Romidepsin (FK228) in a Mouse Model of Lipopolysaccharide-Induced Acute Kidney Injury is Associated with Down-Regulation of the CYP2E1 Gene

Background: Romidepsin (FK228) or depsipeptide, is a selective inhibitor of histone deacetylase 1 (HDAC1) and HDAC2. This study aimed to investigate the effects and molecular mechanisms of romidepsin (FK228) in a mouse model of acute kidney injury (AKI) induced by lipopolysaccharide (LPS).

Material/Methods: The mouse model of AKI was developed by intraperitoneal injection of LPS. The mice were also treated intraperitoneally with romidepsin (FK228) six hours following injection of LPS. Markers of renal injury were measured, including blood urea nitrogen (BUN), serum creatinine (SCR), and serum cystatin C (Cys C) were measured. Histology and transmission electron microscopy were performed to evaluate tissue injury further. Levels of HDACs were detected by quantitative real-time polymerase chain reaction (qRT-PCR) and Western blot. Co-immunoprecipitation (Co-IP) and chromatin immunoprecipitation (ChiP) assays were used to investigate the regulation of CYP2E1 expression.

Results: Treatment with romidepsin (FK228) significantly reduced the levels of BUN, SCR, and Cys C induced by LPS. Histology of the mouse kidneys showed that treatment with romidepsin (FK228) reduced the degree of renal injury. CYP2E1 significantly reduced following treatment with romidepsin (FK228) in the mouse model of AKI. Also, acetylation of H3 was upregulated following treatment with romidepsin (FK228), and binding of hepatocyte nuclear factor-1 alpha (HNF-1α) on the CYP2E1 promoter was significantly increased.

Conclusions: In a mouse model of LPS-induced AKI, treatment with romidepsin (FK228) downregulated the expression of CYP2E1 by inhibiting the binding if HNF-1α with the CYP2E1 promoter to reduce renal injury.

MeSH Keywords: Histology • Histone Deacetylase Inhibitors • Pharmacology • Reactive Oxygen Species

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/918528
ANIMAL STUDY

Background

Acute kidney injury (AKI) is an important clinical condition that results in the loss of kidney function and has been investigated in epidemiologic, clinical, translational, and basic science research studies. Worldwide, the incidence of AKI in hospitalized adult patients has been reported to be as high as 21.6%, with a mortality rate of approximately 23.9% [1, 2]. Also, AKI is strongly associated with accelerating chronic kidney disease (CKD) to end-stage renal disease (ESRD) [3, 4]. However, improved methods of prevention and treatment of AKI remain to be identified.

Sepsis is a systemic inflammatory response caused by bacterial infection, and is a common cause of AKI. Approximately 40% of patients with severe sepsis and septic shock develop sepsis-associated AKI [5]. Lipopolysaccharide (LPS), a constituent of the Gram-negative bacterial cell wall, is widely used in establishing rodent models of sepsis-associated AKI by intraperitoneal injection [6]. LPS that is released during sepsis is an important cause of AKI, and is involved in the pathogenesis of renal damage by inducing the release of pro-inflammatory cytokines and increasing oxidative stress with the development of reactive oxygen species (ROS) [7]. Therefore, the identification of drugs that suppress inflammation and oxidative stress might be potential treatments for sepsis-associated AKI.

Romidepsin (FK228) or depsipeptide, is a selective inhibitor of histone deacetylase 1 (HDAC1) and HDAC2, and is derived from the Gram-negative, facultative anaerobic coccobacillus, Chromobacterium violaceum [8]. Romidepsin (FK228) has several biological and pharmacological activities against tumor cell growth [9], and inflammation [10], and also has antiviral properties [11]. In a mouse model of liver fibrosis, the administration of romidepsin (FK228) significantly reduced liver injury and fibrosis by inhibiting the expression of alpha-smooth muscle actin (α-SMA) [12]. However, the effects of romidepsin (FK228) on AKI remain unknown.

Therefore, this study aimed to investigate the effects and molecular mechanisms of romidepsin (FK228) in a mouse model of AKI induced by LPS.

Material and Methods

Reagents and antibodies

Romidepsin (FK228) (S3020), was purchased from Shanghai Selleck Chemicals Co., Ltd. (Shanghai, China). Lipopolysaccharide (LPS) derived from Escherichia coli O55: B5 (L2637) was purchased from Sigma-Aldrich (St Louis, MO, USA). Antibodies to acetyl-histone H3 (4499) were purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA). Anti-KIM-1 (AF1817) was purchased from R&D Systems (Chengdu, China). Antibodies to CYP2E1 (ab28146), HDAC1 (ab7028), HDAC2 (ab12169), HDAC3 (ab7030), hepatocyte nuclear factor-1 alpha (HNF-1α) (ab96777) and Nrf2 (ab62352) were purchased from Abcam (Cambridge, UK). Anti-GAPDH (TA-08) was purchased from ZSGB Biotechnology (Beijing, China).

The mouse model of lipopolysaccharide (LPS)-induced acute kidney injury (AKI)

Ten-week-old mice were housed with 12-hour light/dark cycle, fed regular chow, and given water ad libitum. All animal procedures and care were carried out in accordance with the Institutional Animal Care and Use Committee (IACUC) of North Sichuan Medical College (approval number: NSMC-2017-0061), and followed national and international laws and policies on laboratory animal care. To assess the role of romidepsin (FK228) in AKI, the LPS-induced mouse model of AKI was established, as previously described [5]. LPS (10 mg/kg) was injected intraperitoneally into the mice, and the control mice were injected with an equivalent volume of normal saline. Romidepsin (FK228) (20 µg/kg) was injected intraperitoneally 6 h later. Then, 24 hours after LPS administration, the mice were euthanized, and the kidney tissues were removed for further experiments.

Detection of indicators of renal function

Tail vein blood samples from each mouse were centrifuged to obtain the serum samples. Mouse urine was collected using diuresis metabolic cages [13]. Blood urea nitrogen (BUN) and serum creatinine (SCR) were measured using a 7600 Automatic Biochemical Analyzer (Hitachi Ltd., Tokyo, Japan). Serum cystatin C (Cys C) (XY-SJH-XS1441) and kidney injury molecule-1 (KIM-1) (XY-SJH-XS1225) ELISA kits were purchased from Xuanya Biotechnology Co., Ltd (Shanghai, China), and the levels were detected according to the manufacturer’s instructions.

Kidney histology

The kidney tissues of the mice were sampled for histology. Samples were fixed with 10% neutral buffered formalin, dehydrated with an equivalent volume of normal saline. Romidepsin (FK228) (20 µg/kg) was injected intraperitoneally 6 h later. Then, 24 hours after LPS administration, the mice were euthanized, and the kidney tissues were removed for further experiments.

Transmission electron microscopy

Mouse kidney tissue was fixed in cacodylate buffer containing 2% glutaraldehyde at 4°C, post-fixed in 1% osmium tetroxide, and following the manufacturer’s instructions.
and stained with 2% uranyl acetate. Samples were embedded in Poly/Bed® 812 Araldite resin (Polysciences Inc., Eppelheim, Germany), and were sectioned with an ultramicrotome to obtain ultrathin sections at 100 nm in thickness. Transmission electron microscopy was performed and photography was undertaken at a magnification of ×20,000 using a Tecnai 10 microscope (FEI Company, Eindhoven, the Netherlands).

Western blot

The mouse kidney tissues were lysed in RIPA buffer (Beyotime, Shanghai, China). The protein concentration was measured using a bicinchoninic acid (BCA) protein assay kit (CW Biotech Co. Ltd., Beijing, China), according to the manufacturer’s instructions. The samples were heated at between 98–100°C for 5 min. 30 μg of total protein underwent sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), and then transferred onto PVDF membranes. The membranes were blocked with 5% dried skimmed milk powder, and the blots were incubated with primary antibodies overnight at 4°C. Antibodies to Ac-H3 (1: 1000), KIM-1 (1: 2000), CYP2E1 (1: 5000), HDAC1 (1: 1000), HDAC2 (1: 1000), HDAC3 (1: 1000), HNF-1 α (1: 2000), Nrf2 (1: 1000) and GAPDH (1: 5000) were used. After washing three times with TBS-Tween solution, the blots were incubated with horseradish peroxidase-conjugated secondary antibodies for 60 minutes at 20°C. An enhanced chemiluminescent (ECL) detection kit was used (GE Healthcare Life Sciences, Logan, UT, USA) to analyze the blots.

Quantitative real-time polymerase chain reaction (qRT-PCR)

All primers were designed using the OligoArchitect™ Online design tool (Sigma-Aldrich, St. Louis MO, USA) (www.oligoarchitect.com/LoginServlet) and synthesized by Huada Company (Shanghai, China) (Table 1). TRIzol reagent was used to isolate total RNAs, and reverse transcription was performed using an iScript™ cDNA synthesis kit (Bio-Rad, Hercules, CA, USA). SYBR™ Green PCR Master Mix (Thermo Fisher Scientific, Waltham, MA, USA) and the Opticon® 2 System (Bio-Rad, Hercules, CA, USA) were used to perform qRT-PCR, according to the manufacturer’s instructions.

Immunoprecipitation

Kidney tissue lysates were prepared using RIPA buffer containing a phosphatase inhibitor and protease inhibitor cocktail. A Reversible Immunoprecipitation System kit (Merck Millipore, Burlington, MA, USA) was used, according to the manufacturer’s instructions.

Chromatin immunoprecipitation (ChIP) assay

A ChIP assay kit (17-611) (Merck Millipore, Burlington, MA, USA) was used to detect the transcription factors that bound with the CYP2E1 promoter, according to the manufacturer’s instructions. Briefly, mouse kidney tissues were collected, and DNA fragments (200–500 bp) were obtained using ultrasound disruption. Transcription factor binding profiles were

Table 1. Quantitative real-time polymerase chain reaction (qRT-PCR) primers for different histone deacetylase (HDAC) mRNA.

| Gene   | Forward sequence | Reverse sequence | Product size (bp) |
|--------|------------------|------------------|-------------------|
| HDAC1  | 5'-TGTCACATCTCGTCCTAC-3' | 5'-GTACTTGGTCATCTCCCTAC-3' | 77 |
| HDAC2  | 5'-GACTCATACCTGGCTGTTA-3' | 5'-ACTCATCGCTGTGGTATT-3' | 104 |
| HDAC3  | 5'-GCTTCTATAAGAGTATG-3' | 5'-GATGTAGTCCTCAGAATG-3' | 84 |
| HDAC4  | 5'-CTCTGAGTCAGAAGAATG-3' | 5'-ACACTGTCACACCAATTTC-3' | 118 |
| HDAC5  | 5'-AAGGAGAAGCAGACAG-3' | 5'-ACTTGGAACAGGAAAT-3' | 76 |
| HDAC6  | 5'-AATCATGTGAGTGCATCA-3' | 5'-AGGATTCTTCTCCTGTC-3' | 80 |
| HDAC7  | 5'-CAAGAATTCGACCAATCT-3' | 5'-CTTCTGCTGTTGACCAACT-3' | 75 |
| HDAC8  | 5'-CAAGGTGTCGAGTAGTG-3' | 5'-GTTGTAACAGGGATTAG-3' | 78 |
| HDAC9  | 5'-GAACATCATCCTCATTG-3' | 5'-AGATCATCACCAGGAG-3' | 81 |
| HDAC10 | 5'-GATTCTGCTCTCCTTGA-3' | 5'-TGAGAATGCTACACCAAT-3' | 102 |
| GAPDH  | 5'-CGGAGTCACGGATTGTTGTCAT-3' | 5'-AGCTTCTCCTCAGGTTGGTAAG-3' | 114 |
| Nrf2   | 5'-AAGCAAGAGGCGGAGAAT-3' | 5'-CACATCACAGTGAGGATGTT-3' | 101 |

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analyzed by the JASPAR 2018 open-access database [14]. An antibody against HNF-1α was used to immunoprecipitate with the sheared chromatin. The immunoprecipitation product was subjected to qRT-PCR using primers specific to the promoter. The primer pairs of the CYP2E1 promoter were as follows: Forward: 5'-GACAGGTGCCAGCAACCA-3'; Reverse: 5'-CCTCTACTCACCAATAACCGAC-3'.

**Statistical analysis**

Data were analyzed using SPSS version 13.0 software (IBM Corp., Armonk, NY, USA). Significant differences were calculated using t-tests or one-way analysis of variance (ANOVA) for paired samples. P<0.05 was regarded as significant, and P<0.01 was highly significant.
Expression and location of class I HDACs in the mouse model of lipopolysaccharide (LPS)-induced acute kidney injury (AKI)

Recent studies demonstrated that class I HDACs are required for kidney development and proliferation of embryonic proximal tubular cells [15]. However, the expression of HDACs also increased tissue injury. The LPS-induced mouse model of AKI was used to determine the levels of HDAC mRNA and protein in the kidney tissue. As shown in Figure 1A, quantitative real-time polymerase chain reaction (qRT-PCR) showed that HDAC mRNA levels varied in AKI. HDAC1, 2, 3, 9, and 10 were significantly upregulated in the AKI model when compared with the control mice, and the HDAC1 and 2 levels were the greatest. HDAC7 and 8 were significantly downregulated. However, only HDAC1 and 2 proteins showed a two-fold upregulation, while HDAC3 was not upregulated when compared with the control mice (Figure 1B). These results indicated that selective inhibition of HDAC1 and 2 had a protective effect in the mouse model of AKI.

Romidepsin (FK228) improved kidney microstructure in the mouse model of LPS-induced AKI

LPS-induced AKI has previously been reported to be associated with renal microvascular hypoperfusion and tissue hypoxia [16]. In this study, in the mouse model of AKI, the degeneration of renal tubular epithelial cells and shrinkage, vacuoles, cell swelling, necrosis, and cell loss were observed. Microvascular congestion was found in the glomerulus, and around the renal tubules, and renal interstitial inflammatory cell infiltrates were present (Figure 2A, 2B, 2D, 2E, 2G, 2H). However, congestion in the glomerular microvasculature and swelling of the renal tubular cells were present in the LPS-treated and romidepsin (FK228)-treated mice, but the degree of injury was less than that in the mouse model of LPS-induced AKI (Figure 2C). Transmission electron microscopy showed renal tubular lumen occlusion with mitochondrial damage, but...
Treatment with romidepsin (FK228) significantly reduced renal injury (Figure 2F, 2I).

Romidepsin (FK228) improved renal function in the mouse model of LPS-induced AKI

The levels of blood urea nitrogen (BUN), serum creatinine (SCR), and serum cystatin C (Cys C) were evaluated in the mouse model of LPS-induced AKI, and these serum markers significantly increased in the 24 hours following LPS injection when compared with the control mice (P<0.05). The levels of BUN, SCR, and Cys C in mice treated with romidepsin (FK228) decreased with significant differences between the LPS-treated group and the LPS and romidepsin (FK228)-treated group (P<0.05), as shown in Figure 3A–3C. Also, the expression of kidney injury molecule-1 (KIM-1) in kidney tissue, which is a marker of tubular injury, was evaluated by Western blot and quantitative real-time polymerase chain reaction (qRT-PCR).

Both Western blot and qRT-PCR showed that the expression of KIM-1 was significantly increased in the mouse model of LPS-induced AKI when compared with the control mice (P<0.001). However, treatment with romidepsin (FK228) significantly reduced the expression of KIM-1 when compared with the LPS-treated group (Figure 3D, 3E) (P<0.001). Finally, analysis of the mouse urine showed that when compared with the control mice, urine KIM-1 levels in the LPS-treated group were increased by seven-fold, but there was only a 2.5-fold increase in the LPS and romidepsin (FK228)-treated group (Figure 3F).

Romidepsin (FK228) inhibited CYP2E1 transcription by blocking hepatocyte nuclear factor-1 alpha (HNF-1α) binding to its promoter

CYP2E1 and Nrf2 have previously been shown to have roles in the generation of reactive oxygen species (ROS), which are involved in sepsis-mediated AKI [17,18]. In this study, the
expression levels of kidney CYP2E1 and Nrf2 were determined by qRT-PCR and Western blot to evaluate the effects of treatment with romidepsin (FK228). LPS administration resulted in the upregulation of the mRNA and protein levels of CYP2E1 and Nrf2 24 h, which supported the role of CYP2E1 in reducing ROS injury due to LPS. However, romidepsin (FK228) treatment reduced CYP2E1 levels without affecting Nrf2 expression, which indicated that romidepsin (FK228) reduced the LPS-induced ROS injury by inhibiting CYP2E1 expression (Figure 4A, 4B).

Levels of acetyl-histone H3 following treatment with romidepsin (FK228)

There was no significant difference in the acetylation level of the histone H3 between the control group and the LPS-treated group. However, romidepsin (FK228) treatment significantly increased the level of acetylated histone H3 (Figure 4B). The transcription factor, hepatocyte nuclear factor-1 alpha (HNF-1α), has been previously shown to increase CYP2E1 expression [19,20]. Therefore, a co-immunoprecipitation (Co-IP) assay was performed to evaluate whether HNF-1α directly binds to acetylated histone H3. The results showed that HNF-1α combined with acetylated histone H3 in the kidney. (D) The chromatin immunoprecipitation (ChIP) assay showing the downregulated level of HNF-1α that combined with the CYP2E1 promoter in the AKI kidney. Bar graphs represent the mean±SEM between each experimental group. * P<0.05 was considered to be statistically significant. * P<0.05, ** P<0.01 and *** P<0.001. N=3 independent experiments in each group.
HNF-1α by deacetylating histone H3 on the CYP2E1 promoter and reduced the levels of ROS in the mouse kidney tissue.

Discussion

The aim of this study was to investigate the effects of romidepsin (FK228), a selective inhibitor of histone deacetylase 1 (HDAC1) and HDAC2, and the molecular mechanisms of its action, in a mouse model of acute kidney injury (AKI) induced by lipopolysaccharide (LPS). The results showed that romidepsin (FK228) protected the mouse kidney from acute injury by downregulation of CYP2E1. The kidney is the site of metabolism of many drugs, and it is also vulnerable to toxic damage. Impaired kidney function can result in the accumulation of metabolic endproducts in vivo.

AKI is a common and severe disease that can result in acute renal failure. Serum markers of AKI include increased blood urea nitrogen (BUN) and increased serum creatinine (SCR) levels in more than 50% of cases [21]. The mechanism of AKI is a complex process that includes renal cell apoptotic, necrosis, and inflammation, all of which may be new targets for potential therapy [2]. However, the relationship between inflammation and oxidative stress on the adaptive response of AKI remains controversial. This study analyzed the therapeutic effect of romidepsin (FK228) on LPS-mediated AKI in a mouse model. The findings showed that LPS-induced renal injury in mice was significantly reduced by romidepsin (FK228), with a significant reduction in the levels of BUN, SCR, and serum cystatin C (Cys C) and kidney tissue levels of hepatocyte nuclear factor-1 alpha (HNF-1α) and CYP2E1 in kidney tissue. Romidepsin (FK228) treatment also reduced acute renal injury by reducing the generation of ROS.

Histone deacetylase inhibitors have roles in reducing fibrosis, inflammation, oxidation in several diseases. Advani et al. showed that vorinostat, or suberoylanilide hydroxamic acid (SAHA), reduced kidney injury by reducing the levels of reactive oxygen species (ROS) in mice with diabetes mellitus [22]. Li et al. and Van Beneden et al. showed that valproic acid (VPA) could effectively reduce the degree of renal injury in rats and mice in a model of renal fibrosis and renal hypertension and in a mouse model of adriamycin nephropathy treated with histone deacetylase inhibitors [23,24]. Wang et al. showed that SAHA could prevent the formation of kidney stones and reduce the degree of renal damage by downregulation of osteopontin and CD44 and reduced the levels of oxidative stress [25]. Both SAHA and VPA are broad-spectrum HDAC inhibitors, but they are limited as potential therapeutic agents due to unstable pharmacodynamics and their side effects [26].

Based on these previous studies, the present study investigated the effects of romidepsin (FK228), a class I HDAC-specific inhibitor, on renal injury in the mouse model of AKI. Romidepsin (FK228) is a histone deacetylase inhibitor, which can inhibit the deacetylation of both HDAC1 and 2 [8], and inhibits the proliferation of tumor cells by upregulating cyclin-dependent kinase inhibitor 1A [27]. In this study, the levels of blood urea nitrogen (BUN), serum creatinine (SCR), and kidney injury molecule-1 (KIM-1) in the urine of LPS-induced kidney injury mice were decreased after intraperitoneal injection of romidepsin (FK228), suggesting that romidepsin (FK228) has an inhibitory effect on kidney injury. Also, the levels of HNF-1α and CYP2E1 in kidneys tissues were significantly decreased with the use of romidepsin (FK228), suggesting that romidepsin (FK228) may promote the repair of oxidative damage by regulating the acetylation level of histone, thus promoting the metabolism of romidepsin (FK228) toxicity.

CYP2E1 and Nrf2 are two key factors involved in response to oxidative damage and are specifically expressed in the liver and kidney [28]. CYP2E1 expression levels rise during drug injury and are associated with an increase in the intracellular oxidative stress response. Wang et al. showed that inhibiting CYP2E1 expression reduced the degree of AKI by inhibiting the release of catalytic iron and the formation of ROS [29,30]. However, activation of Nrf2 has previously been shown to reduce oxidative stress and has a protective effect on the kidney in AKI [29,30]. The increased expression of CYP2E1 results in increased expression levels of Nrf2 protein and mRNA, which can be considered as a response to oxidative damage caused by CYP2E1 [31]. In the present study, during LPS-mediated AKI in the mouse model, the increase in CYP2E1 and Nrf2 protein levels indicated that the accumulation of intracellular ROS was increased and was associated with cell damage. Following treatment with romidepsin (FK228), the mRNA and protein levels of CYP2E1 decreased significantly, but the levels of Nrf2 were not, and serum levels of indicators of renal function, including BUN and SCR, showed a downward trend. These findings indicated that the therapeutic mechanism of romidepsin (FK228) on AKI in the mouse model might be achieved by down-regulating the expression of CYP2E1, but not Nrf2.

Histone deacetylase usually does not bind DNA directly but changes the conformation of chromatin by forming a complex with transcription factors, or by regulating the deacetylation of histone lysine sites, thereby affecting the interaction between transcription factors and DNA [31]. Previous studies have reported that histone regulation can affect the binding of HNF-1 and HNF-3 beta to CYP2E1 promoter by altering acetylation levels, which control the expression of CYP2E1 [19,32]. In the present study, the histone deacetylase inhibitor, romidepsin (FK228), directly increased the level of acetylated histone H3 in the mouse kidney tissue. The results of the co-immuno-precipitation (Co-IP) assay showed that the acetylation level of H3 regulated the binding level of the transcription factor...
hepatocyt nuclear factor-1 alpha (HNF-1α) to histone H3. The chromatin immunoprecipitation (ChIP) assay further confirmed that HNF-1α was the critical transcription factor regulating CYP2E1, and the levels of acetylated histone H3 regulated its binding ability with CYP2E1 promoter. The findings from this study showed that in a mouse model of AKI, romidepsin (FK228) reduced kidney injury by increasing the binding ability of HNF-1α to the CYP2E1 promoter, and down-regulated the expression of CYP2E1 by upregulation of the acetylation level of histone H3 to inhibit the oxidative stress reaction in kidney tissue in a mouse model of LPS-induced AKI.

Conclusions

This study aimed to investigate the effects and molecular mechanisms of romidepsin (FK228), a selective inhibitor of histone deacetylase 1 (HDAC1) and HDAC2, in a mouse model of acute kidney injury (AKI) induced by lipopolysaccharide (LPS). The results showed that romidepsin (FK228) protected the mouse kidney from acute injury and that the mechanism involved downregulation of CYP2E1, which is a phase I toxic metabolic protein. The findings from this study support the need for further studies on the mechanisms of HDAC inhibitors, including romidepsin (FK228), in the reduction of AKI.

Conflict of interest

None.

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