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Oxidation and Absorption of Glucose and Fructose Component Ingested as a Low Glycemic Sucrose-Isomer Isomaltulose (Palatinose) in Human.

KEYWORDS: Palatinose, Glucose, Fructose, 13C -breath test, Sparing effect

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ABSTRACT *It has been less clear how the monosaccharides glucose and fructose are metabolized when consumed together as the disaccharide isomaltulose (palatinose), which is composed of alpha-1,6-linked glucose and fructose. The aim of this study is to investigate the acute metabolism of the monosaccharide components of palatinose. At endoscopy, 20 ml of water containing 100 mg of [1-13C] glucose, [1-13C] fructose, [1-13Cglu] palatinose, or [1-13Cfru] palatinose was sprayed into the duodenum. Breath samples were taken at 10 min-intervals for 90 min. The 13CO2 excretion rose more sharply after ingestion of [1-13Cfru] palatinose than that after ingestion of [1-13Cglu] palatinose, and was significantly higher after ingestion of [1-13C] fructose than that after ingestion of [1-13Cfru] palatinose and remained higher throughout the study period. These results illustrate a sparing effect of fructose component of palatinose on absorption and oxidation of glucose component and should cause a gradual increase in blood glucose after ingestion of palatinose.*

1. Introduction

Different starchy foods are digested at different rates, which are related to the glucose and insulin responses. This varied glycemic response is quantified according to the glycemic index (GI), which is a measure of how much each carbohydrate-containing food raises blood glucose compared with a standard food of either glucose or white bread (Jenkins and others 1981). High-GI forms of carbohydrate produce high concentrations of plasma glucose and increased insulin demand and may therefore contribute to an increased risk of type 2 diabetes. In contrast, low-GI carbohydrates may have acute effects on the clinical management of people with diabetes. It has been reported that low-GI diets reduced HbA1c by 0.43 percent points above that produced by high-GI diets (Liu and others 2000; Montonen and others 2003). In theory, low-GI foods may benefit weight control by promoting satiety.

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Palatinose is a natural occurring disaccharide composed of alpha-1,6-linked glucose and fructose, which has been found in honey and sugar cane extract. It is particularly suitable as a non-cariogenic sucrose replacement and is favorable in products for diabetics (Ooshima and others 1983). Although palatinose has been reported to be completely hydrolyzed and absorbed in the small intestine in rat, the rate of hydrolysis is very slow compared with sucrose and results in slower and lower rise in blood glucose. It has been reported that more slowly digested and absorbed carbohydrates lead to improved profiles of postprandial metabolism and, in the long term, can have benefitical health consequences (Livesay and others 2008; Ludwig 2007). However, it has been less clear how the monosaccharides glucose and fructose are metabolized when consumed together as the disaccharide palatinose and also in comparison with other sources of commonly consumed carbohydrates, such as starches. Monosaccharides are rapidly oxidized and converted to carbon dioxides, which are expired into the breath air. Based on this metabolic theory, stable carbon isotopes have been extensively used to study exogeneous carbohydrate oxidation from the production of $^{13}CO2$ at the mouth. Since palatinose is composed of alpha-1,6-linked glucose and fructose, it is difficult to determine whether CO2 is originated from glucose or fructose. In order to evaluate the absorption and metabolism of palatinose and its components in human, we investigated the acute metabolism of the monosaccharide components of palatinose using ^{13}C-disaccharide.

2. Materials and methods

2.1. Substrates

Palatinose composed of unlabelled glucose and [1-^{13}C] fructose that has carbon isotope in position 1 is expressed as [1-$^{13}C^{fru}$] palatinose, whereas that composed of unlabelled fructose and [1-^{13}C] glucose that has carbon isotope in position 1 is expressed as [1-$^{13}C^{glu}$] palatinose. Both [1-$^{13}C^{glu}$] and [1-$^{13}C^{fru}$] palatinose were provided by Mitsui Sugar Co., Ltd. (Tokyo, Japan). [1-^{13}C] glucose and [1-^{13}C] fructose were purchased from Omicron Biochemicals, Inc. (IN, U.S.A.). Distilled water was purchased from Ohtsuka Pharmaceutical Factory, Inc. (Tokushima, Japan).

2.2. Patients

A total of 58 consecutive patients who underwent diagnostic upper endoscopy were recruited. None of the subjects had a history of use of PPI, H_2-receptor antagonist, antibiotics, steroids, or nonsteroidal anti-inflammatory drugs for a period of at least six month before the investigation. Subjects who had a previous history of partial gastrectomy were excluded from the study. Patients who had abnormal endoscopic findings, including peptic ulcers and gastric cancer, were also excluded regardless of any anti-ulcer treatment. Written informed consent was obtained from all patients. The study was approved by Toho University Ethical Committee.

2.3. Endoscopic breath test

All patients are asked to collect their breath samples before an endoscopic procedure as baseline. At the end of endoscopy, a tip of endoscope was placed to the second part of the duodenum and 20 ml of water containing 100 mg of [1-^{13}C] glucose (n=18), [1-^{13}C] fructose (n=18), ^{13}C-palatinose ([1-$^{13}C^{glu}$] palatinose or [1-$^{13}C^{fru}$] palatinose; n=11 in each) was sprayed into the duodenum. Breath samples were taken at 10 min-intervals for 90 min. ^{13}C was measured as the $^{13}CO2/^{12}CO2$ isotope ratio using non-dispersive infrared isotope spectrometry (Ubit-IR 300; Otsuka Electrics, Osaka, Japan) and was expressed as delta over baseline per mil (‰).

The results were converted to the percentage $^{13}CO2$ recovery in breath per hour (% dose/h) based on the body surface area (BSA) and the assumed CO2 production (VCO2) as follows (Ghoos et al., 1993):

$$\% \text{ dose/h} = \Delta‰ \times VCO2 \times 0.01123 \times 10/(A \times APE/MW)$$

where MW (molecular weight) is 46, VCO2 is 300 (BSA mmol/h, BSA is $0.024265 \times wight^{0.5378} \times height^{0.3964}$ m^2, A (dose) is 80 mg and APE (atom% excess) is 99.5 atom%. The areas under the curve at each time point (AUC; %dose/h□min) were calculated, which reflect the absorption and oxidation of labeled substrate.

2.4. Statistical analysis

Results are reported as means (SD) unless otherwise indicated. Repeated measures analysis of variance was used to compare the groups with respect to changes in breath $^{13}CO2$ excretion since we had measurements for all subjects at 11 time points. After repeated measures analysis of variance, comparisons between different time points were made by tests with contrasts. Data monitored over time were also compared by the area under the curve among four groups. All analyses were performed by the Statistical Package (JMP v 6.0 in Japanese edition). Ethics approval was given by the ethical committee of Toho University, Omori Medical Center (17-64).

3. Results

3.1. Metabolism of monosaccharide components of palatinose

Comparison of appearance of $^{13}CO2$ in breath after the intraduodenal administration of 5 ml of water containing 100 mg of [1-$^{13}C^{glu}$] palatinose and [1-$^{13}C^{fru}$] palatinose were shown in Fig.1. The $^{13}CO2$ excretion increased over time in both breath tests. The onset of $^{13}CO2$ enrichment in the breath rose more sharply and was higher throughout in the [1-$^{13}C^{fru}$] palatinose breath test than in the [1-$^{13}C^{glu}$] palatinose breath test. $^{13}CO2$ excretion was significantly higher after ingestion of [1-$^{13}C^{fru}$] palatinose than that after ingestion of [1-$^{13}C^{glu}$] palatinose and remained higher throughout the study period. Significant differences were found between 10 and 60 min. The areas computed under the curve of $^{13}CO2$ excretion during study period was significantly greater after ingestion of [1-$^{13}C^{fru}$] palatinose than that after ingestion of [1-$^{13}C^{glu}$] palatinose ($p<0.01$) (Fig.2).

3.2. Comparison of absorption and oxidation of glucose and fructose

Fig.3 shows changes in $^{13}CO2$ excretion after intraduodenal administration of [1-^{13}C] glucose and [1-^{13}C] fructose. Analysis of variance revealed a significant breath test × time interaction for $^{13}CO2$ excretion ($p<0.01$). The $^{13}CO2$ excretion increased from the beginning after intraduodenal administration of [1-^{13}C] glucose at an almost constant rate through the study period and reached a peak value of 7.51±1.67 %dose/h at 90 min. In contrast, intraduodenal administration of [1-^{13}C] fructose resulted in the three peaks of $^{13}CO2$ excretion at 15, 40, and 80 min. $^{13}CO2$ excretion levels were significantly higher in the [1-^{13}C] fructose breath test between 10 and 30 min, compared to in the [1-^{13}C] glucose. After 50 min and later, $^{13}CO2$ excretion increased at a similar rate in both two tests. There was no significant difference in the AUC of $^{13}CO2$ excretion between [1-^{13}C] fructose breath tests and [1-^{13}C] glucose breath tests (Fig. 4).

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4. Discussion

It has been reported that palatinose has been reported to be completely hydrolyzed and absorbed in the small intestine, the rate of hydrolysis is very slow compared with sucrose and results in slower and lower rise in blood glucose (Livesay and others 2008; Ludwig 2007). The metabolic superiority of palatinose to sucrose is presumably related to its slower digestion and hence slower absorption of the resulting glucose and fructose, which was evidenced by the generally lower levels of these two hexoses in the plasma after ingestion of palatinose test meals (Lina and others 2002). Furthermore, Kashimura et al (Kashimura and others 2008) demonstrated that palatinose inhibited the hydrolytic activity of α-glucosidases in the small intestine, resulting in slower and lower rise in blood glucose when a mixture of palatinose and sucrose is ingested. These suggest that carbohydrates might affect absorption of the other ones coexisted in the small intestine. It has been suggested that the absorption capacity of glucose in the intestine is a limiting factor for the oxidation of ingested glucose (Jeukendrup and others 1999; Jeukendrup and others 2000). Furthermore, oral ingestion of fructose increases the carbohydrate oxidation rate and thermogenesis more than does ingestion of glucose (Schwarz and others 1992; Sharief and others 1982). It is, however, less clear how the monosaccharides glucose and fructose are metabolized when consumed together as the disaccharide. Then we investigated the acute metabolism of the monosaccharide components of palatinose to evaluate the absorption and metabolism of palatinose and its components in human in the present study.

After [1-$^{13}C^{fru}$] palatinose was directly administered into the duodenum, the onset of $^{13}CO2$ enrichment in the breath rose more sharply and were higher throughout than after [1-$^{13}C^{glu}$] palatinose was done (Fig. 1). It seemed that these differences were resulted from the greater $^{13}CO2$ excretion in the [1-^{13}C] fructose breath test between 10 and 30 min, compared to in the [1-^{13}C] glucose breath test (Fig.2). The difference in absorption and oxidation, when ingested alone as a monosaccharide, may make clear differences in results of palatinose breath test between two hexoses originated from palatinose. As shown in Fig.3 and Fig.4, $^{13}CO2$ excretion rose more rapidly after intraduodenal ingestion of [1-^{13}C] monosaccharides than that after intraduodenal ingestion of [1-^{13}C] palatinose and remained higher throughout the study period, suggesting that glucose is converted from palatinose as rapidly as fructose. It is possible that there are some differences in absorption of monosaccharides when various kinds of monosaccharides are derived into the small intestine together. Burelle et al (Burelle and others 1992) reported that glucose and fructose released from sucrose ingested could reduce the oxidation of glucose or fructose ingested previously by competing for intestinal absorption, for conversion of fructose into glucose by the liver, and for uptake and oxidation in peripheral tissues.

A recent in vitro study (Kashimura and others 2007) has shown the inhibitory effect of palatinose on glucose absorption, suggesting that palatinose may inhibit glucose absorption by directly influencing the active absorption mechanism of glucose or by physically inhibiting glucose absorption using its long combination period with palatinose. However, intestinal transport of glucose occurs via a sodium-dependent glucose transporter (SGLT1) located in the brush-border membrane (Fwrraris and others 1997), whereas fructose is absorbed from the intestine by a sodium-independent facilitative fructose transporter (GLUT-5) (Burant and others 1992). It is, therefore, unlikely that there is much competition for absorption when a mixture of glucose and fructose, compared with the ingestion of an isoenergic amount of monosaccharide. In contrast, it has been also shown that fructose absorption is stimulated by the presence of glucose in the small intestine although glucose and fructose are absorbed by separate intestinal transport mechanisms (Rumessen and others 1986). Since more rapid rises in $^{13}CO2$ excretion after intraduodenal administration of [1-^{13}C] fructose and [1-$^{13}C^{fru}$] palatinose compared with after intraduodenal administration of [1-^{13}C] glucose and [1-$^{13}C^{glu}$] palatinose, respectively, both exogenous fructose ingested as a monosaccharide and that originated from palatinose may be absorbed more rapidly than exogenous glucose ingested as a monosaccharide and that originated from palatinose. Thus, absorption interaction between glucose and fructose has been unclear. However, since the upper limit for glucose absorption at rest is 1.0 g/min (Radziuk and others 1982), the results of breath test are influenced by not only intestinal absorption but also metabolism and oxidation of ^{13}C-substrates. Daly et al (Daly and others 2000) reported that the fructose component of sucrose is oxidized much more rapidly than is the glucose component after a high-sucrose meal and concluded that fructose might have a sparing effect on oxidation of exogenously supplied glucose. The rapid metabolism of fructose may be explained in part by the fact that it bypasses one of the key regulatory enzymes in glycolysis, 6-phosphofructokinase. In addition, fructose is rapidly phosphorylated in the liver to fructose-1-phosphate, a reaction catalyzed by the enzyme fructokinase (Henry and others 1991). Since the activity of fructokinase is higher than the activity of hexokinase and glucokinase, resulting in a large increase in the fructose-1-phosphate concentration after ingestion of fructose, fructose is rapidly phosphorylated and oxidated, probably resulting in a rapid rise in $^{13}CO2$ after intraduodenal administration of [1-^{13}C] fructose.

When ^{13}C-substrate breath tests are used for estimating oxidation of substrates, the size of the bicarbonate pool should be considered because $^{13}CO2$ produced as the end product of oxidation reactions is in equilibrium with the body's bicarbonate pool. It has been reported that a considerable proportion of ^{13}C-bicarbonate can be sequestered in the body (Wolf, 1992). This would lead to a lower estimation of the rate of glucose and fructose oxidation. Furthermore, when carbohydrates are ingested well at rest, a significant portion of the glucose molecules provided from these carbohydrates could have been incorporated into glycogen stores (Jandrain and others 1984). Taylor et al (Taylor and others 1996) also reported that approximate 19% of carbohydrate ingested with a mixed meal was stored as hepatic glycogen in healthy volunteers. The amount of glucose and fructose ingested, but not oxidized, is disposed of non-oxidatively and is presumably stored as liver and muscle glycogen.

Based on the method used in the present study, oxidation rates of ^{13}C-substrates can be estimated regardless of liver and splanchnic uptake. The advantage of our study is that $^{13}CO2$ excretion is not affected by gastric emptying, that is one of the various influencing factors involved from oral ingestion to tissue uptake and oxidation (Rehrer and others 1990). Therefore, the result that onset of $^{13}CO2$ enrichment in the breath rose more sharply and were higher throughout in the [1-$^{13}C^{fru}$] palatinose breath test than in the [1-$^{13}C^{glu}$] palatinose breath test reflects more rapid absorption and/or oxidation of [1-$^{13}C^{fru}$] palatinose. As shown

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in Fig.2, $^{13}CO2$ excretion levels were significantly higher in the [1-^{13}C] fructose than in the [1-^{13}C] glucose breath test between 10 and 30 min. This suggests that fructose is absorbed and oxidized more rapidly than glucose when ingested as a monosaccharide. Similarly, $^{13}CO2$ excretion was significantly higher after ingestion of [1-$^{13}C^{fru}$] palatinose than that after ingestion of [1-$^{13}C^{glu}$] palatinose, indicating that fructose is also absorbed and oxidized more rapidly even when ingested as palatinose. Since glucose component of palatinose is oxidized more slowly, lower glycemic response with palatinose should not be due to the rapid oxidation of glucose. As shown in Fig. 5, there are no significant differences in AUC for 90 min, reflecting total oxidation of ^{13}C-substrate, between [1-$^{13}C^{glu}$] palatinose and [1-$^{13}C^{fru}$] palatinose. These suggest that both ^{13}C-disaccharides were finally oxidized regardless of the differences in speed of absorption or acute fuel selection in response to 100mg of disaccharides. Therefore, the greater differences in $^{13}CO2$ excretion after intraduodenal ingestion of ^{13}C-disaccharides compared to ^{13}C-monosaccharides might be caused by interaction between glucose and fructose (Schwarz and others 1992; Sharief and others 1982). This should contribute the beneficial effect on glucose metabolism of palatinose.

Conclusions

It is concluded that fructose component of palatinose might have a sparing effect on absorption and oxidation of glucose component and should cause a gradual increase in blood glucose after ingestion of palatinose.

Author Contributions

Watanabe T, Kawagoe N, Sasaki Y, Ishii T, Nakajima H, and Goto M collected test data. Tonouchi H, Uchida M, Yamaji T, and Sasaki H designed the study. Kashimura J synthesized ^{13}C-substrates. Urita Y and Kaneko H drafted the manuscript.

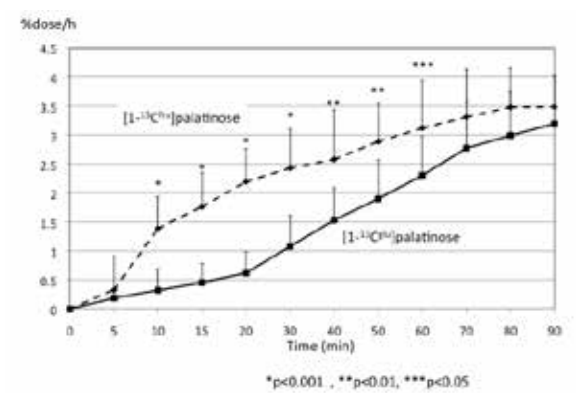

Figure 1 Comparison of appearance of $^{13}CO2$ in breath after the intraduodenal administration of 5 ml of water containing 100 mg of [1-$^{13}C^{glu}$]palatinose and [1-$^{13}C^{fru}$]palatinose. $^{13}CO2$ excretion was significantly higher at 10 min after ingestion of [1-$^{13}C^{fru}$]palatinose and remained higher throughout the study period.

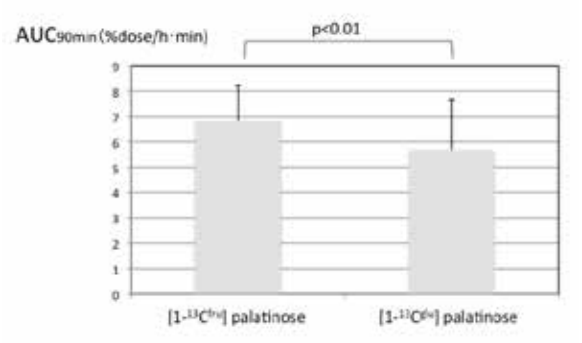

Figure 2 Area under curves (AUC) of $^{13}CO2$ excretion for 90 min after intraduodenal ingestion of ^{13}C-substrates. The areas computed under the curve of $^{13}CO2$ excretion during study period was significantly greater after ingestion of [1-$^{13}C^{fru}$] palatinose than that after ingestion of [1-$^{13}C^{glu}$] palatinose ($p<0.01$).

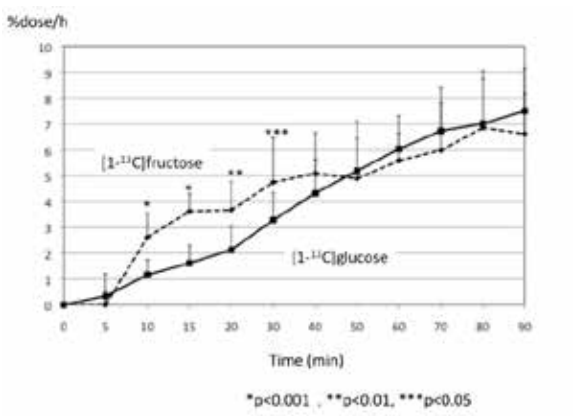

Figure 3 Changes in $^{13}CO2$ excretion after intraduodenal administration of [1-^{13}C] glucose and [1-^{13}C] fructose. $^{13}CO2$ excretion levels were significantly higher in the [1-^{13}C] fructose breath test between 10 and 30 min, compared to in the [1-^{13}C] glucose.

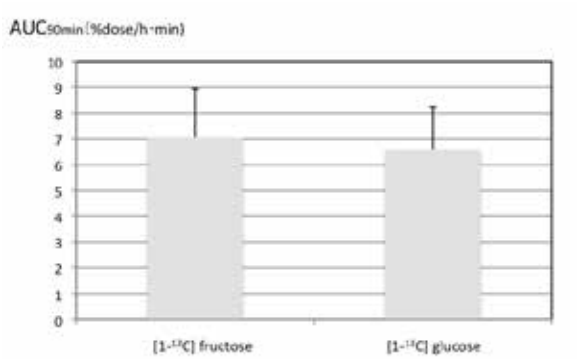

Figure 4 In comparison between monosaccharide breath tests, no significant differences in the AUC were found between [1-^{13}C] fructose and [1-^{13}C] glucose breath test.

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