NEWS

Excitatory neurons may underlie some aspects of Rett syndrome

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Mice that lack the Rett syndrome gene, **MeCP2**, in a subset of neurons that activate neural circuits develop tremor and anxiety-like behaviors, two characteristics of the syndrome. By contrast, mice that lack the gene everywhere in the brain except for in this subset of cells don't have these

symptoms.

The findings, presented today at the **2015 Society for Neuroscience annual meeting** in Chicago, suggest that defects in these ‘excitatory’ neurons may underlie certain symptoms of Rett syndrome, and those in other types of neurons may contribute to a different set of symptoms.

Rett syndrome shares many features with autism, including **repetitive behaviors**, social deficits and problems with language. It is caused by mutations that inactivate MeCP2.

MeCP2 is expressed in many different cell types in the brain. Mice that lack MeCP2 throughout the brain display many Rett-like symptoms, including repetitive behaviors and problems with social interaction, motor coordination, learning and memory. They are also overweight and die young.

Researchers are only beginning to figure out whether certain cell types in the brain are responsible for certain symptoms of the disorder.

In 2010, researchers **selectively deleted MeCP2** from a subset of neurons that suppress the activity of other neurons through the ‘inhibitory’ chemical messenger gamma-aminobutyric acid (GABA). These mice display most, but not all, of the symptoms that mice lacking MeCP2 everywhere do. In particular, they do not appear to show anxiety-like behaviors or tremor.

In the new study, researchers led by **Huda Zoghbi** at Baylor College of Medicine in Houston examined the role of MeCP2 in excitatory neurons, which enhance the activity of other neurons using the chemical messenger glutamate.

“We hope that by studying the roles of MeCP2 in excitatory neurons we will gain a comprehensive understanding of how dysfunction of these cells contributes to Rett syndrome,” says **Xiangling Meng**, a graduate student in Zoghbi’s lab who presented the findings.

Tremor trigger:

The researchers found that male mice lacking MeCP2 in excitatory neurons show an obvious tremor by 8 weeks of age and are overweight, similar to animals that lack the gene throughout the brain. Both the full- and the partial-knockout animals also have trouble balancing on a rotating rod, indicating that they have problems with motor coordination, and opt to spend time in a darkened chamber over a brightly lit one, which is thought to represent an anxiety-like behavior.

Unlike mice that lack MeCP2 throughout the brain, however, mice missing the gene only in excitatory cells do not appear to have problems with learning and memory. They have no difficulty learning to associate a certain sound with a foot shock, and can remember the context in which the shock occurred.

Using brain slices from both sets of mice, the researchers found that neurons in the cortex — the brain's outer layer — of both sets of mice fire at a lower rate than in control mice that have MeCP2.

Restoring MeCP2 only in excitatory cells in animals that otherwise lack the gene protects them from developing tremor and anxiety-like behavior, and restores neuron firing to normal.These animals still have problems with motor coordination and are underweight.

The findings suggest that dysfunction in excitatory neurons leads to anxiety, tremor and obesity. Loss of MeCP2 in this subset of cells also leads to problems with motor coordination, but expressing the gene in only these cells is not sufficient to protect the mice from this problem.

Mice lacking MeCP2 in either excitatory or inhibitory neurons share some similar features, including obesity, motor problems and premature death. But each model recapitulates a unique subset of Rett-like symptoms.

"It's surprising to us, especially when you think of the intensive cross talk between the two types of neurons," Meng says. "But this phenomenon may underlie the pathogenesis of Rett syndrome."

For more reports from the 2015 Society for Neuroscience annual meeting, please ***click here****.*