# 5

# 192 IgG-Saporin-Induced Partial Cortical Cholinergic Deafferentation as a Model for Determining the Interactions Between Brain Aging and Neurodevelopmental Defects in the Cortical Cholinergic Input System

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## INTRODUCTION

The anti-p75-immunotoxin 192 immunoglobulin G-saporin (192 IgG-sap) has been instrumental in testing the hypothesis that the integrity of the cortical cholinergic input system is necessary for the mediation of a wide range of attentional functions and capacities *(1–10)*. As discussed elsewhere *(11)*, attentional functions represent a crucial set of cognitive variables that contribute to the efficacy of learning and recalling of declarative information. Thus, impairments in attentional abilities rapidly yield escalating impairments in learning and memory. Different types of dysregulation of cortical cholinergic transmission have been hypothesized to mediate the diverse attentional impairments that are characteristic of major neuropsychiatric disorders and that contribute to the manifestation of the main cognitive symptoms of these disorders *(12–16)*.

The relationships between the degeneration of basal forebrain cholinergic neurons and the onset and progression of dementia have remained a matter of debate, although some aspects of this debate have been extensively substantiated. Specifically, the status of cortical cholinergic inputs predicts the cognitive status of patients with senile dementia unlike any other measure of cortical integrity, including the density of senile plaques *(17–24)*.

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The role of the cortical cholinergic input system in dementia has been questioned primarily on the basis of psychopharmacological evidence. For example, the fact that the acute administration of muscarinic receptor antagonists to healthy humans does not reproduce the entire spectrum of impaired cognitive functions observed in Alzheimer's disease (AD; *25,26*) has been interpreted as reflecting a rather limited role of the cholinergic system in AD. However, an acute drug effect cannot model decades of escalating decline, and a proper psychopharmacological model in fact would need to assess the effects of chronically administered muscarinic antagonists. It can be safely predicted that such a treatment would cause a devastating and comprehensive decline in cognitive functions, even more so in aged subjects *(27)*.

A second major critique has been based on the narrow therapeutic potential of cholinesterase inhibitors which, likewise, has been interpreted as reflecting the limited involvement of the cholinergic system in the cognitive decline in AD. However, as discussed elsewhere *(13,28)*, there are many fundamental reasons to predict the restricted beneficial cognitive effects of these drugs, including the facts that they further dissociate postsynaptic cholinergic signaling from presynaptic cholinergic activity and that muscarinic receptor signal transduction cascades are disrupted in AD *(29–31)*. Studies continue to substantiate the relationship between decreases in cortical cholinergic innervation and cognitive decline *(17,32)*.

Based largely on the finding that, in patients with mild cognitive impairments, basal forebrain cholinergic neurons exhibit a strikingly reduced level of expression of trkA receptors *(33–35)*, hypotheses have emerged that describe the accelerating decline of the basal forebrain cortical cholinergic input system as a result of disruption of earlier trophic factor support and of reciprocal interactions between a declining cholinergic system and other converging, age-related cellular and vascular processes, including the processing and metabolism of amyloid precursor protein, and the regulation of the microvascular system *(36–48)*.

An important component of this major hypothesis refers to the age-related reregulation of (residual) cortical cholinergic inputs. Neurochemical and behavioral experiments have indicated that the regulation and function of the residual cortical cholinergic input system are robustly altered by the aging process. Specifically, in the aging brain, residual cortical cholinergic inputs no longer respond to activating behavioral or neurochemical manipulations and thus are no longer capable of mediating demands on attentional processing.

These hypotheses were tested by assessing the regulation and function of the (residual) cortical cholinergic input system in aging animals suffering