RESEARCH HIGHLIGHT

A new molecular target for antidepressants

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The mode of action of drugs used to treat depression has long remained mysterious. A new study now shows that unexpectedly, this diverse group of chemicals binds to a well-studied growth factor receptor in the brain.

Depression negatively impacts the everyday lives of very large numbers of people worldwide. Alongside with psychotherapy and related approaches, drugs are also extensively used to improve the well-being of patients suffering from depression. These drugs typically target major neurotransmitter systems in the brain, including those using monoamines such as serotonin in particular.¹ The decade-long focus on monoamines to treat depression started with observations made in the early 1950s that chemicals used to fight tuberculosis dramatically improved the mood of some patients. This unexpected outcome was rightly interpreted to go beyond the relief experienced by individuals liberated from the debilitating effects of *Mycobacterium tuberculosis*. Previously identified enzymes degrading monoamines, designated monoamine oxidases, were found to be inhibited by the hydrazine derivatives initially used to treat tuberculosis.¹ Later drugs focused mostly on the inhibition of the re-uptake of the monoamine serotonin, with fluoxetine, best known under the trade name Prozac, being one of the most widely prescribed medication worldwide. As it typically takes antidepressants a few weeks to improve the mood of patients whilst inhibition of neurotransmitter uptake is immediate, it has long been hypothesized that more complex mechanisms likely underlie the action of antidepressants. Questions about how they work became even more pressing following the observation that drugs targeting other neurotransmitter systems such as those using ketamine and its metabolites were also effective, and more rapidly so than those targeting monoamines.²

Starting in the mid-90s, attention began to focus on more elaborate aspects of neurotransmission, including in particular the remodeling of synapses by brain-derived neurotrophic factor (BDNF). Synaptic plasticity was then proposed to be a key aspect of the mode of action of antidepressants³ as by that time, a link had been established between this growth factor and the serotonergic system.⁴ In animal models, BDNF injections into the brain were shown to improve depressive-like symptoms⁵ and the activation of the BDNF tyrosine kinase receptor TrkB to be essential for antidepressants to work.⁶ What this previous work did not predict is the extraordinary finding reported by Casarotto and colleagues that antidepressants, including those that are structurally unrelated, all bind to TrkB with micromolar affinity and potentiate its activation by BDNF (see Fig. 1).⁷ A second important observation is that cholesterol modulates the activation of TrkB, both by antidepressants and BDNF.⁷ Fractionation studies indicate that only a small proportion of TrkB resides in cholesterol-rich lipid rafts thought to be a component of the post-synaptic membrane

where TrkB is waiting to be activated by the pre-synaptic release of BDNF.⁸ Using a TrkB mutant unable to bind cholesterol and antidepressants, the study also includes suggestive in vivo work indicating that various forms of synaptic plasticity are impaired in mice carrying one mutant allele of TrkB. In particular, long-term potentiation (LTP), a widely used cellular model of memory, is impaired in these animals and previous work has long established that in the rodent hippocampus, both BDNF and TrkB are involved in LTP.^{9,10} Antidepressants improve the performance of animals undergoing memory tests and restore plasticity in the visual system, but not so in animals carrying the TrkB mutation that inhibits antidepressant binding or in wild-type animals treated with the cholesterol-depleting drug pravastatin.⁷ In addition, the generation of new neurons in the hippocampus, previously proposed to be part of the mode of action of antidepressants,¹¹ is shown to be compromised in TrkB mutant animals.⁷

Whilst the study does not identify the sites of contact between TrkB and antidepressants or cholesterol by direct structural observations, it does include molecular modeling and predictions about the impact of different cholesterol concentrations on the conformation of TrkB dimers and the binding sites of antidepressants. Some of these predictions are also verified by single amino acid replacements.⁷

The report by Casarotto and colleagues not only gives novel and exciting explanations for a number of previous observations, but also opens the possibility to use TrkB as a molecular target to develop novel classes of antidepressants. Surely the most surprising aspect of this report is that none of the antidepressants used today have been developed on the basis of their ability to bind to TrkB and potentiate BDNF signaling. The focus on the transmembrane domain of TrkB is also novel as hitherto, most of the work on the three known Trk receptors in mammals focused on their extracellular and intracellular domains, respectively comprising the neurotrophin binding and the tyrosine kinase activity of the receptors. Like their neurotrophin ligands, the Trk receptors are closely related, except for the transmembrane domain of TrkB compared with both TrkA and TrkC. In line with this notion, Casarotto et al. show that the substitution of the transmembrane sequence of TrkB by the corresponding TrkA sequence abrogates antidepressant binding.⁷ Major functional differences between the Trk receptors have been previously documented: in the absence of their respective ligands, TrkA and TrkC cause the death of neurons whilst TrkB does not.¹² Transmembrane domain swapping experiments revealed that the transmembrane domain of TrkA used to replace the corresponding domain of TrkB confers a death-inducing activity to TrkB that can be suppressed by BDNF addition.¹³ More generally, it seems likely that the transmembrane domains of growth factor receptors will receive more attention in the future.

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Fig. 1 The BDNF homodimer binds to the second immunoglobulin-like domain of TrkB, thereby favoring a conformation of TrkB that leads to the phosphorylation of tyrosine residues by the kinase domain. Both cholesterol and antidepressants (AD) promote this configuration thereby potentiating BDNF signaling activity and synaptic plasticity.

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