“The word on the street on preventing or delaying the onset and progression of Alzheimer’s Disease is: 1. Use your brain, stay intellectually challenged, and 2. Be physically active. A recent publication in *Science* utilizing the optimal murine model of Alzheimer’s Disease provides evidence that the mechanism by which physical activity favorably modifies this neurodegenerative model is by increasing neurogenesis and BDNF in the brain. Here’s the publication for you.”

**NEURODEGENERATION**

**Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer’s mouse model**


**INTRODUCTION:** Alzheimer’s disease (AD) is the most common form of age-related dementia, characterized by cognitive impairment, neurodegeneration, β-amyloid (Aβ) deposition, neurofibrillary tangle formation, and neuroinflammation. The most popular therapeutic approach aimed at reducing Aβ burden has not yet proved effective in halting disease progression. A successful therapy would both remove the pathological hallmarks of the disease and provide some functional recovery. The hippocampus contains neural progenitor cells that continue to generate new neurons, a process called adult hippocampal neurogenesis (AHN). AHN is impaired before the onset of classical AD pathology in AD mouse models. Human AHN has also been reported to be altered in AD patients. However, evidence supporting a role for AHN in AD has remained sparse and inconclusive.

**Rationale:** Two fundamental questions remain: (i) whether AHN could be enhanced and exploited for therapeutic purposes for AD, and (ii) whether AHN impairment mediates aspects of AD pathogenesis. To address these questions, we increased AHN genetically (WT) and pharmacologically (PC12) in AD transgenic 5xFAD mice and explored whether promoting AHN alone could ameliorate AD pathology and behavioral symptoms. We assessed the role of exercise, a known neurogenic stimulus, and explored whether promoting AHN in conjunction with the salutary biochemical changes induced by exercise can improve AD pathology and behavioral symptoms in mice. We also investigated whether AHN suppression, by irradiation, temozolomide, or dominant-negative Wnt, contributes to AD pathogenesis and assessed the functional roles of AHN in AD.

**RESULTS:** Inducing AHN alone conferred minimal to no benefit for improving cognition in 5xFAD mice. Exercise-induced AHN improved cognition along with reduced Aβ load and increased levels of brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), fibroblast growth factor (FGF), and synaptic markers. However, AHN activation was also required for exercise-induced improvement in memory. Inducing AHN genetically and pharmacologically in combination with elevating BDNF levels mimicked beneficial effects of exercise on AD mice. Conversely, suppressing AHN in early stages of AD exacerbated neuronal vulnerability in later stages of AD, leading to cognitive impairment and increased neuronal loss. However, no such effects from AHN ablation were observed in nontransgenic wild-type (WT) mice, suggesting that AHN has a specific role in AD.

**CONCLUSION:** Promoting AHN can only ameliorate AD pathology and cognitive deficits in the presence of a healthier, improved local brain environment, e.g., stimulated by exercise. Increasing AHN alone combined with overexpression of BDNF could mimic exercise-induced improvements in cognition, without reducing Aβ burden. Adult-born neurons generated very early in life are critical for maintaining hippocampal neuronal populations in the hostile brain environment created by AD later in life. Thus, AHN impairment may be a primary event that later mediates other aspects of AD pathogenesis. Future attempts to create pharmacological mimetics of the benefits of exercise on both increased AHN and BDNF may someday provide an effective means for improving cognition in AD. Moreover, increasing neurogenesis in the earliest stages of AD pathogenesis may protect against neuronal cell death later in the disease, providing a potentially powerful disease-modifying treatment strategy for AD.
RESEARCH CORNER

Timothy A. McKinsey, Ph.D.
Associate Professor and Associate Division Head for Translational Research
Director, Consortium for Fibrosis Research & Translation (www.cfret.org)
Department of Medicine, Division of Cardiology

Work in the McKinsey lab focuses on understanding the signaling and gene regulatory mechanisms that control heart failure, as well as the interface between obesity, diabetes and cardiovascular disease. We are particularly interested in the role of epigenetics in regulating the pathological fibrosis (scarring) that underlies organ dysfunction. Nuclear DNA is wound around proteins called histones to form chromatin, and post-translational modifications of histones represents one epigenetic mechanism for altering gene expression. Among the enzymes that target histones are histone deacetylases (HDACs), histone acetyltransferases (HATs) and histone methyltransferases. We use molecular biology, biochemistry and pharmacology to address the roles of these and other epigenetic modifiers in the control of gene expression, and extend our findings to surgical, environmental, transgenic and gene knockout models of cardiometabolic disease. We are also interested in the mechanisms whereby signals derived from cell surface receptors are conveyed to histone-modifying enzymes and epigenetic ‘reader’ proteins by kinases and phosphatases. The long-term goal of our work is to translate basic science discoveries into novel therapies for patients with heart failure, which afflicts millions of adults in the U.S. and is associated with a 5-year mortality rate of nearly 50%. As such, our lab has also established core expertise to enable in vitro, cellular and in vivo assessment of experimental small molecule compounds (obtained in high throughput screens) in support of early stage drug discovery. Our lab emphasizes teamwork and camaraderie, thus creating an exciting environment for students and postdoctoral trainees.

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