Pesticides and Parkinson's: Researchers uncover further proof of a link

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(Medical Xpress)—For several years, neurologists at UCLA have been building a case that a link exists between pesticides and Parkinson's disease. To date, paraquat, maneb and ziram—common chemicals sprayed in California's Central Valley and elsewhere—have been tied to increases in the disease, not only among farmworkers but in individuals who simply lived or worked near fields and likely inhaled drifting particles.

Now, UCLA researchers have discovered a link between Parkinson's and another pesticide, benomyl, whose toxicological effects still linger some 10 years after the chemical was banned by the U.S. Environmental Protection Agency.

Even more significantly, the research suggests that the damaging series of events set in motion by benomyl may also occur in people with Parkinson's disease who were never exposed to the pesticide, according to Jeff Bronstein, senior author of the study and a professor of neurology at UCLA, and his colleagues.

Benomyl exposure, they say, starts a cascade of cellular events that may lead to Parkinson's. The pesticide prevents an enzyme called ALDH (aldehyde dehydrogenase) from keeping a lid on DOPAL, a toxin that naturally occurs in the brain. When left unchecked by ALDH, DOPAL accumulates, damages neurons and increases an individual's risk of developing Parkinson's.

The investigators believe their findings concerning benomyl may be generalized to all Parkinson's patients. Developing new drugs to protect ALDH activity, they say, may eventually help slow the progression of the disease, whether or not an individual has been exposed to pesticides.

The research is published in the current online edition of Proceedings of the National Academy of Sciences.

Parkinson's disease is a debilitating neurodegenerative disorder that affects millions worldwide. Its symptoms—including tremor, rigidity, and slowed movements and speech—increase with the progressive degeneration of neurons, primarily in a part of the mid-brain called the substantia nigra. This area normally produces dopamine, a neurotransmitter that allows cells to communicate, and damage to the mid-brain has been linked to the disease. Usually, by the time Parkinson's symptoms manifest themselves, more than half of these neurons, known as dopaminergic neurons, have already been lost.

While researchers have identified certain genetic variations that cause an inherited form of Parkinson's, only a small fraction of the disease can be blamed on genes, said the study's first author, Arthur G. Fitzmaurice, a postdoctoral scholar in Bronstein's laboratory.

"As a result, environmental factors almost certainly play an important role in this disorder," Fitzmaurice said. "Understanding the relevant mechanisms—particularly what causes the selective loss of dopaminergic neurons—may provide important clues to explain how the disease develops."

Benomyl was widely used in the U.S. for three decades until toxicological evidence revealed it could potentially lead to liver tumors, brain malformations, reproductive effects and carcinogenesis. It was banned in 2001.

The researchers wanted to explore whether there was a relationship between benomyl and Parkinson's, which would demonstrate the possibility of long-lasting toxicological effects from pesticide use, even a decade after chronic exposure. But because a direct causal relationship between the pesticide and Parkinson's can't be established by testing humans, the investigators sought to determine if exposure in experimental models could duplicate some of the pathologic features of the disease.

They first tested the effects of benomyl in cell cultures and confirmed that the pesticide damaged or destroyed dopaminergic neurons.

Next, they tested the pesticide in a zebrafish model of the disease. This freshwater fish is commonly used in research because it is easy to manipulate genetically, it develops rapidly and it is transparent, making the observation and measurement of biological processes much easier. By using a fluorescent dye and counting the neurons, the researchers discovered there was significant neuron loss in the fish—but only to the dopaminergic neurons. The other neurons were left unaffected.

Until now, evidence had pointed to one particular culprit—a protein called α-synuclein—in the development of Parkinson's. This protein, common to all Parkinson's patients, is thought to create a pathway to the disease when it binds together in "clumps" and becomes toxic, killing the brain's neurons. (See UCLA research using "molecular tweezers" to break up these toxic aggregations.)

The identification of ALDH activity now gives researchers another target to focus on in trying to stop this disease.

"We've known that in animal models and cell cultures, agricultural pesticides trigger a neurodegenerative process that leads to Parkinson's," said Bronstein, who directs the UCLA Movement Disorders Program.

"And epidemiologic studies have consistently shown the disease occurs at high rates among farmers and in rural populations. Our work reinforces the hypothesis that pesticides may be partially responsible, and the discovery of this new pathway may be a new avenue for developing therapeutic drugs."

More information: www.pnas.org/content/early/201 … 399110.full.pdf+html

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