Ashok K. Shetty, Ph.D.
Medical Research Scientist, **Durham VA Medical Center**, Durham, NC
Professor, Division of Neurosurgery, **Duke University Medical Center**, Durham, NC
E-mail: ashok.shetty@duke.edu

Information on the Previous Project

Title: Behavior of stem/progenitor cells in a rat model of Gulf war syndrome
Funding source: Department of Veterans Affairs
Start and end dates: 4/1/2007 to 3/31/2010

Brief description of purpose and results:

Major Goal: The major aim of this study was to investigate the long-term changes in the behavior of hippocampal neural stem cells, the extent of hippocampal neurogenesis, and the spatial learning and memory function in rats exposed to a combination of Gulf War Illness (GWI) related chemicals such as DEET, permethrin and pyridostigmine bromide and a mild stress for 28 days.

Results: The results of these studies demonstrated that a combined exposure to GWI-related chemicals (DEET, permethrin and pyridostigmine bromide) considerably dampens hippocampal neurogenesis from neural stem cells for prolonged periods. This stem cell dysfunction was found to be associated with impairments in hippocampal-dependent functions such as learning, memory and mood.

The adverse effects on hippocampal function appeared to be due to an interaction of the three chemicals as exposure to any of these chemicals alone had no significant effect on neurogenesis. A combined exposure to the three chemicals appeared to have a specific effect on stem cell function, as this exposure reduced the numbers of granule cells in the dentate gyrus but did not reduce the numbers of CA1 and CA3 pyramidal neurons in the hippocampus.

Addition of mild stress (such as five minutes of restraint stress) during the exposure to GWI-related chemicals enhanced the adverse effects of these chemicals on hippocampal neurogenesis, which was associated with worsening of the functions such as learning, memory and mood and greater reductions in the numbers of neurons in the DG, CA1 and CA3 cell layers. Interestingly, application of mild stress alone has beneficial effects on hippocampal neurogenesis, and memory and mood function.

Publications:

(1) Parihar VK, Hattiangady B, Kuruba R, Shuai B, **Shetty AK** (2011): Predictable chronic mild stress improves mood, hippocampal neurogenesis and memory. ***Molecular Psychiatry***, 16, 171-183.
(2) **Shetty AK**, Parihar VK, Hattiangady B, Babb E, Shuai B (2010). Neural stem cell dysfunction and its implications on memory & mood function in a rat model of Gulf War illness. ***Soc. Neurosci. Abstracts***, 29.17. San Diego, USA.
(3) Parihar VK and **Shetty AK** (2010). Rolipram treatment alleviates learning, memory & mood dysfunction with enhanced hippocampal neurogenesis in a rat model of Gulf War Illness. ***Soc. Neurosci. Abstracts***, 29.10. San Diego, USA.
(4) Parihar VK, Hattiangady B, Shuai B, and **Shetty AK** (2009). Hippocampal Neurogenesis is Impaired in a Rat Model of Gulf War Syndrome. ***Soc. Neurosci. Abstracts,*** Chicago, USA.

Information on the Approved New Project

Title: Memory and Mood Enhancing Therapies for Gulf War Illness
Funding source: Department of Veterans Affairs
Start and end dates: 4/1/2011 to 3/31/2014

Brief description of purpose:

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. In an animal model of Gulf War Illness (induced through exposure to chemicals such as DEET, permethrin and pyridostigmine bromide for 28 days), these symptoms are associated with a greatly decreased hippocampal neurogenesis, a substrate believed to be important for hippocampal dependent cognitive and mood function.

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 hippocampal neurogenesis and 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 (Rolipram or fluoxetine) and a dietary supplement compound having antioxidant and anti-inflammatory properties (resveratrol or curcumin), and combined applications of an anti-depressant drug and physical therapy such as the voluntary physical exercise (using running wheels). 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.