**SEROTONIN SIGNALING REGULATES AMYLOID-BETA METABOLISM IN VIVO**

**J.R. Cirrito**¹,², Y.I. Sheline²,³, D.K. Verges¹, J.L. Restivo¹, W.D. Goebel¹

¹Neurology, ²Alzheimer’s Disease Research Center, ³Psychiatry, Washington University, St. Louis, MO, USA

**Introduction:** Synaptic activity is an important regulator of amyloid-beta (Abeta) generation. We have previously demonstrated a presynaptic mechanism whereby endocytosis of APP near the synaptic terminal leads to enhanced Abeta generation then secretion into the brain interstitial fluid (ISF).

**Aims:** Here we demonstrate a postsynaptic mechanism that requires activation of serotonin receptors on the cell surface and leads to intracellular signaling pathways that downregulate Abeta production.

**Methods:** Three-month old PS1APP +/- mice were implanted with hippocampal microdialysis probes to assess ISF Abeta levels in a living mouse.

**Results:** Mice were administered serotonin directly to the hippocampus, which caused a 30% reduction in ISF Abeta levels over several hours. Selective serotonin reuptake inhibitors (SSRIs) are antidepressants that increase serotonin signaling. When administered systemically, three SSRIs also reduced ISF Abeta levels. Serotonin receptors are G-protein coupled receptors, which can activate MAPK/ERK signaling pathway. Pharmacological inhibition of the MAPK/ERK signaling cascade blocks the serotonin-dependent change in brain Abeta levels.

**Conclusions:** We propose that ERK activation alters the processing of APP and subsequent generation of Abeta. Preliminary data in cognitively-normal human patients demonstrates that individuals with a history of antidepressant use have lower amyloid PIB binding in cortical regions compared age-matched controls. Given that SSRIs are a reasonably well-tolerated class of neuroactive drugs, it may be possible to reduce Abeta production and beneficially affect AD processes using this type of compound in AD patients.

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