Control of Rat Renal Vascular Resistance at Reduced Perfusion Pressure

PAUL A. JOHNSTON, NANCY S. PERRIN, DAVID B. BERNARD, AND NORMAN G. LEVINSKY

SUMMARY Determination of the factors influencing renal vascular resistance (RVR) at very low perfusion pressures (RPP) is of interest, since prolonged periods of reduced perfusion can lead to acute renal failure. We have studied the effects of inhibition of the renin-angiotensin system on renal blood flow (RBF), measured by electromagnetic flow probe, over a subautoregulatory pressure range of 90-25 mm Hg. These studies were carried out in rats on low sodium diets (LS), in which angiotensin II (AI) is increased, and high sodium diets (HS), in which AI is suppressed. We have also studied the effect of altering the kallikrein-kinin system, since our previous studies have indicated an interaction between this system and AI in control of RVR at normal RPP. Variations in sodium intake did not alter the regression of RBF on RPP over the entire low pressure range, RVR in LS rats increased from 15.8 ± 0.4 between 65 and 90 mm Hg to 21.2 ± 1.2 mm Hg/ml per min at pressures <45 mm Hg (P < 0.05). In HS rats, RVR rose from 13.8 ± 0.5 at RPP between 65 and 90 mm Hg to 18.6 ± 0.9 mm Hg/ml per min at RPP <45 mm Hg (P < 0.001). Saralasin, an AI antagonist, increased RBF, and thus reduced RVR, over the entire low pressure range in LS rats, but had no effect on RVR in HS rats. Captopril, which inhibits the formation of AI as well as the degradation kinins, increases RBF in both LS and HS rats. Aprotinin, an inhibitor of kallikrein, reduced RBF, and thus increased RVR over the entire low pressure range in LS rats. Aprotinin had no effect on RVR in HS rats, but pretreatment with this agent blocked the vasodilatory effect of captopril. Infusion of kinins raised RBF in HS rats but had no effect on RBF of LS rats. We conclude that RVR is not fixed or minimal in the subautoregulatory pressure range. All acts as a vasoconstrictor throughout this low pressure range in LS rats, but its effect is countered by the vasodilator influence of kinins. Neither hormone substantially influenced RVR in HS rats. Parallel changes in the activity of these two hormones maintains a relatively constant RVR despite changes in dietary sodium intake. Circ Res 48: 734-739, 1981

RECENT studies from our laboratory have been focused on the control of renal vascular resistance (RVR) in the rat during hypoperfusion at arterial blood pressures of 40 mm Hg or less (Johnston et al., 1979a). In the course of these studies, we observed that teprotide (SQ20881), an inhibitor of angiotensin-converting enzyme (kininase II) reduced RVR markedly in rats whose kidneys were being perfused at these very low pressures. In recent studies of several antagonists of the renin-angiotensin system, Arendshorst and Finn (1977) report that neither saralasin nor teprotide reduced RVR at perfusion pressures of 65 mm Hg in rats on varying levels of dietary sodium intake. At normal or elevated perfusion pressures, renal vascular response to these blockers depended on sodium intake. In low sodium rats, both teprotide and saralasin reduced RVR whereas, in high sodium rats, neither agent affected RVR. Elevated sodium intake has been shown to greatly inhibit the renin-angiotensin system, even when renal perfusion pressure (RPP) is reduced (Hall et al., 1977; Fray et al., 1977; Mason et al., 1979). In contrast, reduced sodium intake produces significant stimulation of the renin-angiotensin system (Flamenbaum and Hamburger, 1974; Granger et al., 1972). Because clarification of the role of various hormones in control of RVR at very low perfusion pressure may improve our understanding of the pathogenesis of the "pre-renal" type of acute renal failure, we have more fully evaluated the renal vascular action of saralasin and captopril over a subautoregulatory pressure range from 90 to 25 mm Hg in rats maintained on high and low sodium diets. In addition, we have studied the role of the kallikrein-kinin system, since recent work from our laboratory has demonstrated the importance of the balance between angiotensin II (AI) and kinins in controlling RVR at normal perfusion pressures in rats on varying sodium intake (Johnston et al., 1981).

Methods

Charles River CD rats, weighing 220-350 g, were placed on two diets of varying sodium content. Group I (HS) consumed normal laboratory chow and drank 1.7% NaCl. Each rat received 5 mg deoxycorticosterone acetate (DOCA) in one weekly injection. These rats remained on this diet for a period of at least 3 weeks, and were studied no sooner than 1 week after the final DOCA injection.
Group II rats (LS) consumed low sodium chow (Purina laboratory rat chow, Na+ = 9 μEq/g) and drank distilled water. These rats also remained on this diet for a period of 3 weeks prior to study.

Rats were anesthetized, intraperitoneally, with ketamine hydrochloride (100 mg/kg) and inactin (25 mg/kg). Body temperature was maintained between 36 and 38°C. Isotonic saline was infused continuously through a jugular vein catheter at 0.04 ml/min, and renal perfusion pressure (RPP) was monitored through a catheter placed in the femoral artery and attached to a strain gauge pressure transducer and recorder. The left kidney was isolated through a suprapubic incision, the renal artery dissected free from its attachments, and the kidney placed in a Lucite cup. Renal blood flow (RBF) was monitored continuously with an electromagnetic flow probe system (EP 401.5, model meter 501, Carolina Medical Electronics). Blood flow zero was determined periodically by completely occluding the renal artery distal to the probe (Johnston et al., 1979b).

To assess the pressure-flow relationship in the subautoregulatory range, we reduced arterial pressure progressively by placing a clamp on the aorta above both renal arteries. Observations at 4–7 different pressure levels between 90 and 25 mm Hg are reported. Flow was allowed to stabilize for 2–5 minutes at each pressure level before observations were recorded. Typically, a series of pressure-flow relations (observations at 4–7 different pressures) was determined twice before and twice after an experimental maneuver. Between each series of pressure-flow determinations, the aorta was unclamped and RPP allowed to stabilize at a level which averaged 106 ± 2 mm Hg.

Four different agents were administered intravenously to rats in each diet group. The drugs were given initially while the kidney was being perfused normally and continued in the following doses throughout the pressure-flow determinations. Saralasin, a competitive inhibitor of angiotensin II, was infused at 3–4 μg/kg per min. Captopril, a converting enzyme inhibitor, was given as injections of 250 μg every 30–45 minutes (2–3 injections/rat). Aprotinin, (Boehringer-Mannhein) used to inhibit kallikrein, was given as a priming dose of 15 × 10^3 kallikrein inhibitor units (KIU), followed by an infusion of 150 KIU/min. Kinins (bradykinin, ICN Pharmaceuticals, or lysyl-bradykinin, Protein Research Foundation) were infused at 4 μg/kg per min. Pressure-flow measurements over the range of 90–25 mm Hg were made 30–60 minutes after administration of each agent was begun. Adequacy of the doses of saralasin and captopril as angiotensin inhibitors, and aprotinin as an inhibitor of kallikrein, was tested in separate studies. Angiotensin I (AI), infused at 100–200 μg/min, increased blood pressure by 32.1 ± 6 mm Hg, in eight rats and decreased RBF by 1.6 ± 0.2 ml/min. in four rats maintained on a high sodium intake. The same dose of AI caused blood pressure to rise by 21.5 ± 3 mm Hg in nine rats and RBF to fall by 1.2 ± 0.2 ml/min in five rats maintained on a low sodium intake. Captopril inhibited 93 ± 3% of the blood pressure elevation in four rats on high salt, and 96 ± 2% in five rats on low salt diets. The effect of AI on RBF was completely eliminated (100 ± 1%) in the four rats (two on each diet) in which it was studied. Saralasin inhibited 80 ± 3% of the blood pressure elevation in eight rats on each diet. The reduction in RBF due to AI was inhibited by 90 ± 3% in four rats on low salt, and 75 ± 1% in three rats on high salt intake. In five HS and six LS rats, aprotinin completely eliminated measurable kallikrein activity from urine. Urinary kallikrein was determined by the method of Chung et al. (1979).

The relation of pressure and flow before and after a specific intervention was determined by regression analysis of all individual pressure-flow measurements in all rats in the experimental series. The statistical significance of differences between pressure-flow regressions before and after an intervention was determined by covariance analysis, which provided an “adjusted mean RBF” (Snedecor and Cochran, 1967). This represents mean RBF over the entire pressure range when the effect of pressure variation is held constant. A P < 0.05 was considered to be significant.

**Results**

Figure 1 describes the relation between pressure and flow for HS and LS rats over the range 90–25 mm Hg. Mean adjusted RBF for the entire pressure range was 3.6 ml/min for HS rats and 3.7 ml/min for LS rats. These were not different by covariance analysis. Likewise, the slopes of the two regression lines (equations given in Fig. 1) were not different. Individual RBF-RPP observations from all rats in

![Figure 1](http://circres.ahajournals.org/)

**Figure 1**  Effect of dietary salt intake. Open points and broken line, high salt (n = 13); solid points and lines, low salt; (n = 15). Regression equation for high salt is, y = 0.09 x −1.08; for low salt is, y = 0.08 −1.0.
both LS and HS were used to calculate mean RVR at pressures less than 45 mm Hg and between 65 and 90 mm Hg. In LS rats, RVR rose from a value of 15.8 ± 0.4 (n = 36) at pressures between 65 and 90 mm Hg to 21.2 ± 1.2 mm Hg/ml per min (n = 27) at pressures less than 45 mm Hg. This change was significant (P < 0.001). In HS rats, RVR rose from a value of 13.8 ± 0.5 (n = 34) at pressures between 65 and 90 mm Hg to 18.6 ± 0.9 mm Hg/ml per min (n = 43) at pressures less than 45 mm Hg. Again this change was significant (P < 0.001).

Figure 2 shows the effect in HS rats of treatment with saralasin and captopril over the pressure range 90–25 mm Hg. Saralasin had no significant effect. The adjusted mean RBF values from covariance analysis were 3.7 and 4.1 ml/min for control and experimental data, respectively; the slopes of the regression lines were not different. In contrast, captopril caused a significant increase in the adjusted mean RBF from 3.9 to 5.5 ml/min (P < 0.001). The slopes of the two regression lines were not different. Data from the captopril study were also analyzed for RPP of 65 mm Hg and below. Over this pressure range, as well, captopril caused a significant rise in RBF (decreased RVR). Adjusted mean RBF rose from 2.9 to 4.3 ml/min (P < 0.001).

Figure 3 shows the effect of saralasin and captopril on RBF in LS rats over the same low pressure range. Both agents caused a significant increase in adjusted mean RBF from 3.5 to 5.3 and from 3.1 to 5.5 ml/min, respectively (P < 0.001 for both). The slopes for both regression lines after drug treatment were significantly greater than the respective controls (P < 0.05). The vascular response to captopril was not statistically different from the response to
The vascular response to each agent was also analyzed at a pressure equal to or less than 65 mm Hg. Treatment with saralasin resulted in an increase in the adjusted mean RBF from 2.2 to 4.2 ml/min (P < 0.001), and captopril from 2.6 to 4.2 (P < 0.001). Thus, both agents caused a rise in RBF (decreased RVR) over the very low perfusion pressure range as well.

Figure 4 describes the relation between RPP and RBF in LS rats before and after treatment with aprotinin. Adjusted mean RBF fell from 3.5 to 3.0 ml/min, a small but significant effect (P < 0.001), after treatment with aprotinin. The slopes of the two regression lines were not different. At pressures of 65 mm Hg and below, aprotinin also reduced adjusted mean RBF from 2.6 to 2.2 ml/min (P < 0.05). Thus, treatment with aprotinin resulted in a fall in RBF (an increase in RVR) at very low pressures as well. In two HS rats (data not shown), aprotinin, while having no effect on the RPP-RBF relation, eliminated the vasodilator effect of captopril (see Fig. 2).

Figure 5 summarizes the effect on RBF of kinin infusion during reduction in RPP. Kinin infusion resulted in marked vasodilation in HS rats. Adjusted mean RBF rose from 3.7 to 4.9 ml/min (P < 0.001). The slopes of the two regression lines were not different. Vasodilation also occurred at pressures of 65 mm Hg and below. Adjusted mean RBF increased from 3.0 to 4.2 ml/min (P < 0.001). In LS rats, however, kinin infusion failed to elicit a response at any subautoregulatory perfusion pressure.

**Discussion**

As renal perfusion pressure is reduced within the autoregulatory range, RVR decreases progressively (Thurau, 1964; Rothe et al, 1971; Johnson, 1974; Arendshorst et al., 1975). At lower perfusion pressures, in the range of 90–60 mm Hg, RBF falls more or less in proportion to RPP so that RVR appears to be constant. Failure of the renal vasculature to respond to certain vasodilators, such as papaverine (Thurau, 1964), has been interpreted to mean that RVR is minimal and fixed in this lower pressure range. The results of the present study confirm and extend previous observations from our laboratory, and by others, that RVR is not fixed and minimal in the subautoregulatory pressure range of 90–25 mm Hg. Studies in the rat and dog have shown that RVR can be reduced by isoncotic volume expansion (Robertson et al., 1972), by extracellular volume...
expansion with mannitol (Johnston et al., 1979b), or by the administration of vasodilators such as acetycholine and prostaglandin E₂ (Baer and Navar, 1973). We now report that both saralasin and captopril lower RVR throughout the subautoregulatory pressure range in rats on a low sodium diet.

Our present data also confirm and extend our earlier observations, and those of other investigators, that RVR increases in the lower range of subautoregulatory pressures (Nahmod and Lenari, 1964; Robertson et al., 1972; Arendshorst et al., 1975; Navar, 1978; Johnston et al., 1979b). In recent observations in our laboratory, RVR of rats on a normal sodium diet rose from 17.4 ± 0.4 at normal RPP to 30.4 ± 1.6 mm Hg/ml per min after 30-45 minutes of hypoperfusion at 40 mm Hg.* In the present study RVR of HS rats increased from 13.8 ± 0.5 at RPP between 65 and 90 mm Hg to 18.6 ± 0.9 mm Hg/ml per min at pressures equal to or less than 45 mm Hg (P < 0.05). In LS rats, RVR increased from 15.8 ± 0.4 at RPP between 65 and 90 to 21.2 ± 1.2 mm Hg/ml per min at pressures of 45 mm Hg or less (P < 0.005). These values of RVR at very low RPP for both groups are significantly less than RVR of rats on a normal sodium diet after 30-45 minutes of hypoperfusion (P < 0.001). Since in the present study hypoperfusion at very low RPP was carried out for 10–15 minutes, and in our previous observations the duration of hypoperfusion was 30-45 minutes, these data taken together suggest that RVR may increase progressively with increased duration of hypoperfusion. The factors responsible for this increased resistance have not been delineated. Our observations in LS rats, and those of others (Arendshorst and Finn, 1977), on the effect of saralasin on RVR at reduced RPP suggest that the renin-angiotensin system may be involved in the increased RVR. However, an increase in RVR also occurred in HS rats, in which the renin-angiotensin system is known to be suppressed even when RPP is reduced (Hall et al., 1977; Mason et al., 1979). Further, saralasin failed to have an effect in HS rats, indicating no role for the renin-angiotensin system in this phenomenon. Neither does the kallikrein-kinin system appear to be involved in the increased RVR at reduced RPP. Increased RVR at very low RPP would have to be the result of a reduction in the activity of the system. However, aprotinin caused vasoconstriction in LS rats at very low RPP, indicating a significant vasodilator effect of the system. In HS rats, aprotinin failed to have an effect at any pressure level, ruling out a role for the kallikrein-kinin system in the increase in RVR in this group of rats. Thus, the current studies do not define the factors responsible for this phenomenon. However, since prolonged periods of partial ischemia may lead to acute renal failure (Stein et al., 1978), elucidation of factors influencing RVR at greatly reduced RPP is important.

Our present observations suggest that the renin-angiotensin and kallikrein-kinin systems may be important determinants of RVR in sodium-restricted rats in the subautoregulatory pressure range. In LS rats both saralasin and captopril caused vasodilation over the entire low pressure range. Therefore, since AII appeared to play a significant role in determining renal vascular tone in these rats, the observation that alterations in sodium intake which dramatically affect the activity of the renin-angiotensin system (Granger et al., 1972; Flamenbaum and Hamburger, 1974; de Rouffignac et al., 1974; Arendshorst and Finn, 1977; Hall et al., 1977) did not reduce RVR indicates that some factor must be antagonizing the vasoconstrictive effect of angiotensin II. It is well documented in rats and humans that urinary kallikrein activity is increased by low sodium intake (Margolius, 1974; Johnston et al., 1976).

In a recent study (Johnston et al., 1981), we observed a significant elevation of urinary kallikrein activity in LS rats confirming these previous observations. In addition, aprotinin increased RVR in LS rats whose kidneys were normally perfused. In the present study, inhibition of kallikrein by aprotinin in LS rats increased RVR to a small but significant extent at sub-autoregulatory pressures (Fig. 4). These data suggest that, in sodium-restricted rats during hypoperfusion, kallikrein is liberating physiologically significant amounts of kinins which antagonize the vasoconstrictor effect of AII. Further support for this hypothesis is the resistance to the vasodilator action of kinins in sodium-restricted rats (Fig. 5). We have previously found in experiments at normal RPP that resistance to kinins in sodium-restricted rats is overcome by blockade of endogenous kinin synthesis with aprotinin (Johnston et al., 1981). These data indicate that resistance to the vasodilator action of kinins is probably due to supra-maximal activity of endogenous kinins caused by sodium restriction. Thus, our present data at sub-autoregulatory pressures are in agreement with our more extensive observations at normal RPP. We suggest that enhanced activity of the kallikrein-kinin system balances increased angiotensin activity and maintains RVR constant during wide variations in sodium intake both at normal and at sub-autoregulatory pressures.

In rats on high sodium intake, saralasin did not alter RVR (Fig. 2). This is consistent with the concept that AII is suppressed in such rats, even when RPP is acutely reduced. On the contrary, captopril reduced RVR throughout the sub-autoregulatory range. Since aprotinin, a kallikrein inhibitor, blocked this vasodilatory effect of captopril, it seems likely that the effect is mediated by the ability of captopril to potentiate kinins by inhibiting

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* RVR = 30 ± 1.6 mm Hg/ml per min represents observations from the last 40 rats studied after 30-45 minutes of hypoperfusion. These animals were studied subsequent to those used in our original study (Johnston et al., 1979b) in which we observed an RVR after 30 minutes of hypoperfusion of 53.1 ± 3.2 mm Hg/ml per min.
kininase II. This observation plus the fact that kinins are effective vasodilators in rats on a high sodium diet, fits the hypothesis that endogenous kinin activity is low in these rats. These observations, as well, are consistent with our more extensive observations at normal RPP.

Most of our observations confirm and extend those reported by Arendshorst and Finn (1977) on the effects of saralasin and the converting enzyme inhibitor, teprotide, on RBF at pressures within and immediately below the autoregulatory range. However, there are two points of disagreement. First, they report no significant effect of either saralasin or teprotide, on RBF, and therefore RVR, at pressures of 65 mm Hg in rats on high or low sodium intake. However, they did not study RBF at pressures below 65 mm Hg. Observations from the two studies are in agreement at pressures above 75 mm Hg. Second, they report no effect of teprotide on RBF at any perfusion pressure in rats on a high sodium diet. The reasons for these differences are unclear. Small variations in protocol may be important; for example, they used a different converting enzyme inhibitor, and their rats were subjected to carotid artery occlusion to generate high arterial pressures.

In conclusion, we have confirmed that RVR is neither fixed nor minimal in the sub-autoregulatory pressure range. As at normal arterial pressures, the RVR at reduced RPP is, in part, controlled by the balance between AII and kinins. Variations in sodium intake alter the degree of hormonal influence but have little effect on RVR. However, RVR can be manipulated by administration of agents that alter the activity of either of these hormone systems. Since renal ischemia appears to be a factor in the pathogenesis of acute renal failure, pharmacological tools which alter RVR at very low pressures are of pathophysiological and therapeutic interest.

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References

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