Press Release

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Date: 9/6/2016

CRF Overexpression Increases Anxiety in Primates

Reports new study in Biological Psychiatry

Philadelphia, PA, September 6, 2016 – A new study in *Biological Psychiatry* reports that overexpression of corticotropin-releasing factor (CRF), a stress-related gene, increases anxious temperament in monkeys. According to Ned Kalin from the University of Wisconsin-Madison who led the study, the findings provide a direct link in primates between alterations in stress-related systems in the brain and the development of anxiety disorders.

Anxiety disorders often begin early in life and anxious temperament during childhood is considered a risk for later development of anxiety and depression. “Young children with extreme anxious temperament have about a 50% chance of developing stress-related psychopathology,” said Kalin.

Researchers have thought that overactivity of the CRF system mediates symptoms associated with anxiety and depression. But early excitement over treating the disorders by altering brain CRF systems turned to disappointment when the approach failed to produce positive outcomes in clinical trials. The new study makes the case that CRF may be an important signaling mechanism for anxiety in primates, which may help reignite interest in targeting CRF for treatment of anxiety and depression.

“This study helps to keep the CRF story alive. Blocking CRF signaling may yet be an important path for reducing anxiety and promoting resilience,” said John Krystal, Editor of *Biological Psychiatry*.

Previous studies on the role of CRF in anxiety used rodents, but Kalin emphasized the value of nonhuman primates, which provide the best model of human anxious temperament, and because humans share critical features of the CRF system with monkeys but not rodents.

This study was the first to alter the CRF system in monkeys to study the effect on anxious temperament. The researchers caused the brains of five monkeys to overproduce CRF by injecting a viral vector, which alters the genome at a very specific region. They targeted the central nucleus of the amygdala, a fundamental component of the neural circuit that regulates anxious temperament. To see what changes occurred in the central nucleus of the amygdala and its connected regions after altering CRF, the researchers performed behavioral tests and imaged the brain with combined metabolic and functional and structural magnetic resonance imaging.

Chronically increasing the activity of CRF in the central nucleus of the amygdala increased anxious temperament in the monkeys. Overexpression also increased brain metabolism in the region, as well as in other regions that play a role in anxious temperament. The findings suggest that the effects of CRF overexpression on increasing anxious temperament involve activation of the neural circuit that underlies the childhood risk to develop anxiety and depression.

“By understanding the neural circuits and molecular mechanisms that underlie this childhood risk, our hope is to use these insights to conceptualize novel early interventions aimed at preventing the long term suffering associated with these disorders,” said Kalin.

He added that their findings take an important step in this direction by demonstrating the ability to modulate the function of CRF in monkeys, and point to the potential for new therapeutics that target overactivity of the CRF system, and other stress-related genes, in the central nucleus of the amygdala.

Notes for editors
The article is "Overexpressing Corticotropin-Releasing Factor in the Primate Amygdala Increases Anxious Temperament and Alters Its Neural Circuit," by Ned H. Kalin, Andrew S. Fox, Rothem Kovner, Marissa K. Riedel, Eva M. Fekete, Patrick H. Roseboom, Do P.M. Tromp, Benjamin P. Grabow, Miles E. Olsen, Ethan K. Brodsky, Daniel R. McFarlin, Andrew L. Alexander, Marina E. Emborg, Walter F. Block, Julie L. Fudge, and Jonathan A. Oler (doi:10.1016/j.biopsych.2016.01.010). It appears in *Biological Psychiatry*, volume 80, issue 5 (2016), published by Elsevier.

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at +1 214 648 0880 or biol.psych@utsouthwestern.edu. Journalists wishing to interview the authors may contact Ned Kalin at +1 608 263 6079 or nkalin@wisc.edu.

The authors’ affiliations, and disclosures of financial and conflicts of interests are available in the article.

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The journal publishes novel results of original research which represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also encouraged.

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