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Researchers provide definitive proof for receptor's role in synapse development

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Jackson Laboratory researchers led by Associate Professor Zhong-wei Zhang, Ph.D., have provided direct evidence that a specific neurotransmitter receptor is vital to the process of pruning synapses in the brains of newborn mammals.

Faulty pruning at this early developmental stage is implicated in autism-spectrum disorders and schizophrenia. The definitive evidence for N-methyl-D-aspartate receptor (NMDAR) in pruning has eluded researchers until now, but in research published in the Proceedings of the National Academy of Sciences, Zhang's lab had serendipitous help in the form of a mouse model containing brain cells lacking NMDAR side-by-side with cells containing the receptor.

Soon after birth, mammals' brains undergo significant development and change. Initially, large numbers of synapses form between neurons. Then, in response to stimuli, the synaptic connections are refined—some synapses are strengthened and others eliminated, or pruned.

In most synapses, glutamate serves as the neurotransmitter, and NMDAR, a major type of post-synaptic glutamate receptor, was previously known to play an important role in neural circuit development. Previous research has implicated the importance of NMDARs in pruning, but it remained unclear whether they played a direct or indirect role.

Zhang and colleagues focused on the thalamus, a brain region where

synapse pruning and strengthening can be monitored and quantified with relative ease. They got unexpected help when they realized the mouse model they were using had thalamus cells lacking NMDARs right next to cells with normal NMDAR levels.

The researchers showed that the refinement process was disrupted in the absence of NMDARs. At the same time, neighboring neurons with the receptors proceeded through normal synaptic strengthening and pruning, clearly establishing the necessity of NMDARs in postsynaptic neurons for synaptic refinement.

"Whenever I give a talk or meet colleagues," Zhang says, "the first question that comes up is whether the NMDA receptor is important. It's good that this is now settled definitively."

There has been extensive research into synaptic strengthening, and most of these studies indicate that the presence of NMDARs may support the recruitment of larger numbers of another kind of glutamate receptor to strengthen the synaptic connections. How NMDARs regulate the pruning process remains largely unknown, however.

Provided by Jackson Laboratory