Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors

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Mots-clés ACEI [16], Alzheimer disease [17], amyloid peptide [18], angiotensin AT1-receptor blocker [19], angiotensin peptide [20], angiotensin receptor [21], c-Met receptor [22], calcium channel blocker [23], centrally acting sympatholytic antihypertensive [24], Cognition [25], diuretic [26], Hepatocyte Growth Factor [27], insulin degrading enzyme [28], insulin regulated aminopeptidase [29], mas receptor [30], renin inhibitor [31], β-blocker [32]
Our review of cohort studies and clinical trials evaluating antihypertensive drugs in the prevention of cognition decline and all dementia in patients with hypertension indicates that two antihypertensive drug classes have greater protective effects, independent of blood pressure decrease: dihydropyridine calcium-channel blockers as shown in the Syst-Eur trial and angiotensin-AT1 receptor blockers as found in the MOSES and ONTARGET trials. By contrast, diuretics and angiotensin-converting enzyme-inhibitors (ACEIs) prevent dementia only in patients with a stroke history, provided they are combined, and prevent stroke recurrence. A Japanese cohort study and a small trial in patients already suffering from Alzheimer’s disease (AD) suggest, however, that the BBB-penetrating ACEI may slow down cognitive decline. Only cohort studies support the hypothesis that diuretics, (especially potassium-sparing diuretics), may decrease the risk of AD. β-blockers worsen cognition decline, or are neutral, according to whether or not they cross the BBB. Centrally-acting sympatholytic agent have a negative impact on cognition as BBB-penetrating β-blockers, probably by blunting the adrenergic pathways. The AD protective effect of DHP appears related to the blockade of neuronal calcium channels. The ambiguous effect of ACEI on cognitive decline and dementia prevention may be explained by the fact that brain ACE is not specific for angiotensin-I. Brain ACE also catabolizes cognition-enhancing brain peptides, amyloid peptides and converts toxic $\beta_42$ into less toxic $\beta_40$. Therefore, ACEIs may have short-term cognition-enhancing properties and may increase in the long term $\beta_40$, brain burden and cognitive decline. The clinical relevance of this scenario, mainly observed in animals, cannot be excluded in man, since the ACE gene has been associated with AD via the human whole genome analysis. To support the hypothesized deleterious effect of ACEI on human AD, confirmation that the ACE gene polymorphism DD is associated with protection against AD is necessary, since this polymorphism increases ACE activity.

Independently of their preventive impact on β-amyloid degenerative neuropathological process by overexpressing insulin degrading enzyme which catabolyses amyloid, the angiotensin AT1-receptor-blockers may have greater cognition protective effects than ACEI (observed in the ONTARGET trial), as they share with ACEI cognition-enhancing effects directly linked with a common AT1-blunting effect. In addition, they increase angiotensin II and IV formation and therefore stimulate non-opposed AT2 and AT4 receptors, whose activation in cognitive processes is well established.

**Résumé en anglais**

Our review of cohort studies and clinical trials evaluating antihypertensive drugs in the prevention of cognition decline and all dementia in patients with hypertension indicates that two antihypertensive drug classes have greater protective effects, independent of blood pressure decrease: dihydropyridine calcium-channel blockers as shown in the Syst-Eur trial and angiotensin-AT1 receptor blockers as found in the MOSES and ONTARGET trials. By contrast, diuretics and angiotensin-converting enzyme-inhibitors (ACEIs) prevent dementia only in patients with a stroke history, provided they are combined, and prevent stroke recurrence. A Japanese cohort study and a small trial in patients already suffering from Alzheimer’s disease (AD) suggest, however, that the BBB-penetrating ACEI may slow down cognitive decline. Only cohort studies support the hypothesis that diuretics, (especially potassium-sparing diuretics), may decrease the risk of AD. β-blockers worsen cognition decline, or are neutral, according to whether or not they cross the BBB. Centrally-acting sympatholytic agent have a negative impact on cognition as BBB-penetrating β-blockers, probably by blunting the adrenergic pathways. The AD protective effect of DHP appears related to the blockade of neuronal calcium channels. The ambiguous effect of ACEI on cognitive decline and dementia prevention may be explained by the fact that brain ACE is not specific for angiotensin-I. Brain ACE also catabolizes cognition-enhancing brain peptides, amyloid peptides and converts toxic $\beta_42$ into less toxic $\beta_40$. Therefore, ACEIs may have short-term cognition-enhancing properties and may increase in the long term $\beta_40$, brain burden and cognitive decline. The clinical relevance of this scenario, mainly observed in animals, cannot be excluded in man, since the ACE gene has been associated with AD via the human whole genome analysis. To support the hypothesized deleterious effect of ACEI on human AD, confirmation that the ACE gene polymorphism DD is associated with protection against AD is necessary, since this polymorphism increases ACE activity.

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