NEWS

Diabetes drug eases fragile X features in mice

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3 JULY 2017

A drug used to treat type 2 diabetes reverses behavioral and brain abnormalities in a mouse model of **fragile X syndrome**[1].

The drug, called metformin, has few side effects, so there is little risk in expanding its use to fragile X syndrome.

“It’s low-hanging fruit,” says lead researcher **Nahum Sonenberg**, a professor of biochemistry at McGill University in Montreal, Canada. “You see something like this in the mouse, it’s a no brainer to take this kind of drug and get it into humans.”

Fragile X syndrome is the most common inherited cause of intellectual disability. It also accounts for about 5 percent of autism cases. The syndrome stems from mutations in **FMR1**, a gene that regulates several signaling pathways in neurons. One of these, called the ERK pathway, regulates the production of proteins that help to form and maintain **synapses**, or the junctions between neurons. Mutations in FMR1 send the ERK pathway into overdrive.

Metformin is known to dampen the ERK pathway. A study published last year showed the drug **eases sleep and memory problems** in a fruit fly model of fragile X[2].

The new work, published in May in *Nature Medicine*, bolsters the notion that metformin might ease features of fragile X syndrome in people, says **Thomas Jongens**, associate professor of genetics at the University of Pennsylvania in Philadelphia. Jongens led the fruit fly research but was not involved in the new work. “That really is very exciting because it suggests that what’s true in the fly and in the mouse should probably be true in humans as well,” he says.

Normal neurons:

Mice with a silenced copy of FMR1 exhibit a range of features seen in people with fragile X syndrome, such as seizures, hyperactivity and excessive grooming — a **repetitive behavior**. They also lack the innate preference to interact with an unfamiliar mouse over a familiar one — a social impairment.

Sonenberg and his team injected adult fragile X mice with either metformin or saline daily for 10 days. A full 24 hours after the last injection, they performed a battery of behavioral tests.

The mice treated with metformin spent significantly less time grooming themselves than did those that received saline. They also spent more time sniffing unfamiliar mice than familiar ones. “Social interaction was not impaired anymore,” says **Ilse Gantois**, a research associate in Sonenberg’s lab.

The researchers also looked at brain tissue from the mice. Fragile X mice tend to have unusually dense and immature **dendritic spines**, the neuronal protrusions that receive signals from other neurons. Metformin, but not the placebo, reversed these abnormalities. “The spine density changed,” Sonenberg says. “That’s what’s amazing; they look normal.”

Appealing treatment:

Metformin also decreases the number of seizures in fragile X mice but does not appear to have any effect on hyperactivity.

The fact that metformin reverses problems in adult mice is particularly encouraging, Jongens says. “Traditionally, this disorder has been considered to be a developmental disorder, and that’s always kind of closed everyone’s mind to thinking that anything can be done once the kid is born,” he says. “These sorts of findings change that thinking.”

Metformin’s excellent safety record makes it appealing as a treatment for children. Some clinicians already prescribe it to **curb the weight gain** associated with antipsychotic medications in children with autism[3].

However, only a carefully designed trial can prove whether the drug safely eases features of fragile X syndrome, says **Mark Bear**, a professor of neuroscience at the Massachusetts Institute of Technology, who was not involved in the study. “As wonderful as this is, other approaches that have been successful in animal models have yet to succeed in the clinic,” he says.

Several researchers, including Sonenberg and Jongens, are seeking funding to begin clinical trials of metformin.

REFERENCES:

1. Gantois I. *et al. Nat. Med.* **23**, 674-677 (2017) **PubMed**
2. Monyak R.E. *et al. Mol. Psychiatry* Epub ahead of print (2016) **PubMed**
3. Anagnostou E. *et al. JAMA Psychiatry* **73**, 928-937 (2016) **PubMed**