

The Changes in Active and Inactive Renin Induced by Various Maneuvers in Hypertensive Patients

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GOTO, T., ABE, K., TSUNODA, K., SEINO, M., YASUJIMA, M., IMAI, Y., CHIBA, S., SATO, M., HARUYAMA, T., OMATA, K., SATO, K., TAJIMA, J., TANNO, M., KUDO, K. and YOSHINAGA, K. *The Changes in Active and Inactive Renin Induced by Various Maneuvers in Hypertensive Patients*. Tohoku J. exp. Med., 1986, 149 (2), 169-181 — The changes in active and inactive renin after captopril ($n=29$) or furosemide administration ($n=10$) were studied in hypertensive patients. Furthermore, after percutaneous transluminal angioplasty (PTA) in 3 cases of renovascular hypertension (RVH), and after nephrectomy in a case of juxtaglomerular cell tumor, the time course of the changes in these two types of renin was investigated. Inactive renin was activated by trypsin treatment. Plasma renin concentration was measured by using an excess of sheep substrate. In patients with essential hypertension or primary aldosteronism, inactive renin was unchanged, irrespective of response in active renin, after the administration of captopril and furosemide. In patients with RVH, inactive renin was markedly decreased by furosemide but unchanged by captopril, in spite of significant increase in active renin. After PTA and nephrectomy, inactive renin decreased slower than active renin. These data support the idea that in patients with RVH, the increase in active renin by furosemide is at least partly due to the activation of inactive renin. It is also suggested that the increase in active renin by captopril is mainly due to the promoted release of active renin from the kidney. Furthermore, it seems likely that the metabolic clearance of inactive renin is slower than that in active renin. — inactive renin; captopril; furosemide; percutaneous transluminal angioplasty; juxtaglomerular cell tumor

Inactive type of renin, other than ordinary active type of renin, is present in human plasma (Skinner et al. 1975; Sealey et al. 1977; Weinberger et al. 1977). Although true nature of inactive renin is not clear, it has been thought to be a proenzyme of normal active renin (Sealey et al. 1977; Hsueh et al. 1981), or renin bound to an inhibitor (Leckie and McGhee 1980). Inactive renin can be activat-

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ed *in vitro* by acidification (Skinner et al. 1975), low temperature (Osmond et al. 1973; Sealey and Laragh 1975), or trypsin and other proteolytic enzymes (Day et al. 1975; Sealey et al. 1979). However, *in vivo*, the conversion of inactive renin to active renin is not yet proved or disproved.

If an increase in active renin and a concomitant decrease in inactive renin are observed in some physiological conditions, it might suggest the possibility of activation of inactive renin *in vivo*. In the present study, to investigate whether inactive renin is converted to active form *in vivo*, renin release was promoted by two different stimulations, i.e., captopril or furosemide with orthostasis in hypertensive patients. We also studied the time course of changes in inactive renin after percutaneous transluminal angioplasty (PTA) and after nephrectomy in juxtaglomerular cell tumor (JGT), to clarify the clearance of inactive renin.

MATERIALS AND METHODS

Captopril administration under recumbent position

Twenty-nine hypertensive patients (18 men and 11 women aged from 16 to 71 with a mean of 39) were studied. They consisted of 17 cases of essential hypertension (EH) (11 men and 6 women aged from 16 to 71 with a mean of 40), 5 of renovascular hypertension (RVH) (4 men and a woman aged from 23 to 61 with a mean of 38), 4 of primary aldosteronism (PA) (2 men and 2 women aged from 27 to 50 with a mean of 39) and 3 of hypertension due to chronic glomerulonephritis (CGN) (a man and 2 women aged from 33 to 48 with a mean of 41). The study was carried out in the morning on fasted patients. Peripheral venous blood was drawn after 1 hr of recumbent position (control) and at 1 hr (SQ 1), 2 hr (SQ 2) after the oral administration of 50 mg captopril (SQ 14,225).

Furosemide administration with ambulation

Ten patients (9 men and a woman aged from 23 to 64 with a mean of 42) were studied. They consisted of 5 cases of EH (5 men aged from 28 to 50 with a mean of 43), 4 of RVH (3 men and a woman aged from 23 to 64 with a mean of 42) and 1 case of PA (a woman aged 41 years). Peripheral venous blood sampling was done after 1 hr of recumbent position, and after 30 min or 1 hr of standing following the intravenous administration of 40 mg furosemide. The time of blood sampling after furosemide administration is different in each patient, because the tolerable time length for standing position is various from patient to patient. In the patient in whom blood sampling was done both at 30 min and 1 hr after the furosemide administration, the value of renin concentration at 1 hr was selected for the calculation of the mean value after the furosemide administration.

After percutaneous transluminal angioplasty and nephrectomy of juxtaglomerular cell tumor

In 3 cases (2 men and a woman aged from 32 to 61 with a mean of 47) of RVH, and one case of JGT (a man aged 71 years), peripheral venous blood sampling was done after PTA and after the nephrectomy in affected side, respectively. And the time course of two types of renin was studied.

Blood sampling

Blood sample was collected into a heparinized syringe. The plasma was separated immediately by centrifugation at 3,000 rpm for 15 min and stored at -20°C until the assay.

Activation of inactive renin

Plasma (100 μl) was mixed with 10 μl of trypsin solution (8 mg/ml in 1/mMole/liter HCl, stored in the frozen state) and incubated for 5 min at 4°C . Thereafter, 10 μl of soyabean trypsin inhibitor (40 mg/ml) was added to inhibit the trypsin (Goto et al. 1984).

Active renin concentration, total renin concentration, and inactive renin concentration

Active (ARC) and total renin concentrations (TRC) were measured by determining the rate of angiotensin I (AI) formation when plasma or activated plasma was incubated with an excess of sheep substrate. Inactive renin concentration (IRC) was defined as the difference between TRC and ARC.

For the enzyme reaction, 100 μ l of plasma or 100 μ l of activated plasma was incubated at 37°C for 4 hr with 500 μ l of a premixed solution consisting of sheep substrate (0.5 μ g AI equivalents dissolved in 400 μ l of 100 mmole/l phosphate buffer, pH 6.5), EDTA·Na₂ (50 μ l of a 250 mmole/l solution, pH 6.5), and PMSF (50 μ l of 200 mmole/l, in ethyl alcohol). Abnormally high renin samples, as the plasmas obtained from a patient with JGT were assayed after dilution with a 1% bovine serum albumin solution. The reaction was terminated by cooling. Plasma proteins were precipitated by adding 500 μ l of 250 g/liter polyethylene glycol dissolved in 80% ethyl alcohol and removed by centrifugation at 5,000 rpm for 15 min. The amount of the AI generated and recovered in the slightly turbid supernatant was estimated by radioimmunoassay (Goto et al. 1984). Renin concentration was expressed as ngAI/ml/hr. Active renin ratio (AR ratio) was calculated as follows: ARC/TRC \times 100 (percent). Values were given as mean \pm s.e. The significance of differences between mean values were evaluated by Student's *t*-test. The level of significance was taken as 0.05.

RESULTS

Captopril administration

As a whole, average value of ARC increased significantly at SQ 1 and SQ 2 (Table 1). IRC also increased significantly at SQ 1 but not significantly at SQ 2 (Table 2). Both TRC and AR ratio increased significantly (Tables 3 and 4).

In patients with EH, ARC increased at SQ 1 and SQ 2 (Table 1, Fig. 1), but IRC did not change significantly (Table 2, Fig. 1). TRC did not alter

TABLE 1. *Changes in active renin concentration in 29 hypertensive patients after 50 mg of captopril administration*

	n	ARC (ngAI/ml/hr)		
		Control	SQ 1	SQ 2
EH	17	4.4 \pm 0.9	11.4 \pm 3.3*	14.4 \pm 4.7*
Responders	5	8.0 \pm 2.6	29.0 \pm 6.0*	39.8 \pm 7.8*
Non-responders	12	2.9 \pm 0.6	4.1 \pm 0.9	3.4 \pm 0.7
RVH	5	16.6 \pm 3.1	168.6 \pm 34.9**	211.8 \pm 47.5*
PA	4	0.9 \pm 0.4	0.5 \pm 0.3	0.4 \pm 0.2
CGN	3	4.5 \pm 2.4	9.2 \pm 3.9	5.4 \pm 1.2
Total	29	6.0 \pm 1.1	34.9 \pm 12.0*	43.1 \pm 15.4*

ARC, active renin concentration; n, number of the patients; SQ 1, 1 hr after captopril administration; SQ 2, 2 hr after captopril administration; EH, essential hypertension; RVH, renovascular hypertension; PA, primary aldosteronism; CGN, chronic glomerulonephritis. See text about the criteria of responders and non-responders.

* $p < 0.05$, ** $p < 0.01$.

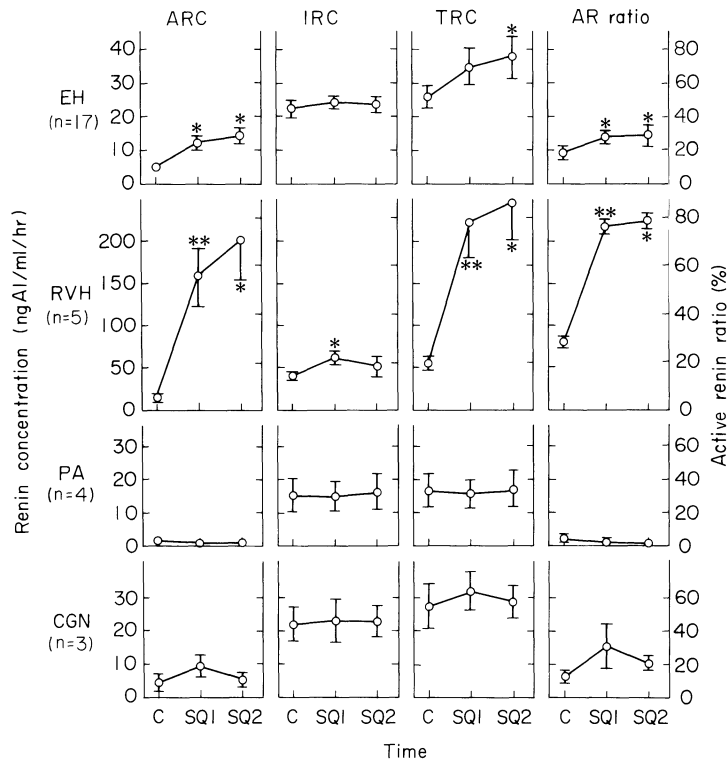


Fig. 1. Changes in active, inactive or total renin concentration and active renin ratio in 29 hypertensive patients after 50 mg of captopril administration. C, control; SQ 1, 1 hr after captopril administration; SQ 2, 2 hr after captopril administration. EH, essential hypertension; RVH, renovascular hypertension; PA, primary aldosteronism; CGN, chronic glomerulonephritis. ARC, active renin concentration; IRC, inactive renin concentration; TRC, total renin concentration; AR ratio, active renin ratio.

* $p < 0.05$, ** $p < 0.01$.

TABLE 2. Changes in active renin concentration after the captopril administration

	n	IRC (ngAI/ml/hr)		
		Control	SQ 1	SQ 2
EH	17	21.7 ± 3.5	24.8 ± 4.2	23.9 ± 4.1
Responders	5	29.3 ± 10.7	38.3 ± 10.6	33.6 ± 11.5
Non-responders	12	18.6 ± 2.3	19.2 ± 3.1	19.9 ± 3.1
RVH	5	40.1 ± 5.1	64.2 ± 10.8*	52.0 ± 14.2
PA	4	16.3 ± 4.9	15.6 ± 4.5	16.8 ± 5.0
CGN	3	22.9 ± 5.8	23.1 ± 7.9	23.3 ± 4.1
Total	29	26.1 ± 2.9	31.5 ± 4.1*	28.2 ± 3.7

IRC, inactive renin concentration. Otherwise, as in Table 1.

TABLE 3. *Changes in total renin concentration after the captopril administration*

	n	TRC (ngAI/ml/hr)		
		Control	SQ 1	SQ 2
EH	17	26.1±3.6	35.9± 6.9	38.0± 7.6*
Responders	5	37.3±9.3	65.2±16.4	73.4±16.7
Non-responders	12	21.4±2.5	23.3± 3.3	23.2± 3.3
RVH	5	56.7±7.8	232.9±41.8**	263.8±50.9*
PA	4	17.2±5.3	16.0± 4.6	17.2± 5.2
CGN	3	27.3±8.2	32.3± 8.6	28.7± 5.0
Total	29	32.1±3.5	65.9±15.3*	71.3±17.7*

TRC, total renin concentration. Otherwise, as in Table 1.

TABLE 4. *Changes in active renin ratio after the captopril administration*

	n	AR ratio (%)		
		Control	SQ 1	SQ 2
EH	17	18.2± 3.9	26.7± 4.5*	27.5± 6.0*
Responders	5	29.8±11.2	47.3± 5.1	58.0±10.9*
Non-responders	12	13.3± 2.4	18.2± 3.8	14.8± 2.3
RVH	5	28.2± 3.0	71.5± 2.9**	77.4± 6.0**
PA	4	4.8± 1.6	2.3± 2.1	1.8± 0.7
CGN	3	14.2± 4.2	30.4±15.5	20.3± 3.6
Total	29	17.2± 2.5	30.3± 4.6**	31.2± 5.2**

AR ratio, active renin ratio. Otherwise, as in Table 1.

significantly at SQ 1 but a significant increase in TRC was observed at SQ 2 (Table 3, Fig. 1). AR ratio also increased significantly (Table 4, Fig. 1).

Patients with EH were divided into 2 groups according to the response of ARC to captopril, as responders and non-responders. Patients who had a value of ARC above 20 ng/ml/hr and also more than 2.5 times control value at SQ 2 were classified as responders (Table 1). Five patients (3 men and 2 women aged from 16 to 63 with a mean of 41) were responders. In them, IRC and TRC also tended to increase (Tables 2 and 3), but did not reach a statistical significance. AR ratio increased significantly only at SQ 2 (Table 4). The remaining 12 patients (8 men and 4 women aged from 21 to 71 with a mean of 39) were non-responders. In these patients, neither ARC nor IRC changed significantly (Tables 1 and 2).

In patients with RVH, ARC increased remarkably in each subject after captopril administration (Table 1, Figs. 1 and 2). IRC increased in 4 cases out of

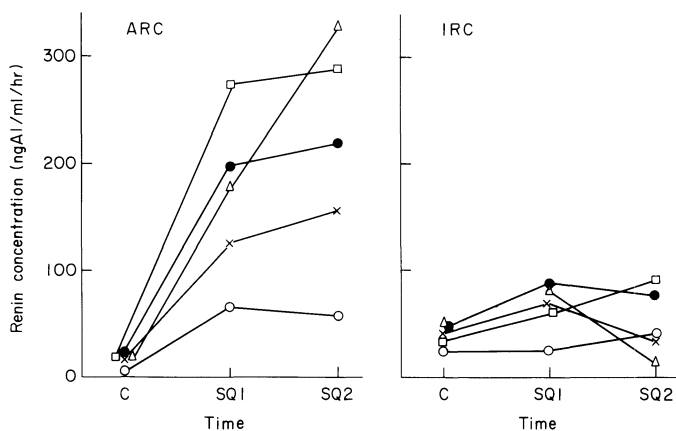


Fig. 2. Changes in active and inactive renin concentration in each patient with renovascular hypertension after the captopril administration. \circ , \bullet , \triangle , \square , \times represents respective case. Otherwise, as in Fig. 1.

TABLE 5. Changes in active renin concentration in 10 hypertensive patients after 40 mg of furosemide administration with ambulation

	n	ARC (ngAI/ml/hr)	
		Control	After
EH	5	3.1 \pm 1.3	10.8 \pm 5.8
RVH	4	34.2 \pm 12.9	92.8 \pm 34.8
PA	1	1.8	3.4
Total	10	15.4 \pm 7.0	42.9 \pm 18.8

Otherwise, as in Table 1.

5 at SQ 1. Therefore, the average value at SQ 1 increased significantly, but the increase was slight and IRC at SQ 2 did not show any significant change (Table 2, Figs. 1, 2)

In 4 cases with PA, neither ARC nor IRC responded to captopril, no changes in TRC and AR ratio either (Tables 1-4, Fig. 1).

In 3 cases with CGN, ARC, TRC and AR ratio tended to increase at SQ 1, but they returned to the control level at SQ 2 (Tables 1, 3 and 4, Fig. 1). IRC did not change after the administration of captopril (Table 2, Fig. 1).

Furosemide administration with ambulation

As a whole, average value of ARC increased. But the change was statistically not significant (Table 5). IRC decreased significantly (Table 6). TRC tended to increase (Table 7), while AR ratio increased significantly (Table 8).

TABLE 6. *Changes in inactive renin concentration after the furosemide administration with ambulation*

	n	IRC (ngAI/ml/hr)	
		Control	After
EH	5	23.7±6.7	20.8±4.1
RVH	4	33.1±6.9	2.0±2.0*
PA	1	18.0	16.2
Total	10	26.9±4.4	12.8±3.6*

Otherwise, as in Tables 1 and 2.

TABLE 7. *Changes in total renin concentration after the furosemide administration with ambulation*

	n	TRC (ngAI/ml/hr)	
		Control	After
EH	5	26.8± 7.7	31.6± 9.2*
RVH	4	67.2±19.5	94.8±33.5
PA	1	19.8	19.6
Total	10	42.3±10.5	55.7±16.8

Otherwise, as in Tables 1 and 3.

TABLE 8. *Changes in active renin ratio after the furosemide administration with ambulation*

	n	AR ratio (%)	
		Control	After
EH	5	11.1± 3.1	26.8± 8.8*
RVH	4	67.2±19.5	94.8±33.5
PA	1	9.2	17.3
Total	10	24.6± 7.1	51.1±13.3**

Otherwise, as in Tables 1 and 4.

In 5 cases with EH, the average value of ARC increased, but the change was not significant (Table 5). The average value of IRC did not alter (Table 6). Both TRC and AR ratio increased significantly (Tables 7 and 8). And in one case, in whom ARC increased markedly, decrease in IRC was observed (Fig. 3).

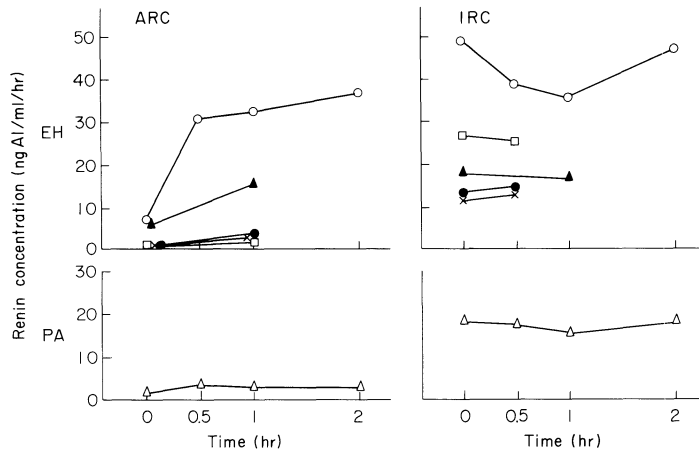


Fig. 3. Changes in active and inactive renin concentration in the patients with essential hypertension and primary aldosteronism after 50 mg of furosemide administration with ambulation. ○, ●, △, ▲, □, × represents respective case. Otherwise, as in Figs. 1 and 2.

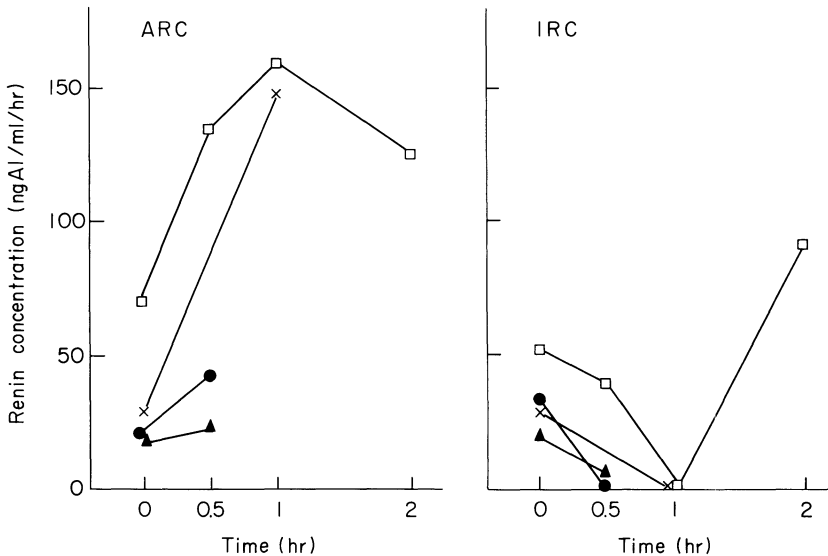


Fig. 4. Changes in active and inactive renin concentration in the patients with renovascular hypertension after furosemide administration with ambulation. Otherwise, as in Figs. 1-3.

In one case with PA, neither ARC nor IRC changed (Tables 5-8, Fig. 3).

In 4 cases with RVH, increase in ARC and concomitant decrease in IRC were observed in each subject at 30 min or 1 hr after furosemide administration. In 3 of 4 cases, IRC was not detected after the administration. However, in one case, in whom blood sampling was done at 2 hr after furosemide administration, IRC increased markedly (Fig. 4). AR ratio increased at 30 min or 1 hr according to

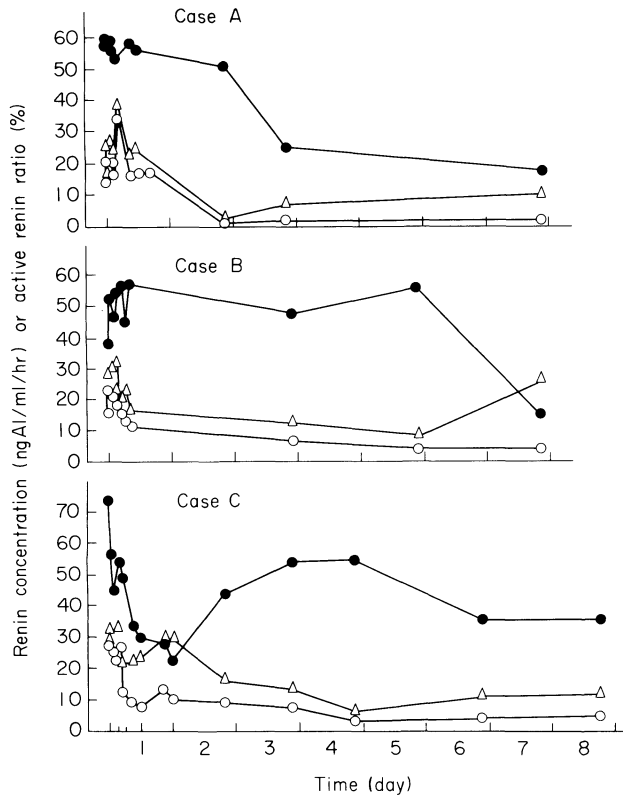


Fig. 5. Changes in active or inactive renin concentration and active renin ratio after percutaneous transluminal angioplasty in 3 cases with renovascular hypertension.

○—○, active renin concentration ;
 ●—●, inactive renin concentration ;
 △—△, active renin ratio.

the concomitant change of active and inactive renin (Table 8).

After PTA and removal of JGT

In 3 cases with RVH, ARC was decreased from 6 to 8 hr after PTA. In 2 patients, transient increase in ARC from 30 min to 4 hr after PTA was observed. Decrease in IRC was slower than that in ARC. In case A, IRC began to decrease 3 days after PTA, and in case B, 7 days after PTA. In case C, IRC decreased transiently from 9 to 24 hr, and increased again 2 days after PTA. Due to the slower decrease of IRC, AR ratio decreased in each case (Fig. 5).

In a case of JGT, nephrectomy in the affected side caused a rapid fall of both ARC and IRC. And the rate of decrease in IRC was slower than that of ARC. The approximate half-lives for ARC and IRC were calculated to be 2 and 4 hr, respectively (Fig. 6).

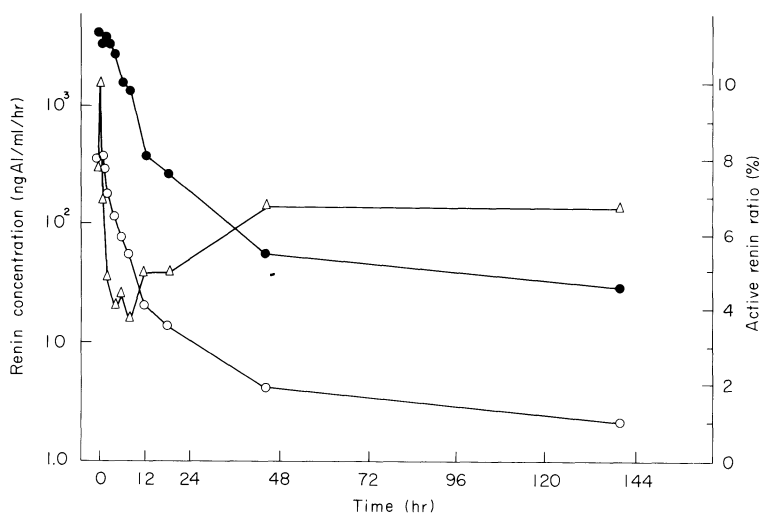


Fig. 6. Changes in active or inactive renin concentration and active renin ratio after nephrectomy in a case with juxtaglomerular cell tumor.

- , active renin concentration ;
- , inactive renin concentration ;
- △—△, active renin ratio.

DISCUSSION

In the literature, in normal subjects or patients with EH, an increase or no change in inactive renin after furosemide administration has been reported (Kappelgaard et al. 1978 ; Millar et al. 1978 ; Rumpf et al. 1978). But there is no study about the patients with RVH.

In the present study, inactive renin was unchanged after furosemide in patients with EH and PA. But in one case of EH and 4 cases of RVH, a marked decrease in inactive renin accompanying the increase in active renin was observed.

This different change in inactive renin in the present study could be explained by the magnitude of the increase in active renin. In the patients with RVH, the response of active renin by furosemide was much greater than that in the patients with EH and PA. Therefore, it is suggested that if an increase in active renin by furosemide is acute and marked as in patients with RVH, the conversion of inactive renin to active form operate mainly to increase active renin in the circulation.

There are many conflicting results concerning captopril induced acute changes in inactive renin. Some authors reported the reciprocal change in active and inactive renin in normal subject (Goldstone et al. 1983) and EH or RVH (Glorisso et al. 1982 ; Derkx et al. 1983). But others observed no change in inactive renin accompanying an increase in active renin in normal subjects (Millar et al. 1980) and in patients with EH or RVH (Linjin et al. 1980 ; Sealey et al. 1981). We also observed previously a reciprocal change in the two forms of renin

(Goto et al. 1980, 1983). But in the previous study, we used cold storage to activate the inactive renin. It has been reported that only 30% inactive renin can be activated by cryoactivation (Hsueh et al. 1978). Moreover, in the previous study, we measured the renin content not as 'concentration' but as 'activity', incubating plasmas with no addition of substrate. Under this condition, renin substrate may be insufficient, resulting in an underestimation of inactive renin. In the present study, we could not detect the reciprocal changes in the two forms of renin. As previously reported, the assay method used in the present study is completely satisfactory for the estimation of renin 'concentration' (Goto et al. 1984). The data described above suggest that captopril increases active renin not by conversion of inactive renin but by another mechanism, perhaps by promoting the secretion of active renin itself from the kidney.

In the present study, discrete changes in inactive renin were observed by furosemide with orthostasis and captopril administration in patients with RVH. In the mechanisms known as stimulating renin release, baroreceptor mechanism and sympathetic nervous system would be commonly brought into action after furosemide with orthostasis and captopril administration following the fall in blood pressure (Davis and Freeman 1976; Keeton and Campbell 1984). Further, it has been postulated that furosemide promotes macula densa mechanism by the blockade of sodium and chloride transport into chemoreceptor cells, while the inhibition of negative short feedback mechanism of angiotensin II works after captopril to promote the renin release from the kidney (Keeton and Campbell 1984; Case et al. 1978). So our present results suggest that the macula densa mechanism may promote the activation of inactive renin, whereas the inhibition of negative short feedback mechanism promote the release of active renin directly from the kidney to increase active renin in the circulation.

After PTA or removal of JGT, inactive renin decreased slower than active renin. This is consistent with the result observed by Derkx after bilateral nephrectomy (Derkx et al. 1978). Our data confirmed that the metabolic clearance of inactive renin is slower than that of active renin.

Acknowledgments

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