Antiketogenic Action of Fructose in Man

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SUMMARY

The effect of fructose infusion (10 gm. every five minutes as a bolus followed by 0.5 gm. per kilogram × hours) on arterial concentrations and hepatic balances of ketones was studied in four juvenile diabetics 24 hours after the withdrawal of insulin. Arterial and hepatic venous concentrations of β-hydroxybutyrate, acetoacetate, free fatty acids, fructose, and oxygen were measured. Hepatic blood flow was also determined.

At constant rates of splanchnic fructose extraction, an 82 per cent diminution of the arterial hepatic venous concentration difference of the ketones was observed but the arteriovenous difference of free fatty acids rose moderately. Since hepatic blood flow was only slightly increased (17 per cent) there was no doubt that total hepatic ketone body formation was reduced. The magnitude of this antiketogenic action became apparent from the continuous fall of the arterial ketone concentrations. Since splanchnic oxygen uptake rose 40 per cent, it is suggested that the antiketogenic effect of fructose was due not only to enhanced re-esterification but also to accelerated oxidation of free fatty acids. DIABETES 27:709-14, July, 1978.

In 1874, Külz suggested for the first time that diabetics were able to metabolize oral fructose better than other sugars.[1] Not until 25 years later was this suggestion supported by well controlled clinical investigations demonstrating that oral fructose was able to abate the acidosis and ketosis of diabetic patients.[2] More recently, these clinical observations have been confirmed when ketone body concentrations were found to be reduced after intravenous administration of fructose to diabetic subjects.[3] Experiments with mitochondria,[4] isolated cells,[5] and slices of the rat liver [6-9] and with the isolated perfused organ[10,11] provided evidence that this effect was at least due partly to reduction of hepatic ketone body formation. Although several studies on the hepatic utilization of fructose have been performed in man,[12-15] it has not yet become clear whether this hepatic antiketogenic action was also operative in man.

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METHODS

Subjects

Four diabetics, recruited from hospitalized patients, were informed about the aim and the risks of the study, and they gave their consent. They were clearly characterized as juvenile diabetics (table 1). Physical examination as well as laboratory tests excluded other diseases; liver function tests, in particular, were normal. Metabolism had been well controlled by injection of insulin s.c. twice daily and by a dietary regimen for two weeks before the test. Serum triglycerides and cholesterol values were also within the expected ranges. Before the test the patients had been fasting overnight (15 hours). They received no drugs and no premedication. The last insulin injection was given at 0700 the day before the test. The protocol for this study was reviewed and approved by the Investigation and Ethical Committee of the Sonderforschungsbereich 51 of the Deutsche Forschungsgemeinschaft according to the Code of Ethics of the World Medical Association.[21]

Catheterization, Infusion Procedure, and Blood Flow

All the studies were performed under sterile condi-

TABLE 1

CLINICAL DATA

PATIENT	SEX	AGE (years)	HEIGHT (cm)	WEIGHT (kg)	PERCENT OF IDEAL BODY WEIGHT* (%)	ONSET OF DIABETES (years of life)	INSULIN† (units/24h)	DIETARY REGIMEN‡ (Kcal/24h)
B.J.	M	45	178	67.3	97	20	40	2 800
K.H.	M	31	181	69.8	97	4	48	2 600
S.T.	F	33	175	66.4	99	19	36	2 200
S.K.	M	32	165	52.5	87	8	48	2 900

*From the Metropolitan Life Insurance Tables, 1959.
†Monocomponent bovine insulin (Depot).
‡45 per cent carbohydrates, 20 per cent protein, and 35 per cent fat.

tions and local anesthesia between 0830 and 1130 with the subject in a supine position. A woven Dacron Goodale-Lubin catheter (type 125 C, size 7 F, USA Catheter and Instrument Corporation, Glenforce, New York) was placed from an antecubital vein into the right hepatic vein under fluoroscopic control. Arterial blood was drawn through a Seldinger cannula (size PE 160, Kifa, Sweden) from the right femoral artery. Patency was maintained by infusion of heparin, the rate of which (0.1 U. per kilogram × minutes) guaranteed no significant effect on lipoprotein lipase activity.[16] Arterial and hepatic venous blood samples were collected simultaneously throughout a 30-minute control period at 10-minute intervals. Fructose solution was infused into an antecubital vein at a rate of 10 gm. per five minutes and then of 0.5 gm. per kilogram per hour. Additional blood samples were obtained at 10-minute intervals for 50 minutes. Total blood loss was less than 250 ml.

Since conventional dye clearance as a technique for the measurement of hepatic blood flow (HBF) could not be applied without risk (for a review see reference 17), and hepatic dye excretion was supposed to be impaired when hepatic metabolism was altered by fructose infusion,[13] a gas exchange technique was employed which had been used before successfully [18-21] and could be supposed to remain valid during fructose infusion.[22] As a tracer, ^{133}xenon was applied by inhalation for six minutes in a closed circuit system containing an O_2:^{133}xenon mixture (500 μCi. ^{133}xenon per liter O_2). Then, with the help of a valve, the volunteer inhaled room air, and the exhaled ^{133}xenon passed through a hose into the open air. CO_2 was trapped by an absorber. During the following 20 minutes, the washout of ^{133}xenon from the liver was registered by a sodium iodide crystal (1¾ × 2 inches). This washout was analyzed according to the rules for the measurement of blood flow with radioactive labeled gases developed by Kety[22] and by Morales and Smith,[23] handling recirculation either by analogue computer[19] or by graphic analysis.[18,20,21] The resulting monoexponential washout process exhibited a constant K that could be considered to be directly proportional to the HBF* and indirectly to the hepatic partition coefficient λ for ^{133}xenon (HBF = K × λ), which had earlier been found to be 0.74.[24] Precision of the method was proved by 20 serial determinations revealing a standard deviation of 3.5 per cent.

During the basal period, HBF was estimated between 0 and 20 minutes and, during the infusion of fructose, between 10 and 30 minutes and 40 and 60 minutes (see table 3).

Analytic Procedures

Glucose (4.8 ± 0.01 mmol per liter),† fructose (2.41 ± 0.01 mmol per liter), β-HOB (0.17 ± 0.002 mmol per liter), and ACAC (0.10 ± 0.002 mmol per liter) were determined enzymatically,[25-28] the FFA (0.46 ± 0.006 mmol per liter) by a colorimetric method,[29] and oxygen (O_2) (7.8 ± 0.05 mmol per liter) oxymetrically.[30] From each blood sample, determinations of the individual substrates were performed at least in duplicate. Hepatic uptake of substrates was generally estimated from the arterial hepatic venous concentration differences of the substrates that had been registered during the measurement of HBF. Before calculating uptake of FFA, plasma concentrations of FFA were corrected for total blood using the corresponding hematocrit. Wilcoxon's rank test was applied to the results.[31] Two means were considered to be significantly different when the mean difference was lying within the 95 per cent confidence limits. All the means were given with the standard error of the mean (S.E.M.).

Materials

Fructose was used as a sterile solution containing 10 gm. of D-fructose in 100 ml. distilled water (Department of Pharmacy, Schwabing City Hospital, Munich, FRG). Radioactive ^{133}xenon (Radiochemical Centre, Amersham, England) was purchased as a sterile solution in 0.9 per cent sodium chloride (10 mCi. per milliliter) with a specific activity of 44.8 Ci. per mmol at a given reference date. Heparin was used as a sterile solution of sodium heparinate containing 2,500 U.S.P. units per milliliter (Hoffmann-La Roche, Grenzach, FRG). Insulin had been used as a sterile solution of chromatographically purified and

*Abbreviations used in this article are as follows: β-hydroxybutyrate (β-HOB), acetoacetate (ACAC), free fatty acids (FFA), hepatic blood flow (HBF), citric acid cycle (CAC), and adenosinetriphosphate (ATP).

†The figures in parentheses represent means ± S.E.M. of 10 repeated measurements of the individual substrate.

crystallized bovine insulin in bis (4-aminochinaldin-6) N,N′-urea-HCl, 1 ml. containing 40 I.U. (Hoechst-AG, Frankfurt, FRG).

RESULTS

Arterial Concentrations of Metabolites

Arterial concentrations of glucose (7.22 ± 0.76 mmol per liter), FFA (0.70 ± 0.06 mmol per liter), and β-HOB (0.33 ± 0.08 mmol per liter) were found to be lower than those seen in severe diabetic ketoacidosis[32] but higher than those of healthy volunteers under identical circumstances.[21,33] Arterial oxygen (7.90 ± 0.81 mmol per liter) and acetoacetate concentrations (0.11 ± 0.03 mmol per liter) were not altered.

The infusion schedule (10 gm. of fructose within five minutes as a bolus followed by 0.5 gm. per kilogram × hours) resulted in a steady state of the arterial fructose concentrations (10 minutes: 2.37 ± 0.22; 30 minutes: 2.34 ± 0.19; 60 minutes: 2.31 ± 0.17 mmol per liter). These concentrations are in good accord with those seen by others employing similar schedules.[13-15] Corresponding to the enhanced hepatic glucose formation from fructose,[14,15] the arterial glucose concentration rose continuously (10 minutes: 8.06 ± 0.63; 30 minutes: 8.45 ± 0.70; 60 minutes: 9.11 ± 0.67 mmol per liter). While arterial oxygen concentrations did not change (10 minutes: 7.85 ± 0.43; 30 minutes: 7.76 ± 1.38; 60 minutes: 7.72 ± 0.71 mmol per liter) and those of FFA rose almost continuously (figure 1), ketones were found to decline continuously (figure 1).

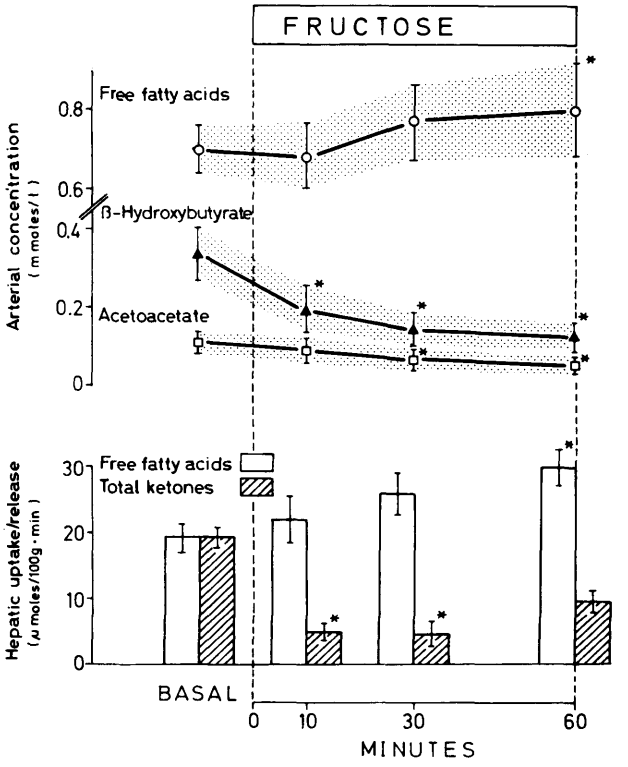

FIG. 1. *Arterial concentrations and hepatic balances of free fatty acids and ketones during the infusion of fructose.* **The values are indicated as means ± S.E.M. of four juvenile diabetics. Production of ketones was calculated on the values obtained for β-HOB and ACAC. The asterisk indicates a significant difference from basal.**

TABLE 2
ARTERIAL HEPATIC VENOUS CONCENTRATION DIFFERENCES OF OXYGEN AND METABOLITES*

	BASAL §	FRUCTOSE INFUSION †		
		10 MIN.	30 MIN.	60 MIN.
FRUCTOSE	---	1.19 ± 0.16	1.15 ± 0.14	0.99 ± 0.15
OXYGEN	2.59 ± 0.33	3.48 ± 0.53 ‡	3.13 ± 0.40 ‡	3.33 ± 0.55 ‡
FREE FATTY ACIDS	0.209 ± 0.023	0.222 ± 0.058	0.284 ± 0.086	0.295 ± 0.061 ‡
β-HYDROXYBUTYRATE	-0.186 ± 0.024	-0.014 ± 0.008 ‡	-0.016 ± 0.002 ‡	0.050 ± 0.012 ‡
ACETOACETATE	-0.088 ± 0.006	-0.034 ± 0.014 ‡	-0.031 ± 0.012 ‡	0.051 ± 0.011 ‡

*Mmoles/liter.
‡Significant as compared to basal.
†10 gm./5 min.; 0.5 gm. per kilogram × hours.
§Four samples obtained at 10 min. intervals, averaged for each subject.

Hepatic Venous Concentrations of Metabolites and Hepatic Blood Flow (tables 2 and 3)

Corresponding to the slightly elevated arterial FFA concentrations of the diabetics, their arterial hepatic venous concentration differences were also found to be slightly increased above that observed in healthy volunteers previously.[21,33,34] As could be expected from the short interval of insulin restriction,[32] the baseline values for the arterial hepatic venous concentration differences of β-HOB were only slightly enlarged while those of acetoacetate were not different from those of healthy subjects.[21,33,34] This was also true for the arterial hepatic venous oxygen difference. The HBF was in good accord with those from earlier studies, in which other indirect techniques for its estimation were employed.[35,36] Hepatic blood flow of the diabetics (table 3) was not significantly different from that of healthy subjects.[21,33] This was in good agreement with the results obtained by others[27] although some contradictory results have been reported.[32]

During fructose infusion, the basal value of HBF was scarcely altered as had been demonstrated earlier in healthy volunteers.[12-14] Corresponding to the steady state of the arterial fructose concentration, a constant fraction of fructose was extracted by the splanchnic bed during the whole test period. In spite

of the slightly faster perfusion, the hepatic venous oxygen concentration declined rapidly, leading to a distinct rise of the arterial hepatic venous difference. The arterial hepatic venous concentration difference of β-HOB was reduced to one tenth of its basal value and that of ACAC was also diminished within 30 minutes of fructose infusion (table 2).

Hepatic Uptake of Metabolites (figure 1)

From arterial hepatic venous concentration differences of substrates (table 2) and the corresponding blood flow data (table 3), hepatic rates of uptake were calculated. As compared with the values obtained in normal persons under identical conditions,[21] acceleration of FFA uptake and of ketone production was observed in the diabetics examined (figure 1). While production of total ketones was immediately reduced on fructose infusion, hepatic uptake of FFA was maintained or even rose at the end of the test period (figure 1). Hepatic oxygen consumption, starting from normal values during baseline conditions (201.0 ± 14.5 μmol/100 gm. × minutes), was distinctly increased during fructose infusion (10 minutes: 315.8 ± 18.9 μmol; 60 minutes: 329.8 ± 34.3 μmol/100 gm. × minutes).

DISCUSSION

The aim of this study was to explore whether the well known ketone-lowering effect of fructose was due to a reduction of the rate of ketogenesis, as could be expected from earlier studies in vitro.[5-11]

Lipolysis and ketogenesis were both slightly accelerated and arterial FFA and β-HOB concentrations were elevated (figure 1) compared with normal volunteers,[21,32] as could be expected 24 hours after the withdrawal of insulin.[32]

Since a comparable fructose infusion had previously been found to be accompanied by a rise of the hepatic venous insulin concentration,[15] these experiments were performed in juvenile diabetics 24 hours after the withdrawal of insulin to eliminate this complicating factor. Fructose was applied according to the permitted dose range for parenteral nutrition.[38] As found in earlier studies in man,[12,14,15] arterial fructose reached concentrations (table 1) that had been found to depress ketone concentrations.[3] As in the isolated perfused organ,[39] about 40 to 50 per cent of the applied fructose was continuously extracted by the liver throughout the test period suggesting a steady hepatic fructose metabolism (table 2). Its antiketogenic action was observed within 10 minutes of infusion and influenced β-HOB more markedly than ACAC (table 2), as was observed earlier.[5-11] The arterial hepatic venous concentration difference of β-HOB was reduced by 90 per cent and that of ACAC by half. The extent of the antiketogenic action of fructose was apparent from the finding that the arterial concentrations of β-HOB and ACAC fell continuously during fructose infusion (table 1), while ketone body concentrations are known to rise during early fasting.[33,40] From experiments in vitro the antiketogenic action of fructose was attributed to an accumulation of glycerol-1-phosphate in the liver which promotes the synthesis of triglycerides and thereby decreases the amount of FFA available for oxidation to ketone bodies.[5,9-11,39,41] In addition, accumulation of glycolytic intermediates was supposed to suppress β-oxidation of FFA.[11] A participation of enhanced re-esterification in the antiketogenic effect presented here cannot be shown to occur by the technique employed. However, enhanced glycolytic activity of the human liver was previously demonstrated to occur during fructose infusion since hepatic lactate uptake was changed into lactate output.[15]

On the other hand, it has also been postulated from studies in vitro[4,5,11] that fructose lowers ketone body formation by speeding up oxidation of FFA via the CAC. This activation of respiration is accomplished by a drop in ATP and a concomitant increase in ADP, which occurs by the rapid phosphorylation of fructose[39,42,43] and, more specifically, in the mitochondrial compartment of the liver cell.[44] It has been observed previously that hepatic phosphorylation of fructose is accelerated four times faster than equimolar glucose in the normal and diabetic human liver.[15]

TABLE 3 HEPATIC BLOOD FLOW*

PATIENTS	BASAL§	FRUCTOSE INFUSION† 10-30 MIN.§	FRUCTOSE INFUSION† 40-60 MIN.§
B.J.	78	81	86
K.H.	71	90	109
S.T.	78	97	97
S.K.	86	96	103
MEAN ± SEM	78.3 ± 3.1	91.0 ± 3.7	98.8 ± 4.9‡

*Milliliters per 100 gm. × minutes.
†10 gm./5 min.; 0.5 gm per kilogram × hours.
‡Significant difference as compared to basal.
§Calculated from a 20-min. tracer washout (see METHODS).

Thus increased ATP turnover may also activate respiration in human liver, as indicated by the data obtained on hepatic oxygen consumption (see RESULTS). Consistent with this, it was found that fructose increases hepatic carbon dioxide production in vitro[5,11] and in vivo.[13] The increased hepatic blood flow observed during fructose loading may be mediated by the release of degradation products of ATP, which have been shown to modulate organ perfusion.[45]

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