Challenging the Cholinergic Hypothesis in Alzheimer Disease

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The idea that some of the symptoms of Alzheimer disease are due to a deficiency of the neurotransmitter acetylcholine in the brain first surfaced in 1976 and 1977. Several groups of investigators reported that the activity of enzymes involved in the synthesis (choline acetyltransferase [ChAT]) and degradation (acetylcholinesterase [AChE]) of acetylcholine were markedly reduced in activity in autopsy brain tissue from patients with end-stage Alzheimer disease, and many subsequent studies have confirmed these findings. A few groups have reported deficits in ChAT activity or acetylcholine release in biopsy tissue from living patients with Alzheimer disease and several reports have shown that the extent of the deficits in autopsy brain tissue correlate with the severity of the disease (as determined by the density of neuritic plaques, neurofibrillary tangles, or both). The cholinergic hypothesis of Alzheimer disease that evolved from these studies simply postulates that at least some of the cognitive decline experienced by patients with Alzheimer disease results from a deficiency of acetylcholine, or cholinergic neurotransmission. This hypothesis has been the stimulus for a great deal of effort in experimental pharmacology and a large number of clinical trials.

In this issue of THE JOURNAL, Davis and colleagues report that cholinergic deficits do not appear to be present in patients with the early stages of Alzheimer disease. With some relatively minor caveats, this work seems likely to seriously undermine support for the cholinergic hypothesis. The main finding is that patients who were already experiencing the characteristic signs and symptoms of Alzheimer disease at death showed no evidence of deficiency of either ChAT or AChE activity. The possibility that other pathologic findings, such as vascular dementia or less common neurological conditions, account for the symptoms appears to have been ruled out. Neuritic plaques and neurofibrillary tangles were present in tissue from the patients with early Alzheimer disease, although in smaller numbers than in patients with end-stage disease. This work suggests that the symptoms of Alzheimer disease, at least in the early stages, are not primarily caused by a loss of cholinergic transmission, even though there is abundant evidence, including in the study by Davis et al, that such deficits do occur as the disease progresses.

Does the work presented by Davis and colleagues dispute more than 2 decades of neurochemical work on cholinergic transmission in Alzheimer disease? Not necessarily. Davis and colleagues show that there are correlations between loss of the cholinergic marker enzymes and the clinical measures of dementia severity (as well as correlations with numbers of plaques and tangles) if and only if the patients with severe dementia are included in the analysis. The study is heavily weighted toward cases with mild cognitive impairment and a correspondingly small number of plaques and tangles. Cholinergic neurotransmission is affected by Alzheimer disease but apparently not early in its course.

The minor caveats about this study include the nature of the patient population, which comprised mostly women and which had a mean age older than usual for this type of study. There was also no reported examination of cholinergic neurons in the ventral forebrain, which provide the major source of cholinergic innervation to the cerebral cortex. It is possible that significant cell loss did occur in these early Alzheimer disease cases but that surviving neurons increased the production of the enzymes necessary to maintain neurotransmission. Another issue is that the only 2 drugs approved by the US Food and Drug Administration (FDA) for treatment of the cognitive deficit in Alzheimer disease (tacrine and donepezil) are both inhibitors of AChE. The approval by the FDA was based on the demonstration of efficacy of these agents. Why do these compounds appear to have beneficial effects if there is no demonstrable cholinergic deficit? Davis et al suggest that these agents may be effective only in moderate- to late-stage cases, presumably cases in which a cholinergic deficit has developed. But the same research group showed 20 years ago that a cholinesterase inhibitor given to young, healthy volunteers could improve memory test scores, indicating that perhaps a cholinergic deficit is not necessary for beneficial effects of compounds of this type.

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If cholinergic neuron loss or dysfunction is not responsible for the early symptoms of Alzheimer disease, what is? The work of Braak et al during the last few years has increasingly focused attention on the fact that entorhinal cortex and hippocampal neurons are among the earliest to show signs of degenerative changes in this condition. Clinical symptoms appear to correlate with the spread of the disease from the hippocampus into the association areas of the neocortex. Disruption of hippocampal circuitry has been suggested previously as an explanation of the impairments of memory that are characteristic of Alzheimer disease. Perhaps therapeutic efforts to treat the early cognitive decline in this disease will have to be directed toward restoration of these circuits, which, for the most part, use glutamate as the neurotransmitter. However, exploring ways to restore these circuits will be difficult because of their complex structure. The pharmaceutical industry, aside from the efforts currently under way to develop new and better cholinergic drugs, appears to be focused on developing drugs to slow or prevent neuronal degeneration in Alzheimer disease. Hopefully, for the sake of patients and their caregivers, these efforts will make drugs to treat the symptoms of this disease unnecessary.

REFERENCES