Effects of Oral D-Tagatose, A Stereoisomer of D-Fructose, on Liver Metabolism in Man as Examined by ^{31}P-Magnetic Resonance Spectroscopy

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D-tagatose, which is a stereoisomer of D-fructose, is phosphorylated to D-tagatose-1-phosphate by fructokinase in the liver. Because of a slow degradation rate of D-tagatose-1-phosphate, this substance may accumulate, and ingested D-tagatose may therefore cause a longer lasting reduction in inorganic phosphate (P_i) and adenosine triphosphate (ATP) levels in the liver compared with D-fructose. Similar to what is seen in patients with hereditary fructose intolerance, this may increase purine nucleotide degradation and thereby increase uric acid production. The effect of 30 g D-tagatose or D-fructose administered orally on ketohexose-1-phosphates, ATP, and P_i levels in the liver was studied by ^{31}P-magnetic resonance spectroscopy (PMRS) in 5 young male volunteers. Blood and urine were collected to detect a possible increased uric acid production. A peak at 5.2 ppm assigned as D-tagatose-1-phosphate equivalent to about 1 mmol/L was found in the spectrum within 30 minutes after D-tagatose was administered in all subjects. Concomitantly, ATP was reduced by about 12% ($P < .05$). Both effects had vanished after 150 minutes. Serum uric acid concentration was increased by 17% 50 minutes after D-tagatose ($P < .05$) and did not reach baseline level when the experiment was terminated 230 minutes after the load. Although renal fractional extraction of uric acid decreased by approximately 12%, this could not explain the acute hyperuricemic effect of D-tagatose. No changes in ^{31}PMRS spectra or serum uric acid concentration were found after D-fructose. These results suggest that a moderate intake of D-tagatose may affect liver metabolism by phosphate trapping despite the fact that the sugar may only be incompletely absorbed in the gut.

PHOSPHORYLATION of ketohexoses in the liver at a rate, which is higher than the subsequent degradation of the phosphorylated compounds, may cause metabolic disturbances due to the accumulation of the phosphorylated intermediates. The best known example is the hereditary fructose intolerance syndrome, which is a genetic defect in the aldolase B enzyme responsible for the cleaving of fructose-1-phosphate into D-glyceraldehyde and dihydroxyacetone phosphate.[1] In these patients, moderate doses of fructose may cause severe hypoglycemia and hyperuricemia,[2] which are explained by impaired glycogen phosphorylase activity and increased purine nucleotide degradation, respectively.[3] Large oral doses of fructose may also have a slight hyperuricemic effect in normal individuals.[4] Hereditary fructose intolerance patients respond to fructose by decline in the inorganic phosphate (P_i) and adenosine triphosphate (ATP) levels in the liver.[5] These changes in hepatic metabolism after fructose can also be seen in normal subjects, but the effect is smaller and more transient.[4,5] However, with intravenous infusion of fructose, this effect was clearly seen.[6] Some fructose isomers show impaired degradation of the phosphorylated intermediaries and may for that reason induce metabolic derangements, which are more pronounced than those of fructose. Thus, the 2 fructose analogues, 2,5-anhydro-D-mannitol (2,5-AM) and D-tagatose, trap phosphate and reduce the ATP level in isolated rat hepatocytes or the intact liver more effectively than D-fructose.[7,8] Furthermore, both analogues inhibit glycogenolysis in the liver[9,10] and increase uric acid excretion.[11,12] The hyperuricosuric effect of D-tagatose was also found in humans after a 30-g oral dose, and the increase uric acid excretion was more pronounced than after the same dose of D-fructose, despite the fact that only part of the sugar may be absorbed.[13] An increase in uric acid production as a result of an elevated purine degradation rate has previously been shown in humans with the sugar alcohol xylitol, which is marketed as a dietetic sugar. Although caused by a different enzymatic reaction, this was also explained by a decline in hepatic ATP due to phosphate trapping.[14] A potential to affect hepatic metabolism of certain phosphate trapping bulk sweeteners is therefore an acknowledged phenomenon.

The present study was conducted to clarify if the acute increased blood concentration and renal excretion of uric acid, which have previously been shown,[12,15] can be associated with an accumulation of D-tagatose-1-phosphate and alterations in ATP in the liver of normal subjects.

MATERIALS AND METHODS

Design

The effect of 30 g D-tagatose or D-fructose administered orally was studied by ^{31}P-magnetic resonance spectroscopy (^{31}PMRS) in 5 apparently healthy fasting male subjects (body mass index [BMI], 24.0 ± 0.6 kg/m^2; age, 23 to 37 years). The 2 sugars were dissolved in 400 mL water and given in a randomized double-blind crossover design with a time lag of more than 1 week between the 2 experiments. ^{31}PMRS recordings were obtained shortly before the ingestion and every 17 minutes after intake of the sugar solution. Blood was sampled shortly before and 20, 50, 80, 110, 140, 170, 200, and 230 minutes after the load for serum uric acid, creatinine, and albumin analyses. Urine was collected for a period running from about 90 minutes before to 240 minutes after dosing for uric acid and creatinine analyses. For technical reasons, urine could only be collected and analyzed as 1 sample for this complete interval, which meant that the effect of the sugars was slightly diluted by the 90-minute preload period.

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31PMRS Recording

The measurements took place in a 1.5 T Siemens scanner (Erlangen, Germany). The volunteers lay supine in the scanner, and a single tuned surface-coil, diameter 16 cm, was placed over the region of the liver. The exact location of the coil was assessed by proton magnetic resonance imaging (MRI). The magnet was shimmed by optimizing on the water signal. ^{31}PMRS spectra were acquired by a sequence where the major part of the signal originated from the liver, eliminating most of the signal from the overlying muscle by spin saturation.[16] Each spectrum consisted of 256 free induction decays (FIDs) with an interpulse delay of 4 seconds, ensuring fully relaxed signals from the liver. Unfortunately, for 1 of the 5 subjects (the first), the nuclear magnetic resonance (NMR) data were lost from the storage disk by mistake. For that subject, only the hard copies of the recorded spectra exist. For that reason, the analysis on the NMR data was performed on only 4 subjects.

NMR Data Analysis

The composite spectra were analyzed by the method of linear prediction (LP), implying estimation of 500 LP coefficients of the time domain signal, providing the frequency of the resonances of the signal.[17] This rather time-consuming procedure is ideally suited for the spectra obtained in the present experiments with relatively low resolution, because the calculation makes no a priori assumptions about the frequency content of the raw data.[17] Subsequently, the intensities of the resonances identified by the LP procedure were obtained by a least square fitting routine on the Fourier transformed signal. Absolute quantitation of the data was obtained by assuming a resting concentration of ATP in the liver of 2.5 mmol/L.[18]

Despite the attempt to eliminate the muscle signal from the muscle covering the liver by means of a special pulse sequence (see above), there was still some muscle signal present in the spectra. However, because the liver does not express the enzyme creatine kinase and consequently does not contain phosphocreatine (PCr), it is possible to correct for the muscle contribution to the liver signal. The correction relies on the fact that resting muscle display ratios of PCr/ATP of approximately 5.[19] Consequently, liver ATP was calculated as spectral-ATP $-$ (0.2 $\times$ PCr). Because of the relatively broad lines of the present spectra (about 80 Hz), it is not possible to accurately differentiate the P_i resonance at about 3 ppm and the phosphomonoesters (PME), primarily consisting of adenosine monophosphate (AMP) alpha-glycerol phosphate, and phosphocholine, which resonances at 3.5 to 4.2 ppm (see Quistorff et al[20] for more elaborate information of which resonances are seen in the liver in that region of the spectrum).

The effects of the 2 sugars were tested on difference spectra, ie, the actual postload spectra subtracted by the spectrum acquired shortly before the sugar was administered. Such difference spectra can be expected to represent the signal changes attributable only to the intake of the test sugar.

Blood and Urine Analyses

Serum and urine uric acid concentrations were enzymatically determined by a quinone-imine dye reaction (kit from Boehringer Mannheim, Diagnostica, Copenhagen, Denmark). Creatinine was determined in serum and urine by the Jaffé method without deproteinization.[21] Serum albumin concentration was measured according to Laurell.[22]

RESULTS

NMR Data

No effects of D-fructose ingestion could be detected, while a marked peak developed at about 5.2 ppm after D-tagatose (Fig 1b). In all subjects this peak, which is assigned as D-tagatose-1-phosphate, was clearly visible in the first spectrum integrating the 0 to 17-minute time interval after D-tagatose was administered (Table 1). The tagatose-1-P peak reached the maximum level in the second or third spectrum (17 to 51 minutes) and started to decline thereafter. After about 150 minutes, the D-tagatose-1-phosphate peak had disappeared again in all subjects. Figure 1 shows a typical difference spectra for D-fructose and D-tagatose, respectively. While the D-fructose difference spectrum did not show any signal changes, a D-tagatose-1-phosphate peak at 5.2 ppm corresponding to about 1 mmol/L was clearly visible in the difference spectrum with D-tagatose after 30 minutes [Fig 1(b-a)]. It also appears that there were only minor changes in the ATP and PME/P_i peaks. However, analyses of all difference spectra showed a small, but consistent, decrease in the β-ATP ($\simeq$ 12%, $P < .05$ when tested

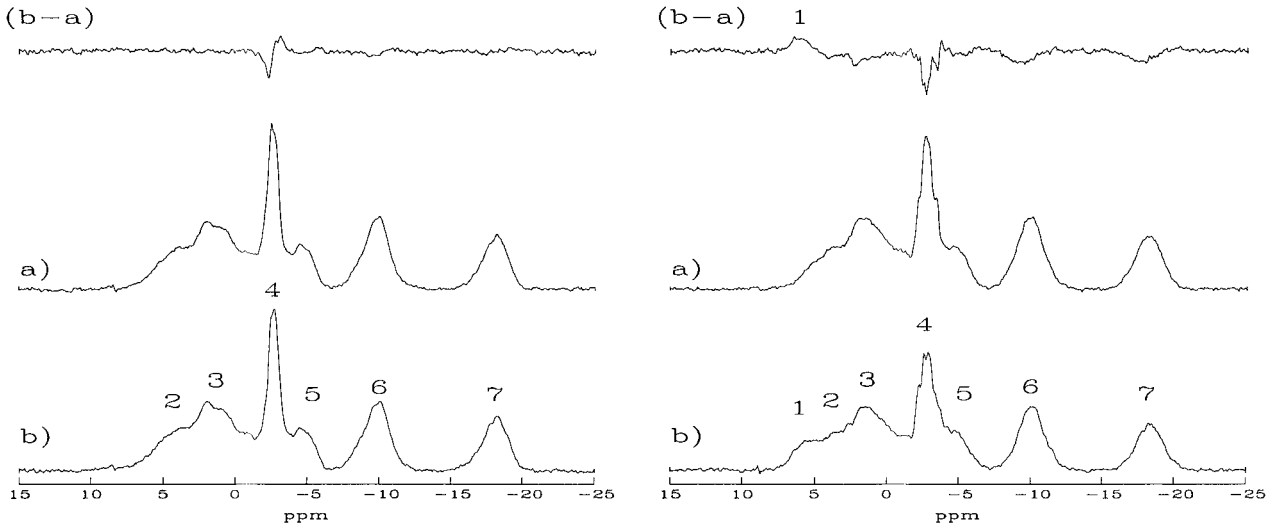

Fig 1. ^{31}PMRS spectrum of human liver recorded before and after ingestion of 30 g D-fructose (left) or D-tagatose (right). (a) Recorded before and (b) 30 to 45 minutes after the intake of the sugar. (b-a) Represents the difference between the 2 spectra in each panel. The peak assignments are: (1) D-tagatose-1-P, (2) phosphomonoesters, (3) inorganic phosphate, (5) phosphorcreatine, (6, 7, and 8) α-, β-, and γ-peaks of ATP. Note that tagatose-1-P is clearly visible in the difference spectrum, while fructose-1-P is not.

Table 1. Changes in Liver ATP and D-Tagatose-1-Phosphate After a 30-g Oral Load of D-Tagatose

Time (min)	ATP (%)	D-Tagatose-1-P (mmol/L)
0 (baseline)	100	0
17	97 ± 3.3	0.27 ± 0.18
34	92 ± 3.1*	1.18 ± 0.29
51	89 ± 3.5*	1.02 ± 0.13
68	91 ± 2.2*	0.64 ± 0.25
85	92 ± 2.0*	0.66 ± 0.30
102	93 ± 2.8	0.50 ± 0.37
119	93 ± 1.5*	0.51 ± 0.47
136	94 ± 2.9	0.30 ± 0.34
170	96	0.24
221	101	0

NOTE. Mean ± SD.

*$P < .05$ tested against baseline values by 2-sided paired *t* test (n = 4). The concentrations of ATP and D-tagatose-1-P were calculated as relative changes, assuming a resting-ATP level of 2.5 mmol/L.[18] The values at minutes 170 and 221 represents only 2 observations.

against baseline values by two-sided paired *t* test). The decline in β-ATP was maximal for the 17 to 85-minute interval, which coincides with the maximum of the D-tagatose-1-phosphate peak (Table 1). A similar decrease of the PME/P_i signal could not consistently be observed.

Blood and Urine Analyses

Figure 2 shows average serum uric acid data. An increase in serum uric acid concentration of 0.059 mmol/L (from 0.355 ± 20 to 0.414 ± 17 mmol/L) was seen during the first 50 minutes after D-tagatose, whereas no such effect was observed after D-fructose. A repeated measures analysis of variance (ANOVA) showed an overall effect of D-tagatose on serum uric acid concentration ($P < .05$). A subsequent contrast analysis yielded significant differences at 50, 80, 110, 140, 170, and 230 minutes after the load in the uric acid response to the different sugars, using preload values as baseline. After D-tagatose, serum uric acid level remained higher than the preload value in the last blood sample at 230 minutes postload ($P < .01$).

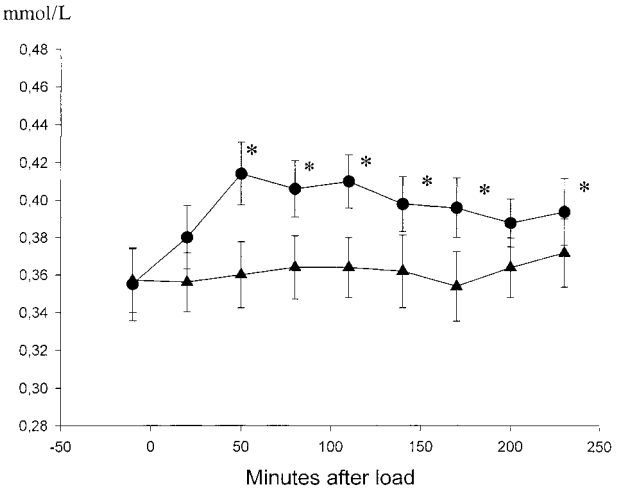

Fig 2. Serum uric acid concentrations before and after 30 g oral D-fructose (▲) or D-tagatose (●). *$P < .05$ *v* D-fructose by repeated measures ANOVA with preload values as reference.

Renal excretion rate of uric acid did not differ between the 2 sugars (D-tagatose *v* D-fructose: 2.50 ± 0.42 *v* 2.65 ± 0.47 μmol/minute, $P = .58$). However, fractional extraction of uric acid calculated as uric acid clearance over creatinine clearance was slightly, but significantly, reduced by D-tagatose (D-tagatose *v* D-fructose: 5.2 ± 1.0 *v* 5.9% ± 1.0%, $P = .004$). Individual data for the calculation of fractional extraction of uric acid are shown in Table 2.

Serum albumin concentration (Fig 3) increased significantly by 4% from baseline to 50 minutes after D-tagatose, whereas the increase after D-fructose was not significant at any time. Diuresis tended to be lower after D-tagatose (D-tagatose *v* D-fructose 1.02 ± 0.32 *v* 1.98 ± 0.42 mL/minute, $P = .07$).

DISCUSSION

No accumulation of D-fructose-1-phosphate in the liver after D-fructose could be detected in the present study by ^{31}PMRS, whereas a peak corresponding to D-tagatose-1-phosphate was obvious after D-tagatose. Accordingly, no decline in β-ATP was seen after D-fructose, while we found a 12% decrease on average 17 to 34 minutes after the ingestion of 30 g D-tagatose, corresponding to about 0.30 mmol/L ATP.[18] The absent effect of D-fructose may seem at variance with a previous study in which a 26% decline in ATP in the liver was shown in humans after intravenous fructose infusion.[6] However, the fructose concentration presented to the liver in that study was probably much larger than in the present study with oral sugar administration of 30 g D-fructose, thereby, causing a much smaller rate of fructose phosphorylation (fructokinase has a Km of 0.2 mmol/L). Furthermore, a previous ^{31}PMRS study with larger oral doses of D-fructose (50 g) has shown a hepatic effect also in normal subjects by an approximately 20% decline in P_i associated with the accumulation of sugar-phosphates.[4] In the present study, in contrast to the lacking effect of D-fructose, a hepatic effect of D-tagatose was observed despite the fact that the entrance to the liver of D-tagatose could be expected to be much slower, as its absorption in the gut is believed to be incomplete.[13] The greater potency of D-tagatose than D-fructose to trap phosphate is probably due to a much slower degradation rate of D-tagatose-1-phosphate.[8] No change in PME/P_i peak was detected with D-tagatose despite the observed decline in ATP. A current replenishment of P_i from the blood to the liver may, therefore, be speculated, but our data do not support a conclusion on this point.

Serum concentration of uric acid increased by 16% during the first 50 minutes after D-tagatose, while no such effect was found after D-fructose. The hyperuricemic effect of D-tagatose, which was similar to what was found with the same dose in a previous study,[12] could not solely be explained by a hemoconcentrating effect of the sugar, ie, plasma volume only decreased by about 4%, as judged from the increase in serum albumin concentration. Uric acid production may be increased after D-tagatose as a consequence of an accelerated purine degradation. A rate-limiting step of this process is the deamination of AMP to inosine mone phosphate (IMP) by AMP deaminase, an enzyme that is inhibited by P_i.[23] A reduced P_i level in the liver may, therefore, be directly responsible for the hyperuricemic effect of phosphate trapping sugars. However, in the present study, the decrease in hepatic ATP could maximally account for approximately 0.30 mmol/L uric acid. Assuming a liver volume

Table 2. Individual Urine Excretion and Uric Acid Data

Subject No.	Collecting Period (min)	Diuresis (mL/min)	Urine Volume (L)	Uric Acid Concentration in Urine (μmol/L)	Uric Acid Excretion Rate (μmol/min)	Creatinine Excretion Rate (μmol/min)	Mean Serum Uric Acid Concentration (mmol/L)	Mean Serum Creatinine Concentration (μmol/L)	Uric Acid Clearance (mL/min)	Creatinine Clearance (mL/min)	Fractional Extraction of Uric Acid (%)
1											
Fructose	−140-240	2.62	0.996	1200	3.1	7.86	0.361	85.2	8.72	92	9.5
D-tagatose	−125-240	2.25	0.820	1600	3.6	8.99	0.391	84.9	9.18	105	8.7
2											
Fructose	−78-242	2.09	0.668	2000	4.2	16.71	0.387	92.4	10.78	181	6.0
D-tagatose	−77-243	0.83	0.265	4000	3.3	14.41	0.372	90.1	8.89	156	5.7
3											
Fructose	−85-240	1.89	0.616	900	1.7	9.47	0.388	84.1	4.40	113	3.9
D-tagatose	−95-235	0.47	0.156	2700	1.3	8.05	0.430	88.0	2.98	92	3.3
4											
Fructose	−115-240	0.45	0.161	3700	1.7	8.18	0.300	77.0	5.61	106	5.3
D-tagatose	−75-240	0.64	0.202	3200	2.1	11.24	0.337	80.8	6.10	139	4.4
5											
Fructose	−75-240	2.85	0.898	900	2.6	11.40	0.361	77.2	7.10	148	4.8
D-tagatose	−90-240	0.91	0.300	2500	2.3	11.84	0.385	78.3	5.91	151	3.9

of 1½ L, this would only correspond to an excess uric acid production of 0.45 mmol. This also assumes that all of the purine of the ATP decrease was degraded to uric acid rather than remaining in the purine pool. This is less than a quantity of 0.92 mmol, which can be calculated by assuming that the 59 μmol/L increase in serum uric acid concentration occurring during the first 50 minutes is distributed in an extracellular volume constituting 20% of the subjects body weight.

The difference may be explained by an increased de novo purine synthesis in which IMP is synthesized from glutamine and ribose-5-phosphate. The so-formed IMP may subsequently contribute to the total purine degradation. The first rate-limiting step in de novo purine synthesis is the formation of 5-phosphoribosyl-1-pyrophosphate (PRPP), which is inhibited by adenine nucleotides. In fact, PRPP concentration in isolated hepatocytes has been shown to be positively associated with the reduction in ATP induced by D-fructose, xylitol, or D-tagatose.[23] Furthermore, extrahepatic metabolism of D-tagatose (gut and kidneys, which in addition to the liver, are also able to catabolize

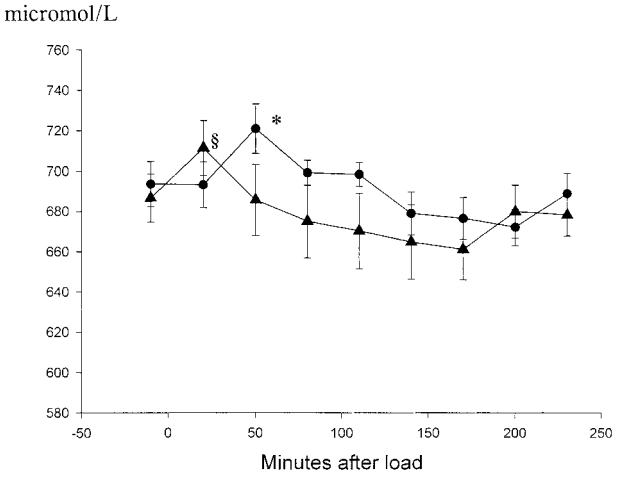

Fig 3. Serum albumin concentrations before and after 30 g oral D-fructose (▲) or D-tagatose (●). *$P < .01$ and §$P = .10$, when tested versus baseline.

D-fructose) could also have contributed to the uric acid production.

Average renal fractional extraction of uric acid across the entire urine collection period was significantly lower after D-tagatose than after D-fructose. Retention of uric acid may, therefore, have contributed to the hyperuricemic effect. However, if an average renal uric acid production rate of 2.65 μmol/minute, corresponding to the uric acid excretion rate during the fructose trials, is assumed as a probable maximal baseline production rate in the tagatose experiment, this would only explain 0.13 mmol of the 0.92 mmol increase in the uric acid pool calculated from the increase in serum concentration even if we assume that renal excretion is totally abolished during the initial 50-minute postload period. On the other hand, an impaired renal excretion may be an important factor in prolonging the hyperuricemic response.

The lower fractional extraction rate of uric acid with D-tagatose is in contrast to the fact that renal clearance of uric acid is normally increased if the blood level of uric acid is elevated experimentally by other means (uric acid infusion or intake of purified RNA) as indicated by a curvilinear relationship between the serum level and excretion rate of uric acid.[24] D-fructose was used as reference in the present study, and an increased renal fractional extraction of uric acid after infusion of D-fructose has, in fact, been found in a previous study.[25] However, in that study, fructose was infused very rapidly causing hyperuricemia, which in turn, may have resulted in the greater fractional extraction of uric acid. No hyperuricemic effect of the D-fructose was seen in the present study, and the D-fructose dose was probably not sufficient to increase fractional extraction of uric acid and hence explain the difference between the 2 sugars. The apparent slightly impaired renal clearance of uric acid after D-tagatose may rather be attributable to a reduced urine flow. A positive relationship between diuresis and excretion of uric acid has been shown in humans[26] and increased serum uric acid levels have, indeed, been found in diarrhea dehydrated patients.[27] This may be associated with a reduced extracellular volume causing an increased tubular reabsorption of uric acid.[28] Although the transient hemoconcentration of about 4% after D-tagatose in the present study, as

calculated from changes in serum albumin concentrations, may seem trivial compared with the more severe dehydration caused by prolonged diarrhea, a (minor) osmotic effect of D-tagatose cannot be excluded.

Although the hyperuricemic effect of D-fructose apparently is more modest than that of D-tagatose,[12] a slightly increased serum uric acid concentration after acute oral administration of D-fructose has previously been reported also in healthy subjects.[12,29,30] The lack of a significant serum uric acid response to fructose in the present study may be explained by the low dose. In another study, a hyperuricemic effect of oral D-fructose was detected with 50 g, but not with 25 g.[30]

In conclusion, a 30-g oral D-tagatose load resulted in a significant intracellular accumulation of D-tagatose-1-phosphate on the order of 1 mmol/L in the human liver within 30 minutes. A similar accumulation of D-fructose-1-phosphate was not seen after the same amount of D-fructose. The metabolic changes in the liver caused by the D-tagatose disappeared in about 2 hours. There was a small decrease of liver ATP, which under the conditions of the present study was 12%, corresponding to about 0.30 mmol/L. Also, a rapid increase in serum uric acid concentration was observed after D-tagatose, whereas no such effect was found after D-fructose. The maximal decline in hepatic ATP after D-tagatose measured by ^{31}PMRS corresponded to a production of about 0.45 mmol uric acid and could, *per se*, only account for about 50% of the observed increase in plasma uric acid concentration, which occurred within the first 50 minutes after the load.

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