

ORIGINAL ARTICLE

Carbohydrate intolerance in patients with self-reported food hypersensitivity: Comparison of lactulose and glucose

JØRGEN VALEUR^{1,2}, METTE HELVIK MORKEN¹, ELISABETH NORIN³,
TORE MIDTVEDT³ & ARNOLD BERSTAD^{1,2}

¹Institute of Medicine, University of Bergen, Bergen, Norway, ²Department of Medicine, Haukeland University Hospital, Bergen, Norway, and ³Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

Abstract

Objective. Malabsorption of low-digestible carbohydrates is physiological, but poorly tolerated in some patients. We investigated symptom anticipation and microbial fermentation as possible mechanisms of carbohydrate intolerance in patients with self-reported food hypersensitivity. **Material and methods.** In a randomized, double-blind, cross-over study, 27 consecutive patients with unexplained, self-reported food hypersensitivity were given 10 g lactulose and 10 g glucose (placebo). Symptoms and pulmonary excretion of hydrogen and methane were assessed. Short-chain fatty acids (SCFAs), lactate and prostaglandin E₂ (PGE₂) were analyzed in rectal dialysis fluid, and compared to dialysates from nine healthy volunteers. **Results.** Post-lactulose symptom scores were correlated with habitual symptom scores ($r = 0.6$, $p = 0.001$), significantly higher than post-glucose symptom scores ($p = 0.01$) and significantly higher in patients than controls ($p = 0.0007$). Levels of SCFAs, lactate and PGE₂ in rectal dialysates were not significantly different after lactulose and glucose, or between patients and controls. Hydrogen excretion was not correlated with symptom scores. **Conclusions.** The findings suggest that self-reported food hypersensitivity is related to microbial fermentation of malabsorbed carbohydrates and not to symptom anticipation solely. Levels of SCFAs, lactate and PGE₂ in rectal dialysates could not explain the fermentation-associated hypersensitivity.

Key Words: Dialysis, dietary carbohydrates, fermentation, food hypersensitivity, irritable bowel syndrome, rectum

Introduction

Symptoms of irritable bowel syndrome (IBS) are often meal-related, and commonly attributed to intake of specific foods [1], i.e. self-reported food hypersensitivity. Foods rich in carbohydrates may be a particular problem [2]. Fat and protein are normally well digested and absorbed in the small intestine, while parts of carbohydrates enter the colon: dietary fiber, resistant starch, sugar alcohols (e.g. sorbitol and xylitol) and some mono-, di- and oligosaccharides (e.g. fructose and lactose). This physiological carbohydrate malabsorption seems to be poorly tolerated in patients with functional gastrointestinal disorders [3], and disturbed microbial fermentation has been postulated as a cause of IBS [4].

However, psychological factors are involved, particularly in self-reported food hypersensitivity [5], and may play an important role in symptom generation.

The main goal of the present study was to clarify whether the response to a small dose of an indigestible, but fermentable, carbohydrate, the disaccharide lactulose [6,7], is related to fermentation or merely reflects psychological factors, primarily symptom anticipation. We thus performed a randomized, double-blind, cross-over study with lactulose and the easily absorbable monosaccharide glucose as placebo in patients with self-reported food hypersensitivity. As symptoms suggestive of disturbed distal bowel functions (e.g. urgency, feeling of discomfort and incomplete evacuation, passing of flatus and sometimes mucus) are common in these patients, an additional

Correspondence: Jørgen Valeur, MD, Institute of Medicine, University of Bergen and Department of Medicine, Haukeland University Hospital, NO-5021 Bergen, Norway. Tel: +47 55 973 031. Fax: +47 55 975 890. E-mail: jorgen.valeur@med.uib.no

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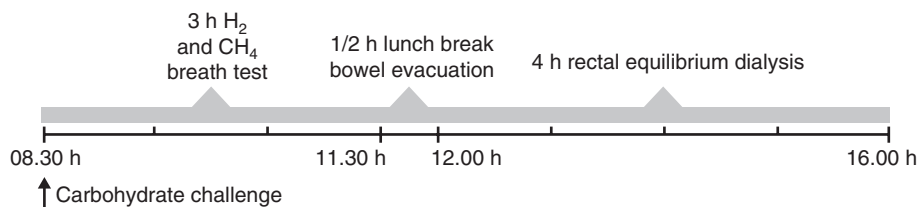


Figure 1. Study protocol.

aim was to measure prostaglandin E₂ and bacterial fermentation products [short-chain fatty acids (SCFAs) and lactate] in the rectum by means of luminal equilibrium dialysis. Intestinal gas production was quantified by analysis of exhaled hydrogen and methane.

Material and methods

Patients and controls

Patients referred to Haukeland University Hospital for investigation of abdominal complaints self-attributed to food hypersensitivity were recruited consecutively from February to September 2008. They were thoroughly examined, and food allergies and other organic gastrointestinal diseases were ruled out by methods described previously [8]. Exclusion criteria were age < 18 years, pregnancy/lactation, organic gastrointestinal disease and prior use of antibiotics (in the past month). Healthy volunteers were recruited from the hospital staff and students at the University of Bergen. They were included if they considered themselves to be healthy, and were not examined further. They were, however, specifically excluded if they had IBS according to the Rome II criteria or had used antibiotics during the past month. The study was performed in accordance with the Declaration of Helsinki and approved by the Regional Committee for Medical Research Ethics.

Study design

Patients were tested with 10 g of lactulose and 10 g of glucose with a 1-week interval in between. The order was randomized (StatMate; GraphPad Inc., San Diego, CA), and both patients and investigators were blinded as to the carbohydrate used. Controls were tested only once, with 10 g of lactulose. Carbohydrate was dissolved in 120 ml of tap water which the participants drank, immediately followed by 60 ml of pure tap water for mouth cleaning. All subjects were asked to avoid fiber-rich foods the day before, and not to take any food for 10 h prior to the challenge.

Examinations followed the outlined study protocol (Figure 1), with 3 h for breath test sampling, 30 min for a lunch break and 4 h for rectal equilibrium dialysis. The participants were not allowed to eat, drink, smoke, sleep or walk around during the breath test, but they were not restricted in any way during the rectal dialysis period. Lunch was not standardized, as most of the patients had special demands (self-imposed) and preferred to bring or select their own food. As preparation for rectal dialysis, the subjects were asked to evacuate their bowels completely during the lunch break (food intake also triggers the gastro-colic reflex).

Analysis of breath samples

Breath test sampling was performed using collection bags from the Quintron Instrument Company (Milwaukee, WI) at baseline and every 15 min for 3 h following carbohydrate intake. Pulmonary excretion of hydrogen and methane was quantified after correction for alveolar quality, based on CO₂ concentration, using a Quintron Model SC Gas Chromatograph (Quintron Instrument Company). Individuals with methane excretion >1 ppm above the atmospheric methane concentration (≈ 1.8 ppm [9]) were classified as methane producers. Hydrogen excretion curves were evaluated with respect to increments above baseline concentrations: Increase in H₂ > 20 ppm within 90 min was denoted "early H₂ increase" and increase in H₂ > 20 ppm within 180 min was denoted "all-time H₂ increase".

Rectal equilibrium dialysis

Dialysis bags (12 cm, 4 ml) were made of cellulose membrane tubing (Visking code DVT12000.01.000; molecular weight cut-off 12–14 kDa; Medicell International Ltd., London, UK), filled with Rheomacrodex® [10% dextran (mean molecular weight 40 kDa) in saline; Meda A/S, Norway] and inserted into the empty rectum. The procedure has been described in detail by Egan et al. [10]. Dialysis bags were stored overnight at +4°C and bathed in

Rheomacrodex solution; there was no need for additional lubrication upon insertion. The dialysis bags were left for 4 h to obtain equilibrium with rectal luminal fluid [11], and dialysate was thereafter aspirated from the bags using a syringe and needle, transferred into plastic vials and stored at -80°C until analysis.

Analysis of SCFAs

The dialysis fluid was mixed with double the amount of distilled water, containing 3 mmol/l 2-ethyl butyric acid (as internal standard) and H_2SO_4 (0.5 mmol/l), and was vacuum-distilled according to a method described by Zijlstra et al. [12], as modified by Höverstad et al. [13]. Dialysates were then analyzed using gas-liquid chromatography with a flame ionization detector. The results were expressed in mmol/kg wet weight. The following SCFAs were analyzed: acetic acid, propionic acid, n-butyric acid, i-butyric acid, n-valeric acid, i-valeric acid, n-caproic acid and i-caproic acid.

Analysis of D- and L-lactate

D- and L-lactate levels were measured using an UV assay kit (Cat. No. 11112821035; Boehringer Mannheim/R-Biopharm, Darmstadt, Germany), following the manufacturer's instructions. Intra-assay coefficients of variation were 5.0% and 5.4% for D- and L-lactate, respectively.

Analysis of prostaglandin E_2

Prostaglandin E_2 (PGE_2) levels were measured using an enzyme immunoassay kit (Cat. No. 514010; Cayman Chemical Company, Ann Arbor, MI), following the manufacturer's instructions. The intra-assay coefficient of variation was 5.6%.

Symptom assessment

Habitual symptom score. IBS was diagnosed according to the Rome II criteria, and habitual symptoms were scored (from 0 to 500) using a translated version of the irritable bowel symptom severity scoring system (IBS-SSS), developed by Francis et al. [14].

Post-test symptom score. A written questionnaire, slightly modified from Farup et al. [15], was completed after each test and returned by mail the next

day. Participants were asked whether they had developed any gastrointestinal symptoms following the carbohydrate challenge and, if yes, when these started (during the test, or 0–2 h, 2–4 h, 4–8 h or > 8 h after the test). They were also requested to indicate whether the post-test symptoms were of the same kind as those usually experienced, and whether the intensity was worse. Pain, borborygmi, bloating, diarrhea and constipation were given a score for severity (absent = 0; mild = 1; moderate = 2; severe = 3) and duration (0–2 h = 1; 2–4 h = 2; 4–8 h = 3; > 8 h = 4). For each symptom, the severity score and duration score were multiplied, and a total post-test symptom score (ranging from 0 to 60) was obtained by adding these values. In addition, the number of so-called “early and long-lasting (ELL)” symptoms [15], i.e. symptoms starting within 5 h and lasting for > 2 h after carbohydrate ingestion, were reported. Importantly, the participants were not informed about the test results until they had completed their post-test symptom reporting.

Statistics

Data were analyzed using Graphpad Prism version 5 (Graphpad Software Inc., San Diego, CA). Data are expressed as mean $\pm$ standard deviation (SD), unless otherwise stated. We used paired *t*-tests for within-group comparisons and unpaired *t*-tests to compare mean values between the two groups. Proportions were compared using Fisher's exact test. Correlations were evaluated using Pearson's correlation coefficient. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Subject characteristics

Thirty patients were referred to our hospital during the recruitment period. Three patients refused to participate (because they felt that the investigations were too cumbersome), and a total of 27 patients were therefore studied [four males, 23 females; mean age 36 years, range 18–64 years; mean body mass index (BMI) 23.7 kg/m^2 , range $17.3\text{--}33.7 \text{ kg/m}^2$]. None of the patients had evidence of food allergies or other organic diseases that could explain their symptoms, and 25 (93%) had IBS according to the Rome II criteria. Nine healthy volunteers (without IBS) agreed to participate (two males, seven females; mean age 26 years, range 22–38 years; mean BMI 22.9 kg/m^2 , range $18.3\text{--}27.8 \text{ kg/m}^2$).

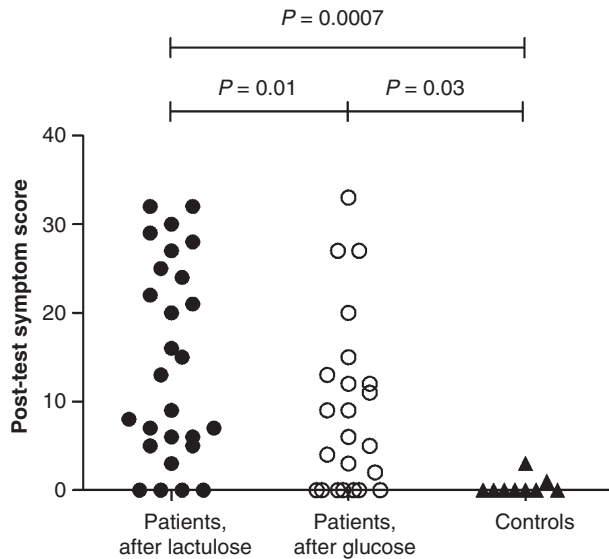


Figure 2. Symptom scores in response to carbohydrate challenge in patients with self-reported food hypersensitivity ($n = 27$) and healthy controls ($n = 9$). Patients were challenged with both 10 g of lactulose and 10 g of glucose, while controls were tested only with 10 g of lactulose.

Symptoms

As expected, habitual symptom scores (IBS-SSS) were higher in patients than in healthy controls (265.0 ± 42.1 vs 50.6 ± 42.1 ; $p < 0.0001$). Post-test symptoms (Figure 2) were worse in patients after both lactulose and glucose than in controls given lactulose (14.3 ± 11.2 and 7.7 ± 9.6 vs 0.4 ± 1.0 ; $p = 0.0007$ and $p = 0.03$, respectively) and the patients developed

significantly more severe symptoms after lactulose ingestion than after glucose ingestion (14.3 ± 11.2 vs 7.7 ± 9.6 ; $p = 0.01$). Also, more ELL symptoms developed in response to lactulose than after glucose challenge (2.4 ± 1.5 vs 1.3 ± 1.6 ; $p = 0.009$). Four patients did not develop any symptoms after either carbohydrate challenge, and seven patients reported more severe symptoms after glucose than after lactulose. Post-test symptom scores were not affected by the order of carbohydrate challenge (i.e. whether the patient ingested lactulose or glucose on the first day). Post-test symptoms replicated habitual symptoms in 21 patients following lactulose ingestion and in 14 following glucose ingestion ($p = \text{NS}$). Post-test symptoms were worse than usual in four patients following lactulose ingestion but in none following glucose ingestion ($p = \text{NS}$). Interestingly, post-test symptom scores after lactulose were significantly correlated with habitual symptom scores (Pearson's $r = 0.6$; $p = 0.001$), whereas post-test symptom scores after glucose were not (Figure 3).

Breath excretion of hydrogen and methane

Excretion levels of hydrogen after lactulose challenge were not significantly different between patients and controls at any time point (Figure 4A), and the areas under the hydrogen excretion curves (AUCs) were not significantly different ($p = 0.2$). "Early H_2 increase" was present in six patients and three controls following lactulose ingestion, whereas "all-time

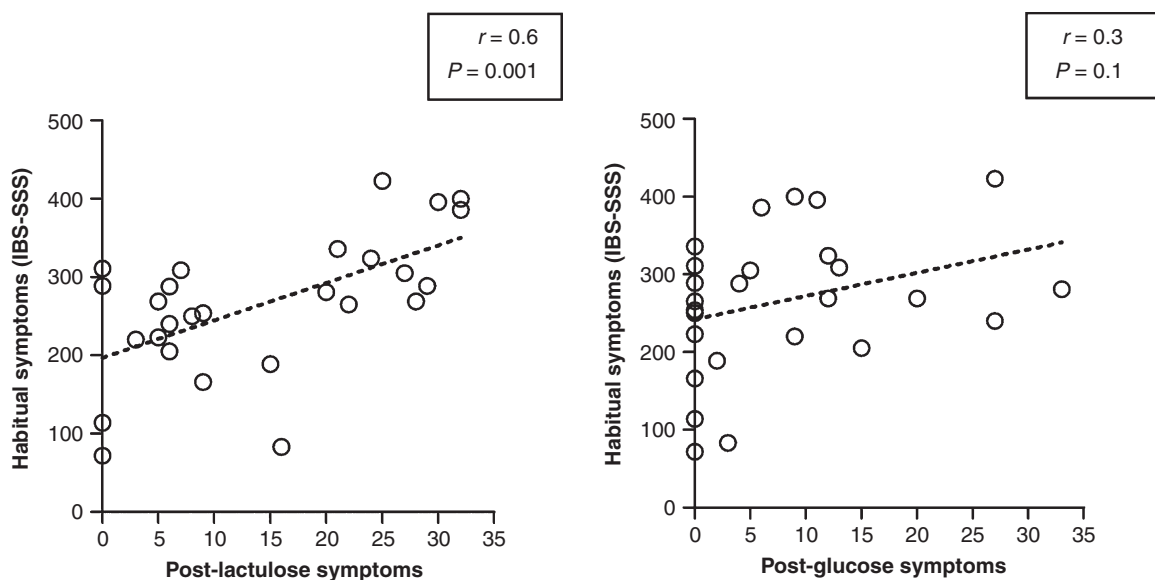


Figure 3. Relationship between post-test symptom scores and habitual symptom scores in patients with self-reported food hypersensitivity ($n = 27$) following ingestion of lactulose (left panel) and glucose (right panel). Note, post-lactulose symptom scores are significantly correlated with habitual symptom scores (Pearson's $r = 0.6$; $p = 0.001$).

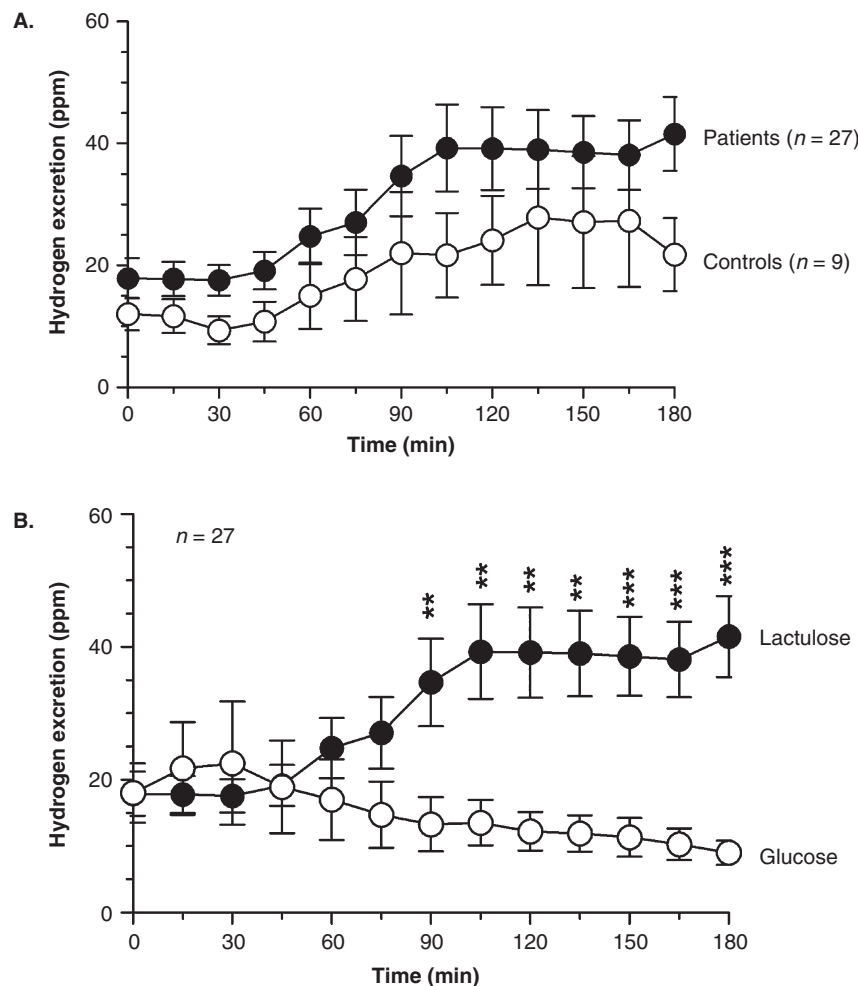


Figure 4. Hydrogen excretion curves: (A) patients ($n = 27$) and controls ($n = 9$) following ingestion of 10 g of lactulose; (B) patients ($n = 27$) following ingestion of 10 g of lactulose and 10 g of glucose. Excretion levels are shown as mean values with error bars representing the SEM. Significant differences between means are indicated (** $p < 0.01$; *** $p < 0.001$).

H₂ increase" was found in 19 patients and four controls (proportions not significantly different).

Although patients excreted more hydrogen in response to lactulose than in response to glucose (Figure 4B; $p = 0.01$), post-test symptoms were not correlated with hydrogen excretion measured as AUC for the individual hydrogen excretion curves (data not shown). Interestingly, three patients showed evidence of glucose fermentation, measured as H₂ increase >20 ppm above baseline concentration, which occurred before 90 min in two of them and at 106 min in one of them. This unexpected phenomenon was associated with symptoms in two of them (post-test symptom scores of 33 and 13, respectively), whereas the third remained asymptomatic. Notably, the two symptomatic patients were among the seven patients who developed more symptoms after glucose ingestion than after lactulose ingestion.

Seven patients and two controls were classified as methane producers, and methane excretion levels

(AUC) were similar in these groups ($p = 0.8$). Levels of methane excretion (AUC) were similar after lactulose and glucose ($p = 0.3$). Post-test symptoms were not correlated with methane excretion measured as AUC for the individual methane excretion curves (data not shown).

SCFAs, lactate and PGE₂ in rectal dialysis fluid

Levels of individual and total SCFAs, D- and L-lactate and PGE₂ after lactulose ingestion were not significantly different from levels after glucose ingestion, and were not significantly different between patients and controls (Figure 5). Levels of PGE₂ tended to be higher in the control group, although not significantly so ($p = 0.06$). There were no correlations between SCFAs, lactate or PGE₂ levels and symptoms scores (habitual and post-test) or gas excretion (including methane-producing status).

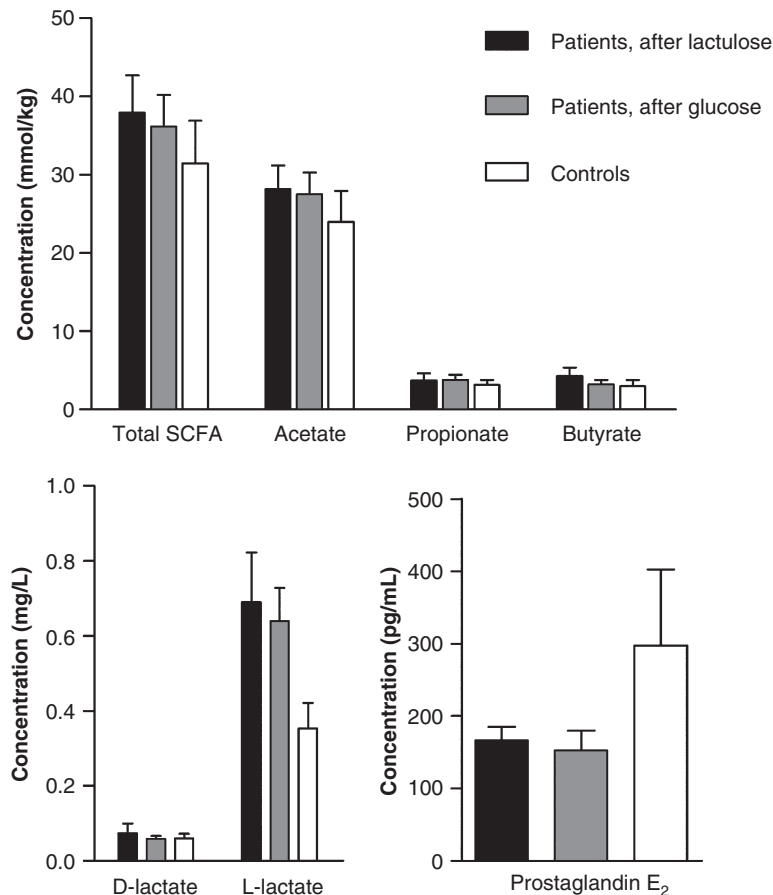


Figure 5. Levels of SCFAs, lactate and PGE₂ in rectal dialysates from patients ($n = 27$; after 10 g of lactulose and after 10 g of glucose) and controls ($n = 9$). Results are shown as mean values with error bars representing the SEM. Mean levels are not significantly different. Low concentrations of i-butyric acid, n-valeric acid, i-valeric acid, n-caproic acid and i-caproic acid are not shown.

Discussion

Self-reported or perceived food hypersensitivity without apparent organic findings also denoted "subjective food hypersensitivity" [5], is a prevalent, but poorly understood condition. Although psychological mechanisms seem to be important, they may not fully explain all symptoms. In the present double-blind, placebo-controlled study, ingestion of lactulose clearly elicited more symptoms than placebo (glucose), indicating that intolerance to a low-digestible carbohydrate has greater impact on symptom generation than symptom anticipation. Symptom anticipation may explain some of the differences between patients and controls, but not the different responses to lactulose and glucose in the patients. Furthermore, lactulose ingestion seems to replicate the patients' habitual IBS-like complaints. Conceivably, habitual symptoms are provoked, at least in part, by fermentable carbohydrates, consistent with the hypothesis that self-reported food hypersensitivity is caused by enterometabolic disturbances [16]. Recently, IBS due

to "malfermentation" has been proposed as a discrete subgroup [17]. In the present study, both gas excretion and levels of rectal fermentation products were evaluated as explanatory variables.

More hydrogen was excreted in exhaled air after lactulose than after glucose, but there was no significant difference between patients and controls in hydrogen excretion after lactulose and, among the patients, the amount of excreted hydrogen was not correlated with symptoms. Hence, intestinal hydrogen gas production as measured by hydrogen excretion in exhaled air does not explain carbohydrate-induced symptoms in our patients. This finding is in accordance with previous findings of others [18] and of our group [6–8]. Since only a fraction of the gas produced in the intestines is excreted via the lungs [19], it is possible that a 3-h quantification of exhaled gas post-challenge is a poor estimate of the actual gas production throughout the following day. However, most of the post-test symptoms started within the 3-h measurement period and often coincided with the onset of rise in pulmonary hydrogen excretion. Overproduction of gas has indeed

been documented in some IBS patients by using 24-h indirect calorimetry [20] and, although cumbersome and costly, this method seems superior to the conventional and widely used hydrogen breath test [21].

Impaired intestinal gas transport could be involved in symptom generation [22,23], as well as production and trapping of gas in parts of the gut where gaseous distension is poorly tolerated, for instance in the small intestine [24]. However, small intestinal bacterial overgrowth (SIBO) does not seem to explain the observed difference in post-lactulose symptoms in our study, because the prevalence of “early H₂ increase”, a widely used criterion for diagnosing SIBO, was similar in patients and controls. Nevertheless, three patients produced excessive amounts of hydrogen (>20 ppm above baseline concentration) in response to 10 g of glucose, which was accompanied by symptoms in two of them, that could signify clinically relevant SIBO. It should be emphasized, however, that the use of hydrogen breath test criteria alone are probably insufficient for diagnosing SIBO [25], as the observed response might also be caused by rapid orocecal transit [26].

Normally, bacterial fermentation of low-digestible carbohydrates takes place mainly in the proximal colon. Conceivably, this process may in part be displaced distally in the colon in patients reporting symptoms that theoretically could be ascribed to rectal irritation by SCFAs [27]. This prompted us to measure fermentation products in the rectum. Alterations in fecal SCFA concentrations have indeed been described previously in patients with IBS [28–30]. However, we did not find any significant differences in rectal SCFA levels in our study, which notably were measured after complete rectal emptying.

Rectal equilibrium dialysis has previously been used to determine luminal levels of D- and L-lactate [31]. D-lactate derives from non-mammalian cells, whereas both bacteria and epithelium produce L-lactate. Both isomers could be produced during carbohydrate malabsorption [32], and conceivably mediate symptoms of carbohydrate intolerance [33]. D-lactate levels were generally much lower than L-lactate levels in our subjects, but there were not any significant differences between patients and controls, or after challenge with lactulose compared to glucose.

A role for PGE₂ in food hypersensitivity has been proposed [34–41]. Interestingly, exogenous administration of a PGE analogue provokes IBS-like symptoms [42], and endogenous PGE₂ can be produced by irritating the mucosa with stimulant laxatives [43], and possibly with SCFAs [44]. In our study, however, PGE₂ levels tended to be lower, rather than higher, in

the patient group, although not significantly different from those in the control group.

We conclude that the symptoms provoked by the indigestible carbohydrate lactulose in patients with self-reported food hypersensitivity could not be accounted for by symptom anticipation alone. Enterometabolic activity seems to be involved, but further studies are necessary to determine the underlying mechanisms of the fermentation-associated hypersensitivity.

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