The Effects of Intra-arterial and Intraportal Injections of Vasopressin on the Simultaneously Perfused Hepatic Arterial and Portal Venous Vascular Beds of the Dog

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SUMMARY The hepatic arterial and hepatic portal venous vascular beds of the chloralose-urethane anesthetized dog were perfused simultaneously in situ. Vasopressin (10 mU = 1 unit) was injected in graded increasing doses into the hepatic artery and into the portal vein. Both intra-arterial and intraportal vasopressin elicited both hepatic arterial vasoconstriction and hepatic venous dilation; the delay in onset of both hepatic vascular effects was significantly shorter than that for any succeeding systemic effects (a rise in systemic arterial pressure and fall in heart rate), showing that they were not attributable to recirculation or to arterial baroreceptor reflexes. Injections of vasopressin into the inferior vena cava at the level of the hepatic veins consistently produced smaller hepatic vascular effects than either intra-arterial or intraportal injections of the same doses. The results are discussed in the context of the therapeutic role of vasopressin in controlling gastrointestinal bleeding and portal hypertension.

VASOPRESSIN is known to elicit vasoconstriction in most peripheral vascular beds; a consequence of its vasoconstrictor properties in the intestinal and splenic vascular beds is a reduction of portal blood flow with a fall in hepatic portal venous pressure. Although these vascular effects occur on administration of doses of vasopressin in excess of the physiological concentrations, they provide an explanation of its established therapeutic role in relieving the symptoms of many conditions, especially portal hypertension with bleeding esophageal varices.

However, the direct effects of vasopressin on the hepatic circulation have received little experimental attention. Vasoconstriction of the hepatic arterial bed occurs in sympathetically denervated preparations when the drug is administered intra-arterially, a response which is inhibited by glucagon. Whereas some reports suggest that vasopressin is without effect on the mesenteric venous system, others have shown that vasopressin relaxes the isolated rabbit portal vein. Moreover, intraportal injections of vasopressin in the dog reduce the calculated portal vascular resistance, an effect postulated to be due to direct portal vasodilatation.

The present series of experiments were performed on dogs in which both hepatic inflow circuits, arterial and portal, were simultaneously perfused with blood under controlled conditions. In addition, the outflow of blood from the superior mesenteric vein was measured. Thus it was possible to establish, quantitatively, the extent to which both liver inflow circuits are influenced by the presence of vasopressin in either the hepatic artery or the portal vein. From the results, the relative potency of vasopressin in altering hepatic arterial, hepatic portal, and superior mesenteric vascular resistances was assessed and a more certain explanation of its therapeutic efficacy in portal hypertension established.

Methods

Observations were made in 9 dogs that had not been fed for 24 hours but that had been allowed unrestricted access to water prior to the injection of methohexital sodium (Brietal, Lilly), 5–8 mg/kg body weight, to induce anesthesia. Anesthesia was maintained by an i.v. injection of chloralose (50 mg/kg; Kuhlmann) and urethane (500 mg/kg; BDH) followed by supplements in the same proportion as necessary to maintain a constant level of anesthesia. The techniques for perfusing the sympathetically innervated hepatic arterial and portal venous vascular beds in situ were a combination of those published previously for the individual perfusion of the two circuits, and only brief details are given here.

Hepatic Arterial Perfusion

The hepatic artery was cannulated and perfused with blood derived from a cannulated femoral ar-
tery. The hepatic artery therefore received arterial blood at essentially constant pressure; hepatic arterial blood flow and perfusion pressure were monitored continuously.

**Hepatic Portal Venous Perfusion**

The portal vein was cannulated and perfused at constant inflow 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 inflow as the superior mesenteric venous outflow and with blood of normal portal venous composition in the anesthetized dog. If drugs entered the systemic arterial circulation, they could alter the outflow from the mesenteric vein, and so the inlet side of the pump used to perfuse the portal vein was also connected via the cannulated external jugular vein to the right atrium, to ensure a constant inflow of blood to the portal vein despite alterations in mesenteric outflow.

**Measurements**

Hepatic arterial perfusion pressure (HAPP) was measured from a “T”-piece close to the point of cannulation of the hepatic artery, using a Consolidated Electrodyamics (L-0001) transducer, and the hepatic arterial blood flow (HABF) was measured with a cannulating flow probe in the cannula connecting the femoral artery to the hepatic artery, and a Cardiovascular Instruments (3765T) electromagnetic flowmeter.

Hepatic portal venous pressure (HPVP) was measured from a T-piece close to the point of cannulation of the portal vein, using a Statham (P23V) transducer, and the hepatic portal venous flow (HPVF) was monitored with a cannulating flow probe on the outflow side of the perfusion pump, and a Cardiovascular Instruments electromagnetic flowmeter.

The superior mesenteric venous flow (SMVF) was measured with a cannulating flow probe in the cannula draining the mesenteric blood via the splenic vein. The purpose of this measurement was to give an indication of blood flow changes in a vascular bed other than the liver. Another electromagnetic flow probe was incorporated into the cannula leading to the right atrium to ensure that, under control conditions, there was no blood flow in either direction in this cannula, so that the portal vein was perfused at exactly the same flow as the superior mesenteric venous outflow.

In addition to these measurements, the systemic arterial blood pressure (BP) was recorded from a cannulated femoral artery with a Statham (P23Gb) transducer; the heart rate (HR) was derived electronically from the pulsatile arterial pressure waveform with a Devices (4520) ratemeter. The pressure in the inferior vena cava (IVCP) at the level of the hepatic veins was measured from a cannula advanced through the femoral vein to the level of the hepatic veins, using a Statham (P23Bb) transducer.

Except for the BP which was recorded as pulsatile pressure, the flow and pressure signals were passed through averaging circuits with time constants of 0.5–0.6 second before being recorded on rectilinear hot-wire recorders (Devices, M-19 and M-2). Mean BP was derived as diastolic + ½ pulse pressure, a derivation giving values in agreement with electronically averaged BP. Calibrations and zeroing of the instruments were carried out as described previously.9,12

**Calculations**

Hepatic arterial vascular resistance (HAVR) was calculated as (hepatic arterial mean perfusion pressure: mm Hg) divided by (hepatic arterial mean blood flow: ml/min or ml/min per 100 g) and expressed in mm Hg/ml per min or mm Hg/ml per min per 100 g.

Hepatic portal vascular resistance (HPVR) was calculated as (hepatic portal mean perfusion pressure – inferior vena cava pressure: mm Hg) divided by (hepatic portal mean blood flow: ml/min or ml/min per 100 g). The pressure gradient across the portal venous system (HPVP-IVCP) is referred to as the hepatic portal perfusion pressure (HPPP).

The interpretation of drug-induced changes in hepatic arterial and portal venous vascular resistances has been considered previously.12,13 Changes in both HAVR and HPVR reflect hepatic arterial and portal vasoconstriction and vasodilation in these preparations.

**Drug and Hormone Administrations**

In three experiments, vasopressin was administered as Pitressin (Parke-Davis), and in the remaining six experiments, pure lysine vasopressin (Sandoz) was used. Since the experiments revealed no differences in the responses of the liver circulation to the two preparations used, for statistical purposes the results have been grouped. In three experiments, the effects of the preservative, chloroform, which has been suggested to possess vasoactivity, also were examined, using a dose equivalent to that administered with the highest dose of vasopressin.

Vasopressin solutions were diluted with isotonic (154 mmol/liter) NaCl solution (saline) and injected into the cannulas leading to the hepatic artery or portal vein in volumes not exceeding 0.5 ml and washed in with saline to make the total injected volume 1.5 ml. These injections were made in graded increasing doses from 10 mU to 500 mU or 1 U both intra-arterially (i.a.) and intraportally (i.p.v.) and, in addition, in seven experiments, 1 U of vasopressin was injected into the inferior vena cava at the level of the hepatic veins.

External vascular circuits were primed with low molecular weight dextran solutions (Lomodex, Fi-
sons, or Rheomacrodex, Pharmacia) and blood coagulation was prevented by an i.v. injection of heparin (Weddel: 250 IU/kg) prior to cannulation of the blood vessels, followed by 100 IU/kg hourly.

Statistical Analyses

Initial control values are expressed as means ± 1 SD, and all other values as means ± SEM. Unless stated to the contrary, n refers to the number of experiments in which observations were made, and not the number of individual vasopressin injections. The significance of differences between paired sets of data was assessed by Student's t-test.

Results

Initial Control Values

When both hepatic arterial and portal venous perfusions had been established in nine dogs weighing 17.0 ± 2.9 kg, the BP was 126.8 ± 20.0 mm Hg, the HR was 181.8 ± 30.9 beats/min, the IVCP was 1.66 ± 1.53 mm Hg, and the systemic arterial hematocrit was 47.6 ± 2.8%. Postmortem, the livers weighed 328.7 ± 62.6 g.

The hepatic arterial perfusion pressure was 116.2 ± 17.4 mm Hg, and the hepatic arterial blood flow 139.1 ± 36.2 ml/min, giving a calculated hepatic arterial vascular resistance of 0.87 ± 0.15 mm Hg/ml per min, or 2.83 ± 0.63 mm Hg/ml per min per 100 g. The hepatic portal venous pressure was 7.19 ± 1.0 mm Hg and the hepatic portal perfusion pressure (HPPP = HPVP - IVCP) 5.53 ± 1.63 mm Hg, which, at a hepatic portal venous blood flow of 209 ± 41.6 ml/min, gave a calculated hepatic portal vascular resistance of 0.027 ± 0.009 mm Hg/ml per min, or 0.090 ± 0.036 mm Hg/ml per min per 100 g. These initial control values are similar to those reported previously from this laboratory in which one inflow circuit alone was perfused.12

Injections of Vasopressin into the Hepatic Artery

Responses of the Hepatic Arterial Vascular Bed

Intra-arterial injections of 10 mU to 1 U of vasopressin caused only dose-dependent reductions in hepatic arterial blood flow which, at constant or slightly increased hepatic arterial perfusion pressure, indicate dose-dependent hepatic arterial vasconstriction. In no experiment was there any sign of a secondary vasodilator response to vasopressin injected into the hepatic artery. The responses of the sympathetically innervated hepatic arterial vascular bed therefore were similar in character to those previously reported for the sympathetically denervated bed.9 The lowest dose (10 mU) was above threshold in all but one experiment, and the maximum increase in calculated hepatic arterial vascular resistance occurred at 0.5 or 1 U i.a.

Responses of the Hepatic Portal Vascular Bed

Injections of vasopressin into the hepatic artery caused dose-dependent reductions in hepatic portal venous pressure which, at a constant inflow and IVCP, reflect a reduction in calculated portal vascular resistance. This was the only portal response observed with doses of vasopressin above threshold. The threshold dose of vasopressin injected i.a. to cause a fall in calculated HPVR was between 10 and 500 mU in different experiments (10-50 mU in 8 of 9 experiments), and the maximum reduction in HPVR over the dose range, 10 mU-1 U i.a., was 15.6 ± 2.7% (n = 9). A typical response is shown in Figure 1, and the dose-response curve in Figure 2.

Extrahepatic Effects of Intra-arterial Vasopressin

Doses of vasopressin of up to 100 mU injected into the hepatic artery were not associated with any measurable systemic effects, although the higher doses produced small increases in systemic arterial pressure and reductions in heart rate and superior
Figure 2 Dose-response curves for the hepatic arterial (upper panel) and portal venous (lower panel) responses to vasopressin injected intra-arterially (filled symbols and continuous lines) and intraportally (open symbols and broken lines). Abscissa scale: log₁₀ scale showing doses of vasopressin injected intra-arterially and intraportally. Upper ordinate scale: % rise in calculated hepatic arterial vascular resistance (HAVR), i.e., hepatic arterial vasoconstriction. Lower ordinate scale: % fall in calculated hepatic portal vascular resistance (HPVR), i.e., portal dilation. Points represent the means of 6-8 observations, and vertical bars show the SEM.

Latency of the Responses to i.a. Vasopressin

When 1 U of vasopressin was injected into the hepatic artery, the first effect observed was a reduction in hepatic arterial blood flow, the onset of which followed 6.8 ± 1.2 sec after the injection. The response of the hepatic portal vascular bed occurred with a significantly longer latency at 9.9 ± 1.5 sec (P < 0.001). However, both hepatic vascular effects significantly preceded the changes in systemic arterial pressure (21.4 ± 2.0 sec; P < 0.005), heart rate (25.9 ± 1.2 sec; P < 0.001), and superior mesenteric venous flow (21.9 ± 1.3 sec; P < 0.001). The relative times to onset (latencies) of the vascular effects of vasopressin are illustrated in Figure 3.
Time Course of the Portal and Arterial Vascular Responses to i.a. Vasopressin

The time courses of the responses of the hepatic arterial and portal vascular beds to i.a. vasopressin were very different (Fig. 1). The hepatic arterial vasoconstrictor response had a short time course from onset to peak, with a quick recovery. The mean time from the injection to the peak of the arterial response to 1.0 U of vasopressin i.a. was, in six experiments, 19.8 ± 0.5 sec, which, after subtraction of the latency, gives a mean time course from onset to peak of 13.1 ± 0.9 sec.

In contrast, the portal dilator response to arterial vasopressin was prolonged in time both from onset to peak and to recovery (Fig. 1). The time from injection to peak for the portal response to 1.0 U of vasopressin i.a. was 42.5 ± 2.8 sec, a value significantly greater (P < 0.001) than that for the arterial response and which, after subtraction of the portal latency gives a time course of the portal dilator response from onset to peak of 32.0 ± 2.9 sec, which is also significantly (P < 0.001) greater than the corresponding value for the arterial response.

Injections of Vasopressin into the Hepatic Portal Vein

Responses of the Hepatic Portal Vascular Bed

The response of the portal vascular bed, a reduction in hepatic portal venous pressure at constant inflow and IVCP, was similar in character and extent to that observed previously when the portal vascular bed was perfused alone.12 The threshold for this effect was either 10 or 50 mU, and the maximum fall in HPVR of 15.3 ± 2.2% occurred on injection of 0.5 or 1.0 U. The dose-response curve for this effect is shown in Figure 2; for each dose, the portal response to vasopressin is very similar whether the peptide is injected into the hepatic artery or the portal vein (Figs. 1 and 2).

Responses of the Hepatic Arterial Vascular Bed

Intraportal injections of vasopressin produced reductions in hepatic arterial blood flow at constant or slightly increased hepatic arterial perfusion pressure (Fig. 1), effects indicative of vasoconstriction (Fig. 2). The threshold dose of vasopressin injected intraportally producing increases in hepatic arterial vascular resistance was between 10 and 500 mU (in 4 of 9 experiments, 500 mU), and the maximum increase in hepatic arterial vascular resistance attained over the dose range, 10 mU-1 U intraportally, was 49.9 ± 10.8%. However, since higher doses were not injected intraportally because they would have resulted in marked systemic effects, it has not been established that this is the maximum possible hepatic arterial response to intraportal vasopressin. Nevertheless, it is clear (Fig. 2) that the hepatic arterial responses to doses of vasopressin injected into the hepatic artery are very much greater than those to the same doses injected into the portal vein.

Extrahepatic Effects of Intraportal Vasopressin

The higher doses within the range injected intraportally produced systemic effects due to the peptide passing through the liver and the cardiopulmonary circuit to enter the systemic circulation. The peak changes after intraportal injection of 1 U of vasopressin were as follows: a rise in blood pressure from 122.8 ± 4.6 to 133.8 ± 5.2 mm Hg, a fall in heart rate from 162.1 ± 13.0 to 151.4 ± 12.3 beats/min, and a reduction in superior mesenteric blood flow from 204.3 ± 15.8 to 149.7 ± 17.3 ml/min, all of which were statistically significant (P < 0.005).

Latency of the Responses to Intraportal Vasopressin

The delay to the onset of the hepatic portal response to intraportal vasopressin was 14.9 ± 1.4 sec, which was not significantly different from the delay to onset of the hepatic arterial response to intraportal vasopressin (11.7 ± 1.2 sec; P > 0.05). In 7 experiments, the onset of the hepatic arterial response preceded even the onset of the portal response to intraportal vasopressin (Figs. 1 and 3). The hepatic vascular effects of intraportal vasopressin significantly preceded the onset of the changes in blood pressure (27.0 ± 2.7 sec; P < 0.001), heart rate (35.3 ± 4.2 sec; P < 0.001) and superior mesenteric venous blood flow (28.5 ± 1.0 sec; P < 0.001).

Time Course of the Hepatic Vascular Responses to Intraportal Vasopressin

The time courses of the hepatic arterial and portal vascular responses to intraportal vasopressin again were very different. The time to peak of the arterial response to the intraportal injection of 1.0 U of vasopressin was 23.3 ± 0.9 sec which, after subtraction of the latency, gives a time course from onset to peak of 11.7 ± 1.3 sec. The time course of the arterial response was therefore rapid both to peak and recovery (Fig. 1). In contrast, the portal dilator responses were prolonged in both phases. The mean time from injection to peak was 57.8 ± 4.2 sec, significantly longer than the arterial response to the same intraportal injections (P < 0.001) and, after subtraction of the latency, yields a time course from onset to peak of the portal dilator effect of 42.6 ± 3.1 sec, a value significantly (P < 0.001) longer than the corresponding value for the hepatic arterial response to intraportal vasopressin.

Injections of Vasopressin into the Inferior Vena Cava

A single dose of 1 U of vasopressin was selected for these injections, the same dose as that used for
analysis of the time courses of the responses to intra-arterial and intraportal vasopressin.

Responses of the Hepatic Arterial Vascular Bed

Intra-arterial vasopressin produced small and very variable changes in the hepatic arterial vascular resistance; in 6 experiments, the calculated changes in HAVR were between +10.0 and −9.7%, the mean response of the hepatic arterial bed to i.v.c. vasopressin being 0.0 ± 3.3%, in contrast to the hepatic arterial responses to intra-arterial (+186.0 ± 54.3%) or intraportal (+43.3 ± 10.0%) injections of 1 U of vasopressin.

Responses of the Hepatic Portal Vascular Bed

Intravenous injections of vasopressin caused a mean fall in calculated HPVR of 6.5 ± 2.7% (range, 0−16.2%) which was consistently less than the reductions in HPVR due to the same dose of vasopressin injected either into the hepatic portal vein (15.0 ± 2.5%) or the hepatic artery (15.2 ± 2.7%) in the same experiments.

Extrahepatic Responses to Intravenous Vasopressin

The systemic responses to intravenous vasopressin consisted of a rise in BP from 115.0 ± 6.0 to 122.0 ± 5.0 mm Hg, a fall in HR from 174.4 ± 7.0 to 162.6 ± 9.8 beats/min, and a fall in SMVF from 213.3 ± 22.2 to 161.0 ± 31.3 ml/min, effects which were similar to those elicited by intra-arterial or intraportal injections of the same doses of vasopressin.

Latency of the Responses to Intravenous Vasopressin

The temporal relationship between the responses to intravenous vasopressin was quite different to those for intra-arterial or intraportal vasopressin (Fig. 3). The first responses to be seen were the increases in BP (latency = 9.0 ± 1.3 sec) and decreases in superior mesenteric venous flow (latency = 9.0 ± 2.8 sec). Following significantly later (P < 0.01) were the changes in hepatic arterial blood flow (14.0 ± 1.6 sec) and hepatic portal venous pressure (26.9 ± 11.3 sec). The latency for the heart rate responses was 16.5 ± 5.4 sec.

Vasopressin Solvent

To examine the possibility of solvent vasoactivity contributing to the responses described, a solution containing chlorobutanol equivalent to that administered with 1 U of vasopressin was injected into the hepatic artery and the portal vein in 3 experiments. Intra-arterial injection produced a reduction in hepatic arterial vascular resistance of 1.5 ± 1.0% (range, 0–3.5%) and no change in portal resistance in any experiment. Intraportal injections caused no change in portal resistance and a fall in hepatic arterial vascular resistance of 0.5 ± 0.5% (range, 0–1.6%).

Discussion

Intra-arterial injections of vasopressin into the sympathetically denervated hepatic arterial vascular bed of the dog cause dose-dependent hepatic arterial vasoconstriction, and this effect is now confirmed for the sympathetically innervated vascular bed; in addition, hepatic arterial vasoconstriction results from the intraportal injection of vasopressin. It has been shown previously that intraportal administration of vasopressin reduces portal vascular resistance; this observation has been confirmed in the present series and extended, since a reduction in portal vascular resistance occurs on injection of vasopressin into the hepatic artery; we term these effects on the inflow circuit not receiving the direct injection “transhepatic” effects.

A hydrodynamic relationship exists between the hepatic artery and the portal vein such that a reduced perfusion in one circuit occasions a reduction in the vascular resistance of the other. These hydrodynamic changes in one circuit occur immediately on alteration of the perfusion of the other and the marked difference in the time courses of the hepatic arterial and portal venous responses to both intra-arterial and intraportal injections of vasopressin shows that the transhepatic drug effects cannot be dependent to any significant extent upon the hydrodynamic relationship between the two circuits.

It is clear from the analyses of the vascular effects and their latencies from injection to onset that the transhepatic effects of vasopressin do not depend on the hormone surviving passage through the liver after intra-arterial or intraportal injection, then surviving passage through the cardiopulmonary circuit, to reenter the liver via the systemic circulation. On both i.a. and i.p.v. injection, both hepatic vascular effects significantly precede any systemic effects, a time course which is qualitatively different from that seen on intravenous injection of vasopressin. That the two hepatic vascular effects precede any systemic effects, including a rise in systemic arterial pressure and a reduction in heart rate, also eliminates the possibility that the transhepatic effects might be a consequence of reflexes elicited by alterations in systemic arterial pressure consequent to the entry of vasoactive material into the systemic circulation.

Whereas it is possible that the portal vascular responses to intra-arterial injection may be the result of the passage of vasopressin through arteriportal anastomotic channels to reach the sites controlling portal vascular resistance, it is not possible to offer a converse explanation for the effects on the hepatic arterial resistance sites after intra-portal administration, because the pressure gradients within the liver would oppose transmission of vasoactive material from portal to arterial systems. A possible explanation of the transhepatic effects of vasopressin lies in the observation of Rappaport and Schneiderman that the inlet...
“sphincter” sites which control the entry of material into the hepatic sinusoids from the arterial and portal systems exhibit cyclic patterns of alternating opening and closing. Vasoactive material present in either inflow circuit may gain access to these inlet sphincter sites and influence the cyclic opening-closing sequences to cause longer periods in either phase and thereby affect the calculated vascular resistances of the two inflow circuits.

Another possible explanation of the transhepatic effects of vasopressin lies in the existence, in the dog, of sphincter sections at the outlets from the hepatic sinusoids into the hepatic venules.17,18 The fact that both intra-arterial and intraportal vasopressin elicited quantitatively similar changes in portal vascular resistance (Fig. 2) might suggest that the alterations in portal vascular resistance were due to effects on a common outlet resistance site where, following mixing of the hepatic arterial and portal venous blood streams, the concentration of vasoactive material would be the same whether it was administered intra-arterially or intraportally. In contrast, the hepatic arterial responses to i.a. injection were much greater than to i.p.v. injection, perhaps suggesting that the main arterial resistance sites are located upstream from the point of confluence of the two inflow circuits, at the sphincters guarding the inlets to the hepatic sinusoids.

It is difficult to correlate the doses of vasopressin injected acutely in the present experiments with the hormone concentrations reported to occur under physiological circumstances. In the dog, intravenous infusions of 8–32 mU kg per min produced systemic blood concentrations of vasopressin of the same order of magnitude as those elicited by hemorrhage and other stressful conditions—that is, about 50–200 μU/ml, and in addition, elicited mesenteric vasoconstriction and slight reductions in hepatic portal venous pressure.10 Although clearly high by physiological standards, the lower levels of vasopressin injected in our experiments are not very different from those reported to produce systemic concentrations similar to those occurring under stressful conditions.19 In both dogs20 and cats,21 severe hemorrhage may elevate systemic blood vasopressin levels by as much as 1 μU/ml.

These and other experiments have shown that elevation of systemic vasopressin levels would bring about significant reductions in total liver blood flow, due to hepatic arterial vasoconstriction, coupled with a reduced inflow to the portal vein due to intestinal and splenic vasoconstriction.22,23 These observations, together with an established metabolic stimulant effect,24 indicate a disadvantage of continuous infusion of high doses of vasopressin which might result in liver hypoxia and possible hepato-cellular damage.

The present series of experiments support the view that the primary cardiovascular action of intravenous vasopressin may be on the gastrointestinal tract. The single i.v. dose used in these experiments evoked little change in hepatic arterial flow but elicited decreases in mesenteric venous flow and hepatic portal vascular resistance. Vasopressin is known to cause a greater degree of intestinal precapillary, as compared with postcapillary, vasoconstriction resulting in the absorption of water from intestinal pericapillary spaces into the vascular lature.25 Such water reabsorption from the perivascular spaces of the intestine could be functionally related to a primary stimulus for the physiological release of vasopressin, i.e., reductions in circulating fluid volume.

Vasopressin is a well-established therapeutic agent controlling severe hemorrhage of the upper and lower intestine, and portal hypertension,26 effects usually ascribed to its mesenteric vasoconstrictor activity. The present experiments suggest that the direct portal vasodilator effect may also contribute to the beneficial effects of therapeutic administration of vasopressin in these conditions.

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References

Subpressor Angiotensin Infusion, Renal Sodium Handling, and Salt-Induced Hypertension in the Dog

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SUMMARY We studied the combined effect of subpressor amounts of angiotensin and long-term sodium chloride infusion on arterial pressure in 16 dogs for periods of 2–8 weeks. In dogs receiving 3.5 liters of isotonic NaCl daily, but no angiotensin, the arterial pressure increased an average of only 3 mm Hg. When angiotensin was infused continuously at a rate of 5 ng/kg per min (a rate too small to cause an observable immediate increase in pressure), subsequent infusion of 3.5 liters of saline daily then increased the pressure by 39 mm Hg. The urinary output of sodium increased to the same extent in both instances, that is, there was no extra sodium loss because of the elevated pressure. This suggests that the angiotensin significantly blocked the normal "pressure natriuresis" usually seen with such large increases in pressure. However, the plasma aldosterone levels during angiotensin infusion were not found to be different from those in the absence of angiotensin. Therefore, we have suggested that the tendency of the kidneys to retain sodium under the influence of angiotensin was probably caused mainly by a direct effect of angiotensin on the kidney itself. Such a direct renal sodium-retaining effect also could be a contributing factor in the marked hypertension that results from salt administration in the presence of small amounts of angiotensin.

SEVERAL investigators, including Dickinson and Ye,1 McCubbin et al.,2 Cowley and DeClue,3 and Trippodo et al.,4 have shown that infusion of angiotensin at a rate that will not cause a significant immediate rise in arterial pressure will nevertheless cause hypertension over a period of 5 days to 2 weeks. Furthermore, Cowley and DeClue5 showed that the level to which the pressure rises is highly dependent on salt intake. In another type of study, Yeyati et al.,6 Waugh,6 and Pagard et al.7 demonstrated that infusion of nonpressor doses of angiotensin either intravenously or into the renal artery can cause as much as a 50% decrease in renal sodium and water output. This effect occurs within a few minutes, presumably before the angiotensin can cause aldosterone secretion. More recently, Hall et al.,8 Lohmeier et al.,9 and Trippodo et al.10 have shown that salt-depleted dogs given appropriate amounts of angiotensin antagonists may in...
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