NEWS

Breathing issues in Rett stem from distinct neural circuits

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Each of the various breathing difficulties seen in people with Rett syndrome arises from a distinct circuit in the brainstem, a new mouse study suggests[1].

Rett syndrome is an autism-related disorder that primarily affects girls. The syndrome appears in children by 18 months, when their development dramatically regresses. They lose speech and use of their hands, for example.

In addition to communication problems and **repetitive behaviors**, individuals with the syndrome develop breathing problems. They breathe rapidly, hold their breath and fail to regulate their breathing rate in response to drops in oxygen. These issues can cause people with the syndrome to develop an irregular heart rate or faint.

The brainstem, the way station between the brain and spinal cord, regulates breathing. The new study found that separate circuits in the brainstem govern breath holding, rapid breathing and adapting to low oxygen levels.

The results, which appeared in May in *The Journal of Neuroscience*, add to others tracing the **critical circuits in the brain** and **body** that give rise to different features of Rett.

A better understanding of the neural basis of breathing in Rett might point the way to therapies, says lead researcher **Jeffrey Neul**, professor of neurosciences and pediatrics at the University of California, San Diego.

“We may be able to identify particular cell types and particular circuits and maybe provide insight into drug targeting or other methods to improve breathing in people with Rett syndrome,” Neul says.

Bad breaths:

Mice with a mutation in the Rett syndrome gene **MeCP2** show the same sort of breathing behaviors as people with the syndrome do. Neul and his colleagues selectively restored expression of MeCP2 to certain brainstem regions in these mice, including the lower pons, medulla and part of the spinal cord. They then placed the mice in a chamber to record how often the mice breathed and how often they held their breath.

Mice with MeCP2 restored in these brainstem regions respond normally to low oxygen levels — that is, they immediately breathe more rapidly. This finding is consistent with that from a 2011 study by the same team[2]. But in their new work, the researchers found that this adaptive response disappears by the time the mice reach 35 weeks old.

Restoring MeCP2 also stops the mice from holding their breath. The mice still breathe unusually rapidly, however.

The researchers then tried restoring the gene to only the lower brainstem, which houses a relay center for sensory signals about oxygen as well as cells that drive rhythmic breathing. This approach does not reduce any of the breathing abnormalities in the mice.

The findings suggest that the circuit governing breath holding resides in the lower pons and medulla, but additional brainstem areas, such as the upper pons, control the other breathing behaviors.

“All the neurons are working in unison,” says **Lucas Pozzo-Miller**, professor of neurobiology at the University of Alabama at Birmingham, who was not involved in the study. “Losing MeCP2 in each [population] gives rise to specific irregular patterns.”

Respiratory repair:

The study also clarified another feature of Rett syndrome: **sudden death**.

Restoring MeCP2 expression to the lower brainstem of mice with a mutation in the gene triples their life span, extending it to more than a year from about 4 months. Many experts attribute the sudden death that can occur in people with Rett syndrome to breathing problems, but the fact that mice can live longer despite serious breathing difficulties calls this connection into question, Pozzo-Miller says.

Heart rate fluctuations and other cardiac problems associated with the syndrome are other **possible causes of sudden death**.

Breathing patterns in the mice are not stable. When they are 20 to 26 weeks old, the mutant mice

with MeCP2 restored in the lower brainstem show temporary improvement: They breathe steadily and hold their breath less.

“But it can’t keep it going,” Neul says. “Ultimately, that system starts to fall apart.” Tracing the remodeling of this circuit over time may provide clues to **the regression seen in Rett syndrome**, he says.

Treating the regression in breathing may require drugs that target several faults in brainstem circuitry, Pozzo-Miller says. “There is not going to be a single silver bullet.”

REFERENCES:

1. Huang T.W. *et al. J. Neurosci.* **36**, 5572-5586 (2016) **PubMed**
2. Ward C.S. *et al. J. Neurosci.* **31**, 10359-10370 (2011) **PubMed**