Synaptic Imbalance in Mild Cognitive Impairment and Alzheimers Disease

https://neurodegenerationresearch.eu/survey/synaptic-imbalance-in-mild-cognitive-impairment-and-alzheimers-disease/

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USA

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Synaptic Imbalance in Mild Cognitive Impairment and Alzheimers Disease

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1

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Research Abstract

PROJECT SUMMARY Initial stages of Alzheimer’s disease (AD) appear to be correlated with elevated electrical activity and synaptic abnormalities in brain regions first affected by pathology. This pathologically shifting towards excitation suggests that there are alterations in the synaptic excitation and inhibition balance (E/I ratio) within these areas (e.g., entorhinal cortex), which in

turn may accelerate activity-dependent AD pathology. However, there are no quantitative, regional measurements of the E/I ratio in the human brain, and alterations in this measure in AD are unknown. In preliminary work leading to this proposal, we have found evidence of inhibitory signaling disturbances at early stages of AD. Levels of Gephyrin expression, an inhibitory postsynaptic synaptic density (iPSD) protein, are reduced in entorhinal cortex neuronal cell bodies of postmortem brain from donors diagnosed with mild cognitive impairment (MCI), a prodromal stage of AD. In addition, by microtransplanting receptors from temporal cortices of human AD donors into Xenopus oocytes, we discovered electrophysiological abnormalities of GABA receptors (GABAARs) suggesting that inhibitory tone is reduced in AD. Importantly though, it is not known whether these collective alterations also occur at the level of synapses in AD or if they are emergent in MCI. Given these preliminary findings, we hypothesize that 1) MCI is characterized by abnormally large E/I ratios in brain regions particularly affected early on in AD and 2) E/I ratio imbalance is driven by impairment in the clustering of synaptic excitatory or inhibitory receptors, or by alteration of the electrophysiological properties of major synaptic glutamate and GABA receptors (GluRs and GABAARs). This general hypothesis will be evaluated in two Specific Aims. Aim 1 will test whether there are specific pro- excitatory alterations in the ratio of excitatory to inhibitory postsynaptic density (ePSD/iPSD) proteins in MCI and AD versus controls. Studies will use Fluorescence Deconvolution Tomography (FDT), developed by part of our research group, whereby immunolabeling of PSD markers are measured within the size constraints of synapses from 3D reconstructions; FDT analysis will determine if pro-excitatory E/I ratios based on counts, volume, and intensity of synaptic markers characterize and differentiate MCI from control and AD cases. Complementing the anatomical work, Aim 2 will test whether electrophysiological alterations of synaptic receptors contribute to larger E/I ratio in MCI and AD using the Microtransplantation of Synaptic Membranes (MSM), a novel technique that allows for electrophysiological studies of GluRs and GABAARs from postmortem human brain tissue. Understanding the degree to which abnormal synaptic E/I ratios are present in MCI and/or AD, and which PSD receptors or proteins are affected, would greatly facilitate targeted pharmacological interventions aimed at restoring E/I balance and may provide substantial benefit to patients showing early signs of cognitive decline by delaying or stopping the progression to AD which currently affects ~5.3 million Americans.

Further information available at:

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