—Regular Articles—

Possibility as Monosaccharide Laxative of Rare Sugar Alcohols

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Allitol, D-talitol and L-iditol are sugar alcohols that are rare in nature. Due to their previous rarity, little is known about the laxative effects of these rare sugar alcohols. Therefore, reliable data on the laxative effect that these sugar alcohols cause in experimental animals could help to evaluate the effectiveness of new monosaccharide laxative drugs. To investigate the laxative effect of rare sugar alcohols, the study was designed to observe the diarrhea that occurred after oral administration of these sugar alcohols in mice. Moreover, to investigate the influence on intestinal function of rare sugar alcohols, the study was designed to examine small intestine transit and the luminal water content. Results indicated that rare sugar alcohols have a laxative effect in mice. Diarrhea started at a dose of 4.95 g/kg of rare sugar alcohols. There was a statistically significant laxative effect for D-talitol and L-iditol at a dose of 9.9 g/kg as compared to vehicle. Moreover, rare sugar alcohols significantly increased the small intestinal transit and the luminal water content of the small intestine and cecum in mice as compared to each vehicle. Overall, L-iditol greatly changes the function of intestine. In conclusion, rare sugar alcohols increase water content in small intestine and accelerate small intestine transit. These results support laxative effect of rare sugar alcohols. Therefore, rare sugar alcohols may be useful as monosaccharide laxatives and may be used to treat constipation.

Key words——allitol; D-talitol; L-iditol; D-sorbitol; monosaccharide laxative

INTRODUCTION

Allitol, D-talitol and L-iditol are rare sugar alcohols having six carbon atoms. Due to their scarcity, there are limited amounts available for research and the cost of obtaining them is quite high. The processes for producing allitol and D-talitol have been previously reported and involve isolation and identification from *Iteailcifolia* and *Himanthalia elongate*.[1] In addition, the fermentation and production of allitol and D-talitol from D-psicose, a ketohexose, by *Enterobacter agglomerans*[2] and *Candida famata*[3] and L-iditol from L-sorbose, a ketohexose, by *Candida intermedia*[4] have been reported. However, even with these processes, it is very difficult to produce large amounts of these sugar alcohols.

Recently, our group has developed new processes to produce ketohexoses on a large scale using enzymatic methods.[5,6] Ketohexoses are the raw materials for allitol, D-talitol and L-iditol, and as a result, it has become possible to obtain large amounts of these rare sugar alcohols. For example, allitol, D-talitol and L-iditol can be produced from D-psicose and L-sorbose by oxidoreductases (Fig. 1). It is expected that these rare sugar alcohols to be used as a monosaccharide laxative. However, due to their previous rarity, little is known about the laxative effects of these alcohols. Reliable data on the laxative effect that these rare sugar alcohols cause in experimental animals could help to evaluate the effectiveness of new monosaccharide laxative drugs.

On the other hand, D-sorbitol, which is a major sugar alcohol, is known to have a laxative effect. D-Sorbitol is a major photosynthetic product and a major phloem-translocated component in Rosaceae (*e.g.*, apple, pear, peach, and cherry). It also has been produced on a large scale from D-glucose by hydrogenation (Fig. 1). This sugar alcohol is widely used as a sweetening agent in the food industry because of its lower calorific value and its various beneficial effects on health. It is also used as a monosaccharide laxative in the treatment of constipation. Because D-sorbitol is cheaper than lactulose as a synthetic disaccharide laxative, it is preferred by several formularies in the treatment of constipation in the elderly.[7] The mechanisms of D-sorbitol's laxative effect have been previously reported by a number of different investigators, although in most of the studies, it was reported there was an increased colonic osmolality when higher doses were consumed. Soergel reported that in-

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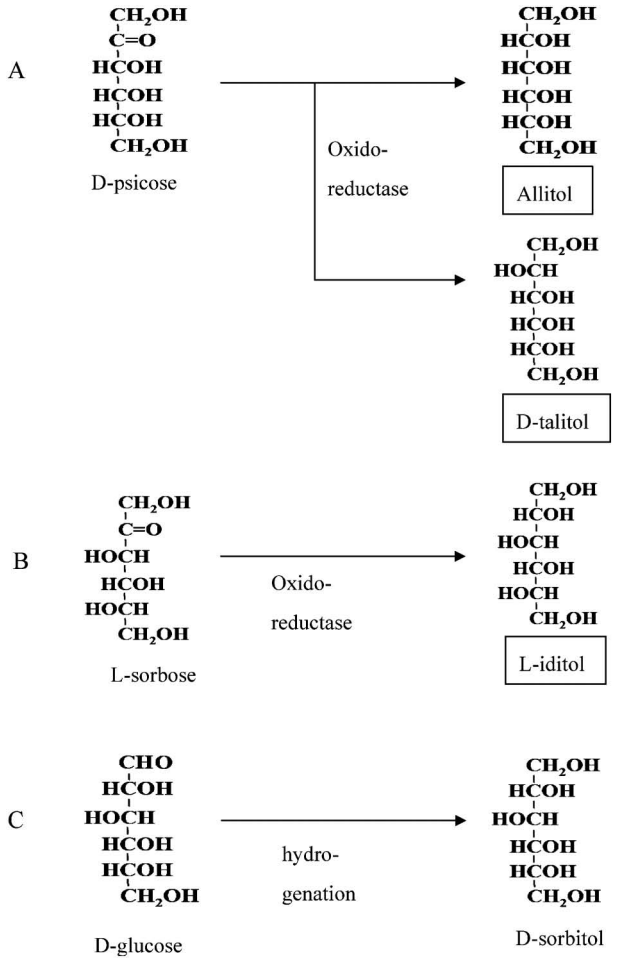

Fig. 1. Conversion of Hexoses to Sugar Alcohols

Conversion of D-psicose to allitol and D-talitol (A). Conversion of L-sorbose to L-iditol (B). Conversion of D-glucose to D-sorbitol (C). Boxed rare sugar alcohols used in the present study.

digestible carbohydrate-induced diarrhea occurs when the amount of carbohydrate entering the colon exceeds its fermentation capacity.[8] In another report, it was stated that intestinal malabsorption is the main reason for the laxative effect.[9]

In the present study, we investigated the laxative effect of allitol, D-talitol, and L-iditol by evaluating the diarrhea that occurred in mice after oral administration of the compounds. Moreover, to investigate the influence on intestinal function of rare sugar alcohols, the study was designed to examine small intestine transit and the luminal water content as compared to the vehicle (Carboxymethylcellulose (CMC) and distilled water) and a positive control (D-sorbitol).

MATERIALS AND METHODS

Reagents Fushimi Seiyakusho, Ltd. (Kagawa, Japan) supplied the rare sugar alcohols, including allitol, D-talitol, L-iditol and the major sugar alcohol, D-sorbitol. Allitol was suspended in 0.5% w/v CMC solution. D-talitol, L-iditol and D-sorbitol were dissolved in distilled water. In order to avoid sudden expansion of the gastric wall, the administration volume was kept at 0.2 ml/animal, and the maximum dose of each sugar alcohol was maintained at 9.9 g/kg, as this was the maximum possible that could be given through the catheter with a suspended solution of allitol. Charcoal and gum arabic were purchased from Wako Pure Chemical Industries Co. (Osaka, Japan).

Animals Male 5-week-old ICR mice (30–35 g) were purchased from Crea Japan, Inc. (Tokyo, Japan). The animals were housed under standard conditions at a room temperature of 20–26°C and a humidity of 30–70% with a 12-h light-dark cycle (lights on at 7:00 AM). They were given solid food for laboratory animals (Oriental Yeast Co., Ltd., Tokyo), and water *ad libitum*. The animals were allowed to acclimate to the environment for at least 7 days and were then put into individual acryl cages before initiating the study. Mice were divided into six groups: group 1, vehicle 1 (0.5% CMC); group 2, vehicle 2 (distilled water); group 3, allitol; group 4, D-talitol; group 5, L-iditol; group 6, D-sorbitol. For the small intestine transit study, animals were fasted overnight but allowed free access to water before the experiments. Water was removed after dosing. The animal experiments in this study were conducted in accordance with the institutional guidelines of Kagawa University and were approved by the Animal Care and Use Committee.

Laxative Effect of Rare Sugar Alcohols The method of Turumi *et al.*[10] was used, with slight modification. Groups of five mice were placed individually in acryl cages with filter paper on the bottom of each cage. Each sugar alcohol (3.3, 4.95, 6.6, 8.25, 9.9 g/kg) and an equal volume of each vehicle were administered by gavage. The consistency of the stools expelled within three hours after the administration of each sugar alcohol or vehicle were investigated. When the feces became unformed, *i.e.*, muddy or watery, this was judged to be diarrhea. The number of mice with diarrhea was reported as the number of animals producing unformed stools as compared to the number tested.

Transit of Charcoal Marker in the Small Intestine The method of Ueda *et al.*[11] was used, with slight

modification. Groups of five animals were used. Mice were orally administered a charcoal marker (distilled water suspension containing 5% charcoal and 10% gum arabic). The mice were sacrificed by cervical dislocation 20 min after administration of the marker and the abdomens were immediately opened, with excision of the entire small intestine from the pylorus to cecum. The length of the small intestine and the distance between the pylorus region and the front of the marker were measured in order to obtain the marker transport percentage. Each of the sugar alcohols (9.9 g/kg, *p.o.*) and an equal volume of each vehicle was administered orally 1.5 h before administration of the marker.

Effect of Luminal Water Content in the Small Intestine, Cecum and Colon The method of Matsuoka *et al.*[12] was used, with slight modification. Groups of five mice, which had already taken part in the small intestine transit study, were used. The cecum and colon were excised from each mouse after the ileocecal junction and the portions of the colon 0.5 cm distal to the ileocecal junction were ligated. The small intestine had already been isolated in the small intestine transit study. The wet weight of the isolated small intestine, cecum, and the colon with luminal water were immediately measured, with the dry weight subsequently measured after these isolated tissues were dried for more than 8 h at 90℃ in a ventilated oven. The luminal water content of the small intestine, cecum and colon were calculated from the difference between the weight of the wet tissues and the weight of the dry tissues.

Data Analyses The data are reported as the mean±S.E.M. A paired *t*-test was used when comparisons were made between two groups. Fisher's exact test for the laxative effect of sugar alcohols was used. A value of p less than 0.05 was considered to indicate statistical significance.

RESULTS

Laxative Effect of Rare Sugar Alcohols The laxative effect of allitol, D-talitol and L-iditol was assessed by observing the diarrhea that occurred in mice after administration of each of the sugar alcohols. In this study, the rare sugar alcohols, allitol, D-talitol and L-iditol, were found to have a marked laxative effect in mice. In fact, as seen in Fig. 2, more than half of the mice exhibited diarrhea after the maximum dosing of these alcohols. There was a statistically significant laxative effect for D-talitol and L-iditol

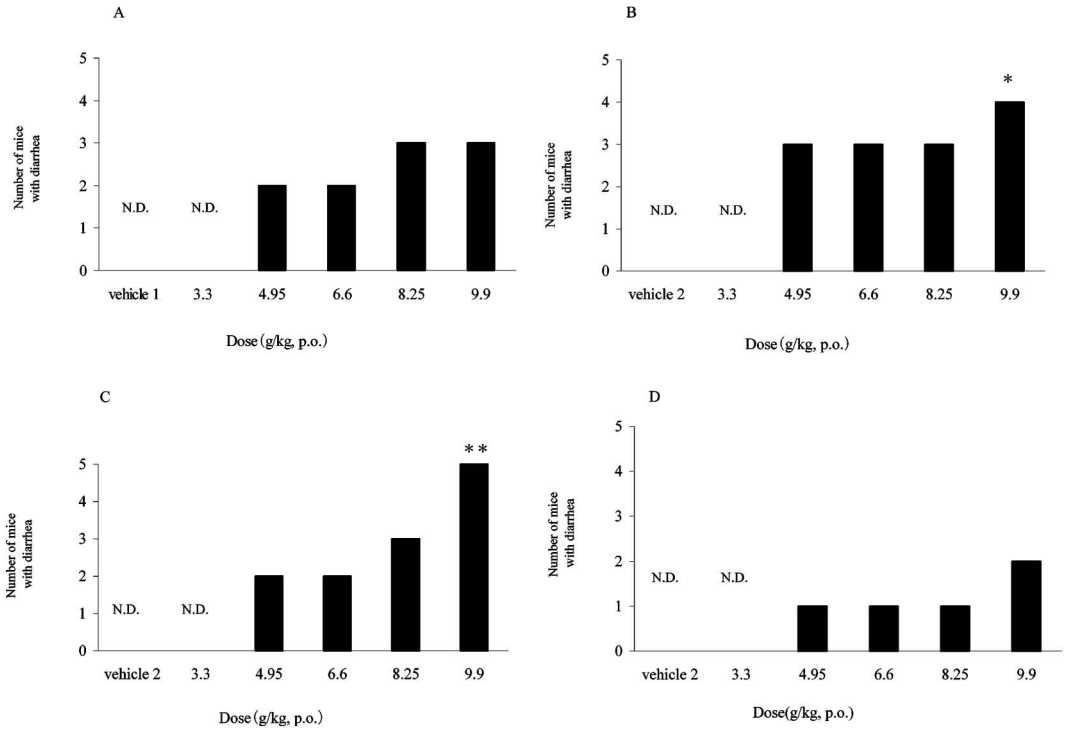

Fig. 2. Laxative Effects on Diarrhea in Mice

Allitol (A), D-talitol (B), L-iditol (C) and D-sorbitol (D). The vehicle animals orally (0.2 ml/animal) received CMC (vehicle 1) and distilled water (vehicle 2). Values are reported as the mean±S.E.M. of 5 animals. $^{*}p<0.05$, $^{**}p<0.01$, *versus* each vehicle.

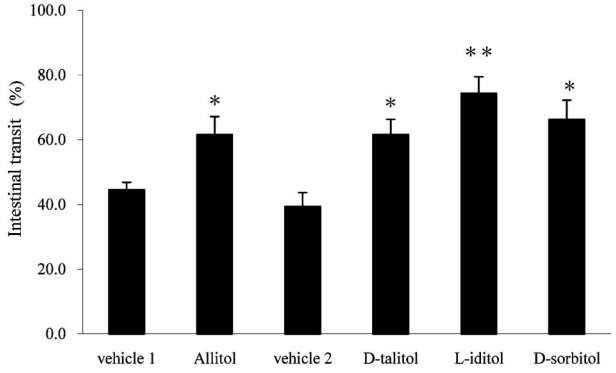

Fig. 3. Effects of Allitol, D-talitol, L-iditol and D-sorbitol on Transit of the Charcoal Marker in the Small Intestine

The vehicle animals orally (0.2 ml/animal) received CMC (vehicle 1) and distilled water (vehicle 2). Values are reported as the mean±S.E.M. of 5 animals. $^{*}p<0.05$, $^{**}p<0.01$, *versus* each vehicle.

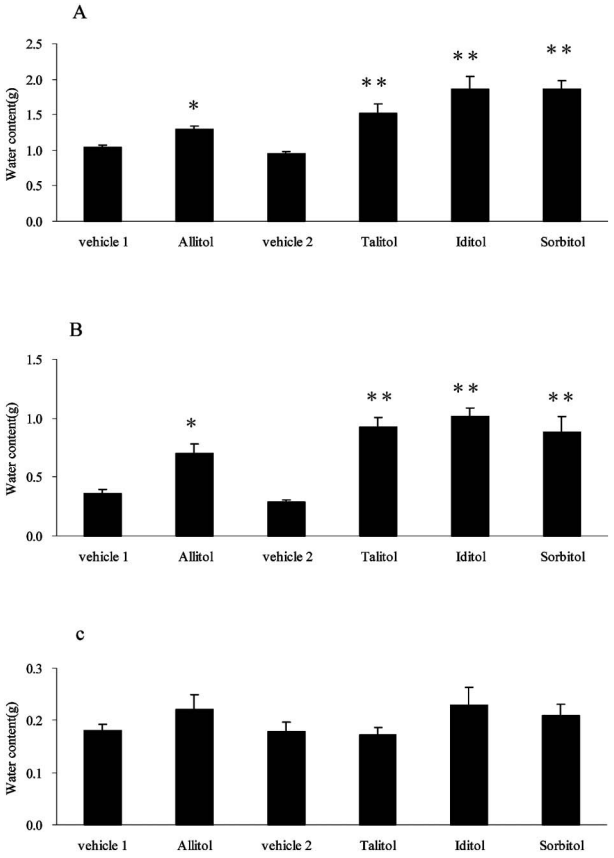

Fig. 4. Effects of Allitol, D-talitol, L-iditol and D-sorbitol on Luminal Water Content in mice

Small intestine (A), cecum (B) and colon (C). The vehicle animals orally (0.2 ml/animal) received CMC (vehicle 1) and distilled water (vehicle 2). Values are reported as the mean±S.E.M. of 5 animals. $^{*}p<0.05$, $^{**}p<0.01$, *versus* each vehicle.

at a dose of 9.9 g/kg. On the other hand, D-sorbitol only induced the diarrhea in less than half of the mice tested when a 9.9 g/kg dose was administered. Mice with muddy diarrhea were observed from the dosage of 4.95 g/kg of rare sugar alcohols and D-sorbitol. Each sugar alcohol also induced the watery diarrhea when a 9.9 g/kg dose was administered.

Transit of Charcoal Marker in the Small Intestine A charcoal marker was used to determine each sugar alcohol's influence on small intestine transit. At a dose of 9.9 g/kg, allitol, D-talitol and L-iditol significantly increased the transit of the charcoal marker in the small intestines of mice (Fig. 3). The distances traveled by each of the vehicle controls (CMC and distilled water) were 44.6±2.2% and 39.4±4.3%. With allitol, D-talitol and L-iditol the charcoal markers moved 61.6±5.5% ($p=0.04$ *vs.* CMC), 61.6±4.7% ($p=0.03$ *vs.* distilled water) and 74.3±5.2% ($p=0.009$ *vs.* distilled water) of the small intestine length. There was also significant movement of the charcoal marker caused by D-sorbitol, 66.3±6.0% ($p=0.03$ *vs.* distilled water) of the small intestine length.

Effects of Luminal Water Content in the Small Intestine, Cecum and Colon The luminal water content in the small intestine, cecum and colon of the mice were studied by examining the differences between the wet and the dry weights of the tissues. Rare sugar alcohols significantly increased the luminal water content in the small intestine and cecum of mice at a dose of 9.9 g/kg (Fig. 4). The luminal water content in small intestine, cecum and colon after administration of vehicle control (CMC) were 1.035±0.032 g, 0.362±0.036 g and 0.180±0.013 g and in the other vehicle control (distilled water) were found to be 0.953±0.036 g, 0.283±0.026 g and 0.179±0.018 g. Allitol significantly increased the luminal water content in the small intestine and cecum to 1.293±0.044 g ($p=0.011$) and 0.703±0.076 g ($p=0.012$), while D-talitol significantly increased the content in these organs to 1.524±0.126 g ($p=0.005$) and 0.923±0.082 g ($p=0.0005$), respectively, L-iditol significantly increased the luminal water content in the small intestine and cecum to 1.859±0.173 g ($p=0.003$) and 1.012±0.072 g ($p=0.0002$), and D-sorbitol also significantly increased the content in these organs to 1.857±0.130 g ($p=0.003$) and 0.880±0.136 g ($p=0.008$). Rare sugar alcohols and D-sorbitol did not significantly increase the luminal water content in the colon, however.

DISCUSSION

The rare sugar alcohols, allitol, D-talitol and L-iditol, have rarely been available for research purposes due to the very limited derivations and exorbitant cost. Therefore, the physiological functions of these compounds are largely unknown. Recently, it has become possible to obtain large quantities of all these alcohols using oxidoreductases on a large scale for the quantitative production of ketohexoses, which are the raw materials for these alcohols. As a result, large amounts of these alcohols have become available, and this is the first study that has been able to focus on their laxative effect.

It has been reported that the best way to test the laxative effect is to examine the fecal condition in experimental animals.[13] Fecal consistency can best be described as the ratio of the water holding capacity of insoluble solids to the total water in the lumen. When there are sufficient water holding solids and/or little non-bound water, stools remain thick and formed. On the other hand, if there are too few of these water-holding solids to bind all of the water present, stool consistency becomes loose, eventually to the point of being like water.[14] In the present study, at a dose of 4.95 g/kg, allitol, D-talitol and L-iditol induced muddy diarrhea and at a dose of 9.9 g/kg induced watery diarrhea in mice within 3 h after the administration of these rare sugar alcohols; the number of mice with diarrhea was more than that induced by the D-sorbitol. The location of the hydroxyl that composes sugar alcohols may influence the laxative effect. These results indicate that rare sugar alcohols have the potential to treat constipation and may be used as monosaccharide laxatives.

It has also been reported that unabsorbed carbohydrates from D-sorbitol may serve as an osmotic load that draws fluid into the intestinal lumen,[15] and this intestinal malabsorption may be main reason for the diarrhea.[9] Diarrhea can be characterized as abnormal frequent expulsion of feces of low consistency, which can be due to a disturbance in the transport of water and electrolytes within the intestines.[16] Despite the multiplicity of possible etiologies, four major mechanisms have been postulated to be responsible for the water and electrolyte transport pathophysiology. These are (i) an increased luminal osmolarity (osmotic diarrhea), (ii) an increased secretion of electrolytes (secretory diarrhea), (iii) a decreased absorption of electrolytes, and (iv) a deranged intestinal motility that causes a decreased transit time.[16] In order to clarify the influence on intestinal function of allitol, D-talitol and L-iditol, it is necessary to determine small intestine transit and the luminal water content within the intestine. We showed that rare sugar alcohols significantly increased the small intestinal transit in mice as compared to vehicle (CMC and distilled water). We also showed that 1.8 h after the administration of rare sugar alcohols, there was a significant increase in the luminal water content of the small intestine and cecum in mice, except for the colon, when compared with vehicle. These results indicate that increase of water content in the small intestine is involved in the acceleration of transit. Similarly, D-sorbitol also caused a significant increase in small intestinal transit and the luminal water content of the small intestine and cecum, except for the colon. Therefore, we found no significant difference between rare sugar alcohols and D-sorbitol.

Each sugar alcohol used in this study has a relation to the structural isomer. The physical properties of each alcohol differ greatly. For example, allitol is insoluble to water as compared to other sugar alcohols. However, it is still unclear whether the physical properties of each alcohol influence the laxative effect. On the other hand, rare sugar alcohols did not influence the contraction of small intestine tissues in a preliminary study (data not shown). It was speculated that these alcohols do not have an irritative action on intestinal lumen. Skoog *et al*. reported that a single dose of sorbitol markedly accelerated colonic transit in healthy humans.[17] In this study, the colonic transit was not measured, because the luminal water content of the colon was not increased in any group. However, the possibility to potentiate the colonic motility by rare sugar alcohols cannot be excluded. Further investigation is needed to determine whether rare sugar alcohols influence colonic motility.

Rare sugar alcohols increase water content in the small intestine and accelerate small intestine transit; these results support their laxative effect. Therefore, these alcohols may be useful as monosaccharide laxatives and may be used to treat constipation.

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