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Oral intake of glucose plus galactose and erythrocyte galactose-1-phosphate
A nutritional evaluation of hydrolyzed lactose

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Summary: This study deals with the metabolic effects of hydrolyzed lactose: After an overnight fast 5 healthy adult volunteers consumed a glucose-galactose mixture equivalent to 61.4 g of lactose (or 125 g of a dried skim milk powder with hydrolyzed lactose). The postprandial rise of erythrocyte galactose-1-phosphate (gal-1-P) never exceeded 22.3 μmol per liter packed red blood cells. This amounts to no more than 22 % of the levels known from galactosemic children to be safe, concerning ocular, neural or hepatic damage. We conclude that the consumption of the hydrolyzed lactose does not cause a risk for consumer's health as judged from this galactose metabolite. A considerably higher risk, however, may accompany the consumption of galactose alone which causes around 17-fold higher plasma galactose levels and around 8-fold higher erythrocyte gal-1-P concentrations for more extended time periods.

Zusammenfassung: Wir haben die Wirkung einer Glukose-Galaktose-Zufuhr, wie sie bei Aufnahme von Lebensmitteln mit hydrolysierter Laktose auftreten kann, untersucht. Dazu erhielten 5 gesunde erwachsene Versuchspersonen morgens nüchtern je 32,3 g Glukose plus 32,3 g Galaktose (entsprechend 125 g eines Magermilchpulvers mit hydrolysierter Laktose). Die postprandialen erythrozytären Galaktose-1-Phosphat-(Gal-1-P-)Spiegel stiegen bei keinem der Probanden höher als 22,3 μmol/l gepackter Erythrozyten an. Damit erreichten die Konzentrationen dieses Indikatormetaboliten lediglich 22 % der Spiegel, die sich bei galaktosämischen Kindern als sicher herausgestellt haben, was die Entstehung von Leber- oder Hirnschäden bzw. Katarakten angeht. Wir schließen daraus, daß das Kriterium der erythrozytären Gal-1-P-Spiegel kein Stoffwechselrisiko beim Konsum von hydrolysierter Laktose erkennen läßt.

Hingegen ist die Aufnahme von Galaktose allein ohne Glukose von 17fach höheren Plasma-Galaktosespiegeln und einer ca. 8fach höheren erythrozytären Gal-1-P-Konzentration begleitet. Die Zufuhr von Galaktose allein dürfte daher ein erheblich höheres Stoffwechselrisiko verursachen.

Key words: risk, galactose, hydrolyzed lactose, toxicity, galactose-1-phosphate

Introduction

Depending on ethnic origin between 15 and 80 % of adults have low intestinal β-galactosidase (E.C. 3.2.1.23) activities and are prone to the

Abbreviations: gal-1-P = galactose-1-phosphate p.v. = packed volume

adverse effects of lactose intolerance (1). This has led the dairy industry to develop products in which lactose is split into the component monosaccharides by enzymatic or chemical hydrolysis (2). This procedure has the additional advantage of increasing the sweetness of the product or producing "lactose syrups" as sweeteners.

Several reports have described the nutritional effects of dairy foods with hydrolyzed lactose (HL). Whereas several groups did not report evidence substantiating the need to lower the lactose concentration in dairy products (3–7), others have repeatedly observed that milk with hydrolyzed lactose led to a higher weight gain when fed to undernourished Australian Aboriginef infants instead of full-cream milk (8, 9). Several investigators have reported reduction of gastrointestinal symptomatology by lactose-reduced milk in adult lactose-malabsorbers (10, 11).

Because of studies which suggest a higher incidence of osteoporosis in lactose-malabsorbers (12, 13) procedures that overcome the adverse effects of lactose malabsorption – such as lactose hydrolysis – may be a valuable technology for preventive medicine.

However, concerns may be raised against any food technology which may contribute to a too rapid entry of galactose into the plasma compartment because consumption of hydrolyzed lactose may lead to overshooting, abnormally high blood galactose concentrations and so be a health hazard because of its toxicity (14).

We have therefore embarked on a study to evaluate the safety of dietary glucose-galactose mixtures in healthy human volunteers by measuring cellular galactose-1-phosphate.

In choosing red blood cell galactose-1-phosphate (gal-1-P) concentrations as indicator of galactose toxicity we were led by the following reasoning:

1. The hepatotoxic action of galactose is very probably caused by gal-1-P (14).
2. There is evidence that erythrocyte gal-1-P levels parallel, and therefore signalize, toxic amounts in liver parenchymal cells (15).
3. The sum of therapeutic experience with galactosemic patients has led pediatricians to conclude that no mental, hepatic or ocular symptoms occur if erythrocyte gal-1-P levels do not exceed 3 mg/dl p.v. (= 0.115 mM) (16, 17).

Materials and Methods

Materials:

All reagents used in this study were of reagent grade quality and obtained from Merck, Darmstadt, Germany. Enzymes and coenzymes were obtained from Boehringer, Mannheim, Germany. Centrisart filters were purchased from Sartorius, Göttingen, Germany.

Subjects and experimental procedure:

5 healthy volunteers (1 female, 4 male) who had been fully informed about the risks, aged between 23 and 49 years, drank 32.3 g galactose plus 32.3 g glucose (if not stated otherwise) in 500 ml water within 20 min after an overnight fast. The study

Table 1. Plasma galactose following oral intake of 2 doses of lactose hydrolysate (n = 2) and of galactose alone (n = 1).

		Plasma galactose (μmol/l)						
Carbohydrate consumed	Subject	Minutes						
		0	30	60	90	120	150	180
12 g galactose	D	–	–	11.99	–	–	–	–
+ 12 g glucose	A	1.33	86.42	28.14	24.15	6.33	5.99	1.33
32.3 g galactose	C	–	260.32	186.5	87.09	12.32	9.94	1.33
+ 32.3 g glucose	A	–	231.96	288.41	173.51	171.85	–	–
32.3 g galactose	B	1.33	3392.65	4087.69	981.96	98.13	81.26	14.71

started between 7:30 and 8:30 a.m. The dose corresponds to the consumption of 125 g skim milk powder with all lactose hydrolyzed and containing 44 g protein.

At the times indicated heparinized blood samples of 1 ml were taken and RBC were sedimented at 3000 rpm for 10 min and washed 3 times with saline. The cell pellet was hemolyzed subsequently at −20 °C for 25 min after adding 0.5 ml distilled water.

Analysis

0.5 ml hemolysate plus 2.0 ml 0.2 M glycine-HCl, pH 8.7, was treated for 5 min at 90 °C. The supernatant was further deproteinized by centrifuging twice for 30 min at 3000 × g in a Centrisart No. 1 ultrafilter. This procedure proved to be superior to previously published protocols (18, 19) because the ultrafiltrates were free of colour and turbidity and gave absorption values of less than 0.2 at 334 nm.

Gal-1-P analyses in the ultrafiltrates were done enzymatically (18). Recovery of gal-1-P was better than 82 %.

Plasma glucose, galactose and uric acid were determined according to established procedures with a centrifugation analyzer (20).

Results

There was a considerable rise of plasma galactose levels up to 4 mmol/l within 60 min following the consumption of 32.3 g galactose (Table 1). However, the rise was reduced by more than 90 % if galactose was consumed simultaneously with glucose. This confirms earlier observations by Stenstam (21).

There was a postprandial rise of erythrocyte gal-1-P following the intake of galactose plus glucose (Fig. 1). Neither the average, nor the range comprising two standard deviations, nor any value observed in the five subjects studied reached the safety limit of 115 µmol/l gal-1-P (16, 17). The highest value observed amounted to 22.3 µmol/l and was less than 22 % of the safety limit value.

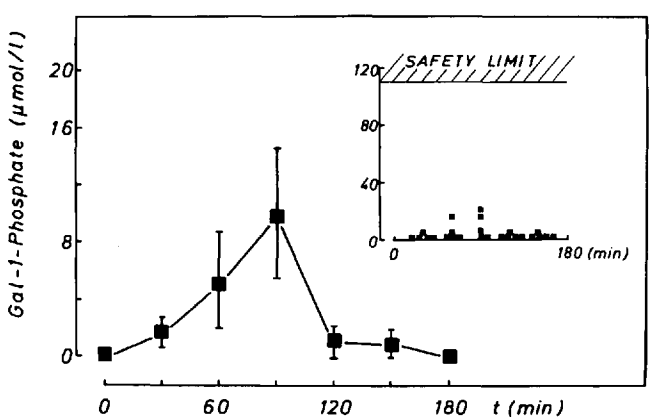

Fig. 1. Erythrocyte gal-1-P levels following consumption of galactose plus glucose. $\bar{x} \pm$ S.E.M. of gal-1-P levels per packed red blood volume are given. Values were obtained from 5 subjects consuming 32.3 g galactose plus 32.3 g glucose. Insert shows individual values.

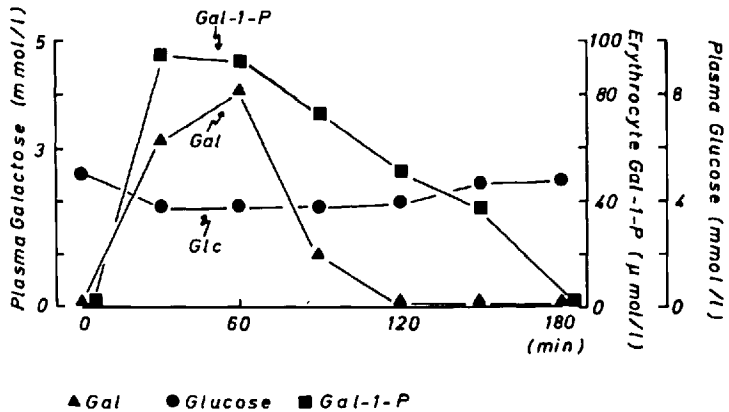

Fig. 2. Metabolite levels following oral galactose intake. Postprandial concentrations of galactose (▲), glucose (●) and red blood cell gal-1-P (■) after consumption of 32.3 g galactose (n = 1).

Erythrocyte gal-1-P reached 82 % of the safety limit values within 30 min when galactose alone was consumed (Fig. 2). This considerably higher rise of erythrocyte gal-1-P as compared to the response following galactose plus glucose again shows the profound influence of glucose ingestion on galactose metabolism.

Interestingly, gal-1-P levels are not only lower but also reach their maximum at a later time (90 min) following galactose plus glucose (Fig. 3) if compared to galactose alone (peak at 30 to 60 min) (Fig. 2). Correspond-

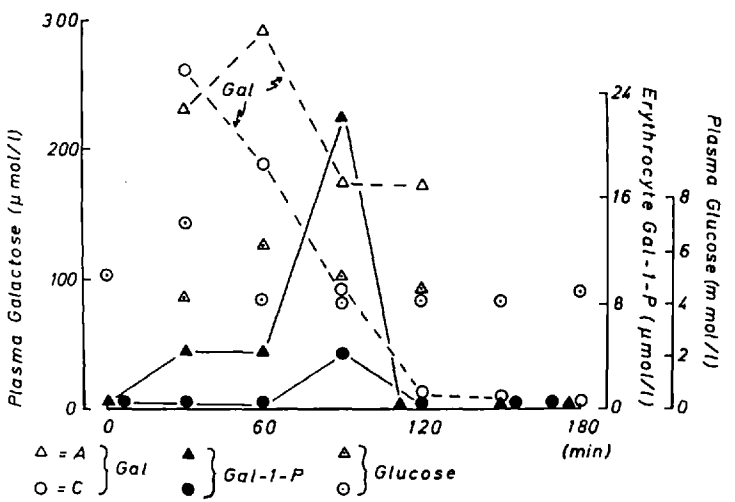

Fig. 3. Metabolite levels following oral intake of galactose plus glucose. Galactose (△, ○), gal-1-P (▲, ●) and glucose (△, ⊙) levels following the oral consumption of 32.3 g galactose plus 32.3 g glucose in 2 subjects (△ and ○). Individual responses of each subject are displayed separately.

Table 2. Plasma glucose following 2 doses of lactose hydrolysate (n = 2) and of galactose alone (n = 1).

		Plasma glucose (mmol/l)						
Carbohydrate consumed	Subject	Minutes						
		0	30	60	90	120	150	180
12 g galactose	D	–	7.92	5.74	4.19	4.54	4.79	–
+ 12 g glucose	A	4.39	6.75	5.50	4.79	4.54	4.38	4.57
32.3 g galactose	C	5.18	7.24	4.17	4.19	4.31	4.07	4.57
+ 32.3 g glucose	A	–	4.39	6.42	4.66	4.55	–	–
32.3 g galactose	B	5.02	3.88	3.89	3.90	3.99	4.73	4.78

Table 3. Plasma uric acid following 2 doses of lactose hydrolysate (n = 2) and of galactose alone (n = 1).

		Plasma uric acid (mmol/l)						
Carbohydrate consumed	Subject	Minutes						
		0	30	60	90	120	150	180
12 g galactose	D	305.7	318.3	–	–	277.8	258.1	–
+ 12 g glucose	A	293.2	326.5	298.0	319.5	338.5	312.9	333.1
32.3 g galactose	C	316.5	317.6	318.3	317.0	310.5	273.6	331.9
+ 32.3 g glucose	A	–	261.7	251.0	255.8	242.7	–	–
32.3 g galactose	B	261.2	268.9	246.9	249.3	318.3	274.2	247.5

ingly, the peaks last for shorter periods (less than 60 min) in the former case and for more extended periods (more than 90 min) in the latter.

Initially plasma glucose rose slightly above fasting values following glucose plus galactose and tended to decrease following galactose alone (Table 2). However, due to the small number of observations, no conclusion concerning statistical significance could be drawn. No changes of plasma uric acid concentrations were observed (Table 3).

Discussion

We have explored whether (and to what extent) the consumption of equimolar mixtures of glucose and galactose as occurring in dairy products with hydrolyzed lactose may constitute a health hazard. For this purpose we have made use of the observation that tissue damage is not observed in galactosemic patients when the erythrocyte gal-1-phosphate concentrations are kept below 115 μmol/l by an appropriate diet (16, 17).

We have observed that the maximal erythrocyte gal-1-P concentrations ever reached in our group of subjects amounted to less than 22 % of the concentration defined as the safe limit. Hence we consider that the consumption of dairy products with hydrolyzed lactose cannot be harmful to consumer's health.

The dose of dietary carbohydrate as applied in this study was chosen because it corresponds to the consumption of 44 g of milk protein. This constitutes a maximum amount which may be conceived to be consumed per 24 h in emergency situations. In this respect the dose chosen represents a maximum challenge to carbohydrate metabolism which can be anticipated. This implies that no health hazard may be expected for any conceivable situation because no harmful metabolic effects were observed under the conditions chosen in this study.

Interestingly, low levels of erythrocyte gal-1-P are only observed if galactose is consumed together with glucose. Galactose alone causes about eightfold higher values. We do not know yet whether this is due to the simultaneous reduction of plasma galactose or whether glucose gears cellular galactose metabolism directly towards lower steady state concentrations of gal-1-P.

It is noteworthy that only glucose, not fructose lowers blood galactose (22). We do not know yet how fructose influences erythrocyte gal-1-P levels. However, caution is advised concerning any food technology which transforms glucose to fructose following lactose hydrolysis.

Macdonald and coauthors have reported earlier that the plasma disappearance of galactose was equally rapid in lactose-tolerant and in lactose-intolerant subjects (23). Accordingly, no obvious health hazard can be anticipated whether or not a subject consuming galactose plus glucose is lactose-tolerant or -intolerant.

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