# REGULATION OF TRANSCRIPTIONAL ACTIVITY IN HIPPOCAMPUS OF GLUCOCORTICOID RECEPTOR IMPAIRED TRANSGENIC MICE: EFFECTS OF RESTRAINT STRESS

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Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin with an important role in synaptic plasticity of adult CNS. The gene codifying for BDNF is a stress-responsive gene: alterations in its expression may be important in producing some of the pathophysiological effects of stress in the hippocampus described in stress-related pathology like depression. While the effects of stress procedures on the regulation of BDNF expression has been widely investigated in hippocampus of control animals, the stress-induced effects on BDNF hippocampal expression in a "pathological" condition are still lacking. Here, we used glucocorticoid receptor impaired (GRi) transgenic mice [1], created as a model to study the neuroendocrine changes observed in stress-related disorders. These mice are characterized by dysfunctional glucocorticoid inhibitory feedback and an excessive activation of the hypothalamic-pituitary-adrenal (HPA) axis, that can be restored by antidepressant drugs treatment. The aim of this study was two-folds 1) to determine whether BDNF expression in the hippocampus is differently influenced by 30 minutes of restraint stress in GRi mice compared to wild-type (WT) mice, and 2) how altered BDNF expression is regulated at the transcriptional level. Initially, a RNAse protection assay was used to evaluate BNDF gene expression. An increase in BDNF mRNA in GRi mice was observed after a single period of restraint stress as compared to non restrained TG mice. In contrast, the same short period of restraint stress did not alter BDNF expression in WT mice.
BDNF is a very complex gene regulated by a wide array of stimuli and signalling pathways. Using an electrophoresis mobility shift assay, the DNA-binding activity of three transcription factors implicated in the regulation of BDNF was studied: cAMP response element binding (CREB) protein, nuclear factor kappaB (Nf-kB), calcium responsive transcription factor (CaRF). Taken together, our results show a different binding activity of these transcription factors in GRi mice with respect to WT mice both under basal and following brief stressful conditions. Our data demonstrated that, in the presence of psycho-physiological stress GRi mice display altered hippocampal regulation in BDNF gene expression. Thus, life-long central GR dysfunction results in an altered sensitivity, at transcriptional level, with respect to restraint stress and this could be a predisposing or determining factor in depression.

[1] Pepin M.C., Pothier F. and Barden N. (1992) Nature 355: 725-8.