Researchers identify key brain cell in antidepressant action

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(Medical Xpress) -- Antidepressant medications such as Prozac have helped improve mood and lessen anxiety in millions of people with major depression. But scientists know surprisingly little about how these drugs work.

Now researchers have discovered that a specific type of cell in the outer layers of the brain is crucial for Prozac's action. The study, a collaboration led by Howard Hughes Medical Institute (HHMI) investigator Nathaniel Heintz and Paul Greengard, both at Rockefeller University, is the first demonstration that genetic profiling of specific neural cell types can lead to new insights into the cause of brain disease. The study is published in the May 25, 2012, issue of the journal *Cell*.

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“There may be many different cell types whose activity you can alter to have a beneficial impact in depression, and this is one of them," says Heintz. More broadly, he says, "it's proof-of-concept that this approach can give you tremendous information about both the causes of disease and strategies for treatment."

Brain scanning studies over the past decade or so have revealed abnormal patterns of neural activity in people with major depression. More specifically, electrical activity in the front of the brain, which is

responsible for reasoning and attention, seems to be out of balance with activity in deeper regions involved in regulating emotions in those individuals.

After many months of use, antidepressants called selective serotonin reuptake inhibitors, or SSRIs, can gradually balance out those brain signals. These drugs increase the amount of serotonin, a chemical messenger, outside of cells. But low serotonin doesn't cause depression, and no one knows why increasing the chemical leads to positive effects.

"These SSRIs increase serotonin in many places in the brain," Heintz says. "So the question is, how do they have such a strong clinical impact on one particular aspect of behavior?"

The answer, according to two decades of work in Heintz's lab, lies in the remarkable diversity of cells in the brains of humans and other mammals. According to classical studies and his team’s findings, he estimates that there are roughly 500 cell types, from the classic pyramidal neurons that fire off electrical impulses, to inhibitory interneurons that block these signals, to microglia that trigger an immune response during injury or infection. Each cell type may respond differently to specific genetic mutations, environmental exposures, and drugs.

"Some cells deal with a specific situation just fine, they adjust and compensate and their function is normal," Heintz says. "But some cell types can't do that, and as a result, they cause disruptions in a circuit."

The first step in sorting out these cell-specific pathways is cataloging all of the various kinds of cells. Until recently, researchers could only do that by growing isolated cells in culture, outside of the animal. Heintz and his colleagues developed an alternative technique, called TRAP, or translating ribosome affinity purification, which they described in

articles published in collaboration with Paul Greengard's laboratory in 2008, also in Cell. TRAP works by capturing all of the proteins expressed by a particular cell when it's still in a live animal, nestled in its natural environment in the presence of many other types of cells. So far, Heintz's team has used the molecular profiles revealed by TRAP to characterize about 120 different types of cells in the nervous system.

In the new study, the researchers focused on a particular cell that's found in an outer layer of the brain's cortex and produces a protein called p11, which binds to serotonin receptors. Mice lacking p11 are lethargic and anxious, similar to people with depression, and do not respond to antidepressant drugs. What's more, postmortem studies have found that suicide victims have decreased levels of p11 in the outer layers of their brains.

Eric Schmidt, a postdoctoral fellow in Heintz's lab, first used fluorescent tags to trace the projections of these p11-producing cells in the mouse brain. He found that the projections go from the cerebral cortex down into the striatum, a deep region. This suggested that these cells were plausible candidates for influencing the signaling imbalance in those areas that's been linked to depression.

When Schmidt exposed these cells to an SSRI called fluoxetine (better known as Prozac), they responded by drastically increasing their production of a protein called HTR4, which is a serotonin receptor. In other words, once the cells sense a surge in serotonin, they adjust so that they can be even more sensitive to the chemical.

Intriguingly, drugs that activate HTR4 already exist and are known to have antidepressant effects. Unfortunately, because many other cells throughout the body also express this receptor, the drugs are quite toxic. "So now the search is on for other molecules that are expressed in this same cell type whose activity could be targeted as an alternative

treatment," Heintz says.

This kind of cell-by-cell analysis will be useful beyond the study of depression, Heintz says, noting that Envoy Therapeutics, a biotechnology company he co-founded, is using TRAP to hunt for new treatments for Parkinson's disease, schizophrenia, and addiction. "We feel that you can't make real progress without targeting individual cell types," Heintz says. "This study is just the tip of the iceberg."

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