Reduced intrarenal resistance and autoregulatory capacity after hyperoncotic dextran

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DEXTRAN SOLUTIONS have been previously used in renal experiments to alter the plasma colloid osmotic pressure, blood volume, and hematocrit in studies examining the control of salt and water excretion (1, 3, 12, 29, 30) and renal hemodynamics (1, 3, 20, 21), but distinction has not always been made between the renal effects due solely to the oncotic properties and those due to other properties (11). However, renal hyperemia following dextran loading has been a relatively consistent observation. This effect has been attributed to dextran leakage into the tubules cannot be discounted.

METHODS

Large mongrel dogs of either sex were anesthetized with sodium pentobarbital at a dose of 30 mg/kg body wt. A tracheotomy was performed, and polyethylene catheters were inserted into the left jugular vein for administration of fluid and into the right femoral artery for the measurement of arterial pressure and for collection of arterial blood samples. Through a left flank incision, the renal artery, vein, and ureter were exposed. The ureter was catheterized with a polyethylene catheter leading to a linear fraction collector (LKB Instruments). An electromagnetic flow transducer, connected to a square-wave flowmeter (Carolina Medical Electronics), was placed around the renal artery, and an adjustable plastic occluder was placed on the artery distal to the flow transducer. As previously described (22), the renal vein was punctured with an 8-inch 20-gauge Becton Dickinson Teflon needle catheter, and the catheter was passed retrograde into the kidney for measurement of intrarenal venous pressure. In experiments where renal blood flow-perfusion pressure relations were obtained, a Becton Dickinson Teflon needle catheter was inserted into the renal artery distal to the occluder. The femoral arterial, renal arterial, and renal venous catheters were connected to Statham pressure transducers. All flows and pressures were recorded on a Grass model 5 polygraph.

After collection of control blood and urine samples, inulin was administered with an isotonic saline solution at 2-4 ml/min to establish appropriate plasma inulin concentration and moderate diuresis. Following a 30- to 40-min equilibration period, blood and urine samples were taken. In four experiments, pressure flow relations were determined by progressively occluding the renal artery to decrease renal arterial pressure in steps of 15-25 mm Hg. In five experiments recovery blood flow patterns following 1
min of total renal arterial occlusion were obtained as previously described (24). Steady-state values for the measured variables were followed in seven experiments.

After control measurements had been completed, 300–500 ml of hyperoncotic, 12% dextran solution in isotonic saline was infused. Clinical grade dextran was obtained from Sigma and had an average molecular weight of 135,000. Blood and urine samples were collected when the renal blood flow response had reached a maximum level. The pressure-flow relations or renal blood flow recovery patterns were repeated in the respective experiments.

At the end of the experiments, the renal artery was catheterized and the flow transducer was calibrated in situ by collecting timed blood sample volumes in a graduated cylinder. Calibration of the flow transducers was performed in each individual experiment, and thus calibration errors were minimized except for the effect of decreases in hematocrit resulting from the dextran infusions. The control blood flow determinations were not corrected for this effect and are thus underestimated by approximately 10%. Plasma colloid osmotic pressure was measured by a modification of Hansen’s technique as previously described (27). A PM-30 Amicon membrane with a molecular weight cut-off point of 30,000 was used in the instrument. Inulin analysis of plasma and urine samples was performed by an automated anthrone method similar to that previously described (32), and standard clearance techniques were used to estimate glomerular filtration rate (GFR).

Control studies indicated that dextran in concentrations achieved in the plasma following infusions did not interfere with the inulin determinations. Intrarenal resistance was determined as the quotient of the renal arterial pressure-intrarenal venous pressure difference divided by the renal blood flow and was expressed as millimeters Hg per milliliter per minute per gram kidney. Hematocrit measurements were made on all blood samples.

Analysis of data was performed with the aid of a PDP-9 digital computer using standard statistical methods. A computer graphics program was utilized to plot the pressure-flow and pressure-resistance curves.

RESULTS

Renal hemodynamic and urine flow responses to hyperoncotic dextran loading. The changes in the steady-state values of arterial pressure, intrarenal venous pressure, renal blood flow, intrarenal resistance, glomerular filtration rate, urine flow, blood hematocrit, and plasma colloid osmotic pressure following infusions of the hyperoncotic solutions of dextran were evaluated. Figure 1 shows the responses of renal blood flow and glomerular filtration rate plotted against the increase in plasma colloid osmotic pressure. In each experiment there was a marked increase in renal blood flow following the infusion of dextran. In every instance, this increase in renal blood flow was associated with an increase in plasma colloid osmotic pressure and a decrease in blood hematocrit. The changes in glomerular filtration rate were not as consistent as the renal blood flow changes, and the individual experiments showed variable results. In some experiments, urine flow decreased to such an extent that GFR determinations by standard clearance methods were not possible.

Figure 2 depicts the intrarenal venous pressure and urine flow responses in the individual experiments to the changes in colloid osmotic pressure following infusion of dextran. The changes in intrarenal deep-venous pressure were quite consistent and showed a marked elevation following the infusion. Urine flows were measured at the time of the maximum RBF following the hyperoncotic infusion and, in almost every case, there was a decreased urine flow. However, in several of the experiments in which observations were continued for some time following the dextran loading, this response was reversed and a diuresis slowly ensued. In almost every instance, the urine excreted following the infusion of the hyperoncotic dextran solution became quite viscous as has previously been described (10). In three of the experiments, the urine samples were analyzed for colloid osmotic pressure.
osmotic pressure. In control samples this was only about 1 mm Hg, but samples collected following the infusion of the dextran solutions yielded colloid osmotic pressures ranging from 44 to 96 mm Hg.

Table 1 presents the average results of the experiments described. With the exception of arterial pressure and glomerular filtration rate, there was a significant change in all variables measured. To facilitate comparison, the average differences are presented in actual units and as percent of the control values. Analysis of the relationship between the increases in colloid osmotic pressure and the increases in renal blood flow revealed a correlation coefficient (r) of 0.71 and a regression coefficient (b) of 1.38 % increase in renal blood flow per 1 % increase in colloid osmotic pressure. These values were significant at the 5 % level.

Renal autoregulatory responses to hyperoncotic loading. In four experiments, the effect of the hyperoncotic dextran loading on the renal autoregulatory phenomenon was investigated. All of the experiments responded in a similar manner with only slight quantitative differences. Figure 3 illustrates the results of one of these experiments in detail. Renal blood flow is plotted both as a function of renal arterial pressure and of the renal arterial-intrarenal venous pressure difference. The difference between these curves is attributed to the effects of passive venous pressure changes (22). In the top portion of Fig. 3, the intrarenal resistance is plotted as a function of the arterial pressure. In each of the graphs, the control curve demonstrates the presence of typical autoregulatory behavior. Infusion of 400 ml of a hyperoncotic dextran solution resulted in a marked diminution of renal autoregulatory capability with pressure-flow and pressure-resistance relationships indicative of a nearly passive system. With infusion of about 200 ml of the dextran solution, the observed responses were less marked. Renal blood flow increased, but autoregulatory behavior could still be observed at the higher arterial pressures. Under these more moderate conditions, the autoregulation range appeared to be reset at a higher pressure level due to the fall in the base-line resist-

Table 1. Average results from 7 experiments subjected to infusions of hyperoncotic dextran solutions

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Before Dextran, Mean ± SEM</th>
<th>Expt After Dextran, Mean ± SEM</th>
<th>Average Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pressure, mm Hg</td>
<td>128 ± 6.1</td>
<td>134 ± 4</td>
<td>+6 ± 4</td>
<td>&lt; .2</td>
</tr>
<tr>
<td>Intrarenal venous pressure, mm Hg</td>
<td>14.6 ± 2.0</td>
<td>14.6 ± 3.0</td>
<td>+20 +137</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>RBF, ml/min per g</td>
<td>3.3 ± 0.3</td>
<td>6.9 ± 0.5</td>
<td>+3.6 +110</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Intrarenal resistance, mm Hg/ml per min per g</td>
<td>37.8 ± 6.3</td>
<td>15.2 ± 1.9</td>
<td>-22.6 -60</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>GFR, ml/min per g</td>
<td>55 ± 10</td>
<td>41 ± 0.5</td>
<td>-14 -28</td>
<td>&lt; .1</td>
</tr>
<tr>
<td>Urine flow, al/min per g</td>
<td>16.9 ± 5.3</td>
<td>5.7 ± 1.3</td>
<td>-11.2 -66</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>39 ± 8</td>
<td>21 ± 9</td>
<td>-18 -46</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Plasma colloid osmotic pressure, mm Hg</td>
<td>17.9 ± 88/98</td>
<td>6.6 ± 10.7</td>
<td>+60 +60</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

FIG. 3. Effects of hyperoncotic dextran loading on relationship between arterial pressure and RBF (lower), between arteriovenous pressure difference and RBF (center), and between arterial pressure and intrarenal resistance (upper). Control curves are designated by C. Those designated by E demonstrate effects of infusion of 400 ml of a 12 % dextran in saline solution.

Influence of hyperoncotic dextran loading on renal blood flow recovery patterns. Renal blood flow recovery patterns were observed in five experiments. Figure 4 shows examples of renal blood flow and intrarenal venous pressure recovery responses to a 1-min renal artery occlusion under normal conditions, contrasted with the recovery responses following dextran loading. The dextran infusions markedly increased the steady-state renal blood flow, but the transient responses
to occlusion were similar in several respects. In either condition, a large flow overshoot occurred immediately upon release of the obstruction, followed by transient reduction of flow to less than the preocclusion level and a gradual reestablishment of the steady-state preocclusion level. The changes in the intrarenal venous pressure also reflected this pattern, which was particularly demonstrable following the dextran infusions. These recovery patterns thus demonstrated maintenance of contractile capability even though steady-state resistance and autoregulatory behavior were markedly diminished.

**DISCUSSION**

These experiments demonstrate that infusion of a hyperoncotic dextran solution causes marked alterations in renal hemodynamics. Both renal blood flow and intrarenal venous pressure were increased markedly, but there was little change in the glomerular filtration rate and urine flow was decreased. The arterial pressure-renal blood flow relation changed from one demonstrating renal autoregulatory capacity to one indicative of passive behavior. These results have been evaluated in relation to several mechanisms, including the possibility that dextran infusions in some manner alter renal hemodynamics by affecting the controlling mechanisms normally responsible for the regulation of renal vascular resistance.

Consideration of the mechanisms involved in the renal blood flow autoregulating system encompasses three aspects. First, there must be some sensor capable of recognizing the resultant effects of an alteration in blood flow, and capable of generating a signal in response to these alterations. Second, some transmitting system must exist to carry that signal from the sensor element to the site of regulation. Third, there must be some effector element that responds to the signal by altering renal resistance to return blood flow to the regulated level. Disruption of any of these three components will compromise the ability of the system to adjust renal vascular resistance to compensate for altered renal perfusion pressure. This in turn allows renal blood flow to vary to a greater than normal degree with perfusion pressure changes. In addition, alteration of any of the factors that can affect the steady-state level of the sensed variable will also result in compensatory renal vascular resistance adjustments. This type of disturbance would alter the relationship between blood flow and the sensed feedback variable and could be expected to cause a resetting of the base line flow but allow the system to maintain some ability to adjust resistance with variations in arterial pressure. When a specific disturbance results in decreased resistance, the autoregulatory pressure range would be progressively offset to higher arterial pressures. Under these conditions, autoregulatory behavior might not be observed at arterial pressures normally achieved in these preparations.

Direct vasodilator agents, such as acetylcholine and papaverine, are believed to affect the effector component directly, by making the vascular smooth muscle less capable of altering resistance in response to signals from the sensor elements (2, 6). In addition to the nearly passive renal blood flow-renal perfusion pressure relationship resulting from this effect, infusion of direct vasodilator agents causes two characteristic responses. First, renal blood flow is increased at pressures below, as well as within the autoregulatory range (2). Second, urine flow is always increased if massive diuresis is not established prior to vasodilatation.

It is also possible to diminish renal autoregulatory capacity without directly affecting vascular smooth muscle contractile capability. Such an effect is seen with ureteral occlusion (23). In this case it has been suggested that the flow or composition of fluid in some part of the tubular network is altered and that this disturbance is monitored by the sensor component of the autoregulatory system, resulting in pregglomerular vascular dilation. It should be recognized that this effect on the vascular elements is secondary to the initial disturbance resulting from the ureteral obstruction.

Dextran, like ureteral occlusion, does not affect renal vascular smooth muscle contractile capability. As shown by the blood flow and intrarenal venous pressure recovery patterns in Fig. 4, capability for adjustment of vascular resistance was still present following the dextran infusions, despite reduction of steady-state resistance and loss of autoregulatory capacity. Because the effector component of the system was apparently intact, the observed disruption of blood flow autoregulation must have resulted from some effect on either the sensing or the transmitting component. Two other observations distinguish the responses to dextran infusion from the responses to infusion of direct vasodilator agents. First, urine flow rate was not increased, despite the increase in blood flow. Second, blood flow at perfusion pressures below the autoregulatory range was unchanged or decreased. These are in direct contrast to the effect of infusion of direct vasodilator agents. Thus, it would appear that the mechanism of renal vasodilation in response to the dextran infusions is more complex than that due to vasodilator infusions. The evaluation of certain findings of this study indicates possible mechanisms.

Changes in the pressure-flow relation caused by dextran infusion occurred primarily at pressures within the normal autoregulatory range. It has been shown that intrarenal resistance reaches a minimal value in the normal kidney at pressures just below the autoregulatory range (29), and it is
apparent from the top portion of Fig. 3 that dextran loading did not alter the minimal intrarenal resistance. These observations are interpreted as evidence that infusion of hyperoncotic dextran primarily affects the components of the renal vascular resistance responsible for autoregulation of renal blood flow.

One explanation compatible with the experimental results is that increased colloid osmotic pressure at the glomerular capillary reduces effective filtration pressure and transiently diminishes the glomerular filtration rate. Decreased filtration rate in turn would result in decreased tubular fluid flow and perhaps alter the composition of fluid delivered to some segment of the tubular system (14). The increased peritubular capillary oncotic pressure could augment this effect by increasing the net peritubular fluid reabsorption (6, 16, 29, 32). This alteration in tubular fluid flow or tubular fluid composition could be responsible for elicitation of some feedback signal to effect a decreased predglomerular resistance and an elevated glomerular hydrostatic pressure. In this manner, the increased oncotic pressure would be offset and filtration rate would return toward normal. To the extent that they can be compared, the findings of the present study are in general agreement with those in which concentrated albumin solutions have been infused (4, 8, 10, 26). It has generally been assumed that the concentrated albumin in some manner exerts its effects through changes in the plasma colloid osmotic pressure. The decreased urine flow under these conditions could be partially due to an increased peritubular capillary oncotic pressure which is thought to increase net fluid reabsorption (6, 16, 25, 29, 30, 31).

Leakage of dextran across the glomerular capillaries into the tubular system has been observed previously (7, 10, 11, 28) and could contribute in some indirect manner to the responses observed. Because of the polydispersity of molecular weight, this appears to be a problem common to all dextrans (13). It was apparent in these experiments that some dextran leakage occurred since the urine became quite viscous following the dextran infusions. Measurements of urine colloid osmotic pressures substantiated this observation. Following filtration of dextran molecules, continued reabsorption of tubular fluid could result in concentration of dextran in the tubules, possibly increasing the viscosity of the tubular fluid (13) to such an extent that urine flow would be diminished and tubular pressure would be increased. Assuming that the intrarenal venous pressure can be used as an index of proximal tubular pressure (9), the increased pressure following dextran loading would indicate that the proximal tubular pressure was markedly increased following the infusions. The finding of an increased intrarenal venous pressure associated with a decreased urine flow suggests some degree of tubular obstruction, since one would normally expect to obtain increased urine flows in association with increased intrarenal venous pressures (6, 16). It is possible that increased tubular fluid viscosity and resistance to flow due to concentration of the filtered dextran could lead to decreased tubular fluid flow and increased tubular pressure. This interpretation could also be utilized to explain the marked decrease in renal vascular resistance. The increased tubular pressure could be expected to cause some obstruction at the individual nephron level. The similarity of the present results with those occurring in response to ureteral obstruction provide additional support for this possibility (23). Alteration in tubular fluid dynamics could thus be responsible for the generation of some feedback signal to the predglomerular vessels, resulting in afferent vasodilation and increased glomerular capillary pressure offsetting the increased proximal tubular pressure and tending to bring glomerular filtration rate back toward normal.

Both of the possibilities that have been discussed are in accord with the experimental observations and with the concept that there is a direct association between either tubular fluid flow or some factor directly associated with tubular flow and the level of predglomerular resistance. However, the results of these experiments do not allow us to evaluate which of the above mechanisms could be primarily responsible for the responses that occurred following the infusion of the hyperoncotic dextran solutions.

This investigation was supported by Public Health Service Research Grant HE 11428 and HE 11678.

P. G. Baer is a postdoctoral fellow of the Mississippi Heart Association.

S. L. Wallace is a predoctoral trainee.

Received for publication 16 November 1970.

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