Unique protein bond enables learning and memory

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Two proteins have a unique bond that enables brain receptors essential to learning and memory to not only get and stay where they're needed, but to be hauled off when they aren't, researchers say.

NMDA receptors increase the activity and communication of brain cells and are strategically placed, much like a welcome center, at the receiving end of the communication highway connecting two cells. They also are targets in brain-degenerating conditions such as Alzheimer's and Parkinson's.

In a true cradle-to-grave relationship, researchers have found the scaffolding protein, SAP102, which helps stabilize the receptor on the cell surface, binds with a subunit of the NMDA receptor called GluN2B at two sites, said Dr. Bo-Shiun Chen, neuroscientist at the Medical College of Georgia at Georgia Health Sciences University.

While one binding site is the norm, these proteins have one that's stronger than the other. When it's time for the normal receptor turnover, the stronger bond releases and the lesser one shuttles the receptor inside the cell for degradation or recycling.

"One binding site is involved in stabilizing the receptor on the cell surface and the other is important in removing the receptor. We think it's a paradigm shift; we've never thought about the same scaffolding protein having two roles," said Chen, corresponding author of the study in the journal *Cell Reports.*

"We believe by understanding the normal turnover of these receptors, we can learn more about how to prevent the abnormal receptor loss that occurs in debilitating diseases such as Alzheimer's." In Parkinson's, the receptors inexplicably move away from where the synapse, or information highway, connects to the neuron, making them less effective. NMDA receptors are supposed to cluster where the synapse hooks into the receiving neuron; in fact, it's part of what anchors the synapse, Chen said.

Interestingly, this pivotal protein, SAP102, a member of the MAGUK family of scaffolding proteins, is the only family member known to directly contribute to maladies: its mutation causes intellectual disability.

While all cells have a system for managing the number of receptors on their surface, in Alzheimer's, this removal process appears accelerated, with increased engulfing of receptors and less neuron-to-neuron communication. The neurotransmitter glutamate helps establish and maintain the synapse and also binds with GluN2B.

GluN2B-containing NMDA receptors stay open to receive information for a long time, enabling the type of vigorous and sustained communication that enables learning and memory. In fact the number of these receptors naturally decreases with age, which may be one reason young people learn easier. When it's time to remove a receptor, phosphorus gets added to GluN2B, changing its function so it no longer binds to the scaffolding protein.

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