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# RESPONSES OF THE SIMULTANEOUSLY-PERFUSED HEPATIC ARTERIAL AND PORTAL VENOUS VASCULAR BEDS OF THE DOG TO HISTAMINE AND 5-HYDROXYTRYPTAMINE

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**1** The sympathetically-innervated hepatic arterial and portal venous vascular beds of the dog were perfused simultaneously *in situ*.

**2** Histamine and 5-hydroxytryptamine (5-HT) were injected intra-arterially and intraportally in graded, increasing doses.

**3** Intra-arterial histamine evoked decreases in hepatic arterial vascular resistance (HAVR) and increases in hepatic portal vascular resistance (HPVR).

**4** Intraportal injections of histamine caused increases in HPVR and decreases in HAVR.

**5** The time courses of the arterial responses to intraportal histamine and of the portal responses to intra-arterial histamine, compared with any systemic effects, showed that these effects on the liver vasculature could not be the result of recirculation of histamine.

**6** Intra-arterial 5-HT evoked biphasic changes in HAVR and small falls in HPVR. Intraportal 5-HT caused falls in HPVR at low doses and rises at high doses, together, typically, with biphasic effects on HAVR.

**7** It is unlikely that the arterial effects of intraportal 5-HT and the portal effects of intra-arterial 5-HT were due to recirculation of the vasoactive material.

**8** Pathophysiologically, both histamine and 5-HT are released from the gastrointestinal tract into the portal vein. These experiments show that such release may affect the hepatic arterial vascular resistance (and therefore blood flow) even though vasoactive levels of the autacoids are not attained in the systemic circulation.

## Introduction

Vasoactive substances administered into the hepatic portal venous bloodstream may affect the vascular resistance not only of the hepatic portal venous but also of the hepatic arterial vascular bed (Hirsch, Ayabe & Glick, 1976). Further, in experiments in which both the hepatic arterial and the portal venous vascular beds have been perfused simultaneously, it has been demonstrated that injections of noradrenaline, isoprenaline or vasopressin into either inflow circuit evoke changes in both the hepatic arterial and portal venous vascular resistances (Richardson & Withrington, 1978a, b). We have termed the effects on the circuit not receiving the direct injection 'transhepatic' as it has been shown that they are not the result of recirculation of the vasoactive material.

Histamine and 5-hydroxytryptamine (5-HT) are distributed throughout the gastrointestinal tract and related organs, and may be released in a variety of pathophysiological conditions. Both amines are vasoactive, and it has been shown previously, with preparations in which only one inflow circuit to the liver was perfused, that intra-arterial injections of histamine cause changes in hepatic arterial, and intraportal injections elicit changes in hepatic portal vascular resistance. However, it is generally considered that physiological release of neither substance results in adequate systemic concentrations for vasoactivity (Vane, 1969).

The present experiments were performed in dogs where both the hepatic arterial and portal venous vascular beds were perfused simultaneously, *in situ*. Injections of histamine and 5-HT were made separ-

ately into both inflow circuits to study the transhepatic responses in the circuit not receiving the direct injection.

The significance of the observations that both histamine and 5-HT when present in elevated concentrations in the portal venous bloodstream, but not in the systemic circulation, may provoke alterations in hepatic arterial blood flow is discussed with reference to the roles of both amines in physiological and pathological states.

## Methods

Experiments were performed in 10 dogs weighing between 13.8 and 23.5 kg which had been allowed unrestricted access to water, but not food, for 24 h before the induction of anaesthesia by an intravenous injection of methohexitone sodium (Brietal, Lilly: 5 to 8 mg/kg). Anaesthesia was maintained with chloralose (Kuhlmann: 50 mg/kg) and urethane (BDH: 500 mg/kg) injected intravenously and followed by supplements in the same proportion as necessary to maintain a constant level of anaesthesia.

The systems used for perfusion of the sympathetically-innervated hepatic arterial and portal venous vascular beds have been described previously, and only brief details are given here (Richardson & Withrington, 1976; 1977b).

### *Hepatic arterial bed*

The cannulated hepatic artery was perfused at essentially constant arterial pressure from a cannulated femoral artery. Hepatic arterial blood flow and perfusion pressure were measured continuously and the hepatic arterial vascular resistance calculated as (hepatic arterial mean perfusion pressure)/(hepatic arterial mean blood flow) and expressed in mmHg $ml^{-1}$ min, or mmHg $ml^{-1}$ min 100 g.

### *Hepatic portal bed*

The hepatic portal vein was cannulated and perfused at constant flow by means of a Watson-Marlow MHRE200 roller pump with blood derived from the superior mesenteric vein *via* the retrogradely-cannulated splenic vein. Under control conditions, the portal vein was perfused at the same flow as the outflow from the superior mesenteric vein, but during drug effects, the mesenteric blood flow could alter, so the pump perfusing the portal vein was also connected *via* a cannulated external jugular vein to the right atrium.

The hepatic portal venous blood flow and perfusion pressure were monitored continuously, as was the pressure in the inferior vena cava (IVC) at the level of the hepatic veins. The hepatic portal vascular resistance was calculated as (hepatic portal venous pressure-IVC pressure)/(hepatic portal venous blood flow) and expressed in the same units as the hepatic arterial vascular resistance.

### *Extrahepatic measurements*

Systemic arterial blood pressure was recorded from a cannulated femoral artery and heart rate derived electronically from this measurement. Mean systemic arterial pressure (BP) was derived as diastolic + 1/3 pulse pressure, a derivation giving values in agreement with those obtained by passing the pulsatile signal through an averaging circuit. The pressure in the IVC at the level of the hepatic veins was measured from a cannula passed through a cannulated femoral vein; the catheter tip position was confirmed *post mortem*. The outflow from the superior mesenteric vein was measured in order to assess blood flow changes occurring in a non-hepatic vascular bed after drug administrations into the hepatic artery or the portal vein.

Intravascular pressures were measured with Statham or Consolidated Electrodynamics transducers and averaged by use of circuits with time constants of about 0.6 s. All blood flows were recorded with cannulating flow probes and electromagnetic flowmeters (Cardiovascular Instruments), mean flows being obtained by passing the signals through averaging circuits with time constants of about 0.6 s.

### *Drug administration*

Animals were heparinized before cannulation of blood vessels (Weddel Pharmaceuticals: 250 iu/kg i.v. followed by 100 iu/kg hourly), and all perfusion systems were primed with low molecular weight dextran solutions in 154 mmol/l NaCl solution (saline) (Lomodex, Fisons or Rheomacrodex, Pharmacia).

The agonist drugs used were: histamine acid phosphate (BDH) and 5-hydroxytryptamine creatinine sulphate (serotonin creatinine sulphate; BDH). Both were dissolved in saline and doses are expressed in terms of the salts used which have molecular weights of 307.1 (histamine) and 405.4 (5-HT). Drugs were injected directly into the cannulae leading to the hepatic artery (intra-arterially: i.a.) or portal vein (intraportally; i.p.v.) in volumes not exceeding 0.5 ml, washed in with saline to a total injectate volume of 1.5 ml. Injections of saline alone produced small injection artifacts on the pressure and flow records, but were without subsequent effects. Drug responses were analysed and dose-response curves constructed as described previously by Richardson & Withrington (1976, 1977b, c).

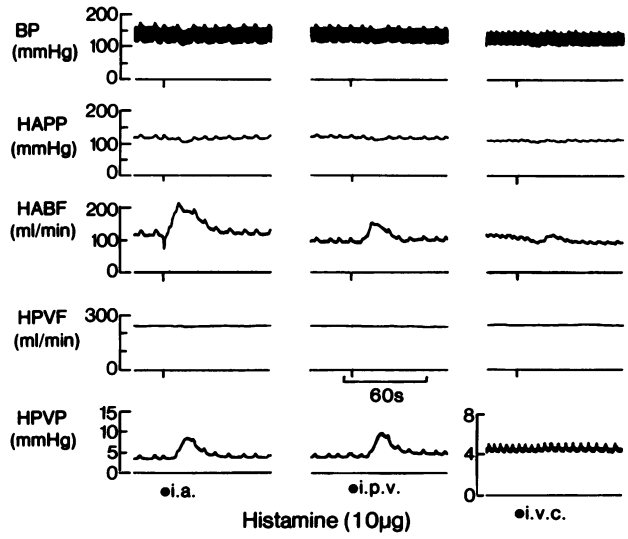


**Figure 1** Effects of injections of 10 μg histamine into the hepatic artery (i.a.), the hepatic portal vein (i.p.v.) and the inferior vena cava at the level of the hepatic veins (i.v.c.). The variables shown are: phasic systemic arterial pressure (BP), hepatic arterial mean perfusion pressure (HAPP), hepatic arterial mean blood flow (HABF), hepatic portal venous blood flow (HPVF: remains constant as the portal vein is perfused with a roller pump) and hepatic portal venous pressure (HPVP). Dots and small vertical lines below zero lines show the points of injection and the bar shows the time scale (1 min).

*Time courses*

In addition to the peak pharmacological responses, the times from injection to onset of the responses to selected doses of histamine and 5-HT were measured from the experimental records. The times to onset of changes in hepatic arterial blood flow, hepatic portal perfusion pressure, blood pressure, heart rate and superior mesenteric blood flow were measured. This information helped to separate direct effects on the liver vasculature following i.a. or i.p.v. injections from effects which could be attributed to vasoactive material passing through the liver and cardiopulmonary circuit to re-enter the liver ('recirculation').

*Statistical analyses*

Initial control data are presented as means $\pm 1$ s.d., and all other variables as means $\pm$ s.e. means. The significance of differences between paired sets of data samples was assessed by Student's $t$ test.

## Results

*Initial control values*

The dogs weighed 18.1 $\pm$ 2.7 kg and *post mortem* the livers weighed 338.4 $\pm$ 58.6 g. The systemic arterial mean pressure (BP) was 125 $\pm$ 18 mmHg, the heart rate (HR) 183 $\pm$ 29 beats/min and the inferior vena cava pressure (IVCP) 2.0 $\pm$ 1.6 mmHg. The hepatic arterial perfusion pressure (HAPP) was 115 $\pm$ 16 mmHg and the hepatic arterial blood flow (HABF) 41.1 $\pm$ 12.9 ml $min^{-1}$ 100 $g^{-1}$, giving a calculated hepatic arterial vascular resistance (HAVR) of 2.9 $\pm$ 0.8 mmHg $ml^{-1}$ min 100 g. The hepatic portal venous pressure (HPVP) was 7.2 $\pm$ 0.8 mmHg and the pressure gradient across the hepatic portal venous bed (HPVP-IVCP) was 5.5 $\pm$ 1.6 mmHg; the hepatic portal venous flow was 66.3 $\pm$ 10.5 ml $min^{-1}$ 100 $g^{-1}$, giving a calculated hepatic portal vascular resistance (HPVR) of 0.09 $\pm$ 0.03 mmHg $ml^{-1}$ min 100 g. The superior mesenteric venous flow (SMVF) was 223 $\pm$ 38 ml/min, and the systemic arterial haematocrit 47.6 $\pm$ 2.5%.

*Effects of intra-arterial injections of histamine*

(a) *Hepatic arterial vascular bed* Intra-arterial injections of histamine over the dose range 0.1 to 50 μg caused dose-dependent hepatic arterial vasodilatation of rapid onset, confirming previous observations (Richardson & Withrington, 1976). The maximum reduction in HAVR was 44.2 $\pm$ 4.3%; a typical re-

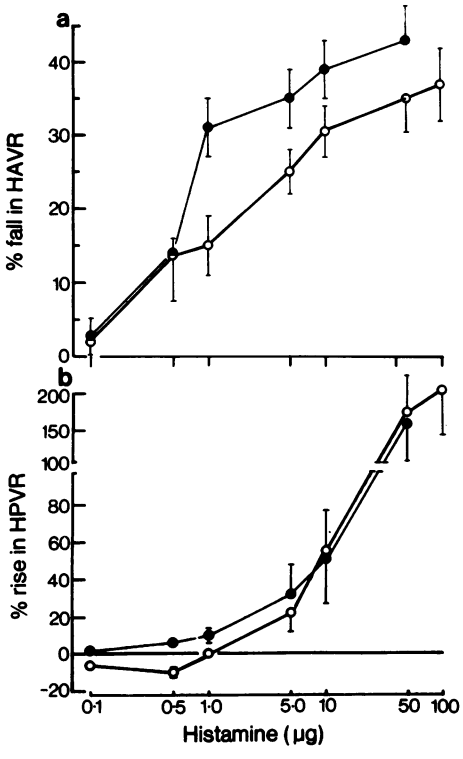


**Figure 2** Dose-response curves for the hepatic arterial (a) and portal venous (b) responses to histamine injected into the hepatic artery (●) and the portal vein (○). Points show the means of 6–8 observations and vertical bars the s.e. means. Abscissa scale: $\log_{10}$ scale showing weight of histamine injected. Upper ordinate scale: % reduction in hepatic arterial vascular resistance (HAVR). Lower ordinate scale: % increase in hepatic portal vascular resistance (HPVR).

sponse is shown in Figure 1 and the dose-response curve in Figure 2.

(b) *Hepatic portal vascular bed* Intra-arterial injections of histamine caused dose-dependent increases in hepatic portal venous pressure, which at constant inflow and IVCP reflect increases in portal vascular resistance. The onset of the effect was rapid and its duration short (Figure 1); the threshold for this effect was between 0.1 and 5.0 μg histamine i.a. in different preparations, and the greatest effect, attained at 50 μg i.a. was an increase in calculated HPVR of 161.6 ± 54.5%. Larger doses were not injected i.a. because of the pronounced systemic effects that would result from higher doses surviving passage through the liver to enter the systemic circulation. It is therefore probable that this effect of 50 μg histamine i.a. does not represent the maximum possible portal effect of intra-arterial injections of histamine.

(c) *Time courses of the responses* One dose, 10 μg, was selected for analysis of the time courses of the responses to i.a. histamine. The delay from injection to onset of the increase in hepatic arterial blood flow was 2.4 ± 0.3 s; this effect was followed significantly later ($P < 0.01$) by the increase in hepatic portal venous pressure at 7.7 ± 1.2 s. However, both liver vascular responses significantly preceded the reduction in BP resulting from the i.a. injection of 10 μg histamine which occurred at 12.8 ± 2.0 s ($P < 0.005$) and which represented a fall of 5.0 ± 1.2 mmHg. This dose of histamine resulted in an increase in heart rate in 3/7 experiments which had a latency of 15.6 ± 1.2 s, significantly ($P < 0.005$) longer than that for the hepatic arterial responses, but not significantly different in three experiments from that for the portal responses ($P > 0.10$) (Figure 3). The rise in HR was of 13 ± 2 beats/min. In no experiments did these injections of histamine result in any measurable change in the outflow from the superior mesenteric vascular bed, through which any histamine injected i.a. to the liver would have to pass to gain access to the portal vascular bed.

*Effects of intraportal injections of histamine*

(a) *Hepatic portal vascular bed* Intraportal injections of histamine (0.1 to 100 μg) resulted in dose-dependent increases in hepatic portal vascular resistance (HPVR), as described previously (Richardson & Withrington, 1977c) and which attained a maximum effect of a rise in HPVR of 220.5 ± 75.7%. Over the dose-range used, the portal responses to intraportal histamine were of the same order of magnitude as the portal responses to intra-arterial injection of the same doses (Figure 2).

(b) *Hepatic arterial vascular bed* Intraportal injections of histamine caused dose-dependent reductions in HAVR which over the dose range 0.1 to 100 μg i.p.v. attained a maximum fall of 37.8 ± 4.1%. The arterial responses to intraportal histamine were similar in character to the arterial responses to intra-arterial injections, though at all doses in excess of 0.5 μg the arterial responses were greater to histamine injected i.a. than to the same doses injected i.p.v. (Figures 1 and 2).

(c) *Time courses of the responses* On intraportal injection of 10 μg histamine, the first response to be manifest was the increase in hepatic arterial blood flow (Figure 1) which had a latency of 7.2 ± 0.8 s,

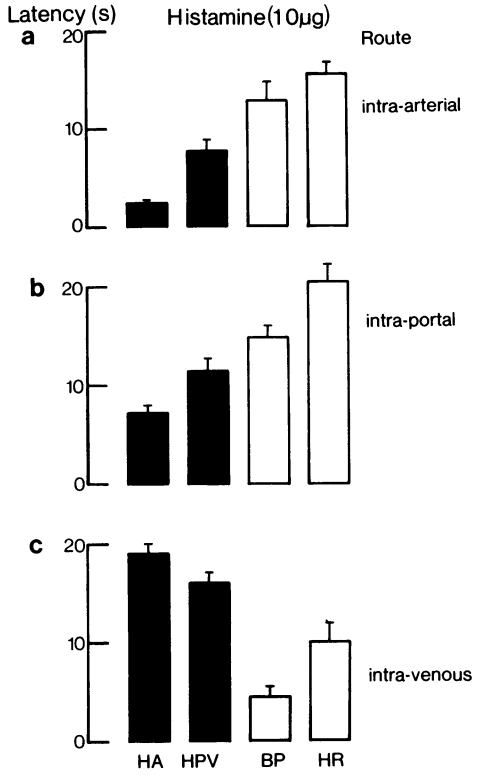


**Figure 3** Times to onset after injection of the responses to histamine, i.e. latencies (expressed in seconds). The responses of the hepatic arterial (HA), and hepatic portal venous (HPV) vascular beds are shown (solid columns) with the changes in systemic arterial pressure (BP) and heart rate (HR) (open columns). The effects of injections into the hepatic artery (a) the hepatic portal vein (b) and into the inferior vena cava at the level of the hepatic veins (c) are shown. Columns show the mean latencies of each variable ($n$ 6 to 8), s.e. means are indicated by the vertical bars.

and was followed significantly ($P < 0.005$) later by the increase in hepatic portal venous pressure at 11.4 ± 1.3 s. Both hepatic vascular effects, however, significantly preceded any changes in BP at 14.6 ± 1.2 s ($P < 0.02$) which represented falls of 7 ± 2 mmHg. Changes in heart rate were observed in only 3/7 experiments on intraportal injection of 10 μg histamine; these occurred significantly later ($P < 0.02$) than the arterial responses at 20.4 ± 1.8 s, but not significantly later than the portal responses to intraportal histamine ($P > 0.05$), and represented increases of 8 ± 3 beats/min. In no experiments did measurable changes in superior mesenteric blood flow result from the intraportal injection of 10 μg histamine, suggesting that there was no significant entry of histamine into the systemic circulation.

*Intravenous histamine*

In 4 experiments, 10 μg histamine was injected into the IVC at the level of the hepatic veins; this caused a different pattern of responses from those seen on either i.a. or i.p.v. injection of the same dose. The HAVR fell by 21.0 ± 6.5%, and the HPVR rose by 5.3 ± 2.1%, effects smaller than those seen on i.a. or i.p.v. injection of this dose. In contrast to the temporal sequence of effects seen on i.a. or i.p.v. injection, the first effect to be manifest was a fall in BP of 20 ± 5 mmHg at 4.5 ± 1.0 s which preceded ($P < 0.001$) the changes in hepatic arterial blood flow (18.9 ± 0.9 s) and hepatic portal venous pressure (16.0 ± 1.1 s) and which was greater than the fall in BP occurring on i.a. or i.p.v. injection. A rise in HR occurred in each experiment (at 10.0 ± 2.0 s), of 15 ± 5 beats/min, though in only 2 experiments were small rises in superior mesenteric blood flow observed.

*Effects of intra-arterial injections of 5-hydroxytryptamine*

5-HT was injected i.a. in doses from 1.0 to 100 μg in each of 7 experiments.

(a) *Hepatic arterial vascular bed* I.a. injections of 5-HT produced dose-dependent hepatic arterial vasoconstriction attaining a maximum increase in HAVR of 98.3 ± 14.5%. The time-course of these vasoconstrictor responses from onset to peak was longer than that of other constrictor agents studied so far and the maximum effect small. In 4/7 experiments, the hepatic arterial vasoconstrictor effect was preceded by a small hepatic arterial vasodilator response which was not in any experiment clearly dose-dependent and which in the 4 experiments attained a maximum effect of a fall in HAVR of 21.3 ± 3.9% at 5–100 μg i.a.

(b) *Hepatic portal vascular bed* In addition to effects on the HABF, i.a. injections of 5-HT caused a small reduction in portal venous pressure, which at constant portal inflow and IVCP, represented falls in calculated portal vascular resistance. The maximum fall in HPVR in 7 experiments was 11.0 ± 2.2% and occurred at either 50 or 100 μg; the threshold for this effect was between 1 and 10 μg in different experiments, and unlike the initial arterial vasodilatation, the reduction in HPVR was dose-dependent and observed in each of 7 experiments. The dose-response curves are shown in Figure 4.

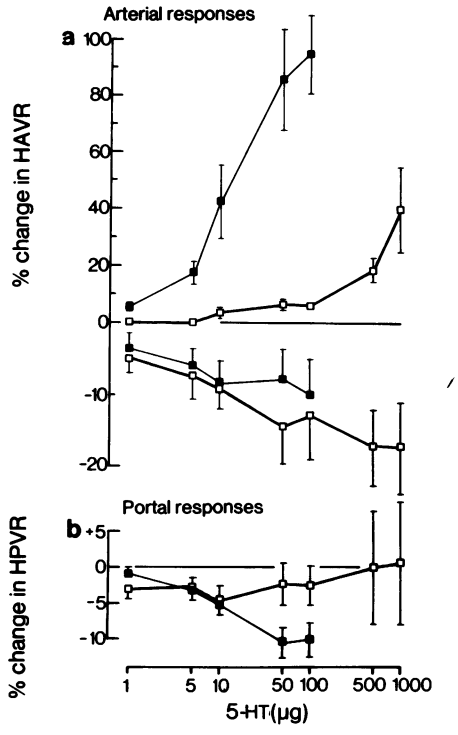


**Figure 4** Dose-response curves for the hepatic arterial (a) and portal venous (b) responses to intra-arterial (■) and intraportal (□) injections of 5-hydroxytryptamine (5-HT). Points show the means of 5 to 7 injections and vertical bars the s.e. means. Abscissa scale: $\log_{10}$ scale showing weight of 5-HT injected. Upper ordinate scale: % change in hepatic arterial vascular resistance (HAVR). Both the initial hepatic arterial vasodilatation (fall in HAVR) and the secondary vasoconstriction (rise in HAVR) are shown, the mean representing the effects observed over the series of 7 experiments. Lower ordinate scale: % change in hepatic portal vascular resistance (HPVR).

(c) *Extrahepatic effects* One dose (100 μg) of 5-HT was selected for analysis of the extrahepatic effects; this dose, whilst producing marked changes in the hepatic arterial and portal venous vascular beds (Figure 4), caused only small and variable changes in systemic arterial pressure ($-3 \pm 2$ mmHg), heart rate ($-5 \pm 3$ beats/min) and in superior mesenteric venous flow ($-0.3 \pm 3.3$ ml/min).

*Effects of intraportal injection of 5-hydroxytryptamine*

5-HT was injected intraportally in graded increasing doses from 1.0 μg to 1.0 mg in each of 7 experiments.

(a) *Hepatic portal vascular bed* The lower doses of 5-HT within the range injected i.p.v. caused small reductions in HPVR whilst the higher doses elicited, in some experiments, small increases in HPVR. All of the portal responses were monophasic. The maximum reduction in HPVR was $12.1 \pm 2.7\%$ (at 10 to 1000 μg) and the maximum increase in HPVR in those experiments ($n = 3$) where it occurred was $22.7 \pm 11.4\%$, at 1.0 mg i.p.v. In 4/7 experiments, however, only the small hepatic portal dilatation was evoked throughout the entire dose range so that, when including all the experiments (7), the mean rise in HPVR to 1 mg 5-HT was $+0.6 \pm 8.6\%$. These observations confirm the previous reports in separate perfusions studies (Richardson & Withrington, 1977c) that the hepatic vascular effects of 5-HT are variable and weak compared with those of other substances.

(b) *Hepatic arterial vascular bed* Intraportal 5-HT elicited changes in hepatic arterial blood flow which reflected changes in the hepatic arterial vascular resistance. In 5/7 experiments, there was an initial hepatic arterial vasodilatation attaining a maximum reduction in HAVR of $28.5 \pm 5.1\%$ (Figure 4); in 4 of these 5 experiments the initial vasodilatation was succeeded by vasoconstriction. In 2/7 experiments only hepatic arterial vasoconstriction was observed. The vasoconstrictor response to i.p.v. 5-HT observed in the hepatic arterial vascular bed of 6/7 dogs, reached a maximum increase in HAVR of $42.3 \pm 15.6\%$. Quantitatively, therefore (Figure 4) the hepatic arterial vasodilator responses to intraportal 5-HT were about the same or slightly greater than the responses to the same doses injected directly into the hepatic artery, whilst the arterial vasoconstrictor response to intraportal 5-HT was much smaller than the effect of the corresponding doses injected intra-arterially.

Confirming our previous observations, the hepatic vascular responses to 5-HT were characterized by being of both slow onset and long duration and small and variable in magnitude. The extra-hepatic responses (BP, HR and SMVF) due to either i.a. or i.p.v. 5-HT were, because of the avidity of the removal processes in the liver and pulmonary circuit, also very small. Such characteristics necessarily prevent a sufficiently discriminating comparative analysis to be made on the time-courses to onset of all these responses.

(c) *Extrahepatic effects* Intraportal injection of 100 μg of 5-HT brought about marked changes in hepatic portal and hepatic arterial vascular resistances (Figure 4) but only small and variable changes in systemic arterial pressure (less than 1 mmHg), heart rate ($3 \pm 6$ beats/min) and superior mesenteric venous flow ($-8.6 \pm 12.2$ ml/min).

## Discussion

These experiments show that intra-arterial and intraportal injections of histamine and of 5-HT cause changes not only in the vascular resistance of the liver inflow circuit which receives the direct injection, but also in the other inflow circuit. These effects are not dependent upon a purely hydrodynamic response of one inflow circuit to altered perfusion in the other, since although such interactions do occur, they are quantitatively extremely small, and could not account for the effects described in this paper (Richardson & Withrington, 1978b).

The relative time-courses of the effects of histamine eliminate the possibility that the effects on the circuit not receiving the direct injection are due to recirculation of vasoactive material., since the portal responses to i.a. injection and the arterial responses to i.p.v. injection precede the systemic effects; this pattern of effects is not seen if histamine is injected intravenously, when systemic effects occur before the hepatic vascular effects. Furthermore, when histamine is injected intraportally, the first effect to be seen is the hepatic arterial response; this eliminates the possibility that this transhepatic effect is due to recirculation or to a reflex triggered by alterations in systemic arterial pressure.

Such an analysis of the temporal relationship of the responses to 5-HT is more difficult since they are both very small and of prolonged time-course, compared with histamine or with either noradrenaline or isoprenaline (Richardson & Withrington, 1978b). However, both the intra-arterial and intraportal injection of 100 μg 5-HT caused significant changes in the resistance of the hepatic inflow circuit not receiving the direct injection, whilst there were no significant changes in BP, HR or SMVF, this indicates that the transhepatic effects must arise from access within the liver rather than from elevated levels of systemic arterial 5-HT. Indeed it has been shown on the basis of bioassay techniques (Vane, 1969) that approximately 95% of 5-HT is removed in passage through the liver and cardiopulmonary circuit.

The underlying mechanisms of the transhepatic effects, that is of the arterial responses to intraportal injection and the portal responses to intra-arterial injection, are as yet not clear. One possibility lies in the observation of Rappaport & Schneiderman (1976) that the inlet sphincter sections to the hepatic sinusoids (Greenway & Stark, 1971) exhibit cyclic opening and closing sequences; it is possible that drugs introduced by either arterial or portal route gain access to these inlet sphincteric sites, and influence the periodicity of the opening and closing movements. Since the measurements made in these experiments (i.e. vascular resistance) represent an integrated measurement of the responses of the microcirculatory units in the liver, changes in the inlet sphincter cyclic movements would be reflected as changes in the respective inflow resistances.

Another explanation of the portal changes on i.a. injection is that the vasoactive material could be conveyed from the arterial high pressure system to the low pressure portal system, through arterioportal anastomotic channels which have been observed, and in which unidirectional arterioportal blood flow has been described.

A further possibility is that intra-arterial or intraportal injections of the autacoids stimulate sensory receptors within the hepatic parenchyma which in turn elicit alterations in vascular dimensions by a reflex effect, either locally or systemically.

In the dog, sphincteric sections exist at the outlet of the hepatic sinusoids into the hepatic veins, in addition to the sphincteric sections at the entry of the two inflow circuits into the hepatic sinusoids, and these outlet sphincters have been shown to constrict in response to histamine, effecting 'hepatic outflow block' (Greenway & Stark, 1971; Greenway & Oshiro, 1973). A part of the transhepatic effect by which intra-arterial histamine elicits portal vasoconstriction may be attributable to increases in resistance in the outflow sphincter sections of the hepatic microvasculature; concomitant with this might be a reduction in the resistance of the arterial inflow sphincter sites, resulting in simultaneous increases in calculated portal vascular resistance and decreases in calculated hepatic arterial vascular resistance. This contention that the changes in calculated portal resistance receive a contribution from changes in outlet sphincter dimensions receives support from the fact that the increases in HPVR are very similar whether the histamine is injected intra-arterially or intraportally; after both routes of injection, it would be expected that the autacoid's concentration at the outflow sphincter sites would be similar, giving rise to quantitatively similar effects. However, it might also be supposed that outflow sphincter constriction ('outflow block') would limit the observed decreases in hepatic arterial vascular resistance: in fact, the maximum reductions in calculated hepatic arterial vascular resistance on injection of histamine (i.a.) are very similar to the maximum reductions obtained with agents which are not established to cause 'outflow block', such as isoprenaline, prostaglandin $E_2$, glucagon, secretin, CCK-PZ and bradykinin (Richardson & Withrington, 1976; 1977a, c).

Pathophysiologically, the importance of these observations may be considerable since they imply that material present in the portal vein in vasoactive amounts can cause hepatic arterial effects without the need to enter the systemic circulation in vasoactive amounts. It is well-established that both autacoids are present in the gastrointestinal tract and may be

released from these sites in shock and anaphylactic reactions (Best, Dale, Dudley & Thorpe, 1927; Erspamer, 1954; Zweifach, 1962; Burks & Long, 1966; Gabella & Juorio, 1973; Douglas, 1975). However, there is no clear evidence that these substances attain vasoactive systemic levels except in the most extreme forms of experimental 'shock' conditions. Attention has therefore not been directed towards the possible pathophysiological implications to the cardiovascular system of these substances. The present experiments demonstrate unequivocally that changes in portal venous blood concentrations of histamine and 5-HT can modulate hepatic arterial blood flow. Indeed, since both autacoids are metabolized actively in the liver (Vane, 1969) the increase in hepatic arterial blood flow seen with histamine may contribute to the liver's ability to detoxify histamine itself and other concomitantly-released autacoids, thereby preventing potentially hazardous increases in systemic levels of these substances.

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