Countermeasures for Human Seizures

Pamela Lein, a developmental neurobiologist and neurotoxicologist in the Department of Molecular Biosciences, directs the $17 million CounterACT Center of Excellence, part of the NIH Countermeasures Against Chemical Threats Research Network.

Medical countermeasures–The center's team is identifying medical countermeasures for neurotoxic chemicals that cause seizures in humans. The project will develop tools and treatments so that emergency responders and medical professionals can protect themselves when responding to chemical emergencies and be able to minimize neurological damage in individuals exposed to such toxic compounds. The multi-layered research effort also aims to improve medical treatment for people with seizure disorders.

Research emphasis–The research emphasis is on a group of chemicals known as organophosphates as well as tetramethylenedisulfotetramine (TETS). TETS is a powerful neurotoxin once used as a rat poison. It is now banned in most parts of the world.

Organophosphates can cause seizures–Used in pesticides like parathion, organophosphates can inhibit the enzyme that normally regulates muscle contractions and critical pathways of communication in the brain. Inhibition of this enzyme causes overstimulation or over-excitation of the downstream cell in the circuit. This increased excitability triggers seizures.

Long-term benefits–The program will produce additional benefits, including improved understanding of the biological mechanisms that cause seizures, new neuroimaging techniques and biomarkers for monitoring neurological damage following chemically induced seizures, and novel approaches for controlling seizures in people with epilepsy.

Major initiatives

- Drugs and treatment procedures to minimize brain damage in patients who survive seizures (led by Lein)
- Improved treatments for preventing seizures (led by Michael Rogawski, School of Medicine)
- Rapid-throughput tests and high-resolution imaging techniques to screen compounds for potential anticonvulsant and anti-inflammatory activity (led by Isaac Pessah, Department of Molecular Biosciences)

Proven track record–With an established track record for bringing together researchers from different backgrounds to focus their diverse expertise on a common research question, the researchers bring 10 years of success in identifying the mechanisms by which organophosphorus pesticides cause neurotoxicity. The goal is to identify biomarkers of neurotoxicity and therapeutic strategies following developmental, occupational or acute exposures. Previous research has yielded novel insights that have been used to set regulatory limits for organophosphorus pesticide applications, and for informing the value of traditional biomarkers of exposure in identifying individuals at risk for neurotoxicity.

State-of-the art instruments for analysis–The center faculty have secured several sophisticated pieces of equipment that facilitate screening of compounds for therapeutic efficacy against chemical convulsants. The instruments include an automated patch system for the pharmacology group and a high-content imaging system.

Initial accomplishments–Well-versed in the use of diverse model systems ranging from cell-based to whole animals, faculty have developed specific tools that will help them to predict the efficacy of new therapies and preventive strategies that emerge from the center.

New data on imaging techniques–In just the first year of the center's existence, neuroscientists have generated new data demonstrating the feasibility of using high-technology imaging of nerve inflammation to track the progression of neurological damage in the brain from DFP, an organophosphate.

Multidisciplinary team–Other UC Davis researchers include Bruce Hammock, a toxicologist and distinguished professor of entomology; Heike Wulff, associate professor of pharmacology in the School of Medicine; Danh Nguyen, a statistics expert in the UC Davis Clinical and Translational Science Center; and Bora Inceoglu, a biochemist and pharmacologist in the Department of Entomology.

Contact: Trina Wood, (530) 752-5257
3/2013