6. Abstract

Brain-derived neurotrophic factor (BDNF) is implicated in clinical depression and its treatment. Administrations of antidepressants have been shown to enhance BDNF expression and phosphorylation of its cognate TrkB receptor. In contrast, stress exposure and depression is associated with down regulation of BDNF (Castren and Rantamäki, 2008). The Ras-mediated extracellular signal-regulated cascade (ERK) pathway is considered as a major BDNF/TrkB intracellular signalling pathway. To investigate the possible contribution of the BDNF/Ras/ERK-pathway on antidepressant activity we utilized a synRas transgenic mouse model expressing constitutively activated human Ha-Ras in differentiated neurons under the control of a synapsin I promoter (Heumann et al., 2000). The synRas mice show elevated levels of activated Ras and activating phosphorylation levels of ERK in the cortex and hippocampus. This is associated with an increased density of cortical spines and synapses as well as increased spontaneous synaptic release frequencies (Arendt et al., 2004). Immunoblotting analysis revealed that 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. Consistently, our results obtained in animal models of depression show an antidepressant-like behavior of the synRas transgenic mice compared to their wild type littermates. Furthermore, the synRas mice exhibit a normal basal HPA-axis activity, but a suppression of corticosterone release in response to acute restraint stress. However, chronic mild stress reversed the antidepressant-like phenotype.

Recently, an up regulation of adult neurogenesis in the hippocampus has been proposed by others to be correlated with drugs effective in the treatment of depressions (Malberg et al., 2000; Santarelli et al., 2003). Interestingly, the synRas mice displayed a reduction of the number of new born cells within the dentate gyrus of the hippocampus and deficient morphology of the DCX-positive immature neurons. This indicates that the antidepressive-like behavior is not linked to increased neural progenitor proliferation. Furthermore, we obtained some general aspects concerning neurogenesis and hippocampus dependent learning and memory. We could show that the neurogenesis of synRas-mice is not a static system. Chronic fluoxetine treatment increased the proliferation of progenitor cells and physical running activity
stimulated the dendritic branching of DCX-positive immature cells. Even the observed decline in working memory abilities in the hippocampus dependent radial maze task of the synRas mice could be abrogated by breeding with erythropoietin overexpressing mice.

Taken together our data support the idea, that the BDNF/Ras/ERK-pathway is critically involved in mood disorders and antidepressant activity. The results indicate that drugs that activate the Ras/ERK-Pathway should produce an antidepressant response. Furthermore, these results raise the eventuality that genetic variations in the Ras, MEK or ERK genes, could contribute to genetic vulnerability that results in depression. In addition, we obtained some general insights into the role of Ras in adult hippocampal neurogenesis, which could be useful for future neurogenesis research.