

Researchers identify new type of depression

June 11 2018



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Depression is a mental disorder that affects over 300 million people around the world. While treatments exist, many of them are based on one hypothesis of how depression arises. Patients that do not fit this mold may not be getting benefits. A study led by Hiroshima University (HU), which was published online this May in *Neuroscience*, sheds light on how one protein called RGS8 plays a role in depression behaviors.

Scientists think depression occurs because of the monoamine hypothesis,



so named for the type of two chemicals that depressed people lack: serotonin and norepinephrine (NE). Ninety percent of <u>antidepressant</u> <u>drugs</u> are made based on this idea. They aim to recalibrate these two monoamines. For some of these patients, however, it may not be enough.

Thirty percent of people on these drugs do not experience an effect, according to Yumiko Saito and Yuki Kobayashi. Both are neuroscientists in HU's Graduate School of Integrated Arts and Sciences. "Obviously, we need a new <u>drug</u>. We need another explanation for what could cause depression."

This study builds upon previous work in which her team found that RGS8 controls a hormone receptor called MCHR1. Parts of the brain involved with movement and mood regulation show signs of RGS8 expression. MCHR1, when active, helps regulate sleep, feeding and mood responses. The researchers found that RGS8 inactivates MCHR1 in cultured cells.

Thus, the idea is that less RGS8 means increased depressed behavior. However, this effect had never been examined in a living organism. Here Saito's group studied depression in mice in two scopes: at the behavioral level, and at the immunohistological level.

First, the mice did a swim test, which is a common behavioral analysis method to assess depressive behaviors in animals. Researchers measure the time each mouse was active, then subtract it from the total test time, leaving researchers with an immobility time period.

Mice with more RGS8 in their nervous system recorded shorter immobility times than those with a normal amount of RGS8. When given an antidepressant drug that acts on monoamines, though, the RGS8 mice had even shorter immobility times. However, when the mice were given a drug that stops MCHR1 from working, immobility time did not



change.

"These mice showed a new type of <u>depression</u>," Saito says. "Monoamines appeared not to be involved in this depressive behavior. Instead, MCHR1 was."

With that conclusion, the team looked at the mice's brains under the microscope to determine the relationship between MCHR1 and RGS8. More specifically, they examined the size of cilia sprouting from cells in a region of the hippocampus called the CA1, where RGS8 concentration was highest. Cilia are TV antennae-like organelles involved in cellular communication.

The team found that RGS8 mice not only had less depressed behavior than those without extra RGS8, but they also had longer cilia. That is, <u>mice</u> that took the drug that stopped MCHR1 from working had longer cilia.

In the past 10 years, scientists have observed that dysfunctional cilia are associated with disorders like obesity, kidney disease and retinal disease. Not much is known about their relationship with mood disorders. These findings led Saito's group to think that RGS8 is a promising candidate toward the development of new antidepressant drugs, which is a focus for future experiments.

More information: Yuki Kobayashi et al. Depression-resistant Phenotype in Mice Overexpressing Regulator of G Protein Signaling 8 (RGS8), *Neuroscience* (2018). DOI: 10.1016/j.neuroscience.2018.05.005

Provided by Hiroshima University



Citation: Researchers identify new type of depression (2018, June 11) retrieved 5 May 2024 from <u>https://medicalxpress.com/news/2018-06-depression_1.html</u>

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