

Field: Chemistry/Biochemistry

Session Topic:

Chemistry of Neuro-disorders: Their mechanism, diagnostics and drug development

Speaker:

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Title: Alzheimer's disease and metabolism of amyloid- β peptide ($A\beta$)

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that robs patients of their memory and cognitive abilities, and even their personalities. These changes are due to the progressive dysfunction and death of neurons that are responsible for learning and memory processes. Accumulation of amyloid- β peptide ($A\beta$) in the brain is a triggering event leading to the pathological cascade of AD, including dementia. It is necessary for overcoming AD to inhibit $A\beta$ production and/or promote the degradation and clearance of $A\beta$ in the brain.

2. Neprilysin is a rate-limiting enzyme in $A\beta$ degradation in the brain. As demonstrated by gene-targeting techniques, disruption of the neprilysin gene causes elevation of endogenous $A\beta$ levels in the mouse brain in a gene-dose-dependent manner. Therefore, reduction of neprilysin activity will contribute to $A\beta$ accumulation/deposition and thus to AD development. Evidence that expression levels of neprilysin were reduced in the hippocampus and cerebral cortex of AD patients and aged laboratory mice suggests a close association of neprilysin with the etiology and pathogenesis of AD. Indeed, reduced activity of neprilysin in the mouse brains elevates $A\beta$ oligomers, which is highly toxic forms of $A\beta$ aggregates, at the synapses, and leads to impaired hippocampal synaptic plasticity and cognitive function. Thus, a decline in neprilysin activity appears to be a causative event that is at least partly responsible for the memory-associated symptoms of AD, and up-regulation of neprilysin represents a promising strategy for therapy and prevention.

3. We have identified somatostatin, which is one of neuropeptides and acts via G-protein-coupled receptors, as a modulator that increases brain neprilysin activity, resulting in a decrease of $A\beta$ levels. It was discovered that somatostatin levels were significantly reduced in the brains of AD patients in 1980s, and this observation has been confirmed repeatedly by others so far, whereas its pathogenic significance remains uncertain. However, recent study showed that about 4% of approximately 11,000 human genes exhibited aging-dependent changes in expression (1.5-fold or more), and one of them was indeed the somatostatin gene, of which the expression level was reduced 2~3-fold from the age of 40 years old. A similar aging-dependent decrease in somatostatin expression level is observed in other primate brains. Because accumulation of $A\beta$ in the human brain occurs from the age of 40 years old, and the $A\beta$ level in normal brain

becomes close to that of clinically AD-affected patients with progression of aging, differences in the velocity of the age-dependent A β accumulation would differentiate the onset of AD pathogenesis among different individuals. Thus, the observation in 1980s appears to support, beyond several decades, our finding that somatostatin controls brain A β levels through modulating the activity of the major A β -degrading enzyme, neprilysin. Taken together, now we propose a possible mechanism for the AD development as follows, down-regulation of somatostatin expression in the human brain at the early stage of aging initiates a gradual decline in neprilysin activity, resulting in a corresponding elevation in the steady-state levels of A β , over a decade or more, and this causes A β accumulation that triggers the AD pathological cascade. This cascade causes progressive neuronal dysfunction and neurodegeneration over a long period, generating a vicious cycle of positive feed-back that further lowers the somatostatin level and neprilysin activity, elevates the A β levels, and accelerates AD development.

Conclusion

Up-regulation of brain neprilysin by blood-brain barrier-permeable non-peptidic agonists selective to somatostatin receptor(s) localized in AD-affected regions might break the vicious cycle through lowering A β levels. Thus, it may be possible to pharmacologically control brain A β levels with somatostatin receptor agonists.

References

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Keywords

Alzheimer's disease (AD), neurodegeneration, brain aging, amyloid- β peptide (A β), aggregation and accumulation of proteins, degradation, neprilysin, somatostatin, hippocampus, brain, gene-knockout