Glucocorticoid action in the brain: from modified histones to modified behaviour

Reul JMHM
Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, University of Bristol, Bristol, UK

Glucocorticoids act on numerous processes in the brain including those underlying stress coping. Coping with stress involves changes in gene expression. Control of gene expression is tight and normally most of the genome is silent with the chromatin being structurally organized in nucleosomes. The nucleosomes consist of highly organized complexes of DNA and histone molecules and represent a barrier to transcription by blocking access of transcription factors. Based on mainly *in vitro* work, nuclear receptors such as the glucocorticoid receptor (GR) seem nevertheless to be able to access their hormone responsive elements, thereby unlocking the nucleosome and rendering it accessible for molecules involved in chromatin remodeling and gene transcription. Recently, substantial progress has been made in obtaining insight into the role of chromatin remodeling in the control of gene expression. The concept has been developing that distinct post-translational modifications in the N-terminal tails of histone molecules (e.g. phosphorylation of histone H3 at serine-10) play a decisive role in chromatin remodeling and making the underlying genome accessible for transcription factors and other molecules involved in gene transcription. Recently, we obtained evidence for the involvement of chromatin remodeling in distinct hippocampal neurons in stress-related behavioural responses. It was found that the acquired immobility response after forced swimming was associated with an increase in the number of neurons showing nuclear immuno-staining for phosphorylated histone H3. Intact GR signaling proved to be a prerequisite for both the histone modification response and the behavioural response. Thus, detection of distinct histone modifications can be used to identify those neurons in which transcriptional activation of formerly inactive genes is taking place. Our observations indicate that chromatin remodeling in neurons participates in neuroplasticity processes underlying stress coping. Moreover, GR appears to play a critical role in stress-induced chromatin remodeling, possibly corresponding with its alledged role in nucleosome unlocking.

Johannes M.H.M. Reul, Henry Wellcome Laboratories for Integrative Neuroscience and Endocrinology, The Dorothy Hodgkin Building, Whitson Street, University of Bristol, Bristol, BS1 3NY, United Kingdom, t +44 117 331 3137, e-mail hans.reul@bristol.ac.uk

Plenary Session 5