Role of Somatostatin Interneurons in Alzheimer's Disease

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The neural circuits that subserve odorant processing are susceptible to dysregulation/attrition in neurodegenerative diseases such as Alzheimer’s Disease (AD). Studies have shown that early olfactory phenotypes reflect memory impairment, and have been shown to correlate with loss of Somatostatin (Sst) interneurons in vital areas of odorant and memory processing. These neurons broadly populate the main olfactory bulb (MOB) and anterior olfactory nucleus (AON, an area crucial to odor mixture processing), but they have received relatively little attention. This project was geared towards determining whether the 5x-FAD model of AD (AD mouse model with 5 point mutations) in the mouse recapitulates the Alzheimer’s phenotype in odor discrimination ability and amount of Sst interneurons, and whether activation of Sst interneurons in the AON rescues this Alzheimer’s phenotype. To determine if Sst interneurons are lost in 5xFAD mice, cell counts were performed on 5xFAD-SstCre animals injected with flex-tdtomato, and immunohistochemistry was performed to reveal early amyloid deposition. The AD model portrayed a loss of Sst interneurons over time, showed impairment in odor discrimination of mixtures, and accumulation of Aß plaque deposition. A cross-habituation task (an assessment of olfactory acuity) was conducted as a behavioral assay. 5xFAD-SstCre animals injected with HM3d and treated with CNO (chemical genetic manipulation in which a drug-modulated receptor on Cre-expressing Sst interneurons and activated by CNO) revealed improvement on the cross habituation task. By determining the connectivity of Sst interneurons in a system involved in AD, potential biomarkers for early disease diagnosis and targets for therapeutic intervention can be identified.

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