Role of beta adrenergic receptors in modulation of cognition, pathology and neuroinflammation in Alzheimers Disease

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Research Abstract

Project Summary The failure of experimental therapeutics for Alzheimer’s disease (AD) in clinical studies emphasizes the need for validation of novel therapeutic targets with new mechanism of action. One strategy is to look to the body’s natural defense mechanisms.

Postmortem studies of AD patients and aged-matched controls have confounded researchers for years with evidence of known pathological markers of AD in control groups with lack of cognitive impairments. Rather than asking if elevated beta-amyloid and neurofibrillary tangles are detrimental for neuronal function and survival, since this has collectively and repeatedly been demonstrated, a more interesting question is, “Why do many individuals have normal cognition, despite these pathological abnormalities?” The noradrenergic (NE) system is a key modulator of cognitive function, neuroinflammation and the systemic immune system. Severe degeneration of NE neurons in AD patients may underlie disease progression at many levels. Adrenergic receptors on microglia play critical roles in regulating neuroinflammation and governing protective mechanisms for neuronal function and survival. Migration of peripheral immune cells to the brain is also regulated by NE tone and may be impaired in AD patients. This proposal will determine the role of NE and beta adrenergic 1 and 2 receptor subtypes (ADRB1 and ADRB2) in AD-like cognitive deficits, neuroinflammation, and pathology using a platform of well-established learning and memory paradigms, transgenic models of mice overexpressing human amyloid precursor protein, and DREADD technology specifically targeting NE neurons in the locus ceruleus to reduce NE tone followed by restoration of tone at ADRB1 and ADRB2 with selective pharmacology. Innovative flow cytometry analysis of brain, blood, spleen and bone marrow will identify effects of modulation of NE tone on resident microglia, systemic immune cells and recruitment of systemic immune cells to the brain. Development of transgenic mice in which ADRB1 and ADRB2 can be conditionally deleted in myeloid lineage cells (e.g., microglia and macrophages, but not neurons) will enable the exploration of the cell-type and receptor subtype specificity of previously described effects of NE in modulation of AD-related behavior and pathophysiology in vivo. Subsequent experiments using an in vitro culture platform of isolated microglia/macrophages from transgenic and wildtype mice, with the ability to conditionally delete ADRB1 and ADRB2, will examine the receptor subtype dependent effects of NE on microglia/macrophage proliferation and phagocytosis.

Further information available at:

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