Peripheral Dopamine Synthesis and Metabolism in Spontaneously Hypertensive Rats

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SUMMARY. We have studied several parameters of peripheral dopamine synthesis and metabolism in spontaneously hypertensive rats during the development of hypertension. Compared to Wistar-Kyoto rats, there was an increased dopamine content in 8-week-old spontaneously hypertensive rats in the adrenals (1.6 ± 0.1 vs. 1.2 ± 0.1 nmol/pair in Wistar-Kyoto rats) and kidneys (97 ± 12 vs. 63 ± 7 pmol/g tissue in Wistar-Kyoto rats), but the dopamine content in peripheral organs from normotensive 4-week-old spontaneously hypertensive rats did not differ from Wistar-Kyoto rats. In the heart, the dopamine increase was observed in 14-week-old spontaneously hypertensive rats (systolic blood pressure: spontaneously hypertensive rats, 189 ± 9; Wistar-Kyoto rats, 106 ± 2 mm Hg) in both atrium (spontaneously hypertensive rats, 133 ± 14; Wistar-Kyoto rats, 86 ± 20 pmol/g tissue) and ventricle (spontaneously hypertensive rats, 41 ± 6; Wistar-Kyoto rats, 23 ± 5 pmol/g tissue). Urinary free dopamine and dihydroxyphenylacetic acid, but not norepinephrine or normetanephrine, in spontaneously hypertensive rats significantly increased between the ages of 7 and 11 weeks, reflecting the dopamine changes in tissue and suggesting a selective increase of the rate of dopamine synthesis and release. The selectively increased dopamine synthesis was confirmed in the adrenals by pulse injection of [3H]tyrosine (700 μCi/kg) which showed a significantly shorter half-life of adrenal dopamine in 8-week-old spontaneously hypertensive rats (68 ± 4 vs. 86 ± 9 minutes in Wistar-Kyoto rats) and 14-week-old spontaneously hypertensive rats (46 ± 2 vs. 67 ± 8 minutes in Wistar-Kyoto rats), while the adrenal norepinephrine and epinephrine content and turnover were not significantly increased compared to Wistar-Kyoto rats. The results suggest that an increased peripheral dopamine synthesis and release is associated with the sequence of events resulting in the appearance of hypertension in spontaneously hypertensive rats. (Circ Res 58: 889-897, 1986)

THERE is substantial evidence for a sympathoadrenal dysfunction in spontaneously hypertensive rats (SHR). Of the several mechanisms that may result in alterations within the central and peripheral catecholaminergic system (Haeusler et al., 1972; Nagatsu et al., 1977; Saavedra et al., 1978; Maemura et al., 1982; Grobecker et al., 1982), a centrally initiated facilitation of the sympathetic nervous system activity has been strongly implicated (Haeusler et al., 1972; Nagatsu et al., 1977). Although many studies suggested that plasma catecholamines (CA) are normal in SHR, the stress-related CA release to the general circulation has been shown to be exaggerated in these animals (McCarty and Kopin, 1978). The adrenal gland, an important source of peripheral CA, has been the subject of numerous studies designed to study the roles of CA at various stages of hypertension. When compared to Wistar-Kyoto (WKY) rats, the 4-week-old SHR had lower norepinephrine (NE) and epinephrine (E) content as well as biosynthetic enzyme activities in their adrenal glands (Grobecker et al., 1972, 1982). At the advanced hypertensive stage (8 weeks of age), the activities of dopamine-β-hydroxylase and phenylethanolamine N-methyltransferase in SHR remained low, whereas tyrosine hydroxylase increased (Grobecker et al., 1982), indicating a non-uniform change in biosynthetic enzyme activities during the course of hypertension. Other reports also suggested a critical importance of the age of SHR, as well as of the type of control strains, in considering the role for the sympathetic nervous system in this experimental model of hypertension (Haeusler et al., 1972; Lovenberg et al., 1973; Chalmers, 1975; Nagatsu et al., 1977). The possibility that the sympathetic nervous system may regulate the blood pressure (BP) in SHR was supported by the observation that pharmacological abolition of the catecholaminergic neurons by 6-hydroxydopamine resulted in a decrease of BP (Haeusler et al., 1972; Yamori et al., 1972). Finally, further support for this proposal was provided by measurements of action potentials in visceral sympathetic nerves (Judy et al., 1976) and in posterior hypothalamus (Takeda and Bunag, 1978). There are only a few reports on the synthesis, tissue content, and metabolism of dopamine (DA) in SHR (Ablad et al., 1977; Lutold et al., 1979; Maemura et al., 1982; Ozaki et al., 1982). Although a selectively decreased DA metabolism in sympathetic ganglia of young normotensive SHR has been
suggested to play a role in the development of hypertension (Lutold et al., 1979), the levels of DA in peripheral tissues were found to be low, and it has therefore been difficult to evaluate the pathophysiological significance of a dopaminergic mechanism in BP regulation. However, more recent studies indicated that dopaminergic mechanisms may participate in BP regulation of SHR. The activity of the renin-angiotensin-aldosterone system may be regulated by the endogenous dopaminergic tone, since pharmacological inhibition of the dopaminergic activity by DA receptor antagonist may modulate the aldosterone response to angiotensin II (AII) (Gordon et al., 1983). Other experiments suggested that SHR have high plasma renin activity (PRA) and AII levels compensatory to a decreased aldosterone responsiveness to AII (Williams et al., 1982). The increased AII may undoubtedly contribute to hypertension in SHR since administration of AII antagonist resulted in a significant decrease of BP in SHR (Munoz-Ramirez et al., 1978). In the present study, we report consistent increases of several indices of the peripheral DA synthesis and release in SHR which could account for the compensatory increase in the activity of the renin-angiotensin system and thus promote the development of hypertension.

Methods

All chemicals used were of the highest purity (analytical grade). Buffers and aqueous solutions were prepared in distilled deionized water. Reference standard catecholamines and metabolites were purchased from Calbiochem, 1-[3H]tyrosine (ring 2,3,5,6; specific activity, 72 Ci/mmol) was from Amersham Corp., Tris (free base) was from Schwarz/Mann, alumina was from Woelm Pharma, and fusaric acid was from Sigma Chemical Co.; other chemicals were from Fisher Scientific Co.

Male SHR and Wistar-Kyoto (WKY) rats were obtained from Charles River Canada Inc. and were housed in our animal room five or six per cage, with ordinary rat chow and water ad libitum and a 12-hour dark-light cycle. Systolic BP was measured in unanesthetized rats using a tail plethysmograph (Pfeffer et al., 1971). At the ages of 4, 7, 9, 11, and 13 weeks, equal numbers of SHR and WKY rats were placed in metabolic cages and, after an overnight accommodation period, urine samples were collected 24 hours. Tissue catecholamines (CA) were determined in 4-, 8-, and 14-week-old rats. After decapsulation, the heart, kidneys and adrenals were removed and immediately frozen until required.

In another series of experiments, the adrenals of 12-week-old SHR and WKY rats were separated into capsular (mainly capsule and zona glomerulosa) and decapsulated (mainly zona fasciculata-reticularis plus medulla) portions using a method described by Tait et al. (1974). After the adrenals were freed from fat, the decapsulation was accomplished by bisecting the glands, then gently squeezing out their inner portion.

Twelve SHR and 12 WKY rats at each age of 4, 8, and 14 weeks were divided into two groups, were administered the same iv injection of [3H]tyrosine (700 μCi/kg, body weight; specific activity, 72 Ci/mmol), and were sacrificed at 15 minutes (group 1) or 75 minutes (group 2) thereafter.
1983), consisted of a wash with 3.5 ml of 0.01 M formic acid and 1.0 ml of sodium phosphate buffer (0.01 M, pH 8.5) followed by elution with 2.0 ml of the above buffer into 50 μl of 6 M formic acid. The sample preparation and the HPLC mobile phase were as described for urinary HVA (Westerink et al., 1982). Chromatography was accomplished on a system similar to that for CA, equipped with a Spherisorb ODS-2 packed column (25 × 0.46 cm, CSC Inc.) and a glassy carbon electrode at a potential of +0.700 V relative to Ag/AgCl reference electrode. The concentration of DOPAC and HVA in each sample was calculated from the respective peak heights in relation to the same sample spiked with standards (1.5 μg/ml DOPAC and 2.5 μg/ml HVA).

Data are presented as the mean ± SE. Tissue CA values are expressed in pmol/g or nmol/g tissue (heart, kidneys); the CA content in adrenals is presented in pmol/g or nmol/pair. Because of the similar adrenal weight of SHR and WKY rats of the corresponding ages, we found the same statistical differences between SHR and WKY rats when the adrenal CA were calculated in nmol per organ weight. The statistical significance of the differences between mean values of SHR and WKY rats was analyzed by Student's t-test for unpaired observations. P < 0.05 was considered to be a significant difference.

Results

Blood Pressure and Weight of Organs

At 4 weeks of age, the mean systolic BP of both SHR and WKY rats was comparable (106 ± 3 and 109 ± 3 mm Hg in SHR and WKY rats, respectively). The systolic BP of WKY rats remained constant between the ages of 4 and 14 weeks. At the ages of 8 and 14 weeks, the systolic BP of SHR was, respectively, 147 ± 5 and 189 ± 9 mm Hg (P < 0.001 compared to WKY rats of the same age).

The body weights of SHR and WKY rats at the ages of 4, 8, and 14 weeks were not significantly different. In contrast, we found significantly higher weights of kidneys and heart in SHR compared to those in WKY rats at ages of 4 and 8 weeks (Table 1). As might be expected, at 14 weeks of age, the heart of SHR also weighed more than the WKY's heart. In contrast to younger animals, the weight of the kidneys was inferior in SHR to that in WKY rats at 14 weeks of age, but this difference was not statistically significant.

Tissue CA content

As shown in Figure 1, there was a similar range of kidney DA in the SHR as in WKY rats at 4 weeks of age, but it greatly exceeded the controls at other ages (8-week-old SHR: 97 ± 12; WKY rats: 63 ± 7; 14-week-old SHR: 108 ± 11; WKY rats: 67 ± 6 pmol/g tissue). The kidney NE was also higher in SHR than in WKY rats, but the difference was not statistically significant at these same ages.

Figure 2 shows the changes in heart DA and NE content between the ages of 4 and 14 weeks. Increases in heart DA content (both atrium and ventricle) were found in 14-week-old SHR: (atrium: SHR, 133 ± 14 vs. 86 ± 20 pmol/g tissue in WKY; ventricle: SHR, 41 ± 6 vs. 23 ± 5 pmol/g tissue in WKY); at this stage of hypertension, NE had not increased, compared to WKY rats of the same age.

The adrenal content of DA showed no difference between normotensive SHR and WKY rats at the age of 4 weeks (Fig. 3). However, adrenal DA had increased significantly in SHR at 8 weeks (1.6 ± 0.1 vs. 1.2 ± 0.1 nmol/pair in WKY) and 14 weeks of
FIGURE 2. Dopamine (top) and norepinephrine (bottom) content in heart, both atrium and ventricle, from SHR and WKY rats of different ages. Each column represents the mean for 10-12 rats. For symbols see Figure 1.

age (1.8 ± 0.1 vs 1.3 ± 0.1 nmol/pair in WKY). Also, although the adrenal NE content was higher at all of the times studied, it was not significantly different from that of WKY rats of the corresponding ages. The adrenal E content was similar in SHR and WKY rats at each age.

Table 2 shows that the high adrenal DA content of hypertensive SHR was accounted for by an increase of DA in the decapsulated portion of the gland. The capsular tissue had a lower but significant content of DA in both groups of rats.

Adrenal CA Synthesis and Turnover Rate

In the present study, we have tried to determine whether the high DA content in adrenals of hypertensive SHR was due mainly to increased DA synthesis, or whether the adrenal DA, as a precursor of NE and E, simply reflected changes in NE and E synthesis. The synthesis of adrenal DA was studied in 4-, 8-, and 14-week-old SHR and WKY rats following a pulse iv injection of [3H]tyrosine (Fig. 4). From 15-75 minutes after the injection, the [3H]DA markedly decreased in the adrenals; during the same period of time, the NE and E labeling significantly increased in all groups of animals, indicating that [3H]DA, formed from [3H]tyrosine, was probably converted to [3H]NE and [3H]E. By comparing the disappearance rates of [3H]labeled DA in SHR and WKY rats, we found no significant differences in 4-week-old animals. However, the adrenals of 8- and 14-week-old hypertensive SHR displayed an accelerated disappearance of [3H]DA, suggesting a shorter half-life and increased turnover of adrenal DA. (The apparent half-lives of adrenal DA were as follows: 4-week-old SHR and WKY rats, 86 ± 9 and 96 ± 9; 8-week-old SHR and WKY rats, 68 ± 4 and 86 ± 9; 14-week-old SHR and WKY rats, 46 ± 2 and 67 ± 8 min, respectively.) These significant differences in the time-course of the labeled DA disappearance between hypertensive SHR and age-matched WKY rats could not be explained by differences in the amounts of [3H]tyrosine supplied by the plasma (Table 3), or by an increased conversion of [3H]DA to [3H]NE and [3H]E (Fig. 4).

In the next series of experiments, we administered

TABLE 2

<table>
<thead>
<tr>
<th>12-wk-old WKY (nmol/pair)</th>
<th>0.97 ± 0.08</th>
<th>0.09 ± 0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-wk-old SHR (nmol/pair)</td>
<td>1.63 ± 0.11*</td>
<td>0.08 ± 0.02</td>
</tr>
</tbody>
</table>

Data are means ± se from groups of 11 SHR and 11 WKY rats. * P < 0.001 between the two groups of rats.
fusaric acid, an inhibitor of dopamine-β-hydroxylase (Nagatsu et al., 1970), intraperitoneally, to 8-week-old SHR and WKY rats in order to determine the turnover of adrenal NE and E. This drug is a specific inhibitor of dopamine-β-hydroxylase in vivo, although it may inhibit tyrosine hydroxylase at high concentrations in vitro (Nagatsu et al., 1970). From 0-120 minutes, the adrenal E decline rate was similar in SHR and WKY rats (Fig. 5) indicating that the turnover of E was not increased in 8-week-old hypertensive SHR, as might have been expected from the accumulation of adrenal 3H-labeled E formed from [3H]tyrosine. The decrease of adrenal NE was faster in WKY rats than in SHR: the difference in adrenal NE content between the two groups of rats was significant at 120 minutes.

The injection of fusaric acid resulted in an approximate 5-fold increase of adrenal DA content (Fig. 5). Although the SHR had significantly higher DA content than WKY rats prior to the treatment, the accumulation of adrenal DA in response to fusaric acid did not differ between SHR and WKY rats. This finding might be justified if the changes in adrenal DA of hypertensive SHR occur independently of changes in its precursor function. Therefore, we attempted to confirm whether the fusaric acid treated SHR could have, despite the similar response to the drug treatment in both groups of rats, an increased DA synthesis. Table 4 illustrates that the adrenals of fusaric acid-treated 8-week-old SHR and WKY rats did not contain 3H-labeled NE and E after the infusion of [3H]tyrosine, suggesting that there was complete inhibition of the dopamine-β-hydroxylase. The nonlabeled DA accumulation was indistinguishable between the two groups of rats, which might indicate that the utilization of DA for NE plus E synthesis was not different between SHR and WKY rats. However, the 3H-labeled DA content arising from [3H]tyrosine was significantly higher in SHR than in WKY rats, confirming the excessive DA synthesis in the hypertensive animals.

### Urinary Excretion of CA and CA Metabolites

Figure 6 summarizes the urinary free DA and DA metabolites in SHR and WKY rats between 4 and 13 weeks old. The urinary excretions of normotensive SHR were not different from those of WKY rats of the same age. In hypertensive SHR, however, the free DA and DOPAC excretions were consistently higher than in WKY rats at all ages between 7 and 11 weeks. At the age of 13 weeks, the difference in free DA excretion between SHR and WKY rats disappeared, although the urinary DOPAC remained significantly higher in SHR (63 ± 8 vs. 31 ± 4 nmol/24 hours in WKY rats). The urinary HVA excretion decreased slightly with age in both SHR and WKY rats, but this DA metabolite showed no difference between the two groups of animals.

### Table 3

Specific Activities of Tyrosine in Plasma after the Injection of 3H-Labeled Tyrosine

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>8-wk-old WKY</th>
<th>8-wk-old SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>5.7 ± 0.37 (n = 6)</td>
<td>5.3 ± 0.37 (n = 6)</td>
</tr>
<tr>
<td>75</td>
<td>0.47 ± 0.18 (n = 6)</td>
<td>0.63 ± 0.07 (n = 6)</td>
</tr>
</tbody>
</table>

After iv pulse injections of [3H]tyrosine (700 μCi/kg), rats were sacrificed at 15 or 75 minutes. Specific activities are expressed in fmol 3H-labeled/nmol total tyrosine (mean ± se), n = number of rats. No significant differences existed between mean values of SHR and WKY rats.
Figure 5. Logarithmic plot of accumulation of dopamine and disappearance of epinephrine and norepinephrine in adrenals of 8-week-old SHR and WKY rats after synthesis inhibition with fusaric acid. Rats receiving fusaric acid (single intraperitoneal dose, 100 mg/kg) were killed at various times between 0 and 120 minutes after the injection. Shown are the means ± SE each point represents the mean for four to six rats. *P < 0.05.

Urinary free NE and NM excretion was never elevated in SHR as compared to controls between the ages of 4 and 13 weeks (Fig. 7). In addition, there was no increase in the NE and/or NM excretion with an increase of BP in SHR: normotensive 4-week-old and hypertensive 13-week-old SHR had significantly less urinary free NE and NM than WKY rats of the corresponding ages (NE: 4-week-old SHR and WKY rats, 2.5 ± 0.5 and 4.1 ± 0.5 nmol/24 hours, respectively; 13-week-old SHR and WKY rats, 4.8 ± 0.5 and 6.9 ± 0.4 nmol/24 hours, respectively; NM: 4-week-old SHR and WKY rats, 3.8 ± 0.5 and 6.2 ± 0.2 nmol/24 hours, respectively; 13-week-old SHR and WKY rats, 6.5 ± 0.5 and 9.2 ± 1.2 nmol/24 hours, respectively), whereas both NE and NM in 7-, 9-, and 11-week-old SHR were in a range similar to WKY rats.

Discussion

Data from the present experiments confirm and extend previous studies indicating an increased DA content in adrenals of hypertensive SHR (Ablad et al., 1977; Maemura et al., 1982; Ozaki et al., 1982) without concomitant increases in adrenal NE and E content (Ozaki et al., 1982). However, the increase in DA content could be due to several mechanisms involved in the adrenal DA synthesis, release, storage, and metabolism. In the present work, it was
possible to study the adrenal synthesis of DA separately by pulse labeling of the adrenal CA with $[^3H]$tyrosine. These experiments revealed an increased decline rate of $[^3H]$DA in the adrenals of hypertensive animals. It was unlikely that a change in the formation of NE and/or E might be responsible for the accelerated disappearance of $[^3H]$DA from adrenals of hypertensive SHR, since the $[^3H]$-NE and $[^3H]$E accumulations were similar in the SHR and WKY rats at each age. On the other hand, the possibility could not be ruled out that an increase in the adrenal release and/or metabolism of labeled NE plus E subsequent to their synthesis in hypertensive SHR could escape attention by the measured indices. Apposed to this possibility is the finding that the decline of endogenous NE and E after inhibition of the synthesis with fusaric acid was not greater in 8-week-old SHR than in WKY rats (that of NE was even slower), indicating that the turnover rate of adrenal NE and E was not increased. Further supporting the selectivity of changes in adrenal DA of hypertensive SHR was the finding that in hypertensive (8-week-old) SHR, the utilization of DA for NE plus E synthesis had not changed, although those rats had an excessive adrenal DA synthesis.

The increase of DA in hypertensive SHR was not exclusive to the adrenals: we found that the kidneys of 8- and 14-week-old SHR, as well as the heart of 14-week-old SHR, contained more DA than those of WKY rats of the corresponding ages. A report by Gianutsos and Moore (1978) showed that the DA content of sympathetic ganglia was also higher in hypertensive SHR than in WKY rats, although Lutold et al. (1978) reported different results in those same tissues. The increased kidney content of DA may be responsible for the most recently observed reduced renal cortical DA receptor binding in hypertensive (8-week-old) but not normotensive (4-week-old) SHR (Beck and Sowers, 1984), by provoking a down-regulation of dopaminergic receptors in this organ.

The increased activity of the peripheral dopaminergic system may have pathogenetic significance in the course of development of hypertension in SHR. It has been shown that administration of the DA antagonist metoclopramide during high-salt intake increased the adrenocortical sensitivity to All (Gordon et al., 1983), suggesting that the adrenocortical responsiveness to All may be regulated by the endogenous dopaminergic tone. Conversely, infusion of DA (Aguilera et al., 1984) and a DA agonist (Whitfield et al., 1980) reduced the aldosterone response to All, best documented in the sodium-restricted state. The increased dopaminergic tone in SHR may be an important factor in determining their adrenocortical sensitivity, since these rats exhibit a decreased adrenocortical responsiveness to All (Williams et al., 1982). The marked reduction of BP with angiotensin antagonist in SHR (Munoz-Ramirez et al., 1978) supports a role for this adrenocortical abnormality, since the BP regulation of SHR may be highly All-dependent, owing to a compensatory increase in PRA and All concentrations (Williams et al., 1982).

To investigate further the possible significance of DA in adrenocortical regulation, we determined the cortical and medullary content of DA in SHR and WKY rats. These studies indicated that a significant proportion of DA was present in the outer adrenal cortex in both groups of rats, but the high adrenal DA content of hypertensive SHR was accounted for by an increase of DA in the decapsulated portion of the gland. However, our study did not rule out that the changes in SHR represent alterations in both
cortical and medullary DA content, since the method used for the dissection provided only an approximate separation of the outer cortex. By analogy with the above All-responsiveness studies, it would appear that the differences in cortical DA between SHR and WKY rats could be better evaluated during changes in dietary sodium intake.

Other possible mechanisms by which the increased peripheral dopaminergic activity could be related to the BP elevation of SHR, are not fully understood. The increase in peripheral DA may be involved in stress-related CA responses (Snider et al., 1974; Waldeck et al., 1975) which were found to be exaggerated in SHR (McCarty and Kopin, 1978). It is possible that the rise in DA may be a marker of the sympathetic discharge not always reflected by increases in the concentrations of NE and E (Kuchel et al., 1982), which could be related to the previously mentioned disbalance of CA-synthesizing enzymes. However, an activation of the peripheral dopaminergic system in the course of BP increase in SHR might also represent a compensatory mechanism in which DA acts against the usually opposite actions of NE on the renovascular (McDonald et al., 1964; Goldberg, 1972), renal tubular (Davis et al., 1968), cardiovascular (Eble, 1964; Goldberg, 1972), and adrenocortical (McKenna et al., 1978; Carey et al., 1979) targets. Finally, a direct relationship between increased peripheral DA and hypertension cannot be excluded: DA can also raise BP in SHR, but this requires very high doses of DA (De Palma and Ackerman, 1982); this hypothesis is therefore very improbable.

In summary, this study demonstrates consistent increases of several indices of peripheral DA synthesis and release during the hypertensive stage of SHR. Only dynamic interventions into the dopaminergic system and studies on other models of experimental hypertension will permit researchers to determine whether this increased release of DA is causally related to hypertension, is a homeostatic response to the increase of BP, or a simple marker of the sympathetic discharge unrelated to hypertension.

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