Bipolar disorder and epilepsy linked to turning down an inhibitory switch in brain circuits

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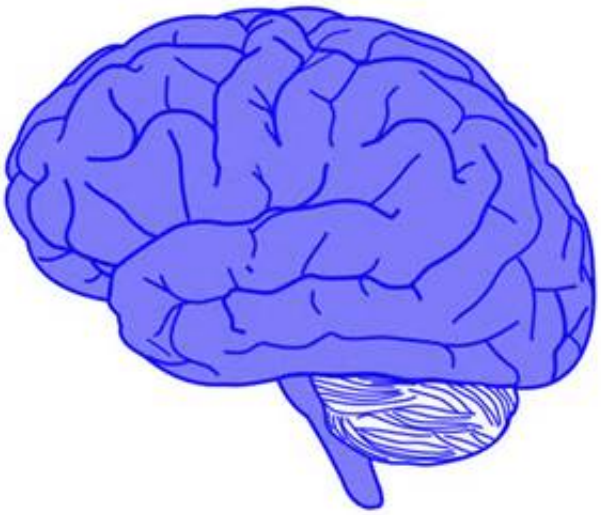

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People with bipolar disorder suffer from excessive emotional highs and lows that can cycle uncontrollably, severely distorting their awareness of self and others, impairing social and work ability and causing high risk of suicide. Current treatments are only partly effective. Researchers at Baylor College of Medicine have used mouse models and advanced molecular mapping studies in both mouse and human to learn how a

gene associated with bipolar disorder controls the balance between brain excitation and inhibition and shown for the first time that it also is linked to epilepsy.

The findings, appearing recently in the early online edition of *Molecular Psychiatry*, open new treatment strategies for both bipolar disorder and epilepsy.

"We became very interested in a gene called ankyrin 3, or ANK3, a decade ago when we discovered it coded for a partner of two other genes that are mutated in some people with epilepsy. Soon afterward, ANK3 was connected with bipolar disorder by genetic testing of thousands of psychiatric patient volunteers around the world," said Dr. Edward C. Cooper, associate professor of neurology, molecular and human genetics, and neuroscience at Baylor. "Although there are important differences, we noted similarities between bipolar disorder and epilepsy: both cycle, both are risk factors for the other, and both are currently treated using many of the same drugs. Reasons behind these overlaps were mysterious, and the specific parts of the ANK3 gene linked with bipolar had no known function. We decided to take a much closer look at the human brain and mice with bipolar-like behavior. In our study we found that reduced expression of one type of ANK3 removes a brake on the output of brain neurons, leading to excesses in firing in circuits for emotions, memory and epilepsy."

Within each ANK3 gene are bits of DNA containing information coding for severaldifferent proteins. The research team found that, in both mice and human, different ANK3-coded proteins were expressed on brain cells responsible for increasing output (excitation) and holding back output (inhibition). Working with Cooper, Baylor genetics graduate student Angel Lopez discovered that an ANK3 type found in lower amounts in bipolar disorder patients was selectively lost by inhibitory neurons, lowering their output. Activity of neighboring excitatory cells

proved unaffected. So, what scientists call "excitation/inhibition" balance was shifted in the direction of excessive excitation.

When Lopez and colleagues engineered mice to lose this inhibitory form of ANK3, they found that the imbalance caused both frequent epileptic seizures and an increased risk of sudden death across the lifespan.

"This showed us that imbalance in ANK3 function can result not only in excessive circuit sensitivity and output leading to bipolar disorder, but also severe epilepsy," Cooper said.

Although diagnosis and care for bipolar disorder and epilepsy often are viewed as distinctly psychiatric and neurological issues, respectively, the study highlights an example of common genetic and biological underpinnings at a frontier between medical disciplines. The results open the door to additional lab and clinical research and could lead to new treatment options for both conditions by targeting ANK3 and its molecular partners in the brain.

"Our work also provides an example of how conducting and participating in unbiased human genetic studies, such as those that implicated ANK3 in bipolar disorder, can illuminate unforeseen connections between disease categories and the benefits of research that crosses disciplinary borders" said Cooper.

Provided by Baylor College of Medicine