Retraction

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D-Psicose Inhibits Intestinal α -Glucosidase and Suppresses the Glycemic Response after Ingestion of Carbohydrates in Rats

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Summary D-psicose is one of the rare sugars present in small quantities in commercial carbohydrates and agricultural products. In this study, we investigated the effects of D-psicose on the activities of α -amylases and α -glucosidases *in vitro*, and evaluated the effects of D-psicose on the *in vivo* postprandial glycemic response using rats. In the *in vitro* study, D-psicose potently inhibited the intestinal sucrase and maltase, however, slightly inhibited the intestinal and salivary α -amylase activities. Male Wistar rats (6 months old) were administered 2 g/kg of sucrose, maltose or soluble starch together with 0.2 g/kg of D-psicose or D-fructose. The D-psicose significantly inhibited the increment of plasma glucose concentration induced by sucrose or maltose. The starch-induced glycemic response tended to be suppressed by D-psicose, however the suppression was not significant. These results suggest that D-psicose inhibits intestinal sucrase and maltase activities and suppresses the plasma glucose increase the normally occurs after sucrose and maltose ingestion. Thus, D-psicose may be useful in preventing postprandial hyperglycemia in diabetic patients when foods containing sucrose and maltose are ingested.

Key Words: D-psicose, sucrase, maltase, plasma glucose, rat

Introduction

D-psicose (D-ribo-2-hexulose), a C-3 epimer of D-fructose, is a “rare sugar” present in small quantities in commercial mixtures of D-glucose and D-fructose obtained from the hydrolysis of sucrose or isomerization of D-glucose [1]. Because of the very small amounts of D-psicose in natural products, few studies have examined D-psicose metabolism in animals. Recently, we developed a new method for producing D-psicose enzymatically on a large scale [2], making it possible to conduct such studies. We have since demonstrated that D-psicose is a sweet carbohydrate that provides no energy to growing rats [3–5] and that it causes little toxic effect in rats [6–7]. Thus, D-psicose may be useful as a sweetener for obese people seeking to lose weight.

On the other hand, it has been proven that strict glycemic control is associated with a low incidence of microvascular and macrovascular complications in diabetes [8], and a delay or inhibition of carbohydrate digestion could be helpful for avoiding postprandial hyperglycemia in diabetic patients [9, 10]. Specific inhibitors of α -glucosidases have shown a definite therapeutic value in suppressing the postprandial glycemic increase by delaying carbohydrate digestion [9–11]. Acarbose [9–13] and L-arabinose [14–17] are known to be competitive and uncompetitive inhibitors of the intestinal α -glucosidases, ie, sucrase, and maltase. It has also been shown that pancreatic amylase is inhibited by acarbose [13]. Although the majority of dietary carbohydrates are starch, daily ingestion of sucrose is large in many advanced countries, however, agents that inhibit neither starch nor sucrose digestion have been used.

Previously, we reported that a diet containing 5% D-psicose increased liver glycogen content in rats fed a high-fat or a low-fat diet for 16 weeks [18]. We also observed that D-psicose significantly suppressed the increment of plasma

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Table 1. Inhibitory effect of rare sugars on glucose release by α -amylase and α -glucosidase

Enzymes	Substrate/ inhibitor	D-Fructose	D-Psicose	D-Allose
		Relative rate (%)		
α -Amylase (rat small intestine)	1	100.8 $\pm$ 1.0 ^a	83.0 $\pm$ 1.9 ^c	89.5 $\pm$ 1.9 ^b
	10	101.2 $\pm$ 2.0	100.2 $\pm$ 1.4	100.4 $\pm$ 0.6
α -Amylase (rat pancreas)	1	100.7 $\pm$ 0.4	100.4 $\pm$ 1.1	101.6 $\pm$ 1.1
	10	98.5 $\pm$ 1.7	98.0 $\pm$ 1.2	101.3 $\pm$ 2.9
α -Amylase (human saliva)	1	101.3 $\pm$ 1.5	96.2 $\pm$ 3.3	103.7 $\pm$ 3.3
	10	101.5 $\pm$ 0.9	99.9 $\pm$ 2.3	99.3 $\pm$ 2.3
α -Amylase (<i>bacillus subtilis</i>)	1	102.4 $\pm$ 3.1	102.3 $\pm$ 5.3	101.7 $\pm$ 2.9
	10	99.1 $\pm$ 0.2	99.1 $\pm$ 0.2	98.3 $\pm$ 0.8
α -Amylase (<i>aspergillus oryzae</i>)	1	95.0 $\pm$ 1.7 ^a	89.3 $\pm$ 0.6 ^b	95.3 $\pm$ 1.1 ^a
	10	98.8 $\pm$ 0.5	97.5 $\pm$ 0.3	98.0 $\pm$ 1.0
Sucrase (rat small intestine)	1	99.6 $\pm$ 2.6 ^a	74.5 $\pm$ 3.9 ^b	77.9 $\pm$ 1.3 ^b
	10	98.1 $\pm$ 1.5 ^a	92.2 $\pm$ 2.3 ^b	96.4 $\pm$ 1.3 ^{ab}
Maltase (rat small intestine)	1	99.5 $\pm$ 3.4 ^a	85.4 $\pm$ 2.6 ^b	90.2 $\pm$ 5.6 ^{ab}
	10	100.9 $\pm$ 0.5	101.0 $\pm$ 0.3	99.7 $\pm$ 0.2

Values are the means $\pm$ SD of four experiments. Relative rates are shown as 100% without inhibitor. Means with different superscripts within a column are significantly different ($p < 0.05$, one-way ANOVA and Fisher's PLSD tests).

glucose concentration induced by oral carbohydrate (sucrose, maltose or starch) tolerance tests [19]. In addition, we demonstrated that plasma glucose and insulin concentrations were lower in all days the rats were fed a D-psicose diet than in the rats fed a sucrose diet for 8 weeks [20]. These findings suggest that D-psicose may inhibit the activities of α -amylase and α -glucosidase. However, inhibitory effects of D-psicose on enzymes in the digestive tract were not clarified. In this study, we investigated the effects of D-psicose on the activities of α -amylases and α -glucosidases *in vitro*, and evaluated the effects of D-psicose on the *in vivo* postprandial glycemic response using rats.

Materials and Methods

All procedures involving animals were approved by the Animal Care Committee of Kagawa University.

Inhibitory effect of D-psicose on activities of α -amylases and α -glucosidases in vitro

D-Psicose and D-allose were donated from Rare Sugar Research Center, Kagawa University. α -Amylases from *bacillus subtilis* and *aspergillus oryzae* were purchased from Wako Pure Chemical Industries (Osaka, Japan). Three male Wistar rats (3-week-old) obtained from Japan SLC (Shizuoka, Japan) were killed by decapitation. The small intestines and pancreases of the rats were obtained immediately after death, rinsed with ice-cold saline, and stored at -40°C until use. All of the collected mucosa from the three rats was homogenized together with a 5 mmol/l EDTA-phosphate buffer (pH 7.0) and centrifuged at 4°C for

10 min at $15000 \times g$. The extract was used to assay of the activities of α -amylase, sucrase, and maltase by methods of Caspary and Graf [12] and Dahlqvist [21]. For the pancreatic α -amylase assay, the tissues were homogenized together with a 10 mmol/l phosphate buffer (pH 7.0), and the homogenate was used for amylase assay using the method of Whelan [22]. The standard assay mixture contained a 40 μl substrate solution (20 mg/ml soluble starch, sucrose, and maltose, for assay of α -amylase, sucrase, and maltase, respectively), and 80 μl of a test carbohydrate solution (final concentration, 0.4–4.0 mg/ml D-fructose, D-psicose, and D-allose). The reaction was initiated by the addition of 80 μl of appropriate dilutions of dried enzyme powders (from *bacillus subtilis* and *aspergillus oryzae*) or enzyme solutions (from the small intestine and pancreas). The reaction mixture was incubated for 60 min at 37°C , and then the glucose concentration of the mixture was determined by the kits (Glucose CII-Test, Wako Pure Chemical Industries). The relative enzyme activities were calculated from glucose release. Relative rates were shown as 100% without inhibitors.

Effect of D-psicose on plasma glucose concentrations after carbohydrate loading in rats

To evaluate the potency of D-psicose *in vivo*, the effects of D-psicose on plasma glucose concentrations after glucose, sucrose, maltose, and soluble starch loading, were examined. One hundred forty-four male Wistar rats (6 months old) were purchased from Japan SLC (Shizuoka, Japan) and acclimatized for a week under standard laboratory conditions ($22 \pm 2^{\circ}\text{C}$, 60% humidity). The light/dark cycle was 12 h with lights on from 8:00 h to 20:00 h. Rats were

Table 2. Effects of D-psicose on plasma glucose concentrations (mg/dL) after oral carbohydrate loading in rats

Test carbohydrates	Time after administration (min)					Δ AUC (h·mg/dL)
	0	30	60	90	120	
Glucose	99 ± 7	148 ± 14	157 ± 15	159 ± 7	168 ± 18	6087 ± 1160
Glucose+Fructose	92 ± 8	139 ± 12	154 ± 17	156 ± 18	159 ± 18	6530 ± 1194
Glucose+Psicose	92 ± 10	140 ± 14	154 ± 10	154 ± 16	155 ± 13	5866 ± 1434
Sucrose	102 ± 8	135 ± 13	151 ± 27 ^a	148 ± 14	146 ± 17	5235 ± 1692
Sucrose + Fructose	102 ± 12	134 ± 13	142 ± 11 ^{ab}	146 ± 10	144 ± 9	4109 ± 1106
Sucrose + Psicose	95 ± 9	129 ± 11	138 ± 12 ^b	146 ± 16	142 ± 17	4433 ± 1654
Maltose	94 ± 9	146 ± 12 ^a	157 ± 19	163 ± 17 ^a	159 ± 12 ^a	6855 ± 1383
Maltose + Fructose	88 ± 12	140 ± 12 ^{ab}	155 ± 15	152 ± 9 ^{ab}	147 ± 12 ^{ab}	6386 ± 1430
Maltose + Psicose	87 ± 9	133 ± 18 ^b	149 ± 13	147 ± 12 ^b	141 ± 16 ^b	5895 ± 1061
Starch	98 ± 10	131 ± 10	133 ± 18	130 ± 17	125 ± 19	4035 ± 1233
Starch + Fructose	93 ± 4	128 ± 14	134 ± 16	127 ± 12	126 ± 11	3836 ± 1330
Starch + Psicose	92 ± 9	124 ± 11	125 ± 15	121 ± 12	120 ± 12	3098 ± 1138

Values are the means ± SD for 12 rats. Fructose and psicose (0.2 g/kg body weight) were administered with glucose, sucrose, maltose or starch (2 g/kg body weight). Means with different superscripts within a column are significantly different ($p < 0.05$, one-way ANOVA and Fisher's PLSD tests).

randomly divided into the 12 groups shown in Table 1. Twelve rats were fasted overnight for 12 h before the experiments. D-Psicose, or D-fructose (0.2 g/kg) was orally administered via gavage with 2 g/kg glucose, sucrose, maltose, or soluble starch. At 0, 30, 60, 90, and 120 min after loading, blood was collected from the tail vein to obtain the plasma. The plasma glucose concentration was determined by the kits (Glucose CII-Test, Wako Pure Chemical Industries).

Statistical analysis

All values are expressed as the mean ± SD. The data was assessed by one-way ANOVA and Fisher's PLSD tests. All analyses were performed with a commercially available statistical package (StatView J-5.0, SAS Institute Inc., Cary, NC).

Results

Inhibitory effect of D-psicose on activities of α -amylases and α -glucosidases in vitro

Relative enzyme activities shown in Table 1 are 100% without inhibitors (D-fructose, D-psicose, or D-allose). D-Fructose (0.4–4.0 mg/ml) showed no inhibition of each enzyme activity (Table 1). D-Psicose and D-allose (4.0 mg/ml) significantly inhibited intestinal α -amylase, sucrase, maltase, and α -amylase from *aspergillus oryzae* (Table 1) except for in the maltase inhibition induced by D-allose. The inhibitory effect of D-psicose was greater than that of D-allose (Table 1). Neither D-psicose nor D-allose inhibited the pancreatic α -amylase, and α -amylase from *bacillus subtilis* activities (Table 1). D-Psicose (4.0 mg/ml) slightly

inhibited the salivary α -amylase activity, but D-allose did not suppress this enzyme (Table 1).

Effect of D-psicose on plasma glucose concentrations after carbohydrate loading in rats

D-Psicose significantly suppressed the increase of plasma glucose levels after sucrose and maltose loading in fasted rats, however, no suppression was found after glucose loading (Table 2). After 60 min after ingestion, the plasma glucose concentration was significantly lower in the Sucrose + Psicose group than in the Sucrose group, the suppression lasted from 30 to 90 min in the Sucrose + Psicose group (Table 2). At 30, 90 and 120 min after ingestion, the plasma glucose concentration was significantly lower in the Maltose + Psicose group than in the Maltose group, and the suppression lasted from 30 to 120 min in the Maltose + Psicose group (Table 2). The plasma glucose level was also suppressed by D-psicose after starch loading in fasted rats, however, the suppression was not significant. D-Fructose did not suppress the increase of plasma glucose levels after either carbohydrate loading (Table 2).

Discussion

We demonstrated in this study that D-psicose selectively inhibited the intestinal α -amylase, sucrase, and maltase activities. We also showed that D-psicose suppressed the increase of plasma glucose after ingestion of sucrose, maltose, and starch in rats, but the plasma glucose suppression was not significant after starch ingestion. Semenza and Balthazar [23] and Seri *et al.* [14] reported a similar inhibi-

tion of sucrase activity by L-arabinose in rabbits [23] and rats [14], however, they did not examine the intestinal α -amylase activity. We also showed that D-allose selectively inhibited the activities of intestinal enzymes *in vitro*, but no *in vivo* examination was performed in this experiment. In our previous study, we demonstrated that a diet containing 5% D-psicose increased liver glycogen content in rats fed a high-fat or a low-fat diet for 16 weeks [18]. We also observed that D-psicose significantly suppressed the increment of plasma glucose concentration induced by oral carbohydrate (sucrose, maltose or starch) tolerance tests [19]. The present study supports our previous findings.

Other α -glucosidase inhibitors [9–13, 24] such as acarbose are recognized as potent inhibitors of the activities of intestinal glucoamylase, maltase, and sucrase, and it has also been shown that acarbose has an inhibitory effect on pancreatic amylase activity [13]. In many advanced countries, starch accounts for approximately 60% of ingested carbohydrates, with sucrose accounting for 30%, and lactose accounting for 10% [12]. Since the digestion of both starch and sucrose are delayed by acarbose and D-psicose, these α -glucosidase inhibitors have valuable therapeutic effect in reducing postprandial hyperglycemia in diabetic patients.

The majority of dietary carbohydrates are from starch, but sucrose is used in many foods as a sweetener or as another ingredient, and its daily intake in many advanced countries is large. It has been shown that Tris competitively inhibits intestinal sucrose ingestion in rats and human subjects [25], however, Tris is of no practical use, because of its unpleasant taste and the necessity of large doses. Thus, there are few known inhibitors of practical use such as L-arabinose that selectively inhibit intestinal sucrase and delay the ingestion of sucrose.

D-Psicose is a rare natural sugar with a sweet taste. In this study, it suppressed the increase in plasma glucose after sucrose (–15%, calculated by area under the curve, Table 2), maltose (–14%), and starch (–23%) but showed no suppression of the increase in plasma glucose after oral glucose loading in rats. These results suggest that D-psicose does not affect glucose absorption or gastric emptying. Among hexose structurally related to D-psicose, D-allose was equally potent in its inhibitory effect on the sucrose and maltose activities of intestinal mucosa in this study. Neither D-psicose nor D-allose inhibited amylases from rat pancreas, *bacillus subtilis*, or *aspergillus oryzae*. These results suggest that some specific interaction may exist among the enzymes, inhibitors, and the substrate to elicit the inhibitory action of D-psicose or D-allose.

D-Psicose is prevalent in nature as a component of some plants and agricultural products [26–30]. It has a potent, sweet taste and low toxicity; the LD₅₀ value was 16g/kg orally in rats in our previous tests [6]. D-Psicose caused no diarrhea at a dose of 10% of the dietary intake in the rat

study [6]. Although a definite therapeutic value of other known α -glucosidase inhibitors in diabetic patients has been demonstrated, unpleasant side effects associated with incomplete absorption of dietary carbohydrates, ie, flatulence, abdominal discomfort, diarrhea [9, 10], and ileus-like symptoms [31], have been reported. These side effects may be due to the potent inhibition of pancreatic amylases and many intestinal enzymes, which in turn strongly inhibits the digestion of both sucrose and starch. As shown in this study, D-psicose only inhibited intestinal enzymes and the suppression of amylase was weak, resulting in little adverse effect on the gastrointestinal tract.

Recently, there have been skeptical studies concerning the long-term effects of α -glucosidase inhibitors, e.g. acarbose, in type 2 diabetes patients. Kaiser *et al.* [32] and Van De Laar *et al.* [33] reported that the long-term trials and meta-analysis studies have been criticized for the effects of α -glucosidase inhibitors. Furthermore, a recent systematic review of α -glucosidase inhibitors in patients with type 2 diabetes concluded that there was no evidence of any effect on morbidity or mortality [34]. It is not clear the hypoglycemic effects and side effects of D-psicose in diabetic patients for long-term. However, these effects were clarified in our previous animal studies [6, 20, 35]. Therefore, we will examine the long-term effects of D-psicose in clinical studies in future.

In conclusion, the present study demonstrated that D-psicose inhibits intestinal sucrase and maltase activities and suppresses the plasma glucose increase after sucrose and maltose ingestion. Thus, D-psicose may be useful in preventing postprandial hyperglycemia in diabetic patients when foods containing sucrose and maltose are ingested. This is the first report indicating inhibition of sucrase and maltase activities by D-psicose both *in vitro* and *in vivo*.

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