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## Toxic Chemical Sarin Damages Genes That Control Brain, Nervous System

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### Brain

A toxic chemical called sarin that is often used in chemical warfare inflicts widespread damage to genes that control memory, thinking, mood, muscle control and a range of other brain functions, a new animal study has shown.

The study could explain many of the physical ailments people experience following sarin exposure, said the researchers from Duke University Medical Center. Such exposures have occurred through on-the-job use with insecticide analogues in the agriculture industry, during the Persian Gulf War, and in the 1995 Tokyo subway terrorist attack.

"We have witnessed and catalogued the severe symptoms that victims of sarin exposure have experienced, and we have studied the severe damage sarin imposes on brain cells," said Mohamed Abou Donia, M.D., Duke pharmacologist and senior author of the study. "Now, we have evidence that implicates the specific genes that are damaged when one is exposed to sarin."

Abou Donia said the results of the study could ultimately lead to a blood test for sarin exposure and could identify potential genes to target with new therapies that ameliorate the damage. He also said the results further emphasize that sarin should be handled with extreme care and used only by professionals with appropriate protective gear.

Results of the study, funded by the Department of Defense, are published in the March 15, 2006, issue of the journal *Biochemical Pharmacology*. Other members of the Duke team include T.V. Damodaran, Ph.D., Holly K. Dressman, Ph.D., and Simon M. Lin, Ph.D.

Abou Donia's team used gene profiling techniques to examine the effects of sarin on all known genes related to brain and nervous system function. Within 15 minutes of a single exposure to sarin, 65 different genes in the brains of rats showed altered expression, meaning their protein levels either increased or decreased. Three months later, expression of a total of 38 genes remained altered. The study time point of three months in rats is the equivalent to 20 years in humans, demonstrating that the effects of sarin are widespread and long-lasting, he said.

"Early reports indicate that some individuals exposed to low levels of sarin during the Tokyo attack suffered persistent neurological and psychiatric abnormalities for more than five years after exposure," said Abou-Donia. "In addition, many of the Gulf War veterans were exposed to low-level sarin during destruction of the enemy's chemical arsenal, and a percentage of them have continued to complain of chronic fatigue, muscle and joint pain, weakness, headaches, loss of concentration, forgetfulness, and irritability.

"Our new findings confirm that the duration of sarin exposure can continue for years or even decades after the initial exposure because it alters gene expression of proteins critical to brain function," he said.

Sarin was developed during World War II as a nerve agent tailor-made to irreversibly inhibit the enzyme acetylcholinesterase. This enzyme's normal role is to halt the signal between a nerve cell and a muscle cell once it has been transmitted. When acetylcholinesterase is inhibited, the nerve signal continues unabated, causing excitability and over-stimulation. This hyper-stimulation initiates the release of additional neurotransmitters that further excite the cells and ultimately cause them to degenerate or die, said Abou-Donia.

It has long been known that chemicals like sarin – called "organophosphates" because they have a phosphorus atom attached to them – can cause brain cell death in high enough doses, said Abou-Donia. Until now, though, global genes affected by sarin have been unidentified, he said.

Abou-Donia's team identified a primary gene responsible for immediate neuronal cell death following sarin exposure. The gene, Cam Kinase II, is overactivated after sarin exposure, resulting in an influx of calcium into the cell. The calcium migrates to the cell's mitochondria, resulting in the release of reactive oxygen species and ultimately cell suicide, characteristic of long-term, chronic sarin exposure. Mitochondria are the power plants of the cell, generating chemical energy through the breakdown of glucose.

The process is among many that occur following sarin exposure, said Abou-Donia. In addition, sarin induces changes within:

- genes that maintain the blood-brain barrier, a membrane that protects the brain from toxic substances;
- genes that help scavenge reactive oxygen species or "oxygen-free radicals" from inflicting irreparable damage in cells and contributing to the aging process;
- genes that control programmed cell death, called apoptosis;
- genes that produce growth hormones and stress hormones; and
- genes that control the electrophysiology of cells, directly increasing excitability of membranes by blocking peripheral nerve conduction.

"We knew that organophosphates inflicted irreparable damage in the brain and nervous system, but now we know how," said Abou-Donia.

He said the current study results apply to other chemicals classified as organophosphates, including chlorpyrifos and related insecticides. High-level exposures to chemicals in this class have been known to produce a variety of symptoms, such as excessive sweating and salivation, severe tremors, seizures, and convulsions. Long-term exposure to these chemicals results in fatigue, muscle contractions, muscle weakness, memory and cognitive deficits, mood changes, and a host of other nervous system changes, researchers said.

In fact, a single high-dose of sarin injected into the muscles of rats caused excessive salivation, severe tremors, seizures, convulsions and, ultimately, death in half of the animals. Animals that received a low dose of sarin did not display the severe symptoms but became inactive, the study showed. Previous studies have shown that low doses result in fewer acute symptoms but more of the chronic, persistent deficits, such as muscle weakness, and memory deficits said Abou Donia.

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