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Insights into neurons that cause symptoms of Rett syndrome could guide new therapy search

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Two studies in mice from Baylor College of Medicine, Texas, reveal new insights into neurons that mediate symptoms typical of the postnatal neurological disorder Rett syndrome.

Rett syndrome is a childhood disorder that typically manifests after the first birthday. Early symptoms include delayed development and poor coordination while, during the second stage, a child will gradually or suddenly develop severe problems with communication, language, learning, co-ordination and other brain functions. It can cause seizures, breathing difficulties and sometimes premature death.

Rett syndrome is caused by mutations in the MECP2 gene which makes a protein with a similar name, MeCP2, that is essential for proper function of neurons in the brain. When MeCP2 is missing from all cells, mice develop symptoms similar to those seen in Rett syndrome and male mice die prematurely.

The two major types of neurons in the brain are excitatory neurons, which send signals to other neurons telling them to be active, and inhibitory neurons, which stop or dampen the activity of other neurons to control the timing and rate of incoming information. These neurons must act in balance with each other for the brain to work correctly, otherwise disruptions can lead to the onset of neurological disorders.

One study in mice, published in the journal *eLife*, shows that expressing MeCP2 only in inhibitory neurons increases lifespan and rescues most but not all behavioral deficits.

A second study, published at the same time in *eLife*, shows that removing MeCP2 only from excitatory neurons in mice contributed to the onset of several Rett-like symptoms, some of which are distinct and complementary to those mediated by inhibitory neurons.

"Together, our findings show that rescuing the activity of MeCP2 in certain cell types can have a profound effect on improving symptoms," says Huda Zoghbi, senior author of both papers and a recent winner of the Shaw Prize for her research leading to the discovery of the gene causing Rett syndrome.

Approximately one in every 10-12,000 females are affected by the disorder, while it is much rarer in males who have more severe symptoms and die early in life. The two studies showed that MeCP2 is important for both inhibitory and excitatory neurons in terms of motor function and survival, but also revealed that each type of neuron is key for distinct neuropsychiatric features.

For the first study, the team asked if expressing MeCP2 in inhibitory neurons, while the gene remains missing from the rest of the body, would be enough to prevent some or all of the symptoms seen in the Rett syndrome mouse model.

"Our data suggest that when a brain is missing MeCP2 everywhere, turning on the gene in inhibitory neurons can make the brain network nearly normal and prevent most Rett-like symptoms," says Kerstin Ure, Postdoctoral Fellow and lead author of the study.

"However, when both normal cells and cells with mutated MeCP2 are

present in the same brain, as seen in female mutant mice, the abnormalities caused by this mixture cannot be overcome just by rescuing the function of inhibitory neurons. This highlights the importance of doing future studies in female mice to better understand how Rett syndrome develops."

Taking these new insights into account, the authors of the second paper set out to learn what aspects of the syndrome would appear or recover if MeCP2 was removed or re-expressed in excitatory neurons.

"We showed that mice lacking the gene from these neurons develop tremor and anxiety-like behaviors, abnormal seizure-like brain activity, severe obesity, and early death, which is surprisingly different from mice missing MeCP2 in inhibitory neurons," says Xiangling Meng, a neuroscience graduate student at Baylor College of Medicine, and lead author of the second study.

"When the gene was re-expressed in excitatory neurons, the female mice were almost completely recovered. In the case of more severe males, their anxiety and tremors were rescued, suggesting that impairment of excitatory neurons by removing MeCP2 contributes to the onset of specific symptoms such as these."

The team believes the next steps will be to investigate if drugs that improve the function of both inhibitory and excitatory neuron activity can be used for treating patients with Rett syndrome. Further studies will be focused on improving the function of these neurons in the hope of restoring the balance between them.

Zoghbi adds: "For now, we are looking at different ways of activating inhibitory neurons in the female mouse brain, including testing drugs and special channels that can activate a cell when a specific chemical is given to the mice. We hope these methods will help us refine a path forward

for potential new therapies for patients."

More information: Kerstin Ure et al, Restoration of Mecp2 expression in GABAergic neurons is sufficient to rescue multiple disease features in a mouse model of Rett Syndrome, *eLife* (2016). DOI: 10.7554/eLife.14198

Xiangling Meng et al. Manipulations of MeCP2 in glutamatergic neurons highlight their contributions to Rett and other neurological disorders, *eLife* (2016). DOI: 10.7554/eLife.14199

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