Effect of Vasoactive Intestinal Polypeptide on Active and Passive Transport in the Human Jejunum

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ABSTRACT The effect of intravenous vasoactive intestinal polypeptide (VIP) on normal transport mechanisms in the human jejunum in vivo was examined with the triple-lumen, steady-state perfusion technique. By using special test solutions that revealed different aspects of jejunal transport, we were able to evaluate the effect of VIP on specific transport processes, such as active bicarbonate absorption, active chloride secretion, and passive absorption or secretion of sodium chloride. At an infusion rate of 200 pmol/kg per h, VIP inhibited active bicarbonate absorption by ~42%, stimulated active chloride secretion to a slight extent, and slightly reduced passive sodium chloride absorption. A larger dose of VIP, 400 pmol/kg per h, had essentially the same effect on active bicarbonate absorption and active chloride secretion, but it markedly depressed passive sodium chloride absorption and also inhibited passive secretion induced by mannitol. VIP reduced the lumen-to-plasma unidirectional sodium and chloride flux rates, while the plasma-to-lumen flux rates were decreased to a lesser extent or remained unchanged. The potential difference became more lumen-negative with VIP, but the sodium diffusion and glucose-stimulated potential were not affected. We conclude that the major effect of VIP in the human jejunum is to decrease the normal absorption of water and electrolytes—not only active bicarbonate-mediated absorption, but also the passive absorption in response to osmotic forces generated by active or facilitated absorptive processes. Although an increase in chloride secretion does occur, this does not appear to be of major importance.

INTRODUCTION

Previous work has shown that high mucosal concentrations of cyclic AMP stimulate active chloride secretion and inhibit sodium chloride absorption in the intestine of laboratory animals in vitro (1). Since vasoactive intestinal polypeptide (VIP)[1] causes an increase in mucosal concentration of cyclic AMP (2), it is generally assumed that severe diarrhea seen in patients with VIP-producing tumors is caused by stimulation of active chloride secretion and by a simultaneous inhibition of normal sodium chloride absorption. It was the purpose of this study to determine the relative importance of each of these cyclic AMP effects in man in vivo. This was done by examining the response of the human jejunum to intravenously infused VIP. The jejunum was selected for study because it is in this part of the intestine that water and electrolyte transport is most deranged in patients with diarrhea due to VIP-secreting endocrine tumors (3).

It is known from previous work that the normal human jejunum in vivo actively absorbs bicarbonate via a Na/H exchange (4), and that to a lesser extent it actively secretes chloride (5). The mucosa is highly permeable to sodium chloride (6), and passive sodium chloride absorption or secretion is quantitatively a major mechanism for salt transport in this part of the human intestine (7). Therefore, in our studies we paid particular attention to the effect of VIP on active bicarbonate absorption, on active chloride secretion, and on passive absorption and secretion of sodium chloride.

VIP was infused intravenously at a rate of 200 or 400 pmol/kg per h, since previous studies have shown that this rate of infusion elevates plasma VIP concentration into the range found in patients with diarrhea associated with VIP-producing tumors (8). Use of higher doses is limited by side effects which include tachycardia, intense flushing, headache, and fatigue.

METHODS

Subjects. Normal volunteers, aged 21–37 yr, were studied. Informed written consent was obtained from each subject.

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[1] *Abbreviations used in this paper*: PD, potential difference; PEG, polyethylene glycol; VIP, vasoactive intestinal polypeptide.

TABLE I
Composition of Test Solutions

Solution	A Bicarbonate-containing	B Bicarbonate-free	C Saline-mannitol	D Saline-fructose	E Saline-mannitol	F Saline-mannitol	G Saline-glucose
				mM			
Na	135	135	125	125	75	50	100
K	5	5					
Cl	105	105	125	125	75	50	100
HCO_3	35						
SO_4		17.5					
Mannitol		30	40		140	170	
Fructose				40			
Glucose							80
Measured osmolality±SE	276 ±1	274 ±1	280 ±2	274 ±1	300 ±1	272 ±1	272 ±1

All test solutions contained PEG 2 g/liter.

This project was approved by a Human Research Review Committee on 1 June 1979.

Jejunal perfusion. Using the triple-lumen tube method, jejunal perfusion was carried out in the standard manner (9) when the infusion site was located at the ligament of Treitz. The mixing segment was 10 cm, and unless otherwise stated, the test segment was 30 cm, and the test solutions were perfused at 10 ml/min. The makeup of the test solutions is shown in Table I. Polyethylene glycol (PEG), 2 g/liter, was added as the nonabsorbable volume marker. A study consisted of a 40-min equilibration period, followed by a 60-min collection period. Samples of the perfusate were aspirated at a rate of 1.5 ml/min from the proximal and distal ends of the test segment. Test solutions and aspirated samples were analyzed for PEG, electrolytes, and solutes by previously published methods (5). Net water and electrolyte movement was calculated by standard nonabsorbable marker equations (6).

In some studies (see Results), the test solutions contained 0.5 μCi/liter of ^{24}Na and ^{36}Cl, which were assayed in a Packard 2425 liquid scintillation spectrometer (Packard Instruments, Downers Grove, Ill.). Unidirectional fluxes were calculated by the equation of Berger and Steele (10).

In all perfusions, an initial control study, during which saline was infused intravenously, was followed by a VIP period during which VIP was infused intravenously. Previous studies have shown that under control conditions absorption rates are consistent during two consecutive perfusion experiments (11).

VIP. Pure porcine VIP (Viktor Mutt, Karolinska Institute, Stockholm, Sweden), dissolved in normal saline that contained 0.5% albumin, was infused intravenously at a rate of 200 or 400 pmol/kg per h with a Harvard Apparatus constant infusion pump (Harvard Apparatus Co., Inc., S. Natick, Mass.).

Potential difference. Potential difference (PD) was measured between the perfusion solution, which served as a flowing intraluminal electrode, and a subcutaneous reference electrode (5). Briefly, the reference electrode consisted of saline in a Medicut catheter (Sherwood Medical Industries, St. Louis, Mo.) inserted into the subcutaneous tissue of the dorsal aspect of the forearm. This subcutaneous reference and the flowing intraluminal catheter were connected via 3 M KCl agar bridges and calomel half-cells to the input terminals of a battery-powered electrometer (model 602, Keithley Instruments, Inc., Cleveland, Ohio), and the output was displayed on a chart recorder (model 281, Rikadenki, Tokyo, Japan).

RESULTS

Effect of VIP during perfusion of a bicarbonate-containing solution. When a bicarbonate-containing balanced electrolyte solution (solution A, Table I) was perfused in the jejunum, intravenous infusion of VIP at 200 pmol/kg per h resulted in a significant reduction in water and electrolyte absorption when compared with the control period (Table II). When VIP was infused at 400 pmol/kg per h, the reduction in absorption of water and sodium was even greater, and mean net chloride secretion was observed. Bicarbonate absorption rate was reduced to approximately the same extent by the two doses of VIP; in both instances, bicarbonate absorption was reduced even though mean luminal bicarbonate concentration was higher during the VIP period than during the control period (due to less bicarbonate absorption in the mixing segment). If bicarbonate absorption from the test segment is expressed as a percentage of total bicarbonate which entered the test segment, VIP reduced bicarbonate absorption by 42 and 51% with the 200 and 400 pmol/kg per h rate of infusion, respectively.[2]

[2] Our conclusion that VIP inhibits bicarbonate absorption conflicts with an earlier conclusion from our group (8). This discrepancy is probably due to the fact that VIP inhibition of bicarbonate absorption results in higher luminal concentration of this ion during VIP test periods than during control test periods (Table II). This then mitigates the inhibitory

TABLE II

*Effect of VIP during Perfusion of a Bicarbonate-containing Solution**

	Water	Sodium		Chloride		Bicarbonate		
	Net‡ movement	Mean Na§ test segment	Net Na‡ movement	Mean Cl§ test segment	Net Cl‡ movement	Mean HCO_3§ test segment	Net HCO_3‡ movement	PD‖
	ml/h/30 cm	*meq/liter*	*meq/h/30 cm*	*meq/liter*	*meq/h/30 cm*	*meq/liter*	*meq/h/30 cm*	*mV*
VIP (200 pmol/kg/h) (n = 6)								
Control	−154 ±18	135.4 ±0.6	−19.6 ±2.1	126.3 ±1.3	−13.0 ±2.1	10.5 ±0.7	−7.0 ±0.4	−1.1 ±0.6
VIP	−84 ±17	138.5 ±0.6	−10.2 ±2.0	122.5 ±1.7	−5.9 ±1.9	16.3 ±1.2	−4.8 ±0.5	−2.2 ±0.4
P¶	<0.005	<0.025	<0.001	NS	<0.001	<0.02	<0.005	NS
VIP (400 pmol/kg/h) (n = 5)								
Control	−130 ±24	140.2 ±0.8	−17.9 ±3.4	126.1 ±3.1	−10.7 ±3.0	16.7 ±2.1	−7.8 ±0.7	−4.0 ±0.8
VIP	−26 ±21	141.9 ±1.1	−3.1 ±3.0	121.1 ±3.8	+1.4 ±2.3	23.2 ±3.0	−4.7 ±0.9	−6.3 ±0.8
P¶	<0.001	NS	<0.001	<0.005	<0.001	<0.005	<0.01	<0.025

* See Table I for composition.

‡ (−) net absorption; (+) net secretion.

§ Mean test segment concentration is the arithmetic mean of the concentration at the proximal and distal collecting sites.

‖ (−) indicates lumen negative PD.

¶ Significance of difference determined by Student's paired t test.

Both doses of VIP caused the PD to become more lumen-negative, but the difference reached statistical significance only with the larger dose.

Effect of VIP during perfusion of a bicarbonate-free solution. To evaluate the effect of VIP on active chloride secretion, it was necessary to perfuse an electrolyte solution that contained no bicarbonate; otherwise, normal absorptive processes conceal secretion (5).

During jejunal perfusion of a bicarbonate-free solution (solution B in Table I), water, sodium, chloride, and bicarbonate were secreted during the control period, when saline was infused intravenously (Table III). During intravenous VIP infusion, at either 200 or 400 pmol/kg per h, the jejunal secretion rate of water and electrolytes was enhanced, and the potential difference became more lumen-negative. Although most of these differences were not statistically significant with either dose of VIP, when all the data were combined (regardless of the VIP infusion rate) it was clear that VIP did enhance secretion rate to a small extent during perfusion of the bicarbonate-free solution ($P < 0.05$ for net water, sodium, chloride, and bicarbonate secretion and PD).

As can be seen by comparing data in Tables II and III, VIP had much more effect on water and electrolyte movement when the jejunum was perfused with an absorbable balanced electrolyte solution than when it was perfused with a bicarbonate-free solution.

Effect of VIP on unidirectional fluxes of sodium and chloride. During perfusion of the bicarbonate-containing solution, the chloride lumen-to-plasma flux was reduced with both the 200 and 400 pmol/kg per h dose of VIP when compared with the control period (Table IV). The plasma-to-lumen chloride flux was not significantly changed when either 200 or 400 pmol/kg per h VIP was infused, though there was a tendency for it also to decrease with VIP. More or less similar changes occurred in the sodium unidirectional fluxes: there was a significant reduction of sodium lumen-to-plasma flux with 400 pmol/kg per h VIP, while the plasma-to-lumen sodium flux was not altered to a statistically significant extent.

During perfusion of the bicarbonate-free solution, there was a significant reduction in both lumen-to-plasma and plasma-to-lumen chloride fluxes with the 200 and 400 pmol/kg per h VIP infusion (Table IV). There was no significant change in the sodium fluxes.

effect of VIP on further net bicarbonate absorption. In the earlier study (8), VIP did inhibit bicarbonate absorption if the latter is expressed as percent of the total load entering the test segment (Krejs and Fordtran, personal communication).

TABLE III

*Effect of VIP during Perfusion of a Bicarbonate-free Solution**

	Water	Sodium		Chloride		Bicarbonate		
	Net‡ movement	Mean [Na]§ test segment	Net Na‡ movement	Mean [Cl]§ test segment	Net Cl‡ movement	Mean [HCO_3]§ test segment	Net HCO_3‡ movement	PD‖
	ml/h/30 cm	*meq/liter*	*meq/h/30 cm*	*meq/liter*	*meq/h/30 cm*	*meq/liter*	*meq/h/30 cm*	*mV*
VIP (200 pmol/kg/h) (n = 6)								
Control	+12	137.9	+3.0	110.0	+2.5	0.5	+0.3	−2.7
	±6	±0.9	±0.8	±0.8	±0.8	±0.1	±0.2	±0.7
VIP	+31	139.8	+5.6	111.4	+4.8	1.0	+0.7	−3.8
	±10	±0.8	±1.8	±0.7	±1.8	±0.4	±0.5	±0.7
P	NS	NS	NS	NS	NS	<0.05	NS	NS
VIP (400 pmol/kg/h) (n = 5)								
Control	+1	139.3	+1.5	110.0	+1.0	1.4	+0.5	−3.3
	±16	±0.6	±2.0	±0.4	±2.3	±2.3	±0.5	±0.8
VIP	+34	140.4	+6.5	113.9	+5.8	3.6	+1.7	−4.8
	±31	±0.4	±4.4	±1.3	±4.7	±0.6	±0.9	±0.4
P	NS	<0.02	NS	NS	NS	<0.01	<0.05	<0.05
VIP (200 and 400 pmol/kg/h) (n = 11)								
Control	+7	138.5	+2.3	110.4	+1.8	0.9	+0.4	−3.0
	±7	±0.6	±1.0	±0.5	±1.1	±0.3	±0.2	±0.5
VIP	+32	140.1	+6.0	112.5	+5.3	2.2	+1.4	−4.2
	±13	±0.4	±2.1	±0.8	±2.2	±0.5	±0.5	±0.4
P	<0.025	<0.05	<0.025	<0.05	<0.05	<0.005	<0.05	<0.05

See legend of Table II for footnote designation.

We have previously provided evidence of active chloride secretion by the normal human jejunum during perfusion of a bicarbonate-free solution (5). Part of the evidence for this was a discrepancy between the observed chloride flux ratio (L → P/P → L) and the chloride flux ratio that would be expected if chloride movement were passive (calculated by Ussing's equation) (12). As shown in Table V, a similar discrepancy was noted in the present control experiment during perfusion of the bicarbonate-free solution. This discrepancy was also seen during VIP infusion. Although quantitative inferences must be interpreted with caution, it is interesting to note that the difference between the calculated and observed flux ratios (Δ flux ratio) was significantly greater during the 400 pmol/kg per h VIP infusion than during the control period ($P < 0.05$). (The Δ flux ratio was also significantly different when all 11 studies, regardless of VIP dose, were combined [$P < 0.01$].) These results would be compatible with increased active chloride secretion during VIP infusion.

Effect of VIP on fructose and fructose-stimulated water and electrolyte absorption. Fructose is absorbed from the jejunum by facilitated diffusion by a mechanism that does not (in contrast to glucose) stimulate active sodium absorption (13). Fructose absorption stimulates the passive absorption of sodium chloride. To evaluate the effect of VIP on absorption of fructose and fructose-stimulated water and electrolyte absorption, the jejunum was perfused in random order with a saline-mannitol solution (solution C, Table I) and on a separate test day with a saline-fructose solution (solution D, Table I). On each test day the subject received intravenous saline during control period, followed by intravenous VIP at a rate of 200 or 400 pmol/kg per h. The difference in absorption of water and electrolytes between the two solutions when the subject was under the same test condition (i.e., intravenous saline or VIP) represented fructose-stimulated water and electrolyte absorption.

The saline-mannitol solution was infused at a rate of 10 ml/min, whereas the saline-fructose solution was infused at a rate of 13 ml/min. This difference in infusion rates compensated for differences in absorption/secretion rates with fructose and mannitol, so that similar flow rates would be obtained in the test segment (13), which was 20 cm in this group of studies.

TABLE IV
Effect of VIP on Unidirectional Sodium and Chloride Fluxes

	Bicarbonate-containing solution*				Bicarbonate-free solution*			
	Chloride fluxes		Sodium fluxes		Chloride fluxes		Sodium fluxes	
	L→P‡	P→L	L→P	P→L	L→P	P→L	L→P	P→L
	meq/h/30 cm test segment							
VIP (200 pmol/kg/h) (n = 6)								
Control	40.3 ±4.1	27.2 ±2.2	62.8 ±2.1	43.2 ±2.0	25.0 ±2.4	27.6 ±2.1	47.1 ±4.6	50.0 ±4.5
VIP	29.8 ±4.2	24.0 ±2.5	53.2 ±4.7	43.0 ±3.8	17.9 ±2.4	22.7 ±3.0	41.3 ±5.3	46.9 ±5.9
P§	<0.01	NS	NS	NS	<0.025	<0.01	NS	NS
VIP (400 pmol/kg/h) (n = 5)								
Control	34.4 ±5.3	23.8 ±3.7	50.1 ±6.1	32.2 ±3.0	33.3 ±2.7	34.5 ±3.4	52.9 ±2.3	54.4 ±2.4
VIP	14.7 ±1.7	16.1 ±1.7	33.6 ±3.8	30.5 ±3.5	20.2 ±3.3	26.1 ±2.6	45.7 ±5.2	52.3 ±7.1
P§	<0.01	NS	<0.05	NS	<0.005	<0.01	NS	NS

* See Table I for composition.
‡ L→P, lumen-to-plasma; P→L, plasma-to-lumen.
§ Significance of difference determined by Student's paired t test.

TABLE V
*Effect of VIP on Chloride Flux Ratios during Perfusion of a Bicarbonate-free Solution**

	Chloride flux ratio			Δ Flux ratio¶
	Observed‡	Calculated§	P‖	
200 pmol/kg/h (n = 6)				
Control	0.9±0.1	1.1±0.1	<0.01	0.2±0.1
VIP	0.8±0.1	1.2±0.1	<0.01	0.4±0.1
P‖				<0.1
400 pmol/kg/h (n = 5)				
Control	1.0±0.1	1.2±0.1	<0.025	0.2±0.1
VIP	0.8±0.2	1.3±0.1	<0.05	0.5±0.2
P‖				<0.05

When all 11 studies are combined, the difference between the Δ flux ratio during VIP infusion and the control period is statistically significant ($P < 0.01$).
* See Table I for composition.
‡ Observed flux ratio is L→P flux divided by P→L flux.
§ Calculated flux ratio for passive ion movement as determined by Ussing equation (12).
‖ Significance of difference determined by Student's paired t test.
¶ Δ flux ratio is the arithmetic difference between calculated and observed flux ratio.

At 200 pmol/kg per h , VIP did not affect fructose absorption in six normal subjects; this infusion rate of VIP slightly decreased mean fructose-stimulated water and sodium chloride absorption, but this effect was statistically significant only for sodium (8.1–6.7 meq/h per 20 cm, $P < 0.02$). When VIP was infused at 400 pmol/kg per h, there was again no significant effect on fructose absorption, but fructose-stimulated water and sodium chloride absorption was markedly reduced, as shown in Table VI.

Effect of VIP on mannitol-induced secretion. We next determined to what extent VIP affected mannitol-induced passive secretion. Only the larger VIP infusion rate was studied. As shown in Table VII, when the jejunum was perfused with a saline solution containing 140 mM mannitol (solution E, Table I), there was net secretion of water and sodium chloride during intravenous infusion of saline. VIP infusion (400 pmol/kg per h) inhibited this secretion (Table VII).

Effect of VIP on sodium diffusion and on glucose-stimulated electrical potential. The jejunum was perfused sequentially with three isotonic test solutions, two containing either mannitol or glucose and a low concentration of sodium chloride (solutions F and G in Table I) and another that was a balanced electrolyte solution (solution A in Table I). Each solution was perfused for 1 h, at a rate of 10 ml/min. The first 30 min of each perfusion was con-

TABLE VI

Effect of VIP on Fructose and Fructose-stimulated Water and Electrolyte Absorption in Five Normal Subjects

	Mean luminal concentration/flow rate‡				Absorption/secretion rates§						
	i.v. Saline		i.v. VIP (400 pmol/kg/h)		i.v. Saline			i.v. VIP (400 pmol/kg/h)			
	Man*	Fru*	Man	Fru	Man	Fru	Δ‖	Man	Fru	Δ‖	P value¶ for Δ
Fructose	—	20.5 ±0.8	—	20.0 ±1.5	—	−4.9 ±0.8	4.9 ±0.8	—	−4.0 ±0.7	4.0 ±0.7	NS
Water	11.2 ±0.2	9.6 ±0.2	12.2 ±0.4	9.9 ±0.2	+27 ±9	−70 ±16	97 ±22	+19 ±11	−8 ±6	27 ±8	<0.02
Sodium	126.3 ±0.5	128.2 ±0.8	128.9 ±0.9	131.4 ±1.4	+3.5 ±0.9	−5.6 ±1.8	9.1 ±2.2	+3.4 ±1.2	+1.7 ±0.9	1.7 ±0.8	<0.025
Chloride	131.8 ±0.8	132.9 ±1.1	133.4 ±1.4	134.1 ±1.7	+3.7 ±1.3	−5.2 ±1.5	8.9 ±2.3	+3.3 ±1.5	+1.4 ±1.0	1.9 ±1.3	<0.05

* See Table I for composition of solutions. Man, saline-mannitol C; Fru, saline-fructose D.

‡ Arithmetic mean of concentration (mmol or meq/liter) and flow rates (ml/min) at proximal and distal ends of the 20-cm test segment.

§ (+) net absorption, (−) net secretion in mmol, ml, or meq/h/20 cm for fructose, water, and electrolytes, respectively.

‖ Δ is the difference between the transport rates with fructose and mannitol solutions.

¶ Significance of difference determined by Student's paired *t* test; NS, not significant ($P \geq 0.1$).

sidered an equilibration period, whereas during the final 30-min period PD was recorded continuously. The entire experiment was repeated on the same test day in the same subjects, while VIP (instead of saline) was infused intravenously at 200 pmol/kg per h. On a separate test day the entire sequence was repeated in separate subjects using the 400 pmol/kg per h rate of infusion of VIP.

During intravenous saline infusion, the PD was lumen-positive (+5.0±0.6 mV) when the jejunum was perfused with a saline-mannitol solution, lumen-negative (−3.8±0.4 mV) when perfused with a balanced electrolyte solution, and even more lumen-negative (−9.0±0.8 mV) when perfused with a saline-glucose solution. The PD was slightly more negative with VIP during perfusion of the balanced electrolyte solution with both the 200 (−4.7±0.9 mV) and 400 (−4.1±0.4 mV) pmol/kg per h dose than during the control period. Neither infusion rate of VIP had any statistically significant effect on the lumen-positive PD during perfusion of solution F (+6.0±1.3 mV, +7.0±1.1 mV, respectively, for the low and high dose of VIP) or on the lumen-negative PD during perfusion of solution G (−10.3±1.4 mV, −10.1±0.9 mV, respectively, for the low and high dose of VIP).

DISCUSSION

Under normal conditions in man, jejunal absorption of a balanced physiological electrolyte solution in vivo is dependent on bicarbonate absorption. Sodium and bicarbonate are absorbed by an active process involving Na/H exchange (4), and water and sodium chloride

TABLE VII

Effect of VIP on Passive (Mannitol-induced) Secretion

	Water	Sodium		Chloride		
	Net secretion	Mean [Na] test segment	Net Na secretion	Mean [Cl] test segment	Net Cl secretion	PD*
	ml/h/20 cm	*meq/liter*	*meq/h/20 cm*	*meq/liter*	*meq/h/20 cm*	*mV*
Control	88±11	94.1±1.3	13.4±1.6	97.3±1.6	13.8±2.0	+3.8±0.7
VIP (400 pmol/kg/h)	46±10	94.7±1.1	8.3±1.2	97.1±1.1	7.3±1.1	+3.8±0.5
P‡	<0.05	NS	<0.05	NS	<0.05	NS

$n = 6$.

* (+) lumen-positive PD.

‡ Significance of difference determined by Student's paired *t* test.

are then absorbed passively in response to osmotic pressure and concentration gradients (7). If bicarbonate absorption is eliminated, by substitution of sulfate for bicarbonate in the perfused test solution, the jejunum no longer absorbs water, sodium, or chloride.

The present studies show that VIP inhibits jejunal bicarbonate absorption, presumably by inhibition of Na/H exchange. However, it appears unlikely that this is the only mechanism by which VIP inhibits jejunal absorption. This is most evident when one compares the effect of the high and low doses of VIP. Both doses inhibited bicarbonate absorption by ~50%, yet the high dose inhibited water and sodium chloride absorption to a much greater extent than the small dose (Table II). Therefore, the larger dose of VIP must inhibit absorption by some nonbicarbonate-mediated mechanism.

The most obvious possibility, in light of previous work in animal experiments in vitro (2), was that the large dose of VIP might induce more active chloride secretion than the small dose. To evaluate the effect of VIP on active secretion, we perfused the jejunum with a bicarbonate-free solution, which allows active chloride secretion to be revealed (5). We found that VIP does stimulate active chloride secretion (this is discussed further in the next to last paragraph of this Discussion); however, the magnitude of this enhanced secretion was rather small, and was not clearly greater with the large than with the small dose of VIP. It thus seemed unlikely that stimulation of active secretion played a major role in the marked inhibition of absorption by the high dose of VIP during jejunal perfusion of the balanced electrolyte solution.

Since inhibition of active bicarbonate absorption and stimulation of active chloride secretion appeared inadequate to explain the observed effect of the large dose of VIP, it seemed possible that VIP might inhibit passive salt and water absorption. To test for this, we evaluated the effect of VIP on fructose-stimulated absorption. Fructose was chosen for study because it is rapidly absorbed by the jejunum by a mechanism that does not enhance active electrolyte absorption (13); fructose stimulation of water and electrolyte absorption is mediated passively. Fortunately for our purposes, VIP did not inhibit fructose absorption rate, so the extent to which fructose absorption was accompanied by absorption of salt and water could be used to assess the effect of VIP on passive water and salt absorption. The results revealed that the large dose of VIP markedly inhibited fructose-stimulated absorption of sodium chloride and water, whereas the small dose had only a slight inhibitory effect (Table VI).

The hypothesis that the large dose of VIP inhibits passive movement of sodium chloride and water was tested by an additional experiment. When isotonic solutions containing mannitol are perfused through the jejunum, the jejunum secretes water and sodium chloride. This secretion results from passive forces (6). If VIP inhibits passive absorption of water and sodium chloride in response to fructose absorption, it should also inhibit passive secretion of water and sodium chloride in response to perfusion with mannitol. The results of the experiment supported the hypothesis (Table VII).

These results offer an explanation for the effect of VIP on jejunal absorption of physiological test solutions. The small dose inhibits absorption mainly because it inhibits bicarbonate absorption, presumably via inhibition of Na/H exchange. This dose of VIP also inhibits passive absorption of water and sodium chloride, and it probably stimulates active chloride secretion, but these effects of the small dose of VIP are relatively unimportant. The large dose of VIP inhibits bicarbonate absorption and stimulates active chloride secretion to about the same extent as the small dose, but it inhibits passive water and sodium chloride absorption to a much greater extent than does the small dose of VIP.

As far as we are aware, no one has previously suggested that the effect of VIP (or any other disorder of intestinal transport) is mediated in part by inhibition of passive movement of water and electrolytes. Others have noted that conductance across in vitro mucosa is reduced by cholera toxin (1); however, as far as we are aware, it is not known whether conductance, as measured in vitro, and passive net water and electrolyte movement, as measured in vivo, are controlled and determined by the same factors.

How VIP reduces passive movement of water and sodium chloride is unknown from our studies. VIP could be reducing passive movement through either paracellular or transcellular pathways by making these transport routes functionally more restrictive or by reducing accessibility to them. Previously it was shown that there is narrowing of the intercellular spaces during VIP administration to dogs in vivo (14), but whether this anatomical change represents a mechanism for functional change is uncertain; it may be the result and not the cause of alterations in water and electrolyte transport.

Regardless of the manner by which VIP alters passive movement, the fact that VIP does not influence the direction or magnitude of the PD change resulting from perfusion of the jejunum with solutions containing a low sodium chloride concentration (sodium diffusion potential) suggests that VIP does not alter the cation-selective nature of the major channels for passive diffusion of anions and cations. We also demonstrated that VIP does not change the direction or magnitude of the glucose-stimulated potential.

This suggests that glucose absorption and glucose stimulation of sodium movement across the brush border and lateral membranes are qualitatively intact during VIP infusion.

During perfusion of either the balanced or the bicarbonate-free solution, the PD was significantly more negative during VIP infusion. This may be due to a stimulation of active chloride secretion (assuming that chloride secretion is electrogenic), since flux ratio analysis suggested enhanced active chloride secretion during VIP infusion. It may seem contradictory to postulate a stimulation of active chloride secretion when plasma-to-lumen flux of chloride tended to fall rather than rise (Table IV). However, this apparent discrepancy is probably explained by the simultaneous inhibitory effect of VIP on passive chloride movement. In other words, VIP reduces passive chloride diffusion from plasma-to-lumen (and from lumen-to-plasma) and increases active plasma-to-lumen flux; the reduction in passive diffusion is quantitatively greater, so total plasma-to-lumen chloride flux falls in spite of the stimulated active chloride secretion.

From our studies we conclude that the major effect of VIP in the human jejunum in vivo is to decrease normal absorption of water and electrolytes—not only active bicarbonate absorption, but also passive absorption of water and sodium chloride in response to osmotic forces generated by active or facilitated solute transport. Although an increase in active chloride secretion does occur, this does not appear to be of major importance, at least not with these doses of VIP. It is possible that larger doses might induce an important, or even dominant, active electrolyte secretion by the jejunum. However, it should be noted that the infusion rates of VIP that we employed result in steady-state plasma VIP concentrations which are well within the range of values found in patients with severe secretory diarrhea apparently caused by VIP-secreting endocrine tumors (8). So, the doses of VIP which we infused are in the pathophysiological range of interest, even though they do not constitute a full dose-response study. Studies with significantly larger doses of VIP (in terms of a dose-response curve) will probably never be possible in humans because they result in intolerable side effects.

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