Journal of Cardiology 60 (2012) 489–494

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Telmisartan protects against cognitive decline via up-regulation of brain-derived neurotrophic factor/tropomyosin-related kinase B in hippocampus of hypertensive rats

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ARTICLE INFO

Article history:
Received 10 April 2012
Received in revised form 24 May 2012
Accepted 20 June 2012
Available online 2 September 2012

Keywords:
Hypertension
Cognitive function
Brain
Angiotensin receptor blocker

ABSTRACT

Background and purpose: Cognitive decline may occur as a result of hypertension, and is dependent on the function of hippocampus. Brain-derived neurotrophic factor (BDNF) mediated by angiotensin II-induced oxidative stress protects against cell death in hippocampus. Angiotensin II receptor blocker (ARB), candesartan, activates BDNF in the hippocampus. Furthermore, peroxisome proliferator-activated receptor (PPAR)-gamma activation in the brain prevents brain damage. Telmisartan, a unique ARB with PPAR-gamma stimulating activity, protects against cognitive decline partly because of PPAR-gamma activation. The aim of the present study was to determine whether telmisartan protects against cognitive decline via up-regulation of BDNF and its receptor tropomyosin-related kinase B (TrkB) in the hippocampus of hypertensive rats, partly because of PPAR-gamma activation.

Methods and results: We divided stroke-prone spontaneously hypertensive rats (SHRSPs), as hypertensive and vascular dementia model rats, into five groups, telmisartan-treated (TLM), TLM + GW9662, a PPAR-gamma inhibitor, -treated (T + G), GW9662-treated (GW), TLM + ANA-12, a TrkB antagonist, -treated (T + A), and vehicle-treated SHRSPs (VEH). After the treatment for 28 days, systolic blood pressure did not change in all groups. However, BDNF expression in the hippocampus was significantly higher in TLM than in VEH to a greater extent than in T + G. Cognitive performance was significantly higher in TLM than in VEH to a greater extent than in T + G, and was not different between T + A, GW, and VEH.

Conclusion: Telmisartan protects against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus of SHRSPs, partly because of PPAR-gamma activation independent of blood pressure-lowering effect.

Introduction

One of the important organ damages related to hypertension is cognitive decline. In the brain, angiotensin II contributes to the physiological regulation of many different functions, including cerebral circulation, integrity of the blood–brain barrier, central sympathetic activity, hormonal production and release, response to stress, behavior, and cognition [1–5]. In the treatments for hypertension, angiotensin II type1 receptor (AT_1R) blockers (ARB) are widely used [6]. A previous clinical study demonstrated that antihypertensive drugs that act via the renin–angiotensin system have potential in preventing, delaying, or decelerating the onset and progression of cognitive decline in hypertensive patients [7]. In the treatments for hypertension, cognition should be focused as a target of the antihypertensive treatment. Among ARBs, telmisartan has a beneficial effect in rats treated with repeated cerebral ischemia [8,9], Alzheimer model [10,11], diabetic model [12], and coronary plaque vulnerability [13]. However, no benefit was found in cognitive performance after administration of telmisartan after stroke [14]. In ONTARGET and TRANSCEND, telmisartan did not provide positive effects on cognitive function [15]. The mechanisms of the protection against cognitive decline in cerebral ischemia by telmisartan should be discussed further. Telmisartan is a unique ARB with a partial peroxisome proliferator-activated receptor (PPAR)-gamma agonistic property in its antihypertensive effect [16]. Anti-inflammatory and anti-oxidant effects of telmisartan that were exerted in part by PPAR-gamma activation, but not its

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0914-5087/$ – see front matter
http://dx.doi.org/10.1016/j.jjcc.2012.08.004

blood pressure-lowering effect, have protective roles against cognitive decline in cerebral ischemia [8,9]. PPAR-gamma activation is reported to reduce oxidative stress and inflammatory response in the vasculature and adipose tissue [17], and PPAR-gamma activation in the brain has been reported to prevent brain damage via anti-inflammatory effects in neurons [18].

Previous studies have suggested that the underlying mechanisms of the beneficial effect of ARBs in stroke may not only be the consequence of improved hemodynamics and vascular function, but may also involve a blood pressure-independent element of neuroprotection [19–22]. In the brain, brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TrkB) are known to be involved in the protective mechanisms against stress and cell death as an antioxidant [23–26]. Angiotensin II induces superoxide-dependent down-regulation of BDNF via phosphorylation of cAMP response element binding protein [27]. Candesartan at sub-hypotensive and renin–angiotensin system blocking dose affords neuroprotection after focal ischemia, associated with increased activity of BDNF [28]. Telmisartan improves memory impairment and reduces neural apoptosis in hippocampus via a PPAR-gamma-dependent anti-apoptotic mechanism in rats with repeated cerebral ischemia [8]. However, it has not been determined whether telmisartan has protective effects on cognitive decline via up-regulation of BDNF/TrkB in the hippocampus.

Combined with these previous studies, we had the hypothesis that the beneficial effects of telmisartan on cognition are not only because of its established effect of antihypertensive and systemic blockade of AT_1R but also because of the benefits on BDNF in the hippocampus via PPAR-gamma agonistic effect in hypertension. The aim of the present study was to determine whether telmisartan protects against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus of stroke-prone spontaneously hypertensive rats (SHRSPs) as hypertensive and vascular dementia model rats [29], partly because of PPAR-gamma activation. Previous studies have demonstrated that ARBs have benefits on brain damage and vascular inflammation in SHRSPs [30–32], as well as organ damage in spontaneously hypertensive rats [33]. Telmisartan also has anti-oxidant effects in vasculature [34] and brain [35] of SHRSPs. We divided SHRSPs into five groups, telmisartan-treated (TLM), TLM + GW9662, a PPAR-gamma antagonist, -treated (T + G), GW9662-treated (GW), TLM + N-[2-[[(hexahydro-2-oxo-1H-azepin-3-yl) amino] carbonyl] phenyl]-benzothiophene-2-carboxamide (ANA-12), a TrkB antagonist, -treated (T + A), and vehicle-treated SHRSPs (VEH). Cognitive function was assessed by the Morris water maze test, which has been widely used as a test of spatial memory and cognition [36].

Methods

Animals

This study was reviewed and approved by the committee on ethics of Animal Experiments, Kyushu University Graduate School of Medical Sciences, and conducted according to the Guidelines for Animal Experiments of Kyushu University. Male SHRSPs (12–14 weeks), weighing 350–425 g and fed standard feed were used (SLC Japan, Hamamatsu, Japan). They were housed individually in a temperature-controlled room (22–23 °C) with a 12-h/12-h light-dark cycle (lights on at 7:00 AM). We divided SHRSPs into 5 groups: TLM, T + G, T + A, GW, and VEH ($n = 5$ for each). Systolic blood pressure and heart rate were measured daily using the tail-cuff method (BP-98 A; Softron, Tokyo, Japan).

Oral administration of drugs

SHRSPs were treated for 4 weeks. TLM group was administered telmisartan (1 mg/kg/day, Sigma Aldrich, St. Louis, MO, USA). GW group was administered GW9662 (1 mg/kg/day, Sigma Aldrich). T + G group was administered telmisartan (1 mg/kg/day) plus GW9662 (1 mg/kg/day). T + A group was administered telmisartan (1 mg/kg/day) plus ANA-12 (0.5 mg/kg/day, Sigma Aldrich). VEH group was administered 0.5% methylcellulose. All drugs were dissolved in 0.5% methylcellulose and administered by gastric gavage every day. The dose of telmisartan was selected as a low dose and non-depressor dose [37,38]. The dose of GW9662 was according to the previous studies examining the partial effect of telmisartan on PPAR-gamma activation [9,37]. The dose of ANA-12 was determined to blockade BDNF according to a previous study [39].

Western blotting analysis

To obtain the hippocampus tissues, the rats were deeply anesthetized with sodium pentobarbital (100 mg/kg IP) and perfused transcardially with PBS (150 mol/L NaCl, 3 mmol/L KCl, and 5 nmol/L phosphate; pH 7.4, 4 °C). The brains were removed quickly, and the hippocampus tissues obtained according to a rat brain atlas were homogenized and sonicated in a lysing buffer containing 40 mmol/L HEPES, 1% Triton X-100, 10% glycerol, and 1 mmol/L phenylmethanesulfonyl fluoride. The tissue lysate was centrifuged at 6000 rpm for 5 min at 4 °C with a microcentrifuge. The lysate was collected, and protein concentration was determined with a BCA protein assay kit (Pierce, Rockford, IL, USA). An aliquot of 20 μg of protein from each sample was separated on 12% SDS-polyacrylamide gel. Proteins were subsequently transferred onto polyvinylidene difluoride membranes (Immobilon-P membrane; Millipore, Billarica, MA, USA). Membranes were incubated for 2 h with a rabbit polyclonal antiserum against BDNF (1:1000; Abcam, Cambridge, UK) or α-tubulin (1:1000; Cell Signaling, Danvers, MA, USA). Membranes were then washed and incubated with a horseradish peroxidase–conjugated horse anti-mouse IgG antibody (1:10,000) for 40 min. Immunoreactivity was detected by enhanced chemiluminescence autoradiography (plus Western blotting detection kit; GE Healthcare Bio-Sciences AB, Uppsala, Sweden), and was expressed as the ratio to α-tubulin protein.

Analysis of cognitive function

Spatial learning and memory function of the rats were investigated with the Morris water maze test in a circular pool filled with water at a temperature of 25.0 ± 1 °C [36]. In the hidden platform test, a transparent platform was submerged 1 cm below the water level. Swimming paths were tracked with a camera fixed on the ceiling of the room and stored in a computer. All the procedures of the Morris water maze were performed for 7 days. A pre-training session was carried out at day 0, in which animals were given 60 s free swimming without the platform. In the hidden-platform test for 4 days, the rats were given 2 trials (1 session) on day 1 and 4 trials (2 sessions) per day on days 2, 3, and 4. The initial trial interval was about 30 min and the inter-session interval was 2 h. During each trial, the rats were released from four pseudo-randomly assigned starting points and allowed to swim for 60 s. After mounting the platform, the rats were allowed to remain there for 15 s, and were then placed in the home cage until the start of the next trial. If a rat was unable to find the platform within 60 s, it was guided to the platform and allowed to rest on the platform for 15 s. Probe trials were performed at day 5. In the probe trial, the hidden platform was removed and the rats was released from the right quadrant and allowed to swim freely for 60 s. The time spent in the target

Table 1
Physiological data.

	VEH	TLM	T+G	T+A	GW
SBP (mmHg)	240 ± 28	228 ± 17	229 ± 16	231 ± 19	243 ± 21
HR (bpm)	338 ± 30	331 ± 26	340 ± 29	343 ± 30	329 ± 37
BW (g)	282 ± 15	280 ± 14	288 ± 17	276 ± 19	291 ± 22
Calorie intake (Kcal/day)	77 ± 5	74 ± 8	72 ± 4	78 ± 6	74 ± 9
Water intake (ml/day)	32 ± 4	29 ± 4	30 ± 5	30 ± 3	28 ± 5

Data are expressed as the mean ± SEM.
SBP, systolic blood pressure; HR, heart rate; BW, body weight; VEH, vehicle; TLM, telmisartan; T+G, telmisartan+GW9662; T+A, telmisartan+ANA-12; GW, GW9662; $n=5$ for each.

quadrant, where the platform had been located during training, and the time spent in the other quadrants were measured. In the visible-platform test which was performed at day 6, the platform was elevated above the water surface and placed in a different position.

Statistical analysis

All values are expressed as mean ± SEM. Comparisons between any two mean values were performed using Bonferroni's correction for multiple comparisons. ANOVA was used to compare all the parameters in all groups. Differences were considered to be statistically significant at a p-value of <0.05.

Results

Physiological data

Systolic blood pressure and heart rate were not changed in TLM, T+G, GW, T+A, and VEH after the treatments (Table 1). Body weight, dairy calorie intake, and water intake were also not different in all groups (Table 1).

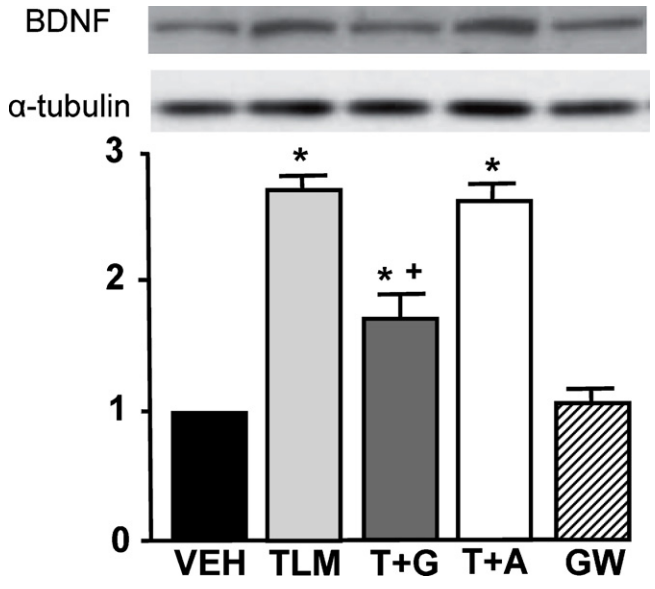

Fig. 1. Expression of BDNF in the hippocampus in each group. BDNF/α-tubulin expression was expressed relative to that in VEH which was assigned a value of 1. $^{*}p<0.05$ versus VEH, $^{+}p<0.05$ in T+G versus TLM, $n=5$ for each. BDNF, brain-derived neurotrophic factor; VEH, vehicle; TLM, telmisartan; T+G, telmisartan+GW9662; T+A, telmisartan+N-[2-[[(hexahydro-2-oxo-1H-azepin-3-yl) amino] carbonyl] phenyl]-benzothiophene-2-carboxamide (ANA-12); GW, GW9662.

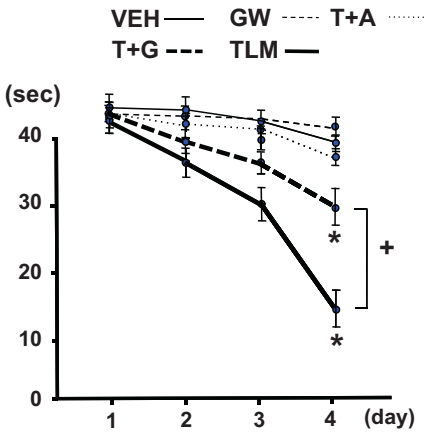

Fig. 2. Escape latency in the hidden platform test of Morris water maze. $^{*}p<0.05$ versus VEH, $^{+}p<0.05$ in T+G versus TLM, $n=5$ for each. VEH, vehicle; TLM, telmisartan; T+G, telmisartan+GW9662; T+A, telmisartan+N-[2-[[(hexahydro-2-oxo-1H-azepin-3-yl) amino] carbonyl] phenyl]-benzothiophene-2-carboxamide (ANA-12); GW, GW9662.

Expression of BDNF in the hippocampus

The expression of BDNF in the hippocampus was significantly higher in TLM than in VEH (Fig. 1). The up-regulation of BDNF in the hippocampus in TLM was attenuated in T+G, but not in T+A (Fig. 1). However, the expression of BDNF in the hippocampus was not different between GW and VEH (Fig. 1).

Morris water maze test

In the hidden platform test, escape latency was significantly lower in TLM than in VEH to a greater extent than in T+G (Fig. 2), and was not different between in VEH, GW, and T+A (Fig. 2). In the probe test, TLM resulted in significantly more time in the target quadrant as compared with VEH, GW, and T+A to a greater extent than in T+G (Fig. 3). In the visible platform test, there were no significant differences in escape latency among all of the groups.

Discussion

In the present study, we have demonstrated two major findings. First, telmisartan has a protective effect on the cognitive decline via up-regulation of BDNF/TrkB in the hippocampus of SHRSPs without depressor effect. Second, co-administration of a PPAR-gamma antagonist with telmisartan partially attenuated the telmisartan-mediated protective effect on the cognitive decline. These results suggest that telmisartan has a possibility of protective effect against cognitive decline via activation of BDNF/TrkB through blockade of AT_1R and part activation of PPAR-gamma in the hippocampus of SHRSPs independent of blood pressure-lowering effect.

In the hippocampus, BDNF protects against ischemic cell damage [32]. Angiotensin II blocks long-term potentiation in the

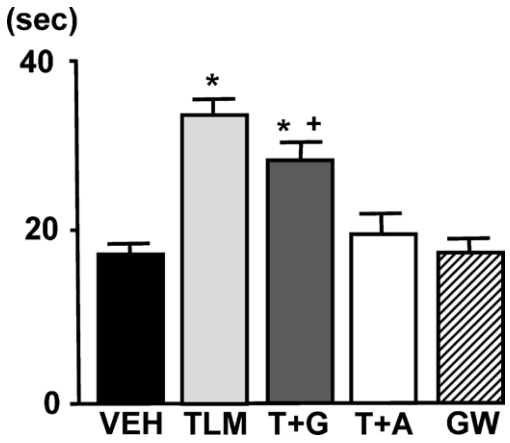

Fig. 3. Time in the target quadrant of the probe test of Morris water maze. $^{*}p < 0.05$ versus VEH, $^{+}p < 0.05$ in T + G versus TLM, $n = 5$ for each. VEH, vehicle; TLM, telmisartan; T + G, telmisartan + GW9662; T + A, telmisartan + N-[2-[[(hexahydro-2-oxo-1H-azepin-3-yl) amino] carbonyl] phenyl]-benzothiophene-2-carboxamide (ANA-12); GW, GW9662.

hippocampus [40–44], and induces superoxide-dependent down regulation of BDNF [27]. In the present study, low-dose telmisartan caused the protective effect against cognitive decline with the increase in BDNF expression in hippocampus of SHRSPs, and the effects were attenuated by TrkB antagonist. These results suggest that telmisartan has a protective effect on the cognitive decline via up-regulation of BDNF/TrkB in the hippocampus of SHRSPs without a depressor effect. Among ARBs, candesartan at sub-hypotensive and renin–angiotensin system blocking dose affords neuroprotection after focal ischemia, associated with increased activity of the BDNF [28]. Interestingly, ramipril at sub-hypotensive, hypotensive, and renin–angiotensin system blocking doses showed no significant neuroprotective effects [28]. Oxidative stress and/or antioxidant deficiency cause cognitive decline [45], and oxidative stress in hippocampus impairs cognitive function [46]. Combining the previous studies with our results in the present study, we consider that the telmisartan-induced up-regulation of BDNF/TrkB is caused by the blockade of AT_1R-induced superoxide in the hippocampus, and that ARBs have a potential to be preferable agents for the treatment of hypertension with the protection against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus.

We also demonstrated that, in the present study, telmisartan-induced protection against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus was partially attenuated by co-administration of PPAR-gamma antagonist with telmisartan. In a previous study, low-dose telmisartan without depressor effect protected against focal brain ischemia partly through activation of PPAR-gamma as well as AT_1R blockade [12]. Telmisartan improves memory impairment and reduces neural apoptosis in hippocampus via a PPAR-gamma-dependent anti-apoptotic mechanism in rats with repeated cerebral ischemia [8]. In other studies, co-administration of PPAR-gamma antagonist had no effect on the losartan-mediated reduction in ischemic area [8,12]. Our results are comparable with those previous studies, and suggest that telmisartan could exert protective effects against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus through AT_1R blockade and partly PPAR-gamma stimulation. Interestingly, in the present study, PPAR-gamma antagonist alone did not change cognitive performance and the expression of BDNF in the hippocampus. There is a possibility that AT_1R blockade has a synergistic effect of PPAR-gamma activation. If so, ARB with partial PPAR-gamma agonist, telmisartan, has a potential to be a preferable agent for the treatment of hypertension with the protection against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus.

The protective effect against cognitive decline is not specific in telmisartan among ARBs. Candesartan has a positive effect on cognitive decline in hypertensive patients [47] or diabetic model [48], and also significantly reduced the incidence and progression of dementia [49]. In SHRSPs, candesartan improves hippocampal CA1 neuron cell reduction, and superoxide production in the hippocampus [50]. In the brain, AT_1R-induced superoxide decreases BDNF [27]. Both telmisartan and candesartan are reported to reduce oxidative stress via blockade of AT_1R in the brain [51–53]. Although candesartan was not examined in the present study, we consider that the protective effect against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus is also caused by candesartan, not only telmisartan among ARBs, through the blockade of AT_1R in the hippocampus. However, the change in permeability of the blood–brain barrier by ARBs has not been well assessed to date. Ischemic brain damage enhances blood–brain barrier permeability and penetration of ARBs into the brain, and blood–brain barrier is disrupted in SHRSPs [54,55]. Telmisartan is expected to readily shift to organs compared with other ARBs, due to its high lipid solubility [56,57]. Moreover, telmisartan is a unique ARB with a partial PPAR-gamma agonistic property [16]. From the results obtained in the present study, AT_1R blockade with PPAR-gamma agonist is considered to be preferable to the protection against cognitive decline via up-regulation of BDNF/TrkB in the hippocampus.

Although the present study could demonstrate a beneficial effect of low-dose telmisartan on cognitive function, depressor dose of telmisartan could not provide positive effect on cognition in previous clinical studies [14,15]. This discrepancy could not be due to the difference in the dose of telmisartan, because the beneficial effects in the present study were obtained with the low and not depressor dose of telmisartan. We could not fully clarify the reasons of the discrepancy in the present study. We used the Morris water maze test in SHRSPs to evaluate cognitive function instead of the shuttle avoidance test. A spatial working memory task, such as Morris water maze test, depends on hippocampus function [58,59]. Because we focused on cognitive performance via BDNF/TrkB in the hippocampus of SHRSPs, we used the Morris water maze test. However, it has not been determined whether other cognitive function tests could obtain similar beneficial effects in other models, such as Alzheimer, diabetes, or cardiovascular disease models. We consider that the cognitive decline in cardiovascular diseases has various clinical backgrounds, and that multi-targeted therapy by combination of agents is necessary to protect against cognitive decline. In these aspects, AT_1R blockade with PPAR-gamma agonist, telmisartan, might be considered to be preferable among ARBs.

Limitations

There are several limitations in the present study. First, we could not determine the dose dependency of telmisartan and not demonstrate the direct data indicating that telmisartan penetrates blood–brain barrier and reaches the hippocampus. Telmisartan used in the present study was at a low and not depressor dose, and we consider that the higher and depressor dose of telmisartan would provide more beneficial effects. It is necessary in a further study to determine whether the telmisartan-induced depressor effect is synergistic to the present results or not, and to measure the concentration of telmisartan in the hippocampus. Second, we did not quantify superoxide in the hippocampus, and did not determine whether telmisartan reduced superoxide in the hippocampus. Furthermore, we examined only cognitive function and BDNF expression in the hippocampus in the present study, and we did not examine the brain damage in the other areas and vascular inflammation. Previously many studies have already demonstrated

that ARBs could prevent brain damage [5,8,10–12] and vascular inflammation [30–32]. Telmisartan also has benefits in SHRSP [34], and anti-oxidant effects in the brain [35,51]. Because of these previous studies, we consider that the benefits of ARBs on brain damage and vascular inflammation are established, and focused on only cognitive function and BDNF expression in the hippocampus in the present study. Third, we did not perform histochemical experiments to determine the expression of PPAR-gamma and changes in CA1 neuron in the hippocampus, and performed only pharmacological inhibition of PPAR-gamma or BDNF/TrkB in the hippocampus. Although previous studies suggested the expression of PPAR-gamma in the hippocampus of cerebral-ischemia models [8,60] and GW9662 or ANA-12 have been used as reasonable agents to inhibit PPAR-gamma or TrkB [8,9,37,39,61], It would strengthen the results of the present study to determine the expression of PPAR-gamma and changes in CA1 neuron in the hippocampus and to do the specific PPAR-gamma or BDNF/TrkB-targeting methods (such as gene transfer methods) locally in the hippocampus.

Conclusion

Telmisartan has a possibility of protective effect against cognitive decline via activation of BDNF/TrkB through blockade of AT_1R and part activation of PPAR-gamma in the hippocampus of SHRSPs independent of blood pressure-lowering effect, which might not be a class effect of ARBs. These results could provide a new aspect that telmisartan may be more effective to prevent cognitive decline compared with other ARBs, and might contribute to improve quality of life in hypertensive patients.

Conflict of interest

None.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (22790709) and, in part, a Kimura Memorial Foundation Research Grant.

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