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## **Why antidepressants don't work for so many**

### ***Northwestern research finds drugs aim at wrong target***

CHICAGO --- More than half the people who take antidepressants for depression never get relief.

Why? Because the cause of depression has been oversimplified and drugs designed to treat it aim at the wrong target, according to new research from the Northwestern University Feinberg School of Medicine. The medications are like arrows shot at the outer rings of a bull's eye instead of the center.

A study from the laboratory of long-time depression researcher Eva Redei, presented at the Neuroscience 2009 conference in Chicago this week, appears to topple two strongly held beliefs about depression. One is that stressful life events are a major cause of depression. The other is that an imbalance in neurotransmitters in the brain triggers depressive symptoms.

Both findings are significant because these beliefs were the basis for developing drugs currently used to treat depression.

Redei, the David Lawrence Stein Professor of Psychiatry at Northwestern's Feinberg School, found powerful molecular evidence that quashes the long-held dogma that stress is generally a major cause of depression. Her new research reveals that there is almost no overlap between stress-related genes and depression-related genes.

"This is a huge study and statistically powerful," Redei said. "This research opens up new routes to develop new antidepressants that may be more effective. There hasn't been an antidepressant based on a novel concept in 20 years."

Her findings are based on extensive studies with a model of severely depressed rats that mirror many behavioral and physiological abnormalities found in patients with major depression. The rats, after decades of development, are believed to be the most depressed in the world.

### **Little Overlap Between Stress and Depression Genes**

Redei used microarray technology to isolate and identify the specific genes related to depression in these animals. She examined the genes in the brain regions -- the hippocampus and amygdala -- commonly associated with depression in rats and humans.

Then she took four genetically different strains of rats and exposed them to chronic stress for two weeks. Afterwards, she identified the genes that had consistently increased or decreased in response to the stress in all four strains in the same brain regions.

Redei now had one set of depression-related genes that came out of an animal model of depression and one set of stress-related genes that came out of her chronic stress study.

Next she compared the two sets of genes to see if there were any similarities. "If the 'stress causes depression theory' was correct, there should have been a significant overlap between these two sets of genes," she said. "There weren't."

Out of a total of over 30,000 genes on the microarray, she discovered approximately 254 genes related to stress and 1275 genes related to depression, with an overlap of only five genes between the two.

"This overlap is insignificant, a very small percentage," Redei said. "This finding is clear evidence that at least in an animal model, chronic stress does not cause the same molecular changes as depression does."

### **Antidepressants Treat Stress Not Depression**

Most animal models that are used by scientists to test antidepressants are based on the hypothesis that stress causes depression. "They stress the animals and look at their behavior," she said. "Then they manipulate the animals' behavior with drugs and say, 'OK, these are going to be good anti-depressants.' But they are not treating depression; they are treating stress."

That is one key reason why current antidepressants aren't doing a great job, Redei noted. She is now looking at the genes that differ in the depressed rat to narrow down targets for drug development.

She said another reason current antidepressants are often ineffective is that they aim to boost neurotransmitters based on the popular molecular explanation of depression, which is that it's the result of decreased levels of the neurotransmitters serotonin, norepinephrine and dopamine. But that's wrong, Redei said.

#### Drugs Aim at Wrong Molecular Target

In the second part of the study, Redei found strong indications that depression actually begins further up in the chain of events in the brain. The biochemical events that ultimately result in depression actually start in the development and functioning of neurons.

"The medications have been focusing on the effect, not the cause," she said. "That's why it takes so long for them to work and why they aren't effective for so many people."

Her animal model of depression did not show dramatic differences in the levels of genes controlling neurotransmitter functions. "If depression was related to neurotransmitter activity, we would have seen that," she said.

#### **Similarities Between Human and Rodent Brains**

Her findings in depressed rats, she said, are very likely applicable to humans.

"The similarities between these regions of the human and rodent brain are remarkable," Redei explained. "The hippocampus and amygdala are part of the so-called ancient lizard brain that controls survival and are the same in even primitive organisms."

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Contributors to the study from Redei's lab include Brian Andrus, Kristen Dennis and Daniel Schaffer, research assistants, and Pradeep Shukla, a postdoctoral fellow. Jelena Radulovic, M.D., Dunbar Scholar and associate professor in psychiatry and behavioral sciences at the Feinberg School, also contributed as did Peter Vedell, a postdoctoral associate in professor Gary Churchill's group at The Jackson Lab, Bar Harbor.

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