

James & Esther King Biomedical Research Program

Chan, Sic

*Biomolecular Science Center
University of Central Florida*

*2007 Program
New Investigator (3-year project)*

Project Title: Nicotine Disrupts Adult Hippocampal Neurogenesis

Project Summary: Nicotine, the neuroactive compound responsible for tobacco addiction, has recently been shown to reduce adult hippocampal neurogenesis. The hippocampus is a brain structure that plays a critical role in learning and memory processes and is a site of neuronal degeneration in Alzheimer's disease, stroke, and epilepsy. It has been shown that this brain structure contains populations of neural progenitor cells that are particularly concentrated in the subventricular zone and the dentate gyrus of the hippocampus. Neurogenesis is the process that involves the proliferation, migration, and differentiation of progenitors into neurons. Several factors such as growth factors, age, environmental, and pharmacological stimuli can regulate neurogenesis. Adult hippocampal neurogenesis decreases during aging, an alteration which could conceivably account for deficits in hippocampus-mediated brain functions and for the declining ability of the nervous system to recover from injury and disease with advancing age. Several lines of evidence also suggest that impairments in neurogenesis may be involved in the pathophysiology of stroke, Alzheimer's and Parkinson's disease. Because nicotine-induced inhibition of neurogenesis can adversely impact the brain to respond to functional demands and injury, concerns have been raised for the potentially serious consequences of tobacco addiction and nicotine abuse. The underlying molecular and cellular mechanisms whereby chronic nicotine exposure impairs neurogenesis have not been established. We have recently found that CREB signaling is reduced in the adult dentate gyrus of rats chronically treated with nicotine. Our goal is to investigate how chronic nicotine treatment blocks the molecular CREB response and whether restoring CREB activity or the expression of downstream genes can reverse nicotine-induced inhibition of neurogenesis. The specific aims are as follows: we will (1) employ neurospheres or neural progenitor cultures to more directly determine the effects of nicotine on cell proliferation, differentiation, and survival and to investigate how chronic nicotine exposure impacts downstream signaling cascades that follow activation of neuronal nicotinic acetylcholine receptors. Given the importance of CREB signaling in the maintenance of progenitor survival in vivo, we will (2) investigate whether rescuing CREB signaling prevents the adverse effect of nicotine on adult hippocampal neurogenesis. Because BDNF may directly link CREB activation with neurogenesis in the dentate gyrus of rats, we will (3) determine if expression of BDNF rescues adult hippocampal neurogenesis following long-lasting administration of nicotine. These studies will provide insights into the molecular basis of nicotine-induced inhibition of neurogenesis and support strategies for enhancing CREB function as a means to preserve neurogenesis in habitual smokers and chronic nicotine users.