Depressed mice could aid research on drug-resistant depression in humans

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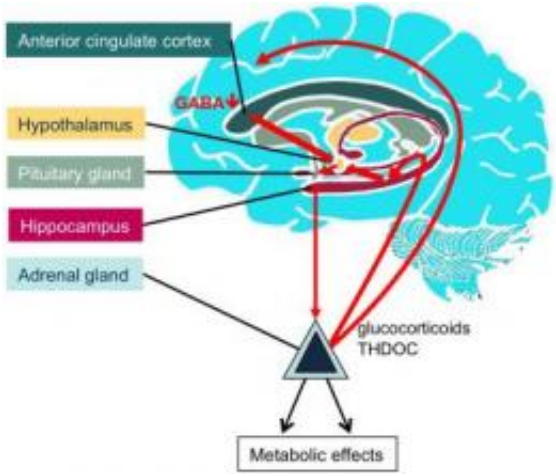

This illustration shows the interaction between the brain's HPA axis (hypothalamus, pituitary, and adrenal glands) and GABAergic deficits of the hippocampus and cortex, which underlie the pathology of major depressive disorder. Credit: Bernhard Luscher, Penn State University

New research shows that a unique strain of laboratory mice characterized at Penn State University has behavioral, hormonal, and neurochemical characteristics that are similar to those of human patients with drug-resistant forms of depression. The mice -- which have a defect in a gene -- are expected to be useful as a new model organism in the effort to develop more effective medications for specific forms of depression. The research, led by Bernhard Luscher, a professor of biology at Penn State, will be published in the journal *Biological*

Psychiatry.

"A mouse can't tell us if it is feeling depressed, so we used a number of different kinds of tests -- including some new ones that we developed -- to gauge behavioral and hormonal changes, or phenotypes, of a type of depression that, in humans, does not respond well to some antidepressant drugs," Luscher said. "These indicators include reduced exploration of novel or otherwise aversive environments, failure to escape from a highly stressful situation, and reduced pleasure-seeking behavior such as a reduced preference for sweet over plain water."

The genetic defect in the depressed mice interferes with the function of a protein in the brain called the GABA-A receptor, which controls the response to the neurotransmitter gamma-aminobutryic acid. Reduced function of these receptors has been known to be be involved in anxiety disorders -- but not in depression -- because currently available drugs that activate the GABA-A receptor are ineffective as antidepressants. "We have shown in this paper that this long-held conviction is flawed," Luscher said. "Our research shows that the GABA-A receptor is, in fact, an important part of the brain circuitry that is not working properly in depression."

The genetically defective, GABA-A-receptor-deficient mice in Luscher's lab previously had been shown to be a good model organism for studies of anxiety, which often occurs along with depression. "About 70 percent of people who are treated for depression also are treated for anxiety at some time during their lives, and the drugs that are used in people as antidepressants act not only to reduce depression but also to reduce anxiety," Luscher said. "These facts suggests that whatever mechanism is defective in the brain is similar in both anxiety and depression."

One of the interesting results of Luscher's new research is that some

antidepressant drugs completely reverse the behavioral and hormonal symptoms of depression in the GABA-A-receptor-deficient mice, bringing their behavior to the level of normal, "wild-type" mice. At the same time, the normal mice had almost no reaction to the drugs. "This result is expected of a mouse model that mimics depression because normal people do not seem to gain anything from taking antidepressants," Luscher explained. These experiments show that this strain of genetically defective mice is a useful animal model for laboratory studies that could be useful for understanding human depression.

One of the major gaps of knowledge about depression in humans is that scientists do not know why some antidepressant drugs fail to help about 30 percent of depressed patients. Because doctors don't have a way of knowing which drug has the best chance of working for a particular patient, they resort to trying one after another hoping to find one that will work. This problem is compounded by the fact that it can take weeks before the drugs show any measurable benefit.

Vincent van Gogh's painting,"On the Threshold of Eternity," often is used to illustrate the despair that those suffering from major depressive disorder

experience. Credit: Wikimedia Commons

Luscher's team tested two kinds of antidepressant drugs in the mice and found that one of the drugs reduced symptoms of anxiety, but not of depression, whereas the other drug reduced both anxiety and depression symptoms. "The one that did not normalize depression-related behaviors is fluoxetine -- the generic name for Prozac -- which works on the neurotransmitter serotonin," Luscher said. The drug that reduced both depression and anxiety symptoms in the mice is desipramine, which works on a different neurotransmitter, noradrenaline. These results are interesting because there is a large group of depressed patients that do not respond well to Prozac. "In human patients with a type of depression called melancholic depression, fluoxetine/Prozac doesn't work as an antidepressant but desipramine does work. These mice are a bit like those patients who don't respond to Prozac," Luscher said.

Patients who don't respond to Prozac have increased serum levels of the hormone cortisol, which in mice is called corticosterone. "Our mice also showed abnormal corticosterone levels analogous to those patients who don't respond to Prozac," Luscher said. "In people, the cortisol level is corrected by drugs such as desipramine, and so it is in our mice. Desipramine corrects corticosterone levels in our mice but fluoxetine does not."

Luscher's paper also describes how he has begun to use this mouse model of drug-resistant depression to learn about the role of developmental factors in the onset of depression. His research suggests that the hormonal defect alone is not sufficient to produce the behavioral symptoms of depression, at least not if the hormonal abnormality is present only in adulthood. "Some research indicates that if you are born with certain types of risk factors, and something highly stressful happens

in your life, such as a war experience -- then that event can trigger a mood disorder if you already have a risk factor," Luscher said.

"One of the many things we now want to explore is whether a slightly different strain of GABA-A-receptor-deficient mice, which are behaviorally normal but have increased levels of stress hormones, are at risk of developing depression if they experience additional excessive stress," Luscher said. "We also want to understand in greater detail what happens in these mice biochemically -- to understand which genes throughout the entire genome are affected by the defect in this one gene, and the resulting depression-like brain state."

Provided by Pennsylvania State University