NEURODEGENERATIVE DISEASE

BDNF copycats

Brain-derived neurotrophic factor (BDNF) has an important role in supporting neuronal survival, which has encouraged studies of its therapeutic potential for neurodegenerative disorders such as Alzheimer's disease. However, its clinical application has been hampered by factors such as a short half-life and low rate of transport across the blood–brain barrier (BBB). Now, Longo, Massa and colleagues have developed an approach to generate and screen small-molecule BDNF mimetics that could overcome some of these limitations.

First, the authors generated a pharmacophore based on a loop domain of BDNF that previous studies on chimeric BDNF mutants had shown binds to a key receptor of the molecule, neurotrophic tyrosine kinase receptor type 2 (NTRK2; also known as TRKB). Using this pharmacophore, an *in silico* screen of a library of ~1 million commercially available small molecules was performed. The screen identified 1,800 hits on the basis of correspondence to the pharmacophore, which were then filtered using criteria such as molecular mass. Following *in vitro* screening of seven compounds for neurotrophic activity, four candidate molecules, designated LM22A1–LM22A4, were selected for further study.

In mouse hippocampal neuronal cultures, the compounds increased cell survival with an efficacy comparable to that of BDNF. The neurotrophic activity of the candidate compounds was decreased by the NTRK2 inhibitor K252a and by an NTRK2-specific antibody, supporting the involvement of this BDNF receptor. The necessity of NTRK2 for LM22A4-mediated neuronal survival was shown by a lack of compound effect in cell lines engineered to express only receptors of other key neurotrophins. Furthermore, fluorescence anisotropy, together with additional binding studies, showed that LM22A4 binds directly to NTRK2. Importantly, unlike BDNF, LM22A4 did not bind to the general neurotrophic factor receptor, p75NTR, which is thought to mediate the pain-promoting effects of BDNF.

Western blot analysis established that, like BDNF, LM22A4 activated protein kinase B (AKT) and extracellular signal-regulated kinase (ERK). This effect was inhibited by blocking LM22A4 with a specific antibody or with K252a, further validating LM22A4 as a BDNF mimetic.

In *in vitro* models of Alzheimer's disease, Parkinson's disease and Huntington's disease, LM22A4 substantially reduced neuronal death, an effect that was inhibited by K252a. For *in vivo* experiments, LM22A4 was administered intranasally to mice owing to its low rate of transport across the BBB. Once-daily dosing of the compound for 7 days increased the activation of NTRK2, AKT and ERK in the hippocampus and striatum. In addition, the impairment in motor learning observed following traumatic brain injury in rats was significantly improved over a 3-week LM22A4 treatment regimen, suggesting that this compound could restore higher brain functions after trauma.

Together, these studies provide a promising new strategy to generate small-molecule mimetics of BDNF that might unlock the potential of NTRK2 activation to treat a broad range of neurological diseases.

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ORIGINAL RESEARCH PAPER Massa, S. M. *et al.* Small molecule BDNF mimetics activate TrkB signaling and prevent neuronal degeneration in rodents. *J. Clin. Invest.* **120**, 1774–1785 (2010)