Metabolism of Circulating Disaccharides in Man and the Rat *

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Summary. The metabolism of circulating disaccharides was studied in adult humans and rats. After iv infusions of 10 g of either lactose, sucrose, or maltose in four adults, no rise in blood glucose was noted. A mean of 8.7 ± 1.89 g of the lactose and 6.3 ± 1.39 g of the sucrose was excreted in the 24–hour urine sample. Only 0.11 ± 0.03 g of the infused maltose was recovered in the urine, suggesting that the maltose was metabolized.

After injection of ^{14}C–labeled lactose and sucrose in rats, 6.2 ± 2.7 and $7.6 \pm 2.4\%$, respectively, was oxidized to $^{14}CO_2$ in 24 hours; 62.1 ± 13.5 and $68.4 \pm 10.8\%$ of the respective disaccharides was excreted into the urine. Conversely, after injection of ^{14}C–labeled maltose $54.6 \pm 7.0\%$ was oxidized to $^{14}CO_2$ and $4.8 \pm 3.9\%$ excreted in the urine. The per cent of maltose oxidized to CO_2 was similar to that of glucose.

In addition to small intestinal mucosa, homogenates of rat kidney, brain, and liver as well as serum were found to have measurable maltase activities. The role of these tissue maltases in the metabolism of circulating maltose and maltosyloligosaccharides is discussed.

Introduction

The hydrolysis of disaccharides by disaccharidases in the intestinal mucosa is usually so complete that only a small fraction of the ingested disaccharide is absorbed intact and excreted in the urine (1, 2). An increase in the absorption and urinary excretion of unhydrolyzed lactose and sucrose has been reported in patients with celiac disease (3, 4), tropical sprue (5, 6), and a variety of other gastrointestinal disorders (4, 7–9) usually associated with a deficiency of intestinal disaccharidases. The purpose of the present study was to compare the metabolic fate of circulating lactose, sucrose, and maltose in adult humans and rats. The results suggest that circulating maltose, unlike lactose and sucrose, may be hydrolyzed by extraintestinal maltases and subsequently metabolized.

Methods

Studies in man. Normal individuals and patients with untreated celiac disease fasted overnight and, after voiding, ingested 25 g of either lactose, sucrose, or maltose in 500 ml of water. All urine was collected for the next 5 hours and a sample frozen for subsequent assay. Urinary disaccharides were determined by incubating 0.1 ml of desalted urine (10) with 1 mg of commercial lactase, sucrase, or maltase dissolved in 0.2 ml of appropriate buffer for 1 hour at 37° C. The buffer for lactase was 0.35 M sodium phosphate, pH 7.25; for sucrase, 0.05 M sodium acetate, pH 4.77; and for maltase, 0.05 M sodium acetate, pH 5.20. After incubation, the net increase in glucose was measured by the glucose oxidase method (11) and used to calculate the amount of disaccharide present in the urine. Experiments with standard disaccharide solutions yielded a 90 to 95% recovery.

Four adult subjects were given iv infusions of 10 g in 100 ml of water of either lactose, sucrose, or maltose
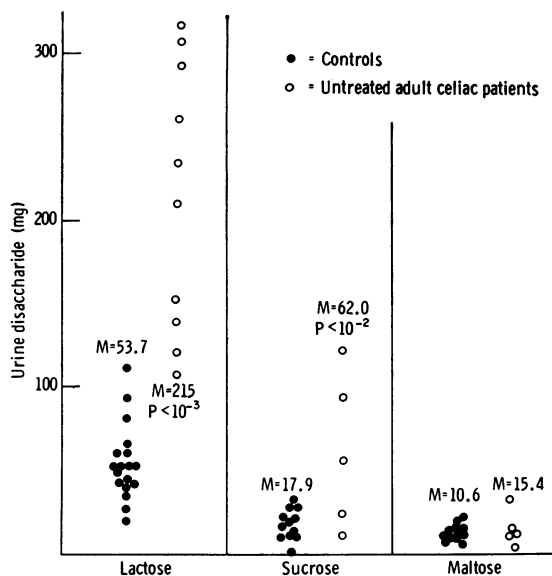
FIG. 1. DISACCHARIDE RECOVERED IN 5-HOUR URINE SAMPLE AFTER INGESTION OF 25 G OF LACTOSE, SUCROSE, OR MALTOSE. M = mean.

over a 30-minute period. Blood was collected at 0, 15, 30, 60, 90, 120, 150, and 180 minutes, and urine was collected under refrigeration for 24 hours. Blood sugar (12), true blood glucose (11), and urinary disaccharides were determined.

In vivo studies in rats. Experiments were performed on nonfasting male Sprague-Dawley rats weighing approximately 250 g and fed a standard ad libitum diet.[1] Five mg of either lactose, sucrose, maltose, or appropriate monosaccharides dissolved in 0.5 ml of water was injected into the tail vein. Each injection contained 0.5 μc of the respective ^{14}C-labeled disaccharide or monosaccharide.[2] Radiopurity of the ^{14}C-labeled sugars was verified by descending paper chromatography and found to be greater than 98%. Before injection, some animals were anesthetized with ether and underwent either complete resection of the small bowel, bilateral nephrectomy, 70% hepatectomy, or a sham operation. After injection the rats were placed in a metabolic chamber, and the CO_2 expired over a 24-hour period was assayed according to the method of Fredrickson and Ono (13). [14]CO_2 in Hyamine was assayed in a Packard liquid scintillation spectrometer at 90% efficiency. Urine was also collected under refrigeration for 24 hours for determination of radioactivity. Quenching was corrected by the channels ratio method (14).

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[1] Rockland mouse/rat diet, distributed by Tekland, Monmouth, Ill.

[2] Lactose-1-^{14}C, sucrose-U-^{14}C, maltose-1-^{14}C, glucose-1-^{14}C, glucose-U-^{14}C, galactose-1-^{14}C, and fructose-1-^{14}C were obtained from Calbiochem, Los Angeles, Calif. Maltose-U-^{14}C was obtained from Nuclear-Chicago, Des Plaines, Ill.

Urine was desalted by stirring with Rexyn 1-300 (H-OH)[3] and then subjected to descending paper chromatography on Whatman 1 filter paper for 16 hours. The solvent systems were *a*) butanol, ethanol, and water (40 : 10 : 50, lower phase) and *b*) isopropanol and water (160 : 40). The dried chromatograms were cut into strips and radioactive peaks detected by a Vanguard automatic chromatogram scanner. Glucose-1-^{14}C and appropriate ^{14}C-labeled disaccharides were used as reference compounds and the migration distances calculated as Rg [(distance sugar travels from the origin/distance glucose travels from the origin) × 100].

In other experiments the jugular vein of rats was cannulated under light Pentothal anesthesia, and 100 mg of either lactose, sucrose, or maltose in 0.5 ml of water was infused over a 5-minute period. Glucose was measured in blood collected from the tail at 0, 5, 15, 30, 45, and 60 minutes (11).

In vitro studies in rats. Experiments to determine maltase content of various organs were performed in nonfasting male Sprague-Dawley rats weighing approximately 250 g. The rats were stunned by a blow on the head and exsanguinated by decapitation. Tissue slices from liver, kidney, and brain were prepared with a Stadie-Riggs tissue slicer. Triplicate incubations were carried out in 25-ml Erlenmeyer flasks containing 2.5 ml Krebs-Henseleit bicarbonate buffer, pH 7.4 (15), 5 mg of disaccharide or monosaccharide, and 0.5 μc of ^{14}C-labeled disaccharides or monosaccharides. After being gassed with 95% O_2 and 5% CO_2 for 10 seconds, the flasks were capped with serum stoppers fitted with a center well. The incubations were carried out in a Dubnoff shaking incubator for 1 hour at 37° C. At the end of this time, 0.5 ml of 1 M Hyamine was injected through the serum stopper into the center well, and 0.3 ml of 6 M sulfuric acid was similarly added to the incubation mixture. The flasks were then incubated for an additional 45 minutes at 37° C to permit diffusion of the liberated [14]CO_2 into the hyamine. The Hyamine in the center well was then transferred quantitatively to 20-ml counting vials, and 14 ml of a solution of 0.3% 2,5,-diphenyloxazole and 0.01% 1,4-bis-2-(5-phenyloxazolyl) benzene in toluene was added. Radioactivity of the [14]CO_2 was counted in a liquid scintillation spectrometer as described above.

Organ homogenates were prepared by homogenizing 1 g of tissue with 4 ml of chilled distilled water in a Potter-Elvehjem tissue grinder. Maltase activity in whole homogenates diluted 1 : 50 or 1 : 100 was measured according to the method of Sols and De la Fuente (16). Protein was determined by the method of Lowry, Rosebrough, Farr, and Randall (17). One U of maltase activity was equal to 1 μmole of maltose hydrolyzed per minute per g of tissue protein.

Results

Studies in man. Normal subjects ingested 25 g of lactose, sucrose, or maltose and excreted

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[3] Fisher Scientific Co., New York, N. Y.

TABLE I

Disaccharide recovered in 24-hour urine sample after iv administration of 10 g in adult humans

Subject	Disaccharide infused		
	Lactose	Sucrose	Maltose
	g	*g*	*g*
J.S.	10.5	7.2	0.09
I.R.	7.1		0.08
B.B.	8.6	4.8	0.12
B.G.		6.8	0.15
Mean ± SD	8.7 ± 1.8	6.3 ± 1.3	0.11 ± 0.03

(mean ± SD) 53.7 ± 22.8, 17.9 ± 9.6, and 10.6 ± 2.1 mg, respectively, in the 5–hour urine sample (Figure 1). After lactose and sucrose ingestion, 215 ±80 (p < 0.001) and 62.0 ± 49 (p < 0.01) mg, respectively, was excreted by patients with untreated celiac disease (Figure 1). This amount was a fourfold increase of urinary disaccharide excretion over normal and suggested enhanced intestinal absorption of unhydrolyzed lactose and sucrose. After maltose ingestion celiac patients excreted a mean of 15.4 ± 10.6 mg, not significantly different from the controls (0.3 > p > 0.25).

These findings suggested that, unlike lactose or sucrose, the intestinal absorption of unhydrolyzed maltose was either not increased in celiac disease or its metabolic fate was different from that of the other disaccharides. To study this further, we measured the concentration of blood sugar after the infusion of 10 g of lactose, sucrose, or maltose in four adult subjects. As shown in Figure 2, copper–reducing substance rose after iv lactose and maltose, reflecting the increase in circulating disaccharide (sucrose is not a copper–reducing

FIG. 3. OXIDATION OF 1-^{14}C–LABELED DISACCHARIDE TO ^{14}CO$_2$ AFTER IV INJECTION IN THE RAT. Each curve represents mean of five animals.

sugar). No significant increase in true blood glucose was noted after any of the disaccharide infusions. A mean of 8.7 ± 1.8 g of the lactose and 6.3 ± 1.3 g of the sucrose was excreted in the 24–hour urine sample (Table I). In contrast, only 0.11 ± 0.03 g, or 1%, of the infused maltose was excreted into the urine.

Studies in the rat. After the iv injection of lactose-1-^{14}C (Figure 3), or sucrose-U-^{14}C, only small amounts of isotope appeared in the expired CO$_2$ over a 24–hour period. On the other hand, after maltose-1-^{14}C or maltose-U-^{14}C injection, excretion of the isotope as ^{14}CO$_2$ was rapid, comparable to that found after the injection of glucose-1-^{14}C or other monosaccharide mixtures. These monosaccharides were selected because they are the hydrolytic metabolites of the injected disaccharides. Peak ^{14}CO$_2$ excretion after maltose-1-^{14}C was noted between 50 and 70 minutes after injection.

The results of the metabolism of disaccharides are summarized in Table II. After lactose-1-^{14}C and sucrose-U-^{14}C injection (mean ± SD), 6.2 ± 2.7 and 7.6 ± 2.4%, respectively, was oxidized to ^{14}CO$_2$ in 24 hours; 62.1 ± 13.5 and 68.4 ± 10.8% of the respective disaccharide was excreted into the urine. After the injection of maltose-1-^{14}C and maltose-U-^{14}C, 54.6 ± 7.0 and 58.6 ± 5.8%, respectively, was oxidized to ^{14}CO$_2$ and only 4.8 ± 3.9 and 3.2 ± 3.0%, respectively, was excreted in the urine. The per cent of maltose-^{14}C oxidized to ^{14}CO$_2$ was similar to that of ^{14}C–labeled monosaccharides.
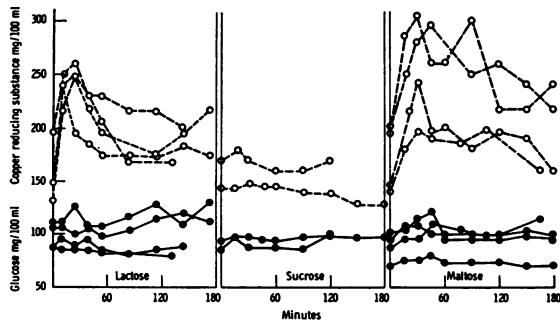

FIG. 2. NONSPECIFIC COPPER–REDUCING SUBSTANCE AND TRUE BLOOD GLUCOSE CONCENTRATION AFTER IV INFUSION OF 10 G OF LACTOSE, SUCROSE, OR MALTOSE IN ADULT HUMANS.
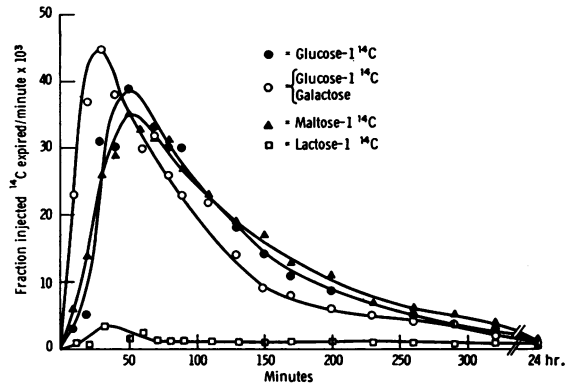
TABLE II

Metabolism of ^{14}C-labeled disaccharides after iv administration in the rat**

Sugar	No. animals	$^{14}CO_2$	Urine ^{14}C
		% dose/24 hours	
Glucose-1-^{14}C	5	62.0 ± 11.6	5.3 ± 4.7
Glucose-U-^{14}C	5	64.0 ± 12.0	14.8 ± 10.3
Glucose-1-^{14}C + galactose†	4	52.0 ± 9.7	9.8 ± 6.6
Glucose-U-^{14}C + fructose-U-^{14}C‡	5	50.7 ± 7.9	19.3 ± 4.6
Maltose-1-^{14}C	5	54.6 ± 7.0	4.8 ± 3.9
Maltose-U-^{14}C	5	58.6 ± 5.8	3.2 ± 3.0
Lactose-1-^{14}C	6	6.2 ± 2.7	62.1 ± 13.5
Sucrose-U-^{14}C	5	7.6 ± 2.4	68.4 ± 10.8

* Animals received 5 mg of sugar in 0.5 ml (1 μc per ml).
† Mixture contained 2.5 mg of each sugar and 0.5 μc glucose-1-^{14}C.
‡ Mixture contained 2.5 mg and 0.25 μc of each sugar.

Paper chromatography of the urinary ^{14}C recovered after injection of each of the disaccharides revealed compounds with Rg values similar to the injected disaccharide. In addition, after maltose injection, 5 to 10% of the urinary ^{14}C migrated with an Rg similar to glucose.

The extensive metabolism of injected maltose to CO_2 suggested that tissue other than small bowel mucosa might possess maltase activity; therefore, the maltase activity in homogenates of organs from three rats was measured (Table III). As expected, maltase activity in small bowel mucosa was high; however, kidney, and, to a lesser extent, brain, pancreas, and liver also had measurable maltase levels. Rat serum likewise demonstrated enzyme activity, whereas human serum assayed for comparison had virtually none.

TABLE III

Maltase activity in homogenates of rat organs

Organ	Maltase		
	1	2	3
	U*	U	U
Intestinal mucosa	485	390	205
Kidney	17	61	73
Brain	14		4.0
Liver	2	1.6	1.7
Pancreas		4	5.6
Spleen	1	0.1	0.2
Muscle	0.1	0.3	0.3
Serum	9.1	12.5	8.9
Human serum	0.3	0.1	0.2

* One U equals 1 μmole maltose hydrolyzed per minute per g protein.

TABLE IV

Oxidation of ^{14}C-labeled disaccharides* to $^{14}CO_2$ by rat organ slices

Experiment no.	Sugar	$^{14}CO_2$†		
		Liver	Kidney	Brain
		cpm/g tissue		
1	Glucose-1-^{14}C	32,000	105,000	288,666
	Maltose-1-^{14}C	9,000	58,900	110,066
2	Glucose-1-^{14}C + galactose‡	45,930	243,300	
	Lactose-1-^{14}C	3,000	15,000	
3	Glucose-U-^{14}C + fructose-U-^{14}C§	45,000	362,000	
	Sucrose-U-^{14}C	4,330	37,000	

* Five mg containing 0.5 μc in each flask.
† Mean of triplicate experiments.
‡ Flask contained 2.5 mg of each sugar and 0.5 μc glucose-1-^{14}C.
§ Flask contained 2.5 mg and 0.25 μc of each sugar.

Tissue slices were prepared from some of the organs having maltase activity and were incubated with either ^{14}C–labeled disaccharide or a control mixture of ^{14}C–labeled monosaccharides. The amount of $^{14}CO_2$ produced by liver, kidney, and brain slices during incubation with maltose-1-^{14}C was 30, 56, and 40%, respectively, of the amount recovered from the incubation with glucose-1-^{14}C (Table IV). The amount of $^{14}CO_2$ recovered from the incubation of lactose-1-^{14}C and sucrose-U-^{14}C with liver and kidney slices was about 10% or less of that recovered after incubation with the respective control monosaccharides. This was in agreement with negligible lactase and sucrase measurement in those tissues. It would appear that organs containing maltase activity are capable of utilizing maltose *in vitro* as a substrate for metabolism to CO_2.

In an effort to determine whether any one of these organs was responsible for the hydrolysis and subsequent metabolism of circulating maltose, we performed experiments on partially eviscerated animals. The selective removal of either the kidneys, 70% of the liver, or entire small bowel had little effect on the oxidation of injected maltose-1-^{14}C to $^{14}CO_2$ (Table V). The effect on the oxidation of injected glucose-1-^{14}C and lactose-1-^{14}C is shown for comparison. After removal of the kidneys, the oxidation of injected lactose-1-^{14}C to $^{14}CO_2$ increased fivefold.

The presence of serum maltase activity sug-

TABLE V

Oxidation of ^{14}C-labeled sugars to $^{14}CO_2$ after iv injection in partially eviscerated rats

Organ removed	$^{14}CO_2$		
	Maltose-1-^{14}C	Glucose-1-^{14}C	Lactose-1-^{14}C
	% dose/24 hours		
Sham	48.3 ± 7.7 (4)*	55.3 ±19.5 (3)	2.9 ±0.9 (3)
Kidneys	46.2 ±11.3 (4)	45.5 ±17.6 (3)	16.9 ±5.9 (3)
Liver (70%)	50.1 ± 9.2 (5)	43.9 ± 4.7 (3)	2.4 (1)
Small bowel	45.0 ± 2.7 (3)		

* Number of rats is given in parentheses.

gested that intravascular hydrolysis of circulating maltose, providing glucose for further metabolism, might explain its low urinary excretion. The blood glucose concentration was therefore measured in rats after iv infusion of 100 mg of either glucose, lactose, sucrose, or maltose. After glucose infusion the expected rise in blood glucose was readily observed (Figure 4). A similar rise in blood glucose was noted only after maltose infusion.

Discussion

The minimal amounts of lactose, sucrose, and maltose that are absorbed intact after oral ingestion reflect the over–all efficiency of intestinal hydrolysis and, to a lesser extent, the relatively poor transport of unhydrolyzed disaccharide across the intestinal mucosa. Studies in man (18, 19) have shown that the rates of hydrolysis for sucrose and maltose are appreciably greater than the rate for lactose and that lactose hydrolysis is rate limiting for over–all lactose absorption.

Our studies show that after an oral load of lactose, more of the unhydrolyzed disaccharide is excreted in the urine than after comparable loading with sucrose or maltose. These observations are consistent with a less efficient hydrolysis of lactose resulting in increased absorption of the intact disaccharide. In normal mucosa an increasing level of activity exists between lactase, sucrase, and maltase (3, 20, 21). The amount of unhydrolyzed disaccharide absorbed and excreted into the urine seems to be inversely proportional to the level of its disaccharidase activity. After oral loading, patients with untreated celiac disease excreted increased amounts of urinary lactose and sucrose, but not maltose. The previous demonstration that lactase activity is most severely reduced in
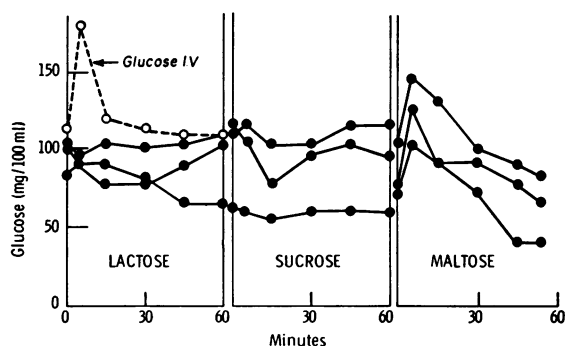

FIG. 4. BLOOD GLUCOSE CONCENTRATION AFTER IV INFUSION OF 100 MG OF LACTOSE, SUCROSE, OR MALTOSE IN THE RAT.

untreated celiac disease and maltase is least affected could explain this difference (3, 4). However, a difference in the metabolic fate of absorbed maltose may also be responsible for its low urinary excretion.

Previous studies in man and animals have shown that parenterally administered lactose or sucrose is rapidly excreted into the urine (22–25). Furthermore, the increase in blood lactose that occurs during lactation is associated with marked lactosuria (26). Unlike lactose and sucrose, the intravenously administered maltose was not followed by a significant excretion of the disaccharide in the urine of our subjects. Similar findings have been noted in the rat after ip injection of maltose (27). None of our adult subjects showed a rise in blood glucose after the iv administration of any of the disaccharides. In the rat, however, the rise in blood glucose noted only after maltose infusion suggests that some of the disaccharide is hydrolyzed intravascularly, particularly since rat serum possesses maltase activity.

The results of the experiments in which ^{14}C-labeled disaccharides were administered to the rat indicate that injected maltose can be metabolized to CO_2 almost as completely as glucose. On the other hand, lactose and sucrose are poorly oxidized to CO_2 and are mainly excreted in the urine. Similar findings with lactose-1-^{14}C have been reported by Carleton, Misler, and Roberts (28). Although all of the urinary isotope after injection of lactose-1-^{14}C was identified chromatographically as lactose, studies performed with lactose-U-^{14}C have shown that other radioactive peaks may be present in the urine (29).

It is unlikely that the circulation of injected maltose to small bowel mucosa played a significant part in its over–all metabolism. One would expect on this basis that at least injected sucrose would also be metabolized. Furthermore, the removal of the small bowel did not affect the over–all metabolism of maltose to CO_2. Several other organs also had maltase activity, but removal of these tissues did not significantly alter the oxidation of maltose to CO_2. It therefore seems unlikely that a single tissue maltase was responsible for hydrolyzing circulating maltose. It is also possible that maltose may be metabolized via other pathways than through hydrolysis to glucose.

Previous reports of maltase activity in organs other than small bowel (30–34) have raised questions regarding its function. Since maltosyloligosaccharides have been isolated from rat liver (35, 36), an amylase–oligoglucosidase (maltase) pathway of glucose production from glycogen has been proposed (37), but thus far this hypothesis lacks convincing support (38). Hers (39) reported an absence of lysosomal acid maltase in tissues of patients with generalized glycogen storage disease and suggested that this enzyme deficiency is responsible for the accumulation of glycogen. Others have proposed that the maltosyloligosaccharides are glycogen precursors, but here also the evidence is conflicting (40–42).

In our experiments, maltase activity in rat kidney was greater than in any of the other organs studied with the exception of small bowel. The amount of $^{14}CO_2$ produced from maltose-1-^{14}C compared with glucose-1-^{14}C by tissue slices was roughly proportional to the tissue maltase activity, i.e., kidney > brain > liver. It is also possible that, unlike liver (43), the kidney cell may be permeable to maltose. These findings suggest that maltase may have a more important metabolic role in the kidney than in liver.

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