Fingolimod Causes Antidepressant-like Effects and Corrects the Reduction in Hippocampal BDNF Levels in Mice Exposed to Chronic Unpredictable Stress

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Recent evidence suggests that fingolimod, the first oral drug approved for the treatment of relapsing-remitting multiple sclerosis, exerts a direct effect on the CNS independently of its peripheral action on the immune system. It has been shown that nanomolar concentrations of fingolimod protect cultured neurons against excitotoxic death through the activation of type-1 sphingosine-1-phosphate (S1P1) receptor (Di Menna et al., 2013; Deogracias et al., 2012). Systemic treatment with fingolimod also enhances hippocampal levels of brain-derived neurotrophic factor (BDNF) (Deogracias et al., 2012). Hippocampal BDNF levels have been associated to the pathophysiology of major depression and to responses to antidepressant medication. Hence, we decided to examine whether fingolimod could cause antidepressant-like effects in the chronic unpredictable stress (CUS) model of 'reactive' depression. C57BL/6J adult male mice were exposed to a 4-week CUS protocol, which was sufficient to induce depressive-like behaviour at the forced swimming test (FST). CUS mice showing an increased immobility time at the FST also displayed a substantial reduction in hippocampal BDNF levels. Fingolimod (3 mg/kg, i.p.) was administered daily in the last week of CUS and the treatment was prolonged for 3 weeks after the discontinuation of the stress protocol. Fingolimod reduced the time spent immobile at the FST in about 30% of treated animals, which are considered 'responders' to the drug. In these responder mice, Western blot analysis showed an increase of hippocampal BDNF protein levels, which were restored to values similar to control animals. Fingolimod did not show any effect on BDNF concentrations in mice that did not respond to the drug at the FST. These data show for the first time an antidepressant-like activity of fingolimod. This raises the interesting possibility that fingolimod may relieve depressive symptoms associated with multiple sclerosis.

Di Menna et al. (2013) *Pharmacol Res.* 67:1-9
Deogracias et al. (2012) *Proc Natl Acad Sci USA* 109:14230-5.