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Why some antidepressants may initially worsen symptoms

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New research helps explain a paradoxical effect of certain antidepressants—that they may actually worsen symptoms before helping patients feel better. The findings, highlighted in a paper publishing online December 17 in the Cell Press journal *Trends in Cognitive Sciences*, may help investigators fix the problem as well as create new classes of drugs to treat depression.

Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed class of antidepressant drugs, and they work by increasing levels of a brain chemical called serotonin. While this boost in serotonin occurs within minutes to hours after an SSRI is taken, patients usually have to take the medication for about 2 weeks before experiencing any relief of symptoms. During this delay, the drug may actually aggravate depression, in some cases even increasing the risk for suicide.

Researchers and clinicians have been puzzled by this, but Adrian Fischer of Otto-von-Guericke University in Germany and his colleagues now point to evidence from recent studies showing that serotonin neurons transmit a dual signal that consists of the release of serotonin as well as glutamate, another brain chemical. The investigators say that SSRIs may affect these two components of the dual signal in different ways.

"While the serotonergic component is immediately amplified following SSRI administration, the glutamate component is acutely suppressed and is only normalized after several days of drug treatment," says Fischer. He notes that the serotonin component of the dual signal has been linked

to motivation, while the glutamate component has been linked to pleasure and learning. "These differential time courses may help to explain the paradox of acute versus chronic SSRI effects."

A better understanding of serotonin neurons' dual signal and its varied response to acute and chronic drug treatment may help resolve some of the paradoxes observed with SSRIs. Delineating the contributing factors of each aspect of the dual signal may point to new drug targets for reducing the delay in effectiveness of SSRIs or even to completely new types of antidepressants. Also, the discovery of the dual signal helps explain why the delayed onset of clinical efficacy that's seen with SSRIs is not evident with other antidepressant drugs that instead target glutamate receptors.

More information: Dual serotonergic signals: a key to understanding paradoxical effects? *Trends in Cognitive Sciences*, 2014.

Provided by Cell Press

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