New target for antidepressants revealed in animal study

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University of Michigan scientists have provided the most detailed picture yet of a key receptor in the brain that influences the effectiveness of serotonin-related antidepressants, such as Prozac.

The findings, which appear online Monday ahead of print in the journal Proceedings of the National Academy of Sciences, open the door to providing a more targeted treatment of depression and anxiety with fewer side effects.

Depressive disorders change a person's mood, emotions and physical well-being and can co-occur with anxiety disorders and substance abuse.

"There are big drawbacks in the current therapies for depression," says senior author John Traynor, Ph.D., professor of pharmacology at the U-M Medical School and director of the U-M Substance Abuse Research Center. "Therapeutic benefits are delayed, there are unwanted side effects, and it's not unusual for depressive symptoms to return."

Authors say the high relapse rate indicates a need for additional treatment options for the estimated 20.9 million Americans with depression.

The best current treatments for depression are selective serotonin reuptake inhibitors, or SSRIs. These drugs work by flooding the brain's synapses with serotonin, a neurotransmitter linked with mood, and increasing signaling through the more than 20 serotonin receptors in the brain.

However the team of researchers showed that one particular pathway, the serotonin 5HT1a receptor is linked with antidepressive and antianxiety behavior in mice.

"Rather than activating all serotonin receptors as SSRIs do, one could increase signaling through the one critical serotonin receptor that our research shows is important for anti-depressant behavior," says co-author Richard R. Neubig, M.D., Ph.D., co-director of the U-M Center for Chemical Genomics and professor of pharmacology at the U-M Medical School.

The new research details the complex actions of a family of proteins, known as RGS proteins, that act as brakes on neurotransmitter signaling.

Researchers created a mutant mouse to boost serotonin signaling at the 5HT1a receptor. This was done by genetically inhibiting the activity of braking proteins. Without the normal brake on serotonin signaling, these mutant mice showed antidepressive behavior even without being given antidepressant drugs. The mice were also more responsive to SSRIs.

Authors say that further research could lead to drugs capable of inhibiting the RGS proteins and which would target the antidepressant signal where it is required on critical 5HT1a receptors.

More information: Proceedings of the National Academy of Sciences, "RGS inhibition at Gai2 selectively potentiates 5-HT1A-mediated antidepressant effects," doi 10.1073/pnas.1000003107

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