

# Is Preservation of Cholinergic Activation a Mechanism Underlying Cognitive Reserve?

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## Abstract

The cognitive reserve, despite having abundant pathological change of Alzheimer's disease, some patients can preserve cognitive function, is a new concept to puzzle Alzheimer's pathogenesis. Interestingly, some recent epidemiological study has shown that diet, exercise, cognitive training and vascular risk monitoring interventions may reduce cognitive decline in at-risk elderly people in the general population. However, the mechanisms underlying this cognitive function preservation are still unknown. Our recent data suggest that differences in the persisting degree of cholinergic activity might be, at least in part, involved in the decorrelation between the extent of cognitive deterioration and AD pathological changes. This fact might raise a possibility of cholinergic modulation for hippocampal glutamatergic activity in a mechanism of "cognitive reserve".

Previous research suggests that amyloid- $\beta$  ( $A\beta$ ) assemblies can inhibit glutamatergic neuronal activity in the hippocampus and increase neurofibrillary tangle (NFT) formation via phosphorylation of tau protein in Alzheimer's disease (AD), forming the basis of the amyloid hypothesis [1]. However, several therapeutic interventions for reducing  $A\beta$  in patients with AD have failed to ameliorate the decline of cognitive function. Meanwhile, some patients have been reported to exhibit preserved cognitive function despite pathological changes in the brain; for example, a nun named Sister Mary maintained cognitive function within the normal range until just prior to death in spite of abundant senile plaques (SPs) and NFTs in the brain [2]. Other studies have reported that some individuals can tolerate more Alzheimer's-related pathological changes than others, a phenomenon known as "cognitive reserve". Epidemiological studies have suggested that a range of factors, including education (intelligence quotient: IQ), occupation, leisure activity, mental activity and exercise, could be involved in cognitive reserve [3]. However, the details of the molecular mechanisms underlying this cognitive functional preservation are still unknown.

Memory dysfunction is the main neurological sign in AD and the primary lesion is thought to be related to glutamatergic neuronal activity in the hippocampus. The synchronization of hippocampal neuronal oscillation through neural connections between the cortex and hippocampus via the subiculum is involved in memory function [4]. Glutamatergic activation in the hippocampus is modulated by several neuronal networks, including adrenergic and cholinergic neurons [5]. In the AD brain, glutamatergic neuronal activity may be impaired and incompletely suppressed by  $A\beta$  oligomers as glutamatergic neurons are in an unsaturated condition [6].

Interestingly, enriched environments have been found to prevent the impairment of hippocampal long term potentiation (LTP), the classical electrophysiological model of memory [7]. This process is thought to occur via  $\beta$ 2-adrenergic signals, when LTP is incompletely suppressed by synthetic  $A\beta$  oligomers [7].

The modulatory effect of cholinergic activity on hippocampal synaptic plasticity may be concentration-dependent [8]. Interestingly, sub threshold cholinergic stimulation via low doses of a cholinergic agonist, can also enhance unsaturated glutamatergic activity in hippocampus, but not saturated LTP [9].

From the early stages of Alzheimer's disease, the concentration of acetylcholine is decreased in the brain and the cholinergic neurons in

the basal forebrain, medial septal nucleus and nucleus basalis of Meynert are degenerative; these findings have led to formation of the choline hypothesis [10]. Interestingly, cholinergic agonists, particularly the stimulation of the muscarinic M1 receptor, can, at least in part, prevent LTP impairment by synthetic  $A\beta$  oligomers as well as  $\beta$ 2-adrenergic stimulants [9]. The effects of cholinergic activation on the amelioration of cognitive function via cholinesterase inhibitors have been confirmed in clinical settings, whereas cholinesterase inhibitors do not ameliorate memory function in individuals without dementia.

However, the effects of cholinesterase inhibitors are limited, and were found to disappear 10-12 months after beginning medication once cognitive function was ameliorated [11]. To utilize cholinergic activation for cognitive preservation for prolonged periods, the degenerative process of cholinergic neurons in the forebrain would need to be inhibited in the Alzheimer's brain. Several neurotrophic factors have been proposed as candidates, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). However, the details of the underlying mechanisms of these factors in the human brain remain unclear.

Previously, we reported the importance of a cholinergic regulator gene in the medial septal nucleus (MSN) called hippocampal cholinergic neurostimulating peptide (HCNP) [12,13]. Recently, we demonstrated that cholinergic neural activation enhanced glutamatergic neuronal activity during unsaturated LTP, but not saturated LTP, using hippocampal sections from mice. Synthetic  $A\beta$  oligomers also suppressed the hippocampal glutamatergic activity in a concentration-dependent manner. Furthermore, HCNP over-expression as well as a cholinergic agonist, through the muscarinic M1 receptor, appeared

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to prevent the suppression of hippocampal glutamatergic neuronal activity induced by synthetic A $\beta$  oligomers [9].

Our data suggest that the neural modulation network projecting hippocampal glutamatergic activation, including cholinergic as well as  $\beta$ 2-adrenergic nerve fibers, could play at least a partial role in the mechanisms underlying cognitive reserve. The clinical fact, cholinesterase inhibitors could ameliorate memory function in only patients with AD, in not individuals without dementia, might also accord with our experimental event that cholinergic stimulation can only enhance unsaturated glutamatergic activity in hippocampus, but not saturated it. These findings indicate that preservation of cholinergic neurons in the forebrain in the AD brain might be a new therapeutic target for treating Alzheimer's disease.

## Conclusion

Differences in the persisting degree of cholinergic activity might be involved in the decorrelation between the extent of cognitive deterioration and AD pathological changes. In addition, the mechanisms of cognitive decline in late-onset sporadic AD should be reconsidered based on clinical and epidemiological findings indicating the involvement of cholinergic activation, diabetes mellitus, atrial fibrillation and/or head trauma, as well as A $\beta$  oligomers.

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