Aging, High Salt Intake, and Renal Dopaminergic Activity in Fischer 344 Rats

Maria A. Vieira-Coelho, Tahir Hussain, Vikram Kansra, Maria P. Serrao, Joao T. Guimaraes, Manuel Pestana, Patricio Soares-da-Silva, Mustafa F. Lokhandwala

Abstract—The present study examined renal dopaminergic activity and its response to high salt (HS) intake in adult (6-month-old) and old (24-month-old) Fischer 344 rats. Daily urinary excretion of L-3,4-dihydroxyphenylalanine (L-DOPA), dopamine, and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid was similar in adult and old rats; by contrast, daily urinary excretion of norepinephrine in old rats was almost twice that in adult animals. HS intake (1% NaCl) over a period of 24 hours resulted in a 2-fold increase in the urinary excretion of dopamine, DOPAC, and norepinephrine in adult animals but not in old animals. Norepinephrine and L-DOPA plasma levels did not change during HS intake and were similar in both groups of rats. The natriuretic response to an HS intake in old rats (from 4.7±0.4 to 10.7±2.0 nmol·kg⁻¹·d⁻¹; Δ=6.0±0.9 nmol·kg⁻¹·d⁻¹) was less than in adult rats (from 5.2±0.4 to 13.5±2.5 nmol·kg⁻¹·d⁻¹; Δ=8.3±0.8 nmol·kg⁻¹·d⁻¹). A diuretic response to HS intake was observed in adult rats (from 20.9±2.3 to 37.6±2.8 mL·kg⁻¹·d⁻¹) but not in old rats (from 37.7±5.7 to 42.3±6.0 mL·kg⁻¹·d⁻¹). Dopamine levels and dopamine/L-DOPA ratios in the renal cortex of old rats were greater than in adult rats. HS intake increased both dopamine levels and dopamine/L-DOPA ratios in the renal cortex of adult rats but not in old rats. Aromatic L-amino acid decarboxylase activity was higher in old rats than in adult rats; HS intake increased L-amino acid decarboxylase activity (nmol·mg protein⁻¹·15 min⁻¹) in adult rats (from 67±1 to 93±1) but not in old rats (from 86±2 to 87±2). Dopamine inhibited Na⁺,K⁺-ATPase activity in proximal tubules obtained from adult rats, but it failed to exert such an inhibitory effect in old rats. It is concluded that renal dopaminergic tonus in old rats is higher than in adult rats but fails to respond to HS intake as observed in adult rats. This may be due in part to the inability of dopamine to inhibit Na⁺,K⁺-ATPase activity in old rats. (Hypertension. 1999;34:666-672.)

Key Words: aging ■ kidney ■ dopamine ■ sodium ■ Na⁺,K⁺-ATPase

Dopamine exerts natriuretic and diuretic effects by activating D₁-like receptors located at various regions in the nephron. At the level of the proximal tubule, the overall increase in sodium excretion produced by dopamine and D₁ receptor agonists results from inhibition of Na⁺,K⁺-adenosine triphosphatase (Na⁺,K⁺-ATPase) and the Na⁺/H⁺ exchanger. Inhibition of Na⁺,K⁺-ATPase by dopamine occurs via a phospholipase C–coupled protein kinase C–linked pathway. Stimulation of D₁ receptors leads to inhibition of the Na⁺/H⁺ exchanger as a result of increased adenosine 3’,5’-cyclic monophosphate formation and subsequently via protein kinase A–mediated phosphorylation.

The physiological importance of the renal actions of dopamine depends on the sources of the amine in the kidney and on the availability of this dopamine to activate the amine-specific receptors. The proximal tubules are endowed with high aromatic L-amino acid decarboxylase (AADC) activity, and epithelial cells of the proximal tubules synthesize dopamine from circulating or filtered L-3,4-dihydroxyphenylalanine (L-DOPA). This nonneuronal renal dopaminergic system appears to be highly dynamic, and the basic mechanisms for the regulation of this system are thought to depend mainly on the availability of L-DOPA, its rapid decarboxylation into dopamine, and the precise and accurate cell-outward amine-transfer mechanisms. High levels of metabolic enzymes such as types A and B monoamine oxidases (MAO-A and MAO-B) and catechol-O-methyltransferase (COMT) have also been considered as important determinants in the overall availability of renal dopamine. The aging kidney undergoes structural changes that result in quantitative alterations in some renal functions such as decline in renal blood flow and glomerular filtration rate. High blood pressure or edema formation may be linked to abnormalities in the function of the renal dopaminergic system, such as decreased ability to synthesize dopamine and deficient coupling of dopamine receptors to effector mechanisms. Despite their normal blood pressure, an
increasing number of studies have revealed that old rats may present particular deficiencies in the renal handling of L-DOPA, its subsequent conversion to dopamine, and at the level of receptor number or coupling to G proteins. Recently, 24-month-old Fischer 344 rats were reported to have an impairment in dopamine receptor-mediated inhibition of renal Na+,K+-ATPase. This deficient response to dopamine is accompanied by a decreased number of dopamine receptors and a marked attenuation of D1-receptor-mediated activation of G proteins but a significant increase in the levels of Gs and Gα11α in the basolateral membranes.

Because tubular epithelial cells responsible for the production of dopamine are endowed with specific receptors for the amine, it was thought appropriate to estimate the status of tubular renal dopaminergic system activity in 24-month-old Fischer 344 rats and compare it with that in adult animals (6 months old). Because one of the important factors regulating the synthesis of dopamine is the amount of sodium delivered to the kidney, it was decided to assess the activity of the renal dopaminergic system in adult and old Fischer 344 rats during normal salt (NS) and high salt (HS) intake. We report here the tissue levels and the urinary excretion of water and electrolytes, dopamine, its immediate precursor L-DOPA, and its metabolites, dopamine, its immediate precursor L-DOPA, and its metabolites. Dopamine, L-DOPA, its subsequent conversion to dopamine, and at the level of receptor number or coupling to G proteins. Recently, 24-month-old Fischer 344 rats were reported to have an impairment in dopamine receptor-mediated inhibition of renal Na+,K+-ATPase. This deficient response to dopamine is accompanied by a decreased number of dopamine receptors and a marked attenuation of D1-receptor-mediated activation of G proteins but a significant increase in the levels of Gs and Gα11α in the basolateral membranes.

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pH 8.6 by addition of Tris buffer. The adsorbed catecholamines were then eluted from the alumina with 200 μL of 0.2 mol/L HClO 4 on Costar Spin-X microfilters; 50 μL of the eluate was injected into an HPLC (Gilson Medical Electronics, Villiers le Bel, France). The lower limit of detection of L-DOPA, dopamine, norepinephrine, epinephrine, metanephrine, 3,4-dihydroxyxynadecacid, DOPAC, HVA, 5-HT, and 5-hydroxyindoleacetic acid ranged from 350 to 1000 fmol.

**Plasma and Urine Ionomogram**

Urinary sodium and potassium were measured by flame photometry (model FML3) connected to a diluter (model A 6241, Radiometer, Copenhagen, Denmark), and urine and plasma osmolality values were measured by means of an osmometer (model 3 MO, Advanced Instruments, Inc).

**Statistics**

Results are expressed as mean±SEM of values for the indicated number of determinations. \( V_{max} \) and \( K_m \) values for the decarboxylation of L-DOPA, the \( \beta \)-methylation of epinephrine, or the deamination of \([1^{H}]\)-HT and \([1^{C}]\beta\)-PEA were calculated from nonlinear regression analysis by using the GraphPad Prism statistics software package. Geometric means are given with 95% confidence limits, and arithmetic means are given with SEM. Statistical analysis was performed by 1-way ANOVA followed by the Newman-Keuls post hoc test. A value of \( P<0.05 \) was assumed to denote a significant difference.

**Results**

**Effect of HS Intake on Urinary Sodium and Dopamine Excretion**

Old rats were \( \approx 100 \) g heavier than adult rats, but HS intake for 24 hours did not affect body weight in both groups of rats. Liquid intake in both old and adult rats did not differ, either during NS intake or HS intake. The urine volume in old rats on NS intake was almost twice that in adult rats; however, during HS intake, adult rats responded with an increase in urine volume, but similar diuresis was not seen in old rats (Figure 1). Fractional excretion of sodium during HS intake increased significantly, and this increase was similar in adult and old rats (Figure 1). Urinary excretion of potassium (mmol \( \cdot \) kg \( ^{-1} \) \( \cdot \) 24 h \( ^{-1} \)) and the fractional excretion of potassium did not change during HS intake, and these values were also similar between adult and old rats (Urinary K\(^+\) from NS adult rats 7.1±0.7, HS adult rats 10.7±1.9, NS old rats 7.0±0.7, and HS old rats 7.0±0.7; fractional excretion of K\(^+\) from NS adult rats 34.7±5.1, HS adult rats 21.9±3.8, NS old rats 35.5±5.7, and HS old rats 32.2±8.0). Urine osmolality in old rats on an NS intake was considerably lower than that in adult rats. During HS intake, adult rats responded with a slight decrease in urine osmolality and an increase in the osmolar clearance, whereas old rats showed no change when compared with values observed on an NS intake (Figure 1). There were no significant changes in plasma sodium, potassium, and chloride levels and plasma osmolality between adult and old rats on both NS and HS intakes.

Data on the urinary excretion of catecholamines and metabolites are given in Figure 2. The urinary excretion of dopamine and DOPAC in adult rats on an NS intake did not differ from that in old rats. However, when adult rats were placed on an HS intake, the urinary excretion of both dopamine and DOPAC was twice that observed during NS intake, and such an increase was not observed in old rats (Figure 2). Old rats failed to respond to an HS intake by an increase in the urinary excretion of dopamine and of its deaminated metabolite, despite the observation that their basal excretion during NS intake did not differ from that in adult rats (Figure 2). In both adult and old rats, the urinary excretion of L-DOPA and HVA were similar during NS intake and not affected by HS intake. It is interesting to note that the urinary excretion of norepinephrine, but not that of epinephrine, in adult rats on an NS intake was half that in old rats, and that HS intake produced a significant increase in the urinary excretion of this amine in adult but not in old animals (Figure 2). The urinary excretion of 5-hydroxyindoleacetic acid (in nmol \( \cdot \) kg \( ^{-1} \) \( \cdot \) 24 h \( ^{-1} \)) in both adult (281±43) and old (354±36) rats on an NS intake did not significantly differ from that observed during HS intake (adult rats 508±127, old rats 458±28). There were no significant changes in plasma L-DOPA, norepinephrine, and DOPAC levels between adult and old rats on both the NS and HS intake.

Data on tissue levels of catecholamines and metabolites are given in the Table. It was found that tissue levels of dopamine and of its deaminated metabolite DOPAC in fragments from

![Figure 1](http://hyper.ahajournals.org/Downloaded/1999/10/668)

![Figure 2](http://hyper.ahajournals.org/Downloaded/1999/10/668)
the renal cortex of adult rats on an NS intake were significantly lower than those in old rats under the same experimental conditions. Placing adult but not old rats on an HS intake resulted in an increase in dopamine tissue levels; DOPAC tissue levels, however, were not affected by different regimens in sodium intake. By contrast, tissue levels of epinephrine in adult rats on an NS intake were higher than in old rats, and HS intake was found to significantly reduce epinephrine levels in both adult and old rats.

In Vitro Studies

AADC Activity
Incubation of homogenates of renal cortex with L-DOPA (50 to 5000 μmol/L) resulted in a concentration-dependent formation of dopamine (Figure 3). The V_max values for AADC with the use of L-DOPA as the substrate in adult rats on an NS intake were found to be significantly (P<0.01) lower than those observed in old rats under the same salt regimen. The effect of HS intake was a marked increase in V_max values in adult but not in old rats (Figure 3). In all experimental conditions, the decarboxylation reaction was a saturable process, with K_m values of the same magnitude.

MAO Activity
Homogenates of renal cortex from both adult and old rats were found to deaminate quite actively both [3H]5-HT and [14C]-β-PEA. Deamination of [14C]-β-PEA was a high-affinity process when compared with that for [3H]5-HT, as expected for specific substrates of MAO-B and MAO-A, respectively. It is interesting to note that V_max and K_m values were similar in both age groups and were not affected by HS intake (data not shown).

COMT Activity
Incubation of homogenates of rat renal cortex in the presence of increasing concentrations of epinephrine resulted in a concentration-dependent formation of metanephrine (data not shown). The kinetics, V_max, and K_m values for COMT were similar in adult and old rats. In all experimental conditions, the O-methylation reaction was a saturable process, with K_m values of the same magnitude (data not shown).

Na^+,K^+-ATPase Activity
Basal Na^+,K^+-ATPase activity (in nmol·min^{-1}·mg protein^{-1}) in the proximal tubules of adult rats on an NS intake

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Adult NS</th>
<th>Adult HS</th>
<th>Old NS</th>
<th>Old HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-DOPA</td>
<td>58.8±5.5</td>
<td>54.2±9.0</td>
<td>51.1±6.1</td>
<td>37.9±5.2</td>
</tr>
<tr>
<td>Dopamine</td>
<td>74.0±4.8*</td>
<td>96.3±11.0†</td>
<td>97.9±8.3</td>
<td>101.4±8.2</td>
</tr>
<tr>
<td>DOPAC</td>
<td>24.6±5.6*</td>
<td>39.5±9.6</td>
<td>50.0±5.5</td>
<td>59.6±12.9</td>
</tr>
<tr>
<td>DA/L-DOPA</td>
<td>1.31±0.15*</td>
<td>2.09±0.20†</td>
<td>2.17±0.39</td>
<td>2.93±0.44</td>
</tr>
<tr>
<td>DOPAC/dopamine</td>
<td>0.32±0.06*</td>
<td>0.40±0.08</td>
<td>0.52±0.06</td>
<td>0.59±0.11</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>1537.9±80.5</td>
<td>1487.0±149</td>
<td>1410.1±83</td>
<td>1399.2±136</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>95.6±8.4*</td>
<td>58.4±7.8†</td>
<td>71.1±6.9</td>
<td>48.0±4.6†</td>
</tr>
</tbody>
</table>

Values are mean±SEM (n=6).

*Significantly different from corresponding values in old rats (P<0.05).
†Significantly different from corresponding values in NS (P<0.05).
was similar to that observed in old rats under the same sodium regimen (adults 127±6, old rats 105±6) and was found not to be significantly changed with the increase in sodium intake (adult 120±5, old 120±20). As shown in Figure 4, dopamine caused a concentration-dependent reduction of Na⁺,K⁺-ATPase activity in the proximal tubules of adult rats on either the NS or HS intake (Figure 4). However, it failed to inhibit enzyme activity in either group of old rats (NS or HS intake).

**ALKP and γ-GT Activities**

There were no significant changes in ALKP between adult and old rats on both NS and HS intakes. However γ-GT activity in adult rats (2.01±0.17 U/mg protein) on the NS intake was significantly greater than that observed in old rats (1.64±0.11 U/mg protein) under the same experimental regimen. However, HS intake failed to alter γ-GT activity in either group of rats.

**Discussion**

The findings of the present study show that old Fischer 344 rats have an increased renal dopaminergic tonus; however, the animals failed to respond to an HS intake with a subsequent increase in dopamine synthesis, which is accompanied by changes in water and electrolyte metabolism. This increased renal dopaminergic tonus, when viewed collectively with the failure of dopamine to inhibit Na⁺,K⁺-ATPase activity as shown in the present and previous studies,21 and a marked decrease in the number of dopamine receptors may be related to an attempt of the renal epithelial cells from old Fischer 344 rats to induce a compensatory response and overcome the reduced expression of dopamine receptors and the functional consequences of this phenomenon.

The increased renal dopaminergic tonus in old Fischer 344 rats was evidenced by high AADC activity, high dopamine and DOPAC levels, and high tissue dopamine/L-DOPA ratios. It is interesting to note that the renal dopaminergic system in old rats failed to respond to an HS intake with an increase in AADC or urinary excretion of dopamine and its deaminated metabolite DOPAC, as it did in the adult rats. On the other hand, the presence of an increased dopaminergic activity in old rats was accompanied by an increase in the urinary excretion of neither dopamine nor its metabolites. Our present findings of a similar urinary excretion of dopamine and DOPAC in adult and old rats are at variance with a previous report showing that urinary dopamine and DOPAC excretion values were lower in old than adult rats.17 This discrepancy may be due to differences in the strain of rats; ie, we used Fischer 344 animals, whereas Armando et al17 used Wistar rats. Also, the age of the animals in the 2 studies was different, in that although we used 6- and 24-month-old rats, the previous study used 3- and 12-month-old rats.17 Unlike the findings of an increase in urinary dopamine excretion during HS intake in Fischer 344 adult rats, in our previous study in Wistar rats placed on an HS intake, we did not see a significant increase in urinary excretion of dopamine.25 We...
believe this discrepancy is related to the strain of animal used, as we have repeatedly failed to observe this type of an effect of an increase in urinary dopamine when Wistar rats are placed on an HS intake (M.A.V.-C., unpublished observation, 1999). In a previous study, we have shown that old rats decarboxylate less L-DOPA in kidney slices, but this was not true of kidney homogenates. Also, old Wistar rats had a reduced ability to take up L-DOPA into tubular cells, similar to findings of another group of investigators. Again, these discrepancies are most likely due to the different strains of animal used in the different studies. It is also interesting to note that although we were able to detect basal levels of DOPAC in the present study in Fischer 344 rats, we were unable to detect basal DOPAC levels in Wistar rats, which may be due to the fact that basal DOPAC levels in Wistar rats are beyond the limit of detection of our assay procedure. The lack of correlation between renal AADC activity and urinary levels of dopamine contrasts with the positive correlation between renal AADC activity and the tissue levels of dopamine and DOPAC and the dopamine/L-DOPA tissue ratios. One possible explanation could be deficient renal delivery of L-DOPA in old rats, particularly during HS intake, as a result of a reduced ability to mobilize L-DOPA from internal stores. Alternatively, it may be related to a reduced ability to take up L-DOPA at the level of the renal tubular epithelial cells. The finding that urinary and plasma levels of L-DOPA were quite similar between old and adult rats on NS and HS intakes suggests that deficient delivery of L-DOPA to the kidney could not account for this phenomena. On the other hand, a deficient uptake of L-DOPA by renal tubular epithelial cells is supported by the finding of reduced dopamine/L-DOPA ratios in both the urine and renal tissues. This suggestion is substantiated by the observation that renal tubular cells from old rats take up less exogenous L-DOPA. The inability of old rats on an HS intake to increase urinary dopamine excretion may be related to the reduced uptake of L-DOPA by tubular cells. In fact, several groups have shown an association between renal delivery of sodium and the ability to form dopamine, and in vitro studies have shown that L-DOPA uptake by renal epithelial cells is a sodium-dependent process. If the uptake of L-DOPA by tubular epithelial cells in old rats became defective, then it would not be able to respond to an increase in sodium by synthesizing more dopamine.

As mentioned above (see the introductory section), there is evidence to suggest that the renal availability of dopamine may depend on the activity of metabolic processes involved in the degradation of the amine, and these include deamination to DOPAC by MAO and methylation to HVA by COMT. The urinary excretion of DOPAC followed quite closely the urinary excretion of the parent amine in all of the 4 experimental conditions. This suggests that deamination of dopamine was not compromised and that an HS intake did not interfere with this process. This finding further supports our previous suggestion that urinary DOPAC is a good marker of renal production of dopamine and simultaneously a good index of cell integrity and viability, since MAO is a mitochondrial enzyme and is quite sensitive to changes in tissue oxygen tension. However, DOPAC/dopamine tissue ratios, another marker of the deamination process, in old rats were found to be greater than those in adult rats. This was observed only during NS intake and not during HS intake and, therefore, may not represent a difference in the activity of renal MAO between old and adult rats. Similarly, no changes in COMT activity were observed between these 4 groups of rats, except for the observation of a lower V_{max} value in old rats on HS intake compared with those on NS intake. This change may not have dramatic consequences on the O-methylation of dopamine, since this was not accompanied by changes in urinary levels of HVA and DOPAC.

These findings reported here for old Fischer rats are different from the observations made in old Wistar rats in several aspects, but both studies show that aging is accompanied by a 2.3-fold (Wistar rats) and a 1.3-fold (Fischer 344 rats) increase in AADC. Obviously, the increase in AADC activity was greater in Wistar than in Fischer 344 rats, but this difference may be due to the fact that AADC activity in the study of Armando et al was performed with a single concentration of substrate (100 μmol/L L-DOPA), which is clearly a nonsaturating concentration. The same criticism applies to determination of MAO activity, wherein a single, nonsaturating concentration of tyramine was used. By contrast, COMT activity in the study of Armando et al was performed with a saturating concentration of substrate, and their result is quite similar to that reported here, i.e., no change in COMT activity between old and adult rats.

Another interesting observation of the present study was that urinary norepinephrine excretion was almost twice as high in old rats compared with adult rats. One possible explanation could be a selective increase in renal sympathetic tone in old rats; the mechanism of and reasons for such an increase remain to be determined. In a previous study, no differences were found in urinary norepinephrine between adult and old rats, which may be due to differences in the strain and age of the animals. The finding that plasma and tissue levels of norepinephrine in adult and old rats were similar can be explained on the basis that circulating levels of norepinephrine mainly reflect release of the amine during a limited period of time, whereas urinary levels give a better indication over a longer period of time. Similarly, tissue levels do not always reflect the rate of norepinephrine synthesis or release. The reason for the increase in urinary excretion of norepinephrine in adult rats placed on an HS intake remains to be determined.

In terms of urinary excretion of electrolytes, we found that old rats had larger urine volumes over the 24-hour period than did adult rats; however, the urine from the former group had a lower osmolality compared with that from adult rats. During an increase in sodium intake, old rats appear to slightly retain sodium, as evidenced by a less-pronounced increase in urinary excretion of sodium compared with adult rats. This may be due to the inability of dopamine in old rats, on either an NS or HS intake, to inhibit Na⁺,K⁺-ATPase (Figure 4). The basal activity of Na⁺,K⁺-ATPase was not different between rats on either NS or HS intake, and although this finding agrees with 1 report, it differs from other published reports in which the authors found a decrease in basal Na⁺,K⁺-ATPase activity in rats placed on an HS intake.

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However, it should be noted that Bertorello et al.\(^3^2\) observed a decrease in basal Na\(^+\),K\(^+\)-ATPase activity in rats after 10 days of HS intake, whereas in the present study, we conducted our measurements after 24 hour of HS intake. It is likely that the exposure to HS intake needs to be of longer duration before changes in basal Na\(^+\),K\(^+\)-ATPase activity in rats can be observed. Although in the present study dopamine was able to inhibit Na\(^+\),K\(^+\)-ATPase in rats placed on both NS and HS intakes, Bertorello et al.\(^3^2\) found that the inhibitory effect of dopamine on Na\(^+\),K\(^+\)-ATPase was diminished in rats placed on an HS intake. Again, this discrepancy may be due to differences in the amount of time that the rats were exposed to HS intake.

In conclusion, it is suggested that old Fischer 344 rats have an increased renal dopaminergic tonus, which does not respond to HS intake by a subsequent increase in dopamine synthesis, and is accompanied by changes in water and electrolyte metabolism. The failure of dopamine to inhibit Na\(^+\),K\(^+\)-ATPase may be one explanation for this derangement and for the water and electrolyte excretion observed in old rats.

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