New approaches and targets in psychiatry: hippocampal neuroplasticity pathways in an animal model of depression: influence of chronic fluoxetine and Δ-9-tetrahydrocannabinol administration

Several intracellular pathways involved in cell proliferation in adult hippocampus, including the endocannabinoid (EC) system, are modulated by antidepressants. To extend our knowledge on the regulation of neuroplasticity by antidepressants and the implication of EC in these responses, we have evaluated the effects of chronic in vivo exposure to the SSRI drug fluoxetine (F) alone or in combination with Δ-9-tetrahydrocannabinol (T) on the expression of several neuroplasticity-related systems (β-catenin, AKT, pCREB and BDNF), in an animal model of depression. We measured protein levels by western blot in male Sprague Dawley bulbectomized rats, treated for 21 days with vehicle (saline), T (10 mg/kg/day, i.p.), F (10 mg/kg/day, p.o.) and T plus F. Olfactory bulbectomy resulted in a significant motor hyperactivity (open field test), reversed by chronic F. Bulbectomized animals exhibited a clear decrease (p< 0.05) in the levels of expression of β-catenin, AKT, BDNF and pCREB. Both F and T treatments produced an increase of hippocampal β-catenin (F= 159±17%, T= 142±70%, p<0.05), AKT, pCREB and BDNF (F= 318±97% T= 329±90%, p<0.05) levels in bulbectomized rats, with respect to the untreated group. A significantly higher effect (P<0.01) was observed following T+F association. Our results suggest the existence, in depressive disorders, of a reduced activity of proliferative pathways in the hippocampus, that could be reversed by both F and T treatments, indicating the possible implication of the EC system in the therapeutic antidepressant responses.