

NEWS

Drug in trials for one autism-linked condition may worsen another

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The drug rapamycin, which is in clinical trials for tuberous sclerosis (TSC), exacerbates features of fragile X syndrome, another condition related to autism, a new study suggests¹.

Rapamycin increases anxiety, shortens sleep and worsens social skills in a mouse model of **fragile X syndrome**, the researchers found. And the drug does not alleviate seizures or cognitive problems in these mice.

The work should serve as an alert to researchers testing rapamycin for conditions related to autism, says lead investigator **Carolyn Beebe Smith**, senior investigator at the U.S. National Institute of Mental Health.

“We do have to be cautious,” she says. “We have to look carefully at those [conditions] on an individual basis.”

The work was published 12 January in *Frontiers in Molecular Neuroscience*. An independent study published in November reported that a drug similar to rapamycin doesn’t appear to improve most features of TSC in 32 children with that condition².

Both studies suggest that the drug may not benefit all people with autism or related conditions says **Mustafa Sahin**, who led the TSC study.

Rapamycin works by inhibiting a pathway led by the mammalian target of rapamycin (mTOR). This pathway is overly active in TSC because the proteins mutated in the condition normally serve as its brakes.

Some studies suggest that the pathway’s activity is also elevated in fragile X mice. However, the new study casts doubt on its role in fragile X.

“In science, some things become a hot topic. And when you have a hammer, everything looks like a nail,” says **Mark Bear**, professor of neuroscience at the Massachusetts Institute of Technology in Cambridge. “I just feel like the mTOR involvement in fragile X has been overhyped.” Bear was not involved in the work but has tested other drugs for fragile X syndrome.

High anxiety:

Smith and her colleagues added rapamycin to the food of typical and fragile X mice when the mice were 21 to 90 days old.

Untreated fragile X mice are hyperactive, prone to seizures and have problems with learning and memory. Rapamycin does not ease these problems; rather, it makes the mice more anxious than usual. It also increases anxiety in typical mice.

It is unclear whether the drug would affect people similarly, however. People with fragile X syndrome tend to be anxious, whereas fragile X mice have low anxiety levels, notes **Rachel Saré**, a postdoctoral fellow in Smith’s lab.

Fragile X mice typically sleep less than controls — and rapamycin shortens their sleep even more. It has the same effect on controls.

The drug also worsens the animals’ social problems. Like controls, fragile X mice spend more time with another mouse than with an object when given a choice. But the fragile X mice given rapamycin do not show a preference for the mouse over the object. The drug has a similar effect on controls in a second social test.

Clinical questions:

A few previous studies have also cast doubt on mTOR’s involvement in fragile X syndrome³. And the new study only found elevated levels of a molecule that works downstream of mTOR, but not mTOR itself.

“It certainly suggests that mTOR isn’t primary, because we didn’t find an increase,” Smith says.

The behavioral results point in the same direction.

“The fact that rapamycin, which is effective in mouse models of TSC, made these animals worse in some respects and didn’t reverse any of the other phenotypes is indicative that this is a not a good target,” Smith says.

It’s too premature to dismiss mTOR as a fragile X target, but the study does suggest that treating with rapamycin for more than a month is not effective for fragile X syndrome, says **Eric Klann**,

professor of neuroscience at New York University, who was not involved in the work.

“We know a chronic dosing regimen like this is probably not something you want to do,” Klann says. “But a question might be: What if you dosed shorter duration and went on and off the drug? That’s how a lot of disorders are treated.”

Smith and her colleagues plan to test the effects of the diabetes drug metformin on fragile X mice. The drug has been shown to **reverse behavioral problems** in fragile X mice.

REFERENCES:

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