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# EFFECTS OF VASOACTIVE INTESTINAL POLYPEPTIDE ON INTESTINAL ABSORPTION AND BLOOD FLOW

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## SUMMARY

1. Intestinal absorption and blood flow in anaesthetized dogs was determined after I.V. infusion of vasoactive intestinal polypeptide (VIP) (1·75–175 ng/min) to determine the contribution of the cardiovascular changes to transport.

2. $^{22}Na$ and $^{3}H_2O$ were utilized to determine the unidirectional fluxes of Na and $H_2O$ from saline perfused through the ileal lumen and the clearances of $^{3}H_2O$ were used to determine total and absorptive site blood flow.

3. Net Na and $H_2O$ absorption were reversed to secretion by VIP at 175 ng/min due to a significant decrease in unidirectional absorptive fluxes and smaller increases in secretory fluxes.

4. Arterial pressure and absorptive site blood flow were reduced in proportion to the changes in Na and $H_2O$ fluxes.

5. Total and absorptive site blood flow decreased and the blood flow resistances increased.

6. Prior treatment with guanethidine to suppress sympathetic effects did not greatly affect the responses to VIP. Prior treatment with atropine to suppress cholinergic effects inhibited most of the effects of VIP.

7. Absorptive site blood flow was linearly related to absorptive fluxes of Na and $H_2O$ but with different slopes for results from atropinized dogs as compared to those from dogs given VIP alone or VIP plus guanethidine.

8. It was concluded that VIP reduces gut absorption through a generalized cardiovascular effect and also through a mechanism which depends on the release of ACh by the gut.

## INTRODUCTION

Several hormones of splanchnic origin have been shown to increase secretion or to reduce absorption by the gut (Makhlouf, 1974; Bynum, Jacobson & Johnson, 1971; Hubel, 1972) and under some conditions the effect seems to be physiological (Bussjaeger & Johnson, 1973; Helman & Barbezat, 1977; Bynum *et al.* 1971). Vasoactive intestinal polypeptide (VIP), a hormone that is chemically related to glucagon and secretin (Said & Mutt, 1972), increases gut secretion (Barbezat & Grossman, 1971) and has been implicated as the diarrhoeal agent in certain disease states (Bloom, Polak & Pearse, 1973; Seif, Sadowski, Heni, Fischer, Bloom, & Polak, 1975). Glucagon has previously been shown to decrease absorption by the canine gut, at least partly, through a change in the magnitude of Starling forces and

blood flow at the absorptive site (MacFerran & Mailman, 1977). Part of this effect was attributed to reduced blood pressure and stimulation of baroreceptors and consequent sympathetic stimulation. Because of the above considerations, the effect of VIP and the influence of autonomic activity on gut transport and blood flow was determined.

## METHODS

The basic techniques have been described elsewhere (Mailman & Jordan, 1975; MacFerram & Mailman, 1977). Briefly, isotonic saline containing $^3H_2O$, [$^{14}$C]inulin and $^{22}$Na was perfused at a known rate through the lumen of ileal segments ($42 \pm 4$ cm from ileocaecal junction, $48 \pm 4$ g) of dogs anaesthetized with pentobarbitone. The effluent was collected and $^3$H, $^{14}$C and $^{22}$Na measured by liquid scintillation counting. Net and unidirectional Na and $H_2O$ fluxes were calculated by the method of Berger & Steele (1958). Na was determined by flame photometry. Total segmental blood flow (TBF) was calculated from the clearance of $^3H_2O$ as (1) TBF = $^3H_2O$ absorbed/($[^3H_2O]_V - [^3H_2O]_A$). Absorptive site blood flow was calculated as (2) ASBF = $^3H_2O$ absorbed/($[^3H_2O]_L - [^3H_2O]_A$). $[^3H_2O]$ represents the concentration of $^3H_2O$ and A, V and L represent mesenteric artery, vein and gut lumen respectively. All appropriate data are expressed per gram of wet gut wt. In a few expts. the transmural potential difference was measured with a high impedance electrometer (Keithley) and agar–1 M-KCl salt bridges but no appreciable change in the voltage of about 6 mV (lumen negative) occurred with VIP infusion and these measurements were discontinued.

In the present experiments, a 60 min control period of three 20 min periods was followed by I.V. infusion (0·15 ml./min) of VIP at 1·75, 17·5, and 175 ng/min for three 20 min periods at each infusion rate which were followed in turn by three 20 min periods in which the VIP infusion was stopped. In one group of animals ($n = 8$) no pre-treatment was given. In a second group ($n = 5$) guanethidine (10 mg/kg, subcutaneously) was administered, as a sympatholytic agent, 12 hr prior to the experiment. In one animal, phenoxybenzamine (5 mg, I.V.), an $\alpha$ receptor blocker, was used and since the results were the same as with guanethidine it is included with the guanethidine group. In a third group ($n = 4$), atropine (0·5 mg plus 0·1 mg/hr) was infused I.V. beginning 30 min before the control period. The degree of sympathetic block by guanethidine was assessed at the end of each experiment by bilateral carotid occlusion which did not raise blood pressure by more than 10 mmHg within 1 min as compared to an increase of 50 mmHg within 15 sec in control animals. The degree of parasympathetic block by atropine was assessed by infusing ACh I.V. at 0·5 mg/min which did not lower blood pressure by more than 10 mmHg within 3 min as compared to a decrease of 50 mmHg within 1 min in control animals.

Arterial and mesenteric vein blood pressures were determined with mercury and saline manometers, respectively. Blood flow resistance for TBF or ASBF was determined as (3) resistance = $(BP_A - BP_V)$/TBF or ASBF, where BP represents blood pressure. Capillary pressure at the absorptive site was calculated by the method of Pappenheimer & Soto-Rivera (1948). The postcapillary/precapillary resistance ratio during control periods was taken as 1/4 and any subsequent changes in overall resistance were considered as due to changes in precapillary resistance (Folkow, 1967). It should be emphasized that this is an indirect measurement and only an approximation of capillary pressure.

Statistical analysis was carried out by paired $t$ test in which each animal served as its own control. The average of the three 20 min control periods was subtracted from each subsequent period and the significance of the differences determined. Linear regression analysis was employed to determine the relationship between the variables.

## RESULTS

*Control periods.* Guanethidine had little effect on control period gut Na, $H_2O$ fluxes or blood flow but did decrease arterial pressure and blood flow resistance as compared to untreated animals (Table 1). Atropine did not greatly affect net transport of Na, $H_2O$ fluxes or blood flow but did increase their secretory and absorptive fluxes and decreased the absorptive site but not total blood flow resistance.

*Time course.* In general, VIP had little effect during the first 20 min of its infusion. In dogs not given pre-treatment, the values of the parameters were similar after 20–40 and 40–60 min of VIP infusion. In animals given atropine or guanethidine the values of the parameters at 20–40 min were intermediate between those at 0–20 and 40–60 min. In the Figures showing the effects of VIP only the values at 40–60 min are shown. In the Figures showing the relationship between the fluxes and blood flow or estimated capillary pressure the values at both 20–40 and 40–60 min are shown.

TABLE 1. Control period values for intestinal fluxes and blood flow after atropine and guanethidine (mean ± S.E. of mean)

| | | | |
|---|---|---|---|
| Net Na absorbed ($\mu$equiv. $g^{-1}.min^{-1}$) | 1·55 ± 0·29 | 1·62 ± 0·39 | 1·30 ± 0·41 |
| Secretory Na flux ($\mu$equiv. $g^{-1}.min^{-1}$) | 1·45 ± 0·19 | 1·28 ± 0·23 | 2·21 ± 0·74 |
| Absorptive Na flux ($\mu$equiv. $g^{-1}.min^{-1}$) | 2·70 ± 0·30 | 2·93 ± 0·42 | 3·50 ± 0·52 |
| Net $H_2O$ absorbed ($\mu$l. $g^{-1}.min^{-1}$) | 11·1 ± 1·3 | 10·1 ± 3·1 | 8·5 ± 2·2 |
| Secretory $H_2O$ flux ($\mu$l. $g^{-1}.min^{-1}$) | 19·5 ± 1·5 | 20·7 ± 1·9 | 31·2 ± 6·0 |
| Absorptive $H_2O$ flux ($\mu$l. $g^{-1}.min^{-1}$) | 30·6 ± 2·4 | 30·8 ± 1·6 | 39·7 ± 5·0 |
| Absorptive site blood flow ($\mu$l. $g^{-1}.min^{-1}$) | 38·9 ± 3·3 | 42·7 ± 2·8 | 64·2 ± 14·2 |
| Total blood flow (ml. $g^{-1}.min^{-1}$) | 0·72 ± 0·13 | 0·74 ± 0·07 | 0·74 ± 0·15 |
| Arterial blood pressure (mmHg) | 133 ± 5 | 109·0 ± 7 | 139·0 ± 7 |
| Venous blood pressure (mmHg) | 10·1 ± 1·4 | 10·7 ± 2·1 | 10·0 ± 1·0 |
| Absorptive site resistance (mmHg. $ml.^{-1}$. g.min) | 3803 ± 434 | 2600 ± 228 | 2564 ± 495 |
| Total resistance (mmHg.$ml.^{-1}$.g.min) | 226 ± 43 | 153 ± 15 | 226 ± 52 |

*Na fluxes.* Below 175 ng/min, VIP tended to decrease net Na transport, and at 175 ng/min Na transport decreased sharply and significantly (Fig. 1) and was converted from net absorption to net secretion. Net Na transport returned toward control values after stopping the VIP infusion but was still significantly below control period values.

Decreased net Na transport was due primarily to a decrease in the absorptive Na fluxes and secondarily to a smaller increase in the secretory fluxes (Fig. 1). Guanethidine did not greatly alter the effects of VIP on the Na fluxes. Atropine prevented the decrease in net Na absorption due to VIP. The decrease in the absorptive flux of Na, although not significant, was of similar magnitude to the decrease seen in the other two groups. The small effect on the net flux was due mainly to inhibition of the VIP-induced increase in the secretory flux.

*$H_2O$ fluxes.* $H_2O$ absorption tended to parallel the changes in Na absorption (Fig. 2). VIP, at 175 ng/min, decreased net $H_2O$ absorption in untreated and guanethidine treated animals due to decreases in the absorptive $H_2O$ fluxes. The secretory and absorptive $H_2O$ fluxes were also significantly decreased at 17·5 ng/min VIP

in untreated animals. After stopping the VIP infusion the $H_2O$ fluxes returned toward control period values although the fluxes were, in general, still significantly different from control values. Atropine blocked the changes due to VIP but when VIP was stopped the absorptive $H_2O$ fluxes became significantly less than controls. As with the Na fluxes, the lack of effect of VIP on the net $H_2O$ fluxes in the presence of atropine was due mainly to a non-significant decrease in the secretory flux rather than to any change in the absorptive fluxes.

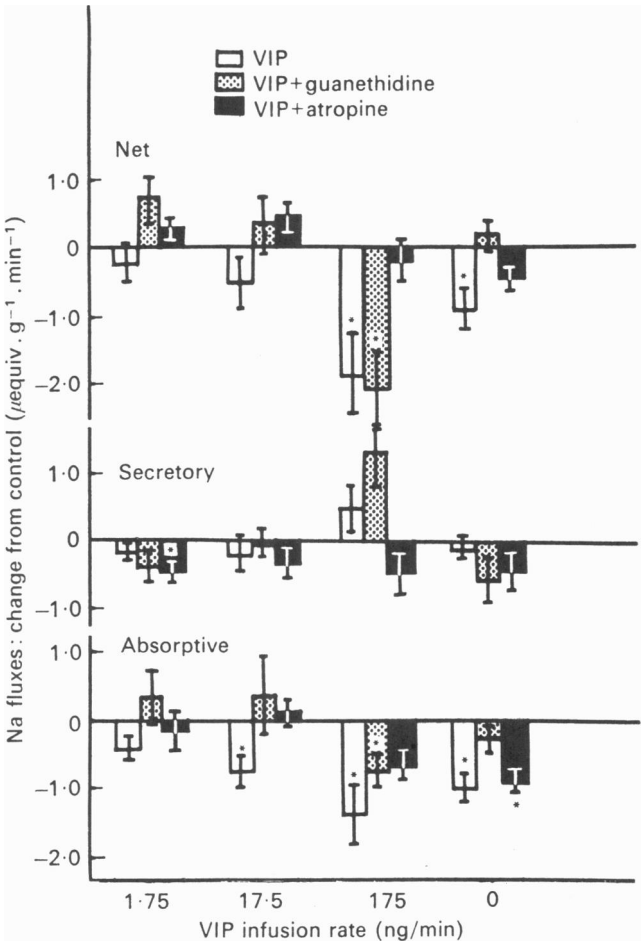


Fig. 1. Effect of I.V. infusion of VIP on Na fluxes across canine ileum in animals given no pre-treatment ($n$ = 8), guanethidine ($n$ = 5) or atropine ($n$ = 4). * indicates a value significantly different from control at the 5% level; vertical bars denote ± S.E. of mean.

*Blood flow.* Both total and absorptive site blood flows were decreased at 175 ng/min VIP infusion, as was arterial pressure (Fig. 3). After treatment with guanethidine, VIP did not alter the total blood flow, but the absorptive site blood flow and arterial pressure were also decreased. The total blood flow did not return towards control values after stopping the VIP infusion. After treatment with atropine, neither the absorptive site blood flow nor arterial pressure were significantly changed

by VIP but total blood flow decreased significantly at 17·5 ng/min VIP. The absorptive site blood flow even though not significantly changed, decreased more in the atropine treated dogs than in the other two groups.

Absorptive site and total blood flow resistance were significantly increased by VIP at 17·5 and 175 ng/min (Fig. 4). Guanethidine prevented the increase in both

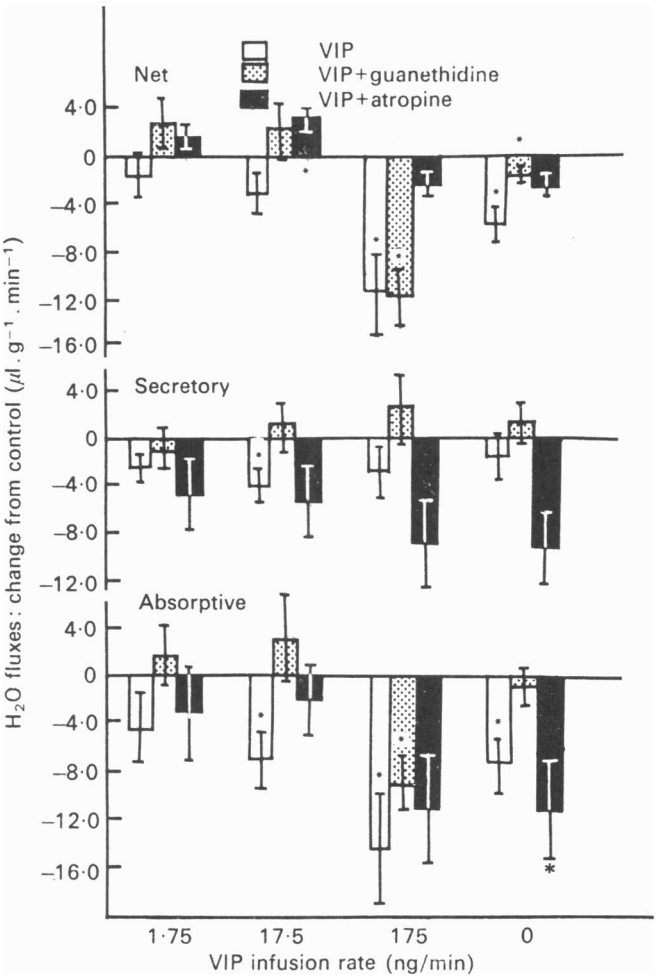


Fig. 2. Effect of I.V. infusion of VIP on $H_2O$ fluxes canine ileum in animals given no pretreatment ($n$ = 8), guanethidine ($n$ = 5) or atropine ($n$ = 4). * indicates a value significantly different from control at the 5% level; vertical bars denote ± S.E. of mean.

resistances. Atropine prevented the increase in absorptive site blood flow resistance but there was a small but significant increase in total blood flow resistance by VIP at 175 ng/min. Mesenteric vein pressure was not significantly changed in any group (data not included).

There was a significant correlation between changes in the absorptive site blood flow and absorptive fluxes of both Na and $H_2O$ associated with VIP infusion (Fig. 5). The relationship between these was very similar for dogs given guanethidine and

those given no pre-treatment. In dogs given atropine there was a different relationship between the absorptive site blood flow and the absorptive fluxes but the relationship was still linear. At any given absorptive site blood flow there was less of a decrease in absorptive flux of both Na and $H_2O$ due to VIP after atropine pre-treatment.

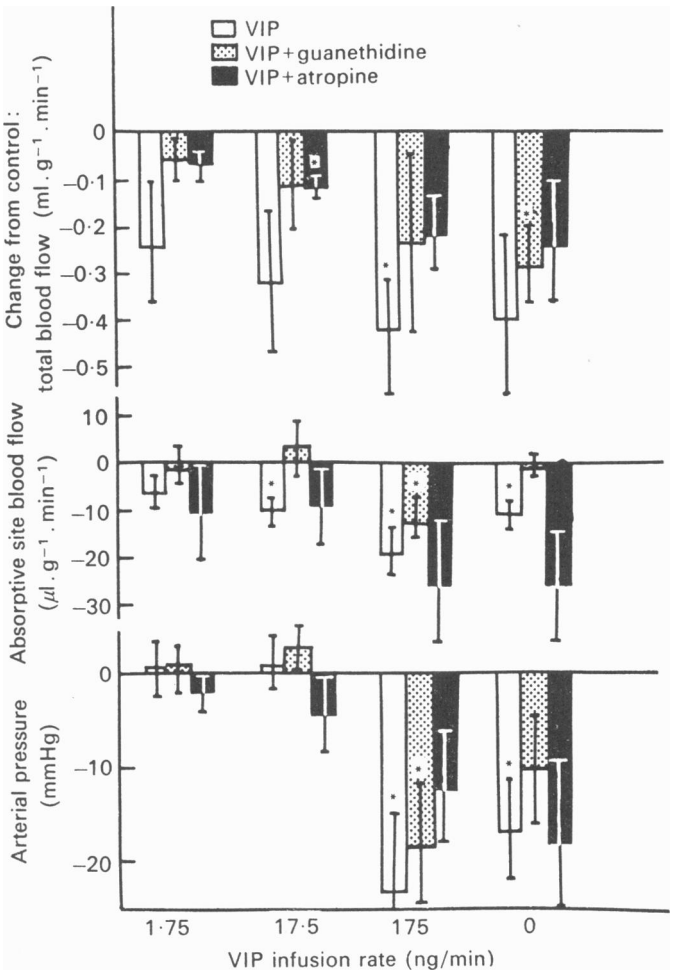


Fig. 3. Effect of I.V. infusion of VIP on cardiovascular parameters in dogs given no pre-treatment ($n$ = 8), guanethidine ($n$ = 5) or atropine ($n$ = 4). * indicates a value significantly different from control at the 5% level; vertical bars denote ± S.E. of mean.

The secretory fluxes of Na were significantly negatively correlated with the estimated capillary pressure in guanethidine-treated and in untreated animals but not in animals given atropine (Fig. 6). The secretory flux of $H_2O$, but not the secretory flux of Na, was significantly positively correlated with capillary pressure in atropine-treated animals, but there was no significant correlation between the secretory $H_2O$ fluxes and estimated capillary pressure in untreated or guanethidine treated animals.

## DISCUSSION

VIP, at a dose of 175 ng/min, caused reduced gut absorption (net secretion) of Na and $H_2O$, due mainly to significant decreases in the unidirectional absorptive fluxes in untreated dogs and also in dogs given guanethidine to block sympathetic reflexes. Associated with the reduced absorption were a decrease in absorptive site blood flow and a decrease in arterial pressure. Atropine blocked most of the

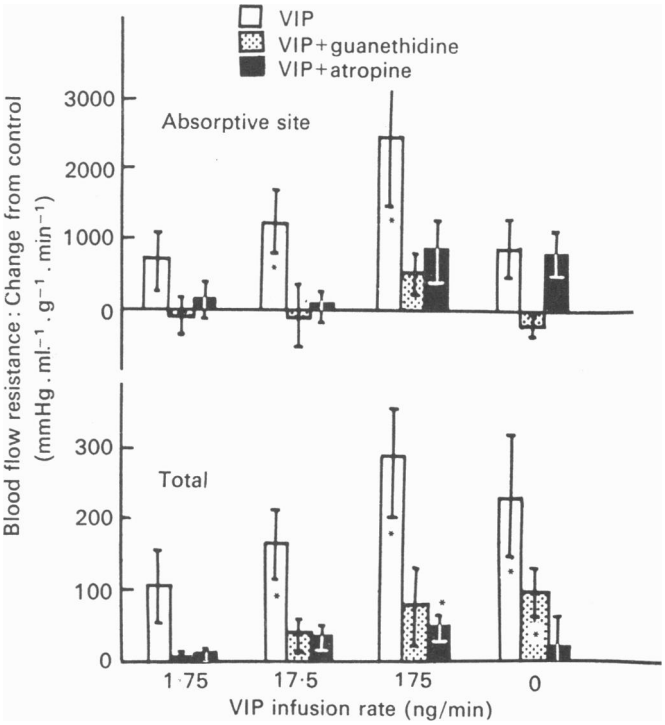


Fig. 4. Effect of I.V. infusion of VIP on intestinal absorptive site blood flow resistance or total blood flow resistance in dogs given no pre-treatment ($n$ = 8), guanethidine ($n$ = 5) or atropine ($n$ = 4). * indicates a value significantly different from control at the 5% level; vertical bars denote ± S.E. of mean.

effects of VIP. Increased secretion following VIP infusion has been observed by others in dogs at doses of 13 $\mu$g/min (Barbezat & Grossman, 1971). In humans, VIP at plasma levels of 0·7–30 ng/ml., as compared to normal values of below 0·5 ng/ml., has been associated with diarrhoea in disease states (Sief, *et al.* 1975; Udall, Singer, Huang, Nichols & Ferry, 1976).

VIP is one of the few gastrointestinal hormones which has been shown to increase intestinal adenylate cyclase activity *in vitro* (Schwartz, Kimberg, Sheerin, Field & Said, 1974; Klaveman, Conlon, Levy & Gardner, 1975) which has been associated with increased active secretion. However, even the hormones which do not activate adenylate cyclase will reduce net absorption primarily by reducing mucosal to serosal fluxes (Gardner, Peskin, Cerda & Brooks, 1967) as does VIP (Schwartz *et al.*

1974). This raises the question of whether the changes in gut transport associated with VIP are due to a direct effect on secretion and/or another effect, perhaps cardiovascular.

VIP decreased arterial pressure to about the same extent in the presence or absence of guanethidine, most likely due to its direct vasodilator activity (Kitamura, Yoshida & Said, 1975; Said & Mutt, 1970). Absorptive site blood flow resistance was

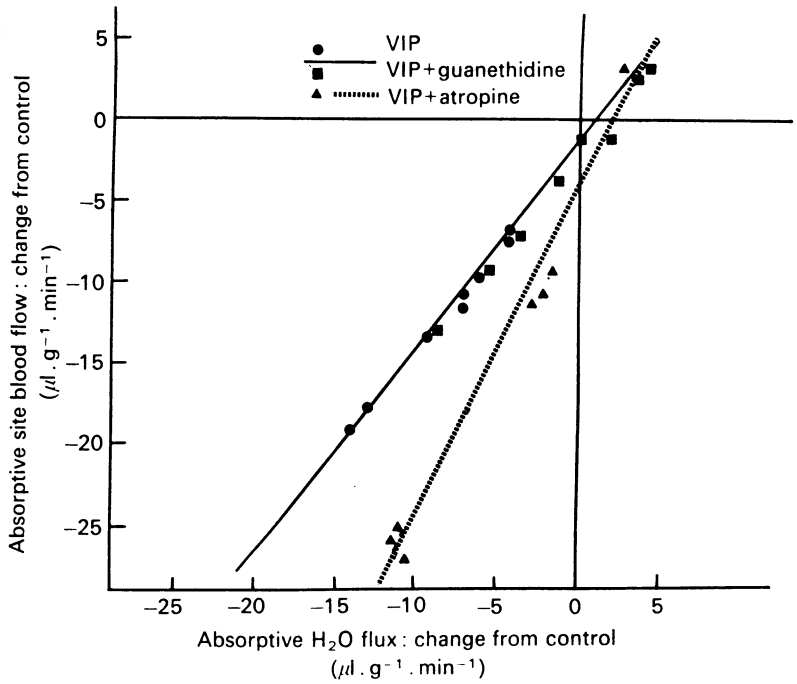


Fig. 5. The relationship between the absorptive fluxes of $H_2O$ in dogs given no pre-treatment (●), guanethidine (■) or atropine (▲), respectively. The lines represent the combined least squares regression lines for dogs given no pre-treatment or guanethidine and those given atropine. The regression lines for the Na fluxes paralleled those of $H_2O$ (not shown). The correlation coefficients were at least 0·91 ($P < 0{\cdot}1\%$).

increased by VIP in the absence of guanethidine but was not affected by VIP in the presence of guanethidine, suggesting that the resistance increases were due to sympathetic stimulation consequent to decreased arterial pressure. VIP did nct overcome the increased blood flow resistance attributed to sympathetic stimulation which was different from the effect of glucagon (MacFerran & Mailman, 1977) and may be related to the finding that VIP slightly increases superior mesenteric artery resistance but decreases hepatic artery and portal vein resistance (Thulin & Olsson, 1973) but glucagon can selectively decrease intestinal resistance (Ulano, Treat, Shanbour, & Jacobson, 1972). Thus, the relative vasodilating ability of these hormones will determine the extent to which sympathetic vasoconstriction is overcome in a certain vascular bed. Considering that guanethidine blocks sympathetic responses which raise blood pressure it would be expected that the decrease in arterial pressure caused by VIP would be greater in guanethidine-treated animals

rather than slightly less, as was the case. But arterial pressure in the guanethidine-treated dogs was, initially, 25 mmHg less in the control period and therefore may not be able to be decreased below a minimal level. A surprising finding was that atropine also significantly blocked the increase in absorptive site blood flow resistance and the decrease in arterial pressure but not the increase in total blood flow resistance, although the magnitude of the latter was greatly decreased. Possibly, there is a cholinergic component of the peripheral vasodilating action of VIP.

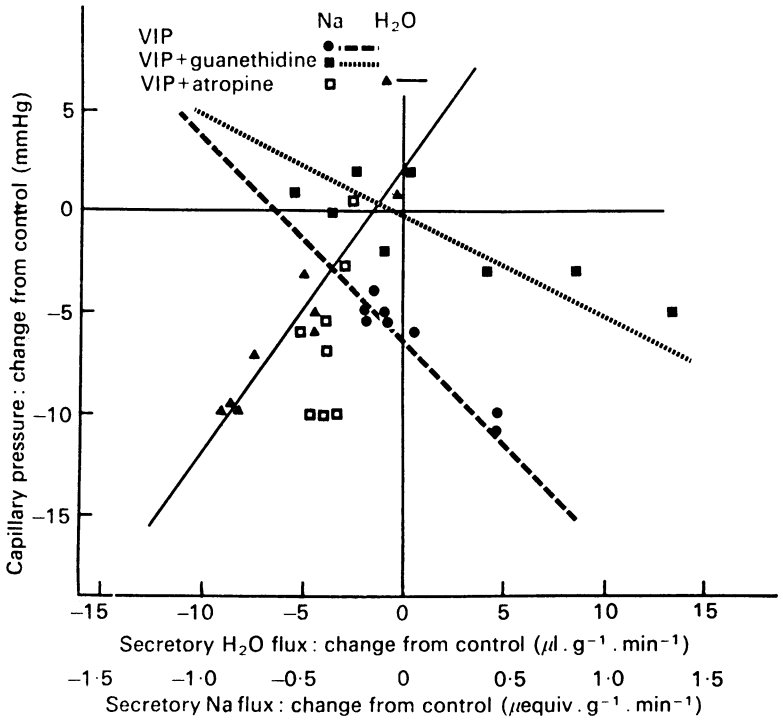


Fig. 6. The relationship between capillary pressure and the secretory Na fluxes in dogs given no pre-treatment (●) or guanethidine (■) or atropine (□), and the secretory $H_2O$ flux in dogs given atropine (▲). The lines represent the least squares regression line only for those relationships showing statistically significant correlations (the smallest correlation was $-0{\cdot}83$, $P < 1\%$). The secretory Na fluxes in atropine-treated dogs are shown for reference and the secretory $H_2O$ fluxes in dogs given no pre-treatment or guanethidine which did not show a statistically significant correlation with capillary pressure, are not shown.

The net effect of VIP was to decrease the absorptive fluxes of Na and $H_2O$ in proportion to the resulting decreases in the absorptive site blood flow. This relationship is consistent with the absorptive fluxes being partly dependent on the washout by blood flow as suggested by others (MacFerran & Mailman, 1977; Winne, 1972; Dobson, Sellers, & Thorlacius, 1971). However, the changes in absorptive site blood flow cannot solely explain the changes in absorptive fluxes because their relationship has a different slope in atropine-treated dogs as compared to guanethidine-treated or untreated dogs. There may be a cholinergic component in the effects of VIP on gut

transport such that when cholinergic stimuli are blocked there is less of a decrease in the absorptive fluxes due to VIP.

The relationship between the secretory Na and $H_2O$ fluxes and estimated capillary pressure is different from that observed in previous expts. (Mailman & Jordan, 1975; MacFerran & Mailman, 1977). In general, the secretory Na and $H_2O$ fluxes parallel each other and also capillary pressure when the body fluid volume is expanded with saline or when glucagon is infused, and this relationship was attributed to changes in the magnitude of Starling forces and a consequent effect on passive movement across the gut. But, when VIP is infused, capillary pressure is inversely correlated to the secretory Na flux and not significantly correlated to the secretory $H_2O$ flux in guanethidine-treated or untreated animals. After atropine, the change in the secretory $H_2O$ fluxes associated with VIP infusion are directly correlated to capillary pressure but the secretory Na fluxes are not significantly correlated. Starling forces would affect the movement of Na and $H_2O$ from blood to lumen independent of other ongoing influences. The increased secretory fluxes of Na in the presence of decreasing capillary pressure may represent a direct effect of VIP on the secretory movement of Na across the epithelial cell which is sufficiently large that it overcomes the simultaneous tendency for the secretory fluxes of Na to decrease because of decreasing capillary pressure.

Effects of atropine in inhibiting the gastrointestinal responses to hormones, analogous to those observed here, have been observed by others. Pentagastrin, cholecystokinin (CCK) octapeptide, glucagon and ACh increase blood flow and oxygen consumption by the gut *in vivo* and the effects, except those of glucagon, are blocked by atropine (Bowen, Pawlik, Fang & Jacobson, 1975). Blockers of $\alpha$ or $\beta$ adrenergic responses did not alter the responses to pentagastrin. CCK and gastrin release ACh from intestinal muscle (Vizi, Bertaccini, Impiccitore & Knoll, 1973), and preventing the release of ACh inhibits the effects of the hormones on contractility. Stimulation of extrinsic nerves has been shown to increase absorption by the gut, and cutting them increases secretion which is further increased by physostigmine but reduced by atropine (Wright, Jennings, Florey & Lium, 1940). Also, pilocarpine increases secretion of Na and $H_2O$ into the ileum and atropine blocks these effects (Hubel, 1976). Atropine by itself did not significantly affect ileal absorption of NaCl or $H_2O$ although it tended to increase their absorption. If VIP does act partly through release of ACh the effect could be either local or through vagal influence, or VIP may act through a cholinergic receptor.

The infusion rate of VIP, 175 ng/min, does not seem an unphysiological rate judging by analogy to similar hormones (Helman & Barbezat, 1977). However, the decrease in blood pressure of about 24 mmHg does seem unphysiological even though ingestion of food in adult dogs is associated with a 10–15 mmHg decrease in blood pressure (Bloom, Edwards, Hardy, Malinowska & Silver, 1975). Also, VIP is largely inactivated in the liver and thus any released from the intestine would not recirculate back to the gut (Kitamura *et al.* 1975). VIP may act locally upon ACh release and the concentration within the tissue could be relatively high without affecting blood pressure and its attendant effects on gut blood flow and capillary pressure. If VIP alters epithelial transport the effect could be on the transcellular transport process or on the conductance of the tissues (Sheerin & Field, 1977).

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