

Original Research

Enhancement of Absorption by Gum Arabic in a Model of Gastrointestinal Dysfunction

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Objective: Diarrhea is a common and deadly threat to millions of infants and children. Similarly, malabsorption can aggravate the health status of the chronically sick and especially the elderly. Prompt recovery from intestinal dysfunction may have a substantial impact on many populations. The aim of this study was to test the hypothesis that, in an animal model of cathartic-induced diarrhea, the previously shown proabsorptive effects of gum arabic (GA) could directly reduce and ameliorate intestinal dysfunction.

Methods: Young male rats were offered a standard solid feed and as a sole source of fluid a phenolphthalein-magnesium citrate solution for 3 or 6 days (PC), or the same plus either 10 (GA1) or 20 (GA2) g/L of GA. Other groups had tap water without (CTL) or with 20 g/L GA (CTL + GA), after which the animals were jejunally perfused under anesthesia to test their absorptive capacity. Similarly treated rats were killed and the small intestinal mucosa scraped and processed for nitric oxide synthase (NOS) determination.

Results: In 6-day studies addition of GA to the cathartic solution led to increases in net water, sodium and glucose absorption with the higher GA2, relatively to the PC rats. For water (means \pm SEM): PC = 42.4 ± 3.6 ; GA2 = 57.9 ± 3.9 nmol/g.min, $p < 0.05$. For sodium: PC = $2,139 \pm 334$; GA2 = $4,465 \pm 444$ nmol/g.min, $p < 0.05$. After only 3-day exposure, effects were less marked. Total NOS activity was increased in the PC, GA1 and GA2 groups (333 ± 26 ; 334 ± 27 ; 336 ± 23 nmol/h.g) compared to CTL (233 ± 27 nmol/h.g, $p < 0.05$), while CTL + GA showed a further reduction of activity (190 ± 18 nmol/h.g, $p < 0.05$ vs. CTL).

Conclusions: These findings substantiate earlier physiologic and biochemical effects of GA on the gastrointestinal tract, presently conducted in a model of gastrointestinal dysfunction. The data further suggest that a natural proteoglycan such as GA can reduce secretory effects induced by cathartics and, hence, are predictive of potential effectiveness in the context of diarrhea or malabsorption by infectious or functional causes.

INTRODUCTION

In preceding studies conducted in our laboratory we focused on the physiologic effects of gum arabic (GA) on the gastrointestinal tract, especially its significant proabsorptive properties [1–5]. GA is a water-soluble, branched polymer of galactose, rhamnose, arabinose, and the magnesium and calcium salts of glucuronic acid. It can be considered an arabinogalactan containing <5% of glycoprotein. It is obtained as an exudate from several species of *Acacia* sp. trees [6]. We previously showed that GA, added to an oral rehydration solution (ORS),

enhanced water, electrolyte and glucose absorption during jejunal perfusions in healthy rats, or following induction of intestinal dysfunction in variously treated animals. A similar preparation with GA also accelerated weight recovery subsequently to several days of chemically induced diarrhea in rats [3]. In addition, GA reduced chloride secretion and normalized sodium transport in the small intestine of rats infused with cholera toxin under anesthesia [4]. Under these conditions it has now been shown that GA modulates nitric oxide (NO) release, acting both as a scavenger of NO diffused from the enterocyte into the lumen [5,7], and as a competitive inhibitor

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of NO synthase (NOS) [8]. There is also evidence that GA increases paracellular intestinal transport [9,10].

In view of the positive results obtained in experiments involving recovery from intestinal dysfunction [3], mimicking treatment of diarrhea, the goal of the present study was to test the hypothesis that GA could act in a preventive or therapeutic way, tempering the effects of cathartic agents used to induce NOS activity, leading to intestinal dysfunction.

MATERIALS AND METHODS

Experimental Animals and Treatments

1. Animals and Treatments. Male rats (Sprague-Dawley, 100–120 g; Taconic, Germantown, NY) were acclimatized and maintained with a standard feed (Rodent Chow, Harlan-Teklad, Madison, WI) and water for at least 48 h prior to the initiation of the experiments. Animals were assigned to one of the following groups according to the type of fluid they were offered as an *ad libitum* drink, as well as free access to solid food. The PC group was given, in lieu of drinking water, a solution containing a 1:1 dilution of U.S.P. magnesium citrate solution (Eckerd Drug Co., Clearwater, FL) containing 29.5 g/L of magnesium citrate (= 4.8 g/L of magnesium) to which additional 100 mg/L phenolphthalein was incorporated. This animal model is characterized by soft stools and fluid accumulation in the cecum, as well as by weight loss. The latter can be related to a reduced feed intake, although fluids are normally consumed, as evidenced by cecal contents. The longer period was consistent with preceding studies and the shorter span probed how soon deleterious effects could be observed. The GA1 treatment consisted of the same solution, but including 10 g/L GA. The GA2 group was offered the cathartic mixture described above, but also containing 20 g/L GA. These concentrations of GA have been used effectively in jejunal perfusion experiments [1–5,7–9]. Rats drinking tap water were the control (CTL) group. An additional treatment consisted of water with 20 g/L GA in solution (CTL + GA). GA was a premium spray-dried product (Importers Service Corp., Jersey City, NJ). This protocol was approved by the Institutional Animal Care and Utilization Committee (IACUC). Histological and ultrastructural observations of cathartic mixture use indicate mucosal damage comparable to that reported in chronic diarrhea of childhood, namely patches of very pale staining goblet cells on villi, reflecting decreased cytoplasmic density [2]. The weight of the rats was monitored daily. The percent weight changes were also corrected by subtracting the weight of the respective cecum, which was clamped, excised and weighed.

2. Intestinal Perfusions. After 3 or 6 days of having been given the solutions precedently described, the rats were anesthetized with urethane (130 mg/mL, 1.0 mL/100 g body weight i.p.). A segment of the jejunum, immediately distal to the ligament of Treitz, estimated to be 20–30 cm, was cannulated

with an entry port at the proximal point and a collecting tube attached at the distal end. One of the solutions described below was infused using a peristaltic pump (Harvard Inst., Boston, MA, USA, model 1203) at 10–12 mL/h, warmed at approximately 50°C so it would enter the abdominal cavity at body temperature. Perfusion rates were determined by weighing the amount of fluid pumped during a known period before and after the experiment. The procedure involved a 1 h equilibration phase to achieve steady state absorption, followed by five separate 15 min collection periods, which were individually analyzed. After completion of the experiment, the rats were killed by exsanguination from the abdominal aorta and the perfused segment removed and measured while extended with a 3 g clip. The excised length of small intestine was weighed wet, but drained of fluid. Only animals with perfused intestinal segments ranging between 15 and 35 cm were considered acceptable, based on previous experience showing that these values allowed for proportionality between length/weight and absorption rate [1,2]. The number of animals in each study is indicated in the legend of Tables and Figures.

3. Experimental Solution. Groups of rats treated as described above were perfused with a standard rehydrating solution containing 60 mM NaCl, 10 mM sodium citrate, 20 mM KCl and 111 mM glucose. All chemicals were obtained from Sigma-Aldrich (St. Louis, MO). Tritiated water (2 μ Ci/L [74 kBq/L]; New England Nuclear, Boston, MA) was added to all solutions to determine unidirectional water fluxes, as indicated in the analytical determinations section.

4. Analytical Determinations. Net water absorption (J_{net}) was obtained by weighing the fractions collected as compared to the amount entering the perfused segment, normalized to length units and expressed as μ L/min \cdot g. Disappearance of tritiated water was used to calculate water influx (J_{in}) by isotope dilution. Serosa-to-lumen efflux (J_{eff}) was estimated by the difference between J_{in} and J_{net} . The influx/efflux ratio (I/E) was obtained as an additional, more sensitive index of unidirectional flux changes [11]. Sodium and potassium were assayed by atomic absorption spectrophotometry (SpectrAA10: Varian Inst., Inc., Mountain View, CA, USA) using external standards, and its absorption corrected for fluid exchanges. A single value was obtained for each rat, averaging the results of the five collection fractions. Glucose was determined by a spectrophotometric method (Sigma 510-DA; Sigma-Aldrich, St. Louis, MO). Formulas used for absorption rate calculations have been previously published, as well as their validation [1,2,4,9,11]. Results are expressed as means \pm SEM. NOS was determined by the conversion of 14 C-labeled L-arginine (Arg) to L-citrulline (Cit) under conditions designed to assay both inducible NOS (iNOS) and constitutive NOS (cNOS). Unreacted Arg was retained by passage through a small column of Bio-Rad AG 50W-X8 (Bio-Rad Laboratories, Inc., Hercules, CA) resin equilibrated with a quench buffer pH 5.5 used to stop the action of the enzyme [12].

Table 1. Body Weight Changes and Cecum Weights in Rats Receiving Oral Fluid Treatments for 6 Days[†]

Treatment	Initial weight (g)	Final weight (g)	Weight changes (%)	Corrected body weight changes (%)	Cecum weight (% body weight)
PC (N)	113.8 ± 1.8 ^a (45)	85.8 ± 1.4 ^a (45)	-24.5 ± 0.8 ^a (45)	-18.6 ± 1.3 ^a (28)	5.36 ± 0.43 ^a (28)
GA1 (N)	110.1 ± 1.9 ^a (36)	82.2 ± 1.9 ^a (36)	-25.5 ± 1.2 ^a (36)	-18.3 ± 2.0 ^a (20)	6.84 ± 0.57 ^b (20)
GA2 (N)	111.8 ± 1.4 ^a (40)	85.3 ± 1.7 ^a (40)	-23.8 ± 1.2 ^a (40)	-17.0 ± 1.8 ^a (29)	7.07 ± 0.53 ^b (29)
CTL (N)	104.5 ± 1.8 ^a (34)	152.3 ± 2.5 ^b (34)	45.7 ± 1.5 ^b (35)	42.4 ± 2.1 ^b (19)	3.12 ± 0.12 ^c (19)
CTL + GA (N)	105.3 ± 1.4 ^a (25)	155.2 ± 1.6 ^b (25)	47.6 ± 1.3 ^b (25)	42.8 ± 1.3 ^b (21)	3.71 ± 0.19 ^c (21)

[†] Data represent the means ± SEM. Values in the same column not sharing superindexes are significantly different ($p < 0.05$).

5. Tissue Harvest for Enzymatic Assays. After 3 or 6 days of the treatments described above, the animals were killed by CO₂ overdose. For the NOS assay, an approximately 40 cm segment of the upper small intestine, immediately distal from the ligament of Treitz, was rapidly removed and handled as fully described in [8]. Mucosal samples were stored at -20°C and analyzed within two weeks.

Morphology

Morphological assessment was conducted on segments of perfused intestine fixed immediately after removal from the abdomen in 2% glutaraldehyde in 0.05 M cacodylate buffer pH 7.3, and prepared for light and electron microscopy [3,10].

Statistical Analysis

Data were analyzed by either a one-way analysis of variance followed by Tukey's test for critical differences, or the Kruskal-Wallis test with multiple comparisons [13]. Treatments were contrasted against each other. The threshold of significance was set at $p < 0.05$.

RESULTS

1. Somatic Changes in Rats Given the Cathartic Solutions and their Controls

[a] Six-Day Experiments. The animals exposed for 6 days to either the PC, GA1 and GA2 solutions lost similar amounts of weight over that period (Table 1). In contrast, the CTL and CTL + GA rats gained weight, both at a comparable rate. Another significant difference among treatments was that all rats receiving the cathartic solution accumulated more fluid in

the cecum than the CTL and the CTL + GA groups. Moreover, rats that ingested GA with the cathartic (groups GA1 and GA2) presented with higher cecal contents than those rats that did not receive GA (PC), but their weight loss excluding the ceca was similar.

[b] Three-Day Experiments. Rats exposed to the same treatments for only 3 days showed a proportional change in weights, respect to the 6-day test, with all animals taking the cathartic mixture losing weight, regardless of the presence or absence of GA, while the CTL, as well as the CTL + GA, gained weight (Table 2). Similarly, fluid accumulation in the cecum was exacerbated in the cathartic groups.

2. GA as an Absorption Modifier during Jejunal Perfusions in Rats Given Cathartics

[a] Six-Day Experiments. There was increased net water absorption at the higher concentration of GA (20 g/L), in the presence of cathartics in the drinking fluid (Fig. 1). This effect was not shown in control rats. Actually all rats drinking cathartic solutions, either modified by GA nor not, exhibited higher net water absorption rates than the CTL or the CTL + GA. There was no difference between the two latter solutions. Addition of GA to water (CTL + GA group) did not alter water influx (Table 3). The addition of 10 g/L of GA (GA1) resulted in an increase in water influx over the rate observed in CTL rats. Potassium absorption exhibited little variation among groups. The major difference was that GA added to cathartic-containing solutions produced greater potassium absorption than when GA was added to plain water (Table 3).

Sodium absorption paralleled net water absorption (Fig. 2) in the finding of increased uptake of the electrolyte with the cathartics, and maximal values were achieved in the GA2 group. Addition of GA to water (CTL + GA) did not increase

Table 2. Somatic Changes and Cecum Weights in Rats Receiving Oral Fluid Treatments for 3 Days[†]

Treatment	Initial weight (g)	Final weight (g)	Weight changes (%)	Corrected body weight changes (%)	Cecum weight (% body weight)
PC (N)	109.7 ± 2.5 ^a (11)	97.0 ± 2.3 ^a (11)	-12.7 ± 1.2 ^a (11)	-6.1 ± 1.4 ^a (11)	6.22 ± 0.58 ^a (11)
GA1 (N)	108.7 ± 2.1 ^a (12)	95.3 ± 2.5 ^a (12)	-12.3 ± 1.3 ^a (12)	-7.6 ± 1.7 ^a (12)	5.73 ± 0.63 ^a (12)
GA2 (N)	111.7 ± 2.4 ^a (15)	100.9 ± 2.3 ^a (15)	-10.8 ± 0.8 ^a (15)	-3.9 ± 1.0 ^a (15)	6.65 ± 0.42 ^a (15)
CTL (N)	99.8 ± 5.4 ^a (11)	126.1 ± 6.3 ^b (11)	26.7 ± 0.9 ^b (11)	22.9 ± 0.9 ^b (11)	2.98 ± 0.24 ^b (11)
CTL + GA (N)	102.5 ± 3.2 ^a (11)	129.5 ± 3.6 ^b (11)	26.5 ± 1.2 ^b (11)	22.2 ± 1.1 ^b (11)	3.37 ± 0.20 ^b (11)

[†] Data represent the means ± SEM. Values in the same column not sharing superindexes are significantly different ($p < 0.05$).

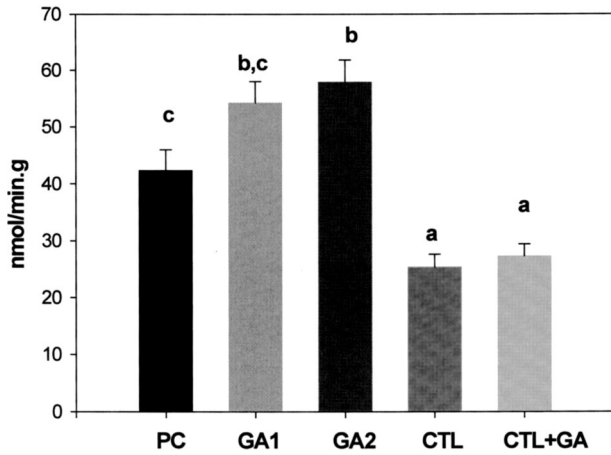


Fig. 1. Net water absorption rates in rats exposed for 6 days to either a cathartic mixture (PC), the same containing 10 g/L of GA (GA1), or 20 g/L GA (GA1). Control rats (CTL) were offered water, or water with 20 g/L GA (CTL + GA). Brackets represent the SEM. N = 14 for each group. The lettering on the bar signifies that those not sharing a letter are different ($p < 0.05$).

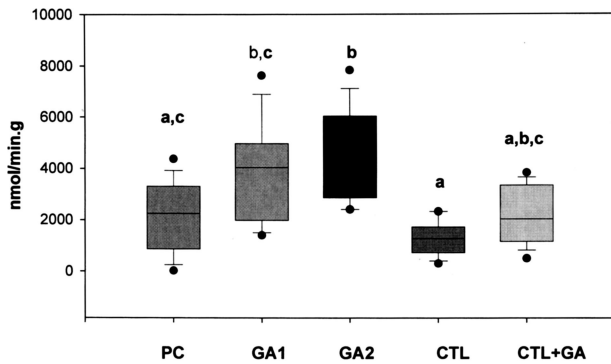


Fig. 2. Sodium absorption under conditions similar to those described under Fig. 1 and for the same treatment groups. The boxes and the error brackets show the median, the 25/75, and the 10/90 percentiles. Significance of differences is indicated as in Fig. 1. Each group had 13 rats.

this parameter. Glucose presented a pattern comparable to that of sodium and net water absorption (Fig. 3), that is, a trend to increase absorption when GA was added to either the cathartic (PC) drink or to water. Thus, the GA2 solution resulted in

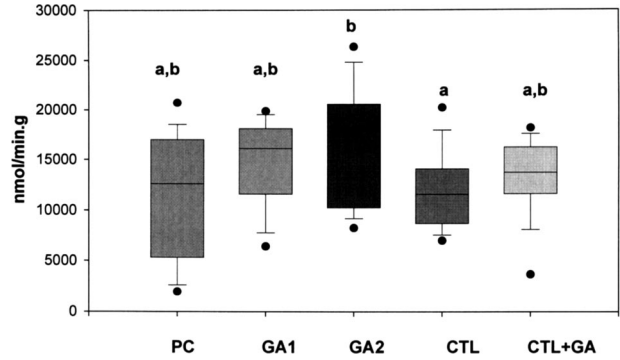


Fig. 3. Glucose absorption rates for rats subjected to the treatment described under Fig. 1 and represented as indicated in the legend of Fig. 2 with the same number of animals than the latter.

higher glucose absorption than the CTL, but it could not be differentiated from the CTL + GA.

[b] Three-Day Experiments. This shorter experimental period sufficed to establish differences between treatments with cathartics and controls, with or without the two concentrations of GA. This is in agreement with the known rapid changes occurring in rat weights when their solid food or fluid intake is altered. No differences within either the cathartic or the control sets could be attributed to GA (Table 2). The only differences were observed between the GA2 treatment and the CTL groups for net water absorption (Table 4).

3. NOS Data. Exposure to the cathartics produced an increase in intestinal mucosal NOS that was not altered by the presence of GA at either concentration in the cathartic mixture (Fig. 4). This was observed after 3 or 6-day long exposures. However, addition of GA to water in the CTL groups produced a reduction of mucosal NOS that was apparent as early as after 3 days and was similarly observed when treatments lasted for 6 days.

DISCUSSION

The results presented here are consistent with previous findings showing that GA has absorption enhancement properties. In this study this was demonstrated following ingestion of GA, concurrently with the cathartics magnesium citrate and

Table 3. Unidirectional Water Movement and Potassium Absorption in Rats Undergoing Oral Fluid Treatments for 6 Days[†]

Treatment	N	Water Influx [†] ($\mu\text{L}/\text{min} \cdot \text{g}$)	Water Secretion ($\mu\text{L}/\text{min} \cdot \text{g}$)	$J_{\text{in}}/J_{\text{eff}}$ (I/E) [‡]	Potassium ($\text{nmol}/\text{min} \cdot \text{g}$)
PC	16	$95.8 \pm 4.9^{\text{a,b}}$	$53.5 \pm 3.6^{\text{a}}$	$1.801 \pm 0.108^{\text{a,b}}$	$1,505 \pm 132^{\text{a,b}}$
GA1	13	$108.2 \pm 5.9^{\text{b}}$	$54.1 \pm 3.6^{\text{a}}$	$2.085 \pm 0.087^{\text{b}}$	$1,914 \pm 113^{\text{b}}$
GA2	14	$101.7 \pm 5.2^{\text{a,b}}$	$43.9 \pm 4.4^{\text{a}}$	$2.587 \pm 0.235^{\text{b}}$	$1,930 \pm 121^{\text{b}}$
CTL	14	$80.5 \pm 11.2^{\text{a}}$	$55.0 \pm 3.8^{\text{a}}$	$1.513 \pm 0.069^{\text{a}}$	$1,475 \pm 109^{\text{a,b}}$
CTL + GA	16	$81.8 \pm 3.8^{\text{a}}$	$54.3 \pm 4.2^{\text{a}}$	$1.569 \pm 0.085^{\text{a}}$	$1,224 \pm 88^{\text{a}}$

[†] Data represent the means \pm SEM.

[‡] The data of these columns were not normally distributed and were analyzed by the Kruskal-Wallis test. Values in the same column not sharing superindexes are significantly different ($p < 0.05$).

Table 4. Fluid Transport, Sodium, Potassium and Glucose Absorption in Rats Undergoing Oral Fluid Treatments for 3 Days[†]

Treatment	N	Net Water Absorption ($\mu\text{L}/\text{min} \cdot \text{g}$)	Water Influx ($\mu\text{L}/\text{min} \cdot \text{g}$)	Water Secretion ($\mu\text{L}/\text{min} \cdot \text{g}$)	$J_{\text{in}}/J_{\text{eff}}$ (I/E) [‡]	Sodium Absorption ($\text{nmol}/\text{min} \cdot \text{g}$)	Potassium Absorption [†] ($\text{nmol}/\text{min} \cdot \text{g}$)	Glucose Absorption ($\text{nmol}/\text{min} \cdot \text{g}$)
PC	12	$40.1 \pm 3.2^{\text{a,b}}$	$93.4 \pm 5.2^{\text{a}}$	$53.3 \pm 4.3^{\text{a}}$	$1.931 \pm 0.239^{\text{a}}$	$2,540 \pm 316^{\text{a}}$	$1,644 \pm 132^{\text{a}}$	$13,723 \pm 1433^{\text{a}}$
GA1	13	$43.0 \pm 3.6^{\text{a,b}}$	$102.4 \pm 6.4^{\text{a}}$	$59.4 \pm 5.2^{\text{a}}$	$1.781 \pm 0.082^{\text{a}}$	$2,712 \pm 416^{\text{a}}$	$1,863 \pm 155^{\text{a}}$	$15,065 \pm 1692^{\text{a}}$
GA2	14	$46.8 \pm 2.9^{\text{a}}$	$98.3 \pm 3.5^{\text{a}}$	$51.4 \pm 3.5^{\text{a}}$	$1.984 \pm 0.087^{\text{a}}$	$3,137 \pm 323^{\text{a}}$	$1,833 \pm 116^{\text{a}}$	$18,454 \pm 1088^{\text{a}}$
CTL	14	$32.0 \pm 4.3^{\text{b}}$	$81.5 \pm 5.7^{\text{a}}$	$49.5 \pm 4.6^{\text{a}}$	$1.763 \pm 0.131^{\text{a}}$	$2,484 \pm 260^{\text{a}}$	$1,695 \pm 170^{\text{a}}$	$15,893 \pm 1011^{\text{a}}$
CTL + GA	13	$38.3 \pm 2.9^{\text{a,b}}$	$96.6 \pm 5.9^{\text{a}}$	$58.3 \pm 5.7^{\text{a}}$	$1.754 \pm 0.110^{\text{a}}$	$2,187 \pm 245^{\text{a}}$	$1,968 \pm 197^{\text{a}}$	$17,691 \pm 1697^{\text{a}}$

[†] Data represent the means \pm SEM.

[‡] The data of these columns were not normally distributed and were analyzed by the Kruskal-Wallis test. Values in the same column not sharing superindexes are significantly different ($p < 0.05$).

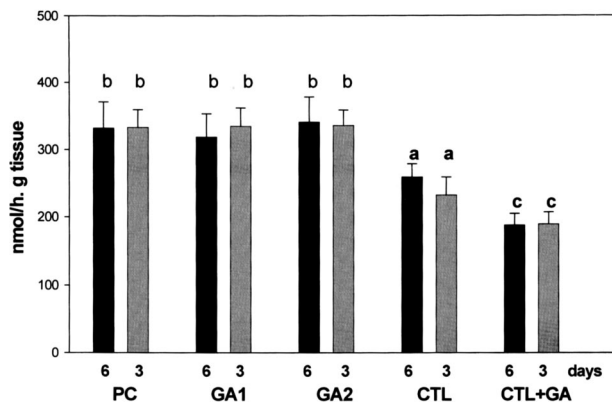


Fig. 4. NOS data for rats exposed for either 6 or 3 days to the treatments described under Fig. 1. N = 11–13 per group for the 6 day treatment; N = 9–12 per group for the 3 day treatment. Bars not labeled with the same letters are different ($p < 0.05$) signifying no differences between the PC, GA1 and GA2 groups, and higher activity than the CTL and CT + GA.

phenolphthalein, over a 6-day period, to induce intestinal dysfunction in rats. However, a concentration of GA as low as 10 g/L still increased the absorptive capacity of the small intestine. Doubling the concentration of GA had some effect on absorption, although it did not correct the exacerbation of NOS activity. The proabsorptive characteristics of GA do not make it an anti-diarrheal agent, but a potential adjuvant in maintaining nutrient absorption in intestinal dysfunction.

The results of jejunal perfusions after 6 days of oral intake of the various fluid preparations showing that the cathartic combination (PC) resulted in a greater water uptake than animals receiving no cathartics in their drinking water could be partly attributed to the technique used for the assessment, which pumps test solutions through an intestinal segment, albeit at a low speed to minimize hydrostatic pressure. Under these conditions, the tight junctions between epithelial cells may allow for a greater lumen-to-serosa transport. Nevertheless, since addition of GA at the higher of the two concentrations produced an extra increase of water and sodium absorption, and to a lesser extent, glucose absorption, this could be attributed to a specific effect of GA. Earlier studies have indicated that GA increases paracellular absorption, either by

decreasing the thickness of the unstirred layer and/or by reducing the surface tension of the luminal contents [10].

Since with shorter exposures to cathartics (3 days), with or without GA, the only changes were in net water absorption, it appears as if a time factor is operational in these experiments. The 6-day experimental period is consonant with earlier studies in our laboratory where generally rats were offered 5-day long treatments, and then perfused with isotonic solutions containing or omitting GA [3,14]. Presently, an additional day was added in order to compare with half that time in the 3-day exposure regimen.

It has been shown that cathartics disrupt the normal absorptive ability of the small intestinal mucosa as a consequence of increased NO production [15,16]. This was confirmed indirectly in this study by the NOS data that revealed consistently higher NOS activity in the PC, GA1 and GA2 groups as compared to the CTL and CTL + GA treatments. For this enzyme, NOS, a 3-day exposure to cathartics sufficed to make the change significant and 6-day treatments did not induce further changes. However, in the absence of cathartics NOS was partially inhibited by exposure to GA. This finding is in agreement with NOS inhibition *in vitro* by GA, as recently reported by our laboratory [8]. However, it is apparent that the presence of GA cannot fully offset the strong NOS-stimulatory action of cathartics. Earlier studies showing that intestinal perfusion of GA partially reversed the secretory effects of *V. comma* toxin [4] suggest that the chemically-induced stimulation of NOS is a more severe insult than the bacterial toxin, and that is not reversed by GA under conditions similar to the present experiments.

Proteoglycans such as GA have a structural relationship with plant-derived beta glucans. The latter have recently received increased attention in their capacity as immunomodulators and adjuvants to monoclonal antibodies [17]. Dietary beta-glucans have been shown to shift inflammatory profiles, *in vitro*, and in animal studies, provide an enhanced resistance against bacterial and parasitic infections [18]. On the other hand, since GA is essentially not absorbed in the small intestine, it may conceivably be either interacting with microfold (M) cells in the ileum, blocking the “sampling” of bacteria by

small intestinal dendritic cells, or also preventing their adherence, and triggering the transcription of pro-inflammatory genes [19,20].

Clinical trials in the use of non-digestible carbohydrates for the treatment of infantile diarrhea had mixed outcomes. A proprietary hydrolyzed form of guar gum, which per se is poorly soluble, improved the outcome of diarrhea when given to young children either in an ORS, or with a triturated chicken diet [21,22]. In contrast, a complex mixture of non-digestible, soluble and insoluble carbohydrates, including less than one-fifth of GA (final concentration ± 2 g/L of GA) was ineffective as a therapeutic additive to alter the course of infantile diarrhea [23]. The latter approach was based on the rationale that short-chain fatty acids produced by fermentation in the colon would have beneficial effects. This premise was not supported.

However, the potential of a non-absorbable natural substance such as GA to act as a modulator of the immune response, as much as an absorption coadjuvant, merits to be further evaluated. The safety, solubility, price accessibility and taste acceptance of this type of substances militates in its favor and offers advantages that remain yet to be fully exploited.

REFERENCES

1. Wapnir RA, Teichberg S, Go JT, Wingertzahn MA, Harper RG: Oral rehydration solutions: enhanced sodium absorption with gum arabic. *J Am Coll Nutr* 15:377–382, 1996.
2. Wapnir RA, Wingertzahn MA, Moyses J, Teichberg S: Gum arabic promotes rat jejunal sodium and water absorption from oral rehydration solutions in two models of diarrhea. *Gastroenterology* 112:1979–1985, 1997.
3. Teichberg S, Wingertzahn MA, Moyses J, Wapnir RA: The effect of gum arabic in an oral rehydration solution on recovery from diarrhea in rats. *J Pediatr Gastro Nutr* 29:411–417, 1999.
4. Turvill JL, Wapnir RA, Wingertzahn MA, Teichberg S, Farthing MJG: Cholera toxin-induced secretion is reduced by a soluble fiber, gum arabic. *Dig Dis Sci* 45:946–951, 2000.
5. Wingertzahn MA, Teichberg S, Wapnir RA: Role of nitric oxide and gum arabic in the regulation of intestinal absorption of water and sodium. In Arnaud MJ (ed): “Hydration Throughout Life.” Montrouge, France: John Libbey Eurotext, pp 199–204, 1998.
6. Anderson DM: Evidence for the safety of gum arabic (*Acacia senegal* [L.] [Wild.]) as a food additive—a brief review. *Food Addit Contam* 3:225–230, 1986.
7. Wingertzahn MA, Teichberg S, Wapnir RA: Jejunal nitric oxide (NO) levels are reduced by gum arabic (GA). *J Am Coll Nutr* 17:509, 1998.
8. Rehman KU, Codipilli CN, Wapnir RA: Modulation of small intestinal nitric oxide synthase by gum arabic. *Exper Biol Med* 229:895–901, 2004.
9. Wingertzahn MA, Teichberg S, Wapnir RA: Stimulation of non-sodium dependent water, electrolyte and glucose transport in rat small intestine by gum arabic. *Dig Dis Sci* 46:1105–1112, 2001.
10. Rehman KU, Wingertzahn MA, Teichberg S, Harper RG, Wapnir RA: Gum arabic (GA) modifies paracellular water and electrolyte transport in the small intestine. *Dig Dis Sci* 48:755–760, 2003.
11. Wapnir RA, Wingertzahn MA, Teichberg S: L-arginine in low concentration improves rat intestinal water and sodium absorption from oral rehydration solutions. *Gut* 40:602–607, 1997.
12. Hevel JM, Marletta MA. Nitric oxide synthase assays. *Meth Enzymol* 233 (Part C): 250–258, 1994.
13. Zar JH: “Biostatistical Analysis,” 2nd ed. Englewood Cliffs: Prentice-Hall, pp 185–205, 1984.
14. Wingertzahn MA, Teichberg S, Wapnir RA: Modified starch enhances absorption and accelerates recovery in experimental diarrhea in rats. *Pediatr Res* 45:397–402, 1999.
15. Gaginella TS, Mascolo N, Izzo AA, Autore G, Capasso F: Nitric oxide as a mediator of biscacodyl and phenolphthalein laxative action: induction of nitric oxide synthase. *J Pharmacol Exp Ther* 270:1239–1245, 1994.
16. Izzo AA, Gaginella TS, Mascolo N, Capasso F: Nitric oxide as a mediator of the laxative action of magnesium sulfate. *Br J Pharmacol* 113:228–232, 1994.
17. Hong F, Hansen RD, Yan J, Allendorf DJ, Baran JT, Ostroff GR, Ross GD: Beta-glucan functions as an adjuvant for monoclonal antibody immunotherapy by recruiting tumoricidal granulocytes as killer cells. *Cancer Res* 63:9023–2031, 2003.
18. Plat J, Mensink RP: Food components and immune function. *Curr Opin Lipidol* 16:31–37, 2005.
19. Sansonetti PJ: War and peace at mucosal surfaces. *Nature Rev Immunol* 4:953–964, 2004.
20. Rescigno M, Chieppa M: Gut-level decisions in war and peace. *Nature Med* 11:254–255, 2005.
21. Alam NH, Meier R, Schneider H: Partially hydrolysed guar gum-supplemented oral rehydration solution in the treatment of acute diarrhoea in children. *J Pediatr Gastro Nutr* 31:503–507, 2000.
22. Alam NH, Meier R, Sarker SA, Bardhan PK, Schneider H, Gyr N: Partially hydrolysed guar gum supplemented comminuted chicken diet in persistent diarrhoea: a randomized controlled trial. *Arch Dis Child* 90:195–199, 2005.
23. Hoekstra JH, Szajewska H, Abu Zikri M, Micetic-Turk D, Weizman Z, Papadopoulou A, Guarino A, Dias A, Oostvogels B: Oral rehydration solution containing a mixture of non-digestible carbohydrates in the treatment of acute diarrhea: a multicenter randomized placebo controlled study on behalf of ESPGHAN working group on intestinal infections. *J Pediatr Gastro Nutr* 39:239–245, 2004.

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