NEWS

Drug duo delivers brain, behavioral benefits for fragile X syndrome

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Administering a cholesterol drug alongside an antibiotic eases atypical behavior and restores the signaling balance in the brains of people with fragile X syndrome.

Researchers presented the preliminary results yesterday at the **2018 Society for Neuroscience annual meeting** in San Diego, California.

In the wake of **failed clinical trials** for **fragile X syndrome** drugs, researchers are increasingly turning to new approaches that **combine treatments** targeting different biological pathways.

“It’s interesting to combine treatments because we don’t have just one signaling pathway that is defective in fragile X,” says Amal Loudghi, a graduate student in **Jean-François Lepage**’s lab at the University of Sherbrooke in Quebec, Canada, who presented some of the results.

The new trial, dubbed LovaMiX, combines lovastatin, which treats high cholesterol, with the antibiotic minocycline. Both drugs have proven promising in small trials and animal studies of fragile X syndrome. Minocycline **dampens anxiety** and **eases the severity of traits** in people with the syndrome. And lovastatin **relieves seizures** in fragile X mice.

The researchers gave 23 people with fragile X syndrome, aged 13 to 40 years, either lovastatin or minocycline for eight weeks — first a low dose and then a higher one; roughly half of the participants received lovastatin first, and the other half minocycline first. The team then gave the participants daily doses of both lovastatin and minocycline for 12 weeks.

Mission accomplished:

This 20-week treatment eased the severity of the participants’ traits, including social withdrawal, hyperactivity and inappropriate speech, according to a parent survey.

The findings suggest that the combination of lovastatin and minocycline improves behavior in children with fragile X syndrome.

The researchers also scanned the brains of 11 of the participants for changes in their functional connectivity — the degree of co-occurring activity between pairs of brain regions.

The participants showed a small increase in connectivity between regions in the salience network, which plays a role in directing attention. By contrast, connectivity within the default mode network, which governs self-reflection, decreased with the treatment. Both networks have been shown to be altered in people with fragile X syndrome.

In a subset of 18 participants, the researchers explored whether the drug combination influences the balance between excitatory and inhibitory signals in the brain; the signaling balance is known to be **perturbed in fragile X syndrome**.

“This imbalance is thought to be at the root of several features typical of the syndrome,” says Angélina Lacroix, another graduate student in Lepage’s lab who presented the findings. For example, people with fragile X syndrome often display hyperactivity and experience seizures.

Twitchy signals:

Lacroix and her colleagues used **transcranial magnetic stimulation** over the motor hub of the brain to produce muscle twitches in the hands of the participants. The signals emitted by these twitches serves as an index of excitatory and inhibitory neural circuits.

Before treatment, participants with fragile X showed weakened inhibitory signals and exaggerated excitatory ones compared with those of controls.

Lovastatin and minocycline may mitigate the signaling imbalance in fragile X, the researchers found. The treatment restores the participants’ inhibitory signaling to the level of the controls. However, excess excitatory signaling remained unchanged.

The findings suggest that the duo-drug approach is moving in the right direction for fragile X treatment, Lepage says. But there’s more work to be done: “It’s encouraging results, but that’s not a panacea.”

*For more reports from the 2018 Society for Neuroscience annual meeting, please **click here**.*