Review Article
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Anti-teratogenic potential and curtailing toxicity of valproic acid

Abstract

Valproic acid (VPA) is widely used as an anticonvulsant and mood-stabilizing drug. It is highly prescribed drug, particularly for epilepsy. However, besides beneficial VPA have a number of side effects due to affecting several signaling pathways through different mechanisms. VPA act as a potent teraogen causing birth defects via interfering with folate metabolism or oxidative stress generation, and histone deacetylase inhibition. However, this article aims to give an overview of the these adverse consequences of VPA are significantly curtailed by the various substances like Vitamin E, Ascorbic Acid, Folic acid, Pantothenic acid, S-adenosyl methionine (SAM) and Curcumin etc which can be focus on its therapeutic use in future against it because of no such other alternative.

Keywords: VPA, vitamin, epilepsy, birth defects, anticonvulsant

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Introduction

VPA has become one of the most widely prescribed antiepileptic drugs worldwide in the management of long-term epilepsy, as well as controlling several neurological disorders including tonic-clonic seizures, idiopathic generalized seizures, juvenile myoclonic epilepsy, and childhood absence seizures and migraines.[1,2] Valproic acid, VPA (2-n-propylpentanoic acid, $C_8H_{15}NaO_2$, MW-166.19) a branched short-chain fatty acid derived from naturally occurring valeric acid was first synthesized in 1882.[3] It is known teratogenic agent for women of childbearing age and classified as a Type Dcategory indicating that human fetal risk has been documented but the use of the drug may still be warranted.[4]

Teratogenic profile and potential mechanisms

The teratogenic potential of VPA has been highlighted by numerous case reports[5] and in epidemiological studies.[6,7] These clinical findings suggest that VPA therapy during pregnancy may produce neural tube defects, most notably spina bifida (in human), as well as cardiovascular, urogenital, craniofacial, and digital abnormalities. An assortment of malformations related to prenatal VPA exposure have also been reported in laboratory species, including mice,[8,9] rats,[10] rabbits,[11] and rhesus monkeys.[12] The incidence associated with NTDs in exposed infants use VPA treatments, which is 10-20 times higher the rate of occurrences in general population.[13] In addition with congenital malformations,[14] a characteristic facial phenotype in VPA-exposed infants which have facial appearance like a broad nasal root, long and thin upper lip, epicanthic folds, small upturned nose, minor abnormalities of the ears and downturned angles of the mouth.

VPA-induced teratogenicity is too much complicated beside this the studies have been demonstrate that the VPA affect several signaling pathways through different mechanisms. Generally, birth defects due to VPA exposure reported three major hypotheses are i.e. Folate deficiency, oxidative stress, and histone deacetylase inhibition. VPA interfering with folate metabolism reported earlier thereby inhibiting the production of one-carbon units for DNA synthesis and methylation.[15] If used daily about 4-5 mg folic acid during pregnancy decreased the incident of spontaneous abortion in women, although the rate of congenital malformations was not affected.[15,16] Modification of histone post-translationally by acetylation, methylation along with other process such as, phosphorylation, and ubiquitination can modify the chromatin conformation, consequential in changes in gene activity. The nucleosome (functional unit of chromatin) is consists of about 146 base pairs of DNA wrapped around the octamer of histone consisted H2A, H2B, H3, and H4 in dual.[17] These modifications lead to altered DNA and histone proteins interactions, or trigger recruitment of chromatin remodeling complexes to further regulate gene activity. During acetylation masks the positive charge on lysine residues on histone tails resulting in a weakened DNA/histone interaction, thereby inducing a relaxed chromatin structure that allows DNA access to transcription factors.[18] Furthermore, acetylation can serve as a marker for other proteins that can then recruit chromatin remodeling and other functional complexes to modulate gene expression.[19] Histone acetylation is dictated by the balance of histone deacetylases (HDACs) and histone acetylases (HATs). HDACs are responsible for the removal of acetyl groups on histones as well as other proteins. Histone acetylation is carried out by HATs by transferring an acetyl group from acetyl coenzyme A (acetyl CoA) onto lysine residues on histone tails. Treatment with HDAC inhibitors could be de-repressing transcription about 2% of genes, out of which many regulate cell cycle and cellular differentiation.[20] Its inhibition is to be expected explanation for their effects on proliferation and differentiation in transformed cells.[21] Many example of HDAC inhibitors block proliferation and induce differentiation in cancers models such as leukemia and colon, lung, and prostate carcinoma.[22] HDAC inhibition as factors for teratogenicity first time reported by Phiel et al.[23] Similar result reported by Gurvich and colleagues in Xenopus and zebrafish embryos. He explained VPA induced teratogenicity via changing gene expression; using microarray for genes targeted which is also targeted by TSA inducing teratogenesis, and finally suggested that gene expression changes were being induced by structurally unrelated two drugs via a similar mechanism.[24]

Valproic acid-induced teratogenesis via oxidative stress

Oxidative stress responsible for causing damage in the building material of cellular macromolecules such as DNA, lipids, and proteins, along with changing redox-sensitive signaling pathways

leading malformation during development.[25] Hydroxyl ion (OH-) is react with nitrogenous bases and it one of the facts of oxidative DNA damage. Generated free radicals can also react with polyunsaturated fatty acids to form electrophilic aldehydes such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE) that adducts bind with the amino acids like cysteine, lysine, or histidine residues and thus interfere with protein function. Beside this, the gene expression is precisely regulated during development; ROS can change the pathway of transcription factors by disturbing cell signaling, therefore disrupt normal embryonic development and result in a teratogenic effect.[26] Oxidative stress is one of the significant mechanisms that involves in embryonic metabolism or bioactivation of an exogenous agent such as drugs or chemicals, which produced ROS, inducing cellular damage or altered signaling and finally teratogenesis.[25,27] Many works have reported that the levels of catalase, superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) are low during organogenesis period embryos as compared to adult.[28] During early embryonic development Cytochrome P450s (CYPs) are the most important enzymes implicated in the metabolism of drugs and some of the forming metabolite involve in generating ROS. Hence applying antioxidative compounds and enzymes would protect harmful effects against ROS and this has also been supported by reports of various workers.[29]

During embryonic period, occurred anaerobic metabolism in embryo so, the risk of oxidative tone is toxic for them. Supply of oxygen required for the rapid growth and weight gain which come from utero-placental circulation. If any fluctuations in the development period due to oxidation are referred to as redox switching, because oxygen levels are maintained to sustain the cellular actions during critical periods of organogenesis. For the rapid proliferation of cells low oxygen levels are required and generated mild oxidative tone leads to cellular differentiation whereas at high oxidative environment results in apoptosis or necrosis of the developing cells.[30] If in this time (organogenesis period) any xenobiotics or drugs which enhance oxidative stress which very sensitive to oxidative tone, causing necrosis or apoptosis or uncontrolled differentiation ultimately resulting very harmful effects in the form of teratogenic effect or birth defects. Previous studies have reported VPA can induce oxidative stress and this is one of the reasons for occurring teratogenicity.[31] The VPA metabolites such as 4-ene VPA, 2-ene VPA and 2, 4-diene VPA, form by CYP metabolism in liver. This metabolite interact with GSH depleted their levels, so the balance of cellular system in antioxidant decrease and condition become very sensitive but by supplementation with any natural or synthetic antioxidants such as catalase, vitamin C, and vitamin E protected against damage induced by 4-ene VPA was reported in various study.[32] VPA induced ROS formation has been determined by measurement of the conversion of the non-fluorescent ROS-sensitive dye 5-(and-6)-chloromehtyl-2‟7‟-dichlorodihydrofluorescein diacetate (CM-H2DCFDA) to the fluorescent dichlorodihydrofluorescein (DCF) in various cell line and it attenuated by antioxidant such as PEG-catalase[33] or with vitamin E[34] or vitamin C[35] was reported, which clarify the role of protective effects (Table 1).

Anti-teratogenic agents against VPA induced teratogenesis

Women taking anticonvulsant medications during gestation of the first trimester[36] have a 3-5% greater risk of birth defect in an infant than whom not taking[37] VPA during pregnancy. The risk of spina bifida occurring is more than or 20 times greater risk than in the general population and about 10 times more observed in other antiepileptic drugs.[38] Various compounds have been used against VPA to reduce or compensate its toxic/teratogenic effects in various animal models. In NMRI mice combination of the three vitamins (Folinic acid, vitamin B6, and vitamin B12) was found effective in reducing VPA (500 mg/kg, subcutaneous) induced exencephaly, spina bifida occulta, palate and rib malformations.[39] In1996, Methionine (70 mg/kg) reduces VPA-induced spina bifida in mice without altering VPA kinetics.[40] Methionine, an essential amino acid is required for normal growth and development in mammals.[41] Coelho and co-workers (1989) found it also important for neural tube development, in cultured rat embryos. Further studies revealed that in the absence of methionine the neural tube failed to close in cultured rat embryos[42] because methionine may be required for the methylation of microfilament proteins involved in neural fold apposition. In humans, methionine metabolism or derangement of homocysteine metabolism has been reported as a possible risk factor in neural tube defects.

In 2000, Al Deeb and its co-worker studied with vitamin E and reported concomitant administration of vitamin E (250 mg/kg) significantly attenuated VPA (700mg/kg, subcutaneous) induced decrease in the fetal weight, crown rump length and malformations (exencephaly, open eyelid, and micrognathae) in Balb mice (Table 1) and another study also reported that its alteration on glutathione homeostasis (GSSG/ GSH ratio) along with inhibiting Hoxa2 expression induced teratogenesis prevented after Pretreatment with ascorbic acid.[34] In 2003, three doses of 4 mg/kg folic acid (FA) (total 12 mg/kg) supplementation during gestation (GD 7) or FA (4 mg/kg) was administered thrice daily starting on GD 5 and continued through GD 10 substantially reduced exencephaly in mouse fetuses[43] (Table 1). Later protective effects of folic acid and pantothenic acid against valproic acid-induced neural tube defects in CD-1 mice has been also reported.[16] In 2001, Fenech reported low levels of folic acid causes breaks of chromosome, hypomethylation of DNA and micronucleus formation. Low levels of methionine increase the level of homocysteine that have been implicated in NTD.[44] Homocysteine was a biomarker of folate status.[45] It has been observed elevated moderately levels of homocysteine in maternal blood and amniotic fluid of pregnancies causing neural tube defects, NTD.[46] Homocysteine has been shown to induce malformations in chick and rat embryos,[47,48] observed that folic acid and vitamin B 12 are independent risk factors for NTD.

Another mechanism exhibited with one of the key enzyme Methylenetetrahydrofolate reductases (MTHFR) involve in folate interconversion and homocysteine metabolism. VPA might interfere with folate metabolism through MTHFR modulation that increase teratogenicity rate.[49] The enzyme methylenetetrahydrofolate reductase (MTHFR) catalyses the production of 5- methytetrahydrofolate, a substrate for methionine synthase in folic acid cycle. Reduced activity of MTHFR results in elevated levels of homocysteine and thus diminishes the supply of methyl groups to macromolecules via folate-homocysteine cycle. A thermolabile variant of MTHFR is reported to occur frequently among NTD cases and their families than among controls.[50,51] So, NTD in fact after administration of folic acid cannot prevent because of many reason for its happening. Further studies are required to clarify certain basic issues in the nutritional requirements of embryos during normal and abnormal morphogenesis of the neural tube defects and other various congenital malformations.

Another in *invivo* study done in rats further supported it by attenuating VPA-induced skeletal malformations by pretreatment of

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vitamin E.[52] In human patients VPA therapy increased the oxidative stress by lower antioxidant activities,[53,54] in various cell line.[33] Recently published study on administration Valproic acid (VPA) at a dose of 300 mg per kg body wt significantly decreased the levels of GSH, SOD and catalase and increased the levels of ROS, TBARS, mRNA expression and the levels of the CYP2C9 enzyme which is involved in the formation of the toxic metabolite (*E*)-2,4-diene-VPA. However, upon the co-administration of curcumin at the dose of 100, 150 and 200 mg per kg body wt. along with 300 mg per kg body wt of VPA, confirmed the significant increase levels of GSH, SOD and catalase and reduced the ROS, TBARS, mRNA expression and the level of CYP2C9 enzyme with respect to VPA (Table 1). This study also conclude the formation of toxic metabolite (*E*)-2,4-diene-VPA is involved in the generation of oxidative stress subsequently contributing in the induction of malformations and anomalies. However, curcumin affords dose dependent amelioration of the anomalies in fetus exerted by VPA.[56] A number of plant products have been reported to have excellent source of antioxidant with no side effects, in most of the published articles. Folic acid, vitamins and various plant products in various form now used as protective, prophylactic or ameliorative form.[57–59]

Table 1 List of herbal products acting antiteratogen activity

Antiteratogen	Dose of antiteratogen	Teratogen	Dose of teratogen	Species/ System	Reported effects	Source
Folinic acid (FA)	4 mg/kg/d on days 8, 9, and 10	Valproate (VPA)	300 mg/kg/d on days 8, 9, 10 of GD	Wistar rat	VPA induced skeletal malformations in skull, vertebrae and ribs were able to prevent by Folate administration.	Ubeda et al.[58]
Vitamin E	250 and 500 mg/kg (oral)	Valproic acid (VPA)	700 mg/kg (sc)	Balb mice	Concomitant administration of vitamin E significantly attenuated VPA induced decrease in the fetal weight, crown rump length and malformations.	Al Deeb et al.[29]
S-adenosyl methionine (SAM)	10 mg/kg/d from days 1-10	Valproate (VPA)	300 mg/kg/d on days 8, 9, 10 of GD	Wistar rat	VPA induced skeletal malformations in skull, vertebrae and ribs whereas SAM-co administration did not show more protective action.	Ubeda et al.[58]
Folic acid (folinic acid)	12 mg (Single); 3 doses of 4 mg; 4 doses of 3 mg / kg on GD 5-10	Sodium Valproate	400 mg/kg on GD 7 or 8	TO mouse	The substantially doses of Folic acid reduced the VPA-induced exencephaly in the fetuses observed.	Padmanabhan and Shafiullah,[44]
Folic acid and Pantothenic acid	3 x 4 mg per kg ip GD 5-10 3 x 200 mg/kg ip GD 9	Valproic acid	400 mg/kg GD 9 (s.c.)	CD-1 mice	Folic acid and Pantothenic acid protect NTDs by independent, but not mutually exclusive mechanisms.	Dawson et al.[17]
Ascorbic Acid	5 mM	Valproic Acid	50,100,200, 400 µg/ml	CD-1 mouse	The presence of ascorbic acid in the culture media was effective in protecting embryos against oxidative stress induced by VPA and prevented VPA-induced inhibition of Hoxa2 gene expression.	Zhang et.al.[36]
Curcumin	100, 200 and 300 mg/kg b wt.	Valproic Acid	400 mg/kg b. wt. (GD6-15)	CF Rat	Curcumin affords dose dependent amelioration of the anomalies in fetus exerted by VPA	Akhilesh Kumar et al.[56]

Conclusion

In light of all these observations and considering ongoing overview it appears that although the work on Antiteratogen is inadequate, scanty, and showing an initial and perfunctory interest in this field yet the data regarding the mechanisms of oxidative stress and oxidative damage was involve in VPA-induced teratogenesis are concluded the responsible for it, however more mechanistic studies are require for searching any others possibility for toxicity. So, more studies are also required to reveal the curtailing its oxidative damage and interactions in signaling pathways that inducing by VPA or its metabolites in the developing embryo causing teratogenicity or birth defects.

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Conflict of interest

The author declares that there is no conflict of interests regarding the publication of this paper.

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