New brain-chemistry differences found in depressed women

November 6 2006

A new brain study finds major differences between women with serious depression and healthy women in a brain-chemical system that's crucial to stress and emotions.

The study adds further evidence that depression has its roots in specific alterations within the brain -- specifically in the endogenous opioid system that is a central part of the brain's natural pain and stress-reduction system. The findings also show significant variation between individuals with depression – variation that seems to be linked to whether or not the patients respond to an antidepressant medication.

The study, performed by researchers at the University of Michigan Medical School affiliated with the U-M Depression Center, is published in the November issue of the Archives of General Psychiatry. It's based on brain imaging, blood chemistry and other data from 14 women with major depression, and 14 healthy women of about the same age and background. The women with depression were not taking antidepressants when the study began.

"This work gives further evidence of individual differences in brain mechanisms that are altered in major depression," says senior author Jon-Kar Zubieta, M.D., Ph.D., the Jenkins Research Professor of Depression and associate professor of psychiatry and radiology. "We found these differences in the response of the endogenous opioid system. Some women, but not others, with major depression, showed exaggerated responses in this system when undergoing an emotional challenge."

That emotional challenge was the summoning of memories of a very sad event in their lives, which the researchers asked the women to recall while they were lying in the positron emission tomography (PET) scanner having their brains imaged. The women recalled the death or serious illness of a friend or family member, a past divorce or breakup with a boyfriend, or other major difficulties. They also had their brains imaged during a neutral emotional state.

Just before the brain scans, the women also had their blood tested to measure levels of two hormones that are released in response to stress. The depressed women were then prescribed an antidepressant drug and reported regularly about their depression symptoms for the next ten weeks. Those whose depression hadn't eased by the end of the first month received a prescription for an increased dose of antidepressant.

"Women who had more pronounced responses in their stress response mechanisms during brain imaging also showed alterations in hormones, like cortisol, that are sometimes over-secreted in depression," Zubieta explains. "In addition, these women responded poorly to treatment with medication."

The research builds on previous studies that found differences in the body's and brain's stress-response system among people with depression. But this is the first time that specific differences in the mu-opioid system have been shown between people with depression and those without.

Zubieta performed the work with former doctoral student, Susan Kennedy, Ph.D., who is first author on the new paper. They used a brain-imaging technique that the U-M team has previously used to see how the brain responds to pain – and to placebo pain treatment.

The technique uses a form of a drug called carfentanil, which binds to

the same receptors on the surface of brain cells that brain chemicals called mu-opioids bind to. Mu-opioids, sometimes also called endorphins, reduce or block the spread of messages related to pain, stress and emotional distress between the body and the brain. They have been called the body's "natural painkillers." The drug is modified to allow it to be "seen" by the PET scanner, so that the researchers can create maps of the specific brain areas where the natural mu-opioids are more or less active at any given time.

In the new study, the researchers also found that the mu-opioid system was overactive in women with depression, even at baseline, when they weren't being asked to recall sad memories.

During the "sadness challenge", the non-depressed women did not show any activation of their mu-opioid system, but the depressed women had a significant activation of that system, and the level of that activation correlated with the intensity of their negative emotional state brought on by the sad memories. Among the non-depressed women, the mu-opioid system was actually less active in some parts of the brain than it had been before they recalled sad memories.

The researchers found differences among the depressed women, too, in some areas of the brain. In the rostral anterior cingulate, which is involved in mood regulation and the integration of sensations and emotions, women who later responded to antidepressant treatment had far lower mu-opioid responses than women who did not respond to medication.

The new findings add the mu-opioid system to the list of brain systems that appear to be altered in depression. Others include the corticotrophin-releasing hormone system, and those involved in noradrenaline, dopamine and serotonin production.

"Further research on these differences, and their relationship to patients' responses to various depression treatments, is crucial to the continued improvement in the understanding of depression and the development of better treatment strategies for patients," Zubieta says.

Source: University of Michigan