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Teratogenic Effect of Valproic Acids on Neural Tube Development: A Review

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Abstract

Valproic acid (VPA) is a well-established antiepileptic drug used worldwide. However, its teratogenic effects on neural tube development have raised significant concerns in both clinical and research settings. Therefore, the aim of this review was to comprehensively summarize the current knowledge regarding the teratogenic effects of VPA on neural tube development. Valproic acid is a simple branched-chain fatty acid with eight carbons, exhibits significant teratogenic effects when exposed during pregnancy. This can result in various neurodevelopmental abnormalities in offspring, collectively known as "fetal valproate syndrome." These abnormalities include cleft palate, atrial septal defects, polydactyly, craniosynostosis, hypospadias, and spina bifida, observed in both humans and animals. The mechanisms underlying its teratogenicity involve disruption of folate metabolism via methyl enetetrahydrofolate reductase (MTHFR) inhibition, leading to increased homocysteine levels and folate deficiency. Valproic acid also induces oxidative stress, DNA damage, and inhibits histone deacetylases (HDACs), resulting in altered gene expression. Its antiangiogenic properties may contribute to its teratogenic effects. So, continued efforts are essential to understand the underlying mechanisms, develop preventive strategies, and enhance prenatal care to improve maternal and fetal health outcomes.

Keywords: *Teratogenic effects of Valproic acid, Valproic acid*

1. Introduction

Teratology is the study of deviant fetal growth, emerged as a scientific field in the mid-20th century with the realization that environmental influences could lead to congenital deformities. Initially limited in clinical

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application, it faced challenges such as infectious diseases and difficulties in identifying congenital deformities (Dicke, 1989). Dietary deficiencies, like low vitamin A intake in pigs leading to eye defects, highlighted the multifaceted causes of anomalies. Genetics, environmental factors, and their combination contribute to anomalies, with genetics accounting for 30%, environmental factors for 15%, and both for 55% in humans (Calado and Pires, 2018). Unlike other forms of prenatal harm induced by drugs, teratogenesis specifically pertains to structural deformities during fetal development (Jamkhande, 2014).

Teratogens are believed to disrupt normal development through various pathways, exploiting different targets and processes (Wlodarczyk *et al.*, 1997). Valproic acid (VPA), an anticonvulsant medication frequently prescribed for various convulsive disorders, has demonstrated effectiveness in treatment. Despite being considered relatively safe, it has been associated with specific developmental defects and rare but severe hepatotoxicity (Bennett *et al.*, 2000). Originally discovered for its antiepileptic properties in 1963, VPA is used in epilepsy treatment and explored for its potential in cancer therapy and other conditions. Maternal use of VPA during pregnancy is linked to an increased risk of congenital defects in the fetus (Kratke and Kirschbaum, 1996).

Maternal use of VPA during pregnancy is linked to an increased risk of congenital defects in the fetus (Matalon *et al.*, 2002). Beyond epilepsy, VPA is under investigation for its potential as an anticancer agent and is also utilized in treating bipolar disorder, anxiety, and migraine prevention (Lee *et al.*, 2015). VPA inhibits the citric acid cycle and increases gamma-aminobutyric acid levels, exerting anticonvulsive effects (Chuang *et al.*, 2012). However, it's associated with hepatotoxicity and various prenatal abnormalities, including neural tube defects (Nau *et al.*, 1991; Okada *et al.*, 2005).

Numerous substances that induce NTDs have been studied in the past (Umur *et al.*, 2012). Neural tube defects (NTDs) rank second in frequency of malformations following congenital cardiac problems (Mallela and Hrubec, 2012). Neural tube defects (NTDs), like anencephaly and spina bifida, result from failures in the neurulation process. Exposure to VPA during pregnancy increases the risk of NTDs (Verrotti *et al.*, 2006; Periodicals *et al.*, 2012; Shafique and Winn, 2020; Lee *et al.*, 2023). Neural tube closure in mouse embryos is known to start at several distinct closure starting locations and happens between GDs 8 and 10 (Okada *et al.*, 2005). Despite its effectiveness in treating epilepsy and bipolar disorders, VPA carries a teratogenic risk, causing NTDs and other malformations during pregnancy. The exact mechanism remains unclear, but hypotheses include histone deacetylase inhibition and folate antagonism, emphasizing the need to understand these mechanisms in clinical decisions regarding VPA use during pregnancy (Defects *et al.*, 2015). Therefore, the aim of this review was to comprehensively summarize the current knowledge regarding the teratogenic effects of VPA on neural tube development.

2. Chemical Structure of Valproic Acid

Dipropylacetic acid, another name for valproic acid, is a simple branched-chain fatty acid with eight carbons that is used to treat epilepsy in patients. It is not structurally connected to other anticonvulsants (Lammer *et al.*, 1987). With a propyl group bonded to the second carbon, the molecule has eight carbons total, with the backbone of pentanoic acid. At physiological pH, 99.8% of the molecule is ionized by this weak organic acid (pKa = 4.8) (Mishra *et al.*, 2022). Valproic acid (VPA), a short-chain fatty acid, is one medication used to treat bipolar disorders, migraines, and epilepsy. It might also be beneficial for treating mental and neurological illnesses (Tiboni *et al.*, 2013).

3. Teratogenic Effect of Valproic Acid

Prenatal VPA exposure was revealed to be associated with neurodevelopmental abnormalities in the offspring in a rat model (Ito, 2021). The International Clearinghouse for Birth Defects Monitoring Systems, http://www.icbd.org/index.html, reports that there is a systematic clinical association between drug exposure during pregnancy and birth defects (teratogenesis), even though the etiology of almost all birth defects is unknown. Two different pathways could be responsible for these drug-induced malformations: one is based on the drug's pharmacological activity, while the other is either unknown or not related to it. Structural alteration can be employed to prevent teratogenic effects while preserving pharmaceutical efficacy

when the impact is brought on by circumstances other than pharmacological activity (Okada and Fujiwara, 2006).

The pharmacological and teratological efficacy of a medicine must be structurally divided into distinct regions, as indicated by this fact. A substance that is not only stronger but also safer in clinical settings for this kind of medication may be produced through structural alteration. Under the umbrella title "fetal valproate syndrome," a group of birth abnormalities includes cleft palate, atrial septal defects, polydactyly, craniosynostosis, hypospadias, and, most commonly spina bifida caused by recognized teratogen valproic acid (VPA) (Tung and Winn, 2011). Valproic acid (VPA) has been shown to cause teratogenic effects in a wide range of animal species, including the mouse, rats, hamsters, rabbits, and rhesus monkeys. It is structurally unrelated to any other anticonvulsant drugs (Wlodarczyk *et al.*, 1997).

The broad category of pharmaceuticals known as psychotropic drugs has various effects on the nervous system. They are capable of passing through the placenta and into the fetal central nervous system (CNS) when taken during pregnancy. Because of this, they may alter the unborn brain's function while it is still inside the uterus and potentially have long-term impacts on brain function because they may easily pass the fetal blood-brain barrier. Regarding their potential teratogenic effects, as well as their potential impact on neonatal adaption and long-term neurodevelopmental results, the quantifiable quantities of most psychoactive drugs identified in the amniotic fluid as a measure of transplacental passage raise concerns (Ornoy *et al.*, 2017). There is a higher chance of significant congenital defects in the fetus when a mother uses antiepileptic medications during pregnancy (Matalon *et al.*, 2002).

Valproic acid is teratogenic in both humans and animals, despite its extensive usage and effectiveness (Defoort *et al.*, 2006). Due to the developing neural system's heightened sensitivity to VPA, in-utero exposure to the chemical during the first trimester of pregnancy unfortunately increases the chance of both significant and small congenital abnormalities. Newborns exposed to VPA in utero have a neural tube defect (NTD) rate that is 10-20 times higher than the whole population (Tung and Winn, 2010).

All of the deformities linked to antiepileptic drugs (AEDs) occur during the first trimester of pregnancy, and NTDs start to appear around day 28 following conception. Any interference with the development of the embryo would cause the biochemical networks and coordinated signaling to be disrupted, leading to a variety of birth abnormalities (Hsieh *et al.*, 2014). In clinical settings, valproic acid (VPA) is frequently used to treat a variety of neuropsychiatric conditions, including bipolar disorder and epilepsy. However, due to its ability to produce embryos with malformations, VPA treatment has garnered a lot of attention. The aberrant development of the neural tube and the axial skeleton in animals are common abnormalities brought on by VPA exposure (Okada and Fujiwara, 2006).

Many drugs, especially antiepileptic drugs (AEDs) and mood-affecting drugs are to be taken throughout pregnancy, potentially affecting the conceptus before and after the period of active organogenesis. Moreover, although the most sensitive period to teratogens is during active organogenesis at post-conception weeks 3-8, several organs (e.g., teeth, external genitalia, brain) continue to be very active developmentally beyond that period and may therefore still be affected by teratogens (Ornoy and Echefu, 2024).

3.1. Mechanism of Teratogenic Action of Valproic Acid

There are several theories as to how congenital abnormalities are induced by VPA. According to one study, the fetal abnormalities brought on by VPA treatment during pregnancy may have been caused by toxic metabolites of the substance (Marc *et al.*, 2009). About 30% of the approximately 200 genes linked to neural tube abnormalities in genetic mice models may be viable. This suggests that the teratogenicity of VPA may be caused by the combined dysregulation of several genes (Kultima *et al.*, 2009). Numerous biological and developmental processes, as well as the pathogenetic mechanisms of numerous congenital malformations and diseases, including numerous neurobehavioral and psychiatric disorders, are currently linked to epigenetic mechanisms. Furthermore, a range of epigenetic modulators are being proposed for potential treatment of "epigenetic diseases (Ornoy *et al.*, 2020). Epigenetics is a branch of genomics that refers to the heritability of gene expression without modifying the DNA sequence (Article *et al.*, 2022).

Mest/Peg1 (mesoderm-specific transcript/paternally expressed gene 1) is a maternal imprinted gene that is widely expressed throughout the embryonic period, including the developing nervous system, and Mest/Peg1-knockout mice exhibited embryonic and placental growth retardation and postnatal growth inhibition, and loss of the gene imprinting resulted in postnatal weight gain and multiple organ hypertrophy (Shaoyan *et al.*, 2020). These studies hint that Mest/Peg1 has a crucial effect on embryonic development. It was found that the Mest/Peg1 gene was expressed in the testis and mature sperm of mice and human beings, presumably playing a role in fertilization (Nakabayashi *et al.*, 2002).

The neural tube's failure to close during development is the cause of anencephaly and spina bifida. In mice, nonspecific stimulation of the maternal immune system can reduce a variety of fetal defects induced by various physical and chemical causes, as well as diseases like diabetes mellitus (Mallela *et al.*, 2018).

Gene-gene and gene-environment interactions are becoming more widely recognized as contributing factors to neural tube defects (NTDs). Over 200 genes have been linked to NTDs in mice, and human NTDs are considerably more complex, involving several factors and polygenic disorders (Article *et al.*, 2022). When the neural tube, which eventually produces the brain and spinal cord, fails to shut properly during the first few weeks of development, common congenital abnormalities known as neural tube defects (NTDs) result. One or more of these processes may fail, impairing correct neural fold fusion and causing harmful or even fatal repercussions for the growing embryo. This failure is most likely the cause of the neural tube defects (NTDs) family of congenital deformities (Dicke, 1989).

NTDs are among the most prevalent birth abnormalities, which may be explained by the intricate synchronization of several morphogenetic processes necessary for appropriate NTC and the very short developmental time frame permitted for completion. Furthermore, NTDs continue to be among the birth abnormalities with the least understanding due to their intricate origin. NTD prevention is a major task for society since over 400 genetic variants and other environmental factors have been identified as mouse NTD risk factors. The complex process of neural growth involves many different cells and mechanisms. Teratogens can change a variety of cellular processes and activities, including cell cycle progression, apoptosis, viability, and interactions between the extracellular matrix and the cell surface. Neural tube abnormalities could result from changes to these processes (Murali, 2011).

There is a lack of knowledge on the precise mechanisms by which neural tube defects are caused by genes linked to these processes, despite recent studies showing that changes in their expression may result in neural tube defects. It will be possible to create intervention strategies to prevent NTDs by identifying the precise molecular, metabolic, or signaling pathways that cause teratogen-induced NTDs. Gene transcription switches, cell migration, differentiation, proliferation, and growth are a few of the intricate, coordinated cellular processes involved in neural tube closure (NTC) (Darya *et al.*, 2018). Numerous investigations have confirmed the complex genesis of isolated NTDs, with both genetic and environmental factors playing a significant role (Glauben *et al.*, 2011).

Heart and neural tube defects are the most prevalent abnormalities. There is no one known mechanism underlying the teratogenicity of VPA. Several theories have been put forward, such as the encouragement of folate deficiency, an increase in the levels of oxidative stress in the body, and the inhibition of histone deacetylases, which have anti-angiogenic effects during development. In addition, research has shown that VPA affects many signaling pathways via various mechanisms, making VPA-induced teratogenicity an excessively complex phenomenon. In general, there are different main theories about birth abnormalities linked to VPA exposure: i.e., Lack of folate, oxidative damage, and suppression of histone deacetylase (Kumar, 2018).

The antiepileptic medication valproic acid (VPA), a strong teratogen that most famously causes neural tube abnormalities (NTDs) in human, mouse, and other vertebrate embryos, was tested in this work using spotted cDNA microarrays to track changes in global gene expression (Kultima *et al.*, 2004).

3.1.1. Disruption of Methylene Tetrahydrofolate Reductase

One of the important enzymes involved in homocysteine metabolism and folate interconversion, methyl tetrahydrofolate reductase (MTHFR), is another mechanism described. Due to MTHFR modification, which

raises the teratogenicity rate, VPA may disrupt the metabolism of folate. In the folic acid cycle, methionine synthase uses 5-methyltetrahydrofolate as a substrate. This process is catalyzed by the enzyme methylenetetrahydrofolate reductase (MTHFR). Methyl groups are less readily available to macromolecules through the folate homocysteine cycle when MTHFR activity is reduced, leading to increased homocysteine levels (Kumar, 2018). The activity of methylene tetrahydrofolate was also observed to be decreased by VPA (Chen *et al.*, 2014).

Since MTHFR converts N5 and N10-methyleneTHF to N5-methylTHF, it has an impact on the distribution of folate forms. Hyperhomocysteinemia, decreased and elevated non-methylated methylation folates are caused by decreased MTHFR activity. Moreover, a mild MTHFR deficit is linked to an increased risk of NTDs, pregnancy difficulties, and possibly additional birth abnormalities (Marc *et al.*, 2009).

In mice, MTHFR activity is reduced to 60-70% of that of wild-type littermates in heterozygous mice and missing in homozygous mice with MTHFR deficiency. This is in line with the levels of MTHFR enzymatic activity found in those who carry the polymorphism. Comparing heterozygous and homozygous mice to their wild-type littermates, both show hyperhomocysteinemia and decreased global DNA methylation (Blumkin *et al.*, 2011). From 5,10-MTHF, 5-methylenetetrahydrofolate (5-MTHF) can be produced because of MTHFR. Since 5-MTHF guarantees that homocysteine is converted to methionine, decreased MTHFR production results in hyperhomocysteinemia (Karakus, 2023).

3.1.2. Folic Acid Deficiency

Neural tube defects (NTDs) can be prevented in humans and rats by taking supplements of folic acid (Dawson *et al.*, 2006). One of the most thoroughly researched dietary components directly linked to neural tube closure (NTC) is maternal folate. The prevalence of NTDs has significantly decreased as a result of folic acid fortification of food on a global scale (Article *et al.*, 2022). The metabolism of carbon has received considerable attention, with the discovery that folic acid supplementation during pregnancy lowers the incidence of neural tube defects (NTDs) being one example. Preconceptional phase folate-dependent NTD incidence has been significantly decreased by folic acid treatment (Li *et al.*, 2023).

Recently, it was discovered that the hippocampal regions of newborn rat pups exposed to VPA during pregnancy showed altered folate metabolism, as evidenced by an increase in 5-methyl-tetrahydrofolate (THF) and a decrease in 5-10-methenyl-THF (Koren *et al.*, 2018). Additionally, in mice, homocysteine increases the exencephaly caused by VPA (Padmanabhan, 2006). It is generally known that folic acid supplementation during pregnancy lowers the incidence of neural tube defects (NTDs) and other specific congenital abnormalities in women carrying infants. Fatty acid deficiency also raises the risk of NTDs (Smith and Whitehall, 2008).

Numerous research studies have also linked the teratogenicity of VPA to potential alterations in a treated individual's folate levels. When female animals or humans are treated with VPA, the overall serum folate levels are shown to decrease (Robert and Rose, 2017). A deficit in folate causes hyperhomocysteinemia, which has been implicated in the teratogenic potential of VPA, resulting in conditions such as spina bifida aperta and neural tubular defect (NTD) (Hsieh *et al.*, 2013).

3.1.3. Oxidative Stress

Oxidative stress is the cause of damage to the building blocks of cellular macromolecules, including DNA, lipids, and proteins. Oxygen damage to DNA occurs when hydroxyl ions combine with nitrogenous bases. As a result of their reaction with polyunsaturated fatty acids, generated free radicals can also produce electrophilic aldehydes like 4-hydroxy-2-nonenal and malondialdehyde, which can bond with amino acid residues like cysteine, lysine, or histidine and hinder protein function (Kumar, 2018).

Increased oxidative stress has the potential to inflict irreparable harm on the developing embryo and fetus because their antioxidant defense systems are young and develop slowly as gestational age increases. Furthermore, our research showed that, compared to other embryonic tissues, the rat brain is more vulnerable to elevated oxidative stress. Moreover, research on mice and rats has revealed that hypoxia with subsequent embryonic oxidative stress from the production of free radicals may be caused by phenytoin-induced embryonic

bradycardia (Ornoy, 2009). Oxidative stress has been implicated in the mechanisms of teratogenesis of several compounds including phenytoin, hydroxyurea, and 5-bromo-2-deoxyuridine (Tung and Winn, 2011). So far, direct proof of this mechanism being responsible for the VPA teratogenicity is missing. However, VPA has been found to reduce Superoxide Dismutase (SOD) activity and reduce glutathione levels (Koren *et al.*, 2018).

3.1.4. Inhibition of Histone Deacetylases (HDAC)

The regulation of gene expression through the mediation of changes in nucleosome conformation is greatly aided by histone deacetylases or HDACs. Histone acetyltransferase (HAT) enzymes work in the opposite way from HDACs: HDACs deacetylate lysine residues on histone tails and cause transcriptional repression by chromatin condensation, whereas HATs act as transcriptional co-activators by acetylating histone lysine–NH2 groups (Menegola *et al.*, 2005).

Both in vitro and in vivo exposure to VPA causes histone deacetylases (HDACs) to be inhibited and histones H3 and H4 to become hyperacetylated (Shafique and Winn, 2020). In addition, the teratogenic potential of VPA and its derivatives has been linked to its HDAC inhibitory activity (Gotfryd *et al.*, 2011). Histones are nuclear proteins that firmly attach to and arrange DNA in the nucleosome, which is made up of several histone complexes (including H1, H2A, H2B, H3, and H4) that build higher-order structures in the DNA. Lysine residues that have undergone histone acetylation loosen the tight binding between the DNA and histones, changing chromatin condensation and perhaps improving gene transcription. Histone deacetylases (HDACs) control this intricate and dynamic interaction by reversing the decondensed chromatin state and reducing transcriptional activity (Hornig *et al.*, 2016).

The reduction of histone acetylation by histone deacetylases results in chromatin modifications. Consequently, transcription factors and their teratogenic counterparts can disrupt the cell cycle and stimulate RNA polymerase to bind with DNA, thereby influencing gene transcription. VPA, growth arrest, and apoptosis are examples of HDAC inhibitors. Its teratogenic impact may be explained by VPA's inhibition of cell growth (Ornoy, 2009). A variety of congenital abnormalities and altered gene expression can result from demethylation of DNA. In fact, VPA changed the way that many genes were expressed by down-regulating the expression of protein kinase C isoforms, inducing the expression of other genes such as Hoxa1 and bcl-2, and activating Wnt-dependent gene expression. Similarly, the teratogenic effects of trichostatin, another well-known HDAC inhibitor, were similar to those of VPA.

3.1.5. Deoxyribonucleic Acid Damages

Excessive reactive oxygen species (ROS) production can cause direct damage to cellular macromolecules such as DNA, protein, and lipids and can alter normal signaling pathways through the activation of redox-sensitive transcription factors (Tung and Winn, 2011). One of the consequences of increased ROS production is oxidative DNA damage (Klaunig and Kamendulis, 2004). Both external DNA-damaging chemicals and cellular metabolites continuously modify the fundamental structure of DNA. These modifications can result in aneuploidy, deletions, fusions, translocations, or more complicated changes such as simple base shifts. Such modifications may ultimately result in degenerative changes and aging in multicellular creatures, or the demise of cells in unicellular species. In addition to activating or amplifying specific biochemical pathways that control cell growth and division and processes that help coordinate DNA replication with damage cleanup, DNA damage can disturb the cellular steady-state quasi-equilibrium. DNA repair, DNA damage checkpoints, transcriptional response, and apoptosis are the four categories of mechanisms that DNA damage triggers and are known or believed to mitigate detrimental damage effects (Sancar and Lindsey-Boltz, 2004).

DNA transcription is regulated by a variety of processes. Transcription is not possible when DNA is entangled with histones. On the other hand, transcription can occur when the nucleosome's DNA becomes detached. Since DNA is negatively charged due to the number of phosphate groups, and histones are basic proteins that are positively charged due to their abundance of basic amino acids like lysine and arginine, the two interact non-covalently to bind DNA. Histones can be post-translationally changed by certain enzymes that can result in the acetylation, methylation, phosphorylation, ubiquitination, and sumoylation of their tail lysines. Histones are distinguished by their tails, which contain lysine residues. Gene transcription is either aided or hindered by these modifications to the nucleosome's structure (Giavini and Menegola, 2014).

According to earlier studies, an increase in oxidative DNA damage may be the cause of teratogenesis for both phenytoin and thalidomide. DNA double-strand breaks may occur during the repair process of oxidized bases, which can be fixed by base excision repair and nucleotide excision repair (Defoort *et al.*, 2016). As an alternative, single-strand breaks that occur when oxidative DNA damage is repaired can transform into double-strand breaks when replication occurs. Chemotherapeutic drugs, like methotrexate and cyclophosphamide, cause cell death and DNA damage, which is probably one of the processes behind the formation of NTDs (Wang *et al.*, 2023).

Consequently, DNA damage repair pathways may directly influence the molecular and cellular processes involved in the correct formation of neural tubes. A single radiation track can cause two or more lesions that are separated by fewer than 20 base pairs, or two helical turns of the DNA molecule, which are referred to as clustered DNA damages or locally multiple damage sites (LMDS). Pyrimidine and purine lesions also known as base damages, basic (AP) sites, single-strand breaks (SSBs), and combinations of these lesions can all be found in LMDS. These combinations can happen in the same or opposite strands and are not limited to double-strand breaks (DSBs) (Zheng, 2019).

For instance, a double-strand break may occur from the simultaneous removal of damaged bases during base excision repair and nucleotide excision repair of oxidized bases on opposite strands that are near to one another (Pfeiffer *et al.*, 2000). The optimal functioning of certain enzymes is also necessary for one-carbon metabolism. These enzymes include 5 and 10-methylenetetrahydrofolate reductase (MTHFR), which directs the folate pool toward methylation or DNA repair (Sharp *et al.*, 2008).

3.1.6. Antiangiogenics

A novel therapeutic approach that is being actively and assiduously investigated is antiangiogenesis, or the pharmaceutical inhibition of the growth and production of new blood vessels. There are numerous research investigating angiogenesis inhibitors as potential therapies for macular degeneration because they block growth factors from entering blood vessel cells. The chemical processes involved in controlling blood vessel formation have been demonstrated to be influenced by several growth factors (Ciardella *et al.*, 2002). One well-known natural inhibitor of angiogenesis is thrombospondin-1 (TSP-1), and in many tumor types, the angiogenic switch is largely dependent on the down-regulation of TSP-1. As demonstrated earlier, TSP-1 is expressed in neuroblastoma tumors with morphologic indications of neuroblast differentiation, but it is epigenetically suppressed in a subgroup of undifferentiated, advanced-stage tumors and cell lines (Yang *et al.*, 2007).

Short-chain fatty acids' capacity to inhibit histone deacetylase (HDAC) activity is a typical mechanism underlying their anticancer actions (Rada-Iglesias *et al.*, 2007) as well as angiogenesis (Pili *et al.*, 2001). The HDAC inhibitors Trichostatin A have been shown in recent studies to have antiangiogenic effects. These effects were associated with a decrease in endothelial cell production of nitric oxide and a significant decrease in the expression of endothelial nitric-oxide synthase (Rössig *et al.*, 2002). Because HDAC-dependent transcriptional repression is relieved by VPA (Michaelis *et al.*, 2004).

4. Conclusion

This review highlights the complex and multifaceted teratogenic effects of valproic acid (VPA) on neural tube development. It explores various mechanisms such as disruptions in folate metabolism, oxidative stress, histone deacetylase inhibition, and gene expression alterations that contribute to VPA-induced neural tube defects (NTDs). Insights from animal studies and advancements in teratogenicity testing methods shed light on dose-dependent effects and critical periods of vulnerability. Its antiangiogenic properties may contribute to its teratogenic effects. Therefore, continued efforts are essential to understand the underlying mechanisms, develop preventive strategies, and enhance prenatal care to improve maternal and fetal health outcomes.

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Conflicts of Interest

The authors report no conflicts of interest in this work.

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