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Current Neuropharmacology, **2020**, *18*, **153-166**

REVIEW ARTICLE

Epigenetic Effects Mediated by Antiepileptic Drugs and their Potential Application

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ARTICLE HISTORY

Received: June 16, 2019
Revised: August 01, 2019
Accepted: October 03, 2019

DOI:
10.2174/1570159X17666191010094849

Abstract: An epigenetic effect mainly refers to a heritable modulation in gene expression in the short term but does not involve alterations in the DNA itself. Epigenetic molecular mechanisms include DNA methylation, histone modification, and untranslated RNA regulation. Antiepileptic drugs have drawn attention to biological and translational medicine because their impact on epigenetic mechanisms will lead to the identification of novel biomarkers and possible therapeutic strategies for the prevention and treatment of various diseases ranging from neuropsychological disorders to cancers and other chronic conditions. However, these transcriptional and posttranscriptional alterations can also result in adverse reactions and toxicity *in vitro* and *in vivo*. Hence, in this review, we focus on recent findings showing epigenetic processes mediated by antiepileptic drugs to elucidate their application in medical experiments and shed light on epigenetic research for medicinal purposes.

Keywords: Antiepileptic drug, DNA methylation, histone modification, untranslated RNA, molecular mechanism, application.

1. INTRODUCTION

Antiepileptic drugs (AEDs) commonly act on diverse molecular targets to selectively attenuate the excitability of neurons and provide adequate seizure control in epileptic patients. There are multiple mechanisms of action of AEDs that can be categorized by their regulatory functions on voltage-gated ion channels and control of synaptic excitability [1]. However, current findings have shown that AEDs can exert their regulatory effects on gene expression as epigenetic modifiers, making them active in different studies of human medicine.

Epigenetics can be interpreted as heritable changes in gene function without alterations in the activity state of a DNA sequence [2]. Significant epigenetic markers include DNA methylation, modifications of histone proteins, and functions of untranslated RNAs. These epigenetic phenomena are usually followed by the identification of biomarkers that can translate molecular and genomic data into clinical practice, especially in oncology [3]. For example, aberrant expression levels of histone deacetylase (HDAC) 1, 2, and 3 are correlated with ovarian cancer and myeloma prognosis [4, 5]. Meanwhile, epigenetic modifiers targeting these biomarker proteins such as valproate acid (VPA) and tacedinaline, have been put into phase III clinical trials of ovarian cancer and myeloma therapy [6, 7]. Additionally, biomarker discovery can be regarded as an advance in the novel possibilities for the treatment of patients with epilepsy and psychological disorders [8, 9].

VPA, carbamazepine (CBZ), and other AEDs can exert epigenetic action in animal models and cells to develop potential drug targets for diseases. Through the genetic or pharmacologic targeting of DNA methyltransferase enzymes, specific gene loci can become hypomethylated, which may lead to the reactivation of silenced gene expression [10]. AEDs can also act as histone deacetylase inhibitors that induce different phenotypes in various transformed cells [11, 12]. Moreover, noncoding RNAs, such as microRNAs (miRNAs), can be modulated to silence chromatin, degrade mRNA, and block translation [13]. These drug effects have been widely used in various research fields.

Regarding the drugs themselves, adverse drug reactions (ADRs) and toxicity are associated with their epigenetic modifications [14, 15]. These epigenetic pathways can help researchers determine possible methods to predict and prevent adverse events and toxicity caused by AEDs.

In this review, we summarize recent data regarding the epigenetic effects mediated by AEDs with clinical implications in human diseases and pharmaceutical research. We searched PubMed and Web of Science for publications in English from Jan 1, 2010, to Apr 1, 2019. The search terms included “antiepileptic drugs”, “acetazolamide”, “benzobarbital” “brivaracetam”, “carbamazepine”, “clonazepam”, “diazepam”, “cannabidiol”, “felbamate”, “gabapentin”, “lacosamide”, “lamotrigine”, “levetiracetam”, “lorazepam”, “mephobarbital”, “oxcarbazepine”, “phenobarbital”, “phenytoin”, “primidone”, “riluzole”, “rufinamide”, “tiaga-

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1570-159X/20 $65.00+.00

bine", "topiramate", "valproic acid", "zonisamide", "retigabine", "eslicarbazepine", "perampanel", "epigenetic effect*", "DNA methylation", "histone modification", "untranslated RNA", "DNMT", "HDAC", "HAT", "HDACI", "MBD", "SAM", and "non-coding RNA". In addition, we also used the Mesh terms in Medline such as "DNA (Cytosine-5-)-Methyltransferases"[Mesh], "epigenomics"[Mesh], "S-Adenosylmethionine"[Mesh], "Methyl CpG Binding Domain"[Mesh], "epigenesis, genetic"[Mesh], "histone acetyltransferases"[Mesh], "histone deacetylases"[Mesh], "Histone Deacetylase Inhibitors"[Mesh], "rna, untranslated"[Mesh], "DNA methylation"[Mesh] OR "histone code"[Mesh], and "anticonvulsants"[Pharmacological Action]. Then, the pivotal clinical studies and experiment article were selected to describe our main topic. We also used some earlier reviews if they were principally relevant to the discussion.

2. THE EPIGENETIC EFFECTS OF ANTIEPILEPTIC DRUGS

2.1. DNA Methylation

DNA methylation is perhaps the best characterized chemical modification of chromatin. In mammalian genes, most methylation processes occur on the cytosine residues of CpG dinucleotides [16]. *De novo* or maintenance DNA methyltransferases (DNMTs) play a significant role in gene regulation and chromatin organization during ontogenesis. DNMTs add methyl groups to hemimethylated DNA during or after DNA replication. Three active DNA methyltransferases have been identified in mammals, named DNMT1, DNMT3a, and DNMT3b [17]. In general, DNA methylation delivers a stable, inherited, and crucial constituent of epigenetic regulation [18].

However, this transient inherited change can be influenced by the environment, chemicals, cancer, and diseases [19]. Furthermore, drug exposure can also affect the methylation process and induce hypermethylation or hypomethylation in gene promoter regions, thereby regulating cellular activities [20].

How do medications such as AEDs function in the epigenome? The DNA methylation pattern is copied by independent enzymatic machinery (*i.e*., DNMTs). DNA methylation occurs immediately after replication by transfer of a methyl moiety from the donor S-adenosyl-l-methionine (SAM) in a reaction catalysed by a DNMT [13]. VPA is a commonly used broad-spectrum antiepileptic drug and an inhibitor of DNMT1, DNMT3a and DNMT3b. This finding also shows that VPA upregulates Reelin protein and glutamic acid decarboxylase 67 (Gad67) mRNA expression by reducing the methylation of their promoters, and dysregulation of these proteins may influence the processes of neuronal migration and positioning in the developing brain [21]. In contrast, the expression of DNMT1 and DNMT3a is elevated in chronically treated ethosuximide-exposed epileptic rats. However, the biological process of this modifying effect is still unclear [22].

In addition to DNMTs, nutrients (*e.g*., folate, homocysteine and vitamin B12) involved in one-carbon metabolism (OCM) can also modify methylation patterns because they can ensure provision of the universal methyl donor SAM for subsequent methylation reactions [23]. A clinical trial showed that VPA or lamotrigine (LTG) monotherapy led to lower serum folate levels in epilepsy patients. Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in OCM because it reduces N5,10-methylenetetrahydrofolate to methyltetrahydrofolate, which can affect the DNA methylation process. In addition, methylation status of the MTHFR amplicon was shown to correlate with serum folate levels, indicating that AEDs may have an effect on methylation by reducing folate levels [24]. Another study showed that VPA-treated patients had both higher serum homocysteine and vitamin B12 levels, which can both affect the OCM [25].

The first-generation AED phenobarbital (PB) is associated with a variety of epigenetic alterations. In a toxicological experiment, PB served as a chemical to investigate the relationship between the apical and epigenetic endpoints. Specific endpoints, such as the transposable element long interspersed element 1 (LINE-1), were found to be hypomethylated in the hepatocytes of rats after exposure to PB. The expression of three genes involved in DNA methylation, DNMT1, DNMT3b and methyl-CpG-binding domain 1 (MBD1), showed a dose-dependent decreasing trend in expression after treatment with PB [26]. Although methyl-binding proteins such as MBD1 do not directly interfere with the methylation process of DNA, they can bind to methylated gene loci and repress their expression [27].

Cannabidiol (CBD), which is used to treat Dravet syndrome, has also been found to increase the expression of DNMT1 to control global DNA methylation levels [28].

2.2. Histone Modification

Histone modifications manipulate transcription and other DNA template functions. This process is regulated by specific enzymatic mechanisms that entail metabolites to serve as cosubstrates or act as activators/inhibitors. One of the most common modes of histone modification is acetylation. Histone acetylation neutralizes positively charged lysine residues, which are highly abundant in histone proteins, thereby "opening up" chromatin and making the DNA more accessible to other protein factors [29]. The acetylation status of histones is regulated by a balance between the activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Mammalian HDACs are divided into 4 classes based on their homology to yeast orthologues and their cofactor dependence (class I, IIa, IIb, III, and IV) [30].

An inhibition in HDACs causes the accumulation of acetylated forms of proteins, thus regulating gene expression, cell proliferation and cell death. HDAC inhibition has the potential to treat diverse diseases, especially in anticancer areas [11]. Many AEDs can act as HDAC inhibitors (HDACIs) and play a critical role in the plurality of gene expression mechanisms. VPA is the first known AED that exhibits nonselective inhibition of HDACs [31]. Carbamazepine (CBZ) and topiramate (TPM) were later discovered to also be HDACIs [12, 32]. In a recent study, HDAC levels were decreased in rodent brain tissues after treatment with lacosamide (LCM), which supports that the effect of LCM can suppress HDAC activity and enhance the cognitive function of experimental animals [33]. Although levetiracetam (LEV) cannot directly affect HDAC activity,

2-pyrrolidinone-n-butyric acid (PBA), the main metabolite of LEV, promotes histone deacetylation in HeLa cells [34].

2.3. Untranslated RNA

Untranslated RNA is also a critical component of epigenetic modifications. Although these RNAs lack the potential to encode proteins, they can impinge on the expression of other genes through a variety of mechanisms [35]. miRNAs form a major class of functional, noncoding RNAs. Accumulating evidence has demonstrated miRNA changes in animal models or patients with different conditions, which reveals the potential for miRNAs to serve as novel biomarkers for the diagnosis or treatment of epilepsy, cancer, and other human diseases [36-38]. AEDs such as VPA can exert anticancer and neuroprotective actions by regulating miRNA levels [39, 40].

However, aberrant miRNA expression may lead to abnormal protein expression, and these unintended reactions can be mediated by AEDs. For example, prenatal exposure to VPA causes an immediate augmentation of miR-132 levels in the mouse embryonic brain and then decreases its molecular targets, methyl-CpG-binding protein 2 (MECP2) and Rho GTPase-activating protein (p250GAP), which may result in autism-like behaviour and pathological changes in the mouse cortex [41]. Phenobarbital can cause changes in the expression levels of delta-like homologue 1 gene and type III iodothyronine deiodinase gene (Dlk1-Dio3). These genes are capable of expressing non-coding RNA clusters. And fluctuations in these RNAs can be associated with hepatocyte hypertrophy and recoding and eventually induce liver cancer [42]. Additional experiments support the robust linkage between miRNA changes induced by PB and liver cancer in rodent models [26]. Similarly, cutaneous adverse reactions, such as Stevens-Johnson syndrome (SJS), caused by CBZ are believed to be related to the dysregulation of miRNAs in an immune cell experimental analysis [43]. This finding will be restated in subsequent chapters.

Encouragingly, recent experimental studies and reviews have shed light on the use of synthetic miRNA mimics or antagonists to slow the progression of chronic diseases, such as cancer, epilepsy and metabolic diseases, in animal models and clinical trials [35, 37, 44, 45] However, disadvantages such as off-target effects and poor cellular uptake still challenge the practical transformation that must be addressed. Unlike lipophilic drugs, antimiRNAs cannot move into cells by passive diffusion; size and polarity impede their ability to diffuse across lipid bilayers. For example, doxorubicin is smaller than 600 Daltons, while full-length antimiRNAs are ten times bigger than them in size. Due to miRNA structure and function, miRNAs may not work in combination with proteins. Even though miRNAs enter cells, they may combine with other proteins or nucleic acids, resulting in off-target effects [46]. In other words, these findings indicate that miRNA-based therapeutic strategies will have a promising future if such problems are resolved.

3. APPLICATION OF THE EPIGENETIC EFFECT OF ANTIEPILEPTIC DRUGS

As depicted in Fig. **1**, the importance of epigenetics throughout the pathogenesis and treatment of various diseases suggests that AEDs may be used to exert epigenetic effects in various diseases and research fields other than epilepsy, such as tumours, cardiovascular diseases, stem cell research, kidney disease, ADRs and toxicity. Their application in disease and stem cell research can be seen in Table **1**. ADRs and toxicity are shown in Table **2**.

3.1. The Treatment and Diagnosis of Different Diseases

3.1.1. Epilepsy

Epilepsy is a clinically common neurologic condition, which over 50 million people worldwide at present are believed to experience [47]. Pharmacotherapy is an essential part of controlling seizures, but nearly 30% of patients develop drug-resistant epilepsy [48]. Hence, the search for biomarkers of epilepsy has become a novel focus of studies on the treatment and diagnosis of this disease [49].

This issue raises a question as to whether the epigenetic effects of AEDs are related to their antiseizure effects or the formation of drug resistance. Mathew *et al*. indicated that promoter variants and epigenetic factors determine the transcriptional overexposure of drug targets and may contribute to pharmacoresistance to LEV [50]. Multidrug resistance protein 1 (MDR1), a kind of efflux transporter involved in the occurrence of drug-resistant epilepsy, is overexpressed with exposure to HDACIs, including VPA. Transporter upregulation is associated with histone acetylation, as shown by increased levels of acetylated histone H3 [51].

Epigenetics may explain the mechanism of action of AEDs. A previous study demonstrated that the expression of the sodium channel SCN3A can enhance the excitability of neurons and aggravate the condition of epilepsy, while VPA can downregulate the expression of SCN3A *in vitro*. Results surprisingly show that VPA increases the methylation of the -39C site in the SCN3A promoter. Furthermore, VPA can upregulate fat mass and obesity-associated (FTO) protein, which may repress the expression of MBD2 and NaV1.3. This finding provides a new explanation for the mechanism of VPA exerting its anticonvulsant action [52]. Dezsi *et al.* discovered ethosuximide antiepileptogenic effects in the genetic absence rat model of genetic generalized epilepsy, which is related to its increased expression of DNMT mRNA in the cortex [22].

miRNAs such as miR-134, miR-181a, miR-124, miR-199a, miR-128, miR-15a-5p and miR-194-5p play important roles as diagnostic and therapeutic biomarkers in patients with epilepsy [53]. In addition, preclinical data have described miRNA therapy and its curative effects in animal models [44]. Therefore, we can see that a novel trend in epigenetic therapy has been used in preclinical experiments of epilepsy. Will the next AED be an epigenetic modifier? Based on the latest report on AED development, adenosine kinase (ADK) inhibitors and adenosine should be investigated because of their demethylation function in obstructing the SAM-dependent transmethylation pathway [54].

3.1.2. Tumours

Epigenetic alterations allow a tumour cell to adapt to changes in its microenvironment, and these changes are reversible. Hence, some dormant, hypermethylated tumour

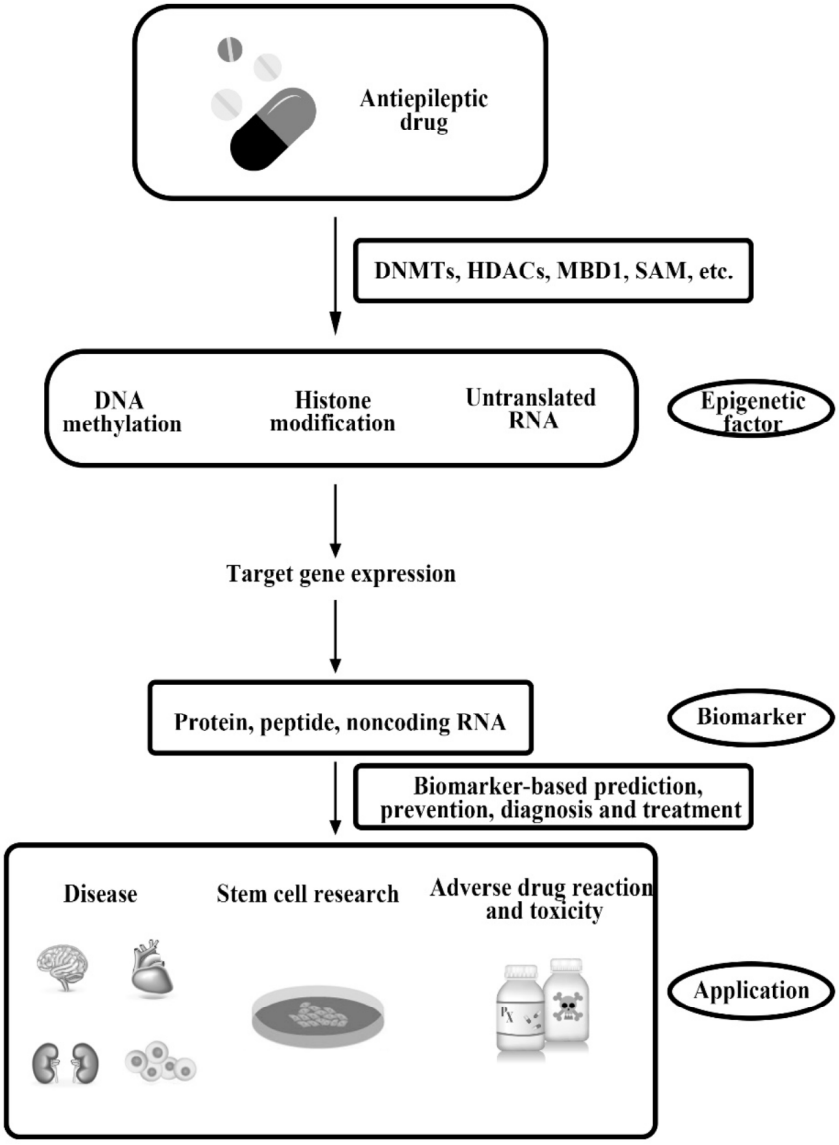

Fig. (1). Mechanisms of epigenetic effects mediated by AEDs and how their epigenetic effect applies to diverse research fields. AEDs affect DNA methylation and histone modification by intervening with enzymes such as DNMTs, HDACs, methyl-binding proteins, such as MBD1, and the methyl donor SAM. They also affect the expression levels of noncoding RNAs. DNA methylation, histone modification, and noncoding RNA regulation can act as epigenetic factors that subsequently influence the expression of target genes. Expression products, such as proteins, peptides and noncoding RNAs, exert biomarker-based predictive, preventive, diagnostic and therapeutic functions in miscellaneous diseases, stem cell research, adverse drug reactions and toxicity. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

suppressor genes can be awakened with drugs [3]. In addition, HDACIs can induce differentiation, cell cycle arrest, and apoptosis *in vitro* [55], which makes it possible to apply demethylating agents and HDACIs in the treatment of patients with cancer.

VPA is a powerful HDACI with the potential to serve as an effective drug for cancer therapy due to its functional induction of cell differentiation [31]. A recent study also emphasized the direct suppression of cancer proliferation by an HDACI to glioblastoma, small cell lung cancer and breast cancer [56-58]. Interestingly, HDACIs may also promote the growth of cancer cells. La Noce *et al.* suggested that VPA induces an expansion of osteosarcoma, while decreasing expression of HDAC2 is a key factor regulating both phenotype and cancer cell growth *in vivo* [59].

Another antitumour mechanism is that VPA enhances the sensitivity to chemotherapy drugs or radiotherapy. For example, VPA can enhance the efficacy of fluoropyrimidine-based chemical radiotherapy in colorectal cancer by increasing the expression of p53. The p53 gene is the critical factor that causes the resistance of cancer cells [60]. In addition, VPA augments paclitaxel-mediated photodynamic therapy in colorectal cancer, overcoming resistance to paclitaxel and reactivating the expression of CDKN1A epigenetically [61]. Evidence demonstrates that tumour necrosis factor-related apoptosis-inducing ligand (TRAIL)-VPA combination

Table 1. Epigenetic-based functions of AEDs associated with disease and stem cell research.

Drug	Gene	Molecular Effect	Functional Effect	Species	Refs.
VPA	P53	Histone acetylation	Antitumour effect	Human	[60]
	M65, M30	H3 acetylation	Antitumour effect	Human	[58]
	cdk1, cyclin B, Raptor, others	H3 and H4 acetylation	Antitumour effect	Human	[63]
	CDKN1A	H3 acetylation	Antitumour effect	Human	[61]
	cdc25a, cdc2, others	Histone acetylation	Antitumour effect	Human	[57]
	MDR1	H3 acetylation	Formation of drug-resistant epilepsy	Human	[51]
	SCN3A	DNA methylation	Treatment of epilepsy	Mouse	[52]
	BRD1	DNA methylation	Biomarker of psychological disorder	Human	[76]
	RELN, SLC1A2, MTNR1A, others	DNA methylation	Biomarker of psychological disorder	Human	[81]
	HDAC2/3/5	H3 acetylation	Biomarker of psychological disorder	Mouse	[79]
	Ube3a	H3 and H4 acetylation	Psychotropic effect	Mouse	[100]
	MT1	H3 acetylation	Psychotropic effect	Rat	[80]
	STAT1, p65	Histone acetylation	Neuroprotective function	Rat	[101]
	HIF1a, HSP70, p-mTOR, Tubulin	Histone acetylation	Neuroprotective function	Mouse, Swine	[82]
	Pitx3, Nurr1	H3 acetylation	Neuroprotective function	Rat	[85]
	FGF21	H3 acetylation	Neuroprotective function	Rat	[83]
	Ang Ⅱ	H3 and H4 acetylation	Treatment of hypertension	Mouse	[91]
	CREM	H4 acetylation	Treatment of atrial fibrillation	Mouse	[92]
	FoxO1	Histone acetylation	Treatment of type 2 diabetes	Rat	[93]
	ECM	H3 acetylation	Treatment of renal disease	Mouse	[94]
	CD133, OCT4, SOX2, NANOG, others	DNA methylation，H3 acetylation	Cell proliferation	Human	[59]
	Scx	H3 acetylation	Cell proliferation	Mouse	[99]
	Nestin, Notch2, Sox10, others	H3 acetylation	Cell differentiation	Bovine	[98]
	miR-122-5p	Upregulation	Cell differentiation	Human	[102]
	Ngn1	DNA methylation	Cell differentiation	Rat	[97]
	miR-145-5p	Upregulation	Antitumour effect	Human	[72]
	miR-125a, miR-125b, miR-205, miR-133b	Upregulation	Antitumour effect	Mouse	[40]
	miR-124	Upregulation	Neuroprotective function	Mouse	[39]
CBZ	BRD1	DNA methylation	Biomarker of psychological disorder	Human	[76]
	HDAC2/3/5	H3 acetylation	Biomarker of psychological disorder	Mouse	[79]
LEV	MGMT	Histone acetylation	Antitumour effect	Human	[70]
	HDAC2/3/5	H3 acetylation	Biomarker of psychological disorder	Human	[79]
LCM	HDAC1	Histone acetylation	Neuroprotective function	Rat	[33]
	miR-195-5p	Upregulation	Antitumour effect	Human	[71]
	miR-107	Downregulation	Antitumour effect	Human	[71]

(Table 1) contd….

Drug	Gene	Molecular Effect	Functional Effect	Species	Refs.
CBD	CB1	DNA methylation	Psychotropic effect	Rat	[78]
	mitochondrial ferritin	DNA methylation	Neuroprotective function	Rat	[84]
BRV	miR-195-5p	Upregulation	Antitumour effect	Human	[71]
	miR-107	Downregulation	Antitumour effect	Human	[71]
OXC	GABRB2	DNA methylation	Psychotropic effect	Human	[77]
LTG	HDAC2/3/5	H3 acetylation	Biomarker of psychological disorder	Mouse	[79]
ESX	DNMT1, DNMT3a	DNA methylation	Treatment of epilepsy	Rat	[22]

Representative examples of studies and epigenetic effects are summarized. VPA valproate acid, CBZ carbamazepine, LEV levetiracetam, LCM lacosamide, ESX ethosuximide, LTG lamotrigine, BRV brivaracetam, OXC oxcarbazepine, CBD cannabidiol.

Table 2. Epigenetic-based application of AEDs associated with adverse drug reactions and toxicity.

Drug	Gene	Molecular Effect	ADR or Toxicity	Species	Refs.
VPA	BMP-7	Histone acetylation	Antitoxic effect	Mouse	[121]
	PPARγ, PPARα, AHR, CD36	DNA methylation	Induces hepatocyte steatosis	Human	[117]
	Keap1	DNA methylation	Induces cataracts	Human	[118]
	MTHFR	DNA methylation	Affects folate metabolism	Human	[25]
	Sox9	H3 acetylation	Induces pancreatitis	Mouse	[119]
	miR-134-5p	Upregulation	Induces autism	Rat	[114]
	miR-132	Upregulation	Induces autism	Mouse	[41]
PB	LINE-1	DNA methylation	Carcinogenesis	Rat	[26]
	Ugt1a6, Ugt1a7	H3 acetylation, H3 methylation	Affects drug metabolism	Rat	[120]
	Dlk1-Dio3, IncRNAs	Upregulation	Carcinogenesis	Mouse	[42]
	miR-200b	Upregulation	Carcinogenesis	Rat	[26]
	miR-221	Downregulation	Carcinogenesis	Rat	[26]
CBZ	CYP3A4	Histone acetylation	Affects drug metabolism	Human	[79]
	miR-155, miR-18a, miR-21	Upregulation	Induces a cutaneous reaction	Human	[43]
LTG	MTHFR	DNA methylation	Affects folate metabolism	Human	[25]

Representative examples of studies and epigenetic effects are summarized. ADRs adverse drug reactions, VPA valproic acid, CBZ carbamazepine, LEV levetiracetam, LCM lacosamide, PB phenobarbital, LTG lamotrigine.

therapy can induce the apoptosis of papillary thyroid cancer (PTC) cells by activating caspases. The apoptosis of drug-resistant PTC cells mediated by VPA can be explained by its participation in the regulation of Nrf2 and Bcl-xL expression, indicating the potential for VPA in combination chemotherapy for the treatment of drug-resistant PTC [62]. In a previous experiment, VPA significantly hindered the growth of temsirolimus-resistant prostate cancer cells *in vitro*. An evaluation of the histone acetylation status revealed increased aH3 and aH4 expression in the resistant and sensitive cells, suggesting an epigenetic mechanism [63]. Recent investigations have shown that VPA also promotes cisplatin sensitivity [64] and restores erlotinib [65], sorafenib [66], gemcitabine, and vincristine responsiveness [67, 68]. However, the specific molecular mechanisms need to be verified in future research.

A retrospective cohort study suggested that LEV may have a survival advantage in patients with glioblastoma who receive temozolomide (TMZ) chemotherapy [69]. Scicchitano *et al*., found that LEV reduces the expression of O6-methylguanine-DNA methyltransferase (MGMT), which promotes the nuclear translocation of the HDAC4 gene, activates the apoptotic pathway and enhances the effect of temozolomide (TMZ) on the proliferation of glioblastoma multiforme (GBM) cells, indicating that TMZ combined with LEV may improve TMZ clinical efficacy in GBM [70].

miRNA regulation also plays a significant role in the epigenetic therapy of cancer. Manifold pathways involved in tumour initiation, progression and metastasis will malfunction if certain miRNAs are altered [37]. Rizzo *et al*. discovered that brivaracetam and lacosamide regulate the expression of miRNAs in glioma cells; in particular, the regulation of miR-195-5p seems to affect the cell cycle, while the regulation of miR-107 seems to be involved in the inhibition of cell migration; therefore, these two drugs also have the potential to be an adjuvant treatment for glioma [71]. A recent study demonstrated that the VPA-induced simultaneous downregulation of EGFR, ErbB2, and ErbB3 in pancreatic cancer cells could slow the progression of pancreatic cancer, which was mainly attributed to the induction of ErbB family member-targeting miRNAs [40]. Moreover, recent evidence has shown that miR-145-5p upregulation in thymoma cells mediated by VPA exhibits antitumour effects as well as better responsiveness to chemotherapy [72].

3.1.3. Psychological Disorders and Neuroprotective Function

Genetic mechanisms may explicate underlying factors of psychological disorders such as depression and schizophrenia. The epigenetic consequences of early conditions can be eliminated using pharmacological interventions, which give great hope to the treatment of psychiatric disorders [8].

AEDs have psychotropic potential. Their pharmacological actions are multiple, and their genetic regulatory functions, especially epigenetic modifications, play an important role in these functions [73, 74]. BRD1 is a susceptibility gene for schizophrenia and bipolar disorder [75]. VPA or CBZ exposure can induce the transcriptional upregulation of BRD1 *in vitro* by demethylating the BRD1 promoter, but CBZ has no such effect on demethylation. This finding indicates that BRD1 can be a potential drug target in schizophrenia [76]. Drugs that show the potential for the treatment of schizophrenia through epigenetic effects include oxcarbazepine (OXC) [77] and CBD [78], which act as an HDACI and DNA demethylating agent, respectively. However, the role of OXC seems to be less effective than that of other potent HDACIs such as VPA and 5-azacytidine. Preclinical experiments have shown that VPA, CBZ, LEV, and LTG can inhibit HDAC2/3/5 in different brain regions, which sheds light on the relationship between antidepressant-like effects and HDACIs [79]. One mechanism reported recently is that VPA upregulates the melatonin receptor MT1, which may have an antidepressive effect [80]. Another common psychological disorder, bipolar disorder, may be related to the epigenetic effects of VPA. VPA treatment influences DNA methylation patterns over and above cell type composition in patients with bipolar disorder, indicating the biological mechanisms underlying drug efficacy [81].

Epigenetic modifications are also involved in basic aspects of brain function in addition to their association with psychiatry. They are commonly reflected in neuroprotective function in drug administration. A preclinical experiment indicated that a decrease in HDAC1 levels in rat and mouse brain tissues treated with lacosamide enhanced cognitive function and exerted a potential neuroprotective effect in Alzheimer's disease [33]. VPA can reduce traumatic neural injuries *in vivo* and *in vitro* as an HDACI, and specific isoforms of HDAC serve as possible targets of the molecular mechanism [82]. In addition, an augmentation in epigenetic regulatory factors such as FGF21 and BDNF may also be a mechanism by which VPA exerts its robust neuroprotective function [39, 83]. da Silva VK *et al*'s research found that CBD can reduce the methylation of mitochondrial DNA, thereby reducing the loss of mitochondrial ferritin in rats. This protein loss is thought to be associated with some neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases [84]. In Parkinson's disease, the key pathogenic factor is the lack of dopamine. Green and colleagues discovered that VPA can upregulate the expression of dopamine transporters, thereby increasing the content of dopamine. This effect may elucidate VPA's neuroprotective potentialities in models of Parkinson's disease [85]. However, since VPA also causes reversible Parkinson's symptoms in clinical applications [86], its efficacy needs to be further evaluated in an *in vivo* model.

3.1.4. Cardiovascular Disease, Diabetes and Renal Disease

In the cardiovascular system, HDACs control processes such as hypertrophy, fibrosis, apoptosis, and energy metabolism. Accumulating evidence has shown their remedial effect in the heart in preclinical models [87, 88]. The HDAC9 gene is thought to be associated with atherosclerosis in preclinical data [89]. An analysis of prospective cohort studies showed that VPA reduces the risk of recurrent ischaemic stroke in patients with a previous stroke or transient ischaemic attack, suggesting that exposure to VPA, an inhibitor of HDAC, may be associated with a lower recurrent stroke risk [90]. The efficacy of VPA for the prevention of recurrent ischaemic stroke is worth further clinical assessment. In a mouse model, Choi *et al*. found that VPA prevented hypertension caused by a high-fat diet by inhibiting HDAC1 and downregulating the expression of angiotensin II and its receptor, which implies a new treatment option for hypertension [91]. A recent study showed that another gene, HDAC2, is related to cardiac fibrosis and apoptosis in muscle cells. VPA can act as an inhibitor to restrain the dysregulation of specific pathways, such as oxidative phosphorylation or RhoA signalling, suggesting that VPA has the potential to delay arterial remodelling and the onset of atrial fibrillation in patients at risk [92].

The application of VPA as an HDACI extends to other disease areas. For example, recent studies have found that VPA inhibits HDAC in different isoforms as an antidote for attenuating renal fibrosis and type 2 diabetes [93, 94].

3.2. Stem Cell Research

Epigenetic reprogramming occurs in primordial germ cells and in the early embryo. DNA methylation of a few crucial loci is required to restrict their differentiation potential [95]. However, these inheritable changes are reversible when epigenetic modifiers are present.

The antiepileptic drug VPA has the powerful ability to induce neural differentiation and neural axis growth in pluripotent stem cells [96]. However, the underlying mechanisms are unknown. Based on this finding, Zhang *et al*. found that VPA activated the mTOR signalling pathway, increased

mTOR activity, and demethylated the Ngn1 promoter region, which significantly enhanced the differentiation of rat and neural stem cells [97].

The method of inducing stem cell differentiation and proliferation is also applied to the study of various preclinical stem cell therapies. For instance, VPA treatment decreases the neural progenitor markers Nestin, Notch2 and Sox and improves the differentiation of sympathoadrenal progenitor cells into catecholaminergic neurons with significantly elevated levels of epinephrine. The induction of chromaffin progenitors may be used in the transplantation therapies of neurodegenerative diseases [98]. Another study showed that HDACIs such as VPA may represent a simple and straightforward strategy for the expansion of phenotypic mouse tendon stem cells and retain the function for tendon repair [99].

3.3. ADRs and Toxicity

3.3.1. Carcinogenicity

Although some drugs have been determined to be nontoxic in traditional toxicity tests, they are reported to have a certain "biological effect". Therefore, some researchers believe that it is necessary to consider a new concept of toxicity, namely, "epigenetic toxicity" [103, 104]. Chemical compounds are anticipated to be able to be classified as epigenetic carcinogens based on mechanistic evidence [105]. Then, we can search for a preventive approach to this carcinogenic effect in the clinic for further analysis of the carcinogenic mechanism.

The International Agency for Research on Cancer classifies PB as a nongenotoxic toxicant, an absolute mammal carcinogen [106]. PB can cause abnormalities in gene expression in hepatocytes; therefore, researchers have also tried to use biomarkers to predict the effect of PB-induced liver cancer in rodent models [107]. Pouche *et al*'s study suggested that the regulation of noncoding RNAs, such as miR-200b and miR-221, can predict the development of liver cancer [26]. The unique mechanism may be that PB alters the expression of specific noncoding RNAs (ncRNAs) by activating CAR. Then, these ncRNAs regulate their target proteins and eventually cause cancer [42].

3.3.2. Developmental Neurotoxicity

AEDs might affect foetal growth. Tomson and Battina summarized different studies suggesting a slightly increased risk of congenital malformations among newborn babies exposed to AEDs during pregnancy [108]. The mechanisms of developmental neurotoxicity mediated by AEDs are also thought to be associated with multiple factors, such as folate metabolism [109] and the expression of placental transporters [110], and epigenetic effects are a non negligible part of this process, which may shed light on possible prevention and treatment strategies of these toxic effects [111]. VPA has the highest risk of teratogenesis among all AEDs [108]. Many studies aim to unravel the link between epigenetic modifications of VPA exposure and the mechanism of teratogenesis. Previous studies have shown that the acetylation and methylation of histones, as well as DNA methylation, in the embryonic neuroepithelium in mice may be related to teratogenic effects [112].

Another neurodevelopmental disorder mediated by AEDs is autism spectrum disorder (ASD). VPA can induce and fabricate an ASD model of rodents, which has been widely used in autism research [113]. In addition to its function in HDAC and DNA methylation, two studies have shown elevated levels of miR-132 and miR-134-5p in brain tissue of the VPA-induced mouse ASD model [41, 114]. In summary, these findings suggest that targets for epigenetic biomarkers may contribute to the prevention and treatment of congenital diseases.

Interestingly, in preclinical studies, researchers have also begun to use folic acid, alpha-linoleic acid and other substances to prevent malformations or developmental disorders caused by VPA [115, 116]. The epigenetic mechanisms of these therapies should be explored in future studies.

3.3.3. Inflammatory Effect

AEDs can cause inflammatory damage to organs in multiple ways. The liver damage caused by VPA can be explained by epigenetic effects. In a previous study, VPA exposure to human primitive liver cells caused a decrease in the methylation levels of the PPARγ, PPARα, CD36 and AHR genes, thereby inhibiting β-oxidation and increasing fatty acid entry into hepatocytes, possibly explaining the molecular mechanism of VPA-induced hepatic steatosis [117]. VPA-induced cataracts are a rare side effect. Palsamy *et al*. discovered hypomethylated loci of the Keap1 promoter that may lead to the enhanced expression of Keap1. In addition, overexpressed Keap1 decreases the Nrf2 level, thereby abolishing Nrf2-dependent antioxidant protection, which might be responsible for oxidative lenticular proteins and cataracts [118]. In addition, VPA is a cause of pancreatitis. However, unlike oxidative stress, VPA interferes with the proliferation of acinar cells and reprograms embryonic cells through the inhibition of HDAC [119]. Activating inflammatory cells can also cause inflammatory effects. CBZ-induced hypersensitivity reactions, such as SJS, are associated with the activation of $CD4^+$ T-cells. A recent study found that miR-18a and miR-155 may be epigenetic factors [43].

3.3.4. Drug Metabolism

An individual's susceptibility to ADRs can be determined by epigenetic effectors, such as pharmaceutical compounds, because of variants in certain genes. The occurrence of an ADR can indicate the epigenetic regulation of metabolic genes [14].

PB and CBZ are both liver enzyme inducers. In a recent study, PB (80 mg/kg)-treated rats had higher expression of Ugt1a6 and Ugt1a7 in brain regions. A marker analysis showed that oxidative stress and histone modifications may promote the transcriptional activation of the Ugt1a6 and Ugt1a7 genes [120]. Ookubo *et al*., suggested that the mechanisms underlying CBZ-induced CYP3A4 expression may be associated with its inhibition of HDAC1 [79].

CONCLUSION

AEDs have contributed to neural stabilization in many ways in epilepsy patients for many years. With the development of epigenetics, there is a growing interest in the func-

tions of AEDs, and they are not limited to the prevention of abnormal discharge. Although this article also mentioned that the toxic effects mediated by AEDs seem to have increased the alertness of researchers, similar epigenetic modifications also have beneficial effects. For example, VPA inhibits the apoptosis of renal tubular epithelial cells by targeting HDAC2 and increasing BMP-7 levels. HDACIs may be potentially effective therapeutic agents for preventing cisplatin nephrotoxicity [121]. However, many drugs lack selectivity for epigenetic targets [122], and AEDs are no exception. These drugs may have both beneficial and harmful effects; for example, valproic acid not only has psychotropic effects (300 mg/kg in mice) [100] but also produces teratogenic effects (400 mg/kg in mice) [112]. The occurrence of negative reactions is often related to factors such as dose, environment, age, sex, and disease of the subject. These negative reactions are a major obstacle to limit the epigenetic role of drugs in clinical applications and require more specific trials to verify drug safety before clinical use.

Another issue to be addressed is that many patients with epilepsy often experience varying degrees of cognitive impairment after receiving antiepileptic drugs [123]. Different antiepileptic drugs may have different effects on cognitive function, among which lamotrigine and levetiracetam are better than first-generation antiepileptic drugs such as VPA, PHT and PB in the cognitive recovery of epilepsy patients [124]. Therefore, what if epigenetic factors could influence this procedure? Additional studies are needed to fill this "gap". However, for these antiepileptic drugs in various fields of research, the answer will eventually be revealed.

In summary, there are plentiful preclinical data that have been obtained in recent years that may provide implications for future clinical studies aiming to elucidate the potential preventive and therapeutic role(s) of AEDs in human medicine.

LIST OF ABBREVIATIONS

ADK	=	Adenosine kinase
ADRs	=	Adverse drug reactions
AEDs	=	Antiepileptic drugs
ASD	=	Autism spectrum disorder
CBD	=	Cannabidiol
CBZ	=	Carbamazepine
Dlk1-Dio3	=	Delta-like homologue 1 gene and the type III iodothyronine deiodinase gene
DNMTs	=	DNA methyltransferases
FTO	=	Fat mass and obesity-associated protein
Gad67	=	Glutamic acid decarboxylase 67
GBM	=	Glioblastoma multiforme
HATs	=	Histone acetyltransferases
HDAC	=	Histone deacetylases
HDACIs	=	Histone deacetylase inhibitors
LCM	=	Lacosamide
LEV	=	Levetiracetam
LINE-1	=	Long interspersed element 1
LTG	=	Lamotrigine
MBD1	=	Methyl-CpG-binding domain 1
MDR1	=	Multidrug resistance protein 1
MECP2	=	Methyl-CpG-binding protein 2
MGMT	=	6-methylguanine-DNA methyltransferase
miRNAs	=	microRNAs
MTHFR	=	Methylenetetrahydrofolate reductase
ncRNAs	=	noncoding RNAs
OCM	=	One-carbon metabolism
OXC	=	Oxcarbazepine
p250GAP	=	Rho GTPase-activating protein
PB	=	Phenobarbital
PBA	=	2-pyrrolidinone-n-butyric acid
PTC	=	Papillary thyroid cancer
SJS	=	Stevens-Johnson syndrome
TMZ	=	Temozolomide
TPM	=	Topiramate
TRAIL	=	Tumour necrosis factor-related apoptosis-inducing ligand
VPA	=	Valproate acid

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This project was supported by the National Science Foundation for Youth Scientists of China (Grant No. 81703613) and Shanghai "Rising Stars of Medical Talent" Youth Development Program (Youth Medical Talents-Clinical Pharmacist Program).

CONFLICT OF INTEREST

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or a financial conflict with the subject matter of the materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

ACKNOWLEDGEMENTS

The authors sincerely thank the medical staff of the Huashan Hospitals of Shanghai, China, for their help.

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