Effect of Gum Arabic (Acacia Senegal) on Glucose Metabolism and Body Weight Gain in Mice

Omaira Nasir
Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Turabah, Taif University
Kingdom of Saudi Arabia

Abstract

**Background:** A diet rich in fibers has been associated with reduced body weight, prevention of metabolic syndrome and improved glycemic control in patients with type 2 diabetes mellitus. Gum arabic (GA) is a dietary fiber of mainly polysaccharide composition derived from the dried exudates from *Acacia senegal*. Methodology: In this study, we investigated the effects of GA on glucose metabolism and body weight gain in wild-type C57Bl/6 mice. GA treatment was delivered as a 10% drinking solution. Results: During GA treatment oral glucose tolerance with 3mg/g bw was significantly improved compared to control mice (AUC 29700±1018 min·mg/dl vs. 27207±892 min·mg/dl) whereas intra-peritoneal glucose tolerance test was unaffected by GA treatment. Also the insulin level was increased during oral and inter-peritoneal glucose tolerance test. Fasting blood glucose concentrations were increased significantly following challenge with a 20% glucose solution (172±63 mg/dl) which was blunted by simultaneous treatment with GA (120±88 mg/dl). Conclusions: GA was found to have affected the consequence of body weight gain during glucose and high fat diet and prevented glucose-induced obesity.

Keywords: Gum arabic, Glucose, Body weight, High fat diet

Introduction

Dietary fibers are the edible constituents of plant foods (or analogous carbohydrates) that escape digestion in the upper intestine and undergo complete or partial fermentation in the large intestine (FAO Food Nutr Pap 1998). A diet rich in fibers has been associated with reduced body weight (Koh-Banerjee et al., 2004) and prevention of metabolic syndrome (McKeown et al., 2004.). In patients with diabetes mellitus type 2, an increased intake of dietary fiber improved glycemic control and reduced hyperinsulinenemia (Chandalia et al., 2000). Proposed explanations for the beneficial effects of dietary fibers include interaction with food intake and body weight through satiation, glycemia and insulinemia, blood lipids and blood pressure (Delzenne et al., 2005).

Gum Arabic (GA) is a water-soluble dietary fiber derived from the dried gummy exudates from the stems and branches of *Acacia senegal* (Younes et al, 1995). Chemically, GA is a polysaccharide based on branched chains of (1-3) linked β-D-galactopyranosyl units. Side chains of 2-5 units in length are attached by (1-6) links to the main chain. Both the main chain and the side chains contain α-L-arabinofuranosyl, α-L-rhamnopyranosyl, β-D-lucuronopyranosyl and 4-O-methyl-β-D-glucuronopyranosyl units (Deckwer et al., 2006). GA is readily soluble in water without increasing viscosity (Tiss et al., 2001). GA is widely used in both the pharmaceutical and the food industry to serve as an emulsifier and stabilizer of various products for human consumption.

GA is primarily indigestible for both humans and animals and after passing the small intestine, it is fermented in the colon under the influence of microorganisms to short chain fatty acids (Phillips, 1998). The US Food and Drug Administration recognized it as one of the safest dietary fibers (Anderson, 1986). GA has also pharmacological effects related to interference with the gastrointestinal absorption of nutrients. The previous study showed that GA affected the intestinal absorption of Na⁺ and water in healthy mice while enhancing calcium and magnesium uptake (Nasir et al., 2008). In a rat model of chronic osmotic-diarrhea GA exerted pro-absorptive properties by increased sodium and water absorption (Teichberger et al., 1999; Wapnir et al., 1997).

GA treatment indeed modifies the body weight, decreased body mass index and body fat percentage among healthy adult females, and effect, which could be exploited in the treatment of obesity (Babiker R et al., 2012). The effect of GA on obesity in humans, may possibly be in part due to an influence on satiety. GA treatment decreases the caloric intake and increases the subjective ratings of feeling satiated (Calame W, et
al., 2011). Additional studies were performed on GA in diabetic animals, i.e., in heterozygous akita (akita−/+) mice developing spontaneous diabetes due to gradual destruction of the pancreas β-cells. GA treatment of the akita+/− mice tended to slightly blunt the hyperglycemia (Nasir O, 2012).

Given the beneficial effects of dietary fibers on the prevention of metabolic syndrome and obesity, we investigated whether the GA treatment have an effect on glucose, insulin levels as well on course of body weight gain during glucose rich or high fat diet in healthy wild-type C57Bl/6 mice.

Material and Methods

Animals

Experiments were carried out on male of 5-7 weeks old wild-type C57Bl/6 mice (Charles River, Germany). The animals were housed under controlled environmental conditions (22-24°C, 50-70% humidity and a 12-h light/dark cycle). Throughout the study, mice had free access to standard pelleted food or high fat diets (C1310, Altromin, Lage, Germany) and tap water, glucose or Gum Arabic from (DarSavanna/Nature Gums Co., Sudan, www. darsavanna.com.). All animal experiments were conducted according to the guidelines of the American Physiological Society and the German law for the care and welfare of animals and were approved by local authorities.

Animal experimentation

Animals were provided with 10% (w/v) GA dissolved in tap water (100 g/l), preparations were refreshed every 3 days during the treatment. The intake corresponded to a dose of approximately 20g/kg bw/day.

To study the effects of GA treatment on glucose tolerance, one week treated and untreated mice were fasted overnight with free access to drink and were loaded with 3 mg/g bw glucose in a volume of 10 µl/g bw by either intra-peritoneal or oral gavage. For the latter mice were shortly sedated using diethylether. Blood glucose was measured after tail-vein bleeding using a glucometer (Accutrend, Roche, Mannheim, Germany) before and at 15, 30, 45, 60, 90, 120 and 180 min after the injection of glucose. Blood samples for the determination of plasma insulin were taken before glucose loading. Plasma insulin was measured using an ELISA method (Crystal Chem INC, USA).

To investigate the effects of GA treatment on the development of obesity, mice were housed individually and the drink of the mice was switched to either 20% (w/v) glucose by 10% GA or 20% glucose only. Control groups received tap water or 10% GA. During the treatment of 4 weeks, body weight, food and fluid intake were monitored.

To test, whether GA is similarly effective in high fat diet animals were provided with a control diet (C1310, 4 kcal% fat, 0.25% Na+, 0.36% Cl−, 0.71% K+, Altromin, Heidenau, Germany) or a high fat diet (C1000, 45 kcal% fat, 0.25% Na+, 0.36% Cl−, 0.71% K+, modified according D12451 from Research Diet, Altromin, Heidenau, Germany) and received 10% (w/v) GA dissolved in tap water (100 g/l) as indicated; preparations were refreshed every 3 days during the treatment. During the treatment of 4 weeks, body weight, food and fluid intake were monitored.

Glucose and insulin concentrations were determined in blood drawn after tail-vein bleeding. Plasma glucose was determined using a glucometer for investing and after an overnight (Accutrend, Roche, Mannheim, Germany); plasma insulin was measured using an ELISA (Crystal Chem INC, USA).

Statistics

Data are provided as means ± SEM, n represents the number of independent experiments. All data were tested for significance with parametric or non-parametric repeated measures ANOVA, paired or unpaired Student t-test or Mann-Whitney test where applicable using GraphPad InStat version 3.00 for Windows 95, GraphPad Software, San Diego California USA, www.graphpad.com. A p-value < 0.05 was considered statistically significant.

Results

To investigate the effect of GA treatment on glucose tolerance, both oral and peritoneal glucose tolerance tests were performed with 3 g/kg bw. As illustrated in (Fig. 1A&B) oral application of glucose led to significantly higher plasma glucose concentrations in untreated mice compared to GA-treated mice. The calculated area-under-the-curve for glucose was significantly higher in untreated than in GA-treated mice (34755±2068 min · mg/dl vs. 29973±778 min · mg/dl, resp.), indicating improved glucose tolerance under GA treatment. However, the positive effects of GA were not evident during intra-peritoneal loading (Fig.1B). The calculated area-under-the-curve was similar in untreated and in GA-treated mice during IPGTT (46897±3440 min · mg/dl vs. 38541±2815 min · mg/dl, resp.).The insulin concentrations were increased during the time course of OGTT and IPGTT (Fig. 2A&B).
Fig. 1A&B: Effect of GA treatment on blood glucose concentration during OGTT and IPGTT.

To test the in vivo relevance of this observation, blood glucose concentrations were determined as a surrogate of glucose uptake. To this end mice were treated with tap water, 10% GA or a 20% (w/v) glucose solution with or without 10% GA for 1 week. During GA treatment, the un-fasting blood glucose concentrations showed non-significant reduction (138±5 mg/dl vs 125±4 mg/dl, resp.; Fig.3A). The addition of 20% glucose significantly increased fasting blood glucose concentration to (153±8 mg/dl), an effect which was significantly blunted under combined treatment with glucose and GA (126±9 mg/dl), Fig.3B.
Further experiments were performed to investigate the course of the body weight under these treatments over 4 weeks. Addition of glucose significantly increased fluid intake and decreased food intake to a similar extent in both GA+glucose-treated and GA-treated mice compared to both untreated and GA-treated mice (Fig. 4A&B). However, glucose-treated mice gained significantly more body weight compared to GA+ glucose-treated mice (Fig. 4B). Addition of glucose significantly increased fluid intake and decreased food intake to a similar extent in animals treated without or with GA (Fig. 5A&B).

Fig. 4 A & B: Effect of GA treatment on Course and delta of body weight gain
Fig. 5 A & B: Effect of GA treatment on drink volume and food intake.

To test whether GA is similarly effective in high fat diet, the body weight was monitored in animals receiving a high fat diet with or without GA. However, the mice treated with high diet alone showed significant increase in body weight gain mice (+13.98±0.98 g), compared to non treated mice (+10.97±0.76 g), Fig. 6A&B.

Fig. 6 A & B: Effect of GA treatment on course and delta of body weight gain during high fat diet.

As illustrated in Figure 6, high fat diet was paralleled by hyperglycemia and hyperinsulinism, effects significantly blunted by GA treatment, Fig. 7A&B.
Discussion
The present study reveals that GA decreases the weight gain as shown in previous studies that GA inhibits intestinal glucose absorption by down-regulation of the membrane abundance of SGLT1 which is the major route for intestinal glucose absorption (Nasir et al., 2010). This was shown in our study by the improved oral glucose tolerance while inter-parenteral glucose loading was unaffected in GA-treated mice, indicating that effects of GA on the glucose metabolism are related to interaction with the intestine. Indeed, The Na⁺-D-glucose cotransporter SGLT1 plays a key role in intestinal glucose absorption as illustrated by defective mutants of SGLT1 in humans, which lead to glucose-galactose-malabsorption in the newborn (Wright et al., 2003). The expression and activity of SGLT1 were increased following a carbohydrate-rich diet (Ferraris et al., 1989). Regulation of SGLT1 can be mediated by adrenergic innervation (Ishikawa et al., 1997), insulin (Stümpel et al., 1996), glucagon-like peptide 2 (Cheeseman et al., 1997), cholecystokinin (Hirsch and Cheeseman, 1998), and insulin-like growth factors (Lane et al., 2002). It has been shown that SGLT1 can be regulated by changes in transcription (Martin et al., 2000), mRNA stability (LoFlin and Lever, 2001), amount of transporter within the plasma membrane (Hirsch et al., 1996), and transporter activity (Vayro et al., 2002). It has been shown that the PI3-Kinase, PI3K, and phosphoinoside-dependent kinase 1, PDK1, (Artunc et al., 2006) or the serum- and glucocorticoid-regulated kinases 1 and 3, SGK1/3, (Artunc et al., 2006) are involved in the regulation of SGLT1 activity. The 67-kDa-protein RS1 is another factor influencing SGLT1 activity by transcriptional and posttranscriptional regulation (Veyhl et al., 2006). The latter has an inhibitory effect on SGLT1 expression while PI3K, PDK1, SGKs stimulate SGLT1 activity and/or expression.

Data from the gene array showed that the transcript levels for the RS1 and SGK3 were significantly reduced, suggesting a possible mechanism for the effects of GA on SGLT1 membrane abundance (Nasir et al., 2010). GA treatment reduced transcript levels of SGLT2, however, the contribution of this finding to the inhibition of glucose uptake is not clear.

In keeping with the electrophysiological and expression data, intestinal glucose absorption was reduced in vivo during GA treatment as evidenced by reducing blood glucose concentrations which were measured as surrogate of glucose uptake. Plasma insulin levels paralleled the blood glucose concentrations ruling out the effects of GA on insulin secretion. Moreover, GA treatment robustly prevented glucose-induced weight gain over 4 weeks despite similar fluid and food intake. The reduction of weight gain was also seen in the absence of glucose. GA treatment significantly reduced urinary glucose excretion, Na⁺ excretion and urinary volume (Nasir et al., 2012). The reduced glucosuria presumably contributed to the blunted diuresis and urinary Na⁺, K⁺ and urea excretion. Glucosuria causes osmotic diuresis with subsequent renal loss of electrolytes (Lang et al., 1987).

Our results indicate that GA treatment does not interfere with peripheral glucose uptake when glucose loading was done inter-parenterally. GA treatment in mice include decreased expression of intestinal Na⁺ coupled glucose carrier SGLT1 with subsequent delay of electrogenic intestinal glucose transport, glucose-induced hyperglycemia, hyperinsulinemia and body weight gain GA treatment has been shown to decrease intestinal Na⁺ coupled glucose transport by downregulating the Na⁺ coupled glucose carrier SGLT1 (Nasir et al., 2010), which determines the rate of intestinal glucose absorption and thus influences glucose-induced insulin release and development of obesity. Addition of GA to the drinking water of C57Bl/6 mice significantly decreased SGLT1 protein abundance in jejunal and ileal brush border membrane vesicles (Nasir et al., 2010). According to gene array data, GA does not decrease SGLT1 protein expression by inhibiting SGLT1 transcription but modifies SGLT1 abundance rather by modifying posttranscriptional regulation (Nasir et al., 2010). Besides altering transcription or mRNA stability SGLT1 could be modified by trafficking into the plasma membrane or by direct regulation of transporter activity (Martin et al., 2000).

GA treatment did not significantly alter food intake and only slightly decreased fluid intake [44]. Addition of 20% glucose in drinking water significantly increases body weight and fasting plasma glucose concentrations, effects significantly blunted by simultaneous treatment with GA. Earlier studies showed that in contrast to chronic GA treatment, direct application of GA to perfused jejunal segments did not influence intestinal glucose uptake (Wingertzahn MA, et al., 2001). Presumably due to downregulation of SGLT1 activity GA treatment blunts the hyperglycemic effect of excessive glucose intake.

Dietary fibers were shown to decrease body weight (Koh-Banerjee P, et al., 2004) to prevent metabolic syndrome (McKeown NM, et al., 2004) and to improve glycemic control as well as hyperinsulinemia in type II diabetes (Chandalia M, et al., 2000). The effect of dietary fibers has been attributed to interaction with food intake and body weight through satiety, glycemia and insulinemia, blood lipids and blood pressure (Delzenne NM, et al., 2005). So far, the beneficial effects of dietary fibers have been explained by interaction with food intake and body weight through satiation, glycemia and insulinemia, blood lipids and blood pressure (Delzenne et al., 2005). GA has been shown to enhance intestinal water and Na⁺ absorption in a rat model of chronic-osmotic diarrhea thus favoring rehydration. Apparently, the effects of GA on intestinal Na⁺ and water absorption are dependent on the condition of the intestine, in addition to other beneficial health effects which have been recently published in a review article by Omaima Nasir, 2013.
In summary, the dietary fiber GA has a favorable effect on glucose metabolism and reduction of body weight gain, which could be used in turn as prophylactic or treatment of obesity and the development of metabolic syndrome.

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References:


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