RENIN RELEASE AND HYPOXIA IN KIDNEY

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TADASHI KAGOSHIMA, AND HIROAKI MATSUI

A great deal of studies have been already made on the control of renin release, and it was pointed out that renin releases were influenced by changes in renal perfusion pressure, in sodium load to macula densa, by sympathetic nervous system, catecholamines and angioten-
sin. However, many problems still remain unsolved. Among them, the effects of renal hypoxia on renin release are still unknown. Systemic hypoxia causes not only renal hypoxia but also reflex sympathetic nervous discharges and increase in secretion of adrenal catecholamines which bring about the alterations in renal hemodynamics and tubular reabsorption. As the result, direct effect of hypoxia becomes obscure. Therefore, the effects of hypoxia were studied on renin release by kidneys in situ which were perfused at a constant pressure, excluding the influence of autonomic nervous system and of catecholamines.

METHODS

Eighteen mongrel dogs weighing 10–18 kg were anesthetized with sodium pentobarbital (30 mg/kg ip). The left flank incision exposed abdominal aorta, renal arteries and left testicular or ovarian vein. After the dogs were heparinized (500 u/kg iv), the double lumens catheter was inserted into the abdominal aorta, and when the tops of inner and outer tubes of the catheter reached the points above and just below the branching of renal arteries respectively, both tubes were ligated around the aorta and connected to the extracorporeal circuit apparatus. By this circuit the kidneys were perfused with arterial blood. The arterial blood was taken from the abdominal aorta by means of inner tube, and was passed through the perfusion-pump, pressure controlling apparatus (which contained Starling's resistance to maintain an arbitrary constant pressure, and the overflow blood was returned into the left jugular vein), probe of electromagnetic flowmeter and outer tube (Fig.1).

Systemic blood pressure and renal perfusion pressure were measured by sphygmomanometer in subclavian artery and in extracorporeal circuit. Renal blood flow was measured by electromagnetic flowmeter (MF-25, Nihonkoden), and renal plasma flow was obtained multiplying the renal blood flow by (1-Hematocrit). Renal vascular resistance was calculated by dividing renal perfusion pressure by renal blood flow. Renal arterial and venous blood were drawn respectively from the extracorporeal circuit and left renal vein which was inserted by a catheter via left testicular or ovarian vein. Blood oxygen tension was measured with IL meter, and oxygen content with Natterson's gasometer.

Plasma renin activities were determined with the improved Skinner method. Pressure activities of incubated plasma were measured with use of the Wistar female rats and were compared with those of standard angiotensin II (Hypertensin; Ciba). Renin release was calculated by multiplying the renal plasma flow by the difference between renal venous and arterial plasma renin activities.

Experiments were arranged as follows.
1. Renal perfusion pressure reduction

Seven dogs were divided into two groups, i.e., the group in which the renal innervation was kept intact, and the one treated previously with hexamethonium (5 mg/kg iv) and dibenamine
TABLE I  RENAL BLOOD FLOW, RENAL VENOUS RENIN ACTIVITY, AND RENAL ARTERIAL RENIN ACTIVITY BEFORE, DURING, AND AFTER REDUCTION IN RENAL PERFUSION PRESSURE

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<th>RBF (ml/min)</th>
<th>vPRA (ng/ml/h)</th>
<th>aPRA (ng/ml/h)</th>
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(200γ/kg/min iv) which suppressed autonomic nervous system and catecholamines.

At first the kidneys were perfused at a constant pressure (120 mmHg) using the extracorporeal circuit. Then renal perfusion pressure was reduced to 90 mmHg for 5 minutes and finally was recovered to 120 mmHg. During those procedures, both systemic blood pressure and renal blood flow were recorded at regular intervals. Before, during and after the reduction in perfusion pressure, the renal arterial and venous blood were sampled, and plasma renin activities were measured.

2. Hypoxic load at a constant renal perfusion pressure

Eleven dogs were also divided into two groups as mentioned above. Renal perfusion pressure was maintained constant at 120 mmHg throughout experiments. Before, during and after the hypoxic load, measurement was made on the renal hemodynamics, plasma renin activities, oxygen tension and/or content in renal arterial and venous blood. As the hypoxic load, the inspiration of gas mixture with low oxygen content (5% oxygen and 95% nitrogen) was carried out for 5 minutes.

RESULTS

1. Renal perfusion pressure reduction

Systemic blood pressure in the control period was lower in the pretreated group than in the non-treated group. Reduction in perfusion pressure caused the elevation of blood pressure in the non-treated, while it caused little change in the pretreated group.

Renal blood flow and plasma flow in the control period were larger in the pretreated than in the non-treated. Renal vascular resistance was inversely lower in the pretreated group. Reduction in perfusion pressure resulted in decrease in the renal blood flow, renal plasma flow and renal vascular resistance in both groups. Moreover the renal plasma flow was significantly lower as compared with the control value (p<0.001).

Those measured values were recovered after the elevation of perfusion pressure to the control level (Table I. Fig. 2).

Renal arterial and venous plasma renin activities, which showed in the control period significantly lower values in the pretreated group as compared with those in the non-treated group (p<0.001), were increased by the reduction in perfusion pressure in both groups and were reduced by recovery of the pressure (Table I). Renin release, which showed no remarkable differences between two groups during the control period, was increased by the reduction in perfusion pressure and the increase was greater in the non-treated group (Fig. 2).

2. Hypoxic load at a constant renal perfusion pressure

Hypoxic load reduced the arterial oxygen

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Fig. 1. Schema of extracorporeal circuit.

Fig. 2. Renal plasma flow and renin release before, during and after reduction in perfusion pressure.

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### TABLE II  
RENAL BLOOD FLOW, RENAL VENOUS RENIN ACTIVITY, AND RENAL ARTERIAL RENIN ACTIVITY BEFORE, DURING, AND AFTER HYPOXIC LOAD

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**non-treated group**

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**pretreated group**


**Diagram**

Fig. 3. Renal plasma flow and renin release before, during and after hypoxic load.

tension (74.4 to 43.8 mmHg average) in the non-treated group, and also decreased the renal oxygen consumption (22.1 to 16.7 ml/min average) in the pretreated group. Systemic blood pressure in control period was lower in the pretreated group. Hypoxic load brought about elevation and/or no changes in blood pressure in the non-treated group but no definite change was observed in the pretreated group. Renal blood flow and plasma flow in the pretreated group,
which were significantly greater than those in the non-treated group during the control period (p<0.001), showed no remarkable changes throughout the experiment, while in the non-treated group hypoxia resulted in the decrease of the values in those measurements (Table II, Fig. 3).

Renal arterial and venous plasma renin activities in the pretreated group showed significantly lower values as compared with those in the non-treated group. Hypoxic load caused no definite change in arterial plasma renin activities, but decreased the renal venous plasma renin activities in two groups except one case in the non-treated. After release of hypoxia, the plasma renin activities were elevated (Table II).

Renin release showed no remarkable differences between two groups during the control period. It was however decreased by hypoxic load except one case in each group (Fig. 3).

Negative coefficient correlations were found during the control period between the renal arterial and venous renin activities and the renal plasma flow in the non-treated group, while the plasma renin activities and renin releases were not correlated with the serum sodium and potassium concentration.

**DISCUSSION**

1. Control of renin release

Two hypotheses were widely accepted on control of renin release. One is the baroreceptor theory, Skinner et al. demonstrated that decrease or increase in mean renal arterial pressure, of as little as 5 or 10 mmHg caused changes in the amount of renin release into venous blood. Further, Blaine et al. found intravascular receptor located in the renal vascular trees employing non-filtering kidney model.

The another hypothesis was known as the macula densa theory. Vander proposed that renin release was controlled by sodium delivery to macula densa but there is no agreement that the special signal that promotes renin release is whether decreased sodium transport by macula densa or increased sodium load or concentration.

Moreover, sympathetic nerve and catecholamines were known to increase renin release. 

In our experiments renal arterial and venous plasma renin activities and renin release were increased when renal perfusion pressure was reduced, and were decreased by the recovery of the pressure. Moreover, those measurements showed lower values in the group pretreated with haxamethonium and dibenamine than in the non-treated group. Those alterations in renin release were similar to those reported by many investigators and the influences of renal nerves and catecholamines were also recognized.

2. Changes in renal hemodynamics induced by hypoxic load

Changes in renal hemodynamics induced by hypoxic load were influenced by the spaces, anesthesia, the degree and duration of hypoxia. Generally, severe hypoxia caused the renal vasoconstriction with reduction both in renal blood flow and in glomerular filtration rate. Those vasoconstrictions were said due to renal nervous discharge and in some reports partially due to humoral effects. Hypoxia was also reported to increase epinephrine excretion from adrenal gland while hypoxia per se is known to have a vasodilating action to renal arteries.

In our experiments hypoxic load caused decrease in renal blood flow and increase in renal vascular resistance in the non-treated group. On the other hand, in the group pretreated with haxamethonium and dibenamine, no remarkable change was observed in those measurements. These results suggest that hypoxic load brought about renal nervous discharge and increase in secretion of catecholamines, and are in conformity with those reported by the predecessors.

3. Alterations in tubular functions induced by hypoxic load

Renal perfusion with venous blood was said to decrease both glomerular filtration rate and sodium reabsorption, and to increase the excretion of sodium, potassium and water.

Hypoxia also decreases sodium filtration in glomerulus and increases sodium excretion. As a result, it may increase sodium load to macula densa and may alter the permeability of macula densa cells, leading to influence on renin release.

4. Hypoxia and renin release

Prolonged hypoxia have been suggested to increase renin release while acute hypoxia, produced by the intravenous administration of KCN or inspiration of low oxygen gas mixture, was reported to yield no influences upon renin release. In ventilation of hypoxic gas, direct effects of hypoxia may be obscured on renin release by the alterations in renal hemodynamics and in tubular reabsorption and by other compensatory factors. Studies on renin
release in hypoxia employing renal tissue culture method revealed no definite findings29,30.

Our experiments, at a constant renal perfusion pressure using the extracorporeal circuit, showed that hypoxic load brought about the decrease in renal venous plasma renin activities and in renin releases in many cases, irrespective of the innervation of the renal nerves or effects of catecholamines.

These findings suggest that hypoxia per se suppresses renin release. We have no explanation on this mechanism but a few inferences will be permitted, i.e. renal oxygen deficiency may decrease the renin release by altering sodium load to macula densa or by changing sodium permeability of macula densa cells, or aerobic metabolism may be involved in the renin release or production.

CONCLUSION

Generalized hypoxic load caused a decrease in renin release at a constant renal perfusion pressure obtained by the extracorporeal circuit. This suggests that oxygen deficiency may give some influences on the control of renin release or that aerobic metabolism may participate in the renin formation in the kidney.

REFERENCES


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