Proceedings of the Nutrition Society (2011), **70**, 119–128 doi:10.1017/S0029665110004039
© The Authors 2011

The Summer Meeting of the Nutrition Society hosted by the Scottish Section was held at Heriot-Watt University, Edinburgh on 28 June–1 July 2010

Conference on 'Nutrition and health: cell to community'

Postgraduate Symposium
Do SCFA have a role in appetite regulation?

Julia Darzi[1]*†, Gary S. Frost[2] and M. Denise Robertson[1]
[1]*University of Surrey, Guildford, Surrey GU2 7WG, UK*
[2]*Imperial College London, London W12 0NN, UK*

The recently discovered SCFA-activated G-coupled protein receptors FFA receptor 2 and FFA receptor 3 are co-localised in L-cells with the anorexigenic 'ileal brake' gut hormone peptide YY, and also in adipocytes, with activation stimulating leptin release. Thus, SCFA such as acetate and propionate show promise as a candidate to increase satiety-enhancing properties of food. We therefore postulate SCFA may have a role in appetite regulation and energy homeostasis. SCFA can be delivered either directly within food, or indirectly via the colon by the provision of fermentable non-digestible carbohydrates. A review of studies investigating the effects of oral SCFA ingestion on appetite suggests that while oral SCFA ingestion is associated with enhanced satiety, this may be explained by product palatability rather than a physiological effect of SCFA. Colon-derived SCFA generated during microfloral fermentation have also been suggested to explain satiety-enhancing properties of non-digestible carbohydrates. However, findings are mixed from investigations into the effects of the prebiotic inulin-type fructans on appetite. Overall, data presented in this review do not support a role for SCFA in appetite regulation.

Acetate: Propionate: Acetic acid: Propionic acid: SCFA: Inulin: Oligofructose: Satiety

Human subjects are living in an increasingly 'obesogenic' environment with easily accessed, energy dense foods and sedentary lifestyles. These 'obesogenic' factors can override homeostatic systems resulting in a gradual increase in the population body weight (BW)[(1)]. The need for strategies to prevent the rise in obesity is therefore becoming increasingly urgent. One strategy is to identify and develop foods that enhance satiety, thereby reducing subsequent energy intake (EI)[(2,3)].

SCFA have been suggested to have satiety-enhancing properties, with some researchers suggesting SCFA may explain the inverse association between dietary fibre intake and BW found in some observational studies[(4–16)]. This review considers the evidence for SCFA having a role in appetite regulation, starting first with the description of SCFA, followed by a discussion of the SCFA-activated receptors FFA receptor 2 (FFA2) and FFA receptor 3 (FFA3), which provide a rationale that SCFA may have a role in energy homeostasis. Finally, studies that have investigated the effects of orally and colonically delivered SCFA on appetite are reviewed.

SCFA

SCFA are organic fatty acids generated in the colon when non-digestible carbohydrates (NDC) such as dietary fibre, resistant starch and inulin resist digestion and absorption in the small intestine, instead proceeding to the colon to undergo bacterial fermentation. The SCFA formed comprise between one and seven carbon units, with acetate (two carbon units) being the most predominant anion in the colon, followed by propionate (three carbon units) and then

Abbreviations: AUC, area under curve; BW, body weight; DP, degree of polymerisation; EI, energy intake; GLP-1, glucagon-like peptide 1; NDC, non-digestible carbohydrate; FFA2 and FFA3, free fatty acid receptor 2 and 3, respectively; OF, oligofructose; PYY, peptide YY; VAS, visual analogue scales.

***Corresponding author:** Dr Julia Darzi, fax +44 20 9848 4171, email julia.darzi@kcl.ac.uk
†**Present address**: Division of Diabetes and Nutritional Sciences, School of Medicine, King's College London, 4th Floor Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK.

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

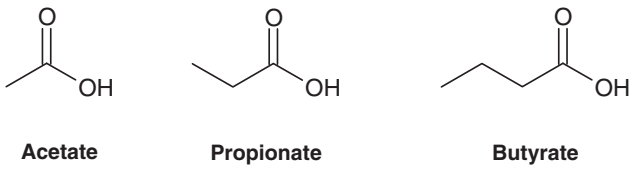

Fig. 1. Chemical structures of acetate, propionate and butyrate.

butyrate (four carbon units)[17,18] (shown in Fig. 1), accounting for approximately 90–95% of total colonic SCFA[19]. Total colonic SCFA concentrations in human subjects are in the range of 60–130 mM; however, relatively low quantities reach the peripheral circulation, with normal blood concentrations in the range of 100–150 μM acetate, 4–5 μM propionate and 1–3 μM butyrate[20].

In addition to being generated from fermentable NDC, dietary SCFA sources include various foods containing SCFA, particularly foods that have been fermented. Examples include sourdough bread, vinegar and vinegar-containing products such as pickles, and some dairy products such as cheese, butter, crème fresh and soured cream. Due to the volatility of SCFA, SCFA-containing products have a distinctive odour and taste associated with them.

The SCFA receptors

In 2003, two orphan G-protein coupled receptors, FFA2 and FFA3 were identified as being activated by SCFA[21–23]. FFA2 and FFA3 were originally known as GPR43 and GPR41, respectively[24]. Initial studies indicate that FFA2 is equally sensitive to activation by propionate, butyrate and acetate, while sensitivity for FFA3 is in the order propionate ≥ butyrate > acetate[21–26]. FFA2 and FFA3 are expressed in a variety of tissues including adipose and the colon[21,22,26,27].

In adipocytes, *in vitro* and *in vivo* evidence from murine models indicate that the activation of FFA3 may mediate leptin expression. *In vitro*, leptin expression was up-regulated following the treatment of murine adipocytes with SCFA solutions, while oral provision of propionate to mice *in vivo* led to elevated circulatory leptin concentrations. Propionate was the most potent ligand *in vitro*, and the stimulatory effects of propionate treatment were abolished in cells infected with a virus that targeted FFA3 mRNA, suggesting that FFA3 is the relevant receptor[26,27].

In the colon, molecular investigations of cell lines of both rat and human origin have shown that FFA2 and FFA3 are co-localised with the anorexigenic 'ileal brake' gut hormone peptide YY (PYY) in enteroendocrine L-cells[28–30]. When administered *in vitro* to a vascularly infused rat colon lumen, solutions of propionate, butyrate, but not acetate stimulate PYY secretion[31], with no significant release of the gut hormone glucagon-like protein 1 (GLP-1)[32]. *In vivo*, luminal administration of SCFA solutions to live rats and large white pigs have been shown to significantly increase subsequent blood PYY concentrations[33,34] and reduce upper gastrointestinal motility[33], an effect reproduced with a PYY infusion[33]. As sensitivity to stimulation *in vitro* is in the order propionate ≥ butyrate > > acetate for PYY secretion[28–30], FFA3 is implicated as the responsible receptor for modulating these effects.

Thus, SCFA may have a role in energy homeostasis via FFA3 activation in adipocytes to stimulate leptin expression[26,27] and via FFA2 and FFA3 activation in the colonic mucosa to enhance production of the anorexigenic gut hormone PYY[28–34].

The role of SCFA in appetite regulation

As outlined above, the presence of the SCFA-activated receptors FFA2 and FFA3 in adipocytes[26,27] and co-localised with PYY in the colonic mucosa[28–34] is suggestive of a role for SCFA in energy homeostasis. The effects of SCFA on appetite have been investigated both by (1) oral provision of SCFA and (2) colonic delivery of SCFA via fermentable NDC such as inulin-type fructans as discussed later.

The effect of orally delivered SCFA on appetite

A number of studies investigating the effects of orally ingested SCFA, in particular acetate (delivered as vinegar)[35–38] and propionate (delivered as sodium (Na) propionate)[39–41], on subsequent satiety have been published (Table 1). These studies will be reviewed below.

Orally delivered acetate and appetite effects. The effects of long-term supplementation with apple cider vinegar as a source of acetate on anthropometric measures in human subjects were reported in a recently published three-way parallel study[38]. In this study, healthy obese Japanese volunteers were randomised to the control (*n* 58, 50 completed), low-dose (*n* 59, 54 completed) or high-dose (*n* 58, 51 completed) treatment, consuming a beverage containing 0, 15 or 30 ml apple cider vinegar, respectively (equivalent to 0, 12·5 and 25 mmol acetate) daily for 12 weeks. At the end of the intervention, those in both the low- and high-dose treatment groups had a significantly lower BW, BMI, % body fat, waist and hip circumference, waist : hip ratio, visceral fat area, subcutaneous fat area and TAG concentrations relative to control. Additionally total fat area and systolic blood pressure were significantly lower in the high-dose group relative to control[38].

This study therefore provides some compelling evidence that vinegar as a source of acetate may influence appetite. The acute effects of vinegar supplementation on appetite and satiety in human subjects have been investigated in a few studies (summarised in Table 1) that will be reviewed later[35–38].

In an acute four-way crossover study, Ostman *et al.* provided human volunteers (*n* 12) bread (containing 50 g carbohydrate) soaked in 0 g (control), 18, 23 and 28 g vinegar (equivalent to 0, 18, 23 and 28 mmol acetic acid) for their breakfast following an overnight fast. They reported a dose–response increase in the area under curve (AUC) for satiety ratings (Fig. 2), with a significantly higher AUC following the 28 g dose relative to control[37].

The same group also investigated the effects of vinegar and form of wheat grain (refined, milled or wholegrain). In this four-way crossover study, participants (*n* 15,

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

Table 1. Summary of human clinical studies investigating the acute effects of oral SCFA supplementation on appetite

Study	SCFA and test products	Design	Participants	Effects on appetite
Ostman *et al.*[37]	Acetate: 18, 23 or 28 mmol soaked in white bread Control: white bread	Acute dose–response crossover study	Healthy (*n* 12)	Dose dependent ↑ in satiety. Satiety AUC significantly ↑ at highest dose relative to control.
Hlebowicz *et al.*[35]	Acetate: 28 mmol soaked in white, wholemeal or wholegrain bread Control: white bread	Acute four-way crossover study	Healthy (*n* 13)	Satiety AUC significantly ↑ for vinegar plus wholegrain compared to other treatments.
Mettler *et al.*[36]	Acetate: 28 mmol +/− added cinnamon in milk rice pudding and glucose drink Control: milk rice pudding and glucose drink	Acute 2 × 2 crossover study	Healthy (*n* 27)	Satiety incremental AUC did not differ between treatments. Main effect of acetate approaching significance ($P = 0{\cdot}064$).
J Darzi, GS Frost and MD Robertson (unpublished results)	Acetate: 25 mmol in unpalatable or more palatable drink alongside standard breakfast Control: drink with no added vinegar alongside standard breakfast	Acute three-way crossover study	Healthy (*n* 16)	Mean *ad libitum* EI 3 h postprandially and appetite VAS for hunger, desire to eat and fullness significantly influenced by treatment. Significant correlations between palatability ratings and appetite measures.
Liljeberg *et al.*[41]	Propionate: 15 mmol (low dose) or 45 mmol (high dose) Na-propionate added to wholemeal bread Control: wholemeal bread	Acute six-way crossover study	Healthy (*n* 11)	Satiety AUC significantly ↑ and acceptability score significantly ↓ with Na-propionate bread (high dose) relative to control.
Liljeberg and Bjorck[40]	Propionate: 45 mmol Na-propionate added to wholemeal bread Control: wholemeal bread	Acute three-way crossover study	Healthy (*n* 12)	Satiety AUC significantly ↑ following Na-propionate bread relative to control.
Frost *et al.*[39]	Propionate: 31 mmol Na propionate plus 30 g sunflower oil +/− psyllium viscous fiber in tomato pasta Control: tomato pasta	Acute 2 × 2 way crossover study	Healthy (*n* 10)	Appetite ratings and *ad libitum* EI 4 h postprandially not significantly different. Significantly ↑ plasma GLP-1 incremental AUC and with psyllium plus oil.
Darzi *et al.*[42]	Propionate: 6 mmol propionate rich sourdough bread jam sandwiches Control: non-sourdough bread jam sandwiches	Acute two-way crossover study	Healthy (*n* 20)	VAS appetite ratings, *ad libitum* EI 3 h postprandially and 24 h EI not significantly different between treatments.

AUC, area under curve; EI, energy intake; VAS, visual analogue scales; GLP-1, glucagon-like peptide 1; ↑, higher; ↓ lower.

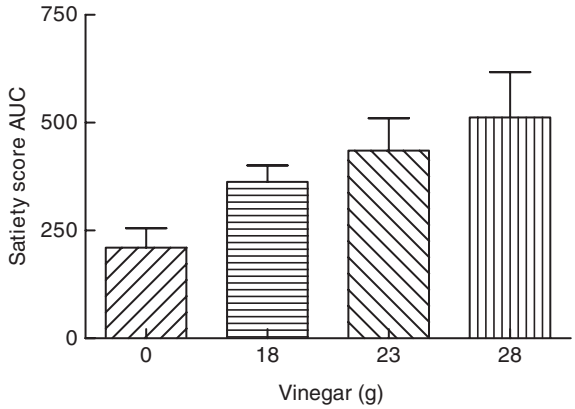

Fig. 2. Postprandial satiety score area under curve (AUC) following ingestion of bread (containing 50 g carbohydrate) soaked in 0, 18, 23 and 28 g white wine vinegar, supplying 0, 18, 23 and 28 mmol acetate, respectively. A dose–response increase in the satiety AUC was observed. Values are mean with error bars representing the SEM. Taken from Ostman *et al.*[37].

13 completed) consumed a test breakfast comprising white, milled grain or wholegrain bread soaked in 28 g vinegar (supplying 28 mmol acetate) compared to white bread without vinegar (control). The postprandial satiety score AUC was significantly higher following wholegrain bread soaked in vinegar relative to the other three treatments, with none of the other treatments altering satiety[35]. However, as wholegrain bread without added vinegar was not investigated, it is not possible to conclude whether the increased satiety arose from the wholegrain structure of the bread alone or it was an additive effect of the grain structure with the vinegar.

A two-by-two crossover study by a different group investigated the additive effects of acetic acid (28 mmol) and cinnamon mixed into a glucose drink and milk rice pudding. This study reported the satiety incremental AUC did not significantly differ between treatments, although a main effect of acetic acid approaching significance ($P = 0{\cdot}064$) was found[36].

However, none of these previous studies investigated quantitative effects on appetite. In addition, subjective effects on appetite were investigated using a single rating bipolar scale[35,37] or point scale[36], rather than a variety of appetite-related visual analogue scale (VAS) questionnaires.

In our own laboratories, we carried out an acute three-way crossover study with two main objectives: to investigate the acute effects of acetate supplementation on

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

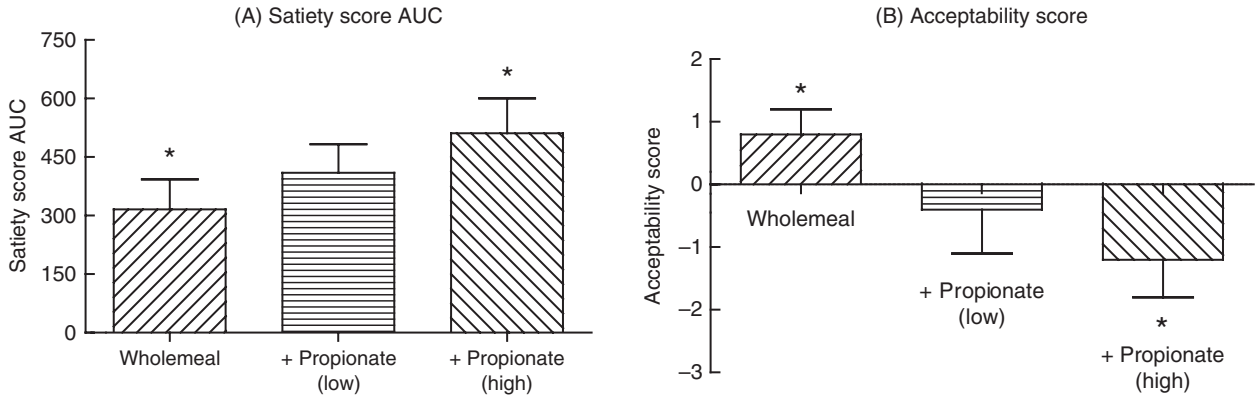

Fig. 3. (A) Postprandial satiety score area under curve (AUC) and (B) acceptability score following ingestion of a mixed breakfast made with wholemeal bread (control) or bread baked with added Na propionate in a low (approximately 15 mmol) and high (approximately 45 mmol) dose. A dose–response increase in satiety was found, which was accompanied by a dose–response decrease in the acceptability score. *Mean values for the high-dose bread differed significantly from control ($P<0{\cdot}05$). Values are mean with error bars representing the SEM. Adapted from Liljeberg *et al.*[41].

subjective and quantitative measures of appetite, and to investigate the influence of product palatability. Subjective appetite effects were assessed using a variety of appetite-related VAS questionnaires. Alongside a standard breakfast (jam sandwiches) normal weight unrestrained eaters (*n* 16) were provided a drink of sugar-free orange squash containing 25 g vinegar (supplying 25 mmol acetate) in a more palatable (Pal, vinegar divided across two drinks) and unpalatable (Unpal, vinegar in a more concentrated form in one drink) form compared to control (drink with no added vinegar). Palatability ratings for the breakfast were significantly lower for the Unpal treatment compared to both control and Pal.

Vinegar treatment significantly lowered subjective appetite VAS ratings for hunger ($P = 0{\cdot}045$) and the desire to eat ($P = 0{\cdot}036$) and increased ratings for fullness ($P<0{\cdot}0001$). Mean *ad libitum* EI of a large pre-weighed homogenous pasta meal provided 3 h postprandially was significantly influenced by vinegar treatment ($P = 0{\cdot}022$). The mean intake was lowest with Unpal treatment, followed by Pal, with the highest mean intake occurring with the control treatment, which was significantly higher than with Unpal treatment. Furthermore, a pooled correlation analysis found significant correlations between breakfast palatability ratings and various appetite measures including 24 h VAS AUC and *ad libitum* EI (J Darzi, GS Frost and MD Robertson, unpublished results). Our findings therefore indicate that while vinegar as a source of acetate may reduce appetite, this effect may be due, at least in part, to palatability effects of the vinegar-containing test products.

Orally delivered propionate and appetite effects. Two acute crossover studies from the same group have examined effects on appetite of bread baked with added Na propionate when consumed as part of a mixed meal for breakfast. In the first study, participants (*n* 11) attended on six occasions and were provided breakfast made using wholemeal bread (control) or the same bread with added Na propionate (low and high dose), sourdough, lactic acid or Ca lactate[41]. In the second study, participants (*n* 12) attended on three occasions and were provided breakfast prepared using wholemeal bread (control) or the same bread with added Na propionate (high dose only) or lactic acid[40]. The actual dose of Na propionate was not reported by the authors, but is calculated as 15 and 45 mmol for low- and high-dose breads, respectively. In both studies, the addition of Na propionate was reported to increase the postprandial satiety rating AUC in a dose–response manner (Fig. 3(A)), with a significantly higher-satiety AUC reported following the high dose of Na propionate bread relative to control[40,41]. However, at the same time, the acceptability rating score was reduced by the addition of Na propionate in a dose–response manner (Fig. 3(B))[41].

The provision of Na propionate is also associated with increased nausea. When volunteers (*n* 10) ingested 3 g Na propionate (equivalent to 31 mmol) combined with 30 g sunflower oil (as a source of PUFA) mixed into a pasta meal at breakfast, postprandial nausea ratings were significantly increased[39]. In this study, the postprandial incremental AUC for the appetite gut hormone GLP-1 was significantly increased by Na propionate and PUFA treatment, although subjective appetite ratings and EI of an *ad libitum* test meal served 4 h postprandially did not differ from the control (pasta with no added Na propionate/PUFA)[39]. However, as PUFA was delivered alongside the Na propionate, it was not possible to determine whether the observed effects were attributed to the added PUFA, propionate, or both and if the higher energy content of the Na propionate/PUFA pasta test meals had an effect.

In our own laboratories we carried out an acute two-way crossover study to investigate the effects of providing a palatable propionate-rich sourdough bread compared to an equally palatable and visually identical non-sourdough control bread on subjective and quantitative measures of appetite. Prior sensory evaluation of the bread products determined the sourdough and control breads to be equally acceptable. Healthy, normal weight unrestrained eaters (*n* 20) were provided a breakfast comprising jam sandwiches made using the palatable sourdough bread (supplying a total of 6·0 mmol propionate) or the non-sourdough control bread. In this study, we found that the palatable propionate-rich sourdough bread did not influence appetite, with no significant differences between

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

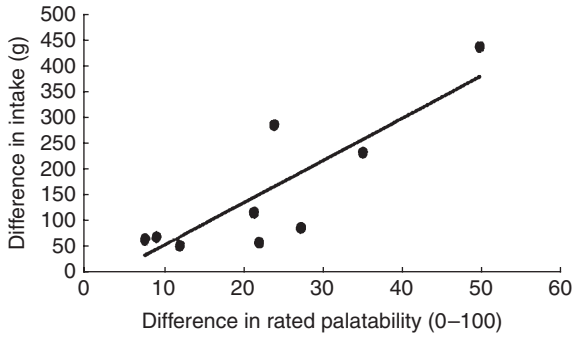

Fig. 4. Relationship between change in palatability ratings and food intake when palatability is manipulated. Each data point represents a published study. Taken from Yeomans[44].

treatments on postprandial appetite VAS ratings, *ad libitum* EI 3 h postprandially or on 24 h intake. Our findings therefore indicate that when provided in a palatable form, propionate does not appear to influence appetite[42]. This implies that previous reports of Na propionate ingestion being associated with increased satiety[40,41] may be a test product palatability effect, at least in part.

Oral SCFA and appetite summary. In summary, initial studies indicate that oral SCFA may enhance satiety[35–41]. However, our findings suggest that product palatability may explain the appetite effects of oral SCFA rather than being a physiological effect of SCFA (J Darzi, GS Frost and MD Robertson, unpublished results).

Studies investigating the link between sensory properties of food and appetite suggest that sensory properties influence food choice and quantities consumed[43]. A pooled analysis of data from studies in which investigators manipulated food palatability concluded there was a strong linear relationship between the change in rated palatability and difference in food intake following food manipulation (Fig. 4)[44]. This provides a rationale for our hypothesis that oral SCFA palatability explains effects on appetite and satiety, most likely via mechanisms mediated at the cephalic phase.

Colonic delivery of SCFA to investigate appetite effects, focusing on inulin-type fructans

There is growing evidence to indicate dietary fibre and other NDC may have a role in BW regulation, with a number of studies suggesting the intake of dietary fibre and/or wholegrains are inversely associated with BW and/or BMI[4–16]. Dietary fibre and other NDC may therefore potentially have a role in the prevention and treatment of obesity.

Furthermore, various studies have demonstrated dietary fibre may enhance satiety and reduce appetite, thus helping to control subsequent food intake[4–6,10,11,45]. However, the mechanisms by which this may occur are not fully understood. It is possible that SCFA generated during colonic fermentation may mediate effects on appetite via interaction with the SCFA-activated receptors FFA2 and FFA3 in colonic enteroendocrine L-cells, and FFA3 in adipocytes to modulate PYY and leptin production, respectively, as discussed earlier.

This review will now focus on a particular group of fermentable NDC, the inulin-type fructans, which as well as being classified as a dietary fibre is also classified as being a prebiotic.

What are inulin-type fructans? Inulin-type fructans are linear oligo- and polysaccharides comprising mainly β-(2→1) fructosyl–fructose glycosidic linkages (Fig. 5)[46]. As digestive enzymes are specific for α-glycosidic bonds, inulin-type fructans resist enzymatic hydrolysis in the small intestine, and therefore proceed undigested to the colon where they are fermented[47]. Inulin-type fructans are considered long chain with a degree of polymerisation (DP) ≥ 10, medium chain with a DP between five and nine and short chain with a DP between two and four. Various inulin-type fructan preparations with differing physical, chemical and physiological properties are available commercially including[47,48]:

High DP inulin (e.g. Inulin HP): Long-chain only inulin-type fructan preparation with a DP ≥ 10 and an average DP of 25;
Oligofructose (OF) (e.g. Raftilose P95): Short- and medium-chain preparation with a DP ranging from 2 to 10 and an average DP of 4;
Mixed inulin-type fructan (e.g. Synergy 1): A mixture of low-, medium- and high-DP inulin-type fructans.

Inulin-type fructans and effects on appetite. Initial rodent model studies give evidence that inulin-type fructans may enhance satiety[49–54]. Chronic OF supplementation in rodents significantly decreases EI[50,51,54], suppresses BW gain[49,51,54] (although not in all cases[50,53]), suppresses fat mass gain[49–51,54], increases proximal colon GLP-1 (7–36) amide concentrations[49–51,53,54], increases portal plasma GLP-1 (7–36)[50,51,54] and gastric-inhibitory polypeptide[53] concentrations, reduces plasma ghrelin concentrations[50] and increases the caecum mass[50,51,53]. Most studies examined OF, with few investigating higher DP inulin-type fructans (e.g. inulin HP)[50,52]. Supplementing rats diets with Synergy 1 (mixture of low- and high-DP inulin-type fructans) resulted in significantly suppressed BW gain[52] and fat mass gain[50], reduced EI[50,52], reduced proximal colon GLP-1 (7–36) concentrations[50] and reduced caecum mass[50]. Furthermore, supplementation with inulin HP significantly suppressed BW gain and increased caecum mass, but did not influence proximal colon GLP-1 (7–36) concentrations or fat mass gain[50].

Following on from these promising data from animal models, a few human studies have investigated acute (Table 2) and more have investigated chronic (Table 3) effects of supplementing with inulin-type fructans on appetite and/or anthropometrics. A review of these studies now follows.

Three different studies have been published that investigated acute effects of ingesting inulin-type fructans on subsequent appetite (Table 2). Peters *et al.* provided volunteers (*n* 21) with a meal replacement bar containing 8 g OF or a non-OF control to be eaten in the free-living setting at breakfast and lunch on day 1 and breakfast only on day 2. No significant effects of treatment were found on satiety ratings or EI at an *ad libitum* buffet meal provided 4 h postprandially[55].

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

Table 2. Summary of human clinical studies investigating acute effects of inulin-type fructan supplementation on appetite

Study	Inulin-type fructan	Design	Participants	Test meals	Effects on appetite
Archer *et al.*[56]	24 g inulin HP	Acute three-way crossover	Healthy (*n* 33)	Sausage patties in muffin matched for mass, protein and available carbohydrate but not E: – Full fat patty (control), inulin HP patty (24 g), lupin kernel fibre patty (24 g)	24 h EI significantly lower following inulin compared to control. No significant influence on satiety ratings.
Peters *et al.*[55]	2 × 8 g OF	Acute four-way crossover	Healthy (*n* 21)	Meal replacement bar given twice on day 1 and once on day 2: – Oat bar (control), OF bar (8 g OF), barley bar (8 g barley), barley + OF bar (8 g barley and 8 g OF)	Appetite ratings AUC and *ad libitum* EI 4 h postprandially did not differ between treatments
Perrigue *et al.*[57]	6 g unspecified inulin-type fructan	Acute six-way crossover	Healthy (*n* 38)	Test product provided 2 h following standard preload: Low-E yoghurt (control 1), high-E yoghurt (control 2), orange juice (control 3) or no yoghurt/drink (control 4) or 6 g inulin-type fructan in low-E or high-E yoghurt	Fullness ratings significantly higher and *ad libitum* EI 2 h postprandially significantly lower following yoghurts with added inulin-type fructan compared to control %.

E, energy; EI, energy intake; OF, oligofructose; AUC, area under curve.

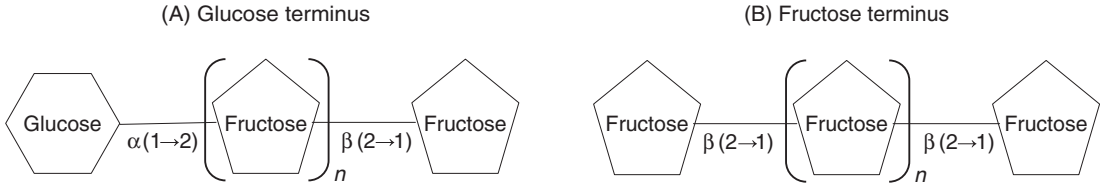

Fig. 5. Structure of inulin-type fructans. Inulin-type fructans are composed of β-(2→1) linked fructose units with either a terminal (A) glucose or (B) fructose unit.

By contrast, Archer and colleagues reported 24 h EI was significantly lowered by supplementation with 24 g inulin HP when supplied to volunteers (*n* 33) as a fat replacer in a sausage patty, relative to a full-fat patty (control). Satiety ratings were not significantly altered[56]. However, control and inulin-containing sausage patties were not matched for energy in this study.

Similarly, consumption of yoghurt containing 6 g inulin-type fructans (type used not specified) significantly decreased subsequent *ad libitum* EI in a controlled setting relative to 'no preload' (control) in healthy volunteers (*n* 38)[57]. However, the overall EI including the preload and the *ad libitum* intake was more than the 'no preload' condition.

A larger number of chronic supplementation studies have been published investigating effects on appetite (Table 3), again with variable results and study limitations, as reviewed below.

Let us first take a look at the chronic effects of OF supplementation on subjective and quantitative appetite measures. In a two-way crossover study, Cani and co-workers reported that daily supplementation of healthy volunteers (*n* 10) with 16 g OF for 2 weeks significantly lowered *ad libitum* EI at breakfast and lunch and the mean daily EI relative to control (16 g maltodextrin)[58]. Relative to control, OF supplementation also significantly increased satiety ratings after breakfast and dinner, and reduced hunger and prospective consumption ratings following dinner[58]. However, as preload test meals were provided *ad libitum* rather than being a fixed, standardised preload, the postprandial appetite ratings are difficult to interpret.

Similarly, a recent parallel study reported supplementation of volunteers (*n* 51) with 14 g Jerusalem Artichoke concentrate (containing OF) daily for 12 weeks reduced rated hunger[59]. However, it was unclear whether effects on hunger were significant.

By contrast, in a two-way parallel study, Parnell and Reimer reported daily supplementation of healthy overweight volunteers (*n* 48) for 12 weeks with 21 g OF did not significantly alter satiety ratings and EI relative to control (7·89 g maltodextrin), although the PYY AUC was significantly higher[60]. However, this parallel study was not sufficiently powered to assess subjective appetite effects[61].

Effects of OF supplementation on gut peptide production have also been investigated by Piche and colleagues in patients with gastrooesophageal reflux disease. In a two-way crossover study, participants (*n* 9) ingested 19·8 g OF or sucrose (control) for 7 d. The postprandial plasma GLP-1 AUC was significantly higher in response to a meal tolerance test following OF supplementation relative to control; however both PYY and cholecystokinin were not significantly influenced by treatment[62].

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

Table 3. Summary of human clinical studies investigating chronic effects of inulin-type fructan supplementation on appetite

Study	Inulin type-fructan and protocol	Design	Participants	Effects on appetite
Piche *et al.* [62]	Supplemented daily for 7 d either: – 3 × 6·6 g OF – 3 × 6·6 g sucrose	Chronic two-way crossover	Patients with GERD (*n* 9)	Significantly ↑ GLP-1 AUC following OF supplementation relative to control with meal tolerance test. No significant changes for PYY and CCK.
Cani *et al.*[58]	Supplemented daily for 2 weeks either: – 2 × 8 g OF – 2 × 8 g DM (control)	Chronic two-way crossover	Healthy (*n* 10)	Satiety ratings significantly ↑ following breakfast and dinner, and hunger ratings significantly ↓ following dinner with OF supplementation. Significantly ↓ *ad libitum* EI at breakfast, lunch and for 24 h period with OF supplementation.
Whelan *et al.*[64]	Consumed daily for 2 weeks as sole source of nutrition either: – Modified formula with added pea fibre, inulin and OF – Standard formula (control)	Chronic two-way crossover	Healthy (*n* 11)	Significantly ↑ mean and minimum fullness, minimum satiety and mean hourly fullness ratings with fibre formula.
Antal *et al.*[59]	Consumed daily for 12 weeks either: – Low E diet + 14 g Jerusalem Artichoke concentrate containing OF – Low E (control)	Chronic two-way parallel	Healthy obese (*n* 51)	Hunger ratings ↓ and significantly ↓ BMI and % body fat with artichoke supplementation.
Cani *et al.* [63]	Supplemented daily for 2 weeks either: – 2 × 8 g OF/inulin mixture – 2 × 8 g DM (control)	Chronic two-way parallel	Healthy (*n* 10)	No differences in satiety ratings or EI between treatments. Significantly ↑ postprandial plasma PYY, GLP-1 and GIP relative to baseline with OF supplementation.
Parnell and Reimer [60]	Supplemented daily for 12 weeks with either: – 21 g OF – 7·89 g DM (control)	Chronic two-way parallel	Healthy overweight and obese (*n* 48)	No differences in satiety ratings between treatments. OF supplementation significantly ↓ 24 h EI, BW, fat mass, central fat mass and postprandial plasma leptin and significantly ↑ postprandial plasma PYY and ghrelin.

GERD, gastrooesophageal reflux disease; ↑ higher; ↓, lower; GLP, glucagon-like peptide; AUC, area under curve; OF, oligofructose; PYY, peptide YY; CCK, cholecystokinin; GIP, gastric-inhibitory polypeptide; BW, body weight.

Let us now take a look at the effects of mixed inulin-type fructans. In a two-way parallel chronic study, Cani and co-workers asked volunteers to supplement their usual diet with 16 g Synergy-1 (*n* 5) or 16 g Maltodextrin (control) (*n* 5) daily for 12 weeks. At the end of the supplementation period volunteers attended a meal tolerance test challenge. The authors reported postprandial subjective appetite ratings did not differ between the two treatments during the meal tolerance test, although the postprandial GLP-1 and PYY response was significantly higher with Synergy-1 treatment[63]. However, this study was underpowered and the meal tolerance test was supplied *ad libitum* making interpretation of postprandial data difficult.

In a two-way crossover study Whelan and colleagues asked healthy volunteers (*n* 11) to consume a standard enteral formula (control) or a modified enteral formula with added pea fibre, inulin and OF for 2 weeks as their sole nutrition source[64]. Significantly increased daily mean and minimum fullness and minimum satiety ratings were observed when the modified enteral formula was consumed relative to control[64]. However, as pea fibre was also included in the active treatment, observed results may not have been solely due to the inulin-type fructans.

Less compelling is anthropometric and food intake data from chronic intervention studies, although these were not the main outcomes of interest for all studies[65–72] except for two[59,60]. One study reported daily supplementation with 14 g Jerusalem Artichoke concentrate (containing OF) for 12 weeks significantly reduced BMI and % body fat levels[59], while another reported daily supplementation with 21 g OF significantly reduced BW, fat mass and central fat mass[60]. However, none of the other studies found a significant influence of inulin-type fructan supplementation on BW post-intervention[59,65,66,68–72] or on food intake during the intervention[65–68].

In our own laboratories, we carried out an acute three-way crossover study to investigate the effects on subjective and quantitative measures of appetite of providing inulin HP or another NDC L-rhamnose as a component of breakfast and lunch compared to a visually identical control (no NDC) following a 6 d run-in period. L-rhamnose was investigated as previously published data suggest propionate production is favoured during L-rhamnose fermentation, both *in vitro*[73] and *in vivo*[74]. Propionate is the most potent ligand for the SCFA receptor FFA3 and appears to promote leptin expression[26,27] and the production of PYY[28–34] as discussed earlier, providing a

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

rationale L-rhamnose may enhance appetite. Inulin HP was investigated due to the lack of previous data regarding effects on appetite.

During an acute meal challenge, healthy, normal weight unrestrained eaters (*n* 13) ingested 22·4 g inulin HP or 25·5 g L-rhamnose as a split dose at a standard breakfast and 180 min later at a standard lunch. We found neither treatment influenced appetite, with no significant differences between treatments for postprandial appetite VAS ratings, *ad libitum* EI 7 h postprandially, intake during the 24 h period following the breakfast preload nor on the mean daily intake during the run-in period (J Darzi, GS Frost and MD Robertson, unpublished results).

Colonic SCFA and appetite summary. While a number of studies have investigated the influence of supplementation with inulin-type fructans on markers of appetite in human subjects, the results to date are contradictory making it difficult to draw firm conclusions. This is in part due to variable dosages and differing choices of inulin-type fructan supplements.

Conclusion

The presence of the SCFA-activated G-coupled protein receptors, FFA2 and FFA3 in adipocytes and the colonic mucosa provide a rationale that SCFA may influence appetite and energy homeostasis. Initial data from observational studies that found dietary fibre and wholegrain intake is inversely related to BW and/or BMI, and from animal studies that found ingestion of inulin-type fructans on reduced EI and BW, provided initial evidence that colonically derived SCFA may influence appetite. However, as reviewed in this paper, these findings are not equivocally corroborated in human intervention studies, and our findings from oral SCFA supplementation studies are suggestive that product palatability may explain the observed effects of oral SCFA ingestion on appetite via cephalic-phase-initiated mechanisms. Therefore, in conclusion, the findings from this review do not support a role for SCFA in appetite regulation.

Acknowledgements

We are grateful to all the volunteers who participated in our studies. J. D. wrote the paper and had primary responsibility for final content. M. D. R. and G. S. F. were involved in refining the paper. All authors read and approved the final manuscript. The authors declare no conflicts of interest. J. D. was supported by an educational fellowship from Premier Foods.

References

1. Foresight. Tackling Obesities: Future Choices – Project Report: Government Office for Science; 2007. 2nd ed.
2. Blundell JE & Halford JC (1994) Regulation of nutrient supply: the brain and appetite control. *Proc Nutr Soc* **53**, 407–418.
3. Cummings DE & Overduin J (2007) Gastrointestinal regulation of food intake. *J Clin Invest* **117**, 13–23.
4. Burton-Freeman B (2000) Dietary fiber and energy regulation. *J Nutr* **130**, 272S–275S.
5. Delzenne NM & Cani PD (2005) A place for dietary fibre in the management of the metabolic syndrome. *Curr Opin Clin Nutr Metab Care* **8**, 636–640.
6. Howarth NC, Saltzman E & Roberts SB (2001) Dietary fiber and weight regulation. *Nutr Rev* **59**, 129–139.
7. Koh-Banerjee P, Franz MV, Sampson L *et al.* (2004) Changes in whole-grain, bran, and cereal fiber consumption in relation to 8-y weight gain among men. *Am J Clin Nutr* **80**, 1237–1245.
8. Koh-Banerjee P & Rimm EB (2003) Whole grain consumption and weight gain: a review of the epidemiological evidence, potential mechanisms and opportunities for future research. *Proc Nutr Soc* **62**, 25–29.
9. Melanson KJ, Angelopoulos TJ, Nguyen VT *et al.* (2006) Consumption of whole-grain cereals during weight loss: Effects on dietary quality, dietary fiber, magnesium, vitamin B-6, and obesity. *J Am Diet Assoc* **106**, 1380–1388.
10. Pereira MA & Ludwig DS (2001) Dietary fiber and body-weight regulation. Observations and mechanisms. *Pediatr Clin North Am* **48**, 969–980.
11. Slavin JL (2005) Dietary fiber and body weight. *Nutrition* **21**, 411–418.
12. Harland JI & Garton LE (2008) Whole-grain intake as a marker of healthy body weight and adiposity. *Public Health Nutr* **11**, 554–563.
13. Good CK, Holschuh N, Albertson AM *et al.* (2008) Whole grain consumption and body mass index in adult women: an analysis of NHANES 1999–2000 and the USDA pyramid servings database. *J Am Coll Nutr* **27**, 80–87.
14. McKeown NM, Yoshida M, Shea MK *et al.* (2009) Whole-grain intake and cereal fiber are associated with lower abdominal adiposity in older adults. *J Nutr* **139**, 1950–1955.
15. Rose N, Hosig K, Davy B *et al.* (2007) Whole-grain intake is associated with body mass index in college students. *J Nutr Educ Behav* **39**, 90–94.
16. Lutsey PL, Jacobs DRJ, Kori S *et al.* (2007) Whole grain intake and its cross-sectional association with obesity, insulin resistance, inflammation, diabetes and subclinical CVD: The MESA Study. *Br J Nutr* **98**, 397–405.
17. Cummings JH, Pomare EW, Branch WJ *et al.* (1987) Short-chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* **28**, 1221–1227.
18. Topping DL & Clifton PM (2001) Short-chain fatty acids and human colonic function: Roles of resistant starch and non-starch polysaccharides. *Physiol Rev* **81**, 1031–1064.
19. Dass NB, John AK, Bassil AK *et al.* (2007) The relationship between the effects of short-chain fatty acids on intestinal motility in vitro and GPR43 receptor activation. *Neurogastroenterol Motil* **19**, 66–74.
20. Cummings JH & Englyst HN (1987) Fermentation in the human large intestine and the available substrates. *Am J Clin Nutr* **45**, 1243–1255.
21. Brown AJ, Goldsworthy SM, Barnes AA *et al.* (2003) The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem* **278**, 11312–11319.
22. Le Poul E, Loison C, Struyf S *et al.* (2003) Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* **278**, 25481–15489.
23. Nilsson NE, Kotarsky K, Owman C *et al.* (2003) Identification of a free fatty acid receptor, FFA2R, expressed on leukocytes and activated by short-chain fatty acids. *Biochem Biophys Res Commun* **303**, 1047–1052.

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

24. Stoddart LA, Smith NJ & Milligan G (2008) International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, −2, and −3: pharmacology and pathophysiological functions. *Pharmacol Rev* **60**, 405–417.
25. Tazoe H, Otomo Y, Kaji I *et al.* (2008) Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *J Physiol Pharmacol* **59**, 251–262.
26. Xiong Y, Miyamoto N, Shibata K *et al.* (2004) Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proc Natl Acad Sci USA* **101**, 1045–1050.
27. Covington DK, Briscoe CA, Brown AJ *et al.* (2006) The G-protein-coupled receptor 40 family (GPR40-GPR43) and its role in nutrient sensing. *Biochem Soc Trans* **34**, 770–773.
28. Karaki S, Mitsui R, Hayashi H *et al.* (2006) Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res* **324**, 353–360.
29. Karaki S, Tazoe H, Hayashi H *et al.* (2008) Expression of the short-chain fatty acid receptor, GPR43, in the human colon. *J Mol Histol* **39**, 135–142.
30. Tazoe H, Otomo Y, Karaki S *et al.* (2009) Expression of short-chain fatty acid receptor GPR41 in the human colon. *Biomed Res* **30**, 149–156.
31. Plaisancié P, Dumoulin V, Chayvialle JA *et al.* (1996) Luminal peptide YY-releasing factors in the isolated vascularly perfused rat colon. *J Endocrinol* **151**, 421–429.
32. Plaisancié P, Dumoulin V, Chayvialle JA *et al.* (1995) Luminal glucagon-like peptide-1(7–36) amide-releasing factors in the isolated vascularly perfused rat colon. *J Endocrinol* **145**, 521–526.
33. Cherbut C, Ferrier L, Rozé C *et al.* (1998) Short-chain fatty acids modify colonic motility through nerves and polypeptide YY release in the rat. *Am J Physiol* **275**, G1415–1422.
34. Cuche G & Malbert CH (2000) Ileal short-chain fatty acids inhibit gastric motility by a humoral pathway. *Am J Physiol* **279**, G925–G930.
35. Hlebowicz J, Lindstedt S, Björgell O *et al.* (2008) The botanical integrity of wheat products influences the gastric distention and satiety in healthy subjects. *Nutr J* **7**, 12–19.
36. Mettler S, Schwarz I & Colombani PC (2009) Additive postprandial blood glucose-attenuating and satiety-enhancing effect of cinnamon and acetic acid. *Nutr Res* **29**, 723–727.
37. Ostman E, Granfeldt Y, Persson L *et al.* (2005) Vinegar supplementation lowers glucose and insulin responses and increases satiety after a bread meal in healthy subjects. *Eur J Clin Nutr* **59**, 983–988.
38. Kondo T, Kishi M, Fushimi T *et al.* (2009) Vinegar intake reduces body weight, body fat mass, and serum triglyceride levels in obese Japanese subjects. *Biosci Biotechnol Biochem* **73**, 1837–1843.
39. Frost GS, Brynes AE, Dhillo WS *et al.* (2003) The effects of fiber enrichment of pasta and fat content on gastric emptying, GLP-1, glucose, and insulin responses to a meal. *Eur J Clin Nutr* **57**, 293–298.
40. Liljeberg HGM & Bjorck IME (1996) Delayed gastric emptying rate as a potential mechanism for lowered glycemia after eating sourdough bread: Studies in humans and rats using test products with added organic acids or an organic salt. *Am J Clin Nutr* **64**, 886–893.
41. Liljeberg HGM, Lonner CH & Bjorck IME (1995) Sourdough fermentation or addition of organic acids or corresponding salts to bread improves nutritional properties of starch in healthy humans. *J Nutr* **125**, 1503–1511.
42. Darzi J, Frost GS & Robertson MD (2008) The acute effects of a propionate-rich sourdough bread on appetite and metabolic response. *Proc Nutr Soc* **67**, E317.
43. Sørensen LB, Møller P, Flint A *et al.* (2003) Effect of sensory perception of foods on appetite and food intake: a review of studies on humans. *Int J Obes* **27**, 1152–1162.
44. Yeomans MR (2007) Chapter 10: The role of palatability in control of human appetite: Implications for understanding and treating obesity. In Appetite and Body Weight: Integrative Systems and The Development of Anti-obesity drugs. pp. 247–269. Liverpool: Elsevier Ltd.
45. Berti C, Riso P, Brusamolino A *et al.* (2005) Effect on appetite control of minor cereal and pseudocereal products. *Br J Nutr* **94**, 850–858.
46. Roberfroid MB (2005) Introducing inulin-type fructans. *Br J Nutr* **93**, S13–S25.
47. Kelly G (2008) Inulin-type prebiotics: a review (Part 1). *Altern Med Rev* **13**, 315–329.
48. Niness KR (1999) Inulin and oligofructose: what are they? *J Nutr* **129**, 1402S–1406S.
49. Cani PD, Knauf C, Iglesias MA *et al.* (2006) Improvement of glucose tolerance and hepatic insulin sensitivity by oligofructose requires a functional glucagon-like peptide 1 receptor. *Diabetes* **55**, 1484–1490.
50. Cani PD, Dewever C & Delzenne NM (2004) Inulin-type fructans modulate gastrointestinal peptides involved in appetite regulation (glucagon-like peptide-1 and ghrelin) in rats. *Br J Nutr* **92**, 521–526.
51. Cani PD, Hoste S, Guiot Y *et al.* (2007) Dietary non-digestible carbohydrates promote L-cell differentiation in the proximal colon of rats. *Br J Nutr* **98**, 32–37.
52. Daubioul C, Rousseau N, Demeure R *et al.* (2002) Dietary fructans, but not cellulose, decrease triglyceride accumulation in the liver of obese Zucker fa/fa rats. *J Nutr* **132**, 967–973.
53. Kok NN, Morgan LM, Williams CM *et al.* (1998) Insulin, glucagon-like peptide 1, glucose-dependent insulinotropic polypeptide and insulin-like growth factor I as putative mediators of the hypolipidemic effect of oligofructose in rats. *J Nutr* **128**, 1099–1103.
54. Cani PD, Neyrinck AM, Maton N *et al.* (2005) Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like peptide-1. *Obes Res* **13**, 1000–1007.
55. Peters HP, Boers HM, Haddeman E *et al.* (2009) No effect of added beta-glucan or of fructooligosaccharide on appetite or energy intake. *Am J Clin Nutr* **89**, 58–63.
56. Archer BJ, Johnson SK, Devereux HM *et al.* (2004) Effect of fat replacement by inulin or lupin-kernel fibre on sausage patty acceptability, post-meal perceptions of satiety and food intake in men. *Br J Nutr* **91**, 591–599.
57. Perrigue MM, Monsivais P & Drewnowski A (2009) Added soluble fiber enhances the satiating power of low-energy-density liquid yogurts. *J Am Diet Assoc* **109**, 1862–1868.
58. Cani PD, Joly E, Horsmans Y *et al.* (2006) Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr* **60**, 567–572.
59. Antal M, Regöly-Mérei A, Biró L *et al.* (2008) Effects of oligofructose containing diet in obese persons. *Orv Hetil* **149**, 1989–1995.
60. Parnell JA & Reimer RA (2009) Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr* **89**, 1751–1759.
61. Flint A, Raben A, Blundell JE *et al.* (2000) Reproducibility, power and validity of visual analogue scales in assessment of

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press

appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord* **24**, 38–48.
62. Piche T, des Varannes SB, Sacher-Huvelin S *et al.* (2003) Colonic fermentation influences lower esophageal sphincter function in gastroesophageal reflux disease. *Gastroenterology* **124**, 894–902.
63. Cani PD, Lecourt E, Dewulf EM *et al.* (2009) Gut microbiota fermentation of prebiotics increases satietogenic and incretin gut peptide production with consequences for appetite sensation and glucose response after a meal. *Am J Clin Nutr* **90**, 1236–1243.
64. Whelan K, Efthymiou L, Judd PA *et al.* (2006) Appetite during consumption of enteral formula as a sole source of nutrition: the effect of supplementing pea-fibre and fructo-oligosaccharides. *Br J Nutr* **96**, 350–356.
65. Alles MS, de Roos NM, Bakx JC *et al.* (1999) Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. *Am J Clin Nutr* **69**, 64–69.
66. Giacco R, Clemente G, Luongo D *et al.* (2004) Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. *Clin Nutr* **23**, 331–340.
67. Pedersen AM, Sandstorm B & Van Amelsvoort JMM (1997) The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. *Br J Nutr* **78**, 215–222.
68. Forcheron F & Beylot M (2007) Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. *Metabolism* **56**, 1093–1098.
69. Davidson MH, Maki KC, Synecki C *et al.* (1998) Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. *Nutr Res* **18**, 503–517.
70. Jackson KG, Taylor GRJ, Clohessy AM *et al.* (1999) The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. *Br J Nutr* **82**, 23–30.
71. Luo J, Rizkalla SW, Alamowitch C *et al.* (1996) Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. *Am J Clin Nutr* **63**, 939–945.
72. Luo J, Van Yperselle N, Rizkalla SW *et al.* (2000) Chronic consumption of short-chain fructooligosacchrarides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. *J Nutr* **130**, 1572–1577.
73. Fernandes J, Rao AV & Wolever TM (2000) Different substrates and methane producing status affect short-chain fatty acid profiles produced by In vitro fermentation of human feces. *J Nutr* **130**, 1932–1936.
74. Vogt JA, Pencharz PB & Wolever MS (2004) L-Rhamose increases serum propionate in humans. *Am J Clin Nutr* **80**, 89–94.

NS Proceedings of the Nutrition Society

https://doi.org/10.1017/S0029665110004039 Published online by Cambridge University Press