STUDIES OF THE METABOLISM OF MANNOSE

THE INFLUENCE OF MANNOSE ADMINISTRATION ON BLOOD SUGAR, BLOOD LACTIC ACID, AND LIVER GLYCOGEN IN THE ADULT RABBIT

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Mannose, glucose, and fructose are closely related and have long been known to be interconvertible *in vitro* (1). The metabolism of glucose and fructose in the mammal has been extensively studied, whereas mannose has been the subject of relatively few, partial studies *in vivo*. The finding of mannose in certain compounds of special physiological import, such as egg white proteins (2), skin collagen (3), human, anterior pituitary gonadotropic hormone (4), and phosphatides of tubercle bacilli (5), adds interest to metabolic studies of this sugar. Mannose has been shown to be readily fermentable by yeast (6–11) and readily glycolyzed by various tissues and tissue extracts *in vitro* (12–18). There are indications in the literature which point to the direct utilization of mannose by the mammal. The results of Mann and coworkers (19) and others (20,21) on the prevention of hypoglycemic shock after hepatectomy are in line with this. Certain workers have shown that mannose is a direct physiological antagonist to insulin (22).

Slow absorption of mannose has made tolerance studies difficult in the rat and in man; in addition doses of 50 gm. produce diarrhea in man (23). Harding *et al.* abandoned their work on man on this account (23). In two experiments conducted on the human subject by the present writers (unpublished) confirmation of the diarrheal effect of mannose was found. For these reasons the rabbit was used as an experimental animal in the present work. The absorption of mannose by the rat has been recently studied by Deuel *et al.* (24); the only available study on the rabbit is that by Hédon in 1900 (25). A reinvestigation of the absorption of mannose in the rabbit by the technique of Cori (26) should be carried out.

Harding and coworkers in 1933 conducted studies on mannose tolerance in man, but found no mannemia and no hyperglycemia (23). Deuel *et al.*

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in 1938 (24) studied the ketolytic and glycogenic ability of mannose in rats, but reported no blood sugar data. In view of the incompleteness of data upon the metabolism of mannose it was considered of interest to follow mannose tolerance and glycogenesis along with the determination of some intermediate blood metabolite. In the present paper three lines of investigation are reported; namely, the effects of mannose administration on blood sugar, blood lactate, and liver glycogen. This work was done on rabbits in an attempt to discover how mannose is utilized.

EXPERIMENTAL

Methods and Reagents

Mannose used in the experiments reported in this paper was prepared by the authors. After a number of studies the method adopted was as follows: Pure α-methylmannoside was prepared from vegetable ivory meal[1] according to the method of Hudson (27). Two recrystallizations were found necessary to give a pure product as judged by specific rotation, $[\alpha]_D^{20} = 80.8°$. 500 gm. of this mannoside were then hydrolyzed by refluxing in 10 liters of 20 per cent formic acid for 50 hours. The orange hydrolysate was then concentrated to 2 liters, decolorized with about 20 gm. of acid-washed norit, and concentrated at 10 mm. of Hg and 40° to a thick, colorless syrup. The syrup was taken up in 500 to 600 cc. of glacial acetic acid and crystallized as in the method of Hudson and Jackson (28). About 200 gm., dry weight (43 per cent yield), of pure *d*-mannose were obtained, $[\alpha]_D^{20} = 14.8°$. The low yield (due to incomplete crystallization of the syrup) was of minor importance, since a product was obtained which was prepared without the introduction of toxic substances such as heavy metals, and which was pure without recrystallization. About 800 gm. of mannose were prepared in the above manner.

Blood sugar was determined by the Benedict 1931 method (29), modified slightly for adaptation to the Evelyn colorimeter; *i.e.*, unknowns and standards were adjusted to contain 0.1 to 0.2 mg. of sugar, and a blank of all reagents was run with each experiment. The glucose used for analytical standards was C.P. anhydrous grade. Glucose for metabolism studies was U.S.P. granular. Fructose was determined by the method of Roe (30). Estimations of urinary sugar in the carbohydrate balance studies were carried out by the Benedict quantitative method (31).

Differential glucose and mannose determinations were carried out by the method of Harding, Nicholson, and Armstrong (23) as modified by Nicholson and Archibald (32); a strain of *Proteus vulgaris* from a collection of desiccated bacteria was used, and the concentration of reducing substances

[1] Kindly donated by the Art-in-Buttons Company, Rochester, New York.

was measured by the Benedict method, as described above. It was found necessary to plan animal experiments after the organisms were cultured to a favorable state of activity as determined by glucose "removal" tests.

Lactic acid was determined on tungstomolybdate (Benedict) blood filtrates by the method of Friedemann, Cotonio, and Shaffer as given by Peters and Van Slyke (33), with the apparatus of West (34). Pure zinc *dl*-lactate was prepared and used as a primary standard for recovery tests run with each group of blood lactate estimations. Liver glycogen was determined by the method of Good, Kramer, and Somogyi (35).

Metabolism Studies

The first problem investigated was the effect of mannose ingestion on blood sugar. This question was studied by experiments on carbohydrate balance in which the concentrations of blood glucose and blood mannose were followed over periods of 4 to 10 hours after mannose administration, and in which total urinary excretion was measured for periods of 24 to 36 hours after the start of each experiment. Eight experiments were carried out on five different animals; in five of these experiments differential glucose and mannose determinations were run on each blood sample.

The procedure used in each case is outlined in the following. Animals were fasted 36 to 48 hours and placed in metabolism cages. Control blood samples were taken and mannose was given by stomach tube within 10 minutes in dosages of 2 to 5 gm. per kilo of body weight in 10 per cent solution in water. Blood samples were subsequently taken at 30 or 60 minute intervals for the duration of the experiment. All samples were obtained by bleeding from the marginal ear vein into oxalated bottles, and were placed in the refrigerator at once. In most cases the protein-free filtrates were made the following day. Animals were kept in the metabolism cages, and after the last blood sample water was allowed during the subsequent period of urine collection. For the differential sugar determinations 5 cc. aliquots of the 1:10 tungstomolybdate filtrates were incubated with *Proteus* as in the method of Nicholson and Archibald (32) and 5 cc. aliquots of each blood sample were treated identically except for the addition of the bacteria. The reducing substance in these filtrates was then determined by the Benedict method, on 2 cc. of the bacterially treated and 1 cc. of the untreated filtrate (plus 1 cc. of water) in Folin-Wu sugar tubes. The observed total sugar is the concentration of reducing substance found for the untreated filtrate read against a glucose standard. The residual reducing substance after incubation with *Proteus* read against a mannose standard is the value for mannose plus saccharoid. The saccharoid value (determined for each experiment) is the concentration of residual reducing substance found for the fasting blood sample after treatment with *Proteus*.

Observed total sugar values are corrected by adding a fraction of the mannose concentration in the same sample. The correction is determined by multiplying the mannose value by the per cent difference in reducing power between glucose and mannose, as in the calculations of Roe and Schwartzman (36). Such a correction is valid, since the mannose fraction of the total blood sugar was underestimated by a similar percentage by being read against a glucose standard. In each experiment the actual difference between the reducing values of the glucose and mannose standards is the factor used in calculating the corrected total sugar. Such a procedure is considered more reliable than using average reduction equivalents, since in this method each experiment acts as its own control. The corrected total

TABLE I

Blood Glucose and Blood Mannose after Mannose Ingestion

Animal 5, male rabbit, 2.14 kilos, fasted 48 hours. Dose, 4 gm. of mannose per kilo, in 100 cc. of H_2O.

Time	Blood sugar values, mg. per 100 cc. whole blood					
	Observed total	After *Proteus*	Correction, (7) × 0.12*	Corrected total sugar	Blood glucose	Blood mannose
(1)	(2)	(3)	(4)	(5)	(6)	(7)
min.						
0	85	14†		85	71	0
60	158	30	1.9	160	130	16
120	138	35	1.6	140	105	21
180	124	29	1.5	126	97	15
255	126	21	0.8	127	106	7

* Copper reduction values: glucose 100, mannose 88.

† Saccharoid value for this experiment.

sugar value minus the "mannose plus saccharoid" value represents blood glucose.

The results of one of the experiments are shown in Table I. Column 4 illustrates the method of calculating the correction explained above. The saccharoid determination serves also as a check upon the activity of the microorganisms. The average saccharoid value found in samples of fasting blood from seven different animals was 10 mg. per cent (range, 6 to 14 mg. per cent). Added mannose was recovered from blood filtrates to the extent of 93 to 107 per cent in tests run on three different batches of bacteria. An assumption made in the differential sugar determinations in these experiments is that the saccharoid value remains the same for the duration of the experimental period. Control experiments on non-glucose reducing substance as determined with *Proteus* showed that it remained very constant over periods of at least 3 hours.

Inspection of Table I shows that the administration of mannose by mouth leads to a prolonged hypersaccharemia (Column 5), an elevation of blood glucose (Column 6), and the appearance of mannose (Column 7) in the peripheral venous blood of an intact rabbit. Four other experiments in this series showed similar results except in the degree of metabolic transformation of mannose. The experiment of Table I showed the greatest increases in blood glucose, but the other four experiments gave significant changes in the same direction. In one of these experiments in which the samplings were continued for 10.5 hours the hyperglycemia and mannemia still persisted.

The total sugar excretion over periods of 24 to 36 hours after mannose administration in doses of 2 to 4 gm. per kilo by the oral and intraperitoneal routes averaged 4 per cent of the dose administered (range, 0 to 8 per cent) in eleven animals tested. Differential sugar determinations were not done on these urines because of the small amounts of reducing substance found.

The specific fructose method of Roe (30) was applied to blood samples in one of the experiments on mannose tolerance. It was found that no measurable fructose was present in any blood sample during the 4 hour period of the test. Blood samples from four other animals receiving doses of mannose of 3 to 5 gm. per kilo of body weight also showed blood fructose values of zero.

The second phase of this investigation was a study of the effect of mannose administration on blood lactic acid. Carpenter *et al.* (37) found that glucose, galactose, and fructose give rise to increased lactate in the blood under basal conditions. Rynbergen and coworkers (38) suggested that lactic acid might be an intermediary in the transformation of fructose to glucose. Therefore, it was considered advisable to study the effect of mannose administration on blood lactate in the resting rabbit. Five experiments on the effect of mannose on blood lactate were carried out, along with two positive controls on the effect of glucose, and one negative control on the effect of mannoheptose. Total blood sugar and blood lactic acid were determined on all samples.

The experimental procedure was as follows: Rabbits weighing about 3 kilos each were fasted for 24 hours. The animals were maintained in a state of mild sedation by means of small doses of veterinary nembutal solution given intraperitoneally every hour or so, depending on the condition of the animal. For the duration of the experiment the animal was in a relaxed, reclining position, the respiration was regular, the pupil responded to bright light, and pain reflexes were never absent. It was felt that such a state was the closest approach to a basal condition that could be obtained. 2 or 3 hours of control period were allowed before the sugar was given to permit the animal to come to a steady state as far as blood sugar

and blood lactate were concerned. Analysis of blood samples taken hourly during the control period showed that the values for blood sugar and blood lactate remained constant or dropped slightly; thus increases after sugar administration could be regarded as true increases above the basal level. Sugars were given in dosages of 2 gm. per kilo of rabbit, and 5 cc. blood samples were taken at hourly intervals over periods of 3 to 6 hours in oxalated bottles containing 50 to 100 mg. of sodium fluoride. The fluoride-preserved bloods were placed at once in the refrigerator and analyzed the following day. The *α-d*-mannoheptose used in Experiment H was prepared in Dr. C. S. Hudson's laboratory and had a specific rotation of +68.8° with sodium light at 20°. Recoveries of pure zinc lactate were run along with six of the eight experiments and 95, 95, 92, 90, 90, and 91 per cent, respectively, of 0.605 mg. samples of lactic acid were recovered by analysis. All lactate values reported are averages of two determinations on the same blood filtrate.

The results of eight experiments are summarized in Fig. 1. Inspection of Fig. 1 reveals that, in general, elevated levels of blood lactate parallel hyperglycemia when a hexose was used. In the case of mannoheptose, Experiment H, no increase in blood lactate was observed even when a saccharemia of 200 mg. per cent was reached. It should be noted that Experiment H not only represented a control on the effect of hypersaccharemia upon the blood lactate level, but it also served as a control on every phase of the experimental technique. The curve obtained for blood lactic acid in this case is practically a straight line at the basal level. Thus, changes observed in blood lactic acid can be considered as due only to the influence of the sugar given and to the level of saccharemia reached. When mannose was administered intraperitoneally (Experiments C and D), marked increases in blood sugar were observed and correspondingly marked increases in blood lactate were found. In Experiments E, F, and G, when mannose was given orally, less hyperglycemia and smaller increases in blood lactate were observed. It appears that the differences in uptake of the mannose into the blood will account for the differences in blood sugar and lactate in these two sets of experiments. Mannose administration always led to a positive increase in blood lactic acid.

The third phase investigated was the effect of mannose administration on liver glycogen in fasted rabbits. This question was studied by determining the changes in liver glycogen produced in periods of 6, 10, and 12 hours after mannose was given in varying dosages by three different routes.

The procedure carried out is outlined in the following. The double laparotomy technique of Cohn and Roe (39) was used on ten of the animals of this series. By this method a control value for fasting liver glycogen was determined on the same animal in which glycogen deposited after

mannose or glucose administration was measured. Rabbits weighing from 1.7 to 3 kilos, unselected as to sex, were fasted 24 hours, anesthetized with nembutal, and operated on. After a 1 gm. sample was taken from the right liver lobe, the wound was closed, the sugar was given, and the animal was kept in a metabolism cage for the duration of the experiment. After a period of 6, 10, or 12 hours the animal was anesthetized, reopened, and sam-

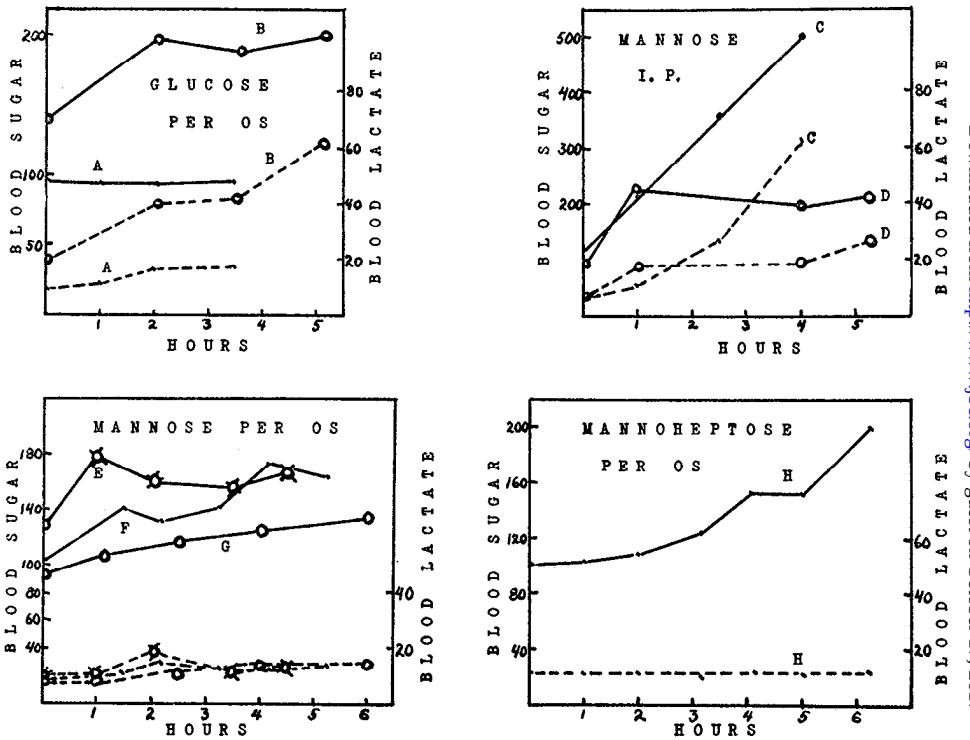

FIG. 1. Influence of administration of various sugars on blood sugar and blood lactate. The doses given in every case were 2 gm. of sugar per kilo of body weight. Each experiment is labeled by letter and represented by a pair of curves. The solid lines refer to blood sugar; broken lines to blood lactate. The units of the vertical axes are mg. per cent.

ples of the right and left liver lobes were taken for analysis. The animal was then sacrificed. All samples were immediately placed in tared tubes containing 5 cc. of 30 per cent KOH, weighed, and subsequently treated as in the method of Good, Kramer, and Somogyi (35). Total sugar excretion was measured on the urines collected during the period of the experiment.

The results of nineteen unselected, serially run experiments are summarized in Table II (Animals 9 and 10 of this series died under anesthesia).

Sugar excretion, when mannose was given by mouth, averaged 4.6 per cent of the dose administered, and 12.2 per cent when mannose was given subcutaneously. The glucose tests serve as positive controls on each of the

TABLE II

Liver Glycogen Formation in Adult Rabbits after Mannose and Glucose Administration by Various Routes

The sugars were given in 20 per cent solution in water; dosages are expressed in gm. per kilo of body weight. The animals are numbered serially.

Sugar	Animal No.	Dose	Liver glycogen, per cent						
			Control	After 6 hrs.	After 10 hrs.	After 12 hrs.	Average		Average increase
							Control	After sugar	
Sugars given *per os*									
Mannose	5	3	1.05			0.81			
"	6	3	1.11			1.69			
"	7	3	0.61			1.31			
"	8	3	0.49			1.28	0.81	1.27	0.46
Glucose	11	3	0.79			1.00			
"	12	3	0.32			3.73	0.56	2.37	1.81
Mannose	13	4			1.40				
"	14	5			2.53			1.97	1.20*
Glucose	18	5			4.03				
"	19	4			4.82			4.41	3.64*
Sugars given subcutaneously									
Mannose	1	3	0.39	2.99					
"	2	3	1.36	2.93					
"	3	3	1.02			3.81			
"	4	3	0.55			2.90	0.83	3.16	2.33
Glucose	20	3				1.99			
"	21	3		2.60				2.29	1.52*
Sugars given intraperitoneally									
Mannose	15	3			2.29				
"	16	5			4.11			3.20	2.43*
Glucose	17	5			4.15			4.15	3.38

* Based upon the average control value for ten rabbits (0.77).

mannose experiments as shown in Table II. Control values for liver glycogen during fasting averaged 0.77 per cent in ten animals. Negative controls on the effects of length of fast, anesthetic, and operation on liver glycogen carried out by Cohn and Roe (39) in this laboratory showed

that at the 12 hour period *total* liver glycogen values by this technique must be greater than 1.08 per cent to be significant (average of nine experiments). Translating this figure into terms of glycogen *increase* due to sugar administration gives a value of 0.31 per cent (1.08 − 0.77) which would be the minimum that could be accepted as significant in these experiments. The last column of Table II, labeled "Average increase," represents glycogen deposited owing to the influence of the sugar administered, and is found by subtracting the value for fasting liver glycogen from the total value found 6, 10, or 12 hours after sugar administration. All values reported for glycogen percentages after sugar administration are averages for samples from two lobes of the liver.

Inspection of Table II shows that mannose given orally at 3 gm. per kilo produced an amount of extra glycogen that is very little greater than the minimum significant value (0.31) under these experimental conditions, but that when the dosage was raised to 4 or 5 gm. per kilo an average of 1.2 per cent of glycogen was deposited during 10 hours. When mannose was given subcutaneously at 3 gm. per kilo it is seen that the glycogen deposited after periods of 6 or 12 hours amounted to 2.33 per cent on the average. The latter figure was higher than that for glucose run under the same conditions. In the last section of Table II it will be seen that the figure for glycogen deposited after mannose administration by the intraperitoneal route compared favorably with that for the glucose experiment. Table II shows in general that in the animals tested mannose raised liver glycogen slightly when given orally, and, when administered parenterally, this sugar was glycogenic to approximately the same degree as glucose.

DISCUSSION

Studies on carbohydrate balance showed that mannose is utilized to a high degree by rabbits, since an average of 96 per cent of varying dosages of the sugar was retained by these animals after administration by the oral or intraperitoneal route. The present studies have shown that mannose was absorbed from the gut and appeared in peripheral venous blood of the rabbit after mannose ingestion. In addition mannose administration produced an elevation of blood glucose. Increases in blood glucose could be interpreted as being due to conversion of mannose to glucose or to stimulation of a glucose-producing mechanism. Stimulation of the formation of blood glucose by a saccharemia of a non-utilizable sugar is unlikely. The data of Roe and Hudson (40) in which a hypersaccharemia was produced by mannoheptose administration showed no significant increase in fermentable reducing substance in the same bloods. Therefore, it is concluded that the data of the present studies can be interpreted as showing conversion of mannose to glucose.

Some insight into a possible mechanism for the metabolic transformation of mannose to glucose is gained from the studies on lactic acid and glycogenesis. Since, by the use of a specific method, no fructose was found in any blood sample from animals tested during the course of hyperglycemia following mannose administration, direct conversion of mannose to glucose by epimerization and attendant Lobry de Bruyn equilibrium appears to be excluded. Rynbergen and coworkers (38) suggested that lactic acid may be an intermediate in the transformation of fructose to glucose. Cori (41) stated that lactate surpasses even fructose in the formation of liver glycogen. The well known lactic acid cycle establishes an important link between the carbohydrate metabolism of muscle and liver. Muscle (and other cellular) glycolysis produces lactate which forms liver glycogen; when liver glycogen is hydrolyzed, glucose results. A plethora of a sugar such as mannose could thus reappear in the blood as glucose after glycolysis in blood and tissues and subsequent glycogenesis and glycogenolysis in the liver. Such a scheme would fit the case of mannose, since blood lactate, liver glycogen, and blood glucose were found to increase after mannose administration.

SUMMARY

1. Studies of the metabolism of mannose in the rabbit have been carried out.

2. Experiments on carbohydrate balance showed an average retention of 96 per cent of doses of mannose of 2 to 5 gm. per kilo when this sugar was administered orally or intraperitoneally. These results indicate a high degree of utilization of mannose by the rabbit.

3. Mannose appeared in the peripheral venous blood and produced an elevation of blood glucose in all animals tested after mannose ingestion. No fructose was found in any blood sample from animals tested during the course of hyperglycemia following mannose administration.

4. Mannose administration led to an increase in blood lactic acid. Elevations in blood lactate produced by mannose were similar to those after glucose administration in that they paralleled increases in total blood sugar. These results were in contrast to those of a control experiment with mannoheptose in which blood lactate remained constant at the basal level even when a saccharemia of 200 mg. per cent was reached.

5. Amounts of liver glycogen found at 6, 10, and 12 hours after mannose administration were approximately of the same order as those found after glucose administration at the same dosage level when these sugars were given parenterally to animals previously fasted 24 hours.

6. The combined results of the experiments carried out indicate that

mannose is fairly slowly absorbed from the gut, well utilized, and convertible to glucose in the intact rabbit. A possible mechanism for the metabolic conversion of mannose to glucose by way of lactic acid and liver glycogen is suggested.

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