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Review

Sex, epilepsy, and epigenetics

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ABSTRACT

Epilepsy refers to a heterogeneous group of disorders that are associated with a wide range of pathogenic mechanisms, seizure manifestations, comorbidity profiles, and therapeutic responses. These characteristics are all influenced quite significantly by sex. As with other conditions exhibiting such patterns, sex differences in epilepsy are thought to arise—at the most fundamental level—from the "organizational" and "activational" effects of sex hormones as well as from the direct actions of the sex chromosomes. However, our understanding of the specific molecular, cellular, and network level processes responsible for mediating sex differences in epilepsy remains limited. Because increasing evidence suggests that epigenetic mechanisms are involved both in epilepsy and in brain sexual dimorphism, we make the case here that analyzing epigenetic regulation will provide novel insights into the basis for sex differences in epilepsy.

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Introduction

Epilepsy refers to a broad spectrum of disease states, including both genetic and acquired disorders, which can be associated with varying pathogenic mechanisms, seizure patterns and frequencies, comorbid conditions (e.g., autism and other neurodevelopmental and neuropsychiatric disorders), therapeutic responses and toxicities (e.g., alterations in sex hormone metabolism), and clinical outcomes. Clinical observations and translational research efforts suggest that these features are all influenced to a significant degree by sex (Veliskova and Desantis, 2013; Perucca et al., 2014b; Savic and Engel, 2014; Kight and McCarthy, 2014; Giorgi et al., 2014; Akman et al., 2014; van Luijtelaar et al., 2014; Scharfman and MacLusky, 2014; Koppel and Harden, 2014; Reddy, 2014; Perucca et al., 2014a; Pitkänen, et al., 2014). For example, epidemiological and genetic studies have revealed that some syndromes are more common in females, including those which are thought to be X chromosome-linked (e.g., Aicardi syndrome, Rett

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syndrome [RS], and protocadherin 19-related infantile epileptic encephalopathy) as well as those that show gender differences due to different genetic and non-genetic factors (e.g., juvenile myoclonic epilepsy). Other syndromes are more common in males (e.g., Ohtahara syndrome, infantile spasms [IS], Lennox–Gastaut syndrome, Landau–Kleffner syndrome, and febrile seizures), with males exhibiting an overall incidence of seizures and prevalence of epilepsy slightly greater than that of females. Additional studies have demonstrated sex-specific patterns of seizure susceptibility, laterality, and generalization; brain regional dysfunction between ictal periods; and seizure-associated neuronal injury in epileptic disorders, such as temporal lobe epilepsy (TLE) (Veliskova and Desantis, 2013; Perucca et al., 2014b; Savic and Engel, 2014; Kight and McCarthy, 2014; Giorgi et al., 2014; Akman et al., 2014; van Luijtelaar et al., 2014; Scharfman and MacLusky, 2014; Koppel and Harden, 2014; Reddy, 2014; Perucca et al., 2014a; Pitkänen, et al., 2014). There is also emerging evidence that common pathological features in epilepsy syndromes are linked with sex differences, such as subtle distinctions in white matter associated with hippocampal sclerosis that can be identified in patients with TLE with diffusion tensor imaging (Oguz et al., 2013). Studying the mechanisms responsible for these selective differences is of great interest for better understanding the onset and progression of epilepsy and for uncovering novel, more effective, and personalized strategies for diagnosis, prevention, and therapy.

As with other conditions exhibiting such patterns, sex differences in epilepsy are thought to arise from the effects of sex hormones. Indeed, many important studies have focused on dissecting the complex and multidimensional influences of androgens, estrogens, and progesterone (along with glucocorticoids and mineralocorticoids) on the process of epileptogenesis and the expression of seizure disorders, including their "organizational" roles during developmental programming and "activational," or acute, effects later in life, which can include modulating neuronal excitability and cell death (Frye, 2008; Veliskova and Desantis, 2013). Their mechanisms can include both canonical genomic functions as well as non-genomic activities. These hormones can even be synthesized locally within the nervous system (i.e., neurosteroids), highlighting their extremely high degree of integration into neurobiological processes (Reddy and Rogawski, 2012; Reddy, 2014). In addition, sex differences in epilepsy are also likely to arise because of the direct effects of sex chromosomes (McCarthy and Arnold, 2011). In fact, recent evidence has shown that cell type- and region-specific gene expression profiles in brain and associated behavioral phenotypes can be sexually dimorphic independent from the effects of gonadal sex hormones. These observations demonstrate that the complement of sex chromosomes and the genes they encode, such as the sex determining region Y (*SRY*) gene, mediate sex differences directly, which represents a paradigm shift away from the classic hormonal milieu model (McCarthy and Arnold, 2011). This insight is specifically relevant for epilepsy as several sex chromosome complement modulated genes are linked with neuronal excitability and neurotransmitter signaling, and many sex chromosome complement modulated behaviors (i.e., social interaction, aggression, anxiety, feeding, habit formation, learning, nociception, circadian rhythms, and visuospatial attention) share underlying modules of neural circuitry with epilepsy and its comorbid conditions (Cox et al., 2014; McCarthy and Arnold, 2011; Seney et al., 2013). Embracing this novel perspective on the basis for sex differences has, in turn, raised important questions about how these hormonal and genetic factors function separately and interactively.

In this review, we introduce the principal epigenetic regulatory mechanisms and discuss how these processes are now emerging as prime mechanisms responsible for integrating hormonal and genetic influences—along with environmental stimuli—at the molecular, cellular, and neural network levels (McCarthy and Nugent, 2013; Qureshi and Mehler, 2010b). Furthermore, we highlight the rapidly expanding body of evidence, which suggests that epigenetic factors and mechanisms (and their deregulation) serve as key players in the pathogenesis of epileptic disorders and the process of epileptogenesis (Hwang et al., 2013; Qureshi and Mehler, 2010a). We believe that, because epigenetic processes are so intimately involved in sexual dimorphism and in epilepsy, analyzing epigenetic regulation will provide novel, clinically relevant, and potentially actionable insights into the basis for sex differences in epilepsy.

Principal epigenetic mechanisms

Epigenetic mechanisms are essentially those cellular processes that regulate the structure and function of the genome in response to interoceptive and environmental stimuli. These mechanisms are responsible for storing, accessing, and selectively utilizing genetic information in a biological context-dependent manner (e.g., during development and cellular differentiation (Tollervey and Lunyak, 2012)). More specifically, epigenetic processes act at a biophysical and biochemical level to promote the execution of genomic programs, such as transcriptional regulation, long term gene silencing, transposable element activity, genomic imprinting, X-chromosome inactivation (XCI), DNA replication and repair, and the maintenance of genomic stability. Because of their roles in these critical functions, epigenetic factors and mechanisms are linked to most, if not all, physiological processes and to nearly every major class of disease (Portela and Esteller, 2010). In particular, recent studies have begun to define how the differential deployment of epigenetic mechanisms underlies brain development and aging, neural cell identity and diversity, synaptic and neural network connectivity and activity-dependent plasticity, and homoeostatic and stress responses; in turn, primary or secondary deregulation of epigenetic processes is increasingly being implicated in the pathophysiology of nervous system diseases, including epilepsy (see below) (Mehler, 2008; Portela and Esteller, 2010; Qureshi and Mehler, 2012).

The foremost epigenetic mechanisms include DNA methylation (and hydroxymethylation), histone protein post-translational modifications (PTMs) and higher-order chromatin remodeling, and non-coding RNA (ncRNA) regulation. These multilayered processes are highly interconnected and exert their regulatory effects through coordinate actions.

DNA methylation describes the covalent modification of carbon atoms at the 5-position in the cytosine aromatic ring, which leads to the formation of 5-methylcytosine (5mC) (Mehler, 2008; Portela and Esteller, 2010; Qureshi and Mehler, 2012). 5mC can be found associated with CpG dinucleotides in gene regulatory regions (i.e., promoters) as well as other genomic sites (particularly in neurons). This epigenetic "mark" is generally thought to promote transcriptional silencing of methylated regions. Mechanistically, several factors can bind to methylated regions (e.g., methyl-CpG-binding domain [MBD] proteins), and these "readers" of methylation marks recruit additional modulatory factors to methylated sites. Many of these effector proteins play roles in transcriptional regulation and chromatin modifications. The methylation reaction is catalyzed by members of the DNA methyltransferase (DNMT) family of enzymes, including those responsible for *de novo* methylation events and for the maintenance of methylation. In addition, profiles of 5mC are dynamic and can be subject to active methylation-demethylation cycles. Specifically, 5mC can be oxidized into 5-hydroxymethylcytosine (5hmC) and other derivatives, which have distinct but still poorly characterized functions that are nevertheless clearly important in brain. Members of the ten-eleven translocation (TET) family of enzymes catalyze these oxidation reactions.

Chromatin is responsible for the compaction of DNA within the cell nucleus (Mehler, 2008; Portela and Esteller, 2010; Qureshi and Mehler, 2012). Dynamic changes in chromatin states into more or less open configurations modulate the accessibility of specific DNA sequences to other nuclear factors, such as those involved in transcription and DNA replication and repair. These alterations in chromatin can occur over multiple hierarchical levels. Histone protein PTMs refer to covalent modifications