Scientists uncover a new pathway that regulates information processing in the brain

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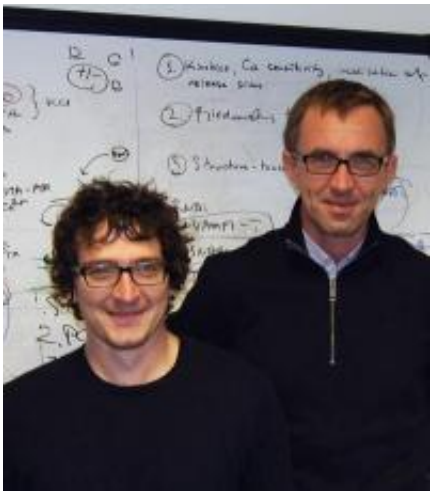

Neuroscientist Anton Maximov (right), graduate student Richard Sando III and colleagues at The Scripps Research Institute are shedding light on the biology of learning and memory. Credit: Scripps Research Institute

Scientists at The Scripps Research Institute (TSRI) have identified a new pathway that appears to play a major role in information processing in the brain. Their research also offers insight into how imbalances in this pathway could contribute to cognitive abnormalities in humans.

The study, published in the November 9, 2012 issue of the journal *Cell*, focuses on the actions of a protein called HDAC4. The researchers found that HDAC4 is critically involved in regulating genes essential for communication between neurons.

"We found that HDAC4 represses these genes, and its function in a given neuron is controlled by activity of other neurons forming a circuit," said TSRI Assistant Professor Anton Maximov, senior investigator for the study.

Searching for Missing Pieces

Synapses, specialized junctions that allow neurons to exchange information, are incredibly complex and built with hundreds of genes. Many of these genes become induced when neurons receive excitatory input from other neurons, including those activated by sensory experiences such as vision, hearing and smell. This process influences the assembly of neural circuits during development, and plays a fundamental role in learning and memory.

The Maximov laboratory is interested in understanding how synapses are formed and regulated. Previous studies have identified several factors necessary for activity-dependent transcription in the brain (transcription is a process of converting genetic information from DNA to RNA), but Maximov notes many puzzles remain to be solved. For example, the majority of synapse-related genes are silent in the embryonic brain, which does not receive direct sensory input from an external world. These genes become de-repressed shortly after birth, yet scientists still know little about the underlying mechanisms of how this happens.

Richard Sando III, a graduate student at the TSRI Kellogg School of Science and Technology, a member of the Maximov lab and the first author of this study, noted the team become interested in class IIa histone deacetylases (HDACs), which include HDAC4, in part because they have been implicated in regulation of transcription of non-neuronal tissues. "Class IIa HDACs are also known to change their cellular localization in response to various signals," he said. "There were hints that, in neurons, the translocation of HDAC4 from the nucleus to

cytoplasm may be triggered by synaptic activity. We found that mutant mice lacking excitatory transmitter release in the brain accumulate HDAC4 in neuronal nuclei. But what was really exciting was our discovery that nuclear HDAC4 represses a pool of genes involved in synaptic communication and memory formation."

Coincidentally, Maximov had been familiar with these same genes since his postdoctoral training with Tomas Sudhof, a neuroscientist whose pioneering work resulted in the identification of key elements of the transmitter release machinery. "It was truly astonishing when their names came up in our in vitro genome-wide mRNA profiling screens for neuronal HDAC4 targets," Maximov said.

A Link to a Rare Human Disease

To learn more about the function of HDAC4 in the brain, the team wanted to study its role in a mouse model. First, however, the scientists had to overcome a serious technical obstacle—HDAC4 also appears to protect neurons from apoptosis (programmed cell death), so complete inactivation of this gene would lead to neurodegeneration. To solve this problem, the team generated mice carrying a mutant form of HDAC4 that could not be exported from the cell nucleus. This mutant repressed transcription independently of neuronal activity.

Another surprise came after the team had already initiated their experiments. Underscoring the team's findings, a human genetic study was published linking mutations in the human HDAC4 locus with a rare form of mental retardation.

"One of these human mutations produces a protein similar to a mutant that we introduced into the mouse brain," said Maximov. "Furthermore, our studies revealed that these mice do not learn and remember as well as normal mice, and their memory loss is associated with deficits in

synaptic transmission. The pieces came together."

Most of the work in the new study was performed at TSRI's Dorris Neuroscience Center, which has state-of-the-art imaging, molecular biology and animal facilities. "Here at the DNC we enjoy a terrific research environment," Maximov said. "It would have been very difficult if not impossible for us to successfully perform these studies without the support of Helen Dorris and our senior colleagues who have assembled a highly productive and collaborative group of molecular neuroscientists."

More information: "HDAC4 Governs a Transcriptional Program Essential for Synaptic Plasticity and Memory," *Cell*, 2012.

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