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The role of class I histone deacetylase (HDAC) on gluconeogenesis in liver

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ABSTRACT

Hepatic gluconeogenesis is crucial for glucose homeostasis. Although sirtuin 1 (Sirt1) is implicated in the regulation of gluconeogenesis in the liver, the effects of other histone deacetylases (HDAC) on gluconeogenesis are unclear. The aim of this study was to identify the role of class I HDACs in hepatic gluconeogenesis. In HepG2 cells and the liver of mice, the expressions of phosphoenol pyruvate carboxykinase (PEPCK) and hepatocyte nuclear factor 4α (HNF4α) were significantly decreased by treatment with a newly designed class I HDAC inhibitor, Ky-2. SiRNA knockdown of HDAC1 expression, but not of HDAC2 or HDAC3, in HepG2 cells decreased PEPCK and HNF4α expression. In HepG2 cells, insulin-stimulated phosphorylation of Akt and forkhead box O 1 (FoxO1) was increased by Ky-2. Pyruvate tolerance tests in Ky-2-treated high-fat-diet (HFD)-fed mice showed a marked reduction in blood glucose compared with vehicle-treated HFD mice. These data suggest that class I HDACs increase HNF4α protein expression and the transcriptional activity of FoxO1, followed by the induction of PEPCK mRNA expression and gluconeogenesis in liver.

1. Introduction

Glucose homeostasis is maintained through the hormonal regulation of hepatic glucose production and peripheral glucose uptake by skeletal muscle and adipose tissue. The liver can produce glucose by breaking down glycogen (glycogenolysis) and by *de novo* synthesis of glucose (i.e., gluconeogenesis) from non-carbohydrate precursors such as lactate, pyruvate, glycerol and α-ketoacids [1]. The rate of gluconeogenesis is a highly regulated process in which phosphoenolpyruvate carboxykinase (PEPCK) is the key rate-controlling enzyme. The expression of PEPCK is controlled by hormones including insulin, glucagon and glucocorticoids at the transcriptional level. Among the complex network of transcription factors and cofactors that contribute to gluconeogenic gene expression in liver, the transcription factors cAMP responsive element-binding protein (CREB), hepatocyte nuclear factor 4α (HNF4α) and forkhead box O 1 (FoxO1), and the coactivators peroxisome proliferators-activated receptor γ coactivator 1 α (PGC-1α), seem to be particularly important [2–4]. CREB induces the expression of PGC-1α, which in turn facilitates the transcriptional activity of HNF4α, glucocorticoid receptor and FoxO1 on the promoters of PEPCK. Insulin activates the serine/threonine kinase Akt through the insulin signaling pathway, and Akt phosphorylates FoxO1, thus decreasing its transcriptional activity and reducing the transcription of the PEPCK gene. Although the mechanisms involved in gluconeogenesis are well understood, it is likely that other, still unidentified molecules or pathways are involved in the regulation of gluconeogenesis.

The structure of chromatin is complex and is made up of DNA, histones and non-histone proteins [5,6]. The "Histone code" is a well-established hypothesis whereby the remodeling of chromatin is a fundamental epigenetic mechanism for regulating gene expression, involving the reversible post-translational modification of amino acids in the histone tails. Acetylation is currently the best characterized histone modification and is performed under the control of histone acetyltransferases (HATs) and histone deacetylases (HDACs) [7,8]. In humans, four HDAC classes have been identified. Class I includes HDACs 1, 2, 3 and 8, class II includes HDACs 4, 5, 6, 7, 9 and 10, and class IV include HDAC11. The third class of HDAC, the Sir2 family of deacetylases, requires NAD and is structurally unrelated to the other HDAC classes. Furthermore, the Sir2 class is not inhibited by compounds that inhibit class I or II HDACs, and does not appear to include histones as a primary substrate.

In addition to the direct effect of HDACs on histone deacetylation, HDACs can also deacetylate various transcription factors

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and regulatory proteins [9,10]. The acetylation status of these non-histone proteins is correlated with protein stability, protein–protein interactions, protein localization and DNA binding activity. These effects of HDACs have been linked mechanistically to the pathogenesis of several diseases, including cancer [10], neurodegenerative disease [11] and lung disease [12]. Thus, small molecules or compounds that inhibit HDAC activity have been investigated in an attempt to establish new treatments for these diseases.

Several studies have reported correlations between glucose homeostasis and HDACs [13,14]. In terms of hepatic glucose metabolism and HDACs, Sirt1 was implicated in the regulation of FoxO1 and/or PGC-1α activity, to thereby regulate gluconeogenesis and glycogen synthesis [15–18]. However, the effects of other HDACs on the regulation of hepatic glucose metabolism are unclear.

We recently developed a new class I HDAC inhibitor, *cyclo*(-L-Asu(NHOH)-Aib-L-Phe-D-Pro-), a chlamydocin-hydroxamic acid analog that we designated as Ky-2 [19]. In the present study, we investigated the potential roles of class I HDACs on the regulation of glucose metabolism, and the potential utility of Ky-2 as a new treatment for diabetes. The results of our study indicate that Ky-2 inhibited gluconeogenesis in the liver of high-fat diet (HFD)-fed mice by suppressing PEPCK expression. We further revealed that the suppression of PEPCK expression by Ky-2 was due to decreases in HNF4α expression and FoxO1 activity.

2. Materials and methods

2.1. Cells and reagents

HepG2 (human hepatoma) cells were purchased from the American Type Culture Collection (Manassas, VA). Polyclonal antibodies for HNF4α, HDAC3, CREB regulated transcription coactivator 2 (CRTC2, also known as TORC2) and PGC-1α were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Antibodies for FoxO1, phospho-FoxO1(Thr24)/FoxO3a(Thr32), Akt, phospho-Akt(Ser473), HDAC1 and HDAC2, CREB and phospho-CREB were purchased from Cell Signaling Technology (Danvers, MA). Ky-2 was generated as previously described [19]. All other reagents were of analytical grade and were purchased from Sigma–Aldrich (Gillingham, UK) or Roche (Mannheim, Germany).

2.2. RNA interference

Small interfering RNAs (siRNAs) against human HDACs, On-TARGETplus HDAC siRNA SMARTpool (L-003493-00-0005, siHDAC1; L-003495-00-0005, siHDAC2; L-003496-00-0005, siHDAC3) and negative control On-TARGETplus siCONTROL Non-targeting pool (D-001810, siNC) were purchased from Dharmacon (Denver, CO). Transient transfection was done using Lipofectamine RNAiMAX reagent (Invitrogen, Carlsbad, CA). HepG2 cells were transfected with HDAC1, HDAC2 or HDAC3 RNAi. After 48–72 h, the cells were subjected to the indicated experiments.

2.3. Experimental animals

Male, 8-week-old C57BL/6 mice were purchased from Clea Japan Inc. (Tokyo, Japan). The mice were fed with the HFD [(HFD32; fat kcal: 56.7% of total kcal), Clea Japan Inc., Tokyo, Japan] for 3 weeks, and Ky-2 (5 mg/kg body weight) or vehicle were injected subcutaneously daily for 1 week. Blood glucose and serum insulin levels were measured using a One-Touch Ultra® glucometer (LifeScan Inc., Milpitas, CA) and enzyme-linked immunosorbent assays (Shibayagi, Gunma, Japan), respectively. After an overnight (10 h) fast, mice underwent glucose tolerance tests with intraperitoneal injection of 1 g/kg body weight glucose. Mice in the fed state underwent an insulin tolerance test, with intraperitoneal injection of 1.25 U/kg body weight insulin. After an overnight fast, mice also underwent pyruvate tolerance tests, with intraperitoneal injection of 2 g/kg body weight pyruvate dissolved in saline. All animal studies were performed in accordance with the Animal Care and Use Committee of Kumamoto University.

2.4. Real-time qRT-PCR

Total RNA was extracted with TRIzol (Life Technologies Inc., Carlsbad, CA). First-strand cDNA was synthesized from 1 μg of total RNA primed with oligo dT. We then quantified the gene transcripts using the LightCycler System (Roche Molecular Biochemicals, Indianapolis, IN). PCR was performed using SYBR Green I master mix and specific primers (Supplementary Table 1). The quantitative results for PEPCK, HNF4α and PGC-1α were normalized by the levels of β-actin mRNA.

2.5. Immunoblotting

The protein concentration was determined by the Bradford method (Bio-Rad Laboratories Inc., Hercules, CA). Proteins (20–160 μg/lane) were electrophoretically separated by SDS–PAGE, transferred onto nitrocellulose membranes, and immunoblotted. Signals were detected using an ATTO Cooled CCD Camera System Light-Capture and quantified using ATTO Densitograph Software CS Analyzer (ATTO Corp., Tokyo, Japan).

2.6. Statistical analysis

Data are given as means ± SEM. Differences between two groups were assessed using unpaired two-tailed *t* tests and differences among more than two groups were assessed by analysis of variance (ANOVA). Data involving more than two repeated measures were assessed by repeated-measures ANOVA. When a significant difference was found with ANOVA, *post hoc* analyses were performed using Fisher's protected least significant difference test. Values of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Effects of the class I HDAC inhibitor Ky-2 on glucose metabolism in vivo

To study the potential role of Ky-2 in glucose metabolism *in vivo*, we treated HFD mice with Ky-2. Although the blood glucose level in the fed state was not significantly affected by treatment with Ky-2, fasting blood glucose was significantly decreased by Ky-2 (Fig. 1A). In comparison, the serum insulin level was not significantly affected by Ky-2 in either the fed or fasted state (Fig. 1B).

As shown in Fig. 1C, Ky-2 did not significantly affect blood glucose during the glucose tolerance test (Fig. 1C). However, in the insulin tolerance test, the blood glucose levels at 60, 90 and 120 min after insulin injection were significantly decreased by Ky-2 treatment (Fig. 1D). Because the fasting blood glucose was improved by Ky-2, we speculated that Ky-2 improved glucose metabolism by reversing insulin resistance, particularly in the liver. Therefore, to examine the effect of Ky-2 on hepatic gluconeogenesis *in vivo*, we performed pyruvate tolerance tests. Blood glucose levels at 15, 30 and 60 min after pyruvate injection were significantly lower in Ky-2-treated mice than in vehicle-treated mice (Fig. 1E). Thus, the results of the pyruvate tolerance test indicate that hepatic gluconeogenesis was suppressed by treatment with the HDAC inhibitor Ky-2 *in vivo*.

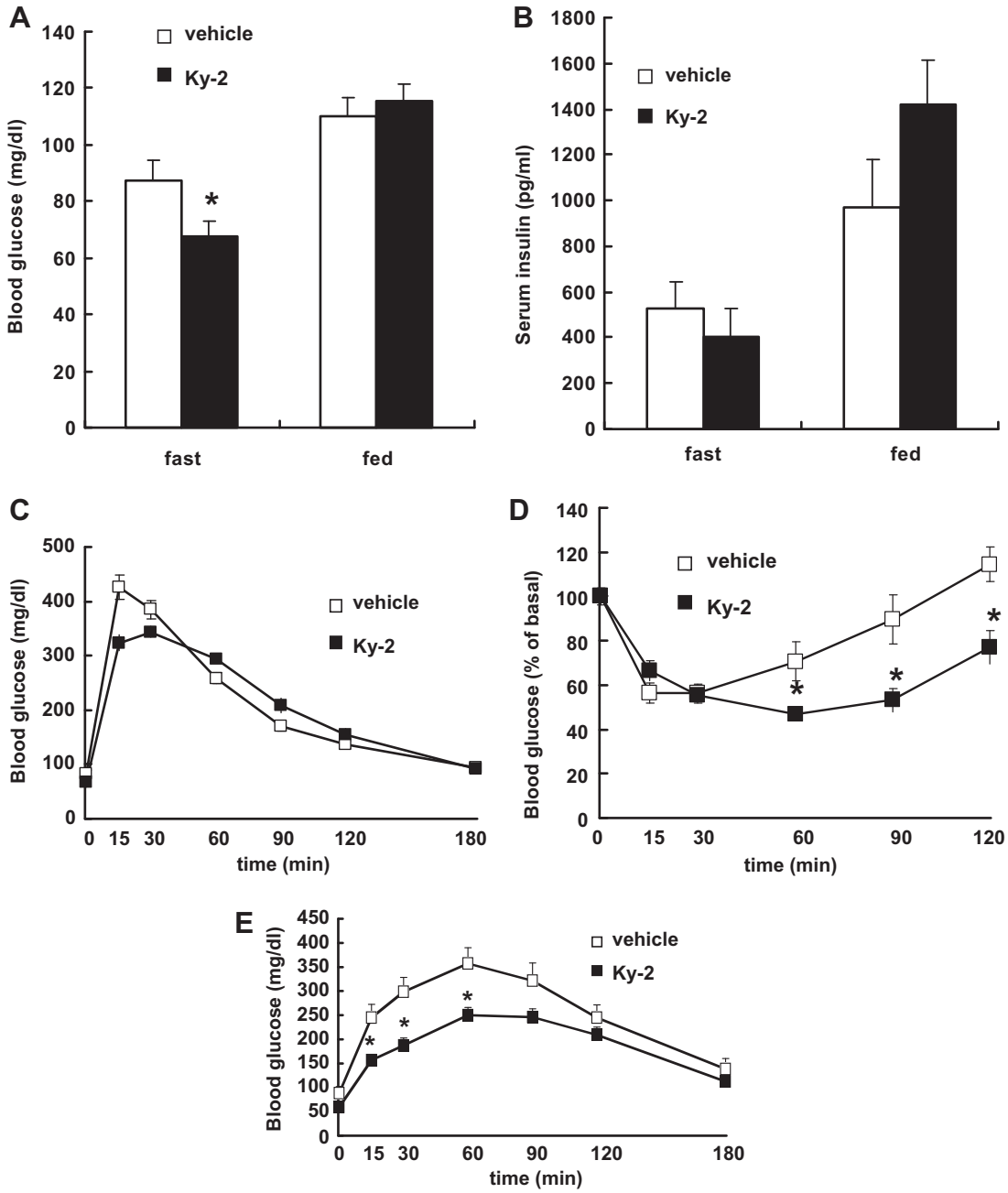

Fig. 1. Effects of the HDAC inhibitor Ky-2 on glucose metabolism in high-fat diet (HFD)-fed mice. (A) Blood glucose and (B) serum insulin levels in HFD mice treated with Ky-2. C57BL/6 mice were treated with HFD for 3 weeks, and vehicle ($n = 20$, white bar) or Ky-2 (5 mg/kg body weight; $n = 20$, black bar) was injected subcutaneously for 1 week. Data are means ± SE; $^{*}P < 0.05$ versus vehicle (two-tailed Student's *t*-test). (C) Glucose (1 g/kg body weight), (D) insulin (1.25 U/kg body weight) and (E) pyruvate (2 g/kg body weight) tolerance tests in HFD mice treated with vehicle ($n = 10$, white squares) or Ky-2 ($n = 10$, black squares). Data are means ± SE; $^{*}P < 0.05$ versus vehicle (repeated-measures analysis of variance and Fisher's protected least significant difference test).

3.2. Effects of Ky-2 on gluconeogenesis-related molecules in HepG2 cells

To evaluate the mechanism responsible for the effects of Ky-2 on hepatic gluconeogenesis, we investigated the mRNA and protein expression, including phosphorylation status, of the key molecules associated with gluconeogenesis using HepG2 cells, a human hepatocyte cell line.

The expression of PEPCK mRNA was significantly decreased by treatment with Ky-2, as compared with vehicle (Fig. 2A). The mRNA and protein expression of HNF4α was also significantly decreased by Ky-2 (Fig. 2A and B and Supplementary Fig. 1A). The expression of PGC-1α tended, although not significantly, to decrease the mRNA and protein levels in response to Ky-2 treatment (Fig. 2A and B and Supplementary Fig. 1B). Because it was reported that PGC-1α expression is regulated by the activation of CREB and CRTC2 [20], we investigated the expression and phosphorylation status of CREB and CRTC2. However, neither the expression nor phosphorylation of CREB and CRTC2 were affected by Ky-2 (Fig. 2C).

Because the transcription factor FoxO1 was reported to regulate the expression of PEPCK gene [4] and Akt phosphorylates FoxO1, resulting in translocation from nucleus to cytosol [21], we evaluated the effects of Ky-2 on FoxO1 and Akt. We found that

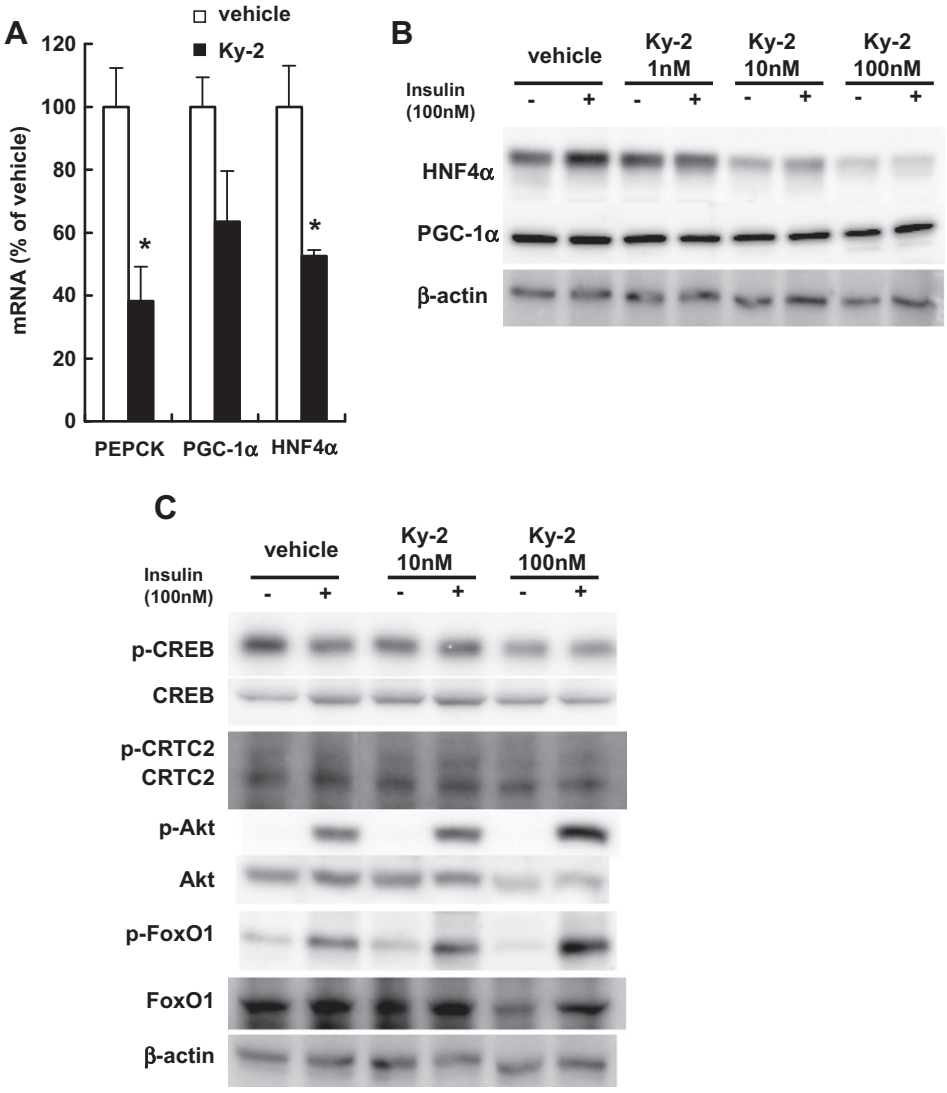

Fig. 2. Effects of Ky-2 on gluconeogenesis-related molecules in HepG2 cells. (A) mRNA expression of PEPCK, HNF4α and PGC-1α in HepG2 cells treated with Ky-2. HepG2 cells were treated with vehicle (white bar) or Ky-2 (100 nM, black bar) for 72 h, and subjected to quantitative-RT-PCR. Data are means ± SE; * $P < 0.05$ versus vehicle (two-tailed Student's *t* test). (B) Protein expression of PGC-1α and HNF4α in Ky-2-treated HepG2 cells. HepG2 cells were treated with Ky-2 (1, 10 or 100 nM) for 72 h and the lysate was subjected to western blotting. (C) Protein expression and phosphorylation status of gluconeogenesis-related molecules in Ky-2-treated HepG2 cells. After stimulation with insulin (100 nM for 15 min), the HepG2 cell lysate was subjected to western blotting.

insulin-induced phosphorylation of Akt and FoxO1 were increased by Ky-2 (Fig. 2C and Supplementary Fig. 2), indicating that Ky-2 suppresses FoxO1 transcriptional activity.

Taken together, these results suggested that the suppression of class I HDAC activity by Ky-2 led to the reduction of HNF4α expression and FoxO1 transcriptional activity, and was followed by a decrease in PEPCK gene expression.

3.3. Effects of class I HDAC siRNAs on gluconeogenesis in HepG2 cells

To confirm the correlation between HDAC and gluconeogenesis, and to identify which isoform of class I HDAC regulates the expression of PEPCK and HNF4α, we performed siRNA-induced knockdown of HDAC1, HDAC2 or HDAC3 expression in HepG2 cells. Suppression of each isoform was confirmed by western blotting, although the magnitude of HDAC3 suppression less than that of HDAC1 and HDAC2 (relative level: HDAC1, 12.4 ± 3.6%; HDAC2, 15.9 ± 6.3%; HDAC3, 57.2 ± 12.4%) (Fig. 3A). The mRNA expression of PEPCK was significantly decreased by siRNA for HDAC1, but not with siRNA for HDAC2 or 3 (Fig. 3B). The mRNA expression of HNF4α was also significantly decreased by siRNA for HDAC1 or HDAC2, but not with siRNA for HDAC3 (Fig. 3C). Consistent with these effects on mRNA, the HNF4α protein was also reduced by HDAC1 knockdown (Fig. 3A and Supplementary Fig. 3). These data suggest that HDAC1 is involved in HNF4α expression and the subsequent increase in PEPCK expression.

3.4. Effect of Ky-2 on hepatic gluconeogenesis-related molecules in vivo

To examine the effect of Ky-2 on molecules associated with gluconeogenesis *in vivo*, we performed quantitative-RT-PCR and western blot analysis of liver tissues from mice treated with Ky-2. Consistent with the experiments in HepG2 cells, PEPCK mRNA expression was significantly decreased by Ky-2 (Fig. 4A). The expressions of HNF4α mRNA (Fig. 4A) as well as HNF4α protein (Fig. 4B) were decreased by Ky-2, whereas PGC-1α protein was not significantly affected (Fig. 4B). Moreover, insulin-stimulated phosphorylation of Akt and FoxO1 was increased by Ky-2 (Fig. 4C). These data confirm that Ky-2 reduces HNF4α expression

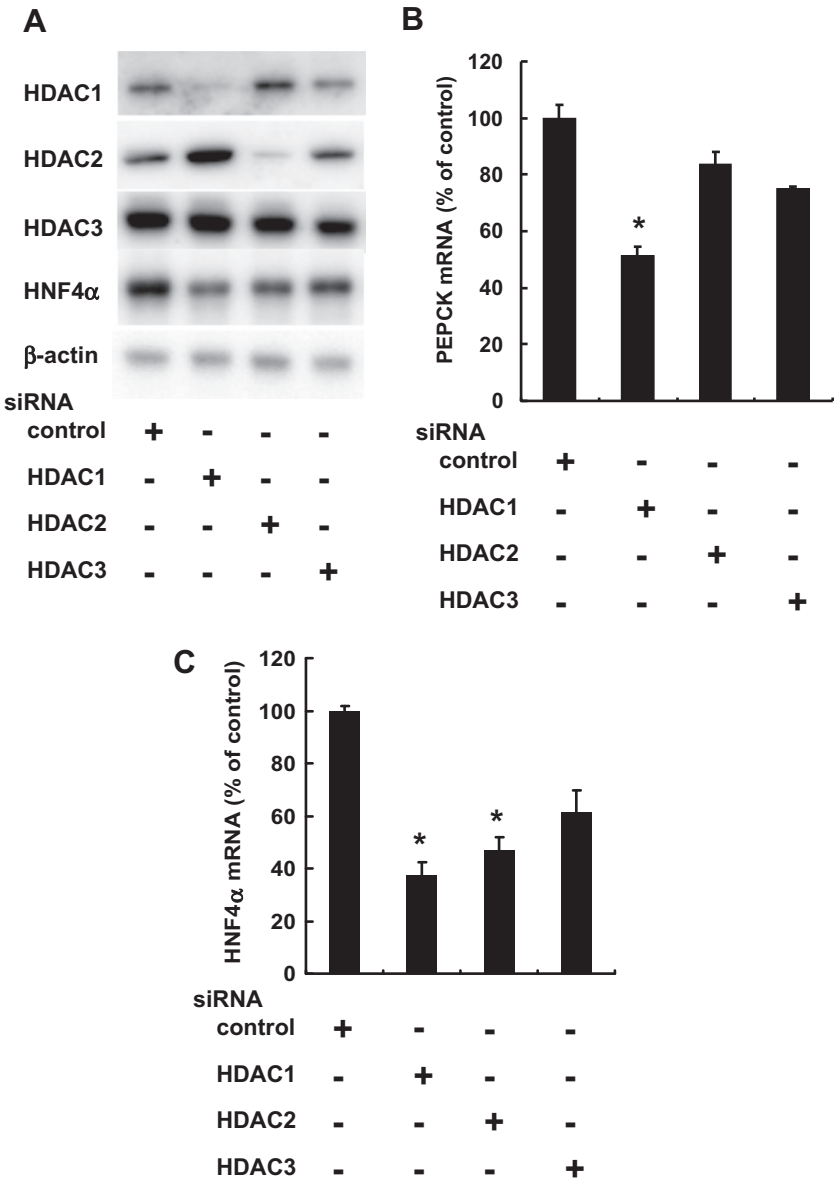

Fig. 3. Effects of siRNA knockdown of HDACs on gluconeogenesis in HepG2 cells. (A) Protein expression of HDAC1, 2 and 3, and HNF4α in HepG2 cells transfected with control siRNA or siRNA for each HDAC. After transfection, the cell lysate was subjected to western blotting. (B) PEPCK and (C) HNF4α mRNA expression in HepG2 cells transfected with the indicated siRNA. HepG2 cells were transfected with the indicated siRNA and subjected to quantitative RT-PCR. Data are means ± SE; $^{*}P < 0.05$ versus basal levels (analysis of variance and Fisher's protected least significant difference test).

and increases the phosphorylation of FoxO1, which is followed by reduced PEPCK expression in the liver *in vivo*.

4. Discussion

In this study, we used a chlamydocin-hydroxamic acid analog, Ky-2, as a specific inhibitor of HDACs. A number of natural and synthetic chemicals, including trichostatin A (TSA), cyclic tetrapeptides and suberoyl anilide hydroxamic acid have been reported to inhibit HDACs, and many of these compounds have entered clinical trials for the treatment of cancer and neurodegenerative diseases [11,22]. Cyclic tetrapeptides are specific inhibitors of class I HDACs, while TSA inhibits HDAC classes I, II and IV [22]. We synthesized a new inhibitor from chlamydocin, a member of the tetrapeptide group of compounds [19]. Since TSA contains a hydroxamic acid, we synthesized the chlamydocin-hydroxamic acid analog by replacing the epoxyketone moiety of chlamydocin with hydroxamic acid. This chlamydocin-hydroxamic acid, Ky-2, is a specific HDAC inhibitor, with IC_{50} values of 8, 20 and 160 nM for HDAC 1, 4 and 6, respectively, indicating that Ky-2 is more specific for class I HDACs [19].

Using Ky-2, we investigated the role of class I HDACs in the regulation of hepatic gluconeogenesis *in vitro* and *in vivo*. We found that class I HDAC mainly acts via two distinct pathways to increase PEPCK expression. The first pathway is that HDAC induces HNF4α expression, while the second involved HDAC-mediated suppression of insulin-induced phosphorylation and activation of Akt, followed by decreased FoxO1 phosphorylation (Fig. 4D). Since phosphorylated FoxO1 was translocated from the nucleus to cytosol, resulting in decreased transcriptional activity, our results suggest that HDAC induces FoxO1 transcriptional activity.

To exclude the possibility that the effects of Ky-2 on gluconeogenesis are independent of HDAC, we evaluated the effects of another HDAC-specific inhibitor, TSA, on gluconeogenesis-related

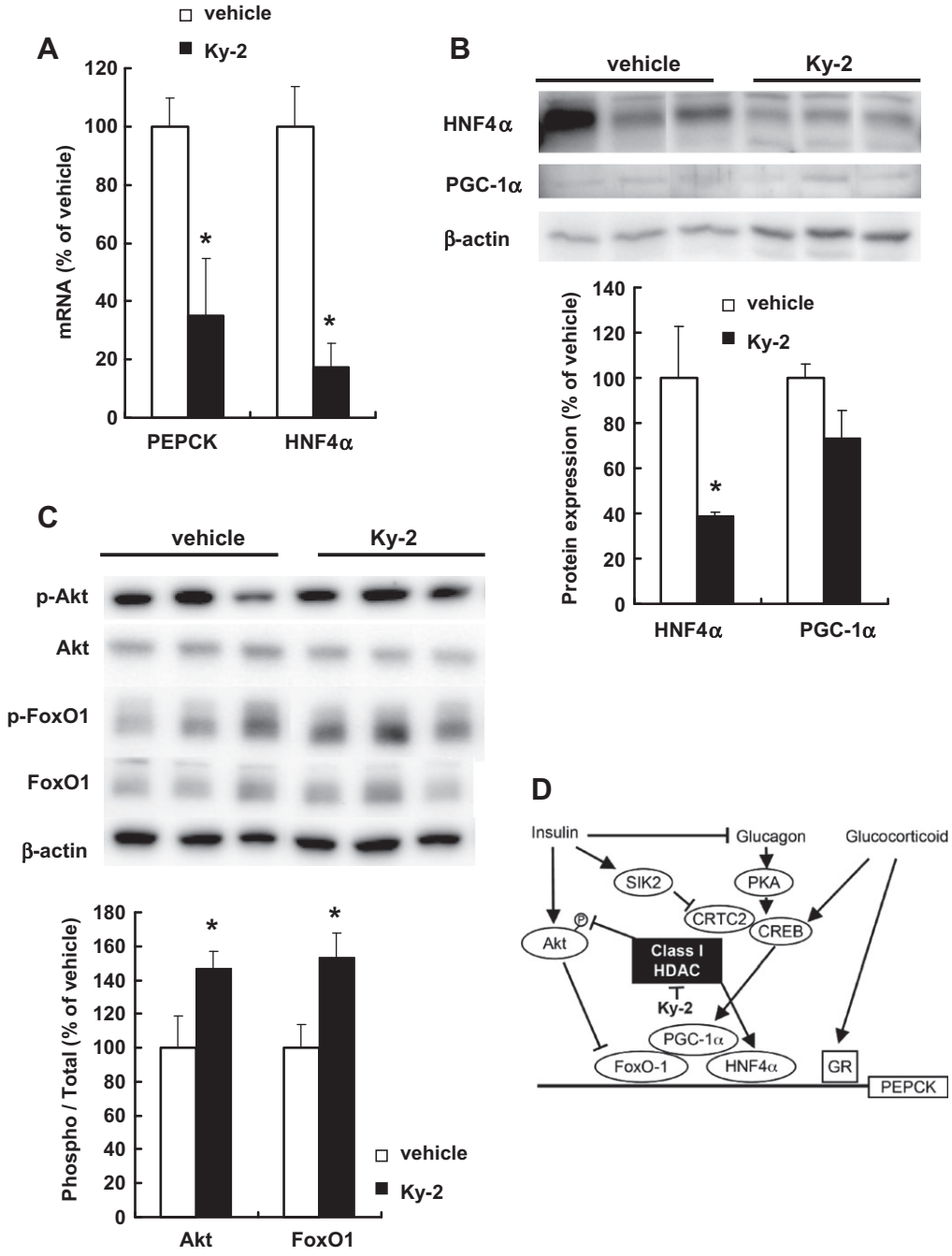

Fig. 4. Effects of Ky-2 on hepatic gluconeogenesis-related molecules *in vivo* in high-fat diet (HFD)-fed mice. (A) Hepatic mRNA expression of PEPCK and HNF4α in Ky-2-treated HFD mice. After treatment with vehicle (white bar) or Ky-2 (5 mg/kg body weight, black bar) for 1 week, the liver was extracted and subjected to quantitative RT-PCR. Data are means ± SE; $^{*}P < 0.05$ versus vehicle (two-tailed Student's *t* test). (B) Protein expression of PGC-1α and HNF4α. After Ky-2 treatment, the liver tissue lysate was subjected to western blotting. (C) Phosphorylation status of Akt and FoxO1 in the liver of Ky-2-treated mice. The Ky-2 treated HFD mice were intraperitoneally injected with saline or insulin (1.25 U/kg body weight), and 15 min later, the liver was removed and subjected to western blotting. Upper panel: representative western blots. Lower panel: densitometric quantitation of the western blot (B, C). Data are means ± SE; $^{*}P < 0.05$ versus vehicle (two-tailed Student's *t* test). (D) Schematic representation of the effect of class I HDAC on PEPCK gene expression.

molecules in HepG2 cells. The expression of HNF4α was decreased by TSA, while that of PGC-1α tended to be decreased by TSA (Supplementary Fig. 4A). However, although the phosphorylation of Akt was increased, the phosphorylation of FoxO1 was not affected by TSA (Supplementary Fig. 4B). The differences in the effects of Ky-2 and TSA might be because TSA inhibits class II and IV HDACs in addition to class I HDAC.

To further investigate the effect of class I HDACs on gluconeogenesis, we used siRNAs to knockdown HDAC1, HDAC2 or HDAC3 expression. In HepG2 cells, knockdown of HDAC1 suppressed the expression of PEPCK and HNF4α, whereas knockdown of HDAC2 and HDAC3 did not. Therefore, these results suggest that at least HDAC1 is involved in the induction of PEPCK via the increase in HNF4α expression.

Regarding the association between HDAC and HNF4α, it was reported that a complex of silencing mediator for retinoid and thyroid receptors (SMRT) and HDAC (HDAC3 or HDAC4) acted as a co-repressor for HNF4α [23]. However, in this study, the expression of

HNF4α was decreased by Ky-2 or siRNA for HDAC1. The discrepancy between our results and those of the previous report might be due to the different cells used in each study. Because HNF4α mRNA was also decreased by Ky-2 and siRNA for HDAC1, we believe that HDAC1 is involved in the increased transcription of HNF4α. It was reported that several *trans*-acting factors, including HNF1α, HNF6 and GATA-6, and repressors, including chicken ovalbumin upstream promoter transcription factor II (COUP-TFII), sterol regulatory element-binding protein 2 (sREBP2) and p53, regulate the transcriptional activity of the HNF4α gene promoter [24–26]. We speculate that HDAC1 affects the *trans*-acting factors and/or repressors that regulate HNF4α gene expression. Further studies are needed to address this hypothesis.

Several investigators have reported that the deacetylation of FoxO1 by the class III HDAC Sirt1 induced FoxO1 activation [16,17]. However, in this study, Ky-2 actually increased Akt activation and FoxO1 phosphorylation, which resulted in the translocation of FoxO1 from the nucleus to the cytosol and thus decreased FoxO1 transcription activity [21]. More studies are necessary to identify the signaling pathway between class I HDACs and Akt.

It was reported previously that PGC-1α plays an important role in the regulation of hepatic gluconeogenesis. For example, Rodgers et al. showed that Sirt1 interacted with and deacetylated PGC-1α, which induced gluconeogenic genes and hepatic glucose output [15]. Meanwhile, Koo et al. reported that the activation of CREB and CRTC2 by glucagon induced hepatic gluconeogenesis via PGC-1α expression [20]. In this study, we observed a trend, although not statistically significant, toward a decrease in PGC-1α expression, which was elicited by Ky-2, but we could not observe the effect of Ky-2 on expression and phosphorylation of CREB and CRTC2. Thus, although it is possible that PGC-1α and the CRTC2–CREB pathway are involved in Ky-2-mediated inhibition of gluconeogenesis, we believe that PGC-1α and the CRTC2–CREB pathway are not the main targets for class I HDAC in the regulation of gluconeogenesis in liver.

In conclusion, the results of our study indicate that inhibition of class I HDACs using Ky-2 suppresses HNF4α protein expression and the transcriptional activity of FoxO1, which is followed by suppressed PEPCK expression and hepatic gluconeogenesis. Therefore, class I HDACs may play an important role in the regulation of hepatic gluconeogenesis, and that class I HDAC inhibitors may offer a novel treatment for diabetes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2010.11.086.

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