Changes of Liver Metabolite Concentrations in Adults with Disorders of Fructose Metabolism after Intravenous Fructose by ^{31}P Magnetic Resonance Spectroscopy¹

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ABSTRACT

A novel ^{31}P magnetic resonance spectroscopy procedure allows the estimation of absolute concentrations of certain phosphorus-containing compounds in liver. We have validated this approach by measuring ATP, phosphomonesters, and inorganic phosphate (P_i) during fasting and after an i.v. fructose bolus in healthy adults and in three adults with disorders of fructose metabolism and by comparing results with known metabolite concentrations measured chemically. During fasting, the ATP concentration averaged 2.7 ± 0.3 (SD, $n = 9$) mmol/L, which, after due correction for other nucleoside triphosphates, was 2.1 mmol/L and corresponded well with known concentrations. Fructose-1-phosphate (F-1-P) could not be measured during fasting; its concentration after fructose was calculated from the difference of the phosphomonoester signals before (2.9 ± 0.2 mmol/L) and after fructose. P_i was 1.4 ± 0.3 mmol/L and represented the one fourth of P_i visible in magnetic resonance spectra. In the three healthy controls after fructose (200 mg/kg, 20% solution, 2.5 min), the fructokinase-mediated increase of F-1-P was rapid, reaching 4.9 mmol/L within 3 min, whereas the uncorrected ATP decreased from 2.7 to 1.8 mmol/L and the

P_i from 1.4 to 0.3 mmol/L. The subsequent decrease of F-1-P, mediated by fructaldolase, was accompanied by an overshooting rise of P_i to 2.7 mmol/L. In the patient with essential fructosuria, the concentrations of F-1-P, ATP, and P_i remained unchanged, confirming that fructokinase was indeed inactive. In the patient with hereditary fructose intolerance, initial metabolic changes were the same as in the controls, but baseline concentrations were not yet reestablished after 7 h, indicating weak fructaldolase activity. In the patient with fructose-1,6-diphosphatase deficiency, initial metabolic changes were the same as in the controls, but normalization was slightly delayed. (*Pediatr Res* 36: 436–440, 1994)

Abbreviations

F-1-P, fructose-1-phosphate
IMP, inosine monophosphate
 P_i , inorganic phosphate
PME, phosphomonoester
PDE, phosphodiester
MRS, magnetic resonance spectroscopy

Traditional investigation of fructose metabolism in human liver is based on the observation of blood parameters in response to fructose infusion or ingestion and on direct and invasive animal studies not feasible in humans. This has changed with the advent of ^{31}P MRS, which renders the direct observation of phosphorus-containing metabolites possible (1–6). We applied this technique to complement present knowledge of normal and disordered fruc-

tose metabolism and examined the metabolic response to fructose in healthy adults and in adult patients with essential fructosuria, hereditary fructose intolerance, and fructose-1,6-diphosphatase deficiency, *i.e.* the three well-known hereditary disorders of fructose metabolism (7). Such studies have not previously been done on essential fructosuria and in fructose-1,6-diphosphatase deficiency. Instead of assessing relative metabolite concentrations expressed by ratios of peak areas (1–6), our efforts have centered on the measuring of absolute concentrations expressed in mmol/L tissue (8).

METHODS

Subjects. All subjects were adults who gave informed consent. They had fasted overnight. Nine healthy volun-

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teers were recruited for the measuring of liver metabolites in the fasting state. Three healthy controls (female, 24 y, 59 kg; male, 26 y, 67 kg; male, 35 y, 74 kg) and one proband each with essential fructosuria (R.K., male, 35 y, 87 kg), hereditary fructose intolerance (V.L., female, 42 y, 55 kg), and fructose-1,6-diphosphatase deficiency (T.M., male, 19 y, 99 kg; originally described in ref. 9) participated in the fructose loading study.

MRS. Two kinds of ³¹P MRS examination were done, one optimized for the determination of absolute metabolite concentrations in the liver of nine fasting healthy volunteers, the other optimized for achieving a high time resolution of metabolite fluctuations in three controls and three patients after a fructose bolus. The average absolute fasting concentrations determined for the nine healthy controls (Table 1) were used as fasting concentrations for the three healthy probands and the three patients given a fructose bolus. All spectra were acquired on a Philips Gyroscan S15 whole-body imager (Philips Medical Systems, Best, The Netherlands) with 1.5-Tesla field strength. For all measurements, a circular plane surface coil 14 cm in diameter was placed under the liver area of the subject in the prone position, and its correct position was verified by magnetic resonance imaging.

For the measurement of the absolute concentrations of the MRS-visible metabolites in liver of the nine fasting healthy volunteers, fully relaxed ³¹P spectra were acquired (repetition time = 10 s, 128 signal averages, adiabatic inversion, and excitation pulses) with volume selection by the image-selected *in vivo* spectroscopy localization technique (10) (selected volume = 120 cm³; 4 cm anteroposterior, 5 cm left-right, 6 cm caudocranial). Absolute metabolite concentrations were determined using new phantom-based calibration procedures that had been evaluated earlier (8). For spectrum analysis, a fully automatic procedure was used for iterative data fitting in the time domain (11).

For the study of metabolite changes in the three controls and the three patients, three to five ³¹P magnetic resonance spectra were acquired in 10-min intervals before the fructose load. Proband was then removed from the magnet, left in the prone position, and given a bolus of 200 mg of fructose (20% wt/vol in water) per kg body weight i.v. within 2.5 min (7, 12). Subsequent time series of spectra were acquired in 5-min intervals for approxi-

mately 1 h and then at longer intervals for up to 3.5 h in all probands and for 7 h in the patient with hereditary fructose intolerance. Venous blood was drawn before fructose and at intervals of approximately 15 min after the bolus for 1 to 2 h for measurements of fructose, glucose, phosphorus, uric acid, magnesium, and potassium (12). For the localization of the spectra, a simple surface-coil technique was applied with square excitation pulses. Their duration (approximately 0.2 ms) was optimized to achieve a flip angle of 90° in the liver and 180° in the thoracic and abdominal muscles to obtain maximum sensitivity for liver and to suppress signal from muscle. For the acquisition of spectra (Fig. 1), 128 measurements were done for each spectrum with a repetition time of 2 s. Partial saturation occurred owing to the relatively short repetition time; yet, assuming a constant relaxation time for each metabolite and comparing each metabolite individually in the time series, saturation did not affect the results. The acquisition time of a spectrum and thus the temporal resolution of the time series of spectra was approximately 5 min. The time indicated for each spectrum (Figs. 1 and 2) is the median of the spectrum acquisition span. For spectrum analysis, the same procedure as above was applied.

Both kinds of spectra were slightly contaminated by signal contributions from muscle, as judged from the phosphocreatine signal. Phosphorus metabolite concen-

Figure 1. ³¹P magnetic resonance spectra of liver metabolites before (–) and after an i.v. bolus of fructose (200 mg/kg in 2.5 min) in a healthy adult (C.G.). The increase in PME is attributed to that in F-1-P.

Table 1. Uncorrected concentrations of phosphorus metabolites (mmol/L) and pH in fasting healthy controls

	Liver (n = 9)*		Calf muscle† (mean ± SD)
	Mean ± SD	Range	
PME	2.9 ± 0.2	2.5–3.4	1.9 ± 0.2
P _i	1.4 ± 0.3	0.9–1.8	2.9 ± 0.2
PDE	9.2 ± 0.6	8.0–10.9	3.8 ± 0.3
Phosphocreatine	null		21.9 ± 1.2
ATP	2.7 ± 0.3	2.2–3.3	5.7 ± 0.3
pH	7.05 ± 0.03	7.00–7.11	7.04 ± 0.03

* Net values (contamination by muscle subtracted).

† Taken from Buchli and Boesiger (8).

Figure 2. Liver metabolite concentrations (mmol/L) by ^{31}P MRS before (—) and after an i.v. bolus of fructose (200 mg/kg in 2.5 min) in three healthy controls (mean) and in one adult proband each with essential fructosuria, hereditary fructose intolerance, and fructose-1,6-diphosphatase deficiency.

trations were measured in the calf muscles of healthy volunteers and averaged (Table 1), and results were used for the estimation of the average contamination of the liver signals by thoracic and abdominal muscles (approximately 3% for PME and for PDE, 13% for P_i and for ATP). Concentrations of metabolites in liver were corrected accordingly. The contamination by fat was cursorily determined, amounted to approximately one tenth that of muscle, and was negligible.

F-1-P is known to resonate in the frequency range of PME; therefore, concentration changes of F-1-P were determined from intensity changes of the PME resonance line. Because IMP also resonates in the same frequency range and its concentration, measured chemically, was 0.12–0.30 $\mu\text{mol/g}$ in human liver during fasting [that of ATP was 2.03–2.74 $\mu\text{mol/g}$ (13)], IMP contributed 4 to 10% to the PME signal. Theoretical calculation indicated that, after fructose, the increase of IMP through nucleotide breakdown was not greater than one half of ATP consumed, *i.e.* ≤ 0.5 mmol/L or approximately one tenth of the increase of PME, in all probands except the fructosuric subject (see Results). The quantitation of ATP was from the β -resonance line; it is understood that the resulting measure comprises not only ATP (although ATP is the main fraction) but also other nucleoside triphosphates making up approximately one fourth of the total (13).

^{31}P MRS-derived metabolite concentrations are given in mmol/L tissue throughout.

RESULTS

Absolute metabolite concentrations in fasting healthy controls. Nine healthy controls were examined after an over-

night fast for concentrations of phosphorylated compounds in liver (Table 1). The concentration of phosphorylated compounds of fat tissue was assumed to be minimal (14), and a potential signal contamination was so small that it could be disregarded.

The ATP concentration (Table 1) was only slightly greater than those reported after chemical analysis for humans (13) and rats (15). Because the ATP signal is contaminated by the other three nucleoside triphosphates making up one fourth of the total, the net ATP concentration averaged 2.1 mmol/L and corresponded well with the published chemically derived concentrations, *i.e.* 2.03–2.74 $\mu\text{mol/g}$ human liver (13) and 2.2 $\mu\text{mol/g}$ rat liver (15).

The reported concentrations of P_i , measured in perfused rat liver *in vivo* and in liver extracts by ^{31}P MRS, differ markedly, the latter being 4 times higher than the former (16). Although other explanations are possible, the MRS-“invisible” P_i may be compartmented, *e.g.* to mitochondria, or tightly bound (16). Thus, the *in vivo* concentration determined in our probands’ livers may similarly have amounted to only one fourth of the total P_i present. Indeed, P_i concentrations estimated here (Table 1), corrected accordingly, match those measured chemically by Bode *et al.* (17): 5.13 ± 1.33 $\mu\text{mol/g}$ liver ($n = 6$).

It has been shown by enzymatic measurements that fasting levels of F-1-P in human liver were approximately 0.2 mmol/kg (17), *i.e.* minimal and insignificant when compared with our PME concentration of 3 mmol/L. Thus, in our experimental setting, F-1-P could not be measured in the fasting proband.

Effects of i.v. fructose in healthy controls. Although in the fasting liver absolute ATP and P_i concentrations

could be determined by using corrections as indicated, this approach could not be validated for rapidly changing concentrations after the fructose bolus. The following measurements are therefore given uncorrected.

In the three healthy controls, within 3 min after the fructose bolus, the PME concentration increased from a mean of 2.9 mmol/L liver to 7.8 mmol/L (range: 6.7–8.5 mmol/L), whereas uncorrected ATP fell from 2.7 to 1.8 mmol/L (range: 1.7–2.0 mmol/L), P_i fell from 1.4 to 0.3 mmol/L (range: 0.2–0.3 mmol/L), and pH fell by 0.15 units (range: 0.12–0.17 units). PDE concentrations remained unchanged (Fig. 2). Time-related concentration changes coincided in the three healthy subjects (Fig. 1). While the subjects were in the fasting state, F-1-P could not be read from the PME signals; the deviations from the fasting level of PME after fructose were attributed to F-1-P. This is reasonable (2), because it is known from human liver biopsies and from animal studies that, after fructose, the concentrations of other sugar phosphates and glycerol-3-phosphate are negligible compared with that of F-1-P (15, 17) and because the observed chemical shift of PME cancels a possible contribution to the signal by phosphorylcholine and phosphorylethanolamine (2). The net average peak F-1-P concentration was 4.9 mmol/L. The initial metabolite changes were as rapid as expected and documented the activity of fructokinase in liver; the individual with the greatest increase in PME experienced the deepest fall of ATP and P_i .

After 3 to 8 min, metabolite concentrations began to revert. Changes of P_i were most rapid, reaching fasting concentrations after 8 to 13 min and remaining above thereafter, in all three subjects during 70 min (Fig. 2). In two of them, one additional spectrum was acquired after 147 min in one and after 210 min in the other; it still showed P_i above fasting levels, +25 and +15%, respectively. PME fell to the fasting level at 20 min and remained there. ATP rose only slowly, and it remained below fasting levels during the entire experimental period, *i.e.* –20, –8, and –4% after 70, 147, and 210 min, respectively. Thus, F-1-P was metabolized promptly, but the reconstitution of ATP was still incomplete at the end of the observation period.

Changes of blood fructose, potassium, glucose, phosphorus, urate, and magnesium, measured during the first 30 to 60 min after the fructose bolus, were as expected (12). Specifically, fructose peaked at 2 to 3 mM. Subjects were encouraged to signal unusual sensations; as witnessed previously (12), all described epigastric discomfort beginning almost immediately after the bolus and lasting several minutes.

Effects of i.v. fructose in adults with disorders of fructose metabolism. In the three adults with essential fructosuria, hereditary fructose intolerance, and fructose-1,6-diphosphatase deficiency, baseline concentrations of PME, P_i , and ATP were assumed to be at the same levels as in the nine healthy volunteers (see Methods). Peak blood fructose was between 2 and 4 mM. Only the

proband with essential fructosuria felt no epigastric discomfort.

In the proband with essential fructosuria, liver metabolites remained unchanged for 2 h (Fig. 2). Blood fructose was 2.29 mM after 15 min, 1.36 mM after 34 min, 0.81 mM after 51 min, 0.49 mM after 73 min, and 0.24 mM after 120 min. In this fructosuric subject, fructose half-life in blood was 26 min (healthy controls: 12.5–17.5 min); fructose extraction from blood was thus markedly delayed compared with normal and compared with the adults with hereditary fructose intolerance (12) and fructose-1,6-diphosphatase deficiency (not shown). Blood metabolites, *i.e.* glucose, P_i , uric acid, magnesium, and potassium, remained at their pretest levels, as had been shown previously (12). Of the test dose of 17.4 g, the subject lost 2.1 g (12%) within 2 h in urine.

In the woman with hereditary fructose intolerance, changes of blood metabolites were as expected and diagnostic of this disorder (12). Liver metabolites changed from normal concentrations as rapidly and to the same degree as in the controls (Fig. 2). However, deviations from the fasting levels lasted far longer, 3 h for P_i and more than 7 h for PME and ATP.

In the subject with fructose-1,6-diphosphatase deficiency, blood metabolite changes were hardly distinguishable from those of the controls, as observed earlier (12). Concentrations of liver metabolites changed in the same sense as in the healthy controls, but the return of PME and P_i to their fasting levels was more protracted (Fig. 2).

Effects of i.v. fructose on metabolites of muscle and fat. Muscle and fat tissue were examined for the same ³¹P metabolites, *i.e.* PME, P_i , PDE, phosphocreatine, and ATP, because they constituted possible additional sites of fructose extraction and disposal. After the fructose load, no significant changes were observed in the healthy controls and in the individual with essential fructosuria.

DISCUSSION

Fructose in blood is rapidly extracted by and metabolized in liver. Its uptake is by a carrier-mediated transport whose affinity constant is more than an order of magnitude higher than the K_m of fructokinase. This and the high V_{max} of fructokinase are major determinants of fructose metabolism, and the rate of fructose entry and thus of phosphorylation is dependent on blood fructose concentration (7). We have shown here and earlier (12) that with an i.v. fructose bolus of 200 mg/kg blood concentrations of 2 to 3 mM are reached, which allow rapid utilization.

In the healthy controls, liver metabolites changed as had been inferred from earlier studies of blood chemistry (12) and was known from animal studies and from ³¹P MRS in humans (1, 2, 7). Nevertheless, the ³¹P MRS approach chosen here allowed for the quantitation of liver metabolites over 2 or more h. F-1-P accumulated quickly and was rapidly metabolized, and the PME frac-

tion fell slightly below the fasting level, perhaps because of a paucity of glucose esters. ATP, a key compound of cell energy metabolism, fell by one third. The decrease was expected and is explained by the phosphorylation of fructose and the rapid breakdown of adenine nucleosides (7). After the initial decrease, the P_i concentration rapidly reversed and remained clearly above its fasting level for as long as 3½ h. This rise of P_i over fasting levels had been observed earlier in humans (1, 3–6) and in isolated rat hepatocytes (18). It was interpreted as an effect of F-1-P catabolism (4), although it exceeded the latter and thus may also signal influx of P_i into the hepatic cytosol from blood, mitochondria, or both. The low ATP level is yet another sign of fructose toxicity for healthy subjects beyond lactic acidemia and hyperuricemia (7).

Our observations in the adult with essential fructosuria bring to light the key role of fructokinase in liver for normal fructose metabolism. Although he excreted only 12% of the test dose, no changes of P_i and phosphorylated metabolites were noted in liver. It is assumed that the nine tenths of a dose of fructose retained by fructosuric subjects are metabolized via fructose-6-phosphate in adipose tissue and skeletal muscle (7). However, in this proband, ^{31}P MRS of calf muscle did not evidence any changes after fructose, but, given the largeness of total muscle mass, concentration changes may have been below the detection limit. The increase of fructose-3-phosphate in this proband's erythrocytes after an oral load in no way made up for the missing fructose (19). Therefore, it still remains obscure how fructosurics dispose of the nine tenths of a fructose bolus that is known to increase their respiratory quotient, although more slowly than in healthy subjects (20, 21).

It has long been known that abdominal pain occurs during rapid administration of fructose solutions (3, 12, 22). It is of special interest that this fructosuric subject felt no discomfort after the fructose bolus. Apparently, the normal functioning of fructokinase is a prerequisite for this sensation and intestinal or hepatic F-1-P, or a metabolite thereof, the cause.

In the woman with hereditary fructose intolerance, changes of PME, P_i , and ATP were the same as those seen in healthy controls, and they reached the same extremes at the same times. Yet, the effects lasted far longer and were still visible after 7 h. Thus, it was demonstrated that fructose is toxic for fructose-intolerant patients as it is for healthy subjects, yet to a higher degree. Conventional diagnostic fructose tolerance tests are recommended at the modest i.v. dose of 200 mg/kg (12), which was also used in this study. It is interesting to note that in a very early study of hereditary fructose intolerance (23), 15 to 30 min after 120 mg of fructose per kg i.v., F-1-P in biopsied liver was approximately 2 mmol/kg, i.e. somewhat less than one half the concentration measured in our patient who received almost twice this dose. Side effects such as pronounced discomfort,

marked hypoglycemia, and renal Fanconi syndrome are extremely rare (12). Considering the long-lasting derangements of key compounds of cell metabolism evidenced in this *in vivo* MRS study, one wonders why they are not more common.

Compared with the effects observed in the fructose-intolerant patient, those of the fructose-1,6-diphosphatase-deficient young adult were minor, but compared with those in the healthy subjects they lasted longer. Here, too, the elevation of P_i outlasted the experimental period, whereas ATP was nearly reconstituted after 2 h in this most distal of the three defects.

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