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Histone deacetylase inhibitors for cardiovascular conditions and healthy longevity

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Histone deacetylase inhibitors (HDACi) regulate gene expression via epigenetic mechanisms. Accumulating evidence suggests that HDACi exert antiproliferative, antioxidant, antineoplastic, and proapoptotic effects through epigenetic mechanisms. Furthermore, HDACi also exert antithrombotic and antifibrotic effects through regulation of thrombotic and fibrotic transduction mechanisms. One of the oldest HDACi is valproic acid, which was first synthesised in 1882. After the discovery of its anticonvulsant properties for the treatment of epilepsy, the use of valproic acid was extended to other conditions, such as bipolar disorder and migraine. Given the accumulating evidence supporting the role of HDACi in the treatment of multiple medical conditions beyond epilepsy, the interest in novel potential indications for HDACi has been renewed. Considering the pleotropic epigenetic effects of HDACi, future studies could assess their efficacy and safety for cardiovascular disease prevention and treatment; treatment of venous thrombosis, Alzheimer's disease, autoimmune and proinflammatory conditions, chronic thromboembolic pulmonary hypertension, and pulmonary arterial hypertension; and as a coadjuvant therapy for cancer. Adequately designed and powered clinical trials are required to assess the efficacy and safety of HDACi before their clinical repurposing.

Introduction

Chromosomal DNA and histone proteins form the chromatin within cell nuclei. The basic unit of chromatin is the nucleosome, which encompasses about 150 DNA base pairs wrapped around a histone octamer.¹ Chemical modifications to nucleosomal DNA and histone tails can influence genetic transcription profoundly—a mode of gene regulation referred to as epigenetics.² Acetylation of histones can alter gene expression by modifying the electrostatic charge of chromatin,³ creating docking sites for acetyl-binding or methyl-binding proteins, which have the capacity to activate RNA polymerases, leading to transcription elongation and formation of cell state-specific enhancers, referred to as super-enhancers.⁴ Histone deacetylases are enzymes that remove acetyl groups from histone tails. In consequence, histone deacetylase inhibitors (HDACi) can block the removal of acetyl groups from histone tails, inducing histone hyperacetylation and regulating genetic transcription via hyperacetylation of histones.⁵

Accumulating evidence suggests that HDACi exert antiproliferative, antioxidant, antineoplastic, and proapoptotic effects through histone hyperacetylation—ie, epigenetic mechanisms.⁶ Other HDACi-mediated mechanisms, including antithrombotic and antifibrotic, have also been documented.⁷

The oldest and most widely studied HDACi is valproic acid, the synthesis of which was described in 1882 by Beverly S Burton.⁸ Valproic acid was initially thought to be pharmacologically inert and was used as a solvent; its anticonvulsant properties were fortuitously discovered in 1963.⁹ The first trial documenting the efficacy of valproic acid in the treatment of epilepsy was published in 1975.¹⁰ Subsequent trials reported the effectiveness of valproic acid in non-epilepsy indications, including bipolar disorder and migraine, and it was later discovered to be an inhibitor of class I histone

deacetylases (comprised of HDAC1 [HD1], HDAC2 [HD2], HDAC3 [HD3], and HDAC8 [HD8]) and, to a lesser extent, of class II histone deacetylases (including HDAC4 [HD4], HDAC5 [HD5], HDAC6 [HD6], HDAC7 [HD7], HDAC9 [HD9], and HDAC10 [H10]).¹¹ Given the accumulating evidence supporting the potential role of HDACi for the treatment of many other medical conditions beyond epilepsy, the interest in novel potential indications for HDACi has been renewed.¹²

We herein review the mechanisms associated with the epigenetic, antithrombotic, and other potential beneficial effects of HDACi in the cardiovascular system and beyond, proposing new areas for future basic and clinical research. Because valproic acid is the most widely studied HDACi, most animal and clinical studies referenced throughout this Review use valproic acid as an HDACi model.

Effects on the coagulation cascade and related pathways

Many cardiovascular conditions are caused by prothrombotic phenomena.¹³ The stability of the thrombotic cascade depends on the balance between fibrinolytic factors, such as the urokinase-type plasminogen activator (uPA), the tissue-type plasminogen activator (tPA), and inhibitors of the fibrinolytic system, such as the plasminogen activator inhibitor 1 (PAI1).¹⁴ The fibrinolytic system is activated by the cleavage of plasminogen to plasmin by serine proteases (mostly tPA) that are released from storage in the vessel endothelium; fibrinolysis is inhibited by circulating PAI1.¹⁵ The thrombotic risk is thus influenced by the balance between PAI1 and tPA; a fine regulation of the endogenous fibrinolytic system is essential for the modulation of fibrin deposition and vascular remodelling.¹⁶ An increase in the plasma concentration of PAI1 can induce a prothrombotic state, as observed in proinflammatory conditions such as autoimmune diseases, chronic obstructive pulmonary disease, cancer,

obesity, or diabetes.¹⁷ Similarly, PAI1 production might be upregulated by proinflammatory factors, such as TNF α , TGF β , and insulin. Furthermore, PAI1 is a marker of endothelial injury and can also serve as an intermediary for the action of other prothrombotic factors and smooth cell migration.¹⁸ PAI1 might also be involved in the pathogenesis of fibrosis because overexpression of PAI1 reduces extracellular matrix degradation by decreasing the proteolytic activity of tPA and uPA.¹⁹

Preclinical and clinical studies have shown that valproic acid might increase endogenous fibrinolysis by stimulation of tPA synthesis and inhibition of PAI1, a mechanism of action that has not been associated with increased risk of bleeding.⁷ For example, valproic acid administration in mice was associated with reduced fibrin accumulation and smaller thrombi, with no increased risk of bleeding.⁷ Supporting in-vitro findings, individuals with increased concentrations of circulating PAI1 have been shown to have a higher risk of thrombotic cardiovascular complications than those with lower concentrations, independently of previous comorbid conditions such as myocardial infarction or diabetes.²⁰ Valproic acid has also been shown to inhibit platelet function by reducing the activity of the arachidonic acid cascade in platelets, inhibiting the cyclooxygenase pathway and the synthesis of thromboxane synthase.²¹

Effects on inflammation, fibrosis, and apoptosis

Fibroblasts and myofibroblasts are essential for the fibrosis process and for the synthesis of extracellular matrix proteins that constitute the fibrotic scar (mainly collagens, fibronectin, and laminins). The activation of TGF β , platelet-derived growth factors, connective tissue growth factor (CCN2), vasoactive compounds (eg, endothelin 1 and angiotensin II), and integrins, which mediate extracellular matrix signalling pathways, has a central role in fibrosis. TGF β , in particular, is responsible for multiple fibrogenic processes, including the conversion of fibroblasts to myofibroblasts, proliferation of myofibroblasts, and the production of extracellular matrix proteins.²² The uPA–plasmin and tPA–plasmin complexes have an important function in the cellular proteolytic degradation of extracellular matrix proteins and in the maintenance of tissue homeostasis.²³ TGF β increases the activity of PAI1 by inhibiting tPA and uPA and by, consequently, diminishing the conversion of plasminogen to plasmin and of promatrix metalloproteinases to metalloproteinases, enhancing their prothrombotic and profibrotic effects.¹⁹ Several studies in animals provide mechanistic insight on the potential role of HDACi in improving profibrotic conditions, not only via PAI1 inhibition but also through antifibrotic and anti-inflammatory mechanisms (eg, suppression of the TGF β pathway), and by suppressing the expression of natriuretic peptides B.²⁴

The antifibrotic and anti-inflammatory effects of valproic acid have been described in multiple organs of animal models, including the heart, lungs (vascular and parenchymal), kidneys, peritoneum, liver, and the conjunctiva of the eye. In hearts of spontaneously hypertensive rats, an increase in inflammatory, hypertrophic, and fibrotic responses has been found, mainly driven by the activation of the mineralocorticoid receptor (MR). The use of valproic acid led to attenuated cardiac hypertrophy and fibrosis in these rats.²⁵ Aldosterone directly increases *PAI1* expression in cardiac muscle cells, an effect that is dependent of MR.²⁶ In humans, the administration of MR antagonists prevented the PAI1 increase induced by furosemide.²⁷ Cardiac hypertrophy induced by chronic infusion of angiotensin II or by aortic banding in mice or rats was significantly reduced by valproic acid administration. The expression of natriuretic peptides A, α -tubulins, and β -myosin heavy chain (MYH7), and the occurrence of interstitial fibrosis were reduced by valproic acid and other HDACi.²⁸ In a mice model of doxorubicin-induced nephropathy, valproic acid attenuated the upregulation of profibrotic and proinflammatory genes, the deposition of collagen, and the infiltration of macrophages into the kidney.²⁹ In a model of thioacetamide-induced hepatic fibrosis, valproic acid prevented the activation and proliferation of hepatic stellate cells and decreased collagen deposition and infiltration of inflammatory cells in the liver.³⁰ A study of rats with induced peritoneal fibrosis showed that valproic acid treatment significantly reduced the peritoneal membrane thickness and the activity of myofibroblasts. A potential mechanism involved in these anti-inflammatory and antifibrotic effects is the suppression of profibrotic factors (TGF β , fibronectin, and SMAD3) and the upregulation of SMAD7, an antifibrotic factor. Furthermore, neoangiogenesis and the expression of proinflammatory cytokines were significantly reduced by valproic acid.³¹ In a rat model of bleomycin-induced lung fibrosis, PAI1 promoted the proliferation and transformation of pulmonary fibroblasts into myofibroblasts, and increased collagen synthesis.³² In other mice models of bleomycin-induced pulmonary fibrosis, inhibiting *PAI1* resulted in a significant downregulation of PAI1 expression and decreased collagen deposition in the lung, which was accompanied by substantial improvement in histopathological and immunohistochemical features.³³ In a mouse model of glaucoma filtration surgery, valproic acid decreased the expression of type I collagen (COL1A1) and suppressed steady-state type I collagen promoter activity. Moreover, valproic acid decreased the expression of the profibrotic SMAD3, decreasing collagen expression, and TGF β did not induce collagen synthesis in the presence of valproic acid treatment.³⁴ The potential antifibrotic effects of HDACi are further discussed in the subsequent disease-specific sections.

Effects on selected cardiovascular conditions and healthy longevity

Arterial hypertension

Reactive oxygen species and proinflammatory cytokines are increased in arterial hypertension, and histone deacetylases can modulate the gene expression of these pro-hypertensive components.³⁵ Valproic acid was compared with hydralazine in spontaneously hypertensive rats: valproic acid reduced blood pressure, proinflammatory cytokines, hypertrophic markers, and reactive oxygen species, whereas hydralazine treatment only reduced blood pressure.³⁵ In a mice model of high-fat diet-induced hypertension, valproic acid prevented the progression of hypertension by downregulating angiotensin II and its receptor via inhibition of HDAC1.³⁶ In the hearts of spontaneously hypertensive rats, the increase in the inflammatory, hypertrophic, and fibrotic responses might be (at least partly) driven by the activation of MR. Valproic acid increased MR acetylation in these rats, not only decreasing the recruitment of MR but also the expression of MR target genes that regulate hypertrophy and fibrosis.²⁵ In rats with induced renovascular hypertension, valproic acid treatment attenuated cardiac dysfunction, hypertrophy, and fibrosis.³⁷ In rats with nitric oxide deficiency-induced hypertension, valproic acid lowered blood pressure, improved the lipid profile, and decreased renal damage.³⁸ These data indicate that valproic acid might reduce blood pressure through epigenetic regulation.

Pulmonary hypertension and chronic pulmonary thromboembolism

Remodelled pulmonary arteries of patients with pulmonary arterial hypertension present with exuberant inflammation, increased proliferation, and decreased apoptosis. In a rat model of severe pulmonary arterial hypertension (induced by monocrotaline and hypoxia), the daily administration of valproic acid prevented and partly reversed the progression of pulmonary arterial hypertension by decreasing the inflammation and proliferation of the remodelled pulmonary arteries.³⁹ Specifically, treatment with valproic acid reduced medial wall thickness and the muscularisation ratio and vascular occlusion score of small pulmonary arteries. Valproic acid also caused downregulation of cell proliferation and inflammation within the vessel wall, resulting in a substantial reduction in apoptotic, inflammatory, and hypoxia-stimulated gene expression.³⁹ These data suggest that the beneficial effects of valproic acid in severe pulmonary arterial hypertension might be due to its epigenetic regulation of cell proliferation, inflammation, and apoptosis. High concentrations of histone deacetylases were also found in the lungs of humans with idiopathic pulmonary arterial hypertension, and in the lungs and right ventricles of rats exposed to hypoxia.⁴⁰ Both the HDACi valproic acid and vorinostat (suberoylanilide hydroxamic acid) mitigated the development of and reduced established hypoxia-induced

pulmonary arterial hypertension in rats. Furthermore, valproic acid and vorinostat inhibited the highly proliferative phenotype of bovine fibroblasts and the growth of human vascular smooth muscle cells in culture.⁴¹ Valproic acid and other HDACi might reduce pulmonary artery hypertension by mitigating pulmonary vascular remodelling through effects on lung endothelial cells and vascular smooth muscle cells, beyond their anti-inflammatory, antifibrotic, and antithrombotic properties.^{42,43}

Atrial fibrillation

HDACi have also been studied in the context of atrial fibrillation, a potentially debilitating and life-threatening condition that increases the risk of stroke, dementia, and, ultimately, death.⁴⁴ The effect of valproic acid in reducing adverse atrial remodelling, dilatation, endothelial dysfunction, fibrosis, and the associated hypercoagulable and prothrombotic state (all of which are associated with atrial fibrillation and its complications, including stroke) has been tested in several experimental models.⁴⁵ Overexpression of histone deacetylases has been associated with the progression of atrial fibrillation.⁴⁶ In a mouse model of extensive atrial fibrosis with age-dependent progression from spontaneous atrial ectopy to paroxysmal and long-lasting atrial fibrillation, valproic acid significantly reduced atrial dilatation, cardiomyocyte enlargement, atrial fibrosis, the disorganisation of myocytes' ultrastructure, and the occurrence of atrial thrombi, and delayed the onset of atrial fibrillation to week 8.⁴⁷ Inhibition of histone deacetylases has also been shown to reverse atrial fibrosis and atrial arrhythmias independently of angiotensin II, and to reduce the total time of fibrillation, atrial fibrosis, intra-atrial adipocytes, and immune cell infiltration without affecting cardiac function in mice.⁴⁸

Stroke

Beyond its aforementioned effects on tPA and PAI1 to restore fibrinolytic capacity, which might prevent thrombi formation and thus reduce the thrombotic risk, valproic acid inhibits the expression of an allele encoding a variant of *HDAC9* that has been associated with carotid plaques and ischaemic stroke.⁴⁹ Moreover, valproic acid and other HDACi might protect the brain from injury progression via anti-inflammatory, antiapoptotic, proangiogenic, and neurotrophic effects.⁵⁰ After transient global cerebral ischaemia in rats, treatment with valproic acid protected against hippocampal cell loss and cognitive deficits through reduction of ischaemia-induced cerebral inflammation, inhibition of the microglia activity, and induction of heat shock proteins.⁵¹ Another study showed that valproic acid reduced neurological deficits and neuronal degeneration by inhibiting inflammation and endovascular injury in hyperglycaemic rats with permanent middle cerebral occlusion.⁵² In a mouse model of ischaemia-reperfusion injury, valproic acid

reduced cell death through anti-inflammatory and antioxidative effects.⁵³ Valproic acid treatment also enhances angiogenesis and promotes functional recovery after brain ischaemia in rats.⁵⁴

Myocardial infarction and atherosclerosis

In a rat model of myocardial infarction, valproic acid reduced infarct size by 50%, preserved systolic function after acute myocardial infarction, and improved myocardial function.⁵⁵ Another study suggested that valproic acid can diminish atherosclerosis in ApoE-deficient mice by inhibiting glycogen synthase kinase 3, a mitogen and growth factor-regulated serine-threonine kinase implicated in the promotion of apoptosis and activation of NF- κ B.⁵⁶

Heart failure

Epigenetic regulation of stress-induced inflammation and fibroblast activation in the heart can lead to, or aggravate, heart failure.² Treatment with valproic acid decreased proinflammatory and fibrotic responses in several experimental models.³⁵ Treatment with trichostatin A and valproic acid also partly reversed cardiac hypertrophy and improved survival in mice with cardiac hypertrophy induced by angiotensin II or aortic banding.²⁸ Treatment with givinostat, a clinical-stage HDACi, blocked left ventricular diastolic dysfunction due to hypertension in Dahl salt-sensitive rats, suppressed ageing-induced diastolic dysfunction in normotensive mice, and was efficacious in improving cardiac myofibril relaxation in a rat model.⁵⁷ Vorinostat treatment of pressure overload cardiac dysfunction in short-haired cats resulted in a significant reduction of left ventricular hypertrophy and left atrial volume, which was linked to an improvement in myofibril relaxation and lysine acetylation of mitochondrial metabolic enzymes, suggesting that acetylation defects in hypertrophic stress can be reversed by HDACi.⁵⁸

Kidney disease

Beyond what has been described in the fibrosis section, treatment with valproic acid ameliorates renal injury and fibrosis in the kidneys of diabetic rats by preventing myofibroblast activation and fibrogenesis.⁵⁹ Furthermore, valproic acid reduced renal cell apoptosis and fibrosis, attenuating renal injury in rat models of renal disease with or without diabetic nephropathy.⁶⁰ Because PAI1 can also contribute to aldosterone-induced renal and cardiac injury, its inhibition might also protect against aldosterone-induced glomerular injury.⁶¹

Diabetes and diabetes-associated metabolic diseases

Histone deacetylases are involved in β -cell differentiation, proliferation, and function, leading to the discovery of a link between diabetes and histone deacetylases.⁶² In rats with type 2 diabetes, treatment with HDACi improved glycaemic control by attenuating the activity of

transcriptional factors associated with dysglycaemia.⁶³ Treatment with valproic acid improved β -cell proliferation and function and reduced β -cell apoptosis in juvenile diabetic rats,⁶⁴ and decreased hepatic fat and serum glucose in obese mice.⁶⁵

Ageing

Ageing is a major contributor to human disease and disability. No drugs so far have been shown to delay human ageing, but some, such as metformin, are being tested for this purpose.⁶⁶ The interplay between epigenetic alterations and ageing can potentially be mitigated: histone acetylation has a major role in the various epigenetic alterations associated with ageing,⁶⁷ and HDACi might therefore revert the natural age-related effects of histone acetylation.⁶⁸ In another model, treating *Caenorhabditis elegans* with valproic acid and the heterocyclic anticonvulsant trimethadione extended the lifespan of this nematode.⁶⁹

Dementia and other neurodegenerative conditions

Ageing and increased amyloid β burden are major risk factors for cognitive diseases (such as Alzheimer's disease), for which effective therapies are scarce. A favourable effect of HDACi on brain function has been described.⁷⁰ Treatment with vorinostat, which exerted an anti-inflammatory action and restored epigenetic balance and transcriptional homeostasis, led to restoration of spatial memory in a mouse model of Alzheimer's disease.⁷¹ Treatment with valproic acid promoted cell proliferation and increased the density of immature neurons in the dentate gyrus of the hippocampus in a mouse model of Alzheimer's disease. Suggestive of enhanced neurogenesis, valproic acid treatment also improved the learning and memory capacity of these mice.⁷² The cognition-enhancing qualities of HDACi, combined with their ability to attenuate the age-related loss of neural cell adhesion molecules, suggest that HDACi might effectively slow the onset of cognitive decline.⁷³

In mice, valproic acid was able to partly prevent striatal dopamine depletion and almost completely protect against substantia nigra dopaminergic cell loss, which might indicate a potential effect of valproic acid to treat Parkinson's disease.⁷⁴

In rats, valproic acid can also attenuate traumatic spinal cord injury-induced inflammation and improve neuronal function and survival after traumatic brain injury.⁷⁵

Cancer

High expression and activity of histone deacetylase are found in some cancers, and research has shown the potential of HDACi in suppressing tumour growth via anti-inflammatory and antiproliferative effects.⁷⁶ In breast cancer cells, for example, valproic acid was found to be a potent antineoplastic agent, inhibiting telomerase activity and inducing apoptosis.⁷⁷ The pan-HDACi vorinostat is approved by the US Food and Drug Administration for the treatment of T-cell lymphoma.⁷⁸

Several other HDACi are being investigated in cancer clinical trials, either as monotherapies or in conjunction with other treatments.⁷⁹

Immunomodulation in autoimmune conditions

Histone deacetylases are highly expressed in the synovium of arthritis patients and correlate with inflammation markers,⁶⁸ suggesting that HDACi might provide benefit in collagen-induced arthritis. In this context, valproic acid has been shown to suppress activation mechanisms in several immune cells that lead to an inflammatory response, by affecting the expression of cell cycle and apoptosis genes through epigenetic modifications.⁸⁰

Vorinostat and entinostat have shown prophylactic activity against swelling and bone erosion.⁸¹ A selective HDAC6 inhibitor, CKD-L (Chong Kun Dang, Seoul, Korea), decreased the arthritis score in a mouse model of collagen-induced arthritis, and reduced the expression of inflammatory markers in patients with rheumatoid arthritis.⁸² In a mouse model of collagen-induced arthritis, valproic acid suppressed the inflammatory response via FOXP3⁺ T_{reg} cells, and it might limit autoimmune disease *in vivo*.⁸³

Other conditions

HDACi have also shown promising results for the prevention and treatment of several other conditions, such as alopecia,⁸⁴ glaucoma,⁸⁵ burn shock,⁸⁶ Duchenne muscular dystrophy,⁸⁷ and autoimmune encephalomyelitis.⁸⁸ For example, valproic acid decreased B-cell response and plasma cell differentiation *in vitro* in nitrophenyl-chicken γ -globulin-immunised and heart transplant recipient mice. HDACi could thus be a therapeutic agent targeting B-cell response after organ transplantation.⁸⁹

The potential effects of HDACi based on animal studies are summarised in figure 1. The link between HDACi mode of action, their intermediate effects, and potential indications are depicted in figure 2.

Epidemiological studies of valproic acid for cardiovascular conditions

Cardiovascular diseases are the leading cause of disability and death worldwide.^{90,91} Epidemiological studies have suggested that the use of valproic acid is associated with a reduction in the risk of stroke and myocardial infarction.⁹² Several population-based and case-control studies provided observational evidence of the potential benefits of valproic acid as antithrombotic agent.

A study of Danish registries compared two age-matched and sex-matched independent cohorts of patients with epilepsy treated with valproic acid with people from the general population without epilepsy and not taking valproic acid. In the first cohort (n=53 086), the relative risk of myocardial infarction was 0.75 (95% CI 0.59–0.97) in favour of valproic acid (compared with

controls). In the second cohort (n=102 003), the relative risk of myocardial infarction was 0.62 (95% CI 0.53–0.73) in favour of valproic acid (compared with controls).⁹³

In another Danish cohort study, the authors assessed the risk of myocardial infarction, stroke, cardiovascular, and all-cause death associated with epilepsy. Patients with epilepsy (compared with those without) had an up to 1.9 times higher risk of major adverse cardiovascular events. However, among those with epilepsy, patients treated with valproic acid (compared with those treated with carbamazepine monotherapy) had a lower associated risk of myocardial infarction (hazard ratio [HR] 0.72 [95% CI 0.59–0.87]) and of stroke (HR 0.86 [95% CI 0.76–0.96]). Carbamazepine and phenobarbital, however, were associated with a higher risk of death (both cardiovascular and of all causes).⁹⁴ Importantly, in this study, patients treated with valproic acid had a lower risk of myocardial infarction than people in the general population without epilepsy and not taking anti-epileptics.

Two separate nested case-control studies with data from electronic health records extracted from the UK Clinical Practice Research Datalink, matched (on age, sex, and follow-up time) participants diagnosed with epilepsy and prescribed antiepileptic drugs with healthy controls. One study assessed incident ischaemic stroke and another assessed myocardial infarction. The stroke study included 2002 cases and 13 098 controls, and the myocardial infarction study included 1153 cases and 7109 controls. Having ever been prescribed valproic acid was not associated with ischaemic stroke (odds ratio [OR] 1.01 [95% CI 0.91–1.12]), but was associated with a lower risk of myocardial infarction (OR 0.78 [95% CI 0.67–0.90]). Moreover, patients with longer valproic acid treatment duration had lower odds of ischaemic stroke (OR 0.57 [95% CI 0.44–0.72]) and myocardial infarction (OR 0.29 [95% CI 0.20–0.44]).⁹⁵

A study comprising data from three different cohorts of patients who had a previous stroke or transient ischaemic attack (South London Stroke Register, Vitamins to Prevent Stroke Study, and Oxford Vascular

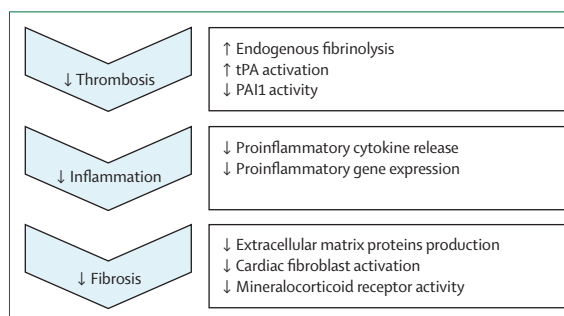


Figure 1: Potential effects of histone deacetylase inhibitors, based on animal studies

For the UK Clinical Practice Research Datalink please see www.cprd.com

Study) assessed the rates of recurrent ischaemic stroke in patients receiving valproic acid compared with patients who received other antiepileptic drugs. The recurrent stroke rate was lower in patients taking valproic acid (10.1%) than in those taking other antiepileptic drugs (19.8%; adjusted HR 0.44 [95% CI 0.30–0.70]).⁹⁶

In a nested case-control study analysing several antiepileptic drugs in 252 407 patients matched with 10 healthy controls per each case of ischaemic stroke or myocardial infarction, the authors found “a trend towards a decreased risk of myocardial infarction” among patients taking valproic acid (relative risk 0.81 [95% CI 0.66–1.00]), with no apparent effect on stroke. The other antiepileptic drugs showed a small increase in the risk of myocardial infarction with prolonged use, but no effect on stroke.⁹⁷

A recent review and meta-analysis also found a reduction in the risk of stroke and myocardial infarction in patients taking valproic acid, compared with patients taking other antiepileptic drugs.⁹²

Which HDACi should be used?

Some HDACi (eg, trapoxin A) are of little therapeutic use because they have poor in-vivo bioavailability and cause toxic side-effects at high doses. Others (eg, butyrate and phenylbutyrate) are degraded rapidly after intravenous administration. Many other compounds are strong

HDACi and have been used as potent anticancer therapies.⁷⁶ Many of these compounds are not specific HDAC inhibitors and also inhibit phosphorylation and methylation of proteins and DNA methylation. On the other hand, valproic acid is an inhibitor of class I (and, to a lesser extent, II) histone deacetylases, and is a well established and generally well tolerated drug.⁹⁸ Moreover, valproic acid might result in a lower risk of QT prolongation compared with other HDACi.⁹⁹

Valproic acid: pharmacology, mechanisms of action, and side-effects

The neurological effects of valproic acid might be mediated by the increased brain concentrations of the inhibitory neurotransmitter γ -aminobutyric acid. Valproic acid is rapidly and almost completely (80–90%) absorbed by the gastrointestinal tract, and is mostly bound to plasma proteins (the free or unbound drug corresponds to 6–15% of total plasma concentrations). Valproic acid is metabolised by the liver and inhibits the liver enzyme CYP2C9, has a half-life of 8–20 h, and up to 50% of circulating valproic acid is eliminated via renal excretion. Hence, hepatic or kidney impairment might increase the concentration of circulating valproic acid. The target daily dose of valproic acid for humans is 20–30 mg/kg per day, and its therapeutic efficacy for neurological conditions is reached at plasma concentrations of 40–100 mg/L (300–700 μ M/L).

Valproic acid is generally well tolerated and the most frequent side-effects (nausea, vomiting, diarrhoea, and dyspepsia) are transient and can be minimised by taking the drug with meals and by increasing the dose progressively. Hepatotoxicity and pancreatitis have been reported but are rare events. Valproic acid increased the risk of teratogenicity or fetal malformations and its use is therefore contraindicated during pregnancy.¹⁰⁰

Future directions and conclusions

The potential antifibrotic effects of HDACi are summarised in the table. Future studies could assess the efficacy of HDACi for other settings, such as primary or secondary cardiovascular prevention (eg, myocardial infarction, stroke, peripheral artery disease, heart failure,

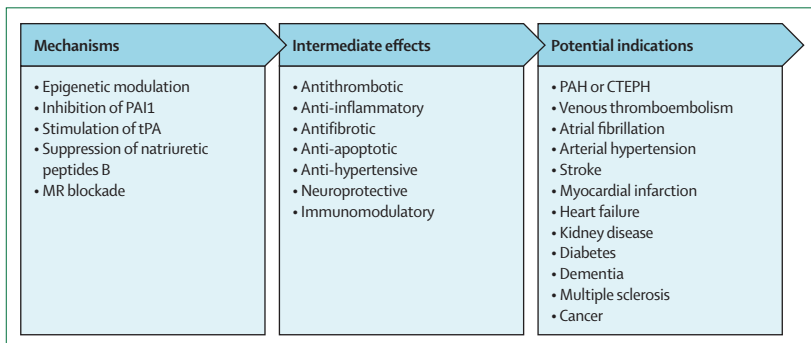


Figure 2: Mechanisms, intermediate effects, and potential indications of histone deacetylase inhibitors. CTEPH=chronic thromboembolic pulmonary hypertension. PAH=pulmonary artery hypertension.

| Pathways or processes | Indications | Potential effects |
|--|--|--|
| Heart ^{25,28,35} Inhibition of mineralocorticoid receptor; reduction of natriuretic peptides; reduction of interstitial fibrosis, proinflammatory cytokines, and reactive oxygen species | Hypertensive heart disease; heart failure; myocardial infarction | Reduction of cardiac hypertrophy, fibrosis, and ischaemia |
| Kidney ^{79,60} | Chronic kidney disease; glomerulosclerosis; proteinuria; ischaemia-reperfusion injury; interstitial fibrosis; tubular damage | Reduction of renal hypertrophy, fibrosis, ischaemia, and proteinuria |
| Liver ^{30,65} Apoptosis of stellate cells; decreased deposition of collagen and inflammatory cells | Cirrhosis; non-alcoholic steatohepatitis | Reduction of hepatic fibrosis and inflammation |
| Peritoneum ³¹ Suppression of profibrotic factors | Peritoneal fibrosis | Reduction of peritoneal fibrosis |
| Lung ^{33,34,2} Downregulation of PAI1 expression; reduced collagen deposition | Pulmonary fibrosis | Reduction of pulmonary fibrosis |
| Eye ³⁴ Reduced collagen deposition | Conjunctival fibrosis | Reduction of eye fibrosis |

Table: Overview of the effects of histone deacetylase inhibitors on fibrosis on various organs (animal models)

Search strategy and selection criteria

We used both Medical Subject Headings terms (controlled language) and free-text terms. The search query included “histone-deacetylase inhibitor” OR “sodium valproate” and we then searched for more specific combinations, such as “histone-deacetylase inhibitor” AND “cardiovascular” OR “heart failure” OR “kidney”. The search was last done on Feb 12, 2021. We did not restrict the search by language, date, or publication status.

atrial fibrillation, diabetes, arterial hypertension, and cardiovascular conditions aggravated by chronic kidney disease); prevention and treatment of venous thrombosis (eg, deep venous thromboembolism, pulmonary embolism, and stroke prevention in atrial fibrillation); treatment of Alzheimer’s disease and other neurodegenerative disorders; treatment of traumatic CNS conditions, such as spinal cord injury or traumatic brain injury; treatment of autoimmune and proinflammatory conditions; and treatment of rare diseases of the lung, such as chronic thromboembolic pulmonary hypertension or pulmonary arterial hypertension. Adequately designed and powered clinical trials are required to assess the efficacy and safety of the drug before any clinical repurposing. The multiple potential indications of HDACi should incentivise the search for newer HDACi with even greater effectiveness and safety.

Given the pleotropic properties of valproic acid and other HDACi through epigenetic modulation and antithrombotic, anti-inflammatory, and antifibrotic properties, repurposed valproic acid (or other HDACi) should be further explored as potential disease-modifying therapies for various indications.

Contributors

JPF drafted the first version of the manuscript and subsequent revisions. BP and FZ drafted and revised the manuscript and provided feedback and input.

Declaration of interests

We declare no competing interests.

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