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Some Effects of Cations and of Water Absorption on Intestinal Hexose, Glycine and Cation Absorption.* (29413)

JOHN H. ANNEGERS
Department of Physiology, Northwestern University Medical School, Chicago, Ill.

Glucose absorption *in vivo* decreased upon the replacement of sodium in the rats' intestine lumen perfusate(1,2). However, various sodium and non-sodium electrolytes at given osmolar concentrations affected differently the intestinal absorption rate for water in the dog(3). Accordingly, the present experiments were designed to test whether hexose or glycine absorption in the dog is influenced by the chemical identity of the accompanying perfusate electrolyte, and whether such influences are related to concomitant changes in water absorption. Additional experiments test whether sodium, potassium and ammonium ions alter the absorption of one another, and whether changes in cation absorption rate are related to changes in net water absorption.

Methods. This technique has been described(3-5). Four dogs with jejunal and 5 dogs with ileal Thiry-Vella fistulas (approx. 20 cm long) were used. Test solutions were perfused through the loops at the rate of about 2 ml/min for one hour in fasted, non-anesthetized dogs. Each dog was tested 2 or 3 times per week. The volume and solute concentrations of solutions were measured before and after loop perfusion. After correction for fluid and solute remaining in the perfused loop, absorption or enterosorption of solute and water was considered to be that amount which disappeared from, or was added to, the perfusate. Hexoses(6) and sodium and potassium (flame photometry) were measured. Ammonium was estimated by microkjeldahl determination on test solutions and on deproteinized, non-digested intestinal effluents; traces of "ammonium N" enterosorbed by dogs receiving ammonium-free perfusates were disregarded. Glycine was estimated (microkjeldahl) on deproteinized, digested effluents, corrected for each dog by that amount of "amino acid N" enterosorbed into N-free perfusates(3,4).

In the first series, changes in water absorption rates were produced by varying the molar concentration of sodium or non-sodium salts in the perfusates while hexose or glycine was approximately 14 mMolar. Absorption rates of the non-electrolytes are reported. In the second series, varying concentrations of NaCl and KCl, NaCl and NH_4Cl, or NH_4Cl and KCl were perfused in solutions made up to approximately 310 mOsmolar by addition of glucose. Net cation sorption rates are reported. The sequence of the various mixtures was randomized in both series.

Results. Table I summarized hexose, glycine and fluid absorption (—values) or enterosorption (+values) rates when sodium, potassium or ammonium salts were present. These salts were chosen because of their differing effects on water sorption in the dog (3). Glycine was not tested with NH_4Cl or K_2SO_4. The data show that the absorption rates for all substances from jejunal and ileal loops were reduced when KCl was substituted for NaCl and when K_2SO_4 was substituted for Na_2SO_4. The substitution of NH_4Cl or 210 mMolar NaCl for 155 mMolar NaCl also reduced hexose and glycine absorption rates in most instances. However, inspection of concomitant hexose or glycine and water sorption data in Table I suggests a positive correlation between non-electrolyte and water

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absorption because there is a tendency for the absorption rates of the non-electrolytes to decrease as fluid absorption rates decrease (or enterosorption increases) regardless of the identity of the electrolyte. Graphic analysis of the original data from individual dogs confirmed this impression and indicated further that over a common range of water sorption rates glucose and glycine absorptive data might differ between NaCl-Na_2SO_4 and KCl-K_2SO_4-NH_4Cl tests. Whether the effects of changing fluid sorption rates on hexose or glycine absorption rates are significant, and whether this relationship differs between sodium and non-sodium experiments was tested by the covariance analysis(7) summarized in Table II. In this analysis, data were pooled for each hexose and for glycine perfusions from each intestinal site according to whether the perfusate contained sodium initially. The *a* constants, columns 2 and 4, estimate rates of absorption for each substance in column 1 when ΔV is zero, and are in agreement with previous results(4,5). Column 3 shows that glucose, galactose and glycine absorption rates from jejunal loops and glucose from ileal loops did not change significantly with changing water sorption. Column 5 shows that with NH_4 and K perfusates hexose absorption decreased with decreasing water absorption except for jejunal fructose.

The covariance analysis also tested whether the 2 *b* coefficients in each line (Table II) differ, and if not, whether hexose absorption rates differ between sodium and non-sodium perfusates when compared at a common value

TABLE I. Hexose, Glycine and Water Sorption in Presence of Various Electrolytes.

	155 mM NaCl		155 mM KCl		155 mM NH_4Cl		210 mM NaCl		100 mM Na_2SO_4		100 mM K_2SO_4	
	Δ Hex.*	ΔV†	Δ Hex.	ΔV	Δ Hex.	ΔV	Δ Hex.	ΔV	Δ Hex.	ΔV	Δ Hex.	ΔV
4 jejunal dogs												
14 mM glucose	-1.46	-34	-.89	+9	-1.60	-40	-1.61	-5	-1.30	-7	-.91	-3
" galactose	-1.23	-35	-.48	+8	-.88	-19	-1.26	-4	-1.36	-27	-.46	-2
" fructose	-.67	-22	-.39	+7	-.59	-9	-.41	+6	-.48	+1	-.36	0
" sorbose	-.28	-20	-.07	+14	-.24	-9	-.03	+9	-.26	-18	.02	+8
" glycine	-2.01‡	-34	-1.23	+8	—	—	-1.31	-2	-1.41	-7	—	—
5 ileal dogs												
14 mM glucose	-1.07	-20	-.41	-2	-.90	-38	-.80	-9	-1.11	-5	-.38	-4
" galactose	-.90	-24	-.26	+3	-.52	-21	-.74	+1	-.88	-23	-.35	-4
" fructose	-.43	-25	-.18	+2	-.40	-25	-.35	-6	-.33	-7	-.21	0
" sorbose	-.13	-16	-.07	+1	-.17	-23	-.09	-2	-.16	-24	-.10	+1
" glycine	-1.21‡	-29	-.88	+2	—	—	-1.13	-9	-1.48	-16	—	—

* Hexose absorption, mM/hr. † H_2O absorption (−) or enterosorption (+), ml/hr. ‡ Glycine absorption, mM/hr.

TABLE II. Effects of Water Sorption on Hexose and Glycine Absorption.

Δ glycine or Δ Hex. = a + bΔV = mM/hr absorbed
a = Δ Hex. or Δ glycine at zero ΔV
b = Δ Hex./ΔV
ΔV = ml/hr water absorbed (−) or enterosorbed (+)

	NaCl, Na_2SO_4		NH_4Cl, KCl, K_2SO_4	
	a	b ± sb	a	b ± sb
Pooled jejunal dogs, n=12				
glucose	−1.52	−.005 ±.009	−.99	.015 ±.003*
galactose	−1.36	−.004 ±.004	−.55	.010 ±.004†
fructose	− .48	.009 ±.003*	−.46	.005 ±.005
sorbose	− .11	.007 ±.003†	−.05	.006 ±.002†
glycine	−1.29	.011 ±.007		
Pooled ileal dogs, n=15				
glucose	−.72	.016 ±.010	−.33	.015 ±.003*
galactose	−.59	.016 ±.005*	−.29	.013 ±.003*
fructose	−.20	.011 ±.002*	−.19	.009 ±.001*
sorbose	−.08	.003 ±.001†	−.08	.005 ±.001*
glycine	−.88	.022 ±.008†		

* Significant at P <.01 † Significant at P <.05

TABLE III. Cation and Water Sorption from Single and Mixed Cation Solutions.

Perfusate, mM/l			Avg 4 jejunal loops mM/hr			ml/hr	Avg 5 ileal loops mM/hr			ml/hr
NaCl	KCl	NH_4Cl	ΔNa	ΔK	$ΔNH_4$	ΔV	ΔNa	ΔK	$ΔNH_4$	ΔV
25	0		1.87	.49		–10	.39	.15		– 4
25	75		.62	–3.78	"0"	–25	1.31	–2.35	"0"	– 7
25	110		2.99	–3.97		–17	2.85	–3.56		– 9
0	25		2.71	– .92		–19	1.74	–1.11		– 2
75	25		–4.14	–1.49		–60	– .95	– .88		–19
110	25		–5.88	–1.50		–55	–1.61	– .68		–18
0	75		2.50	–2.86		–23	2.09	–1.89		– 3
75	0		–2.94	.41		–36	–1.61	.30		–13
75	75		.55	–3.06		–14	.70	–1.98		+ 5
25		0	1.38	.37	.27	–12	.65	.13	.15	– 3
25		75	.66	.29	–4.66	–42	.81	.18	–2.84	–18
25		110	2.92	.38	–7.89	–44	1.58	.24	–5.82	–29
0		25	2.21	.31	– .81	– 6	1.42	.16	–1.06	– 2
75		25	–3.83	.24	–1.61	–56	–1.40	.18	–1.28	–21
110		25	–4.69	.23	–1.44	–53	–2.58	.29	–1.38	–30
0		75	2.32	.32	–4.03	–26	1.90	.19	–3.07	–11
75		0	–2.66	.28	.27	–37	– .98	.14	.14	–11
75		75	– .53	.22	–3.60	–28	– .49	.20	–3.39	–26
	25	0	2.78	– .73	.40	– 9	1.46	– .77	.20	– 2
	25	75	2.06	– .93	–4.07	–33	1.80	– .86	–3.77	–24
	25	110	3.07	– .67	–4.55	–29	2.34	– .63	–4.08	–24
	0	25	2.21	.31	– .81	– 6	1.42	.16	–1.06	– 2
	75	25	2.34	–3.18	–1.18	–31	2.02	2.12	–1.01	–11
	110	25	2.54	–2.99	– .69	–18	1.84	–1.56	– .67	– 5
	0	75	2.32	.32	–3.66	–24	1.77	.17	–4.06	–20
	75	0	2.11	–2.77	.30	–22	2.12	–2.37	.18	– 9
	75	75	4.63	–3.14	–3.18	–13	2.18	–2.40	–3.00	–20

for ΔV. Thus, the effect of decreasing water absorption rates on jejunal glucose and galactose absorption is greater ($P<.05$) for non-sodium (.015 and .010) than for pooled sodium perfusates (—.005 and —.004). This suggests that either sodium aids or K or NH_4 hinders glucose and galactose absorption apart from concomitant changes in water absorption. The *b* coefficients for ileal glucose and galactose were not found to differ between sodium and non-sodium perfusates. However, as shown by the appropriate *a* constants for hexose absorption, at ΔV = zero (—.72 *vs* —.33; —.59 *vs* —.29 mM/hr) glucose and galactose absorption is greater ($P<.01$) from sodium than from non-sodium perfusates. Accordingly, sodium replacement seems to have a specific effect on both jejunal and ileal glucose and galactose absorption rates.

Neither jejunal nor ileal fructose or sorbose absorption differed between the pooled sodium and pooled non-sodium perfusates as judged by the comparison of *b's* or adjusted Δ hexose rates. Therefore, changes in water absorption rates may account for concomitant changes in these hexose absorption rates. The effect of KCl on glycine absorption also seems to be explained by the concomitant change in ΔV. Thus, observed Δ glycine was —1.23 and —.88 mM/hr (column 4, Table I) while predicted (from regression data cols. 2 and 3, Table II) Δ glycine at the observed ΔV for KCl tests is —1.21 and —.87 mM/hr for jejunal and ileal loops, respectively.

The next series of perfusions tested whether the cations Na, K and NH_4 affected the absorption of one another in addition to possible effects incident to changing water absorption rates. The test mixtures are listed in Table III, together with the resulting average cation and water enterosorption (+) and absorption (—) rates. 110 and 150 mMolar NaCl and KCl alone, and 12 mMolar KCl were perfused also. Sodium and potassium enterosorption rates into perfusates initially free of these ions are in agreement with previous results(3). Changes in water absorption rates occurred with changing pro-

TABLE IV. Effects on Cation Sorption of a Second Cation and of Concomitant Water Sorption.

$$\hat{Y} = a + b_{1.23} X_1 + b_{2.13} X_2 + b_{3.12} X_3$$

		mM/hr	mM/l		cc/hr	mM/hr				
Site	n	$\hat{Y}$	X_1	X_2	X_3	a	$b_{1.23}$	$b_{2.13}$	$b_{3.12}$	R
Pooled jejunal	56	ΔNa	Na	K	ΔV	3.62	−.044*	.017*	.076*	.97
″ ″	56	ΔK	Na	K	ΔV	.83	.006	−.042*	.035	.88
″ ″	36	ΔNa	Na	NH_4	ΔV	2.44	−.048*	.035*	.049*	.93
″ ″	36	$ΔNH_4$	Na	NH_4	ΔV	.90	.019*	−.066*	.053*	.93
″ ″	36	$ΔNH_4$	K	NH_4	ΔV	−.28	−.004	−.052*	.033*	.94
″ ″	36	ΔK	K	NH_4	ΔV	.67	−.038*	.005	.039*	.91
Pooled ileal	70	ΔNa	Na	K	ΔV	1.32	−.026*	.018*	.027†	.80
″ ″	70	ΔK	Na	K	ΔV	.11	.006	−.024*	.041*	.69
″ ″	45	ΔNa	Na	NH_4	ΔV	1.20	−.021*	.026*	.063*	.89
″ ″	45	$ΔNH_4$	Na	NH_4	ΔV	−.87	.026*	−.029*	.090*	.88
″ ″	45	$ΔNH_4$	K	NH_4	ΔV	−.29	.010†	−.022*	.092*	.90
″ ″	45	ΔK	K	NH_4	ΔV	−.01	−.022*	.021	.083*	.92

* Significant at $P < .01$ † Significant at $P < .05$

portions of the various cation pairs in the 310 mOsmolar perfusates.

The data from individual dogs, averaged in Table III, together with the appropriate values for average concentration of each cation in the intestine during the perfusion period were treated as follows. It has been shown(3) that the absorption rates for these cations increase nearly linearly with their intestinal lumen concentration over the range used here, although the linear relationship does not hold for higher cation concentrations. Also cation absorption rates changed nearly linearly with changing water absorption rates(3). Assuming that if one cation affected the sorption of a second cation, such an effect is linearly related to the concentration of the "affecting" ion, pooled jejunal and pooled ileal data were evaluated by multiple linear regression analysis(7). In the analyses, sorption rates of cations were treated as dependent variables and the independent variables were considered to be the lumen concentration of that ion whose absorption rate is the dependent variable, the lumen concentration of a second cation, and the concomitant rate of water absorption. The object of the analysis was to identify significant effects of each independent variable on the sorption rates of the various cations.

The analyses are summarized in Table IV. The n values, col. 2, come from the 9 mixtures on 4 jejunal or 5 ileal dogs (Table III) plus 3 additional Na or KCl concentrations in the NaCl-KCl series. In Table IV, col. 3 identifies the dependently-treated cation sorption rate in each line, and the succeeding 3 columns identify the independently-treated variables. The *a* constants predict sorption rates for Y when X_1, X_2 and X_3 are zero. They indicate greater Na enterosorption (+ sign) into Na-free perfusates for jejunal than for ileal loops and relatively small K and NH_4 enterosorption into solutions initially free of these ions, as before (3). The coefficient $b_{1.23}$ indicates the effect of changing X_1 independent of possible effects from changing X_2 or X_3, etc. The multiple correlation coefficient R indicates the relative success in predicting Y from given observations of X_1, X_2 and X_3 in each line. Line 1, Table IV, indicates that Na absorption rate (ΔNa, — sign) increased directly with mM/l sodium (Na), decreased with increasing (K), and decreased with decreasing water absorption (or increasing water enterosorption). The ileal data, line 7, are in agreement. Lines 2 and 8 show that K absorption rates increased directly with (K) and decreased with decreasing water absorption but were not affected significantly by (Na). Thus, (K) either decreased Na insorption or increased Na exsorption rate. The other lines in Table IV show further consistent increasing cation absorption rates directly with their concentrations in the bowel lumen and decreasing cation absorption rates as water absorption rates decrease. In most instances a second cation interfered with the absorption of the dependently-treated cation; the effects of (NH_4) on ΔNa and of (Na) on ΔNH_4 (jejunal and ileal), and of (K) on ΔNH_4 (ileal) are significant statistically.

Discussion. Since sodium enters canine intestinal perfusates which are sodium-free initially(3), complete removal of sodium from the lumen fluid is not achieved by the present technique. Also, "down-gradient" sugar absorption *in vivo* has not been affected consistently by sodium replacement (1,8). Therefore, it was expected that sodium replacement in perfusates would have either no effect on hexose or glycine absorption in the dog, or would have an effect related to concomitant changes in water absorption. However, the present results imply a "specific" effect of sodium replacement on glucose and galactose absorption but fail to show such an effect on fructose, sorbose or glycine absorption. These findings seem to be related to earlier findings that glucose and galactose as well as glucose and glycine compete for intestinal absorption in the non-anesthetized dog, whereas fructose and sorbose do not affect glucose or galactose absorption(4,5). The present results also seem to extend *in vitro* studies showing that sodium replacement depresses the active intestinal transport of glucose, methylglucose, tyrosine and phenylalanine(9-12).

Given molar concentrations of NH_4Cl and NaCl in the canine intestine have similar effects on water sorption whereas KCl produces differing sorption of water(3). The present study shows that the absorption of cations is aided by concurrent and hindered by countercurrent net water movements when varying proportions of 2 cations are perfused through the jejunum or the ileum. In addition, one cation usually has a further inhibitory effect on the absorption of a second cation. The biochemistry of these inhibitory effects is obscure. KCl or NH_4Cl may damage the absorptive processes in some non-specific manner or may increase sodium enterosorption rate. It seems unlikely, however, that (Na) would affect net NH_4 absorption by either action. It is suggested that Na, K and NH_4 share some common step in the absorptive mechanism when mixtures are absorbed.

Summary. Fourteen mMolar hexose or glycine plus 100 to 210 mMolar sodium or non-sodium salts were perfused through jejunal or ileal loops in non-anesthetized dogs. Net water movements changed in response to the chemical identity as well as to the osmolarity of the perfusate. In general, hexose and glycine absorption rates decreased as water absorption rates decreased. At given water absorption rates however, glucose and galactose absorption rates were lower when K or NH_4 salts were substituted for Na salts. Fructose, sorbose and glycine absorption rates did not differ between sodium and non-sodium perfusates. In a second series, .310 osmolar solutions containing varying proportions of NaCl and KCl, NaCl and NH_4Cl, or KCl and NH_4Cl were perfused. Cation absorption rates increased directly with the concentration of the same ion and with water absorption rates. In addition, NH_4 and Na absorption rates decreased as (K) increased, Na and K absorption decreased as (NH_4) increased, and NH_4 absorption decreased as (Na) increased.

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