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Suppression of Postprandial Glycaemia by L-Arabinose in Rats is More Associated with Starch than Sucrose Ingestion – Short Report

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The aim of this study was to verify the glycaemia-lowering activity of L-arabinose. The experiment was conducted on 3 individual days, each separated by a week. At the beginning of each week rats were subjected to an oral glucose, sucrose or starch tolerance test. Five minutes prior to each test rats were gavaged with water (a control), an aqueous solution of acarbose (a positive control) and L-arabinose. There was no effect of L-arabinose on glycaemia in the glucose tolerance test, whereas it reduced postprandial glycaemia after 15 min of the sucrose tolerance test. In the starch tolerance test, the glycaemia after L-arabinose ingestion was significantly decreased both at time intervals and in total. Inhibition of enzyme activity involved in starch digestion (amylase, maltase) may be suggested as the most probable mechanism responsible for the observed effects.

INTRODUCTION

L-arabinose is a pentose broadly present in plants as a structural component of polysaccharides, such as hemicelluloses, pectins and gums, of which it is commonly isolated [Li *et al.*, 2013]. This sugar with a sweet taste is considered to be less absorptive from the intestinal tract as well to provide less metabolisable energy than glucose [Osaki *et al.*, 2001; Krog-Mikelsen *et al.*, 2011]. Animal studies and clinical trials have shown that L-arabinose is able to effectively reduce postprandial blood glucose level and various mechanisms responsible for this effect have been widely suggested [Krog-Mikelsen *et al.*, 2011; Seri *et al.*, 1996; Preuss *et al.*, 2007]. The uncompetitive inhibition of intestinal sucrase by forming enzyme-inhibitor-substrate complex has been proposed as the most probable mechanism of action [Seri *et al.*, 1996; Shibanuma *et al.*, 2011].

Many potential plant-derived, anti-diabetic components have been identified thus far and nowadays research is more and more focused on obtaining dietary supplements that are able to manage postprandial glycaemia in a most effective manner. As a result, mixtures of different plant extracts, phytochemicals and other dietary compounds have been recently tested in animal studies and clinical trials [Collene *et al.*, 2005; Kaats *et al.*, 2011; Said *et al.*, 2008; Loi *et al.*, 2013]. L-arabinose has been used successfully, in combination with chromium, for lowering both circulating glucose and insulin levels after an acute oral sucrose challenge in healthy subjects [Kaats *et al.*, 2011]. In our laboratory, animal studies focused on obtaining a new effective and safe glycaemia-lowering formula, using among others L-arabinose, are in progress. However, the results that have until now been obtained on the bioactivity of L-arabinose suggest a more complex mechanism of action of this compound, which is reported here.

MATERIALS AND METHODS

Preparations

L-Arabinose and acarbose were purchased from Sigma-Aldrich (≥99% and ≥95% purity, respectively, St. Louis, USA). Soluble starch was purchased from POCH Joint-Stock Company (≥99% purity, Gliwice, Poland).

Animals and experiment design

The experiment was conducted on 27 male Wistar rats randomly assigned to one of three groups of nine animals each. Body weights of rats were comparable among groups and equalled 392 g on average (standard deviation = 24.8). The experiment was conducted on 3 individual days, each separated by a week. At the beginning of each week rats were starved overnight and subjected to an oral glucose (at first week, GTT), sucrose (at second week, SuTT) or starch tolerance test (at third week, StTT). Five minutes prior to each test a baseline blood sample was drawn, then rats were gavaged with single portions of water as a control (group C), an aqueous solution of acarbose as a positive control (group AC, 35 mg/kg body weight) and an aqueous solu-

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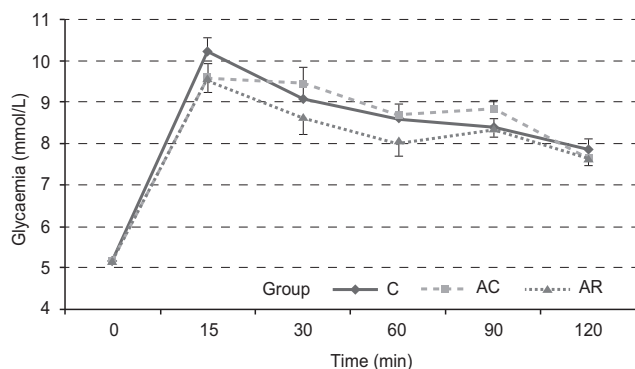E-mail: a.jurgonski@pan.olsztyn.pl (Dr. A. Jurgoński)

FIGURE 1. The oral glucose tolerance test (GTT) of rats. C, control gavaged with water; AC, positive control gavaged with acarbose; AR, experimental gavaged with arabinose.

TABLE 1. Total area under the blood glucose curve (AUC) for the oral glucose (GTT), sucrose (SuTT) and starch (StTT) tolerance test of rats.

	Group		
	C	AC	AR
GTT-AUC (mmol/L×120 min)	1024±19.1	1038±20.6	986±30.2
SuTT-AUC (mmol/L×120 min)	895±21.5[a]	701±19.6[b]	866.0±15.8[a]
StTT-AUC (mmol/L×180 min)	1184±19.1[a]	1012±26.1[c]	1078±13.3[b]

C, control gavaged with water; AC, positive control gavaged with acarbose; AR, experimental gavaged with arabinose. Mean values within a row with unlike superscript letters (a, b, c) are significantly different at $P<0.05$.

tion of L-arabinose as an experimental (group AR, 25 mg/kg body weight). The solution concentrations were so prepared that the amount equalled 1 mL per 350 g of body weight, whereas group C received water in the same way. Acarbose is an α-glucosidase inhibitor widely used in the treatment of diabetes, which delays the absorption of carbohydrates from the small intestine. In between tests, the animals had free access to tap water and a regular rodent chow, whereas during tests rats had free access to drinking water. All animals were maintained in wired cages under a 12-hr light/dark cycle, a controlled temperature of 19°C to 22°C and intensive room ventilation (15 times per h). The animal protocol used in this study was approved by the Institutional Animal Care and Use Committee in Olsztyn, Poland.

Oral tolerance tests

Five min after gavaging with water or the preparations, rats received intragastrically glucose, sucrose or starch in the amount of 2 g/kg body weight. A drop of blood was then collected from the tail tip, and the glucose concentration was measured at time intervals using glucometer (Accu-Chek Go, Roche Diagnostics, Germany). For the oral glucose and sucrose tolerance test (GTT and SuTT, respectively) the following time intervals were chosen: 0, 15, 30, 60, 90 and 120 min; because starch is a complex carbohydrate an additional time interval (180 min) was chosen for the oral starch tolerance test (StTT).

Calculations and statistical analysis

The glycaaemic response during the GTT, SuTT and StTT was evaluated by the total area under the blood glucose curve (AUC) using the trapezoidal rule. The Statistica software (StatSoft Corp., Krakow, Poland) was utilised to determine whether the variables differed among treatment groups. The statistical analysis was performed using a one-way analysis of variance and the Duncan's multiple range *post hoc* test providing that the data were normally distributed and the variances were homogenous. Alternatively, the Kruskal-Wallis test and a *post hoc* analysis using the least significant difference between the mean ranks were applied. Results are expressed as the means and the standard error of the mean and the differences among the groups are denoted as significant at $P\leq0.05$.

RESULTS AND DISCUSSION

There was no effect of L-arabinose on glycaemia in the GTT as is shown both by individual time intervals (Figure 1) and by the AUC (Table 1). This supports other similar studies and confirms that L-arabinose bioactivity is related with an enzyme inhibition, but not with the glucose absorption nor metabolism [Seri *et al.*, 1996; Preuss *et al.*, 2007]. It was also shown that the uncompetitive inhibition of sucrase by L-arabinose can be maintained for several hours in *in vitro* conditions [Shibanuma *et al.*, 2011]. However, in the present study, L-arabinose reduced postprandial glycaemia after 15 min of the SuTT only (Figure 2), whereas the AUC for the SuTT was comparable between the control and the L-arabinose-treated groups and significantly lower in the positive control with acarbose (Table 1). It suggests that L-arabinose can indirectly delay glucose absorption, but without a significant reduction in the absorbed amount of this carbohydrate. More effective reduction in glycaemia by L-arabinose in oral sucrose challenges has been reported in animal studies by other authors [Seri *et al.*, 1996; Preuss *et al.*, 2007]. Our results are similar to those obtained by Krog-Mikkelsen *et al.* [2011] in human subjects, whose postprandial glycaemia after ingestion of sucrose beverages supplemented with L-arabinose was significantly decreased after 30 min of the ingestion, but the AUC was not different from the control. The reduction of postprandial glycaemia was considerably more pronounced for the StTT in the present study (Figure 3). In the AR group, when compared with the control group, the blood glucose level was significantly decreased both at each time interval and in total (StTT-AUC, Table 1). Interestingly, the glucose-lowering effect of L-arabinose was even better at the very beginning of the StTT than that of acarbose. However, taking together the whole time period of the StTT, the acarbose activity was more pronounced than that of L-arabinose as shown by the lower AUC value. Nevertheless, these results suggest that L-arabinose is an effective inhibitor of an enzyme or enzymes responsible for starch breakdown in the gastrointestinal tract. However, Seri *et al.* [1996] did not notice any inhibitory activity of L-arabinose on porcine intestinal maltase nor mouse pancreatic amylase. Moreover, contradictory results to ours were obtained
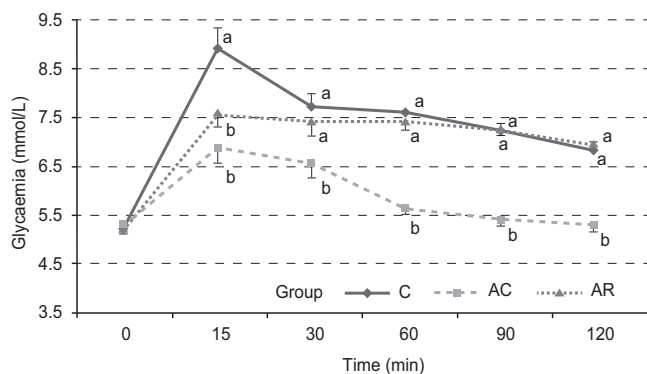
FIGURE 2. The oral sucrose tolerance test (SuTT) of rats. C, control gavaged with water; AC, positive control gavaged with acarbose; AR, experimental gavaged with arabinose. Mean values with unlike letters (a, b) within a time period are significantly different at $P<0.05$.
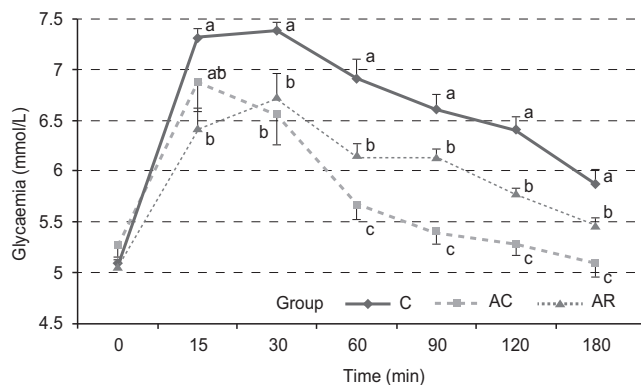

FIGURE 3. The oral starch tolerance test (StTT) of rats. C, control gavaged with water; AC, positive control gavaged with acarbose; AR, experimental gavaged with arabinose. Mean values with unlike letters (a, b, c) within a time period are significantly different at $P<0.05$.

by Preuss *et al.* [2007] who did not find any reduction in blood glucose levels of rats challenged with rice starch and L-arabinose. An explanation of this may be found in methodological differences of that study, because L-arabinose was gavaged both half an hour prior to the starch ingestion and together with the starch ingestion. Moreover, a megadose of L-arabinose was used that equalled 1 g per an adult rat [Preuss *et al.*, 2007], whereas we used on average 9.8 mg L-arabinose per adult rat.

Potentially, the capability of L-arabinose to suppress postprandial glycaemia, as shown in the present study, can be used in the management of diabetes. It is especially important because of well-known adverse events of acarbose and other α-glucosidase inhibitors on the gastrointestinal tract function [Kumar *et al.,* 2012]. However, one of the most important issues is to calculate an effective human dose of a bioactive substance. For an appropriate conversion from animals to humans, the body surface area normalization method has been suggested [Center for Drug Evaluation and Research, 2005; Reagan-Shaw *et al.*, 2008]. This method correlates well across several mammalian species with basic physiological parameters. Accordingly, the dose of L-arabinose ingested by the rats corresponded to 4.52 mg of the preparation per kg for an adult human and could be simply supplied alone or in a combination with another anti-diabetic agents. The doses that have been already tested by Krog-Mikkelsen *et al.* [2011] in a clinical trial on healthy men were more than 3 times higher (up to 39 mg per kg body weight) and in two out of 15 subjects were accompanied by some gastrointestinal side effects, like mild nausea and stomach ache.

CONCLUSIONS

L-arabinose administration to rats at amounts of 25 mg/kg body weight suppressed postprandial glycaemia 15 min after oral ingestion of sucrose. During an oral starch challenge, a significant decrease of AUC values as well as blood glucose concentration at each time point was observed. Inhibition of enzyme activity involved in starch digestion (amylase, maltase) may be suggested as the most probable mechanism responsible for the observed effects.

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