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# EFFECTS OF SUBSTANCE P AND VASOACTIVE INTESTINAL POLYPEPTIDE ON GASTROINTESTINAL BLOOD FLOW IN THE ATLANTIC COD *GADUS MORHUA*

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## Summary

The cardiovascular effects of vasoactive intestinal polypeptide (VIP) and substance P (SP) *in vivo* were studied in the Atlantic cod *Gadus morhua*. Special interest was focused on the distribution of blood to the gastrointestinal circulation.

VIP increased the blood flow to the gut by increasing cardiac output and by decreasing resistance in the vascular bed supplied by the coeliac artery. In addition, VIP had an inhibitory effect on spontaneous stomach motility.

SP induced a triphasic response in the coeliac artery blood flow. An initial increase was followed by a rapid decrease, to the control level or below, and a second increase in flow. The triphasic response was not changed after vagotomy, while atropine blocked the second phase, the decrease, indicating that a local cholinergic mechanism is involved. The significance of this temporary decrease in flow remains to be elucidated. SP also caused an increase in cardiac output and in mesenteric artery blood flow. In addition to the increase in cardiac output, the increase in gastrointestinal blood flow produced by SP is accomplished by a decreased resistance in the coeliac and mesenteric vascular beds.

## Introduction

The innervation of the cardiovascular system was for long considered to involve only adrenergic and cholinergic nerves: all nervous influence on cardiovascular events was explained by more or less complex interactions between adrenergic and cholinergic autonomic nerves. However, following more recent discoveries, primarily from studies of the enteric nervous system, it is evident that the control of the cardiovascular system also depends on non-adrenergic, non-cholinergic factors, notably peptidergic nerves (see Burnstock and Griffith, 1988). Immunohistochemical studies, performed mainly in mammals, have identified a number of neuropeptides in perivascular nerves. Among these are vasoactive intestinal

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polypeptide (VIP), with a widespread distribution in the cardiovascular system (Uddman *et al.* 1981; Della *et al.* 1983), and substance P (SP), with an especially dense distribution in vessels of the abdominal viscera in mammals (Furness *et al.* 1982; Barja *et al.* 1983) and in the toad *Bufo marinus* (Morris *et al.* 1986). Both neuropeptides produce vasodilation in several vascular beds in mammals (Said and Mutt, 1970; Hallberg and Pernow, 1975; Blitz and Charbon, 1983; Rozsa and Varro, 1987), SP probably being involved in the vasodilator response to antidromic stimulation of sensory nerves (Lembeck and Holzer, 1979).

Not much is known about the peptidergic innervation of the cardiovascular system in teleost fishes. Vessels surrounded by nerve fibres containing VIP- or SP-like immunoreactivity have been observed in the gastrointestinal tract of some fishes (Lundin and Holmgren, 1984; Bjenning and Holmgren, 1988; Burkhardt-Holm and Holmgren, 1989). In the cod (*Gadus morhua*), nerve fibres showing VIP-like immunoreactivity have been demonstrated surrounding both the coeliac and mesenteric arteries, which supply the gut with blood (Lundin and Holmgren, 1984; C. Bjenning and S. Holmgren, unpublished observations). SP-like immunoreactivity has, however, not been found in nerves associated with these major vessels, and only a few branches of the stomach vasculature appear to be innervated (J. Jensen, A-C. Jönsson and S. Holmgren, unpublished observations). Porcine VIP and VIP extracted from the gut of rainbow trout (*Salmo gairdneri*) or catfish (*Ictalurus melas*) produce vasodilation in the vascularly perfused intestine of the catfish (Holder *et al.* 1983). Furthermore, VIP induces an increased flow through the perfused gas gland of the cod (*Gadus morhua*) swimbladder and through isolated gill arches from the brown trout *Salmo trutta* (Bolis *et al.* 1984; Lundin and Holmgren, 1984). The cardiovascular effects of SP in fish are, however, largely unknown.

The aim of this investigation was to study the influence of VIP and SP *in vivo* on the cardiovascular system in an unanaesthetized teleost fish, the cod. Special interest was focused on the control of blood flow to the abdominal viscera.

## Materials and methods

Atlantic cod, *Gadus morhua*, of either sex and with a body mass of 900–1700 g, were used in this study. They were kept in recirculating, well-aerated sea water at 10–11 °C, and were used within 10 days of capture.

### *Surgical procedure*

The animals were anaesthetized in MS222 (3-aminobenzoic acid ethylester methanesulphonate; Sigma; 100 mg $l^{-1}$) until all breathing movements ceased. They were then transferred to the operating table, and aerated sea water containing anaesthetic (50 mg $l^{-1}$) was continuously passed over the gills during surgery.

A cannula (PE 50) was inserted into the afferent branchial artery of the third gill arch on the left side for measurement of ventral aortic (prebranchial) blood

pressure ($P_{VA}$) and for recording the heart rate ($f_H$). A second cannula was implanted in the efferent branchial artery of the same gill arch to measure the dorsal aortic (postbranchial) blood pressure ($P_{DA}$). Both cannulae were filled with heparinized (100 i.u. $ml^{-1}$) 0.9 % NaCl and secured with skin sutures. During the experiment, the cannulae were attached to Statham P23 pressure transducers connected to a Grass polygraph (model 7D) for recording blood pressure.

To measure cardiac output (ventral aortic flow) an incision was made at the base of the pectoral fins and the ventral aorta was dissected free from the surrounding tissues without disrupting the pericardium. A cuff-type Doppler flow probe (2.5–3.0 mm i.d., single crystal, P. Pohl International Inc.) was placed around the vessel.

The fish was then placed on its left side and an incision approximately 4 cm long was made between the pectoral and pelvic fins starting 1–1.5 cm posterior to the edge of the operculum. A cannula was inserted into the gonadal vein for the injection of drugs. The cannula was passed through the body wall and sutured to the skin.

To measure blood flow in the coeliac and mesenteric arteries, the vessels were exposed and freed from connective tissue. During this procedure, care was taken not to damage the nerve running along the mesenteric artery. Doppler flow probes (1.3–1.6 mm i.d., single crystal, P. Pohl International Inc.) were placed around the vessels. The leads from the flow probes were taken out *via* a small incision posterior to the pelvic fin. The incision was closed and the leads were sutured to the skin.

For recordings of gastric motility, a balloon attached to a cannula was inserted into the stomach through an incision in the posterior part of the stomach. The incision was closed and the cannula tunnelled through the body wall. The balloon was filled with water and connected to a Statham P23 pressure transducer for recording changes in intragastric pressure.

In one group of fish, small incisions were made dorsal to the opercula, and the vagi were cut bilaterally immediately outside the skull.

After surgery, the animals were transferred to a tank with circulating sea water, where they recovered rapidly from anaesthesia. They were allowed to recover in this tank for 24–48 h before any experiments were started. During this time the effects of MS222 and handling wore off and the flow and pressure recordings stabilized. The flow signal was electrically dampened to obtain a mean blood flow instead of a beat-to-beat flow.

The peptides were injected as bolus doses (0.2 ml) and in the case of SP also infused during a longer period (8–18 min). The doses were calculated per kilogram body mass of the fish.

After the experiments were finished, some of the killed fish ($N$=6) were injected with yellow and red microfil (Canton Bio-Medical Products Inc.) to reveal the distribution of the vascular beds supplied by the coeliac and the mesenteric arteries, respectively. Cannulae were inserted into the proximal part of the coeliac and mesenteric arteries, and connected to syringes containing the microfil. The

microfil was infused simultaneously into the two vessels, and the distribution of microfil was drawn (see Fig. 1).

### *Drugs used*

The following drugs were used: atropine sulphate (Sigma), synthetic substance P (Sigma), natural porcine vasoactive intestinal polypeptide (VIP; a kind gift from Professor V. Mutt, Stockholm).

### *Calculations*

In addition to Grass polygraph recordings, data acquisition software and an IBM PPC computer were used for calculation of mean values during sampling periods. For the statistical tests the control period (2 min) was compared to a 1 min (VIP) or 20 s (SP) period at the maximal flow through the coeliac artery.

A Wilcoxon matched-pairs, signed ranks test was used to evaluate the statistical significance of the recorded effects of SP and VIP. Differences where $P<0.05$ were regarded as statistically significant. Values are presented as means±S.E.M.

The directional pulsed Doppler flowmeter used in the present work accurately measures blood flow velocity in the vessels studied and displays this velocity in kHz Doppler shift. However, there is a direct relationship between the blood velocity and instantaneous volume flow; previous studies on cod visceral arteries (M. Axelsson and R. Fritsche, unpublished results) and ventral aortic blood flow in the hagfish (Axelsson *et al.* 1990), in which the mean blood flow has been calibrated in absolute terms, have demonstrated a high degree of linear correlation between the Doppler signal and mean volume flow. We are therefore confident that the percentage changes in Doppler shift recorded in the present experiments are directly correlated to changes in blood flow in the arteries.

Heart rate was derived from the pulsatile blood pressure signal *via* a Grass 7P44 tachograph unit, and is expressed in beats per minute. Changes in the vascular resistance were calculated as the pressure drop across the vascular bed divided by the percentage change in blood flow through the same vascular circuit, assuming zero pressure in the central venous system.

## Results

The vascular beds supplied by the coeliac artery and the mesenteric artery, as indicated by microfil injections, are shown schematically in Fig. 1.

Resting values for heart rate ($f_H$; 42.9±1.8 beats $min^{-1}$; $N=10$), ventral aortic pressure ($P_{VA}$; 4.9±0.3 kPa; $N=10$) and dorsal aortic pressure ($P_{DA}$; 3.5±0.2 kPa; $N=10$) were similar to the values previously reported in the cod (Axelsson and Nilsson, 1986; Fritsche and Nilsson, 1989).

### *Vasoactive intestinal polypeptide*

Injection of VIP (100 pmol $kg^{-1}$; Fig. 2; Table 1) caused an increase in cardiac output ($\dot{Q}$) and increased flows in the coeliac and mesenteric arteries ($F_{COA}$ and

$F_{MeA}$, respectively). Blood pressures increased in both the ventral and dorsal aorta. The increase in cardiac output was produced solely by an increase in stroke volume ($V_S$) since the heart rate ($f_H$) was unaffected by VIP. The coeliac vascular

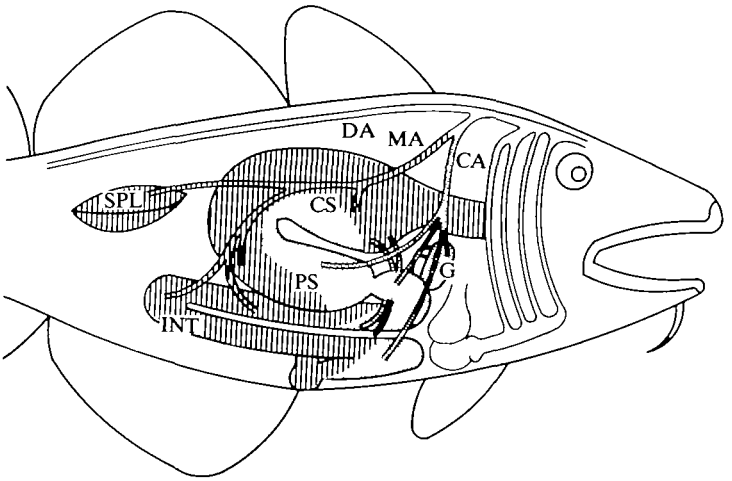


Fig. 1. Schematic drawing showing the parts of the gut supplied by the coeliac artery (stippled area) and the mesenteric artery (cross-hatched area) in the cod. CA, coeliac artery; CS, cardiac stomach; DA, dorsal aorta; G, gallbladder; INT, intestine; MA, mesenteric artery; PS, pyloric stomach; SPL, spleen.

Table 1. *The changes in cardiovascular variables in the cod when injected with SP or VIP*

| | Substance P | | | | Vasoactive intestinal polypeptide | |
|---|---|---|---|---|---|---|
| | 10 pmol $kg^{-1}$ % Change | *N* | 100 pmol $kg^{-1}$ % Change | *N* | 100 pmol $kg^{-1}$ % Change | *N* |
| $P_{VA}$ | 2.2±1.2 | 9 | 0.7±2.0 | 7 | 20.1±2.8* | 9 |
| $P_{DA}$ | −0.5±1.7 | 9 | −2.0±3.3 | 7 | 25.1±4.2* | 9 |
| $f_H$ | 2.8±1.3 | 8 | 1.7±0.9 | 6 | 1.3±1.2 | 9 |
| $\dot{Q}$ | 7.6±2.8* | 6 | 12.4±4.3* | 5 | 16.2±4.3* | 6 |
| $V_S$ | 3.6±2.5 | 6 | 10.5±4.5 | 5 | 15.4±3.5* | 6 |
| $F_{MeA}$ | 11.7±3.6* | 8 | 17.5±5.1* | 6 | 16.7±5.7* | 8 |
| $F_{CoA}$ | 51.1±4.0* | 9 | 78.7±5.9* | 7 | 48.6±11.6* | 8 |
| $VR_{MeA}$ | −10.5±3.2* | 8 | −15.3±5.6* | 6 | 9.0±6.3 | 8 |
| $VR_{CoA}$ | −34.1±2.5* | 9 | −44.8±2.5* | 7 | −12.4±5.4* | 8 |
| $VR_{Sys}$ | −9.6±2.0* | 6 | −10.0±5.3 | 5 | 5.2±4.6 | 6 |

Mean values±S.E.M. are presented.

Asterisks indicate statistically significant ($P<0.05$) changes compared with the control value. $P_{VA}$, ventral aortic blood pressure; $P_{DA}$, dorsal aortic blood pressure; $f_H$, heart rate; $\dot{Q}$, cardiac output; $V_S$, stroke volume; $F_{MeA}$, mesenteric artery blood flow; $F_{CoA}$, coeliac artery blood flow; $VR_{MeA}$, mesenteric circuit vascular resistance; $VR_{CoA}$,coeliac circuit vascular resistance; $VR_{Sys}$, systemic vascular resistance.

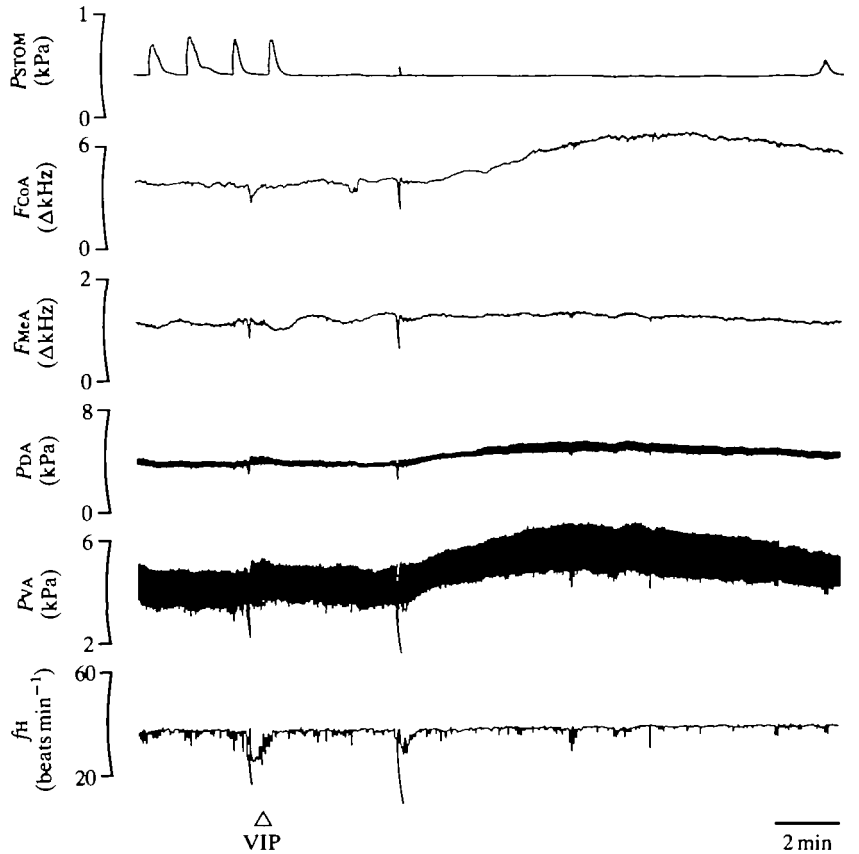


Fig. 2. Recording showing the effect of vasoactive intestinal polypeptide (100 pmol kg$^{-1}$) on the intragastric pressure ($P_{STOM}$), coeliac artery blood flow ($F_{CoA}$), mesenteric artery blood flow ($F_{MeA}$), dorsal aortic blood pressure ($P_{DA}$), ventral aortic blood flow ($P_{VA}$) and heart rate ($f_H$).

resistance ($VR_{CoA}$) was reduced by VIP, while no significant change could be found in the mesenteric vascular resistance ($VR_{MeA}$). The vascular effects of VIP were slow in onset (4–6 min) and longlasting (15–25 min).

Recordings of the intragastric pressure in most cases showed spontaneous contractions of the stomach wall. This activity was abolished when VIP was injected into the fish (Fig. 2; $N$=5).

10 pmol kg$^{-1}$ VIP usually had no effect on the recorded variables ($N$=5).

### *Substance P*

SP (10 or 100 pmol kg$^{-1}$; Fig. 3) produced a triphasic response in coeliac artery blood flow. An initial increase was followed by a rapid decrease, down to or below the initial level, which subsequently reversed to a secondary increase in flow. During these three changes in coeliac artery flow, corresponding changes in the coeliac vascular resistance occurred (Table 2). At the same time as the increase in

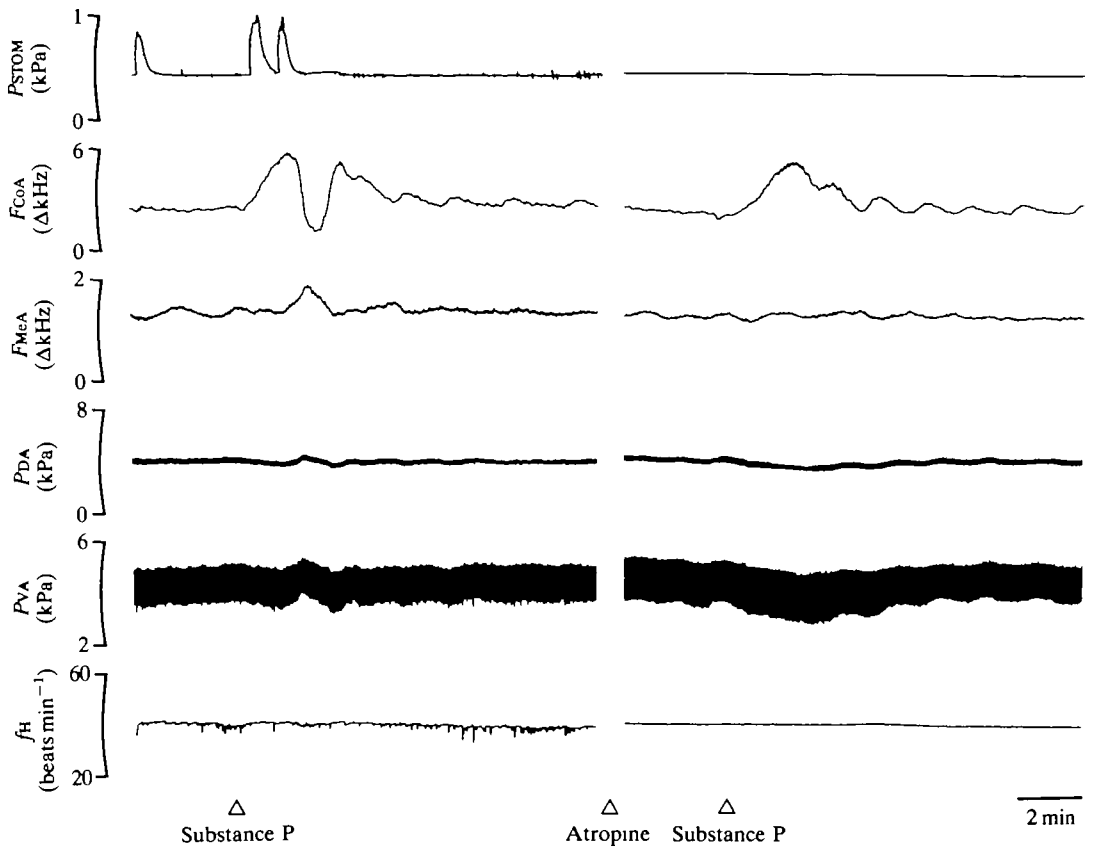


Fig. 3. Recording showing the effect of substance (100 pmol kg$^{-1}$) on the intragastric pressure ($P_{STOM}$), coeliac artery blood flow ($F_{CoA}$), mesenteric artery blood flow ($F_{MeA}$), dorsal aortic blood pressure ($P_{DA}$), ventral aortic blood pressure ($P_{VA}$) and heart rate ($f_H$) before and after treatment with atropine (1.2 mg kg$^{-1}$).

coeliac artery flow, there was a smaller increase in mesenteric artery flow, an increase in cardiac output and a decrease in mesenteric and systemic vascular resistance. No significant change could, however, be found in $P_{VA}$, $P_{DA}$, $f_H$ or $V_S$ during this period (Table 1). During the transient decrease in flow in the coeliac artery, there was often a corresponding small further increase in flow in the mesenteric artery.

Similar, but weaker effects were obtained with 1 pmol kg$^{-1}$ SP in 50% of the animals tested, while the others appeared to be unaffected by this dose, indicating that this dose is within the range of the threshold value of the effects of SP.

Injections of SP had weak excitatory effects on the stomach motility in five out of seven fish. The effect occurred within the first minutes after injection and was recorded as a phasic contraction, if the stomach was previously inactive, or as an enhanced amplitude of spontaneously occurring contractions. Infusion of SP (65–100 pmol kg$^{-1}$; 8–18 min) slightly increased the frequency of the rhythmic

Table 2. *The changes in coeliac artery blood flow ($F_{CoA}$) and coeliac circuit vascular resistance ($VR_{CoA}$) in response to substance P*

| | $F_{CoA}$ % Change | $N$ | $VR_{CoA}$ % Change | $N$ |
|---|---|---|---|---|
| Substance P 10 pmol $kg^{-1}$ | | | | |
| Maximum 1 | 51.1±4.0 | 9 | −34.1±2.5 | 9 |
| Minimum | −31.4±9.4 | 9 | 84.3±27.3 | 9 |
| Maximum 2 | 46.2±2.3 | 9 | −33.3±1.0 | 9 |
| Substance P 100 pmol $kg^{-1}$ | | | | |
| Maximum 1 | 78.7±5.9 | 7 | −44.8±2.5 | 7 |
| Minimum | −9.7±12.5 | 7 | 34.0±25.3 | 7 |
| Maximum 2 | 51.5±9.3 | 7 | −36.5±5.1 | 7 |

Maximum 1, Minimum and Maximum 2 represent the three different phases of the response, the initial increase, the decrease and the second increase, respectively.

The values are presented as means±S.E.M. from a 20 s sampling period from each phase compared to the control period.

contractions of the stomach in five out of six fish during the infusion period. The second change in $F_{CoA}$ in response to SP, the decrease in flow, could not be correlated to the contractions of the stomach, whether induced by SP or spontaneous. The response in $F_{CoA}$ was not due to recirculation of the bolus dose of SP in the cod, since the triphasic response also occurred when SP was infused.

One group of animals was subjected to vagotomy to elucidate whether a vagal reflex was involved in the triphasic response to SP. There was, however, no significant difference between vagotomized and non-vagotomized animals in the response of $F_{CoA}$ (Fig. 4; $N$=5). However, atropine treatment (1.2 mg $kg^{-1}$) blocked the second phase, the decrease, in $F_{CoA}$ in response to SP, while the initial increase in flow remained unchanged (Figs 3 and 5; $N$=6).

## Discussion

Several studies have been performed on fish to investigate the importance of adrenergic control of the cardiovascular system (Nilsson and Axelsson, 1987). The present study is, however, to our knowledge the first report on the influence of regulatory peptides on the cardiovascular system in fish *in vivo*.

The 28 amino acid peptide VIP, originally isolated from pig intestine, has been found to produce a decrease in systemic blood pressure, an increase in cardiac output (both inotropic and chronotropic effects) and to have a vasodilatory effect in gastrointestinal vascular beds in several mammalian species (Said and Mutt, 1970; Eklund *et al.* 1979; Blitz and Charbon, 1983; Unverferth *et al.* 1985). *In vitro* studies in fish have also indicated a vasodilatory role for VIP in different vascular beds (Holder *et al.* 1983; Bolis *et al.* 1984), including the mesenteric-artery-derived swimbladder vasculature of the cod (Lundin and Holmgren, 1984). In the present

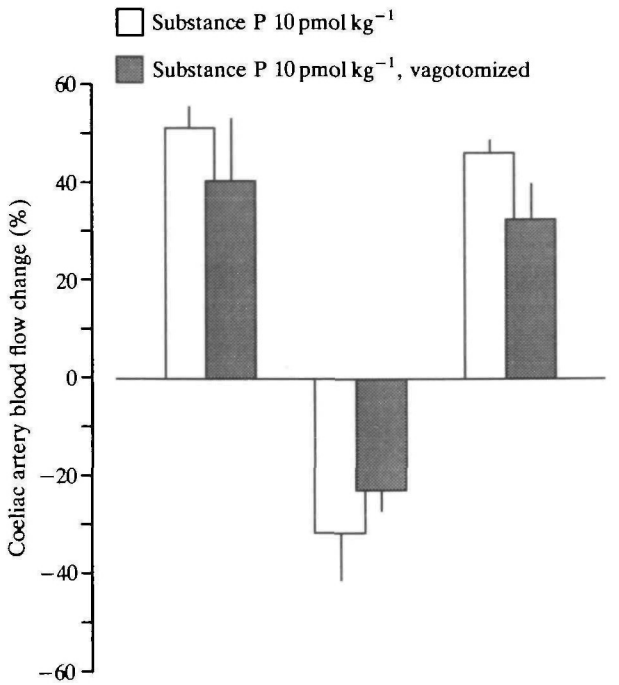


Fig. 4. The effect of substance P on the coeliac artery blood flow in untreated fish (open columns; $N$=9) and in vagotomized fish (stippled columns; $N$=5). The three groups of columns represent from left to right the three phases of the response to substance P: the initial increase in flow, the decrease and the second increase, respectively. Individual columns show mean values+S.E.M. from a 20 s sampling period including the maximal response in each phase. No difference in the type of response to substance P could be found between untreated and vagotomized fish.

*in vivo* study of the cod, porcine VIP increased blood flow in the coeliac artery and the mesenteric artery by 48.6 % and 16.7 %, respectively. This was accomplished by the positive inotropic effect that increases the cardiac output by 16.2 % and, in the case of the coeliac artery, partly by a decrease in vascular resistance. VIP had no significant effect on the mesenteric vascular resistance, which may seem to contrast with the results obtained by Lundin and Holmgren (1984). However, the vasodilatory effect in the isolated swimbladder preparation was only revealed after longlasting infusions of VIP ($10^{-7}$ mol l$^{-1}$) into preparations where the tonus of the vessels was increased by pretreatment with adrenaline, while single injections of VIP (1 ml at $10^{-7}$ mol l$^{-1}$=100 pmol), equivalent to those administered to the whole fish in the present study, had no recordable effect. In any case, the vasodilatory effect of VIP in vascular beds of the gut observed in mammals also seems to be present in the cod, although different vascular beds may be affected by different concentrations and times of exposure, at least under experimental conditions.

The amino acid sequence of the VIP present in the cod differs in five positions

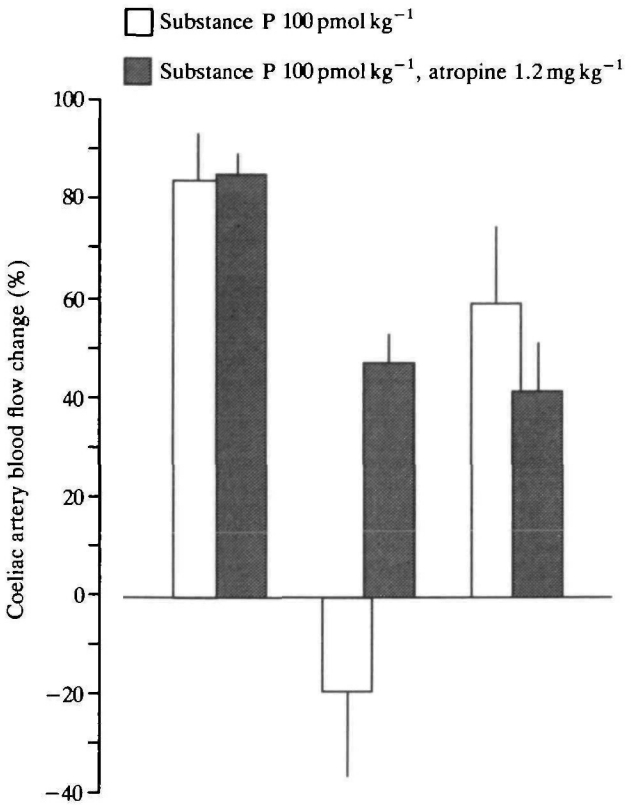


Fig. 5. The effect of substance P on the coeliac artery blood flow in untreated fish (open columns) and after treatment with atropine (filled columns) ($N$=4). The open columns represent from left to right the three phases of the response to substance P: the initial increase, the decrease and the second increase in flow, respectively. Atropine-treated fish showed no triphasic response and the filled columns represent the values matched in time with the three phases obtained before atropine treatment. Individual columns show mean values±S.E.M. from a 20 s sampling period at each phase. The same effect was obtained in another two fish using substance P 10 pmol kg$^{-1}$.

from the porcine VIP used in the present study. Cod VIP and porcine VIP have, however, been found to be approximately equally potent in stimulating amylase secretion from pancreatic acini of the guinea pig, suggesting that the substitutions may be of minor importance for the biological activity (Thwaites *et al.* 1989). This is supported by the observation that the dose range of porcine VIP needed to produce an effect in the cod in the present study agrees well with those used in mammalian (canine) studies *in vivo* (Said and Mutt, 1970; Blitz and Charbon, 1983; Unverferth *et al.* 1985). Furthermore, the measured plasma concentrations of VIP-like immunoreactive material in the cod (125 pmol l$^{-1}$) are similar to the levels found, for example, in the cat (50 pmol l$^{-1}$) (Fahrenkrug *et al.* 1978; Holstein and Humphrey, 1980).

In mammals, VIP is suggested to be the neurotransmitter in the reflex mediating gastric receptive relaxation, which follows distension of the oesophagus (see Dockray, 1987). An inhibitory effect of VIP on the spontaneous motility of the gut was observed in the cod stomach in the present study. VIP is, however, probably not involved in a gastric receptive relaxation reflex in the cod (although this may be the case in other fish species), since the excitatory response to gastric distension is unaffected by VIP (D. J. Grove and S. Holmgren, unpublished observations).

SP has previously been shown to have a vasodilatory effect in the mesenteric vascular bed of mammals (Hallberg and Pernow, 1975; Burcher *et al.* 1977; Schrauwen and Houvenaghel, 1980; Rozsa and Varro, 1987), and in the present study SP produced an increase in flow through both the coeliac and mesenteric arteries. In the coeliac artery the increase in flow was followed by a rapid decrease and a subsequent increase. A similar triphasic response to SP has been described in the mesenteric vascular bed of the pig *in vivo*, when high doses of SP were infused ($1–10\,\mu g\,animal^{-1}\,min^{-1}$; Schrauwen and Houvenaghel, 1980). The mechanism behind this response in the pig was, however, not further examined. In the cod, the decrease in flow could not be attributed to stomach contractions induced by SP. Nor was the response altered by vagotomy. Atropine, in contrast, blocked the rapid decrease in coeliac blood flow without affecting the initial increase, which suggests that a local cholinergic mechanism, rather than a vagal reflex, is responsible for the decrease in flow. The significance of this response needs further investigation.

Nerve fibres and endocrine cells containing SP-like immunoreactivity have been demonstrated in both the stomach and the intestine of the cod. Only very few vessels are, however, innervated by immunoreactive fibres in the stomach and no immunoreactive nerve fibres have been observed innervating the coeliac and mesenteric arteries (Jensen and Holmgren, 1985; Jensen *et al.* 1987; J. Jensen, A.-C. Jönsson and S. Holmgren, unpublished results). This may indicate that, if an endogenous SP-like peptide is involved in vascular control, it is not released from perivascular nerves but acts mainly as a hormone released from endocrine cells or non-vascular nerves in the gut wall.

Studies of the cod stomach, using a preparation vascularly perfused *via* the mesenteric artery, have shown that the threshold dose of SP needed to elicit a contraction is approximately 10 pmol (J. Jensen, A.-C. Jönsson and S. Holmgren, unpublished results). In the present experiments, SP was injected into the gonadal vein *in vivo* in the dose range $1–100\,pmol\,kg^{-1}$, but the effects were weak even with the higher doses. However, considering that part of the injected SP is distributed to other vascular beds and some of it is likely to be degraded, the amount of SP actually reaching the gut smooth muscle is probably considerably reduced towards or below the threshold dose for an effect on stomach motility. The concentration reaching the vascular receptors may be higher, or the vascular receptors may be more sensitive to substance P than the gut wall smooth muscle receptors.

It has been estimated that as much as 40 % of the cardiac output in the cod is directed to the coeliac and mesenteric arteries during resting conditions, and after

feeding there is a marked increase in coeliac and mesenteric flow equivalent to the increase in cardiac output (M. Axelsson and R. Fritsche, unpublished results). In the present study, both VIP and SP increased the cardiac output and the visceral blood flow. Assuming a $\dot{Q}$ value of $18\,ml\,min^{-1}\,kg^{-1}$, an $F_{CoA}$ value of $3.5\,ml\,min^{-1}\,kg^{-1}$ and an $F_{MeA}$ value of $4.1\,ml\,min^{-1}\,kg^{-1}$ (as calculated by M. Axelsson and R. Fritsche, unpublished results), VIP ($100\,pmol\,kg^{-1}$) increases cardiac output by $2.9\,ml\,min^{-1}\,kg^{-1}$. The main part of this increase is distributed to the viscera ($2.4\,ml\,min^{-1}\,kg^{-1}$); this may be partly achieved by the decreased resistance in the coeliac vascular bed. Making the same assumptions for 10 and $100\,pmol\,kg^{-1}$ SP gives increases in cardiac output of 1.4 and $2.2\,ml\,min^{-1}\,kg^{-1}$, respectively, while the corresponding increases in visceral blood flow are 2.3 and $3.4\,ml\,min^{-1}\,kg^{-1}$. This indicates that the increase in visceral blood flow produced by SP is accomplished both by an increase in cardiac output and by a redistribution of blood from other vascular beds. The present results suggest that both VIP and SP may be mediators of postprandial hyperaemia in the gut of the cod.

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