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Review article

The molecular hallmarks of epigenetic effects mediated by antiepileptic drugs

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ABSTRACT

Epilepsy is associated with several epigenetic changes, such as DNA methylation, histone modification, and alterations in the synthesis and functioning of non-coding RNAs (ncRNAs). Paradoxically, antiepileptic drugs (AEDs) that are widely used to control epilepsy may also induce epigenetic modifications and alter the structure of chromatin. As a consequence, changes in the expression of various factors involved in the pathology of epilepsy may positively or negatively affect the course of the disease. It should be noted that while AEDs are widely used in the treatment of epilepsy and other neurological disorders, many of their epigenetic consequences are still unknown. Moreover, an improved understanding of AED-induced epigenetic alterations could provide new targets for future therapeutic interventions. In this review, we give a general overview of the current scientific evidence concerning the epigenetic effects of AEDs that are currently in clinic use and have been evaluated to date.

1. Introduction

Epilepsy is a neurological disorder with a high prevalence worldwide (4.7 to 12 per 1000) (Ngugi et al., 2010). People suffering from epilepsy present with spontaneous recurrent seizures that are a result of brain alterations. The quality of life for people with epilepsy can be impaired due to seizure activity, a high likelihood of mood and psychiatric disorders, cognitive alterations and the side effects of antiepileptic drugs (AEDs).

The purpose of any pharmacological anticonvulsant treatment is to control the epileptic activity and comorbid disorders, as well as to improve the quality of life for the patient (Wei et al., 2015). However, AEDs induce a number of side effects that include cognitive and behavioral disorders (Cavanna et al., 2010; Loring and Meador, 2001) and emotional (Brodie et al., 2016) and endocrine impairments (Hamed, 2016).

People with epilepsy present a high comorbidity of psychiatric disorders including psychosis, neuroses, mood disorders and behavioral changes with epilepsy (Tellez-Zenteno et al., 2007). Depression in epilepsy, the most common comorbidity, is associated with multiple risk factors, specific types of seizures and various biochemical alterations (Gaitatzis et al., 2004). Moreover, people with epilepsy are 2–11 times more likely to have schizophrenia than the people without epilepsy, depending upon the severity of seizures (Fruchter et al., 2014). Personality disorders, especially Borderline Personality Disorder (BPD) and bipolar disorder (BD), have a high prevalence (18%) in people with epilepsy. A number of explanations of the high comorbidity of psychiatric disorders in epilepsy have been put forth, including genetics, structural changes and pharmacological therapies (Sucksdorff et al., 2015; Swinkels et al., 2003). In addition, people with epilepsy may develop treatment-emergent psychiatric adverse events of AEDs, regardless of the mechanism of action of the drug (Mula, 2017; Mula et al., 2007). This information leads to suggest that epigenetic changes induced by AEDs in people with epilepsy may be involved in the high prevalence of comorbid psychiatric disorders (see Section 4), and they have to be considered during clinical therapy.

Epigenetic modifications at the level of DNA or histones that are associated with epilepsy, as well as other mediating factors, could represent new targets for the development of more selective and effective AEDs that have fewer side-effects (Wei et al., 2015). For example, the design of epigenetic therapies that selectively inhibit DNA methylation and thereby reactivate the expression of silenced genes represents an option for epilepsy treatment.

The first section of this review includes a general description of

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epigenetics. The next section presents information regarding the involvement of epigenetic regulation in human epilepsy. The last section focuses on the presentation of evidence of the induction of epigenetic changes by AEDs. This information was obtained through bibliographic searches of PubMed (NIH) and Google Scholar using the following search terms: “epigenetics and epilepsy”, “epilepsy and DNA methylation”, “epilepsy and histones modifications”, “epilepsy and… (each one of the most common histone modifications)”, “epilepsy and ncRNAs”, “epigenetics and AEDs” and “epigenetics and…(each one of the 33 AEDs in clinical use currently)” (Supplementary Table). This search found evidence of involvement in epigenetic changes for only 13 AEDs, while for the remainder (20 AEDs), no such evidence was found.

2. Epigenetic regulation of gene expression

DNA is compressed hierarchically into the cell nucleus via its association with positively charged small alkaline proteins known as *histones*. Each of the histones (H2 A, H2B, H3 and H4) consists of a globular domain, a flexible domain, and a charged amino (NH_2)-terminal end that protrudes from the nucleosome, known as the “histone tail” (Fischle et al., 2003; Jenuwein and Allis, 2001; Marino-Ramirez et al., 2005). In addition, *histone variants* are isoforms of the four canonical histones that also can be incorporated into the nucleosome, undergo modifications and perform specific functions (Marino-Ramirez et al., 2005; Vaquero et al., 2003). Together, DNA and histones are part of the *nucleosomes*, each of which consists of ~147 bp of DNA wrapped 1.75 times around an octamer histone core and constitutes the first level of chromatin compaction (Devaskar and Raychaudhuri, 2007). The second level of chromatin organization is the *pearl necklace*, which is composed of 11-nm beads (nucleosomes) connected by a fragment of DNA of ~10–60 bp (Hansen, 2012; Vaquero et al., 2003). The third level of chromatin organization results when the "pearl necklace" is wrapped approximately six times to form a circular fibrillary structure of ~30 nm in diameter that is stabilized by a histone known as an H1 linker (Vaquero et al., 2003). The fourth level of chromatin compaction consists of 300-nm *loops*. The fifth level of compaction occurs when these *loops* are folded into 250-nm fibers that are packed together to form chromatids, which comprise one-half of the two identical threadlike strands that make up each chromosome (Annunziato, 2008) (Fig. 1).

The mechanism known as chromatin remodeling regulates the transcriptional state of DNA via a coordinated system of ATP-dependent protein complexes that are known as chromatin remodeling complexes (CRCs). These complexes regulate the degree of compaction of the chromatin by moving, expelling or restructuring the nucleosomes (Clapier and Cairns, 2009), in order to favor or prevent the binding of transcription factors to their specific binding sites within DNA (Li et al., 2015).

Chromatin is found in two states: a) *heterochromatin*, which is inaccessible to the transcription process due to its tightly packed condition, and b) *euchromatin*, which is less tightly packed in a way that facilitates the transcription process (Bannister and Kouzarides, 2011; Devaskar and Raychaudhuri, 2007; Grewal and Moazed, 2003) (Fig. 1). The conversion of heterochromatin into euchromatin and vice versa depends on the cell cycle and the environmental requirements of the cell (Bannister and Kouzarides, 2011).

Epigenetics, strictly speaking, is defined as “genetics out of the ordinary" (Jaenisch and Bird, 2003) and refers to heritable changes in gene expression and cell phenotype outside of modifications that affect the Watson-Crick pairing of bases (Goldberg et al., 2007). These modifications can regulate the structure of chromatin and provide a 'fingerprint' based on the environmental experiences of the cell (including its history of exposure to pharmaceuticals). The known epigenetic mechanisms that can modify gene expression without altering the DNA sequence are described below.

2.1. DNA methylation

Methylation is the covalent addition of methyl groups (−CH3) to cytosine residues that reside predominantly in CpG islands. These are regions of greater than 500 bp that are rich in guanine and cytosine (G + C) and are usually located within promoter regions, which are sites involved in the initiation and regulation of transcription (Bannister and Kouzarides, 2011; Egger et al., 2004; Fazzari and Greally, 2004). Over 60% of eukaryotic genes contain CpG islands in their promoters, and most are demethylated or hypomethylated (i.e., having a low proportion or loss of methyl groups) at all stages of development and in all tissues (Antequera, 2003). During aging or in several pathologies, however, a fraction of the CpG islands are liable to be methylated or hypermethylated (i.e., having excessive methyl groups) (Issa, 2000).

Methylation is carried out by DNA methyltransferases (DNMTs), proteins that are responsible for the *de novo* methylation of genes during the early stages of development (DNMT 3A and 3B) as well as the maintenance of established patterns of methylation (DNMT 1) (Bhutani et al., 2011; Tost, 2010). In contrast, the ten-eleven translocation (TET) protein family is primarily responsible for demethylation, which involves the removal or modification of 5mC methyl groups by hydroxylation via the formation of 5-hydroxymethylcytosine (5hmC) and other oxidation processes (Bhutani et al., 2011) (Fig. 1).

The methylation of CpG dinucleotides may induce the inhibition of transcription and thereby repress genes by stabilizing their inactivation (Bird, 2002). Indeed, gene coding regions can also be strongly methylated as a mechanism of silencing alternative promoters, retrotransposons and other functional elements in order to maintain transcriptional efficiency (Yang et al., 2014).

Various factors are involved in the methylation process. Methyl-CpG binding proteins (MBPs, complexes containing proteins such as MBD1, MBD2, MBD3 and MeCP2) mediate transcriptional repression via participation in three mechanisms: a) the addition of methyl groups that interfere with DNA-protein interactions, b) the methylation of CpG islands that attract inhibitory proteins; c) the recruitment of other associated proteins, such as histone deacetylases (HDACs), which are enzymes that remove acetyl groups (Bird, 2002; Nan et al., 1998; Tost, 2010).

2.2. Histone modifications

Histone modification is another type of epigenetic mechanism by which more than 100 different post-translational modifications may occur at the amino (*N*)-terminal ends of the histone tails in nucleosomes. Such modifications include methylation, acetylation, ubiquitination, phosphorylation, citrullination, ADP-ribosylation, sumoylation, and proline isomerization (Li et al., 2007) (Fig. 1). These modifications can result in the activation or repression of gene transcription, depending on the identity and location of the amino acid residue that is modified (Bernstein et al., 2007; Devaskar and Raychaudhuri, 2007; Li et al., 2007). Currently, the most commonly studied modifications are histone methylation, which leads to transcriptional silencing, and acetylation, which leads to transcriptional activation. There are a number of different types of effector proteins that mediate histone modification, including histone methyltransferases (HMTs), which are responsible for histone methylation, histone acetyltransferases (HATs), which mediate histone acetylation, and histone demethylases (HDMets), which remove methyl groups and HDACs (Devaskar and Raychaudhuri, 2007). In particular, the acetylation of lysine 9 in histone 3 (H3K9ac) and the trimethylation of lysine 4 in histone 3 (H3K4me3), as well as the general acetylation of H3, are associated with the active state of euchromatin, while the trimethylation of lysine 27 in histone 3 (H3K27me3) is associated with the silencing of heterochromatin (Lee et al., 2015).

ADP-ribosylation is another post-translational modification of histones that is mediated by ADP-ribose transferases, which transfer single

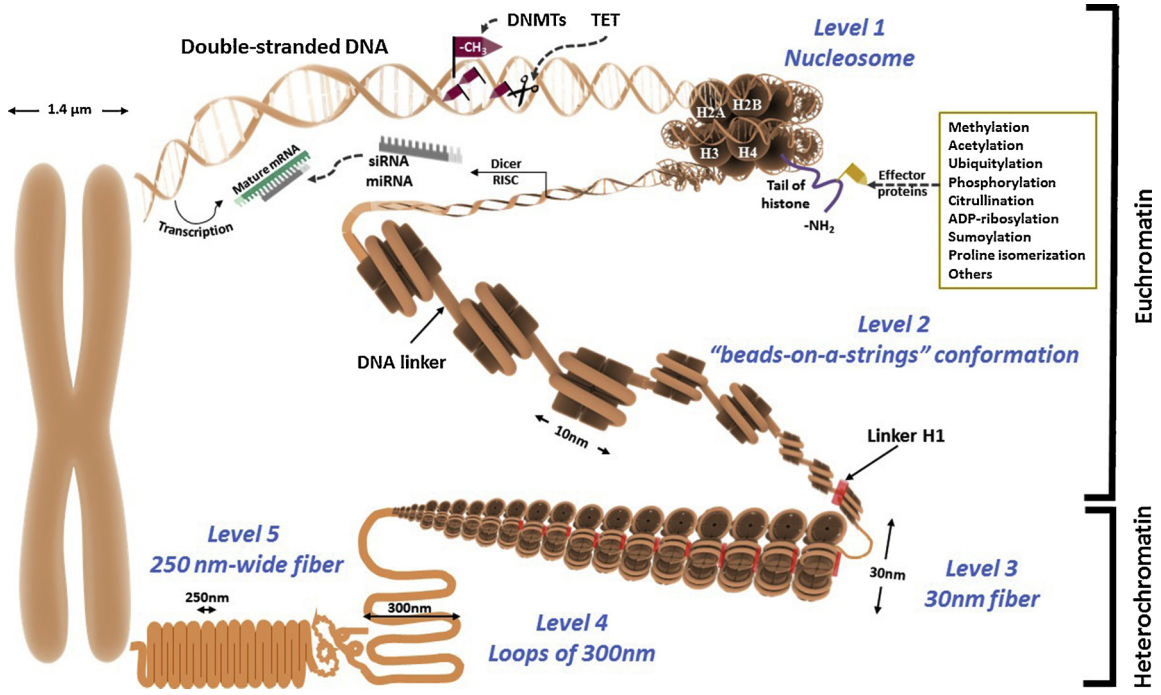

Fig. 1. Spatial organization of the genome and its epigenetic modifications. Chromosomes are formed from DNA "packaged" by histones into nucleosomes, and their structure depends on the degree of chromatin compaction, with heterochromatin being highly compacted and transcriptionally silent, while euchromatin has a more open structure and is transcriptionally active. The state of chromatin compaction can be regulated by epigenetic changes (DNA methylation via DNMTs; histone modifications through effector proteins; and the expression of ncRNAs) and depends on the transcriptional requirements of the cells. -NH2, N (amino)-terminal group; $-CH_3$, methyl group; ncRNAs; DNMT, DNA methyltransferase; H1, histone 1, H2 A, histone 2 A; H2B, histone 2B; H3, histone 3; H4, histone 4; siRNA, miRNA, micro-RNA; non-coding RNAs; small interfering RNA; TET, Ten-Eleven traslocation protein.

or multiple ADP-ribose moieties from NAD^+ to histone tails. This modification is of great biological importance due to its participation in the processes of DNA repair, cell proliferation, apoptosis, gene transcription and signal transduction (Liu and Yu, 2015; Messner and Hottiger, 2011).

In addition, there is a code that can be read and interpreted by the CRCs, known as the *histone code*, that transmits information about the presence of epigenetic changes and how they may influence other modifications (Jenuwein and Allis, 2001; Nightingale et al., 2006) and thereby modifies the rate of gene transcription (Egger et al., 2004; Strahl and Allis, 2000).

2.3. Non-coding RNAs

Non-coding RNAs (ncRNAs) are RNA transcripts that do not encode proteins and therefore cannot be translated (Saetrom et al., 2007). They can be classified as short/micro (< 200 nt) or long/macro (> 200 nt) ncRNAs, depending on their size (Henshall and Kobow, 2015). The most studied ncRNAs are small interfering RNAs (siRNAs) and microRNAs (miRNAs), which are both processed by the proteins Dicer and RISC but differ in their biogenesis (Fig. 1). In their mature form, these ncRNAs are 21–26 nucleotides in length and must be joined to the complementary mRNA sequence to induce effects (Valencia-Sanchez et al., 2006). The regulation of genes by siRNAs is via the highly specific (single target) endonucleolytic cleavage of mRNA. miRNAs, on the other hand, usually induce transcriptional repression via the degradation and proteolytic cleavage of mRNA within the 3′UTR region of as many as 100 target genes (Lam et al., 2015).

In addition to regulating the stability and translation of mRNAs, siRNAs and miRNAs induce gene silencing through the promotion of methylation and the alteration of the structure of chromatin (Castanotto et al., 2005; Godfrey et al., 2007; Holmes and Soloway, 2006; Morris et al., 2004; Suzuki et al., 2005). Specifically, miRNAs are able to bind to histones and induce DNA methylation at specific loci (Egger et al., 2004; Godfrey et al., 2007; Wang et al., 2015), whereas siRNAs regulate the structure of chromatin via their interaction with the nuclease Dicer (Fukagawa et al., 2004)

The long non-coding RNAs (lncRNAs) are a family of molecules located primarily in the nucleus that includes enhancer RNAs (eRNAs), antisense transcripts and intergenic RNAs (Henshall and Kobow, 2015). These lncRNAs control the structure and function of chromatin via the promotion of DNA methylation through the recruitment of DNMTs, the repositioning of the nucleosome and the formation of chromatin loops (Bohmdorfer and Wierzbicki, 2015). They also regulate, both positively and negatively, the transcriptional machinery and the stability of mRNA (Bohmdorfer and Wierzbicki, 2015; Kung et al., 2013). In the brain, the expression of lncRNAs differs depending on the region, stage of development, pluripotential conditions, and the status of neuronal and glial differentiation (Briggs et al., 2015; Quan et al., 2017). lncRNAs are involved in developmental processes, such as X-chromosome silencing and genomic imprinting, as well as diseases such as cancer (Kung et al., 2013) and α-thalassemia (Tufarelli et al., 2003). At present, lncRNAs are considered to be potential targets for the treatment of neurological disorders. In an experimental model of Dravet Syndrome that was caused by a heterozygous loss-of-function mutation in the *SCNA1* gene, Hsiao et al., (2016) demonstrated that the blockage of the repressor effect mediated by a lncRNA known as SCN1ANAT resulted in upregulation of the *SCNA1* gene, leading to subsequent improvement in the control of convulsive activity and the excitability of hippocampal interneurons.

3. Epigenetic regulation in human epilepsy

Epilepsy is a neurological disorder that is associated with great complexity in its epigenetic influences due to the presence of multiple etiologies (Qureshi and Mehler, 2010). The results of studies of both human and experimental models indicate that epileptogenesis and epilepsy itself are associated with the alteration of DNA methylation

Table 1
Epigenetic modifications induced by Antiepileptic Drugs (AEDs).

AED	DNA methylation			
	Specific genes		DNMT	TET family
	Hypermethylation	Hypomethylation		
CBZ	*GABRA1* gene 64 promoters in SK-N-SH neuroblastoma cells.	*SLC6A4* gene 14 promoters in SK-N-SH neuroblastoma cells.	NA	NA
LCM	NA	NA	NA	NA
LMT	Contradictory results	Contradictory results Global *MTHFR* amplicon	NA	NA
OXC	*GABRB2* promoter	NA	NA	NA
PHT	NA	Global	NA	NA
ESX	NA	NA	Induces DNMT 1 and DNMT 3 A	NA
GBP	NA	NA	NA	NA
PB	*CDKN2 A* gene (tumor suppressor protein p16)	Global *HRAS* gene *CYP2D10* gene	Induces DNMT 1	NA
VGB	NA	NA	NA	NA
CBD	Global *KRT10* promoter	NA	Inhibit DNMT 1	NA
LVT	NA	NA	NA	NA
TPM	NA	NA	Inhibit DNMT 1, DNMT 3 A and DMAP1	NA
VPA	64 promoters in SK-N-SH neuroblastoma cells. *RELN* gene.	36 promoters in SK-N-SH neuroblastoma cells. *ALOX5* gene Global in epilepsy patients	NA	Inhibit mitochondrial TET1

AED	Histones Modifications						
	H1	H2A	H2B	H3	H4	HDACs	
						Induction	Inhibition
CBZ	NA	NA	NA	NA	Induction of Acetylation	HDACs 2, 3, 5 and 8 Binding of HDAC1 to *CYP3 A4* promoter	HDACs of class I & II
LCM	NA	NA	NA	NA	NA	NA	YES
LMT	NA	NA	NA	Induction of acetylation	Induction of acetylation	HDACs 2, 3, 5 and 8	YES HDACs 1 and 7
OXC	NA	NA	NA	NA	NA	NA	NA
PHT	NA	NA	NA	NA	NA	NA	NO
ESX	NA	NA	NA	NA	NA	NA	NO
GBP	NA	NA	NA	NA	Does not induce acetylation	NA	NO
PB	Induction of ADP-ribosylation	Not dependent ADP-ribosylation	Induction of ADP-ribosylation	Induces H3K4me3 and inhibits H3K9me3 in *UGT1A* gene. Induces H3K27me3, H3K4me2 and H3K9ac and inhibits H3K27me3 in *CYP2B10* gene. Induces H3K4me3 in *CYP3 A11* gene.	Not dependent ADP-ribosylation	NA	NA
VGB	NA	NA	NA	NA	Induction of acetylation	NA	NO
CBD	NA	NA	NA	Induces H3K9ac	NA	NA	NA
LVT	NA	NA	NA	Induction of acetylation	NA	HDACs 2, 3, 5 and 8	NA
TPM	NA	NA	NA	NA	Induction of acetylation	NA	NO
VPA	NA	Induction of acetylation.	NA	Induction of acetylation Induces H3K9ac and H3K4me3 in *LEPR* gene. Induces acetylation in *GAD1(67), MAGEB2* and *MMP2* genes. Inhibits H3K27me3 in *LEPR* gene.	Induction of acetylation. Induction of acetylation in *CDKN1A* (p21WAF1/CIP1) gene. Induction of acetylation in, *MAGEB2* and *MMP2* genes	NA	HDACs of class I & II HDACs 1, 2, 3, 5 and 7

AED	ncRNAs			
	Short RNAs miRNAs Induction	Inhibition	siRNAs	Long RNAs
CBZ	NA	NA	NA	NA
LCM	NA	NA	NA	NA
LMT	NA	NA	NA	NA
OXC	NA	miR-134	NA	NA
PHT	NA	NA	NA	NA
ESX	NA	NA	NA	NA

(*continued on next page*)

Table 1 (*continued*)

	ncRNAs			
	Short RNAs			Long RNAs
	miRNAs		siRNAs	
	Induction	Inhibition		
GBP	NA	Does not induce miR-107	NA	NA
PB	miR-200a/200b/429 and miR-96/182	miR-122	NA	NA
VGB	NA	NA	NA	NA
CBD	NA	NA	NA	NA
LVT	miR-206, miR-374, miR-142-5p and miR-468	NA	NA	NA
TPM	NA	NA	NA	NA
VPA	miR-144, miR-331, miR-30a-5p, miR-20a, miR-34a, miR-449a, miR-221, miR-15a, miR-16, miR-129, miR-519e, miR-194, miR-214, miR-449a, miR-182, miR-206, miR-133a and miR-10a	let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, miR-885-3p, miR-222, miR-15a, miR-16, miR-144, miR-451, miR-155, miR-127a, miR-124a, miR-128 and miR-137	NA	NA

ALOX5, 5-lipoxygenase gene; CBD, Cannabidiol; CBZ, Carbamacepine; *CDKN1A,* cyclin-dependent kinase inhibitor 1 gene; CDKN2 A, cyclin dependent kinase inhibitor 2 A gene; CYP3 A4, Cytochrome P450 Family 3 Subfamily A polypeptide 4 gene; CYP3 A11, cytochrome P450 family 3 subfamily A polypeptide 11 gene; CYP2D10, cytochrome P450 family 2 subfamily D polypeptide 10 gene; DMAP1, Protein Associated with Dnmt1; DNMT, DNA methyltransferase; ESX, ethosuximide; GBP, gabapentin; GABRA1, $GABA_A$ receptor subunit α1 gene; GABRB2, $GABA_A$ receptor subunit β2 gene; GAD67, Glutamate Decarboxylase 1 (67 kDa) gene; H1, histone 1, H2 A, histone 2 A; H2B, histone 2B; H3, histone 3; H4, histone 4; HRAS, ha-ras proto-oncogene; HDAC, histone deacetylases; *KRT10*, keratin 10 gene; LCM, lacosamide; LEPR, Leptin Receptor gene; LMT, lamotrigine; LVT, levetiracetam; MAGEB2, Melanoma-associated antigen B2 gene; MMP2, Matrix Metallopeptidase 2 gene; MTHFR, methylenetetrahydrofolate reductase gene; miRNA, micro-RNA; NA, No information Available; OXC, oxcarbazepine; PHT, phenytoin; PB, phenobarbital; RELN, reelin gene; siRNA, small interfering RNA; SLC6A4, solute carrier family 6 member 4 gene; TET, Ten-Eleven traslocation protein; TPM, topiramate; UGT1A, UDP-Glucuronosyltransferase Family 1 polypeptide A gene; VPA, valpric acid; VGB, vigabatrine.

signatures throughout the entire genome (Debski et al., 2016; Kobow and Blumcke, 2012). People with drug-resistant temporal lobe epilepsy (TLE) show an increase in the expression of DNMT1 and DNMT3 A in the temporal neocortex, which is associated with alterations in the excitability of neural networks and synaptic plasticity (Zhu et al., 2012). Human TLE is also associated with aberrant methylation of the promoters of genes that are involved in the development of seizures (*Cpa6*) and the dispersion of hippocampal granule cells (*Reln*) (Belhedi et al., 2014; Kobow et al., 2009).

With regard to histone modification, epilepsy has been found to be associated with the overexpression of HDAC2, which is associated with an increase in deacetylase activity and inactivation of chromatin. These processes are involved in the regulation of genes associated with synaptic activity, plasticity and NMDA receptors, in both human (*BDNF*) and experimental models (*Erg1*, *Creb1*, *fos*) (Guan et al., 2009; Huang et al., 2012; Park et al., 2014).

Epilepsy has been associated with modifications of ncRNAs. It has been suggested that a polymorphism in the 3′-UTR of the *AP3M2* gene blocks the miR-422a binding site, which in turn facilitates epileptogenesis in humans (Huang et al., 2007). Fragile X syndrome people who develop epilepsy show changes in the expression of the FMR4 and ASFMR1 lncRNAs (Khalil et al., 2008; Ladd et al., 2007), as well as alterations in the function of FMRP (Fragile X Mental Retardation protein), which is associated with the deregulation of miRNA pathways (Qureshi and Mehler, 2010).

Seizure activity is also associated with the alteration of factors that are involved in regulating epigenetic modification. For example, in Rett syndrome, which is a neurodevelopmental disorder characterized by mental retardation, stereotypical behaviors, and recurrent seizures, there are mutations and duplications of the *MECP2* gene that have functional implications for DNA methylation processes (Amir et al., 1999; Jian et al., 2006; Kinde et al., 2016). Alpha-thalassemia X-linked intellectual disability (ATR-X) syndrome, characterized by mental retardation, altered facial and genital morphology, and the development of epilepsy in 30% of those affected, results from mutation of the *ATR-X* gene that encodes a CRC that is involved in the formation of heterochromatin at mammalian centromeres and telomeres (De La Fuente et al., 2011; Guerrini et al., 2000). People with Sotos syndrome, also known as cerebral gigantism, have a high risk of seizures that is associated with mutations and deletions in the *NSD1* gene, which encodes a histone methyltransferase (Baujat and Cormier-Daire, 2007). Mutations in the *KDM5C (SMCX/JARID1C)* histone demethylase gene have been directly associated with epilepsy and X-linked mental retardation (Abidi et al., 2008; Tzschach et al., 2006). Repressor element 1 (RE1)-silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) represses the transcription of many neurological genes, including those related to epileptogenesis and epilepsy (Tahiliani et al., 2007). The absence of the interaction of REST/NRSF with the LIM domain protein as a consequence of mutations within the REST-interacting LIM domain protein (PRICKLE1/RILP) induces an autosomal-recessive, progressive myoclonus epilepsy-ataxia syndrome (Bassuk et al., 2008).

Overall, there is much evidence to support the fact that epigenetic modifications commonly play a role in epilepsy. However, it is unknown at present whether or not epigenetic alterations are the consequence of treatment with AEDs.

4. Epigenetic modifications associated with AEDs

According to the International League Against Epilepsy (ILAE), there are four types of epilepsy: focal epilepsies, which include unifocal and multifocal syndromes as well as seizures comprising one hemisphere; generalized epilepsies, in which the epileptiform activity appears in the whole brain and is detected by EEG; combined generalized and focal epilepsy; this represents a combination of the first two types; and epilepsy of unknown type, a condition difficult to be determinate due to the lack of information (Scheffer et al., 2017).

Therapy with AEDs focuses on the reduction of excessively fast neural firing during seizures and the avoidance of the spread of epileptic activity to surrounding brain areas through activity against different targets that modulate neuronal activity.

The most important channels that are involved in maintaining neuronal function (Na^+, K^+, Ca^{2+} and Cl^- channels) are critical targets for old and new AEDs (Brodie et al., 2016). The augmentation of inhibitory effects mediated by γ-aminobutyric acid (GABA) or the reduction of neuronal excitation through the blockade of glutamatergic effects are also mechanisms utilized by AEDs (Barker-Haliski and White, 2015). Additionally, AEDs may also induce epigenetic changes that modify the course of the disease. This section describes the presently known epigenetic effects of 13 AEDs that are in wide clinical use. Although other AEDs can induce epigenetic changes, there is not information to support this notion (Table 1, Figs. 2–4).

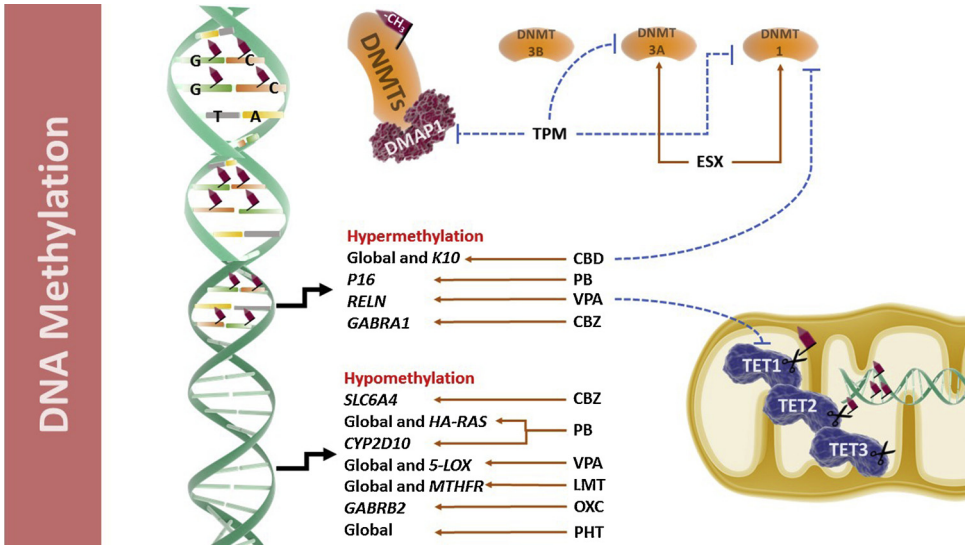

Fig. 2. Changes in DNA methylation elicited by AEDs. AEDs such as carbamazepine (CBZ), phenobarbital (PB) and valproic acid (VPA) can induce both genome-wide and gene-specific hypermethylation and hypomethylation. Cannabidiol (CBD) induces both genome-wide and gene-specific hypermethylation and the inhibition of DNA methyltransferase (DNMT) 1. Genome-wide and gene-specific hypomethylation is induced by lamotrigine (LMT), oxcarbazepine (OXC) and phenytoin (PHT). Ethosuximide (ESX) induces the expression of DNMT1 and 3 A; in contrast, topiramate (TPM) inhibits the expression of DNMT1 and the Protein Associated with Dnmt1 (DMAP1). VPA inhibits the expression of mitochondrial TET (Ten-Eleven traslocation protein) 1. Black arrows indicate active transcriptional processes; brown arrows indicate the induction of processes; and the dashed blue lines indicate inhibition. 5-LOX, 5-lipoxygenase gene; A, adenine; CYP2D10, cytochrome P450, family 2, subfamily d, polypeptide 10 gene; C, cytosine; G, guanine; GABRA1, $GABA_A$ receptor subunit α1 gene; GABRB2, $GABA_A$ receptor subunit β2 gene; HA-RAS, ha-ras oncogene; *K10*, keratin 10 gene; MTHFR, methylenetetrahydrofolate reductase gene; *P16*, P16 gene; RELN, reelin gene; SLC6A4, solute carrier family 6 member 4 gene; T, timine.

4.1. AEDs that target voltage-dependent Na^+ channels

4.1.1. Carbamazepine (CBZ)

The main mechanism of action of carbamazepine is the blockade of voltage-gated Na^+ channels. It is used to control focal or generalized seizures (Cotterman-Hart, 2015a; Sheets et al., 2008; Willow et al., 1984). Regarding its epigenetic effects, there is evidence that CBZ has effects on DNA methylation; the results of an *in silico* study suggested that CBZ modifies the methylation patterns of the $GABA_A$ receptor subunit α1 (*GABRA1)* gene (Houtepen et al., 2016). An *in vitro* genome-wide methylation study analyzing 14,475 genes in SK-N-SH neuroblastoma cells demonstrated that CBZ induced hyper- and hypomethylation in CpGs in 64 and 14 gene promoters, respectively. One of the hypomethylated promoters is that of *SLC6A4*, which encodes a protein that transports serotonin in presynaptic neurons and could therefore affect the therapeutic efficacy of CBZ (Asai et al., 2013) (Table 1, Fig. 2).

Concerning histone modification, observations indicate that CBZ diluted in hydroxypropyl-β-cyclodextrin (HBC) induces H4 acetylation and inhibition of HDAC I and II in HepG2 cells (human liver cancer cell line) (Beutler et al., 2005). However, this effect was not detected in HeLa cells when CBZ was diluted in DMSO (Eyal et al., 2004). In C57BL/6 mice, CBZ induced the synthesis of HDACs in the striatum (HDAC2, HDAC3, and HDAC8), nucleus accumbens (HDAC2 and

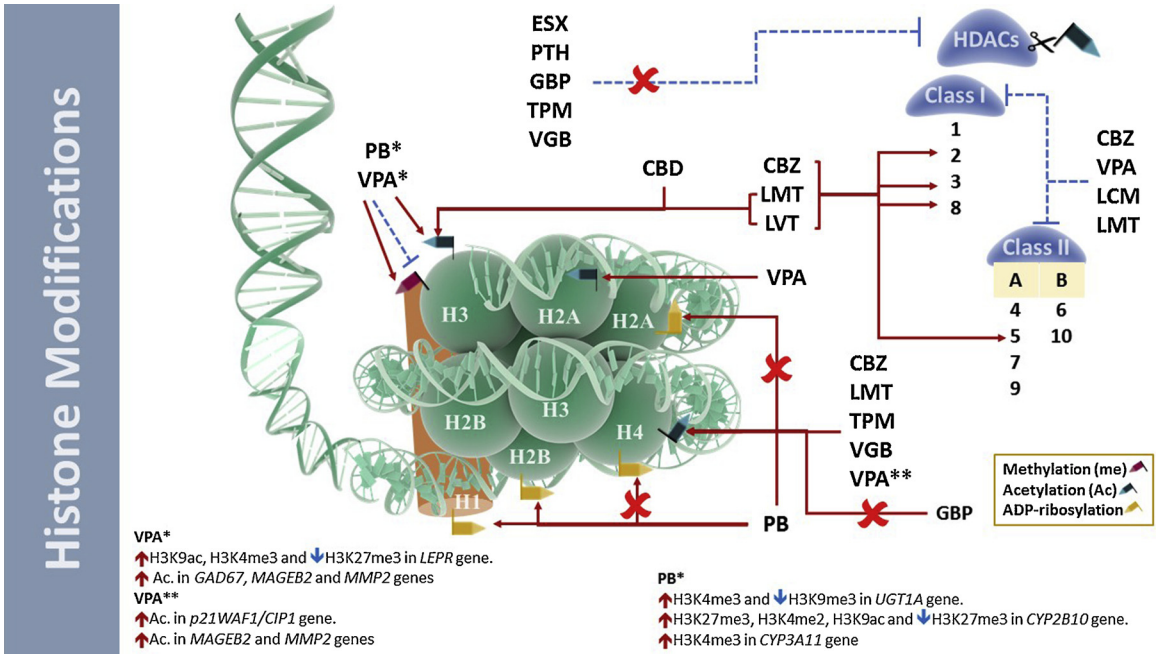

Fig. 3. Histone modifications mediated by AEDs. CBZ, LMT, TPM and vigabatrine (VGB) induce the acetylation (ac.) of H4, while VPA induces the acetylation of H2 A, H3 and H4. Acetylation of H3 is induced by LMT, levetiracetam (LVT) and CBD. PB can induce or inhibit the methylation (me) and acetylation of H3, and it can also affect the ADP-ribosylation of H1 and H2B, but not of H2 A and H4. Gabapentin (GBP) does not induce acetylation of H4. CBZ, LMT and LVT induce the expression of HDAC (Histone deacetylases) 2, 3 5 and 8. The expression of class I and II HDACs is reduced by CBZ, LMT, VPA and lacosamide (LCM). ESX, PHT, GBP, TPM and VGB do not inhibit (red X) HDACs. Some notations and abbreviations are the same as those used in Figs. 1–2 and Table 1.

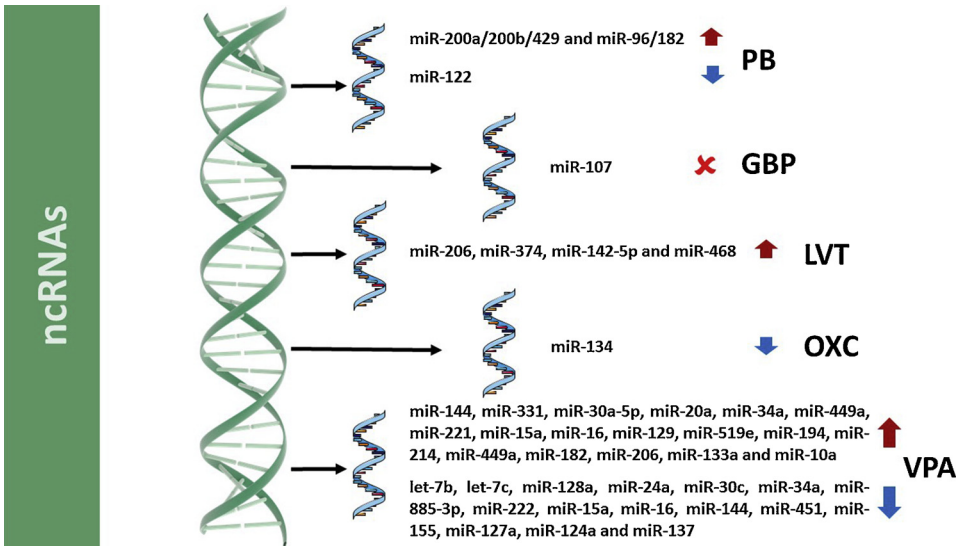

Fig. 4. Regulation of ncRNAs by AEDs. PB can induce and inhibit the expression of miRNAs related to hepatotoxicity. VPA reduces the expression of miRNAs related to neurogenesis, axonal orientation, neurite growth, neurodevelopment, ischemia, cancer, erythropoiesis, psychosis and BPD. LVT induces the expression of miRNAs associated with its pharmacological response. OXC inhibits miR134. GBP does not modify miR-107 expression. Some notations and abbreviations are the same as those used in Figs. 1–3.

HDAC3), and amygdala (HDAC3 and HDAC5) (Ookubo et al., 2013). Furthermore, it is known that CBZ induces the binding of HDAC1 to the *CYP3A4* promoter, which is an isoform of CYP3A that metabolizes various drugs (Wu et al., 2012) (Table 1, Fig. 3). At present, there is no evidence that CBZ regulates the synthesis or function of ncRNAs.

4.1.2. Lacosamide (LCM)

Its pharmacological mechanism involves the inactivation of voltage-gated Na^+ channels (Asconape, 2013; Errington et al., 2008; Sheets et al., 2008). Concerning its role in epigenetic processes, one study has demonstrated its ability to inhibit HDACs in the cerebral cortex of Wistar rats at a dosage of 30 mg/kg (Bang et al., 2015) (Table 1, Fig. 3). No evidence exists that LCM induces DNA methylation or changes in the synthesis or function of ncRNAs.

4.1.3. Lamotrigine (LMT)

The pharmacological activity of LMT involves the blockade of voltage-sensitive Na^+ channels, Ca^{2+} currents and the reduction of the release of excitatory amino acids (Stefani et al., 1996; Xie et al., 1995). It is used to control focal and generalized seizures, such as those associated with Lennox-Gastaut syndrome (Cotterman-Hart, 2015b; Rathaur et al., 2017). Some studies have suggested that LMT does not induce changes in DNA methylation patterns (Ni et al., 2015; Perisic et al., 2010). However, other studies have shown a decrease in genome-wide levels of methylation in the umbilical cord blood and placenta of infants prenatally exposed to LMT and other drugs (Smith et al., 2012). In the peripheral blood of people with epilepsy, LMT induced a reduction in the level of methylation of the methylenetetrahydrofolate reductase (MTHFR) amplicon (Ni et al., 2015). LMT modifies DNA methylation levels in blood cells of people with BPD, supporting epigenetic effects of psychotropic drugs (Houtepen et al., 2016) (Table 1, Fig. 2).

In relation to histone modification, it is known that LMT increases H3 acetylation in the cingulate cortex and the nucleus accumbens of C67BL/6 mice (Ookubo et al., 2013). In cerebellar granule cells, LMT, in association with VPA, induced the hyperacetylation of H3 and H4, the inhibition of HDAC activity, and other effects associated with neuroprotective processes against glutamate-induced excitotoxicity (Leng et al., 2013). In C57BL/6 mice, LMT inhibited the synthesis of HDACs in the hippocampus (HDAC5 and HDAC7) and their activity in the striatum (HDAC2, HDAC3, and HDAC8), nucleus accumbens (HDAC2 and HDAC3), and amygdala (HDAC3 and HDAC5) (Ookubo et al., 2013) (Table 1, Fig. 3). At present, there is no evidence that LMT regulates the synthesis or function of ncRNAs.

4.1.4. Oxcarbazepine (OXC)

OXC acts via the blockade of voltage-gated Na^+ (and possibly Ca^{2+}) channels and is used to control focal seizures (Cotterman-Hart, 2015b; Huang et al., 2008; Wellington and Goa, 2001). Regarding its epigenetic effects, a previous study suggested that OXC induces the methylation of CpG sites in the Alu region of the *GABRB2* (subunit $GABA_{b2}$) gene in people with schizophrenia (Zong et al., 2017) (Table 1, Fig. 2). The results of another study revealed that treatment with OXC inhibited the expression of miR-134 in people with psychosis and BPD (Rong et al., 2011) (Table 1, Fig. 4). There is no current evidence that OXC induces histone modification.

4.1.5. Phenytoin (PHT)

PHT inhibits voltage-gated Na^+ channels and, at high concentrations, augments GABAergic neurotransmission by reducing K^+ efflux (De Weer, 1980; Wong and Teo, 1986). PHT is used to control focal and generalized seizures (Hanaya and Arita, 2016). With regard to DNA methylation, an overall decrease in the level of methylation was observed in neonates prenatally exposed to multiple AEDs, including PHT (Smith et al., 2012) (Table 1, Fig. 2). In addition, an experimental study indicated that PHT does not have inhibitory effects on HDACs in HeLa cells (Eyal et al., 2004) (Table1, Fig. 3). There is no current evidence that suggests that PHT regulates the synthesis or function of ncRNAs.

4.2. AEDs that target Ca^{2+} channels

4.2.1. Ethosuximide (ESX)

ESX is used to control absence seizures, and its main pharmacological action is the reduction of low-threshold T-type Ca^{2+} currents (Cotterman-Hart, 2015a; Coulter et al., 1989; Kostyuk et al., 1992). Regarding its epigenetic effects, chronic treatment with ESX increases the expression of *Dnmt1* and *Dnmt3A* mRNAs in the somatosensory cortex of Strasbourg rats that are used as a genetic model of absence seizures (Dezsi et al., 2013) (Table 1, Fig. 2). ESX does not inhibit HDAC activity, even at concentrations that are five-fold higher than a typical therapeutic dose (Eyal et al., 2004) (Table 1, Fig. 3). Currently, there is no evidence that ESX regulates the synthesis or function of ncRNAs.

4.2.2. Gabapentin (GBP)

GBP is used to reduce focal seizures and neuropathic pain (Czapinski et al., 2005), and its pharmacological effects result from the inhibition of high-threshold Ca^{2+} channel currents and the enhancement of GABA levels (Bryans et al., 1998; Gee et al., 1996; Honmou et al., 1995). GBP is not able to inhibit HDACs or induce H4 acetylation

in HeLa cells (Eyal et al., 2004) (Table 1, Fig. 3). It does not regulate miR-107 in K562 or KCL-22 myeloid leukemia cells (Ruan et al., 2015) (Table 1, Fig. 4). At present, the participation of GBP in DNA methylation processes has not been evaluated.

4.3. AEDs that affect GABAergic neurotransmission

4.3.1. Phenobarbital (PB)

PB is effective in the treatment of multiple types of seizures, including focal, generalized and absence seizures (Czapinski et al., 2005; Macdonald and Barker, 1977), and it induces inhibitory effects as a consequence of the activation of $GABA_A$ receptors.

PB also induces hepatotoxicity as a consequence of epigenetic changes. With regard to DNA methylation, chronic treatment with PB produces hypomethylation throughout the genome, mainly in cells susceptible to liver tumorigenesis (C3H/He and B6C3F1) (Watson and Goodman, 2002); such hypomethylation is also correlated with the transcriptional activation of the Ha-ras gene and other genes associated with angiogenesis, invasion, and metastasis. In B6C3F1 mice, PB induces the demethylation of two CpG islands in the *Cyp2b10* gene, which is involved in drug metabolism (Bachman et al., 2006; Lempiainen et al., 2011; Phillips and Goodman, 2008). PB increases the activity and expresion of DNMTs and induces silencing of the p16 tumor-suppressor gene promoter via hypermethylation (Kostka et al., 2007). DNMT1 mRNA and protein levels have been shown to be augmented in the liver of Wistar rats who were administered PB (Urbanek-Olejnik et al., 2014) (Table 1, Fig. 2).

It has been shown that PB augments H3K4me3 (thalamus and the striatum) and reduces H3K9me3 (thalamus) in Sprague Dawley rats. These variations promote the transcriptional activation of genes that encode UGT1A, which is a drug-metabolizing enzyme (Sakakibara et al., 2016). PB mediates the epigenetic modification of genes encoding other drug-metabolizing enzymes, such as those of the *Cyp450* family. For example, in B6C3F1/Crl mice, chronic PB treatment leads to the conversion of the *Cyp2b10* gene promoter from a repressed state (increased H3K27me3) to an activated state (increased H3K4me2 and H3K9ac, and decreased H3K27me3) (Lempiainen et al., 2011). Also, neonatal exposure to PB was found to induce *Cyp450* gene expression in the liver of adult C57BL/6 mice, a condition that is associated with the presence of H3K4me3 in the *Cyp3 A11* gene promoter (Tien et al., 2016). In Wistar rats, PB induced ADP-ribosylation in H1 and H2B histones but not in H2 A, H3 A, and H4 histones, a state that has been implicated in the regulation of hepatic metabolism (Braz and Lechner, 1986) (Table 1, Fig. 3).

With respect to the regulation of ncRNAs, chronic treatment with PB induces the synthesis of miR-200a/200b/429 and miR-96/182 in the liver of Fisher rats (Koufaris et al., 2013). In contrast, PB inhibited the synthesis of miR-122, which is related to the function and differentiation of hepatocytes in C3H/HeN mice and in HepG2 and HuH-7 human hepatoma cells. Indeed, inhibition of miR-122 was also found to lead to the activation of the constitutive androstane receptor (*CAR*) gene, which regulates the expression of genes such as *CYP2B* and *CYP3 A* (Shizu et al., 2012) (Table 1, Fig. 4).

4.3.2. Vigabatrin (VGB)

VGB enhances GABA levels via the inhibition of GABA transaminase. It is used to control focal seizures and infantile spasms (Cotterman-Hart, 2015b; Jung et al., 1977). Regarding its epigenetics effects, one study in HeLa cells showed that VGB induces an insignificant increase in H4 acetylation and does not inhibit HDACs (Eyal et al., 2004) (Table 1, Fig. 3). At present, there is no evidence that VGB affects DNA methylation or synthesis and function of ncRNAs.

4.4. AEDs with multiple mechanisms of action

4.4.1. Cannabidiol (CBD)

CBD is currently considered a multitargeted drug since it interacts with various endocannabinoid and non-endocannabinoid systems. It is a non-competitive antagonist of CB1 receptors and an inverse agonist of CB2 receptors. CBD acts as an agonist towards TRPV1-4, TRPA1, 5-HT1A, PPAR-γ and the α1 and α3 glycine receptor subunits. It is also an antagonist of TRPM8, GPR55 and voltage-gated T-type Ca^{2+} channels. CBD also modulates the TNFα, VDAC1 and adenosine (A1 and A2) receptors (Ibeas Bih et al., 2015; Perucca, 2017). There is evidence to suggest that CBD is effective in the control of drug-resistant epilepsy (Friedman and Devinsky, 2016).

With regard to its epigenetic effects, CBD increases the methylation of the keratin 10 (*K10*) gene promoter, as well as overall methylation in HaCaT human keratinocytes, via a process mediated by CB1 receptors. It also inhibits the overexpression of the DNMT1 gene without modifying DNMT 3A, 3B, and 3L levels (Pucci et al., 2013) (Table 1, Fig. 2).

CBD induces H3K9 acetylation in the ventral tegmental area (VTA) in C57BL/6 mice, which has been associated with processes related to addiction (Todd et al., 2017) (Table 1, Fig. 3). At present, there is no evidence that CBD regulates the synthesis or function of ncRNAs.

4.4.2. Levetiracetam (LVT)

The antiepileptic effects of LVT result from its inhibition of N- and T-type Ca^{2+} channels and its binding to SV2 A synaptic proteins (Lukyanetz et al., 2002; Lynch et al., 2004; Madeja et al., 2003; Rigo et al., 2002). It has been found to be effective in controlling focal and generalized seizures (Hovinga, 2001).

With regard to its epigenetic effects, studies have shown that LVT induces H3 acetylation in the cingulate cortex and the nucleus accumbens and stimulates the production of HDAC2, HDAC3, and HDAC8 in the striatum and HDAC3 and HDAC5 in the amygdala of C57BL/6 mice (Ookubo et al., 2013) (Table 1, Fig. 3).

There is some evidence to suggest that LVT regulates the expression of miRNAs, especially miR-206, miR-374, miR-142-5p, and miR-468, all of which have been found to regulate pharmacological responses in a murine model of pilocarpine-induced epilepsy (Moon et al., 2014) (Table 1, Fig. 4). At present, there is no evidence that LVT participates in DNA methylation.

4.4.3. Topiramate (TPM)

TPM has been demonstrated to block voltage-dependent Na^+ channels, potentiate GABAergic neurotransmission, antagonize non-NMDA-type receptors and reduce the currents generated by high voltage-activated Ca^{2+} channels (Mula et al., 2006). It is used to control focal and generalized seizures (Cotterman-Hart, 2015b; Czapinski et al., 2005). Concerning its epigenetic effects, there is evidence that indicates that TPM prevents ethanol-induced overexpression of DNMT1, DNMT3 A, and DMAP1 (Dnmt1-Associated Protein 1) in Wistar rats (Echeverry-Alzate et al., 2014) (Table 1, Fig. 2).

An *in vitro* study in HeLa cells revealed that TPM induces H4 hyperacetylation while having no effects on the competitive inhibition of HDACs (Table 1, Fig. 3) (Eyal et al., 2004). There is no evidence that TPM regulates the synthesis or function of ncRNAs.

4.4.4. Valproic acid (VPA)

The pharmacologic effects of VPA include blockade of voltage-gated Na^+ and T-type Ca^{2+} channels and inhibition of GABA degradation via the blockade of GABA transaminase. VPA is used to control generalized and absence seizures (Hanaya and Arita, 2016; Kelly et al., 1990; Macdonald and Bergey, 1978).

With regard to DNA methylation, it has been found that VPA induces the hyper- and hypomethylation of 64 and 14 genes, respectively, in SK-N-SH cells (Asai et al., 2013). In another study, which was conducted in primary cultures derived from cerebellar granule cells, it was

demonstrated that VPA induced hypomethylation of the promoter of the neuronal *5-LOX* (5-lipoxygenase) gene, leading to its transcriptional activation and the consequent stimulation of cell proliferation (Manev and Uz, 2002). In mouse 3T3-L1 fibroblasts, VPA reduced the level of 5-hydroxymethylcytosine in mitochondrial DNA (mtDNA) and decreased the mRNA and protein levels of the mitochondrial demethylation enzyme TET1 (Chen et al., 2012). In people with Major Depressive Disorder, BPD and schizophrenia, VPA was shown to induce hypermethylation (silencing) of the *RELN* gene (approved name reelin), whose protein is involved in neuronal migration and regeneration (Chen et al., 2002; Houtepen et al., 2016). VPA has also been found to induce genome-wide hypomethylation in the peripheral blood cells of people with epilepsy (Tremolizzo et al., 2012) (Table 1, Fig. 2).

VPA has been found to increase H3 acetylation in NIH 3T3 fibroblasts, which leads to subsequent chromatin decondensation in both euchromatin and heterochromatin (Felisbino et al., 2014). The induction of transcriptional repression by H3 hyperacetylation (e.g., by H3K27me3 in the KAT2B and HDAC9 genes) in human embryonic stem cells (hESCs) is mediated by similar changes in chromatin structure (Balmer et al., 2012). In contrast, a study conducted in the rat hippocampal cell line H19-7/IGF-IR demonstrated that VPA increases the levels of H3K9ac and H3K4me3 and reduces the level of H3K27me3 in the *Lepr* (leptin receptor) gene, which leads to alterations in neurogenesis and behavior (Lee et al., 2015). In primary cultures derived from astrocytes, VPA-mediated H3 acetylation increases the expression of Glial Cell-Derived Neurotrophic Factor (*GDNF*), which promotes neuroprotective effects in dopaminergic neurons (Wu et al., 2008). VPA also increases H3 acetylation in the cingulate cortex and the nucleus accumbens of C57BL/6 mice (Ookubo et al., 2013). VPA-induced H3 acetylation in the hippocampus of B6129SF2/J mice was associated with behavioral changes (Yildirim et al., 2003). H3 acetylation mediated by VPA was also shown to have neuroprotective and anti-inflammatory effects in the cortex and striatum of Sprague-Dawley rats affected by cerebral ischemia (Kim et al., 2007; Ren et al., 2004). In the lymphocytes of people with schizophrenia and BPD, VPA induces genome-wide acetylation of H3 as well as the specific acetylation of *RELN* and glutamate decarboxylase 67 (*GAD67)* (Dong et al., 2007; Sharma et al., 2006). VPA-induced H3 acetylation has neuroprotective effects in rats suffering from intracerebral hemorrhage (Sinn et al., 2007). VPA treatment has been found to be associated with an increase in H3 acetylation in the peripheral blood of both people with epilepsy and healthy subjects (Tremolizzo et al., 2012) (Table 1, Fig. 3).

H4 acetylation is also associated with transcriptional activation. It has been shown that VPA increases H4 acetylation and the binding of the transcription factors Ets-1 and Ets-2 to the promoter of FOXP3, which has been found to be indispensable in the regulation of T-reg cells, in human T-cells derived from umbilical cord blood (Fayyad-Kazan et al., 2010). VPA increases genome-wide H4 acetylation (Eyal et al., 2004). Indeed, the antiproliferative effects of VPA in a number of cancer cell lines have been explained by its increase in H4 hyperacetylation in genes such as *p21WAF1/CIP1* (Travaglini et al., 2009) (Table 1, Fig. 3).

It is also known that VPA can induce simultaneous H3 and H4 acetylation in several carcinoma cell lines, including F9 (teratocarcinoma), HeLa (human cervical cancer) (Gottlicher et al., 2001), U937 (human monocytic lymphoma), K562 (human erythroleukemia) (Gurvich et al., 2004), and OVCAR-3 (human ovarian cancer) (Kwiecińska et al., 2014). In MCF-7 cells (human breast cancer), VPA induces the depletion of proteins that comprise the structural support for heterochromatin, including SMCs, DNMT1, and HP1 (Marchion et al., 2005). In H322, H513, and TE12 (thoracic carcinoma) cells, VPA induces cell cycle arrest and apoptosis (Ziauddin et al., 2006). Similarly, in medulloblastoma cells, VPA induces the expression of *p21* and suppresses *TP53, CDK4*, and *CMYC* expression, leading to growth arrest, apoptosis and senescence (Li et al., 2005). This suggests that VPA may be an effective therapeutic agent for use in cancer treatment. However, the H3 and H4 hyperacetylation that is induced by VPA has been shown to also take place in non-neoplastic cells, such as the splenocytes of mice (Gottlicher et al., 2001). In neurons, this effect could modify cell excitability by altering the expression of certain genes, such as *BDNF* and $GABA_AR_{\alpha 4}$ (Fukuchi et al., 2009). In HEK 293 T embryonic kidney cells, VPA induces H3 and H4 acetylation, which leads to the activation of *MAGEB2* (melanoma antigen B2) and *MMP2* (metalloproteinase 2) (Milutinovic et al., 2007) and the inhibition of the JARID1A and EZH2 demethylases; it also leads to the hypo- and hypermethylation of H3K27 and H3K4, respectively (Ganai et al., 2015). VPA also induces the acetylation of H3 and the H2A variant in the peripheral blood of people with epilepsy (Tremolizzo et al., 2012) (Table 1, Fig. 3).

Previous studies have indicated that VPA inhibits the activity of class I and II HDACs, with the exception of HDAC6 and HDAC10, in F9, HEK 293 T (Gottlicher et al., 2001; Gurvich et al., 2004), HeLa (Eyal et al., 2004), and NIH 3T3 cells (Felisbino et al., 2014) via the proteasomal degradation pathway (Kramer et al., 2003). Also, VPA has been demonstrated to inhibit the expression of HDAC1, HDAC2, HDAC5, and HDAC7 in various cancer cell lines (Kwiecińska et al., 2014; Papi et al., 2010). The inhibition of HDACs leads to alterations in the nuclear structure of prostate carcinoma LNCaP, C4-2, DU145, and PC3 cells (Kortenhorst et al., 2009). The teratogenic potential of VPA is mediated by its inhibition of HDACs and induction of H4 hyperacetylation (Eikel et al., 2006). These mechanisms appear to be important to the increase of the formation of GABAergic neurons (GABA neurogenesis) induced by VPA (Laeng et al., 2004). On the other hand, experimental evidence indicates that VPA blocks seizure-induced aberrant neurogenesis (Jessberger et al., 2007). In the hippocampus of C57BL/6 mice, VPA inhibits the production of HDAC5 and HDAC7, whereas in the cingulate cortex, it increases the production of HDAC3 and HDAC5 (Ookubo et al., 2013). In the pancreas, VPA induces a decrease in cell proliferation and differentiation via its inhibition of HDACs, which delays cellular recovery after pancreatitis (Eisses et al., 2015) (Table 1, Fig. 3).

VPA participates in the regulation, synthesis and function of ncRNAs (Detich et al., 2003; Dong et al., 2010; Phiel et al., 2001). VPA reduces the expression of let-7b, let-7c, miR-128a, miR-24a, miR-30c, miR-34a, and miR-221 while increasing the expression of miR-144 in the hippocampus of Wistar rats. These changes involve processes related to neurogenesis, axonal orientation, neurite growth, and neurodevelopment, as well as the PTEN, ERK, Wnt/β-catenin, and β-adrenergic signaling pathways. Additionally, it has been shown that the inhibition of miR-34a by VPA induced the expression of metabotropic glutamate receptor 7 (*GRM7*) (Zhou et al., 2009). In experimental models of ischemia, VPA treatment induces miR-331 overexpression while reducing miR-885-3p overexpression. The functional implications of these changes, however, are not yet well understood (Hunsberger et al., 2012). In SH-SY5Y neuroblastoma cells, combined treatment with lithium and VPA induces the expression of miR-30a-5p, which is a post-transcriptional inhibitor of BDNF (Croce et al., 2014). In LNCaP and PC3 cells, VPA treatment induces the expression of miR-20a, miR-34a, and miR-449a, all of which participate in the regulation of processes underlying epithelial-mesenchymal transition in cancer (Xia et al., 2016). With regard to erythropoiesis-related miRNAs, VPA induces miR-221 and inhibits miR-222, miR-15a, and miR-16 in Epo/TF1 cells. In K562 cells, VPA induces miR-221, miR-15a, and miR-16 and inhibits miR-222. VPA inhibited erythropoiesis via the inhibition of miR-144, miR-451, and GATA-1 transcription factor, while it induced megakaryocyte differentiation via the inhibition of miR-155 and the induction of *GATA-2* and miR-127a (Trecul et al., 2014). In HEK 293 cells, the decrease in miR-92a-1 (and other miRNAs) upon VPA treatment is mediated by the proteasomal degradation of DICER, which is an enzyme that participates in the synthesis of miRNAs. Under the same experimental conditions, VPA was also found to increase the expression of miR-129, miR-519e, miR-194, miR-214, miR-449a, and miR-182,

which most likely occurred via a DICER-independent mechanism, such as the Argonaut-2-dependent synthesis of miRNAs (Zhang et al., 2013). During the neural to myogenic lineage shift, VPA induced the over-expression of muscle-related miRNAs, such as miR-206, miR-133a, and miR-10a, and inhibited specific neurological miRNAs, such as miR-124a, miR-128, and miR-137 (Smirnova et al., 2014). Finally, it has been observed that the inhibition of HDACs by VPA induces changes in the expression of miR-21 and miR-31 in umbilical cord blood T cells (Fayyad-Kazan et al., 2010) (Table 1, Fig. 4).

People with psychosis and BPD were found to have a low level of miR-134, a condition that could be reversed by a number of anti-psychotic drugs, including VPA (Rong et al., 2011). Also, in people with BPD, the administration with VPA facilitates the expression of miR-206, which is associated with *BDNF* gene polymorphisms that contribute to the treatment response and the susceptibility to this particular pathology (Wang et al., 2014) (Table 1, Fig. 4).

5. Concluding remarks

This review provides specific evidence that supports the hypothesis that a number of AEDs induce epigenetic changes. It is important to consider that epigenetic research related to the use of AEDs has been insufficient to reach any definite conclusions. Further research is necessary to fully investigate all of the epigenetic modifications that are induced by each AED. In the future, the epigenetic modifications induced by AEDs, whether they be beneficial or harmful, and their clinical consequences must be considered during clinical use in epileptic people. In addition, epigenetic modifications associated with epilepsy represent potential clues in the search for novel AEDs that are more effective and selective and have fewer side effects (Wei et al., 2015).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2018.11.006.

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