

Antidepressant drugs act by directly binding to TrkB neurotrophin receptors

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Tyrosine kinase receptor 2 (TrkB) fosters neuronal plasticity and the response to antidepressants by acting as a membrane receptor for the brain-derived neurotrophic factor (BDNF). Our biomolecular simulations combined with experimental studies showed [1] that antidepressants directly bind to TrkB and facilitate its synaptic activation by BDNF. A fascinating feature in this binding process is the central role of cholesterol. The study revealed that TrkB senses membrane cholesterol, which modulates the conformation of TrkB and thus regulates the ability of antidepressants to bind to the receptor. For fluoxetine, one of the commonly used antidepressants, biomolecular simulations showed an exact binding site. The results suggest that binding to TrkB and allosteric facilitation of BDNF signaling is the common mechanism for antidepressant action, which may explain how molecular effects of antidepressants are translated into clinical mood recovery.

1. Casarotto PC, et al. Antidepressant drugs act by directly binding to TrkB neurotrophin receptors. *Cell* 184, 1299-1313.e19 (2021). doi:10.1016/j.cell.2021.01.034.

