Sensitivity to antidepressants linked with TrkB-mediated neural proliferation

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Scientists have unveiled a functional link between production of new neurons and the effectiveness of antidepressants (ADs) in an animal model. The study, published by Cell Press in the August 14 issue of the journal *Neuron,* provides exciting insight into a mechanism that might underlie a poor response to antidepressive medications for anxiety or depression.

Depression is a significant public health problem due to both its high prevalence and its devastating impact on individuals and society," says senior author Dr. Luis F. Parada from the University of Texas Southwestern Medical Center. "Despite much excitement generated by recent advances in the knowledge of brain development and function, the mechanisms underlying the pathogenesis of depression, as well as its amelioration by AD treatment, remain poorly understood."

Animal studies have indicated that chronic treatment with ADs leads to production of new neurons in a part of the brain called the hippocampus. Exercise, such as running, which has a documented positive impact on mental health, also stimulates hippocampal neurogenesis. In both cases, new neurons arise from neural progenitor cells (NPCs) that seem to be required for the behavioral response to ADs.

Brain-derived neurotrophic factor (BDNF) is increased in the hippocampus after chronic AD treatment, has been linked with AD-like responses in several behavioral paradigms, and promotes proliferation of hippocampal NPCs. Interestingly, mutant mice with abnormal BDNF exhibit anxiety-like behaviors that are not normalized by AD treatment. Taken together, this research supports a role for BDNF in the response of the brain to chronic AD treatment.

To further investigate the relationship among BDNF, neurogenesis, and AD treatment, Dr. Parada and colleagues removed the gene for the BDNF receptor, TrkB, in a regional and cell type-specific manner. TrkB was expressed in hippocampal cells, including NPCs. Deletion of trkB in mouse embryos or adults resulted in impaired proliferation and neurogenesis in the hippocampus and prevented behavioral improvements induced by AD treatment or wheel running. Conversely, deletion of trkB from only mature neurons in the same brain regions did not impact the production of new neurons or behavioral responses to ADs.

The researchers went on to show that removal of TrkB from adult NPCs alone was sufficient to block sensitivity to chronic ADs. "Our data establish an essential cell-autonomous role for TrkB in regulating hippocampal neurogenesis and behavioral sensitivity to antidepressive treatments and support the notion that impairment of the neurogenic niche is an etiological factor for refractory responses to antidepressive regimen in mice," offers Dr. Parada.

Source: Cell Press