NEWS

Selective enzyme blocker eases fragile X traits in mice

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10 JULY 2020

An experimental drug prevents seizures and improves memory in a mouse model of fragile X syndrome, according to a new study[1]. The drug selectively blocks an enzyme that is overactive in the brains of people with fragile X and could offer a potential treatment for the condition.

“It’s truly a novel target,” says co-lead investigator **Mark Bear**, professor of neuroscience at the Massachusetts Institute of Technology.

Fragile X syndrome is characterized by intellectual disability, seizures, hyperactivity and, in one out of three people, autism. It results from mutations that diminish the gene **FMR1**’s production of FMRP, a protein that limits the synthesis of other proteins at **synapses**, where neurons exchange chemical messages. Without FMRP, according to **one leading theory**, proteins build up at synapses and disrupt this signaling, leading to fragile X’s outward signs.

The new drug helps put the brakes on protein buildup by blocking a specific form of an enzyme called glycogen synthase kinase 3 (GSK3), which plays an important **role during brain development**. Previous trials have prevented protein buildup by blocking a different target, the mGluR5 receptor, which helps control protein production in neurons. But those drugs have **failed in clinical trials** because people have experienced adverse side effects and built up a **tolerance to chronic dosing**.

The drug to block GSK3, called BRD0705, may result in fewer side effects because it is highly selective. The enzyme comes in two forms, known as alpha and beta, and BRD0705 blocks only the former. The findings should stimulate more research on GSK3 alpha, which has not been studied as well as its counterpart, researchers say.

“It’s a very important paper,” says **Randi Hagerman**, medical director of the University of California, Davis MIND Institute, who was not involved in the study. “GSK3 alpha inhibition should

have some good effects in patients, although it's really clear that positive effects in the mouse model doesn't necessarily translate to patient benefit."

Elementary beginnings:

The idea to target GSK3 is not entirely new. It stems from a familiar treatment for a number of neuropsychiatric conditions: lithium, which blocks both forms of GSK3, among other enzymes.

Studies have shown that lithium partially corrects aberrant protein buildup in mouse and fly **models of fragile X syndrome**[2]. Lithium has also helped ease traits in people with fragile X, but its side effects, including kidney damage, limit who can take it[3,4].

Other drugs block both forms of GSK3 more selectively than lithium does, but they can cause cancerous growths[5]. Studies have suggested that blocking only one form of GSK3 could prevent this side effect[6]. But it was unclear which form to block or how to do it without also inhibiting other enzymes.

For the new study, researchers at the Broad Institute in Cambridge, Massachusetts, **designed chemical compounds** that could selectively inhibit either the alpha or the beta form — and little else.

"From a methodology standpoint, this paper is a huge step forward," says **Sean McBride**, assistant professor of cell biology and neuroscience at Rowan University in Stratford, New Jersey. He was not involved in the new work but studies fly models of fragile X syndrome and also sees people with the condition.

A selective process:

The researchers injected fragile X mice with either the alpha or beta inhibitor. Most fragile X mice have seizures when exposed to loud sounds. They also have trouble with learning and memory: Unlike controls, they don't learn to avoid an area where they previously received a painful foot shock.

Blocking the alpha form of GSK3 with BRD0705 eliminated the animals' seizures and caused them to perform as well as controls on the test of learning and memory, the researchers found. The beta inhibitor, on the other hand, had no effect on the mice's fragile X traits.

Fragile X mice produce excess protein in the **hippocampus**, a brain region important for forming and storing memories. The team took tissue from the hippocampi of mice with and without fragile X and incubated it so that protein synthesis would continue. They bathed the tissue in either the alpha inhibitor, beta inhibitor or a neutral solution. They then added a molecule to halt protein

synthesis, and labeled and counted the amount of protein present.

Treating tissue from fragile X mice with the alpha inhibitor lowered protein-synthesis levels to those of controls, whereas treating it with the beta inhibitor and the neutral solution had no effect on protein synthesis.

The brains of fragile X mice also tend to be overly excitable: Neurons in the brain's outer layer, the cortex, fire more often than those of controls. In samples of cortical tissue from the fragile X mice, only application of the alpha inhibitor dampened this hyperexcitability.

The mice treated with the alpha inhibitor did not develop any tolerance to it over time; they received all of the benefits of lithium treatment with none of the side effects. The findings were published in May in *Science Translational Medicine*.

A crucial next step is to make the drug even more selective for the alpha form of GSK3 over the beta form, says co-lead investigator **Florence Wagner**, director of medicinal chemistry at the Broad Institute's Center for the Development of Therapeutics. This would decrease the chances of inhibiting the wrong target once the dose is scaled up to treat people rather than mice.

If the drug is successful in people with fragile X, it might even be applied to other psychiatric conditions **that respond to lithium**, including other forms of autism, Bear says.

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