

Evaluation of the impact of orally administered carbohydrates on postprandial blood glucose levels in different pre-clinical models

Any de Castro Ruiz Marques, Fabiana Percinoto Monteiro Schiavon, Patricia Batista Travassos, Vanessa Fontana Eik, Guilherme Godoy, Christiano Rodrigues Schamber, Roberto Barbosa Bazotte*

State University of Maringá, Department of Pharmacology and Therapeutics, Maringá, PR, Brazil

We developed a pre-clinical model in which to evaluate the impact of orally administered carbohydrates on postprandial blood glucose levels. For this purpose, we compared the effects of different carbohydrates with well-established glycemic indexes. We orally administered (gavage) increasing amounts (0.2, 0.4, 0.6, 0.8, and 1.0 g/kg) of sucrose and lactose to rats which had been fasted for 6 h or 15 h, respectively. In part of the experiments we administered fructose (gavagem). Three different models were compared for measuring postprandial blood glucose levels: a) evaluation of interstitial glucose concentrations by using a real time continuous glucose monitoring system; b) evaluation of glucose levels in blood obtained from the rat tail; c) evaluation of serum glucose levels in blood collected after decapitation. Our results showed that blood obtained from the tails of 15-h fasted rats was the best model in which to evaluate the effect of carbohydrates on postprandial blood glucose levels.

Uniterms: Glycemic index/study. Glycemic index/oral administration. Glycemic load. Interstitial glucose. Real time continuous glucose monitoring system. Carbohydrates/posprandial glucose levels/rats.

INTRODUCTION

It is widely recognized that higher peak postprandial glucose (PPG) levels are associated with type 2 diabetes (Maki, Phillips, 2015), obesity (Thomas, Elliott, Baur, 2007), cardiovascular diseases (Little *et al.*, 2014), liver steatosis (Valtueña *et al.*, 2006), and cancer (Esfahani *et al.*, 2009). Several studies have shown that consuming a diet with a low glycemic index (GI) can reduce insulin resistance (König *et al.*, 2014), blood lipid concentrations (Levitan *et al.*, 2008), body weight (Krebs *et al.*, 2013), and the levels of glycated hemoglobin (Wang *et al.*, 2015a) and pro-inflammatory markers (Feliciano, das Graças, Alfenas, 2014) in blood. Other studies have shown low GI diets to be associated with increased satiety (Pardo-Beutimea *et al.*, 2012) and the incidence of cancer (Truong, Yuet, Hall, 2014).

The GI is a number which reflects how equal quantities of different types of carbohydrates affect

an individual's PPG level (Png *et al.*, 2014; Wang *et al.*, 2015b), and provides a measure of carbohydrate quality (Hollenbeck, Coulston, 1991). Furthermore, the PPG level can be predicted with reasonable accuracy from the GI, when a standard mixed meal (Wolever, Jenkins, 1986) or carbohydrate is consumed (Hashimoto, Noguchi, Furutani, 2014). Another index, glycemic load (GL), is calculated by multiplying the GI by the amount of carbohydrate, and then dividing that result by 100 (Brand-Miller *et al.*, 2003).

Today, GI and GL values are calculated based on the results of tests performed in humans (Frost, Dornhorst, 2000; Jenkins *et al.*, 1981; Recio-Rodriguez *et al.*, 2015). However, these tests require the participation of volunteer subjects, and are expensive and very time-consuming to perform. Because only a few laboratories worldwide can perform these evaluations. GI and GL data are available for only a small number of foods (Foster-Powell, Holt, Brand-Miller, 2002). Interestingly, the GI and GL of the typical diet consumed in the USA appear to have risen in recent years, due to that nation's increased carbohydrate consumption and changes in food-processing technology (Ludwig, 2002).

*Correspondence: R. B. Bazotte. Universidade Estadual de Maringá. Avenida Colombo 5790 - Bloco K68 - sala 101 - 87020-900 - Maringá, PR - Brasil. Tel.: +55-44-3011-5161; Fax: +55-44-3011-5050. E-mail: rbbazotte@gmail.com

When considering that manufacturers are creating new food products at a much faster rate than GI and GL testing can be performed, the utilization of pre-clinical models to reproduce the results obtained from GI and GL tests conducted in humans has become increasingly necessary.

In this regard, non-diabetic rats can be used to evaluate the effect of oral carbohydrates on blood glucose levels (Bassoli *et al.*, 2008). The main advantage of this model is that non-diabetic rats maintain their mechanisms needed to prevent postprandial hyperglycemia, and can be studied without interference caused by insulin deficiency (Kabir *et al.*, 1998).

Our current study was conducted to identify a pre-clinical model in which to evaluate the impact of orally administered carbohydrates on PPG levels, and that better simulates results obtained in humans. For this purpose, we compared the effects of three different carbohydrates with well-established GI values (sucrose, lactose, and fructose), and that represent typical sugars consumed in the Western diet. Additionally, we evaluated the effects of fasting time, the amount of carbohydrate administered, as well as the techniques used to measure glucose concentration.

MATERIAL AND METHODS

Animals

Male Wistar adult rats (*Rattus norvegicus*) weighing 280-330 g were used in this study. The rats were housed under conditions of constant temperature (23 ± 2 °C), an automatically controlled photoperiod (12 h light/12 h dark), and free access to food and water. The rats were fed a standard commercial laboratory diet (Nutrilab CR1, Curitiba, PR, Brazil) *ad libitum* prior to undergoing the experimental procedures.

The rodent chow was composed of the proteins (22%), fibers (8%), minerals (10%), calcium (1.4%) and phosphorus (0.8%). Each kilogram of this product was enriched with the metionine (300 mg), lysine (100 mg), antioxidant (100 mg), vitamin A (12.000 IU), vitamin D3 (1.800 IU), vitamin E (30 mg), vitamin C (800 mg), vitamin K3 (3 mg), vitamin B1 (5 mg), vitamin B2 (6 mg), vitamin B6 (7 mg), vitamin B12 (20 µg), niacine (60 mg), pantotenic acid (20 mg), folic acid (1.0 mg), biotine (0.05 mg), coline (600 mg), iron (50 mg), zinc (60 mg), copper (10 mg), iodine (2 mg), manganese (60 mg), selenium (0.05 mg) and cobalt (1.5mg).

The rats were fasted for either 6 h or 15 h prior to starting the experiments. All procedures used in this study were approved by the Ethics Committee of the

State University of Maringá (Brazil), and were performed in accordance with guidelines provided by the Brazilian Council on Animal Experimentation (protocol number: 005/2013).

Experimental Protocol

Each carbohydrate (sucrose, lactose, and fructose) was dissolved in water (2.0 mL) for oral administration (gavage) to the rats.

Increasing amounts (0.2, 0.4, 0.6, 0.8, and 1.0 g/kg) of either sucrose or lactose were administered. In the final set of experiments, sucrose (0.8 g/kg), lactose (0.8 g/kg), fructose (0.8 g/kg) or both sucrose (0.4 g/kg) and fructose (0.4 g/kg) were administered. In all experiments, rats in the control group received the same volume (2.0 mL) of vehicle (water).

In the first set of experiments, changes in interstitial glucose concentration (IGC) were evaluated with a real-time continuous glucose monitoring system (RT-CGMS). The main advantages of using that system were that it reduced the numbers of animals required for the study, and permitted a greater number of glucose measurements to be obtained from each animal (Sybuia *et al.*, 2014). The RT-CGMS is described in our previously published study (Carrara *et al.*, 2012).

In the second set of experiments, the blood glucose concentrations (BGC) were determined by analyzing blood obtained from the tail of each animal at 0, 5, 15, 30, and 60 min after oral administration of the selected carbohydrate. For this purpose, a drop of blood was obtained after a small incision was made at the tip of the tail, and its glucose level was determined using a home glucometer (Diagnostics Accu-Chek® Active glucometer - Roche Diagnostics; Jaguaré, Brazil).

In the third set of experiments, the animals were sacrificed by decapitation; after which, samples of blood were gathered and examined for their serum glucose concentrations using the glucose oxidase method (Bergmeyer, Bernt, 1974) as previously described (Zubioli *et al.*, 2011). The results reflected blood glucose concentrations at 0, 5, 15, 30, and 60 min after oral administration of the selected carbohydrate.

In the final set of experiments, blood was obtained from the tails of 15 h-fasted rats at 0, 5, 15, 30 and 60 min after oral administration of either sucrose (0.8 g/kg), lactose (0.8 g/kg), fructose (0.8 g/kg), or sucrose (0.4 g/kg) plus fructose (0.4 g/kg).

Depending on their assigned group, the rats were sacrificed by decapitation or euthanized with a high dose (100 mg/kg) of intravenous thiopental (BGC and IGC

groups), and then injected with a lethal dose of potassium chloride (2 mM into the heart).

Statistical Procedures

All data were analyzed by one way ANOVA (Tukey post hoc test) that was performed using Graph-Pad Prism Version 5.0 software. Differences between the glucose concentration values before (time 0) and after (time 0 up to 60 minutes) an oral dose of carbohydrate were calculated as an area under the curve (AUC).

Individual and AUC results (expressed as mg/dL) are reported as the mean \pm standard error of the mean. P-values < 0.05 were considered statistically significant.

RESULTS

There was a significant ($p < 0.05$) increase in the AUC for IGC after oral administration of either sucrose (0.6 or 0.8 g/kg) or lactose (0.6, 0.8 or 1.0 g/kg) to 6-h fasted rats (Table I). There was also a significant ($p < 0.05$) increase in the AUC for IGC after oral administration of either sucrose (0.4, 0.6, 0.8 or 1.0 g/kg) or lactose (0.6, 0.8 or 1.0 g/kg) to 15-h fasted rats (Table II), when compared with the corresponding changes seen vehicle-dosed control rats. However, we did not observe such increased AUCs for glucose

concentrations in samples of tail blood (Table III) or blood collected after decapitation (Table IV).

We also observed a significantly ($p < 0.05$) increased AUC for glucose levels after analyzing samples of tail blood collected from 15-h fasted rats, which after being fasted, received an oral dose of either sucrose (0.4, 0.6, 0.8 or 1.0 g/kg) or lactose (0.2, 0.4, 0.6, 0.8 or 1.0 g/kg) (Table III). A similar increased AUC for glucose was found after analyzing samples of decapitation blood ($p < 0.05$) collected from 15-h fasted rats, which after being fasted, received an oral dose of sucrose (0.2, 0.4, 0.6, 0.8, 1.0 g/kg) or lactose (1.0 g/kg). These increases in glucose AUC values were relative to glucose AUC values which were calculated for control rats that were dosed with vehicle (Table IV).

The greatest differences between sucrose and lactose in terms of glycemic changes (individual values or AUC) were observed in samples of blood collected from 15-h fasted decapitated rats (Table IV). On the other hand, the AUCs that best reflected the GI values of sucrose and lactose were obtained when analyzing blood collected from 15-h fasted decapitated rats which received a 0.8 g/kg oral dose of those same carbohydrates (Table IV).

As shown in Table V, the results for sucrose (0.8 g/kg) and lactose (0.8 g/kg) were very similar to those described in Table IV. Moreover, the results confirm the greater effect of sucrose compared to lactose on

TABLE I - Interstitial glucose concentrations (IGCs) as measured with a continuous glucose monitoring system (mg/dL) in 6-h-fasted rats which received increasing oral doses of sucrose or lactose. The control group received vehicle. Data are expressed as the mean \pm standard error of the mean for results obtained from 3-6 rats. AUC: area under the curve

Time (min)	Vehicle n = 5	Sucrose (g/kg)					Lactose (g/kg)				
		0.2 n = 6	0.4 n = 5	0.6 n = 4	0.8 n = 5	1.0 n = 4	0.2 n = 3	0.4 n = 5	0.6 n = 4	0.8 n = 5	1.0 n = 6
0	89.3 \pm 7.7	95.2 \pm 4.3	84.7 \pm 1.9	87.0 \pm 7.3	86.4 \pm 9.2	81.6 \pm 2.9	82.4 \pm 8.5	84.7 \pm 4.0	90.0 \pm 10.9	68.0 \pm 6.4	80.0 \pm 6.1
5	90.7 \pm 7.4	96.4 \pm 5.5	86.0 \pm 2.4	91.7 \pm 7.8	88.8 \pm 9.5	84.4 \pm 2.4	83.6 \pm 9.1	85.0 \pm 4.9	95.2 \pm 11.1	75.1 \pm 7.2	84.4 \pm 6.7
10	88.0 \pm 7.2	100.8 \pm 6.4	92.3 \pm 2.6	102.0 \pm 8.7	97.2 \pm 9.4	92.2 \pm 2.7	89.6 \pm 9.7	89.0 \pm 5.6	106.0 \pm 10.8	84.3 \pm 8.1	93.6 \pm 5.7
15	86.7 \pm 6.6	104.8 \pm 5.9	100.0 \pm 2.2*	110.0 \pm 8.9	109.0 \pm 9.8	101.6 \pm 2.5*	96.0 \pm 9.4	96.0 \pm 5.8	114.0 \pm 10.7	90.6 \pm 7.8	103.0 \pm 4.7
20	86.7 \pm 5.7	107.6 \pm 5.1	105.0 \pm 1.7*	113.0 \pm 8.8	118.0 \pm 9.7	108.0 \pm 2.0*	99.2 \pm 8.9	103.0 \pm 6.2	118.0 \pm 10.5	93.7 \pm 6.8	109.0 \pm 4.3*
25	87.3 \pm 3.5	107.2 \pm 4.8	105.0 \pm 2.0*	112.0 \pm 8.2	120.0 \pm 9.5	107.6 \pm 2.6*	98.0 \pm 7.7	106.0 \pm 6.9	118.0 \pm 10.6	94.3 \pm 6.2	112.0 \pm 4.7*
30	86.7 \pm 3.5	104.8 \pm 4.1	102.0 \pm 3.0*	107.0 \pm 7.6	118.0 \pm 9.0	104.0 \pm 4.2*	94.8 \pm 6.6	106.7 \pm 7.6	115.6 \pm 10.9	92.8 \pm 6.3	111.6 \pm 5.5*
35	84.7 \pm 3.5	102.0 \pm 4.2	96.7 \pm 4.2*	100.7 \pm 7.3	113.0 \pm 8.0	98.0 \pm 4.7	93.2 \pm 6.5	104.3 \pm 7.4	111.6 \pm 10.6	91.1 \pm 6.5	108.0 \pm 6.2*
40	83.3 \pm 5.2	98.0 \pm 4.0	91.3 \pm 5.3	93.7 \pm 7.3	108.0 \pm 7.1	93.2 \pm 4.7	91.6 \pm 6.3	99.3 \pm 6.1	107.0 \pm 10.5	89.1 \pm 6.7	106.0 \pm 5.8*
45	83.3 \pm 5.9	95.2 \pm 4.0	87.3 \pm 5.3	89.3 \pm 7.5	103.0 \pm 6.7	88.0 \pm 3.9	88.8 \pm 6.1	96.0 \pm 5.6	103.0 \pm 10.6	86.3 \pm 7.0	104.0 \pm 5.3
50	84.7 \pm 5.4	94.0 \pm 4.3	84.0 \pm 5.6	86.3 \pm 7.6	98.4 \pm 7.2	84.0 \pm 4.2	86.4 \pm 5.4	93.0 \pm 5.0	99.6 \pm 10.7	83.4 \pm 7.4	102.0 \pm 5.0
55	83.3 \pm 5.9	93.6 \pm 4.9	81.0 \pm 6.0	85.0 \pm 7.9	94.4 \pm 8.5	82.0 \pm 4.5	84.8 \pm 5.0	91.0 \pm 4.9	97.6 \pm 11.0	80.9 \pm 7.5	101.6 \pm 4.6
60	82.0 \pm 5.2	94.0 \pm 4.7	80.3 \pm 5.4	84.3 \pm 8.1	93.2 \pm 8.3	82.0 \pm 4.2	82.8 \pm 5.3	88.3 \pm 5.5	96.0 \pm 11.8	78.0 \pm 7.9	102.0 \pm 4.7
AUC	6.0 \pm 2.9	20.8 \pm 2.3	33.0 \pm 5.3	48.0 \pm 6.6 ^a	56.6 \pm 3.5 ^a	39.6 \pm 6.3	31.0 \pm 6.0	37.3 \pm 6.9	57.8 \pm 5.4 ^a	59.6 \pm 7.8 ^a	69.8 \pm 7.2 ^a

* In the same column indicate $p < 0.05$ vs. time 0. ^a In the same line indicate $p < 0.05$ vs. vehicle.

TABLE II - Interstitial glucose concentrations (IGCs) as measured with a continuous glucose monitoring (mg/dL) system in 15-h-fasted rats which received increasing oral doses of sucrose or lactose. The control group received vehicle. Data are expressed as the mean \pm standard error of the mean for results obtained from 3-4 rats. AUC: area under the curve

Time (min)	Vehicle n = 4	Sucrose (g/kg)					Lactose (g/kg)				
		0.2	0.4	0.6	0.8	1.0	0.2	0.4	0.6	0.8	1.0
		n = 4	n = 4	n = 4	n = 4	n = 3	n = 4	n = 4	n = 4	n = 3	n = 3
0	82.0 \pm 6.0	85.0 \pm 1.3	69.5 \pm 10.0	68.7 \pm 7.9	67.0 \pm 10.5	75.3 \pm 7.0	84.0 \pm 7.8	80.0 \pm 9.8	82.0 \pm 11.6	83.0 \pm 4.5	79.3 \pm 9.3
5	82.0 \pm 6.9	89.0 \pm 1.3	71.5 \pm 9.3	71.3 \pm 8.5	69.0 \pm 10.9	80.7 \pm 6.7	87.0 \pm 9.4	81.0 \pm 10.1	82.5 \pm 13.0	87.5 \pm 5.1	81.3 \pm 9.3
10	83.0 \pm 7.2	90.0 \pm 2.4	76.5 \pm 9.3	78.0 \pm 8.3	75.5 \pm 10.6	91.3 \pm 7.7	90.5 \pm 9.9	82.5 \pm 10.4	87.5 \pm 13.6	97.0 \pm 6.2	86.0 \pm 8.0
15	83.5 \pm 8.1	91.5 \pm 3.7	84.5 \pm 9.5	87.3 \pm 7.7	85.5 \pm 10.3	106.0 \pm 7.2	94.0 \pm 9.6	87.5 \pm 10.5	93.5 \pm 14.1	107.5 \pm 6.2	93.3 \pm 6.6
20	83.5 \pm 8.1	93.0 \pm 4.2	91.5 \pm 9.7	94.7 \pm 7.0	92.5 \pm 9.1	118.7 \pm 5.7*	95.5 \pm 8.8	93.0 \pm 9.9	99.0 \pm 14.4	114.0 \pm 5.8*	100.7 \pm 7.0
25	82.5 \pm 7.9	94.5 \pm 3.1	94.5 \pm 10.0	98.0 \pm 7.2	95.0 \pm 9.0	122.7 \pm 7.0*	93.0 \pm 7.5	95.5 \pm 10.1	100.5 \pm 13.6	116.5 \pm 5.2*	106.7 \pm 9.0
30	80.5 \pm 7.9	97.5 \pm 0.9	93.0 \pm 10.4	96.7 \pm 7.7	97.5 \pm 8.6	120.0 \pm 9.2*	90.0 \pm 7.0	95.0 \pm 9.2	99.5 \pm 11.5	115.0 \pm 5.4*	109.3 \pm 10.3
35	80.5 \pm 7.1	98.5 \pm 3.8	88.5 \pm 10.9	92.7 \pm 7.7	98.5 \pm 8.6	112.7 \pm 9.2*	87.0 \pm 6.2	92.0 \pm 8.7	98.0 \pm 9.6	111.5 \pm 6.3*	107.3 \pm 12.4
40	80.0 \pm 6.3	95.0 \pm 4.2	83.0 \pm 11.6	88.0 \pm 8.1	95.5 \pm 8.4	107.3 \pm 8.2	85.0 \pm 5.3	87.5 \pm 8.3	96.0 \pm 8.5	106.5 \pm 5.9	104.0 \pm 13.3
45	79.0 \pm 5.1	91.0 \pm 4.4	78.0 \pm 12.6	84.0 \pm 8.1	93.0 \pm 7.5	103.3 \pm 7.0	81.0 \pm 5.2	83.5 \pm 8.3	93.0 \pm 7.3	102.0 \pm 5.0	101.3 \pm 12.7
50	78.5 \pm 4.9	88.0 \pm 4.5	75.5 \pm 12.3	80.0 \pm 8.1	90.0 \pm 8.0	100.7 \pm 5.8	79.5 \pm 5.6	80.5 \pm 8.9	91.0 \pm 7.3	98.5 \pm 4.2	99.3 \pm 11.6
55	77.0 \pm 4.6	84.5 \pm 4.7	73.0 \pm 11.6	77.3 \pm 8.3	86.0 \pm 8.5	97.3 \pm 5.9	78.0 \pm 5.8	78.0 \pm 9.5	89.0 \pm 7.1	96.0 \pm 4.1	98.0 \pm 10.1
60	76.0 \pm 5.7	82.0 \pm 5.0	72.0 \pm 11.1	75.3 \pm 8.3	82.5 \pm 8.6	93.3 \pm 6.4	77.5 \pm 6.7	76.5 \pm 9.9	88.0 \pm 7.5	95.0 \pm 4.0	94.7 \pm 9.7
AUC	10.5 \pm 3.7	21.2 \pm 2.9	41.2 \pm 3.8 ^a	52.6 \pm 1.3 ^a	58.7 \pm 4.5 ^a	89.7 \pm 5.9 ^a	17.0 \pm 2.4	17.2 \pm 2.8	34.2 \pm 2.0 ^a	67.0 \pm 4.7 ^a	53.7 \pm 3.2 ^a

* In the same column indicate p < 0.05 vs. time 0. ^a In the same line indicate p < 0.05 vs. vehicle.

TABLE III - Glucose concentrations in samples of blood collected from the tail as measured with a home glucometer (mg/dL). The rats were fasted for either 6 h or 15 h, and then received increasing oral doses of sucrose or lactose. The control group received vehicle. Data are expressed as the mean \pm standard error of the mean for results obtained from 3-6 rats. AUC: area under the curve

6-h-fasted rats											
Time (min)	Vehicle n = 4	Sucrose (g/kg)					Lactose (g/kg)				
		0.2	0.4	0.6	0.8	1.0	0.2	0.4	0.6	0.8	1.0
		n = 3	n = 3	n = 3	n = 5	n = 3	n = 3	n = 3	n = 4	n = 5	n = 4
0	92.8 \pm 4.5	99.7 \pm 6.2	105.3 \pm 4.8	99.3 \pm 6.5	95.0 \pm 6.4	102.6 \pm 1.2	102.3 \pm 8.5	95.2 \pm 4.1	96.7 \pm 3.7	102.8 \pm 1.4	95.5 \pm 3.0
5	105.8 \pm 8.5	117.0 \pm 6.0	105.3 \pm 3.3	118.7 \pm 18.2	102.7 \pm 9.4	107.8 \pm 4.1	117.3 \pm 12.4	103.6 \pm 8.6	110.7 \pm 4.4	121.3 \pm 4.8*	98.0 \pm 4.3
15	114.5 \pm 3.2*	115.0 \pm 4.5	129.0 \pm 7.8	135.0 \pm 10.5	137.3 \pm 5.8*	125.2 \pm 4.0*	129.0 \pm 11.3	121.8 \pm 7.4*	110.7 \pm 4.7	124.0 \pm 2.5*	109.0 \pm 7.0
30	117.0 \pm 3.2*	116.0 \pm 2.6	132.3 \pm 8.5	131.0 \pm 3.2	128.7 \pm 3.8*	128.6 \pm 2.5*	130.7 \pm 5.4	122.8 \pm 1.3*	119.3 \pm 3.2*	128.5 \pm 1.5*	121.0 \pm 1.9*
60	115.8 \pm 2.1*	115.0 \pm 3.2	115.7 \pm 4.3	110.3 \pm 2.2	114.0 \pm 5.1	125.4 \pm 4.1*	115.3 \pm 2.7	117.4 \pm 1.3	113.3 \pm 4.8	123.8 \pm 4.7*	109.3 \pm 4.2
AUC	74.2 \pm 7.9	56.7 \pm 10.2	68.0 \pm 12.1	92.2 \pm 4.7	93.2 \pm 6.4	67.1 \pm 7.4	73.8 \pm 9.9	75.5 \pm 5.4	59.0 \pm 9.6	76.0 \pm 4.1	51.0 \pm 4.7
15-h-fasted rats											
Time (min)	Vehicle n = 5	Sucrose (g/kg)					Lactose (g/kg)				
		0.2	0.4	0.6	0.8	1.0	0.2	0.4	0.6	0.8	1.0
		n = 4	n = 5	n = 4	n = 5	n = 4	n = 5	n = 5	n = 5	n = 3	n = 6
0	76.2 \pm 3.9	81.7 \pm 3.8	77.5 \pm 1.4	75.5 \pm 3.0	79.3 \pm 5.9	81.0 \pm 2.0	75.8 \pm 2.6	73.4 \pm 1.5	74.2 \pm 2.4	78.0 \pm 2.0	73.7 \pm 3.0
5	78.2 \pm 4.5	86.2 \pm 2.1	83.5 \pm 3.7	77.7 \pm 2.1	94.3 \pm 5.9	79.6 \pm 2.2	85.8 \pm 3.4	77.6 \pm 4.4	89.0 \pm 6.0*	87.4 \pm 2.6	87.7 \pm 3.4
15	83.0 \pm 5.0	108.5 \pm 8.9*	114.5 \pm 6.0 ^a	113.0 \pm 4.3 ^a	131.7 \pm 5.0 ^a	110.0 \pm 6.5*	103.0 \pm 6.3*	96.6 \pm 4.7*	103.6 \pm 2.8*	112.2 \pm 1.1 ^a	104.8 \pm 5.7*
30	96.8 \pm 4.0*	119.0 \pm 5.5*	127.5 \pm 5.7 ^a	147.0 \pm 5.9 ^a	157.7 \pm 11.6 ^a	139.7 \pm 9.9 ^a	115.8 \pm 4.1*	115.8 \pm 3.4*	125.4 \pm 3.2 ^a	130.8 \pm 4.9 ^a	131.2 \pm 4.8 ^a
60	88.4 \pm 0.8	96.75 \pm 3.2	103.8 \pm 2.9*	111.3 \pm 6.3*	114.7 \pm 6.2 ^a	118.7 \pm 4.6 ^a	101.4 \pm 3.6*	106.2 \pm 4.1*	119.4 \pm 7.0 ^a	124.4 \pm 5.5 ^a	127.5 \pm 5.4 ^a
AUC	36.8 \pm 5.8	85.6 \pm 9.8	111.1 \pm 5.9 ^a	134.4 \pm 10.6 ^a	164.8 \pm 13.4 ^a	110.3 \pm 1.7 ^a	90.0 \pm 5.2 ^a	95.5 \pm 9.9 ^a	118.0 \pm 6.7 ^a	123.3 \pm 10.8 ^a	131.1 \pm 15.0 ^a

^a In the same line indicates p < 0.05 vs. vehicle.

TABLE IV - Serum glucose concentrations in blood collected from decapitated rats as measured with standard commercial kits (mg/dL). The rats were fasted for either 6 h or 15 h, and then received increasing oral doses of sucrose or lactose. The control group received vehicle. Data are expressed as mean \pm standard error of the mean for results obtained from 2-6 rats. AUC: area under the curve

Time (min)	6-h-fasted rats										
	Vehicle	Sucrose (g/kg)					Lactose (g/kg)				
		0.2	0.4	0.6	0.8	1.0	0.2	0.4	0.6	0.8	1.0
0	127.7 \pm 3.2 (3)	133.6 \pm 4.5 (4)	138.0 \pm 1.7 (3)	135.0 \pm 6.4 (3)	138.0 \pm 5.2 (3)	130.4 \pm 3.8 (4)	136.6 \pm 6.6 (4)	135.7 \pm 5.7 (4)	137.4 \pm 6.0 (3)	136.4 \pm 3.2 (4)	142.4 \pm 4.2 (4)
5	158.8 \pm 3.4* (3)	158.3 \pm 9.2 (4)	177.6 \pm 16.3 (3)	174.3 \pm 3.7* (3)	176.2 \pm 5.8* (3)	167.9 \pm 6.2* (4)	141.5 \pm 3.6 (4)	157.5 \pm 10.6 (4)	169.7 \pm 5.8* (2)	172.8 \pm 2.8* (4)	161.9 \pm 15.9 (4)
15	154.0 \pm 6.5* (3)	160.2 \pm 4.7 (4)	157.0 \pm 3.2 (3)	152.0 \pm 8.2 (3)	156.7 \pm 8.5 (2)	152.0 \pm 2.6* (4)	142.2 \pm 1.4 (4)	137.0 \pm 4.5 (4)	156.0 \pm 0.9 (3)	162.0 \pm 4.4* (4)	163.7 \pm 3.7 (4)
30	139.6 \pm 6.4 (3)	130.6 \pm 5.2 (4)	130.0 \pm 4.2 (3)	133.0 \pm 8.3 (3)	130.0 \pm 4.0 (2)	150.5 \pm 5.4 (4)	133.0 \pm 12.5 (4)	137.6 \pm 7.2 (4)	141.6 \pm 2.3 (3)	141.2 \pm 9.5 (4)	144.2 \pm 7.2 (4)
60	129.2 \pm 4.4 (3)	132.9 \pm 6.2 (4)	144.7 \pm 11.9 (3)	133.5 \pm 6.4 (3)	136.8 \pm 2.8 (3)	137.2 \pm 4.5 (4)	125.9 \pm 7.7 (4)	122.2 \pm 4.2 (4)	128.9 \pm 5.3 (3)	129.1 \pm 2.8 (4)	137.1 \pm 5.5 (4)
AUC	66.1 \pm 1.9	66.9 \pm 7.2	74.6 \pm 2.7	57.1 \pm 8.5	56.5 \pm 7.5	78.4 \pm 8.2	15.5 \pm 6.0 ^a	28.9 \pm 7.0	45.8 \pm 5.9	58.0 \pm 8.5	63.9 \pm 13.6
Time (min)	15-h-fasted rats										
	Vehicle	Sucrose (g/kg)					Lactose (g/kg)				
		0.2	0.4	0.6	0.8	1.0	0.2	0.4	0.6	0.8	1.0
0	95.0 \pm 1.6 (5)	95.2 \pm 2.1 (6)	91.4 \pm 1.5 (5)	94.3 \pm 3.0 (4)	95.7 \pm 3.1 (5)	94.0 \pm 2.0 (4)	100.0 \pm 5.1 (3)	94.3 \pm 2.5 (5)	89.4 \pm 4.0 (4)	99.2 \pm 3.0 (5)	95.4 \pm 3.6 (6)
5	102.7 \pm 1.9 (5)	126.5 \pm 4.2 ^a (6)	124.1 \pm 7.6* (5)	128.9 \pm 3.8 ^a (4)	138.8 \pm 7.4 ^a (5)	138.7 \pm 5.1 ^a (4)	104.7 \pm 3.7 (3)	115.2 \pm 7.1 (5)	108.6 \pm 5.9 (4)	107.7 \pm 2.4 (5)	117.4 \pm 3.5* (6)
15	111.4 \pm 4.7* (5)	142.4 \pm 6.3 ^a (6)	166.2 \pm 7.6 ^a (5)	164.8 \pm 4.2 ^a (4)	176.6 \pm 6.1 ^a (5)	179.6 \pm 7.8 ^a (4)	129.4 \pm 6.1* (3)	136.1 \pm 6.3* (5)	113.5 \pm 10.3 (4)	131.4 \pm 4.5* (5)	139.3 \pm 5.8* (6)
30	103.4 \pm 4.1 (5)	118.8 \pm 5.3* (6)	134.9 \pm 3.8 ^a (5)	140.5 \pm 7.0 ^a (4)	143.0 \pm 4.5 ^a (5)	160.2 \pm 6.0 ^a (4)	112.6 \pm 7.2 (3)	114.7 \pm 4.5 (5)	115.2 \pm 1.9 (4)	134.4 \pm 6.9 ^a (5)	121.7 \pm 2.3* (6)
60	89.1 \pm 2.7 (5)	102.1 \pm 2.5 (6)	101.6 \pm 1.8 (5)	111.5 \pm 6.1 ^a (4)	111.4 \pm 2.1 ^a (5)	119.6 \pm 4.7 ^a (4)	104.5 \pm 3.5 (3)	109.2 \pm 4.4 ^a (5)	113.9 \pm 5.3 ^a (4)	115.5 \pm 4.3 ^a (5)	114.2 \pm 5.5 ^a (6)
AUC	37.7 \pm 3.0	117.0 \pm 9.0 ^a	156.3 \pm 11.2 ^a	160.0 \pm 15.8 ^a	179.2 \pm 15.2 ^a	207.0 \pm 16.7 ^a	68.3 \pm 10.4	90.7 \pm 13.2	81.5 \pm 19.9	84.2 \pm 5.0	99.7 \pm 11.6 ^a

* In the same column indicate $p < 0.05$ vs. time 0. ^a In the same line indicate $p < 0.05$ vs. vehicle.

TABLE V - Blood glucose concentrations in samples of tail blood obtained from 15-h fasted rats which received sucrose, lactose, fructose or sucrose + fructose, as measured with a home glucometer (mg/dL). The control group received vehicle. The individual values (0, 5, 15, 30, 60 min) and the areas under the curve (AUC) are expressed as the mean \pm standard error for results obtained from 4 rats

Time (min)	Vehicle	Sucrose	Lactose	Fructose	Sucrose + Fructose
		0.8 (g/kg)	0.8(g/kg)	0.8 (g/kg)	0.4 (g/kg) + 0.4 (g/kg)
	n = 4	n = 4	n = 4	n = 4	n = 4
0	79.0 \pm 2.4	79.1 \pm 2.3	77.8 \pm 4.1	77.6 \pm 3.6	76.9 \pm 4.2
5	85.5 \pm 3.5*	87.8 \pm 2.6*	84.1 \pm 4.2*	79.1 \pm 3.3	82.8 \pm 3.2
15	104.3 \pm 4.5*	133.9 \pm 5.5 ^{abc}	105.5 \pm 4.0*	103.1 \pm 6.1*	114.1 \pm 8.2*
30	106.1 \pm 3.1*	159.4 \pm 3.8 ^{abcd}	135.1 \pm 3.5 ^a	124.6 \pm 3.4 ^a	139.4 \pm 4.6 ^a
60	92.1 \pm 3.4*	118.6 \pm 1.9 ^a	123.4 \pm 2.4 ^{ad}	110.9 \pm 2.8 ^a	115.5 \pm 3.8 ^a
AUC	69.9 \pm 12.7	167.7 \pm 11.0 ^{ac}	117.3 \pm 14.6	102.8 \pm 9.8	129.2 \pm 18.0 ^a

* In the same column indicate $p < 0.05$ vs. time 0. Letters in the same line: ^a $p < 0.05$ vs. vehicle, ^b $p < 0.05$ vs. lactose, ^c $p < 0.05$ vs. fructose, ^d $p < 0.05$ vs. sucrose + fructose

post-prandial glucose (PPG) levels. Finally, the amount of sucrose or lactose administered (GL) had minimal influence (individual values or AUC) on the glucose concentrations in blood collected from the tail (Table III) or after decapitation (Table IV), not only in 6-h fasted rats, but also in 15-h fasted rats.

DISCUSSION

We found that the period of fasting influenced the PPG response to an oral dose of sucrose or lactose. However, we did not observe an increase in the AUC of PPG in blood obtained from the tail or after decapitation of 6-h fasted rats which received an oral dose of sucrose or lactose (Tables III and IV).

In contrast, we observed a significant ($p < 0.05$) increase in the AUC for IGC (*vs.* vehicle) after a dose of sucrose (0.6 or 0.8 g/kg) or lactose (0.6, 0.8 or 1.0 g/kg) in 6-h fasted rats (Table I). Taken together, these results suggest that when using a more physiological period of fasting, (*i.e.*, 6-h of food deprivation), IGC measurements more accurately reflect PPG levels after an oral administration of carbohydrates. However, despite our expectation that a higher GL would result in a higher peak PPG level (Atkinson, Foster-Powell, Brand-Miller, 2008; Brand-Miller *et al.*, 2003; Liu *et al.*, 2000; Venn *et al.*, 2006), we did not observe a clear relationship between the GL and PPG levels, not only for the IGC/6-h fasted rats, but for all of the experimental conditions investigated.

On the other hand, increased IGCs ($p < 0.05$ *vs.* vehicle) (Table II), were detected in tail blood (Table III) and decapitation blood (Table IV) obtained from 15-h fasted rats which received an oral dose of sucrose or lactose. The superior accuracy achieved when using a longer fasting period might be attributable to less interference from liver glycogenolysis (Schiavon *et al.*, 2014; Tavoni *et al.*, 2013).

Although the values for interstitial glucose and PPG concentrations in tail blood and decapitation blood obtained from 15-h fasted rats were better correlated with the amount of carbohydrate administered when compared with those values in 6-h fasted rats, the PPG values obtained from tail blood may be preferable to the IGC values obtained from decapitation blood when seeking a reliable test for PPG levels in rats. This notion is based on the fact that the AUC values obtained from tail blood more accurately reflect the GI values of sucrose (GI = 59) and lactose (GI = 46) in humans, and particularly when those carbohydrates are administered at doses of 0.6, 0.8, and 1.0 g/kg. For example, when administered at a dose of 0.8 g/kg, the AUC values obtained for sucrose and lactose in decapitation blood

were 179.2 ± 15.2 mg/dL and 84.2 ± 5.0 mg/dL (Table IV) respectively, *i.e.*, a mathematical proportion of 59 (sucrose) to 28 (lactose). On the other hand, the AUC values for sucrose and lactose in tail blood were 164.8 ± 13.4 mg/dL and 123.3 ± 10.8 mg/dL (Table III), respectively, *i.e.*, a mathematical proportion of 59 (sucrose) to 44 (lactose). Thus, the AUC values obtained with tail blood better reflect the GI values of sucrose (Jenkins *et al.*, 1981) and lactose (Foster-Powell, Holt, Brand-Miller, 2002) in humans.

Despite the advantages of using a RT-CGMS to measure IGC values (Sybuia *et al.*, 2014), that technique less often reproduced the results obtained from GI tests in humans.

In the last set of experiments blood was obtained from the tails of 15 h-fasted which received either sucrose (0.8 g/kg), lactose (0.8 g/kg) or fructose (0.8 g/kg), or a mixture of sucrose (0.4 g/kg) plus fructose (0.4 g/kg).

The results (Table V) obtained when using sucrose (0.8 g/kg) or lactose (0.8 g/kg) were very similar to those shown in Table III. When using tail blood, the AUC values for sucrose and lactose were 167.7 ± 11.3 mg/dL and 117.3 ± 14.6 mg/dL (Table V), respectively; *i.e.*, a mathematical proportion of 59 (sucrose) to 41 (lactose), and once again, better reflected the GI values of sucrose (GI = 59) and lactose (GI = 46) in humans. Moreover, as we expected, fructose (GI = 20) showed a lower ($p < 0.05$) AUC than did sucrose or the 50%/50% mixture of sucrose and fructose, which showed an AUC value intermediate between those of sucrose and fructose.

In contrast to our current results, past investigations concerning the impact of isolated carbohydrates or mixed foods on human blood glucose levels have shown great variability among the tested individuals, which have included healthy subjects, as well as pre-diabetic and diabetic subjects (Atkinson, Foster-Powell, Brand-Miller, 2008). Moreover, inter-individual and intra-individual variations (Vega-López *et al.*, 2007), the placebo effect (Sevenpiper *et al.*, 2007), and several other factors (Foster-Powell, Holt, Brand-Miller, 2002; Wolever *et al.*, 2009) that can influence such results must be taken into consideration. In this context, using rats whose blood had been analyzed using a standardized methodology provides many advantages. For example, it is possible to control several variables which might influence the study results, including age, gender, strain, body weight, feeding schedule, period of fasting, and room temperature (Iannaccone, Jacob, 2009).

CONCLUSION

Tail blood obtained from 15-h fasted rats represents the best pre-clinical model in which to evaluate the impact

of carbohydrates on PPG levels, and then extrapolate the results to humans.

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