The Renoprotective Effects of Sodium Valproate as a Histone Deacetylase Inhibitor on Diabetic Nephropathy

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ABSTRACT

BACKGROUND AND OBJECTIVE: Diabetic nephropathy (DN), as the most common cause of end-stage renal failure, caused by protein kinase C pathway and reactive oxygen species. Recent studies demonstrated importance of epigenetic processes such as histone acetylation and the role of histone deacetylases (HDAC) and histone acetyltransferase in the development of this silent epidemic. Sodium valproate (VA) is known as a histone deacetylase inhibitor(HDACi). DN must be prevented and treated because it is prevalent and important.

METHODS: In this study, scientific articles indexed in databases "Web of science, Scopus, PubMed, SID, ISI" were studied using key words "*Sodium Valproate, Diabetic Nephropathies, Histone Deacetylase Inhibitors*".

FINDINGS: VA can prevent the degradation podocytes and renal cells through the autophagy and reduce proteinuria in the DN condition. In addition, VA, as an HDAC, prevented apoptosis of podocytes, thus it improves DN. Because HDAC class I involved in renal fibrogenesis and fibroblast activation by modulation of TGF-β signaling, sodium valproate promotes antifibrotic effects logically. VA can regulate NF-κB signaling, thereby exert an anti-inflammatory effect in podocytes. HDAC inhibition decreased eNOS mRNA but paradoxically increased activity of eNOS promoter, probably because of inducing an eNOS mRNA-destabilizing factor. Sodium valproate as a HDACi has the high renoprotective effect in laboratory studies with DN models.

CONCLUSION: It is expected that sodium valproate will be used as the prevention or treatment of DN in the future after the clinical trials.

KEY WORDS: *Sodium Valproate, Diabetic Nephropathies, Histone Deacetylase Inhibitors*

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Introduction

Diabetic Nephropathies (DN) is a clinical syndrome characterized by continuous microalbuminuria with insulin-dependent or non-insulin-dependent diabetes (1), glomerular podocytes, mesangial and endothelial cells, tubular epithelium, interstitial fibroblasts and vascular endothelial involvement (2). Having a specific genetic history in 30% of patients with type 1 diabetes and 25-40% of patients with type2 diabetes is effective in the development of diabetic nephropathy (3).

The pathogenesis of this syndrome is multifactorial, but in recent studies, the importance of epigenetic processes associated with histone deacetylase has been emphasized in the development of renal injury (4, 5). Sodium valproate is a histone deacetylase inhibitor (HDACi) (6), histone deacetylases (HDAC) are the types of enzymes that balance the activity of acetylation of histone acetyltransferase by adjusting the state of acetylated/ non- acetylated of histone on the chromatin remodeling, and play an important role in transcription regulation (7-9).

The HDAC can remove the Acetyl group from the lysine residue and non-histone proteins, and can usually act as a suppressor (10), and extensive studies have been carried out on its anticancer effects and mechanisms (11, 12). Sodium valproate is a broad antiepileptic drug that acts through the brain's GABA. This drug was completely accidentally identified in 1963 as an anti-epileptic drug by Pierre Eymard (13), has a fast gastrointestinal absorption and reaches peak blood levels within 1-4 hours. Liver metabolism (conjugation and oxidation) and its major excretion is urinary (14) and teratogenic (15).

Sodium valproate is used in treating migraines in addition to epilepsy and is also used as a stabilizing agent in people with bipolar disorder (16). Recent studies have indicated the effect of sodium valproate on HDAC enzymes, especially class I and II (17-17); therefore, this drug is considered as an HDACi index and its potential effects. A study by Yoshikawa et al. on a culture medium containing proximal epithelial cells of the human kidney tissue known as REGM BulletKit, identified trichostatin A (a type of HDACi) prevents transformation from epithelial to mesangial due to TGF-β1 (22).

In a study by Pang et al., on medium containing interstitial fibroblasts from rat kidney tissue specified, HDACi may exhibit anti-fibrotic properties by disabling these fibroblasts (23). In a study by Marumo et al, on male C57BL / 6J mice, was shown trichostatin A reduces infiltration of the macrophage and changes in fibrotic tissue resulting in a recovery of the interstitial tubular damage of the renal tissue due to ureteral obstruction (24).

In a study by Van Beneden et al., on the model of experimental mice with Adriamycin induced nephropathy, sodium valproate injection reduced the proteinuria, glomerulosclerosis and renal inflammation (25). Advani et al., with long-term treatment with Vorinostat (HDACi) in streptozotocin induced nephropathy mice showed that albuminuria and accumulation of mesangial matrix in diabetic mice are improved through an endothelial nitric oxide synthase mechanism (26). In a study by Cosentino et al, on zebrafish larvae and experimental mice, the onset of phenylthio (a type of HDACi) within 24-48 hours after acute renal injury induced rapid recovery, decreased tubular atrophy, after injury and improvement of interstitial fibrosis (27).

The study by Liu et al. indicated that HDAC class 1 intervenes in fibrogenesis and the activation of renal fibroblasts by modulating the TGF-β messenger (28). Liu et al., in their study on male mice, showed that by deactivation of HDAC, glomerulosclerosis, the release of inflammatory cytokines, podocyte apoptosis, and renal damage decreased (29). Dong et al. also referred to an in vivo experiment for the activation of the Nuclear Factor erythroid 2-related factor (Nrf2) by inhibition of HDAC (30).

Considering previous studies and the association of various HDACi with the development of diabetic nephropathy, and as diabetic nephropathy is developing as an epidemic, it should be carefully investigated on sodium valproate, allowing for creation of a new way to cope with this syndrome in diabetic patients in the medical community. This study was conducted to investigate the most recent evidence available for the use of this anti-epileptic drug to prevent or treat diabetic nephropathy.

Methods

In this narrative review, using electronic-resources such as valid scientific articles indexed in the databases "Web of Science, Scopus, PubMed, SID, ISI" from 1963 to 2017 on the effects of renoprotective of sodium valproate, as histone deacetylase inhibitor in diabetic nephropathy was studied by using sodium valproate, diaphytic nephropathy, histone diastereose inhibitors key words.

Results

A total of 485 articles related to the topic were found, of which about 73 articles were accessible and more relevant to the subject were selected and examined. Diabetic nephropathy is defined as one of the most severe microvascular consequences of diabetes (2) when proteinuria is more than 0.5 g/24h (31). Various factors such as hypertension, hyperglycemia, hyperlipidemia and proteinuria are involved in the development of kidney damage in diabetic nephropathy (1).

Sustained hyperglycemia induces the production of intracellular reactive oxygen species (ROS) in mesangial and tubular epithelial cells through protein kinase C, nicotinamide adenine nucleotide phosphate oxidase, and mitochondrial metabolism (32). In this way, the level of the up regulation process increases the Transforming growth factor beta 1 (TGF-β1) and provides a bed for renal damage (33). Generally, in diabetes, a steady increase in blood glucose leads to hypertrophy of mesangial cells, fibrosis and production of more oxidants, and leads to the development of diabetic nephropathy (34,35). Histone acetylation leads to relaxation of the chromatin structure, and thus paves the way for transcriptional activators and increases the gene expression (36). HDAC enzymes are generally divided into four groups based on their similarity to yeast histonetidistilase (37, 38), which is class 1 (type 1, 2, 3, 8), that is related to the yeast gene and is often found in the nucleus, the second class (HDACs 4,5,6,7,9,10), which are related to the HDAC1 gene of the yeast, and are basically in the cytoplasm, class III (SIRT1-7), known as sirtuins, and are related to the Sir2 gene, which apparently are not affected by HDACi, and the fourth class (HDAC11) that maintains the domain in the catalytic regions of both the first and second class enzymes (8).

Sodium valproate as a class I HDAC inhibitor with different mechanisms (Fig 1) improves diabetic nephropathy in diabetic patients (39).
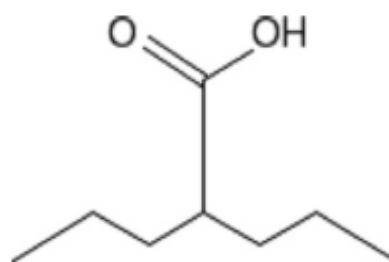

Figure1. Chemical structure of sodium valproate(8)

Therefore, this medication is likely to be used to induce histone acetylation. Studies have also been conducted in recent years on the effects and mechanism of HDAC inhibitors on the improvement of diabetic nephropathy (table 1) (5, 26, 30, 39-41).

Table1. Recent studies on the effects and mechanisms of HDAC inhibitors on the improvement of diabetic nephropathy

HDAC inhibitor	Selective	Effects	Mechanism	References
Sodium Valproate, Trichostatin (2009)	HDAC I/II	Reduction of extracellular fluid accumulation	TGF-β1 suppression caused by HDAC2 activity	(39)
Vorinostat (2011)	HDAC I/II	Reduction of cell proliferation and glomerular hypertrophy	Down regulation of EGFR gene expression	(5)
Saha (2011)	HDAC I/II	Reduction of albuminuria and sedimentation of collagen type 4	Reducing eNOS gene expression in mouse kidneys and inhibiting apoptosis	(26)
Sodium Butyrate (2014)	Pan HDAC	Improve kidney function	Inhibition of apoptosis and DNA damage	(40)
Sodium Valproate (2015)	HDAC I/II	Anti-fibrotic effects	Inhibition of fibrogenesis and improvement of the balance between Pro and anti-fibrotic genes	(41)
Sodium Butyrate (2017)	Pan HDAC	Inhibition of kidney fibrosis caused by diabetes	Increased expression of Nrf2 and renal apoptotic genes	(30)

Discussion

The HDACi was first clinically tested by Johnstone et al. (42). In 2006, the first HDACi, called Suberoyl amid hydroxamic acid, was approved by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL's) (43). Today, many pharmaceutical companies are interested in the synthesis of these compounds due to the potential of HDACi in cancer control and other human pathological conditions (44).

Recent evidence suggests a link between type-1 diabetes mellitus and activity of HDAC enzymes, although HDACi medications play an important role in the reproduction and function of beta cells (45, 46). Hyperglycemia leads to excessive expression of HDAC enzymes and a reduction in histone acetylation, damages podocyte cells and other renal cells and, as a result, impaires glomerular filtration (47). I

n addition, diabetic retinopathy, like diabetic nephropathy, is associated with an epigenetic mechanism (48-50). The present study provides evidence to explain the mechanism of sodium valproate as a renoprotectivein diabetic nephropathy, which is effective in controlling the iNOS / NF-κB signaling pathway and facilitating autophagy through HDAC inhibition (41,51,52).

The first experimental evidence for the treatment of diabetic nephropathy with sodium valproate was presented in the study. By studying rat diabetic nephropathy models, sodium valproate reduces ERS and apoptosis induced by ERS through the regulation of histone H4 acetylation in a promoter of endoplasmic reticulum stress (ERS) proteins such as GRP78 and CHOP (53). ERS is one of the mechanisms responsible for diabetic nephropathy (54, 55).

1.Autophagy: In many studies, the association of abnormal autophagy with the consequences of diabetes has been addressed (56-59). Whereas, sodium valproate reduces proteinuria and renal damage in diabetic rats by facilitating autophagy (47). Autophagy is a catabolic process that destroys and regenerates unnecessary proteins and organelles in the cell to maintain a homeostasis under pathological conditions (60). This process is regulated by epigenetic changes such as histone acetylation (61), which alone has a great importance in the maintenance of podocyte function (57). Therefore, sodium valproate can prevent degradation of podocytes and kidney cells in diabetic nephropathy by an autophagy mechanism. Due to the fact that only SIRT1, HDAC2, HDAC4 and HDAC9 are effective in the development of diabetic nephropathy (29), among the various types of HDAC

enzymes and because only HDAC2 is effective in autophagy among classI HDACs (Table 2), extremely high sodium valproate often inhibits the isoform HDAC2.

Table2. Effect of each class of HDAC in the regulation of autophagy in diabetic nephropathy (63)

HDAC isoforms	An exclusive role in DN	References
HDAC 1	Lack of interference in autophagy	(7)
HDAC 2	Upregulation and interfering with autophagy	(7,47)
HDAC 3	Lack of interference in autophagy	(7)
HDAC 8	Lack of interference in autophagy	(7)

2.Prevention of apoptosis: Because pharmacological inhibition of autophagy in podocyte cell culture induces apoptosis (56), it can be assumed that the prevention of podocyte apoptosis by means of HDACi autophagmechanism, in particular sodium valproate, leads to prevention of diabetic nephropathy. It has been proven that endoplasmic reticulum stress is one of the mechanisms of pathogenesis of diabetic nephropathy; valproate reduces cell apoptosis by relieving this stress, thereby improving renal damage in the diabetic nephropathy model (53).

3.Anti-fibrosis: Given that Class-1 HDACs are involved in modifying TGF-β signaling in renal fibrogenesis and activating fibroblasts, naturally, sodium valproate appears to be anti-fibrotic(8,28). It also reduced the expression of CSF-1 induced by TNF-α in renal tubular cells and reduced fibrotic changes(23).

4.Anti-inflammatory: Inflammatory processes play a key role in the development of diabetic nephropathy. Some studies indicate that the NF-κB signaling pathways are as inflammatory mediators with HDAC enzymes (64) and therefore theoretically it can be concluded that sodium valproate also has anti-inflammatory effects (65).

In general, autophagy, prevention of apoptosis, anti-fibrosis and anti-inflammatory effects are among the mechanisms involved in controlling diabetic nephropathy when taken with sodium valproate (Fig 2); Of course, valproate, like other HDACi, has other mechanisms, such as immunosuppression, prevent cell proliferation, and reduce vascularity (62). The eNOS enzyme, by increasing the production of reactive oxygen species (ROS), may promote tissue damage (66, 67) and compounds that prevent the production of these oxidants can be used to prevent or treat this damage (68).
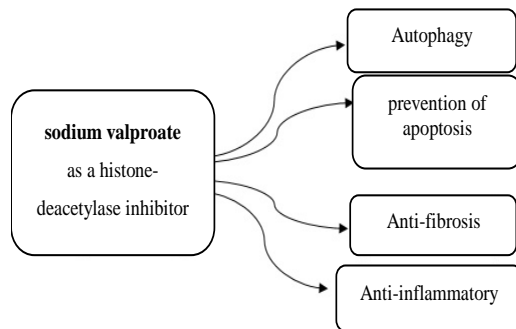
Figure2. Various effects and mechanisms of sodium valproate as a histone-deacetylase inhibitor (62)

Given the fact that in the endothelial cells, the eNOS promoter is rich in acetylated histones (69), in the usual mode of HDAC inhibition, it increases the activity of the desired promoter, but contrary to expectation, the eNOS mRNA in the cell is reduced. This response is likely to be triggered by the induction of unstable eNOS mRNA factors (26). While sodium valproate, decreases oxidative stress, by inhibiting the activation of HDAC2 (39). It is suggested that in future studies, comparing the potential of sodium valproate with other HDACi drugs in the treatment of diabetic nephropathy, as Van Beneden et al. compared the effects of trichostatin A and sodium valproate on the recovery progression of renal fibrosis due to doxorubicin (70).

In addition, due to the relevance of HDAC and HAT, it is recommended to consider the effects of various HAT inhibitors such as curcumin (71-73). The evolution of the subject of previous studies, respectively, is the antifibrotic effects, the prevention of apoptosis and then autophagy for HDACi drugs. Sodium valproate, in turn, as an HDACi, has been shown to have high renoprotective effects in diabetic nephropathy models. It is expected that, if more clinical trials are conducted in the future, the FDA will identify new indications for this drug.

Acknowledgments

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