Researchers Find Brain Pathway of Depression in Rats

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Scientists' hunt for the cause of depression has implicated so many suspects and found so many treatments with different mechanisms that the condition remains an enigma. Now researchers at the Stanford University School of Medicine have identified one unifying principle that could explain how a range of causes and treatments for depression converge.

They found that in rats the differing mechanisms of depression and its treatment in the end appear to funnel through a single brain circuit. Changes in how the electrical signals spread through the circuit appear to be the cause of depression-related behavior, according to their study. Their findings will be published July 6 in *Science Express*, the advance online publication of the journal *Science*.

"I think this will help us make sense of how there can be so many different causes and treatments of depression," said senior author Karl Deisseroth, MD, PhD, assistant professor of bioengineering and of psychiatry and behavioral sciences. "It also helps us understand conceptually how something that seems as hard to get traction on as depression can have a really quantitative, concrete basis."

The work also may have implications for the search for new treatments for depression. "You can use that common pathway as the most efficient, most direct targeted way to find truly specific treatments," he said.

Deisseroth, who sees many depressed patients in clinic, said he has come to appreciate how the bumps in the road that most people see as normal obstacles in life become insurmountable hurdles to depressed people, causing them to lapse into helplessness.

Reasoning that the brain is essentially a complex electrical circuit, Deisseroth's team set out to test the theory of whether brain circuitry malfunction could be at the root of depression. To explore the idea in a precise, quantitative way, they needed to develop a visualization tool that was faster and sharper than brain imaging systems currently available, such as MRI or CT scans.

Raag Airan, an MD/PhD student in Deisseroth's lab and co-first author of the study, led the development of a technique called voltage-sensitive dye imaging for this model. This technique allows intact brain circuits to be viewed in real time, enabling the researchers to watch living neurons in action, across entire brain networks.

The system uses a fluorescent dye, sensitive to brain circuit activity, which the researchers introduce into the animal brain tissue. As dyed circuits light up and darken again in response to electrical activity, very fast high-resolution cameras capture the action. The researchers can observe how different stimuli received by the animal, such as a dose of an antidepressant drug, affect circuit operation.

The researchers used slices of rat brain, Deisseroth said, "like a computer repair technician would take out a circuit board" to test its functional properties. The brain slices, which remain active for many hours, came from parts of the hippocampus, a region long implicated in depression. They also tested slices from rats treated with the antidepressant medications fluoxetine and imipramine.

The team carried out the study using a standard rat model of depression.

Even though the rats do not mimic the entire complexity of genetic and environmental causes of human depression, Deisseroth explained, the animals exhibit similar symptoms and also get better from the same medications that work on humans.

In these rats, they found an alteration in electrical activity flow through the brain that could be corrected by human antidepressants. The extent that the signal spread through the brain sample was diminished in the "depressed" rats, a crucial finding that would not be apparent with other experimental methods, Deisseroth said. They needed to be able to image a whole circuit simultaneously - and very rapidly - to see the effect.

"What surprised me most was how specifically the measure tracked the depression-related behavior," said Airan. "We usually think of psychiatric disorders as fuzzy and intractable, and this study showed me that, with the right tools, we could really put psychiatry on a quantitative framework."

Leslie Meltzer, neurosciences graduate student and co-first author, searched for the cellular basis of these changes in circuitry. An obvious place to start, she said, was to look at the formation of new neurons in the hippocampus, a process that neuroscientists have suggested is at the root of how antidepressants work. What they found was that the growth of new neurons could account for the behavioral improvements seen from treatment as well as the circuitry changes. The converse was not true: Fewer new neurons in that region did not equal depression.

In other words, in their model system, the two states appear to funnel through a common pathway - despite very different cellular mechanisms.

"The holy grail of psychiatry is to try to find final common pathways that can make sense of how genes and life experiences end up with the same result," said Deisseroth. "And the same goes for medications.

There are many treatments that act in fundamentally different ways - how do we make sense of all that complexity""

Deisseroth predicted that, as noninvasive imaging of human brains gets better in the next few years, researchers will be able to measure these same quantitative measures in people as well. "That will be a wonderful thing when that happens," he said.

Source: Stanford University Medical Center