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Epigenetic interventions for epileptogenesis: A new frontier for curing epilepsy

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ABSTRACT

This article highlights the emerging therapeutic potential of specific epigenetic modulators as promising antiepileptogenic or disease-modifying agents for curing epilepsy. Currently, there is an unmet need for antiepileptogenic agents that truly prevent the development of epilepsy in people at risk. There is strong evidence that epigenetic signaling, which exerts high fidelity regulation of gene expression, plays a crucial role in the pathophysiology of epileptogenesis and chronic epilepsy. These modifications are not hard-wired into the genome and are constantly reprogrammed by environmental influences. The potential epigenetic mechanisms, including histone modifications, DNA methylation, microRNA-based transcriptional control, and bromodomain reading activity, can drastically alter the neuronal gene expression profile by exerting their summative effects in a coordinated fashion. Such an epigenetic intervention appears more rational strategy for preventing epilepsy because it targets the primary pathway that initially triggers the numerous downstream cellular and molecular events mediating epileptogenesis. Among currently approved epigenetic drugs, the majority are anticancer drugs with well-established profiles in clinical trials and practice. Evidence from preclinical studies supports the premise that these drugs may be applied to a wide range of brain disorders. Targeting histone deacetylation by inhibiting histone deacetylase enzymes appears to be one promising epigenetic therapy since certain inhibitors have been shown to prevent epileptogenesis in animal models. However, developing neuronal specific epigenetic modulators requires rational, pathophysiology-based optimization to efficiently intercept the upstream pathways in epileptogenesis. Overall, epigenetic agents have been well positioned as new frontier tools towards the national goal of curing epilepsy.

Contents

Abbreviations: AEDs, antiepileptic drugs; BET, bromodomain and extra-terminal domains; CCI, controlled cortical impact; CNS, central nervous system; DG, dentate gyrus; DM, demethylase; DNMT, DNA methyltransferases; EC, electroconvulsive; HAT, histone acetyltransferases; HATi, histone acetyl transferase inhibitor; HCN, hyperpolarization-activated cyclic nucleotide; HDAC, histone deacetylases; HDACi, histone deacetylase inhibitor; IBO, ibotenic acid; KA, kainic acid; KO, knockout; MBD, methyl-CpG-binding domain proteins; miRNA, micro-RNA; NRSF, neuron-restrictive silencer factor; PTZ, pentylenetetrazol; RES, repressor element 1-silencing transcription factor; SE, status epilepticus; TBI, traumatic brain injury; TLE, temporal lobe epilepsy; TSA, trichostatin A; VPA, valproic acid.

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1. Molecular cascades of epileptogenesis

The term 'epileptogenesis' is used to describe the complex plastic changes in the brain that convert a normal brain into a brain debilitated by recurrent seizure activity (Pitkänen, Immonen, Gröhn, & Kharatishvili, 2009; Reddy, 2013). The progression of epileptogenesis can be divided into three phases: the initial injury phase, the latent phase, and the chronic phase (Engel et al., 2007; Goldberg & Coulter, 2013). During the initial injury phase, an insult such as stroke, traumatic brain injury (TBI), brain infection, or exposure to a neurotoxin can activate a host of signaling cascades, triggering the epileptogenic pathway. These signals induce changes that lead to neuroinflammation, oxidation, apoptosis, synaptic plasticity, and functional alterations in the neuronal and neurovascular unit (Pitkänen et al., 2009). The resulting physiological responses alter gene expression in neuronal ensembles by modifying the epigenetic landscape. Next, a dynamic process ensues leading to the rearrangement of synaptic circuitry, neuronal damage, neurogenesis, and synchronic hyperexcitability. These dynamic changes are characteristic of the latent phase, characterized as the most unpredictable phase because it can last several weeks, months, or even years without any clinical symptoms. These changes eventually manifest in spontaneous seizure activity, marking onset of the chronic phase. Intervening in these underlying molecular cascades of epileptogenesis may lead to discoveries and eventual breakthroughs in the development of a cure for epilepsy.

Currently, there is an unmet need for antiepileptogenic agents that truly prevent the development of epilepsy or disease-modifying agents that delay the appearance or severity of epileptic seizures in people at risk (Jacobs et al., 2009). Antiepileptic drugs (AEDs) are the mainstay treatment for epileptic seizures, but about one-third of people with epilepsy show intractable seizures that are resistant to even the best drug therapy (Kwan & Sander, 2004; Löscher & Schmidt, 2011). Moreover, many clinical trials showed a lack of antiepileptogenic efficacy of AEDs in patients at high risk for developing epilepsy (Temkin, 2001, 2009). Some AEDs on the market may be adequate in treating an acute seizure occurrence but have no effect on the underlying cause of the seizure, leading to prolonged and unpredictable seizure activity that can further debilitate the brain (Löscher & Brandt, 2010). Thus, conventional AEDs do not exert a true antiepileptogenic effect, partly because the mechanisms behind anticonvulsant and antiepileptogenic activity are instinctively distinct in the various forms of acquired epilepsy in humans (Reddy, 2011). This is explained by the fact that epilepsy is a spectrum disorder that varies in origin and disease course (Hesdorffer et al., 2013). The heterogenic nature of epilepsy disorders represents both challenges and opportunities for epilepsy research and drug development.

Understanding the causes and halting the progression of various forms of epilepsy are identified as top priorities in the 2014 NIH/NINDS Benchmarks for Epilepsy Research. To fill the gaps in epilepsy research, many labs have been pioneering investigations on the pathophysiology of the mechanisms underlying epileptogenesis. Pinpointing specific targets within the early phases of epileptogenesis may lead to breakthroughs in the development of novel therapies for epilepsy (Löscher, 2002; Pitkänen et al., 2007). It is well accepted that epigenetics, neuroinflammation, and neurodegeneration are the critical players underlying the progression of epileptogenesis (Gibson et al., 2014; Pitkänen et al., 2009; Reddy, 2013). However, there are crucial gaps in knowledge on the fundamental mechanisms of epigenetics and neuronal network pathways that are responsible for the spatial and temporal events ultimately leading to epilepsy. Therefore, a mechanism-based, rational approach through multidisciplinary research is essential for advancing the national goal of curing epilepsy within the next decade.

The central premise of 'epigenetic therapy' is dependent on the potential reversibility of the epigenetic profile, independent of the non-reversible genome. Signaling pathways that regulate epigenetic enzymes are the fundamental targets of epigenetic therapies. Among currently approved epigenetic drugs, the majority are anti-cancer drugs with well-established profiles in clinical trials and practice (Table 1). Thus, the potential side effects and toxic effects of these drugs have been thoroughly explored and reported. Pre-clinical evidence supports that these drugs may be applied to a wide range of central nervous system disorders. In this article, we highlight the emerging therapeutic potential of a growing collection of epigenetic modulators spanning multiple classes as promising antiepileptogenic or disease-modifying agents for epilepsy.

2. Fundamentals of epigenetic mechanisms in epilepsy

Chromatin and epigenetic modifications play a crucial role in the regulation of gene expression underlying several nervous system disorders such as epilepsy (Fig. 1). Epigenetics refers to specific changes in gene expression that are not hard-wired into the genome and are constantly being reprogrammed by environmental factors. The epigenetic landscape is maintained by epigenetic enzymes called 'writers' and 'erasers', which can either encode epigenetic marks or remove them, respectively. These marks are crucial for normal physiological functions during embryogenesis, brain development, and in the day-to-day regulation of gene expression (Hwang, Aromolaran, & Zukin, 2013). Furthermore, a class of 'readers,' the bromodomain and extra-terminal domains (BETs) recognize modifications on histone tails and modulate appropriate gene expression of these epigenetic instructions. This incredibly

Table 1
Epigenetic drugs approved for clinical use and in experimental investigation.

Class	Epigenetic target	Agent name	Developmental stage	Therapeutic target
HDAC inhibitors	HDAC I & II	Valproic acid (VPA)	Approved (1986)	Epilepsy
		Vorinostat (SAHA)	Approved (2006)	T-cell lymphoma
		Belinostat (PXD101)	Approved (2014)	T-cell lymphoma
		Panobinostat (LBH589)	Approved (2015)	Multiple myeloma
		Abexinostat (PCI24781)	Phase II	B-cell lymphoma
		CI994	Phase II	Multiple myeloma
	HDAC I only	Romidepsin (Depsipeptide)	Approved (2009)	T-cell lymphoma
		Entinostat (MS275)	Phase II	Hodgkin's lymphoma
		Mocetinostat (MGCD0103)	Phase II	Hodgkin's lymphoma
		Givinostat (ITF2357)	Phase II	Hodgkin's lymphoma
DNMT inhibitors	DNMTs	5-Azacytidine (Azacitidine)	Approved (2004)	Myelodysplastic syndrome
		5-Aza-2-deoxycitidin (Decitabine)	Approved (2006)	Myelodysplastic syndrome & leukemia
		Zebularine	Preclinical	Various cancers
	DNMT I only	MG98	Phase II	Renal cell carcinoma
BET inhibitors	BRDs 2,3,4	JQ1	Preclinical	Various cancers
		iBET	Preclinical	Leukemia & epilepsy