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Original Communication
Mechanisms of action of β-glucan in postprandial glucose metabolism in healthy men

P Battilana[1], K Ornstein[2], K Minehira[1], JM Schwarz[3], K Acheson[2], P Schneiter[1], J Burri[2], E Jéquier[1] and L Tappy[1]*

[1]*Institute of Physiology, School of Medicine, University of Lausanne, Switzerland;* [2]*Nestle Research Center, Vers-chez-les-Blanc, 1000 Lausanne 26, Switzerland; and* [3]*Department of Nutritional Sciences, University of California at Berkeley, Berkeley, California, USA*

Objective: To assess whether β-glucan (which is fermented in the colon) lowers postprandial glucose concentrations through mechanisms distinct from a delayed carbohydrate absorption and inhibits *de novo* lipogenesis.
Design: Administration of frequent small meals each hour over 9 h allows a rate of intestinal absorption to be reached which is independent of a delayed absorption. A group of 10 healthy men received either an isoenergetic diet containing 8.9 g/day β-glucan or without β-glucan for 3 days. On the third day, the diet was administered as fractioned meals ingested every hour for 9 h.
Setting: Laboratory for human metabolic investigations.
Subjects: Ten healthy male volunteers.
Main outcome measures: Plasma glucose and insulin concentrations, glucose kinetics, glucose oxidation, *de novo* lipogenesis.
Results: On the third day, plasma glucose and free fatty acid concentrations, carbohydrate and lipid oxidation, and energy expenditure were identical with β-glucan and cellulose. Plasma insulin concentrations were, however, 26% lower with β-glucan during the last 2 h of the 9 h meal ingestion. Glucose rate of appearance at steady state was 12% lower with β-glucan. This corresponded to a 21% reduction in the systemic appearance rate of exogenous carbohydrate with β-glucan, while endogenous glucose production was similar with both diets. *De novo* lipogenesis was similar with and without β-glucan.
Conclusion: Administration of frequent meals with or without β-glucan results in similar carbohydrate and lipid metabolism. This suggests that the lowered postprandial glucose concentrations which are observed after ingestion of a single meal containing β-glucan are essentially due to a delayed and somewhat reduced carbohydrate absorption from the gut and do not result from the effects of fermentation products in the colon.
Descriptors: glucose production; *de novo* lipogenesis; substrate oxidation
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Introduction

Administration of soluble fibers (guar gum, β-glucan) together with a mixed meal is known to decrease postprandial glucose and insulin concentrations (Nuttall, 1993). The mechanisms responsible for this effect remain partially unknown. Soluble fibers increase the viscosity of the alimentary bolus, and hence lengthen the gastric emptying and intestinal transit times (Wood, 1990; Cameron-Smith *et al*, 1994; Johansen *et al*, 1996). In addition, the rate of starch digestion by pancreatic amylases is delayed by soluble fibers *in vitro*, an effect which is related to the viscosity of the fibers which may delay the interaction of the enzyme with its substrate (Dunaif & Schneeman, 1981; Hansen & Schulz, 1982; Dutta & Hlasko, 1985). These two mechanisms limit the postprandial rise in plasma glucose concentration by reducing the rate of carbohydrate absorption from the gastrointestinal tract. Two additional mechanisms may also intervene. First, the presence of fibers may actually prevent the digestion and absorption of part of the ingested carbohydrate (Tsuji *et al*, 1992; Jenkins *et al*, 1987). Second, soluble fibers (and any unabsorbed carbohydrate) will be fermented by the bacterial flora in the large intestine, thus releasing short chain fatty acids (acetate, propionate, butyrate) (Barry *et al*, 1995) which may be absorbed into the systemic circulation and exert metabolic effects. It may be hypothesized that such compounds may

*Correspondence: L Tappy, Institut de physiologie, 7 rue du Bugnon, 1005 Lausanne, Switzerland.
E-mail: Luc.Tappy@iphysiol.unil.ch
Guarantor: L Tappy.
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decrease postprandial glycemia by inhibiting endogenous glucose production or by increasing extrahepatic insulin actions.

Dietary fibers also affect plasma lipid profiles. They have been shown to decrease total plasma cholesterol and to reduce postprandial lipemia (Lairon, 1996), and to inhibit lipogenic enzymes responsible for cholesterol synthesis in liver cells (Nishina & Freedland, 1990). It can therefore be hypothesized that short chain fatty acids produced by fermentation of fibers also inhibit hepatic *de novo* lipogenesis (DNL), ie synthesis of fat from carbohydrate. This may contribute to reduction of plasma triglyceride concentrations.

The aim of this study was to determine whether factors other than a delay in carbohydrate digestion and absorption are involved in the decrease in postprandial glucose concentration elicited by β-glucan. A secondary aim was to assess whether such factors may inhibit hepatic DNL. In order to address this issue, a group of healthy human volunteers was studied after 2 days of isoenergetic diets containing either 8.9 g/day β-glucan, or devoid of β-glucan. A carbohydrate-rich, fructose-rich diet was administered to stimulate DNL (Hellerstein *et al*, 1996). On the third day, portions of the diets with or without β-glucan were administered as hourly meals, thus mimicking a slow carbohydrate absorption, irrespective of the actual fiber composition of each diet. In such conditions, the pattern of carbohydrate absorption can be expected to be similar with or without β-glucan, and hence any metabolic difference observed between the two diets should be secondary to mechanisms distinct from the mere lengthening of carbohydrate absorption, ie to metabolic effects of fermentation products of β-glucans. Hormones and substrate concentrations were measured during this period, while substrate oxidations were monitored using indirect calorimetry. After 5 h to allow for a metabolic steady state, ^{13}C glucose was added to the meals to trace exogenous carbohydrate metabolism, whereas whole body glucose kinetics was assessed with intravenous 6,6-^{2}H glucose.

Methods

Ten healthy male subjects were selected to take part to this study. All were in good physical condition and had a family history without diabetes or metabolic disorders. They were not currently taking any medication. The experimental protocol was approved by the ethical committee of Lausanne University School of Medicine and every participant provided an informed, written consent.

Experimental protocol (Figure 1)

At inclusion, resting energy expenditure was measured for 60 min in the morning after an overnight fast using indirect calorimetry (ventilated hood method) (Jallut *et al*, 1990). Every participant thereafter took part in two metabolic investigations, separated by at least 21 days. On each occasion, one of two experimental diets was administered. Both diets had the same macronutrient composition, but

Table 1 Composition of the experimental diets

	β-Glucan	*Cellulose*
Total carbohydrates (percentage energy) of which:	64.8	65.0
complex carbohydrates (percentage carbohydrate)	38	42
simple sugars (fructose, sucrose, lactose, percentage total carbohydrate)	62	58
Protein (percentage energy)	10.1	10.0
Fat (percentage energy)	25.1	25.0
β-Glucan (g/day)	8.9	0.0
Other fibers (cellulose) (g/day)	8.6	8.2
Total dietary fiber (g/day)	17.5	8.2
Energy (1.3×BMR) (kcal/day)	2013.7	2008.4

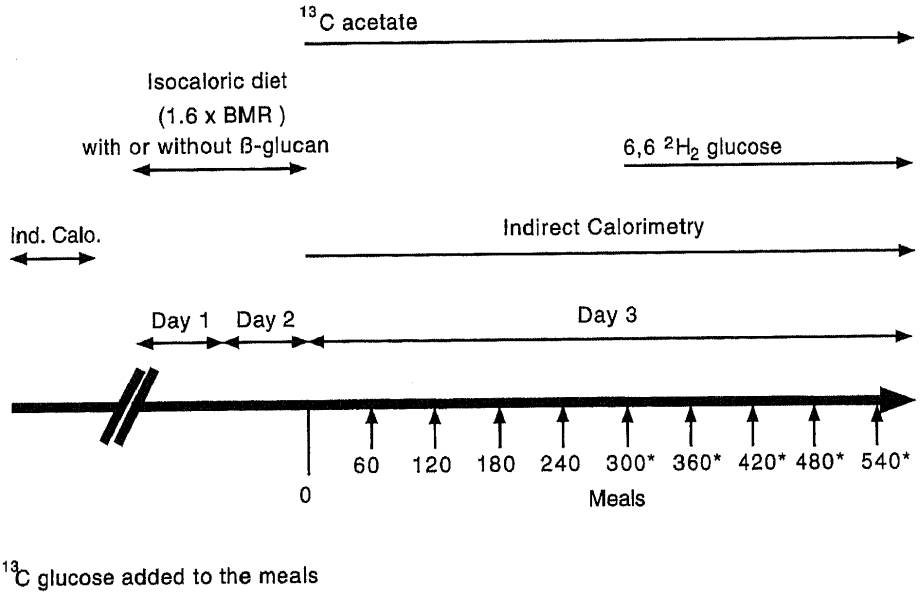

Figure 1 Experimental protocol.

differed in the fiber content: diet 1 contained 8.9 g/day β-glucan + 8.6 g/day cellulose and diet 2 contained 8.2 g/day of cellulose (Table 1). β-glucan had a viscosity of 96 mPa s at a temperature of 40°C, and a molecular weight of 2275 kDa. Each diet was administered for 2 days as three meals taken at 8 am, 12 noon and 7 pm respectively, and one snack in the afternoon. This period of adaptation was estimated to be sufficient for fermentation products of β-glucan to be absorbed systemically. Total energy intake was calculated as 1.6×resting energy expenditure. On the third day, a 10 h metabolic investigation was performed. Subjects came to the metabolic investigation laboratory between 7 and 8 am. They had fasted since 8 pm the day before. A venous cannula was inserted into an antecubital vein for infusion of 6,6-$^2H_2$ glucose. A second venous cannula was inserted into a wrist vein on the other arm for collection of blood samples. After a 60 min period of baseline measurements, meals were administered every hour for nine consecutive hours. Energy intake over 9 h was calculated to cover 24 h resting energy expenditure (approximately 1.3×BMR). Blood samples were collected at 30 min intervals for plasma glucose determination and at 1 h intervals for determination of plasma hormones and other substrate concentrations. In addition, energy expenditure and substrate oxidations were measured using indirect calorimetry throughout the procedure. After 5 h, a primed (6000 $\mu g\,kg^{-1}$) continuous (60 $\mu g\,kg^{-1}\,min^{-1}$) infusion of 6,6-^2H glucose (Tracermass, Worcester, MA) was started to assess whole body glucose kinetics. At the same time, 19.5 mg glucose U-^{13}C glucose (Cambridge Isotope Laboratories, Cambridge, MA) were added to each meal. This amount of ^{13}C glucose was calculated to produce an isotopic enrichment of exogenous glucose (from dissacharides and starch, not including fructose or galactose) of 0.118 atom% excess. Four blood samples were taken thereafter at hourly intervals to assess plasma glucose isotope enrichment.

Analytical procedures

Plasma glucose concentrations were measured by the glucose oxidase method using a glucose analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin concentrations were measured by radioimmunoassay using a kit from Linco (St Charles, MO). Plasma free fatty acids were measured by a colorimetric method using a kit from Wako (Freiburg, Germany). Plasma 6,6-^2H glucose isotopic enrichment was measured by gas chromatography-mass spectrometry (Hewlett Packard Instruments), as described (Schneiter *et al*, 1999). Plasma ^{13}C glucose isotopic enrichment was measured by isotope ratio mass spectrometry (Tracermass CN, Europa Scientific, Crewe, UK), as described (Gay *et al*, 1994). Plasma VLDL-^{13}C palmitate enrichment and mass isotopomers were measured, as described by Hellerstein *et al* (1991). Urinary nitrogen excretion was determined on timed urine samples with the method of Kjeldahl (Hawk, 1947).

Calculations

Energy expenditure and substrate oxidation rates were calculated from respiratory gas exchanges and urinary nitrogen excretion using the equations of Livesey and Elia (1988). Whole body glucose rate of appearance was calculated from 6,6-^2H glucose isotope enrichment using Steele's equations (Wolfe, 1984).

The systemic appearance of exogenous glucosyl (R_a exogenous glucose) units was calculated as:

$$R_a \text{ exogenous glucose} = \frac{\text{plasma } ^{13}C \text{ glucose enrichment}}{\text{calculated exogenous glucose enrichment}} \times \text{glucose rate of appearance}$$

(Tappy *et al*, 1999).

Endogenous glucose production (EGP) was calculated as glucose rate of appearance (R_a glucose) minus the systemic appearance of exogenous glucosyl units:

$$EGP = R_a\text{glucose} - R_a\text{exogenous glucose}.$$

Net non-oxidative glucose disposal was calculated as carbohydrate ingested minus glucose oxidation.

Fractional hepatic de novo lipogenesis was calculated from VLDL-^{13}C palmitate enrichment, as described (Hellerstein *et al*, 1991; Tappy *et al*, 1998). 1-^{13}C acetate was infused to label the intrahepatic acetylCoA pool, and the isotopic enrichment of hepatic acetylCoA was calculated using mass isotopomer distribution analysis (Hellerstein *et al*, 1991).

Statistical analysis

Plasma hormone and substrate concentrations and substrate oxidation were compared by two-way analysis of variance and paired *t*-tests with Bonferroni's adjustment. Glucose kinetics were compared using paired *t*-tests. All results in the text are expressed as mean ± 1 s.e.m. unless stated otherwise.

Results

Fasting plasma glucose, free fatty acids, insulin concentrations, energy expenditure and substrate oxidation were identical after two days of an isoenergetic diet with or without β-glucan (Figures 2–3).

During hourly meal administration, plasma glucose increased after each meal, and remained above basal values throughout the 9 h study period. However, there was no difference between the diets with or without β-glucan. Plasma free fatty acid concentrations were also suppressed similarly with both diets throughout the feeding period. After 7 h of continuous feeding, however, plasma insulin concentrations were significantly higher without β-glucan than with the β-glucan diet (Figure 2). Carbohydrate oxidation was increased to the same extent and with

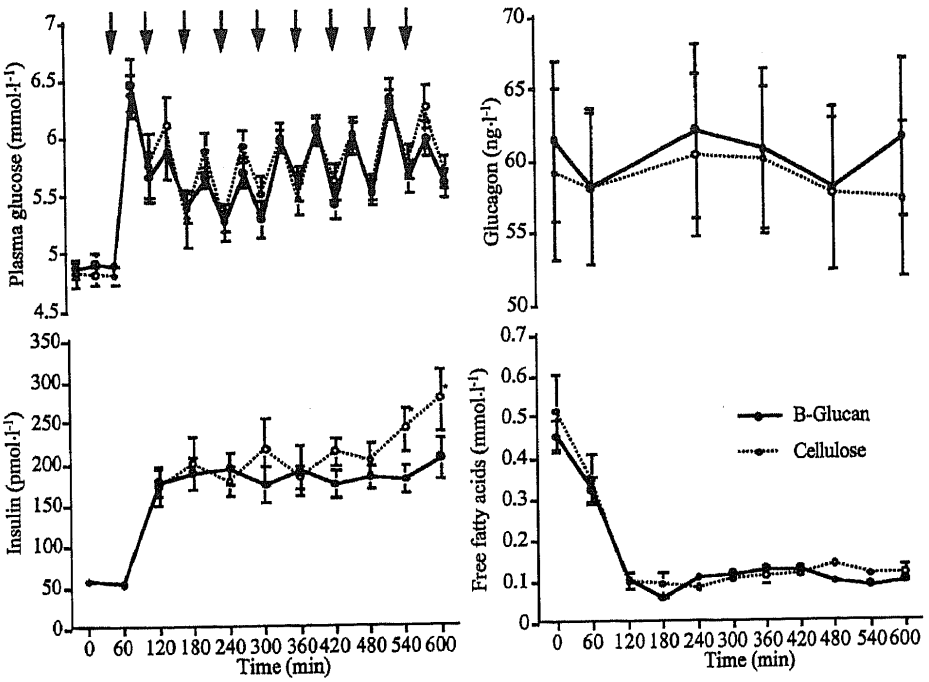

Figure 2 Plasma hormone and substrate concentrations. $^{*}P < 0.05$ β-glucan *vs* control diet.

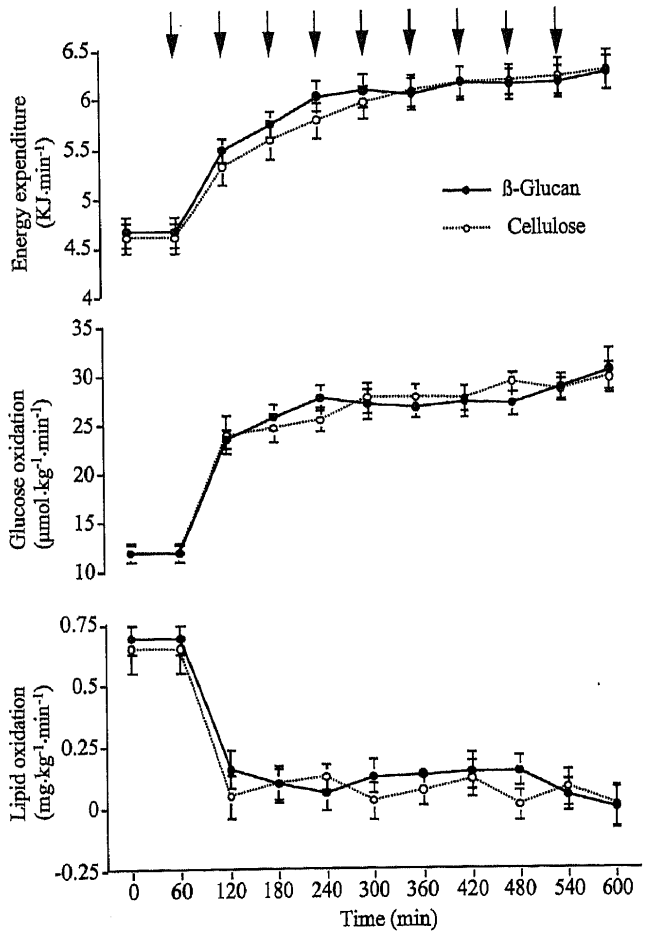

Figure 3 Energy expenditure and substrate oxidation rate.

the same time course with both types of diets. Net non-oxidative glucose disposal calculated during the last hour of the measurements was identical (25.7 µmol kg^{-1} - min^{-1}) with and without β-glucan (NS). Lipid oxidation showed changes which mirrored those of carbohydrate oxidation (Figure 3). The glucose kinetics is shown in Table 2. The whole body glucose rate of appearance was 12% lower with the β-glucan diet than without β-glucan. This was essentially due to a 21% reduction in the systemic appearance of exogenous carbohydrate, while endogenous glucose production was similar with both diets. Fractional hepatic DNL values are shown in Figure 4. β-glucan failed to reduce DNL compared to the diet without β-glucan.

Discussion

β-Glucan (and other soluble fibers) are known to blunt the increase in plasma glucose and insulin concentrations observed after ingestion of a single meal in healthy individuals and in patients with type 2 diabetes (Tappy *et al*, 1996). They have also been observed to improve glucose metabolism and to decrease HbA1c concentrations when administered as part of the diet over several days or weeks in type 2 diabetic patients (Braaten *et al*, 1994; Stilling *et al*, 1999). Our data allow the mechanisms involved in the glucose-lowering effect of β-glucan to be better delineated. In the present study, plasma glucose and insulin concentrations were monitored during a 9 h period during which small meals were ingested every hour. This procedure allows the absorption of dietary carbohydrate to be spread evenly throughout the 9 h study period. In addition, this procedure allows a rate of intestinal absorption which is

Table 2 Glucose kinetics

	β-Glucan	*Cellulose*	P-*value*
Glucose rate of appearance ($\mu mol\,kg^{-1}\,min^{-1}$)	23.6±1.2	26.8±1.5	0.0139
Systemic apparition of exogenous glucosyl units ($\mu mol\,kg^{-1}\,min^{-1}$)	12.9±0.6	16.3±1.0	0.004
Endogenous glucose production ($\mu mol\,kg^{-1}\,min^{-1}$)	10.7±0.9	10.5±0.8	0.7532

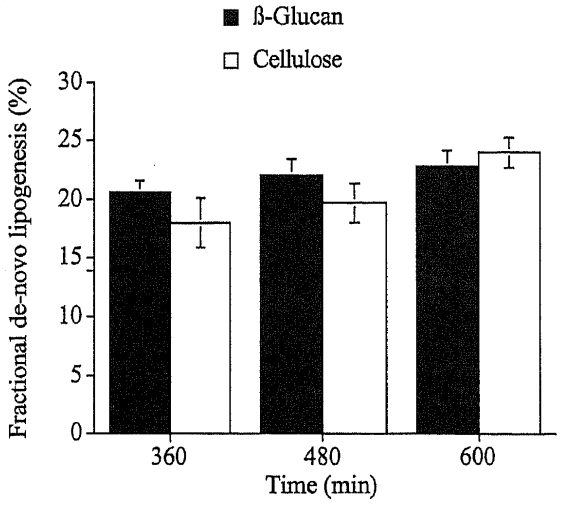

Figure 4 Fractional hepatic *de novo* lipogenesis.

independent of a delayed digestion and absorption to be reached. It has been reported that plasma glucose and insulin concentrations averaged over 24 h periods are markedly reduced during such 'nibbling' regimen in both healthy subjects and type 2 diabetic patients, suggesting that delaying dietary carbohydrate digestion and absorption is an effective way of improving plasma glucose control (Jenkins *et al*, 1989).

β-Glucan has been reported to increase the viscosity of the alimentary bolus within the gastrointestinal tract. As a result the interaction of dietary carbohydrate with pancreatic α amylase is impaired, resulting in delayed starch digestion (Englyst & Cummings, 1985). Additional effects of β-glucan have been postulated as well since it is partially fermented in the large bowel (Lia *et al*, 1996) and short chain fatty acids such as acetate, propionate and butyrate, or other metabolites produced during fermentation may secondarily affect insulin actions (Anderson & Bridges, 1984; McBurney *et al*, 1995). In addition, β-glucan may possibly interfere with carbohydrate digestion within the gastrointestinal tract and reduce carbohydrate malabsorption. The major result of our study is the indirect evidence that such additional mechanisms do not play an important role in the beneficial effects of β-glucan on carbohydrate metabolism. Our experimental protocol, by administering frequent small meals, spread carbohydrate absorption throughout the 9 h study period. This procedure partially reproduces the effects of soluble fibers to delay and lengthen carbohydrate absorption time, and have been shown to decrease average plasma glucose and insulin concentrations observed over 24 h in both healthy individuals and type 2 diabetic patients (Jenkins *et al*, 1989, 1992). The main observation of our study is the loss of postprandial reduction in glucose and insulin concentrations after partitioning a β-glucan containing meal. There was no difference in plasma glucose and insulin concentrations between the two diets over the first 6 h during which meals were ingested at hourly intervals. This absence of effects of β-glucan when meals were partitioned strongly suggests that the 50–60% reduction in plasma glucose and 35–60% reduction in plasma insulin concentrations observed in healthy or diabetic patients after ingestion of a single β-glucan-containing meal were essentially secondary to the effects of β-glucan on the rate of carbohydrate absorption from the gastrointestinal tract (Braaten *et al*, 1991; Tappy *et al*, 1996).

During the last 3 h of the 9 h study protocol, plasma insulin concentrations were significantly, although modestly, lower with the β-glucan than with the diet without β-glucan. This reduction was shown to be associated with a decreased systemic glucose appearance. During this period, the rate of systemic absorption of exogenous carbohydrate was monitored by adding a tracer amount of ^{13}C-labeled glucose to each ingested meal and monitoring of plasma ^{13}C glucose appearance. This procedure assumes that absorption of the ^{13}C-labeled glucose tracer and of digested carbohydrate occurred through comparable mechanisms. This assumption appears reasonable in our particular experimental conditions (Tappy *et al*, 1999). Although it can be expected that the rate of absorption of complex dietary carbohydrate was slower than that of a glucose solution, the repeated administration of meals every hour for several hours can be expected to lead to a steady state during which the whole portion of bioavailable carbohydrate ingested every hour is effectively absorbed at a rate which is independent of the delayed digestion and absorption. In these particular experimental conditions, ^{13}C glucose is therefore expected to trace dietary carbohydrate absorption in spite of kinetic differences between glucose and complex carbohydrates. In our experiments, plasma ^{13}C glucose appearance was 21% lower with than without β-glucan, while endogenous glucose production was identical with the two diets. This suggests that the modest decrease in plasma insulin concentrations observed during the last 2 h of our experimental protocol was essentially due to a modest reduction of carbohydrate absorption from the gut induced by β-glucan.

Surprisingly, the calculated endogenous glucose production averaged 10.6 $\mu mol\,kg^{-1}\,min^{-1}$ with the two experimental diets. This value is very close to the basal glucose production observed in healthy subjects after an overnight fast (Gerich, 1993), and may at first sight suggest that endogenous glucose production was not suppressed by either diet. This interpretation however would be erroneous

for two reasons. First, simultaneous glycogen synthesis and breakdown have been documented in liver cells of both rat and man (Rothman *et al*, 1991; Schneiter *et al*, 1999); a continuing systemic release of unlabeled glucose during ^{13}C carbohydrate absorption therefore reflects a continuing hepatic glycogenolysis at the same time as exogenous ^{13}C-labeled glucose is converted into liver glycogen. ^{13}C glucose appearance allowed us to estimate that approximately 64% of ingested carbohydrate appeared in the systemic circulation, suggesting that the other 36% were extracted by the splanchnic organs and converted into glycogen, at the same time as unlabeled glycogen was released. Such an active glycogen turnover makes it impossible to evaluate quantitatively the amount of carbohydrate malabsorption induced by β-glucan. Second, the diet administered included substantial amounts of fructose which is known to be converted into glucose-6-phosphate in liver cells and released as free glucose in the systemic circulation (Tounian *et al*, 1994). Part of the systemic appearance of unlabeled glucose may therefore correspond to absorption and metabolism of exogenous fructose.

We had also hypothesized that fermentation products of β-glucan may act systemically to inhibit hepatic *de novo* lipogenesis. For this purpose, we labeled intrahepatic acetylCoA by infusing 1-^{13}C acetate, and monitored the enrichment in ^{13}C of VLDL-palmitate. Hepatic fractional DNL was relatively high with the diet without β-glucan (about 20% *vs* 1–5% reported in the literature). This can be explained by the high dietary intake in carbohydrate and fructose (Hellerstein *et al*, 1996) which we used to obtain a stimulation of DNL. β-Glucan however failed to reduce hepatic DNL, indicating no inhibition of the hepatic enzymes involved in fatty acid synthesis.

In summary, our present data indicate that ingestion of diets containing 8.9 g/day β-glucan produced only very modest reductions in plasma glucose and insulin concentrations compared to a diet without β-glucan of similar macronutrient composition with equivalent amounts of insoluble fibers when the diets were administered as small meals every hour. This suggests that mechanisms which specifically concern β-glucan, such as colic fermentation and production of short chain fatty acids, do not significantly influence carbohydrate and lipid metabolism. Thus, these data indirectly support the concept that the reduction in postprandial plasma glucose and insulin observed after ingestion of a single large meal containing β-glucan is mainly secondary to a delay and lengthening of carbohydrate absorption time induced by β-glucan. In addition, a modest decrease in plasma insulin concentrations was observed with β-glucan after 6 h of hourly meal administration, and was shown to be attributable to a modest reduction of exogenous carbohydrate absorption. Our results therefore do not support the hypothesis that metabolites produced during β-glucan fermentation in the large intestine exert beneficial effects on carbohydrate metabolism.

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