

James & Esther King Biomedical Research Program

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New Investigator (3-year project)*

Project Title: Inhibitory Effect of Nicotine on Estrogen-induced Natural Hippocampal Neuroprotection Against Ischemia

Project Summary: Millions of smokers in the U.S. are disabled as a result of stroke. Stroke blocks blood supply to the brain, and neurons in the close vicinity of the vascular blockage may die quickly from oxygen and glucose deprivation. This condition is known as cerebral ischemia. Cerebral ischemia causes delayed degeneration of hippocampal CA1 neurons. The hippocampal CA1 is the most vulnerable region of the brain against global cerebral ischemia. It has been observed that females suffer less post-ischemic damage compared to their male counterparts in their pre-menopausal life owing to circulating levels of estrogen in their body. During the past century, the average life span of women has increased dramatically from 50 years to more than 80 years, yet the age of menopause has remained essentially fixed at 51 years. Hence, a greater proportion and a greater total number of women will spend over 30 years of their lives in the hypo-estrogenic postmenopausal state, which is accompanied with rapid increase in stroke incidences. This suggests greater need for hormone replacement. Importantly, smoking accompanied with hormone replacement therapy elevates adverse effects of smoking in women, and the beneficial effect of estrogen on neurons is lost. Nicotine, tobacco's third main component, is believed to be the primary reason that people consume tobacco products. Nicotine addiction modulates estrogen metabolism, reduces circulating estrogen levels, disturbs normal periodicity of menstrual cycle, and ultimately leads to early onset of menopause in females. We, therefore, hypothesize that chronic nicotine exposure inhibits natural CA1 neuroprotection conferred by estrogen against ischemia. We will investigate the following aims by using two well-characterized models of cerebral ischemia: (1) an in vitro-organotypic slice culture and (2) an in vivo-bilateral carotid occlusion and systemic hypotension in rat. We will determine whether chronic nicotine exposure (1) abolishes estrogen-mediated protection of the selectively vulnerable CA1 region of hippocampus against ischemia, (2) increases ischemic brain damage in female rats under different levels of ovarian hormones, or (3) increases mitochondrial dysfunction in female rat hippocampus. This study intends to increase our understanding of the changes that take place in the hippocampal neurons of females due to nicotine addiction as result of smoking.