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Original article

Theobromine does not affect postprandial lipid metabolism and duodenal gene expression, but has unfavorable effects on postprandial glucose and insulin responses in humans

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SUMMARY

Background & aims: Chocolate consumption is associated with a decreased risk for CVD. Theobromine, a compound in cocoa, may explain these effects as it favorably affected fasting serum lipids. However, long-term effects of theobromine on postprandial metabolism as well as underlying mechanisms have never been studied. The objective was to evaluate the effects of 4-week theobromine consumption (500 mg/day) on fasting and postprandial lipid, lipoprotein and glucose metabolism, and duodenal gene expression.

Methods: In a randomized, double-blind crossover study, 44 healthy men and women, with low baseline HDL-C concentrations consumed 500 mg theobromine or placebo daily. After 4-weeks, fasting blood was sampled and subjects participated in a 4-h postprandial test. Blood was sampled frequently for analysis of lipid and glucose metabolism. In a subgroup of 10 men, 5 h after meal consumption duodenal biopsies were taken for microarray analysis.

Results: 4-weeks theobromine consumption lowered fasting LDL-C (−0.21 mmol/L; $P = 0.006$), and apoB100 (−0.04 g/L; $P = 0.022$), tended to increase HDL-C (0.03 mmol/L; $P = 0.088$) and increased hsCRP (1.2 mg/L; $P = 0.017$) concentrations. Fasting apoA-I, TAG, FFA, glucose and insulin concentrations were unchanged. In the postprandial phase, theobromine consumption increased glucose ($P = 0.026$), insulin ($P = 0.011$) and FFA ($P = 0.003$) concentrations, while lipids and (apo)lipoproteins were unchanged. In duodenal biopsies, microarray analysis showed no consistent changes in expression of genes, pathways or gene sets related to lipid, cholesterol or glucose metabolism.

Conclusions: It is not likely that the potential beneficial effects of cocoa on CVD can be ascribed to theobromine. Although theobromine lowers serum LDL-C concentrations, it did not change fasting HDL-C, apoA-I, or postprandial lipid concentrations and duodenal gene expression, and unfavorably affected postprandial glucose and insulin responses.

This trial was registered on clinicaltrials.gov under study number NCT02209025.

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1. Introduction

Optimizing dietary intake is a cornerstone for the prevention of many non-communicable diseases such as cardiovascular diseases (CVD), diabetes mellitus type 2, and the metabolic syndrome. In this context, chocolate might have beneficial effects, as high chocolate intake was associated with a 37% reduction in CVD events, a 31% reduction in type II diabetes risk and a 29% reduction in stroke risk [1]. In addition, beneficial effects of cocoa on serum lipid profiles have been demonstrated in many intervention studies. In fact, two

Abbreviations: apoA-I, apolipoprotein A-I; apoB100, apolipoprotein B100; apoB48, apolipoprotein B48; CVD, cardiovascular diseases; CYP1A2, cytochrome P450 1A2; CYP2E1, cytochrome P450 2E1; dAUC, decremental area under the curve; DBP, diastolic blood pressure; FFA, free fatty acid; FFQ, food frequency questionnaires; GSEA, gene set enrichment analysis; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitivity c-reactive protein; iAUC, incremental area under the curve; IPA, ingenuity pathway analysis; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; TAG, triacylglycerol.

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different meta-analyses concluded that 2–12 weeks of cocoa consumption significantly decreased low-density lipoprotein cholesterol (LDL-C) and total cholesterol concentrations. However, no effects were found on high-density lipoprotein cholesterol (HDL-C) and triacylglycerol (TAG) concentrations [2,3]. Given the macronutrient composition of chocolate, the potential positive effects of chocolate on serum LDL-C are probably due to one of the minor compounds in cocoa [4]. As dark chocolate contains more cocoa than other chocolate types, dark chocolate should therefore have more favorable metabolic effects than white or milk chocolate. Indeed, Grassi et al. observed that the intake of 100 g of dark chocolate for 15 days increased insulin sensitivity and decreased blood pressure, total cholesterol and LDL-C, while white chocolate did not [5]. Furthermore, Taubert et al. found a decrease in blood pressure, but no changes in plasma lipids or glucose after 18-weeks of dark chocolate consumption compared with white chocolate consumption [6].

Whether cocoa or dark chocolate also influences postprandial lipid and glucose metabolism has only been explored to a limited extent. This is unfortunate, since evidence is accumulating that disturbances in postprandial lipid and glucose metabolism are important risk markers for CVD [7,8]. In type 2 diabetic patients, Basu et al. (2015) showed increased postprandial HDL-C and insulin concentrations, but no differences in LDL-C, TAG, glucose and high-sensitivity C-reactive protein (hsCRP) concentrations after acute cocoa consumption [9]. In contrast, based on an oral-glucose-tolerance test, insulin sensitivity in healthy subjects improved after 100 g of dark chocolate consumption for 15 days [10].

An important question is which component in cacao may be responsible for the suggested beneficial fasting and postprandial metabolic effects. Theobromine, a methylxanthine in cocoa, is a promising candidate [11] given its beneficial effects on blood pressure [10] and fasting plasma lipids [12]. So far, effects of theobromine on postprandial metabolism have not been examined. Therefore, the aim of the present study was to evaluate the effects of 4-weeks pure theobromine intake (500 mg/day) on fasting and postprandial lipid, lipoprotein and glucose metabolism. We were especially interested in changes in HDL metabolism, since theobromine has been reported to increase fasting apolipoprotein A-I (apoA-I) concentrations [12], which may decrease CVD risk [13]. Therefore, overweight and slightly obese subjects with low HDL-C concentrations were included, as these subjects may be more responsive to interventions targeting HDL metabolism. Potential underlying mechanisms were addressed by performing microarray analyses in duodenal biopsies.

2. Material and methods

2.1. Study population

Apparently healthy middle-aged and elderly overweight and slightly obese men and women (BMI 25–35 kg/m^2) were recruited in University and hospital buildings by posters, in local newspapers via advertisements, and among participants who had participated in earlier studies from our Department. They were invited for two screening visits with an interval of $\geq$1 week. During the screening visits body weight without heavy clothing, height, and blood pressure were determined. Blood pressure was measured in fourfold using an Omron M7 (Omron Healthycare Europe B.V., Hoofddorp, The Netherlands). The first measurement was not used and the final three measurements were averaged. Furthermore, a fasting blood sample was taken for analysis of serum total cholesterol, HDL-C, and plasma glucose concentrations. In addition, subjects had to complete a general and medical questionnaire. Inclusion criteria were: men aged between 45 and 70 years, and women aged between 50 and 70 years to exclude pregnant women, since theobromine can cross the placenta [14], BMI between 25 and 35 kg/m^2, fasting serum HDL-C concentrations <1.2 mmol/L for men and <1.5 mmol/L for women so as to include participants with HDL-C concentrations below the 50th percentile of the Dutch population [15], fasting serum total cholesterol concentrations <8.0 mmol/L, fasting plasma glucose concentrations <7.0 mmol/L, stable body weight (weight gain or loss <3 kg in the previous 3 months), no use of lipid-lowering, anti-diabetic or anti-hypertensive medication or a medically prescribed diet, no history or current gastrointestinal diseases or complaints, no use of vitamin or fish oil supplements, no diabetes, no abuse of alcohol or drugs, no smoking, and no active or history of coronary artery disease. In addition, subjects had not participated in another biomedical study for the past 30 days. After information about the aim of the study was given and the potential risks of the experimental procedures were discussed, all participants gave their written informed consent before entering the study. Forty-eight participants were included. After inclusion, subjects were urged not to change their dietary habits, levels of physical exercise, and alcohol intake during the study. The study was performed according to the guidelines laid down in the Declaration of Helsinki. The protocol was approved by the Medical Ethical Committee of the University Hospital Maastricht and the trial was registered on clinicaltrials.gov under study number NCT02209025.

2.2. Study design and product

The study had a randomized, double blind, placebo-controlled, crossover design and consisted of 2 intervention periods of 4-weeks, separated by a 4-week washout period. From 2-weeks before the start of the study and during the study, participants were instructed by a research dietician to avoid products containing cocoa, for which they received a detailed list with products. Furthermore, the consumption of caffeine-containing drinks was restricted to a maximum of 4 cups a day, since theobromine is a metabolite of caffeine. In theory, these 4 caffeine-containing drinks could result in the formation of maximally 80 mg of theobromine [16], which was ±16% of the daily experimental theobromine intake (500 mg) as provided by us. During the test days, caffeine intake was prohibited. Based on a computer-generated randomization scheme, subjects were allocated to a group starting with theobromine or placebo drinks. At breakfast, subjects consumed daily drinks (20 ml) enriched with 500 mg theobromine or placebo. The experimental and placebo drinks were matched for composition, appearance and taste (Supplementary data, Table 1). Theobromine was obtained from Fagron (Uitgeest, the Netherlands) and drinks were produced by Pharmavize (Mariakerke, Belgium). The drinks were provided in boxes of eight 20 ml flasks and participants received 2 boxes at the start of the 4-week intervention period and 2 boxes halfway the intervention period. The drinks and boxes were color-coded to blind the participants and investigators. Subjects were required to return all empty bottles and unused drinks, which were counted to estimate compliance. At the end of the two intervention periods, subjects had to record their habitual food intake of the previous 4 weeks by completing a food frequency questionnaire (FFQ). From these FFQs, energy and nutrient intakes were calculated using the Dutch Nutrient databank [44]. FFQs were immediately checked by the research dietician in the presence of the subjects. Participants recorded in diaries any signs of illness, medication used, alcohol consumption, and any deviations from the study protocol and other complaints.

2.3. Visits, postprandial test, test meal and biopsies

All subjects visited the University at the start of the study (day 1), and twice in the fourth week (days 25 and 28) of both the

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