Introduction

Brain-derived neurotrophic factor (BDNF) is implicated in clinical depression and its treatment. Administration of antidepressants enhances BDNF expression and phosphorylation of its cognate TrkB receptor. In contrast, stress exposure and depression is associated with down regulation of BDNF expression. Furthermore, an up regulation of adult neurogenesis in the hippocampus has been proposed to be correlated with drugs effective in the treatment of depression. The Ras-mediated extracellular signal-regulated cascade (ERK) pathway is considered as a major BDNF/TrkB intracellular signalling pathway. These studies suggest that BDNF is critically involved in depression and the mechanisms of antidepressants activity, but the contribution of the Ras-mediated ERK intracellular signalling pathway is less clear.

To investigate the role of the Ras/ERK-pathway in depression and antidepressant activity we utilized the synRas transgenic mouse model [1] expressing constitutively activated human Ha-Ras in differentiated neurons via the synapsin I promoter.

The synRAs mice normal cycles between the GTP-bound activated and the GDP-bound inactivated conformation. Due to a point mutation, the inactivation of GTP-bound Ras by Ras GTPase is inhibited, hence leading to a permanent Ras activation.

B) Elements of the transgene consist of the bicistronic gene mutated V12-Ha-Ras and LacZ reporter, both under control of the neuron specific synapsin I promoter.

Summary

SynRas mice showed elevated levels of activated Ras and activating phosphorylation levels of ERK in the cortex and hippocampus.

Exhibited an ‘antidepressant-like’ behavior in depression-associated animal models.

Exhibited a normal basal HPA-axis activity, but a suppression of corticosterone release in response to acute restraint stress.

Displayed a dramatic reduction of proliferating cells within the dentate gyrus of the hippocampus.

Chronic fluoxetine administration to wild type mice led to an increased Ras activation followed with subsequent elevation of ERK phosphorylation thus mimicking the synRas phenotype.

Effects of chronic fluoxetine treatment on proliferation of hippocampal progenitors

SynRas mice displayed a dramatic reduction in the number of proliferating cells within the dentate gyrus of the hippocampus. Fluoxetine treatment (23 days, 1 injection daily, 5 mg/kg) was given at day 23 of fluoxetine treatment, 24 h before perfusion.

Shown are representative photographs of wild type saline (A) or fluoxetine (B) treated and synRas saline (C) or fluoxetine (D) treated mice. SGZ: subgranular zone, H: hilus, GCL: granular cell layer.

Response to restraint stress

SynRas mice exhibited normal basal corticosterone levels in the a.m. and p.m.

SynRas mice exhibited an ‘antidepressant-like’ behavior mimicking the synRas phenotype.

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Taken together, an ‘antidepressant-like’ state was established in a genetic model of enhanced neuronal Ras signalling without correlation to increased hippocampal precursor cell proliferation.