INCREASED PLASMA RENIN SUBSTRATE CONCENTRATIONS IN HUMAN MALIGNANT HYPERTENSION

E. ROSSET, J. R. SCHERRER AND R. VEYRAT

Department of Medicine, Division of Nephrology and Hypertension, and Medical Information Unit, Geneva University, Switzerland

SUMMARY

1. In normal man, in deoxycorticosterone/salt hypertension, and in renal artery stenosis, an inverse relationship between plasma renin activity (PRA) and renin-substrate (RS) is found.
2. PRA and RS were found to be inversely related in primary aldosteronism and in anephric patients.
3. In malignant hypertension, by contrast, the highest PRA levels were associated with the highest RS levels.

Key words: renin activity, renin substrate, hypertension, aldosteronism, malignant phase, anephric.

In normal man, an inverse relationship between plasma renin activity (PRA) and renin substrate (RS) levels is observed (Rosset & Veyrat, 1971). In situations entailing an inhibition of the renin-angiotensin system (RAS), achieved by deoxycorticosterone (DOC) plus salt diet, PRA level is decreased, as RS level is increased; when the RAS is activated, by salt depletion, PRA level is increased and RS level is decreased. Is this inverse relation also present in human pathological conditions characterized by an inhibition or an activation of the RAS? Primary aldosteronism and bilateral nephrectomy were the two conditions chosen for studying a chronic inhibition of the RAS. On the other hand, malignant hypertension (MH) is the chronic condition of extreme elevation of the RAS elicited, because MH is commonly accompanied by a potent activation of the RAS, by the spasm of the small arteries, especially of the kidneys. This activation is responsible for the secondary hyperaldosteronism.

MATERIAL AND METHODS

Control subjects. (a) Sixteen male subjects, in good health, 23–30 years old, on unrestricted

Correspondence: Dr Eric Rosset, Department of Medicine, Hôpital Cantonal, CH 1211 Geneva 4, Switzerland.

291s
sodium intake, (b) four male subjects on constant sodium intake plus DOC (20 mg/day) during 4 days, (c) six male subjects on salt restriction (10 mmol of sodium/day) for 4 days, and administration of one dose of 200 mg of chlorthalidone on the first day of the study.

**Primary aldosteronism.** Seven patients (one man and six women) aged between 35 and 60 years were studied. The diagnosis of primary aldosteronism was based on the high blood pressure (mean value: 218.6/120.0 mmHg), hypokalaemia (mean value 2.3 mEq/l), increased aldosteronuria (mean value: 40.2 µg/24 h), low level of PRA (mean value: 0 ng l⁻¹ min⁻¹), remaining low after salt depletion, and finally by the confirmation of the diagnosis on surgery. Four patients were reinvestigated after correction of the primary aldosteronism (mean blood pressure: 181.3/88.8 mmHg, mean kalaemia: 5.2 mEq/l, mean aldosteronuria: 2.9 µg/24 h).

**Patients with chronic renal insufficiency and anephric patients.** Eight patients (six men and two women) aged 34–52 years, suffering from chronic renal insufficiency (chronic glomerulonephritis in all except one case of renal polycystic disease) were studied before and after binephrectomy. Four other patients (three men and one woman), 25–46 years old, were studied only after binephrectomy. In four other patients only PRA level was measured after binephrectomy.

| TABLE 1 |
|------------------------|------------------------|
| **PRA (ng l⁻¹ min⁻¹)** | **RS (ng/ml)**         |
| Mean ± SD              | Mean ± SD              |
| **Control subjects**   |                        |
| Constant sodium intake | 11.4 ± 5.7             | 590 ± 153             |
| Constant sodium intake + DOC | 0 ± 0           | 744 ± 65              |
| Sodium depletion       | 130.3 ± 89.0           | 446 ± 94              |
| **Primary aldosteronism** |                        |                        |
| Before surgery         | 0 ± 0                  | 793 ± 171             |
| After surgery          | 18.8 ± 15.3            | 618 ± 202             |
| **Anephric patients**  |                        |                        |
| Before surgery         | 94.0 ± 73.9            | 709 ± 477             |
| After surgery          | 1.9 ± 6.7              | 1041 ± 348            |
| **Malignant hypertension** |                    |                        |
| Before binephrectomy   | 228.3 ± 116.8          | 1053 ± 645            |
| After binephrectomy    | 0 ± 0                  | 1593 ± 9              |

**Malignant hypertension.** Six patients (four men and two women), 11–47 years old, were studied; the diagnosis of malignant hypertension was based on the severe diastolic hypertension (mean value 160.8 mmHg) with a retinopathy of grade III or IV, a severe renal insufficiency, and finally a potent activation of the RAS, characterized by high PRA levels (mean value: 228.3 ng l⁻¹ min⁻¹). Two of the patients were binephrectomized, with normalization of the blood pressure.

PRA levels were measured according to the method of Boucher, Veyrat, de Champlain & Genest (1964) with a volume of 5 ml of plasma diluted with EDTA (ammonium salt). RS levels were determined by a method described by Rosset & Veyrat (1971). Aldosteronuria was determined by the method of Kliman & Peterson (1960).
**RESULTS**

*Results on paired observations of mean PRA levels*

Mean PRA level of MH was the highest and significantly different from mean PRA levels of all other groups especially of control subjects on salt depletion ($P<0.05$).

*Results on paired observations of mean RS levels*

- **Control subjects.** Unrestricted diet/salt diet plus DOC: $P<0.05$; unrestricted diet/salt depletion: $P<0.001$.
- **Primary aldosteronism.** Primary aldosteronism/control subjects on unrestricted diet: $P<0.001$.
- **Anephric patients.** Chronic renal insufficiency/anephric patients: $P<0.001$.
- **Malignant hypertension.** Mean RS level was the highest, significantly higher than mean RS level of control subjects on constant sodium intake and on salt depletion ($P<0.05$).

Mean RS level of MH was higher than that of control subjects on salt diet + DOC, of primary aldosteronism and of anephric patients (but without significant difference). These three conditions were characterized by an inhibition of the RAS. On the contrary, in MH the highest RS levels were associated with the highest PRA levels.

**DISCUSSION**

In the two pathological conditions of chronic inhibition of the RAS, primary aldosteronism and anephric patients, there was an inverse relation between RS and PRA levels, as observed in the control subjects.

In contrast, MH, a condition of chronic activation of the RAS, associated a high mean PRA level with the highest mean RS level.

Plasma RS level is the result of a dynamic equilibrium between hepatic synthesis of RS and its consumption in the plasma by the action of renin.

In the conditions of RAS inhibition (control subjects on salt diet plus DOC, primary aldosteronism and anephric patients) PRA was decreased to undetectable levels, the RS consumption was reduced and consequently plasma RS concentration increased.

Conversely in the control subject on salt depletion the decrease of plasma RS concentration could be partly explained by an increased consumption secondary to the high PRA levels.

This interpretation is not valid in MH, a condition of high RS concentration with a simultaneous high PRA level. In MH the consumption of RS is certainly increased, because of the high renin (Brown, Davies, Lever & Robertson, 1964), high PRA (Veyrat, Brunner, Grandchamp, Scholer & Muller, 1969) and high plasma angiotensin II (Boyd, Jones & Peart, 1972) levels. As the RS level is increased, the synthesis of RS must be even more increased than its consumption.

The mode of regulation of RS synthesis is not known. Some animal experiments [increased plasma RS levels in the non-filtrating kidney (Blaine, Davis & Baumber, 1971), and in experimental acute tubular necrosis (Hirasawa, Yamamoto, Matsin, Shisozaki, Kobayashi, Yagi, Morimoto, Yoyo Takedei & Murakami, 1968), without significant modifications of PRA levels] suggest a participation of the kidney in regulating the RS synthesis by the liver (Tateishi & Masson, 1972).

In MH the association of a high RS with high PRA levels increases the velocity of the enzymic
reaction and consequently the angiotensin production. This polypeptide by its direct vasoconstrictive action on the arteries and its stimulant effect on the aldosterone production, may play a role in the development of this phase of hypertension.

REFERENCES


