EVALUATION OF GENE REGULATION AND THERAPEUTIC DRUGS RELATED TO ALZHEIMER’S DISEASE IN DEGENERATING PRIMARY CEREBROCORTICAL CULTURES

EVALUATION OF GENE REGULATION AND THERAPEUTIC DRUGS RELATED TO ALZHEIMER’S DISEASE IN DEGENERATING PRIMARY CEREBROCORTICAL CULTURES

Bailey, Jason A.

Permanent Link: http://hdl.handle.net/1805/2741
Date: 2012-03-16
Committee Chair: Lahiri, Debomoy K.
Committee Members: Du, Yansheng; McBride, William J., 1956-; Zhou, Feng
Degree: Ph.D.
Degree Year: 2011
Department: Department of Medical Neuroscience
Grantor: Indiana University
Keywords: Alzheimer ; synapse ; neurodegeneration ; primary culture ; memantine
LC Subjects: Alzheimer's disease -- Research ; Alzheimer's disease -- Treatment -- Research ; Genetic regulation -- Research ; Nervous system -- Degeneration -- Research

Abstract:

Alzheimer’s disease (AD) is a neurological disorder defined by the presence of plaques comprised mostly of amyloid-β (Aβ), and neurofibrillary tangles consisting of hyperphosphorylated microtubule associated protein tau (MAPT). AD is also characterized by widespread synapse loss and degeneration followed by death of neurons in the brain. Inflammatory

processes, such as glial activation, are also implicated. In order to study mechanisms of neurodegeneration and evaluate potential therapeutic agents that could slow or reverse this process, a tissue culture system was developed based on primary embryonic cerebrocortical neurons. This culture system was observed to exhibit time-dependent neurodegeneration, glial proliferation, and synaptic marker loss consistent with AD-affected brains. The regulatory promoter regions of several genes implicated in AD, including the Aβ precursor protein (APP), β-amyloid cleaving enzyme (BACE1), and MAPT, were studied in this culture model. The MAPT gene promoter activity followed the pattern of neuronal maturation and degeneration quite closely, increasing in the initial phase of the tissue culture, then reducing markedly during neurodegeneration while APP and BACE1 gene promoters remained active. Deletion series of these promoters were tested to give an initial indication of the active regions of the gene promoter regions. Furthermore, the effects of exogenous Aβ and overexpression of p25, which are two possible pathogenic mechanisms of gene regulation in AD, were studied. Response to Aβ varied between the promoters and by length of the Aβ fragment used. Overexpression of p25 increased MAPT, but not APP or BACE1, promoter activity. This neurodegeneration model was also used to study the putative neuroprotective action of the NMDA receptor antagonist memantine. Treatment with memantine prevented loss of synaptic markers and preserved neuronal morphology, while having no apparent effect on glial activation. The protective action on synaptic markers was also observed with two other structurally distinct NMDA receptor antagonists, suggesting that the effects of memantine are produced by its action on the NMDA receptor. It is concluded that this tissue culture model will be useful for the study of gene regulation and therapeutic agents for neurodegeneration, and that the efficacy of memantine may result from preservation of synaptic connections in the brain.

Description:

Indiana University-Purdue University Indianapolis (IUPUI)

This item appears in the following Collection(s)

- Medical Neuroscience Department Theses and Dissertations (/handle/1805/1721)

Show Statistical Information (#)

My Account

- Login
- Register

Statistics

- Most Popular Items
- Statistics by Country
- Most Popular Authors