Molecular 'foreman' discovered for brain wiring

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Researchers have identified a master regulatory molecule that is responsible for triggering the remodeling of neuronal connections that is critical for learning. Malfunctioning of the connection-remodeling machinery that they identified may also play a role in mental retardation, schizophrenia, and drug addiction. Thus, said the researchers, knowledge of the machinery could lead to insights into those disorders.

Peter Penzes and colleagues published their findings in the November 21, 2007, issue of the journal *Neuron*, published by Cell Press.

In their experiments, the researchers sought to understand the biological machinery controlling the enlargement of mushroom-like structures called dendritic spines on neurons. Such spines are the receiving stations for neurotransmitters—signaling chemicals that one neuron launches to trigger a nerve impulse in its neighbor. During learning, these spines strengthen signaling between neurons during the process of laying down memory pathways in the brain.

Spine structure can also be involved in neurological disorders. Researchers have found abnormal dendritic spines in certain types of mental retardation, including autism spectrum disorders, as well as schizophrenia and drug addiction.

Specifically, Penzes and colleagues sought to discover whether a molecule called kalirin-7 plays a role in spine enlargement in mature neurons when they undergo a learning-related strengthening called long-

term potentiation (LTP).

The researchers theorized that kalirin-7 might be a key regulator of spine development because it is found in high concentration in the spines of mature neurons. Also, kalirin-7 was known to play a role in the remodeling of the structural beams and studs of the cell, called the cytoskeleton.

The researchers' experiments with cultured neurons revealed that activation of neurons during LTP does indeed trigger kalirin-7 to turn on the machinery for remodeling spines, causing spines to become enlarged.

What's more, the researchers found that kalirin-7 also regulates the other major process necessary for strengthening neuronal signaling connections. Kalirin-7 controls the number of neurotransmitter-receiving stations, called receptors, that festoon the surface of dendritic spines. The number of these receptors determines the strength of signaling connections between neurons.

The researchers concluded that their findings "strongly suggest that kalirin-7 may be an important regulator of the experience-dependent modifications of forebrain circuits during postnatal development and may play an important role in learning and memory."

They also pointed out that altered spine structures "have been associated with mental retardation, neuropsychiatric disorders, and drug addiction. Specifically, aberrant spine morphology in forebrain occurs in many types of mental retardation, including fragile-X and autism spectrum disorders." Similarly, they noted, studies of schizophrenics have also revealed such alteration of dendritic spines, as well as evidence of defects in the kalirin-7 pathway.

"Therefore, our results may suggest potential strategies for treatments of

these neurodevelopmental and psychiatric diseases," they wrote.

Source: Cell Press