Influence of Dietary Fructose on Glucose Tolerance in Man

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Hill, Baker and Chaikoff[1] have reported that rats that had been fasted for one day and fed a diet in which fructose was the only carbohydrate for the next three days showed almost as great a loss of tolerance for orally administered glucose as did rats that were fasted for four days. These two groups of rats were compared with a group that were fasted for one day and fed a diet in which glucose was the only carbohydrate for the next three days. The results of studies of the utilization of C^{14}-labeled glucose, fructose, and acetate in tissue slices from the glucose-fed and fructose-fed animals suggested that liver glucokinase activity was decreased in the fructose-fed rats. Glucose levels in portal vein blood were found to be lower after fructose ingestion than after glucose ingestion. The authors suggested that the hepatic glucokinase system became adapted to dietary glucose and required the presence of frequent high concentrations of glucose in the portal vein blood to maintain its optimal activity. In the rat it appeared that glucose was the dietary carbohydrate specifically required to maintain the activity of the mechanisms for the disposal of administered glucose. Comparable experiments have been performed in the dog by Hill and Chaikoff[2] who demonstrated a diminished glucose tolerance in animals that were fed a fructose-containing diet for seven days.

These findings were interesting but unexpected. Since it had been shown that fructose could be converted to glucose in intestinal,[3-5] hepatic,[6,7] and renal[8-10] tissue, marked effects of glucose deprivation would not have been anticipated in a fructose-fed animal. It had also been reported that fructose administration restored glucose tolerance to normal in a fasted human subject.[11] The phenomenon demonstrated by Hill and others in the rat and dog might explain the loss of the initial advantage of fructose over glucose which was described in the depancreatized dog after prolonged fructose feeding.[12] If this phenomenon occurred in man, it might account for the reported loss of advantage of fructose after prolonged feeding to diabetic patients.[13] It would also suggest a mechanism of starvation diabetes in man.

With these considerations in mind, the present studies were designed to determine whether or not the ingestion of a diet whose sole carbohydrate was fructose would alter oral or intravenous glucose tolerance in man.

METHODS

The composition of the experimental diets, whose sole carbohydrate was either glucose or fructose,* is listed in table 1. Both diets contained approximately 95 gm. of protein, 75 gm. of fat, 250 gm. of carbohydrate, and a total of 2,055 calories. Their composition was exactly the same except for the different hexoses. One fifth of the meat and butter was eaten at breakfast, two fifths at lunch, and two fifths at supper. One fourth of the hexose was usually ingested with each of the three meals and a similar amount at bedtime. In addition to the diet, one multivitamin capsule† was taken each day.

The subjects for these studies were four healthy male physicians whose ages ranged from twenty-nine to thirty-four years. Three types of studies were performed:

(1) For a period of three days each subject ate the glucose diet. On the morning of the fourth day an intravenous glucose tolerance test was performed. For the next several days the subject consumed his usual mixed diet‡ in order to insure the return of his nutritional

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*The fructose used in these studies was supplied by Mead Johnson and Company.

†Avicaps were furnished by Burroughs *Wellcome* and Company.

‡The term "mixed diet" describes a diet composed of foods one would expect to find in the average American home or in the usual hospital cafeteria. Such a diet contains carbohydrate in several forms, in contrast to the experimental diets used in this study.

TABLE 1

Daily composition of experimental diets

Fructose diet (gm.)		Glucose diet (gm.)	
Ground round steak	500	Ground round steak	500
Butter	20	Butter	20
Fructose*	250†	Glucose*	250†

*In the form of a 10 to 50 per cent aqueous solution.
†The diet of subject J.C. contained only 200 gm. of hexose preceding the intravenous glucose tolerance tests.

status to its usual level. He then ate the fructose diet for three days. On the morning of the fourth day the intravenous glucose tolerance test was repeated. In half of the subjects the order of the experimental diets was reversed and the fructose dietary period preceded the glucose period. On other occasions, three of the subjects ate a mixed diet whose carbohydrate content was 250 gm. daily; after periods of three days on this diet intravenous glucose tolerance tests were performed.

(2) Since the above studies involved only the maintenance of normal glucose tolerance by fructose feeding, another experiment was performed in subject J.C. to determine whether or not glucose tolerance could be restored to normal after impairment by fasting. A control intravenous glucose tolerance test was performed after the subject had been on a mixed diet containing 200 gm. of carbohydrate daily for three days; the test was repeated after a thirty-three-hour period of fasting. The test was performed a third time after one day of fasting and three days on the experimental diet containing 200 gm. of fructose daily.

(3) In order to simulate the conditions of the rat experiments of Hill and others more closely, two of the subjects fasted one day and ate the experimental glucose or fructose diet for the next three days; on the morning of the fifth day oral glucose tolerance tests were performed. After the subjects had been eating the usual mixed diet again for several days, the same experiment was repeated except that the other hexose was used as the sole dietary carbohydrate.

Glucose tolerance tests were performed with the subject resting in the recumbent position following an overnight fast. The intravenous tests were performed by administering one gram of glucose per kilogram of body weight in a 10 per cent solution in water during one hour; an infusion pump was used to insure a uniform rate of administration. Blood samples for glucose, pyruvic acid, and lactic acid determination were obtained through an indwelling needle in an antecubital vein, before and at thirty-minute intervals after the start of the infusion, for a total of three hours. For the oral tests, 100 gm. of glucose in 500 ml. of water were ingested within a five-minute period. Blood samples were obtained at the same intervals as for the intravenous tests. The blood was analyzed for glucose by the method of Somogyi, using Nelson's chromogenic reagent.[14] Pyruvic acid was determined by the method of Friedemann and Haugen[15] and the procedure of Barker and Summerson[16] was used for lactic acid analysis.

RESULTS

Clinical effects of diet. The subjects experienced up to four soft to watery bowel movements during the three-day periods of the experimental hexose diets; diarrhea was experienced in the course of both glucose and fructose diets but more frequently during the latter. It was not felt that the frequency or severity of the diarrhea was sufficient to result in any significant loss of nutrients. Weight losses during the three-day dietary periods varied from zero to 1.3 kg. The weight changes were apparently related to the caloric content of the diet, and were not influenced by changing the form of the dietary carbohydrate.

Intravenous glucose tolerance tests following three days of experimental diet. The results of these tests are contained in the upper section of table 2. In three of the four subjects glucose disappeared somewhat more rapidly from the blood following the fructose diet than after the glucose diet; in the fourth subject (M.M.), the reverse was true. The average glucose tolerance curves of the four subjects after the two different hexose diets are illustrated in figure 1. Under the conditions of these experiments, a diet whose sole carbohydrate was fructose did not produce a significant decrease in the rate of removal of intravenously administered glucose.

Intravenous glucose tolerance tests following three days of mixed diet containing 250 gm. of carbohydrate. The results of these tests are shown in the upper section of table 2. It can be seen that these curves were similar to those obtained following three days of the experimental hexose diets. Changing the dietary carbohydrate from that encountered in the usual mixed diet to the same quantity of a pure hexose did not alter the rate of removal of subsequently administered glucose.

Intravenous glucose tolerance tests following one day of fasting and three days of fructose diet. The results of these tests in subject J.C. are shown in the lower section of table 2. One day of starvation produced the expected decrease in the rate of removal of administered glucose, while fructose feeding for three days restored the glucose tolerance to the previous control level.

TABLE 2

Influence of previous diet on blood glucose, pyruvic acid, and lactic acid concentrations during intravenous glucose tolerance tests* in normal subjects

Subject	Wt. Kg.	Date	Carbohydrate in previous diet	Blood glucose (mg./100 ml.) Minutes after start of infusion							Blood pyruvic acid (mg./100 ml.) Minutes after start of infusion							Blood lactic acid (mg./100 ml.) Minutes after start of infusion						
				0	30	60	90	120	150	180	0	30	60	90	120	150	180	0	30	60	90	120	150	180
J.C.	61	10/9/54	Glucose	94	267	342	180	101	57	57	1.1	1.0	1.5	1.4	1.2	1.1	1.0	3.7	4.5	8.9	10.0	9.4	6.0	6.5
		9/27/54	Fructose	89	241	274	137	55	78	82	0.9	0.9	1.2	1.3	1.0	1.2	1.2	3.9	3.7	6.0	6.8	4.5	9.5	7.3
M.M.	69	11/6/54	Glucose	81	211	275	69	56	48	60	0.9	0.7	1.7	1.3	0.9	1.0	0.8	6.8	8.6	9.3	15.5	7.4	7.4	8.3
		1/18/55	Fructose	88	259	294	143	74	67	71	0.8	0.8	1.1	1.0	0.8	0.8	0.9	1.2	1.6	4.2	5.5	3.9	3.6	3.5
		11/2/54	Mixed	74	240	287	115	45	42	56	1.1	1.1	1.4	1.5	1.2	1.1	1.0	7.0	7.3	8.9	10.0	8.2	6.9	9.6
		1/13/55	Mixed	77	203	245	155	91	63	65	0.9	1.1	1.2	1.5	1.1	0.9	0.8	3.4	4.3	4.9	6.9	6.1	4.0	3.6
W.D.	80	12/3/54	Glucose	78	300	397	238	73	44	57	1.0	1.8	1.4	1.3	1.2	1.1	1.0	6.5	17.7	8.1	11.8	9.7	8.4	9.9
		12/20/54	Fructose	85	283	389	125	42	49	62	0.7	1.3	1.0	1.3	0.7	0.6	0.9	3.5	6.0	9.0	10.5	6.5	3.0	6.6
		11/29/54	Mixed	86	278	359	142	67	38	61	1.1	1.0	1.3	1.1	1.0	0.7	1.0	5.3	4.7	9.5	7.7	6.2	4.7	7.7
		12/16/54	Mixed	91	296	384	146	66	45	65	1.0	1.2	1.2	1.4	1.1	1.3	1.5	9.8	—	9.4	9.7	9.2	10.7	15.5
C.P.	96	2/19/55	Glucose	92	317	424	283	199	129	86	0.8	0.9	1.2	1.2	1.0	0.8	0.5	1.8	1.9	4.2	4.9	3.7	1.9	4.1
		2/11/55	Fructose	96	289	346	174	103	54	80	0.8	1.0	1.0	1.3	0.7	0.4	1.4	3.3	4.5	4.4	6.0	6.9	10.1	7.9
		2/5/55	Mixed	98	298	380	265	142	81	56	1.1	1.0	1.0	1.2	1.1	0.8	0.6	2.5	6.4	7.4	9.3	6.2	5.8	7.7
J.C.		6/13/57	Mixed	87	237	291	146	67	57	71	1.2	0.8	1.4	1.2	0.8	0.9	1.1	5.2	7.6	9.9	8.2	8.2	7.4	8.9
		10/10/57	None (fasting one day)	86	230	327	232	176	118	90	1.3	1.1	0.9	1.2	1.2	1.3	1.2	7.9	7.7	6.9	7.0	6.9	5.8	5.9
		10/22/57	Fructose†	82	234	238	115	83	55	73	1.0	1.0	1.2	1.3	1.3	1.0	1.1	5.6	6.4	8.2	9.9	9.2	7.6	8.1

*One gram of glucose per kilogram of body weight in sixty minutes.
†Preceded by one day of fasting.

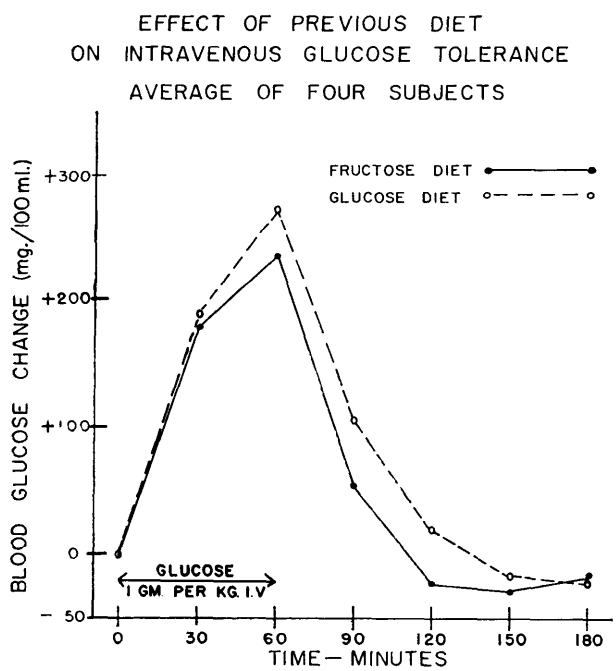

FIG. 1. Average of the intravenous glucose tolerance curves of the four subjects after three days on a diet whose sole carbohydrate was glucose and after three days on a diet whose sole carbohydrate was fructose. Blood sugar concentrations are plotted in terms of variation from the fasting level.

Oral glucose tolerance tests following one day of fasting and three days of experimental diet. The results of these tests are contained in table 3 and in figure 2. Although there was a marked difference between the heights of the blood sugar rises in the two individual subjects, the rate of removal of orally administered glucose from the blood was not impaired by the previous fructose diet in either case.

Changes in blood pyruvic acid and lactic acid during glucose tolerance tests. The usual rises in the concentrations of blood pyruvic acid and lactic acid were observed during the course of the glucose tolerance tests as shown in tables 2 and 3. Although these changes were variable in magnitude, the variations could not be correlated with a change in the form of carbohydrate in the previous diet.

DISCUSSION

The results of these studies suggest that in man dietary glucose* is not required to maintain the activity of the mechanisms for the removal of administered glucose from the blood. Glucose tolerance curves ob-

*The term "dietary glucose" as used here includes not only glucose but other forms of carbohydrate such as starch and glycogen which are converted to glucose in the gastrointestinal tract prior to absorption.

TABLE 3

Influence of fasting and subsequent fructose feeding on blood glucose, pyruvic acid, and lactic acid concentrations during oral glucose tolerance tests* in normal subjects

Subject	Date	Carbohydrate in previous diet	Blood glucose (mg./100 ml.) Minutes after start of infusion							Blood pyruvic acid (mg./100 ml.) Minutes after start of infusion							Blood lactic acid (mg./100 ml.) Minutes after start of infusion						
			0	30	60	90	120	150	180	0	30	60	90	120	150	180	0	30	60	90	120	150	180
J.C.	3/28/55	Glucose†	73	102	107	88	89	68	79	1.2	1.2	1.6	1.8	1.4	1.4	1.0	7.0	5.7	8.8	15.4	19.2	10.4	7.8
	3/7/55	Fructose†	87	104	99	95	90	85	87	0.5	0.6	1.0	0.8	0.7	0.9	1.0	2.4	3.6	8.3	8.4	9.2	9.5	8.1
W.D.	3/21/55	Glucose†	83	155	195	184	166	143	132	1.0	1.2	0.9	1.8	1.0	1.2	0.8	4.2	3.7	7.1	6.8	5.8	5.0	5.4
	4/11/55	Fructose†	92	183	214	176	137	108	81	0.8	1.0	1.2	1.4	1.2	1.2	1.0	7.8	7.1	10.5	13.2	11.7	9.7	10.5

*One hundred grams of glucose was employed as test dose.
†Preceded by one day of fasting.

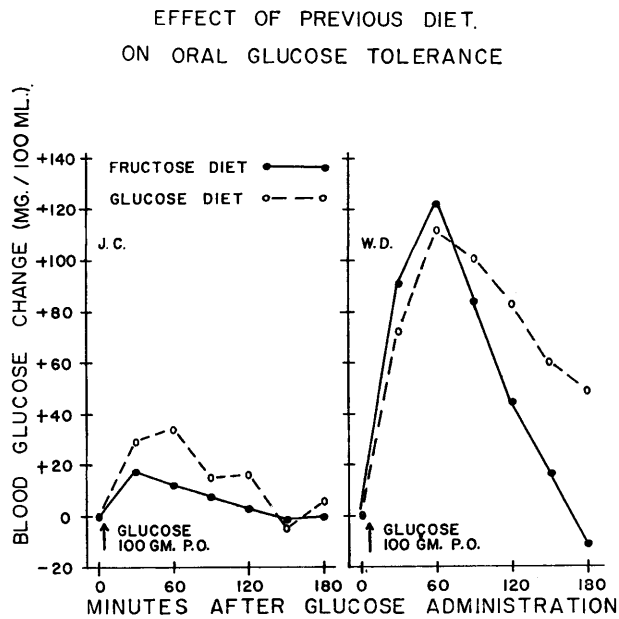

FIG. 2. Oral glucose tolerance curves of subjects J.C. and W.D. after one day of fasting and three days on a diet whose sole carbohydrate was glucose and after one day of fasting and three days on a diet whose sole carbohydrate was fructose. Blood sugar concentrations are plotted in terms of variation from the fasting level.

tained after the subjects had ingested a glucose-free (fructose) diet for three days were similar to those obtained following three days on a diet which was identical except that glucose was the sole carbohydrate. Although the results of these experiments should not be extrapolated to dietary periods longer than four days, one would expect that if a change in glucose tolerance were to occur it would be evident within this period of time, since a definite loss of tolerance has been observed after only two days of fasting or a carbohydrate-free diet.[17-18] The finding of Van Itallie and Shull[19] that the net tolerance for oral glucose was not impaired in normal human subjects after five days of fructose feeding lends additional suport to this conclusion.

However, our results do not exclude the possibility that in the absence of adequate dietary glucose, the activity of the glucose disposal mechanisms may be maintained by glucose formed endogenously from appropriate dietary precursors. This conclusion is based on the knowledge that in man a portion of administered fructose is converted to glucose.[20] The fact that glucose tolerance is more impaired by an antecedent low carbohydrate diet which is high in fat than by one with a high protein content[18] is consistent with this possibility, since dietary protein can furnish more "available carbohydrate" than can fat.

If the conversion of fructose to glucose is to explain the maintenance of normal glucose metabolism during a period when the sole dietary carbohydrate is fructose, one of two conditions must exist: (1) The mechanisms for glucose disposal must be relatively insensitive to a decrease in glucose supply; or (2) a large proportion of administered fructose must be converted to glucose. The studies of Himsworth furnish quantitative information regarding the relationship between dietary carbohydrate and the glucose tolerance curve.[21] This investigator found that as the amount of dietary carbohydrate was increased from 50 to about 150 gm. a marked improvement in glucose tolerance occurred; with further increase of carbohydrate from 150 to 350 gm., improvement in tolerance was relatively slight. These findings suggest that unless at least 150 gm. of glucose is formed from 250 gm. of dietary fructose, the glucose tolerance curve after the fructose diet should be higher than following a diet containing 250 gm. of glucose, assuming that glucose is essential for maintenance of the glucose disposal mechanism. Since precise information is lacking in regard to the portion of administered fructose which is converted to glucose in man, this question cannot be

resolved at the present time.

A study of portal anastomotic vein blood in a patient with Laennec's cirrhosis demonstrated that during the intestinal absorption of fructose less than one fifth of that hexose was converted to glucose.[20] Accordingly, a significantly lower concentration of glucose would occur in the portal blood after ingestion of fructose than after ingestion of an equal amount of glucose. One would therefore have expected a difference in glucose tolerance after the two different experimental diets if the portal blood glucose level in man were of critical significance in this regard, as Hill and his associates have postulated in the case of the rat.

In the present studies as in those of Hill and his associates in the rat and dog only the net tolerance for glucose was tested; no measurements were made of the handling of glucose by individual organs. Fructose feeding might impair the glucose disposal mechanisms of an organ whose quantitative contribution to the total body metabolism is so small that the change would not be detectable in the glucose tolerance curve. Alternatively, if fructose feeding enhanced the rate of glucose removal by one organ and impaired this process in another organ, the net tolerance for glucose might not be altered. Indeed Van Itallie and Shull[19] have concluded from epinephrine-glucose tolerance tests and measurements of the peripheral capillary-venous glucose differences that fructose feeding in man increases the rate of peripheral glucose removal while impairing the ability of the liver to take up glucose.

Three explanations may be proposed to account for divergent results in the rat and human studies:

(1) The mechanisms for glucose disposal may be dependent upon a continued supply of glucose for maintenance of their activity in the rat but not in man.

(2) The difference may be only quantitative in that mechanisms are less sensitive to a decreased supply of glucose in man. As mentioned earlier, a reduction in the total carbohydrate content of the diet produces a prompt decrease in glucose tolerance in both man and the rat, while dietary fructose maintains or restores the tolerance for glucose in man but not in the rat. It is difficult to explain these observations solely on the basis of a quantitative metabolic difference which might be associated with the different body sizes and rates of energy production of the two species.

(3) The glucose disposal mechanisms of the two species may be equally sensitive to changes in available glucose, but a smaller fraction of administered fructose may be converted to glucose in the rat. Relatively less glucose would therefore be available to maintain the disposal mechanisms in the fructose-fed rat as compared to the fructose-fed man. Sufficient data are not available either to exclude or confirm any one of these proposed explanations.

SUMMARY

1. Glucose tolerance tests were performed in normal human subjects who had been fed for three days a diet whose sole carbohydrate was either 200 or 250 gm. of glucose. The tests were repeated in the same subjects after three days on a diet whose sole carbohydrate was an equal quantity of fructose. Control tolerance tests were obtained after normal diets containing the same amount of carbohydrate in mixed form.

2. Fructose feeding for this period of time did not decrease the rate of removal of either orally or intravenously administered glucose. It restored glucose tolerance which had been impaired by fasting for one day.

3. In contrast to findings in the rat and dog, the specificity of glucose as the dietary carbohydrate responsible for maintaining the activity of the glucose disposal mechanisms was not demonstrated in man.

SUMMARIO IN INTERLINGUA

Le Influentia de Fructosa Dietari Super le Tolerantia pro Glucosa in Humanos

1. Tests de tolerantia pro glucosa esseva effectuate in normal subjectos human qui habeva recipite durante tres dies un dieta in que le sol carbohydrato esseva 200 o 250 g de glucosa. Le tests esseva repetite in le mesme subjectos post tres dies durante le quales le sol carbohydrato dietari esseva le mesme quantitate de fructosa. Valores de controlo esseva obtenite per tests de tolerantia post dietas normal continente le mesme quantitate de carbohydrate in forma miscite.

2. Le alimentation a fructosa durante le mentionate periodo de tempore non relentava le elimination de glucosa administrate per via oral o per via intravenose. Illo restaurava le tolerantia pro glucosa que habeva essite compromittite per un die de jejunamento.

3. Per contrasto con le constatationes in rattos e canes, le specificitate de glucosa como le carbohydrato responsabile pro mantener le activitate del mechanismos de elimination de glucosa non esseva demonstrate in humanos.

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The function of insulin as a regulator of permeability of cell membranes is, at present, in the foreground of attention. Nevertheless, experiments such as those reported in the lucid paper by Kipnis and Cori on the change of the temperature coefficient for pentose transfer into diaphragm with insulin addition indicate a possible shift from diffusion to a chemical and therefore probably enzymatic reaction. Such observations suggest that the search for a possible primary metabolic effect of insulin should not yet be fully abandoned. These considerations led us to investigate pigeon breast muscle, where Krebs had found effects of insulin on respiration maintenance which had been confirmed. The fact that such an effect appeared to be unique with pigeon muscle seemed, essentially, not to argue against its possibly reflecting an aspect of insulin activity.

Although with the pigeon breast muscle system no insulin effect could be obtained when measuring glycogen synthesis, we continued because we became aware, during these studies, of some seemingly unresolved problems in the field of glycogen synthesis proper. Certain problematic aspects of the relation of phosphorylase to glycogen synthesis had been brought out already through work on the epinephrine effect on phosphorylase activity. This work, done mainly by Sutherland and his coworkers and by Cori, showed clearly that phosphorylase activation invariably led to glycogen breakdown and never to glycogen synthesis. Since our experiments with breast muscle homogenates gave strong support to the proposition that phosphorylase was not involved in glycogen synthesis, we considered the possibility that the synthesis might go by way of UPDG. The demonstration by Leloir that liver contains an enzyme which will form glycogen from UDPG, made it seem likely that the problem of muscle glycogen synthesis could be explained in terms of a UDPG pathway. In the experiments reported below, results with the pigeon breast muscle homogenate are described, and preliminary data are given on the rabbit and rat skeletal muscle system which synthesizes glycogen from UDPG.

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