Impaired Somatic Inhibition in the Hippocampus in an Animal Model of Alzheimer's Disease

Yu-Chao Liu[1], Irene Han-Juo Cheng[2], Cheng-Chang Lien[1]
[1]Institute of Neuroscience, National Yang-Ming University, Taiwan
[2]Institute of Brain Science, National Yang-Ming University, Taiwan

Alzheimer's disease (AD) is associated with cognitive deficits and increased incidence of seizures. Aberrant increases in excitatory neuronal activity and compensatory inhibitory mechanisms were found in the hippocampus of human amyloid precursor protein (hAPP) transgenic mice[1]. However, hAPP mice have reduced levels of voltage-gated sodium channels in parvalbumin (PV)-positive GABAergic interneurons, a major type of somatic inhibitory interneuron in the mammalian cortex[2]. Such findings pose at least two intriguingly questions: (1) How does reduced GABAergic interneuron excitability contribute to enhanced synaptic inhibition in hAPP mice? (2) What is the functional alteration of synaptic inhibitory output of such PV-positive GABAergic interneurons in early and late stages of AD?

To address these two questions, we first examined somatic inhibition in mature dentate granule cells (DGCs) and CA1 pyramidal cells in the hippocampal slices of hAPP mice (2-11 months old). Compared with non-transgenic mice, hAPP mice showed reduced frequency but not the amplitude of miniature inhibitory postsynaptic currents (mIPSCs) in mature DGCs. Analysis of mIPSC kinetics revealed that fast somatic inhibition in DGCs is preferentially impaired. Using combined extracellular field potential recording and current source-density analysis, we found that somatic GABAergic transmission in the CA1 region from AD (11 months old) mice is 'depolarizing' at resting membrane potentials. These findings suggest that dysfunction of perisomatic inhibitory interneurons could contribute to hyperexcitability and seizures in Aß-induced epileptogenesis.

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References:

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