Effects of long-term soluble vs. insoluble dietary fiber intake on high-fat diet-induced obesity in C57BL/6J mice

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Abstract

Although most of the proposed beneficial effects of fiber consumption have been attributed to viscous and gel-forming properties of soluble fiber, it is mainly insoluble cereal fiber and whole grains that are strongly associated with reduced diabetes risk in prospective cohort studies, indicating that other unknown mechanisms are likely to be involved.

We performed a long-term study investigating potential protective effects of adding soluble guar fiber (10% w/w) vs. insoluble cereal fiber (10% w/w) to an isoenergetic and macronutrient matched high-fat diet in obesity-prone C57BL/6J mice. After 45 weeks, mice fed soluble vs. insoluble fiber showed both significantly increased body weight (41.8 ± 3.0 vs. 33.6 ± 1.5 g, $P=.03$) and elevated markers of insulin resistance. In mice fed soluble fiber, energy loss via the feces was significantly lower and colonic fermentation with production of short chain fatty acids (SCFA) was markedly increased. Gene expression analysis in white adipose tissue showed significantly increased levels of the fatty acid target G-protein coupled receptor-40 in soluble fiber-fed mice. Liver gene expression in the insoluble fiber group showed a pattern consistent with increased fatty acid oxidation. The present results show that soluble vs insoluble dietary fiber added to a high-fat, Western-style diet differently affected body weight and estimates of insulin sensitivity in obesity-prone mice. Soluble fiber intake with increased SCFA production significantly contributed to digested energy, thereby potentially outweighing the well known short-term beneficial effects of soluble fiber consumption.
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1. Introduction

Recent meta-analyses of prospective cohort studies report markedly reduced diabetes risk in subjects consuming diets high in insoluble cereal dietary fiber and whole grains [1,2]. In contrast, and surprisingly, there is no strong support that soluble viscous fibers from fruits and vegetables play a key role in this context [1–3], although most of the proposed protective mechanisms of fiber consumption are either more likely to be relevant with soluble fiber or they are shared by soluble and insoluble fiber [3]. For instance, viscous and gel-forming properties of soluble fibers are involved in hindering of macronutrient absorption, slowing of gastric emptying, reducing postprandial glucose responses and reducing total and low-density lipoprotein (LDL) cholesterol levels. Colonic fermentation of naturally available high-fiber foods with the production of short chain fatty acids (SCFA) can also be

mainly attributed to soluble fiber consumption, whereas effects on inflammatory markers [4] and moderate weight loss due to low energy density and increased satiety have been reported to be comparable with both soluble and insoluble fiber [3,5]. Therefore, it is likely that further mechanisms are involved in conveying reduced diabetes risk after long term insoluble fiber intake. These might include improved whole-body insulin sensitivity, as recently shown in short-term randomized controlled intervention studies [6–8] and several cross-sectional studies in humans [9]. However, no causal relationships can be stated from cross-sectional studies, and long-term dietary interventions in humans face the problem of controlling confounding factors and maintaining dietary adherence [10]. Difficulties investigating signalling pathways in the liver are another problem in human studies. Several relatively short-term studies in animal models reported soluble fiber such as guar gum or psyllium being superior in improving insulin sensitivity, in comparison to insoluble cellulose [11,12]. In a study investigating male Wistar rats, short-term feeding with guar gum vs. cellulose or bran had favourable effects on body weight and carbohydrate tolerance. However, and importantly, in the long term, these effects were absent, with a tendency to reduced body weight and significantly lower pancreatic insulin

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and glucagon concentrations in the cellulose fed rats after 67 weeks [13]. However, different effects may be observed in other species and long-term effects of supplementing a Western-style, high-fat diet with soluble vs. insoluble fiber in obesity prone mouse models are unknown. Potential fiber-induced influences on transcription factors in liver and adipose tissue are of further interest and might provide important insights for the understanding of beneficial effects of fiber consumption. Therefore, in the present study, we investigated in C57BL/6J mice whether a long-term supplementation of a high-fat diet with soluble viscous guar fiber vs. highly purified insoluble cereal fiber differently affects body weight, liver fat, estimates of insulin sensitivity and gene expression of metabolic markers in liver and fat tissue.

2. Methods and materials

2.1. Animals

The protocol for all animal experiments was approved by the local governmental animal ethic review board (State of Brandenburg, Germany). The animals were kept in accordance with the National Institutes of Health guidelines for care and use of laboratory animals. After 45 weeks, mice were sedated using ether inhalation and sacrificed by decapitation.

Experiments were performed in adult (16 weeks old) male C57BL/6J mice obtained by Charles River, Germany. Animals were housed individually at a temperature of 22°C with a 12:12-h light–dark cycle in cages with soft wood bedding. Two groups of animals ($n=7$ per group) received different diets (Table 1) with unlimited access to chow and liquids over 45 weeks. Metabolizable macronutrients of diets were calculated according to the following energy contents: casein 15.7 kJ/g, carbohydrates 16 kJ/g and fat 38 kJ/g. After the experimental period, animals were sacrificed in fed state. Organs were isolated after rapid preparation. Epididymal white adipose tissue and liver tissue were submerged in nitrogen and immediately stored at −80°C until further RNA preparation.

2.2. Diets

The macronutrient composition of the experimental diets is shown in Table 1. The diet enriched with soluble fiber contained 10% (w/w) guar gum, which is an established model for the investigation of soluble fiber diets (64% soluble fiber, 13% insoluble fiber) [14,15]. The diet enriched with insoluble fiber contained 10% of the insoluble fraction of oat fiber, as previously used [8,16,17], providing a mixture of insoluble fibers as found in cereal fiber and whole grain products [3% soluble fiber, 93% insoluble fiber (cellulose 70%, hemicelluloses 25%, lignin 3–5%)]. Food intake rate was recorded every week.

Table 1
Macronutrient composition of experimental diets

	Soluble fiber	Insoluble fiber
Diet (g/kg)		
Casein[a]	200	200
Amylopectin[b]	390	390
Sucrose[c]	50	50
Palm kernel fat[d]	170	170
Thistle oil[e]	10	10
Linseed oil[f]	10	10
Guar fiber[g]	100	–
Insoluble fraction of oat fiber[h]	–	100
Mineral mixture[i]	50	50
Vitamin mixture[j]	20	20
Calculated macronutrient metabolizable energy (%)		
Protein	18	18
Carbohydrates	41	41
Fat	41	41

[a] Dauermilchwerk Peiting, Landshut Germany.
[b] National Starch and Chemical, Hamburg, Germany.
[c] EUCO, Hamburg, Germany.
[d] Kölln KGaA, Elmshorn, Germany.
[e] EUCO, Hamburg, Germany.
[f] Kunella-Feinkost, Cottbus, Germany.
[g] Roeper, Hamburg, Germany.
[h] Rettenmeier, Ellwangen, Germany.
[i] Altromin, Lage, Germany.
[j] Altromin, Lage, Germany.

2.3. Digestibility of diets

Feces of all animals were collected at Week 5, and food intake was recorded for further analysis of energy balance. After drying, energy content of diet samples and feces was determined by bomb calorimetry (IKA C5003, IKA Werke, Germany) and digested energy [defined as diet energy intake (kJ/g) minus energy loss via the feces (kJ/g)] was calculated for all dietary groups. Digestibility of the diet (%) was defined as {[digested energy (kJ/g)/diet energy intake (kJ/g)]×100}. Cumulative digested energy was calculated over the experimental period of 45 weeks by multiplying diet energy intake with digestibility, as measured over 1 week.

2.4. Body composition

Body composition (fat mass, lean mass and free fluids) was measured every 4–6 weeks using nuclear magnetic resonance spectroscopy (Mini Spect MQ 10 NMR Analyser Bruker, Karlsruhe, Germany). Body weight was recorded every week.

2.5. Hydrogen (H_2) breath test as a marker of colonic fermentation

This test was performed twice in all mice in the fed state between 08:00 and 09:00. In order to collect hydrogen exhalation samples, animals were placed individually into 140 ml syringes. After 1 min of equilibration, two samples of 30-ml air breath were drawn of for further analysis. Air breath samples were collected and H_2 concentrations were measured using a breath hydrogen analyser (Quinton Model-12i-Microlyzer; Quintron Instruments, Milwaukee, USA).

2.6. Analysis of hepatic triacylglycerol

Frozen liver tissue was ground in liquid nitrogen to a homogenous powder; 100 mg of tissue was homogenized in 5 ml of 10 mM sodium phosphate buffer containing 1 mM EDTA and 1% polyoxyethylene 10 tridecylethan, using an Ultra-Turrax (IKA Werke, Germany). Samples were centrifuged (10 min, 20,000×g), and the supernatant was incubated at 70°C for 5 min. Triacylglycerols (triglyceride reagent, SIGMA) and protein (DC protein assay, Bio-Rad) levels were analysed in triplicates.

2.7. Insulin tolerance test

Insulin sensitivity was estimated after 44 weeks of dietary intervention in fed mice by intraperitoneal (i.p.) injection of insulin (0.75 IU/kg body mass, Actrapid, Novonordisk) as described previously [18]. There was a 6-day period between insulin tolerance test (ITT) and sacrifice of the animals. Glucose concentrations were measured in tail blood at 0, 15, 30 and 60 min after insulin injection.

2.8. Glucose tolerance test

Glucose tolerance tests were performed at weeks 9/10 and 15/16 by intraperitoneal glucose injection, as described [18]. Plasma was collected before and 10, 30 and 60 min after glucose challenge and immediately frozen at −80°C for measurement of glucose and insulin.

2.9. Plasma analyses

Animals were investigated in the overnight fasted state. Mouse plasma insulin levels were measured by enzyme-linked immunosorbent assay for rat insulin using a mouse insulin standard (both from Crystal Chem, Chicago, IL, USA), as described [19]. Blood was obtained from the retro-orbital sinus during anaesthesia using Isoflurane (Baxter, Unterschleissheim, Germany). Plasma glucose, plasma triacylglycerols, and plasma total cholesterol were measured using commercial kits (glucose HK 125; triacylglycerols and total cholesterol: ABX Pentra, Montpellier France), by using an autoanalyzer (Cobas Mira S, Hoffmann La Roche, Switzerland).

2.10. RNA extraction and real time reverse transcriptase-polymerase chain reaction

Total RNA was extracted from liver and epididymal white fat tissue of animals in nonfasted state by RNeasy lipid tissue kit (QIAgen, Hilden, Germany). DNA digestion was performed using RNase-free DNase (QIAgen). Total RNA (1 µg) was reverse-transcribed to first-strand cDNA using high capacity cDNA Reverse Transcription Kit (Applied Biosystems, USA), according to manufacturer's protocols. Each cDNA sample was applied at a concentration of 0.626 ng of total RNA to the quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) assay wells, using optical 384-well plates, and labelled with Power SYbr Green master mix (Applied Biosystems, Darmstadt, Germany). All samples were measured in triplicates, and nontemplate controls were used to confirm specificity. The quantity of target and the housekeeping gene hypoxanthine-guanine phosphoribosyltransferase (Hprt) were calculated according to a standard curve. In liver tissue, expression of forkhead transcription factor Foxa2, peroxysome proliferator-activated receptor (Ppar)-γ coactivator β (Pgc-1β), L-carnitine palmitoyl transferase1 (Cpt-1), acyl-CoA oxidase (Aox), diacylglycerol acetyltransferase-2 (Dgat-2), uncoupling protein2 (Ucp-2) and Pparα was measured. Expression of G protein-coupled receptors 40, 41 and 43

{Gpr40 [free fatty acid receptor (Ffar)-1], Gpr41 (Ffar-3) and Gpr43 (Ffar-2)} was analysed in white adipose tissue.

The oligonucleotide specific primers were:

Hprt:
up5′-CAGTCCCAGCGTCGTGATTA-3′, lo5′-AGCAAGTCTTTCAGTCCTGTC-3′,
Foxa2:
up5′-GCGGCCAGCGAGTTAAAGTAT-3′, lo5′-TCATTCCAGCGCCCACATA-3′,
Pgc-1β:
up5′-ATGAAGGCGACACACCATCCT-3′, lo5′-TGCCATCCACCTTGACACAAG-3′,
Cpt-1:
up5′-CCTGCATTCCTTCCCATTTG-3′, lo5′-CCCATGTCCTTGTAATGTGCG-3′,
Aox:
up5′-TACTTGAATGACCTGCCGAGC-3′, lo5′-GCAGCAATTTCTACCAATCTGG-3′,
Dgat-2:
up5′-CCAAGAAAGGTGGCAGGAGAT-3′, lo5′-GCAGGTTGTGTGTCTTCACCA-3′,
Ucp-2:
up5′-CCAACAGCCACTGTGAAGTTCC-3′, lo5′-TGACTCTCCCCTTGGATCTGCA-3′,
Pparα:
up5′-CAGTGCCCTGAACATCGAGTGT-3′, lo5′-TTCGCCGAAAGAAGCCCTT-3′,
Gpr40:
up5′-TGGCTAGTTTCATAAACCCGG-3′, lo5′-TCCCAAGTAGCCATGGACCAGT-3′
Gpr41:
up5′-CTTGTATCGACCCCCTGGTTTT-3′, low5′-GCTGAGTCCAAGGCACACAAGT-3′
Gpr43:
up5′-TGTTCAGTTCCCTCAATGCCA-3′, lo5′-CAGGATTGCGGATCAGTAGCA-3′

3. Results

3.1. Different effects of soluble guar fiber vs. insoluble cereal fiber on body weight gain and estimates of insulin resistance in mice fed a high-fat diet

Fig. 1A shows changes in body weight during the experiment. The observed drops in body weight at Weeks 9/10 and 15/16 were induced by overnight fasting procedure for the performance of glucose tolerance tests (GTTs). Area under the curve (AUC) glucose during GTTs showed no significant difference between soluble and insoluble fiber-fed animals ($P=.68$ and $P=.4$, respectively). After 45 weeks, mice fed the soluble fiber diet showed significantly increased body weight, in comparison to mice fed the insoluble
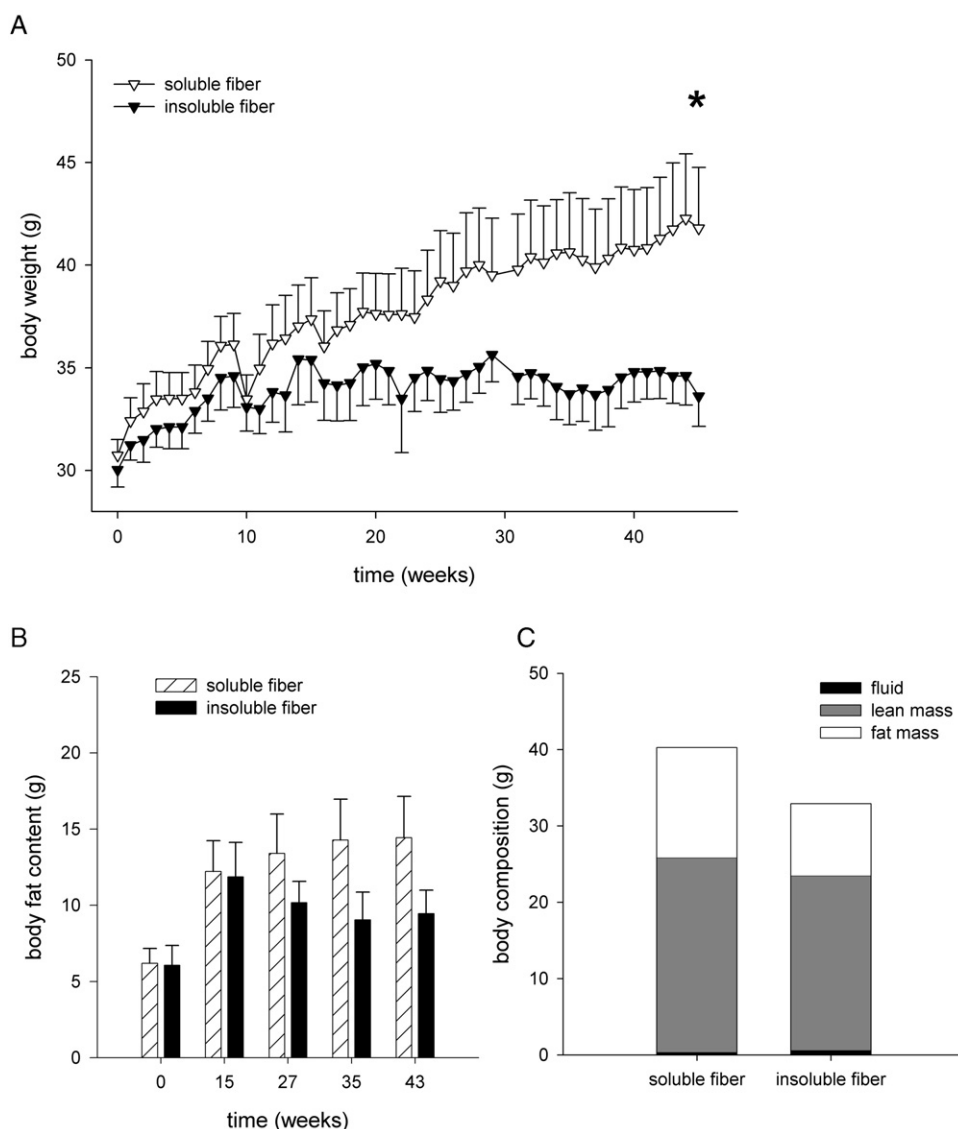

Fig. 1. Change in body composition over 43 weeks of dietary intervention (starting with $n=7$ per group). (A) Changes in body weight. (B) Body fat contents were measured by NMR and are exemplarily shown at 0, 15, 27, 35 and 43 weeks in animals fed soluble vs. insoluble fiber. (C) Body composition measured by NMR after 43 weeks. NMR, nuclear magnetic resonance.

fiber diet (41.8 ± 3.0 vs. 33.6 ± 1.5 g, $P=.03$). Increased body weight was accompanied by a tendency to increased body fat (Fig. 1B, $P=.14$). The exact body composition (free fluid, lean mass and fat mass) in Week 43 is shown in Fig. 1C. In agreement with the observed change in body weight, measurements of insulin sensitivity after i.p. insulin administration (week 44) were significantly lower after soluble vs. insoluble fiber consumption (Fig. 2; $t=60$ min, $P=.044$). AUC glucose during ITT tended to be lower in insoluble fiber-fed animals (299 ± 26 vs. 345 ± 16 mmol/min, $P=.19$). No significant differences were detected in fasting concentrations of plasma cholesterol, plasma triacylglycerols, plasma glucose and plasma insulin (data not shown).

3.2. Increased energy digestion with soluble vs. insoluble fiber

For analysis of digestibility, fecal excretion and food uptake were recorded at Week 5 for further analysis of digested energy. Energy content of the respective diets measured in a calorimeter was 18.8 kJ/g in the group fed with soluble fiber and 17.6 kJ/g in the group fed with insoluble fiber. Food intake was multiplied with these values. Fig. 3A shows no significant difference in diet energy intake during a 1-week period. However, fecal excretion was significantly increased with insoluble vs soluble fiber ($P<.0001$) (Fig. 3B). Energy content in feces was not significantly different between groups ($P=.16$) (Fig. 3C). Digestibility of the diets was 94% with soluble fiber and 89% with insoluble fiber. Digested energy between groups was not significantly different in the short term (Fig. 3D), as measured over 1 week (soluble fiber 365.0 ± 8.0 vs. insoluble fiber 340.8 ± 10.8 kJ/week, $P=.1$). However, long-term cumulative energy digestion over 45 weeks was significantly different between soluble and insoluble fiber consumption (AUC 350577 ± 3919 kJ/mouse vs. 316367 ± 6569 kJ/mouse, $P=.0025$) (Fig. 3E).

3.3. Increased colonic fermentation with soluble fiber

Colonic fermentation of each diet was estimated by using hydrogen breath tests at Week 4 (Fig. 4A). As could be expected, hydrogen exhalation was significantly higher in mice fed the soluble fiber in comparison with mice fed insoluble fiber ($P=.002$).
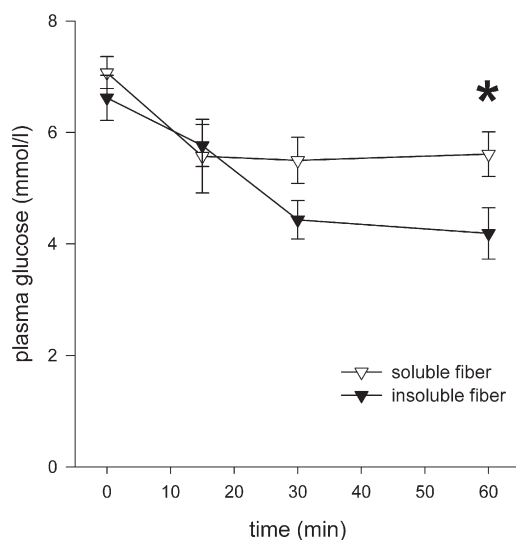
Fig. 2. Increased marker of insulin resistance under diet with soluble vs. insoluble fiber. Glucose levels after i.p. insulin administration during insulin tolerance test in fed state after 44 weeks of intervention in mice fed soluble vs. insoluble fiber ($n=6$ per group). *$P<.05$.

3.4. Fiber-induced changes in adipose tissue mRNA expression of G-protein coupled receptors and Foxa2

The G-protein coupled receptor (Gpr) family Gpr40, Gpr41 and Gpr43 shares approximately 30% identity among members [20] and has recently been shown to be specifically activated by SCFA [20,21]. In agreement with significantly increased colonic fermentation in mice fed soluble vs. insoluble fiber, expression in white adipose tissue of Gpr40 was significantly increased after 45 weeks of dietary intervention ($P=.042$) (Fig. 4B). Gpr41 was not detectable in adipose tissue, as also observed by others [22]. No significant differences were observed in Gpr43 (Fig. 4B, $P=.47$).

Foxa2 was not significantly different between groups in adipose tissue (1.0 ± 0.4 (soluble fiber) vs. 1.5 ± 0.8 (insoluble fiber), arbitrary units, $P=.5$), although the direction of changes was in agreement with the observed significant changes in more metabolic active hepatic tissue.

3.5. Expression of hepatic transcription factors of fat metabolism

After 45 weeks, hepatic triacylglycerol contents tended to be higher in mice fed with soluble vs. insoluble fiber (Fig. 5A) ($P=.11$). We further investigated fiber-induced changes of factors involved in the regulation of liver fat metabolism. Foxa2 is an important transcription factor in liver and fat tissue, regulating, e.g., beta oxidation, triacylglycerol synthesis and fat cell differentiation [23]. After intervention with insoluble fiber, expression of Foxa2 was significantly increased, as compared with the soluble fiber-fed animals (Fig. 5B, $P=.031$). In agreement with this, there was also significantly increased expression of Pgc-1β (Fig. 5B, $P=.006$), which is another transcription factor known to be recruited by Foxa2. Expression of key enzymes of beta-oxidation and triacylglycerol synthesis was further analysed. Dgat-2 was significantly increased in liver tissue of mice fed with insoluble fiber ($P=.045$), whereas Cpt-1 ($P=.07$), Aox ($P=.37$) and Ucp-2 ($P=.12$) were comparable between groups (Fig. 5B). The expression of Pparα, which plays a key role in fatty acid catabolism was significantly higher in insoluble fiber-fed animals ($P=.042$).

4. Discussion

A high fiber intake is emphasised in the recommendations of most nutritional and diabetes associations. Although most of the proposed beneficial effects of fiber consumption have been attributed to viscous properties of soluble fermentable sorts of fiber, results from prospective cohort studies consistently show that insoluble cereal fiber and whole grain consumption, but not soluble fiber intake, is strongly linked to reduced risk of diabetes [1–3,24].

We present novel findings showing that long-term supplementation of a high-fat Western-style diet with soluble highly fermentable guar fiber resulted in an obese phenotype in C57BL/6J mice. In contrast, supplementing the same diet with moderately fermentable insoluble cereal fiber prevented a high-fat diet-induced obese phenotype in these animals.

Weight gain and estimates of insulin resistance were significantly different between groups, although dietary energy intake was comparable.

Mice in the present study had free access to chow. Therefore, significantly lower energy loss via the feces in the soluble fiber group together with comparable dietary energy intake in all mice suggests that more metabolizable energy was extracted from the soluble, highly fermentable fiber diet, without affecting satiety and feeding behaviour. This is supported by earlier studies showing that fiber-induced increases of SCFA do contribute to energy intake both in rodents and humans [25]. Interestingly, colonization of germ-free gnotobiotic mice with a prominent saccharolytic member of the normal human gut microbiota together with the dominant human
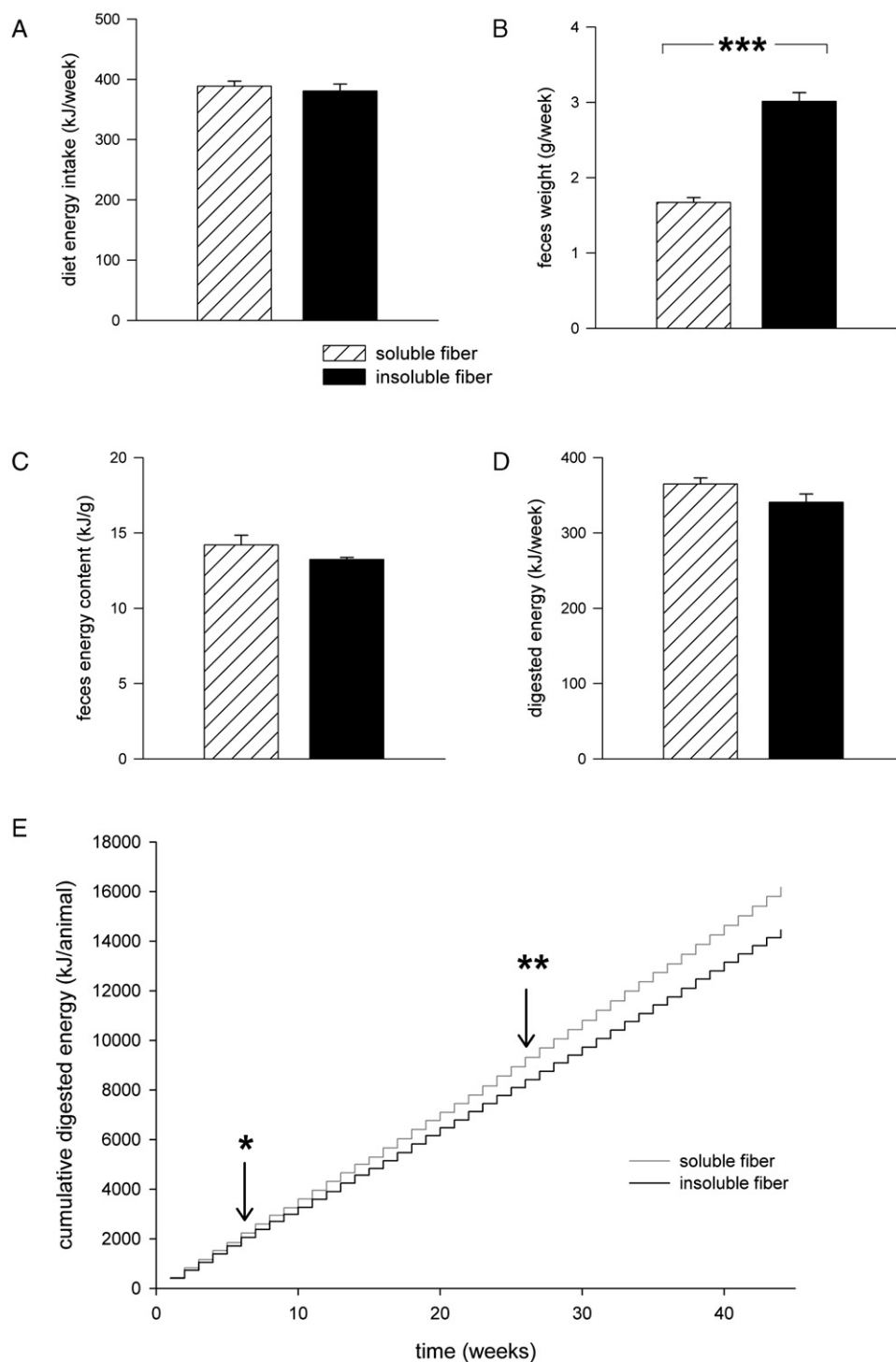
Fig. 3. Energy digestion during one exemplary week and cumulative energy digestion during a whole experimental period. (A) Diet energy intake at Week 5 in groups of animals fed soluble fiber vs. insoluble fiber ($n=7$ per group). (B) Feces excretion during Week 5 of intervention. (C) Feces energy content in the treatment groups. (D) Energy digestion at Week 5 in the dietary intervention groups. (E) Extrapolated cumulative digested energy calculated from diet energy intake over 45 weeks of treatment. Head-down arrows indicate significant differences between soluble vs. insoluble fiber-fed mice. $*P<.05$; $**P<.01$; $P<.001$.

methane-producing germ results in markedly improved colonic fermentation and is associated with an obese phenotype in the host [3,26]. As could be expected, H_2 measurements indicated that colonic fermentation with the production of SCFA was largely increased in mice consuming soluble fiber but not in animals ingesting insoluble cereal fiber. Fiber-induced increases of SCFA production are commonly assumed to be beneficial, e.g., by

reducing hepatic glucose output and beneficially affecting blood lipid profiles [27,28]. Increased insulin sensitivity after relatively short-term consumption of highly fermentable resistant starch has also recently been shown [7]. However, both highly fermentable insoluble resistant starch [7,29] and only moderately fermentable insoluble cereal fiber [8,16] increased insulin sensitivity in humans, indicating that a dose-dependent relation between fermentability of
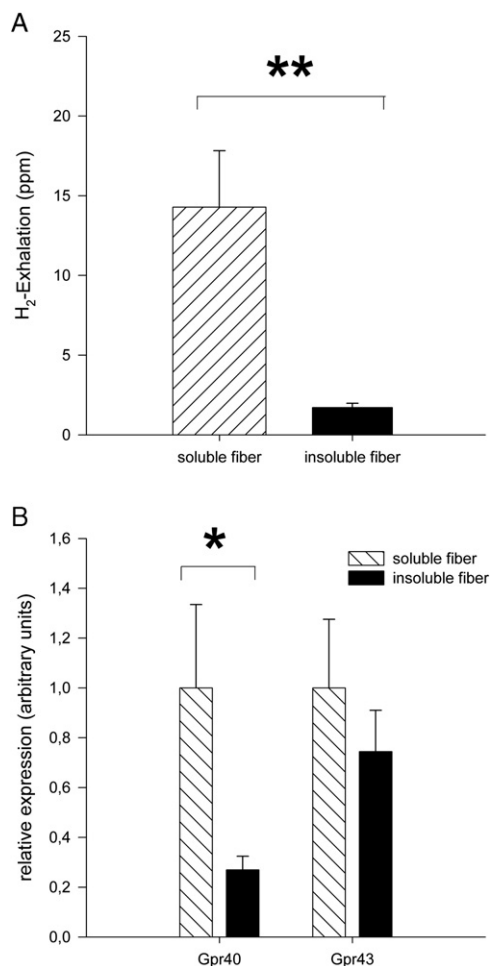
Fig. 4. Marker of colonic fermentation. (A) Hydrogen breath test in week 4 in mice fed soluble vs. insoluble fiber (n=7 per group). (B) Real-time RT-PCR analysis of SCFA targets Gpr40 and Gpr43 in epididymal white adipose tissue after 45 weeks of intervention in mice consuming diets supplemented with soluble vs. insoluble fiber. Results were normalized to internal control Hprt, and the intervention group fed soluble fiber was set to 100% (n=5–6 each group). *P<.05; **P<.01.

dietary fibers and insulin sensitivity is unlikely [3]. Further, available studies indicate that SCFA could contribute to increased de novo lipogenesis [26], probably by stimulating adipogenesis through Gpr43 [20], although in the present study, Gpr43 expression was not significantly increased in fermentable fiber-fed mice. However, expression of Gpr40 representing another recently identified target of fatty acids including SCFA [21] that is mainly expressed in pancreas and brain, but also in monocytes and in adipose tissue, was significantly increased in the soluble fiber group. Loss of Gpr40 protects mice from obesity-induced hyperinsulinemia, hepatic steatosis, increased hepatic glucose output, hyperglycemia and glucose intolerance [30]. Vice versa, increased Gpr40 in soluble fiber-fed mice could provide a potential mechanism contributing to the observed obese phenotype in these animals.

A further novel finding of the present study was liver gene expression in the insoluble fiber group showing a pattern consistent with increased fatty acid oxidation. Mice fed insoluble fiber showed significantly increased expression levels of Foxa2 and Pgc-1β in comparison to soluble fiber-fed animals. These transcription factors are known to play an important role in the regulation of hepatic lipid homeostasis. Coexpression of Foxa2 and Pgc-1b has been reported to concomitantly increase gene expression of key enzymes of mitochondrial beta-oxidation [31]. Significantly increased expression levels in liver of Pparα and Dgat-2 in insoluble fiber-fed mice in the present study were in good agreement with these findings, thus potentially contributing to increased beta-oxidation and reduced fat mass in mice fed insoluble cereal fibers. Differences in liver gene expression were likely caused by fiber-induced differences in body weight and insulin resistance, although a direct influence of fiber types on liver fat metabolism cannot be finally excluded.

It has been suggested that soluble fibers such as guar gum increase postprandial fullness and reduce food intake, e.g., by increasing the viscosity of the bowel content [32]. However, in a meta-analysis of randomized controlled trials in humans, the conclusion was drawn that guar gum was not efficacious for reducing body weight [32]. High SCFA production by the gut microbiota might increase available energy, thereby potentially outweighing the well-known short-term beneficial effects of soluble fiber consumption. Further studies are needed to elucidate whether long-term consumption of soluble, highly fermentable fiber unfavourably affects energy balance also in humans.
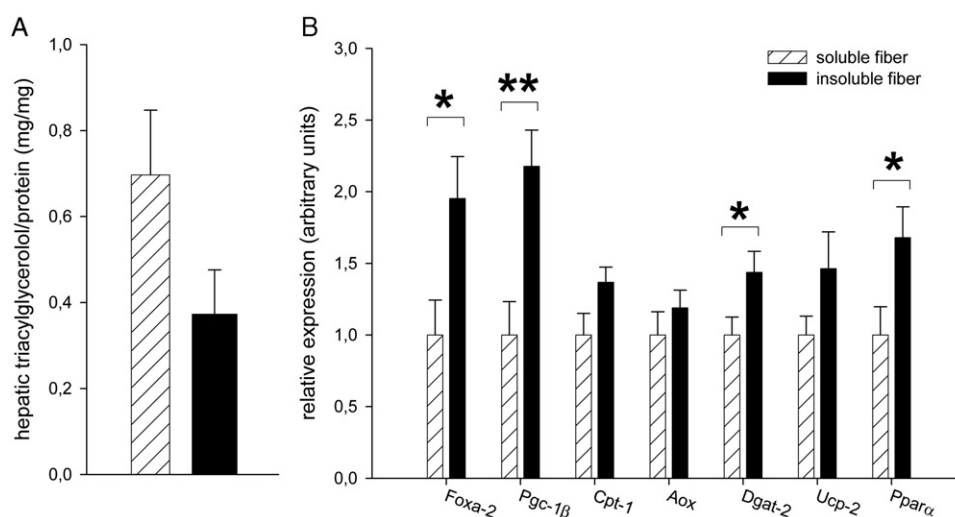

Fig. 5. Hepatic triacylglycerol contents and real-time RT-PCR analysis of transcription factors and enzymes regulating liver fat metabolism in fed state. (A) Hepatic triacylglycerol contents after 45 weeks (n=6 per group). (B) RT-PCR results were normalized to internal control Hprt and the intervention group fed soluble fiber diet was set to 100%. Foxa-2, Pgc-1β, Cpt-1, Aox, Dgat-2, Ucp-2 and Pparα were measured in liver tissue of mice fed soluble vs. insoluble fiber (n=5–6 per group). *P<.05; **P<.01.

In conclusion, long-term supplementation with soluble guar gum leads to an obese phenotype in obesity prone mice fed a Western-style diet. In contrast, supplementing the same diet with insoluble cereal fiber resulted in significantly lower weight gain and improved insulin sensitivity and was further associated with a pattern in liver gene expression consistent with increased fatty acid oxidation. Increased energy digestion with soluble, highly fermentable fiber consumption and increased expression of SCFA target genes might unfavourably affect energy homeostasis in the long term.

Acknowledgments

References

[1] Schulze MB, Schulz M, Heidemann C, Schienkiewitz A, Hoffmann K, Boeing H. Fiber and magnesium intake and incidence of Type 2 diabetes: a prospective study and meta-analysis. Arch Intern Med 2007;167:956–65.

[2] de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of Type 2 diabetes: a prospective cohort study and systematic review. PLoS Med 2007;4:e261.

[3] Weickert MO, Pfeiffer AF. Metabolic effects of dietary fiber consumption and prevention of diabetes. J Nutr 2008;138:439–42.

[4] King DE, Egan BM, Woolson RF, Mainous III AG, Al-Solaiman Y, Jesri A. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. Arch Intern Med 2007;167:502–6.

[5] Howarth NC, Saltzman E, Roberts SB. Dietary fiber and weight regulation. Nutr Rev 2001;59:129–39.

[6] Pereira MA, Jacobs Jr DR, Pins JJ, et al. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. Am J Clin Nutr 2002;75:848–55.

[7] Robertson MD, Bickerton AS, Dennis AL, Vidal H, Frayn KN. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. Am J Clin Nutr 2005;82:559–67.

[8] Weickert MO, Mohlig M, Schofl C, et al. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. Diabetes Care 2006;29:775–80.

[9] Liese AD, Schulz M, Fang F, et al. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. Diabetes Care 2005;28:2832–8.

[10] Jenkins DJ, Kendall CW, Augustin LS, et al. Effect of wheat bran on glycemic control and risk factors for cardiovascular disease in Type 2 diabetes. Diabetes Care 2002;25:1522–8.

[11] Cameron-Smith D, Habito R, Barnett M, Collier GR. Dietary guar gum improves insulin sensitivity in streptozotocin-induced diabetic rats. J Nutr 1997;127:359–64.

[12] Song YJ, Sawamura M, Ikeda K, Igawa S, Yamori Y. Soluble dietary fibre improves insulin sensitivity by increasing muscle GLUT-4 content in stroke-prone spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 2000;27:41–5.

[13] Track NS, Cawkwell ME, Chin BC, Chiu SS, Haberer SA, Honey CR. Guar gum consumption in adolescent and adult rats: short- and long-term metabolic effects. Can J Physiol Pharmacol 1985;63:1113–21.

[14] Kumar C, Rachappaji K, Nandini C, Sambaiah K, Salimath P. Modulatory effect of butyric acid — a product of dietary fiber fermentation in experimentally induced diabetic rats. J Nutr Biochem 2002;13:522.

[15] Owusu-Asiedu A, Patience JF, Laarveld B, Van Kessel AG, Simmins PH, Zijlstra RT. Effects of guar gum and cellulose on digesta passage rate, ileal microbial populations, energy and protein digestibility, and performance of grower pigs. J Anim Sci 2006;84:843–52.

[16] Weickert MO, Mohlig M, Koebnick C, et al. Impact of cereal fibre on glucose-regulating factors. Diabetologia 2005;48:2343–53.

[17] Weickert MO, Spranger J, Holst JJ, et al. Wheat-fibre-induced changes of postprandial peptide YY and ghrelin responses are not associated with acute alterations of satiety. Br J Nutr 2006;96:795–8.

[18] Isken F, Schulz TJ, Mohlig M, Pfeiffer AF, Ristow M. Chemical inhibition of citrate metabolism alters glucose metabolism in mice. Horm Metab Res 2006;38:543–5.

[19] Ristow M, Mulder H, Pomplun D, et al. Frataxin deficiency in pancreatic islets causes diabetes due to loss of beta cell mass. J Clin Invest 2003;112:527–34.

[20] Covington DK, Briscoe CA, Brown AJ, Jayawickreme CK. The G-protein-coupled receptor 40 family (GPR40-GPR43) and its role in nutrient sensing. Biochem Soc Trans 2006;34:770–3.

[21] Stewart G, Hira T, Higgins A, Smith CP, McLaughlin JT. Mouse GPR40 hetero-logously expressed in Xenopus oocytes is activated by short-, medium-, and long-chain fatty acids. Am J Physiol Cell Physiol 2006;290:C785–92.

[22] Hong YH, Nishimura Y, Hishikawa D, et al. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. Endocrinology 2005;146:5092–9.

[23] Wolfrum C, Shih DQ, Kuwajima S, Norris AW, Kahn CR, Stoffel M. Role of Foxa-2 in adipocyte metabolism and differentiation. J Clin Invest 2003;112:345–56.

[24] Jenkins DJ, Kendall CW, Axelsen M, Augustin LS, Vuksan V. Viscous and nonviscous fibres, nonabsorbable and low glycaemic index carbohydrates, blood lipids and coronary heart disease. Curr Opin Lipidol 2000;11:49–56.

[25] McNeil NI. The contribution of the large intestine to energy supplies in man. Am J Clin Nutr 1984;39:338–42.

[26] Backhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci USA 2007;104:979–84.

[27] Thorburn A, Muir J, Proietto J. Carbohydrate fermentation decreases hepatic glucose output in healthy subjects. Metabolism 1993;42:780–5.

[28] Galisteo M, Duarte J, Zarzuelo A. Effects of dietary fibers on disturbances clustered in the metabolic syndrome. J Nutr Biochem 2008;19:71–84.

[29] Robertson MD, Currie JM, Morgan LM, Jewell DP, Frayn KN. Prior short-term consumption of resistant starch enhances postprandial insulin sensitivity in healthy subjects. Diabetologia 2003;46:659–65.

[30] Steneberg P, Rubins N, Bartoov-Shifman R, Walker MD, Edlund H. The FFA receptor GPR40 links hyperinsulinemia, hepatic steatosis, and impaired glucose home-ostasis in mouse. Cell Metab 2005;1:245–58.

[31] Wolfrum C, Stoffel M. Coactivation of Foxa2 through Pgc-1beta promotes liver fatty acid oxidation and triglyceride/VLDL secretion. Cell Metab 2006;3:99–110.

[32] Pittler MH, Ernst E. Guar gum for body weight reduction: meta-analysis of randomized trials. Am J Med 2001;110:724–30.