due to cephalic stimulation of gallbladder contraction (19–21).

The transient, statistically nonsignificant reduction of gallbladder volume at 10 min after 165 mL NaCl solution, amounting to $\sim 10\%$ of the basal volume, is probably due to distention of the upper gastrointestinal tract. Yamamura et al (21) found a maximum reduction in gallbladder volume of $\sim 25\%$ at 20 min after ingestion of 400 mL water. In both that study and ours there were no significant increases in plasma CCK after ingestion of the control solutions. The increases in plasma CCK concentrations exceeded the thresholds for stimulation of gallbladder contraction and pancreatic secretion by exogenous CCK, as reported previously when the same CCK radioimmunoassay was used (22, 23), and could therefore very well explain the present results and those reported by Coffey et al (10) showing stimulation of pancreatic secretion by coffee. In our study we did not investigate the effects on pancreatic secretion directly, but the biological activity of the CCK released was verified by means of gallbladder contraction. In fact, the grade of gallbladder contraction fit well in the dose-response curve previously constructed for exogenous CCK and gallbladder contraction with the same methods as we used in this study (23). Gallbladder contraction and plasma CCK release after coffee were lower than values previously found after a mixed meal (20), after long-chain triglycerides (24), or after an elemental diet (25), but they were higher than after medium-chain triglycerides (24).

It has been demonstrated that CCK stimulates DNA synthesis and growth of the rat pancreas (26, 27) and that chronic stimulation of the pancreas by exogenous and endogenous CCK is able to induce pancreatic neoplasms (8, 9). In those studies, though, the CCK concentrations were not determined and could very well have been considerably higher than those achieved in humans under more or less physiological conditions such as coffee drinking. However, the increases in plasma CCK and decreases in gallbladder volume after ingestion of coffee in this study are certainly not greater than those achieved after ingestion of a normal meal and it is, therefore, unlikely that coffee would render the pancreas more susceptible to carcinogenesis through coffee-induced CCK secretion than would normal eating (22, 28). Furthermore, we demonstrated in this study that both regular coffee and decaffeinated coffee in normal amounts (165 mL) and without additives such as cream or sugar are capable of inducing gallbladder contractions and can indeed be held responsible for colics in patients with gallstones. Thus, this study renders a rational basis for advising patients with symptomatic gallstones to abstain from coffee drinking and also shows that decaffeinated coffee does not offer a clear advantage in this respect. 

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