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RAS Inhibition Attenuates Cognitive Impairment by Reducing Blood-Brain Barrier Permeability in Hypertensive Subjects

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Abstract: Recent studies have suggested that blood-brain barrier (BBB) abnormalities are present from an early stage in patients exhibiting mild symptoms of cognitive impairment during the development of hypertension. There is also growing body of evidence suggesting the potential role of the renin-angiotensin system (RAS) in the pathogenesis of small-vessel disease and cognitive impairment. However, the specific contribution of the RAS to BBB disruption and cognitive impairment remains unclear. We found a significant leakage from brain microvessels in the hippocampus and impaired cognitive functions in angiotensin II (AngII)-infused hypertensive mice, which were associated with increased brain AngII levels. These changes were not observed in AngII-infused AT_{1a} receptor (-/-) mice. We also observed that Dahl salt-sensitive hypertensive rats exhibited hypertension, leakage from brain microvessels in the hippocampus, and impaired cognitive function. In these animals, treatment with an AngII receptor blocker, olmesartan, did not alter blood pressure, but markedly ameliorated leakage from brain microvessels and restored the cognitive decline. These data support the hypothesis that RAS inhibition attenuates cognitive impairment by reducing BBB injury, which is independent of blood pressure changes.

Keywords: Blood-brain barrier, cognitive impairment, hypertension, renin-angiotensin system (RAS), olmesartan.

1. INTRODUCTION

The blood-brain barrier (BBB) neurovascular unit acts as an obstacle for substance delivery to the central nervous system, which is composed of astrocytes, pericytes, a basal membrane and vascular endothelial cells [1]. An increase in BBB permeability is observed as a result of cerebral ischemia [2, 3]. However, BBB permeability also increases with normal aging, and further increases in patients with vascular dementia [3, 4]. Therefore, it is possible that BBB abnormalities are present from an early stage in patients exhibiting mild symptoms of cognitive impairment and minor cerebral microvascular diseases, such as lacunar stroke and hypertension. Indeed, the Honolulu-Asia Aging Study and other clinical studies have shown that high blood pressure is a predictor of reduced cognitive function in later life, as well as a risk factor for vascular dementia [5-7]. Animal studies have also shown that there is a disturbed fence function of tight junctions in BBB endothelial cells of spontaneously hypertensive rats and stroke-prone spontaneously hypertensive rats [8, 9].

A growing body of evidence suggests that augmentation of brain renin-angiotensin system (RAS) activity contributes to the progression of cognitive impairment [10-15]. For example, RAS inhibition with angiotensin II (AngII) type 1 receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors ameliorate impaired cognitive function in hypertensive animals [12, 14, 16, 17]. Furthermore, clinical studies have demonstrated the beneficial effects of RAS inhibitors on cognitive function through both blood pressure-dependent and independent mechanisms [18, 19]. However, plausible within-class differences with regard to the effect of RAS inhibitors on cognitive impairment in hypertensive patients have also been indicated [18, 20-22]. In addition, the precise mechanism by which RAS inhibition improves cognitive function during the development of hypertension remains unclear.

We hypothesize that RAS inhibitors elicit blood pressure-independent protective effects on cognitive impairment through attenuating BBB injury in hypertensive subjects. To support this hypothesis, we performed several preliminary animal studies. This review will briefly summarize these preliminary data as well as our current understanding of the role of the RAS in mediating BBB injury and cognitive impairment during the development of hypertension.

2. ANGII-DEPENDENT HYPERTENSION

2.1. Cognitive Function

Early studies reported a disruption of passive avoidance retention by AngII injection into the brain [23]. Recent

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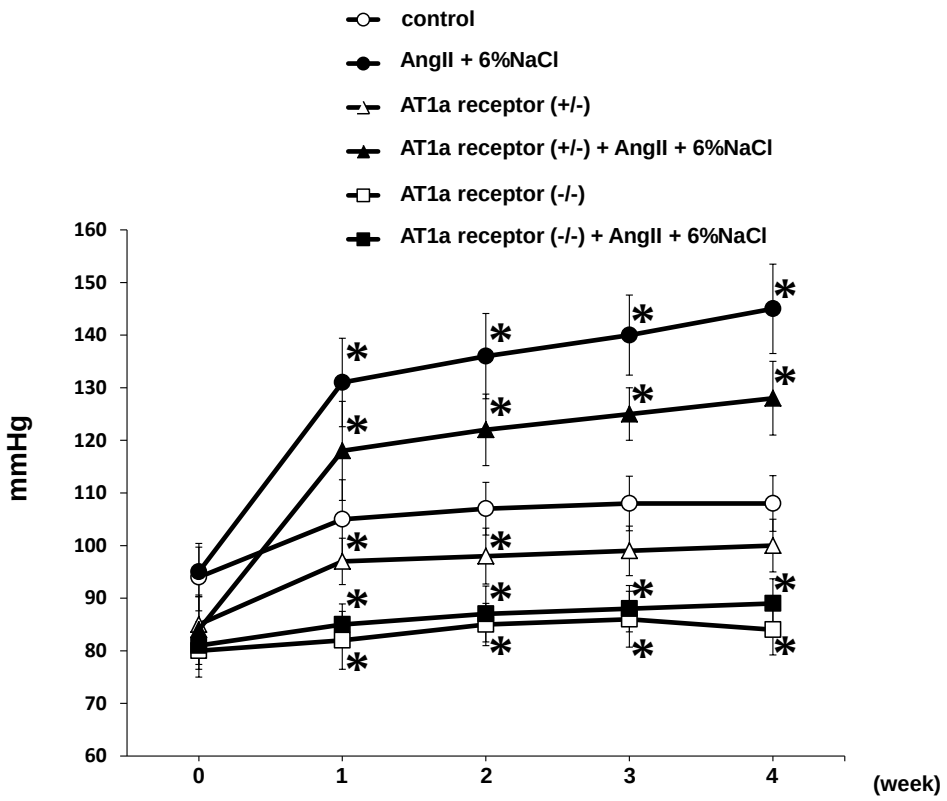

Fig. (1). Effect of chronic infusion of AngII on systolic blood pressure in AT_{1a} receptor deficient mice. Values are presented as means ± SD. Statistical comparisons of the differences between the values were performed using two-way analysis of variance combined with the Newman-Keuls post hoc test. Values of $P<0.05$ were considered statistically significant. *$P<0.05$ vs. control.

studies have also shown impaired cognitive function in renin/angiotensinogen transgenic mice [10]. More recently, we investigated BBB injury and cognitive impairment in AngII-dependent hypertensive mice. All experimental procedures were performed according to the guidelines for the care and use of animals established by the Kagawa University Medical School. To analyze cognitive functions, a shuttle avoidance test was used, as previously described [9, 17, 24]. In 6% NaCl-treated 8-weeks-old C57BL mice, subcutaneous infusion of AngII (20 ng/min) for 4 weeks caused hypertension and impaired cognitive functions (n=11) compared with age-matched vehicle-infused control mice (n=10). On the other hand, AngII-induced hypertension and impairment of cognitive function was not severe in AT_{1a} receptor (+/-) mice (n=8). Furthermore, these changes were not observed in AT_{1a} (-/-) mice (n=7, Figs. **1** and **2**). Interestingly, AngII-induced impairment of cognitive function was associated with increases in brain tissue AngII levels (Fig. **3**). These data suggest that an increase in brain AngII contributes to the pathogenesis of cognitive impairment through the AT_{1a} receptor in mice during the development of AngII-dependent hypertension.

2.2. BBB Permeability

Previous studies have demonstrated that the rapid increase in blood pressure by AngII infusion is associated with BBB injury [25, 26]. AngII also induces blood pressure-independent BBB injury through effects on endothelial cells and the immune system [10, 27]. We previously examined the effects of chronic infusion of AngII on BBB leakage and cognitive functions in the above-mentioned high salt-treated mice. We analyzed microvessel permeability in the hippocampus and corpus callosum by using horseradish peroxidase [9, 17]. All experimental procedures were performed according to the guidelines for the care and use of animals established by the Kagawa University Medical School. We observed significant leakage from brain microvessels in the hippocampus in AngII-infused hypertensive mice (n=11), while no leakage was observed in vehicle-infused control mice (n=10). However, these changes were not observed in AngII-infused AT_{1a} receptor (-/-) mice (n=7, Fig. **4**). Interestingly, cognitive deficits were associated with augmented brain AngII levels and BBB permeability in AngII-infused hypertensive mice. These data support the concept that inappropriate activation of the brain RAS induces cognitive deficits through AT_{1a} receptor-dependent augmentation of BBB permeability during the development of AngII-dependent hypertension.

3. EFFECTS OF RAS INHIBITORS

3.1. Cognitive Function

Hirawa *et al.* [14] reported that long-term treatment with an ACE inhibitor improves memory function in aged, low-salt-treated, normotensive, Dahl salt-sensitive (DSS) rats.

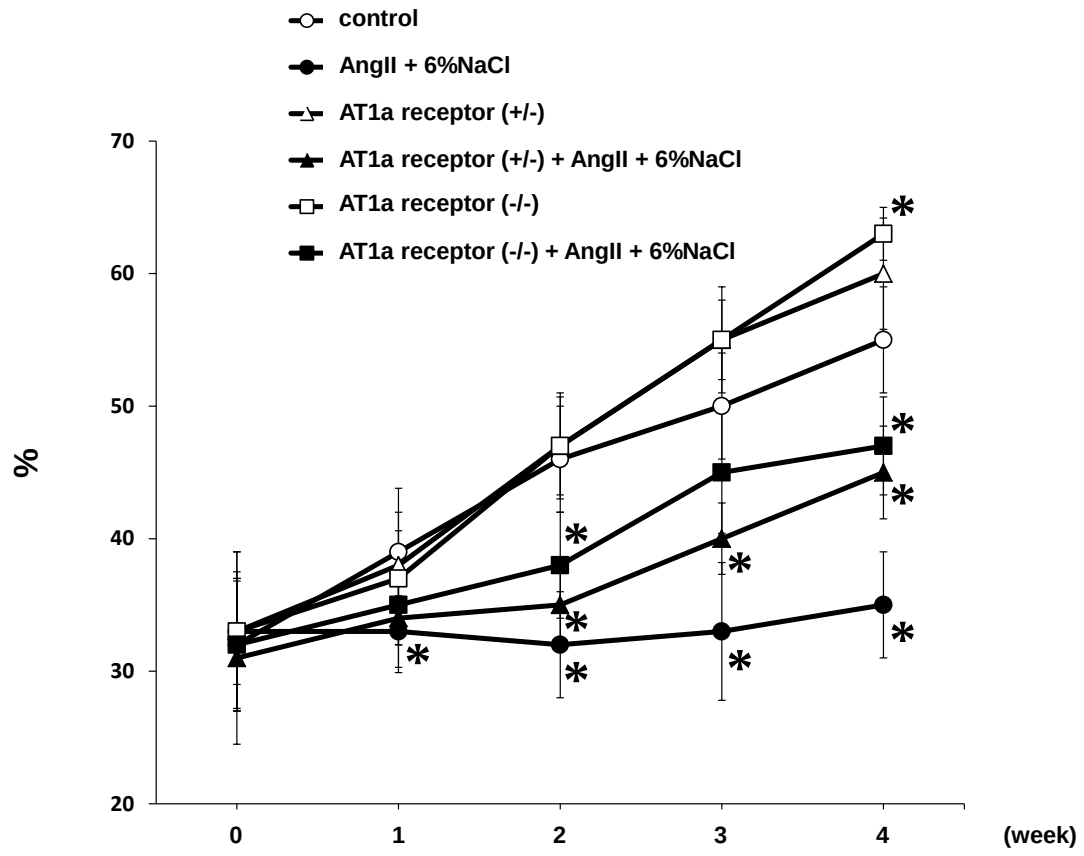

Fig. (2). Effect of chronic infusion of AngII on cognitive functions in AT_{1a} receptor deficient mice. Values of avoidance rate (%) are presented as means ± SE. Statistical comparisons of the differences between the values were performed using or two-way analysis of variance combined with the Newman-Keuls post hoc test. Values of $P<0.05$ were considered statistically significant. *$P<0.05$ vs. control.

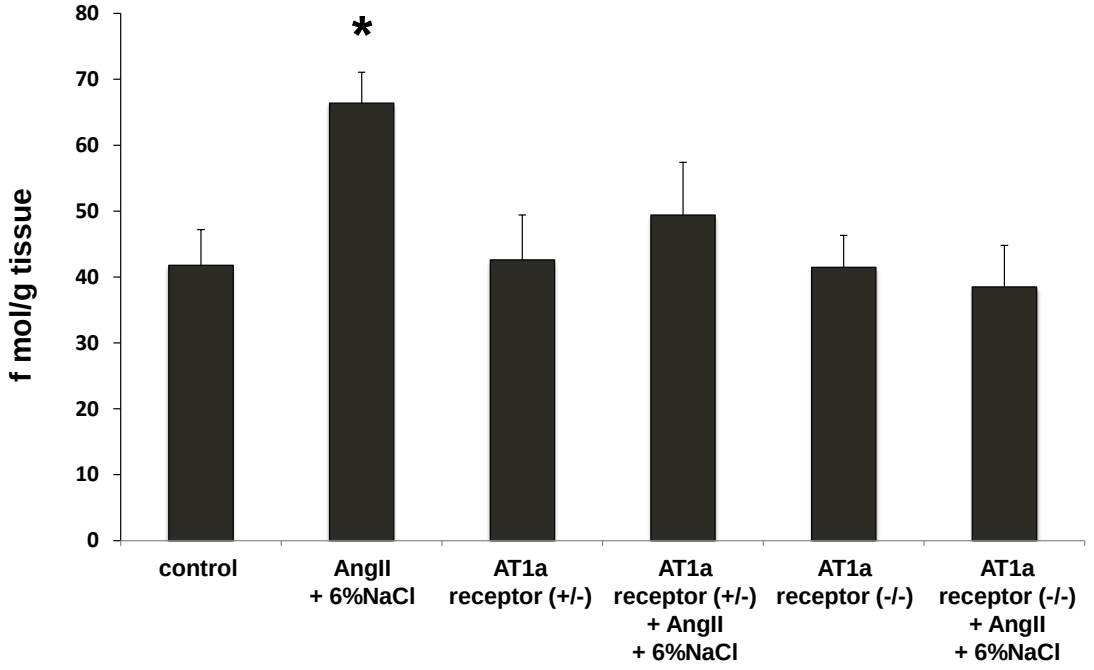

Fig. (3). Effect of chronic infusion of AngII on AngII contents in brain tissue. Values are presented as means ± SD. Statistical comparisons of the differences between the values were performed using paired-t-tests. Values of $P<0.05$ were considered statistically significant. *$P<0.05$ vs. control.

Treatment with RAS inhibitors ameliorates impaired cognitive function in metabolic syndrome [11], hypertensive type 2 diabetic [12] and Alzheimer's disease model mice [28]. Large scale clinical studies have also shown that RAS inhibitors reduce a low risk of developing Alzheimer disease and similar neurodegenerative disorders [29]. However, plausible within-class differences with regard to the effect of RAS inhibitors on cognitive impairment have also been indicated by other studies [18, 20-22, 30, 31].

We have previously shown that cognitive decline is associated with increases in brain tissue AngII levels in DSS hypertensive rats [17]. Furthermore, treatment with an ARB, olmesartan, did not alter blood pressure, but decreased brain AngII levels and attenuates cognitive decline [17]. We

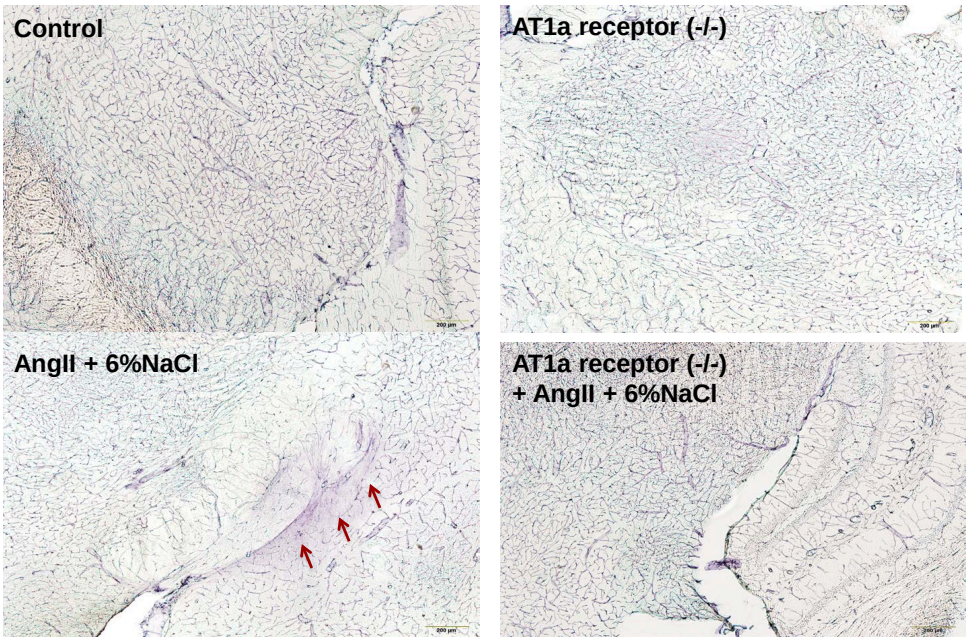

Fig. (4). Effect of chronic infusion of AngII on BBB permeability. BBB permeability as indicated by HRP-TMB reaction (violet stain).

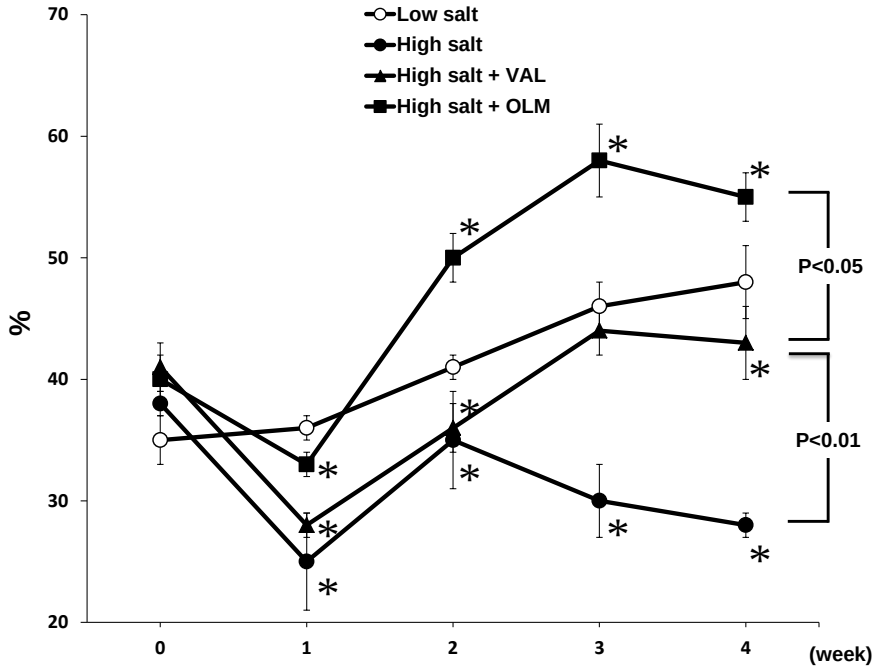

Fig. (5). Effects of valsartan (VAL) and olmesartan (OLM) on cognitive functions in Dahl salt-sensitive hypertensive rats. Values of avoidance rate (%) are presented as means ± SD. Statistical comparisons of the differences between the values were performed using two-way analysis of variance combined with the Newman-Keuls post hoc test. Values of $P<0.05$ were considered statistically significant. *$P<0.05$ vs. control.

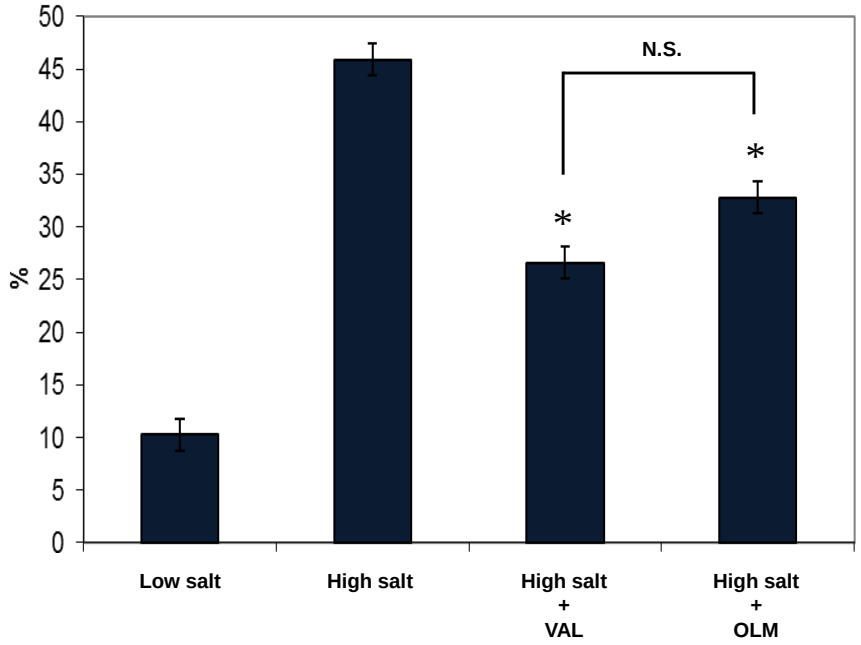

Fig. (6). Effects of valsartan (VAL) and olmesartan (OLM) on BBB permeability. Percentage of the positive area for BBB permeability. Values are presented as means ± SD. Statistical comparisons of the differences between the values were performed using paired-t-test. Values of $P<0.05$ were considered statistically significant. *$P<0.05$ vs. control.

then examined the effects of olmesartan and valsartan on cognitive function in DSS hypertensive rats. All experimental procedures were performed according to the guidelines for the care and use of animals established by the Kagawa University Medical School. Six-week-old DSS rats were treated with 0.3% (n=4) or 8% NaCl (n=12) diet for 4 weeks. Twelve 8% NaCl DSS rats were assigned to three groups: vehicle (n=4), olmesartan (1 mg/kg/day) and valsartan (10 mg/kg/day). The doses of olmesartan and valsartan were determined on the basis of previous studies on DSS rats [17, 32, 33]. Neither olmesartan nor valsartan altered blood pressure in DSS hypertensive rats. As reported previously [17], treatment with olmesartan markedly attenuated cognitive decline (Fig. **5**). These data are consistent with the hypothesis that ARB treatment elicits blood pressure-independent beneficial effects on cognitive impairment in subjects with salt-dependent hypertension. On the other hand, the preventive effect of valsartan on cognitive decline was not so obvious compared with that of olmesartan (Fig. **5**). These data suggest that plausible within-class differences with regard to the effect of ARBs on cognitive impairment might be present under some experimental conditions.

3.2. BBB Permeability

Treatment with an ARB decreases BBB permeability in epinephrine and streptozotocin-induced hypertensive diabetic rats [13]. Our preliminary data also showed significant BBB permeability in type 2 diabetic OLETF rats (data not shown). We have also reported that treatment with olmesartan, at a dose that does not alter blood pressure, markedly restores BBB disruption in DSS hypertensive rats [17]. Furthermore, the above-mentioned preliminary studies showed that valsartan also restored BBB disruption, although the effect of valsartan appears to be weaker than that of olmesartan (Fig. **6**), suggesting possible within-class differences in ARBs. Nevertheless, these preliminary data are consistent with the hypothesis that ARB treatment can cause blood pressure-independent beneficial effects on cognitive impairment by protecting against BBB injury during the development of salt-dependent hypertension.

CONCLUSIONS

In conclusion, the present study supports the hypothesis that RAS inhibition attenuates cognitive impairment through reducing BBB injury in subjects with AngII- and salt-dependent hypertension, independently of blood pressure changes. These data also support the recently introduced clinical concept that the neurovascular unit is an important therapeutic target for brain protection [34].

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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ABBREVIATIONS

BBB	=	blood-brain barrier
RAS	=	renin-angiotensin system
AngII	=	angiotensin II
ARBs	=	AngII type 1 receptor blocker

ACE = angiotensin-converting enzyme

DSS = Dahl salt-sensitive

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