Hydrolysis of lactitol, maltitol and Palatinit® by human intestinal biopsies

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(*Received 3 November 1986 – Accepted 15 May 1987*)

1. The hydrolysis of sugar alcohols of the disaccharide type such as lactitol, maltitol and Palatinit® (the latter an equimolar mixture of 6-O-α-D-glucopyranoside-D-mannitol and 6-O-α-D-glucopyranoside-D-sorbitol) by homogenates of human intestinal biopsies were compared with corresponding natural disaccharides such as lactose, maltose and isomaltose. Seven of the human biopsies were normal with regard to their disaccharidase activities, while twelve biopsies showed decreased levels of disaccharidase activities.

2. All biopsies, normal as well as abnormal, showed essentially the same capacity to hydrolyse the sugar alcohols. Activities towards lactitol (0·34 IE/g protein (where IE = μmol disaccharide hydrolysed/min at 37°)) and Palatinit (2·50 IE/g protein) were only 1·3% of those towards lactose and isomaltose. The activity towards maltitol was much higher (19·1 IE/g protein), approximately 10% of that towards maltose and about as high as the activity towards trehalose. This finding indicates that despite the fact that lactitol and Palatinit were poor substrates, significant amounts of ingested maltitol might be digested and utilized by man.

3. Glucose release was reduced by approximately 25% when maltitol or Palatinit were present at concentrations equal to those of maltose. Palatinit decreased the hydrolysis of sucrose by 12%. Lactitol had no inhibitory effect on the hydrolysis of disaccharides.

Lactitol, maltitol and Palatinit® (the latter an equimolar mixture of 6-O-α-D-glucopyranoside-D-mannitol and 6-O-α-D-glucopyranoside-D-sorbitol) are commercial sugar alcohols produced and used as sweetening agents. Lactitol (4-O-β-D-galactopyranosyl-D-sorbitol) and maltitol (4-O-α-D-glucopyranosyl-D-sorbitol) are manufactured from the disaccharides lactose and maltose by reduction of one glucopyranosyl unit to sorbitol, the sugar alcohol of glucose (Linko, 1982). On hydrolysis lactitol produces equimolar amounts of sorbitol and galactose, while maltitol produces equimolar amounts of sorbitol and glucose.

Palatinit is manufactured from sucrose by enzymic rearrangement to isomaltulose followed by reduction of the fructose unit to mannitol and sorbitol. Hydrolysis of Palatinit liberates glucose (50%), sorbitol (25%) and mannitol (25%).

The reasons for using sugar alcohols as sweetening agents in various foods might be both technological and physiological. Maltitol is significantly sweeter than maltose (Lee, 1977). In contrast to maltose and lactose, maltitol and lactitol are non-reducing compounds and therefore inactive in the Maillard reaction, which reduces protein quality and changes the colour of the product. Another physiological benefit of using sugar alcohols as sweetening agents is their lower cariogenic effect. Sugar alcohols are important as sweetening agents in foods consumed by diabetic subjects. Sorbitol, for instance, gives lower plasma glucose and lower serum insulin levels than sucrose (Akgun & Erthel, 1980).

Sugar alcohols of the disaccharide type such as maltitol, Palatinit and lactitol are believed to require hydrolysis of their glycosidic linkage before absorption just as their corresponding disaccharides. The natural disaccharides maltose and lactose are easily hydrolysed to monosaccharides by intestinal disaccharides. Palatinose (isomaltulose) is hydrolysed by the isomaltase (*EC* 3.2.1.10) enzyme at a rate about 25–30% that of isomaltose (Dahlqvist *et al.* 1963). The question, therefore, is whether the intestinal disaccharidases are also capable of hydrolysing sugar alcohols of the disaccharide type. It

has previously been shown that maltitol can be hydrolysed slowly in vitro by human intestinal biopsies (Dahlqvist & Telenius, 1965). In rats given maltitol orally, sorbitol could also be identified in the urine indicating that hydrolysis had occurred (Lian-Loh *et al.* 1982).

Corresponding information has not been published for Palatinit and lactitol. The purpose of the present study was to compare the hydrolysing activity of human intestinal biopsies towards lactitol, Palatinit and maltitol in relation to the corresponding natural disaccharides maltose and lactose. If not hydrolysed by the intestinal disaccharidases the absorption of these sugar alcohols would even be lower than that of the corresponding simple sugar alcohols sorbitol and mannitol.

MATERIALS AND METHODS

Substrates

Disaccharides and monosaccharides of analytical grade purity were obtained from Kebo Grave, Sweden. The compositions of the sugar alcohols were as follows: lactitol, water content 52 g/kg, composition of dry matter (DM) (g/kg): lactitol 994·3, hydrogenated higher oligosaccharides 3·0, sorbitol 2·7; maltitol, water content 15 g/kg, composition of DM (g/kg): maltitol 766·3, maltotriitol 196·4, hydrogenated higher oligosaccharides 19·7, sorbitol 18·4; Palatinit, water content 58 g/kg, composition of DM (g/kg): 6-O-α-D-glucopyranoside-D-mannitol 473·1, 6-O-α-D-glucopyranoside-D-sorbitol 523·2, hydrogenated higher oligosaccharides 2·0, sorbitol 1·7. Carbohydrate compositions were measured by high-performance liquid chromatography.

Substrate solutions (g/l) for the disaccharidase assays were prepared according to Dahlqvist (1984*c*): lactose 40, maltose 40, sucrose 38·0, trehalose 42·0. In addition, solutions (g/l) of lactitol 40, maltitol 40 and Palatinit 40 were used.

Enzyme sources

Glucose oxidase (*EC* 1.1.3.4)–peroxidase (*EC* 1.11.1.7), used for the determination of glucose release by human small intestinal disaccharidases, was obtained from Kabi Diagnostica AB, Stockholm.

β-Galactose dehydrogenase (*EC* 1.1.1.48), used for measuring galactose release, was obtained as a crystal suspension (5 mg/ml) from Boehringer Mannheim, West Germany.

Human small intestinal biopsies

Human small intestinal biopsies were taken from the duodenal–jejunal flexure by a standard procedure (Crosby & Kugler, 1957), wrapped in Parafilm and kept frozen at −20° until assayed. The disaccharidase activities in an unhomogenized biopsy, stored in this way, are stable for years (Dahlqvist, 1984*c*).

Biopsies were obtained from male and female patients of different ages during diagnosis of various gastrointestinal disorders. Some of them had normal disaccharidase activities and some had different kinds of reduced enzymic activities as specified in Table 1.

Enzymic assays

Analyses of disaccharidase activities in homogenized human intestinal biopsies are routinely performed in our laboratory to serve the hospitals in the region. The disaccharidase activities of the homogenized biopsies were analysed according to the methods of Dahlqvist (1984*b*,*c*) after suitable dilution of each biopsy homogenate. No dilution was necessary, however, when lactitol and Palatinit were used as substrates. When lactitol and lactose were used as substrates released galactose and glucose respectively were

Table 1. *Sex, age and diagnosis of the patients from which small-intestinal biopsies were obtained*

Subject			Biopsy diagnosis		
No.	Sex	Age (years)	Disaccharidases	Histopathological examination*	Clinical diagnosis
A–1	♂	21	Normal	Normal	No malabsorption
A–2	♂	52	Normal	Normal	Nonspecific abdominal complaints
A–3	♂	13	Normal	Mild unspecific enteropathy	Short stature, constipation
A–4	♀	6	Normal	Normal	Nonspecific diarrhoea
A–5	♂	64	Normal	Normal	No malabsorption
A–6	♂	2	Normal	Normal	Nonspecific diarrhoea
A–7	♀	1	Normal	Normal	Nonspecific fibrosis of lungs and hepatomegalia
A–8	♀	40	T and L subnormal	Essentially normal	Irritable colon
A–9	♀	12	L low, T normal	Normal	Nonspecific diarrhoea
A–10	♂	16	L low, T normal	Not performed	Specific low lactase activity
A–11	♂	15	Low	Normal	Short stature
A–12	♂	26	T and L slightly subnormal	Normal	Undiagnosed
A–13	♀	36	T and L slightly subnormal	Normal	Irritable colon
A–14	♀	14	L low, T normal	Normal	Undiagnosed
A–15	♂	6	L low, T normal	Normal	Specific low lactase activity
A–16	♂	17	L low, T normal	Mild inflammatory reaction	Lactose intolerance
A–17	♂	1	T low, T normal	Normal	Suspect malabsorption
A–18	♂	12	L low, T subnormal	Normal	Nonspecific diarrhoea
A–19	♂	8	Subnormal	Normal	Nonspecific abdominal complaints

T, trehalase (*EC* 3.2.1.28); L, lactase (*EC* 3.2.1.23).
* Low magnification direct microscopy.

determined as measures of activity. In some cases both galactose and glucose were measured (for comparison of the methods), while for the remaining substrates only glucose was determined.

The amounts of galactose and glucose released were determined enzymically using β-galactose dehydrogenase and glucose oxidase–peroxidase respectively, as described by Dahlqvist (1984*a*, *b*).

Protein determination

The protein content of the human small intestinal biopsies was determined using the method of Lowry *et al.* (1951) as modified by Eggstein & Kreutz (1955). Human serum albumin was used as the standard protein.

Inhibitory effects of lactitol, maltitol, Palatinit or sorbitol on glucose oxidase–peroxidase

Glucose, 0·28 μmol (in distilled water), was mixed with various amounts (0–1·45 μmol) of lactitol, sorbitol, maltitol or Palatinit (as inhibitors). Water was used to adjust the volume to 1 ml before the addition of 2·0 ml glucose oxidase–peroxidase.

Table 2. *Disaccharidase activities (IE/g)* towards maltitol, Palatinit® lactitol, and disaccharides*

Biopsy no.	Maltitol	Maltose	Palatinit	Isomaltose	Lactitol (galac DH)†	Lactose (galac DH)†	Lactose (Glox)‡	Sucrose	Trehalose
A–1	na[2]	278	na	81·2	0·51	42·8	46·0	70·8	29·0
A–2	na	221	na	76·7	0·29	20·9	22·5	61·0	34·3
A–3	na	217	na	81·8	0·63	36·1	37·3	61·6	17·2
A–4	23·5	192	2·1	63·4	na	na	41·3	45·3	28·6
A–5	29·9	302	na	91·8	na	na	38·6	72·0	31·0
A–6	22·3	220	2·4	75·7	na	na	33·2	53·0	13·4
A–7	na	209	na	73·0	0·53	na	27·2	56·8	23·7
A–8	na	141	na	43·2	0·27	na	18·1	33·1	7·6
A–9	na	173	na	56·0	0·26	20·6	18·6	44·0	14·6
A–10	na	164	na	41·7	0·14	3·2	2·1	26·1	14·1
A–11	na	103	na	33·0	0·13	6·6	5·6	25·9	6·4
A–12	17·0	131	1·8	86·3	na	na	15·4	34·2	11·5
A–13	16·4	140	2·0	60·5	na	na	17·3	36·4	11·1
A–14	22·4	156	1·9	47·1	na	na	14·7	29·7	32·0
A–15	18·4	144	2·0	53·8	na	na	3·5	44·9	20·4
A–16	13·7	141	1·4	44·3	na	na	7·5	35·2	11·3
A–17	18·6	187	2·3	60·3	na	na	19·7	41·4	8·6
A–18	11·5	92	1·4	59·5	na	na	4·0	17·2	10·5
A–19	16·1	59	7·8	22·2	na	na	11·7	25·8	5·0
Mean	19·1	na	2·5	na	0·34	na	na	na	na
SD	4·9	na	1·8	na	0·18	na	na	na	na
Normal values§									
Mean	na	265	na	85	na	na	41	72	28
SD	na	73	na	26	na	na	16	22	8
Range	na	111–407	na	32–139	na	na	21–80	35–131	13–43

na, Not analysed.
* IE = unit of disaccharidase activity, i.e. μmol disaccharide hydrolysed/min at 37°.
† Liberated galactose measured by galactose dehydrogenase (*EC* 1.1.1.48).
‡ Liberated glucose measured by glucose oxidase (*EC* 1.1.3.4)–peroxidase (*EC* 1.11.1.7).
§ Sixteen normal patients (Dahlqvist, 1984*c*).

These mixtures were incubated at 37° for 30 min, and the colour developed was measured spectrophotometrically at 450 nm according to the method described by Dahlqvist (1984*b*).

Inhibitory effects of lactitol, lactose, sorbitol or glucose on galactose dehydrogenase

Galactose (0·1 μmol) was mixed with various amounts (0–0·50 μmol) of lactitol or lactose, or 0–1·00 μmol sorbitol or glucose together with 0·1 μmol galactose. Water was added to adjust the volume to 100 μl. NAD^+ (50 μl), 1·0 ml Tris-EDTA buffer (pH 8·6) and 5 μl galactose dehydrogenase were then added. The activity of the enzyme was measured spectrophotometrically after maximal peak rise as described by Dahlqvist (1984*a*).

Inhibitory effects of lactitol, sorbitol, maltitol or Palatinit on disaccharidase activities

Disaccharidase activities of a normal human biopsy were measured in the presence of lactitol, sorbitol, maltitol and Palatinit. Solutions (g/l) of lactitol (40), sorbitol (20), maltitol (40) or Palatinit (40) in distilled water were used.

Each of the different substrates, one at a time (2·8 μmol in 0·01 M-sodium maleate buffer, pH 6·0), was mixed with various amounts (0–5·6 μmol) of either lactitol, sorbitol, maltitol or Palatinit (as inhibitors). A total volume of 100 μl was obtained by addition of sodium maleate buffer (0·01 M, pH 6·0).

RESULTS

Interaction with assays

Addition of sorbitol, lactitol, maltitol or Palatinit had no effect on the activity of glucose oxidase–peroxidase towards glucose. Glucose, sorbitol, lactose and lactitol did not interfere with the enzymic assay for the determination of galactose release using β-galactose dehydrogenase.

Activities of human biopsies on lactitol, Palatinit and maltitol in comparison with disaccharides

Table 2 shows the disaccharidase activities of nineteen human small-intestinal biopsies. Lactase (*EC* 3.2.1.23) activities have been measured both as glucose release and galactose release in six of these biopsies, as seen in Table 2. The results of the two methods showed good agreement. Biopsies A-1, A-2 and A-3 had normal lactase activity while biopsies A-9, A-10 and A-11 showed low lactase activities. Lactitol as a substrate, however, produced in all cases extremely small amounts of galactose (0·34 IE/g protein, where IE = μmol disaccharide hydrolysed/min at 37°).

The disaccharidase activity of the human biopsies towards Palatinit (Table 2) was also very low (2·27 IE/g protein).

The activity towards maltitol (about 20 IE/g protein; Table 2) was about ten times higher than that towards Palatinit, and about 10% of the activity towards maltose.

Interaction of lactitol, Palatinit and maltitol with disaccharidases in a human biopsy

Hydrolysing activities of the biopsies in the presence of increasing amounts of either lactitol or sorbitol are shown in Table 3. Enzymic activities are expressed as a percentage of the activity when no sugar alcohol was added. Lactitol did not seem to affect glucose release from maltose, but there might have been a slight inhibitory effect with lactose as the substrate. Sorbitol, at increasing concentrations, seemed to have a slight inhibitory effect

Table 3. *Effect of sorbitol and lactitol on the capacities of a normal human small intestine biopsy to hydrolyse lactose and maltose*

Substrate (μmol)	Lactitol (μmol)	Lactitol Activity* (%)	Sorbitol (μmol)	Sorbitol Activity* (%) A†	Sorbitol Activity* (%) B†
		Lactose			
5·6	0	100	0	100	100
5·6	1·2	93·3	1·1	102·3	103·1
5·6	2·9	91·5	2·7	104·7	106·8
5·6	4·7	91·2	4·4	111·3	111·5
5·6	5·6	92·7	5·5	113·2	113·8
		Maltose			
5·6	0	100	0	100	100
5·6	1·2	104·2	1·1	131·5	94·9
5·6	2·9	103·0	2·7	128·2	87·8
5·6	4·7	106·1	4·4	86·9	89·1
5·6	5·6	100·9	5·5	80·3	88·5

* Activity was calculated as a percentage of activity when no inhibitor added.
† Duplicate assays.

Table 4. *Effect of maltitol and Palatinit®* on the capacities of a normal human small intestine biopsy to hydrolyse maltose and sucrose*

Substrate (μmol)	Maltitol (μmol)	Maltitol Activity† (%) A‡	Maltitol Activity† (%) B‡	Palatinit (μmol)	Palatinit Activity† (%) A‡	Palatinit Activity† (%) B‡
			Maltose			
5·6	0	100	100	0	100	100
5·6	1·2	87·4	78·1	1·2	90·6	89·6
5·6	2·9	81·1	78·3	2·9	81·2	82·2
5·6	4·7	76·1	76·1	4·7	75·0	74·7
5·6	5·6	74·7	77·0	5·6	72·5	75·3
			Sucrose			
5·6	0	100	100	0	100	100
5·6	1·2	114·4	118·0	1·2	99·1	97·9
5·6	2·9	122·1	131·9	2·9	92·0	98·6
5·6	4·7	128·9	130·0	4·7	91·5	95·3
5·6	5·6	129·8	130·0	5·6	86·3	90·6

* Equimolar mixture of 6-O-α-D-glucopyranoside-D-manitol and 6-O-α-D-glucopyranoside-D-sorbitol.
† Activity was calculated as a percentage of activity when no inhibitor was added.
‡ Duplicate assays.

on the glucose release from maltose, whereas an increase was observed with lactose as the substrate. There was no evidence of any inhibitory effects of lactitol or sorbitol with sucrose or trehalose as substrates when measured by the glucose oxidase–peroxidase method.

The effects of maltitol and Palatinit on the hydrolysis of maltose and sucrose were also measured (Table 4). Both maltitol and Palatinit seemed to decrease the hydrolysis of maltose. The presence of either sugar alcohol in amounts equal to the concentration of the substrate reduced the activity by about 25%. The hydrolysis of sucrose was affected differently. Palatinit in an amount equal to that of the substrate decreased glucose release from sucrose by about 12%. The presence of maltitol under the same conditions increased glucose release by about 30%.

DISCUSSION

Seven of the human biopsies used in the present study were normal with regard to their disaccharidase activities, and did not differ significantly from the reference values published by Dahlqvist (1984*c*). Some biopsies showed decreased levels of disaccharidase activities (see Table 1).

The disaccharidase activities of homogenates of intestinal biopsies in the present study were estimated by measuring glucose release (by glucose oxidase–peroxidase) or galactose release (by galactose dehydrogenase) depending on the structure of the substrate. In the case of lactose the two methods were compared and the results showed good agreement (see Table 2). The possibility that these methods might be affected by the presence of sugar alcohols or compounds containing sugar alcohols was excluded after studies of inhibitory effects.

As shown in Table 2, the production of galactose from lactitol by intestinal biopsies was extremely low. This finding suggests an almost negligible ability of human small intestinal mucosa to hydrolyse lactitol. There did not seem to be any difference between normal subjects and subjects with lactase deficiency. A lactase activity below 25% of the normal value (41 IE/g protein) gives clinical symptoms in a lactase-intolerant patient. Therefore there is doubt that the extremely low activity towards lactitol leads to any significant hydrolysis.

The activity of the human biopsies towards Palatinit (Table 2) was also very low (2·50 IE/g protein). One patient (A-19) differed by having an activity of 7·8 IE/g protein, which is still a low value compared with the activities towards the disaccharides. This patient was found to have low activities towards all disaccharides but the histopathological examination indicated a normal intestinal mucosa, thereby excluding coeliac disease. Generally, however, both normal and abnormal biopsies showed equally low activities towards Palatinit.

The activity towards maltitol (about 20 IE/g protein; Table 2) was about ten times higher than that towards Palatinit, and about 10% of the activity towards maltose. This finding verifies those of Lian-Loh *et al.* (1982) who showed the occurrence of sorbitol in urine from germ-free as well as from conventional rats given maltitol, indicating a hydrolysis of maltitol by the tissues of the animal. In addition, Dahlqvist & Telenius (1985) demonstrated that maltitol could be hydrolysed by human and rat intestinal enzymes, although at a much slower rate compared with maltose.

The fact that maltitol was more effectively hydrolysed than Palatinit and lactitol might be due to maltase (*EC* 3.2.1.20) being the disaccharidase having the highest activity in the human small intestine, as shown by the control values given in Table 2. The mean maltase activity (IE/g protein) was found to be 265 followed by isomaltase (85), invertase (*EC*

3.2.1.48) (72), lactase (41) and trehalase (*EC* 3.2.1.28) (28). Palatinose (isomaltulose) is hydrolysed by the isomaltase enzyme at a rate which is about 25–30% as fast as that for isomaltose (Dahlqvist *et al.* 1963); the activity towards palatinose would therefore amount to about 23 IE/g. Thus, the maltase activity is more than ten times higher than that expected towards palatinose, and more than six times higher than lactase activity.

The extent of hydrolysis of maltitol was about 10% that of maltose, that of Palatinit was about 10% the expected rate of palatinose and for lactitol was only about 1% of that of lactose. This finding indicates different rates of hydrolysis of different sugar alcohols of the disaccharide type. Consequently this raises the question of their energy value since low-energy sweetening agents are attractive substitutes for sucrose in many food products. Studies of Palatinit in this respect have given it an energy value (for humans) of 40% that of sucrose (Mehnert *et al.* 1978), ascribed mainly to bacterial fermentation of Palatinit to short-chain fatty acids in the colon.

Both maltitol and Palatinit seemed to decrease the hydrolysis of maltose, possibly by competitive inhibition. An inhibitory effect of maltitol towards maltase activity has also been reported by Yoshizawa *et al.* (1975). Palatinose is known to inhibit isomaltase (Dahlqvist *et al.* 1963) and it is possible that Palatinit also acts as an inhibitor, but this possibility was not studied. The hydrolysis of sucrose (measured as glucose release) appeared to increase by 12% in the presence of maltitol. Our interpretation of this finding is that the increase in glucose release is a result of maltase attack on the maltitol.

It is the belief of the authors that lactitol and Palatinit are poor substrates for human intestinal disaccharidases, while significant amounts of maltitol can be digested and utilized by man. The slight inhibitory effect on the hydrolysis of disaccharides is probably of minor importance for a subject showing normal disaccharidase activities.

The authors thank Ms Ulla Lindqvist for excellent technical assistance with the analysis of the human intestinal disaccharidases. Lactitol, maltitol, and Palatinit were kindly supplied by Dr C. J. Booij and R. Kammelar of Borculo Co., The Netherlands.

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Printed in Great Britain