Cellulose Derivatives and Intestinal Absorption of Water and Electrolytes: Potential Role in Oral Rehydration Solutions (44139)

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Abstract. **The physicochemical and structural characteristics of several types of carboxymethylcellulose (CMC) and of methylcellulose (MC) were examined in relation to their capacity to modify water and sodium absorption in oral rehydration solutions (ORS) at various concentrations, using a jejunal perfusion procedure in rats. Comparison of intrinsic low-viscosity CMC of various degrees of substitution (DS) revealed that net water absorption increased as the DS was augmented. A stimulatory effect on sodium absorption occurred only at a low (2.5 g/l) CMC concentration. With products of medium DS, stimulation of net water and sodium absorption was observed only with low-viscosity CMC at 2.5 g/l, but not at 5.0 g/l. In perfusions with CMC of medium and high DS there was a reduction of water and sodium absorption, ultimately resulting in net sodium secretion with 5.0 g/l high-DS CMC. MC perfused at 5.0 or 10.0 g/l reduced net water absorption and reversed sodium transport from absorptive to secretory status. These results show that while low-viscosity-grade, low-DS CMC in low concentrations may facilitate solute uptake and concurrent water absorption from ORS by the jejunum, high intrinsic viscosity and possible chemical interaction of solutes with the modified celluloses tend to block water uptake and produce fluid stasis and electrolyte secretion. Thus, the data suggest that only certain types of CMC may be proabsorptive when added to ORS, while high-viscosity and high-DS CMC or MC induce electrolyte malabsorption and eventual catharsis.**

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In previous studies we showed that carboxymethylcellulose (CMC) of medium viscosity improved net water and sodium absorption when added to oral rehydration solutions (ORS) in small intestinal perfusions of healthy rats and animals with chronic osmotic diarrhea (1) or malnutrition (2). In those studies, relative viscosity (η) appeared to be linked to the rehydrating effectiveness of the preparations. Subsequent work in our laboratory with other vegetable fibers, such as guar gum (GG) (3) and gum arabic (4), showed that an increased η was not an indispensable condition for the enhancement of water and sodium absorption. Differences in chemical composition, including identity of the monomers, chain length, and branching degree of the polymers, could possibly explain the divergency in results.

The present study was intended to clarify systematically the role of inherent viscosity, as determined by chain length, and degree of substitution (DS), an index of the extent of carboxymethylation of cellulose, on the improvement of water and solute absorption from a standard ORS. We used a one-pass *in vivo* jejunal perfusion system to assess the effectiveness of five types of CMC differing in their inherent viscosity and DS. We also evaluated methylcellulose (MC), which is chemically related and produces concentration dependent solutions with $\eta > 1$. Overall, our data indicate that for low-viscosity CMCs there is a positive relationship between DS and the rates of water and sodium

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absorption. By contrast, at a given DS there is an inverse relationship between increasing η and water and sodium absorption. In addition, chemically related MC has a concentration-dependent negative effect on these two parameters.

Materials and Methods

Intestinal Perfusion Procedure. Perfusions were conducted on male Sprague-Dawley rats (Harlan-Sprague-Dawley, Indianapolis, IN), weighing 80–100 g. The animals were allowed to acclimatize for at least 48 hr in the institutional animal facility prior to laparotomy. The perfusions were carried out after an overnight fast. A segment of the jejunum (18–36 cm), just beyond the duodenum, was cannulated with polyethylene tubing under urethane anesthesia (1.3 g/kg ip). The solutions were prewarmed so they reached the jejunum at body temperature, and were delivered with a peristaltic pump (Model 1203; Harvard Instruments, Boston, MA) at a rate of 10–12 ml/hr. Groups of 12 rats were simultaneously perfused, and two or three solutions were tested on the same day. Each rat was perfused with only one solution. After 1 hr of equilibration at the normal pumping rate, perfusates were collected for eight 15-min periods and analyzed for net water absorption; unidirectional fluid movement; sodium, potassium, and calcium transport; and glucose absorption. At the end of the experiments, the rats were sacrificed by exsanguination from the abdominal aorta. The total number of rats used for each treatment is specified in the tables and figures. Other details have been published earlier (1, 2, 4). The protocol was approved the Institutional Animal Care and Utilization Committee.

Solutions Perfused and Chemicals. The basal ORS contained sodium chloride (60 m*M*) and trisodium citrate (10 m*M*), making a total sodium concentration of 90 m*M;* potassium chloride (20 m*M*); and glucose (111 m*M* = 20 g/l). Tritiated water (^3H_2O, 2 μCi/l = 74 MBq/l; NEN-Dupont, Boston, MA) was added to the luminal perfusion solutions to estimate water influx [J_{in}] from lumen to serosa. The varieties of CMC tested were a gift of Akzo Nobel Chemicals (Amersfoort, The Netherlands). These products were described as food grade Akucell with three levels of carboxymethylation, or DS. CMC is manufactured with a DS range from 0.5 to 1.2. The theoretical maximum value is 3. The viscosity grade, determined by the chain length, was assigned by the manufacturer. MC and other chemicals were purchased from Sigma Chemical Co. (St. Louis, MO) and Fisher Scientific (Pittsburgh, PA). Commercial MC has a mean methoxyl content of 29% with a DS of 1.8 (5).

Physicochemical Characteristics of the Solutions. η of the solutions was determined in the laboratory with a Brookfield Viscometer (Model DV-I; Stoughton, MA) and expressed as a relative value against the basal ORS. These figures are presented in Tables I and IV. Osmolality (Wescor vapor pressure osmometer, Model 5500; Logan, UT) was unaffected by the additives and had a mean value of 310 ± 5 mOsm/kg.

Assays and Calculations. Sodium content of CMC was determined by testing the amount of sodium solubilized by water and the total sodium released by treating CMC with a 36 *N* sulfuric acid: 15.5 *N* nitric acid mixture (85:15). Sodium was assayed by atomic absorption spectrophotometry (Spectr AA 10; Varian Instruments Inc., Sunnyvale, CA). The actual inflow ratio was determined gravimetrically before the start and at the end of the perfusion. Each fraction collected was weighed to compute net water absorption, as indicated below. The following formulas were used to compute absorption rates:

$$\text{Net Water Absorption} = \frac{(\text{Inflow Rate} - \text{Outflow Rate}) \times 1000}{I.L.},$$

and

$$J_{in} = \frac{(^3H_2O \text{ dpm ORS} \times \text{Inflow Rate}) - (^3H_2O \text{ dpm sample} \times \text{Outflow Rate}) \times 1000}{^3H_2O \text{ dpm ORS} \times I.L.},$$

where *I.L.* is intestinal length (in cm), net water absorption and [J_{in}] are in μl/min × cm, and inflow and outflow rates are in ml/min.

Water secretion (serosa-to-mucosa efflux) ([J_{eff}]) was calculated by difference between [J_{in}] and net water absorption. The [J_{in}]/[J_{eff}] ratios presented in Tables II, III, and IV were obtained from the values calculated for each rat. Results were expressed as the mean ± SEM.

Statistics. For transport studies, the differences among groups was assessed by the Kruskal-Wallis test followed by nonparametric multiple contrasts (6). Trends were assessed by a Wilcoxon-type test (7). The threshold of significance was 0.05.

Results

Contribution of Sodium to the Perfusates. The sodium content of the various CMC tested, as determined by release into water (soluble sodium) and extraction by acid digestion (total sodium), is presented in Table I. The amount of sodium contributed by CMC did not significantly affect the actual sodium concentration measured in the ORS. Table I also lists η of the modified ORS tested using the CMC-free ORS as the reference value (1.0).

Effect of CMC as a Function of DS. The products manufactured as low viscosity grade were assessed at 3 DS. Figure 1A shows that net water absorption increased with the addition of either 2.5 or 5.0 g/l of CMC of medium or high DS. At 5.0 g/l, net water absorption with CMC of high DS was greater than with the low-DS CMC. Low-viscosity-grade CMC, with low DS, did not alter net water absorption. As shown in Table II, the positive trend relating DS and net water absorption rates, as presented in Figure 1A, was significant (Cuzick's test [7]: $Z = 1.804$, $P = 0.0356$, one

Table I. Concentration of Soluble and Total Sodium, and Actual Sodium Concentration of the CMC Products and ORS Tested

CMC type		Soluble sodium CMC (mg/g)	Total sodium CMC (mg/g)	Actual sodium in ORS (m*M*)	η
No CMC		—	—	89.3 ± 1.5	1.0
LV-LDS	(2.5 g/l)	34	64	91.1 ± 2.4	2.8
	(5.0 g/l)			91.0 ± 3.5	7.0
LV-MDS	(2.5 g/l)	45.6	72	86.3 ± 1.6	2.8
	(5.0 g/l)			88.6 ± 0.5	7.7
LV-HDS	(2.5 g/l)	53	110	92.2 ± 6.3	2.8
	(5.0 g/l)			89.7 ± 0.8	5.6
MV-MDS	(2.5 g/l)	35	85	87.9 ± 1.0	5.6
	(5.0 g/l)			85.2	13.3
HV-MDS	(2.5 g/l)	38	85	90.1 ± 1.6	28.0
	(5.0 g/l)			92.2 ± 5.2	74.1

Note. Data are mean ± SEM. LV, low viscosity; MV, medium viscosity; HV, high viscosity; LDS, low degree of substitution; MDS, medium degree of substitution; HDS, high degree of substitution.

tailed). This stimulatory effect on net water absorption was reflected in the steady rise of the $[J_{in}]/[J_{eff}]$ ratio as DS increased, both at 2.5 and at 5.0 g/l ($Z = 2.021$, $P = 0.0216$, one-tailed for 2.5 g/l; $Z = 2.810$, $P = 0.0025$, one-tailed, for 5.0 g/l). Changes in water $[J_{in}]$ were less informative. However, high-DS CMC at 5.0 g/l had a significantly lower serosa-to-mucosa $[J_{eff}]$ than controls. At 5.0 g/l CMC, both the $[J_{in}]$ and $[J_{eff}]$ of low-DS CMC were lower than the values obtained with 2.5 g/l. With all three DS levels, sodium transport stimulation only paralleled net water absorption changes at the lower concentration of CMC (2.5 g/l) (Fig. 1B). In contrast, at 5.0 g/l a reduction below control rates with the high-DS CMC was observed.

Effect of CMC as a Function of Inherent Viscosity. Net water and sodium absorption declined as the viscosity grade of CMC increased from low to high, at a constant (medium) DS (Fig. 2). The progressive decline in net water absorption was clearly observed with the 5.0 g/l CMC concentration. Addition of 2.5 g/l CMC produced a stimulatory effect only in low-viscosity CMC, but a reduction in net water absorption with medium- and high-viscosity products (Fig. 2A). Sodium transport was comparably affected by the viscosity grade (Fig. 2B): there was a transport increase with 2.5 g/l low-viscosity CMC, but medium and high-viscosity-grade CMC caused a very significant decrease in sodium absorption. At 5.0 g/l, the high-viscosity-grade CMC produced sodium secretion.

The worsening net water absorption values with 2.5 g/l and medium- and high-viscosity CMC was associated with a greater water $[J_{eff}]$ and therefore smaller $[J_{in}]/[J_{eff}]$ ratios (Table III). At the high CMC concentration (5.0 g/l), both $[J_{in}]$ and the $[J_{eff}]$ decreased with medium- and high-DS products; however, $[J_{in}]$ fell to a greater extent than $[J_{eff}]$. The increased net water absorption in low-viscosity CMC at 2.5 g/l appeared due to a greater water $[J_{in}]$ without alteration of $[J_{eff}]$.

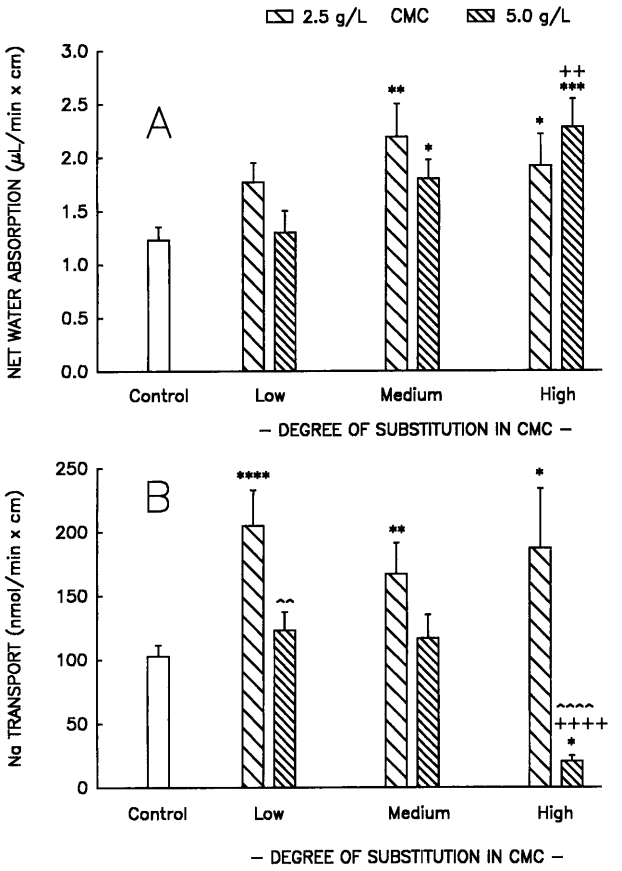

Figure 1. (A) Net water absorption rates during perfusions with low-viscosity-grade CMC of either low, medium, or high degree of substitution (DS). (B) Sodium transport rates under the same conditions. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$ versus controls. $^{++}P < 0.01$; $^{++++}P < 0.0001$ compared with low DS of the same concentration. $^{\wedge\wedge}P < 0.01$; $^{\wedge\wedge\wedge\wedge}P < 0.0001$ versus the same type of CMC at 2.5 g/l. The brackets indicate the SEM. The number of rats per group is indicated in Table II.

Absorption of Water and Solutes in the Presence of MC. As MC concentration increased, the absorption rates for net water and sodium progressively decreased and became significantly lower than controls when either 5.0 or 10.0 g/l MC was added. At these concentrations sodium movement became secretory. The η of the MC containing ORS steadily increased with concentration, but, similarly to CMC (Table I), it did not exhibit colligative properties (Table IV). The decreasing rate of net water absorption was concomitant with a diminishing $[J_{in}]/[J_{eff}]$ ratio. The $[J_{in}]/[J_{eff}]$ ratios for 5.0 and 10.0 g/l MC were significantly lower than those obtained with the basal ORS. This finding appeared to be due to an increasing trend of $[J_{eff}]$, which correlated with the log of η.

Discussion

The experiments conducted were primarily intended to examine further the potential role of modified celluloses as enhancers of sodium and water absorption when added to ORS, and to determine what relationship might exist among chemical composition, physicochemical properties, and

Table II. Unidirectional Water Movement in ORS Containing Low-Viscosity CMC of Various Degrees of Substitution (DS)

	Control	CMC concentration (g/l)					
		2.5			5.0		
		Low DS	Medium DS	High DS	Low DS	Medium DS	High DS
$[J_{in}]$ (µl/min × cm)	4.95 ± 0.30	6.36 ± 0.70	5.98 ± 0.35[a]	5.50 ± 0.61	4.36 ± 0.36[b]	5.79 ± 0.28[c]	4.89 ± 0.14
$[J_{eff}]$	3.72 ± 0.26	4.74 ± 0.69	3.80 ± 0.18	3.58 ± 0.48[c]	3.10 ± 0.22[b]	3.99 ± 0.19[c]	2.89 ± 0.11[d]
$[J_{in}]/[J_{eff}]$	1.43 ± 0.06	1.41 ± 0.08	1.63 ± 0.09	1.69 ± 0.13	1.44 ± 0.08	1.56 ± 0.11	1.81 ± 0.11[c,d]
(*n*)	(11)	(7)	(8)	(8)	(7)	(7)	(7)

Note. Data are mean ± SEM. The $[J_{in}]/[J_{eff}]$ averages in the table are derived from the mean $[J_{in}]/[J_{eff}]$ ratios for each rat.
[a] $P < 0.05$.
[b] $P < 0.01$ compared with same type CMC, 2.5 g/l.
[c] $P < 0.05$ compared with same concentration low DS.
[d] $P < 0.01$ versus control.

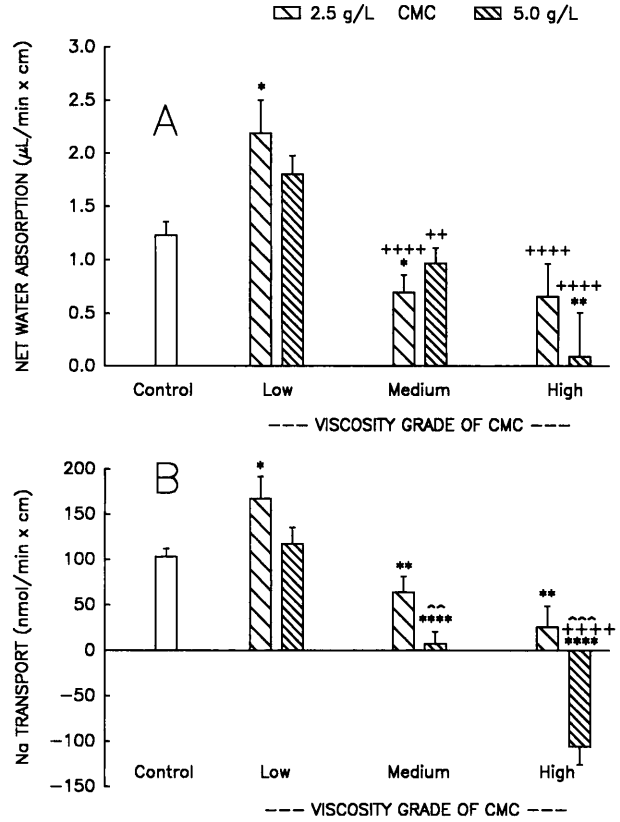

Figure 2. (A) Net water absorption rates during perfusions of medium-DS CMC of three viscosity grades. (B) Sodium absorption rates under the same conditions. The remaining features of the graph are similar to those of Figure 1. The number of animals per group is that listed in Table III.

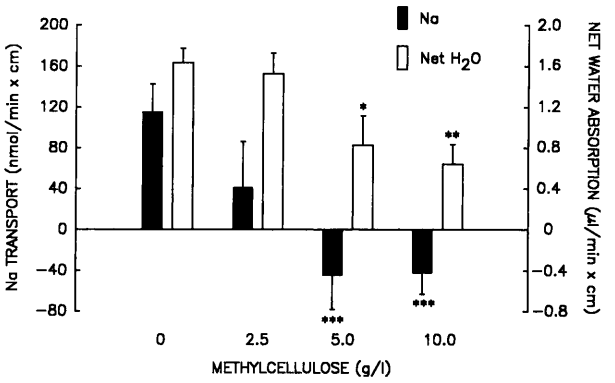

Figure 3. Net water absorption and sodium transport rates of rats perfused with methylcellulose (MC) in the concentrations indicated in the graph. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ versus ORS without MC. The number of rats per group is the same as that of Table IV.

physiologic response. The results reported here show a complex relationship between relative viscosity η and chemical characteristics of solutions presented to the jejunum regarding absorption capacity for water and solutes. The data show that among low-inherent-viscosity CMC products net water absorption improved as the DS of the CMC increased to a medium or high level. Regarding sodium absorption, CMC concentration and its DS were interactive. Only a CMC with a low viscosity grade and medium DS was proabsorptive. The value η of the ORS containing these types of CMC was not a predictive factor. By contrast, MC unequivocally reduced fluid and sodium absorption at concentrations >2.5 g/l.

Cellulose chain length determines the viscosity grade of CMC and MC. Polarity, which is lower when cellulose substituents are methyl groups, i.e. in MC, as compared with carboxymethyl, as in CMC, also alters the response of the intestinal epithelium. In general, increasing the relatively hydrophyllic carboxymethyl residues on CMC had a positive effect of water and sodium absorption. DS appears to be an important variable to be taken into account because CMC products can be manufactured in a variety of substitution levels for a variety of pharmaceutical and industrial applications. Since there is a vast number of possible combinations of chain length and DS, extremely variable physiologic results can be obtained with CMC if the chemical characteristics of the products are not taken into consideration. MC, with a large number of comparatively hydrophobic methyl substituents, is not an additive to enhance water and sodium absorption.

The mechanisms for the very significant reduction of water absorption rates by MC and long chain, high-viscosity-grade CMC may be linked to one or several of the

Table III. Unidirectional Water Movement in ORS Containing CMC of Various Viscosity Grades and Medium Degree of Substitution (DS)

	Control	CMC concentration (g/l)					
		2.5			5.0		
		Low viscosity	Medium viscosity	High viscosity	Low viscosity	Medium viscosity	High viscosity
$[J_{in}]$ (µl/min × cm)	4.95 ± 0.30	5.99 ± 0.35[a]	5.25 ± 0.20	5.50 ± 0.61	5.79 ± 0.28	4.15 ± 0.31[c,d,i]	2.83 ± 0.23[e,f,i]
$[J_{eff}]$	3.72 ± 0.26	3.80 ± 0.18	4.56 ± 0.12[b]	4.48 ± 0.20[a,g]	3.99 ± 0.19	3.19 ± 0.24[e,g]	2.70 ± 0.35[a,e,h]
$[J_{in}]/[J_{eff}]$	1.43 ± 0.06	1.63 ± 0.09	1.17 ± 0.04[b,f]	1.19 ± 0.08[b,c]	1.56 ± 0.11	1.35 ± 0.07[d]	1.18 ± 0.14[g]
(*n*)	(11)	(8)	(8)	(8)	(7)	(11)	(8)

Note. Data are mean ± SEM. The $[J_{in}]/[J_{eff}]$ averages in the table are derived from the mean $[J_{in}]/[J_{eff}]$ ratios for each rat.
[a] $P < 0.05$; [b] $P < 0.01$; [i] $P < 0.0001$ versus control. [c] $P < 0.001$; [f] $P < 0.0001$; [g] $P < 0.05$; [h] $P < 0.01$, compared with low viscosity grade of the same concentration.
[d] $P < 0.05$; [e] $P < 0.0001$, compared with 2.5 g/l same type CMC.

Table IV. Unidirectional Water Fluxes and Glucose Absorption in Perfusions with or without MC

	Methylcellulose (g/l)			
	0	2.5	5.0	10.0
η	1.0	2.7	6.0	32.2
$[J_{in}]$ (µl/min × cm)	5.86 ± 0.42	5.57 ± 0.41	5.39 ± 0.58	5.59 ± 0.73
$[J_{eff}]$	4.22 ± 0.34	4.04 ± 0.37	4.56 ± 0.393	4.95 ± 0.71
$[J_{in}]/[J_{eff}]$	1.43 ± 0.04	1.47 ± 0.12	1.20 ± 0.07[a]	1.20 ± 0.06[b]
(*n*)	(10)	(7)	(7)	(8)

Note. Data are mean ± SEM. The $[J_{in}]/[J_{eff}]$ averages in the table are derived from the mean $[J_{in}]/[J_{eff}]$ ratios for each rat.
[a] $P < 0.05$; [b] $P < 0.01$ vs 0 g/l MC.

following factors: (i) expansion of the unstirred layer because of interaction between the glycocalyx and the hydrated fiber (8); (ii) progressive obstruction of water channels (9); (iii) net sodium losses due to blockage at the brush border of sodium-dependent glucose transport sites. The interaction of CMC with the glycocalyx was documented by electron microscopy in a previous study (1) under proabsorptive conditions. It is possible that access to water channels can be partially blocked by hydrated macromolecules. It is also conceivable that glucose-driven sodium transport is impaired due to the progressive adsorption of the electrolyte to the fiber as the concentration of the latter is increased in the perfusates. In consequence, sodium absorption may be reduced, or net outflow of the ion into the lumen may occur.

High-DS CMC contains a greater number of carboxymethyl groups than low and medium DS; this structural change may alter the chemical gradient of sodium at the intestinal lumen or act as an ion exchanger during intestinal transit. An increased DS appears to have a favorable connotation with low-viscosity-grade CMC as a proabsorptive modifier. Conversely, at constant DS, a higher η value adversely affects water and electrolyte absorption due to the possible mechanisms previously outlined.

The negative impact of high DS on sodium transport is only apparent beyond a threshold concentration, which in these experiments is 2.5 g/l. A comparable negative dose-response was obtained in a preceding study with GG (3), in which we observed sodium secretion when a 10.0 g/l addition of this vegetable fiber was tested under similar conditions, in contrast to a CMC-containing ORS with the same η which was proabsorptive. Those experiments revealed that η should not be considered an overriding factor in determining fluid and electrolyte transport in rat jejunum.

The discrepancy in the changes of sodium and water absorption from ORS with CMC of different DS, and containing a relatively high concentration of glucose, as in the ORS used in these experiments, may also be linked to the putative role of glucose transporters as water channels (10, 11). Although only a fraction of glucose absorption in rat jejunum is paracellular (12), this route may be of importance, as glucose is transported surrounded by water molecules. This movement of solute could result in high net water absorption even with a frankly secretory sodium balance.

MC is unquestionably not an absorption enhancer; it functions as a bulk cathartic and, as such, has found a well-defined niche in fiber-based laxative products (13, 14). It deserves to be noted that MC at 5.0 g/l acts similarly to high-viscosity-grade, medium-DS CMC, also at 5.0 g/l. However, at identical concentration, MC is one order of magnitude less viscous than that type of CMC, which offers an organoleptic advantage. Since the DS of commercial MC is higher than that of any of the CMC tested, this feature and the lower polarity of the methyl group substituents may explain its antiabsorptive effects.

The intestinal absorption of modified celluloses is extremely low. Several of these substances have been long used as stool bulk generators and have an excellent records in terms of toxicity, mutagenicity, and carcinogenicity (13, 15). However, there is very limited previous information regarding the relationship between chemical structure and physiologic effects for semisynthetic fibers, such as CMC, as well as for vegetable gums. Many types of soluble fiber are extensively used in the food industry and, pharmacologically, in the modification of carbohydrate absorption for the dietary control of Type II diabetes (16). Much of the assessment of these products has been empirical, without appropriate consideration of their potential impact on fluid and electrolyte balance.

In summary, absorptive enhancement conditions—the goal of ORS—may be feasible only for certain types of CMC whose physicochemical characteristics favor brush border uptake by greater accessibility to the epithelium, as shown in preceding studies (1, 2). The vast array of potential varieties of CMC demands caution in selecting a specific type for a pharmacologic goal on intestinal function.

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