MedicalXpress

# Research identifies gene with likely role in premenstrual disorder

February 9 2010

Scientists have identified a gene they say is a strong candidate for involvement in premenstrual dysphoric disorder (PMDD) and other maladies associated with the natural flux in hormones during the menstrual cycle. In a paper published Monday in the *Proceedings of the National Academy of Sciences*, Rockefeller University researchers detail experiments in mice showing that a common human variant of the gene increases anxiety, dampens curiosity and tweaks the effects of estrogen on the brain, impairing memory. If applied in the clinic, the work could help diagnose and treat cognitive and mood disorders related to the menstrual cycle and inform treatments during menopause, such as hormone replacement therapy, researchers say.

The experiments homed in on the gene for a protein that, among other things, works with estrogen to enhance the adaptability of neurons in the hippocampus, a brain region that plays a key role in mood, cognition and memory. A change in one amino acid in this gene, called brain-derived neurotrophic factor (BDNF), creates the variant BDNF Met, which is carried by 20 to 30 percent of Caucasian women. Past research showed that it is a risk factor for psychiatric problems such as depression and bipolar disorder and is generally associated with higher anxiety and impaired memory. The Rockefeller scientists and their colleagues at Weill Cornell Medical College now show that the performance of memory tasks by mice with both the variant and the regular gene depends on where they are in their estrous cycles. It is the first time that a genotype has been shown to interact with a hormone cycle to influence a cognitive behavior, one reviewer of the paper wrote. The researchers

also show that mice with the variant gene are more skittish-— they spent much less time in the vulnerable center of a well-lit cage before scurrying to a corner. As a result, they spent less time exploring objects placed in their cage.

"Even though the BDNF Met mice spent less time exploring these objects, they still showed the basic curiosity that all mice show for novel things in their environment," says first author Joanna Spencer, a student in the Tri-Institutional M.D.-Ph.D. Program run by Rockefeller, Weill Cornell and Memorial Sloan-Kettering Cancer Center.

The research compared the performance of mice with the regular BDNF gene and those with BDNF Met on two main tasks, one that challenged them to remember where an object was placed in the cage and another that challenged them to recognize the difference between similar objects placed in the cage five minutes and 30 minutes apart (a real sake cup followed by one built of Legos, for instance, or a small pill bottle and a similar sized bottle of nail polish.) The BDNF Met mice were significantly worse at both tasks, and aptitude for the object-placement test depended on the stage of each mouse's estrous cycle.

When the researchers examined the hippocampus in the mice for clues about the anatomy underlying these differences, they found that the variant gene overall produced more BDNF and the cell receptor for BDNF, called TrkB, and that those in the high-estrogen period of their cycle produced still more BDNF. The researchers believe that this might reflect an effort in the hippocampus, a brain region important for memory of ongoing events, to compensate for a reduction of BDNF secretion that other research has found in the neurons with the BDNF Met gene.

Why these brain changes alter behavior remains murky, but the differences associated with the estrous cycle suggest strongly that BDNF

Met could play an important part in disorders associated with the menstrual cycle, such as PMDD, a condition marked by extreme irritability and mood swings, among other symptoms, and afflicting 5 to 10 percent of women.

"Besides the potential value for better understanding PMDD, these findings add the BDNF system to our understanding of basic cellular and molecular mechanisms that underlie the ability of sex hormones such as estradiol to affect behavioral functions outside of reproduction, such as anxiety and memory," says Bruce S. McEwen, head of the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology at Rockefeller and senior author on the study.

Provided by Rockefeller University