

Inhibitory neurons key to understanding neuropsychiatric disorders

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The brain works because 100 billion of its special nerve cells called neurons regulate trillions of connections that carry and process information. The behavior of each neuron is precisely determined by the proper function of many genes.

In 1999, Baylor College of Medicine researcher Dr. Huda Zoghbi, and her colleagues identified mutations in one of these genes called [MECP2](#) as the culprit in a devastating [neurological disorder](#) called Rett syndrome. In new research in mice published in the current issue of the journal *Nature*, Zoghbi and her colleagues demonstrate that the loss of the protein MeCP2 in a special group of inhibitory [nerve cells](#) in the brain reproduces nearly all Rett syndrome features.

Children, mostly girls, born with Rett syndrome, appear normal at first, but stop or slow intellectual and motor development between three months and three years of age, losing speech, developing learning and gait problems. Some of their symptoms resemble those of autism.

These inhibitory (gamma-amino-butyric-acid [GABA]-ergic) neurons make up only 15 to 20 percent of the total number of neurons in the brain. Loss of MeCP2 causes a 30 to 40 percent reduction in the amount of GABA, the specific signaling chemical made by these neurons. This loss impairs how these neurons communicate with other neurons in the brain. These inhibitory neurons keep the brakes on the communication system, enabling proper transfer of information.

"In effect, the lack of MeCP2 impairs the GABAergic neurons that are key regulators governing the transfer of information in the brain", said Dr. Hsiao-Tuan Chao, an M.D./Ph.D student in Zoghbi's laboratory and first author of the report.

Chao made the discovery by developing a powerful new tool or [mouse model](#) that allowed researchers to remove MeCP2 from only the GABAergic neurons.

"We did this study thinking that perhaps all we would see was a few symptoms of Rett syndrome," said Chao. "Strikingly, we saw that removing MeCP2 solely from GABAergic neurons reproduced almost all the features of Rett syndrome, including cognitive deficits, breathing difficulties, compulsive behavior, and repetitive stereotyped movements. The study tells us that MeCP2 is a key protein for the function of these neurons."

Once the authors determined that the key problem rested with the GABAergic neurons, they sought to find out how the lack of MeCP2 disturbed the function of these neurons. Chao discovered that losing MeCP2 caused the GABAergic neurons to release less of the neurotransmitter, GABA. This occurs because losing MeCP2 reduces the amount of the enzymes required for the production of GABA.

Intriguingly, prior studies showed that expression of these enzymes is also reduced in some patients with autism, schizophrenia and bipolar disorder, said Chao.

"This tells us a lot about what is going on in the brains of people with [Rett syndrome](#), autism or even schizophrenia," said Chao. "A child is born healthy. She starts to grow and then begins to lose developmental milestones. Communication between neurons is impaired, in part due to reduced signals from GABAergic neurons."

"This study taught us that an alteration in the signal from GABAergic [neurons](#) is sufficient to produce features of autism and other neuropsychiatric disorders," said Zoghbi, a Howard Hughes Medical Institute investigator and director of the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital.

More information: www.nature.com

Provided by Baylor College of Medicine

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