

Study reveals structure of key receptors involved in memory and learning

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Scientists have for the first time revealed the structure surrounding important receptors in the brain's hippocampus, the seat of memory and learning.

The study, carried out at Oregon Health & Science University, published today in the journal *Nature*.

The new study focuses on the organization and function of glutamate receptors, a type of neurotransmitter receptor involved in sensing signals between nerve cells in the hippocampus region of the brain. The study reveals the molecular structure of three major complexes of glutamate receptors in the hippocampus.

The findings may be immediately useful in drug development for conditions such as epilepsy, said senior author Eric Gouaux, Ph.D., senior scientist in the OHSU Vollum Institute, Jennifer and Bernard Lacroute Endowed Chair in Neuroscience Research and an Investigator with the Howard Hughes Medical Institute.

"Epilepsy or seizure disorders can have many causes," he said. "If one knows the underlying cause for a particular person's seizure activity, then you may be able to develop [small molecules](#) to modulate that activity."

Working with a mouse model, the OHSU researchers made the breakthrough by developing a chemical reagent based on [monoclonal antibodies](#) to isolate the receptor and the complex of subunits surrounding it. They then imaged the assemblage using state-of-the-art cryo-[electron microscopy](#) at the Pacific Northwest Cryo-EM Center, housed in OHSU's South Waterfront campus in Portland.

Gouaux anticipates the technique will transform structural biology.

"It really opens the door to specifically target the molecules that need to be targeted in order to treat a particular condition," he said. "A great deal of [drug development](#) is structure-based, where you see what the lock looks like and then you develop a key. If you don't know what the lock looks like, then it's much harder to develop a key."

Previously, scientists had to rely on mimicking the actual receptors by artificially engineering receptors by combining DNA segments in tissue

culture. However, that technique has obvious shortcomings.

"It doesn't work perfectly because the real receptors are surrounded by a constellation of additional, sometimes previously unknown, subunits," Gouaux said.

The new monoclonal antibody reagents, also developed at OHSU, enabled scientists to isolate actual glutamate receptors from the brain tissue of mice. They then were able to image those samples in near-atomic detail using cryo-EM, which allowed them to capture the entire assemblage of three types of glutamate [receptors](#) along with their auxiliary subunits.

"Previously, it's been impossible to do this because we had no good way to isolate molecules and no way to see what they looked like," Gouaux said. "So this is a super exciting development."

More information: Hippocampal AMPA receptor assemblies and mechanism of allosteric inhibition, *Nature* (2021). [DOI: 10.1038/s41586-021-03540-0](#)

Provided by Oregon Health & Science University

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