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Comparison of VIP-induced electrolyte secretion at three levels in rat small intestine

AR Chikhlssa *, A Gharzouli **, G Charpin [1], M Descroix-Vagne [1], D Pansu [1***

Hôpital E Herriot, Pavillon H bis, Unité de Recherche INSERM U 45 et École Pratique des Hautes Études, 69437 Lyon Cedex 03, France

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Summary — Duodenal, jejunal and ileal loops were prepared and an iso-osmotic test solution injected, containing 80 mM Na^+, 5 mM K^+, 1.2 mM Ca^{2+}, 77 mM Cl^-, 10 mM HCO_3^- and 136 mM mannitol. ^{14}CPEG 4000 was used as a non-absorbable marker and ^{36}Cl was added to measure the bidirectional fluxes. During the 60-min *in vivo* incubation time, the duodenum actively secreted bicarbonate, a virtually zero flux in the jejunum was observed, whereas the ileum absorbed water and chloride and secreted bicarbonate. The response to the perfused doses of 0.15 to 2.4 nmol•100 g^{-1}•h^{-1} of VIP (vasoactive intestinal peptide) differed qualitatively and quantitatively in the 3 segments: VIP increased bicarbonate secretion and induced chloride secretion in the duodenum, induced chloride secretion in the jejunum without changing bicarbonate minimal influx, induced bicarbonate secretion and suppressed chloride absorption in the ileum. The minimal dose required was lower in the duodenum (0.3 nmol•100 g^{-1}•h^{-1}) than in the jejunum and ileum (1.2 nmol•100 g^{-1}•h^{-1}). The functional heterogeneity of the small intestine was clearly demonstrated after VIP stimulation.

bicarbonate / chloride / intestinal secretion / sodium / rat / VIP

Résumé — Comparaison de la sécrétion induite par le VIP (peptide intestinal vasoactif) à trois niveaux de l'intestin grêle chez le rat. *Des anses duodénales, jéjunales et iléales ont été constituées chez le rat anesthésié et remplies avec un ml de solution test contenant 80 mM de Na^+, 5 mM de K^+, 1,2 mM de Ca^{2+}, 77 mM de Cl^-, 10 mM de HCO_3^- et 136 mM de mannitol. Le ^{14}CPEG4000 a été utilisé comme marqueur non absorbable du mouvement d'eau et du ^{36}Cl a été ajouté pour évaluer les flux bidirectionnels. Au niveau des anses témoins, le duodénum a sécrété activement le bicarbonate, le flux électrolytique était nul dans le jéjunum, l'iléon a absorbé du chlore et sécrété du bicarbonate. La réponse à la perfusion IV de VIP aux doses de 0,15 à 2,4 nmol/100 g•h a confirmé les différences fonctionnelles aux trois niveaux explorés. Le VIP a augmenté la sécrétion de bicarbonate et induit une sécrétion de chlore dans le duodénum, induit une sécrétion de chlore dans le jéjunum, supprimé l'absorption de chlore et d'eau et augmenté la sécrétion de bicar-*

* Present address: University of Damascus, Laboratory of Physiology, Faculty of Medicine, Damascus, Syria

** Present address: Institut de Biologie, University de Sétif, 19000 Sétif, Algeria

*** Correspondence and reprints

bonate et d'eau dans l'iléon. La dose minimale active a été plus basse dans le duodénum (0,3 nmol/100 g•h) que dans le jéjunum et l'iléon (1.2 nmol/100 g•h). Le VIP induit une activation de la sécrétion anionique associée à une inhibition de l'absorption.

bicarbonate / chlore / sécrétion intestinale / rat / sodium / VIP

INTRODUCTION

The stimulation of intestinal secretion by the vasoactive intestinal peptide (VIP) was described shortly after the discovery of the peptide (Barbezat and Grossman, 1971) and has been largely documented, but no simultaneous study on the effects of this peptide on the 3 segments of the small intestine – duodenum, jejunum and ileum – has been published. Studies on the duodenal response to VIP in the rat reported the induction of bicarbonate secretion in the superficial epithelium (Isenberg *et al,* 1984) as well as in Brunner's glands (Kirkegard *et al,* 1984) but did not explore the movement of other ions. In the jejunum and ileum, the increase in water secretion has been shown in the dog (Barbezat, 1973; Mailman, 1978), rabbit (Camilleri *et al,* 1981) and cat (Eklund *et al,* 1981) using isolated loop perfusion in man by triple lumen tube perfusion (Krejs *et al,* 1980), in rat (Coupar, 1976) using the *in situ* ligated loop technique and in pig, in which a watery diarrhea was induced (Modlin *et al,* 1978). The anionic secretion differed according to the species: in the jejunum of the dog VIP induced an active chloride and bicarbonate secretion (Krejs *et al,* 1978) but a chloride secretion in man (Krejs *et al,* 1980). In the ileum a bicarbonate secretion was associated with the suppression of chloride absorption in man (Krejs, 1982) while chloride was the only secreted anion in the rabbit (Schwartz *et al,* 1974). The present study was undertaken to document regional heterogeneity in intestinal transport function and to explore the outcome of such heterogeneity during the same stimulation by VIP at the various levels of the intestine.

MATERIALS AND METHODS

Male Sprague–Dawley rats, purchased from Iffa Credo (L'Arbresle, France) were fed on standard chow (A04, UAR, Villemoisson-sur-Orge, France) until their body weight averaged 200 ± 25 g. Thirty-six h before the experiment, food was withdrawn, and the animals were allowed free access to water. On the day of the experiment, the animals were anesthetized (4 mg sodium pentobarbital / 100 g BW) and an intravenous infusion of VIP in 0.9% saline solution was initiated *via* a jugular catheter. The infusion rate was 0.05 ml/min. Doses of VIP (MW = 3 326, GIH Res Lab, Karolinska Institutet, Stockholm, Sweden) were 0.15, 0.30, 0.60, 1.2 and 2.4 nmol•100 g^{-1}•h^{-1}, respectively.

Three 10-cm intestinal loops were prepared for each animal. Ligation for the duodenal loop began at the pylorus, for the jejunal loop 3 cm distal to the ligament of Treitz, for the ileal loop 10 cm proximal to the ileo-caecal junction. Only the ileal segment that still contained some food residues was rinsed with 0.9% NaCl. The hepatobiliary canal was also tied off. One ml of the test solution was injected into each loop with the aid of a calibrated syringe and an additional ligature was placed proximal to the injection site to avoid leakage of the injected solution. The ligated loops were placed back into the abdominal cavity which was then sutured. Sixty min later, the animals were killed by an intravenous injection of air, the loops were exteriorized, cut proximally to the outside of the ligature. Loop contents were collected, centrifuged and the supernatant was measured and used for the determinations.

Preliminary experiments indicated that when 80 mM NaCl and 140 mM mannitol solution was injected, neither electrolytes nor water moved transmurally in the jejunum. These concentrations were then made the basis of a solution that contained 70 mM NaCl, 5 mM KCl, 1.2 mM $CaCl_2$, 10 mM $HNaCO_3$, 136 mM mannitol, pH 8.1. ^{36}Chloride in HCl (NEN France) was added at a concentration of 0.05 μCi/ml as an influx marker. Tritiated polyethylene glycol 4 000 (^{3}HPEG 4000, NEN France 0.05 μCi/ml) mixed with 5 g/l of cold PEG 4 000 was used as a non-absorbable marker. Only those experiments where recovery of labeled PEG 4 000 was ≥ 88% were analyzed. Recovery of ^{14}C mannitol from the lumen was controlled in a complementary study and exceeded 90%.

The VIP concentration in the blood before and after intravenous perfusion and in the catheter was measured by radioimmunoassay (Chayvialle *et al*, 1980). Na^+ and K^+ content were determined by flame photometry, Cl^- by coulometric titration, bicarbonate by alkali-acid titration and radioactivity by liquid scintillometry.

Comparisons between control and experimental situations were based on means derived from 7–14 loops. Net absorption from the lumen was expressed as a negative and net secretion as a positive value. Statistical analyses of differences were carried out with Student's *t*-test, or the Mann–Whitney test. Linear relationships were derived by least-squares analysis.

RESULTS

Control conditions

In the duodenum, an efflux of sodium, chloride and bicarbonate with 0.24 ml of water was observed (table I). The final luminal concentration of sodium and bicarbonate was increased significantly (table II). The final pH was 7.4. In the jejunum, there was an efflux of sodium and chloride, an influx of bicarbonate with almost no water movement. The luminal concentration of bicarbonate decreased from 10 mM to 6.7 ± 0.4 mM. pH decreased from 8.1 to 6.6. In the ileum, a significant influx of water and chloride and an efflux of bicarbonate was observed. These fluxes induced a significant decrease in luminal chloride concentration and a significant increase in luminal bicarbonate concentration. The final luminal pH was 8.0. In the 3 intestinal segments, the bidirectional fluxes were evaluated by the ^{36}Cl influx which constituted 86% of the ^{36}Cl instilled in the duodenum and jejunum and 93% of the ^{36}Cl instilled in the ileum. The calculated chloride efflux

Table I. Ionic and water fluxes in control rats.

Segment	*n*	*Water (ml)*	*Na (μEq)*	*K (μEq)*	*Cl (μEq)*	*HCO_3 (μEq)*	*36Cl influx (% injected)*
Duodenum	14	0.24 ± 0.07	44 ± 12	2.6 ± 0.6	20 ± 10	16 ± 3	86
Jejunum	14	0.02 ± 0.02	13 ± 4	2.2 ± 0.8	6 ± 4	−3 ± 0.3	86
Ileum	13	−0.13 ± 0.03*	−10 ± 5	−1.2 ± 1.2*	−55 ± 2**	38 ± 5**	93

Fluxes expressed per loop and per h. Secretion is indicated by positive values, absorption by negative values. M ± SEM; * $P < 0.05$; ** $P < 0.01$, significantly different from fluxes in the duodenum and jejunum.

Table II. Final luminal ionic concentration in control and VIP-treated rats.

Ion	*Test solution (mM)*	*Duodenum (mM)*		*Jejunum (mM)*		*Ileum (mM)*	
		T	*VIP*	*T*	*VIP*	*T*	*VIP*
Na^+	80	96.7 ± 4.0*	130.6 ± 1.0***	90.4 ± 1.4*	115.0 ± 2.0***	79.3 ± 2.7	106.8 ± 3.7***
Cl^-	77.6	76.0 ± 4.0	96.7 ± 1.6***	81.8 ± 2.4	109.4 ± 2.0***	25.8 ± 1.3*	58.9 ± 1.5***
HCO_3^-	10	20.2 ± 1.4*	38.8 ± 0.6***	6.7 ± 0.4	8.0 ± 0.4**	53.9 ± 3.3*	56.4 ± 1.0
K^+	5	6.2 ± 0.3	8.4 ± 0.8	6.6 ± 0.3	6.0 ± 0.7	4.6 ± 0.2	5.3 ± 0.2

M ± SEM; T = control loops; $n = 14$; * $P < 0.05$ significantly different from the test solution; VIP = rats perfursed with 2.4 nmol 100 $g^{-1} \cdot h^{-1}$, $n = 7$; ** $P < 0.05$; *** $P < 0.01$, significantly different from the final concentration in control loops.

(^{36}Cl influx – ^{35}Cl net absorption) was significantly lower in the ileum than in the duodenum and jejunum. Potassium was secreted in the duodenum and jejunum and absorbed in the ileum.

The doses of VIP ranged from 0.15 to 2.4 nmol•100 $g^{-1} \cdot h^{-1}$, VIP adhesion to the flask and catheter walls was 70% at the low dose, 30% at the high dose. The basal VIP blood concentration was 1.5–3.6 10^{-12} M at the beginning of the experiment and reached 5.3 10^{-11} M and 5.7 10^{-9} M after the low and high dose respectively.

In the duodenum (fig 1) VIP increased the secretion of sodium, chloride, bicarbonate and water. The increase was significant with doses of ≥ 0.3 nmol•100 $g^{-1} \cdot h^{-1}$. The response to VIP was dependent on the log of the dose. In the jejunum the increase in sodium and chloride secretions was dose-dependent for the doses of 0.6 nmol•100 $g^{-1} \cdot h^{-1}$. In the ileum the absorption reverted to secretion for water and sodium at doses of 1.2 and 2.4 nmol and for chloride at the dose of 2.4 nmol.h^{-1}/100 g. At every level of the intestine final electrolyte concentrations increased (table II). Chloride influx, expressed as ^{36}Cl absorption was inhibited in a dose-dependent manner and decreased to 51, 70 and 66% in the duodenum, jejunum and ileum respectively with the highest dose. On the other hand, chloride efflux was significantly increased.

The potassium secretion augmented with the dose of VIP. The final concentration attained 8 mM in the duodenum, did not change in the jejunum and the ileum, while the potassium flux paralleled the water flux (table II).

DISCUSSION

The *in vivo* ligated loop was shown to be a closed system where anionic and cationic concentrations equilibrated during the 60-min study. The low concentrations of sodium and chloride corresponded to the zero flux ion concentration (Fromm and Hegel,

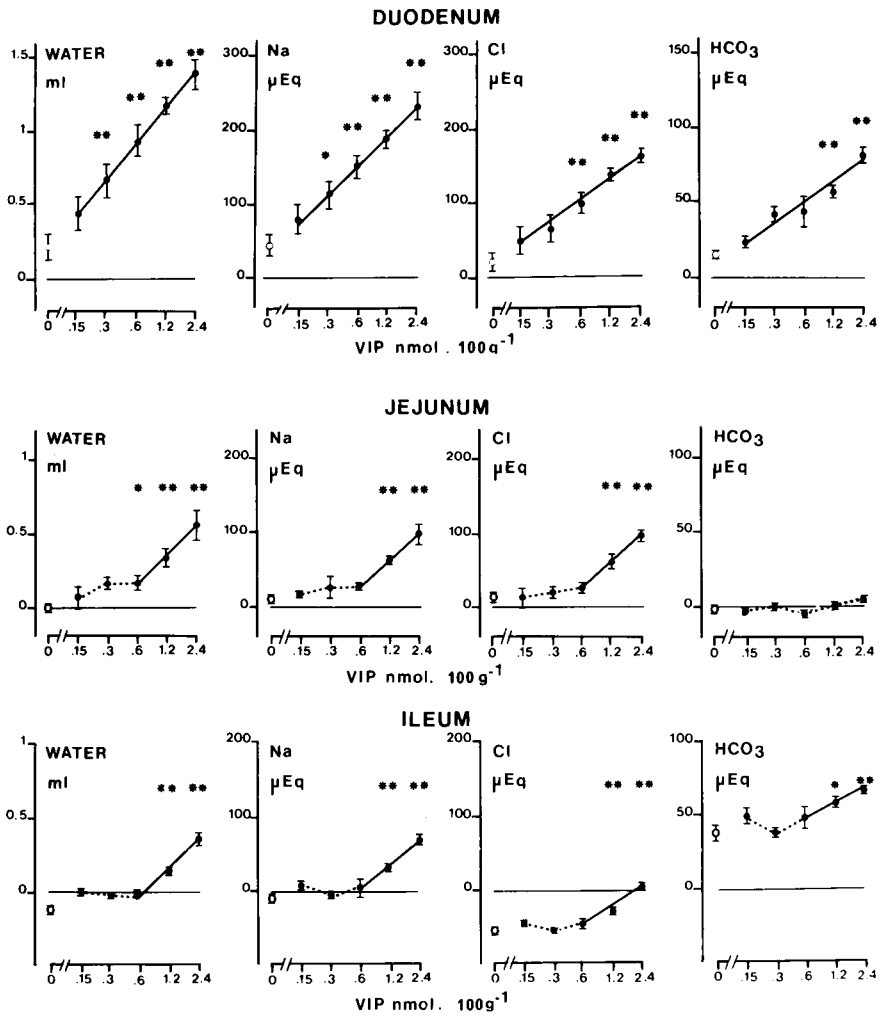

Fig 1. Effect of VIP on ion and water fluxes in the intestinal ligated loops. Positive values indicate a secretion. Doses in nmol•100 g^{-1}•h^{-1}; n = 7 for each treated group, n = 14 for control groups. * $P < 0.05$; ** $P < 0.01$ compared with the control values. The linear relationship between log10 dose and secretion was highly significant for the 5 doses tested in the duodenum, and for the 3 high doses tested in the jejunum and ileum.

1987) in the jejunum, *ie* the concentration where there is no net exchange of ions between the lumen and the blood when the osmolarity is maintained by the presence of mannitol in the test solution.

Heterogeneity of the small intestine was demonstrated in control animals. In the duodenum, an efflux of bicarbonate, sodium and chloride was observed. Sodium bicarbonate was secreted by both Brunner's

glands and epithelial cells, since the bicarbonate flux was quantitatively higher than that measured in a duodenal loop prepared beyond the Brunner's gland region and dependent on epithelial cells only (7 $\mu mol \cdot cm^{-1} \cdot h^{-1}$) (Heylings and Feldman, 1988). Such an efflux was active, since bicarbonate concentration in the efflux was 66 mM. The distension caused by the injected fluid was sufficient to induce vagal stimulation of the secretion (Nylander *et al,* 1987). In the jejunum, the steady state was characterized by the decrease of luminal pH to 6.6. This decrease was sufficient to dissociate bicarbonate and to permit the diffusion of CO_2 from the lumen through the cell. In the ileum the net absorption of water, sodium and chloride created a high sodium gradient between the luminal (79.3 mM) and serosal (140 mM) fluid. The ligated loop model revealed characteristics that were in agreement with the physiological function of the small intestine: neutralization of gastric secretion in the duodenum, reabsorption of bicarbonate in the jejunum, water absorption in the ileum.

The response to VIP was observed with plasma concentrations (53 pM–5.7 nM) that were 10 to 1 000 times higher than the physiologial concentration (a pmol range in our study), and parallelled the plasma concentration of immuoreactive VIP (1.5 nM) measured in patients suffering from a watery diarrhea syndrome induced by VIP-secreting tumors (Said and Faloona, 1975). The values were in the K_d range (1 nM) of the VIP receptors present in plasma membranes of rat enterocytes (Prieto *et al,* 1981) and corresponded to the estimated concentration of VIP created in the vicinity of intestinal cells by paracrine stimulation (Laburthe and Amiranoff, 1989).

A lower dose of VIP was required to induce a significant secretion of water and electrolytes in the duodenum than in the distal parts of the intestine. Since an equivalent number of VIP binding sites was found in epithelial cells obtained from the duodenum, jejunum and ileum (Prieto *et al,* 1981), the duodenal response to the low dose probably represented the bicarbonate secretion of Brunner's glands, known to respond to 0.27 pmol VIP 100 $g^{-1} \cdot h^{-1}$ in the rat (Kirkegaard *et al,* 1984). Chloride concentration in the secreted fluid was 100 mM, *ie* near the systemic value, but the significant increase in luminal chloride concentration argued in favor of an active secretion. In the jejunum, the chloride secretion was active since the chloride concentration in the secreted fluid was 160 mM. The absence of bicarbonate secretion was also observed in human jejunum (Krejs *et al,* 1980) but contrasted with the significant secretion of bicarbonate observed in the dog (Krejs *et al,* 1978). In the ileum, inhibition of basal absorption and water secretion are induced by VIP in all species: in the dog (Mailman, 1978), rat (Wu *et al,* 1979) and man (Krejs *et al,* 1980). Bicarbonate is the only anion secreted in rat and man (Krejs, 1982). The absence of bicarbonate secretion in the jejunum and of chloride secretion in the ileum was demonstrated in man under basal (Turnberg *et al,* 1970) and stimulated (Krejs, 1982) conditions. Our data demonstrate the similar anionic response in rat and in man.

A diagram of the fluxes is presented in figure 2, taking into account the action of recently identified exchangers and channels. In the duodenum a bicarbonate secretion from both epithelial cells and Brunner's glands is observed which depends on 3 mechanisms (Flemström, 1987): a furosemide sensitive HCO_3^-/Cl^- exchange, an active chloride-independent electrogenic HCO_3^- secretion driven by a bicarbonate-sensitive ATPase (Stiel *et al,* 1984), and diffusion through tight junctions. The simultaneous secretion of chloride and bicarbo-

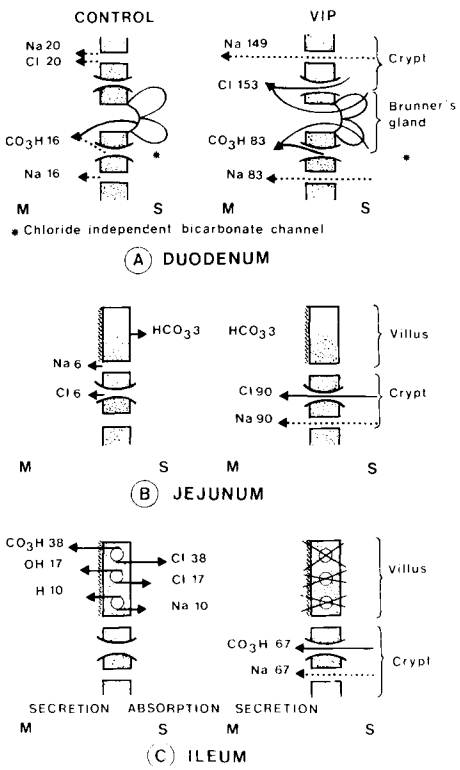

Fig 2. Suggested relationship between net fluxes and possible transport models. Fluxes are those measured in intestinal loops of control rats or rats perfused with 2.4 nmol•100 g^{-1}•h^{-1} of VIP. Representation as used by Tai and Decker (1980). The drawing indicates crypt cells as the unique secretory cells; secretion may in fact occur in both crypt and villus cells (Stewart and Turnberg, 1989). The numerical values are the mean of the net fluxes in µmol/h, ⇝ = exchange; ⋋ = channel; ⊠ = inhibition. The sodium efflux that follows the anionic secretion was described as a diffusion -------> over the paracellular path. A, Duodenum: the anionic active secretion present in the basal state is stimulated by VIP. B, Jejunum: control values are characterized by a zero flux, VIP activates the chloride channel. C, Ileum: absorption in control is the sum of the action of 3 exchangers, VIP suppresses absorption and activates bicarbonate secretion.

nate confirmed that VIP activated both the chloride-independent bicarbonate secretion and a possible apical chloride channel. Evidence of bicarbonate secretion independent of chloride exchange was emphasized by the concomitant reduction in ^{36}Cl influx from 86 to 49% of the quantity injected. In the jejunum the decrease in pH seems to be permitted by the coupled exchangers Na^+/H^+ and Cl^-/CO_3H^- in which the rate of cationic exchange largely exceeds that of the anionic exchange (Hopfer and Liedke, 1987). The VIP-induced chloride secretion depends on the activation of the apical chloride channel by cAMP-dependent protein kinases (Schwartz *et al,* 1974; Laburthe *et al,* 1979). In the ileum, the sodium-independent bicarbonate/chloride exchange could mediate bicarbonate secretion and some of the chloride absorption (Alper, 1991) whereas the coupled exchangers Na^+/H^+ and Cl^-/OH^- may allow the net absorption of sodium chloride and water (Liedke and Hopfer, 1982). The response to VIP is consistent with an inhibition of the absorptive processes located in mature cells, possibly through cAMP production (Eklund *et al,* 1987) and an activation of bicarbonate secretion. This interpretation is in keeping with the presence of VIP receptors throughout the crypt villus axis (Laburthe and Amiranoff, 1989).

In summary, VIP induces water secretion by stimulating anion secretion of both chloride and bicarbonate in the duodenum, chloride only in the jejunum, bicarbonate only in the ileum. The existence of 2 anionic secretions may depend on specific mechanisms, *ie* chloride channel and ATP dependent bicarbonate efflux; nevertheless, it raises the possibility of a unique anion-selective channel that is more permeable to one or the other anion depending on the epithelium (Sullivan and Field, 1991).

The *in situ* ligated loop technique differentiated the movement of ions at 3 levels

of the intestine after administration of VIP. In the duodenum, the increase in bicarbonate and chloride secretion suggests an action on glandular and epithelial cells. In the jejunum, the action may concern chloride channels only. In the ileum, VIP may suppress absorption by villus cells and induce secretion by all cells, or only crypt cells. These findings confirm the plurality of the mechanisms regulating electrolyte secretion and absorption in the small intestine.

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