2ⁿᵈ International Conference on

Brain Disorders and Therapeutics

Chicago, USA   October 26-28, 2016

Alternative models for drug discovery in Alzheimer's disease

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Alzheimer's disease is described as a progressive dementia associated with the extracellular deposits in the brain of a garbage protein, β-amyloid (Aβ) and the intracellular deposits of tangles. The vast majority of the patients develop the disease in old age while a small portion has an early onset, familial form. Since the 1970's it has been generally assumed that the dementia seen in the two forms is due to the neurotoxicity of the Aβ. With the purification and sequencing of Aβ in the 1990's investigators were able to identify the mutations associated with the familial forms. A number of laboratories transfected mice with these mutated genes. Since these animals exhibited many of the pathological and clinical manifestations of the late onset disease, they have been used to screen for new therapeutic agents. Unfortunately, all 244 drugs identified in these models have failed in clinical trials in elderly patients. Work from my laboratory has suggested that plaque deposits of Aβ rather than causing the dementia is merely a biomarker for a decline in the capacity of the endoplasmic reticulum (ER) in the cells to catalyze the posttranslational processing of 40% of cellular proteins, including those synaptic, membrane proteins required for a functioning memory. This paradigm is based on our observation that in the CSF all Aβ is normally N-glycosylated and bound to ER proteins, ERp57 and calreticulin. These data suggest a new direction for drug discovery in which agents are screened for their ability to increase the levels in cell lines of fluorescently labeled components of the ER posttranslational pathway. The development of these cell lines would permit rapid screening for potential therapeutic agents in plate readers.

Biography

Jordan L Holtzman, Graduated from University of Chicago, the Pritzker School Of Medicine in 1959. He Complete internship from University Ill Rsc/Ed in 1960. He Completed Residency training from University of Minnesota in 1973, Department of Medicine, University of Minnesota Minneapolis, MN, USA at present he is in Department of Pharmacology, University of Minnesota Minneapolis, MN, USA. Department of Environmental Health Sciences, University of Minnesota Minneapolis, USA.

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Brain Disord Ther
ISSN: 2168-975X BDT, an open access journal

Brain Disorders 2016
October 26-28, 2016

Volume 5, Issue 3(Suppl)

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