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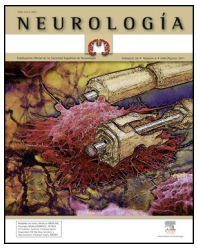

REVIEW ARTICLE

Epigenetics and epilepsy☆

L. Pulido Fontes[a,b,*], P. Quesada Jimenez[a], M. Mendioroz Iriarte[a,b]

[a] Servicio de Neurología, Complejo Hospitalario de Navarra, Pamplona, Navarra, Spain
[b] Navarrabiomed, Pamplona, Navarra, Spain

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Epigenetics;
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Abstract
Introduction: Epigenetics is the study of heritable modifications in gene expression that do not change the DNA nucleotide sequence. Some of the most thoroughly studied epigenetic mechanisms at present are DNA methylation, post-transcriptional modifications of histones, and the effect of non-coding RNA molecules. Gene expression is regulated by means of these mechanisms and disruption of these molecular pathways may elicit development of diseases.
Development: We describe the main epigenetic regulatory mechanisms and review the most recent literature about epigenetic mechanisms and how those mechanisms are involved in different epileptic syndromes.
Conclusion: Identifying the epigenetic mechanisms involved in epilepsy is a promising line of research that will deliver more in-depth knowledge of epilepsy pathophysiology and treatments.

PALABRAS CLAVE
Epigenética;
Neurodesarrollo;
Epileptogénesis;
Epilepsia

Epigenética y epilepsia

Resumen
Introducción: La epigenética es el estudio de los cambios heredables en el ADN sin afectar a las secuencia de nucleótidos. Entre los mecanismos de regulación epigenética, los más estudiados y conocidos hasta la fecha son la metilación del ADN, la modificación de las histonas y los ARN no codificantes. Mediante estos mecanismos se regula la expresividad génica y la alteración de los mismos puede llevar al desarrollo de patologías.
Desarrollo: Describimos los principales mecanismos de regulación epigenética y realizamos una revisión de la bibliografía reciente sobre los mecanismos de regulación epigenética y su implicación en distintos síndromes epilépticos.

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* Corresponding author.
E-mail address: lpfontes7@yahoo.es (L. Pulido Fontes).

Conclusión: La identificación de los mecanismos epigenéticos implicados en la epilepsia constituye una prometedora vía de investigación para profundizar en el conocimiento de la fisiopatología y terapéutica de esta enfermedad.

Introduction

The term 'epigenetics' is attributed to Conrad Waddington, who in 1942 defined it as 'the branch of biology that studies the causal interactions between genes and their products, which bring the phenotype into being'.[1] Today, this area of study is expanding rapidly and delivering results that will hold medical relevance.

In simple terms, we can define epigenetics as the study of inheritance of heritable changes in gene expression that occur with no modifications to the DNA sequence.[2] Epigenetic processes may therefore be understood as gene expression regulating mechanisms that determine not only expression or silencing but also where, when, and how intensely genes are expressed.

Evidence shows that these epigenetic processes may be modified by physical, chemical, nutritional, and even psychosocial factors. As such, our environment and life habits are able to modify genetic expression through epigenetic mechanisms.[3,4]

Epigenetics may help us answer questions that have yet to be fully answered: for example, how is it that 2 individuals with the same genetic load —monozygotic twins, for example— may demonstrate differences in appearance, behaviour, and illness?[5] And how can the environment affect the genome?

Epigenetic regulatory mechanisms in epilepsy

Basic epigenetic mechanisms

Several epigenetic mechanisms are now known. Although novel mechanisms are being discovered, along with new effects produced by known mechanisms, three main types have received the most study: DNA methylation, histone modification, and the action of non-coding RNA.

DNA methylation

DNA methylation is the most thoroughly studied epigenetic mechanism. It consists of the addition of a methyl group to the carbon 5 of those cytosine molecules that are followed by guanine (CpG dinucleotides). These molecules are not distributed in the genome in a uniform manner; rather, they appear in clusters called CpG islands, which are primarily located in gene promoters. CpG islands are not usually methylated, but methylation of these clusters is required by some physiological processes, such as genomic imprinting or X-inactivation in females. In contrast, the other CpG dinucleotides that are not included in CpG islands are methylated and mainly located in repetitive sequences or near the centromere. Methylation is carried out by DNA methyltransferases (DNMT) that catalyse the transfer of a methyl group from S-adenosyl-L-methionine to carbon 5 of cytosine. Five types are known in mammals: DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L.[6] Maintaining correct metabolism of vitamin B_{12}, folic acid, and homocysteine is of vital importance to this process.

Methylation of the gene promoter is generally associated with transcription inhibition, otherwise known as gene silencing. Methylation inhibits transcription through 2 basic mechanisms. The first impedes binding of transcription regulatory factors whose recognition sites contain CpG. The second mechanism involves protein complexes that specifically bind to methylated CpG sites and indirectly prevent transcription factor binding by limiting the access of regulatory elements.[6] These protein complexes are known as methyl-CpG binding domains (MBDs). There are 5 families in mammals: MeCP2, MBD1, MBD2, MBD3, and MBD4. In this way, DNA methylation indirectly regulates the structure of chromatin and DNA accessibility for transcription factors (Fig. 1).[7]

Histone modification

Nuclear DNA is associated with a multiprotein complex that forms chromatin. The nucleosome is the basic structural unit of chromatin. It consists of 146 base pairs of DNA wound around 8 proteins called histones (a H3/H4 tetramer, 2 H2A and H2B dimers, and a H1 molecule). In addition to providing structural support, histones regulate accessibility for transcription factors, thereby determining gene expression. This occurs through epigenetic modifications that take place in each of the N-terminus tails that extend beyond the nucleosome, mainly in the N-terminals of H3 and H4. These modifications include methylation, acetylation, phosphorylation, ubiquitination, and ADP-ribosylation.[8] The best-studied modification is the acetylation of lysine residues. The state of acetylation of H3 and H4 histones increases gene expression by promoting the open configuration of chromatin; the hypoacetylation state is typical of transcriptionally inactive areas of the genome (Fig. 2).[9] This process is carried out by histone acetyltransferase and reversed by histone deacetylases (HDAC). Another modification that takes place is methylation, a process that occurs due to the activity of methyltransferase and by histone demethyltransferase. The effect of this modification depends on the type of modified residue and the degree