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Scientists discover 'thunder' protein that regulates memory formation

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Researchers at Johns Hopkins have discovered in mice a molecular wrecking ball that powers the demolition phase of a cycle that occurs at synapses — those specialized connections between nerve cells in the brain — and whose activity appears critical for both limiting and enhancing learning and memory.

The newly revealed protein, which the researchers named thorase after Thor, the Norse god of thunder, belongs to a large family of enzymes that energize not only neurological construction jobs but also deconstruction projects. The discovery is described in the April 15 issue of *Cell*.

"Thorase is vital for keeping in balance the molecular construction-deconstruction cycle we believe is required for memory formation," explains Valina Dawson, professor of neurology and neuroscience in the Johns Hopkins Institute of Cell Engineering. "It's a highly druggable target, which, depending on whether you enhance or inactivate it, may potentially result in new treatments for autism, PTSD, and memory dysfunction."

The enzyme is one of many AAA+ ATPases that drive the assembly of proteins needed to form specialized receptors at the surfaces of synapses. These receptors are stimulated by neighboring neurons, setting up the signaling and answering connections vital to brain function. The Hopkins team showed how thorase regulates the all-important complementary process of receptor disassembly at synapses, which

ultimately tamps down signaling.

Prolonged excitation or inhibition of these receptors — due to injury, disease, genetic malfunction or drugs — has been implicated in a wide array of learning and memory disorders.

"Change in the strength of the connections between two nerve cells forms the basis of our ability to learn and remember," Dawson says. This phenomenon, called synaptic plasticity, depends upon a balanced alternation of excitation and inhibition of receptors, she adds.

Using a powerful microscope to look at labeled neurons from the brains of mice, the scientists saw that thorase was concentrated in the synaptic regions of cells, leading them to focus studies on the protein interactions that happen there.

First, they cut a protein aptly called GRIP1 — it acts as scaffolding to hold GluR2 receptors to the surface — into various chunks and combined it with thorase. Encouraged by the fact that thorase and the GRIP1 scaffold did indeed bind tightly, they teased out the physiology of that interaction in the presence of lots of thorase and then no thorase.

They discovered that the more thorase, the quicker the scaffolding deconstructed and the faster the surface receptors decreased. Thorase causes GluR2 receptors and GRIP1 to release their hold on each other, and therefore the receptor's grip at the surface of the synapse, they concluded.

To see if the deconstruction of the protein complex had any effect on nerve-signaling processes, they again used cells to record receptor activity by measuring electric currents as they fluxed through cells with and without thorase. In the presence of extra thorase, surface receptor expression was decreased, resulting in reduced signaling.

Next, the team measured the rates of receptor recycling by tagging the protein complex with a fluorescent marker. It could then be tracked as it was subsequently reinserted back into the surface membrane of a cell. In cells in which thorase was knocked out, there was very little deconstruction/turnover compared to normal cells. The scientists reversed the process by adding back thorase.

Finally, the team conducted a series of memory tasks in order to compare the behaviors of normal mice with those genetically modified to lack thorase. When the animals lacking thorase were put into a simple maze, their behaviors revealed they had severe deficits in learning and memory.

"Mice lacking thorase appear to stay in a constant state of stimulation, which prevents memory formation," Dawson explains. "Their receptors get up to the membrane where they are stimulated, but they aren't being recycled if thorase isn't present. If thorase doesn't stop the excitation by recycling the receptor, it continues on and has deleterious effects."

More information: *Cell*: www.cell.com/current

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