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Effects of short chain fatty acids and K on absorption of Mg and other cations by the colon and caecum[1*])

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Summary: The influence of short chain fatty acids (SCFA) on Mg, Na, and water absorption was studied in the rat distal colon and caecum using an in vivo luminal perfusion technique. The effect of SCFA on K absorption by the distal colon and the effect of K on Mg absorption by the distal colon and caecum were also investigated.

Butyrate (60 mmol/l) or a mixture of SCFA (60 mmol/l acetate, 20 mmol/l propionate, 10 mmol/l butyrate) stimulated Mg and K absorption by the distal colon, while Na and water absorption was not affected. The effect on Mg absorption was pH-dependent. In the caecum, butyrate enhanced Na and water absorption, but not Mg absorption. Acetate (60 mmol/l) did not influence electrolyte absorption by either intestinal segment. K (30 mmol/l) inhibited Mg absorption by the distal colon, but not by the caecum.

It is concluded from these findings that SCFA deriving from fermentation of carbohydrates in the large intestine stimulate Mg, K, and Na absorption by delivering protons to Mg^{++}/H^+, K^+/H^+ and Na^+/H^+ exchangers located in the apical membrane of the epithelium. K seems to inhibit Mg absorption in the colon by affecting a mechanism which does not respond to SCFA.

Zusammenfassung: Im distalen Kolon und Zäkum der Ratte wurde der Einfluß von kurzkettigen Fettsäuren (SCFA) auf die Mg-, Na- und Wasserabsorption mittels luminaler Perfusion der Darmsegmente in vivo untersucht. Der Effekt kurzkettiger Fettsäuren auf die K-Absorption im distalen Kolon sowie von K auf die Mg-Absorption im distalen Kolon und Zäkum wurde ebenfalls geprüft.

Butyrat (60 mmol/l) sowie eine Mischung von SCFA (60 mmol/l Azetat, 20 mmol/l Propionat, 10 mmol/l Butyrat) stimulierten die Mg- und K-Absorption im distalen Kolon, während die Na- und Wasserabsorption unbeeinflußt blieben. Der Effekt auf die Mg-Absorption war pH-abhängig. Im Zäkum steigerte Butyrat die Na- und Wasserabsorption, nicht jedoch die Mg-Absorption. Azetat (60 mmol/l) beeinflußte die Elektrolytabsorption in beiden Darmsegmenten nicht. K (30 mmol/l) hemmte die Mg-Absorption im distalen Kolon, nicht jedoch im Zäkum.

Aus diesen Befunden wird geschlossen, daß die bei der Fermentation von Kohlenhydraten im Dickdarm anfallenden kurzkettigen Fettsäuren die Mg-, K- und Na-Absorption durch Bereitstellung von Protonen für die in der apikalen Membran des Epithels lokalisierten Mg^{++}/H^+-, K^+/H^+- und Na^+/H^+-Austauscher stimulieren. K scheint im Kolon die Absorption von Mg durch Beeinträchtigung eines Mechanismus zu hemmen, der nicht auf kurzkettige Fettsäuren anspricht.

Abbreviation index: SCFA = Short chain fatty acids

[1]) Some results were published in a preliminary form (16)

*) In memoriam Prof. Dr. Hermann Zucker

Key words: Mg absorption, Na absorption, K absorption, short chain fatty acids, colon, caecum

Schlüsselwörter: Mg-Absorption, Na-Absorption, K-Absorption, kurzkettige Fettsäuren, Kolon, Zäkum

Introduction

Magnesium is absorbed by the small and large intestines (3, 5, 7, 14, 15, 17, 19, 21, 25). In the small intestine magnesium appears to be mainly absorbed by solvent drag (3), whereas in the colon an active transport mechanism seems to play an important role in magnesium absorption (14, 15, 19). Magnesium is also efficiently absorbed by the caecum, but the mechanism involved is not known (8, 21).

It was one aim of the present study to investigate the influence of short chain fatty acids (SCFA) on Mg absorption by the rat colon and caecum, because SCFA deriving from microbial fermentation of carbohydrates constitute the major anions in the large intestine. To find out whether the degree of dissociation of SCFA affects the results, the experiments were performed using buffer solutions with pH 6.0 or 7.0. Since potassium represents the major cation in the large intestine (9), the influence of potassium on magnesium absorption by the colon and caecum was also studied. In former work, we have already shown that potassium inhibits magnesium absorption by ligated loops of the rat colon (24). An in vivo luminal perfusion technique was used for the present study. Besides absorption of magnesium, absorption of sodium, potassium, and water was also determined.

Material and methods

The distal colon (length: 5 cm, ending 2 cm proximal to the anus) or caecum of anesthetized adult male SIVZ-50 rats (body weight: 200–285 g) fed a commercial rat diet (No. 890, NAFAG, Gossau, Switzerland) was perfused with a buffer solution (0.5 ml/min) as described previously (27). The animals were anesthetized by intramuscular injection of xylazin-hydrochloride (10 mg/kg, Bayer AG, Leverkusen) and ketamine-hydrochloride (50 mg/kg, Parke Davis & Co., Berlin). The buffer solution contained phenolred as unabsorbable marker (20). Net absorption rates were determined following a 30 min equilibration period. The buffer solutions used for studying the effect of SCFA on Mg absorption had the subsequent composition (mmol/l): Control solution (pH 6.0): 60 NaCl, 2.5 Mg Cl_2, 20 $NaHCO_3$, 30 NaH_2PO_4, 30 choline chloride, 10 propionic acid; in the experimental solution (pH 6.0) 60 NaCl was replaced by 60 Na-acetate or Na-butyrate. When studying the influence of a mixture of SCFA on absorption, the solutions were somewhat modified. The control solution (pH 6.0) in addition contained 5 KCl, propionic acid was replaced by 5 lactic acid and choline chloride by NaCl; in the pertinent experimental solution (pH 6.0) 90 NaCl was substituted by 60 Na-acetate, 20 Na-propionate and 10 Na-butyrate. For the experiments performed at pH 7.0 the control solution contained 60 NaCl, 2.5 $MgCl_2$, 20 $NaHCO_3$, 15 NaH_2PO_4, 15 Na_2HPO_4, 30 choline chloride. In the experimental solution (pH 7.0) 60 NaCl was replaced by 60 Na-acetate or Na-butyrate. For studying the effect of potassium on Mg absorption choline chloride in the control solution (30 NaCl, 2.5 $MgCl_2$, 20 $NaHCO_2$ 30 NaH_2PO_4, 60 Na-acetate, 30 choline chloride, 10 propionic acid, pH 6.0) was replaced by KCl (= experimental solution).

Mg was determined photometrically (24) using the test kit of Hoffmann-La Roche, Basel (No. 0 710 199). Concentrations of Na and K were measured with a flame spectrophotometer (model 243, Instrumentation Laboratory Inc.)

Results are presented as means ± SEM. Differences between means were statistically evaluated usingthe Mann-Whitney U test or Student's t-test ($n \geq 10$). P values ≤ 0.05 were considered to be significant.

Results

As shown in Table 1, butyrate, but not acetate, stimulated Mg absorption by the distal colon. The effect was pH-dependent. It occurred at pH 6.0, but not at pH 7.0. Absorption of Na and water by the distal colon was not influenced by acetate or butyrate (Table 1). In the caecum Na and water absorption was stimulated by butyrate, whereas Mg absorption remained unaffected (Table 1).

A mixture of SCFA simulating SCFA concentrations which occur physiologically in the large intestine also stimulated Mg absorption by the distal colon (Table 2). This effect occurred under two different experimental conditions. For one series of experiments, 90 mmol/l NaCl of the control solution was replaced by 90 mmol/l SCFA to obtain the experimental solution. Therefore, the Cl concentrations of the two buffer solutions were very different. To exclude the possibility that the group difference in Mg absorption is due to this difference in the Cl concentration a further series of experiments with buffer solutions of similar Cl concentration was

Table 1. Influence of acetate and butyrate on Mg, Na and water absorption by the distal colon and caecum.

	Control	+ Acetate (60 mmol/l)	Control	+ Butyrate (60 mmol/l)
		Distal colon (pH 6.0)		
Mg[1]	2.24 ± 0.46	2.77 ± 0.40	2.05 ± 0.34	5.23 ± 1.36*
Na[1]	149 ± 6	176 ± 12	147 ± 18	130 ± 14
Water[2]	1115 ± 102	1272 ± 60	1216 ± 94	1241 ± 116
	(5)	(5)	(6)	(6)
		Distal colon (pH 7.0)		
Mg	3.77 ± 0.47	3.08 ± 0.45	–	3.36 ± 0.49
Na	197 ± 10	210 ± 13	–	173 ± 16
Water	1205 ± 49	1240 ± 131	–	1251 ± 118
	(8)	(8)	–	(8)
		Caecum (pH 6.0)		
Mg	1.59 ± 0.27	1.39 ± 0.12	1.88 ± 0.29	2.30 ± 0.41
Na	37 ± 10	39 ± 8	49 ± 9	62 ± 5*
Water	364 ± 71	378 ± 41	443 ± 53	567 ± 41*
	(5)	(5)	(8)	(7)

Values are means ± SEM, number of experiments in parentheses

[1] µmol/100 mg intestinal dry weight · 30 min

[2] µl/100 mg intestinal dry weight · 30 min

* significantly different from the control value ($p < 0.05$)

Table 2. Influences of a mixture of SCFA (60 mmol/l acetate, 20 mmol/l propionate, 10 mmol/l butyrate) on Mg, Na, K and water absorption by the distal colon (pH 6.0).

	Control (90 mmol/l NaCl)	+ SCFA (90 mmol/l SCFA)	Control (90 mmol/l Na-glycolate)	+ SCFA (90 mmol/l SCFA)
Mg[1]	3.33 ± 0,70	5.64 ± 0.57*	2.25 ± 0.54	4.10 ± 0.40*
Na[1]	172 ± 11	186 ± 12	143 ± 13	167 ± 9
K[1]	3.8 ± 1.3	7.9 ± 0.9*	2.0 ± 1.6	9.0 ± 1.2**
Water[2]	1129 ± 72	1226 ± 79	936 ± 84	1114 ± 68
	(10)	(10)	(10)	(9)

Values are means ± SEM, number of experiments in parentheses.
[1, 2] see Table 1
*, ** significantly different from control value (*$p < 0.05$; **$p < 0.01$)

Table 3. Influence of K on Mg, Na, and water absorption by the distal colon caecum.

	Distal colon		Caecum	
	Control	K (30 mmol/l)	Control	K (30 mmol/l)
Mg[1]	3.01 ± 0.45	0.35 ± 0.82*	1.12 ± 0.49	1.02 ± 0.43
Na[1]	141 ± 13	133 ± 13	41 ± 7	32 ± 8
Water[2]	1332 ± 101	1135 ± 125	426 ± 60	343 ± 65
	(14)	(12)	(5)	(5)

Values are means ± SEM, number of experiments in parentheses
[1, 2] see Table 1
* significantly different from the control value ($p < 0.05$)

conducted. In this case the control solution contained 90 mmol/l Na glycolate, which was replaced by 90 mmol/l SCFA to obtain the experimental solution. Under both conditions K absorption could be also studied, because the solutions contained 5 mmol/l K. K absoprtion by the distal colon was also stimulated by the SCFA. Na and water absorption were again not affected (Table 2).

In Table 3 the influence of K (30 mmol/l) on Mg, Na and water absorption by the distal colon and caecum is shown. K clearly inhibited Mg absorption by the distal colon, but not by the caecum. Absorption of Na and water was not significantly affected. At a K concentration of 15 mmol/l no inhibitory effect on Mg absorption occurred (results not shown).

Discussion

The results presented show that SCFA, in particular butyrate, stimulate Mg and K absorption in the distal colon and Na and water absorption in the caecum. Furthermore, K inhibited Mg absorption in the distal colon, but did not affect Mg absorption in the caecum.

In former work, we also observed a stimulatory effect of SCFA on Na and water absorption and the absence of an effect on Mg absorption in the

proximal colon (16). Since the enhancement of Mg absorption by butyrate in the distal colon was observed only under acidic conditions (at pH 6, not at pH 7), the effect appears to be mediated by the undissociated form of SCFA. Due to a pK-value of about 4.8, SCFA occur almost totally (> 99 %) in the dissociated form at pH 7.0. At pH 6.0 about 6.5 % of the SCFA are present in the undissociated form. Because SCFA are predominantly absorbed in their undissociated form (6, 10) their stimulatory effect on electrolyte absorption might depend on their uptake into the epithelium.

The stimulatory effect of butyrate at pH 6 on Na and water absorption in the rat caecum (Table 1) and of a mixture of SCFA in the rat proximal colon (16) is in accord with similar observations of others in the colon of various species (1, 2, 10, 23). It was suggested that this effect is attributable to activation of the Na^+/H^+ exchanger located in the apical membrane of the epithelium (1). As already mentioned, SCFA enter the epithelium predominantly in the undissociated form, although they mainly occur as anions in the intestinal lumen. Therefore, protons are required for absorption of SCFA. These protons appear to be partially delivered by the Na^+/H^+ exchanger (1). After diffusion into the epithelial cells the SCFA release protons because of the relatively high intracellular pH. These protons are then secreted in exchange for Na and thus stimulate Na absorption in the caecum and proximal colon. SCFA, therefore, seem to function as intracellular proton donators for the Na^+/H^+ exchanger. The absence of an effect of acetate on Na absorption by the caecum (Table 1) may be due to its lower lipid solubility in comparison with butyrate, because the ability of undissociated SCFA to pass the cellular membrane and thus to function as intracellular proton donators depends on their lipid solubility (6, 22).

It has been proposed by von Engelhardt et al. (10) that protons may be available in the distal colon for protonation of SCFA from the electroneutral K^+/H^+ pump located in the apical membrane (11, 26). This is in accord with the stimulatory effect of SCFA on K absorption by the distal colon (Table 2). In this intestinal segment SCFA probably function as proton donators for the K^+/H^+ pump. Since Na absorption by the distal colon was neither stimulated by butyrate nor by a mixture of SCFA a Na^+/H^+ exchanger seems not to be operative in the distal colon under the present experimental conditions. This is also in keeping with observations of others (10, 12, 13, 28).

It is of considerable interest that SCFA stimulated Mg absorption by the distal colon in a similar way as Na absorption by the caecum and K absorption by the distal colon. A Mg^{++}/H^+ exchanger in the apical membrane mediating Mg absorption might therefore, in addition, be involved in delivering protons for absorption of SCFA. Such a mechanism apparently does not exist in the caecum (Table 1) and the proximal colon (16), although Mg was absorbed from the caecum (Tables 1 and 3) and proximal colon (16), too. Thus, at least two mechanisms appear to exist in the epithelium of the large intestine for Mg absorption, one being stimulated by SCFA under acidic conditions and one being not affected by SCFA.

It remains to be discussed which of these mechanisms is inhibited by K. Since Mg absorption was inhibited by K in the distal colon, but not in the caecum, the SCFA-sensitive mechanism representing possibly Mg^{++}/H^+ exchange might be impaired by K. This is, however, unlikely, because K

also inhibited Mg-absorption in the proximal colon (24), where the SCFA-sensitive mechanism is lacking (16). Therefore, a mechanism for Mg absorption in the colon is probably inhibited by K which does not respond to SCFA. Since there are K channels in the apical membrane of the colon epithelium (4), K probably reduces the potential difference across the apical membrane (inside negative) and this might inhibit entry of Mg^{++} via channels into the epithelial cell. The absence of an inhibitory effect of K on Mg absorption by the caecum might be due to a lack of K channels in the apical membrane or to the absence of a transcellular mechanism of Mg absorption.

Interestingly, K seems to influence Mg absorption in the rumen in a similar way (18) as in the colon and SCFA also stimulate Mg absorption from the rumen (18).

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