Urinary Excretion of Catecholamine Derivatives in Essential Hypertension

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Urinary excretion of norepinephrine (NE), epinephrine (E), normetanephrine (NMN), metanephrine (MN) and vanillyl mandelic acid (VMA) were measured in 10 hypertensive and 10 normotensive subjects at walking and in sleep. No difference in urinary excretion of each of NE, E, NMN, MN and VMA was observed in sleep between the hypertensive and normotensive subjects. Urinary excretions of NE, E, NMN, MN and VMA at walking were 3 to 6 times higher than those in sleep in both groups. The rate of increase in catecholamine excretion at walking was higher in the hypertensive subjects. At walking, urinary excretion of VMA in the hypertensive group was significantly higher. The ratio of VMA to total catecholamine was lower at walking.

Elevated urinary catecholamine excretion in the hypertensive suggests that the substance plays a role as a causative factor of hypertension.

Studies of hypertension induced by endogenous substances have been carried out with special attention to the adrenal medulla. However, the results of urinary excretion of catecholamines and their metabolites in essential hypertension have been controversial.

It is well established that excretion of catecholamines is increased under various conditions such as upright posture, exercise and emotional tension. Consequently, a proper comparison is possible only when the effects of such conditions are minimized at the measurement.

The present study was made to determine whether or not there are any differences in excretion of catecholamines between patients with essential hypertension and normal subjects by measuring the urinary output of norepinephrine (NE), epinephrine (E), normetanephrine (NMN), metanephrine (MN) and vanillyl mandelic acid (VMA) in sleep and at walking.

MATERIALS AND METHODS

Urinary excretion of NE and E, conjugated NMN and MN, and VMA at walking and in sleep was measured in 10 hypertensive subjects aged 20 to 47 years (averaging 37 years) with systolic blood pressure over 150 mm Hg and/or diastolic
blood pressure over 90 mm Hg and in 10 normotensive subjects aged 20 to 51 years (averaging 39 years).

The hypertensive subjects were company employees. Essential hypertension had been diagnosed by screening examination, but no medication was made until the present study had been performed. The control subjects were laboratory and hospital workers.

Overnight urine samples were collected, regarded as ones during sleep and used as controls. In order to collect urine samples at walking, each subject was led to walk about 3 km in an hour after an hour's rest, and then urine samples were collected.

NE and E were determined by the method of Euler and Lishjako,4 NMN and MN by the method of Janiguchi et al.5 and VMA by the method of Sandler and Ruthvein,6 and the excretion of these substances per one hour was calculated.

RESULTS

The results were summarized in Figs. 1 and 2. No significant difference was found in urinary excretion of NE, E, NMN, MN and VMA between the hypertensive and normotensive subjects in sleep. The urinary excretion of catecholamines

![Graph showing urinary excretion of catecholamines and their metabolites in normotensive subjects.]

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Fig. 2. Urinary excretion of catecholamines and their metabolites in hypertensive subjects. 
VMA: vanillyl mandelic acid. MN: metanephrine. 
S: in sleep W: at walking

in the hypertensive and normotensive subjects was higher at walking than that in sleep, and the normotensive subjects showed lower levels of NE, E, NMN, MN and VMA than those of the hypertensive subjects at walking.

Table 1 shows the averages and standard deviations of NE, E, NMN, MN and VMA excretions in the hypertensive and normotensive subjects. The ratios of (MN+N MN)/VMA and (E+NE)/(MN+N MN) were individually calculated and the mean of the ratios was shown in the table. No significant difference was observed between the hypertensive and normotensive in the urinary excretion of catecholamine, 3-methoxy catecholamine and VMA in sleep. The ratio of (MN+N MN) to VMA was higher in the hypertensive subjects than that in the normotensive subjects in sleep and at walking.

The urinary excretion of VMA at walking was 3 times higher than that in sleep in the normotensive subjects, whereas it was 6 times higher in the hypertensive subjects. Urinary excretion of NE, E, NMN and MN at walking was 3 to 6 times higher than that in sleep in both groups.

In sleep, the ratio of (E+NE) to (MN+N MN) in the normotensive subjects

<table>
<thead>
<tr>
<th>Group</th>
<th>Epinephrine (µg/hr)</th>
<th>Norepinephrine (µg/hr)</th>
<th>Metanephrine (µg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive subjects (sleeping)</td>
<td>0.05±0.08</td>
<td>0.62±0.29</td>
<td>1.87±1.24</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive subjects (walking)</td>
<td>0.15±0.14</td>
<td>3.64±2.04</td>
<td>5.65±2.21</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive subjects (sleeping)</td>
<td>0.04±0.04</td>
<td>0.59±0.38</td>
<td>2.31±1.59</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive subjects (walking)</td>
<td>0.06±0.08</td>
<td>4.26±3.09</td>
<td>8.48±4.02</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


TABLE 2. Endogenous amine metabolism

<table>
<thead>
<tr>
<th>Group</th>
<th>Catecholamine (E + NE)</th>
<th>3-methoxy catecholamine (MN + NMN)</th>
<th>VMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive subjects (sleeping)</td>
<td>1</td>
<td>6.4</td>
<td>150.5</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive subjects (walking)</td>
<td>1</td>
<td>5.2</td>
<td>75.5</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive subjects (sleeping)</td>
<td>1</td>
<td>9.5</td>
<td>141.3</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive subjects (walking)</td>
<td>1</td>
<td>5.4</td>
<td>143.8</td>
</tr>
<tr>
<td>(10 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive subjects (walking)</td>
<td></td>
<td>6.1</td>
<td>110.3</td>
</tr>
<tr>
<td>(7 cases)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These cases were excluded who showed high urinary VMA excretion.

was higher than that in the hypertensive subjects, whereas at walking the ratio in the normotensive subjects was lower than that of the hypertensive subjects.

A comparison of the metabolism of endogenous catecholamine between the hypertensive and normotensive subjects in sleep and at walking is shown in
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catecholamins and their metabolites

<table>
<thead>
<tr>
<th>Normetanephrine</th>
<th>Vanillyl mandelic acid</th>
<th>Total E + NE + MN + NMN + VMA</th>
<th>Ratio of (MN + NMN) / VMA</th>
<th>Ratio of (E + NE) / (MN + NMN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.27±1.93</td>
<td>97.8±35.9</td>
<td>102.0±30.6</td>
<td>0.048±0.035</td>
<td>0.179±0.063</td>
</tr>
<tr>
<td>14.03±5.15</td>
<td>285.5±119.8</td>
<td>308.9±111.6</td>
<td>0.085±0.050</td>
<td>0.196±0.081</td>
</tr>
<tr>
<td>3.69±1.01</td>
<td>99.4±38.3</td>
<td>105.4±41.2</td>
<td>0.069±0.042</td>
<td>0.131±0.086</td>
</tr>
<tr>
<td>14.62±4.95</td>
<td>621.2±312.1</td>
<td>648.9±306.7</td>
<td>0.105±0.072</td>
<td>0.265±0.130</td>
</tr>
</tbody>
</table>

NMN: normetanephrine. VMA: vanillyl mandelic acid.

Table 2. The ratios of 3-methoxy catecholamine and VMA to catecholamine excretion were similar in both groups.

At walking, however, the ratio of VMA to catecholamine in the hypertensive subjects was excessively high.

**DISCUSSION**

Possible relations between the catecholamines and essential hypertension are summarized as follows: a) Oversecretion of catecholamines induces hypertension; b) hyper-reactivity of blood vessels to catecholamines is responsible for the development of hypertension; and c) disturbance of catecholamine metabolism causes hypertension.

The normal urinary excretion of catecholamine was described in a number of the reports. However, some investigators reported that the excretion in hypertensive subjects was higher or lower than that in normal subjects.

VMA excretion in hypertensive subjects has been also said to be normal, high or low, and the excretion of 3-methoxy catecholamine in essential hypertension to be normal or high.

These conflicting results may be due to different conditions at the examination of subjects. In the present study which was performed under different conditions, it was clarified that 1) in sleep there were no differences in the urinary excretion of E, NE, MN, NMN and VMA between the hypertensive and normotensive subjects, 2) at walking, the urinary excretion of E, NE, MN, NMN and VMA was 3 to 6 times higher than that in sleep in both groups, and 3) the rate of increase of catecholamines in the hypertensive subjects at walking was higher than that in the normotensive subjects; especially there was a significant difference in the urinary excretion of
VMA at walking between the hypertensive and normotensive subjects. It means that the hypertensive subjects excrete more catecholamines than the normotensive ones when they were studied under comparable conditions.

The major pathway of catecholamine metabolism is first O-methylation of catecholamines to 3-methoxy derivatives, metanephrine and normetanephrine by catechol-O-methyl transferase, and then deamination by monoamine oxidase. A major end product is vanillyl mandelic acid. O-methylation is the major metabolic route for circulating catecholamine, and oxidative deamination may be the first step in inactivation of NE at the nerve ending.

Brunjes said in his early report that the ratio of 3-methoxy catecholamine to VMA was inversely proportional to monoamine oxidase activity, while the ratio of 

\[ \frac{(E+NE)}{(MN+NMN)} \]

is related to the degree of oxidative deamination. Furthermore, Brunjes said that the hypertensive subjects showed a remarkably elevated ratio of 

\[ \frac{(MN+NMN)}{VMA} \]

indicating anomalous catecholamine metabolism.

Gitlow et al. proposed hypothetically that a deficiency of O-methyl transferase in the vascular wall might delay the decomposition of catecholamine in the arterial wall.

In the present study, the ratio of 

\[ \frac{(MN+NMN)}{VMA} \]

in the normotensives and hypertensives was 0.048 and 0.069 in sleep, and 0.085 and 0.105 at walking, respectively. But it is difficult to conclude that there is abnormality of the catecholamine metabolism in essential hypertension.

As shown in Table 2, the decreased ratio of VMA and 3-methoxy catecholamine to catecholamine at walking may be explained from the fact that monoamine oxidase and catechol-O-methyl transferase activities cannot correspond to the increased concentration of circulating catecholamine following their oversecretion by stress. In the hypertensive group, the relative amount of VMA against catecholamines at walking was not different from that at sleeping. However, the ratio of 

\[ \frac{(E+NE)}{(MN+NMN)} : VMA \]

in these subjects at walking was 1 : 6 : 110, except for 3 cases with high urinary excretion of VMA (Cases No. 3, No. 5 and No. 8). This means that monoamine oxidase activity at walking in the hypertensive subjects as well as normotensive subjects cannot correspond to the increased catecholamine concentration.

The ratio of VMA to catecholamine reported by Brunjes is lower than our ratio. Brunjes determined only free catecholamine so that the ratio of VMA to catecholamine should be naturally higher as compared with our result. On the other hand, the ratio of VMA to catecholamine reported by Anton and Sayre was 132 in the day time and 190 at night, which agreed with our data (Table 3).

No conclusion can be drawn from the present results about the etiology of essential hypertension. However, it is conceivable that the elevated secretion of catecholamine in the hypertensive subjects possibly indicates an enhanced activity of the sympathetic nervous system, which is considered to be one of the causes of hypertension.
Urinary Catecholamine Excretion in Hypertension

TABLE 3. Endogenous amine metabolism

<table>
<thead>
<tr>
<th>Authors</th>
<th>Time</th>
<th>Catecholamine (E+NE)</th>
<th>3-methoxy catecholamine (MN+NMN)</th>
<th>DOMA</th>
<th>VMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brunjes 1964</td>
<td>Day time</td>
<td>(1F)</td>
<td>6.8</td>
<td>8.6</td>
<td>83.3</td>
</tr>
<tr>
<td>Anton &amp; Sayre</td>
<td>Day time</td>
<td>(1F+C)</td>
<td>3</td>
<td>9</td>
<td>132</td>
</tr>
<tr>
<td>1966</td>
<td>Night time</td>
<td>(1F+C)</td>
<td>5</td>
<td>16</td>
<td>190</td>
</tr>
<tr>
<td>Present data</td>
<td>Walking time</td>
<td>(1F+C)</td>
<td>5.2</td>
<td>\</td>
<td>75.5</td>
</tr>
<tr>
<td>1968</td>
<td>Sleeping time</td>
<td>(1F+C)</td>
<td>6.4</td>
<td>\</td>
<td>150.5</td>
</tr>
</tbody>
</table>


References


