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Organophosphate-Related Alterations in Myelin and Axonal Transport in the Living Mammalian Brain

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Institution Receiving Award: GEORGIA HEALTH SCIENCES UNIVERSITY

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PUBLIC ABSTRACT

Among the variety of chronic symptoms that have been reported in those who suffer from Gulf War Illness (GWI), the neurological problems, especially the deficits in attention, concentration, and memory function, may be the most debilitating. Unfortunately, despite more than 20 years of research, the exact cause of these symptoms remains unclear. It has been hypothesized that a significant contributing factor to GWI symptoms may have been exposure to the class of chemicals known as organophosphates. These chemicals are found in many of the insecticides used in the campaign during the Gulf War, as well as nerve agents. Two nerve agents within the class of organophosphates, sarin and cyclosarin, may have been released into the environment at low levels following the destruction of an Iraqi munitions storage complex at Khamsiyah, Iraq, in March 1991. However, it has been very difficult to determine if exposure to organophosphates, specifically, underlie the cognitive deficits or the changes in brain structure (white matter volumetric changes) that have been recently detected in Gulf War Veterans by magnetic resonance imaging (MRI). The uncertainty arises because of the wide variety of other possible contributing factors (multiple vaccinations, treatments with drugs like pyridostigmine bromide, exposure to smoke from oil well fires, infectious organisms, etc.). Accordingly, one goal of the proposed studies is to determine in animals if exposures to organophosphates at levels that do not cause acute symptoms of toxicity (i.e., similar to the situation with Gulf War soldiers) indeed result in changes in the brain that have been documented by MRI studies in Gulf War Veterans. These types of prospective studies can only be conducted in animal models. We have already published several studies in animals showing that such exposures to organophosphates can result in prolonged deficits in cognitive function.

In addition, the diverse and chronic nature of the neurological symptoms of GWI suggests that some basic or fundamental neuronal process was adversely affected while these individuals were stationed in the Persian Gulf area. In previous work we have shown that one such fundamental process, axonal transport, the mechanism whereby important molecules are transported in nerve cells, is impaired in peripheral nerves of animals previously exposed to organophosphates. Our next objective is to determine if axonal transport is impaired in the brains of living animals after exposure to organophosphates, establishing a plausible explanation for the variety of neurological symptoms observed in sufferers of GWI. We have developed the capabilities to investigate each of these phenomena (white matter volumetric and structural changes as well as axonal transport) in the brains of living animals using two magnetic resonance imaging techniques, diffusion tensor imaging (DTI) and manganese-enhanced magnetic resonance imaging (MEMRI). We will study the effects of several doses of a representative organophosphate insecticide that was used during the Gulf War, chlorpyrifos, and a representative nerve agent, diisopropylfluorophosphate. It is expected that the results of these studies will not only contribute to a better understanding of the basis for the neurological symptoms of GWI (the first step before new therapeutic targets can be identified and new treatments can be developed), but also a better understanding of the long-term toxicity of a class of chemicals that continues to pose a significant risk for military personnel as well as millions of civilians worldwide.