

Although many types of neurons are damaged or destroyed in Alzheimer's disease, few seem to fare so badly as the cholinergic cells which arise in the basal forebrain, terminate in the hippocampal and cerebral cortex, and enable some memory functions (compare with reference 1). Identifying the biochemical processes which underlie the selective vulnerability of these cells has been a continuing focus of Alzheimer's disease research. A potential candidate is the propensity of these cells to use choline for two purposes: to phosphorylate it, ultimately generating a major membrane phospholipid, phosphatidylcholine (PC), a pathway they share with all other cells; and to acetylate it to form the neurotransmitter acetylcholine (ACh). Both of the neuronal enzymes which act on choline, choline kinase and choline acetyltransferase, have unusually low affinities for this substrate and are thus unsaturated at normal brain choline levels. Thus, they rapidly synthesize more product when substrate levels increase (e.g., after administration of compounds that raise plasma choline levels [1]). However, when cholinergic neurons are physiologically active, they selectively shunt available free choline to the ACh pathway, increasing the turnover of membrane PC and slowing its synthesis, and, if unchecked by giving supplemental choline, actually decrease the amounts of membrane phospholipids per cell (1). This process, a kind of "autocannibalism" is perhaps analogous to the bone demineralization which occurs with prolonged vitamin D deficiency.

The discovery that providing choline could promote ACh release in model systems (1) generated hope that Alzheimer's disease patients might benefit from supplemental choline sources, much as those with Parkinson's disease show clinical improvement when treated with dopamine's precursor, L-dopa. However, clinical tests of such sources demonstrated only occasional improvement, and drugs that increased brain ACh levels (by blocking acetylcholinesterase) rarely caused dramatic responses. The widespread extracranial distribution of ACh receptors and the continuing unavailability of selective agonists for the brain-specific  $m_1$  receptor (which, when activated, improves memory and suppresses formation of the amyloid-forming peptide, A-beta, in model systems [2]) precluded adequate tests of the hypothesis that drugs which restored cholinergic brain function would bestow clinical improvement on Alzheimer's disease patients. So the "cholinergic hypothesis" of Alzheimer's disease lost its place in the research line to therapeutic strategies based on proteins like APP (the amyloid precursor protein), tau, and the apolipoprotein alleles. Brain levels of choline and of its principal reservoir, PC, were later shown to be reduced in Alzheimer's disease, and those of PC's breakdown product glycerophosphocholine increased (3). However, these discoveries failed to engender new strategies, or drugs, to test in treating the disease.

Now Slotkin and his colleagues (4) present compelling evidence that another macromolecule localized to cholinergic neurons, the high-affinity carrier that transports extracellular choline into cholinergic nerve terminals, also is abnormal in Alzheimer's disease. But the disturbance is opposite to what might have been expected in a disease that reduces the number of terminals: transport activity is too high, not too low. They propose that this change resulted, premortem, from an acceleration

in the frequency with which the surviving neurons were firing, perhaps an adaptive response to the loss of neurons and the impairments in cholinergic neurotransmission that are characteristic of the disease. (It might also constitute an adaptation to the recently demonstrated decrease in choline transport across the blood-brain barrier associated with aging, per se [5].) However, this acceleration in neuronal firing rates, they propose, may be damaging to the cholinergic cells, further diminishing the formation of PC and perhaps accelerating its turnover. They suggest that drugs be developed which will restore cholinergic transmission while decreasing neuronal firing (for example, the cholinergic agonists discussed above): agents which cause the neuron to fire yet more frequently (like GABA antagonists or glutamate agonists) should be avoided, since flogging the dying horse may only hasten its death. This suggestion seems reasonable, and one can only hope that appropriate agents will soon become available for testing.

Should Alzheimer's disease patients also receive supplemental choline, as such or in the form of choline-rich molecules like PC or cytidyldiphosphocholine? Such supplements might cause less of an increment in brain choline levels among old Alzheimer's disease patients than in young subjects (5). However, they have in fact been shown to raise cerebrospinal fluid choline concentrations in such patients (6). Even if they enhanced ACh release and/or protected membrane PC from autocannibalism, they still couldn't correct the deficits in brain levels of the closely related amine ethanolamine, nor of the phospholipid phosphatidylethanolamine (3). However, there is probably little harm (a judgment which must first be confirmed by suitable toxicologic testing) in providing the choline at a dose requirement to the amount that many Americans miss when they give up eggs because of cholesterol content. A stronger argument can be adduced for supplying choline to patients to be treated chronically with drugs like the cholinesterase inhibitors, which further decrease the free choline available to cholinergic terminals. The demonstration by Slotkin et al. (4) of yet another abnormality of cholinergic neurons in Alzheimer's disease should stimulate additional studies on the unique biochemical properties of the cells.

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J. Clin. Invest.

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0021-9738/94/08/0470/01 \$2.00

Volume 94, August 1994, 470