Mechanism of Sodium Load-Induced Hypertension in Non-Insulin Dependent Diabetes Mellitus Model Rats: Defective Dopaminergic System to Inhibit Na-K-ATPase Activity in Renal Epithelial Cells

Hiroki TSUCHIDA, Gorou IMAI, Yoshinori SHIMA, Takeo SATOH, and Shigeru OWADA

Obesity-related non-insulin dependent diabetes mellitus (NIDDM) is frequently accompanied by hypertension. The present study was designed to clarify this mechanism. We first determined the blood pressure in male Wistar fatty rats (WFR), one of the NIDDM model rats, and in Wistar lean rats (WLR) as the control, with a normal (0.7% NaCl) or high (7% NaCl) salt diet. We observed no difference in systolic and mean blood pressures between WFR and WLR. WFR, however, became extremely hypertensive as a result of ingesting the high salt diet. We next investigated the mechanism for sodium sensitivity in WFR. Although the urinary excretion of dopamine (DA), a potent natriuretic factor, which reflects the ability for renal DA production, was preserved in WFR, the sodium balance with the high salt diet was positive. Moreover, Na-K-ATPase activity in isolated proximal convoluted tubules (PCT) from WFR with a normal salt diet was significantly ($p<0.05$) higher than that from WLR. A high salt load produced a significant ($p<0.05$) decrease in Na-K-ATPase activity in WLR but not in WFR. Similarly, Na-K-ATPase activity in WLR with a normal salt diet was significantly ($p<0.05$) inhibited by DA ($10^{-5}$ M), but this was not true in WFR. Furthermore, urinary excretion of norepinephrine in WFR with a high salt diet was the highest among all the groups. These results indicate that WFR tend to develop salt-sensitive hypertension that could be caused by the excessive sodium retention occurring as the result of a defective dopaminergic system in the kidney that fails to inhibit Na-K-ATPase activity. Augmentation of the renal sympathetic nervous system may play some role in this setting. (Hypertens Res 2001; 24: 127-135)

Key Words: non-insulin dependent diabetes mellitus (NIDDM), hypertension, kidney, dopamine, Na-K-ATPase

Introduction

Patients with non-insulin dependent diabetes mellitus (NIDDM) are frequently hypertensive (1). Numerous investigations have been carried out to determine the mechanism of hypertension in NIDDM patients with an emphasis on the insulin-resistance or hyperinsulinemia that was generally considered to be the main pathogenesis of NIDDM (1). Hyperinsulinemia possibly contributes in part to sodium retention leading to blood pressure elevation, as insulin can increase sodium reabsorption in proximal tubules (2). Moreover, activation of the sympathetic nervous system plays some role in insulin-induced increase in blood pressure, as previously reported (3, 4). In salt-sensitive hypertensive patients, the concentration of plasma norepinephrine is augmented by high sodium intake (5). On the other hand, a recent study suggested

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that the effect of obesity on the elevation of blood pressure appeared to be mediated by insulin-resistance rather than by hyperinsulinemia (6). Although they both potentially affect the blood pressure via sodium retention or activation of the sympathetic nervous system, the role of hyperinsulinemia or insulin-resistance in the elevation of blood pressure in NIDDM patients has not been established.

Dopamine (DA) produced in the proximal tubular cells acts on renal tubules in a paracrine fashion and promotes natriuresis mainly by decreasing tubular sodium reabsorption (7). This effect is attributed in part to the inhibition of Na-K-adenosine triphosphatase (Na-K-ATPase), the biochemically equivalent of the Na-K pump that plays a central role in epithelial sodium transport (8). Diminished DA action to inhibit Na-K-ATPase in the kidney was demonstrated in experimental hypertensive model rats, such as spontaneously hypertensive rats (SHR) (9) and Dahl salt-sensitive rats (DSSR) (10). Human essential hypertension also showed a dopaminergic disorder (11, 12). In any case, an aberrant dopaminergic system in the kidney may cause sodium retention, resulting in hypertension. The relationship between the dopamine system in the kidney and NIDDM with regard to the mechanism of blood pressure elevation has not been investigated.

In 1981, Wistar fatty rats (WFR) as an obesity-related NIDDM model were produced (13). This strain was derived from crosses between obese Zucker rats and Wistar Kyoto rats (WKY). A WFR develops obesity and has the characteristics of NIDDM beginning at 6 weeks old, including hyperglycemia, hyperinsulinemia, and insulin-resistance. To determine the mechanism involved in hypertension associated with NIDDM, in this study we used male WFR as a NIDDM model rat and examined blood pressure (BP) changes with or without sodium load and the dopaminergic system in the kidney. We have shown here that a high salt load contributes to elevating BP in WFR but not in Wistar lean rats (WLR). This difference may be caused by augmented sodium retention that is associated with a defective natriuretic effect of the dopaminergic system in the kidneys. Failure of dopamine to inhibit Na-K-ATPase activity in the proximal tubules in WFR has a key role in the mechanism involved in the hypertension associated with NIDDM.

Methods

Animals and Experimental Protocols

All experiments were performed according to the “Guiding Principles for the Care and Use of Laboratory Animals” of the Japanese Pharmacological Society. The WFR was introduced as an obesity-related NIDDM model in 1981 (13). This strain was derived from crosses between obese Zucker rats and Wistar Kyoto rats, which have relatively poor glucose tolerance. The WFR homozygote (fa/fa) develops obesity and has the characteristics of NIDDM at 6 weeks old, such as hyperglycemia, hyperinsulinemia, and insulin-resistance. In this study we used male WFR as the NIDDM model and male WLR as the control. All rats were maintained at consistent humidity (55±5%) and temperature (23±1°C) with a 12-h light-dark cycle. All rats had free access to a normal salt (NS) diet containing 0.7% NaCl and tap water ad libitum until they became 6 weeks old. When they reached 6 weeks old, the rats were divided into four groups: group 1, WLR which were fed a normal salt diet (WLR-NS); group 2, WLR fed a high salt diet (WLR-HS); group 3, WFR fed a normal salt diet (WFR-NS); and group 4, WFR fed a high salt diet (WFR-HS). WLR-NS and WFR-NS continued receiving a NS diet, and rats in the WLR-HS and WFR-HS groups started to be fed a high salt diet containing 7% NaCl. All rats had free access to their respective food and tap water until the end of this study.

When making measurement, we always recorded the rats’ body weight before measuring blood pressure and heart rate. Systolic and mean blood pressures (SBP and MBP, respectively) and heart rate were first measured when the rats were 6 weeks old as a baseline, using the tail-cuff method (ECG Processor BP-98A, Softron, Tokyo, Japan). Thereafter, SBP and MBP were measured in all four groups every two weeks until the rats were 16 weeks old. The median of four or five successive measurements was used as the estimate of blood pressure and heart rate.

Rats were housed in individual metabolic cages after being separated into groups at age 6, 8 and 12 weeks old to measure the food intake and to collect the daily urine. Urine volume and urinary excretion of sodium (Na), dopamine (DA), epinephrine (Epi), and norepinephrine (NE) were measured in each group. Urinary DA, Epi, and NE were measured using the high-pressure liquid chromatography trihydroxindole (HPLC-THI) method (665A-11; Hitachi, Tokyo). The data of all urinary substances were presented as the daily volume and corrected by the respective body weight. Sodium balance was computed by subtracting daily urinary Na excretion from daily dietary Na intake and was expressed as mEq/day.

Microdissection of Proximal Tubules

The procedure of tubule microdissection has been reported previously in detail (14). After anesthesia, the left kidney was perfused in situ through a catheter placed in the left renal artery with cold collagenase solution, a modified HBSS containing (mM) 137 NaCl, 5 KCl, 0.8 MgCl2, 0.33 Na2HPO4, 0.44 KH2PO4, 1 MgCl2, 10 Tris-HCl, 1 CaCl2, at pH 7.4 with 0.05% collagenase (Type I; Sigma Chemical Co., St Louis, USA), and 0.01% BSA. The kidney was then removed and cut along the corti-
Table 1. Body Weight and Sodium Balance in Wistar Lean and Fatty Rats

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Body weight (g)</th>
<th>Sodium intake (μEq/day/g BW)</th>
<th>Urinary sodium excretion (μEq/day/g BW)</th>
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</thead>
<tbody>
<tr>
<td>6 week</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>WLR-NS</td>
<td>5</td>
<td>164 ± 18.8</td>
<td>10.4 ± 0.8</td>
<td>7.3 ± 0.5</td>
</tr>
<tr>
<td>WLR-HS</td>
<td>4</td>
<td>183 ± 8.4</td>
<td>10.9 ± 0.8</td>
<td>7.3 ± 0.8</td>
</tr>
<tr>
<td>WFR-NS</td>
<td>5</td>
<td>215 ± 10.5</td>
<td>12.0 ± 1.0</td>
<td>8.7 ± 0.7</td>
</tr>
<tr>
<td>WFR-HS</td>
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<td>195 ± 23.2</td>
<td>12.0 ± 0.7</td>
<td>8.7 ± 0.6</td>
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<tr>
<td>8 week</td>
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<tr>
<td>WLR-NS</td>
<td>8</td>
<td>229 ± 10.3</td>
<td>9.6 ± 0.4</td>
<td>7.0 ± 0.2</td>
</tr>
<tr>
<td>WLR-HS</td>
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<td>225 ± 11.4</td>
<td>113.6 ± 3.6*</td>
<td>111.1 ± 3.6*</td>
</tr>
<tr>
<td>WFR-NS</td>
<td>6</td>
<td>357 ± 12.0*</td>
<td>9.9 ± 0.3</td>
<td>7.2 ± 0.2</td>
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<tr>
<td>WFR-HS</td>
<td>7</td>
<td>280 ± 4.7*</td>
<td>132.8 ± 2.6*</td>
<td>127.8 ± 0.4*</td>
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<tr>
<td>12 week</td>
<td></td>
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<tr>
<td>WLR-NS</td>
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<td>315 ± 16.1</td>
<td>7.0 ± 0.2</td>
<td>5.1 ± 0.2</td>
</tr>
<tr>
<td>WLR-HS</td>
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<td>302 ± 5.6</td>
<td>83.9 ± 3.4*</td>
<td>82.1 ± 3.4*</td>
</tr>
<tr>
<td>WFR-NS</td>
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<td>471 ± 10.6*</td>
<td>7.85 ± 0.2</td>
<td>5.8 ± 0.3</td>
</tr>
<tr>
<td>WFR-HS</td>
<td>6</td>
<td>430 ± 13.6*</td>
<td>98.4 ± 2.9*</td>
<td>94.6 ± 2.6*</td>
</tr>
</tbody>
</table>

Values are mean ± SE. WLS-NS, Wistar lean rats with normal sodium meal (0.7%); WLR-HS, Wistar lean rats with high sodium meal (7%); WFR-NS, Wistar fatty rats with normal sodium meal; WFR-HS, Wistar fatty rats with high sodium meal. *p < 0.01 vs. WLR-NS, †p < 0.01 vs. WFR-NS.

Statistical Analysis

Data are expressed as the mean ± SEM. Data were analyzed by analysis of variance (ANOVA) followed by the Fisher’s PLSD test for multiple comparisons. P values less than 0.05 were considered to indicate statistical significance.

Results

Body Weight, Sodium Balance, Blood Pressure, and Heart Rate

At 6 weeks old, the rats’ mean body weight was not statistically different among the four groups (Table 1). All groups, and especially the WFR, increased in mean body weight by aging. Body weight in WFR with a normal salt load had already increased significantly more by age 8 weeks than that in WLR with a normal salt load. This was also the case from age 12 to 16 weeks (data not shown). In WFR with a high salt load, body weight was also increased as compared to that of WLR with a high salt load. There was no significant difference in mean body weight between WLR with a normal salt load and those with a high salt load throughout this study. Mean body weight in WFR with a normal salt load was significantly (p < 0.01) more than that in WFR with a high salt load from 8 to 10 weeks old.

As shown in Table 1, at 6 weeks old there was no significant difference in sodium intake or urinary sodium excretion among the four groups at baseline. A high salt load caused enhanced urinary sodium excretion both in WLR and WFR at 8 and 12 weeks old. The highest uri-

Determination of Na-K-ATPase Activity

Tubules were incubated in 1 ml HBSS (0.25 mM CaCl₂) supplemented with 5 mM glucose, 2 mM Na acetate, and 5 mM Na lactate, with or without dopamine at 37°C for 30 min. Tubules were then permeabilized in a hypotonic medium (10 mM Tris), followed by freezing for 1 h at -70°C. Total ATPase activity was determined after 15 min incubation at 37°C in a 2 ml droplet containing (mM) 50 NaCl, 5 KCl, 10 MgCl₂, 1 EGTA, 100 Tris-HCl, 10 Na₂ATP (grade II, vanadate-free; Sigma Chemical Co.), and [γ-32P]ATP (Amersham, Arlington Heights, USA) in tracer amount (∼5 nCi/ml). Mg-dependent ATPase activity was determined in the same solution containing 4 mM ouabain. Phosphate liberated by the hydrolysis of [γ-32P]ATP was separated by filtration through a Millipore filter (0.45μm pore size) after absorption of unhydrolyzed nucleotide on activated charcoal (Sigma Chemical Co.), and radioactivity was counted in a Liquid Scintillation System (Aloka, Tokyo, Japan). Total and magnesium-dependent ATPase activity were each determined on four replicate samples from individual animals, and calculated per millimeter tubule length. Na- and K-dependent, ouabain-inhibitable ATPase was taken as the difference between the means of each group of measurements, and thus represents a single datum point in each animal.
Fig. 1. Changes in Na⁺ balance in Wistar lean and fatty rats with normal or high salt diet (WLR-NS, WLR-HS, WFR-NS, and WFR-HS, respectively). The sodium metabolisms were determined before and after starting the salt load at 6 weeks. *p<0.01 vs. WLR-NS, p<0.01 vs. WFR-NS.

Fig. 2. Systolic blood pressure in Wistar lean and fatty rats with normal or high salt diet (WLR-NS, WLR-HS, WFR-NS, and WFR-HS, respectively). The systolic blood pressures were determined before and after starting the salt load at 6 weeks (N=20 to 22). *p<0.01 vs. WLR-NS, *p <0.01 vs. WFR-NS.

Figure 2 shows systolic blood pressure (SBP) in the four experimental groups from 6 to 16 weeks old. WFR were not hypertensive in comparison with WLR when they ate a normal salt diet. However, a sodium load to WFR caused a significant (p<0.01) elevation of SBP within only 2 weeks of starting load, and after that SBP tended to be increased by aging, reaching a maximum BP (around 170 mmHg) at 14 weeks old. Similarly, there was no difference in mean blood pressure (MBP) among the four groups at baseline (Fig. 3). From age 8 to 16 weeks, MBP in WFR with a high salt load was the highest of all the groups at each age. It was maximally elevated to about 150 mmHg at age 14 weeks.

Heart rate in WFR was greater than that in WLR at each age. No difference was observed between the NS and HS groups of both WLR and WFR except for WLR at 8 weeks old (Fig. 4).

Urinary Dopamine, Epinephrine, and Norepinephrine Excretions

At the baseline of 6 weeks old, there was no significant difference in dopamine (DA) excretion among the four groups (Fig. 5). When WLR and WFR were fed a normal salt diet, the urinary excretion did not alter in either group from baseline reading to the 8- and 12-week readings. The high salt diet, however, produced enhanced urinary DA excretion in both WLR and WFR at 8 and 12 weeks old. DA excretion in 12 weeks old WFR with a high sodium load was markedly and significantly increased in comparison with that in WLR with a normal sodium load.

As shown in Fig. 6, there was no significant difference in epinephrine (Epi) excretion among the four experi-
Fig. 4. Heart rate in Wistar lean and fatty rats with normal or high salt diet (WLR-NS, WLR-HS, WFR-NS, and WFR-HS, respectively). The heart rates were determined before and after starting the salt load at 6 weeks (N = 20 to 22). *p < 0.01 vs. WLR-NS.

Fig. 6. Urinary epinephrine excretion in Wistar lean and fatty rats with normal or high salt diet (WLR-NS, WLR-HS, WFR-NS, and WFR-HS, respectively). The epinephrine excretions were determined before and after starting salt load at 6 weeks.

Fig. 5. Urinary dopamine excretion in Wistar lean and fatty rats with normal or high salt diet (WLR-NS, WLR-HS, WFR-NS, and WFR-HS, respectively). The dopamine excretions were determined before and after starting the salt load at 6 weeks. *p < 0.01 vs. WLR-NS, *p < 0.01 vs. WFR-NS.

Fig. 7. Urinary norepinephrine excretion in Wistar lean and fatty rats with normal or high salt diet (WLR-NS, WLR-HS, WFR-NS, and WFR-HS, respectively). The norepinephrine excretions were determined before and after starting salt load at 6 weeks. *p < 0.01 vs. WLR-NS.

At 8 and 12 weeks, Epi excretion tended to be reduced in all groups, especially in WFR with a normal salt load as compared with the excretion level at baseline. Urinary Epi excretion in WFR with a high salt was highest among the four groups at both 8 and 12 weeks old, but the difference was not statistically significant. Figure 7 shows the changes in urinary norepinephrine (NE) excretion in each group. At 6 weeks old, similar to the findings about urinary Epi excretion, there was no significant difference in NE excretion among the four experimental groups at baseline. At 8 and 12 weeks old, NE excretion also tended to be reduced in each group as compared with the level at the baseline. Urinary NE excretion in WFR with a high salt diet also decreased with aging but was significantly higher than the levels in other groups. At 8 and 12 weeks old, urinary Epi excretion in WFR with a normal sodium load was lower than that in WLR with a normal sodium load (the difference was not significant), but urinary NE excretion was not.
Na-K-ATPase Activity in Proximal Tubules in Response to Sodium Load and Dopamine

As described above, a high salt load produced a marked elevation of blood pressure in WFR. Despite enhanced urinary DA excretion in WFR with a high salt load, the sodium balance was enormously positive. Therefore, we next examined Na-K-ATPase activity that plays a chief role in renal Na reabsorption and is regulated by DA in proximal convoluted tubules (Fig. 8). When rats were fed a normal salt diet, Na-K-ATPase activity in PCT from WFR was higher than that from WLR (2.692 ± 156.3 vs. 1.871 ± 99.3 pmol Pi/mm²/h; p < 0.05). This activity was inhibited by 10⁻³ M of DA in WLR but not in WFR (1.871 ± 99.3 to 1.192 ± 100.6; p < 0.05, 2.692 ± 156.3 to 2.785 ± 122.1 pmol Pi/mm²/h; p = NS, respectively). Similarly, a high sodium load produced inhibition of Na-K-ATPase activity in WLR but not in WFR (1.871 ± 99.3 to 1.076 ± 155.9; p < 0.05, 2.692 ± 156.3 to 2.740 ± 222 pmol Pi/mm²/h; p = NS, respectively).

Discussion

In this study, we first investigated the blood pressure of Wistar fatty and lean rats (WFR and WLR, respectively) with either a normal or a high salt diet. We found that a high sodium load caused hypertension in WFR but not in WLR. Despite the preserved renal production of dopamine, a potent natriuretic factor, the sodium balance became markedly positive in WFR with a high sodium load. Na-K-ATPase activity in an isolated proximal convoluted tubule (PCT) from WLR was inhibited by the sodium load and by dopamine, but that not the case with Na-K-ATPase activity from WFR. These results indicate that WFR experience a characteristic salt-sensitive hypertension that may be caused by excessive sodium retention due to a defective dopaminergic system that does not inhibit Na-K-ATPase activity in PCT.

It has been reported that non-insulin dependent diabetes mellitus (NIDDM) is frequently accompanied by hypertension (1). Although sodium retention may contribute in part to blood pressure elevation in patients with diabetes (15), the precise mechanism involved in the hypertension associated with NIDDM has not been fully elucidated. This study was designed to clarify this mechanism using Wistar fatty rats (WFR), an experimental model for obesity-associated NIDDM (13). We first determined the blood pressure with a high salt load in WFR and WLR. We could show that the extreme elevations of both systolic and mean blood pressures (SBP and MBP, respectively) were identified in WFR when they were fed with a high sodium load (Figs. 2 and 3). A previous study has already shown that an excess of dietary sodium intake may contribute to the rise of blood pressure in WFR with the shift of the pressure natriuresis curve to the right (16). Thus, our result again proved that WFR had a characteristic of salt-sensitive hypertension. A metabolic study of sodium balance demonstrated that the sodium load in both WFR and WLR markedly increased both intake and urinary excretion of sodium. No difference was observed in the net sodium balance between WLR fed with a normal and those with a high sodium load (Fig. 1). In contrast, the net sodium balance in WFR became extremely positive with a high sodium load. These observations indicate that excessive sodium retention plays a central role in the rising of blood pressure in WFR caused by sodium load. We conclude that the urinary excretion of sodium in WFR is relatively insufficient when responding to a high sodium intake.

Several factors are possibly related to sodium retention in WFR that ultimately results in hypertension. It is well known that dopamine is an intrarenal hormone that is mainly produced in the proximal tubular cells (7), and it inhibits Na-K-ATPase activity in several nephron segments in a paracrine fashion (17). This inhibition is caused by a complicated intracellular signaling system via the activation of D1-like receptor (18). Intracellular mechanisms of the dopamine action on Na-K-ATPase are different between the proximal and distal nephron. Phospholipase C and protein kinase C pathways are involved in the proximal tubules (19), whereas adenylate cyclase and protein kinase A pathways are the main signaling in the distal nephron (20). Finally both pathways share the same signaling pathway that is the activation of phospholipase A₂ and arachidonic acid metabolisms (21). It is also generally agreed that a high salt intake produces an increased urinary excretion of dopamine as a result of enhanced extraneural dopamine production by the kidney.
Moreover, during a high salt load, locally generated dopamine in the kidney inhibits Na-K-ATPase activity and contributes to the natriuresis that normally accompanies a high salt load (23, 24). In experimental hypertensive model rats such as spontaneously hypertensive rats (SHR) or Dahl-salt sensitive rats (DSSR), the defective renal dopamine system fails to inhibit renal Na-K-ATPase because of uncoupling of D1-like receptor with adenylate cyclase (9, 10). The failure of dopamine to regulate renal Na-K-ATPase may contribute to the development of hypertension in these strains. In the present study, urinary dopamine excretion was enhanced by a high sodium load, especially in WFR as well as in WLR, indicating that in WFR the capacity for renal dopamine production in response to sodium load is normally preserved (Fig. 5). Despite the maintained dopamine production in WFR, urinary excretion of sodium in WFR was relatively insufficient to handle a high sodium intake, resulting in marked sodium retention. Thus, we next examined renal epithelial Na-K-ATPase activity in response to a high sodium load and dopamine (Fig. 8). A high sodium load produced the inhibition of PCT Na-K-ATPase activity in WLR. Dopamine inhibited Na-K-ATPase activity in WFR as well. In contrast, a high sodium load failed to inhibit Na-K-ATPase activity in WFR in spite of their sufficient generation of dopamine. Moreover, Na-K-ATPase was not inhibited by dopamine in WFR at all. These observations strongly suggest that a defective dopamine system that does not inhibit renal Na-K-ATPase in response to sodium load is closely related with sodium retention followed by the development of hypertension in WFR. A very recent report using obese Zucker rats also demonstrated the reduced dopamine inhibition of Na-K-ATPase activity in the proximal tubules (25). However, the reduced dopamine action to inhibit Na-K-ATPase was extremely mild as compared with that in WFR. Moreover, glucose intolerance and blood pressure elevation in obese Zucker rats are very close to normal in comparison with those in WFR.

Na-K-ATPase activity in WFR was already enhanced without the addition of a high sodium load (Fig. 8). This phenomenon could be related to mild hypertension in WFR when they were fed with a normal sodium load. Numerous investigations have been made of the alteration of renal Na-K-ATPase in an experimental model of diabetes using a streptozotocin (STZ)-treated IDDM model and have demonstrated that Na-K-ATPase activity was increased in the IDDM model (26, 27). Although secondary hyperaldosteronism (26) or glomerular hyperfiltration (27) might be involved in this mechanism, the mechanisms in NIDDM have not been established yet. We were not able to demonstrate glomerular hyperfiltration in WFR (data not shown). Hyperinsulinemia, which was found in WFR (13), is possibly involved in the mechanism of Na-K-ATPase activation in this strain, as insulin has been reported to stimulate Na-K-ATPase activity in PCT in vitro (28). Recently, the Milan hypertensive strain (MHS) has been introduced as an experimental hypertensive model rat, and enhancement of renal Na-K-ATPase caused by a molecular alteration of the cytoskeletal protein adducin plays a central role in the mechanism of hypertension in this strain (29). Moreover, in this strain, increased ouabain-like factor (OLF) levels were observed, and PST 2238, a new antihypertensive compound that antagonizes the pressor effect of ouabain in vivo, reduced blood pressure and normalized Na-K pump alterations, indicating that OLF plays a major role in the pathogenesis of hypertension and augmentation of Na-K-ATPase in MHS (30). The mechanism and its pathogenesis of Na-K-ATPase activation in WFR with a normal sodium condition will be elucidated with especial note taken of hyperinsulinemia, adducing, and OLF.

Sympathetic nerve activity has been reported to affect urinary sodium excretion and blood pressure (3-5). In this study, we attempted to evaluate the sympathetic nerve activity by determining the heart rate and urinary excretions of catecholamines. The heart rate in WFR with or without a sodium load was greater than that in WLR, and no difference was observed between WFR with a normal and that with a high salt diet (Fig. 4). This result suggests that sympathetic nerve activity was possibly augmented in WFR even at the basal condition. A very recent report demonstrated that base sympathetic nerve activity in WFR is enhanced with augmentation of baroreceptor reflex (31), which was in good accordance with this study. However, several factors such as mechanical stimuli during measurement of heart rate might relate to this phenomenon in the present study. On the other hand, urinary excretion of norepinephrine in WFR with a high sodium load was highest among the four groups at ages 8 and 12 weeks (Fig. 7). Norepinephrine is one of the pressor hormones, and it may directly promote renal sodium reabsorption in PCT (32). This result suggested that the renal sympathetic nervous system might contribute in part to the elevation of blood pressure in cases with NIDDM. An earlier study showed that the plasma norepinephrine remained at its stimulated level during high sodium intake in salt-sensitive hypertensive patients (33). Another report demonstrated that marked sympathetic hyperactivity was associated with obesity-related hypertension (34). Available data also suggested that activation of the sympathetic nervous system plays some role in insulin-induced increases in blood pressure (3, 4). Acute administration of insulin increases the blood norepinephrine level and decreases the urinary sodium level (5). However, numerous contradicting opinions are also reported about the relationship among insulin, norepinephrine, and blood pressure. Acute insulin administration may cause peripheral vasodilatation and not increase blood pressure (35, 36). Chronic hyperinsulinemia does...
not increase arterial blood pressure or plasma catecholamines in normal dogs (37). Thus the interpretations of the relationship among hyperinsulinemia, hypertension, and adrenergic activity are controversial, but we can state that the activation of sympathetic nerve activity is possibly involved in the blood pressure elevation in WFR when they are under a high salt load. However, no difference was observed in heart rate between WFR with a normal sodium diet and that with a high sodium diet at each age (Fig. 4), suggesting that sympathetic nerve hyperactivity might be less essential in sodium load-induced hypertension in WFR than is the failure of dopamine to inhibit Na-K-ATPase activity in the proximal tubules. Sympathetic nerve activity in WFR with or without a sodium load will be further determined in detail.

In summary, we found that WFR had characteristically experience salt-sensitive hypertension, mainly caused by excessive sodium retention due to a defective dopaminergic system in the kidney failing to inhibit Na-K-ATPase activity. Moreover, the renal sympathetic nervous system might contribute in part to the elevation of blood pressure in cases with NIDDM. This is the first evidence of a defective dopaminergic system failing to inhibit Na-K-ATPase activity, which may contribute to increased sodium reabsorption and the development of hypertension in WFR with a high salt load. The cause of the dopamine failure to act on renal Na-K-ATPase in this model should be elucidated.

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References


