Scientists identify potential target for treating anhedonia - major symptom of depression

July 11 2012

Stanford University School of Medicine scientists have laid bare a novel molecular mechanism responsible for the most important symptom of major depression: anhedonia, the loss of the ability to experience pleasure. While their study was conducted in mice, the brain circuit involved in this newly elucidated pathway is largely identical between rodents and humans, upping the odds that the findings point toward new therapies for depression and other disorders.

Additionally, opinion leaders hailed the study's inventive methodology, saying it may offer a much sounder approach to testing new antidepressants than the methods now routinely used by drug developers.

While as many as one in six Americans is likely to suffer a major depression in their lifetimes, current medications either are inadequate or eventually stop working in as many as 50 percent of those for whom they're prescribed.

"This may be because all current medications for depression work via the same mechanisms," said Robert Malenka, MD, PhD, the Nancy Friend Pritzker Professor in Psychiatry and Behavioral Sciences. "They increase levels of one or another of two small molecules that some nerve cells in the brain use to signal one another. To get better treatments, there's a great need to understand in greater detail the brain biology that underlies depression's symptoms." The study's first author is Byung

Kook Lim, PhD, a postdoctoral scholar in Malenka's laboratory.

Malenka is senior author of the new study, to be published July 12 in *Nature*, which reveals a novel drug target by showing how a hormone known to affect appetite turns off the brain's ability to experience pleasure when an animal is stressed. This hormone, melanocortin, signals to an ancient and almost universal apparatus deep in the brain called the reward circuit, which has evolved to guide animals toward resources, behaviors and environments — such as food, sex and warmth — that enhance their prospects for survival.

"This is the first study to suggest that we should look at the role of melanocortin in depression-related syndromes," said Eric Nestler, MD, PhD, professor and chair of neuroscience and director of the Friedman Brain Institute at Mount Sinai School of Medicine in New York. Nestler was not involved in the study but is familiar with its contents.

The specific causes of depression are not well understood. There is no laboratory test for depression — the diagnosis is based mainly on patients' own reports of lethargy, despondency, despair and disturbances of appetite and sleep — but a core symptom is anhedonia, also known as the blues.

In their search for new compounds to combat depression, however, drug developers typically have used tests of mouse behaviors that may not truly reflect this key feature of depression — and may also limit the search for effective drugs. "Not all animal models are created equal," said Malenka.

In this study, Malenka and his colleagues instead tested a mouse's ability to experience enjoyment. In another departure from more common practice in studies of depression, the scientists conducted their behavioral measurements after exposing the mice to chronic stress —

the kind that we humans experience all too often — rather than simply placing otherwise happy, normal mice in a single stressful situation.

"Depression in people often involves chronic stress," commented Nestler. "Tossing a person in a swimming pool and telling him to swim doesn't induce despair."

Yet it is precisely tests of this type that have been primarily used in the pharmaceutical industry's hunts for new antidepressants. Common animal assays of depression involve placing normal animals in stressful conditions and then measuring observable outcomes. One example is the "forced swim" test: throwing a rodent into water and measuring how long it takes for the animal to give up trying to swim — an outcome assumed to indicate "behavioral despair."

This assumption is a red herring because it imputes a state of mind, despair, to rats and mice who not only can't talk about their feelings but who may not experience anything remotely like what we mean by the word despair, said Steven Hyman, MD, director of the Stanley Center for Psychiatric Research at the Broad Institute of MIT and Harvard and the former provost of Harvard University. "Who interviewed the mouse? Maybe it stopped swimming to conserve energy."

In 2010, Hyman (who, like Nestler, has seen Malenka's study but played no role in it) and Nestler co-authored a widely acknowledged review in Nature Neuroscience criticizing the way animal assays are used in neuropsychiatric drug development. "Unfortunately, widely used behavioral tests [such as the forced-swim test] are not models of depression at all. Instead, they are rapid, black box tests developed decades ago to screen compounds for antidepressant activity," wrote Nestler and Hyman in their review article.

Moreover, Nestler and Hyman wrote, although a single dose of many

currently used antidepressants can prolong the period during which an animal continues to struggle, single doses of these drugs are never effective in people. To relieve actual cases of human depression, they must be administered for weeks or months.

Assays such as the forced-swim test are relatively fast and cheap. But, said Hyman, they may be inadvertently screening out compounds that could be effective in restoring a depressed person's ability to experience pleasure even though they don't prolong an animal's struggle in response to a dunking.

Tests that directly measure an experimental animal's interest in pleasure-seeking appear to more faithfully reflect a true symptom of human depression, Nestler and Hyman said. One example is the so-called sucrose-preference test. If you give mice a choice between water and water containing dissolved sugar, they usually go for the sugar water. Chronically stressed mice lose that preference, just as people suffering depression induced by life's chronic stresses lose the joy of good food, sex, physical comfort and the like.

Malenka's team decided to use chronically stressed mice to explore the activity of a naturally occurring molecule, melanocortin.

"A few scattered studies had suggested that chronic stress increased melanocortin levels in the brain," he said. "And it was known that stressed animals have heightened numbers of receptors for melanocortin in the nucleus accumbens," a key region of the reward circuit. If this all-important circuit is working properly, it doles out pleasure when an animal achieves a desirable goal or experiences rewarding stimuli, such as food or sex. If it's not working properly, anhedonia is the result.

But it wasn't yet known, Malenka continued, whether melanocortin actually affected the nucleus accumbens or how. "We wanted to find out,

because we were wondering if by modulating melanocortin's activity with a drug we could relieve or prevent a major symptom of depression."

Malenka's team subjected mice to chronic stress by confining them, for three to four hours a day, in small conical tubes with holes in them for air flow over a period of eight days. This stressful confinement clearly reduced the mice's preference for sugar water over plain water. (The animals also lost about 5-10 percent of their body weight, a frequent depression symptom.)

Rather than simply noting the altered sugar-preference behaviors in the stressed mice, the investigators used electrophysiological, biochemical and gene-transferring techniques to manipulate and, ultimately, to delineate the precise brain circuitry involved in the stress-elicited behavioral changes right down to the molecular level.

For example, the researchers scrutinized the nerve cells in the nucleus accumbens that contain receptors for melanocortin. Those nerve cells receive signals from a melanocortin-secreting nerve tract that impinges on them. The scientists found that both chronic stress and the direct administration of melanocortin diminished the signaling strength of some of the tiny electrochemical contacts, known as synapses, on a set of nerve cells in the nucleus accumbens that contain receptors for melanocortin. When these receptors were removed using a sophisticated laboratory trick, the same stressful confinement no longer caused changes in those nerve cells' synapses. Simultaneously, despite the weeklong stressful experience, the mice's sugar preference was returned to normal. Plus, the animals no longer lost weight.

To test whether preventing these stress-elicited biochemical changes in the brain also reduced the effects of stress on the mice's behavioral response to things besides food and sugar water, the research team substituted cocaine for sugar. They got the same constellation of results

with cocaine as they had in their earlier experimentation — further strong evidence that the chronic-stress-induced changes in the brain due to melanocortin action cause an animal to lose its ability to experience pleasure.

Importantly, Malenka and his associates also demonstrated that the brain circuit transmitting melanocortin's morose message to the reward circuitry operates independently of the circuitry responsible for making a mouse give up the ghost when the game gets too tough. Manipulating the melanocortin-associated pathway in the nucleus accumbens had no effect on the mice's performance in the forced-swim test. The stressed mice gave up just as easily when the melanocortin receptors in their nucleus accumbens were depleted as when they weren't.

By looking at the circuits and mechanisms underlying anhedonia, Malenka and his associates thus avoided a pitfall of research on mental diseases, said Hyman. "This study shows how animal research ought to be done," he said.

The melanocortin pathway is already of interest to drug companies, Malenka said, because it appears to be involved in appetite disorders. So companies already have melanocortin mimics and inhibitors at their disposal that could be used in clinical tests to determine whether managing patients' melanocortin signaling relieves anhedonia. This could have implications beyond treatments for depression because anhedonia manifests in other neuropsychiatric syndromes, such as schizophrenia, as well as in terminally ill people who have given up hope.

Provided by Stanford University Medical Center