Dairy products influence gut hormone secretion and appetite differently: A randomized controlled crossover trial

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ABSTRACT

Little is known about how dairy products with different nutrient contents and food matrices affect appetite sensation and gut hormone secretion. The objective of this study was to investigate how appetite sensation and gut hormone secretion in healthy adults are affected by meals with the same amount of fat but from different dairy products. Forty-seven healthy adults (70% women) were recruited to a randomized controlled crossover study with 4 dairy meals consisting of butter, cheese, whipped cream, or sour cream, corresponding to 45 g (approximately 60 energy percent) of fat. Plasma samples were collected for analysis of cholecystokinin (CCK), pancreatic polypeptide (PP), peptide YY (PYY), and ghrelin concentrations at 0, 2, 4, and 6 h after the meals and analyzed as the incremental area under the curve (iAUC_{0–6h}) in a mixed model. Hunger, satiety, and appetite sensations were measured with a visual analog scale (VAS) immediately after finishing the meals and at 4 and 6 h postprandially. Intake of cheese induced a higher level of plasma PP-iAUC_{0–6h} compared with butter or whipped cream, and a higher level of plasma CCK-iAUC_{0–6h} compared with whipped cream. Intake of whipped cream increased VAS appetite at 4 h compared with cheese or sour cream, and at 6 h compared with cheese or butter. No significant meal effect was found for hunger, satiety, plasma PYY, or plasma ghrelin concentration. Intake of cheese increased postprandial plasma PP and CCK concentrations and decreased appetite compared with whipped cream but not with sour cream. These findings encourage further

investigations of how different dairy products affect gut hormone secretion and appetite sensation.

Key words: dairy matrix, gut hormones, appetite, visual analog scale

INTRODUCTION

Obesity is a large global disease burden, as more than 650 million adults have a body mass index (BMI) ≥ 30 kg/m² (WHO, 2011, 2017). Obesity develops due to long-term imbalance of energy intake and energy expenditure (Jéquier and Tappy, 1999; Broskey et al., 2000), and energy intake is partly regulated by gut hormone secretion (Begg and Woods, 2013). The gut hormones cholecystokinin (CCK), peptide YY (PYY), and pancreatic polypeptide (PP) are released during food intake and attenuate appetite (Batterham et al., 2002, 2003a,b; Dhillon and Bloom, 2004; Chandra and Liddle, 2007; Karhunen et al., 2008). Infusion of both PYY and PP in humans has been shown to generate a decrease in food intake for up to 24 h (Batterham et al., 2003a,b), and lower fasting PYY concentrations have been observed in obese subjects compared with lean subjects (Batterham et al., 2003a). Ghrelin, on the other hand, is an appetite-stimulating hormone that is increased during fasting and decreases in response to meal ingestion (Tschöp et al., 2000; Wren et al., 2001; Heinonen et al., 2007; Müller et al., 2015), and infusion of ghrelin in humans has been shown to increase food intake (Wren et al., 2001). In addition to objective measurements of gut hormones, subjective appetite sensations can be measured with a visual analog scale (VAS), which has been proven to be a reliable method in appetite research with postprandial meal studies (Flint et al., 2000; Karhunen et al., 2010).

High dairy intake during energy restriction may favor weight loss and body fat reduction (Zemel, 2005;

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Abargouei et al., 2012; Stonehouse et al., 2016; Geng et al., 2018). For example, an energy-restricted calcium-rich diet with yogurt has been shown to induce a more pronounced loss of fat mass in obese subjects compared with an isocaloric control diet without yogurt (Zemel et al., 2005). However, a recent meta-analysis found that large intake of dairy products can increase not only satiety but also the risk of positive energy balance (Onvani et al., 2017). How different kinds of dairy products affect postprandial appetite and gut hormone secretion is less known, and contradictory results exist. Yogurt has been shown to induce a lower postprandial hunger sensation compared with cheese or milk in an isocaloric and isovolumetric setting, but no differences in plasma PYY or ghrelin concentrations between the dairy products were observed (Dougkas et al., 2012). Another study found a difference in postprandial PYY concentration between fermented milk and whole milk, but with no difference in appetite VAS scores (Sanggaard et al., 2004). Still another study found no difference in subjective appetite sensations when comparing liquid yogurt with semisolid yogurt (Tsuchiya et al., 2006). We recently reported that glucose-dependent insulinotropic polypeptide concentrations were similar after intake of different dairy products with identical fat contents (Hansson et al., 2019). However, because several gut hormones are involved in appetite regulation, the aim of this paper was to further examine any differences in the 0 to 6-h incremental area under the curve for plasma PP, PYY, CCK, and ghrelin concentrations after intake of solid and semisolid dairy products in healthy adults. The aim was also to analyze changes in VAS scores for hunger, satiety, and appetite between 0 and 4 h and 0 to 6 h.

MATERIALS AND METHODS

Subjects

Healthy subjects between 18 and 70 yr of age with a BMI of 18.5 to 25 kg/m² and waist circumference <80 cm for women and <94 cm for men, or BMI of ≥25 kg/m² and waist circumference ≥80 cm for women and ≥94 cm for men, were recruited to a postprandial study conducted at the University of Oslo between 2016 and 2017. Forty-seven subjects attended the first study visit and were included in the analyses. Detailed inclusion and exclusion criteria are presented elsewhere (Hansson et al., 2019).

Study Design

A randomized controlled crossover meal trial with 4 high-fat dairy meals as intervention was performed,

which has been detailed elsewhere (Hansson et al., 2019). In brief, each meal consisted of 3 toasted slices of white bread (Pågen Rosta, Pågen AS, Oslo, Norway), raspberry jam (Nora Bringe bær syltetøy, Orklafoods, Oslo, Norway), and butter (**B**; TINE Smør, TINE BA, Oslo, Norway), medium-hard cheese (**C**; TINE Gräddost, TINE BA, Oslo, Norway), whipped cream (**WC**; TINE Kremfløte, TINE BA, Oslo, Norway), or sour cream (**SC**; TINE Seterrømme, TINE BA, Oslo, Norway), corresponding to total energy contents of 629 kcal, 715 kcal, 652 kcal, and 655 kcal, respectively. Each meal consisted of 45 g, or approximately 60 energy percent (**E%**), of fat. The protein contents of the meals were 8.8 g (5.7 E%), 30.0 g (17.2 E%), 10.9 g (6.9 E%), and 11.2 g (7.0 E%), respectively. The carbohydrate contents of the meals were 45.3 g (30.5 E%), 45.1 g (26.6 E%), 48.4 g (31.3 E%), and 48.6 g (31.3 E%), respectively. The calcium contents were 9.0 mg, 678.0 mg, 85.0 mg, and 94.0 mg, respectively. Subjects were randomly allocated by block randomization (with a ratio of 1:1:1:1) to 1 of 4 test meal orders (order 1: B_C_WC_SC, order 2: C_WC_SC_B, order 3: WC_SC_B_C, order 4: SC_B_C_WC; Figure 1). The principal investigator was responsible for the meal order allocations. Between each test day there was a 3- to 5-wk wash-out period for premenopausal women not taking contraceptives and a minimum wash-out period of 2 wk for other participants. Before each test day, subjects received a text message with instructions to fast for 12 h, not to eat a high-fat meal in the evening, and not to perform any strenuous physical activity or drink alcohol during the 24 h before their visit. Blood samples for gut hormone analysis were collected before ingesting the meal (fasting) and 2, 4, and 6 h after meal ingestion. A VAS form was filled out by the participants immediately after ingesting each meal and along with the postprandial blood sampling. Subjects were instructed to be physically inactive during the 6-h period of blood sampling.

Blood Sampling and Plasma Gut Hormone Analysis

Plasma was collected in EDTA tubes (Becton Dickinson Vacutainer Systems, Plymouth, UK) and kept on ice for less than 15 min before being centrifuged at 2,000 × *g* for 15 min at 4° C (Thermo Fisher Scientific, Waltham, MA) and stored at −80°C until analysis. Ghrelin, PP, and PYY were analyzed using Milliplex Map Kit for human metabolic hormone magnetic bead panel (cat. no. HMHEMAG-34K, EMD Millipore Corporation, Billerica, MA). All samples were measured in duplicate, along with controls, using Bio-Plex 200 system, based on Luminex xMAP technology (Bio-Rad Laboratories Inc., Hercules, CA; Ingerslev et al., 2017).

Figure 1. Overview of study design and flowchart. Fifty-two participants were randomly allocated to 1 of 4 meal orders, starting with butter (dark grey), cheese (grey), whipped cream (light grey), or sour cream (white). n indicates the number of participants fulfilling each meal per each test day.

Figure 2. Changes in plasma pancreatic polypeptide (PP) concentrations in healthy adults after intake of meals containing butter, cheese, whipped cream, or sour cream. Values are mean $\pm$ SEM. B = meal rich in fat from butter (n = 32); C = meal rich in fat from medium-hard cheese (n = 34); WC = meal rich in fat from whipped cream (n = 37); SC = meal rich in fat from sour cream (n = 32); iAUC = incremental area under the curve. P_{meal} = P-value for meal effect; $P_{C > B}$ = P-value for the difference in response between the meal rich in fat from cheese compared with the meal rich in fat from butter; $P_{C > WB}$ = P-value for the difference in response between the meal rich in fat from cheese compared to the meal rich in fat from whipped cream.

We measured CCK using radioimmunoassay with the specific anti-serum no. 92128 with specificity for α -amidated and O-sulfated C-terminus, and measured all bioactive forms of CCK in circulation with equal potency (CCK -8, -22, -33, and -58) without cross-reactivity with any gastrin peptide (Rehfeld, 1998).

Measurement of Appetite Sensations with VAS

Participants' subjective appetite sensations were measured with a simplified and translated VAS form inspired by Flint et al. (2000). The VAS form consisted of 3 questions, each followed by a 10-cm line with ends representing extreme opposite answers. The first question was, "How hungry do you feel?" with a 10-cm scale from "Not hungry at all" to "I have never felt more hungry." The second question was "How full do you feel?" with the scale from "Not full at all" to "I have never felt more full." The last question was "How great is your desire to eat?" with the scale reaching from "No desire at all" to "I have never felt more desire."

Participants marked the lines based on what they felt just after finishing the meal and after 4 and 6 h. Each participant marked the same form for the different time points, and the distances between 0 and 4 h and 0 and 6 h were measured with a ruler.

Ethics

The study was approved by the Regional Committees for Medical and Health Research Ethics (2016/418/REK sør-øst B) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects. The study was registered at www.clinicaltrials.gov as NCT02836106.

Statistics

The original study, with serum triglycerides measured as the incremental area under the curve ($iAUC_{0-6h}$) as main outcome, had a sample size estimation set to 22 lean and 22 overweight participants, with an an-

Figure 3. Changes in plasma cholecystokinin (CCK) concentrations in healthy adults after intake of meals containing butter, cream, or sour cream. Values are mean $\pm$ SEM. B = meal rich in fat from butter ($n = 36$); C = meal rich in fat from medium-hard cheese ($n = 35$); WC = meal rich in fat from whipped cream ($n = 37$); SC = meal rich in fat from sour cream ($n = 35$); $iAUC$ = incremental area under the curve; P_{meal} = P -value for meal effect; $P_{C > WC}$ = P -value for the difference in response between the meal rich in fat from cheese compared with the meal rich in fat from whipped cream.

anticipated dropout rate of 20% based on previous studies (Hansson et al., 2019). In this paper, the subjects were analyzed as a single group with adjustment for BMI, with baseline characteristics presented as medians (25th to 75th percentiles). Gut hormone and VAS data were analyzed with an intention-to-treat analysis by a linear mixed model using Stata Special Edition 15.1 (StataCorp LLC, College Station, TX). All subjects who completed at least 1 test day were included in the analysis. The response variable for the gut hormones was the $iAUC_{0-6h}$, calculated using the trapezoid method (Matthews et al., 1990; Carstensen et al., 2003), whereas delta values were used to present the VAS scores. The model included subject identification number (random effect), meal, visit number, age, sex, and BMI (fixed effects). Significance was set to $\alpha = 0.05$, and Bonferroni correction was applied to adjust for multiple testing of pairwise meal comparisons. Meal comparisons were performed by combining the meal coefficients from the model, and the differences are presented in the text as percentages based on mean values. All data are presented in figures as mean values plus or minus standard error of the mean.

RESULTS

Baseline Characteristics

In total 52 subjects were randomized in the study, and 47 completed the first visit and were included in the final analyses (Figure 1). In total, 31 subjects completed all 4 test meals. Seventy percent of the included subjects were women, the median (25th to 75th percentile) age of the subjects was 32 (25 to 46) yr, and the median (25th to 75th percentile) BMI was 23.6 (21.0 to 25.8) kg/m^2 . The subjects were healthy with normal blood pressure, and lipid parameters, glucose, insulin, and C-reactive protein concentrations within reference intervals (Hansson et al., 2019).

Differences in Plasma PP, PYY, CCK, and Ghrelin Concentrations

We found a significant meal effect on plasma PP- $iAUC_{0-6h}$, with intake of cheese inducing a 139% larger plasma PP- $iAUC_{0-6h}$ compared with butter ($P < 0.001$), and an 80% larger plasma PP- $iAUC_{0-6h}$ compared with

Figure 4. Changes in plasma peptide YY (PYY) concentrations in healthy adults after intake of meals containing butter, cheese, whipped cream, or sour cream. Values are mean $\pm$ SEM. B = meal rich in fat from butter ($n = 23$); C = meal rich in fat from medium-hard cheese ($n = 19$); WC = meal rich in fat from whipped cream ($n = 26$); SC = meal rich in fat from sour cream ($n = 23$); $iAUC$ = incremental area under the curve; P_{meal} = P -value for meal effect.

whipped cream ($P = 0.001$; Figure 2, Supplemental Tables S1 and S2: <https://doi.org/10.3168/jds.2019-16863>). A significant meal effect was also found for plasma CCK-iAUC_{0-6h}, with intake of cheese inducing a 59% larger plasma CCK-iAUC_{0-6h} compared with whipped cream ($P = 0.02$; Figure 3, Supplemental Table S1: <https://doi.org/10.3168/jds.2019-16863>). We discovered no significant meal effect on plasma PYY-iAUC_{0-6h} ($P = 0.24$, Figure 4) or on ghrelin-iAUC_{0-6h} ($P = 0.10$, Figure 5), but butter showed a delayed PYY peak compared with the other dairy products (Figure 4).

Differences in VAS Appetite Sensations

A significant meal effect on VAS appetite (desire to eat) occurred at 0 to 4 h and 0 to 6 h (Supplemental Table S1: <https://doi.org/10.3168/jds.2019-16863>), with intake of whipped cream inducing a 49% larger increase in appetite at 4 h compared with cheese ($P = 0.01$) and a 38% larger increase in appetite at 4 h compared with sour cream ($P = 0.006$; Figure 6, Sup-

plemental Table S2: <https://doi.org/10.3168/jds.2019-16863>). At 6 h, intake of whipped cream induced a 34% larger increase in appetite compared with cheese ($P = 0.006$) and a 27% larger increase in appetite compared with butter ($P = 0.01$; Figure 7, Supplemental Table S2: <https://doi.org/10.3168/jds.2019-16863>). We found no significant meal effect on hunger or satiety at 4 or 6 h (Supplemental Table S1: <https://doi.org/10.3168/jds.2019-16863>).

DISCUSSION

The present study demonstrates that dairy products, in spite of having a similar energy load (629 to 715 kcal) and fat content (45 g), resulted in different postprandial gut hormone responses, indicating that dairy products might play different roles in weight management. Intake of cheese induced the highest plasma concentrations of PP and CCK postprandially, but there were no differences in PYY or ghrelin secretion among the different dairy products. Our study also reveals that dairy products significantly affect appetite to different

Figure 5. Changes in plasma ghrelin concentrations in healthy adults after intake of meals containing butter, cheese, whipped cream, or sour cream. Values are mean $\pm$ SEM. B = meal rich in fat from butter ($n = 31$); C = meal rich in fat from medium-hard cheese ($n = 28$); WC = meal rich in fat from whipped cream ($n = 32$); SC = meal rich in fat from sour cream ($n = 28$); iAUC = incremental area under the curve; P_{meal} = P -value for meal effect.

extents, with intake of whipped cream associated with the largest postprandial increase in appetite.

Whipped cream was associated with a stronger sense of appetite at 4 and 6 h compared with cheese, which was the dairy product associated with the smallest appetite increase. Interestingly, plasma PP- $iAUC_{0-6h}$ was significantly larger after intake of cheese compared with whipped cream, and PP has been shown to attenuate appetite and food intake (Batterham et al., 2003b). Intake of protein is known to stimulate PP secretion (Sirinek et al., 1985; Schmid et al., 1989; Karhunen et al., 2008), and calcium has been shown to augment the postprandial PP response of a protein-rich meal (Sirinek et al., 1985). This might contribute to the large increase in PP after intake of cheese, which has a higher content of protein and calcium compared with the other products. It is currently unclear why sour cream showed a trend ($P = 0.06$) toward higher PP- $iAUC_{0-6h}$ compared with butter, which needs to be further elucidated, but this may partly explain why sour cream significantly attenuated appetite at 4 h compared with whipped cream. The higher protein content of cheese may also explain its larger increase in plasma CCK concentration (Wang et al., 2011). We recently

reported that intake of cheese induced the largest increase in postprandial insulin concentration (Hansson et al., 2019). Previously, CCK has been reported to be insulinotropic (Rushakoff et al., 1987; Lo et al., 2011; Rehfeld, 2011), which might contribute to the insulin release. However, it is intriguing that the CCK increase after intake of cheese was significantly larger only compared with whipped cream and not with sour cream or butter, even though the meals had similar calorie load. This warrants further examination.

Lipids are stronger stimulators of PYY secretion than are proteins or carbohydrates (Zhao et al., 2017), and thus the lack of a significant meal effect on PYY- $iAUC_{0-6h}$ could be explained by the similar fat contents of the meals. Nevertheless, butter exhibited a deviating PYY response, with a delayed peak time compared with the other dairy products. This may be due to a slower gastric emptying from intake of butter, which in turn could result in a delay of the PYY peak, as PYY secretion is dependent on intestinal lipolysis (Feinle-Bisset et al., 2005). In a previous postprandial study with isocaloric and isovolumetric dairy meals, butter seemed to have a slower gastric emptying rate compared with mozzarella cheese (Clemente et al., 2003), suggested by

Figure 6. Changes in appetite visual analog scale (VAS) score in healthy adults from 0 to 4 h after intake of meals containing butter, cheese, whipped cream, or sour cream. Values are mean $\pm$ SEM. B = meal rich in fat from butter ($n = 36$); C = meal rich in fat from medium-hard cheese ($n = 35$); WC = meal rich in fat from whipped cream ($n = 38$); SC = meal rich in fat from sour cream ($n = 36$).

Figure 7. Changes in appetite visual analog scale (VAS) score in healthy adults from 0 to 6 h after intake of meals containing butter, cheese, whipped cream, or sour cream. Values are mean $\pm$ SEM. B = meal rich in fat from butter ($n = 36$); C = meal rich in fat from medium-hard cheese ($n = 35$); WC = meal rich in fat from whipped cream ($n = 38$); SC = meal rich in fat from sour cream ($n = 36$).

the authors to be related to the larger fat aggregates in butter. Furthermore, we found no significant meal effect on ghrelin- $iAUC_{0-6h}$, with similar response patterns likely due to the overall similar calorie loads of the meals.

The strengths of this study include its randomized controlled crossover design, with 4 different dairy product meals that had similar fat content and were close to isocaloric, its analysis of both VAS appetite data and gut hormone values, and its examination of dairy products as whole foods without balancing differing nutrient contents. Study visits were scheduled at approximately 1-mo intervals, to avoid hormonal interference from women's menstrual cycles. A limitation of the study is that the first postprandial blood sample was drawn after 2 h, which means that acute differences in gut hormone concentrations during the first 2 h were missed. Another limitation is the relatively small study population, partly due to a high number of dropouts. Furthermore, because our aim was to investigate the effect of solid and semisolid dairy products as whole foods, the meals were not adjusted for different nutrient contents.

In conclusion, this study demonstrates that intake of dairy products with similar amounts of fat induces different postprandial gut hormone responses and affects appetite to different extents. It remains to be investigated whether this may have an influence on weight regulation.

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GOG is employed at TINE but owns no stock in the company. The other authors have no relevant financial relationships to disclose. PH, KBH, LKLØ, HKB, and SMU designed the study; PH, KBH, and SMU conducted the study; PH and LKLØ performed statistical analyses; GOG provided essential material; JFR, GSR, and KHH performed laboratory analyses; PH, KBH, LKLØ, HKB, GOG, JFR, GSR, KHH, and SMU wrote the manuscript; PH, KBH, and SMU had primary responsibility for the final content of the manuscript. All authors read and approved the final manuscript. We thank Navida Akhter Sheikh for help with blood sampling and all logistics, Anne Randi Enget for help with blood sampling, and Anne Lene Nordengen for preparing meals and blood samples. We also thank all participants for their time and effort. This study was registered at www.clinicaltrials.gov as NCT02836106.

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