D-Tagatose, a Stereoisomer of D-Fructose, Increases Blood Uric Acid Concentration

Benjamin Buemann, Søren Toubro, Jens Juul Holst, Jens F. Rehfeld, Bo Martin Bibby, and Arne Astrup

D-Fructose has been found to increase uric acid production by accelerating the degradation of purine nucleotides, probably due to hepatocellular depletion of inorganic phosphate (P_i) by an accumulation of ketohexose-1-phosphate. The hyperuricemic effect of D-tagatose, a stereoisomer of D-fructose, may be greater than that of D-fructose, as the subsequent degradation of D-tagatose-1-phosphate is slower than the degradation of D-fructose-1-phosphate. We tested the effect of 30 g oral D-tagatose versus D-fructose on plasma uric acid and other metabolic parameters in 8 male subjects by a double-blind crossover design. Both the peak concentration and 4-hour area under the curve (AUC) of serum uric acid were significantly higher after D-tagatose compared with either 30 g D-fructose or plain water. The decline in serum P_i concentration was greater at 50 minutes after D-tagatose versus D-fructose. The thermogenic and lactacidemic responses to D-tagatose were blunted compared with D-fructose. D-Tagatose attenuated the glycemic and insulinemic responses to a meal that was consumed 255 minutes after its administration. Moreover, both fructose and D-tagatose increased plasma concentrations of cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1). The metabolic effects of D-tagatose occurred despite its putative poor absorption.

THE KETOHEXOSE D-tagatose has a structure identical to that of D-fructose except for an inversion around one optical center.[1] The rare sugar has potential applicability as a low-energy bulk sweetener since it appears to be poorly absorbed[2] and was reported in growth experiments to provide no net energy in rats.[3] The absorbed D-tagatose is metabolized in the liver in a way similar to D-fructose. It is phosphorylated to D-tagatose-1-phosphate, which subsequently is degraded by aldolase-B to glyceraldehyde and dihydroxyacetone phosphate.

D-Fructose has been shown to reduce the hepatic level of inorganic phosphate (P_i) in perfused rat livers and healthy humans by trapping P_i by phosphorylation to fructose-1-phosphate.[4] Intake of D-tagatose may also result in hepatic P_i depletion, particularly as the degradation of D-tagatose-1-phosphate occurs at a slower rate than the degradation of D-fructose-1-phosphate, which means a prolonged period in which P_i is trapped after administration of D-tagatose compared with D-fructose[5] (Fig 1).

Hepatic depletion of P_i may induce augmented degradation of purine nucleotides, as P_i is an important inhibitor of adenosine monophosphate (AMP) deaminase, which may be a rate-limiting enzyme in the decomposition of AMP.[6] As a consequence, the release of uric acid from the liver may increase as found after fructose intake in individuals with hereditary fructose intolerance who have an impaired degradation of fructose-1-phosphate due to a deficient aldolase-B enzyme.[7] In a recent study, a 75-g oral dose of D-tagatose has in fact been reported to have an acute hyperuricemic effect,[8] but the effect was not compared with the same dose of fructose. Although it is mediated by a different biochemical mechanism, a hyperuricemic effect, probably involving a hepatic reduction in P_i, has been previously demonstrated in healthy subjects with the sugar alcohol xylitol.[9] This indicates that some sugar substitutes that are already commercially available may have the potential to accelerate purine degradation.

In the present study, we compared the response of the serum uric acid concentration to 30 g D-tagatose against 30 g D-fructose and plain water during a 7-hour period after oral administration. Furthermore, a fixed lunch meal was consumed 4.5 hours after the load to test if a preceding intake of D-tagatose may influence glucose and insulin responses to an ordinary meal. An increase in glucose tolerance has been previously reported after D-tagatose.[10] Finally, we took advantage of the experiment to study the impact of the two sugars on other metabolic parameters and to measure their thermogenic responses. Norepinephrine and epinephrine levels were measured to determine whether catecholamines could be involved in the metabolic findings. Finally, intestinal insulinotropic hormones were assessed, as their responses to D-fructose and D-tagatose may provide new information about the mechanisms for the secretion of these hormones.

SUBJECTS AND METHODS

Following a 30-minute baseline period, the metabolic response during a period of 7 hours to 30 g D-tagatose or 30 g D-fructose dissolved in 400 mL water or plain water was tested after a 13-hour fast. Samples of arterialized blood were obtained throughout the experiment, and indirect calorimetry was performed by the ventilated-hood technique. Four hours and 15 minutes after consumption of the test solution, a controlled lunch was consumed to evaluate the possible interplay between the preceding test sugar consumption and the metabolic response to a meal.

Eight male subjects (body weight, 77.4 ± 2.4 kg; range, 68.0 to 90.8; body mass index, 22.4 ± 0.5 kg/m^2; age, 22.9 ± 0.3 years) participated in the study. All subjects appeared generally healthy, although 1 subject showed post-lunch glucose values of about 10 mmol/L on 2 occasions during the study. However, we decided to include this subject in the analyses, as he had normal fasting glucose and insulin levels and his insulin responses were within the range of values for the other subjects. At least 6 days before the first test day, a screening test with 30 g

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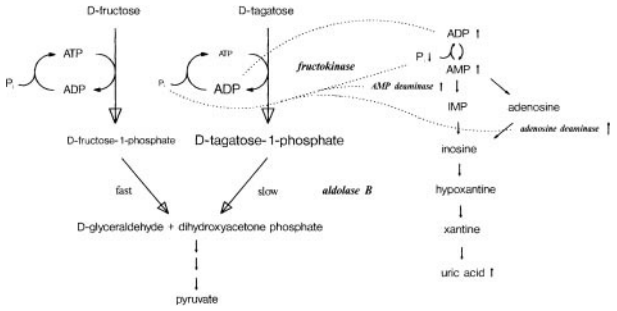

Fig 1. Possible mechanisms to explain an increased purine nucleotide degradation and uric acid production by D-tagatose. A slower cleaving rate of D-tagatose-1-phosphate by aldolase B compared with D-fructose-1-phosphate leads to an accumulation of D-tagatose-1-phosphate and a depletion of P_i. Dotted lines represent how a reduced level of P_i may increase AMP and release the inhibition of AMP deaminase and adenosine deaminase. The increased dephosphorylation of ATP to ADP may also directly increase the supply of purine nucleotides for degradation.

D-tagatose in 400 mL water was performed to exclude subjects showing gastrointestinal symptoms that could disturb the experiment. At that test, 1 of the subjects experienced moderate distention and another subject reported loose stools 7 hours after dosing. However, these symptoms were not regarded as severe enough to exclude the subjects.

The 3 different test solutions were administered orally separated by 5 to 33 days. To balance the study, the 6 different sequence combinations of the test solutions were administered to 6 subjects and the last 2 subjects received the test solution in the order D-fructose/plain water/D-tagatose, and D-tagatose/plain water/D-fructose. Tests involving the test sugars were performed in a double-blind design. When plain water was administered, the subjects were carefully instructed not to disclose its lack of sweetness to the investigators. The experiment commenced at 8 AM with the subject on an antidecubitus mattress after having voided the bladder. A catheter was inserted in a dorsal hand vein, and the hand was wrapped in a heating pad to arterialize the samples. Subsequently, the ventilated hood was placed above the subject's head, and indirect calorimetry was started after at least 30 minutes of supine rest and at least 10 minutes after termination of the preparation for blood sampling. A baseline blood sample was taken 5 minutes before the test solution was administered. After 30 minutes, the gas-exchange measurements were interrupted and the subjects consumed a test solution while sitting on the couch at time 0. The subject remained supine during the next 4 hours and 15 minutes while blood samples were taken at 20, 50, 80, 120, 180, and 240 minutes. To ensure the comfort of the subject, the calorimetry was interrupted for 10 minutes commencing at 90 and 185 minutes, when the hood was removed and the subject was allowed to stretch and turn over on his side.

At 245 minutes, the pre-lunch calorimetry period was terminated and the subject voided the bladder. A 4.0-MJ lunch meal consisting of a hot pot meal made with turkey and a fruit sauce and served with rice was consumed between 255 and 275 minutes, with a macronutrient composition of 56, 24, and 20 energy% carbohydrate, fat, and protein, respectively. The lunch contained 19.4 g glucose and 19.0 g fructose including the contribution from sucrose and calculated according to figures derived from food tables (National Food Agency). The lunch was served at a table in the same room in which the experiment occurred. At 280 minutes, the post-lunch measuring period commenced. Blood samples were drawn at 300, 360, and 420 minutes. Indirect calorimetry was performed from 280 to 365 minutes and from 375 to 425 minutes, and was concluded by voiding the bladder at 430 minutes. The subjects indicated their sensations of hunger, satisfaction, fullness, and a desire to eat on a visual analog scale (VAS) before the pre-lunch measuring period (−60 minutes), at the end of the pre-lunch period before the lunch was presented to the subject (250 minutes), and at the end of the post-lunch period (435 minutes). After the metabolic tests, the subjects completed food records for the remaining and subsequent day. The subject was supplied with a dietetic scale and instructed on how to weigh and record their food intake. During the measurement periods, the subjects watched feature films on video and were instructed to move as little as possible; they were supervised to prevent their falling asleep. They were also instructed not to perform intensive physical exercise on the 3 days preceding each experiment and to use a motorized vehicle for transportation to the department on the days of the experiments. To standardize the preceding food intake, the subjects were supplied with the same diet prepared by the department on the 2 days prior to all experiments. The macronutrient composition of the diet was 60, 25, and 15 energy % as carbohydrate, fat, and protein, respectively. In an attempt to balance the energy requirements, the dietary energy content was estimated from the fat-free mass of the subjects by an algorithm based on previous measurements of energy expenditure (EE) in a respiration chamber on a large group of subjects.[11] The calculated EE was multiplied by 1.2 to allow for free-living physical activity when determining the energy content of the diet. The subjects were instructed to consume the entire diet and nothing additional to the diet.

The study protocol was approved by the Municipal Ethical Committee of Copenhagen and Frederiksberg, Denmark.

Blood Analyses

Serum and urine uric acid concentrations were enzymatically determined in all samples by a quinone-imine dye reaction (kit from Boehringer Mannheim Diagnostica, Copenhagen, Denmark). The P_i level was measured in serum from all samples by precipitation in acid solution by ammonium molybdate (kit from Roche, Basel, Switzerland). Plasma glucose and lactate were enzymatically determined in all samples (kits from Boehringer Mannheim). D-Tagatose was determined in serum from −5, 20, 50, 80, 120, 300, and 420 minutes and in the 2 urine collections by capillary gas chromatography after deactivation of hydroxy groups.[12] Plasma insulin concentrations were determined in all samples by radioimmunoassay ([RIA] kit from Pharmacia and Upjohn, Copenhagen, Denmark). Plasma glucagon concentrations were measured at −5, 20, 50, 120, 240, 300, and 420 minutes, after extraction of plasma with 70% ethanol, by RIA (antibody code no. 4305 directed against the C-terminus of the glucagon molecule, mainly measuring glucagon of pancreatic origin).[13] Plasma concentrations of gastric

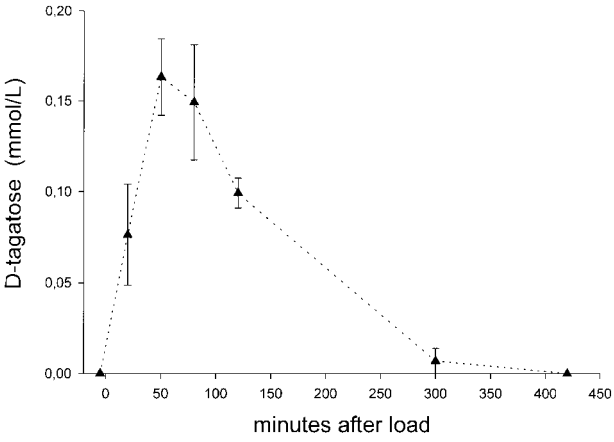

Fig 2. Arterialized serum concentrations of D-tagatose in the test where D-tagatose was administered. (◆), D-fructose, (▲) D-tagatose, (●) plain water (these apply to Figs 2 to 8).

inhibitory polypeptide (GIP) were determined at −5, 50, 120, 300, and 420 minutes by RIA using the C-terminally directed antiserum R 65.[14] Plasma glucagon-like peptide-1 (GLP-1) concentrations were measured in the same samples as GIP by RIA (antiserum code 89390, specific for the amidated C-terminus of GLP-1, which mainly relates to GLP-1 of intestinal origin).[15] Plasma cholecystokinin (CCK) was determined at −5, 50, 120, 300, and 420 minutes by RIA using specific antibodies (antiserum code 92128).[16] To assess plasma norepinephrine and epinephrine concentrations, blood was collected in tubes containing reduced glutathione and EGTA. Epinephrine and norepinephrine were determined at −5, 20, 50, and 120 minutes by a RIA method.[17] The serum albumin[18] concentration was measured at 50, 80, and 180 minutes, on the days when D-tagatose or plain water were administered, to test for a possible effect of D-tagatose on hemoconcentration.

Indirect Calorimetry

Respiratory gas-exchange measurements were performed by the Oxycon ventilated-hood system (Erich Jaeger, Wuerzburg, Germany). All 30-second readings of O_2 uptake and CO_2 production for each measuring period were added, and the nonprotein respiratory quotient (RQnp) was calculated after determining protein oxidation from urinary nitrogen excretion (grams) multiplied by 6.25 g protein/g nitrogen. Energy expenditure (EE) was calculated according to the equation presented by Elia and Livesey.[19] Fat-free mass was calculated from body weight, height, and bioimpedance measured by an Animeter (H.T.S. Engineering, Odense, Denmark) according to an algorithm by Heitmann.[20] The energy content and macronutrient composition of the experimental diet and self-recorded food intake were calculated by Dankost dietary assessment software (Danish Catering Center, Søborg, Denmark). A special database developed for another research project at our department was used to calculate the content of simple sugars for self-reported food intake.

Statistical Analyses

Effects of the 2 test sugars on blood variables (except for glucagon, catecholamines, and albumin), EE, and RQnp were tested by repeated-measures ANOVA using PROC MIXED in SAS 6.12 (SAS Institute, Cary, NC) with time and treatment (D-tagatose, D-fructose, and plain water) as factors and preload values as covariates. Furthermore, the carryover effect, the period effect, and their interactions with time were included in the model. In addition, a person effect was included along with a random person × period effect. Glucose, lactate, insulin, GLP-1, and GIP data were logarithmically transformed to achieve normality. A possible correlation between measurements on the same person was included in the model and validated by comparing the empirical and theoretical semivariograms.[21] If an overall effect of the test sugars or a sugar × time interaction was detected, contrast analyses (treatment × time) were performed to determine the level(s) of treatment that differed. To consider the multiple comparisons between the 3 treatments, only P values less than .017 (.05/3) were accepted as significant in the contrast analyses. As most of the glucagon data were only measured with 1 significant digit, they were analyzed using nonparametric methods. The Friedman repeated-measures ANOVA on ranks was considered in this case using SigmaStat 2.0 (Jandel Scientific, Erkrath, Germany). Glucagon concentrations for the 3 treatments were compared at each time level minus preload data. Additionally to the repeated-measures analysis, the uricemic responses were calculated as the area under the curve (AUC) of delta (Δ) serum uric acid concentrations using the difference between the test sugar and plain water observations. AUCs were calculated from preload to the last pre-lunch sample by the trapezoid method. The presence of a uricemic response was tested for each test sugar, and the 2 test sugars were compared by paired t tests. The response to the test sugars in uric acid excretion during the experiment and self-recorded food intake were tested by repeated-measures ANOVA using plain water as a reference. Appetite scores were tested as the difference between the 2 postload and the preload observations. The tests were performed separately for each of the 2 postload time levels using repeated-measures ANOVA. The latter 3 tests were performed with SPSS 7.5 for Windows (SPSS, Chicago, IL). All data are presented as the mean ± SEM.

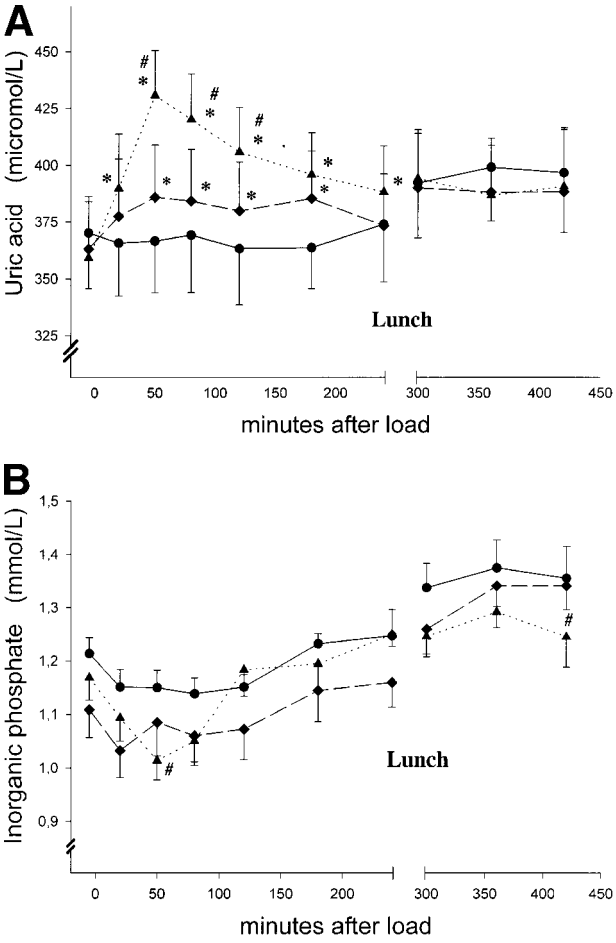

Fig 3. Arterialized serum uric acid and P_i concentrations before and after the test sugar load. *P and #P < .017 *v* plain water and D-fructose, respectively, by contrast analyses. Overall effects by repeated-measures ANOVA: uric acid, treatment, P < .001, treatment × time, P < .001; P_i, treatment, NS, treatment × time, P < .001.

RESULTS

When D-tagatose was administered, its serum concentration peaked after 50 minutes, with a range of 0.05 to 0.28 mmol/L

Table 1. AUC of Δ Serum Uric Acid Concentration in the Pre-Lunch Period

		*P**	*P v* D-Fructose†
Uric acid (mmol · min/L)			
D-fructose	3.63 ± 2.34	.17	
D-tagatose	9.01 ± 2.52	.009	.006

NOTE. Results are the mean ± SEM (n = 8). The pre-lunch period is defined as the interval from −5 to 240 minutes.

*AUC tested against 0 by 2-sided *t* test.

†AUC comparison between D-tagatose and D-fructose by 2-sided paired *t* test.

Table 2. Urinary Uric Acid Excretion (μmol/min) During the Pre-Lunch (−60 to 245 minutes) and Post-Lunch (245 to 430 minutes) Periods

Condition		*P* for Test Sugar *v* Plain Water
Pre-lunch		
Plain water	3.42 ± 0.15	
D-Fructose	3.65 ± 0.26	.30
D-Tagatose	4.53 ± 0.31	.02
Post-lunch		
Plain water	4.21 ± 0.25	
D-Fructose	4.15 ± 0.33	.32
D-Tagatose	4.93 ± 0.15	.046

NOTE. Results are the mean ± SEM (n = 8). The pre-lunch and post-lunch periods included the intervals from t −60 to 245 minutes and from 245 to 430 minutes, respectively. *P* values were obtained by repeated-measures ANOVA as contrasts using plain water as a reference.

(Fig 2). No D-tagatose could be detected in the serum in any subject after 420 minutes. A total of 2.42 mmol (range, 1.66 to 4.03) D-tagatose corresponding to 1.45% of the 30-g dose was detected in the urine. Most of the D-tagatose excreted (2.21 mmol; range, 1.24 to 3.86) was found in the pre-lunch urine collection, indicating that only a minor part of the total D-tagatose excretion could have occurred after the experiment and thereby escaped detection. D-tagatose reduced diuresis relative to plain water during the pre-lunch period from 2.25 ± 0.29 to 1.49 ± 0.23 mL/min ($P = .002$), whereas no such effect was found in the post-lunch period (D-tagatose *v* plain water, 1.51 ± 0.20 *v* 1.37 ± 0.10 mL/min). Diuresis was not affected by D-fructose during either of the 2 periods as compared with plain water. A slight increase from 666 ± 11 to 696 ± 7 μmol/L ($P = .03$) in the serum albumin concentration was observed 50 minutes after administration of D-tagatose as compared with water, whereas no such difference was found in the subsequent samples that were analyzed for albumin (D-tagatose *v* plain water: 80 minutes, 684 ± 9 *v* 676 ± 9 μmol/L, NS, and 180 minutes, 670 ± 9 *v* 676 ± 15 μmol/L, NS, respectively).

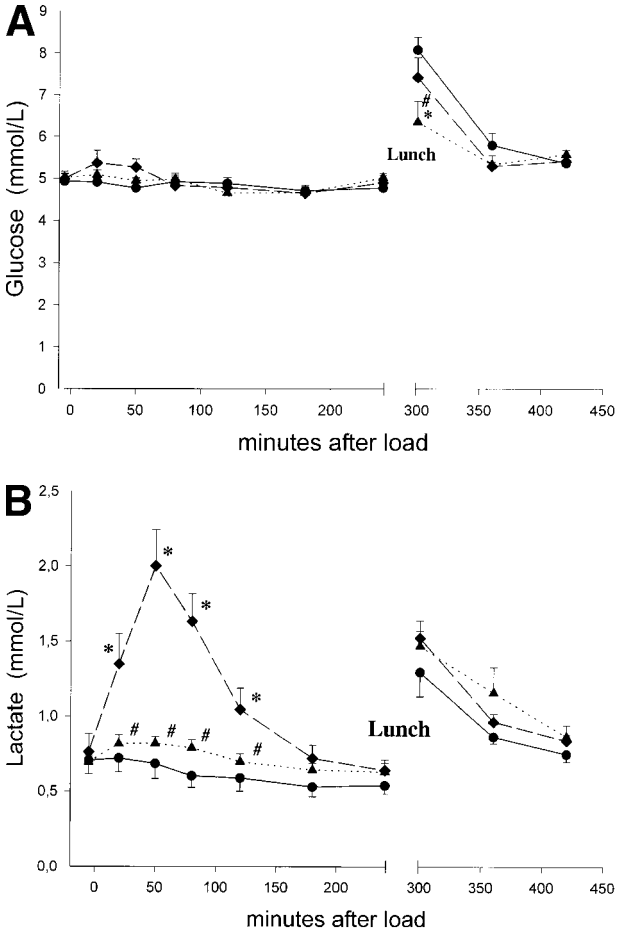

Fig 4. Arterialized plasma glucose and lactate concentrations before and after the test sugar load. *P and #P < .017 *v* plain water and D-fructose, respectively, by contrast analyses. Overall effects by repeated-measures ANOVA: glucose, treatment, NS, treatment × time, P < .001; lactate, treatment, P < .001, treatment × time, P < .001.

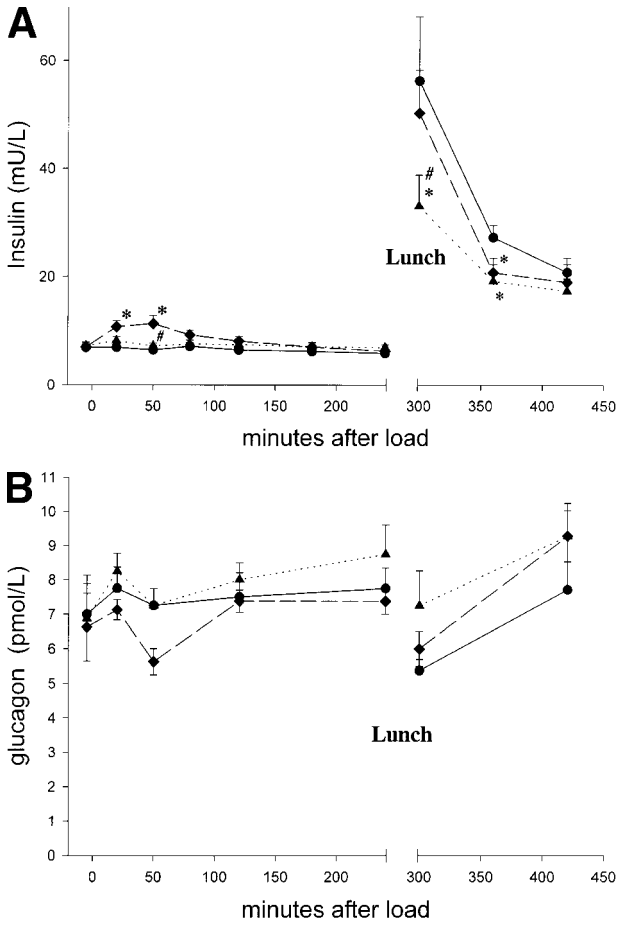

Fig 5. Arterialized plasma insulin and glucagon concentrations before and after the test sugar load. *P and #P < .017 *v* plain water and D-fructose, respectively, by contrast analyses. Overall effect by repeated-measures ANOVA: insulin, treatment, P < .02, treatment × time, P < .001; glucagon, no significant treatment effect at any time by Friedman repeated-measures ANOVA on ranks.

Serum uric acid was increased by D-tagatose throughout the entire pre-lunch period (Fig 3A). The weaker response of serum uric acid to D-fructose was also significant by repeated-measures ANOVA, but the response to D-fructose could not be confirmed by a significant AUC. The AUC of the Δ serum uric acid concentration following D-tagatose was significantly greater than that of D-fructose (Table 1). No effects of the test sugars on serum uric acid were found after lunch. Except for a single subject who displayed slightly elevated serum uric acid levels during all 3 tests, no values exceeded 450 μmol/L, which is the upper limit of the reference interval for healthy Danish males. Urinary uric acid excretion was increased by D-tagatose during both the pre- and post-lunch periods (D-tagatose *v* plain water: pre-lunch, 1,430 ± 102 *v* 1,044 ± 51 μmol, and post-lunch, 899 ± 25 *v* 797 ± 49 μmol), whereas no such effect was found after D-fructose. The pre-lunch excretion of uric acid was significantly higher after D-tagatose compared with D-fructose (Table 2).

Despite great variation in both the effect of D-tagatose on the total excretion of uric acid (range, −22 to 952 μmol) and the AUC of the Δ serum uric acid concentration (range, −1.4 to 18.8 mmol · min/L), no correlation was found between the 2 variables.

In the pre-lunch period, a slight and transient decline in serum P_i was observed after D-tagatose, but the response only reached statistical significance when compared with fructose and only 50 minutes after the load (D-tagatose *v* fructose, $P = .01$; D-tagatose *v* plain water, $P = .03$). A lower serum P_i concentration after D-tagatose compared with D-fructose was also found 400 minutes postload (Fig 3B).

The pre-lunch increase in plasma glucose after D-fructose did not reach significance ($P = .06$). The post-lunch increase of plasma glucose was attenuated by D-tagatose 45 minutes after the start of the meal (Fig 4A). Plasma levels of lactate increased markedly as a result of the fructose load (Fig 4B), while the response to D-tagatose was trivial. The plasma lactate response to lunch was unaffected by the test sugars. There was a small but significant plasma insulin response to the fructose load, whereas plasma insulin remained at the basal level after D-tagatose (Fig 5A). D-Tagatose had a marked suppressive effect on plasma insulin 45 minutes after lunch and the insulin level remained somewhat lower with D-tagatose at 95 minutes after lunch, at which time insulin also was lower with fructose compared with plain water. The test sugars had no significant impact on the plasma glucagon concentration (Fig 5B).

A transient GLP-1 and CCK response was observed with both sugars without a significant difference between fructose and D-tagatose (Fig 6A and B). A slightly lower level of plasma GIP after D-tagatose compared with fructose was found 50 and 120 minutes postload (Fig 6C). No effects were found for administration of the 2 sugars on plasma epinephrine or norepinephrine concentrations.

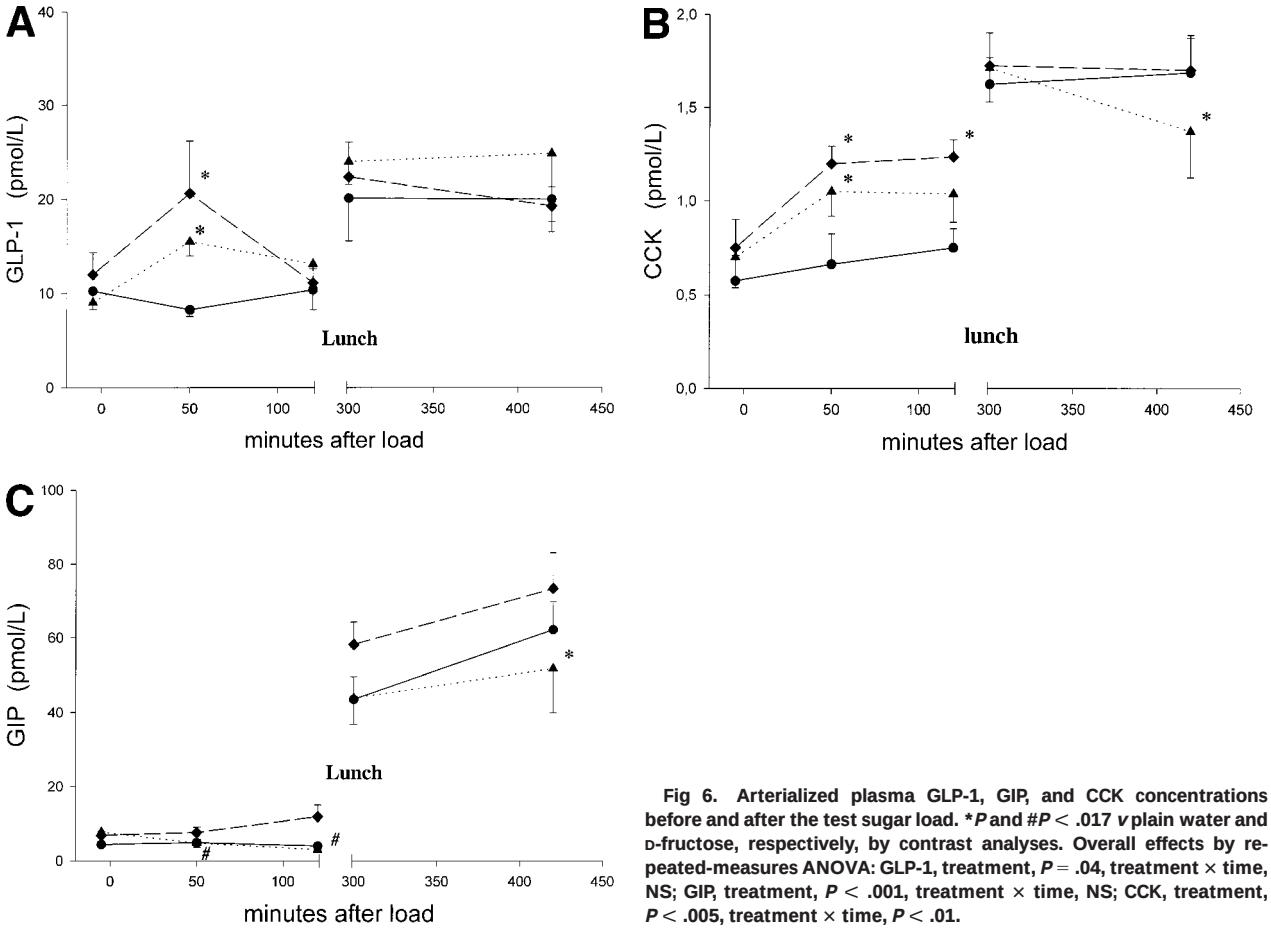

Fig 6. Arterialized plasma GLP-1, GIP, and CCK concentrations before and after the test sugar load. *P and #$P < .017$ *v* plain water and D-fructose, respectively, by contrast analyses. Overall effects by repeated-measures ANOVA: GLP-1, treatment, $P = .04$, treatment × time, NS; GIP, treatment, $P < .001$, treatment × time, NS; CCK, treatment, $P < .005$, treatment × time, $P < .01$.

A slight thermogenic effect of D-fructose was observed during the first 80-minute period after the load, which only reached significance compared with D-tagatose (Fig 7A), whereas D-tagatose did not increase EE. Both test sugars increased the RQnp during the pre-lunch period, but only D-fructose induced a pronounced and immediate peak in the RQnp (Fig 7B).

No significant differences were found between the treatments in pre- or post-lunch appetite scores (Fig 8) or the energy content or composition of the self-recorded post-test diet.

DISCUSSION

Only 1.5% of the administered D-tagatose was recovered in the urine. This indicates that only a minor part of the sugar is absorbed or that it is absorbed and almost completely metabolized. Both the serum level and urine excretion of uric acid were increased during the pre-lunch period after administration of D-tagatose, which is in line with the hyperuricemic effect of the sugar observed in another study.[8] The fact that the increase in serum uric acid was more pronounced after oral D-tagatose administration versus the same dose of D-fructose, despite the fact that probably only a minor fraction of D-tagatose was absorbed, suggests that this sugar has a greater capacity to perturb purine metabolism. This may be explained by the more prolonged lowering effect of D-tagatose on intracellular P_i[5,22] compared with D-fructose, although this has not yet been confirmed in in vivo liver experiments. However, a P_i-depleting effect is supported in the present study by the observation of a transient decline in serum P_i after D-tagatose but not after D-fructose.

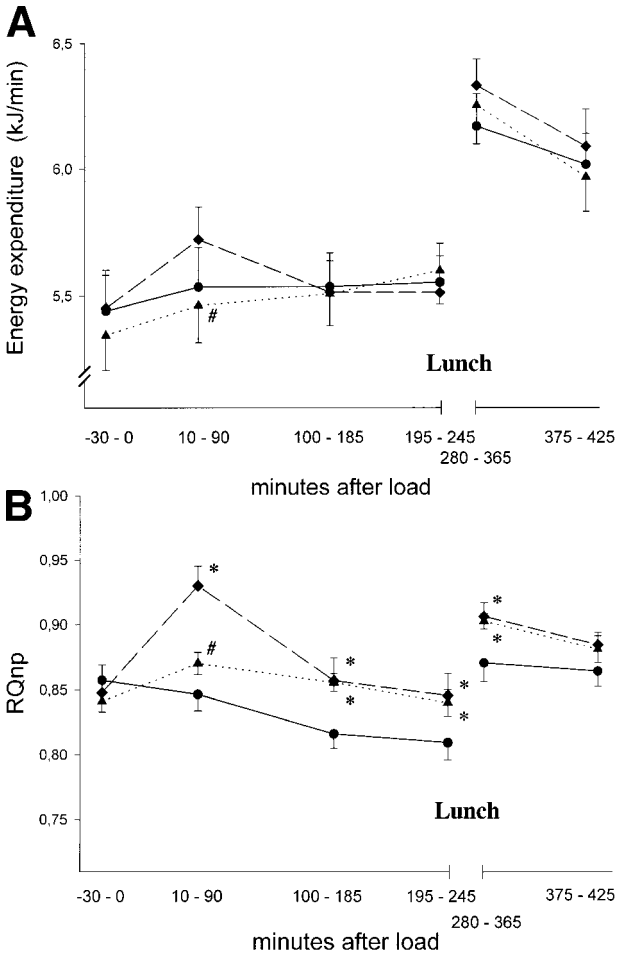

Fig 7. EE and RQnp before and after the test sugar load. *P and #$P < .017$ *v* plain water and D-fructose, respectively, by contrast analyses. Overall effects by repeated-measures ANOVA: EE, treatment, NS, treatment × time, $P = .04$; RQnp, treatment, $P < .001$, treatment × time, $P < .001$.

The study design does not allow any conclusion as to where the additional uric acid production occurred. Most D-fructose given orally is probably metabolized in the liver,[23] although some degradation of the sugar may occur in other tissues. However, due to its putative poor absorption,[2] relatively more D-tagatose compared with D-fructose may be available in the gut lumen to be metabolized by the intestinal epithelium, which therefore may possibly contribute to the uric acid production. Although the observed transient increase in the blood uric acid concentration may be trivial and clinically insignificant in normal healthy subjects, the hyperuricemic effect of D-tagatose may be detrimental to gouty individuals or individuals genetically predisposed to gout, as these groups previously have been found to exhibit an exaggerated blood uric acid response to fructose.[24] Furthermore, studies are required pertaining to the hyperuricemic response of D-tagatose in insulin-resistant subjects, who frequently present an increased basal serum uric acid level[25] and may have a more pronounced uric acid response to sucrose after consuming a high-fructose diet.[26]

The fact that no correlation was found between Δ uric acid excretion and the AUC of Δ serum uric acid contradicts a simple relationship between an increase in serum levels and an increase in urine excretion of uric acid. Variations in the rate of biliary uric acid elimination, which normally constitutes approximately one third of the total excretion,[27] may be one factor. The fact that urinary uric acid excretion remained higher during the post-lunch period after D-tagatose despite the serum concentration return to the plain-water level may suggest that some uric acid may have accumulated in a renal pool.

The 34% reduction in pre-lunch diuresis after D-tagatose compared with plain water is probably attributable to water retention in the small intestine by the osmotic impact of the unabsorbed D-tagatose. Water retention by D-tagatose was also indicated by the higher serum albumin concentration 50 minutes after administration of the sugar as compared with plain water. This apparent relative hemoconcentration was transient, as the difference in serum albumin concentration had disappeared 80 minutes after dosing. The higher level of serum uric acid 50 minutes after D-tagatose could not be solely explained by relative hemoconcentration, as it remained significantly higher when calculated as a ratio to serum albumin concentration. However, as urinary uric acid excretion can be reduced by reducing urinary flow,[28] the decline in diuresis after D-tagatose may have contributed to its hyperuricemic effect. On the other hand, even if a total abolishment of urinary uric acid excretion by D-tagatose is assumed, this would only explain 22% of the increase in serum concentration during the first 50 minutes.

In contrast to D-fructose, which induced both a pronounced plasma lactate response accompanied by an increased EE and RQnp during the first 1.5 hours, the responses of these

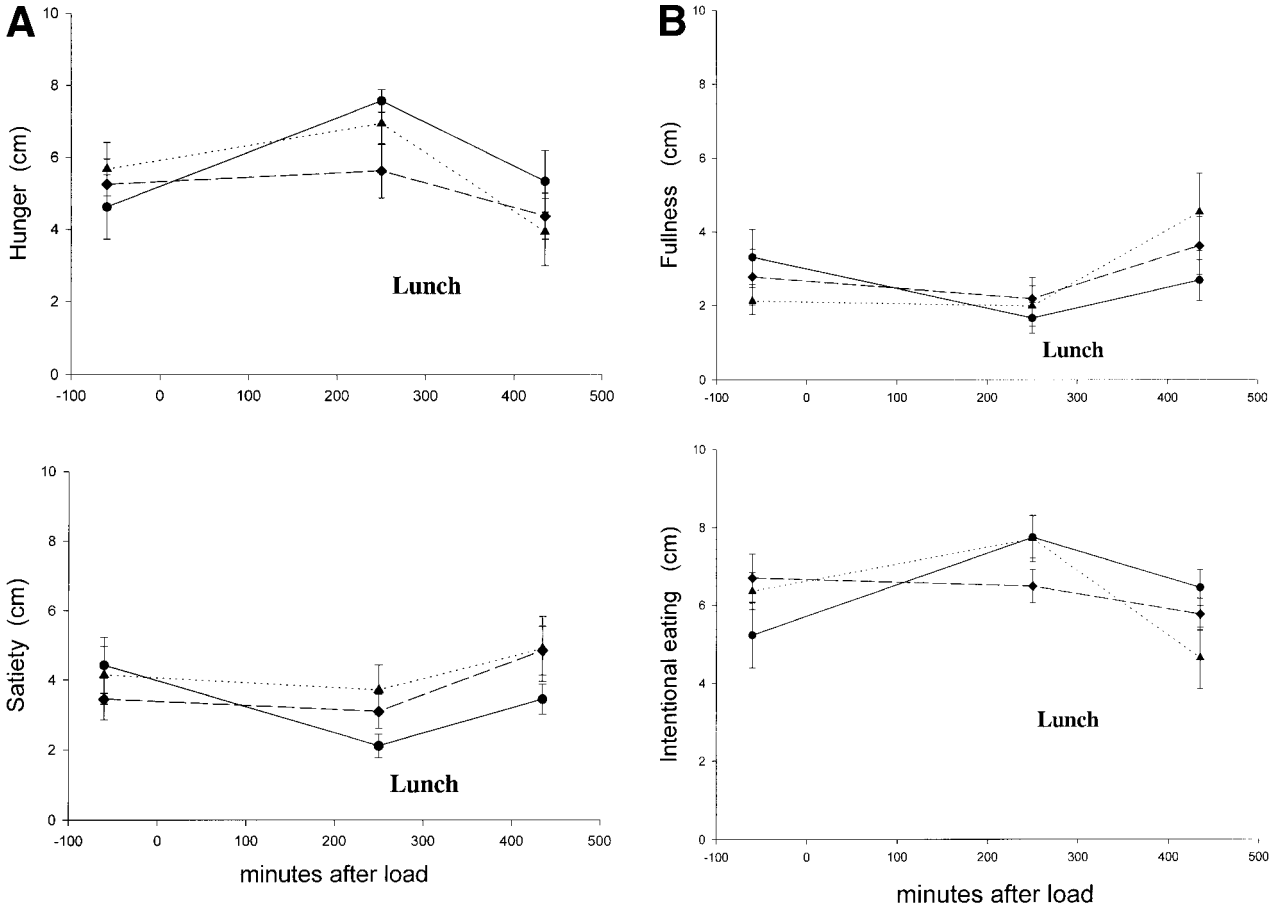

Fig 8. Appetite sensations measured by VAS scores before and after test sugar load. No treatment or treatment × time effects at the $P < .017$ level were found by repeated-measures ANOVA.

parameters were more modest after D-tagatose. The lactacidemic effect of fructose is well recognized,[29] and is explained by a faster phosphorylation and bypassing of the regulatory enzyme phosphofructokinase I when D-fructose enters glycolysis as compared with D-glucose.[30] The small response in blood lactate after D-tagatose implies that the absorption of sugar is small or that it occurs at a rate which does not exceed the capacity for its entry into oxidative metabolism. The attenuated early response in the RQ and absent thermogenesis after D-tagatose further indicate that D-tagatose is poorly absorbed or is metabolized at a slower rate than D-fructose. The RQ after minute 100 was similarly increased with D-tagatose compared with D-fructose, but this could be due to CO_2 produced by fermentation of unabsorbed D-tagatose and therefore does not necessarily reflect oxidation of the sugar.

Both glucose and insulin responses to the lunch meal were attenuated after D-tagatose. D-Tagatose, when given prior to an oral glucose load, has been previously reported to attenuate its glycemic effect,[10] and several mechanisms may explain this effect. A direct impact of D-tagatose on postprandial hepatic glucose metabolism may be hypothesized, as D-tagatose may have the capacity to augment postprandial hepatic extraction of glucose by stimulation of glycogen synthase. Experiments on isolated rat hepatocytes have demonstrated an increased activity of this enzyme when D-tagatose is added to the medium.[31] D-Tagatose may also influence glucose metabolism as a consequence of the short-chain fatty acids (SCFAs) produced by its fermentation, as SCFA has been suggested to improve insulin sensitivity. A study using a diet rich in barley containing a large amount of poorly absorbed carbohydrate, was found to improve glucose tolerance. This may be a result of an increased suppression by insulin of hepatic glucose production.[32]

The increase in plasma CCK after fructose and D-tagatose suggests that the ingestion of pure sugar solutions may stimulate the secretion of this hormone. Administration of D-fructose or D-tagatose caused no increment in the blood concentration of GIP, but GLP-1 increased 50 minutes after administration of both sugars. The lack of increase in GIP is in accordance with the suggestions from experiments with in vivo luminal perfusion of rodent gut preparations, ie, the common structure of the monosaccharide eliciting a GIP response is compatible with the requirements for the sodium-dependent glucose pathway across the mucosal cell brushborder,[33] and the furanose ring of D-fructose and D-tagatose does not fulfill the required configuration. Furthermore, the increase in plasma GLP-1 within 50 minutes after dosing of both sugars implies that the early GLP-1 response does not require a plasma GIP response to be elicited as otherwise suggested.[34] A more frequent sampling of the

gastrointestinal hormones, particularly during the first 2 hours after lunch, may have provided a better picture of their postprandial responses, but the sampling rate was limited to avoid excessive blood loss.

In conclusion, the present data demonstrate a hyperuricemic effect of D-tagatose which could be anticipated from previous observations with fructose intake and the metabolism of ketohexoses. The blunted response to D-tagatose in EE and RQ as compared with D-fructose confirms that the sugar is malabsorbed and may be metabolized at a slower rate than D-fructose. Despite being poorly absorbed, D-tagatose was found to increase GLP-1. Further investigations with regard to the metabolic effects and impact on food intake of D-tagatose, particularly in individuals predisposed to overweight, hyperuricemia, or gout, are required. Furthermore, studies on the impact of D-tagatose on phosphate and carbohydrate metabolism in the liver using noninvasive techniques would be pertinent.

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