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Effect of *Tnf* gene knockout on behavior, BDNF expression, and brain serotonin system during long-term administration of dexamethasone

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Motivation and Aim: The pro-inflammatory cytokine tumor necrosis factor (TNF) is one of the key mediators between the immune and central nervous systems. TNF is involved in the regulation of behavior and the level of BDNF (brain-derived neurotrophic factor, a key neurotrophin within the brain), and the functioning of the serotonin system of the brain. In turn, chronic administration of the synthetic glucocorticoid dexamethasone can lead to changes in brain BDNF levels and behavioral impairments. Thus, the aim of this work was to study the effect of complete knockout of the *Tnf* gene on the sensitivity of mice to long-term administration of dexamethasone.
Methods and Algorithms: Adult C57BL/6J mice (WT) and mice with *Tnf* gene knockout (TNF KO) were injected daily with DEX (4 mg/kg, i. p.) or saline. The behavior of the animals was assessed in the following paradigms: the open field (OF), the tail suspension test (TST), the elevated plus maze (EPM) and the novel object (NO) tests.The level of expression of genes encoding BDNF, its TrkB and p75 receptors and key elements of brain serotonin system in several brain structures (prefrontal cortex, hippocampus, midbrain) were measured by real-time RT-PCR. The levels of BDNF and its precursor proBDNF proteins were measured by Western blot analysis, and the levels of serotonin (5-HT) and its metabolite 5-HIAA in the same brain structures were examined by HPLC. The data were analyzed by two-way ANOVA followed by LSD post-hoc test.
Results: Long-term administration of dexamethasone led to decrease in motor activity in the OF test ($p < 0.05$), an increase in depressive-like behavior in the TST ($p < 0.05$) and in anxiety-like behavior in the EPM test ($p < 0.05$) only in TNF KO mice, but not in WT mice. In contrast, deterioration in cognitive performance in the NO test was observed only in WT mice ($p < 0.05$). An increase in the expression of the *Bdnf* gene at the mRNA level in hippocampus ($p < 0.05$) was observed only in TNF KO mice ; the increase in the proBDNF protein level in the frontal cortex was revealed in both strains of mice ($p < 0.05$ for WT and $p < 0.001$ for TNF KO). Dexamethasone also led to a decrease in the expression of the gene encoding the 5-HT7 receptor ($p < 0.05$) in the midbrain of TNF KO animals.
Conclusion: Thus, the depressive-like and anxiety-like behavior of TNF KO mice caused by long-term administration of dexamethasone can be explained by an increase in the level of proBDNF and the proBDNF/BDNF ratio in the hippocampus, detected only in animals of this strain. This, in turn, may be associated with differences in neurogenesis in the hippocampus in knockout animals. The data obtained allow us to expand our understanding of the influence of the immune system on neurotrophic support and the functioning of the serotonin system of the brain.