Long-Term Inhibition of Renin-Angiotensin System Sustains Memory Function in Aged Dahl Rats

Nobuhito Hirawa, Yoshio Uehara, Yukari Kawabata, Atsushi Numabe, Tomoko Gomi, Toshio Ikeda, Tsutomu Suzuki, Atsuo Goto, Teruhiko Toyo-oka, Masao Omata

Abstract—The Dahl salt-sensitive (DS) rat, a genetic model of salt-induced hypertension in humans, is more likely to develop severe vascular injuries than a rat with spontaneous hypertension. We designed an experiment to scrutinize the effects of renin-angiotensin inhibition on cognitive dysfunction in the aged, normotensive DS with a passive avoidance test. Eighteen months of treatment with a very low dose of the angiotensin-converting enzyme (ACE) inhibitor cilazapril (2.5 μg/mL in drinking water) or the angiotensin II type 1 receptor antagonist E4177 did not reduce blood pressure throughout the experiment, although in the low dose cilazapril group (12.5 μg/mL in drinking water), blood pressure dropped within 6 months after treatment began. The cilazapril treatments dose-dependently improved memory function in the aged, normotensive DS fed a low-salt diet compared with the untreated, control rats. This improvement was associated with significant increases in hippocampal CA1 cells and capillary densities in the CA1 regions compared with those in the untreated DS. Similarly, E4177 slightly improved the memory dysfunction observed in the aged DS. The cells in the hippocampal CA1 region were restored slightly, but the capillary densities were not influenced by the receptor antagonist. On the other hand, the ACE inhibitor and receptor antagonist both attenuated urinary protein excretions with an improvement of glomerular sclerosis. These data suggest that long-term treatment with an ACE inhibitor improves memory dysfunction probably through restoration of capillary and hippocampal cells. The effects are due to the inhibition of the angiotensin II type 1 receptor and probably to the enhancement of the kallikrein-kinin system.


Key Words: cilazapril ■ angiotensin-converting enzyme inhibitors ■ receptors, angiotensin ■ memory ■ cognition ■ rats, aging ■ aging

Recent advances in vascular physiology have emphasized an integration of multiple risk factors that form vascular lesions in patients with various disorders that affect the cardiovascular system. The understanding of the process of vascular lesion development has led to the establishment of pharmacological and nonpharmacological strategies for the prevention of vascular damage in hypertension, hyperlipidemia, or abnormal glucose metabolism. In addition to such acquired forms of risk factors, some inevitable factors, eg, gender, genetic loading, and aging, contribute to the progression of vascular injuries. Among these factors, aging is particularly important. The development of a therapeutic strategy for the aging population is urgently needed. In Japan, by year 2015, people ≥65 years of age will constitute 25% of the population, and worldwide, by year 2025, this population will have doubled. In addition, ≈50% of dementia or cognitive dysfunction in the elderly are attributable to cerebrovascular lesions. The elucidation of the mechanism of cerebrovascular lesions related to the process of aging provides a useful strategy to prevent an increase in the number of elderly with dementia or cognitive dysfunction in the near future.

In this context, it is well documented that long-term treatment with angiotensin-converting enzyme (ACE) inhibitors preserves renal function and delays progression to end-stage renal failure in hypertensive patients with diabetes mellitus. It has been demonstrated that treatment with ACE inhibitors prevents progression of retinopathy in the patients with diabetes mellitus. In addition, ACE inhibitors have been reported to enhance angiogenesis in ischemic heart diseases. These data strongly suggest that treatment with ACE inhibitors protects the vascular wall against various injuries and maintains blood flow in the peripheral vasculature.

On the other hand, we have recently demonstrated that Dahl salt-sensitive (DS) rats are susceptible to vascular injuries even when they are fed a low-salt (0.3% NaCl) diet and exhibit normotension. Alternatively, a blunted response of the kallikrein-kinin system explains this finding. Indeed, angiotensin II (Ang II) receptor (type 1) density in glomeruli

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and the mRNA levels of renal arteries are regulated by the level of salt intake. Considering these data, we hypothesize that normotensive DS fed a low-salt diet are a useful rat model to investigate vascular damage induced by the process of aging and are appropriate for studying the pathophysiologic or therapeutic aspects of age-related disorders in humans.

In the present study, we attempted to test the hypothesis of the usefulness of DS for study of age-related vascular diseases and, in addition, we investigated the effects of long-term treatment with an ACE inhibitor on cognitive function in aged DS with normotension.

Methods

In Vivo Experiment

Four-week-old DS were purchased from Eisai Research Laboratories (Eisai Co, Ltd, Tokyo, Japan). The rats were a recent inbred strain and had been fed a low-salt (0.3% NaCl) diet after they had been weaned. When the DS were 8 weeks of age, 40 DS were divided into 4 groups: (1) 10 rats were given a very low dose of the ACE inhibitor cilazapril (2.5 mg/mL cilazapril in drinking water); (2) 10 rats were given a low dose of cilazapril (12.5 mg/mL cilazapril in drinking water); (3) 10 rats were given the angiotensin II subtype 1 receptor antagonist E4177, 3-[(2'-carboxybi phenyl-4-yl)methyl]-2-cyclopropyl-7-methyl-3H-imidazo[4,5-b]pyridine (AT1Re antagonist; 25 μg/mL in drinking water); and (4) 10 rats were given water alone. Drugs were dissolved in drinking water at appropriate concentrations for each group. The rats were given drinking water ad libitum. The doses used in the present study were reported to inhibit the renin-angiotensin system in vitro. They were maintained for 1½ years. The procedures followed were in accordance with institutional guidelines.

Systolic blood pressure was determined by the tail-cuff method. At the end of the experiment, arterial pressure was determined directly through a catheter placed in the right femoral artery under Inactin anesthesia (100 mg/kg body wt) (Byk Gulden, Konstanz, Germany). A 24-hour urine specimen was collected on 3 consecutive days, and the urine that was collected on the last day was used for determining various parameters. The right kidney was obtained for morphological evaluation. Whole blood samples and organs of interest were also obtained.

Estimation of Learning Ability by Passive Avoidance Task

The behavioral experiments were performed in a quiet, diffusely lighted room (indirect light from 25 watt lamps that were placed 1.5 m above the animals). After the rats were acclimated to the room, they were trained in a conventional step-through passive avoidance apparatus that was divided into 2 chambers: one light and the other dark. The apparatus had a stainless-steel grid floor, and the chambers were separated by a slit door. Each animal was initially placed in a safe and lighted room with the slit door closed. After 60 seconds of equilibrium stabilization, the slit door to the dark chamber was opened. After the rats stepped into the dark room, the door was closed and a foot electric shock (75V, 500 mA) was activated. After 10 seconds, the door was re-opened and the rats had access to the safe light room. Effective electric shock was preliminarily determined according to the previous studies. Through a series of these procedures, the risk and its avoidance were engraved on their memory.

The time until the door was re-opened to permit escape from the dark chamber was estimated as escape reaction time (ERT). ERT is influenced by the ability to recognize the unpleasant environment and the determination of how to escape the unpleasant situation; thus, indicating the electric shock was sufficient for memory creation. To determine preservation of the memory, response latency was measured. Briefly, the shock generator was turned off and the rats were placed in the safe, light chamber. We measured the time passed until they stepped into the dark chamber, which was maximally 400 seconds. The longer the response latency, the better the memory. Basic behavior activity and movement were estimated with the open field test. Briefly, the rats were placed in a quiet and lighted room with a floor divided into 40×50-cm compartments marked by grid lines. The rats were allowed to move freely. We determined how many times the rat crossed the grid lines in a 2-minute period. The experiment was repeated 3 times. The values were averaged to obtain the measurement of the basal movement.

Histological Study of Hippocampal CA1 Region

The whole brain was embedded in paraffin with the cerebrum. Five-micrometer serial sections in the hippocampal CA1 area were stained with Bodian and reticulin. Neurons in the zone of the CA1 region next to the CA2 were counted under a light microscope. The total for 3 areas was averaged to obtain the cell number of neurons in the zone. For comparison, we measured the cell number in the cortical region by the same procedures used for the hippocampal area. To determine vascular density in the CA1 region, we stained the vascular endothelial cells with anti-Factor VIII antibody and horseradish peroxidase–labeled anti–rabbit IgG antibody. The cross-sections of the capillaries that were stained dark gray were detected under light microscopy. The number in the 6 continuous areas was averaged to obtain its capillary density.

Functional and Morphological Alterations in the Kidney

To assess renal function, we determined plasma and urinary levels of creatinine, plasma levels of electrolytes, urinary protein concentrations, and N-acetyl-β-D-glucosaminidase activity (NAG). Glomerular and arterial lesions in the kidney were assessed according to the method as described in previous studies. The severity of these lesions was graded. An overall glomerulosclerosis score was obtained by multiplying the severity score by the percentage of glomeruli that displayed the same degree of injury and adding these scores. The severity of arterial injury was graded according to the previous method. An overall arterial injury score was obtained by multiplying the severity score by the percentage of arteries that displayed the same degree of injury and adding these scores.

Acute and Subacute Experiments on Memory Function

To determine the acute and subacute effects of renin-angiotensin inhibition on the cognitive function, we treated normotensive DS fed a low-salt diet with the same doses of cilazapril or E4177 for 1 week or 6 months. In these rats, we measured the basal activity of movement and latency by use of the passive avoidance test with the same procedures as those in the long-term treatment experiment mentioned above.

Reagents

Cilazapril and E4177 were donated by Eisai Pharmaceutical Co, Ltd, Tokyo, Japan.

Statistical Analysis

Data are expressed as mean±SE. Differences were analyzed by 1-way and 2-way ANOVA and multivariate analysis with the STATISTICA program (StatSoft, Tulsa, Okla.). P<0.05 was considered statistically significant.

Results

Hemodynamics

The drinking water amounts were 35.1±3.2 mL/d for the very low dose cilazapril group, 40.5±5.4 mL/d for the low dose cilazapril group, and 36.9±2.5 mL/d for the E4177 group. On the basis of these data, the dosages taken were
Behavior and Learning Ability

First, we checked the effects of the treatments on the behavior of the rats. Basic behavior activity and movement were assessed with the open-field test according to the method of Braszko and Wisniewski.10 By determining the frequency of crossing in the open-field, it was demonstrated that either cilazapril or E4177 treatment did not alter the basal movement significantly compared with the untreated control rats. This clearly suggested that there were no differences in the searching ability and basic movements among the experimental groups. Second, to assess the ability to recognize alterations in the environment and judge how to escape the electric shock, we measured the ERT. Treatments with ACE inhibitor significantly improved ERT in the very low dose group (16.5±1.5 seconds versus 12.0±0.4 seconds, P<0.01) and in the low dose group (12.5±0.5 seconds versus the control group, P<0.01), which indicated that ACE inhibitor increased recognition and judgment abilities. In contrast, the AT1Rc antagonist E4177 did not influence ERT (15.6±1.9 seconds).

The response latency in the step-through passive avoidance task, a useful index of learning ability, is shown in Figure 2. Eighteen days after electric shock, the latency of the untreated control rats averaged 352±50 seconds. However, cilazapril treatment significantly preserved latency up to 389±11 seconds for the very low dose cilazapril group and 397±3 seconds for the low dose cilazapril group, which suggests that cilazapril treatment sustained cognitive function. This beneficial effect was observed until 113 days after the electric shock.

We determined the number of neuronal cells in the hippocampal area (Figure 3a). The number of cells in the hippocampus was 1258±32 cells/mm² for the untreated control rats. This was significantly lower than the 1466±42 cells/mm² in the very low dose cilazapril group and the 1491±57 cells/mm² in the low dose cilazapril group (Figure 3b). However, no differences existed in the cell densities in the cerebral cortex among the experimental groups. Treat-

Figure 1. Time-dependent alterations in systolic blood pressure in DS. Eight-week-old DS were fed a low-salt diet. The passive avoidance task was performed at month 12, which was at the age of 14 months. CONT indicates DS fed a low-salt diet alone; VL-CLZ, rats given a very low dose of cilazapril; L-CLZ, rats given a low dose of cilazapril; and E4177, rats given E4177. *P<0.05, **P<0.005 vs the control rats. The difference was assessed by least significant difference after 2-way ANOVA.

0.16±0.01 mg/kg body wt per day for the very low dose cilazapril group, 0.94±0.12 mg/kg body wt per day for the low dose cilazapril group, and 1.66±0.11 mg/kg body wt per day for the E4177 group. For acute treatment, >1 mg/d of cilazapril is required to reduce blood pressure in the spontaneously hypertensive rat.8 The dose of cilazapril used in the present study was much below the depressor doses of cilazapril. Similarly, the dose of E4177 was below the doses required to reduce blood pressure in some rat model forms of hypertension.9

Systolic blood pressure time-dependently increased in the untreated control rats (Figure 1). However, the blood pressures were within the range of normotension throughout the study. Very low dose cilazapril treatment did not affect the blood pressure; however, low dose cilazapril treatment gradually but significantly decreased blood pressure during the later period of the experiment. Treatment with E4177 slightly decreased blood pressure; however, the difference was not significant. To assess these points more accurately, at the end of the experiment we directly measured arterial blood pressures through a catheter placed in the femoral artery. No differences existed in the arterial systolic blood pressure between the untreated control group and the group treated with a very low dose of cilazapril or E4177 (137±3 mm Hg for control, 136±3 for very low dose cilazapril, and 132±3 for E4177). Low dose cilazapril significantly reduced the systolic blood pressure compared with the untreated control rats (122±4 mm Hg).

No differences in body weight existed among the 4 experimental groups. Cilazapril treatment dose-dependently reduced heart weight compared with the untreated control rats (0.32±0.01 g/100 g body wt for control versus 0.30±0.01 g/100 g body wt for very low dose cilazapril [P<0.005] and 0.28±0.01 g/100 g body wt for low dose cilazapril [P<0.0005]). Similarly, E4177 treatment significantly decreased heart weight to the level achieved by the low dose cilazapril treatment (0.28±0.01, P<0.005).

Figure 2. Response latency in the step-through passive avoidance task. The response latency was assessed at 1, 7, 18, 29, 46, 60, 81, 99, 113, and 128 days after electric shock. The maximum latency was assessed as 400 seconds. The response latency was time-dependently decreased after electric shock. Abbreviations are the same as in Figure 1. The values were compared with the measurement in the untreated control rats. *P<0.01 vs L-CLZ; †P<0.01 vs VL-CLZ; ‡P<0.01 vs E4177.
ment with the AT1Rc antagonist E4177 slightly increased cell density in the hippocampal area, but the beneficial effects were much smaller than with ACE inhibition and did not reach statistical significance. We determined the number of cross-sectional capillaries in the CA1 region of the hippocampus. Low dose cilazapril treatment significantly increased the capillary density in this hippocampal area compared with the untreated, control DS rats.

**Plasma and Urinary Parameters**

For comparison to brain function, we attempted to investigate the effects of long-term inhibition of the renin-angiotensin system on kidney function (Table 1). The ACE inhibitor treatment significantly decreased plasma creatinine levels. The creatinine clearance ratio was higher in ACE treatment than in the control rats, but the difference was not significant. Serum NAG decreased with ACE inhibitor treatment; however, the difference did not reach significance. The ACE inhibitor groups significantly decreased urinary protein excretion. The E4177 treatment significantly reduced urinary protein excretion to the level attained by low dose ACE treatment.

**Renal Morphology**

We morphologically examined the effects of inhibition of the renin-angiotensin system on renal function in the aged rats. Progression of glomerular sclerotic lesions was observed in the aged, normotensive rats fed a low-salt diet. The glomerular lesions (glomerular sclerotic score) were dose-dependently attenuated by cilazapril treatment (200±10 for the control versus 113±11 for very low dose cilazapril [P<0.001] and 84±6 for low dose cilazapril [P<0.001]). Similarly, E4177 significantly ameliorated the glomerular lesions, which corresponded to the improvement achieved by the ACE inhibitor treatment (73±7, P<0.001). In addition, the ACE inhibitor and AT1Rc antagonist treatments improved the arterial injury score observed in the aged DS (35±7 for control versus 6±3 for very low dose cilazapril [P<0.001], 5±3 for low dose cilazapril [P<0.001], and 6±3 for AT1Rc [P<0.001]).

**Acute and Subacute Experiments**

We demonstrated the acute effects of renin-angiotensin inhibition by use of the passive avoidance task and open-field task (Figure 4). The rats were treated with the ACE inhibitor for 1 week or 6 months. We investigated the effects of the treatment on cognitive function on these rats 0, 1, 4, 8, and 16 days after the electric shock or 0, 1, 3, 5, 7, and 9 weeks after the shock, respectively. Day 0 indicates the time just after the placement of memory. Treatment with the ACE inhibitor or AT1Rc antagonist for 1 week did not alter basal behavior (not shown) or the memory function as indicated by latency time (n=35). Similarly, renin-angiotensin inhibition did not affect the basal behavior (not shown) or the cognitive function in DS rats after 6 months (n=34).

**Multiple Regression Analysis**

We analyzed the predictors of preservation of the neuronal cells in the hippocampus with multivariate analyses. The dependent factor was the number of neuronal cells in the hippocampus. We listed the following as independent factors: capillary density in the hippocampus, the number of cells in the cortex, the glomerulosclerosis score in the kidney, the arterial injury score in the kidney, creatinine clearance rate, systolic blood pressure at month 17, and serum NAG levels. The analyses revealed that the number of neuronal cells in the hippocampus was determined by the number of cells in the cortex (B value=0.377, P<0.025), systolic blood pressure (B value=–0.335, P<0.05), and creatinine clearance rate (B value=0.620, P<0.0002).

**Discussion**

To assess learning ability, we performed the passive avoidance test according to the standard method.10,11 This is an...
established test to assess memory function in the field of behavioral pharmacology. Latency time, the time required to re-enter the dark room again, is influenced essentially by the basic movement of animals and their learning ability. In the present study, however, there were no differences in the basic movement among the 4 experimental groups. These results suggest that the latency time determined in the present study reflect predominantly the learning ability of the aged rats.

The most important finding in the present study was that long-term inhibition of the renin-angiotensin system improved cognitive function in the aged, normotensive rats. Moreover, the beneficial effects on memory function were associated with preservation of the neuronal cells and capillary densities in the hippocampal area. These data strongly suggest that ACE inhibitor treatment maintains cognitive function in the aged rats probably through protection of the vascular vessels and neuronal cells responsible for memory function. In fact, pure inhibition of the angiotensin type I receptor by E4177 slightly but significantly maintained memory function. This indicates that preservation of the memory by ACE inhibitor treatment is attributable at least in part to the inhibition of the Ang II subtype 1 receptor-mediated event.

A series of studies was published reporting disruption of passive avoidance retention by Ang II infusion in the central nervous system.14,15 Wayner et al16 have reported that Ang II inhibits the induction of long-term potentiation in the hippocampus, a frequency-dependent model of learning and memory, when Ang II is administered in the hippocampal area. They have also demonstrated that Ang II–induced inhibition of LTP is an AT1Rc-mediated event in the hippocampal area. On the other hand, some studies have demonstrated that acute administration of Ang II in the central nervous system improves the learning ability in rats.17,18 Moreover, Ang II immunoreactive fibers have been shown in all hippocampal fields.18 The effects of Ang II in the central nervous system are somewhat controversial. These effects of Ang II on the learning function have been explained consistently by direct actions on the neuronal function. To the best of our knowledge, however, there have been few studies that report the long-term effects of Ang II on cognitive function. In addition, because the ACE inhibitor cilazapril and the AT1Rc antagonist E4177 do not penetrate the blood brain barrier, these compounds do not seem to exert direct effects on memory function in the central nervous system. In this context, we demonstrated in the present study that ACE inhibitor treatment for 6 months was unable to improve the learning ability in these rats. This suggests that inhibition of renin-angiotensin for a longer period is needed to produce the beneficial effects on memory function in the central nervous system.

In addition, evidence suggests a major role of acetylcholine in the pathogenesis of memory dysfunction in humans. It has been shown that in Alzheimer’s disease, there is a dramatic decrease in the hippocampus and frontal cortex of choline acetyltransferase and a marked reduction in cholinergic neuron counts in the nucleus basalis. Precursor loading coupled with an agent that accelerates acetylcholine release is reported to possibly attenuate memory dysfunction. In this

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### Parameters Indicating Renal Function

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Creatinine, μmol/L</th>
<th>sNAG, μU/mL</th>
<th>UV, mL/100 g BW/d</th>
<th>UNa, mmol/100 g BW/d</th>
<th>Upro, mg/d</th>
<th>UNAG, U/Cr</th>
<th>Ccr, mL/100 g BW/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>52.2 ± 4.4</td>
<td>20.1 ± 1.9</td>
<td>3.15 ± 0.34</td>
<td>0.55 ± 0.06</td>
<td>215.9 ± 15.3</td>
<td>187.2 ± 54.5</td>
<td>546.3 ± 38.1</td>
</tr>
<tr>
<td>VL-CLZ</td>
<td>10</td>
<td>45.1 ± 1.8*</td>
<td>19.1 ± 1.7</td>
<td>2.59 ± 0.17*</td>
<td>0.47 ± 0.04</td>
<td>204.8 ± 16.0</td>
<td>195.9 ± 54.9</td>
<td>593.3 ± 31.3</td>
</tr>
<tr>
<td>L-CLZ</td>
<td>10</td>
<td>43.4 ± 0.9*</td>
<td>17.0 ± 0.9</td>
<td>2.58 ± 0.38</td>
<td>0.47 ± 0.04</td>
<td>182.9 ± 12.1*</td>
<td>160.3 ± 45.6</td>
<td>649.2 ± 101.1</td>
</tr>
<tr>
<td>E4177</td>
<td>10</td>
<td>40.7 ± 1.8*</td>
<td>17.2 ± 0.9</td>
<td>2.12 ± 0.19**</td>
<td>0.49 ± 0.04</td>
<td>186.0 ± 17.3*</td>
<td>35.8 ± 5.1**</td>
<td>621.7 ± 30.4</td>
</tr>
</tbody>
</table>

sNAG indicates serum level of NAG; UV, urinary volume; BW, body weight; UNa, urinary excretion of sodium; Upro, urinary excretion of protein; UNAG, urinary excretion of NAG; Ccr, creatinine clearance rate; Control, untreated DS fed a low-salt diet alone; VL-CLZ, rats fed a low-salt diet and given a very low dose of cilazapril; L-CLZ, rats fed a low-salt diet and given a low dose of cilazapril; E4177, rats fed a low-salt diet and treated with the receptor antagonist E4177. The group difference was assessed by 1-way ANOVA.

*P < 0.05, **P < 0.01 vs the value in the untreated DS (Control).
context. Wiemer et al20 have demonstrated that Hoe 065, a compound structurally related to ACE inhibitors, increases cholinergic activity within a physiological range through an enhancement of the release of acetylcholine. In the present study, we did not investigate the effects of the angiotensin inhibition on cholinergic activity in DS. However, we note that such cholinergic nerve-mediated mechanisms contribute to the improvement of memory function observed in the present study.

The inhibition of the renin-angiotensin system is primary to the preservation of cognitive function by ACE inhibitor treatment. However, the protection of neural cells and capillary densities in the hippocampal area was much greater in ACE inhibitor groups than in the Ang II receptor antagonism group. The reason for this difference was unclear. However, it was not solely due to a difference in the intensity of the renin-angiotensin inhibition because treatment with the Ang II receptor antagonist attenuated the glomerular lesions as much as the ACE inhibitor treatment and also reduced heart weight to the level achieved by the ACE inhibitor treatment. In fact, recent research on cardioprotection from ACE inhibitor treatment has revealed the role of the kallikrein-kinin system, which is enhanced by ACE inhibitor treatment in angiogenesis in postischemic heart diseases, and improved the prognosis of myocardial infarction.4,5 In consideration of these data, the beneficial effects of ACE inhibitor treatment on the learning system are at least in part due to the enhancement of the kallikrein-kinin system.

The hippocampus is known as the gate to memory. The CA1 region in particular is one of the most important areas for cognitive function and is noted for its susceptibility to ischemia.21,22 Sakanaka and colleagues23 have demonstrated that a relationship exists between the latency of the passive avoidance task and the cell density of the CA1 region. Our results for the cerebral function and morphological changes of the brain are in accordance with the previous studies.21–23 This structural difference in the vascular system may explain the difference in neuronal cell preservation between the CA1 region and the deep cortex.

Interestingly, long-term treatment with a subdepressor dose of ACE inhibitor improved renal function with the resolution of morphological injuries. It is beyond the scope of this study to discuss whether the process of aging per se causes the deterioration in the kidney function. However, we can state that 19-month-old DS rats fed a low-salt diet exhibited kidney dysfunction that was improved significantly by inhibition of the renin-angiotensin system. In this regard, the aged DS rats with normotension are appropriate to study the mechanism of age-dependent organ dysfunction and they are helpful in the development of a strategy to prevent age-related disorders.

There is much interest in the effects of antihypertensive treatment on cognitive dysfunction or dementia in the elderly. Long-term treatment with nitrendipine alone or in combination with an ACE inhibitor or a diuretic reduces the incidence of an Alzheimer-type dementia by $\approx 50\%$.24 Recently, similar effects have been reported with treatment with amlodipine.25 Blood pressure reduction per se contributes to the prevention of dementia in hypertension. Interestingly, we demonstrated that even in the normotensive DS, blood pressure values independently determined in part the preservation of neuronal cells in the hippocampal area. These data suggest that an increase in blood pressure within the normotensive range along with aging become risk factors of age-related vascular injuries and subsequent organ damage. To address these points more directly, it is necessary to investigate the therapeutic effects of calcium channel blockers on cognitive dysfunction in the aged DS with normotension.

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