

Important New Insight Into How Antidepressants Work

Blocking the formation of neurons in the hippocampus blocks the behavioral effects of antidepressants in mice, say researchers funded by the National Institutes of Health (NIH). Their finding lends new credence to the proposed role of such neurogenesis in lifting mood. It also helps to explain why antidepressants typically take a few weeks to work, note Rene Hen, Ph.D., Columbia University, and colleagues.

"If antidepressants work by stimulating the production of new neurons, there's a built-in delay," explained Hen, a grantee of NIH's National Institute of Mental Health (NIMH) and National Institute on Drug Abuse (NIDA). "Stem cells must divide, differentiate, migrate and establish connections with post-synaptic targets – a process that takes a few weeks."

"This is an important new insight into how antidepressants work," added NIMH director Thomas Insel, M.D. "We have known that antidepressants influence the birth of neurons in the hippocampus. Now it appears that this effect may be important for the clinical response."

Chronic stress, anxiety and depression have been linked to atrophy or loss of hippocampal neurons. A few years ago, Hen's colleague and co-author Ronald Duman, Ph.D., Yale University, reported that some antidepressants promote hippocampal neurogenesis. But to what effect? To begin to demonstrate a causal relationship between these newly generated cells and relief from depression, researchers would have to find a way to prevent their formation in a behaving animal.

The researchers first showed that mice become less anxious – they begin eating sooner in a novel environment – after four weeks of antidepressant treatment, but not after just 5 days of such treatment. Paralleling the delay in onset of antidepressant efficacy in humans, the chronically-treated mice, but not the briefly-treated ones, showed a 60 percent boost in a telltale marker of neurogenesis in a key area of the hippocampus.

To find out if the observed neurogenesis is involved in antidepressants' mechanism-of-action, Hen and colleagues selectively targeted the hippocampus with x-rays to kill proliferating cells. This reduced neurogenesis by 85 percent. Antidepressants had no effect on anxiety and depression-related behaviors in the irradiated mice. For example, fluoxetine failed to improve grooming behavior, as it normally does, in animals whose behavior had deteriorated following chronic unpredictable stress. Evidence suggested that this could not be attributed to other effects of x-rays.

Neurons communicate with each other by secreting messenger chemicals, or neurotransmitters, such as serotonin, which cross the synaptic gulf between cells and bind to receptors on neighboring cell membranes. Medications that enhance such binding of serotonin to its receptors (serotonin selective reuptake inhibitors, or SSRIs) are widely prescribed to treat anxiety and depression, suggesting that these receptors play an important role in regulating emotions.

By knocking out the gene that codes for a key subtype of serotonin receptor (5-HT1A), the researchers created a strain of "knockout" mice that as adults show anxiety-related traits, such as a reluctance to begin eating in a novel environment. While unaffected by chronic treatment with the SSRI fluoxetine, the knockout mice became less anxious after chronic treatment with tricyclic antidepressants, which act via another neurotransmitter, norepinephrine, suggesting an independent molecular pathway.

While chronic fluoxetine treatment doubled the number of new hippocampal neurons in normal mice, it had no effect in the knockout mice. The tricyclic imipramine boosted neurogenesis in both types of mice, indicating that the serotonin 1A receptor is required for neurogenesis induced by fluoxetine, but not imipramine. Chronic treatment with a serotonin 1A-selective drug confirmed that activating the serotonin 1A receptor is sufficient to spur cell proliferation.

Although the new findings strengthen the case that neurogenesis contributes to the effects of

antidepressants, Hen cautions that ultimate proof may require a "cleaner" method of suppressing this process, such as transgenic techniques that will more precisely target toxins at the hippocampal circuits involved.

"Our results suggest that strategies aimed at stimulating hippocampal neurogenesis could provide novel avenues for the treatment of anxiety and depressive disorders," suggest the researchers.

Also participating in the study were: Luca Santarelli, Michael Saxe, Cornelius Gross, Stephanie Dulawa, Noelia Weisstaub, James Lee, Columbia University; Alexandre Surget, Catherine Belzung, Universite de Tours, France; Fortunato Battaglia, Ottavio Arancio, New York University.

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