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NEURODEGENERATIVE DISEASE

Could fingolimod provide cognitive benefits in patients with Huntington disease?

The approval of the immunomodulatory drug fingolimod (FTY720) to treat multiple sclerosis has prompted investigators to explore the potential benefits of this drug in other neurological diseases. A new study published in *Human Molecular Genetics* shows that fingolimod, via effects on brain-derived neurotrophic factor (BDNF) signalling, restores hippocampal synaptic plasticity and improves memory function in a mouse model of Huntington disease (HD).

> "...fingolimod-treated mice performed better than ... controls on [memory] tests..."

"Our team has a long track record in the study of the BDNF–TrkB–p75^{NTR} signalling system, a key player in the regulation of synaptic plasticity, learning and memory," explains lead author Andrés Miguez. "In the search for new drugs that modulate this system, a 2012 study by Deogracias *et al.*, in which they reported an increase in BDNF after delivery of fingolimod, attracted our attention."

Miguez and colleagues used R6/1 mice—a validated model of HD—to test the effects of chronic administration of fingolimod. Intraperitoneal delivery of either fingolimod or a vehicle solution was initiated at the presymptomatic stage (8 weeks of age) and continued until the mice were 20 weeks old.

At 17 weeks of age, the fingolimod-treated mice performed better than the vehicle controls on tests of spatial and recognition memory. In addition, the treated animals exhibited reductions in astrogliosis and dendritic spine loss in the hippocampus compared with the controls.

Miguez *et al.* found evidence that fingolimod exerts its effects via the BDNF signalling pathway. In both patients and animals with HD, cognitive and synaptic deficits have been linked to an imbalance in levels of the BDNF receptors p75^{NTR} and TrkB. In fingolimod-treated mice, the normal balance was restored through upregulation of TrkB and concomitant downregulation of p75^{NTR}.

"In the short term, we plan to test fingolimod in a knock-in mouse model of HD, which displays slower progression of the disease," says Miguez. "Given the safety profile of the drug and the fact that it can also rescue motor deficits in HD mice, we believe it could be worthy to carry out clinical trials."

Heather Wood

Original article Miguez, A. *et al.* Fingolimod (FTY720) enhances hippocampal synaptic plasticity and memory in Huntington's disease by preventing p75^{NTR} up-regulation and astrocyte-mediated inflammation. *Hum. Mol. Genet.* doi:10.1093/hmg/ddv218

Further reading Deogracias, R. *et al.* Fingolimod, a sphingosine-1 phosphate receptor modulator, increases BDNF levels and improves symptoms of a mouse model of Rett syndrome. *Proc. Natl Acad. Sci. USA* **109**, 14230–14235 (2012)