

ORIGINAL ARTICLE

Neuronal Activity, TGF β -Signaling and Unpredictable Chronic Stress Modulate Transcription of *Gadd45* Family Members and DNA Methylation in the Hippocampus

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Abstract

Neuronal activity is altered in several neurological and psychiatric diseases. Upon depolarization not only neurotransmitters are released but also cytokines and other activators of signaling cascades. Unraveling their complex implication in transcriptional control in receiving cells will contribute to understand specific central nervous system (CNS) pathologies and will be of therapeutically interest. In this study we depolarized mature hippocampal neurons *in vitro* using KCl and revealed increased release not only of brain-derived neurotrophic factor (BDNF) but also of transforming growth factor beta (TGFB). Neuronal activity together with BDNF and TGFB controls transcription of DNA modifying enzymes specifically members of the DNA-damage-inducible (*Gadd*) family, *Gadd45a*, *Gadd45b*, and *Gadd45g*. MeDIP followed by massive parallel sequencing and transcriptome analyses revealed less DNA methylation upon KCl treatment. Psychiatric disorder-related genes, namely *Tshz1*, *Foxn3*, *Jarid2*, *Per1*, *Map3k5*, and *Arc* are transcriptionally activated and demethylated upon neuronal activation. To analyze whether misexpression of *Gadd45* family members are associated with psychiatric diseases, we applied unpredictable chronic mild stress (UCMS) as established model for depression to mice. UCMS led to reduced expression of *Gadd45* family members. Taken together, our data demonstrate that *Gadd45* family members are new putative targets for UCMS treatments.

Key words: ARC, BDNF, depolarization, depression, DNA demethylation

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