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Exploring the Role of Acetylcholine in Primate Cognition Using Me20.4 IgG-Saporin

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INTRODUCTION

"Do not go gentle into that good night,
Old age should burn and rave at close of day;
Rage, rage against the dying of the light."

Dylan Thomas, 1914–1953

Two factors led to the emergence of the "cholinergic hypothesis of geriatric memory dysfunction" *(1)*: evidence that cholinergic blockade in human volunteers leads to impaired acquisition of new information *(2,3)* and the demonstration of loss of cortical cholinergic activity and loss of cholinergic cell bodies in the basal forebrain of patients dying with Alzheimer's disease *(4–6)*. It has been proposed that it is the loss of the rising cholinergic pathways from the basal forebrain to the cortex (including the hippocampus) that is responsible for the amnesia seen in dementing illnesses *(6)*. This view has been challenged (e.g., in ref. *7*). Cholinergic antagonists also block transmission at cholinergic neurons intrinsic to many subcortical areas and block transmission in the cholinergic projections to noncortical areas; this may affect memory, either directly or via an influence on arousal and attention. Furthermore, studies with rats did not produce a correlation between the magnitude of cholinergic loss in the basal forebrain across various nonimmunotoxic lesion techniques and learning or performance impairments *(8)*.

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However, although these early studies did not establish a role for the basal forebrain cholinergic projections in learning, they did not establish a specific role for it in any other cognitive function because none of the lesion methods used were specific to the cholinergic system. It remains a possibility that the behavioral tasks used in these various studies were inappropriate rather than that these studies demonstrated, unequivocally, that basal forebrain acetylcholine is not involved in any aspect of learning and memory.

Clinical observation has also been unable to determine a specific role for acetylcholine in mnemonic function. Degeneration of many neuronal systems and other pathological changes are found in the brains of patients dying with Alzheimer's disease *(9–11)* and any of these may have contributed to a wide range of cognitive impairments, including memory loss. Although loss of cholinergic markers measured postmortem does correlate with dementia scores premortem *(12,13)*, other aspects of pathology, such as cortical neurofibrillary tangle density and loss of pyramidal cells also correlate with severity of symptoms *(14–16)*.

Patients with Alzheimer's disease show impairment on acquisition of long-term memories and on tests of recent memory *(17)*. Aged monkeys show impairments on a wide range of memory tests, including repeated-trial learning (long-term memory tasks) *(18,19)* and tests of recent memory *(20)*. Thus, either acetylcholine is involved in a wide range of memory functions (and probably other cognitive functions as well) or, if only some of the memory deficits in Alzheimer's disease and aging are caused by cholinergic loss, other memory deficits must be caused by other pathology.

The enhancement of cholinergic neurotransmission using cholinesterase inhibitors (e.g., donepezil) is currently a licensed treatment for the memory impairments of Alzheimer's disease *(21)*. This method is only moderately successful. Efficacy is limited because cholinesterase inhibitors act by preventing the breakdown of acetylcholine and can therefore only be of value when some acetylcholine is still present, and dose is limited by the occurrence of undesirable autonomic side effects and other toxicity. Drugs that specifically target cholinoceptive receptors in neural circuits involved in learning and memory may be much more effective. Such drugs would not compensate directly for loss of noncholinergic neurons in Alzheimer's disease, but if the loss of the rising cholinergic projections does contribute to memory impairment, then it will be necessary to address this loss with effective treatment. Furthermore, there is evidence that immunotoxic cholinergic lesions induce β-amyloid deposition *(22)*, and that cholinergic agonists suppress the production of the β-amyloid precursor peptide *(23)*, suggesting that prolonged cholinergic support may retard pathogenic mechanisms as well as provide cognitive enhancement in Alzheimer's disease.