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# THE VASODILATOR ACTIONS OF ISOPRENALINE, HISTAMINE, PROSTAGLANDIN $E_2$, GLUCAGON AND SECRETIN ON THE HEPATIC ARTERIAL VASCULAR BED OF THE DOG

P.D.I. RICHARDSON & P.G. WITHRINGTON

Department of Physiology, The Medical College of St. Bartholomew's Hospital, Charterhouse Square, London EC1M 6BQ

**1** The sympathetically-innervated arterial vascular bed of the dog's liver was perfused from a femoral artery. Arterial blood flow and perfusion pressure were measured continuously, and the hepatic arterial vascular resistance calculated. The preparation provided a means of assessing hepatic arterial vasodilatation quantitatively.

**2** Isoprenaline, histamine, prostaglandin $E_2$, glucagon and secretin were injected intra-arterially and all evoked dose-dependent vasodilatation of the hepatic arterial vascular bed.

**3** The maximum reduction in the calculated hepatic arterial vascular resistance of 37–38% was the same for each of the five substances.

**4** Comparisons on a weight basis revealed that prostaglandin $E_2$ was the most potent, followed in potency order by secretin, isoprenaline, histamine and glucagon.

**5** Comparisons on a molar basis showed that secretin and prostaglandin $E_2$ were intrinsically considerably more potent than isoprenaline, histamine or glucagon.

**6** The onset of the vasodilatator responses to secretin, isoprenaline, histamine and prostaglandin $E_2$ was rapid, and the duration of their actions was brief.

**7** The onset of the vasodilator effects of glucagon was slow and its duration of action very prolonged.

**8** The implications of these observations with respect to the physiological control of the hepatic arterial vascular bed of the dog are discussed.

## Introduction

In previous publications (Richardson & Withrington, 1975; 1976), the range of vasoconstrictor responses of the hepatic arterial vascular bed to noradrenaline, angiotensin and vasopressin, substances which are likely to be circulating under various physiological circumstances, was established. Those experiments also revealed that glucagon, an established gastrointestinal hormone, had two significant actions on the hepatic arterial vascular bed of the dog. It provoked hepatic arterial vasodilatation, and antagonized the hepatic arterial vasoconstrictor actions of noradrenaline, angiotensin and vasopressin.

We have now studied the actions of another gastrointestinal hormone, secretin, on the hepatic arterial vascular bed. In addition, two potent naturally-occurring vasodilator substances, histamine and prostaglandin $E_2$ have been studied. Although not normally present in the systemic circulation in vasoactive amounts, they may be synthesized within the liver or may enter the liver in the portal vein and so could modify hepatic arterial vascular resistance. The present experiments were designed to examine the dose-response relationships, relative potencies and time-courses of the vascular actions of these naturally occurring agents on the hepatic arterial bed. In addition the vasodilator effects of the synthetic catecholamine, isoprenaline, were examined for comparative purposes in the establishment of the relative activities of the vasodilator hormones.

## Methods

Experiments were performed on 12 dogs weighing between 10.5 and 17.5 kg ($14.7 \pm 2.3$ kg; mean $\pm$ s.d.) which had been deprived of food for 24 h, but allowed unrestricted access to water. Anaesthesia was induced by an intravenous injection of methohexitone sodium (Brietal, Lilly; 7.5–10.0 mg/kg) and maintained with chloralose (Kuhlmann, Paris; 50 mg/kg i.v.) and urethane (BDH; 500 mg/kg i.v.), supplementary doses

of chloralose and urethane being given as necessary to maintain a constant level of anaesthesia.

Following a midline laparotomy, the common hepatic artery was separated from its periarterial sympathetic nerves. In contrast to previous experiments (Richardson & Withrington, 1976) in which these nerves were divided, in the present series of experiments, they were carefully preserved to maintain a sympathetic vasoconstrictor tone to the hepatic arterial vasculature. The animals were injected with heparin (Weddel Pharmaceuticals; 250 i.u./kg, i.v., followed by supplements of 100 i.u./kg hourly), the common hepatic artery cannulated close to its origin from the aorta, and perfused with blood from a cannulated femoral artery. The blood flow through the cannula between the femoral artery and the hepatic artery (hepatic arterial blood flow; HABF) was measured with a cannulated flow probe and electromagnetic flowmeter (Cardiovascular Instruments Limited) and the hepatic arterial perfusion pressure (PP) was measured from a 'T'-piece close to the point of cannulation of the hepatic artery with a Consolidated Electrodynamics L212 strain gauge transducer. The cannula system carried additional 'T'-pieces for the intra-arterial administration of vasoactive substances.

On completion of surgery, the abdominal incision was closed, a thermometer inserted into the abdominal cavity, and the intra-abdominal temperature maintained at 37–38°C with table heaters and radiant lamps; stable control variables were recorded for at least 20 min before the administration of any drugs or hormones.

To monitor possible systemic effects of the vasoactive agents, phasic systemic arterial blood pressure was measured with a Statham P23Gb strain gauge transducer from the cannulated right femoral artery, and heart rate derived electronically from this measurement.

After appropriate amplification, all variables were displayed continuously on a Devices M 19 recorder.

*Calculation of results*

*Liver weight* was obtained immediately after each experiment. Values expressed per 100 g refer to this terminal weight of liver.

*Hepatic arterial mean perfusion pressure (PP)* was derived electronically from the phasic waveform with a Devices model 3502 averaging circuit with time constants of 0.5, 1 and 2 s, selected appropriately. Both mean and phasic pressure records were displayed continuously.

*Hepatic arterial mean blood flow (HABF)* was derived electronically by passing the phasic waveform through an averaging circuit with a time constant of 0.6 second. Both mean and phasic flow records were displayed continuously.

*Hepatic arterial vascular resistance (HAVR)* was calculated as hepatic arterial mean perfusion pressure (mmHg) divided by hepatic arterial mean blood flow (ml/min, or ml $min^{-1}$ 100 $g^{-1}$) and expressed as mmHg $ml^{-1}$ min, or mmHg $ml^{-1}$ min 100 grams.

*Changes in vascular resistance* were calculated as percentage changes from the control values immediately before any procedure, i.e. (change in vascular resistance × 100)/(control vascular resistance).

When large doses of the vasodilator agents were injected intra-arterially to the liver, there were large increases in blood flow accompanied by small reductions in perfusion pressure. Since a change in perfusion pressure itself may cause myogenic and hydrostatic adjustments in the tone of resistance vessels, resulting in alterations in vascular resistance (Bayliss, 1902; Folkow, 1964), the possible contribution of such changes to the effects measured in the present experiments was examined. On 15 occasions in 5 preparations, the PP was reduced by graded occlusions of the hepatic arterial cannula, and pressure/resistance curves constructed. When the PP was reduced in this way, by the same amount as the reduction caused by maximal doses of the vasodilator substances (by $11.3 \pm 0.7$ mmHg from a control of $119.2 \pm 4.8$ mmHg; $n = 28$), the hepatic arterial vascular resistance (HAVR) rose by about 3% from $1.94 \pm 0.15$ to $2.00 \pm 0.17$ (mean ± s.e. mean, $n = 15$) mmHg $ml^{-1}$ min 100 grams.

Since the HAVR fell by about 38% on injection of maximal doses of all the vasodilator substances (see results), the small change in HAVR due to the reduced perfusion pressure is insignificant and correction factors have not been applied.

*Expression of results*

Except where indicated to the contrary, results are expressed as means ± s.e. means.

Where the term $ED_{50}$ is used, it indicates the dose of a drug producing 50% of the maximum response that could be elicited by progressively increasing intra-arterial injections of that drug.

The time course of the responses to each of the substances are expressed numerically as the time taken for 50% recovery from the maximum effect ($T\frac{1}{2}$) of a selected dose of each substance. The dose selected for this analysis was a just-submaximal dose which produced the same reduction in HAVR for each substance.

*Drugs*

The drugs used, and the forms in which their weights

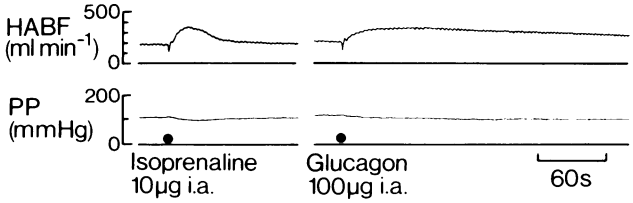


**Figure 1** Time courses of the responses of the hepatic arterial vascular bed to intra-arterial injections of isoprenaline and glucagon. HABF = hepatic arterial blood flow; PP = hepatic arterial mean perfusion pressure.

are expressed were: glucagon hydrochloride (Lilly; base), histamine acid phosphate (BDH; salt), isoprenaline sulphate (MacCarthay; salt), prostaglandin $E_2$ (Prostin $E_2$, Upjohn) and natural secretin (Boots). Doses of secretin are expressed in Crick-Harper-Raper Units where 1 unit is equivalent to 62.5 ng (manufacturer's data).

Drugs were dissolved in, or diluted from ampoules with 0.9% w/v NaCl solution (saline). Intra-arterial injections were made at a point between the flow probe and hepatic arterial cannula, resulting in an injection artefact which was very clearly separable from subsequent drug-induced changes in HABF and PP (Figure 1).

Intra-arterial infusions were from a Watson-Marlow MHRE-200 pump precalibrated to deliver 1.0 ml/min against pressures in excess of 150 mmHg.

The volume of blood in the external circuit was compensated for by injecting an equal volume of a solution of low molecular weight dextran in saline (Rheomacrodex, Pharmacia) intravenously.

## Results

### *Control values*

The livers weighed $312.8 \pm 6.4$ (s.d.) g, representing $2.12 \pm 0.27$ (s.d.) % of the weight of the dogs. Under control conditions, the hepatic arterial mean perfusion pressure (PP) was $124.3 \pm 5.9$ mmHg and the hepatic arterial mean blood flow (HABF) $63.6 \pm 5.9$ ml $min^{-1}$ $100\ g^{-1}$, giving a calculated hepatic arterial vascular resistance (HAVR) of $2.18 \pm 0.25$ mmHg $ml^{-1}$ min 100 grams. The heart rate was $177.0 \pm 12.0$ beats/minute.

### *The effects of the vasoactive agents*

Isoprenaline, histamine, prostaglandin $E_2$, glucagon and secretin were injected into the hepatic artery in increasing doses from below threshold to doses in excess of the maximum responses. From the changes in calculated HAVR, $\log_{10}$ dose-response curves were constructed for each substance, the doses being expressed both in terms of the weight of the substance used and, in order to compare the intrinsic potencies of the five substances, in terms of the fraction of one mole of the agent injected.

*Isoprenaline* was injected into the hepatic artery in increasing doses from 10 ng to 50 μg on 8 occasions in 5 preparations: hepatic arterial vasodilatation, manifest as an increase in HABF with small reductions in PP at the highest doses, was the only effect observed (Figure 1). The reduction in calculated HAVR was dose-dependent (Figure 2a), the lowest dose at which effects were observed being between 10 and 50 ng, and maximum effects being attained on injection of 20 or 50 μg. The maximum reduction in HAVR was $38.1 \pm 1.9\%$ (Table 2) and the changes in HABF, PP and calculated HAVR at maximum vasodilatation are shown in Table 1.

The vasodilatation elicited by isoprenaline was of rapid onset and short duration, the time taken for 50% recovery from the peak changes ($T_{\frac{1}{2}}$) of the test dose being $21.4 \pm 2.7$ s (Figure 1; Table 2).

*Histamine* was injected in doses between 10 ng and 20 μg on 5 occasions in 3 preparations, resulting in hepatic arterial vasodilatation at all doses above the threshold of 50 or 100 ng. The reduction in calculated HAVR was dose-dependent (Figure 2a), reaching a maximum of $37.4 \pm 4.5\%$ at 10 or 20 μg; the changes in blood flow and perfusion pressure at maximal vasodilatation are shown in Table 1.

The effects of histamine were of rapid onset and brief duration, the $T_{\frac{1}{2}}$ for recovery from the vasodilatation being $14.2 \pm 1.4$ s (Table 2).

*Prostaglandin $E_2$* was injected intra-arterially to the liver in doses from 0.5 ng to 5 μg on 8 occasions in 5 preparations, resulting in a reduction in calculated HAVR at all doses above the threshold of 1 or 5 ng (Figure 2a). The maximum reduction in HAVR attained on injection of prostaglandin $E_2$ was $37.4 \pm 1.9\%$, the doses producing the maximum effect being between 0.5 and 5 μg. The changes in HABF and PP at maximum vasodilatation are shown in

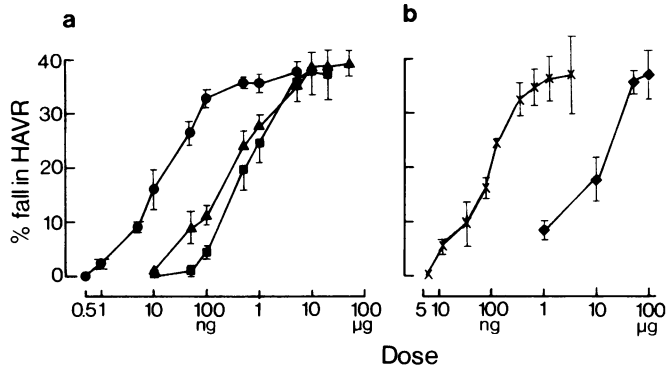


**Figure 2** $Log_{10}$ dose-response curves to the five vasodilators used. The doses are expressed in terms of the weight of each substance injected intra-arterially, and the response is the percentage reduction in calculated hepatic arterial vascular resistance (HAVR). (a) Dose-response curves to isoprenaline (▲), histamine (■), and prostaglandin $E_2$ (●). (b) Dose-response curves to glucagon (◆) and secretin (×). The symbols represent the mean observations (for isoprenaline, $n=8$, for histamine, $n=5$, for prostaglandin $E_2$, $n=8$, for glucagon, $n=4$, and for secretin, $n=3$) and the vertical lines show the s.e. means.

Table 1; the $T_{\frac{1}{2}}$ to recovery from the peak effect of the selected dose of prostaglandin $E_2$, 0.5 µg, was 18.2 ± 1.6 s.

The solution of prostaglandin $E_2$ contained a small amount of ethanol; when 1 µg of prostaglandin $E_2$ was injected, an amount of ethanol equivalent to 0.5 ml of 0.2% ethanol in saline was injected. Whilst this dose of prostaglandin $E_2$ produced 92.9 ± 1.7% of the maximum vasodilator response, injecting the corresponding amount of ethanol did not influence the HAVR.

*Glucagon* (1, 10, 50 and 100 µg) was injected into the hepatic artery, and brought about considerable increases in HABF with small reductions in PP at the higher doses (Figure 2b, Tables 1 and 2). This procedure was adopted in each of 4 experiments and the mean maximum reduction in calculated HAVR

**Table 1** Hepatic arterial perfusion pressure (PP) blood flow (HABF) and calculated vascular resistance (HAVR) immediately before, and at the peak of responses to maximal vasodilator doses of each agent

| *PP (mmHg)* | | *HABF (ml min$^{-1}$ 100 g$^{-1}$)* | | *HAVR (mmHg ml$^{-1}$ min 100 g)* | |
|---|---|---|---|---|---|
| *Control* | *Peak* | *Control* | *Peak* | *Control* | *Peak* |
| *Isoprenaline (n=8)* | | | | | |
| 122.3 ± 9.2 | 109.0 ± 8.0 | 56.8 ± 6.5 | 85.8 ± 8.3 | 2.30 ± 0.24 | 1.34 ± 0.13 |
| *Histamine (n=5)* | | | | | |
| 129.0 ± 9.4 | 116.4 ± 8.6 | 41.2 ± 5.1 | 61.4 ± 6.8 | 3.34 ± 0.47 | 2.04 ± 0.35 |
| *Prostaglandin $E_2$ (n=8)* | | | | | |
| 116.1 ± 5.6 | 107.5 ± 5.6 | 53.0 ± 5.3 | 79.0 ± 8.8 | 2.32 ± 0.23 | 1.46 ± 0.18 |
| *Glucagon (n=4)* | | | | | |
| 111.8 ± 6.1 | 101.3 ± 6.9 | 59.6 ± 7.2 | 90.9 ± 11.1 | 1.95 ± 0.24 | 1.17 ± 0.16 |
| *Secretin (n=3)* | | | | | |
| 107.3 ± 12.7 | 98.3 ± 13.5 | 50.7 ± 4.8 | 74.0 ± 5.3 | 2.20 ± 0.18 | 1.36 ± 0.21 |

Each value is the mean ± s.e. mean immediately before (Control) and at the peak of the responses to maximal vasodilator doses (Peak) of each agent. The number of dose-response curves from which these data were derived is shown in parentheses after the name of the drug.

was 37.1 ± 4.3%. The time course of the effects of glucagon was different from that of the other four agents, being slow in onset and of very long duration (Figure 1), the $T_{\frac{1}{2}}$ for recovery from the peak effects of 100 μg glucagon being 219.0 ± 16.5 s, a value more than ten times larger than for the other four substances examined.

*Secretin.* Complete dose-response curves to secretin were constructed on 3 occasions in 3 experiments by injecting doses between 100 mu (6.25 ng) and 50 u (3.13 μg) intra-arterially to the liver. At doses above the threshold of 200 mu, there were increases in HABF and at the highest doses small reductions in PP, resulting in reductions in the calculated vascular resistance of up to 37.1 ± 4.3% (Figure 2b, Tables 1 & 2). Maximum effects were observed on injection of between 5 and 20 u (0.31 to 1.25 μg), and the effects were of rapid onset and short duration, the $T_{\frac{1}{2}}$ to recovery from the maximum effects of 20 u being 19.8 ± 3.1 s, values similar to those for isoprenaline, histamine and prostaglandin $E_2$.

*Relative vasodilator potency of isoprenaline, histamine, prostaglandin $E_2$, glucagon and secretin*

The maximum reduction in hepatic arterial vascular resistance attained with each agent was the same at about 37–38% (Table 2), but the potencies of the five substances differed considerably. From Figure 1, the weight of each substance which produces 50% of the maximum reduction in HAVR has been measured (Table 2) to give an indication of the potency order. On this weight basis, prostaglandin $E_2$ is the most potent vasodilator, followed by secretin, isoprenaline, histamine and glucagon. A more meaningful indication of the relative intrinsic potencies of the substances is achieved by considering the effects of fractions of one mole of each agent. In Figure 3, the dose-response curves for all five substances are plotted as the fraction of one mole of the substance on a

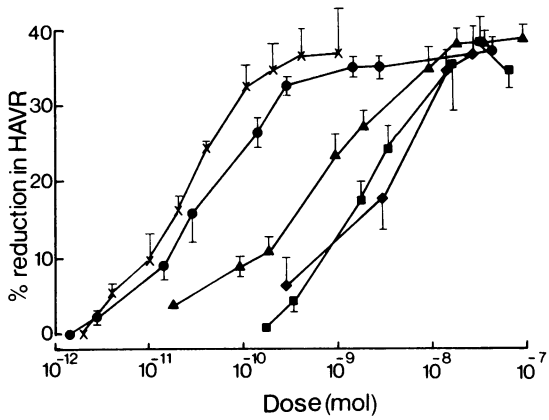


**Figure 3** $Log_{10}$ dose-response curves for isoprenaline (▲), histamine (■) prostaglandin $E_2$ (●), glucagon (◆) and secretin (×) on the canine hepatic arterial vascular bed. The dose is expressed as a fraction of one mole of each agent injected intra-arterially, and the response as the % fall in calculated hepatic arterial vascular resistance (HAVR). The symbols represent the mean observations and the vertical bars show the s.e. means. The numbers of observations are as for Figure 2.

**Table 2** Maximum reductions in calculated hepatic arterial vascular resistance (HAVR), $ED_{50}$ values, and times to half recovery from peak effects of selected doses of the vasodilator agents

| *Substance* | *Maximum fall in HAVR (%)* | *$ED_{50}$ (ng)* | *$ED_{50}$ (mol)* | *Test (μg)* | *Time to 50% recovery from peak effect of test dose (s)* |
|---|---|---|---|---|---|
| *Isoprenaline sulphate (n = 8)* | 38.1 ± 1.9 | 352 | $6.32 \times 10^{-10}$ | 10 | 21.4 ± 2.7 |
| *Histamine acid phosphate (n = 5)* | 37.4 ± 4.5 | 480 | $1.56 \times 10^{-9}$ | 10 | 14.2 ± 1.4 |
| *Prostaglandin $E_2$ (n = 8)* | 37.4 ± 1.9 | 20.5 | $5.82 \times 10^{-11}$ | 0.5 | 18.2 ± 1.6 |
| *Glucagon (n = 4)* | 37.1 ± 4.3 | 1120 | $3.21 \times 10^{-9}$ | 100 | 219.0 ± 16.3 |
| *Secretin (n = 3)* | 37.1 ± 4.3 | 80.0 | $2.62 \times 10^{-11}$ | 1.25 | 19.8 ± 3.1 |

Effects are shown as means ± s.e. mean.

logarithmic scale against the percentage reduction of vascular resistance. The curves to the left therefore represent substances with greater vasodilator potency than those to the right, and again the $ED_{50}$ can be calculated for this type of expression of the dose-response relationships. From Figure 3, it is apparent that on a molar basis, secretin with an $ED_{50}$ of $2.62 \times 10^{-11}$ mol and prostaglandin $E_2$ with an $ED_{50}$ of $5.82 \times 10^{-11}$ mol are the most potent vasodilator substances when injected intra-arterially to the hepatic arterial vascular bed of the dog. Isoprenaline ($ED_{50} = 6.32 \times 10^{-10}$ mol) has less than one-tenth the potency of prostaglandin $E_2$, and histamine with an $ED_{50}$ of $1.56 \times 10^{-9}$ mol, and glucagon ($ED_{50} = 3.21 \times 10^{-9}$ mol) are even less potent as vasodilators.

## Discussion

The present series of experiments were performed on the sympathetically-innervated liver of the dog and the control values for hepatic arterial blood flow, calculated hepatic vascular resistance and liver weights accord well with previously published data in the same species (Green, Hall, Sexton & Deal, 1959; Torrance, 1961; Richardson & Withrington, 1976).

The study of vasodilatation in the hepatic arterial bed has been almost entirely neglected since the low basal tone does not provide a suitable experimental preparation. In the present series it was found that provided care was taken to retain the sympathetic innervation to the liver, considerable increases in blood flow could be elicited regularly and repeatably on the injection of known vasodilator agents. The innervated liver therefore provides a preparation from which quantitative information may be obtained. The functional integrity of the sympathetic innervation to the liver was confirmed in some of the present experiments by temporary occlusion of the common carotid arteries, a procedure which elicited a reflex increase in hepatic arterial vascular resistance.

The present investigation was concerned with the increases in hepatic arterial blood flow due to the presence in the hepatic arterial blood of substances which either are normally present in the systemic circulation such as the gut hormones glucagon and secretin, or which may influence hepatic arterial vascular resistance either by being synthesized and released within the liver or by gaining access to the hepatic arterial bed through the portal vein (histamine, prostaglandin $E_2$). A comparison of the vasodilator properties of these naturally occurring compounds was made with the synthetic catecholamine, isoprenaline, the vasodilator properties of which are well established.

Large doses of isoprenaline injected or infused intra-arterially have been shown to elicit hepatic arterial vasodilatation in the dog (Scholtholt, Lochner, Renn & Shiraishi, 1967) but in the cat $\beta$-adrenoceptor responses have been found to be particularly difficult to elicit (Greenway & Stark, 1971). In the present experiments arterial injections of isoprenaline evoked marked and graded increases in hepatic arterial blood flow of short duration. On a molar basis it was amongst the least potent of the 5 substances tested.

Hepatic arterial vasodilatation in response to histamine has been observed previously (Galindo, 1965; Greenway & Stark, 1971). In the innervated liver histamine causes a dose-dependent increase in hepatic arterial bood flow of short duration. On a molar basis it was amongst the least active group, although the maximum decrease in hepatic arterial resistance was the same as with the other compounds investigated. The contention that histamine may act as a physiological vasodilator in some vascular beds has received considerable attention, particularly with regard to the hindlimb vasculature (Schayer, 1962; Beck, 1965) but it is unlikely to survive in the systemic blood at high concentrations unless histaminase inhibitors are administered (Ghosh & Schild, 1958; Buffoni, 1966). However, histamine is present in the liver under normal conditions (Best, Dale, Dudley & Thorpe, 1927); in addition, the gut contains large quantities of histamine (Roche e Silva, 1966) and under certain circumstances therefore the portal vein may contain detectable amounts. Histamine may alter the distribution of arterial blood in the hepatic parenchyma by having access to, and acting upon, those structures controlling hepatic arterial resistance. Factors which cause the release of histamine within the liver may include inflammation, arterial occlusion and anaphylactic reactions.

Injections of prostaglandin $E_2$ into the arterial supply to the liver caused marked, dose-dependent reductions in hepatic arterial vascular resistance; the time-course of the response was short. Together with secretin it was, intrinsically, the most active molecule in evoking hepatic vasodilatation with an $ED_{50}$ of $5.8 \times 10^{-11}$ mol. The high potency of prostaglandin $E_2$ as a hepatic arterial vasodilator prompts the question of its possible physiological role. Systemic circulating levels are low because of the effective removal by lung and liver (Vane, 1969). However, in the presence of the requisite enzymes synthesis is rapid so that, like histamine, local factors within the liver may stimulate the production of prostaglandin $E_2$ in amounts which could influence the arteriolar smooth muscle of the hepatic bed, modifying hepatic arterial resistance and the distribution of arterial blood within the liver. The gut contains and synthesizes prostaglandin $E_2$ which may be released in response to a number of stimuli (Horton, 1969). In the dog, it has been clearly shown that the spleen, when stimulated to contract by either nerve stimulation or intra-arterial injections of adrenaline, releases prostaglandin $E_2$ into the venous

effluent which consequently enters the liver by the portal vein (Davies, Horton & Withrington, 1968; Gilmore, Vane & Wyllie, 1969). It is possible that the hepatic arterial vascular resistance may be altered by prostaglandins present in the portal venous blood originating from either the spleen or the gastrointestinal tract.

The hepatic arterial vasodilator properties of glucagon in the sympathetically-denervated liver have been reported previously (Richardson & Withrington, 1975, 1976). Normally it enters the liver in the portal blood, its origin being the alpha cells of the pancreatic islets although an immunoreactive glucagon-like material is found to be released from the gut (Bloom, 1974). Some glucagon passes through the liver and pulmonary circuits and re-enters the liver in the hepatic arterial supply. The hepatic arterial vascular responses to glucagon are complicated: injections into the hepatic artery provoke large and dose-dependent reductions in hepatic arterial resistance, the maximum response not being significantly less than to the other compounds tested. However, on a weight basis, it was the least potent of the agents examined and on a molar basis amongst the least active group. A striking observation, possibly with considerable functional significance, is that the duration of action of glucagon on the resistance vessels is very much longer than that of the others. The cumulative activity inherent in prolonged responses implies that glucagon, even in very small concentrations, will evoke sustained increases in liver blood flow. In addition to these direct actions of arterial glucagon on the hepatic arterial resistance is its inhibitory action on the hepatic vasoconstrictor responses to circulating agents such as noradrenaline, angiotensin and vasopressin (Richardson & Withrington, 1975; 1976) and adrenaline (Richardson & Withrington, unpublished observations). The relative importance of these two properties of glucagon in maintaining hepatic arterial blood flow is difficult to ascertain without more information on the circulating systemic arterial and portal blood concentrations.

Secretin is an established gastrointestinal hormone; its presence in the small intestine (Bayliss & Starling, 1902; Bloom, 1974) and its vascular actions (Ross, 1970) have been elucidated. It enters the liver in both portal venous and systemic arterial supplies. Injections of secretin into the hepatic artery result in profound dose-dependent hepatic arterial vasodilatation of very short duration. On a molar basis it is with prostaglandin $E_2$, the most potent vasodilator examined in the present series with an $ED_{50}$ of $2.6 \times 10^{-11}$ mol (80 ng; 1.28 u) and with vasodilatation of the hepatic arterial bed being apparent on intra-arterial injection of as little as 200 mu. Arterial or portal blood concentrations of secretin have not been satisfactorily established in experimental animals; in man normal peripheral blood secretin levels are of the order of 25 pg/ml rising to 250 pg/ml in starvation or when acid is present in the duodenum (Bloom & Ogawa, 1973; Boden & Chey, 1973; Bloom, 1974; Henry, Flanagan & Buchanan, 1975). In the present experiments, hepatic arterial vasodilatation was apparent on injection of 12.5 ng (200 mu) into an arterial blood flow of the order of 200–250 ml/min; it is therefore probable that hepatic arterial vasodilation occurs at physiological levels of secretin. In addition hepatic arterial vasodilatation is clearly elicited by arterial infusions of secretin which produce blood concentrations of 200–300 pg/ml (Richardson & Withrington, unpublished observations).

The results of the present experiments taken in conjunction with previous results (Richardson & Withrington, 1976) show that a number of substances which are present in the hepatic arterial supply have potent actions in either reducing (secretin and glucagon) or increasing (adrenaline, noradrenaline, angiotensin and vasopressin) hepatic arterial vascular resistance. The interaction between some of these substances is not, moreover, one of simple functional antagonism. In the case of glucagon it is considerably more complex (Richardson & Withrington, 1976). In addition, two of the vasodilator substances studied, histamine and prostaglandin $E_2$, although not normally present in the arterial supply in vasoactive amounts may enter the liver in the portal circulation. The extent to which these substances, and other vasoactive agents present in the portal vein, may modify the hepatic arterial vascular resistance and influence the actions of other vasoactive materials on the circulation is the subject of further experiments.

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