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Research reveals new depths of complexity in nerve cells

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Research from the Oklahoma Medical Research Foundation reveals a new complexity to nerve cells in the brain that could affect future therapies aimed at altering mood and memory in humans.

OMRF scientist Kenneth Miller, Ph.D., studied the function of a common protein (known as CaM Kinase II) in tiny roundworms called *C. elegans*. His research appears in the latest issue of the journal *Genetics*.

"CaM Kinase II is very abundant in the brain, so it has been heavily studied," Miller said. "But this is the first time anybody has seen results like this."

Using a method called "forward genetics," Miller's lab randomly screened thousands of mutant worms for defects in neuropeptide storage and unexpectedly identified mutant worms lacking CaM Kinase II. Further analysis revealed that CaM Kinase II plays a significant role in controlling when and where neuropeptides are released from neurons.

Neuropeptides are small protein-like molecules that nerve cells in the brain use to communicate with each other. Disruptions in that communication can affect learning, memory, social behaviors and mood. They are created and stored in containers called dense-core vesicles. Under normal conditions they are only released from those containers in response to appropriate signals in the brain.

"We tagged the neuropeptides with a fluorescent protein so we could see

where they went," Miller said. "In the worms that were missing the gene that makes CaM Kinase II, the neuropeptides were virtually missing altogether in the parts of the neurons where we expected them."

That's because without the protein, the dense core vesicles couldn't hold onto the neuropeptides. Instead they were all released before they got transported to their storage location, he said. In humans, such an event would be extremely unpredictable, possibly even causing a psychotic episode, Miller said.

"This is a very significant demonstration of how neurons and likely other neuroendocrine cells package neuropeptides, move them around the cell, and release them where they will be most effective," said Michael Sesma, Ph.D., of the National Institute of Health's National Institute of General Medical Sciences, which partially funded the research. "The high-resolution visualization inside entire living neurons achieved by Dr. Miller and his colleagues is a technical tour de force, and also demonstrates the enormous value of the genetic model system *C. elegans* for studying the internal workings of living cells."

By understanding more about how neurons work, Miller said physicians and drug developers will be able to finely hone their targets when working with patients.

"Before this research, we didn't even know that neurons had this special mechanism to control neuropeptide function," he said. "This is why we do basic research. This is why it's important to understand how neurons work, down to the subcellular and molecular levels."

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