Br. J. Pharmac. (1976), **58**, 127–135

THE ACTIONS OF NATURAL SECRETIN ON THE SMALL INTESTINAL VASCULATURE OF THE ANAESTHETIZED CAT

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1 A plethysmographic preparation of cat jejunum was used to measure changes in tissue volume and capillary filtration coefficient (CFC), simultaneously with measurements of arterial and venous pressures, and total blood flow.

2 Secretin was infused and injected intravenously and also infused intra-arterially in relatively small doses. Probable resulting blood concentrations were compared with those determined under physiological conditions in other investigations.

3 By intravenous or intra-arterial infusion, secretin caused increases in CFC, indicating an increased functional exchange vessel area, and increases in jejunal volume, indicating increased vascular capacitance. The jejunal blood flow increased whilst the blood pressure remained essentially unchanged.

4 By intravenous injection, secretin caused rises in jejunal volume and reductions in calculated jejunal vascular resistance over the same dose range. Effects were statistically significant at 500 mu/kg and higher doses caused reductions in systemic arterial pressure.

5 The calculated peak blood concentrations of secretin resulting from the lower doses used in this investigation were of the same order of magnitude as those determined under physiological conditions in man.

6 It is possible that at physiological concentrations secretin causes an increased functional exchange vessel area in the small intestine, and may also increase the total blood flow through this tissue.

Introduction

The first report of the physiological and pharmacological properties of an extract of mammalian duodenum and jejunum showed that the active principle in the extract, secretin, caused a reduction in arterial blood pressure when injected intravenously, as well as stimulating pancreatic secretion (Bayliss & Starling, 1902). This early report of the vasodepressor action of this hormone has been extended subsequently by Ross (1970) and Fasth, Filipsson, Hulten & Martinson (1972) who showed that large doses of secretin injected intra-arterially or intravenously to the anaesthetized cat caused increases in superior mesenteric arterial blood flow.

Plethysmographic preparations of the cat small intestine have been used previously for the simultaneous measurement of blood flow, changes in vascular capacitance and capillary filtration coefficient (CFC) by Folkow, Lundgren & Wallentin (1963), and these techniques have been evaluated by Mellander & Johansson (1968) and Folkow & Mellander (1970). It has previously been demonstrated that changes in CFC may be evoked by vasoactive substances adminstered in doses inadequate to affect the recorded intravascular pressures or the total blood flow through a tissue (Folkow *et al.*, 1963; Richardson, 1974, 1975a, 1975b).

Secretin is present in mammalian jejunum in large quantities (Bayliss & Starling, 1902; Bloom, 1974) and relies for its main effect of stimulating pancreatic exocrine secretion on its release into the systemic circulation, thereby reaching its target organ. It is therefore possible that the vascular effects of secretin on the small intestine might be due to the hormone gaining access through the systemic circulation, as well as by local release. For this reason, in the present investigation emphasis has been placed on the effects of secretin injected and infused intravenously to animals in which both the sympathetic innervation to the small intestine and the suprarenal glands have been preserved. In this way, the pattern of responses of the small intestinal vasculature to elevated systemic blood levels of secretin has been established, and this has been compared with the effects of intra-arterial infusions of secretin on this vascular bed.

A preliminary report of part of the results of this investigation has been presented to the British Pharmacological Society (Richardson, 1976).

Methods

The preparations used were similar to those described previously for the measurement of blood flow, changes in tissue volume and capillary filtration coefficient (CFC) in the small intestine (Folkow *et al.*, 1963; Richardson, 1974). Eleven healthy cats of either sex, weighing between 2.40 and 3.87 kg (3.02 ± 0.40, mean $\pm$ s.d., kg) were deprived of food for 24 h but allowed access to water *ad libitum* before the induction of anaesthesia with halothane. The right saphenous vein was cannulated, and anaesthesia maintained by an intravenous injection of chloralose (Kuhlmann, Paris; 70 mg/kg).

Following a midline laparotomy, the spleen, omenta, large intestine, duodenum, pancreas and distal small intestine were extirpated, leaving a loop of proximal jejunum weighing 56.5 ± 17.2 g (mean $\pm$ s.d.). The animals were treated with heparin (Weddel Pharmaceuticals; 250 i.u./kg, i.v., followed by 100 i.u./kg i.v., hourly) and the superior mesenteric vein cannulated. Blood from the superior mesenteric vein was continuously returned to the animal via the cannulated right external jugular vein, using a Watson-Marlow MHRE-200 roller pump (Richardson, 1974).

In most experiments, the superior mesenteric artery and its accompanying sympathetic periarterial nerves were carefully preserved, but in some ('isolated') preparations, the sympathetic periarterial nerves were divided and the superior mesenteric artery cannulated and perfused from a cannulated common carotid artery.

The prepared loop of small intestine was inserted into a rhomboid-shaped Perspex plethysmograph, which was then sealed and connected to a recorder to measure changes in the volume of the tissue (Richardson, 1974). The temperature of the contents of the plethysmograph, and of the animal, was maintained at 37–38°C with table heaters and radiant lamps. All animals breathed spontaneously throughout the experiments, and the volume of the blood localized in the external circuit was compensated for by an intravenous injection of a corresponding volume of low molecular weight dextran in normal saline (Rheomacrodex, Pharmacia) immediately before cannulation of the superior mesenteric vein.

Measurements

Systemic arterial blood pressure was measured from a cannulated femoral artery by means of a Statham P23Gb strain-gauge transducer. Phasic pressure was recorded, and mean pressure either derived as diastolic + $\frac{1}{3}$ pulse pressure, a derivation which gave values in agreement with those obtained by switching the phasic waveform through an averaging circuit with a time-constant of about 3 s, or obtained by passing the phasic signal through a Devices (Model 3502) averaging circuit with selectable time constants of 0.5, 1 and 2 seconds. In this case, both mean and phasic pressures were displayed continuously.

Arterial perfusion pressure was measured in some experiments in addition to the systemic arterial blood pressure. A small branch of the superior mesenteric artery was cannulated and connected to a Consolidated Electrodynamics (Model L212) strain-gauge transducer: electronically averaged mean pressure was recorded continuously.

In the 'isolated' preparations, mean arterial perfusion pressure was measured with the same system from a 'T'-piece in the cannula, close to the point of cannulation of the superior mesenteric artery.

Heart rate was measured with a Devices (Model 4521) ratemeter triggered from the systemic arterial pressure waveform. The calibration was checked by running the recorder at high paper speed and counting the heart rate directly from the arterial pressure waveform.

Superior mesenteric venous pressure was measured just outside the plethysmograph from a 'T'-piece in the superior mesenteric venous cannula, with a Statham P23V or P23Ia strain-gauge transducer. The outlet from the superior mesenteric vein was adjusted so that under control conditions the venous pressure was about + 3 mmHg relative to the level of fluid in the plethysmograph so that the veins within the plethysmograph were patent, thereby preventing an increase in the postcapillary resistance.

All pressure transducers were calibrated with mercury or water manometers immediately before each experiment: zero reference pressures were taken *post mortem* as those recorded with the catheter tips open to air *in situ*.

Blood flow. In all experiments, the superior mesenteric venous flow was recorded continuously with a cannulating flow probe in the superior mesenteric venous cannula, and an electromagnetic flowmeter (Cardiovascular Instruments). Mean blood flow was obtained by passing the phasic waveform through an averaging circuit with a time constant of 0.6 second.

In the isolated preparations, phasic and mean arterial inflow were also recorded, by means of a second cannulating flow probe and electromagnetic flowmeter.

All flow probes were calibrated *in situ* with whole blood; zero positions were established by temporary occlusion of the cannulae downstream from the flow probes.

Changes in jejunal volume were recorded as described previously (Richardson, 1974), by a displacement technique, measuring the upthrust of fluid in continuity with the plethysmograph contents upon the sensor of an isometric transducer, Devices (Model 4151).

After appropriate amplification, all variables were displayed continuously on a Devices (Model M-19) rectilinear recorder.

Calculations

Jejunal vascular resistance was calculated as (mean arterial pressure − mean superior mesenteric venous pressure)/mean blood flow, and expressed as mmHg ml^{-1} min 100 g.

Capillary filtration coefficient was measured essentially as described by Folkow *et al.* (1963): superior mesenteric venous pressure (SMVP) was elevated by 10 cmH_2O for periods of 1 minute. This caused a characteristic increase in the volume of the tissue within the plethysmograph (Figure 1): the volume increases were biphasic, the first phase being due to the passive distension of the capacitance vessels, and the second, slow and continuous phase being due to the transudation of fluid from exchange vessels into perivascular spaces (Folkow *et al.*, 1963; Mellander & Johansson, 1968; Johnson & Richardson, 1974).

The slope of this second phase, expressed as ml of fluid transuded per minute, per mmHg rise in SMVP, per 100 g of tissue (ml min^{-1} $mmHg^{-1}$ 100 g^{-1}) is the capillary filtration coefficient (CFC).

Drug administration

Hexamethonium bromide (BDH), propranolol hydrochloride (Inderal, ICI) and natural secretin (Boots) were used in this study. Doses of secretin are expressed in Crick-Harper-Raper Units (u) or milliunits (mu). One unit is equivalent to 4 clinical units and also equivalent to 62.5 ng (manufacturer's data).

Secretin was infused and injected intravenously, and also infused intra-arterially. Infusions were at a rate of 1.0 ml/min from a Watson-Marlow MHRE-200 pump precalibrated against a static pressure in excess of 150 mmHg to ensure a constant inflow against arterial pressures. Intravenous injections were in volumes not exceeding 0.25 ml, washed in to a total injectate volume of 1.0 ml with 0.9% w/v NaCl solution (saline).

Expression of results

Except where indicated to the contrary, results are expressed as means ± s.e. means; the significance of changes from control data is assessed by use of Student's *t*-test for paired data.

At least 3 and usually 4 determinations of CFC and measurements of other variables were made before and during secretin infusions, and the mean values for each set of variables, together with the percentage changes, were calculated for each experiment. Where *n* is quoted, it therefore refers to numbers of experiments and not to numbers of individual determinations of CFC and measurements of other variables. When secretin was injected, the peak effects were compared with the control values immediately preceding the injection, and percentage changes calculated from these measurements.

Results

Control values

Under control conditions in 7 preparations in which the superior mesenteric artery and periarterial nerves were intact, the systemic arterial mean pressure (BP) was 151.4 ± 4.2 mmHg, and the heart rate (HR) 174.6 ± 10.0 beats/minute. The superior mesenteric venous pressure (SMVP) was 3.14 ± 0.36 mmHg, at which pressures the preparations were isovolumetric under control conditons. The superior mesenteric venous blood flow (SMVF) was 55.7 ± 7.8 ml min^{-1} 100 g^{-1}, and the calculated jejunal vascular resistance (JVR) 3.15 ± 0.57 mmHg ml^{-1} min 100 g. The capillary filtration coefficient (CFC) was 0.060 ± 0.009 ml min^{-1} $mmHg^{-1}$ 100 g^{-1}.

The control values for 4 isolated preparations fell within the ranges found in the intact preparations, the BP being 140.0 ± 4.8 mmHg, the HR 212.3 ± 13.4 beats/min, the SMVF 44.3 ± 9.3 ml min^{-1} 100 g^{-1}, the JVR 3.63 ± 0.70 mmHg ml^{-1} min 100 g, and the CFC 0.048 ± 0.004 ml min^{-1} $mmHg^{-1}$ 100 g^{-1}, values similar to those reported previously for sympathetically-denervated preparations (Folkow *et al.*, 1963; Richardson, 1975b).

No systematic differences were observed between the mean BP and the mean arterial perfusion pressures measured either from a cannulated small branch of the superior mesenteric artery, or from a 'T' piece in the arterial cannulae in 'isolated' preparations.

Secretin by intravenous infusion

Secretin was infused intravenously for 15 min periods at doses of 100 and 500 mu kg^{-1} min^{-1} which were selected on the basis of results from preliminary experiments; the effects are summarized in Table 1.

When secretin was infused at a rate of 100 mu kg^{-1} min^{-1}, there were no consistent changes in BP, HR, SMVF or calculated JVR ($P > 0.30$ for each variable), the changes in individual experiments being very small and not qualitatively consistent in the series of 5 experiments in which secretin was infused at this dose level.

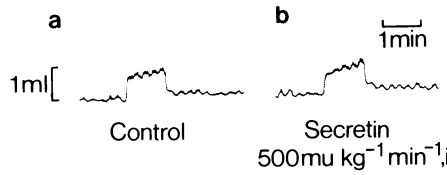

Figure 1 Effects of an intravenous infusion of 500 mu kg^{-1} min^{-1} secretin on capillary filtration coefficient in the sympathetically-innervated cat jejunum. (a) under control conditions, CFC = 0.035 ml min^{-1} $mmHg^{-1}$ 100 g^{-1}; (b) during the secretin infusion, CFC = 0.080 ml min^{-1} $mmHg^{-1}$ 100 g^{-1}. When the superior mesenteric venous pressure was returned to control levels at the end of the 1 min elevation by 10 cmH_2O to determine the CFC, the tissue volume returned to the same value as before the elevation of venous pressure.

However, at the higher infusion of 500 mu kg^{-1} min^{-1} the BP fell by up to 12 mmHg, the HR rose by up to 45 beats/min and the SMVF increased by between 3.2 and 22.5 ml min^{-1} 100 g^{-1}. In no experiment were changes detected in any of these variables which were opposite in direction to the mean changes. The effects of one such infusion of secretin in a typical experiment are illustrated in Figure 2.

At the beginning of the infusions at both dose levels, the jejunal volume increased significantly ($P < 0.05$), the increase persisting throughout the infusion periods. On cessation of the infusion, the volume declined again to its pre-infusion levels.

The capillary filtration coefficient was increased at both infusion levels, the changes being statistically significant ($P < 0.05$) in each case; the typical effect of elevating the SMVP by 10 cmH_2O for 1 min on the volume of a preparation both under control conditions and during the intravenous infusion of 500 mu kg^{-1} min^{-1} of secretin is shown in Figure 1.

When secretin was infused intravenously, the changes in all variables were rapid in onset, persisted for the duration of the infusions, and returned to control values within 5 min after the cessation of the infusions (Figure 2).

Since the BP fell on infusion of 500 mu kg^{-1} min^{-1} secretin intravenously, the possibility of a part of the effects being attributable to a baroreceptor reflex effect (Öberg, 1964) was considered: in 3 experiments the infusions were repeated after hexamethonium (5.0 mg/kg, i.v.). The effects of subsequent secretin infusions were qualitatively identical to those before hexamethonium, though quantitative comparisons are difficult because of the altered control values for all variables (Richardson, 1974).

Many of the effects of secretin on this preparation resemble those of isoprenaline (Folkow *et al.*, 1963; Richardson, 1974), and so in 3 experiments the intravenous infusion of 500 mu kg^{-1} min^{-1} of secretin was repeated after a dose of propranolol previously found adequate to block the effects of exogenous isoprenaline on these preparations (Richardson, 1974): the effects of secretin on the small intestinal vasculature were not appreciably modified by pretreatment with propranolol.

Table 1 The effects of intravenous infusions of natural secretin on the small intestinal vasculature of the cat

Infusion rate *Variable (units)*	*Control*	*During infusion*	*Significance*
(a) 100 mu kg^{-1} min^{-1}			
Blood pressure (mmHg)	152.0 ± 4.7	152.6 ± 5.9	NS
Heart rate (beats/min)	176.4 ± 14.0	180.9 ± 11.6	NS
SMVF (ml min^{-1} 100 g^{-1})	54.6 ± 4.6	56.0 ± 5.4	NS
JVR (mmHg ml^{-1} min 100 g)	2.86 ± 0.24	2.81 ± 0.24	NS
Jejunal volume (ml/100 g)		+0.27 ± 0.06	$P < 0.05$
CFC (ml min^{-1} $mmHg^{-1}$ 100 g^{-1})	0.060 ± 0.009	0.083 ± 0.012	$P < 0.05$
(b) 500 mu kg^{-1} min^{-1}			
Blood pressure (mmHg)	151.6 ± 4.1	146.2 ± 4.3	$P < 0.05$
Heart rate (beats/min)	177.4 ± 13.2	199.6 ± 9.5	NS
SMVF (ml min^{-1} 100 g^{-1})	50.8 ± 3.9	59.9 ± 6.0	$P < 0.05$
JVR (mmHg ml^{-1} min 100 g)	3.06 ± 0.26	2.57 ± 0.32	$P < 0.05$
Jejunal volume (ml/100 g)		+0.83 ± 0.24	$P < 0.05$
CFC (ml min^{-1} $mmHg^{-1}$ 100 g^{-1})	0.060 ± 0.009	0.095 ± 0.011	$P < 0.02$

All variables are expressed as means ± s.e. means; $n = 5$ in all cases. The degrees of statistical significance of the differences between the mean values immediately before (control) and during the infusions of secretin are assessed using Student's *t*-test. NS = $P > 0.05$; for values in Part (a), NS = $P > 0.30$. SMVF = superior mesenteric venous blood flow; JVR = jejunal vascular resistance; CFC = capillary filtration coefficient. Jejunal volume = change in jejunal volume caused by the secretin infusion from control isovolumetric state.

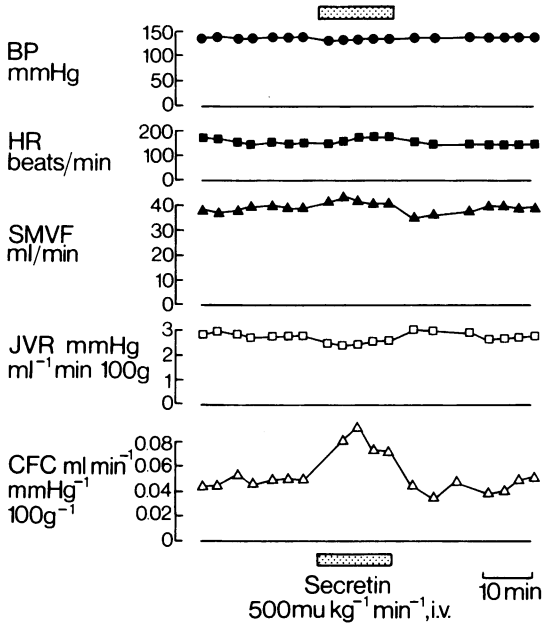

Figure 2 The effects of an intravenous infusion of 500 mu kg^{-1} min^{-1} of secretin on systemic arterial mean pressure (BP), heart rate (HR), superior mesenteric venous blood flow (SMVF), the calculated jejunal vascular resistance (JVR) and the capillary filtration coefficient (CFC). Cat, female, 3.41 kg; weight of jejunum = 78 g.

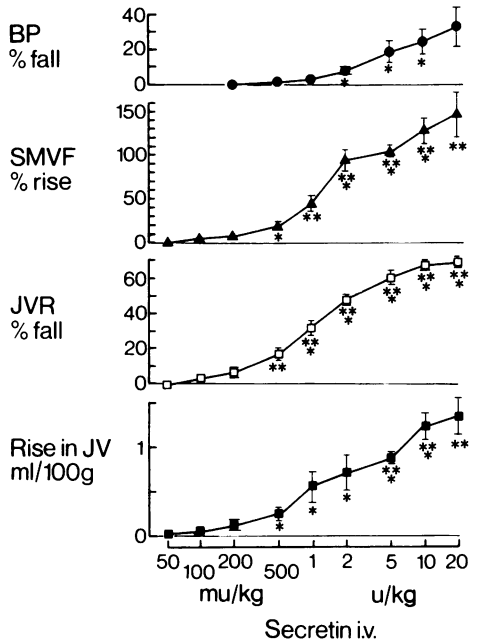

Figure 3 Effects of increasing intravenous injections of secretin on systemic arterial mean pressure (BP; expressed as percentage reduction from pre-injection values), superior mesenteric venous blood flow (SMVF; expressed as % increases from pre-injection values), calculated jejunal vascular resistance (JVR; % reductions from pre-injection values) and the increase in jejunal volume (JV; expressed as ml/100 g of tissue). Points represent the mean of six observations and the vertical lines the s.e. means; the significance of changes from controls is shown by asterisks: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

Secretin by intravenous injection

Secretin was injected intravenously in increasing doses from 10 mu/kg to 20 u/kg on six occasions in order to examine the dose–response relationship of intravenous secretin on the jejunal resistance and capacitance vessels. The results are summarized in Figure 3.

The predominant effects were a transient increase in jejunal volume and a transient reduction in calculated jejunal vascular resistance: both effects occurred over the same dose range, being detectable on injection of 100 mu/kg, and being statistically significant on injection of 500 mu/kg. The reduction in calculated JVR indicates that vasodilatation occurred in the precapillary resistance vessels (Mellander & Johansson, 1968) which resulted in large increases in jejunal blood flow, although particularly at higher doses of secretin there were reductions in systemic arterial pressure (Figure 3). The heart rate rose variably, particularly at the higher doses (5–20 u/kg, i.v.) where rises of between 6 and 28 beats/min occurred in different experiments.

Although the changes in JVR and jejunal volume appear to reach maxima between 10 and 20 u/kg (Figure 3), and correlate well with those reported by Ross (1970) on intravenous injection of a single dose of 40 u/kg (= 10 clinical units/kg) secretin, no attempt was made to establish absolute maxima or to investigate the hypertensive effect which is reported to be apparent at high doses of the hormone (Ross, 1970), since the purpose of this investigation was to concentrate upon the effects of lower doses of secretin.

If the assumption is made that the whole intravenous injection of secretin was uniformly distributed throughout a blood volume of 70 ml/kg body weight, the peak blood concentration attained after injection of 100 mu/kg would have been 1.43 mu/ml (89 pg/ml) and after 500 mu/kg, 7.14 mu/ml (446 pg/ml).

Secretin by intra-arterial infusion

Secretin was infused intra-arterially to investigate two points: (i) whether the effects on all variables were

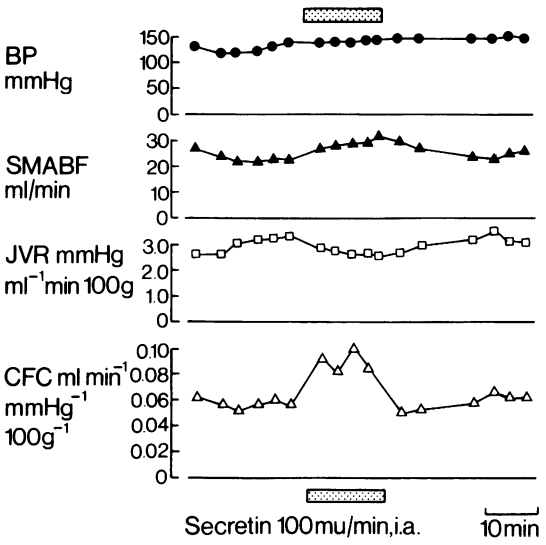

Figure 4 Intra-arterial infusion of secretin to a 52 g loop of jejunum in a 3 kg female cat: effects are shown on systemic arterial mean pressure (BP), superior mesenteric arterial blood flow (SMABF), calculated jejunal vascular resistance (JVR) and capillary filtration coefficient (CFC). The heart rate did not change during the infusion from its control level of 241 beats/minute.

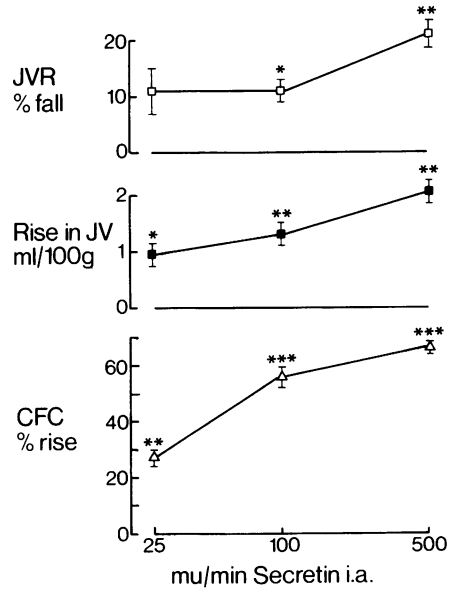

Figure 5 The effects of intra-arterial infusions of secretin on jejunal vascular resistance (JVR; expressed as % reduction), the jejunal volume (JV; increases expressed in ml/100 g) and CFC (expressed as % increase) in four preparations. Points represent the mean values and vertical lines the s.e. means; the significance of changes from control values is shown by asterisks: $*=P<0.02$; $**=P<0.01$; $***=P<0.001$.

qualitatively and quantitatively similar to those observed on intravenous infusion, and consequently whether significant activation or deactivation of the hormone was likely to have occurred in passage through the lungs and other tissues, and (ii) whether the blood concentrations of secretin attained on intra-arterial infusion were of the same order of magnitude as those reported to occur physiologically, for if effects were produced at such concentrations, they could well be of functional significance.

Secretin was infused intra-arterially in doses of 25, 100 and 500 mu/min to each of 4 preparations in random order of doses; all infusions were of 15 min duration. The effects of a typical infusion are shown in Figure 4, and the effects summarized in Figure 5.

When secretin was infused intra-arterially, the perfusion pressure and the systemic arterial pressure remained unchanged at all dose levels employed ($P>0.30$). The heart rate also remained unchanged at all three dose levels of secretin ($P>0.20$). There were, however, significant increases in blood flow through the tissue which resulted in reductions in calculated jejunal vascular resistance (Figure 5), indicating that vasodilatation had occurred. In addition, there were dose-dependent increases in jejunal volume and in capillary filtration coefficient, effects which were statistically significant at all three infusion levels. The effects of intra-arterial infusions of secretin were rapid in onset, persisted for the duration of the infusions without any consistent tendency to increase or diminish, and declined quickly on cessation of infusions, the variables returning to pre-infusion levels within 5 min (Figure 4).

The mean maximum blood concentrations of secretin were assessed by dividing the amount of the hormone infused (mu/min) by the blood flow (ml/minute). For the 25 mu/min infusions, the calculated mean maximum blood concentration was 1.57 mu/ml (98 pg/ml), for the 100 mu/min infusions, 4.20 mu/ml (263 pg/ml) and for the 500 mu/min infusions, 22.19 mu/ml (1.39 ng/ml).

Discussion

Secretin has been shown to cause increases in capillary filtration coefficient and to increase the volume of the small intestine of the anaesthetized cat, effects which were demonstrable whether the hormone was administered intravenously or intra-arterially, and

which were dose-dependent and statistically significant. This extends the observation of Biber, Fara & Lundgren (1973) of the effect of intra-arterial secretin on the denervated intestine to the effects of secretin administered intravenously by injection and by infusion. In the present investigation, the effects are quantitated with respect to the administered doses. Additionally, the effects of secretin on intestinal blood flow and vascular resistance (Ross, 1970; Tibblin, 1971; Fasth *et al.*, 1972) have been confirmed, extended to the effects of much lower doses of the hormone, and the dose-response relationships established.

The use of the present techniques for the measurement of vascular dimensions is well established (Mellander, 1960; Folkow *et al.*, 1963; Mellander & Johansson, 1968; Folkow & Mellander, 1970). The changes in vascular resistance reported in the present investigation were the result of vasodilatation in precapillary resistance vessels, manifest as substantial increases in blood flow at constant arterial pressure, except where secretin was injected intravenously in large doses when a hypotensive effect was apparent (Figure 3).

Changes in CFC indicate changes either in activity of precapillary 'sphincters' or in vascular permeability, or both; it is not possible to differentiate these separate mechanisms *in vivo*, but the fact that there have not been previous reports of secretin increasing vascular permeability, supported by the observation that secretin caused no irreversible increases in intestinal volume at either control or elevated venous pressures (Figure 1) suggests that the predominant effect may well have been for secretin to dilate the intestinal precapillary 'sphincter' vessels rather than to increase vascular permeability.

An increase in tissue volume on administration of a vasoactive hormone does not constitute conclusive proof of a vasodilator action on the capacitance vessels, since the effect may be indirect, resulting from distension of the capacitance vessels caused by precapillary resistance vessel dilatation with a consequent increase in blood flow. As the increases in jejunal volume which were observed in the present experiments occurred over the same dose ranges as the reductions in vascular resistance (Figures 3 and 5), the underlying cause of the observed increase in intestinal volume cannot be ascribed with certainty either to a direct effect on the capacitance vessels, or to an indirect effect on the capacitance vessels resulting from precapillary vasodilatation. Nevertheless, it has been demonstrated that dilatation of the capacitance vessels does occur on administration of secretin, over the same dose range as dilatation of precapillary resistance vessels.

When any vasodilator agent is administered intravenously and results in a reduction in systemic arterial pressure, contributions to the observed changes in vascular dimensions in a single, sympathetically-innervated tissue may arise from myogenic and hydrostatic responses to the altered arterial pressure (Bayliss, 1902; Folkow, 1964), and also from baroreceptor reflex modulations in sympathetic vasoconstrictor tone (Öberg, 1964). The fact that the effects of the intra-arterial infusions of secretin, which did not cause changes in arterial pressure, were very similar to those observed on intravenous infusion of secretin at the dose levels chosen for these experiments suggests that the predominant effects seen on intravenous infusion were direct effects of the hormone on the intestinal vasculature. This view receives support from the similarity of the effects of intravenous secretin before and after hexamethonium, although quantitative comparisons are difficult because of the hypotensive effect of hexamethonium itself.

Significant reductions in arterial pressure did occur on intravenous injection of the larger doses of secretin (> 1 u/kg), and both hydrostatic and reflex modulations in vascular dimensions, as well as direct effects of the hormone, could well have contributed to the observed effects (Figure 3). Reductions in carotid sinus pressure in the cat cause an increase in jejunal vascular resistance and a reduction in jejunal volume, together with a reduction in CFC (Öberg, 1964). Since no attempt was made to elicit maximum responses to intravenously injected secretin, the apparent maxima shown in Figure 3 may not in fact represent the true maximum rises in jejunal volume or maximum reductions in JVR which could be attained in denervated preparations perfused at constant pressure, since the secretin-induced rises in JV and reductions in JVR may have been counteracted in these sympathetically-innervated preparations by baroreceptor reflex effects at the higher doses of secretin when the systemic arterial pressure fell.

It was shown by Ross (1970) that pretreatment with propranolol did not modify the reductions in vascular resistance caused by intravenous or intra-arterial secretin; this observation is confirmed in the present experiments and extended to the effects of secretin on CFC and the jejunal volume, both of which were unaffected by pretreatment with propranolol in a dose previously found adequate to block the effects of exogenous isoprenaline on this preparation (Richardson, 1974). Therefore, although the effects of secretin are superficially similar to those of isoprenaline on this preparation (Folkow *et al.*, 1963; Richardson, 1974), it is unlikely that they are the result of β-adrenoceptor stimulation.

The effects of secretin on the jejunal vascular bed are different from those of the structurally-related hormone, glucagon (Richardson, 1975a) which causes a fall in CFC which is reversible by α-adrenoceptor blockade. Whilst this action of glucagon may be due to the release of catecholamines either from the

suprarenal gland or from the intestine itself (Fasth & Hulten, 1971; Richardson, 1975a, 1975b), the possibility remains that the two hormones may have an essentially dissimilar action on the intestinal vascular smooth muscle, as they do on the hepatic parenchymal cells (Peterson, 1974).

Physiological blood concentrations of secretin do not appear to have been reported for the cat, though radioimmunoassay techniques have been employed to study plasma secretin concentrations in man (Bloom & Ogawa, 1973; Boden & Chey, 1973; Bloom, 1974). Fasting secretin levels range between about 100 and 500 pg/ml plasma: assuming an haematocrit of about 50%, these values correspond to blood concentrations of between 50 and 250 pg/ml. The presence of acid in the duodenum causes a rise in plasma secretin levels to between 200 and 600 pg/ml (Boden & Chey, 1973; Bloom & Ogawa, 1973), and starvation also leads to an increase in plasma secretin levels from about 50 pg/ml in the fed subject to about 175 pg/ml in starvation (Henry, Flanagan & Buchanan, 1975). It is therefore not unreasonable to assume that, in man, normal secretin levels may be about 25 pg/ml blood, rising on starvation to values up to 250 pg/ml, and perhaps even higher if acid is present in the duodenum.

The blood secretin levels in the present experiments when secretin was infused intra-arterially in doses of 25 and 100 mu/min were about 100 and 260 pg/ml respectively, and after intravenous injection of 100 mu/kg if the injected secretin had been distributed evenly throughout the bloodstream, the resultant blood concentration would have been about 90 pg/ml.

If the assumption is made that physiological secretin levels are similar in the cat and in man, the effects which were demonstrated at the lower doses of secretin employed in the present experiments could well be of functional significance, particularly as the effects were clear-cut, and in some cases statistically significant (Figures 3–5).

It is possible, on the basis of the present experiments, that when secretin levels are elevated under 'physiological' conditions, as when acid is present in the duodenum, and in starvation, the capillary filtration coefficient may be increased, causing an increase in the functional exchange vessel area in the small intestine, and particularly at the higher secretin levels falling within the 'physiological range', the total blood flow through the intestine may be increased, due to a reduction in intestinal vascular resistance. It is possible that such a vascular effect of secretin is important in maintaining high blood secretin levels in starvation, a state in which Henry *et al.* (1975) have suggested that the hormone may exert a lipolytic action.

This study was generously supported by the Medical Research Council. The author is pleased to acknowledge the skilful technical assistance of Miss June Pyke and Miss Dorinda Lobenhan, and the help of the Boots Company Limited in a literature search.

References

BAYLISS, W.M. (1902). On the local reactions of the arterial wall to changes in internal pressure. *J. Physiol. Lond.*, **28**, 220–231.

BAYLISS, W.M. & STARLING, E.H. (1902). The mechanism of pancreatic secretion. *J. Physiol. Lond.*, **28**, 325–353.

BIBER, B., FARA, J. & LUNDGREN, O. (1973). Vascular reactions in the small intestine during vasodilatation. *Acta Physiol. scand.*, **89**, 449–456.

BLOOM, S.R. (1974). Progress report: radioimmunoassay of intestinal hormones. *Gut*, **15**, 502–510.

BLOOM, S.R. & OGAWA, O. (1973). Radioimmunoassay of human peripheral plasma secretin. *J. Endocrinol.*, **58**, xxiv–xxv.

BODEN, G. & CHEY, W.Y. (1973). Preparation and specificity of antiserum to synthetic secretin and its use in a radioimmunoassay (RIA). *Endocrinology*, **92**, 1617–1624.

FASTH, S. & HULTEN, L. (1971). The effect of glucagon on intestinal motility and blood flow. *Acta physiol. scand.*, **83**, 169–173.

FASTH, S., FILIPSSON, S. HULTEN, L. & MARTINSON, J. (1972). The effect of the gastrointestinal hormones on intestinal motility and blood flow. *Experientia*, **29**, 982–984.

FOLKOW, B. (1964). Description of the myogenic hypothesis. *Circ. Res.*, Supt. to 14 & 15, I-279 to I-285.

FOLKOW, B., LUNDGREN, O. & WALLENTIN, I. (1963). Studies on the relationship between flow resistance, capillary filtration coefficient and regional blood volume in the intestine of the cat. *Acta physiol. scand.*, **57**, 270–283.

FOLKOW, B. & MELLANDER, S. (1970). Measurements of capillary filtration coefficient and its use in studies of the control of capillary exchange. In *Capillary permeability (Alfred Benzon Symposium II)*, pp. 614–623. Munksgaard, Copenhagen.

HENRY, R.W., FLANAGAN, R.W.J. & BUCHANAN, K.D. (1975). Secretin: a new role for an old hormone. *Lancet*, **ii**, 202–203.

JOHNSON, P.C. & RICHARDSON, J.R. (1974). The influence of venous pressure on filtration forces in the intestine. *Microvasc. res.*, **7**, 296–306.

MELLANDER, S. (1960). Comparative studies on the adrenergic neuro-hormonal control of resistance and capacitance blood vessels in the cat. *Acta physiol. scand., Supplement* **176**, 5–86.

MELLANDER, S. & JOHANSSON, B. (1968). Control of resistance, exchange and capacitance functions in the peripheral circulation. *Pharmac. rev.*, **20**, 117–196.

ÖBERG, B. (1964). Effects of cardiovascular reflexes on net capillary fluid transfer. *Acta physiol. scand., Supplement* **229**, 5–98.

PETERSON, O. (1974). The effect of glucagon on the liver cell membrane potential. *J. Physiol. Lond.*, **239**, 647–656.

RICHARDSON, P.D.I. (1974). Drug-induced changes in capillary filtration coefficient and blood flow in the innervated small intestine of the anaesthetized cat. *Br. J. Pharmac.*, **52**, 481–498.

RICHARDSON, P.D.I. (1975a). The effects of glucagon and pentagastrin on capillary filtration coefficient in the innervated jejunum of the anaesthetized cat. *Br. J. Pharmac.*, **54**, 225P.

RICHARDSON, P.D.I. (1975b). An investigation of the mechanisms responsible for a reduction in capillary filtration coefficient in the innervated cat jejunum on intravenous infusion of histamine. *J. Pharm. Pharmac.*, **27**, 868–870.

RICHARDSON, P.D.I. (1976). The effects of intravenous secretin on the small intestinal vasculature of the cat. *Br. J. Pharmac.*, **56**, 358–359P.

ROSS, G. (1970). Cardiovascular effects of secretin. *Am. J. Physiol.*, **218**, 1166–1170.

TIBBLIN, S. (1971). De intestinala hormoneras effekt på splanknikus-cirkulationen. *Nordisk Medicin*, **85**, 121.

(Received March 4, 1976.)