NEWS

Angelman syndrome drug shows promise in mouse study

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B. Taylor-BlakeGlowing success: A mouse spinal cord treated with topotecan (right) glows where brain cells express UBE3A, the protein missing in Angelman syndrome (left).

Two weeks of treatment with **a cancer drug called topotecan** boosts expression for a year of the gene that's deficient in **Angelman syndrome**, according to unpublished research presented 20 March at the New York Academy of Sciences.

Angelman syndrome is marked by developmental delays, impaired or no speech, seizures and, often, autism. It is caused by a deletion or mutation of the maternal copy of a gene called **UBE3A** and surrounding parts of chromosome 15. The paternal copy of the gene is normally silenced in the brain.

The new findings provide support for an unusual therapeutic approach to the syndrome: unsilencing the paternal copy.

In 2011, **Benjamin Philpot** and his team identified **16 topoisomerase inhibitors**, compounds that interfere with enzymes necessary for DNA replication. At the time, they showed that a two-week treatment with one of these compounds, topotecan, activates the paternal copy of UBE3A in mouse spinal cord and brain cells for at least 12 weeks after the therapy ends[1].

Since then, he and his collaborators have identified about 30 topoisomerase inhibitors that effectively unsilence the gene in mouse neurons.

According to the latest findings, presented at the **Autism Spectrum Disorder: From Genes to Circuits to Behavior** conference, injecting topotecan into mouse spinal cord cells once daily for about two weeks activates the gene in some spinal cord neurons for at least a year.

"We have every reason to believe that, at least in this subset of neurons, the unsilencing of UBE3A is permanent," says Philpot, associate professor of cell and molecular physiology at the University of North Carolina, Chapel Hill.

Unsilencing challenges:

The researchers haven’t yet shown that they can deliver the drug to a human brain, activate enough cells and alleviate Angelman symptoms in mice or in people.

In the mouse study, they injected the drug into the spinal cord rather than the brain. The blood-brain barrier makes it difficult to administer drugs to the brain, and although researchers can inject the drug directly into the brain, they are looking at other, safer methods of delivery.

Studies suggest that topotecan has modest permeability across the blood-brain barrier, but Philpot and his collaborators are working to find a drug that is more permeable and reactivates UBE3A in more neurons in the brain, Philpot says.

"Getting the drug to where it needs to go has been a problem for all of the therapies for Angelman syndrome," says **Lawrence Reiter**, associate professor of neurology at the University of Tennessee Health Science Center in Memphis, who was not involved in the research.

Philpot's team is also trying to find a combination of topoisomerase inhibitors that can be effective with minimal side effects. Surprisingly, topotecan has no widespread effects on other imprinted genes — those genes for which one parent's copy is expressed and the other's copy is silenced — Philpot says.

"That would be the next step, to find a more refined drug,” says Reiter. “[Topotecan] is really a harsh, generalized drug.”

However, topotecan's lasting influence in mice indicates that it may only require a few doses, which would reduce toxicity exposure, notes **Michael Ehlers**, chief scientific officer of neuroscience at Pfizer, who was not involved in the study. "A promising thing about this preliminary data is that it has an enduring effect.”

Researchers don't yet know whether the topoisomerase inhibitors improve symptoms associated

with Angelman syndrome in mice, or whether they will work in people. "We haven't even tried," Philpot says. "We're still working on optimizing delivery of the drug."

If it works in people, the researchers will need to determine whether the drug is age-sensitive, and whether it can be given to older people with Angelman syndrome." There's no way to know that until you get to the clinical trial stage," Reiter says.

References:

1. Huang H.S. *et al. Nature* **481**, 185-189 (2011) **PubMed**