MOOD DISORDERS

Small-molecule neurotrophin antagonist reduces anxiety

The growth factor hormone brain-derived neurotrophic factor (BDNF) and its receptor tropomyosin-related kinase B (TRKB) are involved in the pathophysiology of mood-related disorders. However, it has been difficult to identify compounds that intervene in this protein–protein interaction. A recently published paper in the *Journal of Clinical Investigation* has identified what is probably the first non-peptide antagonist of TRKB, which reduced anxiety- and depression-related behaviours in mouse models.

To identify potential TRKB antagonists, the authors first used *in silico* screening, which was based on the known structural interaction between neurotrophins and TRK receptors. Compounds from the Bioinfo-DB database library were docked onto the so-called 'specificity interaction patch', which is a binding pocket located in the fifth subdomain of TRKB; this binding pocket is thought to drive the selectivity of the interaction with BDNF. The virtual screening identified 22 hits, out of which two compounds (named N-T04 and N-T19) completely inhibited BDNF-induced TRKB phosphorylation in cellular assays. In addition, N-T19 prevented BDNF-induced neurite outgrowth in transfected neuronal cells. However, its low potency meant that the authors undertook further *in silico* screening based on the structure of N-T19, which identified a molecule — called ANA-12 — that shared the same scaffold as N-T19 but displayed increased potency. ANA-12 prevented BDNF-induced neurite outgrowth at nanomolar concentrations and was selective for TRKB over TRKA or TRKC. Furthermore, it was found that ANA-12 and BDNF probably do not bind to the same sites on TRKB.

Following intraperitoneal injection in mice, ANA-12 crossed the blood–brain barrier and was able to partially inhibit TRKB activity homogenously throughout the brain 4 hours after its administration. As inhibition of BDNF–TRKB signalling can induce neuronal death in the central nervous system, it was interesting to note that chronic administration of ANA-12 did not affect neuron survival.

Next, the authors investigated whether ANA-12 (given at a dose of 0.5 mg per kg (bodyweight) via intraperitoneal injection) had anxiolytic properties in mouse models. In the elevated plus maze task, treated mice spent more time in open arms than control mice, and in the novelty-suppressed feeding paradigm, food-deprived mice that were treated with ANA-12 entered the illuminated area and consumed a food pellet twice as fast as controls. Such behaviours are consistent with ANA-12 having anxiolytic properties. In models to assess the potential antidepressant activity of ANA-12, the authors used the forced-swim test and the tail-suspension test. In both models, ANA-12-treated mice spent less time immobile than controls — behaviour that is consistent with ANA-12 having antidepressant activities.

This newly identified TRKB antagonist should be a useful pharmacological tool to allow further investigation of the role of BDNF–TRKB signalling in pathophysiological conditions, and it could serve as a lead compound for the design of potent, oral bioavailable TRKB modulators.

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ORIGINAL RESEARCH PAPER
Cazorla, M. *et al.* Identification of a low-molecular weight TrkB antagonist with anxiolytic and antidepressant activity in mice. *J. Clin. Invest.* **121**, 1846–1857 (2011)