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Potential Role of the Sigma-1 Receptor Chaperone in the Beneficial Effects of Donepezil in Dementia with Lewy Bodies

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TO THE EDITOR

With great interest, I read the article by Mori *et al*.[1] about a randomized, placebo-controlled trial of the cholinesterase (ChE) inhibitor donepezil for dementia with Lewy bodies (DLB). The study randomly assigned 140 DLB patients to receive placebo or donepezil hydrochloride (3, 5, or 10 mg, daily for 12 weeks). The effects on cognition were assessed using the Mini-Mental State Examination (MMSE) and several domain-specific neuropsychological tests. Changes in behavior were evaluated using the Neuropsychiatric Inventory, caregiver burden using the Zarit Caregiver Burden Interview, and global function using the Clinician's Interview-Based Impression of Change-plus Caregiver Input (CIBIC-plus). Donepezil at 5 or 10 mg was significantly superior to placebo on both the MMSE and CIBIC-plus, and 3 mg donepezil was significantly superior to placebo on the CIBIC-plus, but not on the MMSE. Furthermore, a beneficial effect of donepezil was evident in each symptom domain characteristic of delusion, hallucination, and cognitive fluctuation (in DLB). Moreover, patients who received donepezil showed improved global function, as measured by the CIBIC-plus. These results suggest that donepezil (5 and 10 mg/day) produces significant cognitive, behavioral, and global improvements in DLB patients, and that at the highest dose, this drug reduces the caregiver burden.[1]

Cholinergic loss in DLB might be associated with cognitive deficits and neuropsychiatric symptoms,[2] although the precise pathogenesis of DLB is unclear. In contrast, accumulating evidence suggests that the sigma-1 receptor chaperone plays an important role in the pathophysiology of neuropsychiatric disorders, and that sigma-1 receptor agonists are potential therapy for neuropsychiatric disorders.[3-6] In addition to ChE inhibition, donepezil binds to the sigma-1 receptor chaperone in the brain with high affinity.[7] Furthermore, we reported that donepezil potentiated nerve growth factor-induced neurite outgrowth in PC12 cells, and that its effect was antagonized by treatment with NE-100 (4-methoxy-3-(2-phenylethoxy)-N,N-dipropylbenzeneethanamine hydrochloride) a sigma-1 receptor antagonist.[8] Moreover, we found that phencyclidine-induced cognitive deficits in mice were improved by the subchronic administration of donepezil, but not the ChE inhibitor physostigmine, and that its effect was antagonized by the co-administration of NE-100.[7] These findings suggest that the agonistic activity of donepezil at the sigma-1 receptor chaperone plays a role in the mechanisms of this drug in animal models of cognitive deficits. A positron emission tomography study demonstrated that donepezil (5 or 10 mg) binds to the sigma-1 receptor in the living human brain at therapeutic doses, implicating the sigma-1 receptor chaperone in the pharmacological mechanism of donepezil in the human brain.[9]

Given the crucial role of the sigma-1 receptor chaperone in the pathophysiology of neuropsychiatric disorders, the sigma-1 receptor chaperone is likely involved in the beneficial effects of donepezil in DLB.

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