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Transient Intolerance to Exogenous Fructose in the Newborn *

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The normal newborn infant has inadequate homeostatic mechanisms for stabilizing the concentration of glucose in the blood (1, 2). Recent studies of carbohydrate metabolism in this age group have indicated a diminished responsiveness to small doses (30 μg per kg body weight) of exogenous glucagon (3, 4) and a slow rate of disappearance from the blood of either glucose or galactose administered intravenously (4, 5). Similar results have been observed in the premature infant (6). Glucose uptake by the tissues improves with a second dose and with age. The newborn infant is sensitive to exogenous insulin (5, 6), and insulin-like substances have been found in umbilical vein blood (7). We interpret the effects of the injection of either glucagon or galactose, which resulted in a prompt rise in the concentration of glucose in the blood, to indicate functional adequacy of the enzymes of the glycogen cycle in the liver of the newborn infant.

Since the pathway for fructose metabolism in the liver differs from that of galactose or glucose, we wished to evaluate the effect of a rapid infusion of fructose on the concentration of glucose and lactate in the blood of newborn infants. The possible mechanisms involved are elucidated by combining the effects of epinephrine plus glucagon or galactose and fructose infusions.

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Methods

Sixty-one normal, newborn, full-term infants were studied after uncomplicated vaginal deliveries. Seventeen infants were born at the Cleveland Metropolitan General Hospital, the remaining forty-four at the University of Illinois, Research and Education Hospitals. All infants were fasted for 12 hours and given glucose water for 12 hours and then dilute formula, 15 cal per 30 ml, for 24 to 72 hours—routine newborn care. Infants less than 6 hours of age were fasted from the time of delivery. Infants between 6 and 24 hours of age were fasted variable times from a minimum of 3 hours after a glucose feeding to a maximum of 12 hours after delivery. Infants older than 24 hours were fasted 3 to 4 hours before study. All infants tolerated the procedures well, showing no marked alterations in temperature, nor any circulatory, respiratory, or neurological abnormalities. The responses to fructose in these infants were measured after a rapid injection of 25% fructose (1 g per kg body weight) given within a 2- to 4-minute period into a peripheral vein. Blood samples were obtained from punctures of the skin of the unwarmed heel. After 0.2-ml control samples were obtained before any injection, further samples were taken at 5, 10, 20, 30, 45, 60, 75, 90, and 120 minutes after injection. To prevent glycolysis the capillary blood samples were either precipitated immediately with barium hydroxide and zinc sulfate or transferred to sodium fluoride solutions (0.6 mg per tube). Separate 0.1-ml samples were precipitated directly with trichloroacetic acid for the lactic acid determinations.

The infants were grouped according to age and test, as indicated in Table I. Group I infants received fructose only. Group II infants were given 3 μg per kg of epinephrine subcutaneously followed by 300 μg per kg of glucagon intravenously. Samples of capillary blood were obtained at 0, 15, and 30 minutes when a fructose tolerance was superimposed as described above. Group III infants were given fructose intravenously. Capillary blood samples were obtained at 0, 5, 10, and 15 minutes, at which time an iv galactose tolerance (1 g per kg of a 25% solution) was superimposed. Group IV infants were given the galactose initially and the fructose at 15 minutes. Group V infants were initially given fructose intravenously. After the 90-minute blood sample, an

TABLE I

Age grouping of infants studied

Age of infants	Group I Fructose*	Group II Epinephrine plus glucagon before fructose	Group III Fructose before galactose	Group IV Galactose before fructose	Group V Fructose before fructose
a) Less than 6 hours	18	5			5
b) 6–24 hours	6		3	2	
c) 24–72 hours	6	5			
d) 72–168 hours	6				
e) 7–13 days	5				
Total	41	10	3	2	5

* All fructose and galactose administrations were intravenous.

identical fructose dose was given. The observations for the second phase were made for 60 minutes only

Total hexose was determined by the Somogyi-Nelson technique (8, 9). Fructose or galactose or both were determined as residual reducing substance after glucose oxidase digestion (10) or analysis (11). Hexose in the double fructose tests was determined by the ferricyanide technique on a microsugar automatic analyzer designed by Leonards. This method gives results similar to that of Somogyi and Nelson. Blood lactate was determined by the enzymatic technique of Friedland and Dietrich (12).

TABLE II

The effect of a rapid iv injection of fructose (1 g per kg) upon the concentration (mg per 100 ml) of fructose (Fr), glucose (Gl), and lactate (La) in the blood

			Minutes after injection									
			0	5	10	20	30	45	60	75	90	120	K
			mg/100 ml										*%/min*
Group Ia													
<6 hours	Fr	Mean		154.0	161.0	154.0	137.0	111.0	84.0	60.0	51.0	30.0	1.61
(no. = 18)		SEM		4.2	2.7	2.6	3.3	3.3	2.8	7.2	2.6	2.2	0.10
	Gl	Mean	48.0	43.0	39.0	33.0	28.0	30.0	47.0	78.0	83.0	91.0	
		SEM	2.7	3.7	3.8	3.5	3.7	4.8	5.5	9.0	5.7	7.1	
	La	Mean	16.4				33.9		41.2			36.3	
		SEM	1.8				2.9		3.4			3.5	
Group Ib													
6–24 hours	Fr	Mean		141.0	146.0	137.0	125.0	98.0	71.0	55.0	38.0	26.0	1.77
(no. = 6)		SEM		13.9	10.0	12.5	10.6	9.8	8.3	5.8	5.0	4.6	0.15
	Gl	Mean	51.0	51.0	48.0	42.0	38.0	45.0	64.0	77.0	84.0	84.0	
		SEM	2.5	3.2	3.3	3.4	3.2	4.4	4.2	5.1	7.6	7.6	
	La	Mean	21.1				47.2		54.7			44.9	
		SEM	2.7				6.0		8.6			5.6	
Group Ic													
24–72 hours	Fr	Mean		149.0	145.0	127.0	108.0	69.0	42.0	29.0	17.0	10.0	2.88
(no. = 6)		SEM		7.9	3.9	6.6	6.3	6.0	4.6	2.3	2.4	2.5	0.28
	Gl	Mean	58.0	56.0	52.0	50.0	58.0	72.0	76.0	80.0	84.0	79.0	
		SEM	4.4	2.1	2.2	3.3	3.8	1.9	1.6	2.6	2.0	1.9	
	La	Mean	15.7				41.4		38.2			22.0	
		SEM	1.7				2.7		4.0			2.4	
Group Id													
72–168 hours	Fr	Mean		164.0	150.0	128.0	97.0	64.0	36.0	23.0	15.0	8.0	3.01
(no. = 6)		SEM		9.3	12.0	9.2	8.3	8.1	6.0	4.3	3.3	2.1	0.18
	Gl	Mean	71.0	65.0	63.0	61.0	77.0	101.0	98.0	90.0	88.0	80.0	
		SEM	3.3	3.4	2.2	5.8	7.4	3.7	3.5	4.4	1.0	3.6	
	La	Mean	14.9				41.1		37.9			24.3	
		SEM	1.4				4.1		4.7			5.8	
Group Ie													
7 days	Fr	Mean		157.0	142.0	122.0	86.0	55.0	35.0	27.0	21.0	12.0	3.17
(no. = 5)		SEM		4.0	4.0	3.4	5.9	5.3	4.0	4.3	5.9	3.1	0.25
	Gl	Mean	75.0	68.0	64.0	60.0	76.0	105.0	97.0	94.0	88.0	76.0	
		SEM	2.9	2.4	2.7	2.8	6.7	6.5	6.9	7.0	5.4	5.8	
	La	Mean	18.8				47.3		49.9			36.2	
		SEM	2.6				1.0		3.2			6.5	

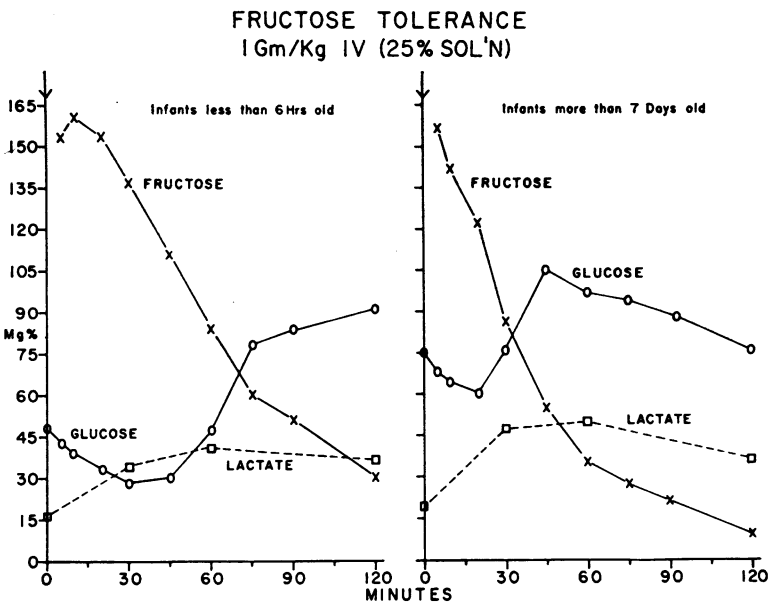

FIG. 1. ARITHMETIC GRAPHS OF FRUCTOSE TOLERANCE FROM NORMAL INFANTS LESS THAN 6 HOURS OF AGE (GROUP IA, LEFT) AND INFANTS OLDER THAN 7 DAYS (GROUP IE, RIGHT). Fructose, glucose, and lactate are expressed as mg per 100 ml.

Results

The administration of fructose to infants in Group Ia was associated with a significant decline in the concentration of glucose in the blood from mean control values of 48 mg per 100 ml to a low of 28 mg per 100 ml at 30 minutes after injection (Table II, Figure 1). After a transient plateau, there was a marked rise in the concentration of glucose in the blood to mean levels of 83 mg per 100 ml at 90 minutes and 91 mg per 100 ml at 120 minutes. The fructose disappeared from the blood at a slow rate. A plateau was evident for

TABLE III

The effects of fructose (1 g per kg, iv) upon the concentration of fructose, glucose, and lactate in the blood after stimulation by epinephrine (3 μg per kg, im) and glucagon (300 μg per kg, iv)*

			Minutes after glucagon and epinephrine			Minutes after fructose injection								
			0	15	30	5	10	20	30	45	60	90	120	K
						mg/100 ml								%/min
Group IIa														
<6 hours	Fr	Mean				161.0	163.0	157.0	140.0	119.0	90.0	51.0	31.0	1.63
(no. = 5)		SEM				12.8	9.5	7.8	7.3	10.6	8.4	5.1	4.4	0.13
	Gl	Mean	55.0	71.0	86.0	86.0	80.0	72.0	64.0	67.0	86.0	97.0	85.0	
		SEM	6.7	10.4	10.3	10.9	10.2	9.2	8.1	8.0	13.4	18.8	13.9	
	La	Mean	21.4		23.8				41.3		47.4		41.2	
		SEM	4.2		4.0				6.1		7.7		7.9	
Group IIc														
31–42 hours	Fr	Mean				182.0	170.0	141.0	110.0	76.0	52.0	25.0	16.0	2.53
(no. = 5)		SEM				6.1	3.4	8.0	7.4	6.5	2.5	7.9	4.1	0.14
	Gl	Mean	59.0	84.0	105.0	97.0	87.0	75.0	82.0	116.0	121.0	107.0	79.0	
		SEM	4.2	3.8	5.7	3.4	2.1	1.1	4.9	7.1	12.9	14.2	12.4	
	La	Mean	17.3		18.6				45.7		45.9		30.9	
		SEM	2.9		2.0				3.7		4.2		6.0	

* Expressed as mg per 100 ml.

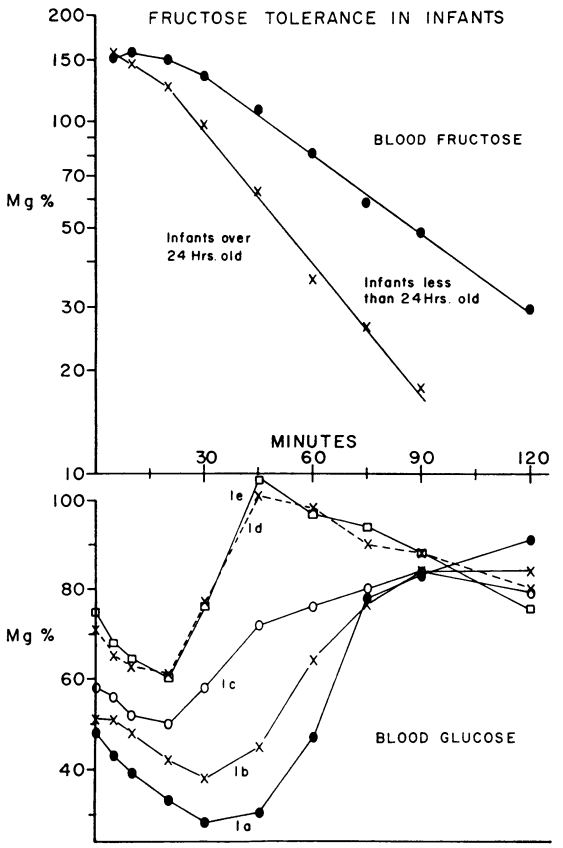

FIG. 2. UPPER FIGURE: A SEMILOGARITHMIC GRAPH COMPARING THE MEAN CONCENTRATION OF FRUCTOSE IN THE BLOOD FOR ALL INFANTS LESS THAN 24 HOURS OF AGE (GROUPS IA, B) TO THOSE OVER 24 HOURS OLD (GROUPS IC, D, E). LOWER FIGURE: THE SIMULTANEOUSLY OBTAINED MEAN VALUES FOR THE CONCENTRATION OF GLUCOSE IN THE BLOOD FOR INFANTS OF VARIOUS AGES (less than 6 hours old to over 7 days of age, i.e., groups Ia to Ie, respectively, as described in Table I).

the initial 20 minutes, followed by a more rapid rate thereafter (Figures 1, 2).

The levels of lactate in the blood of infants in Group Ia rose from mean control values of 16.4 mg per 100 ml to 41.2 mg per 100 ml at 60 minutes, then declined to 36.3 mg per 100 ml at 120 minutes.

The six infants in Group Ib had similar glucose responses, although the nadir was higher. In contrast to these two groups of younger infants, the responses in the older infants (Groups Ic, d, e) were more transient, both in the early hypoglucosemic and in the later hyperglucosemic phases (Figure 2). A slow rate of fructose disappearance was still apparent in the Group Ib infants between 6 and 24 hours of age (Table II); however, an increased rate of fructose disappearance occurred in the older infants of Groups Ic, d, and e. The fructose values plotted semilogarithmically gave a straight line relationship with time beyond the initial 20 minutes and are consistent with first order kinetics (Figure 2). The mean rate constants are given in Table II. Changes in the concentrations of lactate in the blood were similar in all groups.

The administration of epinephrine and glucagon to five infants under 6 hours of age (Group IIa) produced a prompt rise in the concentration of glucose in the blood from a mean of 55 mg per 100 ml to 86 mg per 100 ml by 30 minutes (Table III, Figure 3). At this time the injection of fructose resulted in a prompt fall in the concentration of glucose in the blood from 86 to 64 mg per 100 ml within 30 minutes. A later, secondary rise in glucose concentration to 97 mg per 100 ml occurred after 60 additional minutes. There was no change in the level of lactate in the blood after administration of epinephrine and glucagon, but high mean values of 47 mg per 100 ml occurred 60 minutes after fructose injection. Similar

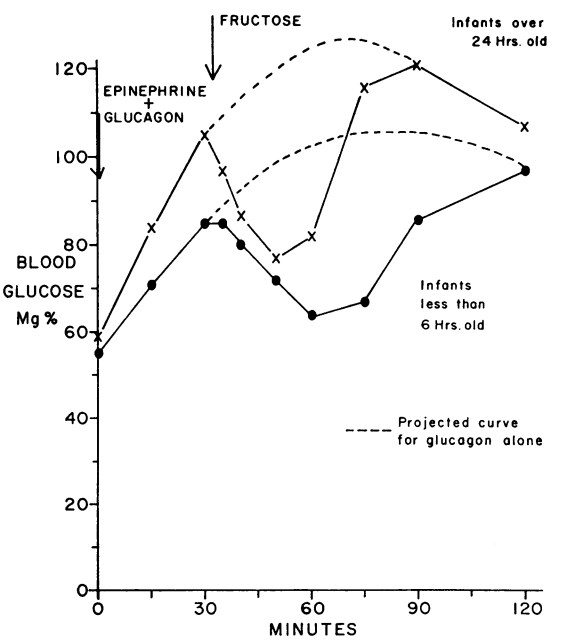

FIG. 3. AN ARITHMETIC GRAPH OF THE EFFECTS OF FRUCTOSE ON INFANTS PREVIOUSLY GIVEN EPINEPHRINE AND GLUCAGON TO STIMULATE HEPATIC GLUCOSE RELEASE.

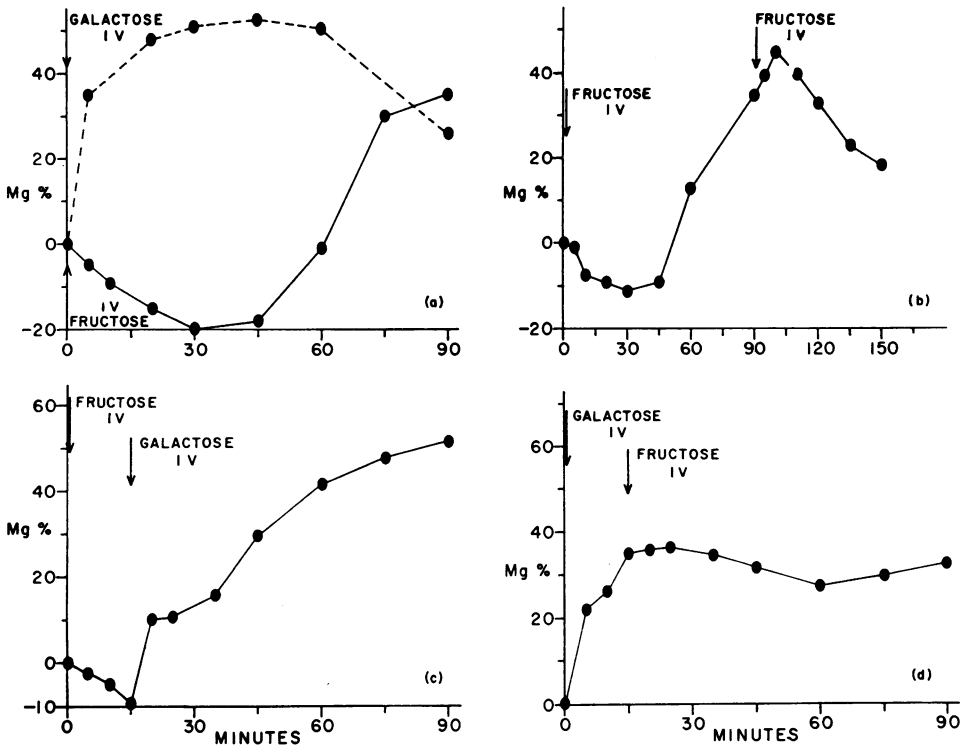

FIG. 4. THE EFFECTS OF GALACTOSE AND FRUCTOSE TOLERANCE TESTS, ALONE OR COMBINED, ON THE MEAN INCREMENT IN THE CONCENTRATION OF GLUCOSE IN THE BLOOD OF NEWBORN INFANTS. (a) The mean responses of infants given either galactose or fructose intravenously. The galactose studies were reported previously for 12 infants under 6 hours of age (4). The fructose studies are Group Ia. (b) The effects of two sequential doses of fructose given intravenously to Group Va, 5 infants, at a 90-minute interval (note difference in the time scale). (c) The effects on glucose in the blood of galactose administered intravenously to infants 15 minutes after fructose infusion (Group IIIb). (d) The effects of fructose on glucose in the blood from infants previously given an injection of galactose (Group IVb).

studies in five infants over 24 hours of age (Group IIc) resulted in higher initial and subsequent levels of glucose in the blood after injection of epinephrine and glucagon. However, a more transient hypoglucosemia occurred after fructose injection in the older infants compared to that in the younger group. The levels of lactate in the blood were similar in both groups. The rates of fructose disappearance from the blood of these infants (Groups IIa, c) were similar to those obtained in infants (Groups Ia, c) given fructose alone.

The iv injection of galactose (Group IVb) resulted in a prompt rise in blood glucose from 49 mg per 100 ml to 84 mg per 100 ml (Figure 4a, d). The superimposition of a fructose tolerance at 15 minutes resulted in a plateau in the level of glucose in the blood for 20 minutes, then a slight decline to 77 mg per 100 ml at 60 minutes, with a return to prefructose administration values of 85 mg per 100 ml for the remaining time of observation (Figure 4d). When fructose was administered before galactose (Group IIIb), the rise in the concentration of glucose in the blood usually observed after galactose administration was delayed for 30 minutes (Figure 4c).

A second injection of fructose, given 90 minutes after the initial fructose infusion (Group Va) during the phase when the concentration of glucose in the blood was rising, did not result in a prompt fall in the level of glucose in the blood. Instead, an initial rise in glucose concentration was observed (Figure 4b). The subsequent delayed fall in the glucose concentration of the blood is not

clearly related directly to either the first or second fructose injection. The rate of fructose disappearance from the blood after the second dose was similar to the rate after the first injection.

Discussion

The physiological mechanisms resulting in the fall in the concentration of glucose in the blood associated with the rapid iv injection of fructose (Figure 1) may be related to an increase in tissue uptake of glucose, a decrease in hepatic output, or a combination of both. There is evidence suggesting that the hypoglucosemia is not due to increased peripheral uptake. Fructose injected directly into the pancreatic artery of the dog does not produce hypoglucosemia, suggesting that fructose does not stimulate the release of insulin (13). Although the infusion of fructose in normal men increases the rate of disappearance of an exogenous glucose load, an increase in insulin-like activity in the serum could not be detected (14). The levels of insulin in the blood decrease concurrently with those of glucose after the administration of fructose to patients with hereditary fructose intolerance (15, 16). Furthermore, studies of iv glucose and tolbutamide tolerances as well as leucine tolerances in newborn infants indicate a delayed or slow glucose disappearance from the blood, suggesting a failure or delay of pancreatic insulin release (5–7).

The data from the combined epinephrine-glucagon and fructose studies (Figure 3) indicate an inhibition of hepatic release of glucose by intravenously administered fructose. Glucagon stimulates hepatic glycogenolysis, and epinephrine, in addition, inhibits peripheral glucose uptake in muscle, resulting in a rise in the concentration of glucose in the blood. Previous studies have indicated that these hormones, alone or in combination, result in a characteristic sustained rise in the level of glucose in the blood in newborn infants (3, 4, 6). In contrast, the responses of older infants and adults are of significantly shorter duration. Thus the fall in the level of glucose in the blood after glucagon and fructose administration must be interpreted to indicate a cessation of hepatic glucose output.

The rate of disappearance of intravenously administered fructose from the blood of the newborn infant is significantly slower than that in older infants and adults (Table II, Figure 2). The adult clears fructose at a rate of 3.4 to 3.8% per minute, assuming first order kinetics. In contrast, the mean rate in infants under 6 hours of age was 1.61% per minute; that in infants between 6 and 24 hours, 1.77% per minute; and the rates in infants older than 24 hours, 2.88, 3.01, and 3.17% per minute. Since the amount of fructose excreted in the urine in older individuals is small (less than 5%) and therefore has little influence on the disappearance rate, the oliguria of the normal newborn cannot contribute significantly to this diminished disappearance rate. Dieckhoff and Schmidt (17) have reported similarly slower rates for fructose disappearance in infants under 10 days of age compared to older infants. The diminished rate for fructose in the newborn infant is similar to that observed previously for both galactose and glucose (4–6).

The transient decreased uptake of fructose by tissues and the associated inhibition of glucose release by the newborn's liver may be analogous to the recently described syndrome of hereditary fructose intolerance (15). Individuals with this disease respond to fructose, oral or injected, with a delayed fructose disappearance from the blood associated with a prompt and persistent hypoglucosemia, often associated with severe symptoms. Biopsy of the liver has indicated an absence of fructose-1-phosphate aldolase in several such patients (18). Thus an accumulation of fructose-1-phosphate and fructose might be expected in the livers of such individuals.

The effect of administered fructose on the concentration of glucose in the blood may be influenced by factors other than the age of the subject. The mode of administration and dose of fructose may be important. For example, when fructose (0.5 g per kg) was given to adults during a continuous infusion lasting 30 to 60 minutes, no depression of the level of glucose in the blood was observed at the end of the infusion (19). In contrast, when the time of injection of a comparable dose was shortened to 10 minutes, a transient hypoglucosemia was found in association with the higher concentrations of fructose attained in the blood (20).

Although the human placenta is capable of fructose secretion *in vitro,* only low concentrations of

fructose (less than 10 mg per 100 ml) have been measured in mixed umbilical cord blood (21). Unlike the sheep and goat, man is nonfructogenic. Substrate induction of enzyme activity necessary for fructose metabolism is therefore unlikely to occur prenatally.

The studies reported suggest that there is in the full-term human infant, in the initial hours after birth, an adaptation of hepatic enzymes to metabolize exogenously administered fructose. Schapira, Schapira, and Dreyfus have reported recently on diminished fructose aldolase activity in a few human fetal liver samples (22). Walker has found absent or diminished hepatic fructokinase in three nonfructogenic species in the first 7 to 10 days after birth (23). He also showed a diminished fructose disappearance rate from the blood of the newborn rabbit, which had decreased enzyme activity in the liver.

The invariable rise in lactate in the blood of infants of all age groups studied is inexplicable. A diminution of glucose-6-phosphatase activity such as occurs in type I glycogen storage disease would be associated with a rise in lactate and a fall in glucose. The failure to demonstrate a lessening of the lactate rise in older infants in whom hypoglucosemia was diminished makes this enzymatic defect unlikely. Our studies do not provide sufficient data to warrant speculation concerning alternative mechanisms such as inhibition of gluconeogenesis by fructose. The possibility of a peripheral tissue origin for the lactate must also be considered.

Possible mechanisms for the fructose-induced hypoglucosemia include the inhibition of phosphoglucomutase by fructose-1-phosphate and the inhibition of glycogenolysis or glucose-6-phosphatase. The administration of galactose intravenously in three patients with hereditary fructose intolerance resulted in a prompt rise in the level of glucose, previously depressed by fructose (16). This would indicate that inhibition of phosphoglucomutase and glucose-6-phosphatase is unlikely. Our studies in infants under 6 hours of age are compatible with this interpretation. Additional support for the hypothesis is obtained from the results of the double fructose tolerance tests, which suggest that glucose-6-phosphatase is not inhibited by fructose administration. The low levels of glucose observed after fructose administration could be explained by an inhibition of glycogenolysis.

Summary

The rapid iv administration of fructose to normal newborn infants results in a prompt transient depression of the concentration of glucose in the blood. This is most evident in infants less than 6 hours of age but occurs in all age groups with rapid infusion.

The rate of disappearance of fructose from the blood diminishes for infants less than 24 hours of age. The rate of disposal of fructose increases with age.

When fructose is administered to infants after epinephrine-glucagon stimulation, the rise in the concentration of glucose in the blood is immediately suppressed and a decline occurs. We interpret this to indicate that fructose inhibits the release of glucose from the liver; combined galactose-fructose tolerance studies further substantiate this conclusion.

We suggest that a maturation or adaptation of fructokinase or fructose aldolase, or both, occurs in the liver of the newborn infant in the initial hours after birth.

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