Editorial Comment

Aegis against Stroke and Dementia by Angiotensin Type 1 Receptor Blockers: New Beneficial Aspects

Ryuichi MORISHITA[1)]

(*Hypertens Res* 2008; 31: 1–3)

***Key Words*: ischemia, angiotensin II, hypertension, peroxisome proliferator–activated receptor-γ, atherosclerosis**

Hypertension is the most significant predisposing factor for cerebrovascular disease (stroke, ischemic white matter lesions, silent infarct) and coronary heart disease (myocardial infarction, angina), which are leading causes of morbidity and mortality worldwide. Hypertension is a major risk factor for cerebrovascular disease including stroke, and may also contribute to the development of vascular dementia (*1*). The incidence of hypertension correlates with advancing age, with an estimated prevalence of 50% in people older than 70 years. In light of the dramatic increase in the elderly populations in Western countries, especially in Japan, the protective effects of antihypertensive drugs on stroke are now subjects of interests.

The renin-angiotensin system (RAS) plays a key role in regulating cardiovascular homeostasis, such as controlling sodium balance, body fluid volume, and arterial blood pressure. Manipulation of this system has emerged as a new therapeutic approach to the management of hypertension. Indeed, recent clinical trial evidence suggests that RAS blockade by angiotensin-converting enzyme (ACE) inhibition or by angiotensin type 1 receptor (AT1) blockade may influence large vessel atherosclerosis as well as cardiovascular morbidity and mortality independent of blood pressure reduction. Moreover, there is accumulating evidence that the brain has its own RAS, which mediates several physiological and pathological brain functions (*2*). Brain angiotensin receptors and endogenous angiotensin peptides have been implicated in neural plasticity and cognitive function such as memory and learning. On the other hand, the neurobiological links between RAS and cerebrovascular disease have been investigated and are becoming a subject of interest in the pathogenesis of this disease (*3*).

Almost all components of RAS have been identified in the brain, and it is believed that endogenous angiotensin peptides are associated with its receptors. The brain has a high concentration of angiotensinogen, especially in the choroid plexus and astrocytes. Angiotensin II (Ang II) has been identified within synaptic vesicles in nerve terminals in those areas with high angiotensin receptor concentrations. Renin and ACE are also widely distributed throughout the brain (*4*). Although recent studies demonstrated that the AT1 receptor mediates the known physiological actions of Ang II in the brain (*2*, *4*, *5*), the angiotensin type 2 (AT2) receptor protein is also associated with vascular growth during development (*6*) and with the regulation of cerebral blood flow (*7*, *8*). The brain has high concentrations of angiotensin receptors in several regions. Binding sites for Ang II have been identified within the circumventricular organs (CVO), specifically in the subfornical organ (SFO), organum vasculosum of the lamina terminalis (OVLT), area postrema (AP), median eminence, and anterior pituitary gland (*9–11*). The AT1 subtype is localized with high densities in the following brain regions: the hypothalamus, the anterior pituitary, lateral geniculate, anterior ventral third ventricle region, subfornical organ, paraventricular, supraoptic, ventral medial nuclei, median eminence, and preoptic region; in the medulla: the nucleus of the solitary

From the [1)]Department of Clinical Gene Therapy, Graduate School of Medicine, Osaka University, Suita, Japan.

Address for Reprints: Ryuichi Morishita, M.D., Ph.D., Division of Clinical Gene Therapy, Graduate School of Medicine, Osaka University, 2–2 Yamadaoka, Suita 565–0871, Japan. E-mail: morishit@cgt.med.osaka-u.ac.jp

Received November 12, 2007.

tract, dorsal motor nucleus of the vagus, and inferior olivary nucleus (*2*). High densities of AT2 receptors are found in the amygdala, medial geniculate, hypoglossal nucleus, inferior olivary nucleus, lateral habenula, caudate putamen, globus pallidus, locus ceruleus, thalamus, inferior colliculus, and ventral tegmental areas (*2*).

In this issue of *Hypertension Research*, Iwai *et al*. reported the effects of an AT1 receptor blocker (ARB), telmisartan, on focal brain ischemia in atherosclerotic apolipoprotein E–deficient (ApoE KO) mice fed a high-cholesterol diet (*12*). They clearly demonstrated that the blockade of the AT1 receptor attenuates ischemic brain damage induced in the atherosclerosis model. This beneficial effect of telmisartan was associated with the attenuation of neurological deficit, superoxide production in the ischemic area, and the reduction of cerebral blood flow in the penumbra without significant changes in blood pressure and serum cholesterol level. Thus, they concluded that this inhibitory action is mediated through attenuation of the reduction in cerebral blood flow and of oxidative stress in the brain as well as through an anti-atherosclerotic effect. Their conclusion was consistent with those of recent large clinical trials. In primary prevention, the LIFE randomized trial showed a significant difference in stroke rate in favor of losartan compared with atenolol, despite similar reductions in blood pressure (*13*). In acute stroke, the ACCESS study found that candesartan, an ARB, seems to be safe in hypertensive acute stroke patients and may offer advantages independent of blood pressure control (*14*). In secondary stroke prevention, the MOSES study showed that eprosartan prevented vascular events more effectively than nitrendipine, despite similar blood pressure–lowering effects. Similarly, in the Jikei Heart Study, the addition of valsartan, an ARB, to conventional cardiovascular treatment was effective for decreasing the incidence of stroke (0.60), while blood pressure level did not differ between conventional and valsartan treatment groups (*15*). Now, interest in ARBs' brain-protective effects is apparently increasing.

Moreover, ARBs' effects on cognitive function are also gaining interest. A growing body of evidence indicates that brain angiotensin peptides and their receptors are involved in cognitive function, especially in memory processing. Long-term potentiation (LTP) is thought to serve as the basic physiological mechanism underlying memory storage. Wayner and co-workers reported that Ang II delivered into the CA1 field of the rat hippocampus inhibited LTP. This inhibition was blocked by losartan or by a non-specific AT1 and AT2 receptor antagonist; however, a specific AT2 receptor antagonist failed to block this Ang II–induced inhibition of LTP (*16–20*). Morgan and Routtenberg reported that Ang II injected directly into the dorsal neostriatum impaired a step-down shock avoidance response (*21*). Similarly, Lee *et al*. observed that direct injection of Ang II into the dentate gyrus disrupted performance of a single trial step-through shock avoidance response (*22*). Losartan significantly attenuated these impairments (*21*, *22*). It is also reported that intracerebroventricularly infused renin impaired performance of a passive avoidance task in a dose-dependent manner (*23*). Although an ARB and an ACE inhibitor attenuated this renin-induced deficit, co-application of an AT2 receptor antagonist failed to influence the deficit.

Neuropathological investigations have shown that people with hypertension more often have large areas of white matter hyperintensity, ventricular enlargement, and silent infarcts compared to normotensive individuals, which could promote cognitive impairment and the clinical expression of dementia (*24–27*). Indeed, in the Perindopril Protection against Recurrent Stroke Study (PROGRESS), a randomized, double-blind, placebo-controlled trial involving more than 6,000 patients with a previous stroke or ischemic attack (*28*), participants treated with an ACE inhibitor (perindopril) showed lower dementia rates. In the Study on Cognition and Prognosis in the Elderly (SCOPE) trial, which included elderly hypertensive subjects aged 70–89 years with a Mini-Mental State Examination (MMSE) score of 24 or more, the score declined significantly less in an ARB (candesartan) group in patients with slightly low cognitive function at baseline (MMSE score 24–28) (*29*, *30*). The present study by Iwai *et al*. may also support these findings (*12*). However, the brain-protective effects shown in their study may not be class effects, since telmisartan has a unique property in addition to blocking the AT1 receptor among recently developed ARBs. As previous papers have indicated that telmisartan acts as a selective modulator of peroxisome proliferator–activated receptor-γ (PPAR-γ) and increases its activity (*31*, *32*), telmisartan may improve ischemic brain damage in an atherosclerotic model not only *via* blockade of AT1 receptor stimulation. Recently, since a PPAR-γ agonist, rosiglitazone, showed neuroprotective effects at least partially mediated by anti-inflammatory action (*33*), the present study using telmisartan might be due to anti-inflammatory action and the regulation of carbohydrate and lipid metabolism *via* PPAR-γ activation, in addition to AT1 receptor blockade. Future basic and clinical studies should test whether or not all ARBs might have the same effects on the brain. Nevertheless, ARBs' protective effects on stroke and cognitive function should be considered one of their most important features as first-line antihypertensive drugs.

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