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Studies on Absorption and Hydrolysis of Ethyl α-D-Glucoside in Rat Intestine

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Ethyl α-D-glucoside (α-EG) is normally contained in Sake, which has been taken by Japanese people since ancient times. In this study, the intestinal absorption of α-EG was investigated using rat everted intestinal sac. Furthermore, the α-EG hydrolytic activity in rat intestine was compared with disaccharides hydrolytic activities, and the effects of α-EG on disaccharides hydrolysis were examined using crude enzyme preparation from rat intestinal acetone powder. Glucose liberated from α-EG was detected in a serosal solution of everted rat intestinal sac, but it was only less than 4% of absorbed intact α-EG. α-EG absorption into small intestinal tissue was reduced by elimination of sodium ion from the mucosal solution or under the presence of phlorizin. The hydrolytic activity for α-EG was detected in crude enzyme preparation from rat intestinal acetone powder, but it showed a low value as compared to those for disaccharides. α-EG showed mixed type inhibition for maltose and sucrose hydrolysis, but inhibitory concentrations of α-EG required for 50% inhibition for the maltose and sucrose hydrolysis were higher than those of arabinose and acarbose. In conclusion, a small amount of α-EG was hydrolyzed and most of it was absorbed via SGLT1 as an intact form in the rat small intestine, and the inhibitory effect of α-EG on disaccharides hydrolysis was weak.

KEYWORDS: Ethyl α-D-glucoside; absorption; hydrolysis; glucose transporter; intestine; rat

INTRODUCTION

Ethyl α-D-glucoside (α-EG) is normally contained in Sake (*1*−*4*), which has been taken by Japanese people since ancient times as an alcoholic beverage and used in cooking as a flavor enhancer. In our previous study, α-EG was detected in plasma and urine of rats fed an α-EG solution (*5*). Imanari and Tamura (*2*) and Teague et al. (*6*) showed that α-EG was detected in the urine of a man who took Sake or rice wine. Thus, α-EG was not hydrolyzed completely in the animal body. On the other hand, ultraviolet B (UVB)-induced epidermal barrier disruption was reduced by oral administration of α-EG or Sake concentrate containing α-EG on mice (*7*), which suggested that α-EG showed physiological effects in the animal body.

In general, disaccharides are hydrolyzed by α-glucosidases localized in the small intestinal mucosa (*8*, *9*). Some glucosides were hydrolyzed by enzymes distributed in the small intestine as well as disaccharides. According to Takenaka and Uchiyama (*10*), (2*S*)-1-*O*-α-D-glucosylglycerol, which was also contained in Sake, was hydrolyzed by sucrase in the sucrase−isomaltase complex in rat intestine. Vitamin glucosides (*11*, *12*) and flavonoid glucosides (*13*) were completely or incompletely hydrolyzed in the animal body, and then, they provide glucose and aglycons. On the other hand, methyl α-D-glucoside (α-MG), nonmetabolic glucoside, is usable for analyzing the transport activity of sodium-dependent glucose transporters (SGLTs) (*14*−*16*).

Released monosaccharides are absorbed through glucose transporters [SGLT and facilitative glucose transporters (GLUTs)] distributed in the small intestinal membrane (*17*, *18*). Brush border membrane transport of monosaccharides in small intestinal mucosa proceeds via SGLT1 and GLUT5, and basolateral membrane transport is also mediated by GLUT2 (*19*, *20*). Landau et al. demonstrated that α-EG was effectively concentrated in everted hamster intestinal sacs (*21*). Ramaswamy et al. demonstrated that hamster intestinal SGLT1 showed affinity to *β*-alkyl glucosides, and the affinity of alkyl glucosides for SGLT1 increased with the increase in the length of the alkyl chain (*22*). Kipp et al. also demonstrated that hog renal SGLTs showed differences of affinity to alkyl chain length in alkyl glucosides (*23*). α-EG might be actively transported via SGLT1 in the small intestine.

In the present study, we examined the intestinal absorption of α-EG by rat everted intestinal sacs. Moreover, we determined

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α-EG and disaccharides hydrolytic activities and effects of α-EG on disaccharides hydrolysis using crude enzyme preparation from rat intestinal acetone powder.

MATERIALS AND METHODS

Reagents and Animals. Reagent grade α-EG (purity > 98%) was prepared by Kanebo Cosmetics Inc. (Kanagawa, Japan). Acarbose, α-MG, α-glucosidase (EC 3.2.1.20) from *Saccharomyces* sp., and Glucose B-Test Wako were purchased from Wako Pure Chemicals Co. Ltd. (Osaka, Japan). Rat intestinal acetone powder was purchased from Sigma Chemical Co. (St. Louis, MO). Other reagents were purchased from Nacalai Tesque Inc. (Kyoto, Japan). Male Wistar ST clean rats were purchased from Japan SLC Inc. (Hamamatsu, Japan), and care and use of the rats in the present study followed the guidelines of governmental legislation in Japan on the proper use of laboratory animals (1980), and animal experiments were approved by the ethical committee of the Faculty of Agriculture in Gifu University (Gifu, Japan).

Preparation of Everted Rat Intestinal Sacs. Wistar ST rats, approximately 8−12 weeks old and approximately weighing 200−350 g, were killed by drawing blood under anesthesia, and the small intestine was excised immediately and rinsed briefly with cold 0.9% KCl. The preparation of everted rat intestinal sacs was performed by the method described by Wilson and Wiseman (*24*). The adherent mesenteric tissue and fat were trimmed off from the jejunum region. The jejunum was divided into tubes of similar size (4 cm in length) and then everted. Both ends of these tubes were bound tightly with silk string after inclusion of 500 μL of Krebs−Ringer buffer. α-EG absorption and sugar determination methods were performed as described in a previous study (*5*). In brief, the everted intestine was dipped into Krebs−Ringer buffer containing 20 mM α-EG, which was bubbled with O_2/CO_2 (95:5, v/v) gas adequately. After incubation for 30 min, glucose in the serosal solution was determined by glucose test kit (Glucose B-Test Wako). The total sugar (α-EG plus glucose) in the serosal solution was determined by the same kit after hydrolysis by α-glucosidase from *Saccharomyces* sp. α-EG absorbed was calculated by subtracting the glucose from the total sugar. The absorption of α-EG was expressed as the μmol of α-EG absorbed per 100 mg of small intestine.

Time Course of α-EG Absorption by Everted Rat Intestinal Sacs. Intestinal sacs were incubated in each experimental solution containing 20 mM α-EG as indicated in parentheses: control (Krebs−Ringer buffer), Na^+-free (Krebs−Ringer buffer replaced sodium ion with equimolar amount of potassium ion), and phlorizin (Krebs−Ringer buffer containing 1.55 mM phlorizin). After incubation for 0 (blank), 1, 5, 15, 30, or 45 min at 37 °C, the serosal solution was collected in a sample tube to determine the absorbed sugars. The same volume (v/w) of ice-cold Krebs−Ringer buffer was added to the residual intestinal tissue and then homogenized with a HG30 homogenizer (HITACHI High-Technologies Co., Tokyo, Japan). After centrifugation at 12000*g* for 10 min at 4 °C with centrifuge MR-150 (TOMY SEIKO Co., Ltd.), the supernatant was collected in a sample tube. Sugars in serosal solution and supernatant from tissue homogenate were determined by the method described above.

Preparation of Crude Enzyme Solution from Rat Intestinal Acetone Powder. The crude enzyme solution was prepared from rat intestinal acetone powder as described by Takenaka and Uchiyama (*10*). The acetone powder was suspended with 10 volumes (v/w) of 0.2 M sodium phosphate buffer (pH 6.0) and then homogenized with a HG30 homogenizer. The homogenate was sonicated for 15 min using a Sharp UT-104 Silentsonic (Sharp Manufacturing System Co., Osaka, Japan) in an ice bath. To remove large particles, the homogenate was centrifuged at 3000*g* for 30 min at 4 °C using a refrigerated centrifuge RS-20IV (TOMY SEIKO Co., Ltd.). The supernatant as a crude enzyme solution was collected in a sample tube and kept on ice until use. The protein concentration in each supernatant was determined by the method of Lowry et al. (*25*) using bovine serum albumin as the standard.

Measurement of Hydrolyzing Activity for α-EG, α-MG, and Disaccharides. The crude enzyme solution was diluted with 0.2 M sodium phosphate buffer (pH 6.0) appropriately. Each substrate solution (α-EG, α-MG, maltose, sucrose, or lactose) was diluted at various concentrations with the same buffer. After preincubation of 200 μL of each sugar solution for 5 min, the reaction was started by adding 100 μL of crude enzyme solution. Incubation was performed at 37 °C for 180 min for α-EG and α-MG or 30 min for disaccharides. To stop the reaction, 100 μL of 1 N NaOH was added and then neutralized with 1 N HCl. The reaction was performed in triplicate. After centrifugation at 12000*g* for 10 min with centrifuge MR-150, and the supernatant was used for glucose determination by Glucose B-Test Wako. The hydrolyzing activity for maltose was expressed as half the amount (μmol) of glucose liberated per mg protein per hour, since 1 mol of maltose is hydrolyzed to liberate 2 mol of glucose.

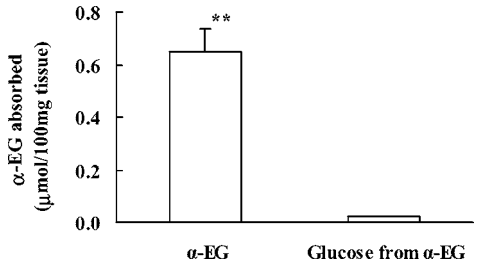

Figure 1. Absorption of α-EG and glucose liberated from α-EG into serosal solution of everted rat intestinal sac was examined. Everted rat intestinal sacs were incubated for 30 min in the Krebs–Ringer buffer containing 20 mM α-EG. α-EG absorption was calculated by subtracting glucose from totally absorbed sugar (glucose plus α-EG). Significant difference was indicated by asterisk (**, $P < 0.01$). Data showed means ± standard errors ($n = 6$).

Assessment of IC_{50} for Disaccharides Hydrolysis by α-EG and α-Glucosidase Inhibitors. To start the hydrolyzing reaction, 100 μL of the crude enzyme solution was added to 200 μL of 50 mM each disaccharide (maltose, sucrose, or lactose) solution containing various concentrations of α-EG, arabinose, or acarbose. The hydrolyzing reaction and glucose analysis were performed by the method described above.

Determination of Inhibition Type of α-EG for Disaccharides Hydrolysis. The reaction mixture consisted of 100 μL of the crude enzyme solution and 200 μL of various concentrations of maltose or sucrose solution containing various concentrations of α-EG. The hydrolyzing reaction and glucose analysis were performed by the method described above.

Statistical Analysis. Statistical significance among means was estimated at $P < 0.05$ according to Student's *t*-test.

RESULTS

Figure 1 shows the absorption of α-EG by everted rat intestinal sacs. α-EG and glucose liberated from α-EG were detected in serosal solution, but absorbed glucose was significantly less than absorbed intact α-EG ($P < 0.01$).

Figure 2 shows the time course of α-EG absorption in small intestinal tissue (cells) and in serosal solution of everted rat intestinal sacs. α-EG absorption in the small intestinal tissue and that in the serosal solution was significantly reduced by elimination of sodium ion from experimental solution or adding phlorizin in the mucosal solution ($P < 0.05$).

α-EG hydrolysis by crude enzyme preparation from rat intestinal acetone powder was indicated in **Figure 3**. α-EG was hydrolyzed by crude enzyme solution prepared from rat intestinal acetone powder.

Table 1 summarizes K_m and V_{max} values for α-EG, α-MG, and disaccharides in this hydrolysis experiment. V_{max} values for the hydrolysis of α-EG, maltose, sucrose, and lactose were 0.09, 13.1, 4.46, and 0.22 μmol/mg protein/h, respectively. The hydrolyzing activity for α-MG was not detected; therefore, K_m and V_{max} values were not determined.

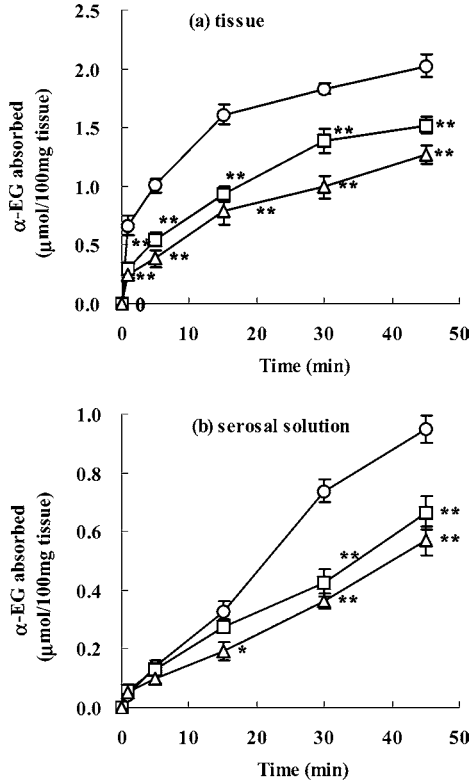

Figure 2. Time courses of α-EG absorption into intestinal tissue (**a**) and serosal solution (**b**) on everted rat intestinal sac were indicated. Everted rat intestinal sacs were incubated for 0 (blank), 1, 5, 15, 30, or 45 min in the Krebs–Ringer buffer containing sodium ion (white circle), in the Krebs–Ringer buffer without sodium ion in which potassium ion was substituted by sodium ion (white triangle), or in the Krebs–Ringer buffer with 1.55 mM phlorizin (white square). α-EG absorption was calculated by subtracting glucose from totally absorbed sugar (glucose plus α-EG). Significant difference at each concentration was indicated by asterisk (**, $P < 0.01$; and *, $P < 0.05$). Each point was the mean ± standard error ($n = 6$).

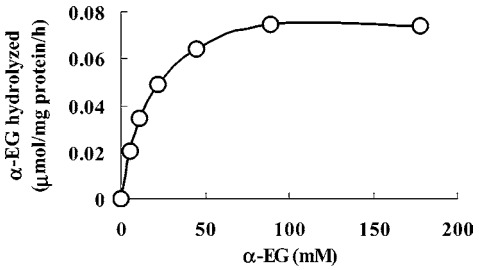

Figure 3. Hydrolysis of α-EG by crude enzyme preparation from rat intestinal acetone powder was examined. Incubation was performed for 180 min at 37 °C. Concentrations of α-EG were set at 0, 10, 21, 42, 83, 167, and 333 mM. Reaction was performed in triplicate.

Figure 4 shows the effect of α-EG on disaccharides hydrolysis by rat intestinal crude enzyme solution. Hydrolyzing activities for maltose (**a**) and sucrose (**b**) were decreased by adding α-EG to the reaction mixture, but that for lactose (**c**) was decreased only slightly in the presence of α-EG at high concentrations. **Table 2** summarizes the concentrations required for 50% inhibition of disaccharide hydrolysis (IC_{50}). The IC_{50} of α-EG for maltose and sucrose was 408 and 101 mM, respectively. The IC_{50} of acarbose for maltose and sucrose was 2.6×10^{-3} and 2.5×10^{-3} mM, respectively. The IC_{50} of arabinose for sucrose hydrolysis was 3.4 mM, whereas that for maltose was not detected (maximal inhibition rate for maltose was 20% even at 600 mM). **Figure 5** shows the Lineweaver–Burk plot for disaccharides hydrolysis by rat intestinal crude enzyme with or without α-EG. α-EG showed mixed type inhibition for the hydrolysis of maltose and sucrose.

Table 1. Kinetics Constants for the Hydrolysis of Glucose Conjugates by Crude Enzyme Preparation from Rat Intestinal Acetone Powder[a]

	K_m (mM)	V_{max} (μmol/mg protein/h)
α-EG	18.7	0.09
α-MG	ND	ND
maltose	14.1	13.1
sucrose	19.9	4.46
lactose	22.5	0.22

[a] Incubations were performed at 37 °C for 180 min for α-EG and α-MG or 30 min for disaccharides. The reaction was performed in triplicate. ND, K_m and V_{max} values were not determined.

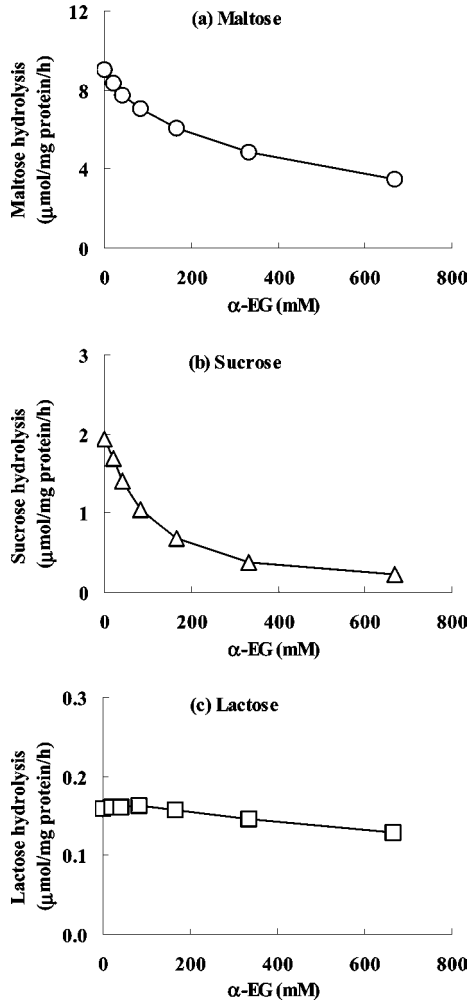

Figure 4. Inhibition of disaccharide hydrolysis by α-EG was indicated. Concentrations of α-EG were set at 0, 21, 42, 83, 167, 333, and 667 mM. Incubations were performed for 30 min at 37 °C. Reaction was performed in triplicate.

DISCUSSION

Disaccharides and oligosaccharides are absorbed as monosaccharides into the blood stream by hexose transport systems distributed in the intestinal membrane after membrane digestion (*19*). In our previous investigation, the hydrolyzing activity for α-EG was detected in a crude enzyme preparation from small intestinal mucosa of Wistar rats (*5*). Landau et al. (*21*) suggested

Table 2. IC_{50} Values of α-EG, Arabinose, and Acarbose for Disaccharide Hydrolysis by Crude Enzyme Preparation from Rat Intestinal Acetone Powder[a]

	IC_{50} values (mM)		
	α-EG	arabinose	acarbose
maltose	408	ND	2.6×10^{-3}
sucrose	101	3.4	2.5×10^{-3}

[a] IC_{50}, inhibitory concentration required for 50% inhibition of the disaccharide hydrolysis. Incubation was performed at 37 °C for 30 min. The reaction was performed in triplicate. ND, IC_{50} was not determined. Inhibition for maltose hydrolysis by arabinose was maximum (20%) at 600 mM.

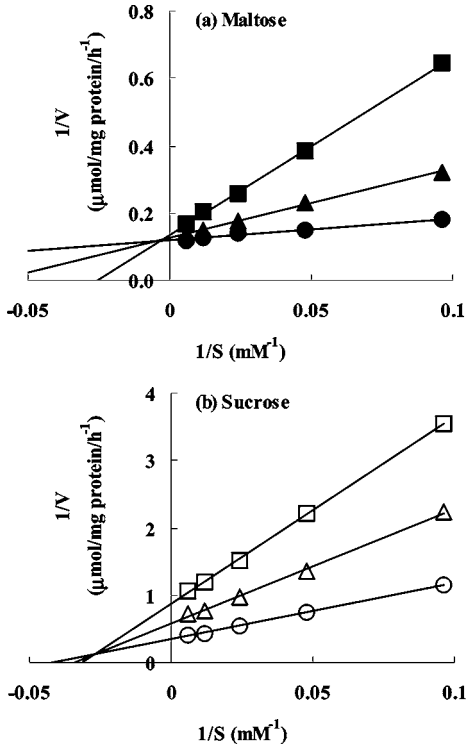

Figure 5. Lineweaver–Burk plot for maltose (**a**) and sucrose (**b**) hydrolysis in the presence and absence of α-EG were indicated. Incubations were performed for 30 min at 37 °C. Concentration of α-EG was set at 0 (black circle), 167 (black triangle), or 667 mM (black square) for maltose hydrolysis and 0 (white circle), 83 (white triangle), or 167 mM (white square) for sucrose hydrolysis. Reaction was performed in triplicate.

the presence of α-EG hydrolyzing enzyme in hamster intestines. As shown in **Figure 1**, glucose liberated from α-EG was detected in a serosal solution of everted rat intestinal sacs, but the glucose absorbed was only less than 4% of absorbed intact α-EG. α-EG was hydrolyzed in rat intestine (**Figure 3**), but the hydrolyzing activity for α-EG showed a low value as compared to that for maltose and sucrose. Our previous study reported that more than 60% of α-EG ingested was excreted into urine (*5*, *26*). These data suggested that α-EG was hardly hydrolyzed and easily absorbed as an intact form in the small intestine.

According to Landau et al. (*21*), α-alkyl glucosides with the small aglycon, i.e., methyl, ethyl, and isopropyl glucosides, were extensively concentrated in everted hamster intestines. Furthermore, hamster intestinal SGLT showed affinity to *β*-alkyl glucosides, and the affinity of alkyl glucosides for SGLT1 increased with the alkyl chain length (*22*). In this experiment using everted rat intestinal sacs, α-EG absorption into the small intestinal tissue was reduced by elimination of sodium ion from the mucosal solution or under the presence of phlorizin (**Figure 2a**), a specific inhibitor of SGLT transporters (*27*, *28*). These data suggested that α-EG was absorbed into small intestinal cells via SGLT1 in a brush border membrane. As shown in **Figure 2b**, α-EG was detected in serosal solution, which suggested that absorbed α-EG into intestinal cells was transported to the serosal side via GLUT2 in basolateral membrane. Reduction of α-EG transport to serosal solution was associated with a reduction of α-EG absorption into intestinal cells via SGLT1. Although the ability of GLUT5 and other transport systems on α-EG transport in the small intestine remained unknown, results in this study showed that α-EG was transported through the small intestinal wall. Therefore, most of the α-EG ingested was absorbed into the blood stream as the intact form (*5*, *26*).

Disaccharides, e.g., maltose and sucrose, are hydrolyzed by small intestinal enzymes (*17*, *19*, *29*), and these enzymes could hydrolyze various glucose conjugates (*11*−*13*, *30*). α-EG showed mixed type inhibition for maltose and sucrose hydrolysis (**Figure 5**), showing the possibility that α-EG might be hydrolyzed by maltase and sucrase in rat intestines. On the other hand, α-MG was not hydrolyzed by the intestinal crude enzyme preparation (data not shown). At present, α-MG is considered as a nonmetabolic glucoside because it was not hydrolyzed by mammalian enzymes (*14*−*16*). Therefore, α-EG hydrolyzing enzymes in rat small intestine might recognize differences in carbon length between ethyl and methyl in aglycon. α-Glucosidase in mammalian small intestine has been reported to catalyze transglucosidation (*10*, *31*−*33*). However, despite extensive research into the metabolic fate of ethanol over many years, glucosidation to ethanol as an acceptor in the mammalian body has not been described. Therefore, α-EG might not be detected in the mammalian body unless it was ingested from Sake or rice wine.

As shown in **Table 2**, IC_{50} values of α-EG for maltose and sucrose hydrolysis were higher than those of arabinose and acarbose. Arabinose showed uncompetitive inhibition for sucrose hydrolysis (*29*); thus, it was expected for the prevention of increasing plasma glucose levels after sucrose ingestion. Acarbose strongly inhibited disaccharides hydrolysis by intestinal enzymes; therefore, it is used as a diabetic medicine, a suppressor of the postprandial increase in blood glucose level (*34*, *35*). α-EG as an inhibitor for disaccharides hydrolysis was less effective as compared to arabinose and acarbose.

In conclusion, most of the ingested α-EG was absorbed through SGLT1 and GLUT2 localized in rat small intestines. The hydrolyzing activity for α-EG was lower than those for disaccharides. α-EG was only slowly hydrolyzed by maltase and sucrase in rat intestines, and effects as an inhibitor on disaccharides hydrolysis were weak as compared to arabinose and acarbose.

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