MedicalXpress

Blocking the effects of amyloid b in Alzheimer's disease

July 30 2012

During Alzheimer's disease, 'plaques' of amyloid beta (Ab) and tau protein 'tangles' develop in the brain, leading to the death of brain cells and disruption of chemical signaling between neurons. This leads to loss of memory, mood changes, and difficulties with reasoning. New research published in BioMed Central's open access journal *Alzheimer's Research & Therapy*, has found that up-regulating the gene Hes1 largely counteracted the effects of Ab on neurons, including preventing cell death, and on GABAergic signaling.

The exact mechanism behind how Ab contributes to Alzheimer's disease is not yet fully understood, however researchers from Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER) in Spain recently discovered that Ab interferes with the normal activity of nerve growth factor (NGF). One of the actions of NGF is activating the protein Hes1, a transcription factor required to turn on other genes. Without this factor GABAergic signaling within the brain decreases.

Using gene therapy techniques, Pedro Chacón and Alfredo Rodríguez-Tébar augmented the amount of Hes1 in cultured neurons. Increasing the amount of Hes1, directly or by activating the protein NF-kB (which in turn up-regulate the cell's own Hes1), abolished the effect of Ab and prevented neuron death. Additionally another growth factor, TGFb, which can also activate NF-kB, was able to prevent the effects of Ab on neurons by improving levels of Hes1.

Pedro Chacón explained, "Ab usually decreases the length of dendrites

and GABAergic connectivity of neurons, however these effects were completely reversed by Hes1, NF-kB, and TGFb. When we grew neurons in a concentration of Ab which normally kills most cells, 50% of the neurons with extra Hes1 were able to survive."

These results demonstrate that neurons can be protected from the effects of Ab by increasing the amount of Hes1 in the cells. By clarifying the roles of NGF or TGFb in Hes1 protection this research provides strategies for limiting the effects of Alzheimer's disease.

More information: Increased expression of the homologue of Enhancer-of-split 1 protects neurons from beta amyloid neurotoxicity and hints at an alternative role for transforming growth factor beta1 as a neuroprotector Pedro J Chacon and Alfredo Rodriguez-Tebar *Alzheimer's Research & Therapy* (in press)

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