

Dihydropyridine calcium channel blockers in dementia and hypertension

Farha Motiwala, MD, Nwakile Ojike, MD, and Steven Lippmann, MD

Dementia affects 34 million people globally, with the most common cause of dementia, Alzheimer's disease (AD), affecting 5.5 million Americans.^{1,2} The connection between cerebrovascular disorders and AD means that antihypertensive agents may play a role in dementia prophylaxis and management.^{1,2}

Hypertension increases the risk of intellectual dysfunction by increasing susceptibility to heart disease, ischemic brain injury, and cerebrovascular pathology.¹ In addition to senile plaques, ischemic brain lesions are observed in autopsies of AD patients,¹ and brain infarctions are more common among AD patients than among controls.² Brain pathology suggestive of AD was found in 30% to 50% of postmortem examinations of patients with vascular dementia.¹

It is useful to note that dihydropyridines, a subgroup of calcium channel blockers, may inhibit amyloidogenesis.³

Hypertension and cognition

Hypertension-induced hyperdense lesions in cerebral white matter reflect pathology in small vessels, inflammatory change, and disruption of the blood-brain barrier, which may precede cognitive decline.¹ Even subclinical ischemic changes may increase the probability of developing dementia.² Hypertension also reduces cerebral perfusion, especially in the hippocampus, which may promote degeneration of memory function.¹ Prolonged cerebral hypoxia increases amyloid precursor protein production and β -secretase activity.^{1,2} Patients who died of brain ischemia show prominent β -amyloid protein and apolipoprotein E in histopathologic analysis of the hippocampus.¹ Compression of vessels

by β -amyloid protein further augments this degenerative process.¹

Inhibition of amyloidogenesis

Long-term administration of antihypertensive medications in patients age <75 decreases the probability of dementia by 8% each year.¹ Calcium channel blockers protect neurons by lowering blood pressure and reversing cellular-level calcium channel dysfunction that occurs with age, cerebral infarction, and AD.

Select dihydropyridines may inhibit amyloidogenesis in apolipoprotein E carriers:

- amlodipine and nilvadipine reduce β -secretase activity and amyloid precursor protein- β production³
- nilvadipine and nitrendipine limit β -amyloid protein synthesis in the brain and promote their clearance through the blood-brain barrier³
- nilvadipine-treated apolipoprotein E carriers experience cognitive stabilization compared with cognitive decreases seen in non-treated subjects.

Dihydropyridines can produce therapeutic effects for both AD and cerebrovascular dementia patients, indicating the potential that certain agents in this class have for treating both conditions.

References

1. Valenzuela M, Esler M, Ritchie K, et al. Antihypertensives for combating dementia? A perspective on candidate molecular mechanisms and population-based prevention. *Transl Psychiatry*. 2012;2:e107.
2. Pimentel-Coelho PM, Rivest S. The early contribution of cerebrovascular factors to the pathogenesis of Alzheimer's disease. *Eur J Neurosci*. 2012;35(12):1917-1937.
3. Paris D, Bachmeier C, Patel N, et al. Selective antihypertensive dihydropyridines lower A β accumulation by targeting both the production and the clearance of A β across the blood-brain barrier. *Mol Med*. 2011;17(3-4):149-162.

Dr. Motiwala is a Clinical Extern, Department of Psychiatry, University of Louisville School of Medicine, Louisville, Kentucky. Dr. Ojike is a Clinical Extern, Department of Psychiatry, University of Louisville School of Medicine, Louisville, Kentucky. Dr. Lippmann is a Professor, Department of Psychiatry, University of Louisville School of Medicine, Louisville, Kentucky.

Disclosure

The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.