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Angiotensin-receptor blockers, hypertension and alzheimer disease: The entangled relationship

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EDITORIAL

Angiotensin-Receptor Blockers, Hypertension and Alzheimer Disease

– The Entangled Relationship –

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Alzheimer disease (AD) is a very common neurodegenerative disorder characterized by progressive dementia, brain atrophy and neuronal loss (especially in the hippocampus), with senile plaques (in which amyloid-β (Aβ) is deposited) and neurofibrillary tangles (in which phosphorylated tau protein accumulates). The basal nucleus of Meynert is also involved and affects the cholinergic neuronal system in the brain, causing memory impairment.

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Acetylcholine esterase inhibitors (donepezil, galantamine and rivastigmine) and an NMDA-type glutamate receptor antagonist (memantine) are widely used for the cognitive dysfunction of AD, but these drugs cannot halt disease deterioration. Therefore, disease-modifying drugs or preventive therapy is needed, but has not yet been established. An anti-Aβ antibody drug is a candidate disease-modifying treatment, but previous reports have noted that it caused encephalitis or brain edema/exudates, which raises safety concerns.[1,2] Other trials targeting tau-protein, beta-secretase or gamma-secretase are in progress,[3] but the situation is not very optimistic.

Another strategy against AD is intervention for putative risk factors such as hypertension (HT), diabetes mellitus (DM), dyslipidemia, smoking and so on.[4] HT (especially in middle age) is a disease risk factor (risk ratio=1.5).[5] The mechanism is still unclear, but the presence of vascular pathology involving arterial stiffness, arteriolosclerosis, endothelial degeneration and blood-brain barrier dysfunction leads to chronic cerebral hypoperfusion. It induces several features of AD pathology, including selective brain atrophy, white matter changes and accumulation of abnormal proteins such as Aβ.[6] Some preliminary studies have reported the effectiveness of angiotensin-receptor blockers (ARBs) against the AD pathological process in mice,[7] but the effectiveness in human beings has not been established. Are ARBs really efficacious against AD?

In this issue of the Journal, Hsu et al report that use of an ARB was not associated with a reduction of risk of AD in Asian patients with essential HT.[8] Their study was based on a nationwide health-insurance database that enrolled a large-scale Asian population. The study also analyzed various ARBs, but none showed a significant effect on risk reduction. The result suggests it is difficult, at least for Asian people, to gain any benefit from ARBs for preventing new onset of AD.

This study has some limitations; for example, it was not prospective double-blinded and placebo-controlled research. In addition, the authors did not set a blood pressure target and did not analyze blood pressure control outcomes, and the study did not include non-Asians. Nevertheless, the results will have an effect on the antihypertensive strategy against AD at the public-health level.

This report is in line with previous studies that suggested

Table. Placebo-Controlled Studies of Antihypertensive Drugs and Cognition

Study	Drug tested	Measurement	Result
Syst-Eur (1998)[9]	Nitrendipine (+enalapril or hydrochlorothiazide)	MMSE, no. of patients with dementia	Reduced the rate of dementia by 50%
PROGRESS (2003)[10]	Perindopril (+indapamide)	MMSE, no. of patients with dementia	NS (for non-stroke dementia)
SHEP (1994)[11]	Chlorthalidone (+atenolol or reserpine)	Short-CARE (Comprehensive Assessment and Referral Examination)	NS
SCOPE (2003)[12]	Candesartan	MMSE, no. of patients with dementia	NS
PRoFESS (2008)[14]	Telmisartan	MMSE, no. of patients with dementia	NS
HYVET-COG (2008)[15]	Indapamide (+perindopril)	MMSE, no. of patients with dementia	NS

MMSE, Mini-Mental State Examination; NS, no significance.

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the effectiveness of antihypertensive drugs against AD is still controversial (**Table**). The Syst-Eur study with nitrendipine demonstrated decreased incidence of new onset of dementia,[9] but further studies by other investigators confirming that result have not been reported. The PROGRESS study with perindopril reported no significant change in new onset of non-stroke dementia,[10] and the SHEP study showed that diuretic chlorthalidone did not have an effect on cognitive function.[11] The SCOPE study did not show a significant effect of candesartan on prevention of AD,[12] although its substudy indicated active treatment achieved less decline in attention and episodic memory.[13] The PRoFESS study with telmisartan described no significant change in Mini-Mental State Examination score and no difference in the numbers of demented patients.[14] The HYVET-COG study of indapamide failed to prove a significant difference in the rate of dementia between treatment and placebo in patients aged 80 years or older.[15] To date, antihypertensive drugs have had little effect on AD prevention or slowing.

It is unclear why antihypertensive drugs are not effective, but there are several possible reasons. First, the contribution of HT to AD is relatively small and other factors such as aging, sex, genotype (eg, apolipoprotein E), education and DM weigh in on the onset of AD. Second, some stages of the AD process (including neuronal loss) are irreversible, so antihypertensive intervention would not be effective. Third, there is still a place for consideration in the process of intervention; previous studies do not negate that other types of antihypertensive drugs could be candidates. Moreover, AD is an insidious disorder and the pathological process starts from the age of 50–60 years, so earlier detection of the at-risk population would be necessary for effective intervention.

The onset of AD is associated with multiple factors, so manifold approaches (not monotherapy) are needed for effective disease-modifying treatment, such as removing amyloid burden, intervening in the amyloid or tau accumulation cascade or repairing vascular pathology, as well as lifestyle correction.

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