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NEURODEGENERATIVE DISEASE

Gene therapy delivers an alternative approach to Alzheimer's disease

The main focus of current drug development efforts for Alzheimer's disease is targeting the amyloid-β (Aβ) brain plaques that are characteristic of the disease. However, there have recently been several disappointments with clinical trials of Aβ-targeted agents. Now, new research has highlighted the neuroprotective effects of brain-derived neurotrophic factor (BDNF) in various models of Alzheimer's disease, which seem to be mediated by an amyloid-independent mechanism.

In Alzheimer's disease, profound neuronal dysfunction in the entorhinal cortex contributes to the early loss of short-term memory. BDNF, which is expressed in the entorhinal cortex and trafficked to the hippocampus, is implicated in mechanisms underlying memory and, furthermore, BDNF levels are reduced in the entorhinal cortex and the hippocampus in Alzheimer's disease. These observations led to the hypothesis that gene therapy involving *BDNF* delivery to the entorhinal region might ameliorate Alzheimer's disease by reducing neurodegeneration in both of these regions.

To test this hypothesis, Nagahara *et al.* first assessed the effects of *BDNF* delivery to the entorhinal cortex in both a transgenic mouse model of Alzheimer's disease and aged rats. *BDNF*-injected rodents showed restoration of spatial memory deficits in both models, although *BDNF* delivery had no effect on neuronal number or Aβ plaque density. Furthermore, *BDNF* treatment partially normalized alterations in gene expression implicated in Alzheimer's disease (mouse model) and ageing (rat model). BDNF also prevented the death of entorhinal cortical neurons induced *in vitro* by Aβ and induced *in vivo* in rats by lesions of the perforant path, which links the entorhinal cortex to the hippocampus.

The authors then examined whether these effects were replicated in primates. A non-human primate model of entorhinal cortex neuronal death was developed by performing bilateral radiofrequency lesions of the perforant path in monkeys; subsequent injection of *BDNF* prevented neuronal death in this model. Cognitive performance was examined in aged monkeys, and *BDNF* treatment was shown to significantly improve their performance in a visuospatial discrimination task.

Overall, these studies provide support for exploring the clinical translation of *BDNF* delivery as a potential therapy for Alzheimer's disease, although caution is warranted as the models and species used do not necessarily replicate the exact causes of neurodegeneration in Alzheimer's disease. Importantly, previous efforts to use neurotrophic factors to treat neurodegenerative disorders have been severely limited by the challenge of safe and effective delivery, but the authors' results in this case suggest that their delivery approach could be successfully translated to human treatment.

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ORIGINAL RESEARCH PAPER Nagahara, A. H. *et al.* Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. *Nature Med.* **15**, 331–337 (2009)