Interactions between Intrarenal Epinephrine Receptors and the Renal Baroreceptor in the Control of PRA in Conscious Dogs

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SUMMARY. We investigated the relationship between plasma renin activity (PRA) and renal arterial pressure (RAP) during (1) control conditions, (2) intravenous epinephrine infusion, and (3) intrarenal epinephrine infusion. In five uninephrectomized conscious dogs maintained on a low-salt diet, we controlled the RAP with an inflatable constricting cuff around the renal artery. (1) The control stimulus-response curve of the renal baroreceptor consists of a relatively flat section (slope = -0.03 ng Al/ml/hr per mm Hg) at RAP's close to control pressure and a much steeper section (slope = -0.48 ng Al/ml/hr per mm Hg) at RAP's below a threshold pressure of approximately 75 mm Hg. (2) Intravenous infusion of epinephrine at a dose that yields physiological plasma concentrations shifts the stimulus-response curve to the right by 10-15 mm Hg without altering either slope. (3) Intrarenal epinephrine infusion also displaces the stimulus-response curve to the right; intrarenal and intravenous epinephrine infusions that produce similar renal arterial epinephrine concentrations shift the response curve by the same amount. (4) However, as previously reported, intravenous administration of epinephrine decreases mean aortic pressure (MAP) (93 to 88 mm Hg, P < 0.05) and increases PRA (1.1 to 1.6 ng Al/ml per hr, P < 0.05), while intrarenal epinephrine has no effect on either MAP or PRA. Taken together, these results demonstrate that both infusions act intrarenally, increasing the threshold pressure, but that only intravenous epinephrine has an additional systemic effect, lowering MAP and, therefore, RAP. The combination of an increase in threshold pressure and a decrease in RAP causes the RAP to fall below the threshold pressure, raising PRA. These observations explain why PRA increases during intravenous but not intrarenal infusion. (Circ Res 50: 477-485, 1982)

THESE experiments were designed to address two questions raised by Vander's early report (1965) that intravenous infusions of epinephrine increase renal venous renin activity. The first question deals with the site of action of circulating epinephrine: is it within the kidney or elsewhere in the body? The second, and perhaps more fundamental, question deals with the physiological systems controlling renin secretion. Adrenergic agonists alter blood pressure through a variety of mechanisms, and, at first thought, it seems quite reasonable that epinephrine should also increase plasma renin activity (PRA). On the other hand, there are clearly many situations, such as mild hypoglycemia, in which plasma epinephrine is elevated in response to a stimulus other than a decrease in blood pressure. Does the system which regulates PRA have the flexibility to adapt to these various requirements, or are elevated levels of plasma epinephrine invariably associated with high PRA's? This paper will attempt to answer both of these questions.

Vander and others have clearly demonstrated that intravenous infusions of epinephrine increase renal venous renin activity (Vander, 1965; Otsuka et al., 1970; Tanigawa et al., 1970). However, it is not clear that this direct intrarenal adrenergic pathway, generally characterized under nonphysiological conditions and at high pharmacological concentrations of β-agonists, is the mechanism through which intravenous infusions of epinephrine act to increase PRA in vivo. Although intrarenal infusions of epinephrine or isoproterenol increase renin release in anesthetized dogs (Wathen et al., 1965; Ayers et al., 1969; Winer et al., 1971; Johnson et al., 1971, 1976), intravenous isoproterenol is more potent than intrarenal isoproterenol in increasing renin secretion (Reid et al., 1972; Johnson et al., 1976). In addition, experiments from our laboratory have demonstrated that epinephrine infusions that produce systemic plasma concentrations within the high physiological range consistently increase PRA, whereas intrarenal infusions of epinephrine that produce similar renal arterial epinephrine concentrations do not affect PRA (Johnson et al., 1976). Since selective stimulation of intrarenal receptors at these concentrations of epinephrine did not raise renin levels, we concluded that the action
of systemic infusions of epinephrine to elevate PRA was not mediated through intrarenal receptors alone. Further investigations led us to conclude that this rise in PRA was not mediated solely through the drop in mean aortic pressure caused by these systemic levels of epinephrine or through changes in renal nerve activity, hematocrit, plasma potassium concentration, or prostaglandin levels (Johnson et al., 1979b). Since earlier work (Eide et al., 1974; Ayers et al., 1969) had suggested that isoproterenol was more potent in increasing renin secretion at lowered renal arterial pressures, we investigated the possibility that the effect of systemic epinephrine infusions on PRA is mediated through an interaction between the renal baroreceptor and intrarenal epinephrine receptors. The results of this study demonstrate that such an interaction can explain the effects of intravenous infusions of epinephrine without requiring any extra-renal \( \beta \)-adrenergic pathways directly affecting renin secretion other than a vasodilation causing a drop in mean aortic pressure.

**Methods**

**Animal Preparation**

Five male mongrel dogs (24–34 kg) were trained to lie quietly for 3 hours on a padded table. Then, in a sterile procedure during which intravenous pentobarbital anesthesia was used (J.A. Webster), catheters were implanted in the aorta, inferior vena cava and one renal artery, as described by Herd and Barger (1964), and an inflatable silastic cuff (Hazen Everett) was placed around the renal artery proximal to the tip of the renal arterial catheter. The contralateral kidney was removed. In four of the five dogs, a noncannulating electromagnetic flowmeter (Zepeda Instruments) was placed around the renal artery proximal to the inflatable cuff.

At least 2 weeks before any experiments, the dogs were placed on a low-salt diet containing 10 mEq sodium/day (Riviana Food Supply, Hill Division) and given 40 mg BID of furosemide (Hoechst-Roussel) orally for 3 days. Total urinary collections were analyzed to determine daily urinary sodium excretion, which ranged between 2 and 6 mEq sodium/day when in balance.

**Experimental Protocols**

Three types of experiments were performed in randomized order within any set of renal perfusion pressures:

1. **Decreased renal perfusion pressure alone:** On the day of an experiment, the dog was brought into the experimental room and made to lie down on a padded table. The flow probe was connected to external leads and the aortic and renal arterial catheters were connected to Statham P23Dc pressure transducers. An infusion of furosemide (Hoechst-Roussel) orally for 3 days began through the renal arterial catheter at a rate of 0.2 ml/min. After 25 minutes, blood samples were drawn for PRA and renin activity. An infusion of 5% dextrose was begun through the renal arterial catheter at a rate of 0.2 ml/min.

   A typical experiment is illustrated in Figure 1. After a 20-minute control period, blood samples (3 ml) were drawn 5 minutes apart through the aortic catheter for later determination of plasma catecholamine concentration and renin activity.

   At this time, the catheter leading to the constrictor cuff was connected to a micrometer syringe filled with sterile water. The cuff was inflated to decrease the renal perfusion pressure (RPP) by a predetermined amount, 15, 20, or 25 mm Hg. The perfusion pressure was kept constant during the experimental period by adding or withdrawing fluid from the cuff. After 30 minutes, when the mean aortic pressure (MAP) and renal blood flow (RBF) had stabilized, two blood samples (3 ml each) were drawn for PRA five minutes apart; a blood sample for plasma catecholamines (5 ml) was drawn with the last PRA sample. After this, the catheters were flushed with 5% dextrose, the baselines were checked, and the infusion into the renal artery was stopped temporarily to ensure that it did not affect the readings of RPP or RBF. Then, if the dog was still quiet, the cuff was inflated further to decrease the perfusion pressure by an additional 15 mm Hg and the procedure was repeated. In this manner, the RPP was decreased in 15 mm Hg steps until the dog became restless or until the next constriction would have resulted in a perfusion pressure less than 40 mm Hg. During a typical experiment, 40–50 ml of blood would be taken from an animal. At the end of the experiment, the blood cells were suspended in 5% dextrose and returned to the dog.

2. **Decreased renal perfusion pressure during intravenous epinephrine infusion:** In these experiments an infusion of epinephrine (125 \( \mu \)g/kg per min, 0.2 ml/min) as the hydrochloride (Adrenalin, Parke-Davis) was begun through the inferior vena caval catheter at the end of the control period and continued throughout the experiment. During the first experimental period, the cuff was not inflated, so that mean aortic and renal arterial pressures were equal. After 25 minutes, blood samples were drawn for PRA and catecholamines. Then the micrometer syringe was connected and the renal perfusion pressure was decreased as described above.

3. **Decreased renal perfusion pressure during intrarenal epinephrine infusion:** The protocol for these experiments was similar to the one described above, except that the epinephrine infusion was through the renal arterial catheter,
replacing the infusion of 5% dextrose. The initial rate of infusion was 0.2 ml/min at a concentration calculated to yield a total dose of 25 ng/kg per min. During the experiment, as the progressive reduction in RPP caused the RBF to decrease, the rate of the intrarenal epinephrine infusion was adjusted to keep the renal arterial epinephrine concentration constant. Measured epinephrine levels are shown in Table 1. In the one dog without a flow probe, the rate of the intrarenal infusion was adjusted, assuming that the RBF was constant at RPP's above 70 mm Hg and was a linear function of RPP below 70 mm Hg.

**Assays**

Blood samples were drawn into 5-ml EDTA Vacutainer tubes for the PRA assay and into chilled 5-ml Vacutainer tubes containing 10 mg EGTA and 6 mg reduced glutathione for the catecholamine assay. The tubes were kept on ice for less than 10 minutes until they could be spun in a refrigerated centrifuge to remove cells and platelets. Plasma samples were frozen until the assays were performed.

PRA was measured by the method of Haber et al. (1969); the results are expressed as nanograms of angiotensin I generated per ml of plasma per hour. Plasma concentrations of epinephrine were measured with a commercially available kit (Cat-A-Kit, Upjohn Diagnostics). In this assay, the enzyme catechol-O-methyl transferase is used to catalyze the addition of a $^3$H-methyl group to epinephrine. The product, $^3$H-metanephrine, is separated by thin layer chromatography from other catecholamine derivatives, oxidized to $^3$H-vanillin, extracted and quantified by liquid scintillation counting. Endogenous catecholamine levels in a plasma sample are determined by comparison with a duplicate sample containing an added 100 pg of epinephrine as an internal standard.

**Calculations**

For each experimental protocol in each dog, all determinations of PRA within a 5 mm Hg interval of renal arterial pressure were averaged; there were three to six experiments per protocol per dog. By plotting the mean PRA against the mean RAP for each interval, we obtained a stimulus-response curve for the renal baroreceptor of that dog (Fig. 2). For purposes of analysis, two straight lines were fitted to each of the curves by standard regression techniques. The intersection of these two lines was defined as the threshold pressure. Comparisons between slopes and intercepts of these lines for the different protocols were performed using the analysis of covariance technique for comparison of regression lines described in Snedecor and Cochran (1978). Direct comparison of PRA levels between different protocols was performed with paired t-tests, pairing mean PRA values obtained within a given 5 mm Hg RPP interval within each dog.

**Results**

Figure 1 illustrates the changes in MAP, PRA, and heart rate (HR) during a typical progressive renal artery constriction which lowered RPP to 70, 55, and 40 mm Hg. The MAP, PRA, and HR reached a steady state at the end of the 35-minute period at each RPP; in preliminary experiments, extending the time at each RPP did not produce significant changes in any of the variables. From a series of such experiments in a single dog, taking the renal arterial pressure to different levels on different days, we could obtain a renal baroreceptor stimulus-response curve by plotting the PRA for all points falling within a 5 mm Hg interval of renal arterial pressure. Such a graph for one of the dogs is shown in Figure 2, where the 11 points shown were obtained from 31 separate determinations of PRA. The two points at the highest renal arterial pressures represent values of PRA at control pressures, whereas all the other points are the results of lowered renal arterial pressures produced by inflating the cuff around the renal artery. Clearly, small reductions of the RPP below control do not affect the PRA significantly, but there is a critical (threshold) renal arterial pressure, approximately 10–20 mm Hg below the animal’s control pressure, below which PRA is a steep and approximately linear function of the RPP. Four parameters describe such a graph: the threshold pressure, the baseline PRA, and the slopes of the lines above and below the threshold pressure (Table 2). Within any one dog, these parameters were relatively stable over periods of days to weeks; the

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Epinephrine concentration in renal arterial plasma (pg/ml) before and during renal artery constriction during (a) intrarenal dextrose infusion, (b) intravenous epinephrine infusion at 125 ng/kg per min, and (c) intrarenal epinephrine infusion at a rate adjusted to keep renal arterial epinephrine concentrations approximately equal to those produced by the intravenous epinephrine infusion.
Renal artery pressure (mmHg)

**FIGURE 2.** Stimulus-response curve of the renal baroreceptor in one dog on a low-salt diet. Individual steady state values of plasma renin activity, obtained from experiments such as the one illustrated in Figure 1, were averaged within each 5 mm Hg range of renal arterial pressure. Two straight lines were fitted by standard regression techniques.

Points shown in Figure 2 were obtained from four experiments performed over a period of 2 weeks. Although these curves were qualitatively similar in all dogs, all these parameters varied quantitatively from dog to dog, as shown in Table 2. The averaged values from 20 experiments, in which over 150 separate determinations of plasma renin activity were made in five dogs, are shown in Figure 3, and clearly follow a similar pattern, with a plateau region, a threshold pressure, and a linear relationship between the renal arterial pressure and the PRA below the threshold pressure.

In the next series of experiments, the renal arterial pressure was decreased in a step-wise fashion, as in the previous protocol, but in the presence of an intravenous infusion of epinephrine. Epinephrine was infused at 125 ng/kg per min, producing plasma epinephrine concentrations similar to those produced by hemorrhage or insulin-induced hypoglycemia, as reported in a previous paper from this laboratory (Johnson, 1979a). The averaged stimulus-response curves for the five dogs are shown in Figure 4, where the points shown were obtained from 115 individual determinations of PRA in 19 experiments. Above threshold pressures, the PRA during an epinephrine infusion (Fig. 4, solid curve) is not statistically different from the PRA during a dextrose infusion (Fig. 4, dashed curve) at the same pressure. However, in each of the five dogs, the values of PRA below the threshold pressure were significantly greater during the intravenous epinephrine infusion (*P < 0.01*), as were the intercepts of the regression lines fitted to these points (*P < 0.05*) and the threshold pressures (*P < 0.05*); the slopes of the lines, however, were not significantly different. All of these effects may be described as a shift to the right of the stimulus-response curve during the intravenous epinephrine infusion.

During the first experimental period, the cuff around the renal artery was not inflated while the epinephrine was infused intravenously. In the five dogs, the systemic epinephrine infusion alone caused a drop in the mean blood pressure (from 93 to 88 mm Hg, *P < 0.05*), an increase in the heart rate (from 71...
to 110 beats/min, $P < 0.05$), and an increase in the PRA (from 1.1 to 1.6 ng Al/ml per hr, $P < 0.05$). This comparison between the PRA at two different conditions and pressures (dextrose infusion at 93 mm Hg compared to epinephrine infusion at 88 mm Hg) is different from that made in the previous paragraph between the two conditions at the same pressures.

In the final series of experiments, epinephrine was infused into the renal artery while the RPP was decreased. The initial rate of infusion was 25 ng/kg per min, which produced renal arterial epinephrine concentrations similar to those seen during the intravenous epinephrine infusions at 125 ng/kg per min (Table 1). During the experiment, the rate of the infusion was adjusted to keep the renal arterial epinephrine concentration constant. In one dog with two renal arterial catheters, epinephrine was infused into the proximal catheter and serial samples for plasma catecholamines were drawn through the distal catheter during the progressive constriction. As Table 1 shows, the renal arterial plasma epinephrine levels are approximately equal despite the decreased renal perfusion pressure. There was no measurable systemic spillover from the intrarenal epinephrine infusion. During control periods, the average plasma epinephrine concentration was 47 ± 32 pg/ml; during intrarenal epinephrine infusion, the systemic plasma epinephrine concentration was 47 ± 14 pg/ml.

The averaged results from this series of experiments are shown in Figure 5 and are similar to those produced by the intravenous epinephrine infusions. Paired $t$-tests, comparing the PRA's at each renal arterial pressure above the threshold value, demonstrated that the intrarenal epinephrine infusions had no significant effect on PRA at pressures above threshold. The PRA's at RPP's below the threshold pressure were significantly elevated with intrarenal epinephrine infusions, as with the intravenous infusions, and the threshold pressures were significantly greater during the intrarenal epinephrine infusion (both $P < 0.01$). The slopes of the regression lines were not significantly different. Thus, intrarenal epinephrine also causes the stimulus-response curve to shift to the right.

During the first experimental period, when the cuff around the renal artery was not inflated, intrarenal infusion of epinephrine alone caused no significant change in the mean blood pressure (from 94 to 97 mm Hg, $P > 0.05$), heart rate (from 70 to 73 beats/min, $P > 0.05$), or in PRA (from 0.7 to 0.9 ng Al/ml per hr, $P > 0.05$).

When we compared the intrarenal and intravenous infusions of epinephrine, we found that the effects on the PRA at any renal arterial pressure were not significantly different in any of the five dogs (Fig. 6). Paired $t$-tests comparing the PRA's at each pressure...
in all the dogs showed no difference between the two infusions, and the regression lines fitted to the values of PRA below the threshold pressures had similar slopes and intercepts. The threshold pressures, as well, were not significantly different in the intravenous and intrarenal infusions (Table 2).

Discussion

This study allows us to draw a number of conclusions that could not be deduced from most of the earlier work, in which the renal perfusion pressure was generally kept at a constant level throughout the experiment or else not controlled at all. Clearly, the conclusions drawn from these earlier investigations could be inconsistent if the experiments were performed at different RPP's. In addition, our analysis not only allows us to conclude that there is an interaction between the renal baroreceptor and a renal epinephrine receptor, but, because it examines a range of pressures, also allows us to describe that interaction in some detail.

The shape of the stimulus-response curve of the renal baroreceptor under control conditions is typical of many biological systems and similar to that predicted by Fray's stretch receptor model for renin release (1976). Schematically, it can be divided into two ranges of pressures, one in which the PRA is relatively unresponsive to changes in the RPP, and another in which small changes in perfusion pressure cause large changes in the PRA. The control MAP of these dogs ranged between 90 and 100 mm Hg, and the slope of the stimulus-response curve was relatively shallow over a range of 10 to 20 mm Hg below the control pressure. This does not imply that the renin-angiotensin system is not involved in the control of blood pressure under normal circumstances; in four of the five dogs, the slope of the stimulus-response curve was negative in this range, suggesting that small changes in PRA do occur as a result of changes in the perfusion pressure around control levels. Although these changes in PRA are much less than those seen at the lower pressures, they may still have important effects on blood pressure and renal function, particularly in cases (such as a high-salt diet) in which animals are more responsive to angiotensin.

One must remember that our experiments were performed on dogs maintained on a low-salt diet, a condition in which renin release is stimulated. The value of the threshold pressure varied from dog to dog (between 70 and 85 mm Hg), as did the sensitivity of the stimulus-response curve for pressures below the threshold value (between -0.20 and -0.80 ng Al/ml per hr per mm Hg). Thus, although the form of the stimulus-response curve was constant...
in each of the dogs, it is difficult to predict the exact shape of the curve for any individual animal. This inter-animal variation may reflect the many other stimuli, such as salt state, basal plasma catecholamine levels, and renal nerve activity, that affect the stimulus-response relationship and which vary from dog to dog.

The stimulus-response relationship seems to be quite different in anesthetized animals following recent surgical trauma. Most acute experiments done under anesthesia have control values of PRA and RPP that are much larger than those of our conscious dogs. Thus, the stimulus-response curves of these experimental preparations seem different from those obtained in unstressed animals. A direct examination of the relationship between RPP and renin secretion in acutely anesthetized, surgically prepared, decapitated dogs by Cowley and Guyton, in 1972, reports results which differ from ours in three respects: (1) there is no plateau phase at the higher renal arterial pressures, (2) the control values of PRA (at perfusion pressures of 100 mm Hg) are much greater than those seen in trained conscious dogs, and (3) in their experiments, arterial renin activity and renin secretion decreased at RPP's below 50 mm Hg. Clearly, there are a number of differences between the two preparations: the authors suggest, among others, the presence of anesthetic agents, the recent surgical trauma, and the constant norepinephrine infusion given to raise blood pressure.

It is possible to reconcile some of the discrepancies between our experiments and those of Cowley and Guyton within the framework put forward in this paper by postulating that the stimulus-response relationship is shifted far to the right in their preparation, raising the threshold value for renin release above 100 mm Hg. This would imply that their control points are already on the steep part of the stimulus-response curve, explaining both the lack of a plateau region and the high initial renin levels. Further evidence supporting this hypothesis can be found in the reports of Fojas and Schmid (1970) and Schmid (1972). These investigators reported that in anesthetized, acutely surgically prepared dogs, reducing the RPP from 130 to 105 mm Hg did not increase renin secretion, whereas reducing it further, to 88 or 80 mm Hg, did raise the rate of renin secretion. These results would be consistent with the suggestion that the threshold value for renin release is between 105 and 90 mm Hg in these acute preparations, approximately the control pressure in the experiments of Cowley and Guyton.

Our next set of experiments examined the renal baroreceptor in the presence of high systemic plasma concentrations of epinephrine. We knew from our previous experiments that intravenous epinephrine raised PRA, but it is clear that epinephrine could affect the stimulus-response relationship in a number of ways. It might increase the gain of the system, in effect multiplying every value on the curve by a given factor. Alternatively, it might simply increase the basal level of renin secretion, raising the entire curve. In fact, we found that the curve was shifted to the right, as shown in Figure 4; thus, smaller decrements in the RPP are required to move onto the steep portion of the stimulus-response curve in the presence of high physiological systemic levels of epinephrine.

Other stimuli will also affect the response of the renal baroreceptor. Thames and diBona (1979) reported that low levels of renal nerve stimulation, which do not affect RBF or MAP, will augment the secretion of renin in response to suprarenal aortic constriction. Nevertheless, although the overall effect (modulation of the response of the renal baroreceptor) is similar, one cannot conclude that these low levels of renal nerve stimulation act through the same mechanism, as does circulating epinephrine; they may, for example, affect the gain, rather than the set point, of the stimulus-response curve.

The final series of experiments investigated the effect of intrarenal infusions of epinephrine on the stimulus-response curve of the renal baroreceptor. We expected that this curve would fall between two extremes. If there were no intrarenal epinephrine receptors, intrarenal infusions would not affect the stimulus-response relationship, and we would expect a curve similar to the control. If, on the other hand, the entire effect of intravenous epinephrine is through an action on intrarenal receptors, selectively raising the renal arterial epinephrine concentration would result in a curve similar to that produced by epinephrine.

As Figure 6 demonstrates, the renal baroreceptor curve is similar in the presence of intravenous and intrarenal infusions. In both the intravenous and the intrarenal (iv and ir) infusions, the curve is shifted to the right to the same extent, decreasing the amount that the perfusion pressure must be reduced before PRA begins to increase steeply. This figure indicates, then, that at any given renal perfusion pressure, iv and ir infusions of epinephrine are equipotent in raising the plasma renin activity, so long as they produce similar renal arterial epinephrine concentrations. In these dogs, once one accounts for the renal arterial pressure, the effect of an iv epinephrine infusion can be explained entirely by its action in raising the renal arterial epinephrine concentration, and, hence, through an action on intrarenal receptors. Consequently, any difference in the response to iv and ir epinephrine can be explained by differences in systemic arterial (and therefore renal perfusion) pressures, without invoking additional extrarenal effects of epinephrine.

We cannot directly exclude the possibility that the increase in PRA seen during the epinephrine infusions is due to decreased hepatic clearance of renin. However, there are at least four strong arguments that would indicate that this is not occurring:

1. If epinephrine affected hepatic clearance, then it should produce similar increases in PRA at both high and low RAP's. However, once one controls for the RAP, epinephrine has no effect on PRA at RAP's greater than 90 mm Hg but does have a considerable
effect at lower RAP’s (Fig. 4). Thus, one would have to postulate an RAP-dependent hepatic clearance of renin, and there is no reason to suppose that epinephrine affects hepatic clearance of renin only at lower renal artery pressures.

2. There is no measurable systemic spillover from the ir infusion. Thus, it is unlikely that the ir infusion would affect hepatic blood flow or clearance of renin, yet it still causes an increase in PRA. In addition, ir and iv epinephrine infusions cause equivalent changes in PRA at all RAP’s, despite the fact that iv epinephrine infusion produces systemic plasma epinephrine levels five times higher than those seen with the ir infusions. If epinephrine increases PRA by affecting hepatic clearance, one would expect that the iv infusion would have a much larger effect than the ir infusion.

3. Others (among them Wathen et al., 1964; Johnson et al., 1971, 1976; Reid et al., 1972; Eide et al., 1974) have measured renin secretion directly, using the RBF and arteriovenous differences. All of these investigators have found that renin secretion increases during either iv or ir infusions of β-adrenergic agonists, which have been said to act through both extrarenal (Reid et al., 1972) mechanisms. The answer to the second question, dealing with the flexibility of the linkage between circulating epinephrine and plasma renin activity, is implicit in the site of action of systemic infusions of β-agonists, which have been said to act through both intrarenal (Ganong, 1972; Johnson et al., 1976) and extrarenal (Reid et al., 1972) mechanisms.

4. Epinephrine (iv or ir) causes PRA to increase by a factor of two to five over the range of RAP’s between 50 and 80 mm Hg. It seems improbable that hepatic blood flow would drop by 80%, which would be necessary to explain the increase in PRA at 80 mm Hg on the basis of decreased hepatic clearance of renin.

In these dogs, as in previous experiments from this laboratory (Johnson, 1979a), intravenous infusions of epinephrine caused a greater increase in PRA than did intrarenal infusions during the first experimental period, when the cuff around the renal artery was not inflated and the RPP was not controlled. Figure 6 demonstrates, however, that these results are not incompatible with the assertion that intrarenal and intravenous infusion of epinephrine have equivalent intrarenal effects. The average control blood pressure for these five dogs was 94 mm Hg, and the average PRA was 0.9 ng AI/ml per hr. After the intrarenal epinephrine infusion, the average MAP (and RAP) increased to 97 mm Hg. Figures 5 and 6 demonstrate that infusing epinephrine into the renal artery shifts the stimulus-response curve of the renal baroreceptor, which moves from the control to the epinephrine infusion curve. However, an intrarenal epinephrine infusion alone does not change the blood pressure, and, at a renal artery pressure of 95 to 97 mm Hg, the two curves are not significantly different; therefore, the PRA does not increase. On the other hand, after the intravenous epinephrine infusion, the average MAP was 88 mm Hg during the first 30-minute experimental period. Thus, a systemic epinephrine infusion not only shifts the stimulus-response relationship from the control to the epinephrine infusion curve, but also decreases the RAP to a point below the threshold value for renin release; at this pressure, the stimulus-response curve becomes steep, and PRA increases to 1.6 ng AI/ml per hr.

An earlier paper from this laboratory (Johnson, 1979a) also reported that intravenous infusions of epinephrine caused greater increases in PRA than did intrarenal infusions adjusted to produce equivalent renal arterial epinephrine concentrations (3.9 ng AI/ml per hr as compared to 0.9 ng AI/ml per hr). The average MAP of these conscious dogs was 95 mm Hg during the intrarenal epinephrine infusions and 87 mm Hg during the intravenous infusions. These results are consistent with our hypothesis that the PRA will increase after epinephrine infusion only when the RPP is below a threshold pressure of about 88 mm Hg.

This scheme is also consistent with a number of other papers. Tanigawa et al. (1972) reported that only those infusion rates of catecholamines which decrease aortic pressure will increase plasma renin activity, and suggested that the effect of catecholamines might be an indirect one acting on the renal baroreceptor. Eide et al. (1974), investigating a possible interaction between isoproterenol and the renal baroreceptor, found that the stimulatory effect of isoproterenol on renin secretion was greater at RPP’s below the range of autoregulation than it was at control pressures, and concluded that a β-adrenergic receptor might potentiate the action of the renal baroreceptor. Clearly, both of these results are consistent with the type of interaction put forth in this paper.

Thus, we have answered the first of the two questions we raised concerning the action of epinephrine in the intact conscious animal: where does it occur? The effect of intravenous epinephrine can be explained as the combination of an extrarenal action, a generalized vasodilation leading to a drop in blood pressure which is sensed by the renal baroreceptor, and an intrarenal action, mediated through intrarenal receptors for epinephrine which affect the stimulus-response curve of the renal baroreceptor. This scheme may be able to reconcile a long-standing disagreement over the site of action of systemic infusions of β-agonists, which have been said to act through both intrarenal (Ganong, 1972; Johnson et al., 1976) or extrarenal (Reid et al., 1972) mechanisms.

The effect of intravenous epinephrine and plasma renin activity, is implicit in the stimulus-response curve of the renal baroreceptor, which moves from the control to the epinephrine infusion curve. However, an intrarenal epinephrine infusion alone does not change the blood pressure, and, at a renal artery pressure of 95 to 97 mm Hg, the two curves are not significantly different; therefore, the PRA does not increase. On the other hand, after the intravenous epinephrine infusion, the average MAP was 88 mm Hg during the first 30-minute experimental period. Thus, a systemic epinephrine infusion not only shifts the stimulus-response relationship from the control to the epinephrine infusion curve, but also decreases the RAP to a point below the threshold value for renin release; at this pressure, the stimulus-response curve becomes steep, and PRA increases to 1.6 ng AI/ml per hr.
pressures, there is a large difference between the two curves. Under such circumstances, the elevated levels of plasma epinephrine will affect renin secretion and help to maintain blood pressure. Thus, this physiological control system has the flexibility to allow plasma renin activity to be either stimulated or unaffected by high physiological levels of circulating epinephrine, depending on whether the increased epinephrine levels are or are not associated with a threat to blood pressure.

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