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Cortical Cholinergic Deafferentation Induces Aβ Deposition

Toward a Physiological Animal Model of Alzheimer's Disease

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INTRODUCTION

There are 4 million Americans with Alzheimer's disease (AD), and the cost of the disease to the United States is estimated at $100 billion annually (Alzheimer's Association). Finding a cure or prevention for AD is therefore an important goal. To do this, however, the cause(s) of AD must first be determined.

Research has established that brain accumulation and histological deposition of a single peptide known as Aβ is a critical event in AD. Many investigators believe that Aβ deposition leads to all of the other relevant pathological changes in the disease, including neurofibrillary tangle formation, loss of synapses, neuronal death, and dementia *(1–3)*. Preventing this accumulation may prevent AD. In simple genetic forms of AD, accumulation of Aβ is caused by inherited gene mutations that result in increased Aβ production *(4)*. Only a very small subset of AD occurs this way, however. In the common, "sporadic" form of AD, the reason for Aβ accumulation is not known.

If Aβ deposition can be considered the essence of AD, then the disease in fact transcends human genetics because Aβ deposition is an aging change

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common to many mammalian species *(5–11)*. The prevalence of AD increases exponentially with age *(12)*, and the histopathology of AD affects all humans who approach the maximum human lifespan *(13,14)*. The initial pathogenic event of AD therefore must lie within the physiological process of aging.

We have developed an animal model of AD that is initiated by a physiological aging change *(15,16)*. In primates, cholinergic afferents to the cerebral cortex are depleted during aging, probably because of the loss or physiological inadequacy of the parent cell bodies in the basal forebrain *(17–30)*. Evidence from human postmortem studies, as well as cell culture and animal experiments, has linked cholinergic neurotransmission to Aβ metabolism and deposition. In aging human cerebral cortex, cholinergic deafferentation begins around ages 40–50 yr *(20,25)* and is shortly followed by biochemically detectable elevations of cortical Aβ (31) and Aβ deposition *(32)*. In aging, nondemented humans, there is a statistical association between the depletion of cortical cholinergic markers and measures of Aβ accumulation *(27,33,34)*.

In vitro studies have shown that m1 and m3 muscarinic receptor activation leads to changes in the cleavage pattern of Aβ's amyloid precursor protein (βAPP) that favor decreased production of Aβ (processing changes that result in more Aβ formation are termed *amyloidogenic*; changes that favor secretory APP [sAPPα], a different cleavage product, are termed *nonamyloidogenic*) *(35–50)*. This effect has been confirmed in vivo in animals *(51–53)* and humans *(54,55)*. Conversely, decreased activation of muscarinic receptors, whether through lesions of cholinergic afferents *(56–63)* or pharmacological blockade *(64)*, leads to increased expression of βAPP or evidence of increased amyloidogenic cleavage. We therefore hypothesized that cortical cholinergic deafferentation would cause increased cortical Aβ production and deposition.

Cortical cholinergic deafferentation, accomplished through lesioning of the nucleus basalis of Meynert (NBM) has long been employed as an animal model of AD. Following the discovery of the cortical cholinergic deficit in AD, many investigators suggested that this could be the initial critical pathogenic event in the disease. Some predicted that degenerating cholinergic fibers might participate in plaque formation *(65–67)*. Two groups even reported the development of Aβ deposition in rats with NBM lesions *(68,69)*, but this was not replicated by others, and these findings were later disputed *(70)*. One group reported that NBM lesions increased amyloidogenic processing of βAPP *(62,63)*, but they did not measure Aβ directly. Our approach differs from these previous efforts in a number of ways.