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Basal Forebrain Cholinergic Lesion by 192 IgG-Saporin

A Tool to Assess the Consequences of Cortical Cholinergic Dysfunction in Alzheimer's Disease

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INTRODUCTION

Alzheimer's disease, the most common neurodegenerative disorder causing senile dementia, is characterized by two major morphopathological hallmarks. The deposition of extracellular neuritic, β-amyloid peptide-containing plaques (senile plaques) in hippocampal and cerebral cortical regions of patients with Alzheimer's disease is accompanied by the presence of intracellular neurofibrillary tangles that occupy much of the cytoplasm of particular pyramidal neurons.

Another hallmark of Alzheimer's disease is a progressive neuronal cell loss associated with region-specific brain atrophy. In particular, the cholinergic projection from the nucleus basalis of Meynert to areas of the cerebral cortex is the pathway that is very early and most severely affected in brains from those with Alzheimer's disease. A number of studies have demonstrated that the learning and memory deficits observed in patients with Alzheimer's disease are caused at least partly by the progressive loss of basal forebrain cholinergic neurons, which led to the cholinergic hypothesis of geriatric memory dysfunction *(1,2)*. For reviews, *see* refs. *3–5*.

Massive loss of basal forebrain cholinergic neurons was demonstrated by reductions in number of cholinergic markers such as choline acetyltransferase, muscarinic and nicotinic acetylcholine receptor binding, as well as levels of acetylcholine. In particular, the activity of choline acetyl transferase is highly

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correlated with the clinical dementia ratings across the neocortex of patients with Alzheimer's disease *(6)*.

However, impaired cortical cholinergic neurotransmission may also contribute to β-amyloid plaque pathology in Alzheimer's disease. This has been evidenced by a number of studies in vitro and in vivo that demonstrated cholinergic control of expression and processing of the β-amyloid precursor protein (APP; *7–15*). The basal forebrain cholinergic system also plays a role in regulation of cerebral cortical blood flow mediated by activation of cholinergic receptors and nitric oxide (NO)-related mechanisms and affects cerebral cortical glucose utilization, which may contribute to the impaired cerebral glucose metabolism observed in Alzheimer's disease.

However, it is still unclear how cognitive deficits, basal forebrain cholinergic cell loss, energy dysfunction, and β-amyloid formation and deposition are interrelated in the pathogenesis of Alzheimer's disease. To address this question, adequate animal approaches are required to produce specific cholinergic deficits in vivo. These would allow detailed evaluation of the neurochemical, neuropathological, and behavioral sequela, as well as functional implications of plastic repair mechanisms following cholinergic hypofunction and provide information that cannot be or can only partially be obtained in humans.

Lesions of the cholinergic basal forebrain complex result in a cortical cholinergic denervation and have been exploited in a number of studies to produce an animal model to mimic dysfunctions of cortical cholinergic neurotransmission; for review, *see* the work of Härtig et al. *(16)*, for instance. Because of the unique topographical organization of the basal forebrain cholinergic system, cholinergic lesion studies face a number of difficulties to selectively and specifically destroy the cholinergic neurons giving rise to the cholinergic basalo-cortical pathway: First, cholinergic cells in the basal forebrain do not comprise a distinct nucleus with sharp boundaries (e.g., like the locus coeruleus for noradrenergic cells), but they are distributed within a number of distinct forebrain nuclei, forming an irregular shaped band of neurons with both a rostral–caudal and ventral–dorsal extension. Second, the basal forebrain nuclei that comprise the cholinergic cell population also contain a variety of noncholinergic cells like γ-aminobutyric acid-(GABA), neuropeptides-, or glutamate-containing neurons intermingled with cholinergic ones. In addition, there are also noncholinergic fiber bundles passing through the basal forebrain in the neighborhood of cholinergic nuclei.

A large number of different experimental paradigms have been introduced to produce cholinergic deficits (*see*, e.g., Schliebs et al. [*17*]*)*, comprising