

A Comprehensive Insight Into the Role of Valproic Acid in Neurodegenerative Disorders: An Updated Review

Hesameddin Razilou¹, Seyyed Sina Hejazian¹, Shahed Meshkini^{1*}

¹Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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*Corresponding Author:

Shahed Meshkini,

Email: shahed.meshkini@gmail.com

Abstract

Degenerative nerve diseases are caused by the progressive loss of the structure and function of neurons. Numerous signaling pathways have been suggested to be involved in neurodegenerative disease. Valproic acid is a branched-chain fatty acid used to treat bipolar disorder and epilepsy. Valproic acid modulates immunity by the activation of monocyte-derived macrophages. The present review study focused on the role of Valproic acid in neurodegenerative diseases such as MS and stroke.

Keywords: Sodium valproate, Neurodegenerative diseases

Introduction

Sodium Valproate

Sodium valproate (VPA, 2-Propylpentanoic acid) is a first-line broad-spectrum anticonvulsant drug with mood-stabilizing properties, which is widely used in the treatment of convulsion and bipolar diseases. VPA is a short-chain (pentameric) 8-carbon fatty acid that was first obtained from *Valeriana officinalis* and is used worldwide.¹ Multiple mechanisms of action have been proposed for VPA, including sodium channel blockade, decreased γ -aminobutyric acid transaminase (GABA-T) activity, increased extracellular GABA neurotransmitter content, decreased succinate semialdehyde dehydrogenase (SSADH), and effect on the T-type calcium channel.^{2,3} Common side effects of VPA in therapeutic doses include nausea, vomiting, gastrointestinal upset, and heartburn. In addition, tremor may be seen at higher doses of the drug. Its rare but deadly complication is hepatotoxicity that occurs idiosyncratically and manifests itself with increased liver enzymes. It also alters the metabolism of several drugs, which limits its use.^{4,5}

Neurodegenerative Diseases

Neurodegenerative diseases are age-related diseases that directly affect the central nervous system and include a wide range of diseases, the most common of which include Alzheimer's disease, Parkinson's disease, Huntington's disease, and multiple sclerosis (MS). Numerous mechanisms have been suggested for the pathogenesis of these diseases and include the involvement of both neuronal and non-neuronal cells of the brain, such as the glial cells. They cause various clinical symptoms, including movement, speech, memory, and cognitive impairment.^{6,7} Given that the prevalence of these diseases

is rapidly increasing due to the increase in the average age of the population and the growth in the number of cases in developed countries, the need for proper treatment has increased considerably. However, in most of the cases, there is no definitive and appropriate treatment. Therefore, the use of alternative drugs to treat these patients has become more important than ever. Among the drugs that have recently been suggested to be effective in neurodegenerative diseases is VPA.⁸⁻¹¹

Valproic Acid and Neuroprotection

The production of new drugs requires lots of money and time. The proposed solution to this problem is to use the unknown properties of existing drugs. VPA is one of the well-known drugs for treating central nervous system diseases. New therapeutic effects in favor of its potential in treating neurodegenerative diseases have been discovered. These effects include neuroprotective effects on dopaminergic neurons by several mechanisms, including increased expression of glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) by inhibiting histone deacetylase (HDAC) activity and anti-inflammatory effects in neurons by attenuating release of pro-inflammatory factors from microglia.¹²⁻¹⁴ It also affects enzymatic pathways of extracellular-signal-regulated kinases (ERK), phosphatidylinositol 3 kinase/akt-1, and glycogen synthase kinase 3B (GSK-3B).¹⁵ In addition, it has neuroprotective effects against glutamate excitotoxicity, which is mediated by increased alpha-synuclein expression following inhibition of HDAC and increased Bcl-2 expression.¹⁶ A study showed that VPA has anti-inflammatory and neuroprotective effects in mice with ischemic stroke.¹⁷ VPA has also been shown to prevent the death of hippocampal cells following ischemic



inflammation.¹⁸ Another mechanism suggested for the neuroprotective properties of this drug is the inhibition of TNF- α release and NO production from microglia cells.¹⁹ This drug is even effective in inhibiting the activity of T cells, which are involved in nerve damage.²⁰ Besides, several other mechanisms and multiple regulatory pathways are involved in the neuroprotective properties of this drug.^{21,22} In the following, we will review the studies that have investigated the role of this drug in neurodegenerative diseases.

Valproic Acid and Alzheimer's Disease

Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia in the elderly, leading to progressive loss of memory, as well as cognitive and behavioral impairments. AD is an irreversible neurodegenerative disease and several mechanisms are involved in its pathogenesis, the most prominent of which are extracellular accumulation of senile plaques (SP), mainly composed of amyloid beta ($A\beta$), and intracellular neurofibrillary tangle (NFT), mainly composed of hyperphosphorylated Tau protein.²³ $A\beta$ is the result of proteolytic cleavage of amyloid precursor protein (APP) and hyperphosphorylation of tau protein is the result of dysfunction of several kinases, including GSK-3B, which is associated with impaired axonal transport.²⁴ In addition, studies have shown cholinergic system impairments in mice models of AD.²⁵ It is estimated that 51.6 million people worldwide suffer from AD, although gender differences in the prevalence and course of the disease have been reported.²⁶ Other common symptoms in AD patients include behavioral and psychological symptoms of dementia (BPSD), which are accompanied by agitation, violence, inappropriate sexual behavior, delusion, and misidentification.²⁷ The most common treatment for BPSD is antipsychotic drugs, especially atypical antipsychotic drugs; however, there are concerns about their side effects.²⁸

Use of Valproic Acid in Alzheimer's Disease

It has been shown that HDAC inhibitors, including VPA, improve spatial learning and memory and cognitive impairments in AD patients; however, VPA does not improve memory in wild-type (WT) mice.²⁹ Numerous animal and human studies have evaluated the efficacy of VPA in the treatment of AD. The study conducted by Yao et al investigated the efficacy of VPA in male and female APP^{swE}/PS1^{dE9} mice as mice models of AD.³⁰ The use of VPA in these mice (100 mg/kg/d for 3 months intraperitoneally) improved long-term recognition memory, spatial learning, and memory. HDAC activity in the hippocampus of these mice was increased by 96% compared to the WT and vehicle mice, which is in accordance with increased acetylation of H3 lysine 9 and H4 lysine 8 by 28% and 32%, respectively.³¹ Considering the role of HDAC2 in increasing the number of neurons and synapses, HDAC2 level was further investigated in this

study. No significant differences in HDAC2 expression were observed between study groups; however, the activity level of this enzyme was elevated among VPA-treated mice.^{30,32} The other mechanism of action introduced in this study for VPA was the increase in the expressions of synaptic plasticity-associated proteins including CRB, CAMKII, and CAM in the hippocampus, which are involved in improving spatial learning and memory.³⁰ In another study that used higher doses of VPA for a shorter period of time (200 mg/kg/d for 2-3 weeks), similar effects were observed in the long-term memory of mice with hypoxia-induced memory deficit.³³ Even low doses of VPA for 4 weeks (30 mg/kg/d) have been reported to be effective in improving spatial learning and memory impairment in mouse models of AD.^{34,35}

Studies have shown the neuroprotective role of VPA in AD. Xuan et al reported that the number of NeuN⁺ cells in the hippocampus and ChAT-immunoreactive neurons in the vertical diagonal band of Broca (VDB) and medial septum in APP/PS1 mice increased after treatment with VPA.^{36,37} It was also shown that the activity of microglia and astrocytes, which are normally seen around $A\beta$ plaques, decreases in these mice, resulting in reduced levels of IL-1 β and TNF α in the hippocampus and cortex.³⁸ In addition, the study by Xuan et al showed reduced levels of cytokines and cytotoxic molecules in VPA-treated mice.³⁹

Both $A\beta$ deposition and soluble form of $A\beta$ are associated with cognitive impairments in AD.⁴⁰ VPA has been shown to be effective in the reduction of both forms of $A\beta$ in transgenic mice. Interestingly, it has been shown that $A\beta$ plaques stimulate the production of inflammatory cytokines by microglia, and these cytokines accelerate the formation of $A\beta$ plaques in AD.^{41,42} Therefore, it can be concluded that VPA prevents further damage to the brain in AD through both mechanisms of reducing the production of cytokines and the formation of $A\beta$ plaques. VPA increases the expression and activity of BCL-2 as a protein involved in neuroprotection, resulting in anti-apoptotic effects of this drug in mouse models of AD.⁴² It has been also reported that VPA inhibits the GSK-3B activity through phosphorylation at serine-9 (producing phospho-GSK-3B-ser9), which is associated with reduced levels of $A\beta$.⁴³ Phosphorylation of NF κ B-p65 around the $A\beta$ plaques causes inflammation. VPA can reverse this process, resulting in neuroprotective effects.^{44,45}

As mentioned before, gender differences are seen in AD. These differences are seen in VPA-treated mice as well. The study by Long et al showed that the improvement of most signs of AD by VPA treatment was greater in male mice than in female mice.⁴⁶ In addition, $A\beta$ plaque, $A\beta$ 40 and $A\beta$ 42 reduction, and improvement in synaptic activity and structure was greater in male mice than in female mice. Moreover, the $A\beta$ cleavage by an increase in neprilysin was greater in male mice. No significant differences were seen in presynaptic vesicle density between the two genders.⁴⁷ It has been shown that melatonin has a great role in $A\beta$ reduction and

Tau protein hyperphosphorylation, which may improve synaptic plasticity and cognitive performance in aged mice.⁴⁸ Circulating melatonin levels and expression of its receptor, M2, in the hippocampus of AD patients are reduced even in preclinical stages.⁴⁹ Hong et al reported that M2 levels in CA1, CA2, CA3, and DG regions of hippocampus in Sprague-Dawley rats increased after 17 days of treatment with VPA. Besides, the efficacy of VPA in different stages of AD was assessed which showed a greater reduction in neurite plaque formation in the early stages of the disease. In addition, they reported that the impact of VPA lasted for about two months after discontinuation.³⁴

In a clinical study, the efficacy of donepezil + VPA in AD patients with BPSD was compared to donepezil + quetiapine, indicating no differences. Both therapies had satisfactory results; however, the first combination therapy was more cost-effective than the other. The same study showed that VEGF increased after VPA treatment, especially in patients with excellent prognosis.⁵⁰ Herrmann et al evaluated the efficacy of VPA in elderly patients with different stages of AD who suffered from aggression and agitation. The patients were treated with an average dose of 1135 mg/d for about 6 weeks. VPA therapy did not alleviate the symptoms, but rather it intensified them.⁵¹ Many studies have used divalproex, a drug similar to VPA, in the treatment of aggressive behaviors in AD patients, which showed no favorable results.⁵²

Valproic Acid and Parkinson's Disease

Parkinson's Disease

Parkinson's disease (PD) is the second most common neurodegenerative disease and the most common movement disorder associated with tremor, stiffness, bradykinesia, and postural instability. Non-motor symptoms in this disease include autonomic disorders, cognitive impairment, and sleep disorders. The main pathological change in this disease is the destruction of dopaminergic cells in the nigrostriatal pathway. The diagnostic hallmark of these cells is the presence of intracytoplasmic inclusions called Lewy bodies (LB) containing α -synuclein (α Syn) and Lewy neurites.^{53,54} The exact mechanism of this disease is not known; however, epigenetic disorders such as DNA methylation or Histon remodeling have been found to be effective in the pathogenesis of PD.⁵⁵ Mutant α Syn in PD patients can promote the translocation of methyltransferase 1 into the cytoplasm, causing hypomethylation of the promoter region of the α Syn gene (SNCA). In addition, the α Syn has been shown to mask histone proteins and thus prevent their acetylation, leading to hypoacetylation, which can ultimately induce apoptosis.^{56,57} There is no definitive cure for this disease; however, treatments may alleviate symptoms and prevent its progression. However, levodopa and dopaminergic drugs have been approved.⁵⁸ PD is a progressive disease and patients' need

for dopamine increases over time which exposes patients to side effects such as on-off fluctuations, dyskinesias, dystonia, psychosis, and/or behavioral syndromes such as impulse control disorders (ICDs). ICDs include unrestrained gambling, hypersexuality, compulsive shopping, compulsive eating, hobbyism, punning, and compulsive medication use.^{59,60}

Use of Valproic Acid in Parkinson's Disease

Many animal studies have evaluated the efficacy of VPA in the treatment of mice models of PD. It has been shown that pretreatment with VPA in PD-induced mice using Rotenone and 6-hydroxydopamine shows neuroprotective effects on striatal dopaminergic neuronal terminals and dopaminergic cell bodies in substantia nigra pars compacta (SNpc). However, PD induction using Rotenone and 6-hydroxydopamine is not based on protein deposition, which is the main pathological mechanism in patients with PD.^{61,62} In another study, the same neuroprotective properties of VPA were shown in PD-induced mice by the mitochondrial toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).⁶³ It is important to note that in mouse models of PD, by the time of symptoms emergence, 60%-70% of SNpc neurons are destroyed and striatal dopamine levels are reduced by up to 80%. Therefore, the use of VPA before the induction of PD in mice may not mimic the exact clinical condition of PD patients; therefore, the results may not be reliable.⁶⁴ In another study by Harrison et al, the neuroprotective properties of VPA were investigated in mice after induction of PD using the neurotoxin Lactacystin (a proteasome inhibitor). This study not only demonstrated that VPA protects neurons against neurodegeneration but also showed that VPA reverses the degeneration of dopaminergic nigrostriatal neurons in these mice. These effects were not limited to nigrostriatal cells and were observed in other brain regions as well. MRI was also used to evaluate neurological change, which showed a decrease in midbrain volume and an increase in ventricular volume following induction of PD, both of which were attenuated in VPA-treated mice. In this study, the levels of BCL2 as an anti-apoptotic factor and BAD as a pre-apoptotic factor were examined, the first of which increased after treatment with VPA and the second decreased.⁶⁵

Studies have shown an increase in neurotrophic factors, BDNF and GDNF, and acetylation of histones in mouse models of PD following VPA use. VPA has also been shown to be effective in alleviating movement disorders in these mice.^{66,67} In a study by Carriere et al, unilateral intrastriatal rotenone injection not only caused movement disorders contralateral to the injection side but also led to an increase in ipsilateral forelimb use, both of which were reversed by VPA.⁶⁸ VPA has also been shown to be effective in the alleviation of non-motor symptoms such as cognitive and emotional deficits in mouse models of PD.⁶⁹ In one of these studies, Castro et al reported significantly increased levels of striatal dopamine following VPA use

in mouse models of PD.⁷⁰ Immunohistochemical studies have shown partial and complete maintenance of tyrosine hydroxylase immunoreactivity in striatum and substantia nigra of PD-induced mice, respectively.⁷¹

The prevalence of pathological gambling, which is defined as excessive uncontrolled gambling despite financial losses and social problems, varies from 3.4% to 6.1% among PD patients.⁶⁹ A case report study by Degirmenci and Kececi reported successful treatment of pathological gambling in a 52-year-old man who had PD for 3 years. The patient in this study had symptoms of inappropriate behaviors such as compulsive shopping, unreasonable selling, and pathological gambling, which had gradually worsened. The patient also suffered terrifying visual hallucinations at night and was treated with levodopa and several other drugs. Assuming the symptoms were side effects of the drugs, their dose was reduced, resulting in alleviation of the sign; however, the pathological gambling remained uncontrolled and treatment with VPA was started for the patient (500 mg/d). In the second week of treatment, the patient's symptoms began to decrease and after 1 month of treatment, they completely disappeared. No side effects after treatment with VPA were seen.⁷²

Dopamine dysregulation syndrome (DDS), also called hedonistic homeostatic dysregulation syndrome, is defined as excessive consumption of dopaminergic drugs by PD patients, which is seen in 1%-2% of these patients.^{73,74} In a study by Sriram et al, 4 cases of DDS were treated with VPA which alleviated their excessive desire for dopaminergic use after a short period of therapy.⁷⁵ In addition, in a case series study by Hicks et al, VPA was used to treat ICD symptoms in three patients with PD, which showed satisfactory results. These patients suffered from hypersexuality, episodes of extreme excitement, and compulsive behaviors and showed signs of DDS. Treatment with VPA reduced inappropriate behaviors of all patients; therefore, the dose of needed levodopa was reduced. In two patients, VPA was discontinued after a period of time, leading to the return of ICD symptoms.^{76,77}

VPA has been evaluated in the treatment of PD patients and the results showed that the number of on-off fluctuations increased in patients.⁷⁸ In another study, Ximenes et al showed that the levels of OX-42 and GFAP (reactive factors of microglia and astrocytes) increased following induction of PD in mice with 6-OHDA, respectively, which were both reversed by the administration of VPA. TNF- α and HDAC levels also decreased following VPA treatment. All of these changes were seen in the CA1 and CA3 regions of the hippocampus and the cortex.⁷⁹

In addition to all these studies, it should be noted that VPA is known as a drug with the potential to induce PD.⁸⁰ In a case report of a 67-year-old male patient with PD, the patient's symptoms worsened following VPA use. In this

study, following the aggravation of the patient's cognitive and psychological symptoms, rivastigmine (3 mg/d) and VPA (500 mg twice a day) were started, which led to severe exacerbation of movement disorders in the patient to the point he was unable to walk without assistance. Cessation of the drug significantly alleviated the movement disorder of the patient after a week. Symptoms completely disappeared after two months. However, the patient's cognitive and psychological disorders returned rapidly.⁸¹

Valproic Acid and Multiple Sclerosis

Multiple Sclerosis

MS is the most frequent chronic inflammatory, demyelinating, and neurodegenerative disease of the central nervous system, which is the most common cause of non-traumatic neurological disability in young people. Multiple mechanisms are involved in the pathogenesis of this disease, including oxidative stress, excitotoxicity, autoimmunity, and hormonal disorders. The main cells involved in the pathogenesis of the disease are TH1 and TH17 cells.^{82,83} The disease typically occurs between the ages of 25 and 45 and presents with a variety of symptoms, all of which are somehow related to the central nervous system.⁸⁴ Numerous attempts have been made to find an effective treatment for the disease; however, no definitive cure has been found to date, and only ocrelizumab and Siponimod among the 17 FDA-approved drugs are relatively effective in reducing the debilitating symptoms of the disease.⁸⁵⁻⁸⁷ In addition, the current treatments are most effective in the relapsing-remitting form and not the progressive form of the disease. Therefore, there is an urgent need for new therapeutic ways for this disease.⁸⁸

Use of Valproic Acid in MS

Numerous studies have attempted to find new therapeutic strategies for the treatment of MS.⁸⁹⁻⁹¹ VPA is among the drugs that have been reported to be useful in the treatment of this disease, which is not unexpected due to its neuroprotective effects.^{92,93} The studies have shown the efficacy of VPA in the treatment of MS by alleviating the symptoms of patients.^{94,95} The most recent two studies on the use of VPA in the treatment of MS patients were performed in 2015, the results of which are inconsistent with each other. In one of these studies, which was a case report study, the effectiveness of VPA in the treatment of pseudobulbar affect in MS patients was evaluated.⁹³ Pseudobulbar affect is a disabling feature of unknown pathophysiology found in many people with central nervous system diseases and manifests itself with sudden episodes of laughter and crying.⁹⁴ The patient treated in this study suffered from incessant crying that was completely alleviated after three consecutive days of treatment with VPA. However, following a change in the patient's medication regimen to an FDA-approved drug, Nuedexta (dextromethorphan plus quinidine) at

discharge, the patient's symptoms returned completely after 6 days, forcing physicians to repeat the course of VPA treatment. Similar to the first course, the patient's symptoms disappeared quickly. The results of this study were in contrast to another study conducted in the same year by Nielsen et al.⁹⁵ In this large retrospective cohort, the risk of developing MS in people of different races using VPA was evaluated for the first time. They found that VPA did not prevent MS from occurring, but rather it increased the risk of developing MS in patients with a previous history of VPA use. The risk was higher in the first year after stopping the drug, and it was no longer observed after five years. This probably occurred in the context of the reversal of the neuroprotective effects of the VPA following its cessation. Therefore, unlike the previous three studies, the finding of this study was not in favor of the therapeutic effects of VPA in MS patients.⁹⁵

In addition to human studies, several animal studies have examined the impact of VPA on MS.⁹⁰ Optic neuritis is the inflammation of the optic nerve that occurs in many patients with MS, and it may be the first manifestation of their disease, which occurs in 20% of cases.⁸⁹ It has been shown that the use of VPA reduces inflammation in the spinal cord and optic nerve and therefore is effective in reducing demyelination and degeneration in MS patients. The ASK1 pathway has been shown to regulate the production of chemokines in astrocytes and the progression of demyelination through the production of pro-inflammatory factors.⁸⁰ In a study, in addition to VPA, ASK1 pathway inhibitors were used to treat EAE mice, which showed synergistic effects with VPA. The mechanism proposed in this study for the neuroprotective effects of VPA in MS was to reduce the infiltration of T cells into the optic nerve and spinal cord and to suppress the activity of glial cells, the latter of which may itself be due to T-cell suppression.

VPA suppresses degeneration and demyelination in the optic nerve in MS models. Additionally, it has been reported to be effective in inducing remyelination and thus improving the neural function of these mice. In two separate studies were shown that the number of myelinated neurons increased in mouse models of MS following VPA treatment.^{91,92} In the same studies, VPA was also shown to be effective in increasing neural stem cells and oligodendrocyte precursors in the brain, which in turn can be useful in reversing neurological damage in MS patients.^{85,86} For the first time, Rossi et al used a combination of two drugs, VPA and α -linolenic acid, in mice models of MS, the results of which were satisfactory.⁸⁷ In addition to the efficacy of VPA in preventing or reversing pathological changes, numerous studies have demonstrated improvements in the performance of MS mouse models. In a study performed on Dark Agouti (DA) mice with EAE, a combination of VPA and T4 was used for three consecutive days in these mice, which significantly

reduced the symptoms and pathology of the rat brain. This study showed that VPA has immunomodulatory properties and reduces the production of oligodendrocyte progenitors. This study is of great importance because it showed that VPA can be therapeutically effective at low doses.⁹⁰

Valproic Acid and Huntington's Disease

Huntington's Disease

Huntington's disease (HD) is an autosomal dominant genetic disorder that occurs due to the replication of the three-nucleotide (cytosine-adenine-guanine) sequence in the Huntington (HTT, OMIM 613004) gene located on chromosome 4, causing corticospinal involvement as cerebral cortex atrophy.⁸⁹ The importance of the disease is primarily due to its progressive and consequently fatal nature within 15 to 20 years from the onset; otherwise, the prevalence of the disease is low and reaches its maximum at 16 cases per million population.⁹² The symptoms of the disease are more common in middle-aged people and include chorea, dystonia, cognitive disorders, and psychological changes, the last two of which usually occur before movement disorders.⁹⁵ Common treatments for this condition include using neuroleptic antidopaminergic (such as haloperidol and olanzapine) or dopamine-lowering drugs (such as tetrabenazine), long-term use of which has always been accompanied by concerns due to their side effects such as extrapyramidal symptoms, difficulty swallowing, and bradykinesia.⁸⁸ Therefore, the use of alternative therapies has received more and more attention and many studies have evaluated the efficacy of different drugs in the treatment of these patients, among which VPA has shown promising effects due to its neuroprotective properties.⁹⁰

Use of Valproic Acid in Huntington's Disease

Among the pathogenic mechanisms of the HD disease, excitotoxicity, decreased medium-sized GABAergic neurons in the striatum, and increased histone deacetylation have been studied,⁹⁰ the three mechanisms shown to be modulated by VPA.⁸⁹ The first study to evaluate the effect of VPA in HD was conducted by Tan et al in 1976, in which the efficacy of VPA and L-Dopa in the treatment of a female patient with HD was compared. It was shown that despite the effectiveness of VPA in alleviating the disease, the effect of the drug decreased after a few weeks, whereas no such change in efficacy was observed in treatment with L-Dopa.⁶⁷ Other clinical studies evaluating the efficacy of VPA in the treatment of HD were performed, in one of which the efficacy of VPA in reducing myoclonus of HD patients was assessed.⁸⁸ Action myoclonus or myoclonic hyperkinesia is one of the rare but debilitating manifestations in HD patients that may be confused with chorea.⁹¹ Studies have shown the role of the GABA neurotransmitter in the development of

myoclonus in HD patients. In this regard, VPA may have beneficial effects on the myoclonus as an extracellular GABA enhancer.⁹² In this study, 8 HD patients with a previous history of myoclonic hyperkinesia were treated with different doses of VPA. Only one of the patients who was treated with a lower dose of VPA (300 mg/d) did not respond well to the treatment and higher doses of the drug were significantly effective on patient's symptoms. Even a patient with a previous history of VPA use (1050 mg/d) experienced reduced symptoms by increasing the dose of VPA to 1800 mg/d. All of this evidence suggests a dose-dependent effect of VPA on HD-induced myoclonus.⁹³ Clinical studies investigated the combined effect of VPA and olanzapine in HD patients.⁹⁴ Two 39- and 52-year-old patients with a history of HD who were treated with Haloperidol and recently had worsening symptoms were admitted to the hospital. They underwent a combination therapy of VPA and Olanzapine (5 mg/d and 1500 mg/d, respectively). They showed significant improvement in symptoms of movement disorders, psychosis, and aggression. However, recovery in these patients took 7-8 weeks. Due to the lack of response to Haloperidol as the standard treatment for HD and the satisfactory results of VPA + Olanzapine use in this study, further investigations of this combination therapy seem reasonable.⁸⁶ The most recent study on the use of VPA in the treatment of HD was the study conducted by Whiting et al in 2018. In this study, they evaluated the efficacy of VPA in the treatment of behavioral disorders in a 59-year-old female patient with an 8-year history of Huntington's disease. The patient suffered from relatively severe choreoathetosis and dysarthria and was hospitalized due to the intensification of aggressive behaviors since a month ago. After initial treatment and observing no improvement, the administration of VPA was started for the patient and a blood level of 95 µg/mL was achieved within 4 days. The patient responded quickly to treatment within a week of treatment, and his aggressive behaviors were significantly reduced. The patient was followed up for only one month when no recurrence of symptoms was observed. However, further studies are needed to evaluate the long-term effectiveness of the treatment.⁸⁷

In addition to numerous clinical studies, several animal studies have been performed to evaluate the effect of VPA in HD, all of which have shown good efficacy. Among them recent study was performed on N171-82Q mice as a mouse model of HD.⁸⁸ In a study, the efficacy of VPA in preventing HD in mice was evaluated and it was shown that the onset of the disease was delayed in mice treated with VPA; therefore, their survival was improved by 31.4% which was higher than the results obtained in another study that examined the efficacy of phenylbutyrate on survival of mice models of HD.⁸⁹ In addition to these effects, VPA reduced huntingtin

aggregate deposition as an underlying cause of brain damage in HD, thereby reducing spontaneous locomotor activity. It is noteworthy that the administration of VPA in this study was performed before the onset of the disease to evaluate its preventive properties in HD, which may explain the conflicting results of this study with some other clinical studies in which VPA did not show efficacy in HD patients.⁹⁰ In addition to this study, another investigation was conducted by Morland et al to assess the preventive effect of VPA in HD. In this study, which used malonate to induce HD, transgenic mice treated with VPA had a smaller brain lesion compared to other mice. In addition, it was shown that the rate of extracellular accumulation of glutamate in mice treated with VPA was lower compared to other mice.⁹¹ Due to the possible role of increased extracellular glutamate in the pathogenesis of HD disease, extracellular glutamate depletion was suggested as a neuroprotective mechanism of VPA, which may be due to increased glutamate transporter activity.⁹²

One of the new therapeutic strategies for treating HD is stem cell therapy. However, due to the differences in efficacy of this method in different patients, there are limitations in its use.¹³⁵ A method used to increase the effectiveness of this treatment is the preconditioning of stem cells before transplantation.⁹³ Therefore, Linares et al used VPA + Li for preconditioning of mesenchymal stem cells (MSCs) before transplanting to mice models of HD. This study showed that MSCs that were preconditioned with VPA + Li showed better migration and homing capacity and that more of these cells remained after transplantation and produced more neuroprotective factors (such as trophic and antiapoptotic factors), which generally improved motor function and survival in N171-82Q mice receiving this treatment. However, the use of this treatment did not improve the weight of the recipient mice, a failure that had been shown in previous studies using stem cells to treat HD mice.⁹⁴ Another study that examined the efficacy of this combination therapy in HD transgenic mice was the study conducted by Chiu et al. In this study, the direct effect of VPA + Li on the improvement of symptoms in mice models of HD was evaluated. Two types of mice were used in this study including N171-82Q and 2AC128. It was shown that the use of this treatment led to improvement in movement disorder and depressive-like symptoms and an increase in motor skill learning and movement coordination. Interestingly, despite the ineffectiveness of Li or VPA monotherapy in reducing anxiety-like symptoms, treatment with both drugs reduced these symptoms. Among the neuroprotective factors that increased in the brain of studied mice were heat shock protein 70 (Hsp70) and BDNF. Contrary to the increase in the survival of mice under the influence of VPA + Li, this increase was not statistically significant, and as in the study of Linares, no favorable effects were

seen on the weight of mice.⁹⁵

Discussion

Based on the content provided, it can be concluded that besides the conventional use of VPA as an anticonvulsant drug, it can be used for other purposes including the treatment of patients with neurodegenerative disorders. However, the efficacy of this drug in different forms of neurodegenerative diseases is not the same and even different manifestations of these diseases do not respond equally to VPA. In addition, as mentioned earlier, the

efficacy of VPA in neurodegenerative disease varies from study to study; therefore, definitive decisions about the use of this drug in patients with neurodegenerative disease need further investigations.

Conclusion

Besides, most of the studies in this field are only animal studies, the results of which cannot be directly generalized to the human population. However, according to many promising results in many studies, it seems that the use of this drug in the treatment of neurodegenerative patients

Table 1. Effects of Valproic Acid on Neurological Diseases

Disease	Characteristic of disease	Effect of valproic acid
AD	<ul style="list-style-type: none"> ✓ Aβ plaque formation ✓ Production of inflammatory cytokines ✓ Phosphorylation of NFκB-p65 around the Aβ plaques ✓ Decreased melatonin production ✓ Tau protein dephosphorylation ✓ M2 (melatonin receptor) reduction 	<ul style="list-style-type: none"> ✓ Increases anti-apoptotic factors including BCL-2 expression ✓ Reducing the production of inflammatory cytokines ✓ Prevents the formation of Aβ plaques ✓ Hyperphosphorylation of NFκB-p65 in the Aβ plaques ✓ Inhibits the GSK-3B activity through phosphorylation at serine-9 (producing phospho-GSK-3B-ser9) ✓ M2 (melatonin receptor) elevation
Parkinson's disease	<ul style="list-style-type: none"> ✓ Destruction of dopaminergic cells ✓ Mutant alpha-synuclein (αSyn) formation ✓ Methyltransferase 1 increased in the cytoplasm and affected the promoter region of the αSyn gene (SNCA) ✓ Increased neuronal apoptosis through preventing histone acetylation ✓ Maintenance of tyrosine hydroxylase immunoreactivity in striatum and substantia nigra 	<ul style="list-style-type: none"> ✓ Protects neurons against neurodegeneration ✓ Reverses the degeneration of dopaminergic nigrostriatal neurons ✓ Decreases midbrain volume and increases ventricular volume ✓ Increases BCL2 levels ✓ Decreases BAD levels ✓ Increases BDNF, GDNF, and acetylation of histones ✓ Increases the levels of striatal dopamine
MS	<ul style="list-style-type: none"> ✓ Dysregulation of oxidative stress pathways, hormones, and excitotoxicity ✓ Dysregulated Th1 and Th17 cells ✓ ASK1 pathway dysregulation ✓ Unbalanced immune system affects astrocytes and causes demyelination 	<ul style="list-style-type: none"> ✓ Prevents MS onset but increases the risk of developing MS in patients with a previous history of VPA use ✓ Reduces remyelination and oligodendrocyte precursors in the brain ✓ Reduces the infiltration of T cells into the optic nerve and spinal cord ✓ Suppresses the activity of glial cells, leading to T-cell suppression
Huntington's disease	<ul style="list-style-type: none"> ✓ Replication of cytosine-adenine-guanine sequence in the Huntington (HTT, OMIM 613004) gene ✓ GABA dysregulation ✓ Decreased medium-sized GABAergic neurons in the striatum ✓ Increased histone deacetylation ✓ Increased extracellular glutamate 	<ul style="list-style-type: none"> ✓ Enhances extracellular GABA ✓ Transgenic mice-treated VPA had a smaller brain lesion ✓ Lowering extracellular accumulation of glutamate ✓ Increases glutamate transporter activity ✓ Decreases histone deacetylation ✓ Increases survival rate in HD

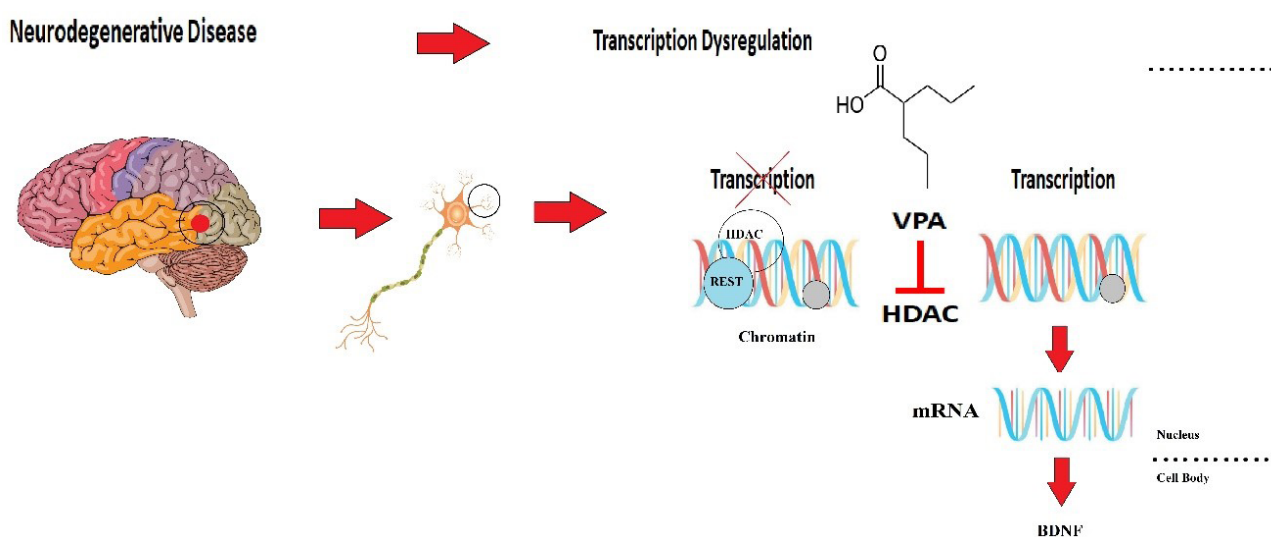


Figure 1. Role of VPA in the Pathogenesis of Neurodegenerative Diseases by Affecting HDAC and BDNF

may be beneficial. Figure 1 demonstrates the efficacy of VPA in neurodegenerative diseases. Table 1 summarizes the primary manifestation of neurodegenerative diseases and the effects of VPA on them.

Authors' Contribution

Conceptualization: Hesameddin Razilou, Seyyed Sina Hejazian.

Data curation: Hesameddin Razilou, Seyyed Sina Hejazian.

Formal analysis: Hesameddin Razilou, Seyyed Sina Hejazian.

Investigation: Shahed Meshkini.

Methodology: Shahed Meshkini.

Project administration: Hesameddin Razilou, Seyyed Sina Hejazian.

Resources: Hesameddin Razilou, Seyyed Sina Hejazian.

Software: Hesameddin Razilou, Seyyed Sina Hejazian.

Supervision: Shahed Meshkini.

Validation: Hesameddin Razilou, Seyyed Sina Hejazian.

Visualization: Hesameddin Razilou, Seyyed Sina Hejazian.

Writing—original draft: Hesameddin Razilou, Seyyed Sina Hejazian.

Writing—review & editing: Shahed Meshkini.

Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the current study.

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