Decreased Basal and n-Butyrate Stimulated Colonic Water and Electrolyte Transport in the Pre- and Postnatal Malnourished Rat

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Abstrak

Telah dilakukan penelitian perfusi kolon in vivo pada 2 kelompok tikus berumur 10 minggu : (1) kontrol, yang diberi makan ad libitum; (2) malnutrisi, yang diberi makan terbatas (50% kontrol) sejak pranatal. Tikus malnutrisi mempunyai berat badan, panjang, berat serta luas permukaan kolon yang lebih rendah dibanding kontrol. Absorpsi air (104,2 ± 14,6 μl/min/g), natrium (20,3 ± 3,2 μmol/min/g) dan klorida (0,21 ± 0,04 μmol/min/g) serta sekresi kalium (-23,2 ± 2,8 μmol/min/g) pada tikus malnutrisi ternyata hanya 50-67% dari nilai kontrol. Penabahan n-butirat menimbulkan peningkatan transport air dan elektrolit pada kedua kelompok, tetapi derajat peningkatan tersebut kurang pada kelompok malnutrisi dibandingkan kontrol (air: 36% vs 22%; natrium: 64% vs 32%; klorida: 58% vs 27%; kalium: 53% vs 26%). Aktivitas enzim Na, K-ATPase pada mukosa kolon yang malnutrisi hanya 35% dari nilai kontrol. Hasil penelitian ini menunjukkan bahwa gangguan utilisasi substrat dan menurunnya Na, K-ATPase agaknya berperan pada gangguan absorpsi air dan elektrolit pada tikus yang menderita malnutrisi kronis.

Abstract

To investigate possible functional changes in colonic water and electrolyte transport during malnutrition, we performed in vivo colonic perfusion studies in 2 groups of 10 weeks old rats: controls fed ad libitum, and experimental animals restricted to 50% of the control maternal and weanling intake. The nutritionally deprived animals had lower body weights, colonic lengths, weights and surface areas than controls. The net absorption of water (104.2 ± 14.6 μl/min/g), sodium (20.3 ± 3.2 μmoles/min/g) and chloride (0.21 ± 0.04 μmoles/min/g) as well as potassium secretion (-23.2 ± 2.8 μmoles) of malnourished animals were 50-67% those of control animals. Addition of n-butyrate increased water and electrolyte transport in both groups, but to a much lesser extent in malnourished animals, increases in control vs malnourished animals were respectively (water: 36% vs 22%; sodium: 64% vs 32%; chloride: 58% vs 27%; potassium: 53% vs 26%). The activity of Na, K-ATPase in the colonic mucosa of malnourished rats was only 35% of control values. The findings suggest that impaired substrate utilization and decreased Na, K-ATPase activity may play a role in the impaired colonic water and electrolyte transport in chronically malnourished rats.

Keywords : Electrolyte transport, Water transport, Colon, Malnutrition, Short chain fatty acids.

INTRODUCTION

The colonic mucosa derives much of its energy from the catabolism of luminally derived substrate, primarily the bacterially produced short chain fatty acids (SCFA), e.g. butyrate, acetate, and propionate.[1] Since sodium absorption in the colon is an energy requiring process mediated by Na,K-ATPase[2,3], altered energy production in the colonic mucosa might affect water and electrolyte absorption. This has been suggested experimentally by studies documenting decreased water and sodium absorption in isolated colon segments depleted of SCFA,[4] and has been discussed as a possible etiologic factor in the pathogenesis of malnutrition-associated diarrhea.[5] In a previous study, we found that chronic malnutrition resulted in decreased utilization of various fuels, including n-butyrate, by isolated rat colonocytes in vitro.[6] To our knowledge, no information is currently available regarding the effect of chronic malnutrition on water and electrolyte

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* *This work was done in International Intitute for Infant Nutrition and Gastrointestinal Disease, Children's Hospital of Buffalo, State University of New York, Buffalo, New York, U.S.A. and supported in part by a grant from the U.S. Agency for International Development (SPE-5940-A-00-4019-00).*

transport in the colon. The present study was designed to investigate the effect of chronic malnutrition on basal and n-butyrate stimulated colonic water and electrolyte transport, and colonic mucosal Na,K-ATPase activity in a previously established rat model of pre- and postnatal nutrient deprivation.[7]

MATERIALS AND METHODS

Animals

Female Sprague-Dawley rats (250-300 g) were bred to obtain timed pregnancies. The success of the breeding was determined by the presence of sperms in the vaginal smears on the following morning. This was then considered day 0 of pregnancy. The animals were housed individually with free access to water in a room maintained at constant temperature and humidity with a 12-h light-dark cycle.

Induction of malnutrition

Pre- and postnatal malnutrition were induced as previously described.[7] Briefly, on day 5 of pregnancy, female rats were divided into 2 groups: (a) control rats fed a standard laboratory diet (Purina Rat Chow, Ralson-Purina Co., St. Louis, MO) ad libitum throughout pregnancy and lactation; (b) malnourished rats fed 50% of the control intake (determined by the weight of food consumed by controls on the previous day) during pregnancy and lactation. At parturition, litter size was adjusted to 8 pups per litter. Pups were fed a diet weaned on day 21 of lactation. Pups from control dams were fed the same laboratory diet ad libitum until 10 weeks of age (control group). Pups from malnourished dams were limited to 50 % of the control intake of the previous day (malnourished group). Animals were weighed on a weekly basis. Colonic perfusion studies were undertaken at 10 weeks of age in both control and malnourished rats. In another series of animals not undergoing perfusion studies, the activity of Na, K-ATPase in the colonic mucosa was measured.

Perfusion technique

The perfusion technique described by Bright-Asare and Binder[8] was used. During the perfusion, the rat was anesthetized with intraperitoneal pentobarbital (30-50 mg/kg body weight). The colon was cannulated immediately distal to the ileo-cecal junction and reinserted into the abdomen. The colon was rinsed of its intestinal contents with warm Ringer's solution and a distal collection catheter tube was placed in the rectum 2-3 cm from the anus. The colon was perfused at a constant rate (0.5 ml/min) by a peristaltic perfusion pump (Masterflex Model 7014.20, Cole-Parmer Instrument Co., Chicago, IL). This perfusion rate was chosen for both control and malnourished animals since preliminary experiments had demonstrated no differences in net water and electrolyte fluxes among controls using 0.7 and 0.5 ml/min and among malnourished rats using 0.5 and 0.35 ml/min. The perfusion solution (Ringer's solution) contained 147 meq sodium (Na), 4 meq potassium (K), 2.3 meq calcium (Ca), and 155.6 meq chloride (Cl) per 1000 ml and had an osmolality of about 290 mosmoles/L. Polyethylene Glycol (PEG 4000, Sigma Chemical Co; 5 g/L) was added as a nonabsorbable marker. The body temperature of the rats was maintained at 37°C with a heating lamp. The perfusion solution was maintained at 38°C. After washing out the intestinal contents and discarding the first 30-min perfusate, the subsequent perfusate was collected in three 20-min periods. The mean result of these 3 collection periods was used to determine the rate of water, Na, K, Cl movement in each experimental group. A second perfusion study for evaluating the effect of SCFA on fluid and electrolyte movement was then performed by adding 10 mmoles/L n-butyrate to the perfusion solution. This concentration was chosen since preliminary studies had shown that water and electrolyte transport did not differ significantly using concentrations of 10, 20 and 30 mmoles/L of n-butyrate in the perfusion solution. The n-butyrate solution was perfused in a fashion identical to the control (Ringer's) solution. At the end of the experiment, the perfused colon segment was removed and its length was measured under 5 g of tension. The colon was opened longitudinally and the width was measured at 5 points to obtain the mean width. Surface area of the colon was calculated by multiplying the length and mean width of the colon. Finally, the colon was dried at 100°C to constant weight. All results were expressed as µl or µmoles/min per g colonic dry weight and µl or nmoles/min per cm2 colonic surface area.

Calculations

Net water transport was determined from changes in PEG concentrations using the following formula :[9,10]

Net water transport = PR (1 - PEGin/PEGeff) where PR is the perfusion rate in ml/min and PEGin and PEGeff are the concentrations of PEG in the infusion solution and the effluent collection, respectively.

Net ionic transport was calculated using the following formula :

Net ionic transport = PR [Iin - Ieff (PEGin/PEGeff)] where Iin and Ieff are the ionic concentrations (mmoles/L) in the infusion solution and the effluent, respectively.

Recovery of PEG

Initial studies were performed to validate the use of PEG as a nonabsorbable marker to quantitate water absorption and secretion. To check the steady state and the accuracy of taking effluent samples, following washing out the intestinal contents, the rat colons were perfused with Ringer's solution. The effusate collected in the first 30-min was discarded and the subsequent effusates were collected in nine 20-min periods; PEG, Na, K, and Cl were measured in each collection sample. Recovery studies of PEG were performed in both control and malnourished rats by a previously described method.[11] After rinsing out the colonic contents with warm Ringer's solution, the colon was perfused with Ringer's solution containing 5 g/L PEG for 60 min, followed by a second perfusion with Ringer's solution (without PEG) for another 60 min at the rate of 0.5 ml/min. The effluent was collected together with the colonic fluid content which was obtained by gently pressing the colon between two fingers to empty it at the end of the perfusion. The collection fluid was measured for volume, centrifuged (600 xg, 5 min) and used to determine the PEG concentration. PEG recovery was calculated by comparing the amount of PEG in the collection fluid with that in the initial perfusion solution.

Biochemical determinations

PEG was measured by the turbidimetric method of Hyden[12] as modified by Malawer.[13] The concentrations of Na and K in the intestinal fluids were determined by a Sodium/Potassium analyzer (Model 1020, Orion Research Inc, Boston, MA) and Cl was measured titrametrically (CMT 10 Chloride Titrator, Radiometer, Copenhagen, Denmark). The Na, K-ATPase activity was determined using Ottolenghi's method.[14] The mucosa was removed by gently scraping the colon with a glass slide and then homogenized with a cold buffer containing 250 mmoles/L sucrose and 30 mmoles/L histidine at 0°C. Each homogenate was diluted 1 : 250 with a solution containing 120 mmoles/L KCl, 5 mmoles/L $MgCl_2$, 30 mmoles/L histidine, 0.2 % bovine serum albumin and 3 mmoles/L adenosine 5'-triphosphate (vanadium free, Sigma Chemical Co., St. Louis, MO) at a pH of 7.4 in the presence and absence of 1 mmoles/L ouabain (Sigma). The solutions were incubated at 37°C for 15 min and the reactions were stopped by adding 500 µl of 10 % ice-cold trichloracetic acid and the cooling to 0°C.

Phosphate determinations were carried out in the resulting supernatants using Baginski's method.[15] The level of ouabain-insensitive Mg-adenosine triphosphatase (Mg-ATPase) was calculated as the amount of inorganic phosphate released per hour from the ouabain-treated sample. The amount of ouabain-sensitive Na, K-ATPase was calculated as the difference between the amount of inorganic phosphate released per hour from the total sample and the amount of inorganic phosphate released per hour from the ouabain-treated sample. The enzyme activities were related to the amount of protein in the homogenates.[16]

Statistics

Results were expressed as means ± S.D. Differences in mean values between two groups were evaluated by the Student's t-test with $p < 0.05$ considered significant.[17]

RESULTS

Recovery of PEG

PEG and ionic concentrations obtained during the subsequent 20- min periods did not differ by more than 10 %, indicating that a steady state had been achieved after the initial 30 min equilibration perfusion and that no significant deterioration of the colonic perfusion preparation had occurred. No differences in the recovery of PEG following perfusion were found between control and malnourished animals (Table 1).

Growth parameters

At 10 weeks of age, the mean body weight as well as mean colonic length, dry weight and surface area of malnourished rats were significantly lower than those of controls (Table 2). There was a strong positive correlation between colonic dry weight and surface area : $y = 18.5x - 163$, $r = 0,89$, $p < 0.001$ for controls and $y = 5.2x - 104$, $r = 0.94$, $p < 0.001$ for malnourished animals.

Water and electrolyte movement

Net water transport, net sodium and chloride absorption as well as net potassium secretion were significantly decreased in malnourished rats compared with controls following perfusion with Ringer's solu-

tion. Adding 10 mmoles/L n-butyrate to the perfusion solution increased all parameters in both groups, but the increase was significantly lower in malnourished than in control animals ($p < 0.01$). The results were consistent, whether related to colonic dry weight (Table 3) or colonic surface area (Table 4).

Colonic mucosal activities of Na, K-ATPase

The activity of Na, K-ATPase in the colonic mucosa of malnourished rats was reduced 65 % compared with controls (Table 5).

Table 1. Recovery of PEG following perfusion studies in control and malnourished rats in vivo[a]

		Effluent and colonic fluids			
Group	N	Volume recovered (ml)	PEG conc. (mg%)	PEG content (mg)	PEG recovery[b] (%)
Control	6	49.3 ± 1.5	294.7 ± 9.1	145.1 ± 2.7	96.7 ± 1.8
Malnourished	6	57.4 ± 0.4	250.3 ± 3.9	143.5 ± 2.0	95.7 ± 1.3

[a] After being rinsed clean with warm Ringer's solution, the colons were perfused with Ringer's solution containing 5 g/L PEG (polyethylene glycol 4000) for 60 min and thereafter with Ringer's solution (without PEG) for another 60 min at a rate of 0.5 ml/min. The total effluent and colonic contents were collected for measuring the volume and PEG concentrations. Values are expressed as means ± SD; n = number of animals.

[b] PEG recoveries were calculated by comparing the amount of PEG in the total effluent fluids and the initial amount of PEG perfused (150 mg).

Table 2. Effect of pre- and postnatal malnutrition on body weight, colonic length, dry weight and surface area in 10 week old rats.

Group	n	Body weight (g)	Colonic length (g)	Colonic dry weight (mg)	Colonic surface area (cm2)
Control	14	304 ± 25	21.3 ± 0.6	346.1 ± 36.8	27.6 ± 1.8
Malnourished	14	170 ± 10[a]	17.3 ± 0.7[a]	197.7 ± 11.0[a]	17.9 ± 2.0[a]

Values are expressed as mean ± SD; n = number of animals
[a]$p << 0.001$ compared with controls.

Table 3. Effect of malnutrition on net water, sodium, potassium and chloride movement during perfusion with Ringer's solution on Ringer's solution containing 10 mmoles/L n-butyrate in 10 week old rats.

	H_2O absorption (μl.min^{-1}.g^{-1})	Na absorption	Cl absorption (μmoles.min^{-1}.g^{-1})	K secretion
Controls (n = 8)				
Ringer's solution	206.7 ± 11.5	31.4 ± 3.6	0.32 ± 0.05	-34.5 ± 4.9
Ringer's + Butyrate	280.6 ± 18.4^{a}	50.9 ± 3.8^{a}	0.49 ± 0.12^{a}	-53.5 ± 3.7^{a}
% increase	36 ± 5 %	64 ± 19 %	58 ± 28 %	53 ± 19 %
Malnourished (n = 8)				
Ringer's solution	104.2 ± 14.6^{d}	20.3 ± 3.2^{d}	0.21 ± 0.04^{d}	-23.2 ± 2.8^{d}
Ringer's + Butyrate	126.3 ± 10.1^{b,d}	26.8 ± 3.6^{a,d}	0.26 ± 0.0^{4b,d}	-28.5 ± 4.6^{c,d}
% increase	22 ± 10 %	32 ± 18 %^{d}	27 ± 7 %^{e}	26 ± 11 %^{e}

Each animal was first perfused with Ringer's solution and then with Ringer's solution containing 10 mmoles/L n-butyrate. Percent increases were calculated by dividing the difference in net absorption/ secretion between the 2 perfusions by the net absorption/secretion during perfusion with Ringer's alone. Values are expressed as means ± SD and related to the colonic dry weight.

$^{a}p < 0.001$, $^{b}p < 0.01$, $^{c}p < 0.05$ compared with Ringer's alone; $^{d}p < 0.001$, $^{e}p < 0.01$ compared with controls.

Table 4. Effect of malnutrition on net water, sodium, potassium and chloride movement during perfusion with Ringer's solution on Ringer's solution containing 10 mmoles/L n-butyrate in 10 week old rats.

	H_2O absorption (μl.min^{-1}.cm^{-2})	Na absorption	Cl absorption (μmoles.min^{-1}.cm^{-2})	K secretion
Controls (n = 8)				
Ringer's solution	2.17 ± 0.93	405.8 ± 50.4	446.0 ± 64.4	-4.07 ± 0.64
Ringer's + Butyrate	3.63 ± 0.28^{a}	657.5 ± 55.6^{a}	689.7 ± 47.8^{a}	-6.28 ± 1.54^{b}
% increase	36 ± 5 %	64 ± 19 %	58 ± 28 %	53 ± 20 %
Malnourished (n = 8)				
Ringer's solution	1.11 ± 0.18^{d}	216.6 ± 38.0^{d}	247.1 ± 35.6^{d}	-2.24 + 0.34^{d}
Ringer's + Butyrate	1.35 ± 14^{c,d}	286.2 ± 42.3^{b,d}	304.7 ± 55.9^{b,d}	-2.81 + 0.40^{b,d}
% increase	22 ± 10 %^{e}	32 ± 8 %^{d}	23 ± 11 %^{e}	26 ± 11 %^{e}

Each animal was first perfused with Ringer's solution and then with Ringer's solution containing 10 mmoles/L n-butyrate. Percent increases were calculated by dividing the difference in net absorption/ secretion between the 2 perfusions by the net absorption/ secretion during perfusion with Ringer's alone. Values are expressed as means ± SD and related to the colonic surface area.

$^{a}p < 0.001$, $^{b}p < 0.01$, $^{c}p < 0.05$ compared with Ringer's alone; $^{d}p < 0.001$, $^{e}p < 0.01$ compared with controls.

Table 5. Effect of pre- and postnatal malnutrition on the colonic mucosal activity of Na, K-ATPase in 10 week old rats.

Group	n	Na, K-ATPase activity (μmoles Pi.h^{-1}.mg protein^{-1})
Control	7	15.22 ± 4.63
Malnourished	7	5.28 ± 2.40^{a}

Values are expressed as means ± SD; n = number of animals; Pi = inorganic phosphate; ^{a}p < 0.001 compared with controls.

DISCUSSION

In this study, combined pre- and postnatal malnutrition has been shown in a rat model to result in decreased body weight, colonic length, weight and surface area, diminished basal and substrate-stimulated absorption of water, sodium, chloride and secretion of potassium, as well as decreased activity of colonic mucosal Na, K-ATPase.

Using an established *in vivo* perfusion technique,[8,9,10,18] this investigation is, to our knowledge, the first report documenting decreased fluid and electrolyte transport in an animal model of pre- and postnatal malnutrition. In order to eliminate the possibility that malnutrition caused increased gut permeability to PEG which was used as a nonabsorable marker to provide the basis for calculating water and electrolyte trans-port, recovery studies were done. The recovery to PEG in this study was similar to that previously re-ported[11,19] and did not differ between the 2 groups, thus eliminating this possibility.

Water and electrolyte movement in the rat colon are complex phenomena, involving both active and passive forces.[20] It has been suggested that sodium is the main cation absorbed in the colon. This transport is largely active and mediated by the energy-requiring Na, K-ATPase pump located at the basolateral membrane of the colonic mucosa. The movement of water is passive and occurs in response to oncotic and hydrostatic forces. The 65 % reduction in specific activity of Na-ATPase in the colonic mucosa of the malnourished animals was consistent with and may have contributed to the decreased sodium and water transport observed.

Our finding that perfusion with n-butyrate stimulated colonic sodium and water absorption agrees with previous reports in rat, goat and human colon.[20,21,22,23] The finding that perfusion with 10 mmoles/L n-butyrate did not have as great a stimulatory effect upon water and sodium absorption in the malnourished as in the control animals suggested that malnutrition may be associated with an impairment of SCFA utilization. In the colon, unabsorbed protein, peptides, carbohydrates and polysaccharides are fermented by bacteria to SCFA, e.g. acetate, propionate and butyrate. These are water-soluble and readily absorbed into the colonic mucosa which utilizes them as major respiratory fuels.[1,5,25] The stimulatory effect of SCFA absorption upon sodium and water uptake is thought to occur via a Na^{+} - H^{+} exchange : The transport of SCFA into the mucosal cell results in the production of intracellular H^{+} ions. These then exit the cell via a mechanism coupled with the inward movement of Na^{+} ions. The intraluminal hydration of CO_2 producing bicarbonate is catalyzed by carbonic anhydrase, which is present in the colonic mucosa.[1] In addition, the active metabolism of SCFA may increase the availability of energy necessary to support active transport. This concept is supported by the results of experiments performed by Roediger, et al., using Thirty-Vella preparations of rat colon which has been depleted of SCFA. In spite of a compensatory increase of Na, K-ATPase activity, absorption of sodium and water was decreased, associated with a diminished oxidation of SCFA to CO_2 and could be partially restored by re-exposure of the mucosa to SCFA.[4] In the present study, the decreased stimulation by butyrate of colonic sodium and water transport in the malnourished compared with control animals is also consistent with some impairment of an active process. The absorption of butyrate is primarily passive and might be expected to occur to a similar extent in both groups which were exposed to equal concentrations of butyrate in the perfusion solutions. However, our previous studies have shown that colonocytes isolated from 6 week old rats subjected to pre- and postnatal malnutrition exhibited significantly diminished oxidative metabolism of butyrate and other substrates.[6] The resulting impairment of energy production may well adversely affect water and electrolyte transport.

In spite of significant biochemical, morphological and functional changes, the malnourished animals in our study did not appear ill and exhibited no overt diarrhea. It must be kept in mind, however, that although organs affected by malnutrition may function well enough to avoid pathological signs under normal circumstances, there is danger of decompensation in periods of stress. A diminished colonic capacity for salvage may be overwhelmed in case of increased spillage of water or undigested carbohydrate into the colon. It remains for future investigations to determine

whether the described changes are severe enough to affect morbidity and mortality. Equally important is the question of potential for reversibility after nutritional rehabilitation.

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