Press Release

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Antidepressants Induce Resilience and Reverse Susceptibility

Reports new study in Biological Psychiatry

Philadelphia, PA, February 2, 2017 – When they work, antidepressant medications may take weeks or months to alleviate symptoms of depression. Progress in developing new and more effective antidepressant treatments has been limited, though a new study published in *Biological Psychiatry* offers new insights into how antidepressants work.

Using a mouse model of depression, researchers found that a therapeutic response to antidepressant medication may stem from changes in gene expression that induce resilience and reverse vulnerability to exhibiting depression-like responses to stress. The study, led by Dr. Eric Nestler of the Icahn School of Medicine at Mount Sinai in New York, teases apart the mechanisms of two different antidepressant drugs– the conventional tricyclic antidepressant imipramine and fast-acting ketamine.

Depression-like symptoms were induced in mice using a chronic social defeat stress model, which causes physiological and behavioral changes that model depression in humans. Using genome-wide assays to study gene transcription in mice that either succumbed to the stress paradigm or were unaffected, the researchers identified specific transcriptional changes associated with susceptibility or resilience. Then they treated the mice exhibiting depression-like symptoms with repeated imipramine or single-dose ketamine, and looked for those susceptible-specific or resilience-specific changes induced by the drugs. Importantly, each treatment reversed the depression-like symptoms of a roughly equivalent fraction of the mice.

Co-first authors Dr. Rosemary Bagot and Hannah Cates and colleagues examined four different emotion-related brain regions implicated in depression, and found that both imipramine and ketamine exerted strong effects in the prefrontal cortex. As a result, this region could be a common and potentially essential target for antidepressant action. The different brain regions also displayed changes in gene expression unique to each of the drugs, which may be the source of drug-specific effects.

“Antidepressant effects on resilience are an important new area of study. This study suggests that both traditional and rapid-acting antidepressant medications induce a biochemical fingerprint of resilience in brain regions associated with the regulation of emotion,” said Dr. John Krystal, Editor of *Biological Psychiatry*. Both drugs also induced patterns of gene expression that strongly opposed susceptible-specific gene expression, suggesting a reversal of susceptibility.

Not all mice showed improvement of their symptoms with antidepressant treatment. Those that lacked a response to treatment failed to show gene expression changes that were observed in treatment-responders. Unique changes in the non-responders also suggest that rather than just failing to respond, alterations in the brain may actually oppose the effects of medication.

“The work provides uniquely broad and novel insight into the mechanism of action of two antidepressant drugs across several brain regions, including why certain individuals respond behaviorally to the treatments while others do not,” said Dr. Nestler. “The findings offer a template for future drug discovery efforts aimed at validating novel targets for antidepressant therapeutics.”

Notes for editors

The article is "Ketamine and Imipramine Reverse Transcriptional Signatures of Susceptibility and Induce Resilience-Specific Gene Expression Profiles," by Rosemary C. Bagot, Hannah M. Cates, Immanuel Purushothaman, Vincent Vialou, Elizabeth A. Heller, Lynn Yieh, Benoit LaBonté, Catherine J. Peña, Li Shen, Gayle M. Wittenberg, and Eric J. Nestler (doi: 10.1016/j.biopsych.2016.06.012). It appears in *Biological Psychiatry*, volume 81, issue 4 (2017), 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 Eric J. Nestler, M.D., Ph.D., at eric.nestler@mssm.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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