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Synaptic Dependent Amyloid-β Generation *in vivo* in Alzheimer's Disease Mouse Model

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Alzheimer's disease (AD) is the most common cause of dementia and is pathologically characterized by toxic amyloid-β (Aβ) oligomers and plaques. Extracellular accumulation of Aβ peptide in the brain appears to precipitate disease onset and the cognitive AD-associated pathogenic cascade. In humans and transgenic models of AD, brain regions with the highest levels of synaptic activity show the greatest amount of Aβ plaques, suggesting Aβ production is closely linked to synaptic transmission. To determine whether changes in synaptic activity alter the amounts Aβ in the brain, we developed novel micro-immunoelectrode (MIE) technology that detects Aβ in the brain ISF with high temporal resolution in the hippocampus of living mice allowing us to examine rapid Aβ kinetics. We custom designed a 3D-printed adaptor to connect the MIE to an injection port which enables us to measure Aβ and locally deliver drugs directly to the dentate gyrus. With these technologies, we pharmacologically manipulated synaptic activity by delivering excitatory and inhibitory drugs. Here, we show that changes in levels of Aβ are closely related synaptic activity in the brain, where large increases in synaptic activity rapidly brought forth higher Aβ levels in the mouse brain, while inhibition of nonspontaneous synaptic activity decreased Aβ levels *in vivo* in a concentration dependent fashion. These findings highlight a close temporal relationship between synaptic activity and Aβ generation in the brain.