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Review Paper

The Neurotoxic Mechanisms of Valproic Acid and Their Association With Neurodevelopmental Disorders: A Narrative Review

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ABSTRACT

Valproic acid (VPA), which is an anticonvulsant and mood stabilizer, has been applied in treating several neurological and psychiatric conditions. However, severe neurotoxic side effects may result from its use, especially when taken at certain developmental stages of a child's brain. Consequently, the present narrative review aimed not only to summarize what is presently known about the neurotoxicity of VPA and the related neuropsychiatric disorders, but also to focus on potential interventions. Most of VPA's neurotoxic effects are due to its ability to increase reactive oxygen species (ROS) production, cause mitochondrial dysfunction, and alter epigenetics. It also facilitates neuronal damage by distorting the excitatory and inhibitory neurotransmission, increasing the excitotoxicity, oxidative stress, and mitochondrial dysfunction. These neurotoxic mechanisms are strongly associated with multiple neurodevelopmental disorders (NDDs). For example, prenatal VPA use is one of the common risk factors in autism spectrum disorder (ASD) that is correlated with complex social and communication deficits. VPA, which is used to treat epilepsy, may paradoxically increase seizure propensity by affecting neuronal excitability and synaptic input. Understanding these pathways can help reduce VPA's neurotoxicity without diminishing its efficacy in sensitized children.

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Highlights

- VPA induces epigenetic dysregulation through HDAC.
- VPA impairs mitochondria, increasing ROS and ATP depletion.
- The impaired balance of GABA/glutamate induces the change in neural circuitry.

Plain Language Summary

Valproic acid (VPA) is a commonly used medicine to treat epilepsy, bipolar disorder and migraine. For many people, it is effective and life-changing. Nonetheless, it has been found that when consumed during pregnancy or in the early life of the brain, VPA can predispose children to some developmental disorders such as autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder, intellectual disability (ADHD), and developmental delays. In this review, we examined how VPA can affect the developing brain. Studies suggest that VPA may interfere with how brain cells grow, connect, and communicate. It is capable of raising the levels of harmful molecules such as reactive oxygen species (ROS) that damage cells and lower the energy production in the brain. VPA can also change how genes are regulated, affecting important processes involved in brain development. In addition, it may disrupt the balance of chemical messengers that allow brain cells to send signals to one another. Together, these effects can alter brain structure and function during critical stages of development. Understanding these mechanisms is important for both doctors and families. It assists in understanding why prenatal exposure to VPA is risky and why its prescription must be the responsibility of care, particularly in women of childbearing age. This information also aids in designing safer treatment plans and protection therapies that can reduce the damage but retain the advantage of the drug. Finally, the most vulnerable children can be safeguarded by enhancing awareness and clinical advice, whereas children requiring effective treatment are not left unattended.

Introduction

Valproic acid (VPA) is an antiepileptic drug used to manage epilepsy, bipolar disorders, and migraine (Chateauvieux et al., 2010; Romoli et al., 2019; Carli et al., 2023) a branched short-chain fatty acid, is widely used as an antiepileptic drug and a mood stabilizer. Antiepileptic properties have been attributed to inhibition of gamma amino butyrate (GABA). This property makes VPA beneficial for managing these conditions despite its associated risks, such as effects on neurodevelopment and documented neurotoxic consequences for the nervous system. VPA has serious teratogenic effects, with research correlating to maternal exposure to VPA, especially in critical developmental stages that have serious neurotoxic effects and are linked to various neurodevelopmental disorders (NDDs) (Cui et al., 2020; Ornoy et al., 2023). Such NDDs are autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and intellectual disability (ID).

Oxidative stress is one of the earliest and most critical pathways involved in VPA-induced neurotoxicity. Exposure to VPA elicits oxidative stress by increasing reactive oxygen species (ROS) production, leading to neurotoxicity and apoptosis by suppressing antioxidant capacity in the brain (Chaudhary & Parvez, 2018). This oxidative stress is exacerbated by VPA's modulation of mitochondrial function, which is crucial for maintaining cellular energy and structural stability (Tong et al., 2005; Salsaa et al., 2020). VPA has been reported to impair energy metabolism and cause neurotoxicity by affecting mitochondrial function (Salsaa et al., 2020; Giulivi et al., 2023).

Another mechanism by which VPA acts is through altering the equilibrium of oxidative stress while also acting as a class I histone deacetylase (HDAC) inhibitor. This inhibition alters chromatin conformation and gene expression of functions vital to neuronal differentiation and synaptic plasticity (Chen et al., 2015; Sandonà et al., 2023). These epigenetic modifications can lead to abnormal neuronal development and function, thereby exacerbating NDDs (Chen et al., 2015; Sandonà et al., 2023).

Another significant activity that is influenced by VPA toxicity is neurogenesis. Research has indicated that VPA antagonistically influences differentiation and pro-

liferation of neural progenitor cells, which are an important part of intrauterine and perinatal brain development (Zhang et al., 2017; Taleb et al., 2021; Meng et al., 2022; Piorczynski et al., 2022). Such disruption results in structural and functional impairments of the brain, leading to cognitive-motor and behavioural changes (Taleb et al., 2021).

Knowledge of these teratogenic and toxic mechanisms is essential for managing VPA-related side effects and enhancing its potential. This review provided a useful general background on how VPA causes neurotoxicity through direct inhibition of HDACs, increased ROS formation, and changes in neurotransmitter profiles. Further, it looked at specific NDDs associated with these mechanisms, including ASD and ADHD, recognizing the need for more studies to devise ways of reducing potential harms before presenting implications for future research with a view to enhancing the desirable therapeutic effects.

Pharmacological properties of VPA

VPA is also known as 2-propylvaleric acid. It is a carboxylic acid, $C_8H_6O_2$, with a molecular weight of around 144.22 g/mol. It is a colourless, pale yellow, oily liquid that dilutes due to its very mild sulphur dioxide-like lethargy (Löscher, 1999; Rahman et al., 2025). It is insoluble in oils but very soluble in water and forms salts with some basic compounds, which affect its pharmacokinetics and formulation (Alsarra et al., 2005; Ghodke-Puranik et al., 2013).

VPA is a weak acid with a pKa of about 4.8 (Mishra et al., 2021). This multiplicity of pKa values indicates that at physiological pH, an acceptable concentration of VPA would be present in the form lacking an acidic proton, valproate, which enhances solubility and permeability in physiological fluids (Ghodke-Puranik et al., 2013; Safdar & Ismail, 2023). The VPA deprotonated form has the potential to bind to other biological partners, such as proteins and enzymes, which might explain the drug's action profile and side effects (Shnayder et al., 2023).

VPA is chemically stable in most situations and is hydrolyzed by heat and light, as well as by the presence of strong acids or bases (Zhu et al., 2017; Shnayder et al., 2023; Rahman et al., 2025). Such stability is critical in its pharmaceutical systems, where stability in drug release and efficacy are required (Tseng et al., 2020; Singh et al., 2021). VPA is administered as a sodium salt (sodium valproate or divalproex sodium) to enhance its bioavailability and its solubility in the bloodstream (Dutta & Reed, 2007; Cipriani et al., 2013).

VPA has lipophilic properties, enabling it to cross the blood-brain barrier, where its antiepileptic effects are observed in disorders of the central nervous system (Vieira & Gamarra, 2016; Wu et al., 2023). This feature also explains its neurotoxicity because VPA can accumulate in neuronal structures and exert toxic effects on neurons (Manthou et al., 2021; Taleb et al., 2021). VPA is metabolized in the liver through several pathways, of which glucuronidation and cytochrome P450-mediated metabolism are the most prevalent (Argikar & Remmel, 2009; Ezhilarasan & Mani, 2022). These protocols are involved in its pharmacokinetics and determine its therapeutic utility and toxicity (Ghodke-Puranik et al., 2013; Zhu et al., 2017).

In the liver, glucuronidation, mitochondrial β-oxidation, and cytochrome P450-mediated oxidation transform VPA into both therapeutic and toxic products (Argikar & Remmel, 2009; Ezhilarasan & Mani, 2022; Shnayder et al., 2023). One of them, 4-ene-VPA (4-en-VPA), is a neurotoxic unsaturated metabolite that forms during the oxidation and desaturation of VPA in the liver (Ghodke-Puranik et al., 2013; Shnayder et al., 2023). It directly suppresses the mitochondrial fatty acid 2-oxidation pathway by inhibiting acyl-CoA dehydrogenases, leading to the production of toxic fatty acyl metabolites and a decrease in cellular ATP (Ezhilarasan & Mani, 2022). The lack of energy increases oxidative stress, ROS production, and disruption of neuronal homeostasis, thereby exacerbating mitochondrial impairment and neuronal apoptosis (Giulivi et al., 2023). Its formation and accumulation are then important biochemical steps that connect VPA metabolism to its neurotoxic and hepatotoxic effects.

In view of this, the solubility, acid strength, stability, and lipid solubility of VPA can be regarded as highly influential in its pharmacokinetics and pharmacodynamics. Knowledge of these properties is crucial for determining the most effective strategies to harness VPA's clinical applications and minimize its adverse effects.

Development of research models with VPA

VPA is commonly used in experiments involving the approximation of NDDs, including ASD and other associated disorders. Particularly relevant to the choice of research model are the administration period and dosage, which determine the validity and generalizability of these models (Table 1).

Table 1. Development of research models with VPA

Model Type	Administration Period	Dose Range (mg/kg)	Observed Outcomes
Prenatal exposure	Gestational days 12.5-14.5	200-600	Increased risk of ASD-like behaviors
Postnatal exposure	Postnatal day 5-7	100-300	Cognitive and attention deficits reflective of ADHD

ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder.

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Administrative phase and gain

VPA-based experimental paradigms normally adopt prenatal or postnatal injections to affect neurodevelopmental endpoints. Prenatal administration is often used to model human exposure during embryonic/fetal development, with toxicological manifestations that resemble clinical findings (Cui et al., 2020; Elnahas et al., 2021). For instance, VPA is given to pregnant dams as a treatment to understand its consequences on the offspring's growth and development. Studies using this model to understand aspects of VPA-induced ASD and other NDDs are reviewed by Cui et al. (2020).

VPA is usually used in prenatal exposure models, with treatment starting on gestational days 12.5-14.5, which are believed to be important developmental stages in rodents (Sato et al., 2022). In these studies, doses normally vary from 200 to 600 mg/kg orally or intraperitoneally, depending on the study design (Dendrinos et al., 2011). Given the current administration schedule, the researchers can assess offspring for long-term alterations in brain structure, function, and behaviour (Cui et al., 2020).

Postnatal models, in contrast, are used to observe the consequences of VPA treatment initiated after birth, which may help evaluate interfering treatments for state disorders such as epilepsy, as well as to analyze the disturbance itself (Mariotti et al., 2019). For example, VPA is injected into neonatal or juvenile animals to study its effects on neurodevelopment and to compare the efficacy of potential therapies for NDDs resulting from early VPA exposure (Mariotti et al., 2019). Doses in postnatal or late prenatal models are generally lower than in prenatal models, typically 12.5–14.5; doses in postnatal or late prenatal models range from 100–300 mg/kg, with multiple doses daily for weeks (Wei et al., 2016; Norton et al., 2020).

Dose and protocol of administration

This paper strongly suggests that the dose and administration schedule of VPA are essential factors in determining study outcomes. The most common approach in the prenatal models is to administer VPA to expectant rodents in the gestational period of 12.5-14.5 days. This period is selected because it falls within critical periods of brain development (Sato et al., 2022). Dosage depends and usually ranges from 200 to 600 mg/kg, based on doses shown in clinical practice to provide similar exposure levels (Dendrinos et al., 2011).

In postnatal models, VPA is usually administered on postnatal days 5 or 7, at doses ranging from 100 to 300 mg/kg, depending on preprogrammed study objectives (Mony et al., 2016; Norton et al., 2020). The dosing regimen may be regular and long-term; in some studies, the drug is given daily for several weeks to evaluate the compound's steady-state toxicity (Dutta et al., 2003). The route of administration, whether oral, intraperitoneal, or intravenous, also affects the study results. Oral administration is often used to reflect human exposure, while intraperitoneal administration provides greater control over the amount of drug delivered and rapid distribution within the body (Dutta et al., 2003).

Species used in VPA studies, whether prenatal or postnatal, help discover the processes that lead to NDDs. These models differ in the timing of the dose, the amount administered, and the method used. Prenatal models tend to use higher dosages and specifically address changes during early development, whereas postnatal models use lower dosages to address late developmental or therapeutic outcomes. It is important to understand these parameters to generate valid, appropriate predictive models that enhance understanding of VPA's impact and inform better therapeutic strategies for NDDs. These models facilitate the interpretation of the influence of VPA-induced neurodevelopmental changes. Still, the field remains in its infancy in identifying how it can be directly applied to human neurodevelopment, which highlights the concern.

Table 1 presents the development of research models with VPA. This research model has been used by several scientists, who have applied it to various NDDs based on their behavioral characteristics.

Mechanisms of neurotoxicity of VPA

VPA is effective in treating epilepsy and bipolar disorder, but has neurotoxic potential in human exposure in the process of brain development (Safdar & Ismail, 2023). There are other neurotoxic effects of cerebral VPA, mostly related to synaptic formation and plasticity (Tursunov et al., 2023) (Table 2). The pathophysiology of neurotoxicity related to VPA is as follows:

Histone deacetylase inhibition and epigenetic changes

VPA has been reported to suppress HDAC activity, which is involved in chromatin remodeling and gene expression regulation (Sixto-López et al., 2020; Singh et al., 2021). Due to the effects of VPA on neuronal development and synaptic function, it was shown that HDACs inhibition changes the expression of genes important for neuronal development (Slaughter et al., 2021). Abnormal regulation of genes required for synapse development, synaptic stability, and plasticity disrupts neuronal connections and their stability (Zhang et al., 2013) a common genetic motor neuron (MN). Epigenetic changes resulting from HDAC inhibition also affect genes involved in neuronal differentiation, potentially leading to improper neuronal circuit formation (Delcuve et al., 2012).

Oxidative stress and mitochondrial dysfunction

Oxidative stress is induced by VPA, which increases ROS production, thereby harming cellular proteins, lipids, and DNA (Jakubczyk et al., 2020). Among these organelles, mitochondria are the most vulnerable to VPA-induced stress, as they are the primary source of ROS and are involved in energy metabolism (Palma et al., 2024). There is decreased ATP production due to mitochondrial dysfunction, which is vital for synaptic plasticity, as synaptic activity depends heavily on energy supply (Videla et al., 2022). The energy shortage at synapses inhibits synaptic vesicle cycling and neurotransmitter release, and impairs synaptic transmission and plasticity (Rizzoli, 2014; Li & Sheng, 2022).

Modulation of neurotransmitter systems

VPA interacts with neurotransmitters and modulates γ-aminobutyric acid (GABA)ergic/glutamatergic transmission (Tursunov et al., 2023). VPA increases the levels of the major inhibitory neurotransmitter GABA, which, in turn, restores neurotransmitter balance in the immature brain and affects essential developmental periods (Sears & Hewett, 2021) stroke, epilepsy and substance abuse. Asymmetry in glutamate and GABA signaling can induce synaptic plasticity, which may correlate with changes in the number and morphology of dendritic spines (Sears & Hewett, 2021) stroke, epilepsy and substance abuse. Such variations may accumulate, leading to unhealthy changes in synaptic plasticity that can impair learning and even cause NDDs (Reddy-Thootkur et al., 2022).

Another mechanistic hypothesis that explains the paradoxical proconvulsant effect of VPA is its regulation of the GABAergic system. VPA boosts the GABAergic neurotransmission by blocking GABA transaminase and boosting the synaptic levels of GABA. It is one of the mechanisms underlying its anticonvulsant action in the adult brain (Johannessen, 2000; Romoli et al., 2019; Rahman et al., 2025). Nonetheless, during early brain development, the neurotransmitter GABA is excitatory rather than inhibitory. The reason is that immature neurons have high intracellular chloride levels, which are maintained by the $Na^{+}K^{+2}Cl^{-}$ cotransporter 1 (NKCC1), thereby creating an inverted chloride gradient (Li & Xu, 2008; de Leon & Tadi, 2025). Under these conditions, activation of GABA A receptors results in neuronal depolarization rather than hyperpolarization due to chloride efflux. It is plausible that the GABAergic signaling, augmented in the developing brain by VPA, enables neuronal overexcitation, synaptic instability, and abnormal circuit formation, which may increase vulnerability to seizures and neurodevelopmental maladaptation following postnatal or early postnatal exposure to VPA.

Alteration of growth factors and signaling pathways

VPA exposure influences signaling pathways, including the activation of brain-derived neurotrophic factor (BDNF) and other growth factors required to stimulate synaptic growth and plasticity (Qi et al., 2022). Such an effect could be ascribed to a change in BDNF concentration, as BDNF is involved in synaptic plasticity, which underlies long-term potentiation and serves as a basis for learning and memory (Lu et al., 2014). Together with alterations in BDNF signaling and other neurotrophic cascades, VPA inhibits synaptogenesis and the formation of strong contacts, which are considered fundamentally important for typical cognitive development (Lu et al., 2014; Wang et al., 2022).

Abnormal synaptic pruning and morphological changes

Synaptic pruning, which is an important process in the maturation of synaptic connections, can be altered by VPA (Faust et al., 2021). Labelling of dendritic spines has revealed that prefrontal cortical neurons of animals exposed to VPA exhibit decreased dendritic spine density and altered spine shape, suggesting impaired synaptogenesis and synaptic plasticity (Takuma et al., 2014). This process may involve the gain or loss of dendritic spines, which is the brain's ultimate capacity to learn and form memories (Moulin et al., 2022).

Neuroinflammation and immune dysregulation

VPA has been linked to neuroinflammation, characterized by enhanced production of pro-inflammatory cytokines and astrogliosis (Taleb et al., 2021). Yet intake and chronic neuroinflammation can further worsen synaptic dysfunction by reducing the likelihood that neurons will communicate effectively and by altering synapse morphology (Rao et al., 2012). Inflammatory cytokines can abolish synaptic plasticity by binding neurotransmitters, altering receptor dimensions, and disrupting synaptic signaling (Bourgognon & Cavanagh, 2020).

Disruption of neurogenesis

VPA impairs neurogenesis in the developing rat brain by reducing both the last mitotic division of neural progenitor cells (NPCs) in the subgranular zone of the hippocampus and in the subventricular zone, and the differentiation of new neurons. Previous studies have established that VPA reduces the total number of NPCs and the ratio of cells that differentiate into neurones or glial cells (Taleb et al., 2021). They also noted that disruption of neurogenesis may lead to structural/functional changes in the brain, which may manifest as behavioral deficits. The study also confirmed that VPA affects neural stem cell proliferation and differentiation, thereby altering brain structure and function (Taleb et al., 2021). Such disturbance in embryonic neurogenesis could lead to poor cognitive or behavioral development, as observed in the VPA-treated animal (Juliandi et al., 2015; Zhao et al., 2019). New investigations have revealed that changes in VPA-induced neurogenesis lead to developmental and functional alterations, suggesting that this particular avenue may help pinpoint the problem of VPA neurotoxicity (Guerra et al., 2023).

Ion channel modulation

VPA modulates different ion channels (sodium and calcium), which are fundamental in action potential propagation and neurotransmission (Ghodke-Puranik et al., 2013; Catterall, 2023). Irritations within these channels may alter excitability and neuronal structure (Ghodke-Puranik et al., 2013).

The cumulative impact of these mechanisms results in impaired synaptic function, leading to abnormal transmission, reduced synaptic plasticity, and altered synapsing (Burke & Bender, 2019; Liu & Wang, 2019). These synaptic changes first affect neurotoxicity and, cumulatively, learning and memory, as well as social behavioral interactions, when exposure to VPA occurs at specific developmental stages (Debanne & Russier, 2019). Knowledge of these mechanisms is important for formulating interventions that might reduce the risk of those adverse effects while enhancing the efficacy of vitamin K antagonists when given concomitantly with VPA. Future studies need to be designed to unravel these pathways and their influence on real-world interventions for VPA-related neurotoxicity and neurodevelopmental disease.

Combined, these mechanisms depict a causal cascade rather than isolated events. VPA is an HDAC inhibitor, with its main action triggering broad epigenetic dysregulation and altering the transcription of genes that play key roles in neuronal differentiation, mitochondrial biogenesis, and antioxidant defense (Chen et al., 2015; Slaughter et al., 2021). This condition impairs mitochondrial metabolism, leading to decreased ATP production and an overproduction of ROS (Salsaa et al., 2020; Giulivi et al., 2023). The increased ROS levels also damage mitochondrial membranes and nuclear DNA, forming a positive feedback loop of oxidative stress and dysfunctional mitochondria (Hong et al., 2024; Palma et al., 2024). These secondary insults result in synaptic instability, impaired neurogenesis, and neuroinflammation, which underlie the cognitive, motor, and behavioral impairments observed in VPA-induced NDDs. The combination model highlights that VPA neurotoxicity arises from the primary epigenetic effects of the compound, which spread to molecular and cellular cascades and generate permanent neurodevelopmental effects.

Table 2 summarizes general information and indicates how each mechanism results in specific developmental disorders. These mechanisms have been described by several scientists, who have related them to various NDDs and have attributed behavioral changes to them.

Table 2. The mechanism of VPA neurotoxicity and the associated disorder

Mechanism of VPA Neurotoxicity	Description	Associated NDDs
Oxidative stress	Elevated ROS production, leading to neuronal damage and apoptosis (Tong et al., 2005; Chaudhary & Parvez, 2018).	ASD, ADHD
Mitochondrial dysfunction	Impairment of mitochondrial energy production and metabolism, contributing to neurodegeneration (Salsaa et al., 2020; Videla et al., 2022).	Intellectual disabilities, epilepsy
HDAC inhibition (epigenetic alterations)	Inhibition of histone deacetylases alters chromatin structure, affecting genes crucial for neuronal differentiation and synaptic function (Chen et al., 2015; Sandonà et al., 2023).	ASD, intellectual disabilities
Neuroinflammation	Chronic microglial activation and elevated pro-inflammatory cytokines disrupt synaptic function and neuronal health (Rao et al., 2012; Taleb et al., 2021).	ADHD, ASD, epilepsy
Neurotransmitter Imbalance	Dysregulation of GABAergic and glutamatergic systems, affecting synaptic plasticity and connectivity (Gobbi & Janiri, 2006; Sears & Hewett, 2021).	ASD, epilepsy
Disrupted neurogenesis	Inhibition of neural stem cell proliferation and differentiation, leading to structural and functional abnormalities in the brain (Zhang et al., 2017; Taleb et al., 2021).	Developmental delay, intellectual disabilities

Abbreviations: ASD: Autism spectrum disorder; ADHD: Attention deficit hyperactivity disorder. NEUROSCIENCE

The impact of VPA on NDDs

It is important to develop relationships between specific pathways implicated in VPA exposure and NDDs to identify potentially useful therapies and potentially harmful long-term effects. The subsequent sections of this article discuss the effects of VPA on specific NDDs/phenotypes, including descriptions of the mechanisms underlying these effects and related clinical and animal studies on therapeutic approaches (Figure 1).

Autism spectrum disorder

The relationship between VPA exposure and ASD has been established; moreover, earlier research has confirmed this relationship. Currently, VPA is a known teratogen that affects ASD, with many of them displaying the features of social and communication impairment (Tartaglione et al., 2019). The pathways by which these connections manifest include changes in neural connectivity and synaptic activity, driven by VPA's effects on epigenetics and exacerbation of oxidative stress (Guerra et al., 2023).

Maternal VPA use has been linked with a significant risk factor for ASD cases in children. As shown, VPA influences some stages of neurogenesis, including the first trimester of pregnancy, when neural connections are formed (Kaye et al., 2024). Animal maternal exposure to VPA also alters brain development factors like synaptic connection deficits and elevated repetitive behaviors, which are definitive symptoms of ASD (Kaye et al., 2024; Udodi et al., 2024; Udodi et al., 2025). In humans, population-based studies prove that the children who ingested VPA during pregnancy have a higher risk of developing ASD than those children exposed to other antiepileptic drugs or no medication at all (Coste et al., 2020). The most proposed pathways by which VPA causes ASD involve impairments in neuronal migration, synaptic plasticity, and autism-related gene expression (Liu et al., 2021; Guerra et al., 2023).

ADHD

There has also been an association between VPA exposure and hyperactivity/attentional concerns that can amount to a diagnosis of ADHD. Neurogenesis and neuroinflammation by the drug can account for the attentional and hyperactivity seen in ADHD patients (Honybun et al., 2021). These behavioral consequences can be linked to disruptions in dopamine signaling pathways and the development of the prefrontal cortex (Kerekes et al., 2021).

ADHD symptoms include inattention, hyperactivity, and impulsiveness because of a disrupted brain circuit dealing with attention and control of behavior (Kerekes et al., 2021). Through influence on neurotransmitter systems, including dopaminergic and serotonergic ones, VPA has been linked to the emergence of ADHD (Cannon Homaei et al., 2022; Tursunov et al., 2023). It has

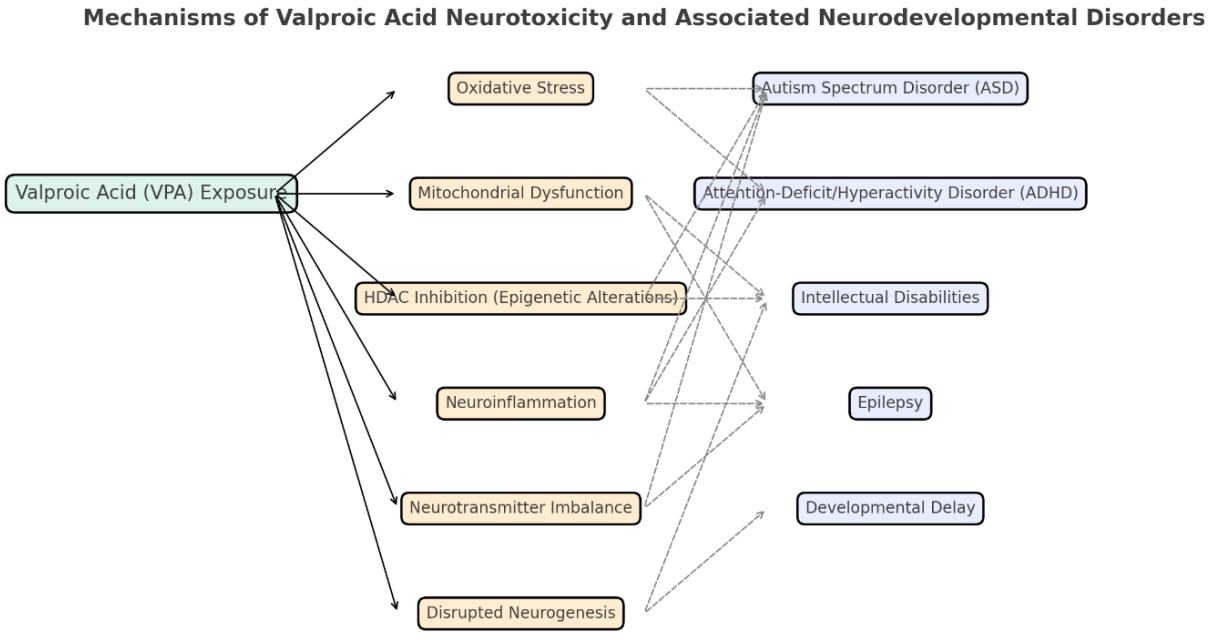

Figure 1. How VPA exposure leads to NDDs

been demonstrated that VPA alters these neurotransmitter systems in such a manner that it interferes with executive control, which is a primary component that makes up ADHD (Cannon Homaei et al., 2022; Tursunov et al., 2023). Thus, data obtained from animal research indicated that VPA use results in deficits in attention and hyperactivity, which may be associated with ADHD (Vatansever Pınar et al., 2024).

ID

Another related risk factor to VPA exposure is ID. The substance's imminent adverse effects on brain development and synaptic plasticity lead to cognitive disorders and developmental delay (Juliandi et al., 2015). Numerous past investigations have revealed that children who were exposed to VPA in utero might also have poor cognitive and adaptive skills (Bromley et al., 2009; Coste et al., 2020). Language, memory, and problem-solving abilities are some of the neuropsychological effects of VPA exposure (Bromley et al., 2009). The detrimental effects of VPA on brain development, especially on synapse and neuronal function, are thought to underlie its effects on cognition (Juliandi et al., 2015).

Epilepsy

Closely related to this point, it is worth mentioning that VPA is an antiepileptic medication, which, however, could trigger seizures. This effect is postulated to be associated with disruption of GABA- and GLU-releasing neurons, altered neuronal excitability, and network communication (Romoli et al., 2019). Various processes by which VPA exhibits therapeutic and neurotoxic effects should be strictly observed and controlled in epileptic patients.

Developmental delay (DD)

Developmental delay refers to the delayed attainment of developmental milestones. Children who were exposed to VPA during prenatal development are often affected by developmental motor delays, in addition to cognitive and language delays (Coste et al., 2020; Cui et al., 2020). It is believed that these delays are caused by abnormal neuronal development, including migration and differentiation (Juliandi et al., 2015; Zhao et al., 2019). These clinical observations have repeatedly shown that children exposed to VPA experience developmental delays that hinder their growth and learning (Bromley et al., 2009; Juliandi et al., 2015; Coste et al., 2020).

Other neu-mes

Besides ASD, ADHD, ID, and HDAC, there are other neurodevelopmental outcomes linked to VPA exposure; these include the effects of VPA on children by exposing them to motor impairments and social communication difficulties (Taleb et al., 2021). These outcomes confirm the extensive effect of VPA on neurodevelopment and the necessity to study these risks if the medication is prescribed to pregnant women (Taleb et al., 2021; Kaye et al., 2024).

Figure 1 presents a hierarchically organized flowchart of the neurotoxic effects of VPA and their relationships with the NDDs mentioned. To link each mechanism to its respective disorders, we've used the patterns explained above.

Discussion

The above findings, summarized in this review, indicate that the neurotoxic effect of VPA has a multi-level causal pathway, starting with HDAC inhibition and proceeding to mitochondrial dysfunction, oxidative stress, and activation of neuroinflammatory pathways. These mechanisms are not independent, as they create a cascade that disrupts neuronal energy metabolism, synaptic plasticity, and gene regulation (Chen et al., 2015; Giulivi et al., 2023; Hong et al., 2024). This combined pathway is important for understanding molecular targets for intervention.

VPA toxicity and its relation to NDDs are topics of great interest, which have been investigated under various aspects. Recently, the impact of oxidative stress, mitochondrial dysfunction, and HDAC inhibition on VPA-induced neurotoxicity during vulnerable developmental stages has been studied (Chaudhary & Parvez, 2018; Salsaa et al., 2020). High ROS levels, which define oxidative stress, can be considered another principal factor in neuronal death and structural changes in VPA-treated models (Tong et al., 2005; Giulivi et al., 2023). This ROS accumulation disrupts mitochondrial function, which in turn worsens the neuron's metabolic state and leads to apoptotic cell death (Giulivi et al., 2023). VPA metabolite 4-en-VPA inhibits mitochondrial fatty acid β-oxidation, further amplifying the oxidative stress cascade, making VPA metabolism an etiological factor in its neurotoxic outcomes (Ezhilarasan & Mani, 2022; Shnayder et al., 2023).

Recent data also shows that VPA metabolic activation is a direct cause of its downstream neurotoxic cascade. Mediator 4-en-VPA is an unsaturated metabolite produced as a result of hepatic ω-oxidation and desaturation. It inhibits fatty acid β-oxidation in mitochondria by blocking acyl-CoA dehydrogenases, leading to the accumulation of fatty acid intermediates, decreased ATP production, and increased ROS release (Ghodke-Puranik et al., 2013). Such a metabolic bottleneck increases oxidative stress and mitochondrial dysfunction, leading to an energetic and redox imbalance that further precipitates neuronal apoptosis and synaptic instability. Therefore, 4-en-VPA is an upstream biochemical stimulus in the pathway of causation linking HDAC inhibition with mitochondrial stress, thereby initiating the neurodevelopmental disabilities associated with VPA exposure.

HDAC inhibition by VPA has also been characterized as the main driver of neurodevelopmental abnormalities, resulting from shifts in gene expression and chromatin remodeling (Chen et al., 2015; Sandonà et al., 2023). It suppresses histone deacetylase activity and enhances gene expression in differentiated neurons, synapse formation, and plasticity (Sixto-López et al., 2020; Slaughter et al., 2021). These epigenetic changes correlate to NDDs, which include ASD, intellectual disabilities, and neuropathological diseases observed among individuals exposed to VPA during gestational periods (Liu et al., 2021; Guerra et al., 2023).

Otherwise, this paper highlights that VPA causes oxidative stress, epigenetic dysregulation, and neuroinflammation, which are major drivers of neurotoxicity (Bourgognon & Cavanagh, 2020; Taleb et al., 2021). Exposure to certain neurotoxicants could cause demyelination, prolonged neuroinflammation, overactivation of microglia, and increased levels of pro-inflammatory cytokines, which become detrimental to neurons, change the structure of synapses, and thus result in cognitive/motor loss and other behavioral changes (Rao et al., 2012; Faust et al., 2021; Udodi et al., 2022a, Udodi et al., 2022b). It is believed that this inflammation hampers neurotransmission, and such dysregulation of neurotransmission hinders synaptic plasticity and affects cognition (Taleb et al., 2021; Sears & Hewett, 2021).

In addition, effects of VPA on neurotransmitter systems, including excess inhibitory GABA relative to excitatory glutamate, are involved in neurodevelopmental consequences (Gobbi & Janiri, 2006; Singh et al., 2021). GABA dysregulation is a potential factor in the main neuropathological characteristics of ASD, including excessive synaptic pruning and decreased dendritic spine number (Takuma et al., 2014; Moulin et al., 2022; Udodi et al., 2025). Altered glutamatergic signaling also enhances synaptic alterations, which seem to affect learning and memory processes important for brain neurodevelopment (Rizzoli, 2014; Tursunov et al., 2023). Despite its clinical use as an anticonvulsant, the GABA-enhancing effects of VPA during neurodevelopment are paradoxical, as GABA can cause neuronal excitation in immature neurons due to the dominance of NKCC1-mediated chloride influx (Romoli et al., 2019; Savardi et al., 2021).

Impairment of neurogenesis is another endpoint affected by VPA exposure, as studies demonstrate diminished NSC proliferation and differentiation in the affected area (Juliandi et al., 2015; Taleb et al., 2021). VPA impairs neurogenesis more severely during prenatal and early postnatal development, as circuits are more vulnerable to its effects (Zhang et al., 2017; Meng et al., 2022). Both animal models proved that VPA exposure leads to cognitive and social deficits, which corroborates the link between the neurotoxicity of VPA and developmental disorders (Zhao et al., 2019; Cui et al., 2020).

Lastly, the various pathways through which VPA elicits its neurotoxicity make it impossible for a single, common strategy to manage the various effects it brings. Future research on protective agents, such as antioxidants and HDAC inhibitors, could offer new approaches to reduce VPA-induced neurotoxicity and improve developmental outcomes (Tursunov et al., 2023; Hong et al., 2024). Since oxidative stress, epigenetic modifications, neuroinflammation, and neurotransmitters are closely linked biomolecules, a multifaceted approach may be needed to address a wide range of neurodevelopmental deficits elicited by VPA treatment (Rao et al., 2012; Wang et al., 2022).

Clinicians should think twice about when to give VPA and other viable options available for consideration to women of childbearing age to reduce the chances of prenatal VPA exposure. Future work should focus on identifying suitable drugs compatible with VPA to reduce its brain toxicity and on improving existing animal models that mimic human brain development.

Potential interventions and preventive measures of VPA neurotoxicity

Knowledge of the neurotoxicity of VPA gives a baseline for developing interventions to counteract its negative side effects without compromising the efficacy of the treatment. Several proposed protective measures in both experimental and clinical research primarily focus on oxidative stress, mitochondrial dysfunction, and epigenetic dysregulation.

Antioxidant therapy

Antioxidants rank among the most researched protective factors against VPA-induced toxicity. Melatonin, vitamin E, N-acetylcysteine, and coenzyme Q10 have been shown to have ROS-scavenging properties, antioxidant enzyme activity, and anti-apoptotic effects in the brain (Chaudhary & Parvez, 2018; Hong et al., 2024). An example is melatonin, which has been reported to reverse VPA-induced synaptic and mitochondrial damage by increasing antioxidant defenses and reducing lipid peroxidation (Chaudhary & Parvez, 2018).

Selective HDAC inhibition and epigenetic control

Because VPA is a broad-spectrum HDAC inhibitor, selective control of specific HDAC isoforms is under development to maintain therapeutic effects and minimize neurotoxicity. In the discovery of isoform-selective HDAC inhibitors, recent studies have shown potential for restoring normal histone acetylation dynamics with no effect on neuronal differentiation (Slaughter et al., 2021; Sandonà et al., 2023). These agents can serve as safer alternatives or supplements to VPA in conditions that require mood stabilization or anticonvulsant treatment.

Neurotrophic and anti-inflammatory agents

It was also found that neurotrophic support factors or neuroinflammation suppressors, such as BDNF mimetics, curcumin, and resveratrol, can alleviate the toxic effects of VPA on synaptic plasticity and neurogenesis (Qi et al., 2022; Wang et al., 2022). They further suppress cytokine-induced neuroinflammation, an effect enhanced by their capacity to regulate intracellular signaling.

Cannabinoid-based neuroprotection

In a recent study, Udodi et al. (2025) found that cannabidiol (CBD) reversed VPA-induced developmental neurotoxicity in the mouse brain by allosterically regulating the CB1 receptor, thereby normalizing GABAergic signaling and attenuating oxidative stress. The outcomes of such studies emphasize the therapeutic properties of endocannabinoid modulators in facilitating recovery from neurodevelopmental abnormalities induced by VPA.

Mitochondrial protection

Coenzyme Q10, L-carnitine, and alpha-lipoic acid are substances that stabilize the mitochondrial performance to reinstate the ATP production and mitigate the damage of mitochondria caused by oxidative stress (Giulivi et al., 2023; Palma et al., 2024). They are also examining these agents as possible adjuncts to reduce mitochondrial and metabolic side effects of VPA.

Combined, these interventions imply that combination interventions targeting oxidative stress, inflammation, and epigenetic dysregulation could be an effective approach to reducing the neurodevelopmental toxicity of VPA. Further studies are required to establish these pro-

tective measures in human models and to define optimal therapeutic windows for use in susceptible groups, such as pregnant women and growing children.

Conclusion

VPA neurotoxicity is a mechanism of polypractical implications in NDDs. Recognizing these pathways is essential to designing measures to reduce the harms associated with VPA and enhance the outcomes for patients who need VPA administration. The development of therapeutic drugs that are safer and more specific to VPA due to its wide application and its neurotoxic properties is important, as well as the improvement of treatment regimes in vulnerable patients, such as pregnant women.

Ethical Considerations

Compliance with ethical guidelines

This article is a review paper with no human or animal sample.

Data availability

This is a narrative review and all informations were properly cited and listed in the reference section.

Declaration of generative AI and AI-assisted technologies in the writing process

No AI tool influenced the scientific content, data analysis, or conclusions of this work.

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Authors' contributions

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Conflict of interest

The authors declared no conflict of interest.

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