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Surplus of serotonin receptors may explain failure of antidepressants in some patients

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An excess of one type of serotonin receptor in the center of the brain may explain why antidepressants fail to relieve symptoms of depression for 50 percent of patients, a new study from researchers at Columbia University Medical Center shows.

The study is the first to find a causal link between receptor number and antidepressant treatment and may lead to more personalized treatment for depression, including treatments for patients who do not respond to antidepressants and ways to identify these patients before they undergo costly, and ultimately, futile therapies.

The research, led by Rene Hen, PhD, professor of pharmacology in the Departments of Psychiatry and Neuroscience at Columbia University, and a researcher the New York State Psychiatric Institute, appears in the January 15 issue of the journal *Neuron*.

Most antidepressants - including the popular SSRIs - work by increasing the amount of serotonin made by cells -- called raphe neurons -- deep in the middle of the brain. Serotonin relieves symptoms of depression when it is shipped to other brain regions.

But too many serotonin receptors of the 1A type on the raphe neurons sets up a negative feedback loop that reduces the production of serotonin, Dr. Hen and his colleagues discovered

"The more antidepressants try to increase serotonin production, the less

serotonin the neurons actually produce, and behavior in mice does not change," Dr. Hen says.

Dr. Hen and his colleagues measured the effect of antidepressants with a commonly used behavioral test that measures the boldness in mice when retrieving food from bright open areas. Mice on antidepressants usually become more daring, but the drugs had no such effect on mice with surplus serotonin receptors.

Recent genetic and imaging studies of depressed patients have suggested that high receptor numbers of the 1A type in the raphe neurons are associated with treatment failure. Until now, no direct test of the association could be performed because the number of receptors in the raphe neurons could not be altered without changing the number of receptors in other parts of the brain.

Using new techniques in genetic engineering, Dr. Hen created a strain of mouse that can be programmed to produce high or low levels of serotonin receptors of the 1A type only in the raphe neuron. The levels present in the mice mimicked the levels found in people who are resistant to antidepressant treatment.

"By simply tweaking the number of receptors down, we were able to transform a non-responder into a responder," Dr. Hen adds.

That strategy also may work for patients resistant to antidepressant treatment, Dr. Hen says, if drugs can be found to reduce the number of receptors or impede their activity.

But first the role of surplus serotonin receptors in people must be confirmed. Dr. Hen's lab is now looking at patients enrolled in clinical trials to see if receptor levels predict response to antidepressants.

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Provided by Columbia University Medical Center

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