Active and Inactive Renin after Captopril (SQ 14225) Administration in Hypertensive Patients

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The changes in active and inactive renin after oral administration of captopril (SQ 14225) were studied in 29 hypertensive patients. Inactive renin was calculated as plasma renin activity (PRA) after cold storage (total renin) minus PRA before cold storage (active renin). The patients were divided into 2 groups, responders and non-responders, according to the response of active renin to captopril. In 9 responders, the active renin increased markedly, while the inactive renin decreased. On the other hand, in 20 non-responders, both renin activities increased only slightly. Total renin increased markedly in responders; it increased in much smaller degree but significantly in non-responders. These data suggest that captopril promotes the conversion of inactive renin to active one and augments the renin release as a whole.

There are different types of renin, active and inactive, in human amniotic fluid (Lumbers 1971; Skinner et al. 1975), in plasma of normotensives, patients with essential hypertension (Skinner et al. 1975; Sealey et al. 1977; Weinberger et al. 1977), anephric patients (Weinberger et al. 1977; Sealey et al. 1977), pregnant women (Skinner et al. 1975) and patients with renal tumors (Day and Leutscher 1974). Inactive renin can be activated by acidification (Lumbers 1971; Skinner et al. 1975), low temperature (Osmond et al. 1973; Sealey and Laragh 1975), or trypsin and other proteolytic enzymes (Morris and Lumbers 1972; Day et al. 1975; Sealey et al. 1979) in vitro. Although the physiological role of inactive renin in hypertension is not clear, it was thought to be a proenzyme (Day et al. 1975; Sealey et al. 1977), or renin bound to an inhibitor (Leckie 1973; Boyd 1974; Morris and Johnston 1976). There are many arguments about alteration in active and inactive renin after various stimulations. An increase in both active and inactive renin after sodium restriction and furosemide administration has been reported (Weinberger et al. 1977; Millar et al. 1978). On the other hand, divergent changes

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in active and inactive renin by isoprenalin, clonidine, diazoxide, propranolol and tilting were reported (Derksen et al. 1976; Atlas et al. 1977, 1978). Atlas et al. (1977, 1978) suggested in their reports that inactive renin can be changed to active renin in vivo.

It is well known that angiotensin converting enzyme inhibitor, captopril (SQ 14225), induces an increase in plasma renin activity by the inhibition of negative short feedback mechanism of renin release (Case et al. 1978). In relation to the mechanism underlying the augmented renin release by captopril, there are two possibilities: one is increment of conversion of inactive to active renin and the other is an increase in release of renin from the kidney. There was no report about the change in inactive renin after the administration of captopril. We already reported that captopril augments the conversion of inactive renin to active one in patients who responded with a marked increase in active renin to captopril administration (Goto et al. 1980). In this paper, we studied further changes in total renin and the percentage of inactive renin in order to investigate the mechanism of augmented plasma renin activity.

**MATERIALS AND METHODS**

Twenty-nine hypertensive patients (15 men and 14 women aged from 14 to 63 with a mean of 38 years) were studied. They consisted of 17 cases of essential hypertension (EH) (9 men and 8 women aged from 16 to 63 with a mean of 41 years), 7 of renovascular hypertension (RVH) (3 men and 4 women aged from 23 to 56 with a mean of 37 years), and 3 of hypertension due to renal parenchymal disease (RPD) (2 men and a woman aged from 25 to 46 with a mean of 33 years). The remaining 2 patients (a man aged 24 years and a woman aged 14 years) were the cases in which RVH was suspected, but the angiography was not done. In 17 cases of EH, were included 5 cases (3 men and 2 women aged from 28 to 63 with a mean of 45 years) of low renin EH, 10 cases (4 men and 6 women aged from 16 to 54 with a mean of 40 years) of normal renin EH, and 2 cases (both men aged 33 and 36 years) of high renin EH. In 3 cases of RPD, 2 cases (a man aged 28 years and a woman aged 25 years) of chronic glomerulonephritis, and 1 case (a man aged 46 years) of systemic lupus erythematosus were included.

The study was carried out in fasted patients in the morning. Peripheral venous blood sampling was performed after 1 hr of recumbent position (control), and subsequently captopril (25 or 50 mg) was given orally. Thereafter the subjects were kept in supine position for 2 hr. The sampling of blood was done at 1 hr (SQ1) and 2 hr (SQ2) after the oral administration. 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. Plasma renin activity (PRA) was measured using radioimmunoassay of generated angiotensin I by incubation of plasma at 37°C, pH 5.5 for 6 hr with disodium ethylenediamine tetraacetic acid (EDTA) and di-isopropyl fluorophosphate (DFP) as previously described (Abe et al. 1972). Plasma renin activity was expressed as ng AngI/ml/hr.

Activation of inactive renin was done by means of cold storage. Inactive renin was calculated as PRA after 10 days of cold (−5°C) storage (total renin) minus PRA before cold storage (active renin) (Saito et al. 1979). The percentage of inactive renin was calculated as follows: (inactive renin)/(total renin) × 100. To evaluate statistical significance, the paired t-test was used. Values were given as mean±s.e.
RESULTS

As illustrated in Fig. 1, the average values of active renin were increased significantly by captopril (control: 2.7±0.5 ng/ml/hr, SQ1: 7.0±1.2 ng/ml/hr, \( p<0.001 \), SQ2: 7.2±1.3 ng/ml/hr, \( p<0.001 \)), while inactive renin decreased at SQ1 and returned to the control level at SQ2 (control: 3.3±0.6 ng/ml/hr, SQ1: 2.0 ±0.4 ng/ml/hr, \( p<0.05 \), SQ2: 3.0±0.6 ng/ml/hr) (Fig. 1). Total renin was increased significantly by captopril (Table 1). The percentage of inactive renin was decreased at SQ1 and returned to the control level at SQ2 (Table 2).

In patients with EH, active renin increased at SQ1 and SQ2 (control: 2.3±0.7
Fig. 3. Change in active and inactive renin, in 5 patients with low renin (left panel), 10 patients with normal renin (middle panel) and 2 patients with high renin (right panel) essential hypertension. Otherwise, as in Figs. 1 and 2.

**Table 1. Changes in total renin after the captopril administration**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Control</th>
<th>SQ1</th>
<th>SQ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EH</td>
<td>17</td>
<td>4.7±0.8</td>
<td>6.7±1.1†</td>
<td>7.9±1.3</td>
</tr>
<tr>
<td>Low renin EH</td>
<td>5</td>
<td>3.2±0.9</td>
<td>5.0±1.9</td>
<td>5.7±2.0</td>
</tr>
<tr>
<td>Normal renin EH</td>
<td>10</td>
<td>4.3±0.7</td>
<td>6.2±1.2</td>
<td>7.1±1.4*</td>
</tr>
<tr>
<td>High renin EH</td>
<td>2</td>
<td>14.6±8.3</td>
<td>15.3±11.2</td>
<td>21.3±13.5†</td>
</tr>
<tr>
<td>RVH</td>
<td>7</td>
<td>9.1±1.6</td>
<td>14.9±1.2†</td>
<td>15.7±2.0*</td>
</tr>
<tr>
<td>RPD</td>
<td>3</td>
<td>9.7±3.1</td>
<td>10.0±3.3</td>
<td>15.4±5.8†</td>
</tr>
<tr>
<td>Responders</td>
<td>9</td>
<td>9.2±1.5</td>
<td>14.5±1.1†</td>
<td>16.3±1.5†</td>
</tr>
<tr>
<td>Non-responders</td>
<td>20</td>
<td>4.6±0.7</td>
<td>6.4±1.0†</td>
<td>7.0±1.1†</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>6.1±0.8</td>
<td>9.0±1.0†</td>
<td>10.2±1.2‡</td>
</tr>
</tbody>
</table>

* p<0.05, † p<0.01, ‡ p<0.001.

**Table 2. Changes in the percentage of inactive renin after the captopril administration**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Control</th>
<th>SQ1</th>
<th>SQ2</th>
</tr>
</thead>
<tbody>
<tr>
<td>EH</td>
<td>17</td>
<td>51.3±8.9</td>
<td>40.8±9.9</td>
<td>52.9±8.8</td>
</tr>
<tr>
<td>Low renin EH</td>
<td>5</td>
<td>80.0±8.2</td>
<td>56.1±16.8</td>
<td>72.5±10.5</td>
</tr>
<tr>
<td>Normal renin EH</td>
<td>10</td>
<td>44.5±12.0</td>
<td>41.3±13.5</td>
<td>51.3±12.8</td>
</tr>
<tr>
<td>High renin EH</td>
<td>2</td>
<td>17.9±42.0</td>
<td>both 0</td>
<td>43.8 &amp; 0</td>
</tr>
<tr>
<td>RVH</td>
<td>7</td>
<td>45.5±13.3</td>
<td>16.6±8.9</td>
<td>11.4±5.8*</td>
</tr>
<tr>
<td>RPD</td>
<td>3</td>
<td>65.4±13.9</td>
<td>31.2±15.7</td>
<td>51.3±10.2</td>
</tr>
<tr>
<td>Responders</td>
<td>9</td>
<td>48.2±12.3</td>
<td>8.9±4.6</td>
<td>4.6±3.1</td>
</tr>
<tr>
<td>Non-responders</td>
<td>20</td>
<td>55.9±7.6</td>
<td>43.0±8.5</td>
<td>55.8±6.6</td>
</tr>
<tr>
<td>Total</td>
<td>29</td>
<td>53.5±6.4</td>
<td>32.4±6.7†</td>
<td>39.9±6.4</td>
</tr>
</tbody>
</table>

* p<0.05, † p<0.01.
Renin after Captopril Administration

ng/ml/hr, SQ1: 4.7±1.4 ng/ml/hr, p<0.05, SQ2: 4.3±1.3 ng/ml/hr, p<0.05). Inactive renin did not change at SQ1 but increased at SQ2 (control: 2.2±0.5 ng/ml/hr, SQ1: 1.9±0.9 ng/ml/hr, SQ2: 3.6±0.8 ng/ml/hr, p<0.05) (Fig. 2). Total renin was increased significantly at SQ1 and slightly but not significantly increased at SQ2. The percentage of inactive renin was not significantly changed (Table 2). In the patients with low renin EH, active renin showed a tendency to increase but the change was not significant (control: 0.4±0.1 ng/ml/hr, SQ1: 3.1±2.3 ng/ml/hr, SQ2: 2.0±1.1 ng/ml/hr). Inactive renin was increased only at SQ2 (control: 2.8±0.9 ng/ml/hr, SQ1: 1.9±0.8 ng/ml/hr, SQ2: 3.7±1.1 ng/ml/hr, p<0.05) (Fig. 3). Total renin also showed a tendency to increase after administration of captopril (Table 1). The percentage of inactive renin showed a tendency to decrease but the change was not significant (Table 2). In the patients with normal renin EH, both active and inactive renin showed a tendency to increase (active renin; control: 1.9±0.5 ng/ml/hr, SQ1: 3.8±1.5 ng/ml/hr, SQ2: 3.7±1.6 ng/ml/hr, inactive renin; control: 2.1±0.6 ng/ml/hr, SQ1: 2.4±0.8 ng/ml/hr, SQ2: 3.4±1.1 ng/ml/hr) (Fig. 3). Total renin also showed a tendency to increase in both periods but the increase was significant only at SQ2 (Table 1). The percentage of inactive renin did not change (Table 2). In 2 cases of high renin EH, no significant change was observed in either active or inactive renin.

Fig. 4. Changes in active and inactive renin in 7 patients with renovascular hypertension. Otherwise, as in Fig. 1.
Total renin increased in both cases (Table 1). No significant change was observed in the percentage of inactive renin (Table 2).

In 7 cases of RVH, active renin increased significantly (control: 4.2±0.9 ng/ml/hr, SQ1: 12.7±1.9 ng/ml/hr, p<0.01, SQ2: 14.4±2.5 ng/ml/hr, p<0.01). Inactive renin decreased but the change was statistically not significant (control: 4.8±1.6 ng/ml/hr, SQ1: 2.2±0.1 ng/ml/hr, SQ2: 1.4±0.7 ng/ml/hr) (Fig. 4). Total renin increased significantly (Table 1). The percentage of inactive renin decreased, but the change was significant only at SQ2 (Table 2).

In 3 cases of RPD, active renin tended to increase but the change was not significant (control: 2.9±1.3 ng/ml/hr, SQ1: 6.6±1.9 ng/ml/hr, SQ2: 7.4±2.6 ng/ml/hr). Inactive renin showed no significant change (control: 6.8±2.5 ng/ml/hr, SQ1: 3.4±2.1 ng/ml/hr, SQ2: 8.0±3.9 ng/ml/hr) (Fig. 5). Total renin did not change at SQ1 but increased significantly at SQ2 (Table 1). The percentage of inactive renin insignificantly decreased (Table 2).

All patients were divided into 2 groups, responders and non-responders, according to the response of active renin to captopril. Patients who had a value of active renin of 10 ng/ml/hr or more at SQ2, and also showed a response of greater than twice the control values at SQ2 were classified as responders. Nine patients (5 men and 4 women aged 14 to 56 with a mean of 33 years), including 5 with RVH, 2 with EH and 2 with suspectable RVH were responders. In these responders, active renin increased markedly (control: 4.0±0.8 ng/ml/hr, SQ1: 13.3±1.2 ng/ml/hr, p<0.001, SQ2: 15.6±1.6 ng/ml/hr, p<0.001), while inactive renin decreased significantly (control: 4.9±1.5 ng/ml/hr, SQ1: 1.3±0.6 ng/ml/hr, p<0.05, SQ2: 0.7±0.5 ng/ml/hr, p<0.01) (Fig. 6). Total renin increased significantly (Table 1). The percentage of inactive renin insignificantly decreased (Table 2). The remaining 20 patients (10 men and 10 women aged 16 to 63 with a mean of 39 years), including 15 with EH, 3 with RPD and 2 with RVH were non-responders.
In these patients, active renin increased (control: 2.0±0.6 ng/ml/hr, SQ1: 4.1±1.1 ng/ml/hr, \( p<0.05 \), SQ2: 3.5±0.8 ng/ml/hr, \( p<0.01 \)), and inactive renin did not change at SQ1 but increased at SQ2 (control: 2.6±0.4 ng/ml/hr, SQ1: 2.3±0.6 ng/ml/hr, SQ2: 4.0±0.7 ng/ml/hr, \( p<0.05 \)) (Fig. 6). Total renin increased significantly (Table 1). The percentage of inactive renin did not show any significant change (Table 2).

**DISCUSSION**

The increase in renin activity in human plasma by low temperature was first reported by Osmond et al. (1973). Sealey et al. (1977) have shown that cryoactivation was accomplished by incubating plasma at \(-5^\circ\text{C}, \text{pH 7.4, for 4 days}\). Recently Saito et al. (1979) reported that the cryoactivation is not complete before 10 days of incubation.

Angiotensin converting enzyme inhibitor, captopril (SQ 14225) induces an increase in plasma renin activity by the inhibition of negative short feedback mechanism of renin release (Case et al. 1978). In the present study, the responses of active renin to captopril were not uniform in hypertensive patients. Nine patients out of 29 showed a hyperresponse. There was no significant difference in control values of either active or inactive renin between responders and non-responders. However, in responders who exhibited a marked increase in active renin by captopril, inactive renin decreased significantly. Moreover, the percentage of inactive renin tended to decrease in non-responders, although the change was not significant. These data suggest that at least in responders the
increase in plasma renin activity by captopril administration may be due to the conversion of active renin to inactive renin.

In this paper we also investigated the change of total renin, namely active renin plus inactive renin. Total renin was increased not only in responders but also in non-responders. It is still unknown in what manner the renin is stored (active, inactive or mixed), and the form of renin released from the human kidney is controversial. But our data suggest that captopril augments the release of renin as a whole.

Inactive renin decreased in responders, but slightly increased in non-responders. The reason of this difference between responders and non-responders is not clear. If inactive renin is released from the kidney and converted to active renin, it may be possible that the conversion of inactive renin to active one in responders is more rapid than the renin release.

It may be concluded from this study that captopril augments the renin release and promotes the conversion of inactive renin to active one.

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References


