Interrogating the link between aging and AD with temporally-controlled transgenes

https://neurodegenerationresearch.eu/survey/interrogating-the-link-between-aging-and-ad-with-temporally-controlled-transgenes/

Principal Investigators

JANKOWSKY, JOANNA L

Institution

BAYLOR COLLEGE OF MEDICINE

Contact information of lead PI
Country

USA

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Interrogating the link between aging and AD with temporally-controlled transgenes

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1

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Alzheimer's disease & other dementias

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Research Abstract

Summary Age is the single greatest risk factor for Alzheimer’s disease (AD), yet we understand little about how it actually contributes to pathogenesis. In order to gain insight into how aging influences pathogenesis, we need a way to experimentally control time. In most animal models of AD-associated pathologies such as amyloidogenesis, the severity of disease is inexorably linked with age. Yet isolating the the effect of aging on disease progression requires a means of uncoupling age from disease onset so that the interaction between them can be manipulated and tested. In the proposed experiments, we will take advantage of a mouse model we developed to provide temporal control over the expression of transgenic APP, and with it, the onset and duration of A? overproduction in the brain. We will use this model to generate young adult and geriatric animals that have been challenged with identical exposure to pathogenic A?. With this system, we can separate age from A? production to create old animals with the same level of pathology as their much younger counterparts. We have already completed extensive characterization of the behavioral and neurophysiological response of young adult tet-off APP animals to increasing periods of amyloid accumulation. These young adult animals display surprising resilience to severe pathology, leading us to question whether we had unwittingly eliminated a critical variable from our model by engineering it for rapid pathology. Here we will test this hypothesis by re-introducing age and aging into our experiments. We expect that many aspects of cognitive function, neurophysiology, and circuit plasticity that were weakly affected or quickly restored upon therapeutic transgene suppression will be more severe and less amenable to recovery when tested in the appropriate context of an aging brain. In Aim 1, we will use behavioral characterization to identify how aging influences the cognitive response to a neuropathological insult by comparing the pattern and speed of functional decline in mice with young adult or geriatric onset of transgenic APP. We will further test whether the aging brain is less resilient to therapeutic intervention when transgene expression is genetically suppressed to mimic the effect of pharmacologic A? reduction. In Aim 2, we will explore whether aging exacerbates A?-associated cognitive decline by restricting the mechanisms available to overcome pathologic insult. In one experiment, we will test whether physical changes to the hippocampal circuit produced through ongoing neurogenesis are more severely affected by A? in aged animals than in young adults exposed to the same transgenic insult. In complementary experiments, we will test whether loss of electrophysiological plasticity also contributes to hippocampal vulnerability in aged mice exposed to A?. Where possible, we seek to quantitatively answer whether the effects of aging and A? are simply additive, or if they interact to increase disease vulnerability. Although our proposal focuses on A? amyloidosis, we believe these studies will yield insight into the effect of aging on the response to neural injury more broadly. We expect our findings will indicate that aging should be restored to models of age-related disease.

Lay Summary

Narrative Our study will test whether aging increases vulnerability to Alzheimer’s-associated cognitive decline by reducing the brain’s ability to overcome pathological injury. Our experiments take advantage of a unique mouse model in which we can stop time to study how equivalent neuropathological damage may cause greater functional impairment with age.

Further information available at:

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Investments > €500k

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United States of America

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