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REVIEW ARTICLE

Effect of Omega-3 against Valproic Acid-Neuroteratogenicity: A Narrative Review

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ABSTRACT

Background: Some retrospective and prospective clinical studies have shown that prenatal Valproic Acid (VPA) exposure can cause signs of autism spectrum disorder (ASD) in children, including social impairment, communication impairments, anxiety, obsessive/repetitive behaviour, and impaired motor abilities.

Bipolar illness, migraine, and epilepsy are all treated with valproic acid (VPA) that act as an inhibitor of histone deacetylases and an epigenetic modulator. VPA is a powerful teratogen for the progeny of human females undergoing pregnancy. The teratogenicity of VPA revealed foetal valproate syndrome, a condition in which offspring have characteristics of ASD, dysmorphic features, cardiac abnormalities, neural tube malformations, and neurodevelopmental delay.

Omega-3 is polyunsaturated fatty acids (PUFAs) present in seafood-like krill and algae as well as fish. These─PUFAs are found in the cell membrane phospholipids.

For some high-fat tissues, such as brain and retina, Omega-3 fatty acids (OM3FAs) have a stabilizing and protective impact. Docosahexaenoic acid (DHA) is one of OM3FAs and it is a crucial component of the brain's phospholipid membranes, that has the capacity to preserve the cell membrane integrity of neural tissues for improving the cognitive function, Alzheimer disease, and dementia.

Conclusions: Valproic acid intake during pregnancy exerted neurotoxic effect on the offspring and Omega-3 may have a protective effect against Valproic acid neurotoxicity.

Keywords:
Valproic Acid; Neuroteratogenicity; Omega-3.

Valproic acid

Bipolar illness, migraine, and epilepsy are all treated with valproic acid (VPA), an anti-epileptic medication. VPA administration during pregnancy can alter gene activity, damage DNA, interfere with mitochondrial energy metabolism, and increase foetal oxidative stress since it is an epigenetic modulator and an inhibitor of histone deacetylases. VPA is therefore a strong teratogen [1].

Exposure to valproic acid during pregnancy raises the risk of significant congenital abnormalities in several organs, such as the brain, heart, and limbs [2].

Teratogenicity of VPA was used to demonstrate foetal valproate syndrome, which comprises neural tube abnormalities, neurodevelopment delay, cognitive deficiencies, dysmorphic characteristics, Intrauterine growth retardation (IUGR), cardiac anomalies, and affection of the cranio-facial complex resulting in facial dysmorphism such as a long and thin upper lip, shallow philtrum, epicanthal folds, and midface hypoplasia, which is characterised by a flat nasal bridge, tiny upturned nose, and downturned angles of the mouth [3,4].

Neurodevelopmental abnormalities are another type of foetal damage brought on by VPA, mostly impacting behaviour and cognitive function [5].

These alterations may have an impact on language development, learning capacities, and perhaps lead to learning problems, attention deficit hyperactivity disorder (ADHD), or autism spectrum disorder (ASD) [6].

Numerous studies documented spina bifida occulta and exencephaly, which reflect Neural Tube Defects (NTD) brought on by prenatal exposure to VPA [7].

It is yet unknown how exactly VPA causes congenital abnormalities. Nonetheless, a number of molecular routes via which VPA results in congenital deformities and neurodevelopmental problems have been hypothesised based on scientific findings. One-carbon metabolism (OCM) is one of these pathways [8] **Figure 1.**

These actions of VPA may impede the transfer of a unit of carbon needed for the relevant cycles to proceed, resulting in aberrant phospholipid, protein, nucleic acid, and methylation reactions [9].

Additionally, it has been demonstrated that this VAL inhibits histone deacetylases and raises oxidative stress in the prefrontal cortex. This suggests that through epigenetic modifications, it may influence the expression of many genes involved in cellular differentiation and cell cycle control [2].

Numerous studies have demonstrated that exposure to VPA prenatally can cause alterations in genes expression linked to the development of the brain, synaptic function, and neurotransmitter signalling pathways. These genes are linked to risk genes for autism spectrum disorder (ASD) [10].

It has been suggested that VPA causes congenital deformities and neurodevelopmental teratogenicity through a number of different molecular routes. Among them, VPA suppresses the histone deacetylases *(*HDAC*)* enzymes that remove acetyl group from the histones for regulation of gene expression [11].

Moreover, VPA causes a disruption in the homeostasis of the one-carbon metabolism (OCM) that is associated with many developmental abnormalities [12].The folate and methionine cycles are included in the progression of OCM [13,14].

Dietary folate (vitamin B9) is converted into dihydrofolate (DHF) by the enzyme dihydrofolate reductase and is then reduced to tetrahydrofolate (THF). THF is converted to 5,10-methyleneTHF, which is converted to 5-methylTHF by the Methylenetetrahydrofolate reductase (MTHFR) enzyme. 5-methylTHF can donate a methyl group to regenerate methionine from homocysteine (Hcy); this reaction is catalysed by methionine synthase (MS), methyltransferase (MTR) and methionine synthase reductase (MTRR) with vitamin B12 as a cofactor.

Thereafter, methionine adenosyltransferase (MAT) catalyses the transfer of adenosine to methionine to generate S-adenosylmethionine (SAMe), which functions in methylation reactions. SAMe is then demethylated and forms S-adenosylhomocysteine (SAH).

SAH is hydrolysed to form Hcy that can enter the transsulfuration pathway to form cystathionine (catalysed by cystathionine beta-synthase (CBS) and cysteine (catalysed by cystathionase). Cysteine is then used to synthesise glutathione (GSH) to combat damage by reactive oxygen species (ROS), **Figure 1**

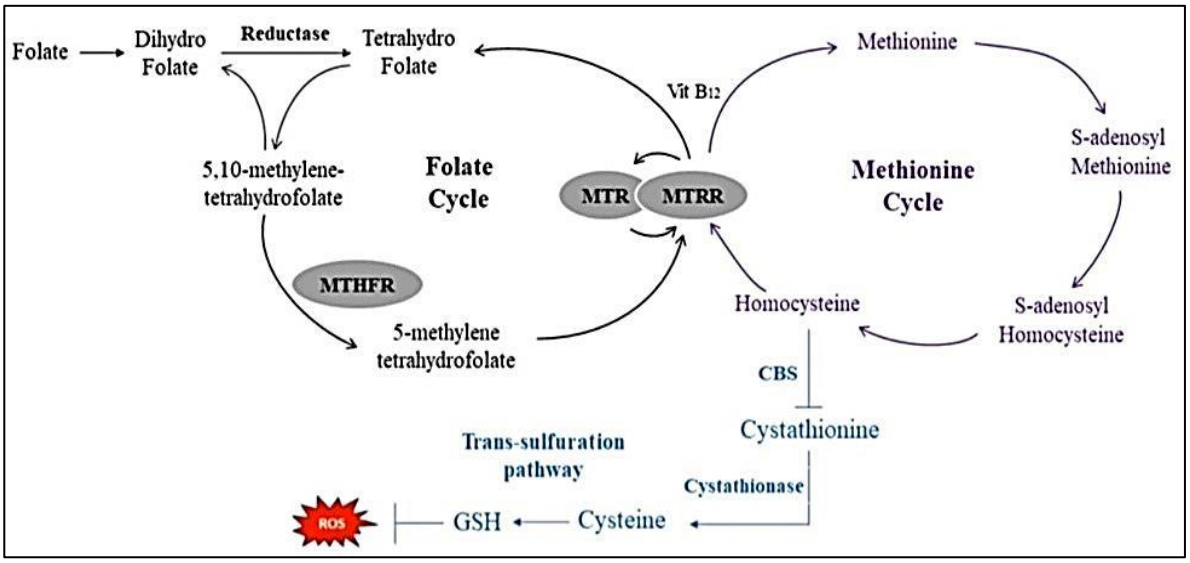


Figure1:

Schematic of One-Carbon metabolism related folate cycle, methionine cycle and transsulfration pathway. MTHFR, methylene tetrahydrofolate reductase; MTR, methyl transferase ; MTRR, methionine synthase reductase; CBS, cystathionine beta-synthase; ROS, reactive oxygen species[14]

VPA inhibits the enzymes dihydrofolate reductase and methyltransferases (MTR) which are involved

in the folate and methionine cycles [15].

As a result, VPA interferences in OCM led to decreased levels of endogenous folate, an imbalance in the S-adenosyl methionine (SAMe) and S-adenosyl homocysteine (SAH) ratio, where greater plasma concentration of SAH compared to lower plasma concentration of SAMe, all of which were detected in pregnancies impacted by NTD [4] **Figure 2.** SAMe is the major methyl donor for the methylation of nucleic acids [16].

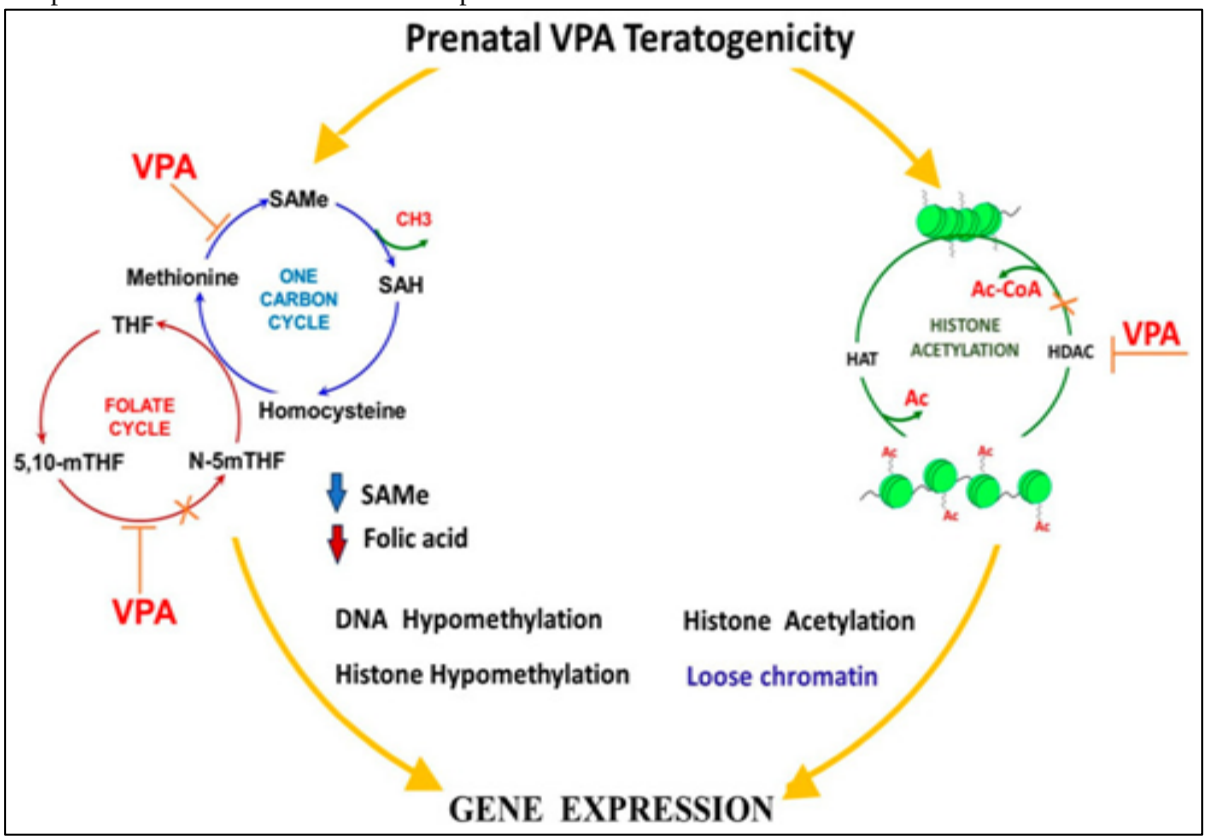


Figure 2: Hypothesised mechanism of VPA-induced epigenetic modifications' teratogenic effects [4].
VPA: Valproic acid; **Ac-Co**: Aacetyl-CoA; **HDAC**: Histone deacetylases; **HAT:** Histone acetyl transferasE;**SAMe**: S-adenosyl Methionine
SAH: S-adenosyl Homocysteine; **THF**: Tetrahydrofolate; **5,10 mTHF**: 5,10 methylene Tetrahydrofolate; **5 mTHF**: 5 methylene Tetrahydrofolate

DNA methylation, one of several post-replication epigenetic changes that occurs in the genome, contributes to the regulation of gene expression and maintenance of genome integrity and stability [17].

Poor methylation of DNA due to SAMe deficiency lead to cell dysfunction and alteration in gene expression with development of birth defects [18].

Omega-3

OMEGA-3 fatty acids are a family of Polyunsaturated fatty acids (PUFAs) having several carbon-carbon double bonds in their backbone. They are present in seafood-like krill and algae as well as fish including sardines, salmon, tuna, and halibut as well as in nut oils, some plants, and lake trout. These PUFAs, which are found in membrane phospholipids, are essential for many physiological processes, such as signaling, cell-to-cell communication, and membrane shape with fluidity preservation [19] **Table 1.**

Strong brain structure and function are necessary for a healthy brain and optimal cognition. The health and efficient operation of brain cells depend on omega-3 fatty acids. Furthermore, compounds generated from omega-3 fatty acids support higher oxygen levels and blood flow to the brain. Additionally, Omega-3 reduces the severity of brain damage and protects against it [20].

In addition to potentially lowering the risk of chronic illnesses including cancer, arthritis, and heart disease, Omega-3 can also decrease inflammation. Additionally, they control the development and activities of the nervous system, blood pressure, hematic coagulation, glucose tolerance. Docosahexaenoic acid (DHA) is a crucial component of the brain's phospholipid

membranes, and it is one of the omega-3 fatty acids. So, omega-3 has the capacity to preserve the cell membrane integrity of neural tissues [21].

Omega-3 is beneficial in age-related cognitive decline, rheumatoid arthritis, diabetes, cancer, depression, and other mental diseases. Additionally, it is critical for the growth of children and nursing mothers [22].

Poor cognitive performance on object recognition memory was the outcome of VPA treatment prenatally. The effects of omega-3 on cognition in various illness models are the subject of conflicting findings. One of the previous studies has shown the therapeutic effects of omega-3 supplementation on a range of neurological illnesses, including Alzheimer's and traumatic brain damage [23].

Moreover, persistent DHA therapy prevented prenatal VPA-induced cognitive impairment, according to Gao et al. The object recognition memory impairments caused by prenatal VPA treatment were shown to be improved by omega-3 [24].

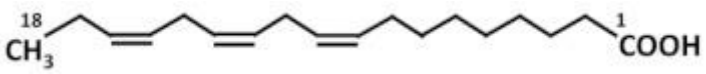
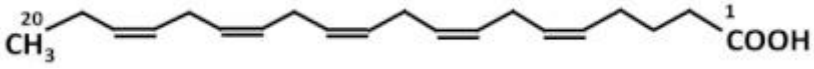
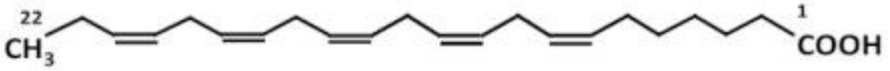
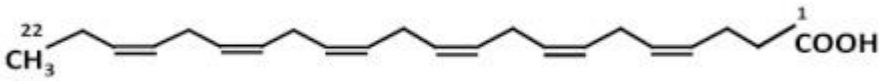
The prefrontal cortex and hippocampus's neuroinflammation caused by a foetal VPA injection is lessened by omega-3 supplementation. The prefrontal cortex and hippocampus are believed to experience severe inflammation with the structural alterations caused by prenatal VPA treatment. Therefore, omega-3 ameliorates the memory deficiencies related to object recognition caused by prenatal VPA treatment [25].

Among the most vital fatty acids needed for brain growth and maturation are polyunsaturated fatty acids (PUFAs). These PUFAs are potent regulators of neuroinflammatory processes, microglia activation, and synaptic plasticity. Their possible ameliorative effects on autism may be related to these processes [26].

Omega-3 supplementation has been demonstrated to inhibit caspase-3 activity in prenatally exposed rats to VPA, therefore ameliorating learning and memory deficits [24].

It is important to note that investigating these pathways pertaining to omega-3 is beneficial for comprehending its preventive and remedial effects against VPA neurotoxicity [26].

Table 1: Names and chemical structures of commonly available omega-3 fatty acids **[27].**

Common Name	Chemical Structure
Alpha-linolenic acid	
Eicosapentaenoic acid	
Docosapentaenoic acid	
Docosahexaenoic acid	

Conflict of interest: The authors reported no conflicts of interest.

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