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THE EFFECTS OF INTRAPORTAL INJECTIONS OF NORADRENALINE, ADRENALINE, VASOPRESSIN AND ANGIOTENSIN ON THE HEPATIC PORTAL VASCULAR BED OF THE DOG: MARKED TACHYPHYLAXIS TO ANGIOTENSIN

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1 The hepatic portal vein of the anaesthetized dog was cannulated and perfused with blood derived from the cannulated superior mesenteric vein.

2 The portal vein was perfused at constant flow, the hepatic portal venous pressure being monitored continuously together with the inferior vena caval pressure. From these measurements, the hepatic portal venous vascular resistance was calculated.

3 Noradrenaline and adrenaline were injected intraportally in graded doses which caused dose-dependent increases in the hepatic portal vascular resistance. At all doses, adrenaline was significantly ($P < 0.05$) more potent than noradrenaline.

4 Intraportal injections of vasopressin caused reductions in calculated hepatic portal venous vascular resistance in most experiments; these effects were dose-dependent.

5 No tachyphylaxis to the effects of noradrenaline, adrenaline or vasopressin was observed.

6 Intraportal injections of angiotensin caused dose-dependent increases in calculated hepatic portal vascular resistance up to 5 μg; thereafter larger doses caused smaller increases in portal resistance.

7 Repeated intraportal injections of angiotensin revealed the existence of tachyphylaxis in the hepatic portal vascular bed.

8 Intraportal infusions of angiotensin caused rises in calculated hepatic portal vascular resistance from which there was almost complete 'escape' despite the continued infusions. Infusions of noradrenaline which caused similar rises in calculated portal vascular resistance did not exhibit equivalent degrees of 'escape'.

9 The development of tachyphylaxis explains the fact that doses of 10 and 20 μg of angiotensin injected after 5 μg doses produced smaller effects. If a much longer time interval was allowed between injections (30 min), the dose-response curve to angiotensin had a sigmoid shape.

10 These findings are discussed with respect to their possible importance in the functional status of the hepatic portal vascular bed in this species.

Introduction

Injections of noradrenaline, angiotensin and vasopressin into the hepatic artery of the dog have been shown to cause constriction of the hepatic arterial vascular bed (Richardson & Withrington, 1976a). Similarly, adrenaline, at even the lowest doses appears to be vasoconstrictor to the denervated hepatic arterial vascular tree (Andrews, Hecker, MaeGraith & Ritchie, 1955; Richardson & Withrington, unpublished observations). In addition to the arterial inflow, the liver receives a large supply of blood which has drained the intestine, pancreas and spleen via the portal vein. Varying amounts of noradrenaline, adrenaline, vasopressin and angiotensin may therefore enter the liver in the portal vein, having passed through the mesenteric, pancreatic and splenic vasculature. These vasoactive agents may affect the portal vascular circuit by actions on structures within the liver which control portal vascular resistance. The present paper describes the actions of these naturally-occurring substances on the portal vascular resistance studied by the use of a perfusion technique where the blood was derived from the mesenteric vein. The portal blood flow was maintained constant despite alterations in the mesenteric and other series-coupled

vascular territories which, normally, would alter portal haemodynamics.

The actions of angiotensin were examined in more detail than those of the other substances because our experiments revealed that successive intraportal injections and infusions resulted in tachyphylaxis, a phenomenon seen neither with the other agents nor in studies of angiotensin on the hepatic arterial vascular bed.

Methods

Experiments were performed on 7 dogs weighing between 9.6 and 20.6 kg (15.7 ± 3.5 kg: mean ± s.d.) which had been starved, but allowed free access to water for 24 h before the induction of anaesthesia with methohexitone sodium (Brietal, Lilly, 7.5–10.0 mg/kg, i.v.). Anaesthesia was maintained with intravenous chloralose (Kuhlmann, Paris: 50 mg/kg) and urethane (BDH; 500 mg/kg), supplements of chloralose and urethane being given as necessary to maintain a constant level of anaesthesia.

Surgical preparation

Following a midline laparotomy, the splenic, superior mesenteric and hepatic portal veins were dissected free of surrounding tissue. The splenic artery and its accompanying periarterial sympathetic nerves were then dissected free, tied off, and the nerves stimulated supramaximally to expel the erythrocytes stored within the spleen into the systemic circulation. After an intravenous injection of heparin (Weddel Pharmaceuticals: 250 iu/kg and hourly supplements of 100 iu/kg) to prevent blood coagulation, the splenic vein was tied. The vessel was then cannulated towards the liver with wide bore tubing, and connected to a small reservoir into which the effluent from the superior mesenteric vein subsequently drained. The hepatic portal vein was tied about 5 mm from the confluence of the splenic and superior mesenteric veins, and the superior mesenteric venous effluent drained via the cannulated splenic vein into the reservoir. The spleen was then removed.

The superior mesenteric venous blood draining into the reservoir was returned to the animal via a cannulated external jugular vein until the hepatic portal vein perfusion was established.

The hepatic portal vein was then cannulated towards the liver with wide-bore tubing, and the hepatic portal venous vascular bed perfused at constant flow with a Watson-Marlow MHRE200 roller pump deriving its supply from the reservoir receiving blood from the superior mesenteric vein. The pump system was set to perfuse the hepatic portal vein at the same flow as that draining from the superior mesenteric vein via the cannulated splenic vein into the reservoir (see Results section). Interposed between the roller pump system and the hepatic portal venous cannula were a cannulating flowhead, 'T'-pieces for the injection and infusion of vasoactive substances into the hepatic portal vein, and a further 'T'-piece close to the point of cannulation of the hepatic portal vein for the measurement of the hepatic portal venous perfusion pressure.

Once perfusion of the hepatic portal venous vascular bed had been established, the laparotomy incision was closed and a thermometer inserted into the abdominal cavity; the intra-abdominal temperature was maintained at 37–38°C throughout all experiments, by the use of radiant lamps and table heaters. The volume contained in the external perfusion circuit was compensated for with a solution of 10% low molecular weight dextran in normal saline (Rheomacrodex, Pharmacia).

Recording of variables

Systemic arterial blood pressure (BP) was measured from a cannulated femoral artery with a Statham P23Gb strain gauge transducer; pulsatile pressure was recorded throughout all experiments.

Heart rate (HR) was measured with a Devices 4521 ratemeter triggered from the pulsatile systemic arterial pressure waveform.

Inferior vena cava pressure (IVCP) was measured from a catheter passed into the inferior vena cava via a femoral vein for a distance estimated to cause its tip to lie close to the entrance of the hepatic vein into the inferior vena cava; the position of the catheter tip was confirmed *post mortem*. The catheter was connected to a Consolidated Electrodynamics L212 strain gauge transducer, and the mean IVCP derived with a Devices 3502 averaging circuit with time constants of 0.5, 1 or 2 s selected appropriately.

Hepatic portal venous blood flow (HPVF) was monitored with a cannulating flowhead and electromagnetic flowmeter (Cardiovascular Instruments, Model 3765T), with the flowhead on the outflow side of the roller pump used for perfusing the hepatic portal venous vasculature. Hydrostatic flow zeroes were established throughout each experiment by diverting the blood through a bypass in parallel with the flowprobe; this avoided interruption of the blood flow whilst establishing zero positions. The flow measuring system was calibrated at the end of each experiment *in situ*, with whole blood. Mean blood flow was obtained by passing the phasic waveform through an averaging circuit with a time constant of 0.6 s; both mean and phasic signals were recorded continuously.

Hepatic portal venous pressure (HPVP) was measured from a 'T'-piece in the cannula just before the point of

cannulation of the hepatic portal vein, using a Statham P23V strain-gauge transducer. Mean hepatic portal venous pressure was obtained by passing the phasic signal through a Devices 3502 averaging circuit with a time constant of 0.5, 1.0 or 2.0 s selected appropriately.

Superior mesenteric venous outflow (SMVF) was monitored with an electromagnetic flowmeter (Cardiovascular Instruments C500) and a cannulating flow-probe in the cannula draining the splenic vein. Flow zeroes and calibrations were obtained as described above.

All pressure transducers were precalibrated with mercury or water manometers: zero reference positions were checked frequently throughout the course of each experiment.

After suitable amplification, all variables were recorded continuously on a Devices M19 rectilinear recorder.

Calculations

Liver weight. The livers were excised and weighed immediately *post mortem*; values expressed per 100 g refer to this terminal weight of liver.

Hepatic portal venous vascular resistance (HPVR). The hepatic portal venous inflow remained constant at all times in each experiment, as did the inferior vena caval pressure. Thus an increase and decrease in HPVP indicated a similar directional change in HPVR. Vascular resistance was calculated as (hepatic portal mean perfusion pressure–inferior vena cava pressure)/(hepatic portal mean blood flow) and expressed as mmHg ml^{-1} min, or mmHg ml^{-1} min 100 g. Changes in HPVR were calculated as the percentage change in vascular resistance from control values immediately before a drug injection to the peak of the response, i.e., (change in HPVR × 100)/(control HPVR).

Expression of results

Except where indicated to the contrary, results are expressed as means ± s.e. means. Degrees of statistical significance were assessed by Student's *t*-test for paired data samples.

Log_{10} dose-response curves were constructed by injecting increasing, graded, doses of vasoactive substances into the hepatic portal vein, the doses being increased either until the maximum response was attained, or until pronounced systemic effects resulted from the drugs passing through the liver and entering the systemic circulation. Unless stated to the contrary in the results, one dose of a drug was injected about 1 min after the complete recovery from the effects of the previous injection.

Vasoactive substances

The following drugs were used in this investigation: adrenaline bitartrate (Macarthays), noradrenaline acid tartrate (Levophed, Winthrop), angiotensin II amide (Hypertensin, Ciba), vasopressin (Pitressin for i.v. injection, Parke-Davis). Doses are expressed in terms of the weight of salt injected (for noradrenaline, the weight of base injected) and for vasopressin in international units (iu) of activity where 1 unit is equivalent to 0.5 mg (manufacturer's data).

Drugs were injected into the cannula between the roller pump and the hepatic portal vein (intraportally) in volumes between 0.5 and 1.0 ml, washed in with 0.9% w/v NaCl solution (saline) to a total injectate volume of 2.0 ml; these injections resulted in small injection artifacts which were clearly separable from the subsequent drug-induced effects.

Infusions were made into the portal vein cannula (intraportally) from a Watson-Marlow MHRE200 pump precalibrated to deliver 1.0 ml/min against the range of pressures encountered in these experiments. All infusions were of 5 min duration.

Results

Control values

In the present experiments, the livers weighed 307.1 ± 55.8 (mean ± s.d.) grams. In each experiment when the hepatic portal venous perfusion was established such that the portal blood flow was equal to the superior mesenteric venous outflow (see Methods section), the following values for the control variables (mean ± s.d.) were obtained: systemic arterial mean pressure (BP) 140.7 ± 13.7 mmHg, heart rate 157.1 ± 38.0 beats/min and hepatic portal venous blood flow 240.7 ± 62.7 ml/min or 78.5 ± 14.3 ml min^{-1} 100 g^{-1} with a portal mean perfusion pressure of 6.6 ± 3.2 mmHg. Under these conditions, the mean inferior vena cava pressure was 1.8 ± 0.8 mmHg. The mean value for the HPVR was 0.066 ± 0.035 mmHg ml^{-1} min 100 g, or hepatic portal vascular conductance of 20.1 ± 12.8 ml min^{-1} 100 g^{-1} $mmHg^{-1}$.

The values for the systemic arterial pressure and heart rate are similar to those reported previously in the anaesthetized dog whilst the mean portal vascular resistance is considerably less than the calculated hepatic arterial vascular resistance in either the sympathetically-denervated (Richardson & Withrington, 1976a) or sympathetically-innervated (Richardson & Withrington, 1976b,c,d) liver preparations reported previously from this laboratory.

Effects of intraportal injections of vasoactive substances on the hepatic portal vascular resistance

In each experiment, the intraportal injection of saline (0.5 or 1.0 ml) washed in, in the same way as for a

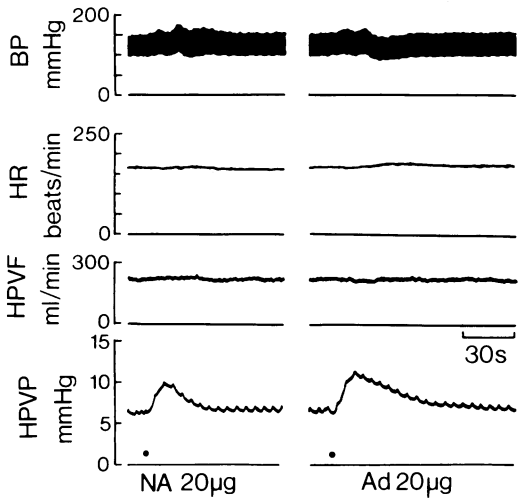

Figure 1 Effects of intraportal injections of noradrenaline (NA) 20 μg, and adrenaline (Ad) 20 μg, on the canine hepatic portal venous vascular bed perfused at constant inflow. BP = systemic arterial blood pressure, HR = heart rate, HPVF = mean hepatic portal venous blood flow, and HPVP = mean hepatic portal venous perfusion pressure. Dots indicate the points of intraportal injections.

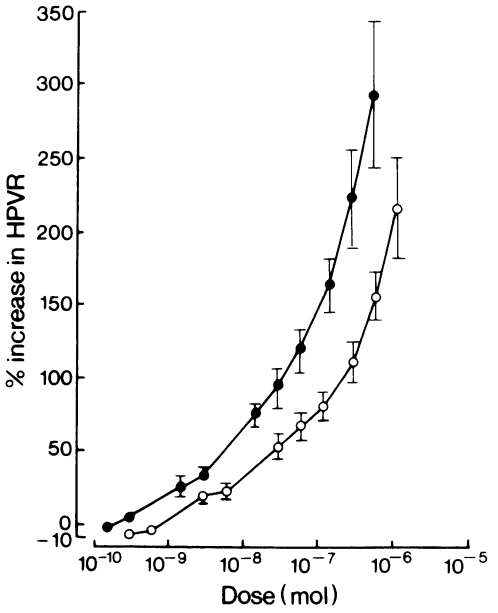

Figure 2 Log_{10} dose-response curves for the increase in hepatic portal vascular resistance (HPVR) to the intraportal injection of adrenaline (●) and noradrenaline (○). Abscissa scale: dose of drug in moles; ordinate scale: percentage increase in hepatic portal vascular resistance. Points represent the mean of 5 determinations; vertical bars show the s.e. means.

drug injection was without measurable effect on the HPVR.

Noradrenaline. In 6 preparations, the log_{10} dose-response relationship between the intraportal injection of increasing graded doses of noradrenaline, and the resulting change in the calculated HPVR was established on 7 occasions. Noradrenaline was injected in selected doses over the range 0.05 to 200 μg in each experiment; intraportal doses of noradrenaline in excess of 10 μg were accompanied by changes in systemic arterial pressure and heart rate. The peak changes in hepatic portal venous perfusion pressure which were used to calculate changes in HPVR (see Methods section) were not temporally related to these systemic effects (Figure 1), and usually preceded them by 10–15 seconds.

Doses in excess of 200 μg were not administered since there were marked systemic cardiovascular effects arising from the noradrenaline passing through the liver into the systemic circulation. The responses of the portal venous vascular bed to the largest doses of noradrenaline used in this study might not, therefore, have been the absolute maximum attainable in other types of preparation.

Of the 7 injections of noradrenaline at or below 0.1 μg, 4 evoked a reduction in hepatic portal venous pressure indicating a reduction in calculated HPVR. The other 3 injections did not cause any measurable change in the calculated portal vascular resistance.

All injections above 0.1 μg evoked increases in HPVP (Figure 1) representing increases in calculated HPVR. The rise in HPVR was graded and increased with increasing intraportal injections of noradrenaline (Figure 2).

There was no evidence in any experiment of tachyphylaxis to repeated intraportal injections of noradrenaline, which were usually made within 1 min of the hepatic portal perfusion pressure returning to the pre-injection baseline level.

Adrenaline. The log_{10} dose-response relationship between intraportal injections of adrenaline and the changes in HPVR were established over the same nominal weight range as for noradrenaline, 0.05 to 200 μg, in each of five preparations. In all of these experiments, the injections of adrenaline were paired with intraportal injections of equal weights of noradrenaline to compare the relative potencies of the two catecholamines.

On 2 out of 6 occasions in which adrenaline was injected in a dose of 0.1 μg or less, there was a

reduction in hepatic portal perfusion pressure representing a reduction in the calculated HPVR.

All intraportal injections in excess of 0.1 μg adrenaline evoked increases in the hepatic portal perfusion pressure and rises in the calculated HPVR. This increase in HPVR in response to adrenaline increased with the dose injected intraportally; doses of adrenaline in excess of 10 μg were accompanied by changes in systemic arterial pressure and rises in heart rate. As with noradrenaline, the peak increase in hepatic portal venous perfusion pressure preceded the peak systemic changes by 10–15 s (Figure 1). Doses in excess of 200 μg were not administered since substantial systemic effects resulted from the intraportal injection of this dose of adrenaline. There was no evidence in any experiment of hepatic portal vascular tachyphylaxis to repeated intraportal injections of adrenaline.

In all five experiments in which paired doses of noradrenaline and adrenaline were injected into the hepatic portal vascular bed, it was evident that at each dose, adrenaline was more potent than noradrenaline in producing increases in hepatic portal perfusion pressure, and consequently in the calculated HPVR. The difference between the response to noradrenaline and adrenaline was statistically significant when paired doses of 1, 5, 10, 20, 50, 100 and 200 μg were injected intraportally ($P < 0.01$, 0.02, 0.05, 0.01, 0.01, 0.05 and 0.05 respectively). These weights of noradrenaline are expressed in terms of the base, and those of adrenaline as the bitartrate salt; if, however, the doses are expressed on a molar basis, the difference in potency between these two catecholamines becomes even more apparent (Figure 2).

Vasopressin was injected intraportally on 24 occasions in 6 experiments in doses from 0.005 to 5.0 iu. On 18/24 occasions, there was a small, slightly delayed reduction in the hepatic portal perfusion pressure and therefore in the calculated hepatic portal vascular resistance. On the remaining 6/24 injections, not restricted to low doses of vasopressin, no change in hepatic portal perfusion pressure was observed subsequent to the intraportal injection of vasopressin. Nevertheless, the mean results from 6 experiments indicate that the reduction in calculated HPVR in response to intraportal vasopressin was graded and dose-dependent (Figure 3). On no occasion in any experiment was intraportal administration of any dose of vasopressin accompanied by an increase in calculated HPVR.

In most experiments, the higher doses of vasopressin administered intraportally evoked a reduction in calculated HPVR and subsequently, after passage through the cardiopulmonary circuit into the systemic arterial system, caused mesenteric vasoconstriction reflected by a reduction in the outflow from the superior mesenteric vein (see Methods section) with either no change or a concomitant rise in the systemic arterial blood pressure.

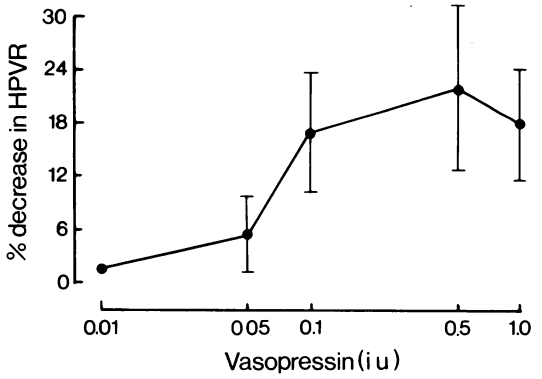

Figure 3 Dose-response curve for the reduction in hepatic portal vascular resistance (HPVR) to intraportal administrations of vasopressin. Abscissa scale: $\log_{10}$ dose of drug in international units (iu); ordinate scale: percentage decrease in hepatic portal vascular resistance. Points represent the means of 5 experiments, vertical bars show the s.e. means.

Angiotensin. The complete $\log_{10}$ dose-response relationship for angiotensin on the hepatic portal venous vascular bed was established in each of 6 experiments by graded, increasing, intraportal injections of between 0.05 and 20 μg. The doses were usually given within 1 min of the hepatic portal perfusion pressure returning to the control level, an interval between injections of approximately 5 minutes. In all experiments, all doses of angiotensin administered in this way caused an increase in the hepatic portal perfusion pressure and in the calculated HPVR. This increase in portal resistance was graded and dose-dependent (Figure 4). However, in all experiments, with the injection procedure described above, the magnitude of the increases in HPVR increased up to doses of 5.0 μg intraportally, but higher doses (10 and 20 μg) resulted in smaller increases in the calculated hepatic portal venous vascular resistance than were elicited by 5.0 μg, and a bell-shaped dose-response curve was obtained (Figure 4). The possibility that this was due to regional tachyphylaxis to angiotensin was therefore examined in detail since the rises in systemic arterial pressure associated with the intraportal injection of the higher doses of angiotensin, in contrast to the changes in calculated hepatic portal vascular resistance, increased with the increasing intraportal doses of angiotensin.

Angiotensin tachyphylaxis: repeated injections of angiotensin. Four successive intraportal injections

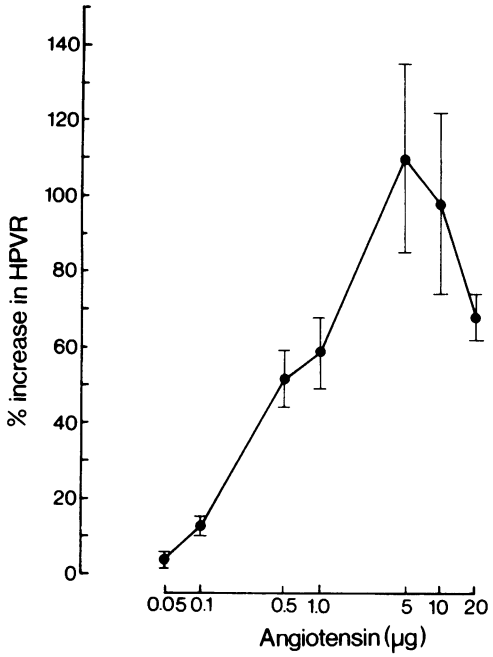

Figure 4 Dose-response curve for the increase in hepatic portal vascular resistance (HPVR) to intraportal administrations of angiotensin. Abscissa scale: $\log_{10}$ dose of drug in μg; ordinate scale: percentage increase in hepatic portal vascular resistance. Points represent the means of 6 observations, vertical bars show the s.e. means.

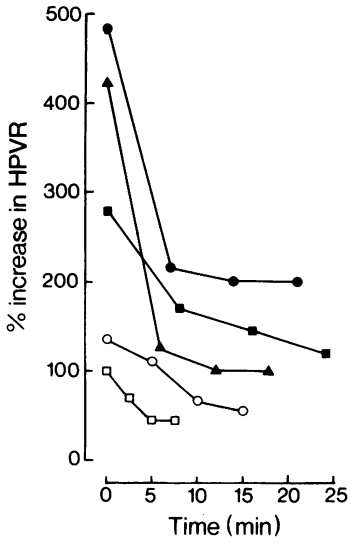

Figure 5 Diminution in the response of the hepatic portal vascular bed to repeated intraportal injections of angiotensin (0.5 μg □; 1.0 μg ○; 5.0 μg ■; 10.0 μg ▲; 20.0 μg ●). Abscissa scale: time in minutes, showing the intervals between successive injections of equal doses. Ordinate scale: percentage increase in hepatic portal vascular resistance. The injections, four at each dose, were separated by approximately 30 minutes.

of each of five selected doses of angiotensin (0.5, 1, 5, 10 and 20 μg) were made in blocks of equal doses. Within each block, the second, third and fourth injections were made as soon as the hepatic portal perfusion pressure had returned to control levels after the preceding injection. The blocks of injections however were separated by much longer intervals, usually of at least 30 minutes.

This procedure revealed pronounced tachyphylaxis to the repeated intraportal injections of angiotensin. The time course and extent of the development of tachyphylaxis is shown in Figure 5: it is apparent that the tachyphylaxis is most marked between the first and second injections of any of the five selected doses, whilst the increases in HPVR to the fourth injection of each series were very similar to those caused by the third injection.

With each block of injections, test doses of noradrenaline were injected intraportally, to assess whether or not the development of tachyphylaxis was specific to angiotensin: injections of noradrenaline, in contrast to those of angiotensin, showed no sign of the development of tachyphylaxis.

That the tachyphylaxis of the hepatic portal vascular bed to angiotensin was a regional variation is illustrated by the fact that the larger intraportal injections of angiotensin, though provoking hepatic portal tachyphylaxis, on reaching the systemic circulation caused mesenteric vasoconstriction judged by the reductions in outflow from the superior mesenteric vein with concomitant increases in systemic arterial pressure. The reductions in mesenteric outflow due to repeated intraportal injections of noradrenaline did not diminish by more than 10% between the first and fourth injections of angiotensin in any series.

Since these experiments revealed clear evidence of a marked portal vascular tachyphylaxis to angiotensin, its influence on the bell-shaped dose-response curve (Figure 4) was ascertained. In one experiment, the interval between successive injections of angiotensin was increased substantially to 5–6 times the duration of the portal vascular response to each injection (i.e. to about 30 min for the larger doses). Although this procedure occupied the entire experiment, the influence of tachyphylaxis was much less apparent, and intraportal injections of 0.1, 0.5, 1, 5, 10 and 20 μg of angiotensin provoked rises in the calculated HPVR of 25, 100, 133, 280, 425 and 485% respectively. Under

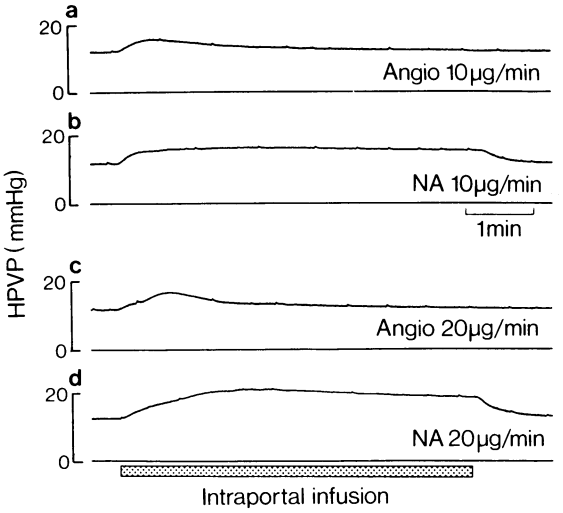

Figure 6 The effects of intraportal infusions of (a) angiotensin (Angio) 10 μg/min, (b) noradrenaline (NA) 10 μg/min, (c) angiotensin 20 μg/min, and (d) noradrenaline 20 μg/min on the hepatic portal perfusion pressure (HPVP) at constant hepatic portal blood flow. The infusions were maintained for 5 min as shown by the horizontal bar.

these conditions, the dose-response curve for angiotensin on the hepatic portal vascular bed assumed the shape typical of substances such as noradrenaline and adrenaline for which there was, in these experiments, no evidence of tachyphylaxis.

Angiotensin tachyphylaxis: intraportal infusions of angiotensin. The specificity of the portal vascular development of tachyphylaxis was further demonstrated by intraportal infusions of both angiotensin and noradrenaline; typical responses are illustrated in Figure 6. The intraportal infusion of 10.0 μg/min of noradrenaline elicited an increase in the hepatic portal perfusion pressure at constant inflow and IVCP, resulting in a peak increase in the calculated HPVR of 33% which was maintained throughout the period of the infusion. Only at higher infusion rates (20 μg/min) was there any sign of 'escape' from the effects of noradrenaline: one such infusion caused a rise in calculated HPVR of 70% which declined to 75% of this value by the end of a 5 min infusion (Figure 6b & d).

In contrast, intraportal infusions of angiotensin (10 μg/min, 20 μg/min) always showed 'escape' from the peak increases in portal vascular resistance: as shown in Figure 6, when 10.0 μg/min was infused, the peak increase of 27% in the calculated HPVR had receded so that the portal resistance returned to control values within 2 min, despite the continued angiotensin infusion (Figure 6a & c). There was no change in the portal vascular resistance when the angiotensin infusion was discontinued at the end of the 5 minutes. Further evidence of the regional variation of the development of tachyphylaxis to angiotensin is the fact that the rises in systemic arterial pressure of 15 and 20 mmHg which accompanied the intraportal infusions of 10 and 20 μg/min respectively of angiotensin were maintained throughout the period of the infusions.

Discussion

The technique of portal vein perfusion used in the present experiments is similar in principle to that employed by Green, Hall, Sexten & Deal (1959), and Shoemaker (1964); the technique ensures that the portal venous vasculature is perfused with blood derived from its normal supply, the superior mesenteric vein, and permits the quantitative examination of the physiological and pharmacological responses of the hepatic portal venous vasculature uncomplicated by the concomitant responses of the series-coupled vascular circuits of the intestine, pancreas and spleen. Once the portal perfusion was established the portal venous pressures and flows were of the same order as those reported previously. At the end of the experiments the livers were of a good red colour and did not show any signs of 'blueness' or swelling. The perfusion continued for 4 to 5 h without change in perfusion pressure and throughout this time the portal vasculature responded quantitatively to intraportal injection of test doses of noradrenaline. After about 5 h perfusion the portal pressure usually increased indicating an increased basal portal vascular resistance; the experiments were then terminated.

In the present experiments, the intraportal injections of both noradrenaline and adrenaline caused, over a considerable part of the dose-response curve, systemic effects of changes in arterial pressure and heart rate resulting from entry of the catecholamines into the systemic arterial supply. That the effects we describe here are the primary actions of catecholamines on the portal vasculature and not secondary effects arising from alterations in hepatic arterial flow after passage through the cardiopulmonary circuit is indicated by the time course of the peak responses: the peak changes in portal perfusion pressure resulting from intraportal noradrenaline or adrenaline preceded the peak systemic effects by 10 to 15 s, and could not, therefore, arise as secondary effects on the hepatic portal vasculature resulting from systemic effects of the catecholamines after passage through the liver.

Previous reports of the effects of single injections of these catecholamines (Green *et al.*, 1959; Shoemaker, 1964) are thereby confirmed and extended to the establishment of the dose-response relationship. Throughout the dose range investigated, adrenaline

was more potent than noradrenaline on both a weight and molar basis, a conclusion reached on isolated preparations of the hepatic portal vein (Hughes & Vane, 1967). Preliminary experiments (Richardson & Withrington, unpublished observations) indicate that paired injections of noradrenaline and adrenaline into the hepatic artery of the dog also cause vasoconstriction, but that in the hepatic arterial vasculature, the relative potency is different from that in the hepatic portal vasculature, noradrenaline being more potent than adrenaline. The effects and the potency order of noradrenaline and adrenaline in the hepatic arterial vascular bed are therefore similar to those in the intestinal (Texter, Chou, Merrill, Laureta & Frolich, 1964; Swan & Reynolds, 1971) and splenic (Davies, Gamble & Withrington, 1973) vascular beds. Systemic release of the catecholamines would therefore cause a profound reduction in total liver blood flow by causing hepatic arterial vasoconstriction (Richardson & Withrington, 1976a) in addition to reducing the inflow to the portal vein by intestinal and splenic vasoconstriction, and causing hepatic portal vasoconstriction.

The present experiments confirm that, in contrast to its action on the hepatic arterial bed, the effects of intraportal injections of vasopressin on the hepatic portal vasculature are weak and somewhat variable, but at high doses dose-dependent reductions in hepatic portal vascular resistance are elicited (Shoemaker, 1964). Isolated preparations of the hepatic portal vein are relaxed by high concentrations (10–100 mu/ml) of vasopressin (Hughes & Vane, 1967), suggesting that the effects seen in the present experiments are due to relaxation of the portal venous vascular smooth muscle.

It is improbable that this effect is of physiological importance, since vasopressin concentrations would be unlikely to approach those shown to be necessary to elicit this effect. Further, it has been known for many years (Clark, 1928) that vasopressin or pituitary extracts cause a reduction in hepatic portal venous pressure which is due to vasoconstriction in the intestinal (Cohen, Sitar, McNeill & Greenway, 1970; McNeill, Stark & Greenway, 1970; Texter *et al.*, 1974) and splenic (Cohen *et al.*, 1970; Davies & Withrington, 1975) vascular beds which occurs at much lower concentrations of vasopressin than are needed to cause reductions in HPVR. The net result of systemic release of vasopressin in the dog is likely to be a reduction in total liver blood flow occasioned by hepatic arterial vasoconstriction (Richardson & Withrington, 1976a) coupled with intestinal and splenic vasoconstriction reducing the hepatic portal inflow and pressure.

Angiotensin injected into the hepatic artery causes a dose-dependent arterial vasoconstriction, responses which remain constant throughout an experiment and are uninfluenced by the interval between successive administrations (Richardson & Withrington, 1976a). Although intraportal injections of angiotensin provoke portal vasoconstriction, in contrast there is a pronounced tachyphylaxis to subsequent intraportal administration. In the present experiments an interval of about 30 min was necessary for the restoration of the portal vascular response to angiotensin subsequent to a single large (10 or 20 μg) intraportal administration. The tachyphylaxis was most apparent over the higher dose range; an observation similar to that of Bock & Gross (1961). The effect of portal tachyphylaxis to angiotensin was even more apparent during intraportal infusions when the portal vascular response declined rapidly after an initial vasoconstriction so that the control portal vascular resistance was restored despite the continued intraportal infusion of the drug. No tachyphylaxis was observed to either intraportal injections or infusions of noradrenaline. Tachyphylaxis to angiotensin has been well established in other vascular territories (Page & Helmer, 1940) and confirmed for angiotensin II amide both *in vitro* (Khairallah, Page, Bumpus & Türker, 1966), and *in vivo* for the pressor response in dogs (Bock & Gross, 1961).

Variations in the development of tachyphylaxis to angiotensin exist between species (Khairallah, *et al.*, 1966) and between different vascular beds in the same species (Jonsson, Svanik & Vikgren, 1967). Jonsson *et al.* (1967) showed that, in the cat, the development of tachyphylaxis to angiotensin was very much more pronounced in the intestinal vasculature than in the hindlimb vessels. In the present experiments, it was consistently observed that intraportal injections of angiotensin which elicited gradually diminishing increases in HPVR were, on reaching the systemic circulation, eliciting almost constant reductions in mesenteric venous outflow and rises in systemic arterial pressure. This implies that the hepatic portal vasculature exhibits this phenomenon to a more marked degree than the intestinal vasculature in the dog.

One consequence of the tachyphylaxis to angiotensin is to ensure an uninterrupted portal blood flow to the liver, which is the main degradative site for angiotensin (Vane, 1969). Whether the portal resistance vessels fail to sustain responses to other vasoactive substances which are destroyed by the liver remains to be established.

The present experiments demonstrate that vasoactive substances either injected systemically or released by physiological mechanisms into the systemic circulation might influence portal vein haemodynamics by a primary action on the portal resistance structures in addition to indirectly affecting the pressure/flow profile of hepatic portal vasculature by direct actions on the series-coupled vascular beds of the intestine, spleen and pancreas. The present experiments reveal, moreover, that both the qualitative

and quantitative aspects of the actions of adrenaline, noradrenaline, vasopressin and angiotensin on the portal resistance structure are different from those on the hepatic arterial resistance vessels.

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References

ANDREWS, W.H.H., HECKER, R., MAEGRAITH, B.G. & RITCHIE, H.D. (1955). The action of adrenaline, l-noradrenaline, acetylcholine, and other substances on the blood vessels of the perfused canine liver. *J. Physiol., Lond.*, **128**, 413–434.

BOCK, K.D. & GROSS, F. (1961). Renin and angiotensin tachyphylaxis. *Circulation Res.*, **9**, 1044–1055.

CLARK, G.A. (1928). A comparison of the effects of adrenaline and pituitrin on the portal circulation. *J. Physiol., Lond.*, **66**, 274–279.

COHEN, M.M., SITAR, D.S., McNEILL, J.R. & GREENWAY, C.V. (1970). Vasopressin and angiotensin on resistance vessels of spleen, intestine and liver. *Am. J. Physiol.*, **218**, 1704–1706.

DAVIES, B.N., GAMBLE, J. & WITHRINGTON, P.G. (1973). Frequency-dependent differences in the responses of the capsular and vascular smooth muscle of the spleen of the dog to sympathetic nerve stimulation. *J. Physiol., Lond.*, **228**, 13–25.

DAVIES, B.N. & WITHRINGTON, P.G. (1975). The responses of the isolated, blood perfused spleen of the dog to angiotensin, oxytocin and vasopressin. *Br. J. Pharmac.*, **54**, 205–212.

GREEN, H.D., HALL, L.S., SEXTEN, J. & DEAL, C.P. (1959). Autonomic vasomotor responses in the canine hepatic arterial and venous beds. *Am. J. Physiol.*, **196**, 196–202.

HUGHES, J. & VANE, J.R. (1967). An analysis of the responses of the isolated portal vein of the rabbit to electrical stimulation and to drugs. *Br. J. Pharmac. Chemother.*, **30**, 46–66.

JONSSON, O., SVANVIK, J. & VIKGREN, P. (1967). Regional differences in vascular tachyphylaxis to angiotensin in the cat. *Angiologica (Basle)*, **4**, 299–309.

KHAIRALLAH, P.A., PAGE, I.H., BUMPUS, F.M. & TÜRKER, R.K. (1966). Angiotensin tachyphylaxis and its reversal. *Circulation Res.*, **19**, 247–254.

McNEILL, J.R., STARK, R.D. & GREENWAY, C.V. (1970). Intestinal vasoconstriction after hemorrhage: roles of vasopressin and angiotensin. *Am. J. Physiol.*, **219**, 1342–1347.

PAGE, I.H. & HELMER, O.M. (1940). Angiotonin-activator, renin- and angiotonin-inhibitor and the mechanism of angiotonin tachyphylaxis in normal, hypertensive and nephrectomized animals. *J. exp. Med.*, **71**, 495–519.

RICHARDSON, P.D.I. & WITHRINGTON, P.G. (1976a). The inhibition by glucagon of the vasoconstrictor actions of noradrenaline, angiotensin and vasopressin on the hepatic arterial vascular bed of the dog. *Br. J. Pharmac.*, **57**, 93–102.

RICHARDSON, P.D.I. & WITHRINGTON, P.G. (1976b). The vasodilator actions of isoprenaline, histamine, prostaglandin E_2, glucagon and secretin on the hepatic arterial vascular bed of the dog. *Br. J. Pharmac.*, **57**, 581–588.

RICHARDSON, P.D.I. & WITHRINGTON, P.G. (1976c). Beta adrenoceptors in the hepatic arterial vascular bed of the dog. *Br. J. Pharmac.*, **57**, 451P.

RICHARDSON, P.D.I. & WITHRINGTON, P.G. (1976d). The influence of glucagon upon the responses of the hepatic arterial vasculature to vasodilator agents. *Br. J. Pharmac.*, **57**, 473P.

SHOEMAKER, C.P. (1964). A study of hepatic haemodynamics in the dog. *Circulation Res.*, **15**, 216–233.

SWAN, K.G. & REYNOLDS, D.G. (1971). Effects of intra-arterial catecholamine infusions on blood flow in the canine gut. *Gastroenterology*, **61**, 863–871.

TEXTER, E.C., CHOU, C.-C., MERRILL, S.L., LAURETA, H.C. & FROLICH, E.D. (1964). Direct effects of vasoactive agents on segmental resistance of the mesenteric and portal circulation. *J. Lab. clin. Med.*, **64**, 624–633.

VANE, J.R. (1969). The release and fate of vaso-active hormones in the circulation. *Br. J. Pharmac. Chemother.*, **35**, 209–242.

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