Epigenetic Effects Mediated by Antiepileptic Drugs and their Potential Application

Fan-Cheng Kong¹, Chun-Lai Ma¹* and Ming-Kang Zhong¹

¹Department of Pharmacy, Huashan Hospital, Fudan University, Shanghai, China

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”, “lacasamide”, “lamotrigine”, “levetiracetam”, “lorazepam”, “mephobarbital”, “oxcarbazepine”, “phenobarbital”, “phenytoin”, “primidone”, “riluzole”, “rufinamide”, “tiaga-
bined, “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, untranscribed”[Mesh], “DNA methylation”[Mesh] OR “histone code”[Mesh], and “anticonvulsants”[Pharmacological Action]. Then, the pivotal clinical studies and experiment articles 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 ANTI EPILEPTIC 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, namely 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 substrates 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 lamotrigine (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-pyridolidinone-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 antineoplastic 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, anti-miRNAs 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 anti-miRNAs 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 ANTI-EPILEPTIC 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 overexpression 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
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

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

| Drug   | Gene                        | Molecular Effect | Functional Effect                  | Species | Refs. |
|--------|-----------------------------|------------------|------------------------------------|---------|-------|
|        | P53                         | Histone acetylation | Antitumour effect                  | Human   | [60]  |
| VPA    | 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] |
|        | Ptx3, 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 | Cell proliferation                  | Human   | [59]  |
|        | Sxx                         | 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                   | Human   | [76]  |
|        | HDAC2/3/5                   | H3 acetylation    | Biomarker of psychological disorder | Mouse   | [79]  |
|        | LEV                         | MGMT              | Histone acetylation                | Human   | [70]  |
|        | HDAC2/3/5                   | H3 acetylation    | Biomarker of psychological disorder | Human   | [79]  |
|        | LCM                         | HDAC1             | Histone acetylation                | Rat     | [33]  |
|        | miR-195-5p                  | Upregulation      | Antitumour effect                  | Human   | [71]  |
|        | miR-107                     | Downregulation    | Antitumour effect                  | Human   | [71]  |

(Table 1) contd....
Clinical investigations have shown that VPA also promotes cisplatin resistance, suggesting an epigenetic mechanism [63]. Recent increased aH3 and aH4 expression in the resistant and sensitive cells, 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 brivaracem 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 LTH 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 down-regulating 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 non-toxic 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 carcinogen, an absolute mammalian 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 folate 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, PH 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

| Abbreviation | Definition |
|--------------|------------|
| 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 iothoridine 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.

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CONFLICT OF INTEREST

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REFERENCES

[1] Rogawski, M.A.; Löscher, W. The neurobiology of antiepileptic drugs. Nat. Rev. Neurosci., 2004, 5(7), 553-564. [http://dx.doi.org/10.1038/nrrneuroscience1340] [PMID: 15208697]
[2] Bird, A. Perceptions of epigenetics. Nature, 2007, 447(7143), 396-398. [http://dx.doi.org/10.1038/nature05913] [PMID: 17522671]
[3] Esteller, M. Epigenetics in cancer. N. Engl. J. Med., 2008, 358(11), 1148-1159.
Current Neuropharmacology, 2020, Vol. 18, No. 2

Weichert, W.; Röske, A.; Geeker, V.; Beckers, T.; Ebert, M.P.; Pross, M.; Dietel, M.; Denkert, C.; Röcken, C. Association of patterns of class I histone deacetylase expression with patient prognosis in gastric cancer: a retrospective analysis. *Lancet Oncol.*, 2008, 9(2), 139-148. [PMID: 18207460]

Rong, H.; Liu, T.B.; Yang, K.J.; Yang, H.C.; Wu, D.H.; Liao, C.P.; Hong, F.; Yang, H.Z.; Wan, Fe; Ye, X.Y.; Xu, D.; Zhang, X.; Chao, C.A.; Shen, Q.J. MicroRNA-134 plasma levels before and after treatment for bipolar mania. *J. Psychiatr. Res.*, 2011, 45(1), 92-95. [PMID: 20546789]

Suraweera, A.; O’Byrne, K.J.; Richard, D. Combination therapy with histone deacetylase inhibitors (HDACi) for the treatment of cancer: Achieving the full therapeutic potential of HDACi. *Front. Oncol.*, 2018, 8, 92. [PMID: 28338948]

Chou, T.C.; Talalay, P. Quantitative analysis of dose-effect relationships: the combined effects of multiple drugs or enzyme inhibitors. *Adv. Enzyme Regul.*, 1984, 22, 27-55. [PMID: 6382953]

Masterpasqua, F. Psychology and Epigenetics. *Rev. Gen. Psychol.*, 2009, 13(3), 194-201. [PMID: 19051947]

Pitkänen, A.; Löschner, W.; Vezzani, A.; Becker, A.J.; Simonato, M.; Lukasiuk, K.; Gröhn, O.; Bankstahl, J.P.; Friedman, A.; Aronica, E.; Gorter, J.A.; Ravizza, T.; Siöditya, S.M.; Kokaia, M.; Beck, H. Advances in the development of biomarkers for epilepsy. *Lancet Neurol.*, 2016, 15(8), 843-856. [PMID: 27302363]

Issa, J-P.J.; Kantarjian, H.M.; Targeting, D.N.A. Targeting DNA methylation. *Clin. Cancer Res.*, 2009, 15(12), 3938-3946. [PMID: 19509174]

Xu, W.S.; Parmigiani, R.B.; Marks, P.A. Histone deacetylase inhibitors: molecular mechanisms of action. *Oncogene*, 2007, 26(37), 5401-5552. [PMID: 18061206]

Eyal, S.; Yagen, B.; Sobol, E.; Altschuler, Y.; Shmuel, M.; Bieler, M. The activity of antiepileptic drugs as histone deacetylase inhibitors. *Epilepsia*, 2004, 45(7), 737-744. [PMID: 15250695]

Szyf, M.; Epigenetics, D.N.A. Epigenetics, DNA methylation, and chromatin modifying drugs. *Annu. Rev. Pharmacol. Toxicol.*, 2009, 49(1), 243-263. [PMID: 18851683]

Kacevska, M.; Ivanov, M.; Ingelman-Sundberg, M. J. C. P. Therapeutics, Perspectives on epigenetics and its relevance to adverse drug reactions 2011, 89(6), 902-932.

Watson, R.E.; Goodman, J.J. Epigenetics and DNA methylation: come of age in toxicology. *Toxicol. Sci.*, 2002, 67(1), 11-16. [PMID: 11961211]

Jones, P.A. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat. Rev. Genet.*, 2012, 13(7), 484-492. [PMID: 22640108]

Bestor, T.H. The DNA methyltransferases of mammals. *Hum. Mol. Genet.*, 2000, 9(16), 2395-2402. [PMID: 10934327]

Vidaki, A.; Daniel, B.; Court, D.S. Forensic DNA methylation profiling—potential opportunities and challenges. *Forensic Sci. Int. Genet.*, 2013, 7(3), 499-507.

Goldberg, A.D.; Allis, C.D.; Bernstein, E. Epigenetics: a landscape takes shape. *Cell*, 2007, 128(4), 635-638. [PMID: 17320500]

Mahn, D.; Puri, S.; Sharma, S. DNA methylation signatures: Biomarkers of drug and alcohol abuse. *Mutat. Res.*, 2018, 777, 19-28. [PMID: 3015428]

Dong, E.; Chen, Y.; Gavin, D.P.; Grayson, D.R.; Guidotti, A. Valproate induces DNA demethylation in nuclear extracts from adult mouse brain. *Epileptogen.*, 2010, 5(8), 730-735.

Dezi, G.; Ozturk, E.; Stanic, D.; Powell, K.L.; Blumenfeld, H.; O’Brien, T.J.; Jones, N.C. Ethosuximide reduces epileptogenesis and behavioral comorbidity in the GAERS model of genetic generalized epilepsy. *Epilepsia*, 2013, 54(4), 635-643. [PMID: 23464891]

Pitkänen, A.; Löschner, W.; Vezzani, A.; Becker, A.J.; Simonato, M.; Lukasiuk, K.; Gorter, J.A.; Aronica, E.; Pitkänen, A. DNA methylation signatures: Biomedical applications. *Epilepsia*, 2013, 54(4), 635-643.
Epigenetic Effects Mediated by Antiepileptic Drugs and their Potential Application

Current Neuropharmacology, 2020, Vol. 18, No. 2 163

A.J. Levitrectam resistance: Synthetic signatures & corresponding promoter SNPs in epileptic hippocampi. Neurobiol. Dis., 2013, 60, 115-125.

[http://dx.doi.org/10.1016/j.nd.2013.08.015] [PMID: 24018139]

Yeo, D.; Wen, X.; Gorczyca, L.; Morris, A.; Richardson, J.R.; Alekseenos, L.M. Increased MDR1 transporter expression in human brain endothelial cells through enhanced histone acetylation and activation of aryl hydrocarbon receptor signaling. Mol. Neurobiol., 2019, 56(10), 6986-7002.

[http://dx.doi.org/10.1007/s12035-019-1565-7] [PMID: 30963442]

Tan, N.N.; Tang, H.L.; Lin, G.W.; Chen, Y.H.; Lu, P.; Li, H.J.; Cao, M.M.; Zhao, Q.H.; Yi, Y.H.; Liao, W.P.; Long, Y.S. Epig-

ese modification therapeutic effects in a model of a
disease. Epilepsy Res., 2000, 41(2), E566.

[http://dx.doi.org/10.1016/s0920-1211(00)0012-5] [PMID: 27302632]

Grimminger, T.; Perlhorn, K.; Surges, R.; Niemann, P.; Priebe, L.; von Lehe, M.; Hoffmann, P.; Ciechon, S.; Schoch, S.; Becker,
regulation of H19 noncoding RNA in ovarian A2780 cells. *Appl. Biochem. Biotechnol.*, 2018, 154(5), 1132-1144.

[65] Zhuo, W.; Zhang, L.; Zhu, Y.; Xie, Q.; Zhu, B.; Chen, Z. Valproic acid, an inhibitor of class I histone deacetylases, reverses acquired Erlotinib-resistance of lung adenocarcinoma cells: A connectivity Mapping analysis and an experimental study. *Am. J. Cancer Res.*, 2015, 5(7), 2202-2211. [PMID: 26328250]

[66] Matsuda, Y.; Wakai, T.; Kubota, M.; Osawa, M.; Hirose, Y.; Sakata, J.; Kobayashi, T.; Fujimaki, T.; Takamura, M.; Yamagishi, S.; Aoyagi, Y. Valproic acid overcomes transforming growth factor-β-mediated sorafenib resistance in hepatocellular carcinoma. *Int. J. Clin. Exp. Pathol.*, 2014, 7(4), 1299-1313. [PMID: 24817927]

[67] Wang, Y.; Kuramitsu, Y.; Kitagawa, T.; Tokuda, K.; Baron, B.; Akada, J.; Nakamura, K. The histone deacetylase inhibitor valproic acid sensitizes gemcitabine-Induced Cytotoxicity in Gemcitabine-resistant pancreatic cancer cells possibly through inhibition of the DNA repair protein gamma-H2AX. *Target. Oncol.*, 2015, 10(4), 575-581.

[68] Blaheta, R.A.; Michaelis, M.; Natshet, I.; Hansenberg, C.; Weich, E.; Relja, B.; Jonas, D.; Doerr, H.W.; Cinat, J.; Jr Valproic acid inhibits adhesion of vincristine- and cisplatin-resistant neuroblastoma tumour cells to endothelium. *Br. J. Cancer.*, 2007, 96(11), 1609-1706.

[69] Kim, Y.H.; Kim, T.; Joo, J.D.; Han, J.H.; Kim, Y.J.; Kim, I.A.; Yun, C.H.; Kim, C.Y. Survival benefit of levetiracetam in patients treated with concomitant chemoradiotherapy and adjuvant chemotherapy with temozolomide for glioblastoma multiforme. *Cancer*, 2015, 121(17), 2926-2932.

[70] [http://dx.doi.org/10.1002/eanc.n.201408393] [PMID: 25975354]

[71] Scicchitano, B.M.; Sorrentino, S.; Proietti, G.; Lama, G.; Dobrowolny, G.; Catizone, A.; Binda, E.; Larocca, L.M.; Sica, V.; Deiervatamid enhances the temozolomide effect on glioblastoma stem cell proliferation and apoptosis. *Cancer Cell Int.*, 2018, 18, 136.

[72] [http://dx.doi.org/10.1186/s12853-018-0626-8] [PMID: 30214378]

[73] Rizzo, A.; Donzelli, S.; Girgenti, V.; Sacconi, A.; Vasco, C.; Salamaggi, A.; Blandino, G.; Maschio, M.; Ciancius, E. In *vitro* antineoplastic effects of brivaracetam and lacosamide on human glioma cells. *Journal of experimental & clinical cancer research.*

[74] [http://dx.doi.org/10.1186/s12943-016-0413-4] [PMID: 27486946]

[75] [http://dx.doi.org/10.1007/s12020-014-1013-4] [PMID: 25094934]

[76] [http://dx.doi.org/10.1111/eanc.12038] [PMID: 20063323]

[77] [http://dx.doi.org/10.1007/s12020-012-1015-7] [PMID: 23588417]

[78] [http://dx.doi.org/10.1038/jn.2011.246] [PMID: 22970921]

[79] [http://dx.doi.org/10.1093/ijnp/pwy035] [PMID: 27207921]

[80] [http://dx.doi.org/10.1016/j.brainresbull.2018.01.014] [PMID: 29374603]

[81] [http://dx.doi.org/10.1093/ijnp/pyw035] [PMID: 27207921]

[82] [http://dx.doi.org/10.1007/s12943-016-0413-4] [PMID: 25094934]

[83] [http://dx.doi.org/10.1038/188-008] [PMID: 17055515]

[84] [http://dx.doi.org/10.1186/s12853-018-0626-8] [PMID: 30214378]

[85] [http://dx.doi.org/10.1093/ijnp/pyw035] [PMID: 27207921]

[86] [http://dx.doi.org/10.1093/brain/brw036] [PMID: 18794555]

[87] [http://dx.doi.org/10.1016/j.brainresbull.2018.01.014] [PMID: 29374603]

[88] [http://dx.doi.org/10.1007/s12928-012-8237-x] [PMID: 21151616]

[89] [http://dx.doi.org/10.1016/j.annurev-pharmaco-tox-010614-134712] [PMID: 21942627]

[90] [http://dx.doi.org/10.1016/j.brainresbull.2018.01.014] [PMID: 29374603]
Epigenetic Effects Mediated by Antiepileptic Drugs and their Potential Application

Vineis, P.; Smith, M.T; Herceg, Z.; Lambert, M.

Development of human umbilical cord derived mesenchymal stem cells.

Cell Res. 2018, 29(7), 2372-2375 [PMID: 30424007] [http://dx.doi.org/10.1016/j.biomaterials.2018.03.043]

Bisphenol A and valproic acid may have epigenetic toxicities: potential public health concerns. 

Crit. Rev. Toxicol. 2016, 46(8), 676-700. [http://dx.doi.org/10.1080/10408444.2016.1175417] [PMID: 27278298]

Role of the histone deacetylase inhibitor valproic acid in high-fat diet-induced hypertension via inhibition of HDAC1/angiotensin II axis.

Int. J. Obesity (2005) 34(9), 1702-1709.

Some thymocyte agents. IARC Monogr. Eval. Carcinog. Risks Hum. 2001, 79, 1-725. [PMID: 11766267]

Towards incorpora-

Food Chem. toxicol., 2016, 109, 2016.

Inhibition of HDAC1/angiotensin II induced hypertension

Lancet Neurol. 2012, 11(9), 803-813.

Hirsch, M. M.; Deckmann, I.; Fontes-Dutra, M.; Bauer-Negrini, G.; Della-Flora Nunes, G.; Nunes, W.; Rabelo, B.; Riesgo, R.; Margis, R.; Bambini-Junior, V.; Gottfried, C. Behavioral alterations in autism model induced by valproic acid and translational analysis of circulating microRNA. 

Food Chemical Toxicology, 2018, 115, 336-343. [http://dx.doi.org/10.1016/j.fct.2018.01.021] [PMID: 29776446]

In vitro revo
cate with a new mecha-

N. K.; van der Laan, A.; Dijkstra, T.; Calabrese, L.; Rijksen, G. The valproic acid induced teratogenesis. 

Toxicol. Appl. Pharmacol. 2010, 248(3), 201-209.

Can our understanding of epigenetics assist with primary prevention of congenital defects? J. Med. Genet. 2010, 47(2), 73-80.

Exp. Neurol. 2018, 299(PT A), 217-227. [http://dx.doi.org/10.1016/j.expneurol.2017.04.017] [PMID: 2878518]

Yu, W.H.; Ho, Y.L.; Huang, P.T.; Chu, S.L.; Tsai, H.J.; Liou, H.H. The phosphorylation state of GSK3β is correlated to the Drosophila antennal organ size. 

Exp. Eye Res. 2014, 121, 170-178. [http://dx.doi.org/10.1016/j.exer.2014.01.021] [PMID: 24525405] [PMID: 25724324]

van Breda, S.J.; Claessen, S.M.H.; van Heurn, M.; Theunissen, D.H.J.; Jenden, D.J.; de Kort, T.J.; Vincken, J.C.S. Integrative omics data analyses of repeated dose toxicity of valproic acid in vitro reveal new mechanisms of steatosis induction. 

Toxicology, 2018, 393, 160-170. [http://dx.doi.org/10.1016/j.tox.2017.11.013] [PMID: 29154799]

Palsamy, P.; Bidasee, K.R.; Shinohara, T. Valproic acid suppresses Nrf2/Keap1 dependent antioxidant protection through induction of endoplasmic reticulum stress and Keap1 promoter DNA demethylation in human lens epithelial cells. Exp. Eye Res. 2014, 121, 26-34. [http://dx.doi.org/10.1016/j.exer.2014.01.021] [PMID: 24525405]

Eisses, J.F.; Criscimanna, A.; Dionise, Z.R.; Orabi, A.I.; Javed, A.; Negrini, G.; van Breda, S.J.; Claessen, S.M.H.; van Heurn, M.; Theunissen, D.H.J.; Jenden, D.J.; de Kort, T.J.; Vincken, J.C.S. Integrative omics data analyses of repeated dose toxicity of valproic acid in vitro reveal new mechanisms of steatosis induction. 

Toxicology, 2018, 393, 160-170. [http://dx.doi.org/10.1016/j.tox.2017.11.013] [PMID: 29154799]
promoted apoptosis of renal tubular epithelial cells in acute kidney injury. *Cell Death Dis.*, **2017**, *8*(10), e3139. [http://dx.doi.org/10.1038/cddis.2017.552] [PMID: 29072686]

[122] Anderson, S.J.; Feye, K.M.; Schmidt-Mc Cormack, G.R.; Malovic, E.; Mlynarczyk, G.S.A.; Izbicki, P.; Arnold, L.F.; Jefferson, M.A.; de la Rosa, B.M.; Wehrman, R.F.; Luna, K.C.; Hu, H.Z.; Kondru, N.C.; Kleinhenz, M.D.; Smith, J.S.; Manne, S.; Putra, M.R.; Choudhary, S.; Massey, N.; Luo, D.; Berg, C.A.; Acharya, S.; Sharma, S.; Kanuri, S.H.; Lange, J.K.; Carlson, S.A. Off-Target drug effects resulting in altered gene expression events with epigenetic and “Quasi-Epigenetic” origins. *Pharmacol. Res.*, **2016**, *107*, 229-233. [http://dx.doi.org/10.1016/j.phrs.2016.03.028] [PMID: 27025785]

[123] Orbinski, P.; Meador, K.J. Cognitive side effects of antiepileptic drugs. *Epilepsy Behav.*, **2004**, *5*(Suppl. 1), S60-S65. [http://dx.doi.org/10.1016/j.yebeh.2003.11.008] [PMID: 14725848]

[124] Barr, W.B. Understanding the cognitive side effects of antiepileptic drugs: Can functional imaging be helpful? *Epilepsy Curr.*, **2019**, *19*(1), 22-23. [http://dx.doi.org/10.1177/1535759718822032] [PMID: 30838926]