An Experimental Renal Acidification Defect in Patients with Hereditary Fructose Intolerance

I. ITS RESEMBLANCE TO RENAL TUBULAR ACIDOSIS

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ABSTRACT In three unrelated patients with hereditary fructose intolerance (HFI), but in none of five normal subjects, the experimental administration of fructose invariably induced a reversible dysfunction of the renal tubule with biochemical and physiological characteristics of renal tubular acidosis. During a state of ammonium chloride-induced acidosis, (*a*) urinary pH was greater than six and the rate of excretion of net acid (titratable acid plus ammonium minus bicarbonate) was inappropriately low, (*b*) the glomerular filtration rate remained unchanged or decreased modestly, and (*c*) urinary excretion of titratable acid increased briskly with diuresis of infused phosphate, although urinary pH changed little. The tubular dysfunction, which also includes impaired tubular reabsorption of alpha amino nitrogen and phosphate, persisted throughout administration of fructose and disappeared afterward. The tubular dysfunction was not causally dependent on hypoglucosemia, ammonium chloride-induced acidosis or osmotic diuresis. Rather, it appeared causally related to the fructose-induced metabolic abnormality of patients with HFI. The causal enzymatic defect, the virtual absence of fructose-1-phosphate aldolase, occurs in the kidney as well as in the liver of patients with HFI.

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INTRODUCTION

So-called renal tubular acidosis (RTA) is a clinical disorder of renal acidification expressed biochemically as a characteristic syndrome which includes hyperchloremia, minimal or no azotemia, and alkaline, or minimally acid urine in the presence of metabolic acidosis (1). Certain physiologic characteristics of the acidification defect (2–6) permit the inference that the renal tubule is unable to maintain a normally steep lumen–peritubular H^+ gradient (2–4, 6–8). A causal mechanism, however, has not been defined. Among those suggested are disturbances in the intracellular metabolic processes of the renal tubules that make hydrogen ion available for exchange (8) or that generate the energy necessary for the postulated mechanism that actively pumps hydrogen ion against a high lumen-peritubular concentration gradient (7, 8). The reported evidence that such metabolic disturbances exist in patients with RTA is circumstantial at best. RTA has been reported in association with such metabolic disorders as "glycogenosis" (9), cystinosis (10), galactosemia (11), Wilson's disease (12), Lowe's syndrome (13) and hereditary fructose intolerance (HFI) (14), but the relationship between the underlying metabolic abnormality and the acidification defect is unclear. Only in galactosemia and HFI is the causal biochemical defect known (15, 16) and the resultant metabolic abnormality reversible and inducible experimentally (15, 17, 18).

In two children with galactosemia, Komrower, Schwarz, Holzel, and Golberg (11) reported that the biochemical characteristics of RTA disappeared after dietary restriction of galactose. Yet, subsequent experimental ingestion of galactose (as milk) for 10 days by these children did not induce a recurrence of hyperchloremic acidosis, nor did it prevent urinary pH from decreasing to levels below 5.5 after administration of ammonium chloride. In two infants with HFI, Levin, Oberholzer, Snodgrass, Stimmler, and Wilmers (18) described metabolic acidosis which presumably disappeared after dietary restriction of fructose. The acidosis in one infant was accompanied by hyperchloremia, but data on urinary acidification was reported in neither. In the one known patient with HFI and persisting renal tubular acidosis, dietary restriction of fructose had no demonstrated effect on the acidification defect (14).

In the present study fructose was administered intravenously to three adult patients with HFI but without persisting RTA. In each patient fructose induced a reversible defect of renal acidification with biochemical and physiologic characteristics of RTA.

METHODS

Subjects. Three unrelated adult patients with HFI were studied (Table I). Each patient had a history characteristic of HFI (17). In each case the diagnosis was established by the demonstration of marked decreases in true blood glucose and serum phosphorus levels within 45 min after intravenous administration of 0.25 g of fructose per kg as a 25% solution over a 5 min period. Serum carbon dioxide content and electrolyte concentrations in the three patients were within normal limits. The patients were maintained on a fructose-free diet in a metabolic ward during each study. Five normal subjects, two women and three men, aged 24–41 yr, served as a control group.

Procedures. 15 separate studies were carried out. In 13 of the 15, ammonium chloride, 0.08–0.1 g/kg, was administered orally at 7 a.m. as a 10% solution or as non-enteric-coated tablets. In an initial study on each patient (studies 1–3), ammonium chloride only was administered, and voided urine was collected under mineral oil at 2-hr intervals for 10 hr. In studies 4–8, fructose was infused intravenously over a 2- to 3-hr period beginning 6 hr after administration of ammonium chloride, first as a 25% solution given over 5 min in an amount calculated to provide 0.25 g/kg, and subsequently as a 10% solution infused at a constant rate calculated to deliver 0.25 g/kg per hr. Throughout the fructose infusion, and for approximately 1 hr before and after, voided urine from the male patient was collected under mineral oil at 30-min intervals. Over the same time course the women with HFI were comfortably supine, and urine was collected at 15-min intervals via an indwelling catheter emptying under a layer of mineral oil. In studies 5 and 6, hypoglucosemia was prevented by intravenous infusion of a 10% solution of glucose, beginning 10 min before the fructose infusion. The glucose solution was infused at a rate calculated to deliver approximately 0.10–0.12 g/kg per hr. In study 8, buffer phosphate was infused approximately 1 hr after the beginning of the fructose infusion.

In the two studies in which ammonium chloride was not administered (studies 9 and 10), fructose was infused as described, but in reduced amount (about one-quarter).

In one study each, on the five normal subjects, ammonium chloride and fructose were administered in the described sequence.

Inulin clearance was measured before and during infusion of fructose. In initial studies on the patients with HFI, infusion of inulin in doses that achieved blood inulin concentrations of 25–35 mg/100 ml resulted in reduced tubular absorption of phosphate and amino acids (see Table II, Results and Appendix). In subsequent studies the patients' blood inulin levels were maintained at approximately 15 mg/100 ml, and this effect was not observed.

Laboratory methods. The following laboratory determinations were carried out: blood fructose (19), phosphate (20), uric acid (21), inulin by a modification (22) of a diphenylamine technic (23), urinary ammonium (24), titratable acid (25), urinary alpha amino nitrogen (26), and plasma alpha amino nitrogen (27). Blood glucose was analyzed by the glucose oxidase method. Serum and urinary carbon dioxide content was determined with a Van Slyke apparatus (28). Serum and urinary sodium and potassium concentrations were measured with a Baird flame photometer with an internal lithium standard; chloride levels were determined with a Cotlove-Aminco automatic titrator. Arterial and urinary pH were each measured anaerobically at 38°C with a model 27 Radiometer pH meter. All biochemical analyses were done in duplicate; if the values did not agree, the analyses were repeated. Urinary bicarbonate concentration was calculated from urinary pH and carbon dioxide content by the Henderson-Hasselbalch equation, pK was taken as $6.33-0.5\ \sqrt{(Na^+) + (K^+) + (NH_4^+)}$ (29).

RESULTS

Studies of renal acidification with ammonium chloride challenge

Without fructose. In the initial study on each patient, urinary pH decreased to normal minima and the rates of excretion of titratable acid and ammonium increased to normal maxima (Table I).

TABLE I

Clinical and Physiologic Findings in Patients with Hereditary Fructose Intolerance

Patient, age and sex	Renal acidification*			GFR
	U_{pH} min	$U_{TA}V_{max}$	$U_{NH_4}V_{max}$	
yr		*mEq/min*		*ml/min*
Normal values‡	<5.3	>25.0	>39.0	
D.M. 41, F	4.89	54.7	77.7	138
E.A. 31, F	4.95	46.9	51.5	88
A.H. 42, M	4.84	30.4	50.0	133

Abbreviations: U_{pH} min = minimal urinary pH, $U_{TA}V_{max}$ = maximal rate of excretion of titratable acid, $U_{NH_4}V_{max}$ = maximal rate of excretion of ammonium, GFR = glomerular filtration rate measured as inulin clearance (average of at least three successive 20-min urine collection periods).

* Renal acidification response after administration of a single oral dose of 0.08–0.1 g of NH_4Cl/kg, procedure of Wrong and Davies (4).

‡ Established in a previous study (5).

With fructose. The effects of fructose on the renal acidification response to ammonium chloride in the patients with HFI and the normal subjects are compared in Fig. 1. The results of a representative study are shown in Fig. 2 and Table II.

In studies 4–8 on the patients with HFI, urinary pH increased from 5.2 or less to greater than 6.2 within 45 min of the beginning of the fructose infusion and remained elevated for as long as the infusion was continued. Within 1½–3 hr after the termination of the infusion, urinary pH had decreased to values of about 5 (Figs. 2 and 3). The rate of excretion of titratable acid, ammonium, and calculated net acid decreased as urinary pH increased and increased as urinary pH decreased. With diuresis of infused phosphate in one patient (Fig. 3), urinary excretion of titratable acid increased to levels greater than those obtained before fructose was infused, despite the continued elevation of urinary pH and essentially unchanging degree of acidosis. In the normal subjects a decrease in urinary pH and increase in excretion of net acid occurred and persisted despite administration of fructose.

Comparable blood fructose levels were achieved in the patients with HFI and the normal subjects (Fig. 4). In the patients who received fructose without glucose, blood concentrations of glucose invarably decreased, although not always to subnormal levels.

At the time of maximal rise in urinary pH and maximal reduction in the rate of urinary excretion of ammonium and titratable acid in the patients with HFI, the arterial pH was in the acidotic range; the serum carbon dioxide content was either unchanged or less than the reduced levels measured immediately before fructose was infused. The glomerular filtration rate, as measured by inulin clearance, did not change or decreased moderately after administration of fructose. In a study on patient D. M. (Table II), the urine flow varied only from 2.16 to 2.78 ml/min over the four periods preceding and the five periods following the institution of fructose. The urine flow was considerably more variable in the other studies in which fructose was administered. In all three patients with HFI who were receiving fructose, urinary pH was greater than 6 during

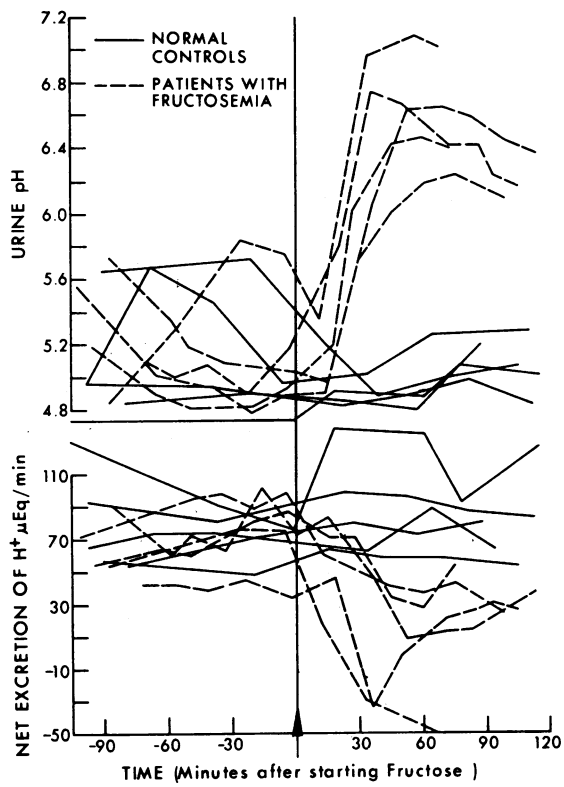

FIGURE 1 Effect of intravenous infusion of fructose on the renal acidification response to ammonium chloride–induced acidosis in normal control subjects and patients with hereditary fructose intolerance. The amount of fructose administered to the normal subjects was approximately 1.25 times greater than the amount the patients received.

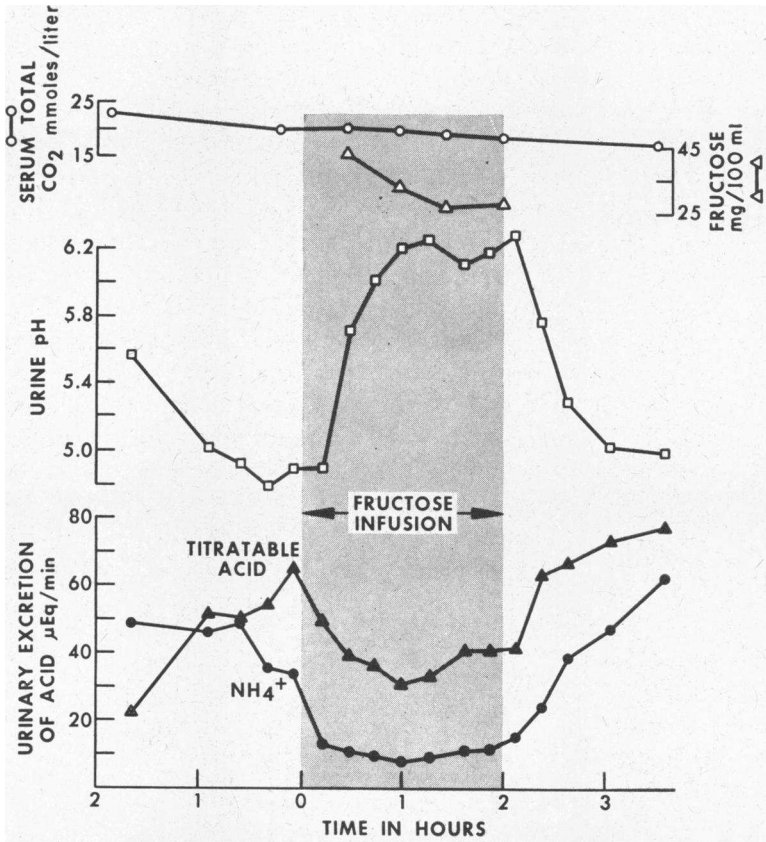

FIGURE 2 Effect of intravenous infusion of fructose on the renal acidification response to ammonium chloride–induced acidosis in a representative study on a patient with hereditary fructose intolerance (study 4).

urine flows of less than 4 ml/min. Conversely, urinary pH was less than 5 during urine flows of greater than 4 ml/min in the normal subjects during fructose infusion.

Studies of renal acidification without ammonium chloride challenge

During the administration of fructose to patient E. A., with and without prevention of hypoglucosemia by simultaneous infusion of glucose, urinary pH became greater than 7, the excretion of both titratable acid and ammonium decreased to less than 10 μEq/min, and the excretion of net acid became sharply and persistently negative despite the apparent occurrence of mild metabolic acidosis (Table III). Soon after discontinuance of the fructose infusion, and presumably because of the acidosis, the rate of excretion of net acid became sharply positive, increasing to a level greater than that obtaining before the administration of fructose, and the urinary pH decreased to values just greater than 5.

Effect of fructose on renal functions other than that of acidification

In both patients and normal subjects (Table IV) the clearance of phosphorus (Cp) increased during the administration of fructose and in the patients during administration of inulin alone. Compared with the Cp values obtained during the pre-inulin control period, those obtained during administration of fructose were increased by a similar magnitude in the patients and the control group. In the patients with HFI, however, the increase in Cp was associated with a mean decrease in the concentration of plasma phosphorus, whereas in the normal subjects the mean concentration of plasma phosphorus did not decrease. Tubular reabsorption of phosphorus, calculated as percentage of phosphate filtered, decreased to a greater extent in the patients with HFI than in the normal subjects, although the concentration of plasma phosphorus was less in the patients. These findings indicate that fructose induced a greater degree of impairment of tubular reabsorption of

TABLE II

Effect of Fructose on the Renal Acidification Response to Ammonium Chloride-Induced Acidosis in Representative Patient with Hereditary Fructose Intolerance (D. M., Study 4)

	Urine										Serum	
Time	Flow	pH	Titratable acid	NH_4^+	Net H^+	Na^+	K^+	P^-	C_{in}	Arterial pH	CO_2	P
min	*ml/min*				*μEq/min*			*μmoles/min*	*ml/min*		*mmoles/liter*	
		60 ml of 10% NH_4Cl administered orally at 0 min										
0–120	1.76	5.45	15.0	42.3	57.3	99	35	6.2		7.4	30.0	1.48
120–188	1.79	5.06	11.9	37.7	48.6	74	38	2.0				
188–261	5.20	5.27	18.2	61.3	79.5	150	66	4.7				
261–330	6.24	5.56	21.8	48.6	70.4	180	65	13.1			23.0	1.90
330		Priming dose: 33.5 ml of 10% inulin over 5-min period i.v.										
		Constant infusion I: 10% inulin at 0.247 ml/min i.v.										
330–376	2.78	5.00	51.0	45.6	96.6	246	115	43.5				
376–395	2.76	4.91	49.8	48.0	97.8	223	104	46.8	142			
395–411	2.31	4.78	54.3	35.1	89.1	220	161	51.4	117			
411–426	2.44	4.88	65.3	33.6	98.9	234	201	59.5	108		20.0	1.81
426		Priming dose: 67 ml of 25% fructose over 5-min period i.v.										
		Constant infusion II: 10% fructose at 1.66 ml/min i.v.										
426–444	2.34	4.89	48.8		61.5	222	187	52.9	117			
444–459	2.50	5.70	39.4	10.7	50.1	201	175	37.1	97		20.5	1.23
459–474	2.46	6.01	35.8	9.1	44.9	213	215	43.5	139			
474–490	2.16	6.18	29.5	7.3	36.8	216	192	42.6	119		20.0	1.26
490–506	2.41	6.24	33.4	9.1	42.6	243	214	47.4	137			
506–528	1.28	6.10	19.1	5.1	24.2	141	121	25.1	77	7.3	19.0	1.16

phosphorus in the patient group than in the control group (30).

During administration of fructose, urinary excretion of alpha amino nitrogen increased markedly in the patients with HFI, the mean increase being 127 μg/min as compared with a mean increase of 17.4 in the control subjects (Table IV). The increased excretion probably reflects diminished renal tubular reabsorption of alpha amino nitrogen, since plasma alpha amino nitrogen changed minimally, if at all, in the one study in which measurements were made. The fructose-induced diminution in tubular reabsorption of alpha amino nitrogen in patients with HFI has been demonstrated previously (18).

In a single study on one patient with HFI, urinary excretion of uric acid quadrupled and uric acid clearance increased from 9.2 to 20.9 ml/min. No change in uric acid clearance was demonstrated in two studies on normal subjects.

In both the patients with HFI and the normal subjects, the administration of fructose had no consistent clear-cut effect on the rates of urinary excretion of Na^+ and Cl^-, already increased by ammonium chloride-induced acidosis (roughly to the same degree in both groups) (Fig. 5). In the patients, in contrast to the normal subjects, urinary excretion of potassium increased slightly ($0.5 > P > 0.10$) during administration of fructose. In one of the studies on patient E. A., in which fructose was initiated without preceding acidosis (study 9), urinary excretion of sodium increased strikingly during administration of fructose (Table III), and a sizable urinary excretion of HCO_3^- occurred. The increase in urinary excretion of chloride was considerably less than that in sodium excretion. These changes can be related to the apparent decrease in the serum concentration of sodium from 138 to 135 mEq/liter, the decrease in serum carbon dioxide from 25 to 21 mEq/liter, and the minimal change in concentration of serum chloride from 104 to 106 mEq/liter.

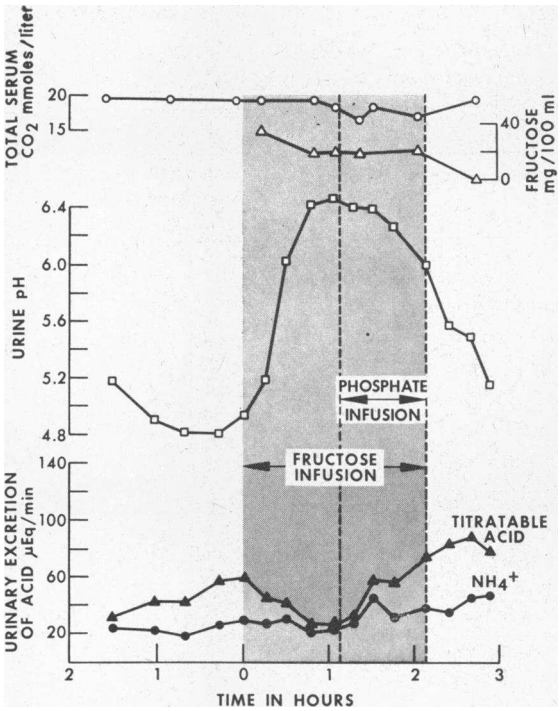

FIGURE 3 Effect of phosphate diuresis on urinary excretion of acid in a fructosemic patient with fructose-induced impairment of renal acidification (study 8). A solution containing 0.15 M Na_2HPO_4/NaH_2PO_4, pH 7.4, was infused intravenously at a rate of 0.75 mmole/min for the 1st 12 min and 0.287 mmole/min for the next 60 min.

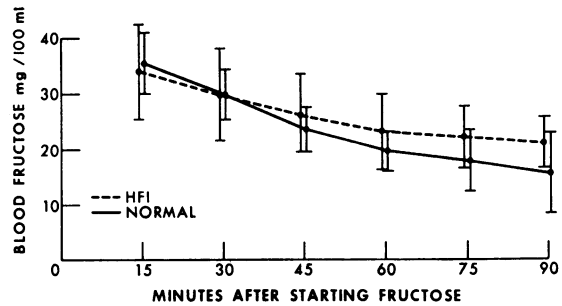

FIGURE 4 Mean blood fructose levels after fructose infusions in normal control subjects and patients with hereditary fructose intolerance challenged with ammonium chloride. Bars indicate 1 SD.

DISCUSSION

The results of the present study indicate that in patients with hereditary fructose intolerance, administration of fructose immediately, but reversibly, converts normal renal function into a state of tubular dysfunction with characteristics like those of renal tubular acidosis (1–6): (*a*) During a state of hyperchloremic acidosis (induced by ammonium chloride), urinary pH increased to values greater than 6 and urinary excretion of net acid (titratable acid and ammonium minus bicarbonate) decreased to rates inappropriate for the degree of acidosis. (*b*) The glomerular filtration rate was fairly well maintained during the state of tubular dysfunction. (*c*) With diuresis of infused buffer phosphate, the rate of excretion of titratable acid increased briskly, although urinary pH remained elevated. The fructose-induced tubular dysfunction also included impaired tubular reabsorption of alpha amino nitrogen and phosphorus. The immediacy with which normal tubular function was disrupted after institution of fruc-

TABLE III

Effect of Fructose Infusion on the Serum Concentration and Urinary Excretion of Electrolytes in a Nonacidotic Patient with Hereditary Fructose Intolerance (E. A., Study 9)*

	Serum				Urine					
Time	Na^+	K^+	Cl^-	Total CO_2	pH	Na^+	Cl^-	K^+	HCO_3^-	C_{cr}
min	*mEq/liter*					*μEq/min*				*ml/min*
−115					5.55	45	48	19		80
−70					6.10	82	75	25		79
−28	138	4.3	104	25.0	6.27	122	105	27		83
Fructose begun	139	4.2	105	25.0	5.91	105	100	39		84
+29	135	4.3	106	24.5	6.26	179	152	37		103
+58	136	4.1	106	23.0	6.92	272	177	37	75	71
+89	135	3.9	106	22.0	7.06	256	170	27	50	72
+117	136	3.9	105	21.5	7.01	355	198	37	76	96

* Fructose was administered at a reduced dosage schedule (see text).

TABLE IV

*Effect of Fructose Administration and Ammonium Chloride-Induced Acidosis on Various Renal Tubular Functions**

	Phosphorus											α-Amino nitrogen			
	Plasma concentration			Renal clearance			Tubular reabsorption‡		Tubular reabsorption§			Serum concentration		Urinary excretion	
Subjects	C_1	C_2	F	C_1	C_2	F	C_2	F	C_1	C_2	F	C_1	F	C_1	F
	mmoles/liter			*ml/min*			%		%			*mg/100 ml*		*μg/min*	
Hereditary fructose intolerance															
D.M.	1.70	1.81	1.23	5.50	32.80	28.6	69.6	70.5	95.8	76.8	67.7			67.2	241.5
	0.83	1.30	0.82	5.75	20.50	36.0	87.3	78.3	96.8	90.1	81.3			95.8	246.6
A.H.	0.94	1.03	0.73	8.88	9.27	19.7	93.3	76.9	94.1	94.3	78.7	4.0	4.2	72.1	128.0
E.A.C.	1.22	1.03	0.86	7.30	10.50	11.0	86.8	89.3	90.1	85.3	87.4			68.5	162.6
	1.33	1.38	1.08	17.90	26.50	25.2	64.9	50.8	82.3	51.6	58.1			77.6	238.3
Mean change															
C_1:C_2	+0.11				+9.1					−12.2					
C_2:F	−0.39				+4.2			−7.2		−5.0					
C_1:F	−0.28				+13.3					−17.2					+127.2
Normal controls															
A.B.	1.16	1.09	1.19	6.00	13.00	17.1	86.5	83.2	94.5	87.3	85.5	4.7	4.7	154.0	117.9
R.C.M.	1.51		1.29	12.80		23.3			89.7		77.5	4.5	5.1	176.2	174.5
A.J.	0.94		1.28	6.30		14.8			93.9		82.8			75.4	96.6
A.W.	1.20		1.06	16.10		25.8			84.5		77.2	3.7	3.9	84.0	167.0
R.L.	0.97		1.18	18.30		41.0			80.4		57.8	4.7	4.5	111.0	131.5
Mean change															
C_1:F	+0.04				+12.5					−8.7					+17.4

* Each horizontal of values was obtained in a separate study. C_1 = mean value of 1–6 successive measurements before initiation of inulin (or fructose in those studies in which inulin was not given); C_2 = mean value of 3–4 successive measurements during inulin infusion but before initiation of fructose; F = mean value of 3–4 successive measurements beginning 15–20 min after initiation of fructose.

‡ Calculated as percentage of filtered load reabsorbed, using GFR = C_{in}.

§ Calculated as percentage of filtered load reabsorbed, using GFR = C_{cr}.

tose infusion and was restored after fructose was discontinued constitutes strong evidence that fructose or one of its metabolites causes the tubular dysfunction. Tubular dysfunction occurred in the absence of either hypoglucosemia or ammonium chloride-induced acidosis and could not be related to osmotic diuresis.

Hereditary fructose intolerance is a genetically transmitted metabolic disorder characterized biochemically by the virtual inactivity of hepatic fructose-1-phosphate aldolase (16, 17). As a result of this enzymatic defect, fructose-1-phosphate (F-1-P), the initial reaction product of administered fructose, accumulates intracellularly (31) (Fig. 6), much as galactose-1-phosphate (Gal-1-P) accumulates intracellularly in galactosemia because of the deficiency of Gal-1-P uridyl transferase (15). The similarities, as well as the kinds, of metabolic and clinical abnormalities in HFI and in galactosemia suggest that the cellular accumulation of hexose-1-phosphate is central in the pathogenesis of the multiple cellular disturbances of both disorders. In patients with either disorder, the respective hexose induces hypophosphatemia unassociated with increased urinary excretion of phosphate and hypoglucosemia resultant in part from diminished hepatic output of glucose (11, 17, 18, 32, 33). In both disorders similar functional and structural abnormalities of the liver and kidney occur, which can be prevented and in some instances reversed by abstention from the specific hexose (17, 18, 34). In both disorders, persisting RTA, as well as reversible hexose-induced proteinuria and aminoaciduria of a "non-overflow" type, has been demonstrated (11, 14, 18, 35, 36). In two children with galactosemia, diagnosed just before death, increased amounts of Gal-1-P were measured in both renal and hepatic tissue (37).

In patients with HFI receiving fructose, it seems likely that F-1-P accumulates in the kidneys. In mammalian kidney, as in liver, the conversion of fructose to glucose (38) presumably occurs only via F-1-P, the triose products of its

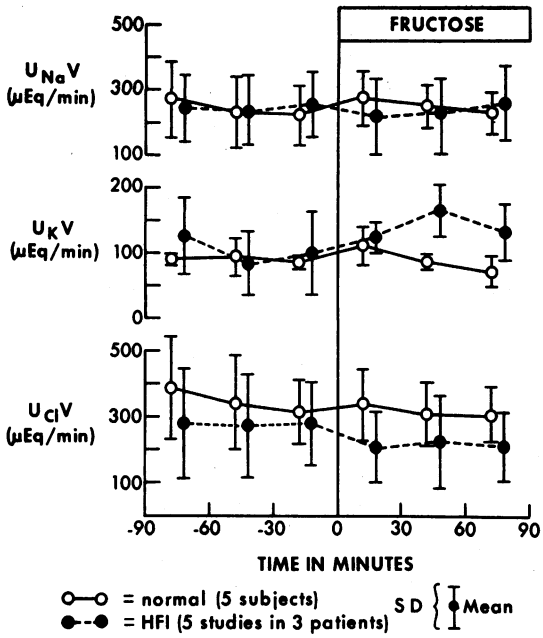

FIGURE 5 Effect of intravenous infusion of fructose on the rate of urinary excretion of sodium, potassium, and chloride in patients with hereditary fructose intolerance (studies 4–8) and normal subjects made acidotic with ammonium chloride. Each pair of values represents the mean rate of excretion during successive 30-min periods before and during administration of fructose.

catalytic cleavage and their recondensation to fructose-1-6 diphosphate (F-1-6 diP) (17, 38). The requisite enzymes, fructokinase (39), F-1-P aldolase and F-1-6 diP aldolase (40, 41), have been demonstrated in mammalian kidney. Renal aldolase activity toward F-1-P and F-1-6 diP, although readily demonstrable in normal man (41), was undetectable and diminished, respectively, in a patient with HFI (41).

Cellular accumulation of F-1-P might disrupt cellular function in several ways. Fructose-1-phosphate is reported to inhibit phosphoglucomutase (42), F-1-6 diP aldolase (17), and hexose phosphate isomerase (43) in vitro; inhibition may also occur in vivo (44). The accumulation of F-1-P might also deplete preformed adenosine triphosphate (ATP), since for each mole of hexose phosphorylated to hexose-1-phosphate, one mole of ATP is converted to adenosine diphosphate (ADP).

Whatever the intimate biochemical and biophysical mechanism, the data obtained in the present study provide compelling evidence that a defect in renal acidification, with physiologic characteristics like those of renal tubular acidosis, can

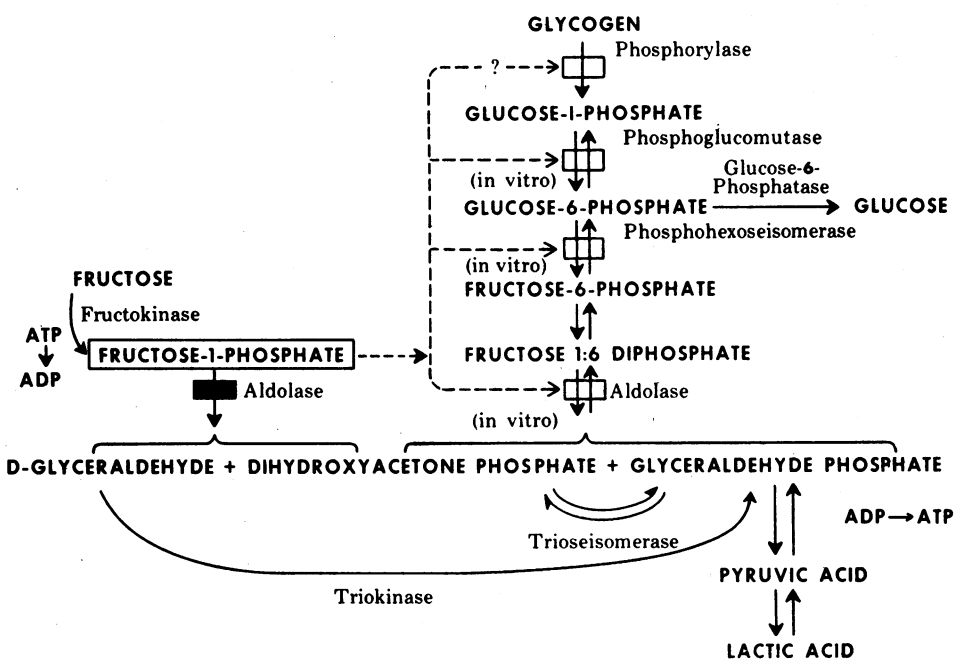

FIGURE 6 Biochemical effects of the aldolase block of fructose-1-phosphate (F-1-P) in hereditary fructose intolerance. The solid rectangle between F-1-P and D-glyceraldehyde + dihydroxyacetone represents the aldolase block; the dotted lines leading to the open rectangles represent F-1-P–mediated enzymatic blocks demonstrated in vitro or proposed.

be caused in man by a disturbance in carbohydrate metabolism in the renal tubule, mediated by the virtually absent activity of a specific renal enzyme.

APPENDIX

The solutions of inulin used for determination of glomerular filtration rate in some of these studies apparently contained substances that were not metabolically inert. One of the patients with HFI experienced nausea and vomiting 15–20 min after inulin infusions were begun. In the patients with HFI, in contrast to the control subjects, aminoaciduria and hyperphosphaturia invariably occurred when inulin was infused in amounts productive of the sustained blood level of 25 mg/100 ml suggested by Smith (22).

The possibility that inulin preparations might contain appreciable amounts of free fructose is suggested by the characteristics and stability of the inulin molecule in solution. Inulin is a fructofurasan and, being a furanocide, is easily hydrolyzed. In chromatograms of unrecrystallized inulin, Phelps (45) reported that the spot reacting as fructose accounted for 10–20% of the total color development. Furthermore, Nilwarangkur and Berlyne (46) found that vials of inulin stored for 1 yr may contain appreciable amounts of noninulin-reducing substances, presumably fructose or fructose polymers. Finally, when vials containing inulin (10%, Warner Chilcott Laboratories, Morris Plains, N. J.) were placed for 1–3 hr in boiling water, the concentration of inulin decreased progressively and the concentration of noninulin-reducing substances increased progressively as a function of time.[1] These observations suggest that inulin solubilized by the customary method of boiling should not be administered to patients with HFI in the amounts usually suggested for measurements of glomerular filtration rate.

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