NEWS

Antidepressant eases some autism features in mice

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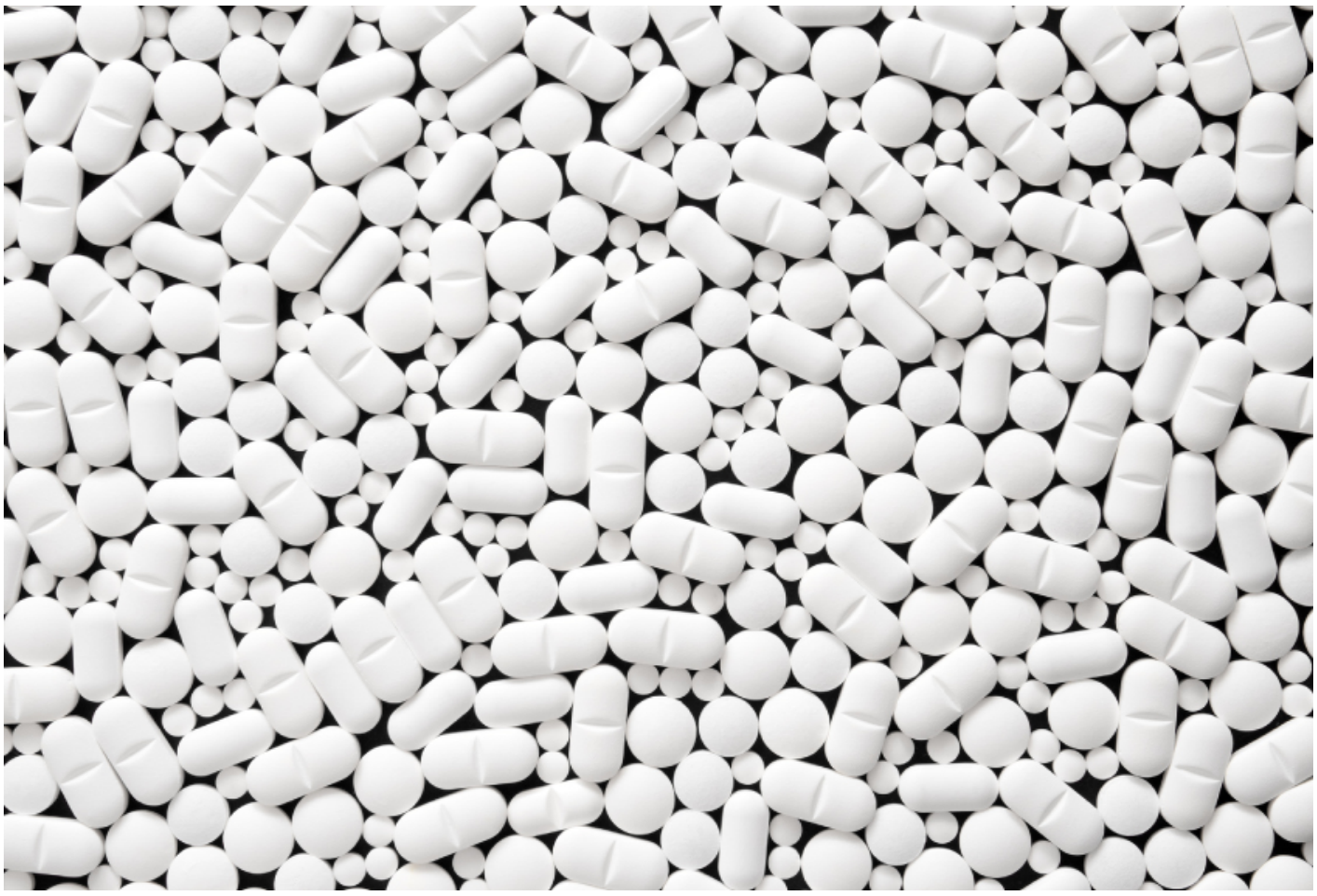

A drug that keeps neurons of newborn mice bathed in the **chemical messenger** serotonin prevents social abnormalities in a mouse model of dup15q syndrome. The findings suggest that low levels of serotonin, which helps regulate mood and sleep, contribute to autism features in the

mice.

Researchers presented the findings yesterday at the **2017 Dup15q Alliance Scientific Meeting** in Los Angeles.

“Our study shows that serotonin is important for developing neurons,” says lead investigator **Toru Takumi**, senior team leader of mental biology at the RIKEN Brain Science Institute in Wako, Japan.

The mutant mice in the study carry an extra copy of a chromosomal region called 15q11-13. About 1 percent of people with autism have duplications of this region. Takumi’s team **debuted the mice** in 2009. Like other mouse models of autism, these mice do not show the usual interest in interacting with a novel mouse.

Serotonin has been implicated in autism for years, but it was unclear whether and how the chemical contributes to features of the condition. Some teams **unsuccessfully tested antidepressants** that boost serotonin levels, such as fluoxetine (commonly marketed as Prozac), as a treatment for autism.

The results, published 21 June in *Science Advances*, hint that drugs that normalize serotonin levels could treat some features of autism[1].

“It is striking that a genetic mouse model shows convergence with long-standing findings pointing to changes in the serotonin system in autism spectrum disorder,” says **Jeremy Veenstra-VanderWeele**, associate professor of psychiatry at Columbia University, who was not involved in the study.

Takumi and others urge caution in interpreting the findings, however. That’s because the mice carry an extra copy of 15q11-13 inherited from their fathers. By contrast, most people with autism who have the duplication inherit the extra copy from their mothers.

“I think that it would be risky to generalize” the findings to people, says **Matthew Anderson**, associate professor of pathology at Harvard University, who was not involved in the work.

Serotonin deficiency:

Takumi and his colleagues reported in 2010 that 1- to 3-week-old dup15q mice have unusually low levels of serotonin in the brain[2].

In the new study, they looked at neuronal activity in the mice. They used positron emission tomography to look for alterations in activity throughout the brains of awake mice.

They found that the mice show reduced activity in the dorsal raphe nucleus, a brain region that is active in the presence of serotonin. Brain slices from the region revealed that neurons sensitive to serotonin are less active in the mutant mice than they are in controls.

The researchers then used a device to vibrate a whisker on the mice. They monitored the activation of neurons in the mice's somatosensory cortex, a brain region that responds to touch and receives signals from the dorsal raphe nucleus. They found that the whisker stimulation activates a larger section of the somatosensory cortex in the dup15q mice than it does in controls.

The team next looked at the balance of brain signals in the somatosensory cortex that excite or dampen neuronal activity. They found that the mutant mice have too few receptors for inhibitory signals. Consistent with this finding, brain slices from the mice show a decrease in the frequency of inhibitory signals, and a corresponding increase in neurons' excitability.

This imbalance is consistent with the theory that the signaling balance is **altered in autism**, Takumi says.

Takumi and his team treated the mothers of newborn pups with fluoxetine, an antidepressant that prevents serotonin uptake into neurons and allows the chemical's effects to last longer. Exposure to the drug for the first three weeks of life — through nursing — normalizes the pups' signaling balance at 5 weeks old.

The treatment also improves the mice's serotonin levels and social behaviors as adults. The mice spend as much time as controls do interacting with a novel mouse.

Takumi says it is unclear how low levels of serotonin in the brain might affect brain signaling. Serotonin has more than a dozen receptors, and the precise functions of many of them are unknown.

*For more reports from the 2017 Dup15q Alliance Scientific Meeting, please **click here**.*

REFERENCES:

1. Nakai N. *et al. Sci. Adv.* **3**, e1603001 (2017) **PubMed**
2. Tamada K. *et al. PLOS One* **5**, e15126 (2010) **PubMed**