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The Transhepatic Response to Noradrenaline in the Rabbit Liver: the Influence of Arterioportal Pressure Gradient

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Abstract

The dose-related responses of the hepatic arterial and portal venous vascular beds to bolus administration of noradrenaline (10^{-10}–10^{-4} mol), injected into the hepatic artery and portal vein, were studied in the isolated dual-perfused rabbit liver at both basal and raised tone. The transhepatic ratio, defined as the ratio between the intra-arterial molar ED50 dose and the intraportal dose required to give the same arterial response, was calculated for arterial and venous responses to noradrenaline.

At basal tone, the transhepatic ratio for hepatic arterial vasoconstrictive responses was 500. Portal venous vasoconstrictive responses were similar in potency independent of injection site but differed significantly in analysis of dose-response slope and maximal response. At raised tone, the arterio-portal pressure gradient increased by 68·5 mmHg and there was a 10-fold increase in the transhepatic ratio for hepatic arterial responses, while the portal venous responses remained unchanged.

These results demonstrate that arterio-portal pressure gradient has a powerful effect on transhepatic action of noradrenaline, and suggest a pre-sinusoidal site for the generation of both hepatic arterial and portal venous vascular resistance.

The interaction between the hepatic arterial and portal venous blood supply of the liver has been divided into three separate components—the autoregulation of blood flow (an increase in vascular resistance in response to an increase in flow), the hydrodynamic or buffer response (a fall in hepatic arterial resistance following a fall in portal venous flow), and the ability of an agent to affect both vascular beds when only injected into one, known as the transhepatic (Withrington & Richardson 1990) or transvascular (Lautt et al 1984) effect.

The transhepatic action of drugs in the vascular beds of the liver can be categorized into two groups—a direct action, the response occurring in the injected vascular bed, and an indirect action, where the response occurs in the opposite vascular bed to the site of injection. The direct and indirect responses may be of different potency and amplitude, and one agent may elicit different responses in each vascular bed. For example acetylcholine is an arterial vasodilator but causes an increase in portal venous resistance following either arterial or portal venous injection (Alexander et al 1994). The route of transmission of an agent, or its effect, from one vascular bed to the other is not known, nor have any factors which might affect this transhepatic route been identified. In certain clinical situations, such as portal hypertension or hypovolaemic shock, the pressure in the hepatic inflows may change. This study was conducted to identify whether alteration of this arterio-portal pressure gradient affects the transhepatic action of drugs.

In general, the potency of most vasoactive substances measured in the portal venous bed seems to be largely independent of injection site while in the hepatic arterial bed, direct injection is much more potent than indirect (intra-portal) injection (Lautt et al 1984). This fact has been used to suggest that portal venous resistance is generated after mixing of the two hepatic inflows, i.e. at a sinusoidal or post-sinusoidal site (Richardson & Withrington 1978a; Lautt et al 1984). There is, however, recent evidence to suggest that much of the venous resistance arises pre-sinusoidally (Maass-Moreno & Rothe 1992). It is unclear whether portal venous injection of a substance reaches the hepatic arterial resistance sites by simple diffusion or by an intravascular route. Such a route could be the peribiliary plexus which seems to be present in most animals (Grisham & Nopanitaya 1981). A study of the effect of the arterio-portal pressure gradient on transhepatic responses may also shed light on the route of transfer of agents from the portal venous to the hepatic arterial vascular bed. Direct pressure dependence would imply an intravascular transfer of the injected agent, while a lack of pressure dependence would suggest drug diffusion as the route of transfer.

The in-vivo study of the transhepatic effect and the mechanism by which it occurs has been limited by two factors—firstly the buffer response (Lautt 1985), which may alter vascular resistance, and secondly the inability to give large doses of injectable agents in an in-vivo or in-situ perfused liver due to the resultant instability of systemic haemodynamics (Withrington 1992). The in-vitro dual perfused rabbit liver (Alexander et al 1992) was developed to avoid such problems. We have shown that this preparation does not have a demonstrable hydrodynamic response (Browse & Alexander unpublished observation), and that this interaction has been reported to be independent of innervation (Mathie et al 1980). In-vitro single pass perfusion also permits any dose of vasoactive agent to be injected, although the liver can take a considerable time to recover

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from very large doses. This model is, therefore, ideally suited to studies into the transhepatic effects of drugs.

This investigation studies the effects of noradrenaline injected via both the arterial and portal route in the isolated dual-perfused rabbit liver. The actions of this vasoconstrictor are compared at a basal and at a raised arterio-portal pressure gradient.

Materials and Methods

Operative procedures

Eight male New Zealand White rabbits, weighing 2·64–3·28 kg (mean 2.92 ± 0.07 kg), were initially sedated with subcutaneous fentanyl-fluanisone (Hypnorm 0·3 mL kg^{-1}), and 15 min later anaesthetized with intravenous midazolam (Hypnovel 1·5 mg kg^{-1}) through a cannulated marginal ear vein. A further 0·3 mL kg^{-1} Hypnorm was injected intramuscularly for continued analgesia during the 40-min operative period. The operative technique has been described in detail elsewhere (Alexander et al 1992) but will be outlined in brief here.

The abdomen was opened through a mid-line incision, and the common bile duct cannulated. After intravenous administration of heparin (300 units kg^{-1}) the common hepatic artery, and the gastroduodenal artery when present, were cannulated (Portex 3FG) and the gastroduodenal vein ligated. Ten millilitres of heparinized saline (20 units mL^{-1}) was infused into the catheters to prevent blood coagulation in the intrahepatic arterial vasculature. The portal vein was then cannulated and 40 mL heparinized saline were flushed through the portal system. The liver was then rapidly excised from the animal, weighed and placed in an organ bath.

Liver perfusion

Livers were perfused at constant flow rates via the hepatic arterial and portal venous cannulae, at 25 and 75 mL min^{-1}/100 g liver, respectively. The perfusate used was Krebs–Bülbring buffer solution of the following composition (mM): NaCl 133, KCl 4·7, NaH_2PO_4 1·35, $NaHCO_3$ 20·0, $MgSO_4$ 0·61, glucose 7·8, and $CaCl_2$ 2·52, at 37°C, from a common oxygenated reservoir (95% O_2–5% CO_2). Homogeneous liver perfusion was indicated by all sections of the liver changing to a uniform colour. Perfusion pressures were measured with Spectramed (Statham) P23XL physiological pressure transducers from side arms of the perfusion circuit and from the gastroduodenal artery cannula. Recordings were made on a Grass 79F polygraph (Grass Instrument Co., Quincy, MA, USA). Perfusion under these conditions maintains liver viability for 5 h (Browse et al 1994).

Drug administration

Noradrenaline bitartrate (Sigma Chemical Co., Poole, Dorset, UK) was dissolved in 0·1 mM ascorbic acid to give doses over the range of 10^{-10}–10^{-4} mol/100 g liver as 0·1-mL bolus injections into either the hepatic artery or portal vein. Subsequent injections were given when the pressure had returned to normal.

Experimental design

Dose-response curves were constructed to alternating hepatic arterial and portal venous bolus administration of noradrenaline at both basal and raised tone. Experiments were randomly assigned to one of two groups. The liver weight and basal perfusion indices did not differ significantly between the two groups.

Raised pressure (four livers). The tone in the vascular bed was increased by the addition of noradrenaline to the perfusate, to a concentration of 5–7·5 × 10^{-7} M. A further dose-response curve to noradrenaline was then constructed.

Control perfusions (four livers). The flow and vascular tone in this group were not altered. Further dose-response curves to noradrenaline were, therefore, constructed at the same basal pressure to exclude changes in responses occurring as a result of duration of perfusion.

Statistics and presentation of data

Responses were recorded as changes in perfusion pressure (mmHg) in each vessel. All results are presented as mean ± standard error. Student's paired or unpaired *t*-test was used, as appropriate, to test for differences between responses, $P < 0.05$ being taken as significant.

Comparison between the direct and transhepatic responses to noradrenaline was made by the method described by Withrington (1992). A transhepatic ratio was calculated by dividing the arterial molar ED50 by the molar portal dose required to give a response equal to the response seen with the arterial molar ED50 (see Fig. 1). In practice this was performed by subtracting the logarithms of these doses to give a log (transhepatic ratio).

Linear regression analysis was also performed on the central (straight) portion of dose-response curves from each individual perfusion (20–80% of maximal responses) when plotted as response vs log (dose). The individual slopes and intercepts from each curve were then calculated.

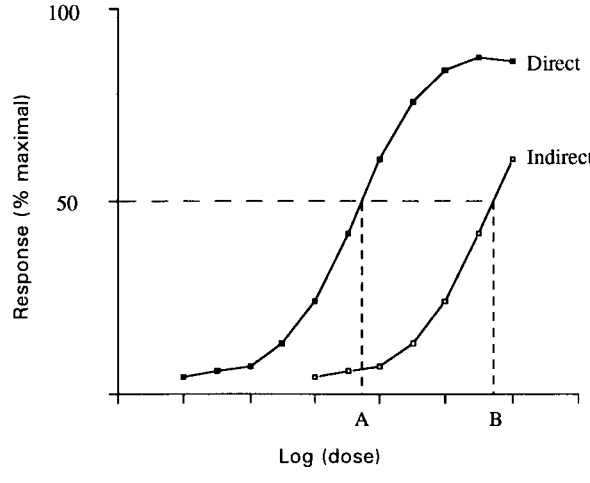

FIG. 1. Demonstration of the transhepatic ratio used to compare the relative efficacy for direct and transhepatic routes of injection. The ratio is calculated by dividing the molar ED50 for direct injection (A) by the molar dose required to give the same response following indirect injection (B).

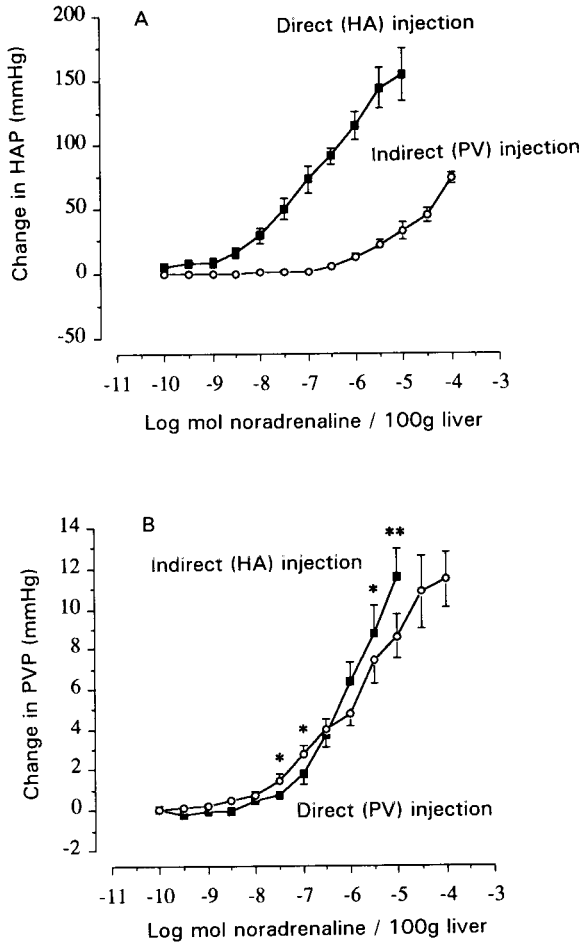

FIG. 2. The hepatic arterial (A) and portal venous (B) response curves to noradrenaline injected into both the hepatic artery and portal vein (HAP = hepatic arterial pressure, PVP = portal venous pressure). The ED50 of the direct hepatic arterial curve differs significantly from the indirect dose required to give an equivalent response ($P < 0.001$). It was not clear whether the same maximum responses would have been reached if sufficient noradrenaline had been given into the portal vein. Significant differences between direct and indirect responses exist for doses above 10^{-9} mol/100 g liver. The portal venous response curves to noradrenaline were similarly independent of injection site, although regression analysis demonstrated a difference between the slopes and y intercepts of the curves ($P < 0.001$). $*P < 0.05$, $**P < 0.01$ for direct vs indirect responses.

Results

Basal tone

The livers of eight rabbits (rabbit wt: 2.92 ± 0.07 kg; liver wt: 106.3 ± 0.3 g) were perfused at initial hepatic arterial and portal venous perfusion pressures of 36.6 ± 0.2 and 0.88 ± 0.41 mmHg, respectively.

The predominant hepatic arterial and portal venous response to noradrenaline was vasoconstriction. At the lowest doses used (10^{-10}–10^{-9} mol) a small degree of vasodilatation was often seen, more obvious in transhepatic responses than in direct responses. The dose-related hepatic arterial responses to noradrenaline are shown in Fig. 2. The mean log (ED50) for hepatic arterial responses to hepatic arterial injection was 6.62 ± 0.19 and for portal vein injection the log (molar dose) required to give an equivalent response to the arterial molar ED50 was 3.91 ± 0.24 ($P < 0.001$). This resulted in a log (transhepatic ratio) of 2.70 ± 0.22, showing that the hepatic arterial vascular bed was 500 times more sensitive to direct than to transhepatic stimulation. The maximal hepatic arterial response to hepatic arterial injection (direct) was an increase in perfusion pressure of 161.8 ± 0.3 mmHg. The maximal hepatic arterial response to portal vein injection was not attained but results from one experiment, where the indirect response to noradrenaline reached 80% of the maximal direct response, suggested that the maximal responses would be similar. Linear regression analysis of the log (dose) vs response lines, however, suggested that a similar maximal response would not be reached (slope 41.29 ± 0.08 vs 39.33 ± 5.24, y intercept 355.73 ± 5.24 vs 235.20 ± 0.26 ($P = 0.02$), with correlation coefficients (r^2) = 0.990 and 0.890 for direct and indirect responses, respectively).

The portal venous responses to noradrenaline were similar in nature, independent of the injection site (Fig. 2). The −log (molar ED50) for direct responses and the molar dose required to give an equivalent response for transhepatic responses were 6.06 ± 0.22 and 6.15 ± 0.12, respectively ($P > 0.05$). The maximal response for portal vein (direct) injection was 10.4 ± 0.2 mmHg, but this could not be attained for hepatic arterial (indirect) injection due to the duration of hepatic arterial response following doses of this magnitude (10^{-4}). Regression analysis showed that both the slope and y intercept for direct and indirect injection were significantly different (slope 2.64 ± 0.07 vs 4.60 ± 0.32, $P < 0.001$, y intercept 21.13 ± 0.44 vs 33.91 ± 0.03, $P < 0.001$, with r^2 for direct and indirect response lines 0.996 and 0.990, respectively) suggesting that the curves were different in slope and maximal response.

The shapes of hepatic arterial and portal venous responses were also different following direct and indirect injection. The hepatic arterial responses were immediate after hepatic arterial injection and often demonstrated a two-phase response (Fig. 3), but this was less defined following portal vein injection. The definition of the first-phase response was variable and often difficult to measure accurately, particularly at higher doses, and so all measurements shown are the maximum deflection of the pressure measurement seen in response to injections. The portal venous responses were of much shorter duration following direct than indirect injection (Fig. 3). The response peak was reached almost immediately at the lower direct doses while this was delayed with indirect injection. No obvious latent period between injection and response could be identified in either vascular bed following injection of noradrenaline.

Raised tone

The addition of noradrenaline ($5–7.5 \times 10^{-7}$ M) raised hepatic arterial pressure and venous portal pressure to 108 ± 8 and 2.9 ± 0 mmHg, respectively, with the arterio-portal pressure gradient increased by 68.5 ± 9.0 mmHg (or by a factor of 2.82 ± 0.15). This resulted in a small leftward shift of the dose-response curve for hepatic arterial responses to direct injection of noradrenaline (Fig. 4).

The amplitude of responses to noradrenaline was decreased at raised pressure compared with those at basal

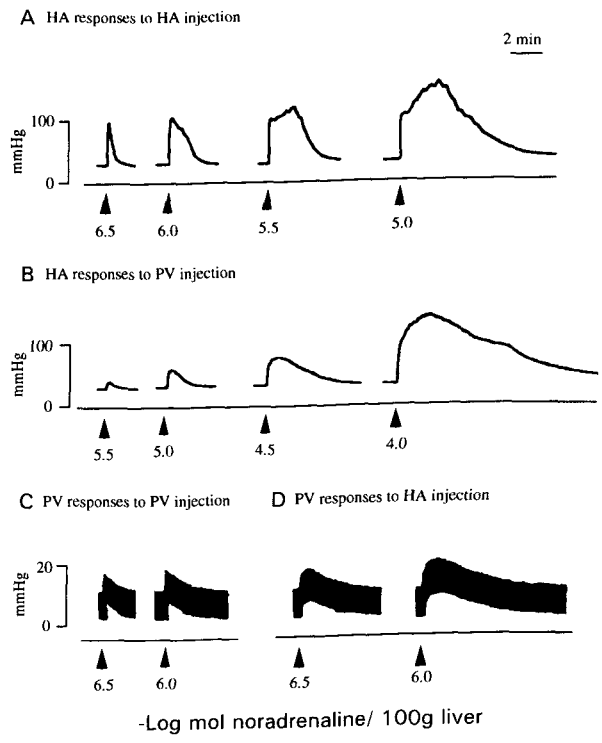

FIG. 3. The shape of pressure responses to noradrenaline. Hepatic arterial responses following direct injection (A), hepatic arterial (HA) responses following indirect injection (B), portal venous (PV) responses following direct injection (C) and portal venous responses following indirect injection (D). Direct hepatic arterial responses (A) were more biphasic than transhepatic hepatic arterial responses (B). Portal venous responses were much shorter and reached a maximum earlier following direct (C) compared with transhepatic injection (D).

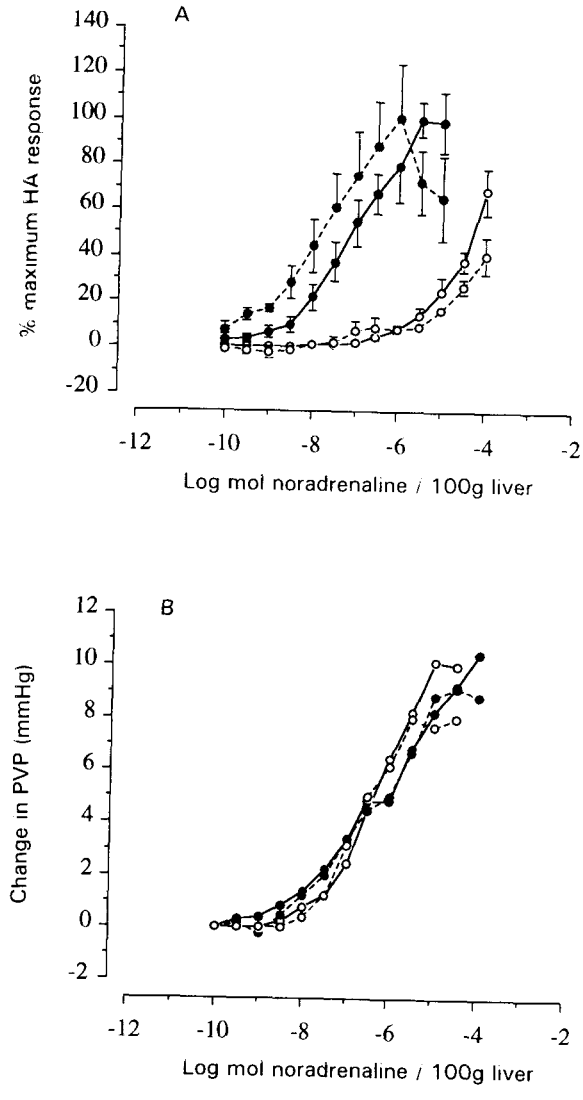

FIG. 4. The effect of increasing arterioportal pressure gradient on (A) hepatic arterial (HA) responses (as % maximum direct hepatic arterial response) and (B) portal venous pressure (PVP) responses (mmHg) to noradrenaline following direct and indirect injection. Increasing the pressure gradient further separates the direct and indirect hepatic arterial responses, but does not affect portal venous responses. Standard error bars are omitted from the portal venous pressure-response curves for clarity. ● Direct (HA) injection; ○ indirect (PV) injection; —— basal pressure; – – – raised pressure.

tone, especially affecting the arterial bed where the maximum response decreased from 178·0 ± 4·4 to 112·0 ± 9·6 mmHg. This fall of 66 mmHg correlated with the increase in perfusion pressure of 68·5 mmHg following noradrenaline constriction. The maximum total response to noradrenaline was, therefore, maintained during the duration of the experiments.

The effect of an increase in arterial to venous pressure gradient on the log-transhepatic ratio, for the hepatic arterial and portal venous responses, compared with control perfusions is shown in Fig. 5. The log (transhepatic ratio) for arterial responses increased from 2·80 ± 0·21 to 3·81 ± 0·35 ($P = 0·02$) with an increase in pressure gradient compared with a non-significant change from 2·64 ± 0·40 to 2·81 ± 0·36 in controls. In this small series there was no direct correlation between the degree of pressure change and the transhepatic ratio ($r^2 = 0·29$). There was no significant change in the transhepatic ratio for the portal venous vasculature.

Control perfusions. The dose-related response curves to noradrenaline did not change with duration of perfusion. The −log (ED50) for the direct hepatic arterial response curves constructed at basal pressure were 6·22 ± 0·17 and 6·46 ● 0·26 and the − log (molar doses) required to give an equivalent response following transhepatic injection were 3·58 ± 0·45 and 3·65 ± 0·27 (Table 1). Maximum arterial responses for direct injection were 154·8 ± 0·1 and 163·0 ± 0·5 mmHg and for transhepatic injection were 73·3 ± 5·9 and 68·3 ± 3·0 mmHg. There was no significant change in the log (transhepatic ratio) (2·64 ± 0·40 vs 2·81 ± 0·36). In one experiment the pressure in the hepatic arterial vascular bed increased during perfusion (hepatic arterial pressure rose from 35 to 50 mmHg) and in this experiment the log (transhepatic ratio) did increase (from 2·69 to 3·51), in keeping with the results from the raised pressure group.

The portal venous responses to noradrenaline remained constant during perfusion. There was no significant change in ED50 maximal response, or the transhepatic ratio between the two response curves.

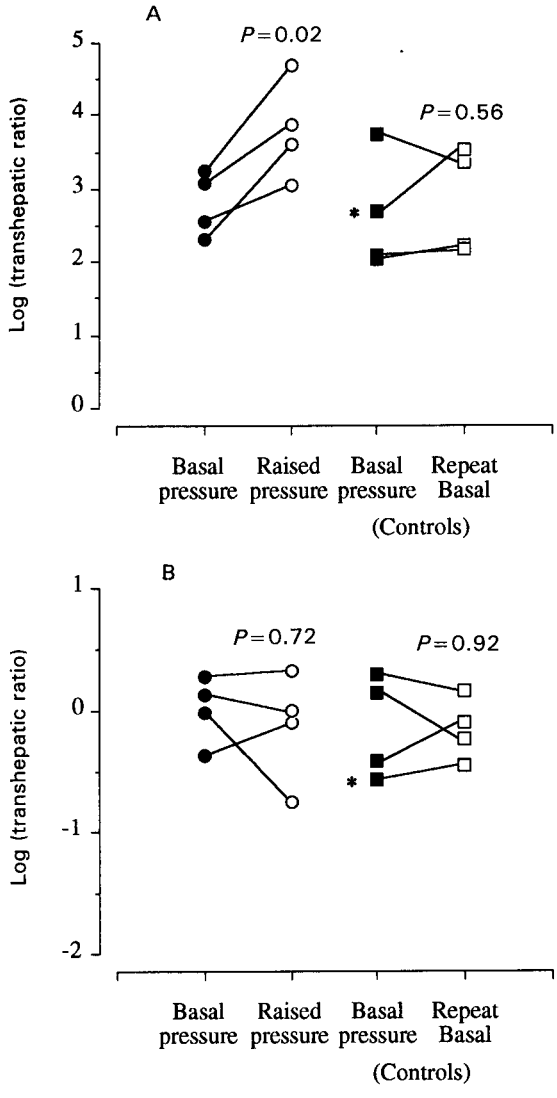

FIG. 5. Comparison of the log (transhepatic ratio) for hepatic arterial responses (A) and portal venous responses (B) during increase of the arterio-portal pressure gradient, against controls where the arterio-portal pressure gradient was not altered. Increasing the pressure gradient only affects the log (transhepatic ratio) for hepatic arterial responses ($P = 0{\cdot}02$). In one control experiment the hepatic arterial basal pressure increased from 34 to 49 mmHg (*), giving results similar to the altered pressure group.

Discussion

A simultaneous comparison of the actions of noradrenaline on both the hepatic arterial and portal venous vascular beds following intra-arterial and intra-portal injection was studied. At basal tone in the Krebs perfused liver, we demonstrated that the direct action of noradrenaline on the hepatic arterial vascular bed was approximately 500 times more potent than the transhepatic action. This figure was higher than that of 50 reported previously (Richardson & Withrington 1978b). The maximum transhepatic response was not reached in our experiments but would appear to be of a similar magnitude to the direct maximum response, suggesting that if sufficient noradrenaline were given most, if not all, the hepatic arterial resistance sites would be accessible from portal venous injection of noradrenaline. However, this did not apply to the portal venous vascular bed. Richardson & Withrington (1978b) found that the transhepatic portal responses never exceeded 80% of direct responses. Our results conformed with this over a comparable dose range, but with higher doses, the transhepatic response and the maximum transhepatic response were actually greater than the direct response. This fact, and the difference in shape of the direct and indirect portal venous responses, may be explained by flow and dilution effects due to the different flows in the hepatic artery and portal vein. The different volume and velocity of flow could result in exposure of the resistance sites to a different concentration of noradrenaline or to a different duration of exposure, but the exact mechanism of this is not clear. The possibility exists that the two sets of hepatic arterial resistance sites were entirely independent, one set being activated by intraluminally applied noradrenaline (hepatic arterial injection) while the other set of muscles may be activated by extraluminally applied noradrenaline (transhepatic). However, pilot studies where noradrenaline was applied extraluminally, i.e. into the organ chamber directly, did not elicit any changes in perfusion pressure (Browse & Alexander unpublished observations) and this therefore remains an unlikely possibility.

Investigations which demonstrated differences in hepatic arterial potency between direct and indirect injection and the similarity of portal venous potency concluded that resistance sites may be located pre-sinusoidally for the hepatic artery and post-sinusoidally for the portal venous vascular bed (Richardson & Withrington 1978b; Lautt et al 1984). There is further evidence to substantiate this assumption by the large pressure drop demonstrable between the hepatic arterioles and the sinusoids, although the situation in the portal venous vasculature may not be so clear. Early results suggested that portal vascular resistance was pre-sinusoidal in origin (Nakata et al 1960) and perhaps due to sinusoidal inlet sphincters (McCuskey et al 1979), but the demonstration of a hepatic venous outlet sphincter responding to histamine in the dog (Greenway & Oshiro 1973) and to sympathetic nervous stimulation in the cat (Lautt et al 1986), suggested it was generated post-sinusoidally. Recent investigations employing new methods of data interpretation (Lautt & Legare 1992a, b) and direct pressure measurement (Bohlen et al 1991), concluded that only one third of the resistance was post-sinusoidal and that pre-sinusoidal resistance predominated.

The particularly interesting feature in the portal venous bed was the similarity in potency between direct and transhepatic actions, as noted previously (Richardson & Withrington 1978a; Lautt et al 1984). This suggested that either the hepatic-arterially-injected noradrenaline had excellent diffusion capabilities which allowed it to reach all the portal venous resistance sites, or that the resistance was generated after mixing of the hepatic arterial and portal venous inflows (i.e. post-sinusoidally). This was in contrast to the relative lack of accessibility, and consequent difference in response potency, of the hepatic arterial resistance sites (pre-sinusoidal). If the portal resistance sites for noradrenaline are pre-sinusoidal then the trans-

Table 1. −Log (molar ED50) changes for direct injection of noradrenaline and the − log (molar dose) required to give an equivalent response by transhepatic injection. There is a leftward shift of the ED50 for direct hepatic arterial responses after the addition of noradrenaline to increase the perfusion pressure ($P < 0.05$). The log (transhepatic ratio) is also shown.

	Direct	Transhepatic	Log (transhepatic ratio)
Hepatic arterial responses			
Control (first)	6·22 ± 0·17* (85·8 ± 6·9)	3·58 ± 0·45 (50·5 ± 8·9)	2·64 ± 0·40
Control (second)	6·46 ± 0·26 (93·8 ± 4·7)	3·65 ± 0·27 (43·5 ± 9·4)	2·81 ± 0·36
Basal pressure	7·01 ± 0·18 (158·7 ± 11·6)	4·21 ± 0·06 (108·8 ± 15·7)	2·80 ± 0·21
Raised pressure	7·77 ± 0·18 (106·0 ± 25·5)	3·96 ± 0·22 (43·3 ± 8·3)	3·81 ± 0·35**
Portal venous responses			
Control (first)	5·89 ± 0·24 (10·3 ± 2·5)	6·02 ± 0·07 (11·1 ± 2·5)	−0·13 ± 0·21
Control (second)	6·11 ± 0·13 (10·3 ± 2·1)	6·27 ± 0·09 (10·0 ± 1·9)	−0·16 ± 0·13
Basal pressure	6·24 ± 0·38 (10·5 ± 0·5)	6·28 ± 0·23 (10·1 ± 0·8)	0·00 ± 0·14
Raised pressure	6·22 ± 0·27 (9·2 ± 1·4)	6·35 ± 0·15 (8·0 ± 1·0)	−0·14 ± 0·22

*$P = 0.02$ compared with basal pressure group, Student's unpaired t-test. **$P \leqslant 0.05$ compared with basal pressure, Student's paired t-test. Although the data suggested that there was a statistical difference between the control (first) and basal pressure group this was not relevant because each perfusion served as its own control before the addition of noradrenaline, i.e. basal pressure for raised pressure and control (first) for control (second). Moreover this difference may be due to the biological variability of the sensitivity of each of the livers used to noradrenaline and that this is far greater than the individual variability which may occur during a single perfusion in one liver (Browse et al 1994). Values quoted in parentheses are the G_{max} values for each respective dose-response curve.

hepatic responses demonstrated during this study must be a result of transfer of noradrenaline either through the tissues or by a direct intravascular route.

Ohtani (1979) demonstrated, using scanning electron microscopy of vascular casts, that terminal arterioles drained directly into the sinusoids in the rabbit, and Grisham & Nopanitaya (1981) showed that arterioles supplied the peribiliary plexus and that this had efferents to the portal venules. Thus, although an intravascular route probably existed for flow from arterial to portal pre-sinusoidal resistance sites, it was unlikely to carry a large proportion of the hepatic arterial supply, most of which entered the sinusoids directly. Therefore, diffusion through the tissues was likely to be the main mechanism for the arterial to venous transhepatic effect. Similarly, these anatomical studies also suggested that direct flow from the portal venous to hepatic arterial vascular bed was unlikely, again making diffusion the probable route.

The increase in hepatic arterial to portal venous pressure gradient during these experiments further separated the direct and transhepatic arterial dose-response curves to noradrenaline. This confirmed that access to the hepatic arterial resistance sites was influenced by this gradient (although a direct correlation between the transhepatic ratio and pressure difference could not be demonstrated in this small series). The fact that pressure gradient had any influence was surprising because diffusion through a liquid is not supposed to be affected by hydrostatic pressure at these concentrations, although diffusion through a semi-permeable membrane has been shown to be dependent on hydrostatic pressure (Parbrook et al 1990). Therefore, either an intra-vascular route does exist for the transhepatic transmission of noradrenaline responses from the venous to arterial vascular bed, despite the pressure gradient against it, or, more likely, the liver can be regarded as a series of semi-permeable membranes forming a barrier to diffusion. The portal venous action of noradrenaline was unaffected by this gradient.

The use of noradrenaline may be criticized as a means of increasing vascular tone in these experiments because of the resultant leftward shift of the arterial dose-response curve, but the comparison of hepatic arterial and portal venous responses independently, using the transhepatic ratio accommodated this shift. The lag times for the onset of responses were very short in these experiments (less than 5 s, independent of injection site); however, we have subsequently shown that there is a significant lag time before the onset of arterial responses from portal injection with adenosine 5′-triphosphate which would seem to confirm the lack of a direct luminal transfer (Browse et al unpublished observation). It is possible, therefore, that a decrease or increase of the pressure gradient could have a significant bearing on the response to vasoactive agents in diseases affecting portal pressure such as cirrhosis or the Budd-Chiari syndrome.

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