Effects of Gum Arabic (*Acacia senegal*) on Renal Function in Diabetic Mice

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Key Words

Calcium • Glucosuria • Hyperglycemia • Phosphate • Proteinuria • Blood pressure

Abstract

Background/Aims: Gum arabic (GA) is a Ca²⁺-, Mg²⁺- and K⁺-rich dietary fiber used for the treatment of patients with chronic kidney disease in Middle Eastern countries. In healthy mice, GA treatment increases creatinine clearance, renal ADH excretion, as well as intestinal and renal excretion of Mg²⁺ and Ca²⁺. GA decreases plasma Pi concentration, urinary Pi and Na⁺ excretion. The present study explored the effects of GA on renal function in diabetic mice. **Methods:** Metabolic cage experiments were performed on Akita mice (*akita*^{+/-}), which spontaneously develop insulin deficiency and thus hyperglycemia. Plasma and urinary concentrations of Na⁺, K⁺ and Ca²⁺ were measured by flame photometry (AFM 5051, Eppendorf, Germany), creatinine by the Jaffé method, phosphate photometrically, urea by an enzymatic method, glucose utilizing a glucometer and an enzymatic kit, aldosterone using an RIA, urinary albumin fluorometrically, and blood pressure by the tail-cuff method. **Results:** GA (10% in drinking water) significantly increased urinary excretion of Ca²⁺ and significantly decreased plasma phos-

phate and urea concentrations, urinary flow rate, urinary Na⁺, phosphate and glucose excretion, blood pressure and proteinuria. **Conclusions:** GA treatment decreases blood pressure and proteinuria in diabetic mice and may thus prove beneficial in diabetic nephropathy.

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Introduction

Gum arabic (GA), a water-soluble dietary fiber [1] derived from the dried gummy exudates from the stems and branches of *Acacia senegal* [2], is a polysaccharide based on branched chains of (1–3)-linked β-D-galactopyranosyl units containing α-L-arabinofuranosyl, α-L-rhamnopyranosyl, β-D-glucuronopyranosyl and 4-O-methyl-β-D-glucuronopyranosyl units [3]. Upon ingestion, GA is fermented in the colon by microorganisms to short-chain fatty acids [4].

GA is considered one of the safest dietary fibers by the US Food and Drug Administration [5]. In Middle Eastern

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Fig. 1. Structural characterization of GA. COSY HR/MAS NMR spectrum of GA in D₂O, 313 K with labeled cross-peaks for the monosaccharide units.

countries GA is widely used in the treatment of patients with chronic kidney disease and end-stage renal disease [6]. GA was found to increase fecal nitrogen excretion [7], to decrease production of free oxygen radicals [6], and to modestly counteract renal injury following acute gentamicin nephrotoxicity in rats [8]. In healthy mice, GA treatment has been shown to increase creatinine clearance and renal ADH excretion as well as intestinal and renal excretion of Mg²⁺ and Ca²⁺ [9]. It has also been shown to lower plasma concentration of 1,25(OH)₂D₃ as well as urinary P_i and Na⁺ excretion [9].

A major cause of end-stage renal disease is diabetic nephropathy [10]. The present study thus explored the effects of GA on renal function in diabetic mice. To this end, metabolic cage experiments were performed on heterozygous Akita (*akita*^{+/-}) mice, which develop spontaneous diabetes due to the gradual destruction of pancreatic β-cells [11]. It is shown that GA treatment of those mice indeed influences renal function. Most importantly, GA treatment decreased proteinuria, an important parameter for the progression of renal disease [12–18].

Fig. 2. Effect of GA treatment on blood glucose concentration and urinary glucose excretion of *akita*^{+/-} mice. Arithmetic means ± SEM of blood glucose concentration (a) and urinary glucose excretion (b) in heterozygous *akita*^{+/-} mice without and with 1 week's or 2 weeks' GA treatment. Asterisk indicates significant difference from control (without GA treatment).

Methods

Gum Arabic

GA in powder form was provided as a generous gift from Dar Savanna Ltd., Khartoum, Sudan (www.ssgums.com). The fully natural extract powder with a particle size smaller than 210 μm was produced mechanically from wildy grown *A. senegal* trees. The quality conforms to the food and pharmaceutical requirements of the Food and Agriculture Organization of the United Nations (FAO), British pharmacopoeia (BP), United States pharmacopoeia (USP) and the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Optical rotation was determined on a Perkin Elmer model 341 polarimeter. GA was dissolved in water and measured at 20°C to obtain a value of -28°.

¹H HR/MAS NMR spectra of GA was recorded on a Bruker ARX 400-MHz spectrometer at a spinning rate of 4 kHz in a 4-mm double-bearing ZrO₂ rotor. The spectrometer was equipped with a deuterium lock setup, which was set on the resonance frequency of D₂O. The 90° pulse length was set to 10.5 μs. Spectra were recorded at 313 K and multiplied by an exponential line broadening function of lb = 0.5 Hz prior to Fourier transformation. Spectrum processing was performed using Bruker TOPSPIN 2.0 software. Assignment of the GA proton COSY HR/MAS NMR spectrum was obtained for a number of cross-peaks starting from the anomeric protons. Figure 1 displays the spectrum with the labeled cross-peaks as reported previously [19]. The obtained data is in accordance with JECFA specifications and provides valuable information on the studied sample [20, 21].

Animals

Experiments were carried out on heterozygous *akita*^{+/-} mice (age: 3–8 months) which spontaneously develop diabetes. Before

Fig. 3. Effect of GA treatment on body weight, food intake, fluid intake, and urinary output of *akita*^{+/-} mice. Arithmetic means $\pm$ SEM of body weight (a), food intake (b), fluid intake (c) and urinary output (d) in heterozygous *akita*^{+/-} mice without and with 1 week's or 2 weeks' GA treatment. Asterisk indicates significant difference from control (without GA treatment).

including the mice in the study the diabetic phenotype was assured by the determination of plasma glucose concentrations. A glucose concentration above 200 mg/dl was considered as diabetic. The animals were housed under controlled environmental conditions (22–24°C, 50–70% humidity and a 12-hour light/dark cycle). Throughout the study the mice had free access to standard pelleted food (Altromin, Lage, Germany) and tap water or GA solution as indicated. 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.

GA Treatment

GA was administered by the addition of 10% (w/w) GA to the tap drinking water (100 g/l). The preparations were refreshed every 3 days during the treatment. The effects of GA administration were investigated before treatment with GA, after 1 week and after 2 weeks of GA treatment. The intake corresponded to a dose of approximately 20 g/kg body weight/day.

Collection of Urine

For the evaluation of renal excretion as well as daily food and fluid intake, the mice were placed individually in metabolic cages

Fig. 4. Effect of GA treatment on urinary excretion and plasma concentration of Na⁺ and K⁺ in *akita*^{+/-} mice. Arithmetic means $\pm$ SEM of urinary excretions (a, c) and plasma concentration (b, d) of Na⁺ (a, b) and K⁺ (c, d) in heterozygous *akita*^{+/-} mice without and with 1 week's or 2 weeks' GA treatment. Asterisk indicates significant difference from control (without GA treatment).

(Techniplast, Hohenpeissenberg, Germany) for 24 h and urine was collected with free access to fluid as well as standard diet. Collections were performed at baseline with tap water, and with GA-containing drinking water for 1 or 2 weeks. The inner wall of the metabolic cages was siliconized, and urine was collected under water-saturated oil.

Determination of Plasma and Urinary Concentrations

To obtain blood specimens, the animals were lightly anesthetized with diethylether (Roth, Karlsruhe, Germany), and approximately 130 μl of blood was withdrawn into heparinized capillaries by puncturing the retro-orbital plexus.

The plasma and urinary concentrations of Na⁺, K⁺ and Ca²⁺ were measured by flame photometry (AFM 5051, Eppendorf, Germany) or by a photometric method according to the manufacturer's instructions (dri-chem clinical chemistry analyzer FUJI FDC 3500i, Sysmex, Norsted, Germany). Urinary creatinine concentrations were measured using a kinetic Jaffé method. The plasma and urinary phosphate concentrations were measured photometrically using kits from Roche Diagnostics (Mannheim, Germany). Plasma urea was measured by an enzymatic method (Lehmann, Berlin, Germany).

Fig. 5. Effect of GA treatment on urinary excretion and plasma concentration of Ca^{2+} and phosphate in $akita^{+/-}$ mice. Arithmetic means $\pm$ SEM of urinary excretion (**a**, **c**) and plasma concentration (**b**, **d**) of Ca^{2+} (**a**, **b**) and phosphate (**c**, **d**) in heterozygous $akita^{+/-}$ mice without and with 1 week's or 2 weeks' GA treatment. Asterisk indicates significant difference from control (without GA treatment).

The blood glucose concentration was determined utilizing a glucometer (Accutrend, Roche, Mannheim, Germany). The urinary glucose concentration was determined utilizing a commercial enzymatic kit (Gluco-quant, Roche Diagnostics, Mannheim, Germany). Plasma aldosterone concentration was measured using an RIA kit (Demeditec, Kiel, Germany).

Urinary albumin was measured fluorometrically using the albumin-sensitive dye albumin blue 580 at 595-nm excitation and 642-nm emission on a Wallac counter (Victor 1420) according to the manufacturer's instructions (microfluoral, Progen, Heidelberg, Germany). Standard curves were generated with mouse albumin (Sigma, Schnelldorf, Germany), and measurements were performed within the linear range (0–156 mg/l).

Blood Pressure Measurements

Systolic arterial blood pressure was determined by the tail-cuff method (IITC, Model 179, Woodland Hills, Calif., USA). Application of this method requires certain precautions to reduce the stress of the animals, including appropriate training of the mice over multiple days and adequate prewarming to dilate the tail artery. The animals were placed in a heated chamber at an ambient temperature of 30–32°C. Animal blood pressure traces were re-

Table 1. Arithmetic means $\pm$ SEM (n = 3–4) of the indicated parameters determined before (control) and following treatment of $akita^{+/-}$ mice with GA for 7 or for 14 days

	Control	7 days' treatment	14 days' treatment
FE (Na^+), %	1.05 $\pm$ 0.58	0.07 $\pm$ 0.01	0.03 $\pm$ 0.02
FE (K^+), %	20.11 $\pm$ 7.02	5.11 $\pm$ 1.41	12.31 $\pm$ 7.27
FE (urea), %	222.15 $\pm$ 67.10	36.33 $\pm$ 7.55*	30.75 $\pm$ 9.8*

* $p < 0.05$. FE = Fractional excretion.

corded in one session until the deviation of a minimum of 5 traces was lower than 5 mm Hg. The readings from 3 days were then averaged to obtain a mean blood pressure under the respective treatment. All recordings and data analysis were done using a computerized data acquisition system and software (PowerLab 400 and Chart 5, both ADInstruments, Colorado Springs, Colo., USA). All measurements were performed by the same person during a defined time.

Statistical Analysis

Data are provided as arithmetic means $\pm$ SEM, and n represents the number of independent experiments. Data were tested for significance using the paired two-tailed Student t test when two-sample means were tested. $p < 0.05$ was considered statistically significant.

Results

As described earlier [11], heterozygous $akita^{+/-}$ mice developed marked and statistically significant hyperglycemia (fig. 2). Treatment of the $akita^{+/-}$ mice with GA tended to slightly decrease the plasma glucose concentration, an effect, however, not reaching statistical significance. The treatment significantly reduced the urinary glucose excretion (fig. 2).

Within the observed treatment period of up to 2 weeks, GA did not significantly modify the body weight of the $akita^{+/-}$ mice (fig. 3) despite a significant decrease of food intake following GA treatment (fig. 3). Similarly, fluid intake and as a result urinary output were decreased following GA treatment of the $akita^{+/-}$ mice (fig. 3).

The decrease of glucosuria and urinary flow rate of the $akita^{+/-}$ mice was paralleled by a significantly decreased urinary Na^+ excretion (fig. 4; table 1). Urinary K^+ excretion tended to decrease following GA treatment, an effect, however, not reaching statistical significance (fig. 4; table 1). Neither plasma Na^+ concentration nor plasma K^+

Fig. 6. Effect of GA treatment on urinary creatinine and albumin excretion of *akita*^{+/-} mice. Arithmetic means $\pm$ SEM of urinary creatinine excretion (**c**), urinary albumin excretion (**a**) and urinary albumin excretion over body weight (**b**) in heterozygous *akita*^{+/-} mice without and with 1 week's or 2 weeks' GA treatment. Asterisk indicates significant difference from control (without GA treatment).

Fig. 7. Effect of GA treatment on plasma urea and aldosterone concentration of *akita*^{+/-} mice. Arithmetic means $\pm$ SEM of plasma urea (**a**) and aldosterone (**b**) concentration in heterozygous *akita*^{+/-} mice without and with 1 week's or 2 weeks' GA treatment. Asterisk indicates significant difference from control (without GA treatment).

Fig. 8. Effect of GA treatment on arterial blood pressure. Arithmetic means $\pm$ SEM (n = 9–11) of arterial blood pressure in heterozygous *akita*^{+/-} mice without and with 1 week's or 2 weeks' GA treatment. **p < 0.01 vs. control.

concentration of the *akita*^{+/-} mice were significantly modified by the GA treatment (fig. 4).

GA treatment of *akita*^{+/-} mice significantly increased the urinary excretion of Ca²⁺ (fig. 5). Plasma Ca²⁺ concentration tended to increase following GA treatment, an effect, however, not reaching statistical significance (fig. 5). GA treatment of *akita*^{+/-} mice was followed by a profound and significant decrease of plasma phosphate concentration paralleled by a significant decrease of urinary phosphate excretion (fig. 5).

As illustrated in figure 6, the diabetic *akita*^{+/-} mice developed albuminuria. Surprisingly, the albuminuria was significantly decreased by GA treatment. Urinary creati-

nine excretion remained constant during GA treatment (fig. 6).

Plasma urea concentration and fractional urea excretion decreased in GA-treated *akita*^{+/-} mice (fig. 7; table 1). Plasma aldosterone concentration was not significantly modified by GA treatment (fig. 7).

As shown in figure 8, GA treatment was followed by a marked and significant decrease of arterial blood pressure.

In wild-type mice, GA treatment significantly reduced urinary Na⁺ excretion (table 2).

Table 2. Arithmetic means $\pm$ SEM (n = 4–5) of the indicated parameters determined before (control) and following treatment of wild-type mice with GA for 7 or for 14 days

	Control	7 days' treatment	14 days' treatment
Body weight, g	28.11 $\pm$ 1.66	27.93 $\pm$ 2.13	27.01 $\pm$ 2.09
Food intake, g/24 h	3.66 $\pm$ 0.52	3.88 $\pm$ 0.16	3.81 $\pm$ 0.24
Fluid intake, g/24 h	5.59 $\pm$ 0.28	6.08 $\pm$ 0.59	5.83 $\pm$ 0.59
Urine output, ml/24 h	1.05 $\pm$ 0.25	1.1 $\pm$ 0.26	1.04 $\pm$ 0.34
Na ⁺ serum, mmol/l	146.54 $\pm$ 1.14	143.35 $\pm$ 1.13	146.78 $\pm$ 1.29
K ⁺ serum, mmol/l	4.14 $\pm$ 0.23	4.27 $\pm$ 0.15	3.82 $\pm$ 0.29
Ca ²⁺ serum, mmol/l	2.24 $\pm$ 0.04	2.52 $\pm$ 0.19	2.40 $\pm$ 0.08
Pi serum, mmol/l	1.61 $\pm$ 0.15	1.44 $\pm$ 0.46	1.03 $\pm$ 0.11*
Urine Na ⁺ , μ mol/24 h	122.15 $\pm$ 15.20	65.82 $\pm$ 7.01**	50.38 $\pm$ 9.04**
FE (Na ⁺), %	1.19 $\pm$ 0.09	0.62 $\pm$ 0.16**	0.45 $\pm$ 0.16*
Urine K ⁺ , μ mol/24 h	541.93 $\pm$ 75.96	591.53 $\pm$ 49.90	539.11 $\pm$ 88.74
FE (K ⁺), %	185.2 $\pm$ 12.34	183.22 $\pm$ 29.26	210.80 $\pm$ 64.61
Urine Ca ²⁺ , μ mol/24 h	18.23 $\pm$ 1.56	29.30 $\pm$ 3.03	23.91 $\pm$ 2.94
FE (Ca ²⁺), %	14.22 $\pm$ 1.93	14.9 $\pm$ 2.77	16.46 $\pm$ 1.26
Urine Pi, μ mol/24 h	6.22 $\pm$ 2.97	2.81 $\pm$ 0.4*	2.77 $\pm$ 0.70*
FE (Pi), %	2.71 $\pm$ 0.33	3.30 $\pm$ 1.20	4.46 $\pm$ 1.79
Creatinine clearance, μ l/min	52.95 $\pm$ 7.48	60.46 $\pm$ 11.1	56.54 $\pm$ 11.65
Urine creatinine, μ mol/24 h	5.78 $\pm$ 0.84	6.89 $\pm$ 0.98	5.9 $\pm$ 1.14

* p < 0.05, ** p < 0.01 vs. control. FE = Fractional excretion.

Discussion

The present study reveals novel effects of GA. In diabetic heterozygous *akita*^{+/-} mice, GA treatment decreased glucosuria without appreciably influencing the plasma glucose concentration. Possibly, GA increased renal tubular glucose transport. Despite the decrease of urinary glucose loss, the plasma glucose concentration was not significantly modified by GA treatment. Presumably, the decreased food intake compensated for the decreased urinary glucose loss and thus, neither plasma glucose concentration nor body weight was significantly modified by GA treatment.

The reduced glucosuria might have contributed to the decrease of urinary volume and urinary Na⁺, K⁺ and urea excretion. Glucosuria imposes an osmotic diuresis with subsequent renal loss of electrolytes [22]. Moreover, GA treatment increases the release of ADH [9], which may have contributed to the decreased fluid, Na⁺ and urea excretion.

The antinatriuresis was paralleled by calciuria, which is presumably secondary to enhanced Ca²⁺ intake. GA is rich in Ca²⁺ salts (table 3) [3]. Accordingly, a calciuric effect of GA treatment has been reported earlier in healthy mice [9]. In this earlier study the increased uptake of cal-

cium was followed by suppression of the secretion of the biologically active 1,25(OH)₂D₃ and a tendency of PTH plasma concentration to similarly decrease [9]. The decrease of plasma PTH and 1,25(OH)₂D₃ concentrations is expected to reduce renal tubular Ca²⁺ reabsorption and thus presumably contributes to or even accounts for the calciuria [23, 24].

A decrease of the plasma 1,25(OH)₂D₃ concentration is expected to decrease intestinal phosphate absorption, which may account for the decline of plasma phosphate concentration. The hypophosphatemia is in turn expected to result in antiphosphaturia, which has indeed been observed in healthy [9] and diabetic mice. The antiphosphaturia would be further fostered by reduced PTH plasma levels [25].

The most striking observation was the marked decrease of albuminuria following GA treatment. The decrease of albuminuria could have been due to a decrease of blood pressure. In an earlier study [9], we did not observe a significant effect of GA treatment on plasma aldosterone concentration or blood pressure of healthy mice. In the present study on diabetic mice, however, GA did significantly decrease blood pressure. Moreover, an antihypertensive effect of GA has been demonstrated earlier in humans [26]. The effect of GA on blood pressure could at least in part be

Table 3. Properties and composition of GA according to the manufacturer

Form	Powder
Particle size	<250 μm
Viscosity of 20% solution	70–110 cP
pH of 20% solution	4.1–4.8
Specific rotation	(oc)D 25c (–26°) to (–35°)
Moisture	<13%
Total ash	<4%
Acid-insoluble residue	<1.0%
Starch or dextrin	Negative
Tannin bearing gums	Negative
Arsenic	<1.0 mg/kg
Lead	<2.0 mg/kg
Cadmium	<1.0 mg/kg
Mercury	0.05 mg/kg
Antimony	<1.0 mg/kg
Tin	<40 mg/kg
Copper	<20 mg/kg
Total dietary fiber (as is)	>85%
Total dietary fiber (dry weight)	>90%
<i>Nutritional information (approximate values per 100 g)</i>	
Energy	200 kcal
Protein	1.9 g
Available carbohydrates	<0.1 g
Fat	0.1 g
Soluble dietary fiber	85.5 g
Soluble dietary fiber (dry basis)	94 g
Cholesterol	<1 mg
Sodium	14 mg
Calcium	1,074 mg
Potassium	914 mg
Magnesium	390 mg
Iron	1.0 mg

due to enhanced Ca^{2+} intake, which has been shown to lower blood pressure, an effect attributed in part to stimulation of the Ca^{2+} -sensing receptor with subsequent inhibition of the Na^+ , K^+ , 2Cl^- cotransport in the thick ascending limb [27] or triggering of vasodilation [28].

The present study does not rule out antiproteinuric effects of GA treatment involving additional mechanisms unrelated to blood pressure. GA treatment was further associated with an increased creatinine clearance [9]. The mechanisms involved in the influence of GA treatment on glomerular function remain elusive. The fermentation of GA by intestinal bacteria leads to the formation of several degradation products including short-chain fatty acids [29]. Accordingly, GA treatment has previously been shown to enhance the serum butyrate concentration in healthy subjects [30]. Infusion of D,L-3-hydroxybutyric

acid and sodium D,L-3-hydroxybutyrate have in turn been shown to increase the glomerular filtration rate and renal blood flow in humans [31]. It is tempting to speculate that the enhanced butyrate formation influences glomerular function during GA treatment.

GA is used in Middle Eastern countries for the treatment of patients with chronic and end-stage kidney disease [6]. The present data indeed disclose some effects of GA treatment, which may be beneficial for patients with renal disease. First, the decrease of proteinuria is expected to delay the progression of renal disease [12]. Second, the decrease of plasma phosphate concentration increases the plasma concentration of ionized Ca^{2+} and thus counteracts hyperparathyroidism, a major pathophysiological parameter in advanced renal disease [32–34]. Third, an increase in creatinine clearance, as has been observed earlier [9], counteracts the decline of renal excretory function. Our data are thus indeed suggestive of a favorable influence of GA treatment on renal function in diabetic individuals. It should, however, be pointed out that the phenotype of the *akita*^{+/-} mice is not that of fully developed diabetic nephropathy. Rather, the renal function reflects that of early diabetes.

At least in theory, the composition and chemical property and thus the biological effects of GA may vary. It remains to be shown whether other preparations of GA are similarly effective.

In conclusion, this present study reveals several effects of GA treatment, which may delay the progression to renal failure in diabetes. Most importantly, GA treatment decreases proteinuria, lowers plasma phosphate concentration and increases the glomerular filtration rate.

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Disclosure Statement

The authors of this manuscript state that they have no conflicts to declare and that the results presented in this paper have not been published previously in whole or in part.

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