Brain needs perfection in synapse number

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Like Goldilocks, the brain seeks proportions that are just right. The proper number of synapses or communication between nerve cells, determined early in life, is crucial to having a healthy brain that can learn and retain information.

Now, researchers at Baylor College of Medicine in Houston have determined that the protein MeCP2 (methyl-CpG binding protein 2), is critical to fine-tuning the number of synapses. In a report that appears in today's issue of the journal Neuron, they said that too little MeCP2, as in the neurodevelopmental disorder Rett syndrome, or too much MeCP2, can result in mental retardation, problems with gait or spasticity and symptoms of autism.

In fact, a common underlying theme in the autism spectrum disorders could be a disruption in neuron-to-neuron communication caused by abnormal amounts of MeCP2, said Hsiao-Tuan Chao, an M.D./Ph.D. graduate student, who worked under the co-mentorship of BCM investigators Drs. Huda Y. Zoghbi and Christian Rosenmund and is first author of the report. Zoghbi is a professor of molecular and human genetics, pediatrics, neurology and neuroscience at BCM and a Howard Hughes Medical Institute investigator, and Rosenmund is an associate professor of molecular and human genetics and neuroscience.

As infants, girls with Rett syndrome seem normal for at least six months. Between the ages of 6 and 18 months, however, their development stops and they begin to regress, losing the ability to talk. Then they begin to have problems walking and keeping their balance and develop typical

hand-wringing behavior. Many of their symptoms mirror those of autism. Zoghbi's laboratory was the first to identify a mutation in the MeCP2 gene that results in too little of this protein, causing girls to develop Rett. Boys who suffer from a disorder linked to too much MeCP2 have spasticity and mental retardation with autism-like behavior.

"MeCP2 has an important role in fine-tuning the amount of synaptic responses," said Chao. Having just the right amount of MeCP2 and the right number of synapses drives healthy brain development.

"Starting life with the right amount of synapses is critical," said Zoghbi. "What determines that and how do we know that we have the right number?"

Chao unraveled that mystery using two different sets of mice – one with too little MeCP2 and one with too much – and asking what was wrong with their neurons.

"We wanted to know if there were changes within the neuron itself or is this a question of the overall network and the way the neurons communicate?" she said.

In Rosenmund's laboratory, she was able to use his assays to look at synaptic communication in individual neurons to find out that loss of MeCP2 caused the neurons to "talk on a lower level, releasing less neurotransmitter per neuron," she said. On the contrary, doubling MeCP2 caused the opposite, an increase in communication between neurons or synapses. Most importantly, she found that synapses were functioning normally, but that too little MeCP2 meant that fewer synapses were formed, while too much MeCP2 meant too many synapses were formed.

"The beauty of this result is that this critical process in the development

of synaptic connectivity in the brain is tightly regulated by the amount of MeCP2," said Rosenmund. "It is one of the strongest pieces of evidence that mental retardation and autism-like diseases originate with problems in synapse formation."

Chao said, "It suggests that the pathways in which MeCP2 is involved and the proteins it regulates are probably critical for how the brain can determine how many synapses to make as it's developing."

"This determination of how many synapses to make happens early in life," said Zoghbi. "If it's not right, then the brain undergoes secondary changes to try to compensate. This is a big important observation and opens up ways to think about adult diseases that involve loss of synaptic function. It is also interesting that patients who lack this protein or have too much have features of autism. More and more, data point to the possiblity that autism is a disorder of abnormal function of the synapse."

"This is important because this is the basic foundation for how we refine our learning," Chao said. "Understanding how MeCP2 is involved in our neurological development is another piece of the puzzle in understanding autism and other neurological disorders."

Source: Baylor College of Medicine