The fermentable fibre inulin increases postprandial serum short-chain fatty acids and reduces free-fatty acids and ghrelin in healthy subjects

Joshua Tarini and Thomas M.S. Wolever

Abstract: It is thought that diets high in dietary fibre are associated with reduced risk for type 2 diabetes, at least in part because the short-chain fatty acids (SCFAs) produced during the colonic fermentation of fibre beneficially influence circulating concentrations of free-fatty acids (FFAs) and gut hormones involved in the regulation of blood glucose and body mass. However, there is a paucity of data showing this sequence of events in humans. Thus, our objective was to determine the effect of the fermentable fibre inulin on postprandial glucose, insulin, SCFA, FFA, and gut hormone responses in healthy subjects. Overnight fasted healthy subjects (n = 12) were studied for 6 h after consuming 400 mL drinks, containing 80 g high-fructose corn syrup (80HFCS), 56 g HFCS (56HFCS), or 56 g HFCS plus 24 g inulin (Inulin), using a randomized, single-blind, crossover design. A standard lunch was served 4 h after the test drink. Glucose and insulin responses after Inulin did not differ significantly from those after 80HFCS or 56HFCS. Serum acetate, propionate, and butyrate were significantly higher after Inulin than after HFCS drinks from 4–6 h. FFAs fell at a similar rate after all 3 test drinks, but were lower after Inulin than after 56HFCS at 4 h (0.40 ± 0.06 vs. 0.51 ± 0.06 mmol·L^{-1}; $p < 0.05$). Compared with 56HFCS, Inulin significantly increased plasma glucagon-like peptide-1 concentrations at 30 min, and reduced ghrelin at 4.5 h and 6 h. The results are consistent with the hypothesis that dietary fibre increases the production of colonic SCFAs, which may reduce type 2 diabetes risk by reducing postprandial FFAs and favorably affecting gut hormones, which regulate food intake.

Key words: dietary fibre, dietary carbohydrates, diabetes, gut peptides, colonic fermentation, acetate, humans.

Résumé : Les régimes riches en fibres alimentaires sont associés partiellement, dit-on, à la diminution du risque de diabète de type 2 parce que les acides gras à chaîne courte (SCFA) produits durant la fermentation colique des fibres ont un effet bénéfique sur les concentrations sanguines des acides gras libres (FFA) et des hormones de l'intestin participant à la régulation de la glycémie et de la masse corporelle. Cependant, il y a très peu d'études sur cette séquence d'événements chez les humains. Par conséquent, cette étude se propose d'analyser l'effet de l'inuline, une fibre fermentescible, sur la concentration postprandiale de glucose, d'insuline, de SCFA, de FFA et sur des hormones intestinales chez des sujets en bonne santé. On étudie chez 12 sujets en bonne santé et à jeun depuis la veille les effets de l'inuline six heures après avoir consommé 400 mL d'une boisson contenant soit 80 g de sirop de maïs à haute teneur en fructose (80HFCS), soit 56 g de HFCS (56HFCS) ou 56 g de HFCS additionné de 24 g d'inuline (Inulin); on utilise un schéma expérimental à simple insu en chassé-croisé. Quatre heures après avoir consommé la boisson, on leur sert un repas standard. Comparativement aux effets de la consommation de 80HFCS ou de 56HFCS, on n'observe pas de différences de réponse du glucose et de l'insuline après avoir consommé la boisson additionnée d'inuline. Les concentrations sériques d'acétate, de proprionate et de butyrate sont significativement plus grandes 4 à 6 h après la consommation de la boisson additionnée d'inuline comparativement aux boissons de HFCS. Quatre heures après la consommation des trois boissons, on observe une diminution similaire de la concentration des FFA, mais la concentration est plus faible après la consommation de la boisson additionnée d'inuline (0,40 ± 0,06 comparativement à 0,51 ± 0,06 mmol·L^{-1}, $p < 0,05$). Comparativement à la boisson contenant seulement 56 g de HFCS, la boisson additionnée d'inuline élève la concentration de GLP-1 à la 30^{e} minute et abaisse la concentration de ghréline à la 4^{e} heure et demie et à la 5^{e} h. Les observations faites dans cette étude appuient la thèse selon laquelle les fibres alimentaires élèvent la production de SCFA dans le côlon, ce qui aurait pour effet de diminuer le risque de diabète de type 2 en abaissant la concentration postprandiale de FFA et en favorisant positivement l'action des hormones intestinales qui contrôlent l'apport alimentaire.

Mots-clés : fibre alimentaire, glucides alimentaires, diabète, peptides intestinaux, fermentation colique, acétate, humains.

[Traduit par la Rédaction]

Received 4 May 2009. Accepted 10 October 2009. Published on the NRC Research Press Web site at apnm.nrc.ca on 20 January 2010.

J. Tarini. Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON M5S 3E2, Canada.
T.M.S. Wolever.[1] Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON M5S 3E2, Canada; Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, ON M5B 1W8, Canada.

[1]Corresponding author (e-mail: thomas.wolever@utoronto.ca).

Introduction

High intakes of dietary fibre are associated with reduced risk for type 2 diabetes (T2DM) (Salmerón et al. 1997). A potential mechanism for this is the fact that the colonic fermentation of fibre produces short-chain fatty acids (SCFA), which may reduce T2DM risk by lowering free-fatty acid (FFA) concentrations and enhancing body mass regulation. Elevated FFAs are associated with the deterioration of glucose tolerance and the development of T2DM (Boden et al. 2002; Charles et al. 1997). Serum FFA concentrations are regulated primarily by the activities of hormone-sensitive lipase and adipose triglyceride lipase (Arner and Langin 2007), but other influences also exist. Increasing the carbohydrate load (Wolever et al. 1995) and slowing the rate of meal ingestion (Jenkins et al. 1990) reduce postprandial FFA responses and reduce the glycaemic response elicited by a subsequent meal, the so-called second-meal effect. Serum FFA concentrations are also reduced by the SCFAs acetate and propionate (Crouse et al. 1968; Ferchaud-Roucher et al. 2005; Wolever et al. 1991), but it is not known whether this mechanism of reducing FFA is associated with a second-meal effect. In addition, it is not known whether circulating concentrations of gut hormones are associated with a second-meal effect.

Obesity is a major risk factor for the development of T2DM (Seidell 2000). The role of colonic fermentation in obesity has recently been highlighted by the discovery that obese and lean individuals have different bacteria in their colons, and that, as the obese lose weight, their bacteriome changes to become more like that of lean individuals (Ley et al. 2006). SCFAs may affect body mass by influencing the secretion of gut hormones involved in food intake regulation. In rats, high-fibre diets have been shown to upregulate the gene expression and secretion of glucagon-like peptide-1 (GLP-1), peptide YY, and ghrelin (Delzenne et al. 2005; Keenan et al. 2006; Reimer and McBurney 1996), effects that were accompanied by either reduced weight or improved glucose homeostasis. However, adding various types of viscous or cereal fibres to test drinks has been shown to have little or no effect on postprandial GLP-1 responses over periods of 2–4 h in humans (Weickert et al. 2005). Nevertheless, this does not disprove the hypothesis that SCFAs influence gut hormones, because cereal fibre is poorly fermented and it takes longer than 2–4 h for the fermentable fibre guar gum to begin to be fermented (Wolever et al. 1992).

It has previously been shown that adding 24 g inulin to 56 g high-fructose corn syrup (HFCS) elicits a rise in breath hydrogen within 2–3 h of consumption, and delays the rebound of serum FFA 3–4 h after eating (Grysman et al. 2008). Therefore, we hypothesized that inulin would raise postprandial SCFAs, reduce FFAs, reduce the glucose and insulin responses elicited by a second meal, and have favorable effects on postprandial gut hormone responses, specifically by increasing GLP-1 and reducing ghrelin responses in healthy human subjects.

Materials and methods

We studied 12 young and healthy volunteers, aged 26 ± 1.8 years (mean ± SEM), with a body mass index (BMI) of 23 ± 0.9 kg·m^{-2} and a waist circumference of 77 ± 1.1 cm in the 7 females and 90 ± 2.1 cm in the 5 males. Subjects were recruited by the authors' word of mouth. Subjects were nonsmokers, free of natural health products and prescription medications (with the exception of oral contraceptives), and had not taken antibiotics in the previous 3 months. They were also not following any unusual dietary patterns, were not anaemic, and had normal blood glucose and lipid concentrations prior to participating in the study. Individuals who reported consuming more than 30 g dietary fibre per day were excluded. All female subjects were premenopausal. Subjects were asked to refrain from alcohol consumption and strenuous physical activity for the 24-h period preceding each study day. The procedures followed were in accordance with the ethical standards of the institutional committees on human experimentation, and approval was granted by the Research Ethics Boards at St. Michael's Hospital and the University of Toronto (Toronto, Ont.). Subjects provided written informed consent prior to their participation, and all 12 completed the study.

Protocol

Overnight fasted subjects came to the Clinical Nutrition and Risk Factor Modification Centre at St. Michael's Hospital at 0730 hours on 3 separate occasions, separated by a 1-week washout. When subjects arrived, they were seated and had their forearms warmed with a heating pad. An indwelling cannula was inserted into a forearm vein; it was kept clear with periodic saline flushes. After a fasting blood sample was drawn, subjects consumed a test drink within 10 min, and further blood samples were drawn at 0.5, 1, 1.5, 2, 3, and 4 h after the start of the test drink. Immediately after the 4-h blood sample, a standard lunch was provided. Subjects ate the lunch within 15 min, and further blood samples were drawn at 4.5, 5, 5.5, and 6 h. Subjects remained seated and awake for the duration of the study.

Analytical methods

Blood for FFAs and SCFAs was drawn into tubes containing spray-coated silica and a polymer gel for serum separation (SST Vacutainer tube, BD Canada Inc., Oakville, Ont.). Blood for glucose, insulin, and C-peptide was drawn into separate SST Vacutainer tubes, to which 40 uL of insulin degradation inhibitor (ingredients not disclosed, Banting and Best Diabetes Centre Core Laboratory, University of Toronto) was added, and the tubes were inverted to mix the contents. Blood for active GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) was collected in 4 mL ice-cooled EDTA tubes; 50 μL DPP-IV inhibitor (Linco Research, Billerica, Mass.) was added, and the tubes were mixed within 30 s. Blood for ghrelin (3 mL) was collected in plain tubes containing 3 mg [4-(2-aminoethyl)-benzenesulfonyl fluoreide] and left to clot for 30 min. Tubes were centrifuged at 4 °C for 15 min at 3000 r·min^{-1} (600*g*), and the serum was removed and stored at –70 °C prior to analysis. Glucose was analyzed using the hexokinase method, the insulin by electrochemiluminecence immunoassay (ECLIA) method, the C-peptide by sandwich enzyme-linked immunosorbent assay (ELISA), and FFA were analyzed using an enzymatic method at the the Banting and Best Diabetes Centre Core Laboratory. SCFAs were measured by gas chromato-

graphy after previous microfiltration and vacuum distillation, as described elsewhere (Vogt et al. 2004*b*). GLP-1 (catalogue no. EGLP-35K), GIP (catalogue no. EZHGIP-54K), and total ghrelin (catalogue no. EZGRT-89K) were measured by ELISA using kits purchased from Millipore Inc. (Billerica, Mass.).

Test drinks

The 3 test drinks (treatments) consisted of 80 g HFCS (80HFCS; containing 42% fructose and 58% glucose; Cargill Inc., Minnetonka, Minn.); 56 g HFCS plus 24 g Oliggo-Fibre Instant Inulin (Inulin; 90% dietary fibre, 10% free fructose, glucose and saccharose; Cargill, Inc.) or 56 g HFCS alone (56HFCS) dissolved in 400 mL bottled water on the morning of the study. Each subject consumed all 3 treatments in random order.

The treatments in this study were designed to distinguish between the effects of adding inulin to HFCS or partially substituting inulin for HFCS. This distinction is relevant and important because inulin and other types of dietary fibre are appearing more and more in the food supply, and are often added to foods at the expense of available carbohydrate, resulting in a product with reduced energy content and (or) reduced glycemic load. While such products may be beneficial, their metabolic effects may differ from those seen when dietary fibre intake is added to a fixed amount of available carbohydrate.

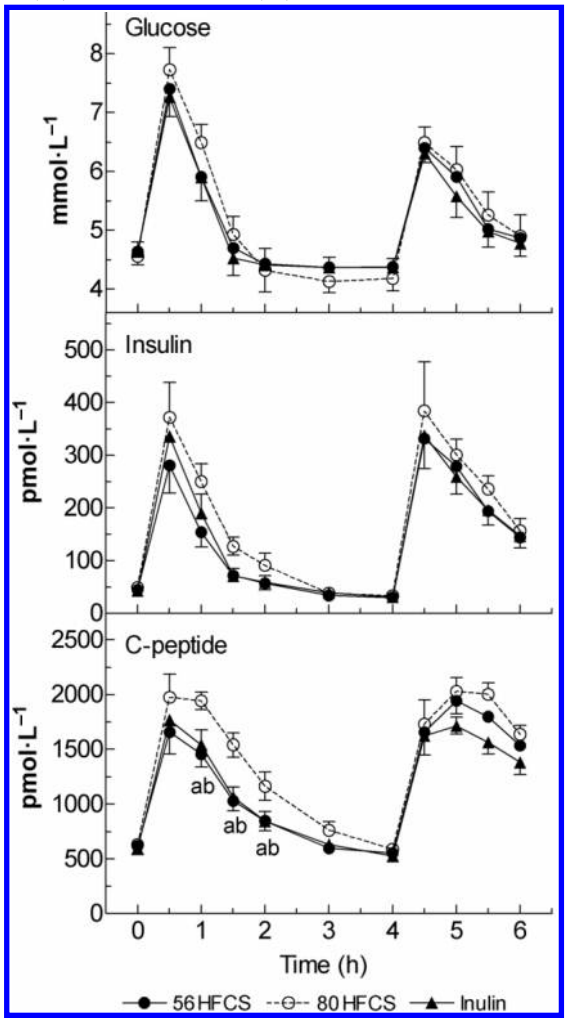
Standard lunch

The standard lunch consisted of a cheese and tomato sandwich (2 slices of whole wheat bread, 65 g fresh tomato, 45 g medium cheddar cheese, 15 g whipped dressing), a drink of apple juice (200 mL), a bottle of water (500 mL), and 2 chocolate cookies (chocolate thins). The lunch provided 551 calories (46% as carbohydrate, 14% as protein, and 40% as fat) and 4 g fibre.

Statistical analyses

Results are given as means ± SEM. Ghrelin and GIP concentrations were considered to be non-normally distributed, based on visual inspection, and were normalized prior to statistical analysis by taking logarithms. The primary statistical analysis, upon which the conclusions were based, was a repeated-measures analysis of variance (ANOVA), examining for the main effects of time (0 through 6 h) and treatment (test drink) and the time × treatment interaction. Significant differences between test meals at individual time points were assessed using ANOVA only if a significant time × treatment interaction was found. Incremental areas under the curve (AUC), ignoring the area beneath the baseline, were calculated geometrically for the 0–2-, 0–4-, and 4–6-h periods, using a Lotus 1-2-3 (97 edition, Lotus Development Corp., Cambridge, Mass.) spreadsheet. For the 0–2- and 0–4-h AUC, the value at 0 h was taken as the baseline; for the 4–6-h AUC, the value at 4 h was taken to be the baseline. AUC values were also subjected to ANOVA. After demonstrating significant heterogeneity, the significance of differences between individual means was assessed using Tukey's test to control for multiple comparisons. Differences were taken to be statistically significant if 2-tailed $p < 0.05$. ANOVA was performed on a Lotus 1-2-3 spreadsheet, with formulae developed and tested using examples provided by Cody and Smith (1997). To investigate a possible relationship between serum FFA and SCFA responses, the difference between concentrations at the 4-h time point after the Inulin treatment and the average of the concentrations 4 h after the non-inulin treatments (56HFCS and 80HFCS) were calculated, and the differences in FFAs were correlated with the differences in acetate, propionate, and butyrate.

Fig. 1. Serum glucose, insulin, and C-peptide responses (means ± SEM) in 12 healthy subjects who consumed 80 g high-fructose corn syrup (80HFCS), 56 g HFCS (56HFCS), or 56 g HFCS plus 24 g inulin (Inulin) at 0 h and after a standard lunch at 4 h. Significant differences: $p < 0.05$, Tukey's test after significant time × treatment interaction by analysis of variance (ANOVA)); a, 80HFCS vs. 56HFCS; b, 80HFCS vs. Inulin; c, 56HFCS vs. Inulin.



Results

Glucose, insulin, and C-peptide

The glycaemic responses elicited by Inulin and 56HFCS tended to be smaller than those elicited by 80HFCS, but the difference was not statistically significant (Fig. 1). There was no significant difference in glucose AUC among treatments (Table 1). There was a main effect of treatment ($p = 0.013$), but no significant time × treatment interaction for insulin. Insulin AUC after 80HFCS was 40% greater than

Table 1. Incremental areas under the curve for glucose, insulin, C-peptide, and short-chain fatty acids (SCFAs) after the 3 treatments.

Variable	Time after intake (h)	80HFCS	56HFCS	Inulin
Glucose (mmol×min·L^{-1})	0–2	174±17	135±20	128±16
	0–4	181±19	141±21	134±17
	4–6	171±23	138±25	124±23
Insulin (nmol×min·L^{-1})	0–2	18.8±2.3b	11.5±1.8a	14.4±2.9ab
	0–4	20.3±2.5b	12.0±1.9a	15.2±2.9ab
	4–6	26.5±2.9	23.2±2.7	22.7±2.6
C-peptide (nmol×min·L^{-1})	0–2	115±5b	72±7a	81±7a
	0–4	141±11b	80±8a	91±7a
	4–6	136±6	127±11	112±7
Acetate (μmol×min·L^{-1})	0–2	138±99	82±57	117±115
	0–4	179±132a	221±179a	1540±580b
	4–6	706±229	718±283	1020±314
Proptionate (μmol×min·L^{-1})	0–2	6±3	7±4	7±5
	0–4	9±4	9±5	17±7
	4–6	69±16a	79±18a	149±40b
Butyrate (μmol×min·L^{-1})	0–2	4±2	5±3	5±4
	0–4	5±2	6±4	11±5
	4–6	21±7a	19±5a	74±15b

Note: Values are means ± SEM for n = 12 subjects. Means in the same row with different letters differ significantly ($p < 0.05$). 80HFCS, 80 g high-fructose corn syrup; 56HFCS, 56 g HFCS; Inulin, 56 g HFCS plus 24 g inulin.

that after 56HFCS for both the 0–2-h ($p < 0.05$) and 0–4-h ($p < 0.05$) time periods; insulin AUC after Inulin was intermediate (Table 1). C-peptide was less after Inulin and 56HFCS than after 80HFCS at 1, 1.5, and 2 h ($p < 0.007$; Fig. 1). AUC after Inulin and 56HFCS was 30% and 37% less, respectively, than after 80HFCS over the 0–2-h period ($p < 0.05$), and 35% and 43% less, respectively, than after 80HFCS over the 0–4-h period ($p < 0.05$; Table 1).

There were no significant differences between treatments for glucose, insulin, or C-peptide responses after lunch (i.e,. between 4 and 6 h).

Free-fatty acids

After inulin, FFAs were less than after 56HFCS at 4 h ($p < 0.05$); after 56HFCS, FFAs were greater than after 80HFCS at 2 h ($p < 0.05$; Fig. 2). FFAs at 4 h after Inulin also tended to be less than after 80HFCS, but the difference just missed statistical significance ($p = 0.07$). During the first 4 h, the minimum FFA concentration attained did not differ significantly among treatments (0.09 ± 0.01, 0.08 ± 0.01, and 0.07 ± 0.01 mmol·L^{-1} for 56HFCS, Inulin, and 80HFCS, respectively). However, the minimum FFA concentration occurred sooner after 56HFCS than after 80HFCS (70 ± 6 vs. 93 ± 9 min; $p < 0.05$); after Inulin, it was intermediate (88 ± 8 min). There was no significant difference in FFAs among treatments after lunch.

Short-chain fatty acids

After Inulin, serum acetate was significantly greater than after both of the other treatments at 3 h, and the concentrations of acetate, propionate, and butyrate were significantly greater from 4–6 h after Inulin than after both of the other treatments (Fig. 2). During the 0–4-h period, acetate AUC was 90% greater after Inulin than after 56HFCS or 80HFCS ($p < 0.05$; Table 1). However, propionate and butyrate AUC were about 50% greater after Inulin than after either other treatment over the 4–6-h period ($p < 0.05$; Table 1).

GIP, GLP-1, and ghrelin

Serum GIP concentrations at 2 and 3 h after Inulin and 56HFCS were significantly less than after 80HFCS (Fig. 3). During the 0–4-h period, GIP AUC after Inulin and 56HFCS (309 ± 24 and 298 ± 24 pg × h·mL^{-1}, respectively) was significantly less than after 80HFCS (377 ± 24 pg × h·mL^{-1}). There was no significant difference in GIP among treatments after lunch. Serum GLP-1 did not differ significantly among treatments at any time, except at 30 min, when serum GLP-1 after Inulin and after 80HFCS was significantly greater than that after 56HFCS (Fig. 3). Serum ghrelin responses did not differ among the test drinks over the first 3 h; however, after Inulin, serum ghrelin was significantly lower than after 80HFCS at 4 and 4.5 h, and significantly less than after 56HFCS at 4.5 and 6 h (Fig. 3).

Correlations

The changes in serum acetate elicited by Inulin at 4 h in individual subjects (value for Inulin minus average of values for HFCS56 and HFCS80) were not significantly related to the changes in FFA or ghrelin concentrations (Fig. 4).

Discussion

It has been suggested that the SCFAs produced by the colonic fermentation of dietary fibre might protect against diabetes in at least 3 ways: increasing insulin sensitivity by reducing postprandial FFAs; increasing β-cell function and insulin secretion by increasing GLP-1 secretion; and reducing weight gain by beneficially influencing the secretion of gut hormones, such as ghrelin, involved in food intake regu-

Fig. 2. Serum free-fatty acids (FFAs), acetate, propionate, and butyrate responses (means ± SEM) in 12 healthy subjects who consumed 80 g high-fructose corn syrup (80HFCS), 56 g HFCS (56HFCS), or 56 g HFCS plus 24 g inulin (Inulin) at 0 h and after a standard lunch at 4 h. Significant differences: $p < 0.05$, Tukey's test after significant time × treatment interaction by ANOVA; a, 80HFCS vs. 56HFCS; b, 80HFCS vs. Inulin; c, 56HFCS vs. Inulin.

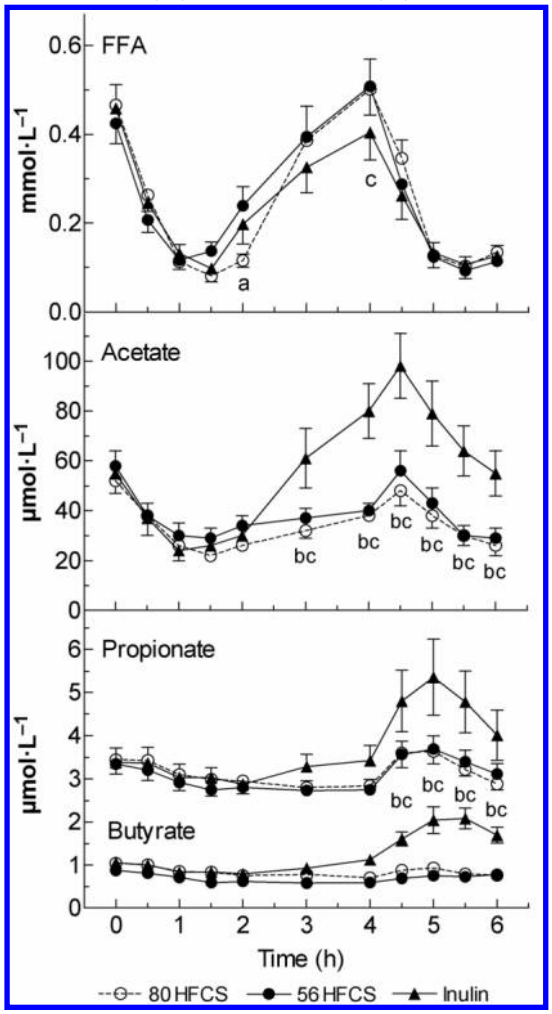
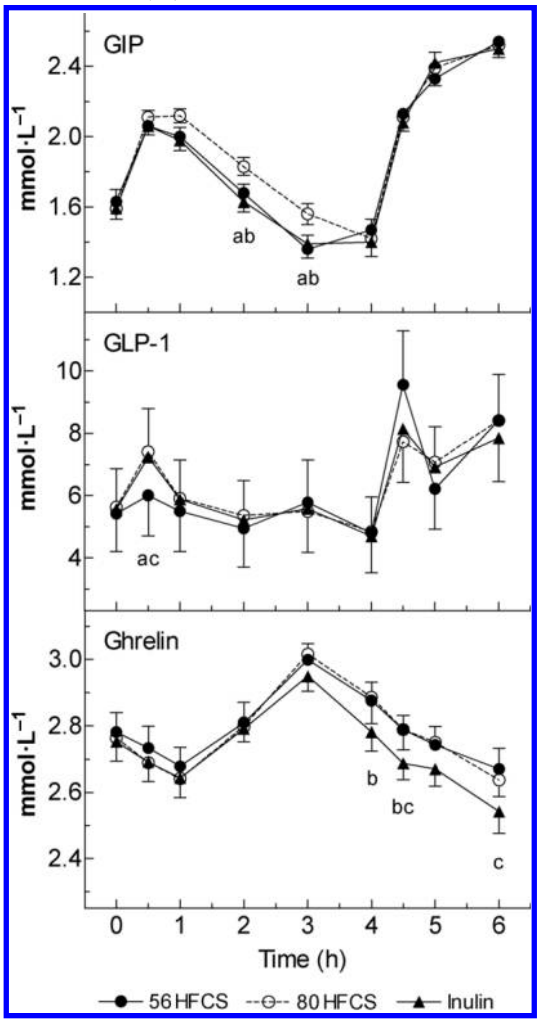


Fig. 3. Plasma glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and serum ghrelin responses (means ± SEM) in 12 healthy subjects who consumed 80 g high-fructose corn syrup (80HFCS), 56 g HFCS (56HFCS), or 56 g HFCS plus 24 g inulin (Inulin) at 0 h and after a standard lunch at 4 h. Significant differences: $p < 0.05$, Tukey's test after significant time × treatment interaction by ANOVA; a, 80HFCS vs. 56HFCS; b, 80HFCS vs. Inulin; c, 56HFCS vs. Inulin.



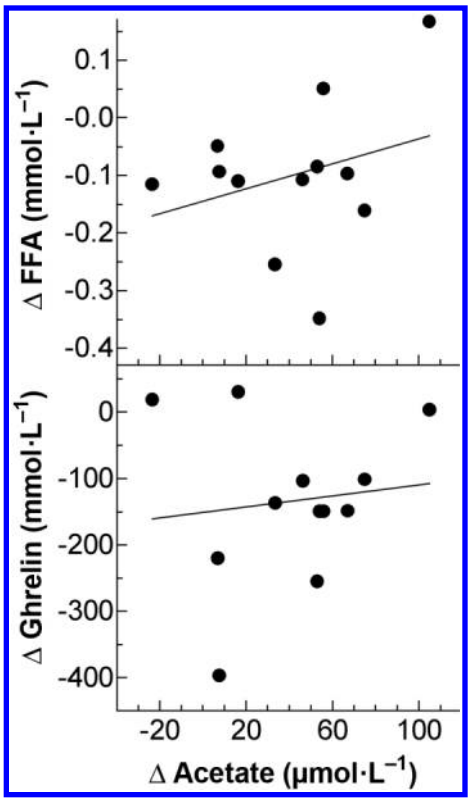
lation (Weickert and Pfeiffer 2008). Our results demonstrate a link between colonic SCFAs and several of these effects by showing that inulin increased postprandial SCFAs, and that this was associated with reduced postprandial FFA and ghrelin concentrations.

The results show that both adding and substituting inulin reduced postprandial FFAs, but did so at different times. Adding available carbohydrate (80HFCS vs. 56HFCS) prolonged the suppression of FFAs for about 20–30 min, but did not affect FFA concentrations 3–4 h after eating. Adding fermentable fibre (Inulin vs. 56HFCS) did not affect the time when FFAs began to rise from the nadir, but did result in a slower rise so that there was a lower concentration 4 h after eating.

Inulin elicited significantly greater serum SCFA concentrations than the inulin-free test drinks as soon as 180 min after eating. This presumably reflects the more rapid transit of inulin through the small intestine and fermentation in the colon, compared with guar, after which it took 8–10 h to detect a rise in serum acetate (Wolever et al. 1992). Apart from work showing a selective increase in serum acetate after oral lactulose and in serum propionate after oral L-rhamnose (Vogt et al. 2004*b*), identification of serum SCFA profiles after individual dietary fibre has received little attention. Our results are of interest because they show that inulin elicits large serum responses from all 3 major SCFAs. It is not clear whether this is due to a difference in the type of SCFA produced after inulin vs. lactulose or rhamnose, or to the larger dose used here (24 g), compared with the 8–9 g of lactulose or rhamnose (Vogt et al. 2004*b*).

Rectal infusion of acetate and (or) propionate reduced serum FFAs in a dose-dependent fashion (Wolever et al. 1989, 1991), possibly via inhibition of hormone-sensitive lipase. Since FFAs reduce muscle glucose uptake, increase hepatic glucose output (Boden et al. 1994; Ferrannini et al. 1983), and chronically reduce glucose-stimulated insulin secretion

Fig. 4. Relationship between changes in serum acetate at 4 h after 24 g inulin (Inulin), compared with controls, and changes in fatty-free acid (FFA) (nonsignificant) and ghrelin (nonsignificant) concentrations. Changes were calculated by subtracting the mean of the values 4 h after 56 g high-fructose corn syrup (HFCS) and 80 g HFCS from the value 4 h after Inulin.



(Carpentier et al. 1999), the ability of colonic SCFAs to lower serum FFAs could be a mechanism by which fibre reduces the risk for diabetes (Venn and Mann 2004). Soluble fibres, such as guar, reduce postprandial FFAs (Jenkins et al. 1980), but this has been attributed to delayed carbohydrate absorption (Jenkins et al. 1990) rather than colonic fermentation. Nonviscous unavailable carbohydrates, such as lactulose or inulin, do not reduce the rate of glucose absorption and, thus, provide an experimental model to test whether SCFAs produced during colonic fermentation (as opposed to intravenous or rectal infusion of SCFAs) reduce postprandial FFAs. Adding small amounts (5–9 g) of lactulose or rhamnose to breakfast meals had no significant effect on postprandial FFAs (Brighenti et al. 2006; Vogt et al. 2004*b*), nor did consuming 25 g·day^{-1} of lactulose or rhamnose for 4 weeks (Vogt et al. 2004*a*). However, increased breath hydrogen and reduced fasting FFAs have been seen on the morning after consuming high-soluble-fibre foods, such as barley or oats, the evening before (Nilsson et al. 2008; Thorburn et al. 1993). Also, when subjects with diabetes increased dietary fibre intake (mixed sources) from 30 to 55 g·day^{-1}, fasting serum acetate increased while FFA decreased, with their concentrations being inversely correlated with each other (Akanji et al. 1989). In our study, the rise in acetate elicited by inulin occurred before the reduction in FFAs, but there was no correlation between changes in serum acetate and changes in FFA concentration. This could be explained if the ability of acetate to reduce FFAs differs in different subjects, or if the reduction in FFAs was mainly due to portal blood acetate reducing FFA release from abdominal adipose tissue; the portal acetate concentration may not be related to the peripheral blood acetate because of differences in hepatic acetate uptake. Akanji et al. (1989) demonstrated a correlation between serum FFA and acetate concentrations in a fasting state, following a 6-week chronic high-fibre diet, a situation quite different from our study.

We measured GLP-1 because animal studies suggest that SCFAs may protect against diabetes by upregulating GLP-1 secretion and increasing insulin secretion (Reimer and McBurney 1996; Tappenden et al. 1996). We measured GIP because the secretion of GLP-1 from L-cells located in the terminal ileum is stimulated both by luminal nutrients (Roberge and Brubaker 1991) and by GIP, via an enteroendocrine loop (Roberge and Brubaker 1993). We found that adding 24 g carbohydrate to 56 g HFCS increased the acute rise of serum GLP-1 to the same extent, whether the carbohydrate was available (80HFCS) or unavailable (Inulin). The rise in GLP-1 at 30 min is difficult to explain, because it occurred presumably before the meal had reached the terminal ileum, and it was not associated with a rise in SCFAs or an increase in GIP. By contrast, GIP was not affected by adding 24 g inulin to 56 g HFCS, but was stimulated by additional available carbohydrate (80HFCS) beginning about 1 h after the meal.

Ghrelin is an orexigenic peptide produced in the stomach and small intestine (Field et al. 2008). Feeding inulin to rats reduces body fat, increases serum GLP-1, and reduces ghrelin (Delzenne et al. 2005). In humans, across a range of intakes of 220 to 1000 kcal, the nadir of postprandial ghrelin was found to decrease by about 2.4% for every 100 kcal increase of energy intake (Callahan et al. 2004). This is consistent with our results because the mean nadir of ghrelin immediately after 80HFCS (320 kcal), 73% of baseline, was about 5% lower than that after 56HFCS (224 kcal), 78% of baseline, but this was not significant because the difference in energy intake was only 100 kcal. However, the mean nadir of serum ghrelin after lunch after Inulin, 63% of baseline, was 12% less than that after 56HFCS, 78% of baseline. This suggests that the fermentation of 24 g inulin, supplying about 50 kcal of energy, has a ghrelin-suppressive effect of about 500–600 kcal of nutrients, which are absorbed from the small intestine. Colonic fermentation may reduce ghrelin via increased peptide YY. We have shown that serum peptide YY increases after rectal infusion of saline or acetate (Freeland and Wolever 2009), and the administration of peptide YY to humans has been shown to reduce serum ghrelin (Sloth et al. 2007).

The current study is not without limitations. Although the study was undertaken to explore physiological mechanisms, the 24 g dose of inulin may be impractically large for inclusion in a food product, with respect to both product composition and potential gastrointestinal side effects; however, no such side effects were reported by the subjects in the study. We did not assess the subjects' habitual fibre intake, or their fibre intake for the 24–48 h preceding the test days; it is possible that acute or chronic fibre intake may have significantly influenced the colonic fermentation results. Finally, it is important to consider the results of the study in the con-

text of a carbohydrate-containing meal, and the fact that the fermentation, and subsequent FFA modulation, may have manifested itself differently if the inulin had been delivered as part of a mixed meal.

In summary, the results show that, in healthy subjects, inulin reduces postprandial FFA rebound and reduces the serum ghrelin response after a subsequent meal, events associated with increased colonic SCFA production. The results are consistent with the hypothesis that dietary fibre increases the production of colonic SCFAs, which may reduce T2DM risk by reducing postprandial FFAs and favorably affecting gut hormones, which regulate food intake.

Acknowledgements

Supported by grant no. OOP-64648 from the Canadian Institutes of Health Research (CIHR). J.T. was supported by a training grant from the CIHR. The authors have no conflicts of interest to declare.

References

Akanji, A.O., Peterson, D.B., Humphreys, S., and Hockaday, T.D.R. 1989. Change in plasma acetate levels in diabetic subjects on mixed high fiber diets. Am. J. Gastroenterol. **84**(11): 1365–1370. PMID:2554722.

Arner, P., and Langin, D. 2007. The role of neutral lipases in human adipose tissue lipolysis. Curr. Opin. Lipidol. **18**(3): 246–250. doi:10.1097/MOL.0b013e32811e16fb. PMID:17495596.

Boden, G., Chen, X., Ruiz, J., White, J.V., and Rossetti, L. 1994. Mechanisms of fatty acid-induced inhibition of glucose uptake. J. Clin. Invest. **93**(6): 2438–2446. doi:10.1172/JCI117252. PMID:8200979.

Boden, G., Cheung, P., Stein, T.P., Kresge, K., and Mozzoli, M. 2002. FFA cause hepatic insulin resistance by inhibiting insulin suppression of glycogenolysis. Am. J. Physiol. Endocrinol. Metab. **283**(1): E12–E19. PMID:12067837.

Brighenti, F., Benini, L., Del Rio, D., Casiraghi, C., Pellegrini, N., Scazzina, F., et al. 2006. Colonic fermentation of indigestible carbohydrates contributes to the second-meal effect. Am. J. Clin. Nutr. **83**(4): 817–822. PMID:16600933.

Callahan, H.S., Cummings, D.E., Pepe, M.S., Breen, P.A., Matthys, C.C., and Weigle, D.S. 2004. Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict intermeal interval in humans. J. Clin. Endocrinol. Metab. **89**(3): 1319–1324. doi:10.1210/jc.2003-031267. PMID:15001628.

Carpentier, A., Mittelman, S.D., Lamarche, B., Bergman, R.N., Giacca, A., and Lewis, G.F. 1999. Acute enhancement of insulin secretion by FFA in humans is lost with prolonged FFA elevation. Am. J. Physiol. Endocrinol. Metab. **276**: E1055–E1066. PMID:10362618.

Charles, M.A., Eschwège, E., Thibult, N., Claude, J.R., Warnet, J.M., Rosselin, G.E., et al. 1997. The role of non-esterified fatty acids in the deterioration of glucose tolerance in Caucasian subjects: results of the Paris Prospective Study. Diabetologia, **40**(9): 1101–1106. doi:10.1007/s001250050793. PMID:9300248.

Cody, R.P., and Smith, J.K. 1997. Applied Statistics and the SAS Programming Language. 4th ed. Prentice Hall, Upper Saddle River, N.J.

Crouse, J.R., Gerson, C.D., DeCarli, L.M., and Lieber, C.S. 1968. Role of acetate in the reduction of plasma free fatty acids produced by ethanol in man. J. Lipid Res. **9**(4): 509–512. PMID: 5725882.

Delzenne, N.M., Cani, P.D., Daubioul, C., and Neyrinck, A.M. 2005. Impact of inulin and oligofructose on gastrointestinal peptides. Br. J. Nutr. **93**(Suppl. 1): S157–S161. doi:10.1079/BJN20041342. PMID:15877889.

Ferchaud-Roucher, V., Pouteau, E., Piloquet, H., Zaïr, Y., and Krempf, M. 2005. Colonic fermentation from lactulose inhibits lipolysis in overweight subjects. Am. J. Physiol. Endocrinol. Metab. **289**(4): E716–E720. doi:10.1152/ajpendo.00430.2004. PMID:16150956.

Ferrannini, E., Barrett, E.J., Bevilacqua, S., and DeFronzo, R.A. 1983. Effect of fatty acids on glucose production and utilization in man. J. Clin. Invest. **72**(5): 1737–1747. doi:10.1172/JCI111133. PMID:6138367.

Field, B.C.T., Wren, A.M., Cooke, D., and Bloom, S.R. 2008. Gut hormones as potential new targets for appetite regulation and the treatment of obesity. Drugs, **68**(2): 147–163. doi:10.2165/00003495-200868020-00002. PMID:18197723.

Freeland, K.N., and Wolever, T.M.S. 2009. Acute effects on intravenous and rectal acetate on glucon-like peptide-1, peptide YY, ghrelin, adiponectin and tumor necrosis factor-α. Brit. J. Nutr. [Epub ahead of print.]. doi:10.1017/S0007114509991863. PMID:19818198.

Grysman, A., Carlson, T., and Wolever, T.M. 2008. Effects of sucromalt on postprandial responses in human subjects. Eur. J. Clin. Nutr. **62**(12): 1364–1371. doi:10.1038/sj.ejcn.1602890. PMID:17717534.

Jenkins, D.J.A., Wolever, T.M.S., Nineham, R., Sarson, D.L., Bloom, S.R., Ahern, J., et al. 1980. Improved glucose tolerance four hours after taking guar with glucose. Diabetologia, **19**(1): 21–24. doi:10.1007/BF00258305. PMID:6248408.

Jenkins, D.J.A., Wolever, T.M.S., Ocana, A.M., Vuksan, V., Cunnane, S.C., Jenkins, M., et al. 1990. Metabolic effects of reducing rate of glucose ingestion by single bolus versus continuous sipping. Diabetes, **39**(7): 775–781. doi:10.2337/diabetes.39.7.775. PMID:2191884.

Keenan, M.J., Zhou, J., McCutcheon, K.L., Raggio, A.M., Bateman, H.G., Todd, E., et al. 2006. Effects of resistant starch, a non-digestible fermentable fiber, on reducing body fat. Obesity (Silver Spring), **14**(9): 1523–1534. doi:10.1038/oby.2006.176. PMID:17030963.

Ley, R.E., Turnbaugh, P.J., Klein, S., and Gordon, J.I. 2006. Microbial ecology: human gut microbes associated with obesity. Nature, **444**(7122): 1022–1023. doi:10.1038/4441022a. PMID: 17183309.

Nilsson, A.C., Östman, E.M., Holst, J.J., and Björck, I.M.E. 2008. Including indigestible carbohydrates in the evening meal of healthy subjects improves glucose tolerance, lowers inflammatory markers, and increases satiety after a subsequent standardized breakfast. J. Nutr. **138**(4): 732–739. PMID:18356328.

Reimer, R.A., and McBurney, M.I. 1996. Dietary fiber modulates intestinal proglucagon messenger ribonucleic acid and postprandial secretion of glucagon-like peptide-1 and insulin in rats. Endocrinology, **137**(9): 3948–3956. doi:10.1210/en.137.9.3948. PMID:8756571.

Roberge, J.N., and Brubaker, P.L. 1991. Secretion of proglucagon-derived peptides in response to intestinal luminal nutrients. Endocrinology, **128**(6): 3169–3174. doi:10.1210/endo-128-6-3169. PMID:2036983.

Roberge, J.N., and Brubaker, P.L. 1993. Regulation of intestinal proglucagon-derived peptide secretion by glucose-dependent insulinotropic peptide in a novel enteroendocrine loop. Endocrinology, **133**(1): 233–240. doi:10.1210/en.133.1.233. PMID: 8319572.

Salmerón, J., Ascherio, A., Rimm, E.B., Colditz, G.A., Spiegelman,

D., Jenkins, D.J., et al. 1997. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care, **20**(4): 545–550. doi:10.2337/diacare.20.4.545. PMID:9096978.

Seidell, J.C. 2000. Obesity, insulin resistance and diabetes – a worldwide epidemic. Br. J. Nutr. **83**(Suppl. 1): S5–S8. doi:10.1017/S000711450000088X. PMID:10889785.

Sloth, B., Davidsen, L., Holst, J.J., Flint, A., and Astrup, A. 2007. Effect of subcutaneous injections of PYY1-36 and PYY3-36 on appetite, ad libitum energy intake, and plasma free fatty acid concentration in obese males. Am. J. Physiol. Endocrinol. Metab. **293**(2): E604–E609. doi:10.1152/ajpendo.00153.2007. PMID:17566112.

Tappenden, K.A., Thomson, A.B., Wild, G.E., and McBurney, M.I. 1996. Short-chain fatty acids increase proglucagon and ornithine decarboxylase messenger RNAs after intestinal resection in rats. J. Parenter. Enteral Nutr. **20**(5): 357–362. doi:10.1177/0148607196020005357. PMID:8887905.

Thorburn, A., Muir, J., and Proietto, J. 1993. Carbohydrate fermentation decreases hepatic glucose output in healthy subjects. Metabolism, **42**(6): 780–785. doi:10.1016/0026-0495(93)90249-N. PMID:8510524.

Venn, B.J., and Mann, J.I. 2004. Cereal grains, legumes and diabetes. Eur. J. Clin. Nutr. **58**(11): 1443–1461. doi:10.1038/sj.ejcn.1601995. PMID:15162131.

Vogt, J.A., Ishii-Schrade, K.B., Pencharz, P.B., and Wolever, T.M.S. 2004*a*. L-Rhamnose increases serum propionate after long-term supplementation, but lactulose does not raise serum acetate. Am. J. Clin. Nutr. **80**(5): 1254–1261. PMID:15531673.

Vogt, J.A., Pencharz, P.B., and Wolever, T.M.S. 2004*b*. L-Rhamnose increases serum propionate in humans. Am. J. Clin. Nutr. **80**(1): 89–94. PMID:15213033.

Weickert, M.O., and Pfeiffer, A.F.H. 2008. Metabolic effects of dietary fiber consumption and prevention of diabetes. J. Nutr. **138**(3): 439–442. PMID:18287346.

Weickert, M.O., Mohlig, M., Koebnick, C., Holst, J.J., Namsolleck, P., Ristow, M., et al. 2005. Impact of cereal fibre on glucose-regulating factors. Diabetologia, **48**(11): 2343–2353. doi:10.1007/s00125-005-1941-x. PMID:16172868.

Wolever, T.M.S., Brighenti, F., Royall, D., Jenkins, A.L., and Jenkins, D.J.A. 1989. Effect of rectal infusion of short chain fatty acids in human subjects. Am. J. Gastroenterol. **84**(9): 1027–1033. PMID:2773895.

Wolever, T.M.S., Spadafora, P., and Eshuis, H. 1991. Interaction between colonic acetate and propionate in humans. Am. J. Clin. Nutr. **53**(3): 681–687. PMID:2000822.

Wolever, T.M.S., ter Wal, P., Spadafora, P., and Robb, P. 1992. Guar, but not psyllium, increases breath methane and serum acetate concentrations in human subjects. Am. J. Clin. Nutr. **55**(3): 719–722. PMID:1312763.

Wolever, T.M.S., Bentum-Williams, A., and Jenkins, D.J.A. 1995. Physiological modulation of plasma free fatty acid concentrations by diet. Metabolic implications in nondiabetic subjects. Diabetes Care, **18**(7): 962–970. doi:10.2337/diacare.18.7.962. PMID:7555557.

This article has been cited by:

1. F. Bertram, D. Menge, V. Andresen. 2017. Die Bedeutung des Mikrobioms für die Adipositas. *Der Gynäkologe* . [CrossRef]
2. F Liu, M Prabhakar, J Ju, H Long, H-W Zhou. 2017. Effect of inulin-type fructans on blood lipid profile and glucose level: a systematic review and meta-analysis of randomized controlled trials. *European Journal of Clinical Nutrition* **71**:1, 9-20. [CrossRef]
3. N. FlochThe Influence of Microbiota on Mechanisms of Bariatric Surgery 267-281. [CrossRef]
4. Isabel Halnes, Katherine Baines, Bronwyn Berthon, Lesley MacDonald-Wicks, Peter Gibson, Lisa Wood. 2017. Soluble Fibre Meal Challenge Reduces Airway Inflammation and Expression of GPR43 and GPR41 in Asthma. *Nutrients* **9**:1, 57. [CrossRef]
5. Betsabe Contreras-Haro, Jose A. Robles-Cervantes, Manuel Gonzalez-Ortiz, Esperanza Martinez-Abundis, Claudia Espinel-Bermudez, Martha P. Gallegos-Arreola, Karina C. Morgado-Castillo. 2016. The Effect of Agave tequilana Weber Inulin on Postprandial Ghrelin Concentration in Obese Patients. *Journal of Medicinal Food* . [CrossRef]
6. Sandra Steensels, Leen Cools, Bert Avau, Laurien Vancleef, Ricard Farré, Kristin Verbeke, Inge Depoortere. 2016. Supplementation of oligofructose, but not sucralose, decreases high-fat diet induced body weight gain in mice independent of gustducin-mediated gut hormone release. *Molecular Nutrition & Food Research* . [CrossRef]
7. Jiamiao Hu, Shaoling Lin, Baodong Zheng, Peter C.K. Cheung. 2016. Short-chain fatty acids in control of energy metabolism. *Critical Reviews in Food Science and Nutrition* 00-00. [CrossRef]
8. Roman M. Stilling, Marcel van de Wouw, Gerard Clarke, Catherine Stanton, Timothy G. Dinan, John F. Cryan. 2016. The neuropharmacology of butyrate: The bread and butter of the microbiota-gut-brain axis?. *Neurochemistry International* **99**, 110-132. [CrossRef]
9. Anne Nilsson, Elin Johansson-Boll, Jonna Sandberg, Inger Björck. 2016. Gut microbiota mediated benefits of barley kernel products on metabolism, gut hormones, and inflammatory markers as affected by co-ingestion of commercially available probiotics: a randomized controlled study in healthy subjects. *Clinical Nutrition ESPEN* **15**, 49-56. [CrossRef]
10. Patrice D. Cani, Claude Knauf. 2016. How gut microbes talk to organs: The role of endocrine and nervous routes. *Molecular Metabolism* **5**:9, 743-752. [CrossRef]
11. Muhammad Shoaib, Aamir Shehzad, Mukama Omar, Allah Rakha, Husnain Raza, Hafiz Rizwan Sharif, Azam Shakeel, Anum Ansari, Sobia Niazi. 2016. Inulin: Properties, health benefits and food applications. *Carbohydrate Polymers* **147**, 444-454. [CrossRef]
12. Marisol Aguirre, Carlota Bussolo de Souza, Koen Venema. 2016. The Gut Microbiota from Lean and Obese Subjects Contribute Differently to the Fermentation of Arabinogalactan and Inulin. *PLOS ONE* **11**:7, e0159236. [CrossRef]
13. Megan W. Bourassa, Ishraq Alim, Scott J. Bultman, Rajiv R. Ratan. 2016. Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health?. *Neuroscience Letters* **625**, 56-63. [CrossRef]
14. Linda M. Samuelsson, Wayne Young, Karl Fraser, Gerald W. Tannock, Julian Lee, Nicole C. Roy. 2016. Digestive-resistant carbohydrates affect lipid metabolism in rats. *Metabolomics* **12**:5. . [CrossRef]
15. Berit Svendsen, Jens Juul Holst. 2016. Regulation of gut hormone secretion. Studies using isolated perfused intestines. *Peptides* **77**, 47-53. [CrossRef]
16. Julia Darzi, Gary S. Frost, Jonathan R. Swann, Adele Costabile, M. Denise Robertson. 2016. l-rhamnose as a source of colonic propionate inhibits insulin secretion but does not influence measures of appetite or food intake. *Appetite* **98**, 142-149. [CrossRef]
17. Maria de Jesus Raposo, Alcina de Morais, Rui de Morais. 2016. Emergent Sources of Prebiotics: Seaweeds and Microalgae. *Marine Drugs* **14**:2, 27. [CrossRef]
18. Nikoleta S. Stamataki, Eirini K. Nikolidaki, Amalia E. Yanni, Maria Stoupaki, Panagiotis Konstantopoulos, Alexandros-Pantelis Tsigkas, Despoina Perrea, Nikolaos Tentolouris, Vaios T. Karathanos. 2016. Evaluation of a high nutritional quality snack based on oat flakes and inulin: effects on postprandial glucose, insulin and ghrelin responses of healthy subjects. *Food Funct.* **7**:7, 3295-3303. [CrossRef]
19. Adriana Souza Torsoni, Marciane Milanski, Marcio Alberto TorsoniDietary Patterns and Insulin Resistance 19-28. [CrossRef]
20. Muhammad Jaffar Khan, Konstantinos Gerasimidis, Christine Ann Edwards, M. Guftar Shaikh. 2016. Role of Gut Microbiota in the Aetiology of Obesity: Proposed Mechanisms and Review of the Literature. *Journal of Obesity* **2016**, 1-27. [CrossRef]
21. Ilaria Peluso, Husseen Manafikhi, Raffaella Reggi, Yaroslava Longhitano, Christian Zanza, Maura Palmery. 2016. Relationship between the Peroxidation of Leukocytes Index Ratio and the Improvement of Postprandial Metabolic Stress by a Functional Food. *Oxidative Medicine and Cellular Longevity* **2016**, 1-10. [CrossRef]

22. Eun Ky Kim, Tae Jung Oh, Lee-Kyung Kim, Young Min Cho. 2016. Improving Effect of the Acute Administration of Dietary Fiber-Enriched Cereals on Blood Glucose Levels and Gut Hormone Secretion. *Journal of Korean Medical Science* **31**:2, 222. [CrossRef]
23. Philippe Gérard. 2016. Gut microbiota and obesity. *Cellular and Molecular Life Sciences* **73**:1, 147-162. [CrossRef]
24. Sarah Heap, Jessica Ingram, Marron Law, Amy J. Tucker, Amanda J. Wright. 2016. Eight-day consumption of inulin added to a yogurt breakfast lowers postprandial appetite ratings but not energy intakes in young healthy females: a randomised controlled trial. *British Journal of Nutrition* **115**:02, 262-270. [CrossRef]
25. Cong Tang, Stefan OffermannsFFA2 and FFA3 in Metabolic Regulation . [CrossRef]
26. M K Hamilton, H E Raybould. 2016. Bugs, guts and brains, and the regulation of food intake and body weight. *International Journal of Obesity Supplements* **6**, S8. [CrossRef]
27. Deepak K. Rajpal, Jean-Louis Klein, David Mayhew, Joyce Boucheron, Aaron T. Spivak, Vinod Kumar, Karen Ingraham, Mark Paulik, Lihong Chen, Stephanie Van Horn, Elizabeth Thomas, Ganesh Sathe, George P. Livi, David J. Holmes, James R. Brown. 2015. Selective Spectrum Antibiotic Modulation of the Gut Microbiome in Obesity and Diabetes Rodent Models. *PLOS ONE* **10**:12, e0145499. [CrossRef]
28. Renata Barczynska, Katarzyna Slizewska, Mieczyslaw Litwin, Mieczyslaw Szalecki, Arkadiusz Zarski, Janusz Kapusniak. 2015. The effect of dietary fibre preparations from potato starch on the growth and activity of bacterial strains belonging to the phyla Firmicutes, Bacteroidetes, and Actinobacteria. *Journal of Functional Foods* **19**, 661-668. [CrossRef]
29. Christine M. Peat, Susan C. Kleiman, Cynthia M. Bulik, Ian M. Carroll. 2015. The Intestinal Microbiome in Bariatric Surgery Patients. *European Eating Disorders Review* **23**:6, 496-503. [CrossRef]
30. Eliana B. Giuntini, Fabiana A.H. Sardá, Maria Cristina Y. Lui, Carmen C. Tadini, Franco M. Lajolo, Elizabete W. Menezes. 2015. Gastrointestinal hormone modulation after a double-blind interventional study with unavailable carbohydrates. *Food Research International* **77**, 17-23. [CrossRef]
31. Eliana B. Giuntini, Milana C.T. Dan, Maria Cristina Y. Lui, Franco M. Lajolo, Elizabete W. Menezes. 2015. Positive impact of a functional ingredient on hunger and satiety after ingestion of two meals with different characteristics. *Food Research International* **76**, 395-401. [CrossRef]
32. L. Tripkovic, N. C. Muirhead, K. H. Hart, G. S. Frost, J. K. Lodge. 2015. The effects of a diet rich in inulin or wheat fibre on markers of cardiovascular disease in overweight male subjects. *Journal of Human Nutrition and Dietetics* **28**:5, 476-485. [CrossRef]
33. Francesca Di Bartolomeo, Wim Van den Ende. 2015. Fructose and Fructans: Opposite Effects on Health?. *Plant Foods for Human Nutrition* **70**:3, 227-237. [CrossRef]
34. E. S. Chambers, D. J. Morrison, M. C. Tedford, G. Frost. 2015. A novel dietary strategy to increase colonic propionate production in humans and improve appetite regulation and bodyweight management. *Nutrition Bulletin* **40**:3, 227-230. [CrossRef]
35. Edward S. Chambers, Douglas J. Morrison, Gary Frost. 2015. Control of appetite and energy intake by SCFA: what are the potential underlying mechanisms?. *Proceedings of the Nutrition Society* **74**:03, 328-336. [CrossRef]
36. Zohre Hashemi, Kaiyuan Yang, Han Yang, Alena Jin, Jocelyn Ozga, Catherine B. Chan. 2015. Cooking enhances beneficial effects of pea seed coat consumption on glucose tolerance, incretin, and pancreatic hormones in high-fat-diet–fed rats. *Applied Physiology, Nutrition, and Metabolism* **40**:4, 323-333. [Abstract] [Full Text] [PDF] [PDF Plus]
37. Huachun Weng, Kosuke Endo, Jiawei Li, Naoko Kito, Naoharu Iwai. 2015. Induction of Peroxisomes by Butyrate-Producing Probiotics. *PLOS ONE* **10**:2, e0117851. [CrossRef]
38. Elena Franco-Robles, Mercedes G. López. 2015. Implication of Fructans in Health: Immunomodulatory and Antioxidant Mechanisms. *The Scientific World Journal* **2015**, 1-15. [CrossRef]
39. C. Morris, A. Lynn, C. Neveux, A. C. Hall, G. A. Morris. 2015. Impact of bread making on fructan chain integrity and effect of fructan enriched breads on breath hydrogen, satiety, energy intake, PYY and ghrelin. *Food Funct.* **6**:8, 2561-2567. [CrossRef]
40. R. Jay Widmer, Andreas J. Flammer, Lilach O. Lerman, Amir Lerman. 2015. The Mediterranean Diet, its Components, and Cardiovascular Disease. *The American Journal of Medicine* **128**:3, 229. [CrossRef]
41. Qing Shen, Vatsala MaitinObesity-Associated Gut Microbiota 149-171. [CrossRef]
42. H.Q. Sun, C.Q. Tan, H.K. Wei, Y. Zou, G. Long, J.T. Ao, H.X. Xue, S.W. Jiang, J. Peng. 2015. Effects of different amounts of konjac flour inclusion in gestation diets on physio-chemical properties of diets, postprandial satiety in pregnant sows, lactation feed intake of sows and piglet performance. *Animal Reproduction Science* **152**, 55-64. [CrossRef]
43. Mechanisms behind bacterial impact on animal models 103-126. [CrossRef]
44. Catalin Chimerel, Edward Emery, David K. Summers, Ulrich Keyser, Fiona M. Gribble, Frank Reimann. 2014. Bacterial Metabolite Indole Modulates Incretin Secretion from Intestinal Enteroendocrine L Cells. *Cell Reports* **9**:4, 1202-1208. [CrossRef]

45. Roxanne Dutia, Blandine LaferrèreIncretin Response after Bariatric Surgery 221-238. [CrossRef]
46. Sabine Ibrügger, Louise Kristine Vigsnæs, Andreas Blennow, Dan Škuflić, Anne Raben, Lotte Lauritzen, Mette Kristensen. 2014. Second meal effect on appetite and fermentation of wholegrain rye foods. *Appetite* **80**, 248-256. [CrossRef]
47. Amandine Everard, Patrice D. Cani. 2014. Gut microbiota and GLP-1. *Reviews in Endocrine and Metabolic Disorders* **15**:3, 189-196. [CrossRef]
48. P.D. Cani, L. Geurts, S. Matamoros, H. Plovier, T. Duparc. 2014. Glucose metabolism: Focus on gut microbiota, the endocannabinoid system and beyond. *Diabetes & Metabolism* **40**:4, 246-257. [CrossRef]
49. J Fernandes, W Su, S Rahat-Rozenbloom, T M S Wolever, E M Comelli. 2014. Adiposity, gut microbiota and faecal short chain fatty acids are linked in adult humans. *Nutrition & Diabetes* **4**:6, e121. [CrossRef]
50. Cathy Signoret, Heidi JacobsChicory Fructans in Nutrition and the Formulation of Foods Dedicated to Blood Glucose Disorder Management 259-300. [CrossRef]
51. Greta Jakobsdottir, Margareta Nyman, Frida Fåk. 2014. Designing future prebiotic fiber to target metabolic syndrome. *Nutrition* **30**:5, 497-502. [CrossRef]
52. Darin Peshev, Wim Van den Ende. 2014. Fructans: Prebiotics and immunomodulators. *Journal of Functional Foods* **8**, 348-357. [CrossRef]
53. Nicole J. Kellow, Melinda T. Coughlan, Christopher M. Reid. 2014. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. *British Journal of Nutrition* **111**:07, 1147-1161. [CrossRef]
54. M L Hartvigsen, H N Lærke, A Overgaard, J J Holst, K E Bach Knudsen, K Hermansen. 2014. Postprandial effects of test meals including concentrated arabinoxylan and whole grain rye in subjects with the metabolic syndrome: a randomised study. *European Journal of Clinical Nutrition* . [CrossRef]
55. Miriam E. Clegg, Amir Shafat. 2014. The effect of agar jelly on energy expenditure, appetite, gastric emptying and glycaemic response. *European Journal of Nutrition* **53**:2, 533-539. [CrossRef]
56. Joel Selkrig, Peiyan Wong, Xiaodong Zhang, Sven Pettersson. 2014. Metabolic tinkering by the gut microbiome. *Gut Microbes* **5**:3, 369. [CrossRef]
57. Kristin M. Nieman, Tia M. Rains, Mary R. Dicklin, Kevin C. MakiWheat Fiber in Postprandial Metabolic Profile and Health 59-66. [CrossRef]
58. Patrice D Cani, Amandine Everard, Thibaut Duparc. 2013. Gut microbiota, enteroendocrine functions and metabolism. *Current Opinion in Pharmacology* **13**:6, 935-940. [CrossRef]
59. Elin V Johansson, Anne C Nilsson, Elin M Östman, Inger M E Björck. 2013. Effects of indigestible carbohydrates in barley on glucose metabolism, appetite and voluntary food intake over 16 h in healthy adults. *Nutrition Journal* **12**:1. . [CrossRef]
60. Maja S. Engelstoft, Won-mee Park, Ichiro Sakata, Line V. Kristensen, Anna Sofie Husted, Sherri Osborne-Lawrence, Paul K. Piper, Angela K. Walker, Maria H. Pedersen, Mark K. Nøhr, Jie Pan, Christopher J. Sinz, Paul E. Carrington, Taro E. Akiyama, Robert M. Jones, Cong Tang, Kashan Ahmed, Stefan Offermanns, Kristoffer L. Egerod, Jeffrey M. Zigman, Thue W. Schwartz. 2013. Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells. *Molecular Metabolism* **2**:4, 376-392. [CrossRef]
61. Wajahat Z. Mehal. 2013. The Gordian Knot of dysbiosis, obesity and NAFLD. *Nature Reviews Gastroenterology & Hepatology* **10**:11, 637-644. [CrossRef]
62. Gustavo D. Pimentel, Thayana O. Micheletti, Fernanda Pace. 2013. Nutritional Targets for Modulation of the Microbiota in Obesity. *Drug Development Research* n/a-n/a. [CrossRef]
63. Danielle M. Stringer, Carla G. Taylor, Paulyn Appah, Heather Blewett, Peter Zahradka. 2013. Consumption of buckwheat modulates the post-prandial response of selected gastrointestinal satiety hormones in individuals with type 2 diabetes mellitus. *Metabolism* **62**:7, 1021-1031. [CrossRef]
64. Camilla Pedersen, Solenne Lefevre, Véronique Peters, Michael Patterson, Mohammad A. Ghatei, Linda M. Morgan, Gary S. Frost. 2013. Gut hormone release and appetite regulation in healthy non-obese participants following oligofructose intake. A dose-escalation study. *Appetite* **66**, 44-53. [CrossRef]
65. Laure B. Bindels, Evelyne M. Dewulf, Nathalie M. Delzenne. 2013. GPR43/FFA2: physiopathological relevance and therapeutic prospects. *Trends in Pharmacological Sciences* **34**:4, 226-232. [CrossRef]
66. Caroline L. Bodinham, Najlaa M. Al-Mana, Leanne Smith, M. Denise Robertson. 2013. Endogenous plasma glucagon-like peptide-1 following acute dietary fibre consumption. *British Journal of Nutrition* 1-5. [CrossRef]
67. Brian T. Layden, Anthony R. Angueira, Michael Brodsky, Vivek Durai, William L. Lowe. 2013. Short chain fatty acids and their receptors: new metabolic targets. *Translational Research* **161**:3, 131-140. [CrossRef]

68. Brian Zambrowicz, Zhi-Ming Ding, Ike Ogbaa, Kenny Frazier, Phillip Banks, Anne Turnage, Joel Freiman, Melinda Smith, Dennis Ruff, Arthur Sands, David Powell. 2013. Effects of LX4211, a Dual SGLT1/SGLT2 Inhibitor, Plus Sitagliptin on Postprandial Active GLP-1 and Glycemic Control in Type 2 Diabetes. *Clinical Therapeutics* **35**:3, 273-285.e7. [CrossRef]

69. J.A. Harrold, G.M. Hughes, K. O'Shiel, E. Quinn, E.J. Boyland, N.J. Williams, J.C.G. Halford. 2013. Acute effects of a herb extract formulation and inulin fibre on appetite, energy intake and food choice. *Appetite* **62**, 84-90. [CrossRef]

70. Jian Shen, Martin S. Obin, Liping Zhao. 2013. The gut microbiota, obesity and insulin resistance. *Molecular Aspects of Medicine* **34**:1, 39-58. [CrossRef]

71. M. Kristensen, F. Savorani, S. Christensen, S.B. Engelsen, S. Bügel, S. Toubro, I. Tetens, A. Astrup. 2013. Flaxseed dietary fibers suppress postprandial lipemia and appetite sensation in young men. *Nutrition, Metabolism and Cardiovascular Diseases* **23**:2, 136-143. [CrossRef]

72. Stefan Offermanns. 2013. Free Fatty Acid (FFA) and Hydroxy Carboxylic Acid (HCA) Receptors. *Annual Review of Pharmacology and Toxicology* **54**:1, 131025102232009. [CrossRef]

73. M.P. Ferreira, F. Gendron, K. KindscherBioactive Prairie Plants and Aging Adults 263-275. [CrossRef]

74. Bruno Melo Carvalho, Mario Jose Abdalla Saad. 2013. Influence of Gut Microbiota on Subclinical Inflammation and Insulin Resistance. *Mediators of Inflammation* **2013**, 1-13. [CrossRef]

75. Abby S. Klosterbuer, William Thomas, Joanne L. Slavin. 2012. Resistant Starch and Pullulan Reduce Postprandial Glucose, Insulin, and GLP-1, but Have No Effect on Satiety in Healthy Humans. *Journal of Agricultural and Food Chemistry* **60**:48, 11928-11934. [CrossRef]

76. S. Schenker. 2012. An overview of the role of rice in the UK diet. *Nutrition Bulletin* **37**:4, 309-323. [CrossRef]

77. Gustavo D Pimentel, Thayana O Micheletti, Fernanda Pace, José C Rosa, Ronaldo VT Santos, Fabio S Lira. 2012. Gut-central nervous system axis is a target for nutritional therapies. *Nutrition Journal* **11**:1. . [CrossRef]

78. G. Hindy, E. Sonestedt, U. Ericson, X.-J. Jing, Y. Zhou, O. Hansson, E. Renström, E. Wirfält, M. Orho-Melander. 2012. Role of TCF7L2 risk variant and dietary fibre intake on incident type 2 diabetes. *Diabetologia* **55**:10, 2646-2654. [CrossRef]

79. J Fernandes, J Vogt, T M S Wolever. 2012. Intravenous acetate elicits a greater free fatty acid rebound in normal than hyperinsulinaemic humans. *European Journal of Clinical Nutrition* **66**:9, 1029-1034. [CrossRef]

80. Jelena Anastasovska, Tulika Arora, Gina J. Sanchez Canon, James R.C. Parkinson, Kieran Touhy, Glen R. Gibson, Nachiket A. Nadkarni, Po-Wah So, Anthony P. Goldstone, E. Louise Thomas, Mohammed K. Hankir, Jan Van Loo, Neena Modi, Jimmy D. Bell, Gary Frost. 2012. Fermentable Carbohydrate Alters Hypothalamic Neuronal Activity and Protects Against the Obesogenic Environment. *Obesity* **20**:5, 1016-1023. [CrossRef]

81. David Sánchez, Marta Miguel, Amaya Aleixandre. 2012. Dietary Fiber, Gut Peptides, and Adipocytokines. *Journal of Medicinal Food* **15**:3, 223-230. [CrossRef]

82. G. Tolhurst, H. Heffron, Y. S. Lam, H. E. Parker, A. M. Habib, E. Diakogiannaki, J. Cameron, J. Grosse, F. Reimann, F. M. Gribble. 2012. Short-Chain Fatty Acids Stimulate Glucagon-Like Peptide-1 Secretion via the G-Protein-Coupled Receptor FFAR2. *Diabetes* **61**:2, 364-371. [CrossRef]

83. D. El Khoury, C. Cuda, B. L. Luhovyy, G. H. Anderson. 2012. Beta Glucan: Health Benefits in Obesity and Metabolic Syndrome. *Journal of Nutrition and Metabolism* **2012**, 1-28. [CrossRef]

84. Erik E. J. G. Aller, Itziar Abete, Arne Astrup, J. Alfredo Martinez, Marleen A. van Baak. 2011. Starches, Sugars and Obesity. *Nutrients* **3**:12, 341-369. [CrossRef]

85. W. Van den Ende, D. Peshev, L. De Gara. 2011. Disease prevention by natural antioxidants and prebiotics acting as ROS scavengers in the gastrointestinal tract. *Trends in Food Science & Technology* **22**:12, 689-697. [CrossRef]

86. J Fernandes, J Vogt, T M S Wolever. 2011. Inulin increases short-term markers for colonic fermentation similarly in healthy and hyperinsulinaemic humans. *European Journal of Clinical Nutrition* **65**:12, 1279-1286. [CrossRef]

87. Edward Chambers, Nicola Guess, Alexander Viardot, Gary Frost. 2011. Dietary starch and fiber: potential benefits to body weight and glucose metabolism. *Diabetes Management* **1**:5, 521-528. [CrossRef]

88. Nathalie M. Delzenne, Patrice D. Cani. 2011. Interaction Between Obesity and the Gut Microbiota: Relevance in Nutrition. *Annual Review of Nutrition* **31**:1, 15-31. [CrossRef]

89. Nathalie M. Delzenne, Patrice D. Cani. 2011. Gut Microbiota and the Pathogenesis of Insulin Resistance. *Current Diabetes Reports* **11**:3, 154-159. [CrossRef]

90. Yi Lin, Inge Huybrechts, Stefanie Vandevijvere, Selin Bolca, Willem De Keyzer, Stephanie De Vriese, Anja Polet, Melissa De Neve, Herman Van Oyen, John Van Camp, Guy De Backer, Stefaan De Henauw. 2011. Fibre intake among the Belgian population

by sex–age and sex–education groups and its association with BMI and waist circumference. *British Journal of Nutrition* **105**:11, 1692-1703. [CrossRef]

91. Silviya Stoyanova, Jan Geuns, Éva Hideg, Wim Van Den Ende. 2011. The food additives inulin and stevioside counteract oxidative stress. *International Journal of Food Sciences and Nutrition* **62**:3, 207-214. [CrossRef]
92. Patrice D. Cani, Nathalie M. Delzenne. 2011. The gut microbiome as therapeutic target. *Pharmacology & Therapeutics* **130**:2, 202-212. [CrossRef]
93. Kristina A. Harris, Penny M. Kris-Etherton. 2010. Effects of Whole Grains on Coronary Heart Disease Risk. *Current Atherosclerosis Reports* **12**:6, 368-376. [CrossRef]