PsychoAAD-2013

OMICS Group Conferences
Accelerating Scientific Discovery

International Conference on
Psychology, Autism and Alzheimer's Disease

September 30 - October 1, 2013 San Antonio, Texas, USA

Synergic roles of amyloid-β and tau oligomers in the development of neurotoxicity involved in Alzheimer's disease progression

Jayakumar Rajadas
Stanford University, USA

Abstract

Accumulation of misfolded proteins in the neuronal cells results in dysregulation of calcium homeostasis and cellular dysfunction in peripheral and brain tissues. We have shown that the prolonged subcutaneous injection of casein amyloid aggregates, triggers beta amyloid accumulation in the mouse brain. This raises a question how an enrichment of one amyloid in the tissue leads to accumulation of another amyloid? We and others groups have shown that the amyloid oligomer on interaction with Ephrin-B2 receptor (Eph2) results in Eph2 depletion. Eph2 depletion would lead to aberrant NMDA signaling with increase in intracellular calcium [Ca^{2+}]. More detailed *in vivo* and *in vitro* studies demonstrate that such up-regulation of calcium results in endoplasmic stress and inhibition of protein phosphatase 2A (PP2A). PP2A is involved in maintaining the tau hyper phosphoyrlation under control. Importantly, we observe PP2A is expressed abundantly in dendritic spines. Inhibition of PP2A would result in higher tau phosphorylation and decrease spine density. We have been developing specific ligands that would modify the toxic structure of oligomers to prevent Eph2 interactions. A class of novel amyloid-beta oligomer binding compounds are developed that would alter the oligomeric populations of A beta and tau converting them into non-toxic conformers thereby preventing their interaction with Eph2 receptors. These molecules also suppress aberrant NMDA receptor activation along with calcium elevation. We have shown toxic to nontoxic amyloid transitions are possible when oligomeric are interacting with small heat shock protein like alpha-crystalline. Thus, small molecules and small heat shock proteins could rescue the PP2A activity and significantly reduce the tau hyper phosphorylation and associated toxicity. This novel mechanistic pathway would help improve substantial and viable therapeutic intervention against AD.

Biography

Jayakumar Rajadas has completed his Ph.D. in 1990 from Indian Institute of Technology, Chennai, India. He was holding visiting professorships and visiting fellowship to various world premier institutes such as ETH, Zürich, NIA (NIH), University of Massachusetts, Amherst, and Stanford University. At present, he is the director of Biomaterials and Advanced Drug Delivery Laboratory (Bio ADD) at Stanford University. He has published more than 125 papers in reputed journals and serving as an editorial board member. Before moving to Stanford, he served as the founding chair of the Bioorganic and Neurochemistry Laboratory at the Council of Scientific and Industrial Research (CSIR) at one of the premier national laboratories in India, where he was responsible for both the organization and management of the division.

jayraja@stanford.edu