Development of BACE1 Inhibitors in Treatment of Alzheimer’s Disease

Alzheimer’s disease (AD) is a neurodegenerative disease discovered in 1906 by Alois Alzheimer and is an escalating health problem among the elderly in the world. AD is considered to be the most common cause of age-related dementia and the pathogenesis of this disease has been extensively studied for over several decades in order to discover targets for therapeutic intervention. However, due to controversial data and the heterogeneous nature of the disease, the underlying cause of AD is still not clearly understood. Based on accumulating data, two hypotheses were formulated by researchers to explain the etiology of AD: the amyloid cascade hypothesis and the alternate hypothesis. The amyloid cascade hypothesis is the oldest and the most accepted hypothesis, which centers on the neurotoxicity of overproduced and aggregated amyloidogenic peptide. The origin of amyloidogenic peptide and its related enzymes were extensively studied and b-site APP cleaving enzyme (BACE1), an aspartyl protease, is one of the enzymes discovered as a result of such efforts. Since the discovery of the enzyme, countless attempts have been made to synthesize an effective inhibitor of BACE1. The first generation of BACE1 inhibitors was peptidomimetic inhibitors which were derivatives of short peptide sequence of its natural substrate. Although these compounds gave promising results in vitro, they were unsatisfactory in vivo due to its molecular size and poor CNS penetration. Many AD research groups are now focusing on the design of inhibitors that are less or non-peptidic in order to overcome the problems encountered in the earlier generation of inhibitors. A novel class of compounds containing isonicotinamide was among the few promising inhibitors, which demonstrated the reduction of Ab in vivo. Such inhibitors are the fruits of several decades of intensive AD research that may be a hallmark of our advancement in medicinal chemistry.

References