Ecogenetics: Understanding

Human Susceptibility to Injury and Disease

Our genes significantly influence how environmental exposures affect our health. One metaphor often cited is that our genetic makeup is a "loaded gun" and the environment "pulls the trigger." With each genetic "switch" set firmly in place from birth, an environmental exposure can "turn it off or on," leading to a cascade of reactions in the body. This is why some workers who have been exposed to beryllium show signs of berylliosis, an occupational lung disease, while others continue to have a clean bill of health, even with the same exposure.

Ecogenetics is the study of how a person's genes influence human ecology, which is the interaction of humans with their environment, explains Professor David Eaton, director of the Center for Ecogenetics and Environmental Health (CEEH). Scientists affiliated with CEEH are investigating genetic variations that cause people to react differently to environmental exposures. CEEH provides administrative and technical support to 99 scientists from a variety of disciplines. The center is supported by the National Institute of Environmental Health Sciences (NIEHS) and is part of the NIEHS Environmental Health Sciences Core Center program.

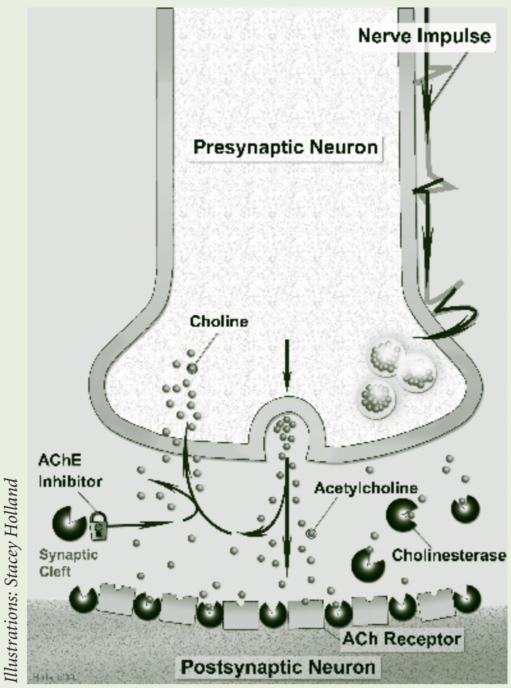
CEEH scientists share a commitment to improving human health by reducing the burden of disease. To identify and protect susceptible groups requires a better understanding of gene-environment interactions. These scientists also strive to involve the community in their work and to consider the ethical, legal, and social implications of their research endeavors.

ECOGENETICS AND PESTICIDES

Some researchers are studying what determines our susceptibility to the harmful effects of neurotoxic chemicals, such as certain pesticides. They are gathering data on population-wide genetic variations that may determine how the body handles exposures to organophosphorus (OP) pesticides, which are widely used across the United States and overseas.

Since 2004, Washington state has mandated cholinesterase monitoring of agricultural pesticide handlers to ensure they are not overexposed to OP pesticides. Washington and California are the only two states to mandate the monitoring. In this program, two forms of cholinesterase are measured in the blood: acetylcholinesterase (AChE) and serum cholinesterase.

Cholinesterase inhibition, or limited activity of the enzyme from a baseline measurement before exposure, suggests the handler has been overexposed. AChE, often referred to as "cholinesterase," is an enzyme essential for normal functioning of the nervous system. It regulates the transmission of nerve signals in the body. OP pesticides can interfere in this process. When AChE activity levels are low, acetylcholine accumulates



Illustrations: Stacey Holland

The acetylcholinesterase (AChE) enzyme regulates the transmission of nerve signals in the body. If a nerve signal were likened to a radio transmission, then AChE would be the "off switch" that ends the transmission after a message has been received. To transmit the nerve signal between neurons, the presynaptic neuron releases acetylcholine, which binds with acetylcholine (ACh) receptors on the postsynaptic neuron. AChE ends the transmission of nerve signals by breaking down acetylcholine into choline and acetate.

and causes continuous stimulation in the nervous system. Overexposure to OP pesticides might result in acute symptoms, such as headaches, muscle twitching, hypersecretion, and nausea. Studies have linked long-term chronic effects of overexposure to neurobehavioral performance problems and cancers.

Some individuals may be especially susceptible to health effects from exposure to OP pesticides. Paraoxonase 1 (PON1), an enzyme in our bodies that plays an important role in breaking down certain OP pesticides into less toxic forms, is of particular interest to CEEH researchers.

Everyone has PON1, but scientists have found that variations in PON1 levels exist in the population. Research suggests that PON1 levels and how efficiently the enzyme can detoxify reagents may be based on an individual's genotype, the genetic identity of an individual—somewhat like an architect's blueprint for a house.

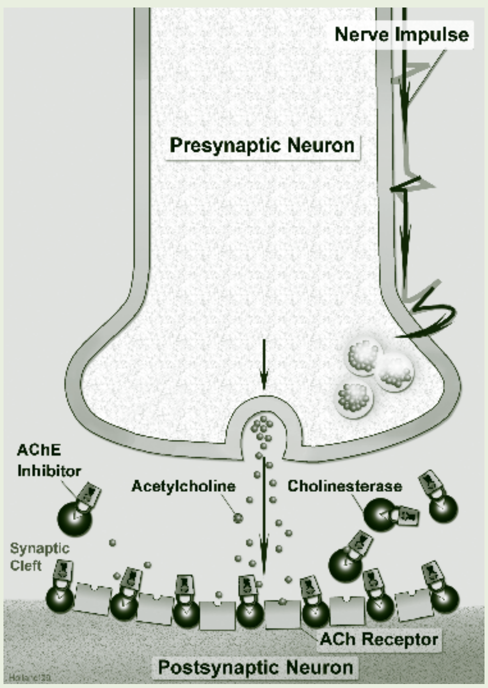
Although animal studies have suggested low PON1 activity is associated with depressed levels of acetylcholinesterase, not many population-based studies of PON1 status among OP-exposed individuals have been done, explains Jonathan Hofmann (MPH, Environmental and Occupational Health, 2004; PhD, Epidemiology, 2008). He wanted to see if the activity level of PON1 and the PON1 genotype were associated with serum cholinesterase inhibition among pesticide handlers. If there was a relationship, then Hofmann hypothesized that PON1 may be an important factor in determining someone's susceptibility to overexposure to OP pesticides.

With support from CEEH, the Pacific Northwest Agricultural Safety and Health Center (PNASH), and the Northwest Center for Occupational Health and Safety (an Education and Research Center), Hofmann evaluated the relationship between PON1 and cholinesterase inhibition among pesticide handlers exposed to OP insecticides. He worked with DEOHS Professors Matthew Keifer, Richard Fenske, Gerald van Belle, and Harvey Checkoway; Associate Professor Anneclaire De Roos (Epidemiology); and Professor Clement Furlong (Genome Sciences) to conduct an epidemiological study. Their study compared PON1 levels and PON1 genotype with serum cholinesterase levels in 163 volunteers recruited in the 2006 and 2007 spray seasons.

CEEH's Functional Genomics and Proteomics Laboratory, under the direction of Principal Research Scientist Federico Farin, processed these samples and developed an assay to characterize the PON1 genotype of study participants. This laboratory provides state-of-the-art technologies that can be used by researchers to investigate gene-environment interactions.

Comparing levels of PON1 and PON1 genotypes to the results of the cholinesterase monitoring, Hofmann found there were differences in the level of serum cholinesterase inhibition by PON1 genotype, suggesting that some pesticide handlers were better able to metabolize OP pesticides than others. He also found that people with high PON1 activity had less cholinesterase inhibition than those with low PON1 activity.

Hofmann, who is now a postdoctoral fellow in the Division of Cancer Epidemiology and Genetics at the National Cancer Institute, says the study's results suggest "we should account for differences in sensitivity to OPs between individuals, including increased sensitivity related to PON1 status, when performing regulatory risk assessments for these chemicals."



OP pesticides "lock" the AChE enzyme. This prevents AChE from breaking down acetylcholine. Overexposure to OP pesticides inhibits AChE activity, interfering with normal nerve signaling. In the cholinesterase monitoring program, the activity level of this enzyme is measured in blood to determine if an agricultural pesticide handler has been overexposed to pesticides.

An agricultural worker applies pesticides

Kit Galvin

From a public health perspective, says Eaton, "laws and policies are designed not only to protect the average person, but also to protect sensitive populations." Environmental health laws enforced by the Environmental Protection Agency, he explains, specifically mandate that exposure limits should ensure even the most sensitive individual is protected.

ETHICAL & LEGAL CONSIDERATIONS

Genotyping is a revolutionary technology, but it raises ethical and legal considerations. Kelly Fryer-Edwards, director of the CEEH Community Outreach and Ethics Core and associate professor in the Department of Bioethics and Humanities in the School of Medicine, worked with the researchers involved in Hofmann's study. She advised them on ethical considerations, such as the kind of information that should accompany genetic results provided to study participants.

CEEH is one of two NIEHS Environmental Health Sciences Centers in the United States that have an ethics core to address the many complex issues that might arise from genetics research. Eaton wanted a group to work alongside the investigators as the research evolved and ethical issues arose.

Only a handful of studies involving genetic tests have included a follow up to investigate participants' impressions of test results, explains Fryer-Edwards. So, with support from PNASH, research team members interviewed the participants after they received the results of their PON1 genetic tests.

They found that the agricultural workers who were interviewed had some gaps in understanding what their test results showed. This led to the production of a video by two graduate students, Rad Cunningham (MPH student, Environmental and Occupational Health) and Coby Jansen (MPH student, Department of Health Services). The six-minute Spanish-language video addresses questions individuals may have about genetic tests, such as the difference between PON1 and an individual's cholinesterase status. Cunningham and Jansen will present a poster about the ethical dilemmas involved in communicating genetic results at the American Public Health Association's 2009 national conference.

In her CEEH role, Fryer-Edwards also works with a community outreach team to share information with outside groups. She describes these discussions as "a two-way conversation;" working together to better communicate the ethical issues keeps the public, our communities, and other stakeholders involved with CEEH research.

Fryer-Edwards and Jon Sharpe, Community Outreach and Ethics Core program manager, developed educational materials based on the PON1 study. An interactive lesson uses role-playing to teach participants about genetic susceptibility to environmental exposures and also give them a sense of the dilemmas involved in genetic testing: who gets to decide who is tested, what is the relationship between research findings and actual health effects, who has access to the results, and what are the consequences to any decision. In the role play, participants have a choice of getting or not getting a genetic test before starting a new job as a pesticide handler. If the test is positive, they will not be offered the job.

The activity sparks animated discussions about what risks are worth taking to feed their families, what responsibility employers have to protect their workers, and freedom of choice around health behaviors. When asked what they learned from the activity, one eighth-grade student wrote "the choices you make [with the information you have] about interacting with hazardous chemicals affect your health and life."

FOR FURTHER READING

Center for Ecogenetics and Environmental Health: *http://depts.washington.edu/ceeh/*

Hofmann JN, Keifer MC, Furlong CE, De Roos AJ, Farin FM, Fenske RA, van Belle G, Checkoway H. Serum cholinesterase inhibition in relation to paraoxonase-1(PON1) status among organophosphate-exposed agricultural pesticide handlers. *Environ Health Perspect* 2009;117(9):1402–1408.

Hofmann JN, Keifer MC, De Roos AJ, Fenske RA, Furlong CE, van Belle G, Checkoway H. Occupational determinants of serum cholinesterase inhibition among organophosphate-exposed agricultural pesticide handlers in Washington state. *Occup Environ Med* 2009 (in press). ■