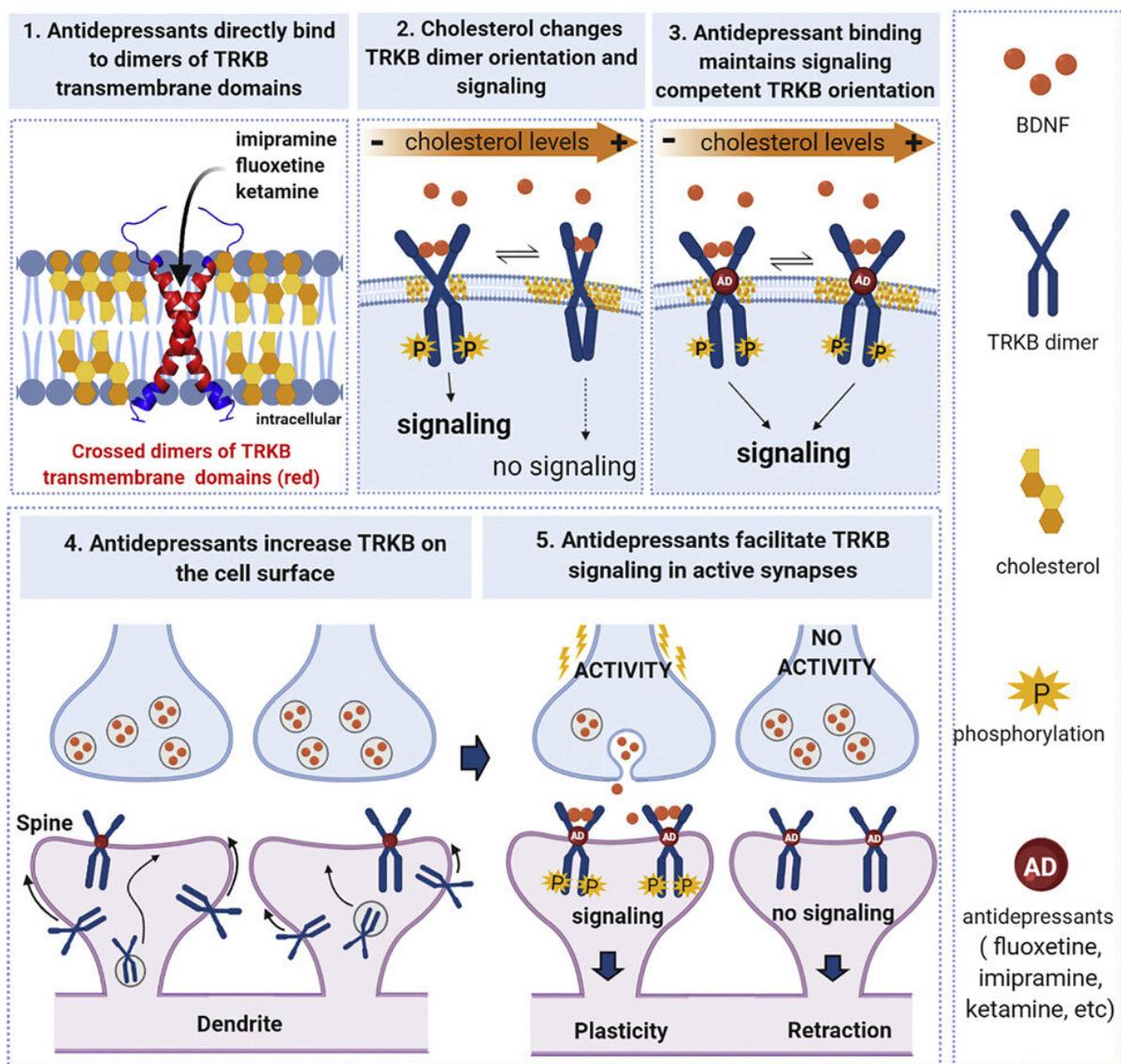


Researchers uncover new information on the effects of antidepressants

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The effects of selective serotonin reuptake inhibitors (SSRIs) and other conventional antidepressants are believed to be based on their increasing the levels of serotonin and noradrenalin in synapses, while ketamine, a new rapid-acting antidepressant, is thought to function by inhibiting receptors for the neurotransmitter glutamate.

Neurotrophic factors regulate the development and plasticity of the nervous system. While all antidepressants increase the quantity and signaling of brain-derived neurotrophic factor (BDNF) in the brain, the drugs have so far been thought to act on BDNF indirectly, through serotonin or glutamate receptors.

A new study published this week in *Cell* demonstrates, however, that antidepressants bind directly to a BDNF receptor known as TrkB. This finding challenges the primary role of serotonin or glutamate receptors in the effects of antidepressants.

The international study, which was collaboratively led by the Neuroscience Center and the Department of Physics at the University of Helsinki, investigated the binding of antidepressants from different drug classes to the TrkB receptor. All the antidepressants examined, including fluoxetine (an SSRI), imipramine (a [tricyclic antidepressant](#)) and the rapid-acting [ketamine](#) interacted with TrkB.

"We found that all antidepressants boost BDNF signaling by binding to its TrkB receptor. This signaling is necessary for the cellular and behavioral effects of antidepressants in our experimental models. The effects of antidepressant on plasticity do not therefore require increases in the serotonin levels or the inhibition of glutamate receptors, as

previously thought," says Professor Eero Castrén, the principal investigator of the study.

Molecular modeling helped to locate the binding site of antidepressants

The binding site of antidepressants in the transmembrane region of TrkB was identified through molecular modeling, performed in Professor Ilpo Vattulainen's research group at the Department of Physics, University of Helsinki. Biochemical binding studies and mutations introduced in the TrkB receptor verified the site.

Molecular modeling also demonstrated that the structure of TrkB is sensitive to the cholesterol concentration of the cell membrane. TrkB is displaced in cholesterol-rich membrane compartments, such as synaptic membranes.

"The drug binding stabilizes dimers, structures composed of two TrkB receptors, inhibiting the displacement of the TrkB receptors and increasing their quantity in synaptic cell membranes, which boosts the effects of BDNF. That is to say that the drugs do not directly activate TrkB. Instead, they sensitize the receptor to the effects of BDNF," Castrén explains.

In addition to findings pertaining to the effects of antidepressants, the study produced a substantial amount of new information on the structure and function of the growth factor receptor.

Why does ketamine have such a rapid effect?

Ketamine, which has been used as an anesthetic, is becoming increasingly utilized as an antidepressant. The researchers were surprised

to find that both slow-acting SSRIs and rapid-acting ketamine act by binding to the same site in TrkB.

SSRI drugs bind to the serotonin transporter protein much more avidly than to TrkB, but the binding of ketamine to the [glutamate receptor](#) and TrkB occurs at similar [drug](#) concentrations.

"Previous studies have shown that in SSRI therapy, drugs gradually reach the high brain concentration needed for binding to the TrkB receptor, whereas intravenously administered ketamine and esketamine as a nasal spray reach the level needed for binding quickly, in a matter of minutes. The difference in the onset of action for SSRIs and ketamine may be caused by their different capacity to reach in the brain the concentration needed for binding with TrkB [receptors](#)," Castrén says.

More information: Plinio C. Casarotto et al, Antidepressant drugs act by directly binding to TRKB neurotrophin receptors, *Cell*, February 18, 2021 doi.org/10.1016/j.cell.2021.01.034

Provided by University of Helsinki

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