Scientists identify machinery that helps make memories

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A major puzzle for neurobiologists is how the brain can modify one microscopic connection, or synapse, at a time in a brain cell and not affect the thousands of other connections nearby. Plasticity, the ability of the brain to precisely rearrange the connections between its nerve cells, is the framework for learning and forming memories.

Duke University Medical Center researchers have identified a missing-link molecule that helps to explain the process of plasticity and could lead to targeted therapies.

The discovery of a molecule that moves new receptors to the synapse so that the neuron (nerve cell) can respond more strongly helps to explain several observations about plasticity, said Michael Ehlers, M.D., Ph.D., a Duke professor of neurobiology and senior author of the study published in the Oct. 31 issue of *Cell*. "This may be a general delivery system in the brain and in other types of cells, and could have significance for all cell signaling."

Ehlers said this could be a general way for all cells to locally modify their membranes with receptors, a process critical for many activities -- cell signaling, tumor formation and tissue development.

"Part of plasticity involves getting receptors to the synaptic connections of nerve cells," Ehlers said. "The movement of neurotransmitter (chemical) receptors occurs through little packages that deliver molecules to the synapse when new memories form. What we have

discovered is the molecular motor that moves these packages when synapses are active."

When neurons fire at the same time, their connections strengthen and a person can associate certain features. "Once you have heard someone's name, seen his face, where he was standing, all these features can be bound into a unified packet of information – a percept – and at a very cellular level this occurs by strengthening synaptic connections between co-active neurons," said Ehlers, who is also a Howard Hughes Medical Investigator.

To learn and make new associations, the brain alters the strengths of the synapses' electrical inputs onto cells that compute these features. Scientists studied the hippocampus, where memories form, but this machinery could operate in other brain areas.

"One of earliest changes in Alzheimer's disease is synapse dysfunction, so this molecule might be a new target for that disease," he said. "Abnormal movement of receptors may be implicated in brain development, in autism." He said the molecule potentially is involved "in the abnormal electrical activity of epilepsy and the overactive brain pathways of addiction."

In a series of biochemistry and microscopic imaging experiments, Ehlers and colleagues found that the myosin Vb (five-b) molecule in hippocampal neurons responded to a flow of calcium ions from the synaptic space by popping up and into action. One end of the myosin is attached the meshlike actin filaments so it can "walk" to the end of the nerve cells where receptors are. On its other end, it tows an endosome, a packet that contains new receptors.

"These endosomes are like little memories waiting to happen," Ehlers said. "They are reservoirs of neurotransmitter receptors that brain cells

deploy to add more receptors to a particular synapse. More receptors equals stronger synapses."

Electrical impulses cause one nerve cell to dump its neurotransmitter, in this case, glutamate, into the small space between neurons (the synapse), which activates neurotransmitter receptors on the receiving side. These are ion channels that open in response to neurotransmitter and generate the electrical impulse.

When the scientists blocked myosin in single cells, this stopped the addition of new receptors and prevented electrical impulses from getting stronger, showing that myosin is essential to enhancing nerve cell connections.

"This is a very basic cellular mechanism of brain plasticity. It is likely fundamental to brain development and disease," Ehlers said. "The myosin Vb molecule gives us a new way to think about designing therapies for treating memory loss, psychiatric disease and brain development."

Source: Duke University