Targeting Beta Amyloid Clearance as Therapeutic Approach for Alzheimer's Disease

Dr. Amal Khalil Kaddoumi

College of Pharmacy,
University of Louisiana at Monroe, 9:00 AM

Development of Casein Kinase 1 Inhibitors as Therapeutics for Alzheimer's Disease

Dr. Jayalakshmi Sridhar

Department of Chemistry
Xavier University of Louisiana, 9:45 AM

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Targeting Beta Amyloid Clearance as Therapeutic Approach for Alzheimer's Disease

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Mentor:
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Significant efforts have been made to elucidate the mechanisms responsible for beta amyloid (Aβ) accumulation in the brain of Alzheimer's disease patients (AD). Possible mechanisms for Aβ pathogenesis include faulty clearance across the blood-brain barrier (BBB). Continuous removal of Aβ from the CNS is important for preventing or delaying Aβ accumulation. Low-density lipoprotein receptor protein-1 (LRP1) and P-glycoprotein (P-gp) are believed to be major Aβ efflux transporters at the BBB, and reduced function of these transporters at the BBB has been observed during normal aging and in AD. A role for LRP1 to Aβ transport across the BBB in AD has been demonstrated, however the specific role and contribution of P-gp to the clearance of Aβ and consequent Aβ toxicity remains largely unknown and poorly defined. Understanding the role of P-gp to Aβ regulation is essential not only for understanding the basis for Aβ fluxes in the brain, but also because it may identify novel roles for P-gp in modulating specific forms or species of Aβ, or potentially serving as a basis for the development of novel therapeutics for regulating the levels of Aβ in the brain. Thus, there is an urgent need to elucidate exact role P-gp plays in the clearance of Aβ. P-gp is an efflux transporter highly expressed at the luminal side of the endothelium at the BBB, reported to play a potential role in regulating Aβ clearance by several groups. The mode of interaction between P-gp and Aβ is undefined, and the mechanism by which P-gp removes Aβ in vivo remains poorly understood, thus further studies in these areas are required to clarify the exact role of P-gp in Aβ regulation in the brain. Our preliminary data confirm a significant role for P-gp in regulating Aβ levels in the brain. Therefore, clarifying such role will be useful to gain valuable clues regarding strategies for treating and/or preventing increased levels of toxic Aβ observed in AD and vascular dementia.
Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with the accumulation of the neurotoxic peptide amyloid β (Aβ). Casein kinase 1 family comprises of eight isozymes, two of which CKιδ and CKιε are predominantly expressed in the brain. CKιδ plays a critical role in AD through phosphorylation of tau, a protein associated with microtubules, which precedes neuritic lesion formation. Thus, CKιδ is implicated in the tau fibrillization reaction pathway. CKιδ is reported to be associated with pathological accumulation of tau in several neurodegenerative diseases including AD, Down syndrome, progressive supranuclear palsy, and parkinsonism dementia complex of Guam. Inhibition of CKιδ by pan CKι inhibitors has been shown to reduce fibrillar lesions and to inhibit Aβ production. These studies show the potential for CKιδ specific inhibitors as therapeutic agents for neurodegenerative disorders. The reports on development of CKιδ small molecule inhibitors as therapeutic agents for neurodegenerative disorders have been far and few. None of the recently reported CKιδ inhibitors been tested for their efficacy in pre-clinical trials. Our recent work investigating quinones as kinase inhibitors revealed a quinone compound that inhibited CKιδ and Pim1 kinase preferentially over CKιγ2 and 98 other human protein kinases. Similarity search and preliminary in vitro CKιδ kinase inhibition assay have yielded a few compounds with good potency. This proposal aims to further refine the structure of the quinones through molecular modeling studies, design of new derivatives, and synthesis of the designed molecules followed by CKιδ inhibition assays to obtain highly selective and potent inhibitors of CKιδ kinase.