The multifaceted therapeutic potential of valproic acid beyond CNS axis

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ABSTRACT

Valproic acid is widely used as an anti-epileptic globally. Anti-epileptic action is mediated by Gamma Amino Butyric Acid (GABA) receptors. In past and recently, several other clinical outcomes have been proposed by various studies. These under-reported clinical actions apart from anti-epileptic activity are mediated by various intracellular and extracellular pathways. Several mechanisms like Histone deacetylase (HDAC) inhibition, inhibition of inflammatory cytokines, angiogenesis inhibition and many more justifies its possible use in variety of disorders like diabetes mellitus, asthma, cancer, shock, hyperlipidemia, fibrosis etc. Present review throws some light on such under-reported, clinically beneficial effects of Valproic acid in various diseases and disorders.

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INTRODUCTION

Valproic acid (VPA) is a branched chain carboxylic acid, and is a broad spectrum antiepileptic drug that has been used for more than 35 years and also prescribed to treat bipolar and schizoaffective disorders, social phobias and neuropathic pain, as well as for prophylaxis or treatment of migraine headache, with a chemical structure similar to that of short chain fatty acids [1-4]. The name Valproic acid comes from 2-propylvalericacid, its alternative chemical name. In the chemical nomenclature, Valproic acid should be named 2-propylpentanoic acid or dipropyl-acetic acid with the formula $(CH_3CH_2CH_2)_2CHCOOH)$. Valproic acid is an endogenous fatty acid and was first synthesized by B.S. Burton, as an organic solvent [5]. Its antiepileptic properties was accidently discovered in 1963 by Pierre Eymard and his colleagues, who were using Valproic acid as a solvent for compound tested as a antiepileptic potential and they realized that this solvent itself inhibits experimental seizures [1, 6]. It was first used clinically in USA in 1978 only for absence seizures and thereafter in 1978 for partial seizure [5]. At first, it was formulated in acid form and thereafter as a sodium and magnesium salt and as an amide. Valproic acid is slightly soluble in water and highly soluble in organic solvents and stable at room temperature. Valproic acid is not sensitive to humidity but its sodium salt is highly hygroscopic [1, 5, 7].

Pharmacology of Valproic acid

It potentiates gamma aminobutyric acid transmission in some specific brain regions, thought to be responsible for control of seizure generation and propagation by inhibition of GABA degradation, increase GABA synthesis and decrease GABA turnover [1, 2, 4, 8-11]. It also reduces release and/or effects of epileptogenic hydroxybutyric acid and attenuates N-methyl-D-aspartate (NMDA)-type glutamate receptors induced neuronal excitation [1, 2, 12, 13]. It was also observed that Valproic acid block voltage-dependent

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Na⁺ channels [14, 15] and modulate the firing frequency of neurons and alter dopaminergic and seratonergic neuro-transmissions [2, 11, 16].

Pharmacokinetics of Valproic acid

Salts of Valproic acid is available in different dosage form including parenteral and oral dosage forms. Its oral dosage forms includes immediate release, sustained release, delayed release and enteric coated preparations [10]. Non enteric coated formulations are freely, rapidly and complete-ly absorbed from gastrointestinal tract. They give peak plasma concentration within 1-4 hrs. after ingestion. It achieves peak plasma concentration after oral solution and enteric coated formulation within 15-60 minutes and 3-7.5 hrs. respectively [2, 5, 10, 17]. Its therapeutic concentration ranges from 50-125 µg/ml and at this concentration, 80-90% bounds to plasma proteins and binding to plasma proteins decreases with increase in concentration of drug in plasma. Valproic acid has very low volume of distribution ranging from 0.13-0.40 l/kg [2, 18-20].

Metabolism: [2, 21-24]

Biological half-life of Valproic acid is 5-20 hrs. Elimina-tion follows first order monophasic exponential kinetics [19, 25] (Table 1).

Adverse drug reactions

Common adverse drug reactions include dyspepsia, weight gain, dysphoria, fatigue, dizziness, drowsiness, hair loss, headache, nausea, sedation and tremor. It can also im-pair liver function, prolongate the blood coagulation time and may also cause thrombocytopenia. It is teratogenic and when used in pregnancy it may cause congenital anomalies mainly spina bifida [1, 26-28]. Some serious side effects may be seen in some individuals who are taking Valproic acid for prolonged use and these includes hepatotoxicity, hyperammonaemic encephalopathy and pancreatitis. It may also result in central nervous system depression and behav-iour abnormalities [10, 29, 30].

Novel Pharmacological actions of Valproic acid

Valproic acid as Anti-inflammatory: Valproic acid has been shown to reduce the COX-I and COX-II levels which are involved in inflammation. Bosetti and co-workers [31] found that chronic Valproic acid treatment reduces rat brain arachidonic acid release and also reduce the COX I and COX II total turnover and thus may be useful in reducing inflammation. In another study, Valproic acid attenuated inflammation in rat model of autoimmune neuritis where VA suppressed the mRNA levels of interferon-gamma, tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-6 and IL-17 [32].

Valproic acid inhibits atherosclerotic lesions: Long term endoplasmic reticulum (ER) stress observed in atherosclerot-ic lesions which is an important contributor to pro-atherogenic progression [33]. Long term ER stress leads to apoptosis of lesional macrophages. During plaque formation, apoptotic cells are quickly phagocytized by macrophages [34] and this process is mediated by anti-inflammatory cyto-kines such as transforming growth factor (TGF)- β and IL-10 [35]. Glycogen synthase kinase-3 (GSK-3) is important potential factor through which ER stress signals and produc-es atherosclerotic lesions [36]. Bowes et al. [37] studied the effect of Valproic acid in hyperglycemic apo-E deficient mice and reported the protective role of Valproate in attenu-ating the atherosclerotic lesions. This effect was mediated by inhibiting the GSK-3 activity and interfering with pro-atherogenic endoplasmic reticulum stress signaling path-ways. The probable mechanism behind regression of athero-sclerotic lesions might be inhibition of GSK-3 inhibition and reduction in ER stress along with lowering of inflammatory markers like TGF- β and COX-II as described earlier The major challenge is population-based clinical study is re-quired to ascertain VPA's anti-atherosclerotic potential and dose titration is utmost important in this condition.

Valproic acid in type I diabetes: Patients with type I dia-betes have deficient β cell function or loss of β cell resulting in decrease in insulin secretion. This loss of pancreatic β cells results in hyperglycemia which if not controlled results in diabetic microvascular and macrovascular complications. Studies have shown that VPA increased insulin secretion from pancreatic β cells. In-vitro study on pancreatic β cells have demonstrated that VPA increased time and dose de-pendent insulin secretion in cell supernatant [38]. This effect of Valproic acid might be useful in patients with type I dia-betes who have few β cells intact or functioning in pancreas. Our group showed significant reduction in blood glucose with two months of VPA (210 mg/kg/day) treatment in dia-betic rats effect of which might be related to induction of estrogen receptors [39]. ER stress is also important factor

Table 1. Metabolism [2, 21-24]

Biochemical Process		Percentage	Metabolite
Direct Glucuronidation		80%	-
Unchanged excretion		3%	-
β- oxidation		17%	
	Mitochondrial Cytosol	70%	-
	ώ- oxidation	14%	5- hydroxyl-2-propyl pentanoic acid, 2-polyglutaric acid
	ώ1- oxidation	16%	4- hydroxyl-2-propyl pentanoic acid, 4- oxo-2-propyl pentanoic acid

that has been linked to development of type I diabetes by destruction of β cells [40]. It has been shown that VLA protects cells from ER stress and prevents apoptosis by inhibition of GSK-3α and GSK-3β. It was observed that in culture of hepatic carcinoma cell line HepG2, when incubated with VPA, there was significant protection of cells from ER stress induced by thapsigargin and this protective effect was mediated by predominantly GSK-3β and to a lesser extent by GSK-3α. This experiment throws light on our understanding that VPA could be used to treat autoimmune type I diabetes by preventing further loss of β cells [41]. The mechanism behind reduction in blood glucose in type I diabetes is mainly due to pancreatic β-cell protection from oxidative stress and HDAC inhibition property of VPA. Further, challenge in use of VPA in type-I diabetes is to carry out large case-control study and its efficacy in combination with other hypoglycemic drugs.

Valproic acid in type II diabetes: Insulin resistance is hallmark of type II diabetes characterized by hyperinsulinemia and hyperglycemia. Recently, a study revealed that Valproic acid significantly reduced plasma glucose level, glycated hemoglobin and insulin resistance in type II diabetic rats. Further, VPA also inhibited gluconeogenesis in liver and all this effect was mediated by inhibition of HDAC activity by VPA [42]. HDAC have been reporting to mediate glucose metabolism and target for insulin sensitivity recently. Class I and III HDAC regulates glucose and fatty acid metabolism [43]. HDAC3 activation by hyperglycemia suppress the Peroxisome proliferator–activated receptor (PPAR)-γ coactivator (PGC)-1α, a transcription co-activator, function and thus insulin sensitivity. Study showed that blocking HDAC3 activity in DIO mice prevented insulin resistance [44, 45]. This study suggests the role of class I HDAC inhibitor in improving insulin sensitivity. Acetylation of Tricarboxylic acid (TCA) cycle enzymes in cytosol was found in type II diabetes. Trichostatin A, a class I HDAC inhibitor was found to regulate acetylation status of TCA cycle proteins and sensitizes insulin thereby reducing plasma glucose [46, 47]. In another study, butyrate, a class I HDAC inhibitor improved energy expenditure and insulin sensitivity in dietary obese C57BL/6J mice through stimulation of PGC-1α activation by HDAC inhibitory action [48]. Valproic acid is well known inhibitor of class I HDAC and may have therapeutic role in type II diabetes as insulin sensitizer. The probable mechanism in type-II diabetes is the ability of VPA to inhibit HDAC which affects glucose metabolism pathway enzymes and increase insulin sensitivity and reduction in oxidative stress which is hallmark in diabetic condition as shown by our group previously [39]. The challenge in use of VPA in type-II diabetes is to conduct large population based studies and comparing its effects with available hypoglycaemic drugs along with deciding suitable dose which should not produce side effects.

Valproic acid inhibits angiogenesis: Anti-angiogenic potential of any compound make it very useful in treatment of proliferative disorders. VPA shown to inhibit endothelial cell proliferation dose-dependently. It also inhibited vascular endothelial growth factor (VEGF) secretion of glioma cells in-vitro [49]. Another study showed similar findings where VPA treatment inhibited umbilical vein proliferation, migration and tube formation. These profound changes were attributed to hyperacetylation of histone H4 which indicates histone deacetylase (HDAC) inhibitory activity as VPA is a well known HDAC inhibitor and a decreased expression of the endothelial nitric-oxide synthase (eNOS) which is confirmed by replacing VPA with its derivative which is not showing HDAC inhibitory activity [50]. In brain tumor model, VPA decreased the synthesis of vessels expressing factor VIII and inhibited glioma cell angiogenesis. This finding supports the role of VPA in treatment of cancer [49]. Pericytes have important function in neo-formation of blood vessels and it maintains angiostasis in other tissue. The effect of VPA on pericyte has been studied and found that VPA treatment inhibits pericyte proliferation and migration without affecting pericyte viability [51]. The mechanism of anti-angiogenic property might involves HDAC inhibition and attenuation of VEGF and eNOS thereby, justify its use in proliferative disorders.

Valproic acid decrease fibrosis: Fibrotic diseases are mainly a result of type I collagen overproduction. It was demonstrated that VPA inhibited collagen production in conjunctival fibroblast by decreasing type I collagen expression by modulating Smad expression where Smad2, Smad3 and Smad4 were decreased and blocked the fibrogenic activation. Apart from this, Smad6 was over-expressed which proved to be beneficial as over-expression of Smad6 reduced the fibrogenic potential of TGF-β [52]. Another study by Mannaerts et al. [53] showed that VPA blocked the hepatic stellate cells activation and ultimately resulting liver fibrosis in chronically injured mouse liver. VPA also halted thiocetamide induced liver fibrosis where VPA increased the DNA damage and apoptosis in the activated hepatic stellete cells along with significantly increase in MMP-2 production [54]. In a model of Adriamycin induced renal fibrosis, VPA attenuated the kidney injury by decreasing the expression of pro-fibrotic and pro-inflammatory genes and accumulation of myofibroblasts in the interstitium. It was observed that α-SMA, TIMP-1, collagen type-1α1, and TGF-β1 induction were significantly abrogated by VPA treatment which are fibrotic markers. It was also studied that these pathological changes were due to histone hyperacetylation [55]. VPA is well known HDAC inhibitor [56] and this inhibitory activity could be responsible behind attenuation of renal fibrosis. Similar results were recorded by different scientists where VPA reduced tubulo-interstitial injury, renal fibroblast activation and interstitial fibrosis and suppresses the epenchymal to mesenchymal transition (EMT) induced by TGF-β1 where TGF-β1 was inhibited by VPA [57-60]. Left ventricular heart failure, a major cardiac manifestation is a consequences of cardiac fibrosis [61]. Further our group showed significant reduction in cardiac and renal collagen with VPA treatment in diabetic rats which was possibly due to increased estrogen receptor expression with VPA treatment [39]. In a model of doxorubicin induced myocardial fibrosis

in rats, VPA reduced collagen synthesis in left ventricle [62]. Another study showed that VPA administration in DOCA salt sensitive hypertensive rat reduced the cardiac hypertrophy and fibrosis which was confirmed by reduction in ANF, BNP and β-MHC in hearts [61]. Of note, cardiac fibrosis was also inhibited by angiotensin infusion and aortic bending in rats where VPA reduced interstitial fibrosis by inhibiting ANF, β-MHC and α-tubulin which were believed due to inhibition of class I HDAC [63] which is well reported by VPA [56]. Above evidences makes the VPA as a candidate for therapeutics of fibrotic disorders. Recently, it has been reported that VPA protects heart functions in model of myocardial infarction where there is significant reduction in oxidative stress and fibrosis observed mediated via Foxm1 pathway [64]. The possible mechanism in reduction in fibrosis involves arrest of fibrotic markers like TGF-β1, ANF and BNP. Apart from this, oxidative stress plays an important role in fibrosis is already shown to be inhibited by VPA in animal model as shown by studies [39, 65].

Valproic acid decrease blood pressure: Systolic and pulmonary hypertension are outcome of several disorders like atherosclerosis, diabetes, hyperlipidemia, heart failure and many more often associated with increased expression of pro-inflammatory cytokines (PICs). Long standing untreated hypertension may damage kidney and retina. VPA has shown some hope in treating systolic hypertension. In a study of L-NAME induced hypertension in rats, VPA treatment normalized the increased blood pressure and heart rate [66]. In another study, VPA treatment in spontaneously hypertensive rats for 20 weeks reduced blood pressure, heart rate and reactive oxygen species (ROS). It is believed that uncontrolled HDAC activity is responsible for hypertension and associated effects. VPA is known HDAC inhibitor and VPA treatment reduced HDAC activity and ROS thereby reduced hypertension. Apart from this, VPA also inhibited PICs like TNF-α and IL-1β and reduced angiotensin-1 receptor expression thereby controlled hypertension by ameliorating the action of angiotensin-II [67]. Right ventricular failure, a most debilitating condition arises when pulmonary hypertension standing long time. In monocrotaline induced severe pulmonary hypertension, VPA attenuated progression of vascular remodeling and reversed the severe pulmonary hypertension. This effect is due to reducing the excessive inflammation and cell proliferation. HDAC inhibitory activity may have played an important role in reversing pulmonary hypertension [68]. As HDAC inhibitor have proven role in cardio-renal axis and cancer [58, 69]. This findings were supported by another study carried out by Cho et al. [70] where VPA reduced right ventricular hypertrophy in monocrotaline induced right sided heart failure. In our study, we also support above findings where VPA (210 mg/kg/day) for two months significantly reduced systolic and diastolic blood pressure, rate of pressure development and decay and hypertrophic index [39]. The mechanism involved in reduction of blood pressure is blocking of angiotensin-1 receptor and attenuation of inflammatory markers with reduction in oxidative stress. The challenge in using VPA in hypertension

is to be justified by properly designed clinical study and suitable dose which should not produce treatment related side effects.

Valproic acid inhibits adipogenesis: Worldwide prevalence of obesity and its increase day-by-day is a serious concern and made health researchers to think for new entity to treat obesity as it is positively correlated with morbidity in patients. Excess fat accumulation is a product of hyperplasia and hypertrophy of adipocyte [71] which cannot be reversed by current therapeutic approach. In an attempt to think for such condition, study was conduct to know the effective role of VPA to inhibit adipogenesis. In 3T3L1 cell line, VPA was shown to inhibit adipogenesis by its HDAC inhibitory activity. It was also shown that VPA mediated this effect by direct activation of PPARγ [72]. Other study carried out to find the molecular mechanism of VPA inhibit adipogenesis where it was found that VPA suppressed adipogenesis through the down-regulation of USF1 (Upstream stimulating factor-1)-activated fatty acid synthesis in adipocytes. Apart from that, expression of fatty acid synthase was noteworthy suppressed with VPA treatment [73]. PPAR-δ has proven role in lipid homeostasis and metabolic regulation [74]. PPAR-δ has also been identified for its role in reduction of adiposity by inhibiting adipogenesis [75]. Another study has concluded that VPA is an activator of PPAR-δ ligand-binding domain in CHO (Chinese hamster ovary) cells [76]. So, as discussed earlier, inhibition of adipogenesis may be due to activation of PPAR-δ ligand. Further, it was noted that HDAC1 increases energy expenditure and reduce the adiposity in obese mice. VPA is proved to be HDAC1 inhibitor and thereby may regulate adipocyte differentiation process [77]. The mechanism may involve in inhibition of adiogenesis is activation of PPARγ and reduction in lipid parameters like LDL, cholesterol and triglyceride which might be related to its HDAC inhibitory activity.

Valproic acid delays aging: Majority of human disability and diseases are due to phenomena of ageing and major contributor for socio-economic burden. Alzheimer's disease, Parkinson's disease and cardiovascular diseases are on top of ageing related disorders. Agents which can delay the ageing process will be an exceptional outcome of modern science. In an attempt to discover such drugs, VPA proved to be a value because in experiment on Caenorhabditis elegans, it was found that VPA extended the life span of C. elegens and delayed diminished age-related body movements. Possible mechanism behind delaying lifespan may be HDAC inhibitory activity of VPA. Other mechanism sorted out by scientist was DAF-1 nuclear localization and modulation of insulin/IGF-1 pathway [78]. Retinal degeneration is also one of ageing related disorder where there is a loss of photoreceptor in retina. It was shown that VPA treatment prevented the loss of photoreceptor induced by N-methyl-N-Nitrosourea (MNU) in mice by its anti-apoptotic action and by preventing the degradation of Heat shock protein-70 (HSP 70) [79] which has crucial role in photoreceptor cell death [80, 81].

Valproic acid increase erythropoiesis: Cell differentiation along the erythroid lineage occurs over a two week span

in humans. The earliest erythroid progenitor, the burst forming unit-erythroid (BFU-E), is small and without distinguishing histologic characteristics. BFU-Es express the cell surface antigen, CD34, as do all other early hematopoietic progenitors allowing for its isolation using anti-CD34 antibodies. The stage after the BFU-E is the CFU-E (colony forming unit-erythroid) which is larger and is the stage right before hemoglobin production begins. Erythropoiesis stimulating agent stimulates red blood cell (RBCs) production which can be helpful in many threatening diseases like anemia, malaria etc. to reduce substantial rate of morbidity [82]. Role of HDAC inhibitors in erythropoiesis is well established [83]. Scientists have shown that VPA enhanced the potential of IL-3 to stimulate megakaryopoiesis and erythropoiesis which could be novel therapeutic approach for hematological disease [84]. VPA also shown capacity for ex-vivo expansion of hematopoietic stem cells which could be useful in stem cell transplantation and therapies [85]. Pace and co-workers [86] found that VPA and other short chain fatty acid induces γ globin and stimulates the proliferation of hematopoietic cells in vitro. Further in-vivo study found increase in γ globin gene expression and induces erythropoiesis which can be pivotal in treatment of the β-hemoglobinopathies and oral treatment of other anemias. VPA also shown to induce fetal hemoglobin synthesis by modulating MAP kinase pathway [87]. The possible mechanism by which VPA stimulates erythropoiesis is to stimulate IL-3 and γ globin gene expression.

Valproic acid in Asthma and Airway disorders: Asthma and airway disorders are more common and debilitating inflammatory illness in developing countries owe to its industrialization which emits harmful gases and destroys airway linings. Apart from this, they are more common in persons who smoke regularly and worldwide problem. Airway remodeling (AR), inflammation and hyperresponsiveness (AHR) as described by thickened and hypersecretory airway walls [88]. AR and AHR suppression are mediated by T$_{reg}$ cells and Th2 as evidenced by animal model [89]. Study has shown that VPA treatment regulated the gene expression of T$_{regs}$ and increased the number of T$_{reg}$ in collagen induced arthritis model in rats and thus indicating a potential role in allergic airway diseases (AAD) [90, 91]. Royce et al. [88] found that in chronic treatment of VPA in mice model of AAD, there was reduced epithelial thickness and fibrosis in airway by reduced TGF-β protein expression and showed complete anti-remodelling effect by VPA. He also shown anti-apoptotic effect in airway epithelial cells as it is a significant marker in asthma for epithelial damage. Another team of researchers take on activity of VPA in hyperoxic lung injury model in neonatal rats where VPA exhibited anti-apoptotic, anti-fibrotic and anti-inflammatory action. VPA also showed anti-oxidant activity and preserved structural damage to lungs. VPA also reduced TNF-α and IL-6 levels and showed anti-inflammatory activity as reported previously [92] and tissue remodeling was due to reduction in TGFβ/Smad activity and apoptosis apart from reduction in HDAC activity which was prominent in lung injury [93, 94].

Further, it was noted that HDAC inhibitors produce its anti-inflammatory action by decreased leukocyte infiltration and reduction in Th2, IL-4 and IL-5 which are elevated in airway hyperresponsiveness (AHR), allergic airway diseases (AAD) and airway inflammation [88, 95, 96]. Clinical trial in human also proved VPA as effective anti-asthmatic agent where he showed complete remission in asthma with improvement in peak-flow rates [88, 97]. VPA inhibits inflammatory cytokines and oxidative stress along with Th2 which exerts positive effects in airway disordes.

VPA in Shock: Trauma and burn, which leads to hemorrhagic shock is most common cause of death after injury which can be prevented if resuscitation is provided immediately. It may lead to tissue hypoxia, hypercapnia and decreased tissue perfusion [98]. Although, resuscitation can help as damage control, it may lead to hemodilution, coagulopaty and edema and sometimes acidosis and hypothermia [99-101]. Hemorrhagic shock distorts acetylation process in cell and increase histone deacetylation [102]. One of the study conducted by Hwabejire et al. [99] showed that VPA at dose of 250 mg/kg resulted in increased histone acetylation and activated prosurvival protein signalling like PI3K, phosphorylated Akt and phosphorylated GSK-3β. In another study, VPA showed protective effects and survival in in-vivo animal model of hemorrhagic shock. This effect was mediated by activation of PPARγ and inhibition of apoptotic signaling [103]. It has also been noted that VPA alone can also mitigate organ specific damage in septic shock, hemorrhagic shock and traumatic brain injury. These protective mechanism is reported to acquire by creating and modulating prosurvival gene expression and anti-inflammatory phenotype by inhibiting histone deacetylation [104-106]. Patrick et al. [107] stated in his report that VPA produced its protective effect in traumatic injury and hemorrhagic shock by increasing the expression of genes associated with cell survival, proliferation, and differentiation and decreasing those associated with cell death and inflammation such as CCR1, IL-1β, TREM2 and TYROBP. If we dwell into detailed molecular mechanism of survival, it has been found that VPA acetylates H3K9 and β-catenin and enhances translocation of β-catenin into the nucleus, where it co-localizes with Ac-H3K9 and stimulates the transcription of survival gene bcl-2 [108]. VPA showed increased survival in burn injury induced shock too. In animal model of burn injury using beagle dogs, VPA treated groups showed 60% survival rate and these may be possibly mediated by lowering of the level of pro-inflammatory factors, amelioration of vasopermeability-induced visceral edema, reduction of blood volume loss, and protection of vital organs through inhibition of histone deacetylase activity of cell of vital organs [109]. Similarly, in rat model of lipopolysaccharide induced septic shock, VPA rescued multiple organ damage by diminishing inflammatory cytokines and restoration of acetylation status in affected tissue [110].

VPA in Hematological Cancer: Multiple myeloma and acute myeloid leukemia is defined as hematological malignancies where there is an unregulated proliferation of termi-

nally differentiated plasma cells which is very difficult to cure [111, 112]. Study conducted on myeloma cell lines and sorted human bone marrow multiple myeloma cells showed that VPA inhibited proliferation and acted as apoptosis inducer in all multiple myeloma cell lines [56, 113]. These effects were attributed to increased levels of acetylated histones and p21 whereas reduction in cyclinD1 has notable effects. VPA arrested G0/1 phase in cell cycle [114]. In support of above study results, another experiment was conducted in which different human myeloma cell lines were used and they found that VPA promoted myeloma cell death by G1 phase arrest and also by apoptosis which is caspase dependent via MEK/ERK and p38 MAPK pathway [112]. If we can further dive into animal study, Neri et al. [115] used multiple myeloma (MM) cells and MM xenografts in two animal models respectively and studied the effects of VPA on them. He found that VPA up-regulated mRNA transcripts of RND3, BTG1 and CREG1and p21 which is known to be apoptotic and anti-proliferative. He also demonstrated that there was down-regulation of cell cycle progression via inhibition of c-MYC, CCND1 and CCND2, which are cell cycle regulators. There was also a reduction in VEGF and VEGF receptor-1 expression and he concluded that VPA mediated cell cycle arrest and cell growth and apoptosis of MM cells by PARP activation which is known to cause cell death [115]. Of note, In chronic lymphocytic leukemia (CLL) cell lines, VPA showed apoptotic cell death via up-regulation of cathepsin-B and increased level of histone-3 acetylation [116]. Another mechanism involved in apoptosis by VPA is mitochondrial membrane damage by cytochrome –c release and cause apoptosis of leukemic cells by over-expression of BCL-2 and BAX proteins [117-119]. There is another mechanism like blocking of angiogenesis where VPA acts. Several studies found that VPA inhibits angiogenesis and arrest tumor growth [50, 120]. As we know that CLL cell are resistant to death receptor mediated apoptosis, VPA showed its potential to kill leukemic cell via caspase-8 dependent apoptotic pathway. VPA treatment sensitized the tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) and it led to reduced expression and down-regulation of c-FLIP [121]. A clinical study was conducted in patients with acute myeloid leukemia (AML) with combination of Azacytidine and VPA. Treatment showed significant clinical improvement with less side effects [122]. Another phase II clinical study targeted 62 patients with high risk Myelodysplastic syndrome (MDS), treated with a combination of azacytidine and VPA showed that VPA increased 5-azacytidine efficiency, and the study concluded that 5-AZA/VPA combined treatment is effective for patients with MDS with a poor prognosis [123]. From all above inferences, we can potentially justify use of VPA in myeloid and leukemic malignancy via its mechanism of anti-apoptotic and cell cycle arrest by modulating various mediators.

VPA in Solid Tumors: Histone deacetylase inhibitors mainly acts through stimulation of silenced tumor suppressor gene. VPA acts on p21WAF1/CDKN1A, a CDK (cyclin dependent kinase) generally associated with cell cycle arrest in G1/S phase and modulates their expression. Further, VPA induces apoptosis, via the extrinsic pathway involving engagement of the caspase-8-dependent cascade, and makes cells more receptive to TRAIL/Apo2L-mediated apoptosis [124].

There are several reports of VPA treatment in solid tumors. VPA inhibited the cell growth in medullary thyroid cancer cells by modifying expression of Notch 1 *in-vitro* [125]. VPA (30 mg/kg/day) has been recently clinically investigated in breast cancer and demonstrated that valproic acid is clinically relevant regarding its HDAC inhibition activity in solid tumor malignancy [126, 127]. A phase II clinical study with VPA (60-90 mg/kg/day) evaluated in prostate cancer and regularly monitored PSA levels. Study found that increasing dose of VPA reduced PSA level and patient s have disease stabilization or remission although some toxicities are reported [128]. In a pancreatobiliary cancer, VPA in combination with 5-Fluorouracil showed antitumor activity at a dose of 30 mg/kg/day with manageable safety profile [129]. In a clinical study with glioblastoma, VPA (15-30 mg/kg/day) showed improved outcomes and increased median survival in patients with low toxicity [130]. Similarly, VPA has been studied in combination with cytotoxic chemotherapy, particularly with DNA-damaging agents: in combination with the epirubicin, responses were seen in 22% of patients [131]. Further, in patients with breast cancer, VPA (120 mg/kg/day) along with epirubicin, cyclophosphamide produced objective responses in 64% of patients with acceptable toxicities [127].

VPA also showed synergistic effects with Doxorubicin in patients with mesothelioma and showed good response rate of 16% [132]. Further, In a small randomized study of 36 patients with advanced cervical cancer, the addition of epigenetic therapy with hydralazine and VPA (30 mg/kg/day) to cisplatin and topotecan led to a statistically significant improvement in the progression-free survival of 10 versus 6 months [133] and further in another study, VPA induced H3 acetylation showed to prevent the emergence of resistance to mammalian target of rapamycin inhibitors in renal cell cancer [134]. In a clinical study with metastatic melanoma, VPA (75 mg/kg/day) with Karenitecin showed disease stabilization in 47% of patients.

So, based on all above context, it can be concluded that VPA has shown some potential in treating solid tumors with varied dose and standard dose still has to be established based on types of tumors that can lead to future use of VPA in these conditions for better treatment outcomes. The major challenge in using VPA in solid tumors is its high dose requirement which may not be suitable for all patients as high dose sometimes shows hematological and gastric adverse events which may force to discontinue its use although positive effects.

CONCLUSION

Valproic acid has numerous, remarkable properties, those can be used to treat variety of disorders. Several clinical trials and studies are going on to check the efficacy and safety
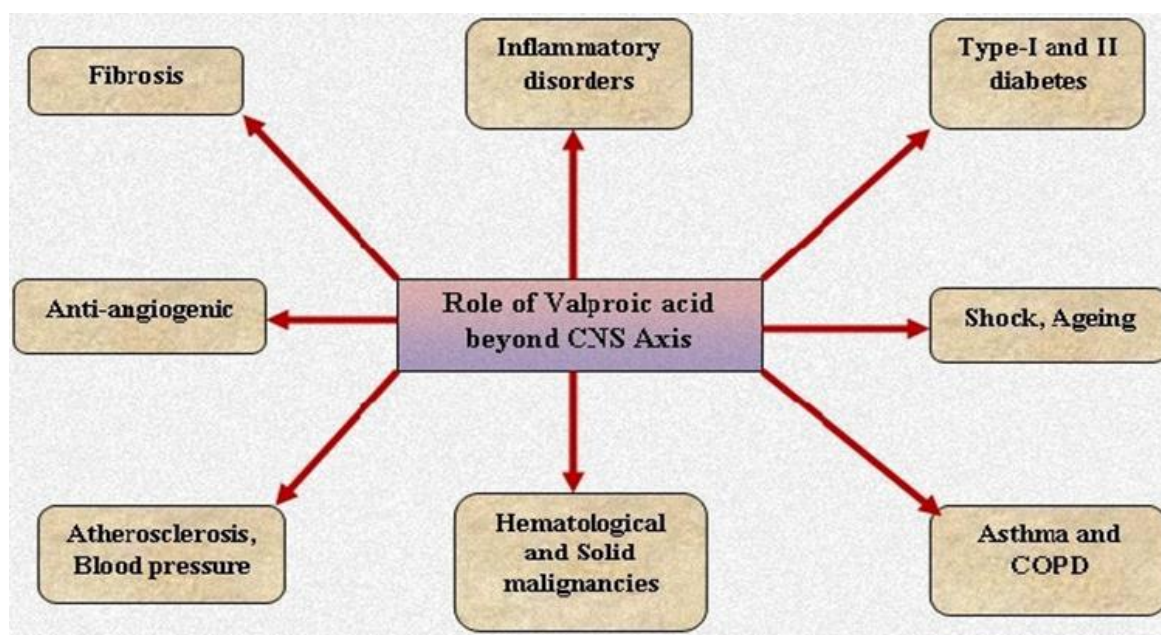
Figure 1. A summary of Valproic acid actions

at higher dose of this molecule. Its role in metabolic and inflammatory diseases has been fully reviewed and tested and justifies its role in adjuvant treatment along with current therapy. Its role in hematological malignancies has been wonderful and may become thirst molecule in coming years by looking at its risk-reward ratio in such cases (Fig. 1).

Future perspectives

Although an outline of various mechanisms of Valproic acid are well-established in various diseases and disorders, several additional aspects regarding its role in metabolic disorders, cancer and cardiovascular diseases are still to be explored. As these diseases are widely prevalent across the globe and involvement of various genetic economy in these diseases, its exact role at genetic structure and molecular pathways should be established which helps in assessing risk-benefit ratio and personalized medicine as high dose of VPA cause some gastric and hematological toxicities. Regulatory authority approval can also be a challenge without exactly known mechanism and lack of human studies. Physicians should look into its effects on metabolic disorders and respiratory disorders based on available human clinical reports and accordingly can look out to prescribe in patients with epilepsy so that patients can be benefited without much drug loading. Further, large population-based clinical studies are strictly warranted to access effects of Valproic acid as mentioned in article which can easily justify its use and efficacy with simultaneously monitoring adverse events.

CONFLICTS OF INTEREST

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article

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