

Unexpected link found between feeding and memory brain areas

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The search for a mechanism that could explain how the protein complex NCOR1/2 regulates memory has revealed an unexpected connection between the lateral hypothalamus and the hippocampus, the feeding and the memory centers of the brain, respectively. The findings, which were published today in the journal *Nature Neuroscience* by a multidisciplinary team led by researchers at Baylor College of Medicine, have implications for studies on brain function, including those related to autism spectrum disorders, intellectual disabilities and neurodegenerative

disease.

"It was not known how NCOR1/2 regulates [memory](#) or other cognitive functions, but there is evidence that NCOR1/2 plays a fundamental role in the activity of many hormones," said corresponding author Dr. Zheng Sun, assistant professor of medicine and of molecular and cellular biology at Baylor and member of Baylor's Dan L Duncan Comprehensive Cancer Center and Center for Precision Environmental Health and of the Texas Medical Center Digestive Diseases Center.

In this project, the researchers worked with mice carrying mutations of NCOR1/2.

"These mice clearly present with memory deficits," said co-first author Dr. Wenjun Zhou, postdoctoral associate in the Sun lab. "The signaling involving GABA, a key inhibitory neurotransmitter in the brain, was dysfunctional in hypothalamus neurons when NCOR1/2 was disrupted."

To explore the cellular mechanism underlying the condition, Sun collaborated with Dr. Yong Xu, associate professor of pediatrics, molecular and [cellular biology](#) and with the USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine.

The researchers conducted a number of electrophysiological experiments to investigate how the lack of NCOR1/2 resulted in memory deficits in mice.

"What struck us the most was that the process by which NCOR1/2 regulates memory involves a new circuit that links two [brain regions](#): the [lateral hypothalamus](#), known as a feeding center of the brain, and the hippocampus, a place that stores memory," Xu said. "It surprised us because the hypothalamus is not traditionally considered to be a major regulator of learning and memory."

The researchers validated the newly discovered circuits in different ways.

"We applied both optogenetics and chemogenetics techniques," said co-first author Dr. Yanlin He, postdoctoral associate in the Xu lab. "The protein complex NCOR1/2 is key to the hypothalamus-hippocampus circuit; when we knock it out the circuit becomes dysfunctional."

In addition, the researchers have connected their findings in mouse models with human conditions.

"We describe here new genetic variants of NCOR1/2 in patients with intellectual disability or neurodevelopmental defects," said co-corresponding author Dr. Pengfei Liu, assistant professor of molecular and human genetics at Baylor and laboratory director of clinical research at Baylor Genetics.

"The gene NCOR1 is located on human chromosome 17, very close to the region that has been previously implicated in the Potocki-Lupski and Smith-Magenis syndromes," Liu explains. "We have always suspected that mutations of this gene could cause [intellectual disabilities](#) or other deleterious neurological consequences. The mouse models in the current study provide the first evidence that this is indeed the case."

These findings have implications for the relationships among endocrine factors, obesity and metabolic disorders and cognitive dysfunctions such as Alzheimer's disease. It is known, for instance, that people with endocrine disruption or metabolic disorders are more susceptible to Alzheimer's disease.

"Mechanisms underlying these associations are not completely clear," Sun said. "We think that the NCOR1/2-regulated neural circuit between the feeding and the memory centers of the brain we have discovered is

worth exploring further in this context."

More information: Loss of function of NCOR1 and NCOR2 impairs memory through a novel GABAergic hypothalamus–CA3 projection, *Nature Neuroscience* (2019). [DOI: 10.1038/s41593-018-0311-1](https://doi.org/10.1038/s41593-018-0311-1)

Provided by Baylor College of Medicine

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