



## Project Information

7101BX000883-02

[Back to Query Form](#) [Back to Search Results](#) [Print Version](#)[DESCRIPTION](#) [DETAILS](#) [RESULTS](#) [HISTORY](#) [SUBPROJECTS](#) [SIMILAR PROJECTS](#) [NEARBY PROJECTS](#) <sup>BETA</sup> [LINKS](#) [NEWS AND MORE](#)**Project Number:** 7101BX000883-02**Contact PI / Project Leader:** SHETTY, ASHOK K.**Title:** MEMORY AND MOOD ENHANCING THERAPIES FOR GULF WAR ILLNESS**Awardee Organization:** OLIN TEAGUE VETERANS CENTER**Abstract Text:**

DESCRIPTION (provided by applicant): While the Gulf war Illness displays multiple central nervous system (CNS) impairments, cognitive dysfunction, memory loss, depression and anxiety are the most common symptoms. Intake of the prophylactic drug pyridostigmine bromide (PB), prolonged exposure to pesticides (such as DEET and permethrin), and the combat-related stress during the Persian Gulf War-1 are believed to be the underlying causes of Gulf war Illness. Consistent with this supposition, studies in our laboratory using a rat model demonstrate that a combined exposure to low doses of the above chemicals (PB, DEET & Permethrin) and mild stress for 28 days causes considerable impairments in the hippocampus- dependent functions, which include impaired ability for new spatial learning, declined ability for making new memories, and increased depressive- and anxiety- like behavior. Analyses of hippocampal tissues further revealed that the behavioral impairments are linked with greatly declined neurogenesis but mostly intact neuronal cell layers in the hippocampus. Considering the role of hippocampal neurogenesis in learning, memory and mood functions, these findings suggest that a greatly declined neurogenesis likely underlies learning & memory impairments and increased depression & anxiety in Gulf war Illness. In this context, strategies that greatly enhance hippocampal neurogenesis appear useful for reversing the cognitive dysfunction and the depression and anxiety observed in Gulf war Illness. Indeed, our preliminary studies suggest that administration of antidepressants such as fluoxetine (FLU) or rolipram (ROL) after a combined exposure to chemicals (PB+DEET+Permethrin) and stress has promise for improving the hippocampal neurogenesis as well as cognitive function. Therefore, using the above rat model of Gulf war Illness, we propose to rigorously analyze the efficacy of distinct clinically applicable strategies for enhancing the hippocampal neurogenesis & cognitive function, and reversing the depressive & anxiety-like behaviors. In Specific Aim 1, we will test the hypothesis that combined applications of an anti-depressant drug (FLU or ROL) and an antioxidant drug (Curcumin [CUR] or Resveratrol [RESV]; dietary supplements having anti-oxidant, anti-inflammatory, and neurogenesis enhancing properties) greatly enhance hippocampal neurogenesis, cognitive function and mood in the rat model of Gulf war Illness. In Specific Aim 2, we will address the hypothesis that combined applications of an anti-depressant drug (FLU or ROL) or an antioxidant drug (CUR or RESV) and physical therapy such as the voluntary physical exercise (PE) greatly boost hippocampal neurogenesis, cognitive function as well as mood in the rat model of Gulf war Illness. In both aims, we will first expose rats to the three chemicals (PB, DEET & Permethrin) and mild stress (i.e. 5 minutes of restraint stress) for 28 days and ascertain the extent of cognitive dysfunction and depressive & anxiety- like behaviors. Animals will then receive the treatments as described above and undergo testing at 6- weeks after the conclusion of the treatment for cognitive function and depressive & anxiety-like behavior. Following this, their performance in the behavioral tests will be correlated with the extent of hippocampal neurogenesis, the proliferative behavior of neural stem cells (NSCs), and the pattern of expression of genes related to neurogenesis and to suppression of oxidative stress. The overall research is designed to ascertain the therapeutic efficacy of different treatment approaches. Thus, the studies proposed in this project are highly relevant to the Gulf war RFA (BX-09-014) because, this project utilizes a rat model that simulates the various exposures experienced by the Persian Gulf War-1 veterans and the experiments are focused on developing therapeutic strategies for reversing several CNS impairments Associated with Gulf war Illness.

**Public Health Relevance Statement:**

Persian Gulf War-1 veterans have a higher prevalence of Chronic Multi-Symptom health problems. These include significant cognitive dysfunction, memory loss, depression and anxiety. Using an animal model of model of Gulf war Illness, this study will rigorously test the efficacy of distinct clinically applicable treatment strategies for enhancing the cognitive function and reducing the depression and anxiety Associated with Gulf war Illness. The treatment strategies include combined applications of an anti-depressant drug and a dietary supplement compound having anti- oxidant and anti-inflammatory properties, and combined applications of an anti-depressant drug and physical therapy such as the voluntary physical exercise (PE). Overall, the major focus is on validating treatment approaches that might be useful for both improving the learning and memory function and reducing the depression and anxiety in Persian Gulf War-1 veterans.

**Project Terms:**

Acetylcholinesterase Inhibitors; Address; Affinity; age group; Aging; Amyotrophic Lateral Sclerosis; Animal Model; Animals; Anti-inflammatory; Anti-Inflammatory Agents; Antidepressive Agents; Antioxidants; Anxiety; Back; base; Behavior; behavior test; behavioral impairment; Biological; Brain region; Bromides; cell behavior; Cells; Chemicals; Chronic; Cognitive; cognitive function; combat; Control Animal; CREB1 gene; Curcumin; Cyclic AMP; Deet; depressive symptoms; design; Devices; Dietary Supplements; Dizziness; Dose; efficacy testing; Environment; Exercise; Exhibits; experience; Exposure to; Fluoxetine; Functional disorder; Gene Expression; granule cell; Grapes; Gulf War; Health; High Prevalence; Hippocampus (Brain); Housing; Impaired cognition; Impairment; improved; Inflammation; inhibitor/antagonist; Insecta; Institute of Medicine (U.S.); Intake; Laboratories; Learning; Link; Major Depressive Disorder; Memory; Memory impairment; Memory Loss; Mental Depression; Modeling; Monitor; Moods; nerve agent; nerve stem cell; nervous system disorder; Neuraxis; neurogenesis; Neurologic; Neurons; neurotrophic factor; Oxidative Stress; Pattern; Performance; Permethrin; Persian Gulf; Pesticides; Pharmaceutical Preparations; Pharmacotherapy; phosphoric diester hydrolase; Physical therapy; phytoalexin; phytoalexins; Property; prophylactic; Prophylactic treatment; Prozac; Published Comment; pyridostigmine; Rattus; Recovery; Research; research study; restraint stress; Resveratrol; Rodent; Role; Rolipram; Running; Selective Serotonin Reuptake Inhibitor; sensor; Simulate; Skin; Sleep; social; Spices; Stress; Study Section; Symptoms; Testing; Therapeutic; Therapeutic Effect; Tissues; Treatment Efficacy; treatment strategy; Tumeric; Veterans