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REVIEW ARTICLE

The Neuroprotective Role of Omega-3 Fatty Acids Against Valproic Acid-Induced Cerebellar Abnormalities: A Narrative Review

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ABSTRACT

Background: Valproic acid (VPA) can easily pass through the placental barrier, exposing the fetus to harmful effects. Exposure to VPA during pregnancy has been associated with various developmental defects, including Neural Tube Defects and neurodevelopmental disorders such as reduced cognitive function, learning difficulties, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). Omega-3 fatty acids are essential for supporting the health and function of the nervous system. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are forms of omega-3 fatty acids. Both EPA and DHA are essential for brain functions; they improve cognitive function, have a positive impact against neural damage, and reduce the risk of neurodegenerative diseases such as Alzheimer's and Parkinson's.

They are incorporated into the cell membranes of brain cells, helping to maintain proper fluidity and signaling. Omega-3 fatty acids also aid in the production of neurotransmitters, which are vital for communication between nerve cells. Additionally, they possess anti-inflammatory properties that can safeguard the brain from damage caused by oxidative stress and inflammation.

Conclusion: Exposure to valproic acid during pregnancy had degenerative structural effects on the offspring's cerebellar cortex. Co-administration of Omega-3 is highly recommended to mitigate the toxic effects of VPA when administered at the lowest effective dose.

Keywords: Omega-3, valproic acid, cerebellum, neuroprotection.

Cortical Development and Synaptic Formation in the Cerebellum

The development of the cerebellum involves transforming a smooth, undifferentiated structure into a highly convoluted one with fissures and folia. This transformation is driven by complex cellular processes, including coordinated movements and interactions between cells. These interactions lead to the development of the cerebellar cortex and nuclei, as well as the assembly of neural circuits within these regions (see Fig. 1). The proliferation, migration, and differentiation of specific cerebellar stem cells are carefully controlled in terms of both location and timing. This control is achieved through a complex interplay of intrinsic morphogenetic programs and the concentration of locally produced signaling molecules [1].

Cerebellar Development in the Mice

The development of the cerebellum in mice begins at embryonic day 9 (E9) with the formation of a neuroepithelial swelling known as the cerebellar primordium at the rostral lip of the roof of the fourth ventricle. This process continues until the third week after birth, when the cerebellar hemispheres are fully formed and expanded. The cells of the cerebellum originate from radial glia progenitors located in two main primary zones: the ventricular zone (VZ) and the rhombic lip (RL). These progenitor cells move to secondary areas where cerebellar neurogenesis continues during early postnatal development. VZ progenitors move into the prospective white matter, which surrounds the cerebellar nuclei and extends into the axis of the developing folds. In contrast, RL progenitors migrate toward the roof of the developing cerebellum [1].

Cerebellar Cell Differentiation

The differentiation of cerebellar cells follows a specific sequence over time. Initially, the caudal rhombic lip (RL) precursors generate glutamatergic projection neurons of the cerebellar nuclei between embryonic days 10.5 and 12.5. These neurons come together in the nuclear transitory zone, which is located beneath the pial surface at the rostral end of the cerebellar plate.

Following this, progenitor cells in the ventricular zone (VZ) differentiate into Purkinje cells (E11–E13), Bergmann glia precursors (E13–E14), and GABAergic interneuron precursors destined for both the cerebellar nuclei and cortex (E13.5–E16.5). Finally, the progenitors in the rostral RL differentiate into the precursors of granule cells (E12.5–E17.5) and unipolar brush cells [2].

Purkinje Cell Organization and Birthdate-Based Placement

The organization and placement of Purkinje cells are determined by their birthdate within the developing cerebellum. Cells born earlier are positioned laterally, dorsally, and posteriorly, while cells born later are situated more medially, ventrally, and anteriorly [3]. Initially, Purkinje cells form multilayered clusters, but around postnatal day 4 or 5, they reorganize into a single layer and undergo significant morphological changes. By the third postnatal week, they develop complex dendritic arborization [4]. The size of the Purkinje cell population is often seen as a reliable indicator of cerebellar growth capacity. There is strong evidence suggesting that the excitatory projection neurons of the cerebellar nuclei play a crucial role in regulating Purkinje cell survival, thus affecting the overall number of these important neurons [5]. The precursors of the Bergmann glia migrate into the Purkinje cell layer until P7. Their migration is facilitated by apical processes that protrude from the subpial surface, allowing them to align with Purkinje cells and form a compact epithelium-like lining. The Bergman glial cells also undergo significant structural changes during the second and third post-natal weeks as they mature [6,7].

Granule Cells Development and Migration

Granule cell precursors initially form a temporary germinal layer called the external granular layer (EGL), located between the pial surface and the molecular layer (ML). Within the EGL, these precursors undergo extensive clonal expansion through multiple rounds of mitotic divisions, resulting in the creation of a significant population of granule cells. Starting around embryonic day 17.5, some granule cell precursors stop proliferating, begin to differentiate, and migrate beyond the Purkinje cell layer (PL) to form the internal granule layer (IGL). This migration process becomes particularly noticeable around postnatal day 5 and is usually completed by postnatal day 20[1] (Fig. 1).

Postmitotic granule cells go through a series of changes in shape, including forming processes that help them move along the radial fibers of Bergmann glia. As the cells mature, they send out an ascending axon that splits within the molecular layer (ML), creating parallel fibers that make connections with the dendrites of Purkinje cells and interneurons. [2].

Sonic Hedgehog and Cerebellar Cortex Development

The Sonic Hedgehog (SHH) lipoprotein pathway promotes the development of cerebellar progenitors in both primary and secondary germinal zones. This pathway also plays a crucial role in determining the initial differentiation of various cerebellar cell types. [8].

Apart from its role in the maturation of cerebellar progenitors, Sonic Hedgehog (SHH) plays a specific part in the formation and arrangement of the cerebellar cortex. SHH encourages the growth of Bergmann glia and the movement of granule cells to the internal granule layer (IGL), which helps in the development of the layers of the cerebellar cortex [9].

The Role of Transcription Factors and Molecules in Cerebellar Development

Researchers have used a combination of gene expression analysis, cell differentiation mapping, and examination of genetically engineered mice to uncover the important role of specific transcription factors and molecules in cerebellar development [1]. Recent single-cell RNA sequencing (scRNA-seq) studies have supported existing models of cerebellar development and provided new insights into the changes in gene expression that occur during cell differentiation. A thorough description of the key factors that coordinate gene expression programs during cerebellar development is needed [10].

Transcriptome profiling at specific developmental time points has revealed important events that take place around E9, E13, and at birth [11]. At E9, genetic signals initiate the specification of cerebellar progenitors in the VZ and RL germinal zones, which have unique gene expression profiles. However, the specification of precursor cells in these zones and the roof plate is not absolute. Recent single-cell analyses have identified distinct

cell clusters with mixed features marked by the expression of several genes of the WNT pathway [12].

Cerebellar Development andNeurodevelopmental Disorders

The cerebellar development, characterized by extensive synaptic connections and a prolonged maturation period, makes it vulnerable to genetic and environmental risk factors. Early postnatal cerebellar defects or injuries are a significant non-genetic risk factor for autism spectrum disorder (ASD), and genes related to ASD are actively expressed during cerebellar development. In ASD mouse models, there is disrupted functional connectivity between the cerebellum and the medial prefrontal cortex, leading to social and repetitive behaviors [13]. Cerebellar dysfunction and structural abnormalities have also been linked to attention deficit hyperactivity disorder (ADHD) and schizophrenia [14]. These neurodevelopmental disorders often involve dysregulation of gene expression at epigenetic, transcriptional, and translational levels, resulting in an altered balance between excitatory and inhibitory synapses. RNA processing steps, including splicing factors and splicing patterns, are frequently abnormal in these diseases.

Valproic Acid

Valproic acid (VPA) is commonly used as an anticonvulsant therapy, but its potential neurotoxicity has raised concerns. Studies have shown that VPA can cause apoptotic neurodegeneration in different brain regions, even at doses relevant to clinical use. It's unexpected that VPA rapidly diffuses into the brain due to its physiochemical properties. VPA can enter the central nervous system through both the choroid plexus (blood-cerebrospinal fluid barrier) and the blood-brain barrier (brain capillary endothelium). While this ability is beneficial for its effectiveness as an anticonvulsant, it also highlights the potential for unintended side effects. Valproic acid (VPA) is mainly metabolized in the liver through cytosolic ω-oxidation, leading to the formation of various reactive metabolites. Some of these metabolites may have biological activity and contribute to VPA-induced toxicity, especially in cases of acute overdose [15].

It has been discovered that VPA causes programmed cell death in cultured microglia. This cell death process is identified by the movement of phosphatidylserine (PS) to the outer membrane, fragmentation of DNA between the cell nuclei, and the presence of TUNEL-positive cells. The decrease in the number of microglia in neuron-glia cultures treated with VPA is likely due to this cell death. Additionally, the limited impact of VPA on the growth of microglia supports this conclusion [16].

Valproic acid has been found to cause fetal valproate syndrome, a collection of abnormalities that can occur in fetuses exposed to VPA during pregnancy. These abnormalities include neural tube defects, delays in neurodevelopment, cognitive impairments, distinctive physical features, reduced fetal growth, heart problems, and abnormalities in the structure of the face. [17].

Previous studies have shown that VPA can damage neurons and affect cognitive function in people and rodents with epilepsy. Additionally, VPA can lead to oxidative stress, disrupt proper central nervous system development, and potentially compromise cognitive function. Furthermore, exposure to VPA during pregnancy has been associated with birth defects and an increased risk of autism [18].

Studies have found that exposure to VPA during pregnancy can cause a noticeable deterioration of the cerebellar Purkinje and granular cells [19]. It was discovered that shrinkage of the Purkinje and cerebellar hemispheres cell number occurred in rats on day 12 of gestation following VPA administration. However, few research studies have investigated how VPA affects gliogenesis in the developing brain. After prenatal VPA injection, changes in the postnatal density of microglia and astrocytes were observed [20]. It was also shown that VPA can induce toxicity in genes and proteins that play crucial roles in controlling development and differentiation during organogenesis by generating several apoptotic cascades [21].

Mechanism of action of valproic acid:

VPA can inhibit the histone deacetylase enzymes (HDAC), which in turn blocks PTEN/PI3K-Akt downstream. This inhibition leads to the expression of caspase-9 and caspase-3, causing apoptosis and autophagy, respectively [22] (Fig. 2). It has been suggested that an increase in the body's overall free radical level causes fetal deformity and cellular damage brought on by VPA. Oxidative stress is thought to play a role in VPA's neurotoxic effects. VPA leads to oxidative damage to proteins and lipids in the brain. Additionally, VPA decreases glutathione—the main non-enzymatic antioxidant defense in the brain. Oxidative stress in the cerebellum and cerebral cortex by VPA may be initiated or exacerbated by alteration in the activities of Na^+-K^+-ATPase [19].

Additionally, Valproic acid (VPA) disrupts the balance of one-carbon metabolism (OCM), a metabolic pathway involved in various developmental processes. While the exact mechanisms are not fully understood, scientific evidence suggests that VPA may disrupt OCM, leading to adverse outcomes. VPA interferes with the transfer of a single carbon unit, a crucial step in various metabolic cycles, which can result in abnormalities in the synthesis of phospholipids, proteins, nucleic acids, and methylation reactions [23,24].

VPA disrupts the folate and methionine cycles by inhibiting dihydrofolate reductase and methyltransferases, leading to impaired one-carbon metabolism. Folate (vitamin B9) undergoes a series of enzymatic reactions to produce 5-methyltetrahydrofolate (5-methylTHF), a key metabolite involved in methionine synthesis. 5-MethylTHF donates a methyl group to homocysteine, regenerating methionine with the assistance of methionine synthase, methyltransferase, and methionine synthase reductase, requiring vitamin B12 as a cofactor. Methionine is further converted into S-adenosylmethionine (SAMe), a crucial molecule for methylation reactions. SAMe is subsequently demethylated to form S-adenosylhomocysteine (SAH), which is hydrolyzed to form homocysteine that enters the transsulfuration pathway to generate cysteine, a precursor for glutathione (GSH). GSH plays a vital role in protecting cells from oxidative damage caused by reactive oxygen species (ROS). By inhibiting key enzymes in the folate and methionine cycles, VPA can disrupt the normal functioning of these metabolic pathways and may contribute to adverse health effects [27].

VPA-induced disruptions in one-carbon metabolism (OCM) resulted in decreased endogenous folate levels and an imbalance in the S-adenosylmethionine (SAMe) to S-adenosylhomocysteine (SAH) ratio, with elevated SAH levels relative to SAMe. These metabolic alterations were observed in pregnancies affected by neural tube defects (NTDs) [17].

Omega-3

Omega-3 (ω-3) essential fatty acids, which include docosahexaenoic acid (DHA, C22:6n-3), eicosapentaenoic acid (EPA, C20:5n-3), and α-linolenic acid (ALA, C18:3n-3), are crucial for the structure and function of the brain. Polyunsaturated fatty acids (PUFAs) like EPA and DHA are commonly found in fish oil, while ALA is more commonly found in vegetable sources such as linseed and soybean oils [25]. Through specific enzyme-catalyzed chain reactions, eicosapentaenoic acid (EPA) can be produced from α-linolenic acid (ALA), and then docosahexaenoic acid (DHA) can be generated from EPA. However, only a small fraction, approximately 5% of ALA, goes through this metabolic pathway. Interestingly, dietary supplementation with ALA raises tissue EPA levels, while DHA levels remain relatively unchanged [26]. Fish products are often recommended as dietary sources of docosahexaenoic acid (DHA). DHA is a vital component of the phospholipid structures within brain cell membranes and is highly concentrated in the brain. It plays a crucial role in the mechanisms that govern neuronal communication. In preterm newborns, docosahexaenoic acid plays an essential role in healthy retinal and brain development. DHA is an important lipid in neural tissues, making up around 15–20% of the total lipid content in the brain cortex. Studies have shown that DHA and other omega-3 fatty acids have neuroprotective effects on brain tissue. DHA oil has been used as an adjuvant cancer treatment for breast and colon malignancies, autoimmune diseases, glomerulonephritis, allergic asthma, hypertension, and rheumatoid arthritis, among other ailments. The usage of DHA and other omega-3 fatty acids as nutritional supplements has grown due to their effects on cardiovascular health, inflammation, and mental health. Studies have shown that they can help with issues such as irritability, hyperactivity, and other troublesome behaviors [28,29].

Oxidative stress occurs when there is an imbalance in the production and accumulation of reactive oxygen species (ROS). There is strong evidence to suggest that fish oil supplements can be beneficial in managing conditions such as cancer and arrhythmia, which are often associated with ROS imbalance. Additionally, these supplements can have a positive impact on uric acid, total cholesterol, HDL, LDL, and plasma triglyceride levels. In female transgenic mice, a dietary regimen incorporating fish oil, which has anti-inflammatory properties, has been shown to inhibit the development of atherosclerotic lesions. Since the human body lacks delta-15 and delta-12 desaturase enzymes, the de novo biosynthesis of essential fatty acids (FAs) is incomplete, and these FAs must be obtained through dietary sources [30].

Recent studies have shown that omega-3 fatty acids have neuroprotective properties. For instance,

Eicosapentaenoic acid (EPA) has been found to significantly reduce radiation-induced and age-related apoptotic changes in the brain. Offspring supplemented with omega-3 fatty acids showed increased superoxide dismutase activity and decreased levels of nitric oxide and xanthine oxidase in the hippocampus and corpus striatum [31].

A study demonstrates that exposure to formaldehyde (FA) can cause neuronal damage in the cerebellum, as indicated by decreased levels of antioxidant enzymes (SOD and CAT) associated with oxidative stress and increased markers of cellular damage (XO and MDA). However, this damage is ameliorated by the administration of omega-3 fatty acids. These findings suggest a potential protective role for omega-3 supplementation against FA-induced cerebellar neurodegeneration [32].

Polyunsaturated fatty acids (PUFAs) are important nutrients for brain development and function. These fatty acids play a crucial role in regulating neuroinflammatory processes, microglial activation, and synaptic plasticity. Their potential benefits for autism spectrum disorder may be due to their influence on these biological pathways. Omega-3 supplementation has been found to inhibit caspase-3 activity in rats exposed to valproic acid (VPA) during pregnancy, which mitigates learning and memory deficits [33,34].

These findings offer additional proof of the potential advantages of omega-3 fatty acids supplementation for brain health. They may aid in the development of new strategies for preventing and treating neurodegenerative diseases.

Conclusion

Valproic acid (VPA) causes oxidative stress by reducing the antioxidant level in brain tissue, which can lead to the death of brain cells. Polyunsaturated fatty acids of omega-3 help to increase the antioxidant levels in neural tissues, suggesting that they may have immunomodulatory and anti-inflammatory properties. This could play a protective role against the neurodegenerative effects of valproic acid on the cerebellum.

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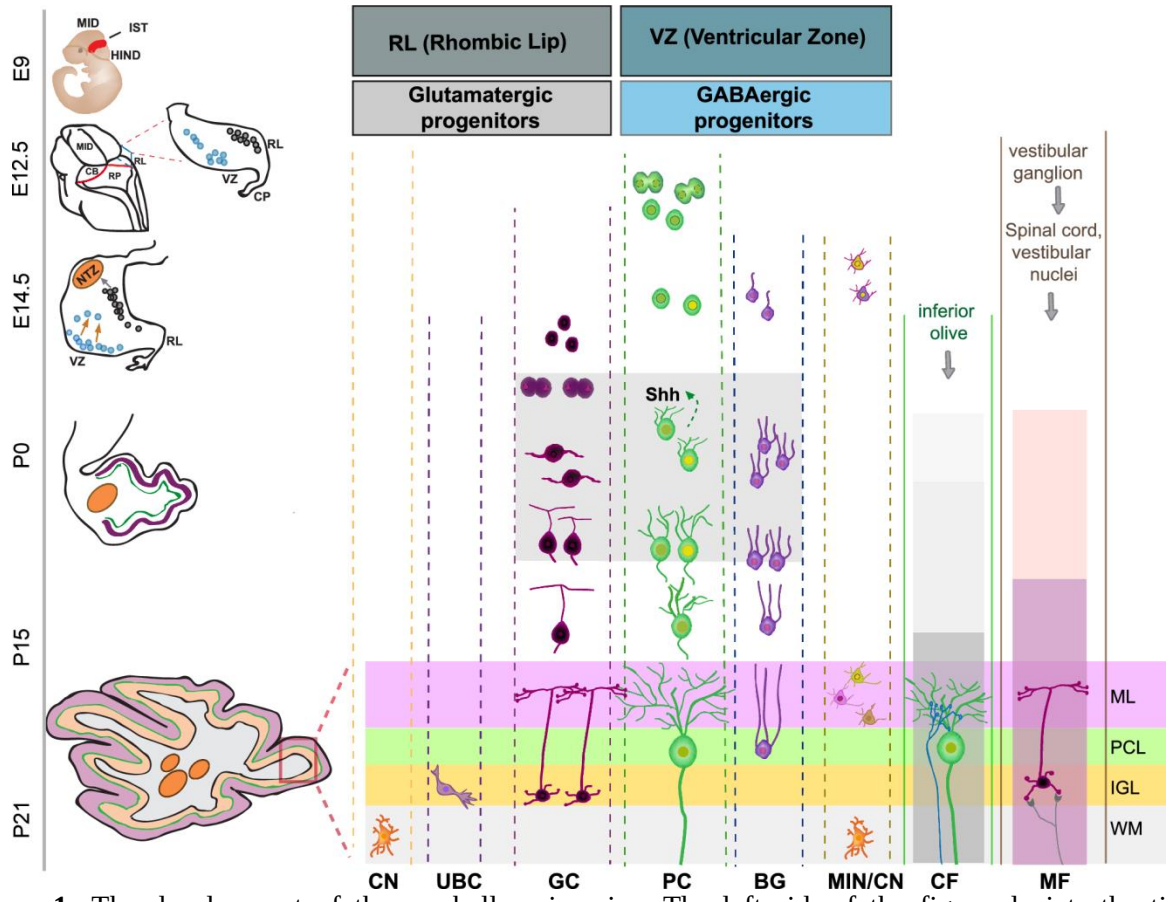

Figure 1: The development of the cerebellum in mice. The left side of the figure depicts the timeline of cerebellar development from embryonic day 9 (E9) to post-natal day 21 (P21). The Progenitor cells (E12.5–14.5) are described as gray (RL progenitors) or turquoise (VZ progenitors), and their migratory course is indicated by arrows (E14.5). MID (midbrain), IST (isthmus); HIND (hindbrain), CB (cerebellum), RP (Roof plate), RL (Rhombic Lip), VZ (Ventricular zone), CP (choroid plexus), NTZ (nuclear transitory zone). The right side of the figure illustrates cerebellar histogenesis. The light gray rectangle represents the timing of SHH secretion from PC, which promotes proliferation and maturation of the nearby cells. From the RL, Glutamatergic precursor give rise to neurons of cerebellar nuclei (CN), unipolar brush cell (UBC) and granule cells (GC), while GABAergic precursor from the VZ differentiate in Purkinje cells (PC), Bergmann glia cells (BG), molecular layer interneurons (MIN) and inhibitory neurons of cerebellar nuclei (CN). Climbing fibers (CF) forming synaptic connections with Purkinje cells and mossy fiber (MF) forming synaptic connections with granule cells are also shown. Rectangles in the CF column indicate timing of: supernumerary innervation (light gray); early phase of pruning (gray) and late phase of pruning (dark gray). Rectangles in the MF column indicate timing of: transient contacts with PC (pink); translocation to GC (light violet). Cerebellar cortical layers are marked (boxed area) in the P21 sketch and illustrated on the right side as follow: IGL internal granule layer (orange rectangle), PCL Purkinje cell layer (light green rectangle), ML Molecular layer (pink rectangle). WM White matter (light gray) [35].

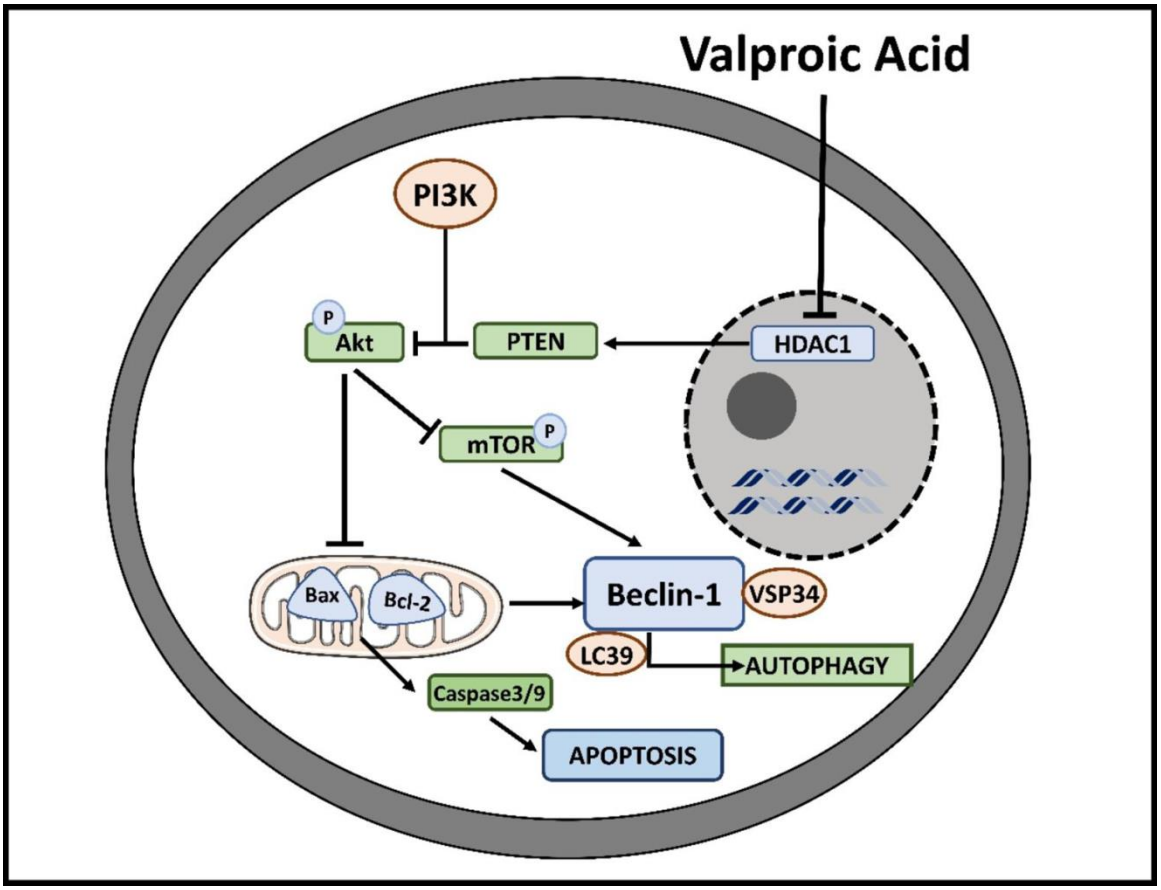

Figure 2: Valproic acid (VPA) works by inhibiting histone deacetylases (HDACs). This inhibition blocks the downstream PTEN/PI3K-Akt signaling axis, leading to the disruption of the mTOR and the proteins Bax and Bcl-2, which promotes the expression of caspase-3 and caspase-9. These changes trigger apoptosis and autophagy [36].

Citation

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