Noradrenergic Mechanisms in the Brain and Peripheral Organs of Normotensive and Spontaneously Hypertensive Rats at Various Ages

KAUSHIK P. PATEL, M.SC., ROBERT L. KLINE, PH.D., and PAUL F. MERCER, PH.D.

SUMMARY Previous studies of noradrenergic mechanisms in spontaneously hypertensive rats (SHR) have yielded conflicting results, as many have used: 1) rats of only one age; 2) a single organ such as heart or brain; or 3) either Wistar-Kyoto (WKY) or an outbred normotensive control rat. We have studied the turnover of norepinephrine (NE) in three brain areas (cortex, hypothalamus, brain stem) and three peripheral organs (duodenum, skeletal muscle, kidney) of SHR, WKY, and Wistar rats at 5, 9, and 18 weeks of age. The rate of decline of norepinephrine [NE] in tissue was determined with a fluorescence assay at 0, 2, 4, and 8 hours after inhibition of tyrosine hydroxylase with α-methyltyrosine. Differences in NE turnover were inferred by comparing slopes of regression lines calculated for the plot of log [NE] (expressed as a percent of the initial concentration) vs time. Systolic arterial pressure of SHR was similar to that of WKY and Wistar rats at 5 weeks of age, but increased to 150 mm Hg by 9 weeks and reached an average of 190 mm Hg by 18 weeks. The turnover of NE in 5-week-old SHR compared to two normotensive strains was significantly lower in the cortex and significantly higher in the kidney and skeletal muscle. By 9 weeks, in SHR, NE turnover had increased significantly in the hypothalamus and brain stem, while decreasing significantly in the kidney and duodenum. No such changes were seen in these organs of WKY or Wistar rats when comparing turnover of NE at 5 and 9 weeks. At 18 weeks, there were no further differences in the organs of SHR when compared to values obtained at 9 weeks. These data support the hypothesis that the turnover of NE may be altered in central and peripheral organs of young SHR, and may initiate or contribute to the development of hypertension. Changes in turnover of NE in the brain and peripheral organs between 5 and 9 weeks in SHR suggest compensatory responses to increasing arterial pressure; however, similar changes in turnover were not seen between 9 and 18 weeks, although arterial pressure continued to increase. (Hypertension 3: 682-690, 1981)

Key Words • norepinephrine turnover • α-methyltyrosine • Wistar rats • WKY rats

NUMEROUS studies have been concerned with catecholamine metabolism in the spontaneously hypertensive rat (SHR) to determine the possible role of central catecholaminergic neurons and the sympathetic nervous system in the development and maintenance of hypertension. The results in the different studies are difficult to interpret and compare, as many investigators have used SHR of different ages, various strains of normotensive control rats, and various combinations of tissues from peripheral organs and brain. Many studies have considered the heart as a representative organ of the cardiovascular system, and few have looked at changes in the brain and peripheral organs simultaneously at different ages. Table 1 summarizes the studies of norepinephrine (NE) turnover in SHR that have been published to date.

In the present study, we have examined the turnover of NE, a dynamic measure of neuronal function, to determine whether differences in noradrenergic mechanisms exist between SHR and two different normotensive controls, Wistar-Kyoto (WKY) and outbred Wistar rats. Furthermore, as several lines of evidence suggest that neurogenic mechanisms may be involved during the early stages of the hypertensive process in SHR, rats of each strain were studied at 5, 9, and 18 weeks of age. These ages were chosen to represent the pre- or early hypertensive, the rapid-development phase, and the steady maintained phase.
of hypertension in SHR. The turnover of NE was measured systematically in several brain areas known to influence arterial pressure, as well as in the intestine, skeletal muscle, and kidney, three organs richly innervated by the sympathetic nervous system.

methods

Four-week-old SHR, WKY, and outbred Wistar rats (n = 72 for each strain) were purchased from Charles River Laboratory (Wilmington, Massachusetts) and randomly assigned to individual cages in a room with a 12-hour light cycle maintained at 20°–22°C. Food (Purina Rat Chow) and water were available ad libitum. Systolic arterial pressure (SBP) was measured using the tail cuff technique in a random sample of six rats from each strain at 5 weeks of age, and at 9 and 18 weeks of age in the SHR used at those ages for determination of norepinephrine (NE) turnover.

Measurement of Disappearance Rate of NE

The rate of decline of tissue NE after inhibition of tyrosine hydroxylase was determined at 5, 9, and 18 weeks of age in all three strains, using the method originally described by Brodie et al., and used more recently by VanAmeringen et al. in DOCA-salt rats and Patel et al. in rats with aortic depressor nerve transection. Briefly, the decline in endogenous NE was measured following inhibition of NE synthesis with the tyrosine hydroxylase inhibitor, DL-α-methyl-p-tyrosine methyl ester HC1 (Aldrich Chemical Company, Milwaukee, Wisconsin) given at a dose of 300 mg/kg i.p. every 4 hours. At each age and in each strain, the rats were randomly selected and killed by cervical fracture at 2 hours (n = 3), 4 hours (n = 5–6), and 8 hours (n = 5–6) after the first dose of the inhibitor. Six rats of each strain were also killed at 0 time to serve as controls. A section of the intestine (duodenum), the left kidney, a piece of skeletal muscle (from hindlimbs), and the whole brain were quickly removed. The brain was further sectioned on ice into three areas: 1) the brain stem (from 1 mm caudal to the obex to just caudal to the mammillary bodies); 2) the hypothalamus (from the optic chiasm to the mammillary bodies rostrocaudally, from the corpus callosum to the ventral surface dorsoventrally, and laterally to the edge of the optic tract); and 3) the cortex. The cerebellum was discarded.

Samples were weighed, homogenized in perchloric acid, and subsequently assayed in duplicate using a fluorescence assay for NE, as previously described. All samples were corrected for percent recovery using internal standards, and results were expressed as ng/g wet weight. The coefficient of variation (calculated from internal standards) between all the assays done over age, among strains, and among organs was less than 5%. Furthermore, the majority of the duplicate samples, which were randomized in different assay batches, when corrected for percent recovery were within 5% of the mean for that sample.

Data Analysis

The rate of decline of tissue NE was determined by expressing the tissue concentration of NE at different times after inhibition of tyrosine hydroxylase as a percent of the mean initial value. Data points (mean ± SE) were plotted on a log scale, and a best fit line was calculated using regression analysis. Correlation coefficients (r) ranged from 0.85 to 0.98, with the variation within an assay of less than 20%, with the variation within an assay of less than 5%. Furthermore, the majority of the duplicate samples, which were randomized in different assay batches, when corrected for percent recovery were within 5% of the mean for that sample.

Table 1. Summary of Studies of the Turnover of Norepinephrine in the Brain and Peripheral Organs of Spontaneously-Hypertensive Rats (SHR)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rat</th>
<th>Control</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>11-14</td>
<td>Wistar</td>
<td>29</td>
</tr>
<tr>
<td>Heart</td>
<td>10-15</td>
<td>Sprague-Dawley</td>
<td>30</td>
</tr>
<tr>
<td>Heart</td>
<td>11-14</td>
<td>Wistar</td>
<td>31</td>
</tr>
<tr>
<td>Ileum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>6,12</td>
<td>Wistar</td>
<td>23</td>
</tr>
</tbody>
</table>

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Results

The SBP was similar in all three strains of rats at 5 weeks of age (SHR, 126 ± 4 mm Hg; WKY, 122 ± 4 mm Hg; Wistar, 128 ± 3 mm Hg; n = 6 for each group). Thereafter, the SHR gradually developed a significantly higher pressure, reaching an average of 150 ± 2 mm Hg at 9 weeks and 190 ± 3 mm Hg by 18 weeks. Thus, the ages chosen corresponded appropriately to the pre- or early hypertensive stage, the rapid development stage, and the steadily maintained hypertensive stage in SHR. Although the body weight of WKY rats more closely resembled that of SHR than did that of Wistar rats, by 18 weeks there were significant differences between the body weights of all three strains. The body weights for SHR, WKY, and Wistar rats at 18 weeks of age were 336 ± 4 g (n = 18), 275 ± 4 g (n = 16), and 513 ± 8 g (n = 16), respectively.

Comparison of Disappearance Rate of Norepinephrine After Inhibition of Tyrosine Hydroxylase Among SHR, WKY, and Wistar Rats at Various Ages

Cortex

At 5 weeks of age, the slope of the regression line for cortex from SHR was significantly (p < 0.05) lower than those obtained for WKY and Wistar rats (fig. 1 and table 2). No differences existed at 9 weeks; at 18 weeks, however, the disappearance rate of NE was greater in the cortex of Wistar rats when compared to that of SHR and WKY rats.

Hypothalamus

No significant difference between the slopes of regression lines obtained for hypothalamus existed for SHR and WKY rats, or between WKY and Wistar rats at 5 weeks; however, there was a significant (p < 0.01) difference between SHR and Wistar rats at this age (fig. 2 and table 2). At 9 weeks no differences were noted, while at 18 weeks the turnover of NE in the hypothalamus of SHR was less than that in Wistar rats (p < 0.01) and greater than that in WKY rats (p < 0.05).

Table 2. Comparison of Slopes of Regression Lines for Disappearance Rate of Norepinephrine in the Organs of SHR, WKY, and Wistar Rats at Various Ages

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rat age</th>
<th>5 wks</th>
<th>9 wks</th>
<th>18 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>SHR vs WKY</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SHR vs Wistar</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>WKY vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>SHR vs WKY</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>SHR vs Wistar</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>WKY vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Brain stem</td>
<td>SHR vs WKY</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SHR vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>WKY vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Kidney</td>
<td>SHR vs WKY</td>
<td>p &lt; 0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SHR vs Wistar</td>
<td>p &lt; 0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>WKY vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Duodenum</td>
<td>SHR vs WKY</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SHR vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>WKY vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>SHR vs WKY</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>SHR vs Wistar</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>WKY vs Wistar</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Brain Stem

The turnover of NE in the brain stem was not significantly different among the three strains at 5 weeks of age, but at 9 weeks, NE turnover in the brain stem of SHR was significantly (p < 0.05) higher than...
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that in Wistar rats (fig. 3 and table 2). At 18 weeks,
the Wistar rats had a significantly (p < 0.01) higher
turnover of NE in the brain stem than did both SHR
and WKY rats.

Kidney

The rate of disappearance of NE was significantly
higher in the kidneys of SHR when compared to that
in kidneys of WKY rats (p < 0.01) and of Wistar rats
(p < 0.05) at 5 weeks of age (fig. 4 and table 4). No
differences in the turnover of NE in the kidney was
found among the three strains at 9 or 18 weeks of age.

Duodenum

No significant differences were found between
slopes of regression lines obtained for duodenum from
SHR and WKY rats at any age (fig. 5 and table 2).
There was a significant (p < 0.05) difference between
regression lines for duodenum from WKY and Wistar
rats at 18 weeks of age.

Skeletal Muscle

The turnover of NE in skeletal muscle was
significantly higher in SHR when compared to that in
Wistar rats at all three ages (fig. 6 and table 2).
Similarly, NE turnover in skeletal muscle of SHR was
significantly greater than that found for WKY rats at
5 and 9 weeks, but did not differ significantly at 18
weeks.

Comparison of Disappearance Rate of Norepinephrine After
Inhibition of Tyrosine Hydroxylase Within SHR, WKY, and
Wistar Rats

Spontaneously Hypertensive Rats (SHR)

Comparing changes in turnover with age, we
observed that, in the hypothalamus and brain stem,
there was an increase in the turnover of NE between 5
and 9 weeks of age, as shown by a significant
(p < 0.05) difference between the slopes of regression
lines (table 3). The half-life values changed from 5.5 to
4.2 hours and 4.8 to 4.2 hours in the hypothalamus.
and brain stem, respectively. On the contrary, in the kidney and duodenum, the slopes of the regression lines decreased significantly \((p < 0.05)\) over the same time. Half-life values changed from 3.3 to 4.8 hours and 4.0 to 5.6 hours, respectively. No further differences were noted between 9 and 18 weeks. Similarly, there were no differences noted for cortex and skeletal muscle with age.

**Wistar-Kyoto (WKY) Rats**

The turnover of NE in skeletal muscle and hypothalamus decreased significantly \((p < 0.01\) and \(p < 0.05\), respectively) in WKY rats between 5 and 9 weeks of age (table 4). No other changes were observed in any other organs with respect to age.

**Wistar Rats**

The turnover of NE in the brain stem of Wistar rats increased significantly \((p < 0.01)\) between 9 and 18 weeks of age, while that in the skeletal muscle decreased significantly \((p < 0.05)\) between 5 and 9 weeks of age (table 5). No other differences were noted.

**TABLE 3.** Slopes of Regression Lines for Disappearance Rate of Norepinephrine in the Organs of SHR at Various Ages

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rat age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 wks</td>
<td>9 wks</td>
<td>18 wks</td>
</tr>
<tr>
<td>Cortex</td>
<td>-0.061 ± 0.003</td>
<td>-0.068 ± 0.005</td>
<td>-0.064 ± 0.013</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>-0.054 ± 0.006</td>
<td>-0.072 ± 0.008†</td>
<td>-0.061 ± 0.007</td>
</tr>
<tr>
<td>Brain stem</td>
<td>-0.062 ± 0.002</td>
<td>-0.071 ± 0.004*</td>
<td>-0.056 ± 0.025</td>
</tr>
<tr>
<td>Kidney</td>
<td>-0.090 ± 0.032</td>
<td>-0.062 ± 0.014*</td>
<td>-0.057 ± 0.012†</td>
</tr>
<tr>
<td>Duodenum</td>
<td>-0.075 ± 0.029</td>
<td>-0.053 ± 0.013*</td>
<td>-0.048 ± 0.010*</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>-0.050 ± 0.005</td>
<td>-0.053 ± 0.006</td>
<td>-0.044 ± 0.005</td>
</tr>
</tbody>
</table>

Mean ± standard error (SE) for plot of log % mean initial NE concentration vs time.

*\(p < 0.05\) when compared to value for 5 weeks.
†\(p < 0.01\) when compared to value for 9 weeks.

There were no significant differences between slopes for 9 and 18 weeks.

**TABLE 4.** Slopes of Regression Lines for Disappearance Rate of Norepinephrine in the Organs of WKY Rats at Various Ages

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rat age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 wks</td>
<td>9 wks</td>
<td>18 wks</td>
</tr>
<tr>
<td>Cortex</td>
<td>-0.072 ± 0.006</td>
<td>-0.065 ± 0.003</td>
<td>-0.058 ± 0.003*</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>-0.068 ± 0.005</td>
<td>-0.066 ± 0.008†</td>
<td>-0.045 ± 0.007*†</td>
</tr>
<tr>
<td>Brain stem</td>
<td>-0.067 ± 0.004</td>
<td>-0.065 ± 0.002</td>
<td>-0.063 ± 0.005</td>
</tr>
<tr>
<td>Kidney</td>
<td>-0.056 ± 0.013</td>
<td>-0.059 ± 0.013</td>
<td>-0.059 ± 0.017</td>
</tr>
<tr>
<td>Duodenum</td>
<td>-0.057 ± 0.016</td>
<td>-0.065 ± 0.018</td>
<td>-0.046 ± 0.009†</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>-0.031 ± 0.004</td>
<td>-0.035 ± 0.004</td>
<td>-0.039 ± 0.007</td>
</tr>
</tbody>
</table>

Mean ± SE for plot of log % mean initial NE concentration vs time.

*\(p < 0.05\) when compared to value for 5 weeks.
†\(p < 0.01\) when compared to value for 9 weeks.

**TABLE 5.** Slopes of Regression Lines for Disappearance Rate of Norepinephrine in Organs of Wistar Rats at Various Ages

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rat age</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 wks</td>
<td>9 wks</td>
<td>18 wks</td>
</tr>
<tr>
<td>Cortex</td>
<td>-0.072 ± 0.003</td>
<td>-0.072 ± 0.006</td>
<td>-0.081 ± 0.005</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>-0.068 ± 0.007</td>
<td>-0.070 ± 0.009</td>
<td>-0.082 ± 0.005*</td>
</tr>
<tr>
<td>Brain stem</td>
<td>-0.061 ± 0.004</td>
<td>-0.059 ± 0.006</td>
<td>-0.077 ± 0.002† , †</td>
</tr>
<tr>
<td>Kidney</td>
<td>-0.062 ± 0.033</td>
<td>-0.068 ± 0.007</td>
<td>-0.075 ± 0.019</td>
</tr>
<tr>
<td>Duodenum</td>
<td>-0.058 ± 0.006</td>
<td>-0.062 ± 0.009</td>
<td>-0.065 ± 0.014</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>-0.038 ± 0.006</td>
<td>-0.023 ± 0.004*</td>
<td>-0.030 ± 0.009</td>
</tr>
</tbody>
</table>

Mean ± SE for plot of log % mean initial NE concentration vs time.

*\(p < 0.05\) when compared to value for 5 weeks.
†\(p < 0.001\) when compared to value for 5 weeks.
‡\(p < 0.01\) when compared to value for 9 weeks.
**Figure 4.** Turnover of norepinephrine (NE) in kidney of SHR, WKY, and Wistar rats after inhibition of tyrosine hydroxylase with α-methyltyrosine. Format as in figure 1. See table 2 for statistical comparisons.

**Figure 5.** Turnover of norepinephrine (NE) in duodenum of SHR, WKY, and Wistar rats after inhibition of tyrosine hydroxylase with α-methyltyrosine. Format as in figure 1. See table 2 for statistical comparisons.

**Figure 6.** Turnover of norepinephrine (NE) in skeletal muscle of SHR, WKY, and Wistar rats after inhibition of tyrosine hydroxylase with α-methyltyrosine. Format as in figure 1. See table 2 for statistical comparisons.
Discussion

The turnover of NE represents the net effect of synthesis (strongly affected by impulse traffic), catabolism, uptake, and storage of NE at the nerve ending, and is thus a dynamic measure of neuronal function. In this study, the rate of decline of endogenous NE after inhibition of tyrosine hydroxylase (expressed as a percent of the initial value) was used as an index of NE turnover. We have recently tested the usefulness of this technique in detecting changes in sympathetic nerve activity in hypertensive animals, using a neurogenic model of hypertension produced by bilateral transection of the aortic depressor nerve in rats. As would be predicted on the basis of loss of specific inhibitory input to noradrenergic neurons involved in the regulation of arterial pressure, NE turnover was increased in the hypothalamus, midbrain, and medulla, as well as in the kidney and skeletal muscle, but not in the duodenum. The changes in NE turnover in the peripheral organs agreed well with changes in vascular resistance reported due to neurally-mediated vasoconstriction in similarly daffferentiated animals.

However, differences in the turnover of NE between SHR and normotensive rats, or changes over age within a given strain, may not necessarily be due to altered neuronal activity alone, although it has been reported that there are no differences in catabolism or uptake of NE in SHR when compared to those processes in normotensive control rats. Unfortunately, systematic studies of these variables among various strains at different ages have not been reported. Recently, Collis et al. provided evidence that the release of NE in response to nerve stimulation is increased in SHR compared to that in WKY rats, suggesting that differences in neuronal function do exist. In addition, as effector organ responses are a complex function of various neuronal processes plus receptor numbers and characteristics, the functional interpretation of differences in NE turnover is difficult, especially when comparing animals with possible genetic differences. Nevertheless, the measurement of NE turnover does provide useful information about neuronal function and may suggest possible alterations in noradrenergic mechanisms that are related to the cause or the effect of the hypertensive process.

Comparison of Norepinephrine Turnover in SHR, WKY, and Wistar Rats

Various investigators have suggested that WKY rats should be used as normotensive controls for SHR on the basis of their similar genetic background and hemodynamic characteristics such as cardiac output. In this study, WKY rats seemed more closely related to SHR in terms of body weights, but significant differences still existed. It is of interest that, of the 18 possible comparisons of regression lines between any two of the three strains at three ages, there were 10 differences noted between SHR and Wistar rats, five differences between SHR and WKY rats, and four differences between WKY and Wistar rats.

It is clear from these data that the use of different normotensive strains may lead to different conclusions about noradrenergic mechanisms in SHR. Similarly, it is clear that studies in which only one organ was examined, or in which only one age of SHR was used, lead to conclusions that cannot be generalized to the whole animal at any age. For example, the turnover of NE in the duodenum did not differ with age in SHR nor was it different from that in WKY rats at any age, leading to the possible conclusion that the turnover of NE is not different in SHR and WKY rats. The present study was an attempt to give a better overall picture of NE turnover in the brain and peripheral organs of SHR at various ages, and how it may or may not differ from similar measurements made in normotensive rats. It is recognized that the use of large brain sections does not permit specific conclusions to be made about central noradrenergic mechanisms. In the cases where no significant differences were found, it is entirely possible that only small changes occurred in specific nuclei or that opposing changes cancelled each other.

The significantly lower turnover of NE in the cortex of SHR before the elevation of arterial pressure (5 weeks of age) compared to that in WKY and Wistar rats suggests a possible initiating role of higher brain structures in the hypertensive process. Yamori et al. reported similar results in 6-week-old SHR. At the same age, SHR showed an increased turnover of NE in the kidney and skeletal muscle compared to either WKY or Wistar rats, suggesting a possible involvement of the sympathetic nervous system in these areas in the early stages of hypertension. These data for the kidney support the finding of increased renal nerve activity in young SHR compared to age-matched Wistar rats and are compatible with the idea that more NE is released during renal nerve stimulation in SHR than in WKY rats at 6 weeks of age. Although none of these data permits conclusions about enhanced renal nerve influence on renal function in SHR, the data are of interest in light of the findings that renal denervation at an early age delays the development of hypertension in SHR, but has no effect on the arterial pressure of WKY rats. The differences in NE turnover in peripheral organs at 5 weeks are similar to those seen in rats with aortic depressor nerve transection, i.e., increased turnover in skeletal muscle and kidney but no difference in duodenum, suggesting a possible differential alteration of sympathetic activity. The reciprocal relation between turnover of NE in the brain and peripheral organs of SHR has been reported previously, and has been suggested as being involved in the hypertensive process. A similar reciprocal relation has been reported for rats made hypertensive with DOCA-salt. However, we have recently shown in rats with aortic depressor nerve transection that increased turnover of NE in peripheral organs was associated with increased turnover in the brain as well. These differences suggest that different central noradrenergic mechanisms may
be involved in different types of hypertension or that the reciprocal changes are not a cause and effect relationship.

In rats at 9 weeks of age, when arterial pressure was increasing rapidly in SHR, there were no differences noted in the turnover of NE in the brain or peripheral organs between SHR and WKY rats except in skeletal muscle. These studies agree reasonably well with recent studies reported by Touw et al., in which the neural component of vascular resistance was assessed in conscious SHR and WKY rats at 8 and 13 weeks of age. Using the percent change of vascular resistance after ganglionic blockade as an index of neural tone, they found no significant difference between SHR and WKY rats for renal, mesenteric, and hindlimb vascular beds, and concluded that, functionally, there was no greater sympathetic component in SHR than in WKY rats at either age. However, Judy et al. reported increased renal nerve activity in SHR at this age (compared to Wistar rats), and Fink and Brody provided evidence to suggest that there was a decreased release of NE in response to nerve stimulation in 12-week-old SHR when compared to responses obtained in WKY rats. These results are compatible with those reported by Touw et al. and the results of the present study, as increased renal nerve activity with decreased release of NE would not necessarily increase NE turnover, nor would it increase sympathetic influence on the effector organ. The differences in turnover of NE in skeletal muscle at 9 weeks are difficult to explain and require further study.

In 18-week-old rats, SHR and WKY differed with respect to turnover of NE only in the hypothalamus. If noradrenergic mechanisms within the hypothalamus are concerned with maintaining the elevated arterial pressure, it appears that increased sympathetic influence on peripheral organs is not involved.

Comparison of Norepinephrine Turnover in SHR at Various Ages

Due to the persistent problem of deciding upon the proper normotensive control for SHR, perhaps more meaningful comparisons can be made between SHR at various stages of the hypertensive process. The reciprocal relation between central and peripheral NE metabolism is again evident when comparing results obtained in SHR at 5 to 18 weeks of age. There was a significant increase in the turnover of NE in the hypothalamus and brain stem from 5 to 9 weeks, and during the same time there was a significant reduction in NE turnover in kidney and intestine. During this time, the arterial pressure rose from 120 to 150 mm Hg. It is conceivable that the decrease in the NE turnover in certain peripheral organs may be part of a mechanism involved in attempting to compensate for the rising arterial pressure. It is interesting to note, however, that although arterial pressure continued to rise in SHR between 9 and 18 weeks of age, there were no further changes in NE turnover in the brain or peripheral organs. This would suggest that: 1) the changes observed between 5 and 9 weeks were not related to a compensatory response to increasing pressure; 2) maximum compensation was reached by 9 weeks; or 3) neural mechanisms had adapted to the elevated arterial pressure. The well-known adaptation of arterial baroreceptors to elevated arterial pressure would support the latter possibility.

In summary, the data reported in our study provide the basis for a systematic comparison of NE turnover in the brain and peripheral organs of SHR and two normotensive control strains at various ages. The data in general support the hypothesis that a neurogenic component is involved in the early stages of development but not in the maintenance of hypertension in SHR. In addition, the data clearly show the necessity of studying several organs at various ages in SHR if one is interested in determining whether differences in noradrenergic mechanisms exist in this model of hypertension. Similarly, one cannot measure changes in NE turnover in the brain and assume that these changes are translated to altered sympathetic nerve activity in peripheral organs. Finally, the problem of appropriate controls for SHR was considered by using both inbred WKY rats and outbred Wistar rats. Interpretation of results may differ depending upon which normotensive rats are used, as we found twice as many differences between SHR and Wistar rats as between SHR and WKY rats. It may be more meaningful to compare SHR at various ages rather than between strains.

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