The endocrine control of histone acetylation in regulating gonadotropin gene expression

Rendicontazione

Informazioni relative al progetto

HATS

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Progetto chiuso

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Final Report Summary - HATS (The endocrine control of histone acetylation in regulating gonadotropin gene expression)

The focus of this project was the central regulation of reproduction through the hypothalamic regulation of the pituitary gonadotropic hormones, luteinising hormone (LH) and follicle stimulating hormone (FSH), and the role of the chromatin structure in this regulation. Our hypothesis was that activation of LH and FSH synthesis by the hypothalamic gonadotropin releasing hormone (GnRH) involves targeting of the chromatin, through acetylation of histones. Histones can be acetylated by histone acetyl transferases (HAT) which are recruited to the gene promoters by gene-specific transcription factors. These enzymes play an integral role in determining chromatin structure through altering the interaction of the histones with the deoxyribonucleic acid (DNA) wrapped around them and/or by providing a signal for the binding of additional regulatory proteins including other chromatin modifying and remodelling enzymes. Accordingly, we aimed to study the HATs involved in this regulation, they mechanisms through which they are recruited to the gonadotropin gene promoters and their regulation by GnRH treatment. We also sought to understand their role and relationship in respect to other histone modifications.

We have established the basal levels of histone H3 acetylation at a number of lysines in unstimulated gonadotrope cells for all three subunit genes, and shown how this correlates with expression levels and other features of the chromatin. We have demonstrated GnRH-induced H3 acetylation at the LH-beta gene promoter and have elucidated likely mechanisms of HAT recruitment. This appears to involve both interactions with gene-specific transcription factors and cross-talk between additional histone modifications that are stimulated by GnRH. The FSH-beta gene was recently reported to be activated by the HAT CREB binding protein (CBP), which can be recruited by the transcription factor CREB. However our findings indicate that CBP recruitment is also regulated via competition with a different CREB coactivator, TORC1.

TORC is activated by the phosphatase calcineurin which, as we have shown, comprises a major part of the GnRH signalling pathway to FSH-beta gene expression. We also discovered that GnRH has a novel effect on TORC, initially causing its rapid degradation, followed by protection of the N-terminus of the newly synthesized protein, which appears degraded or inaccessible in the untreated cells. As the N-terminus is involved in TORC protein-protein interactions, this GnRH effect serves to enhance TORC activity. TORC interacts also with Nur77 at the FSH-beta gene promoter, and the three factors, TORC, Nur77 and CREB have a strong synergistic effect on promoter activity, without need for the CREB phosphorylation and/or the HAT activity of CBP.

We have thus furthered our understanding of the role and regulation of histone acetylation in transcription of the LH and FSH beta-subunit genes. However histone acetylation is likely centrally linked to other histone modifications, and we will continue to integrate these findings with our other work on the regulation of the chromatin at these genes by GnRH. In this way, we are addressing two aspects of particular interest: first, the mechanisms through which a membrane-bound receptor can induce modifications in the chromatin at a specific gene locus, which is of major interest to the basic biologist and has wide implications in all biological systems involving the extracellular-mediated regulation of gene expression. Despite its fundamental nature, this aspect of gene regulation is still very poorly understood. Secondly, the research addresses quite specifically the mechanisms through which GnRH activates the gonadotropin genes. The clarification of these processes should lead to a better understanding of various disorders in reproductive function.

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