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ORIGINAL ARTICLE

Dexmedetomidine ameliorates high-fat diet-induced nonalcoholic fatty liver disease by targeting SCD1 in obesity mice

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Abstract

Fatty liver disease is one of the main hepatic complications associated with obesity. To date, there are no therapeutic drugs approved for this pathology. Insulin resistance (IR) is implicated both in pathogenesis of nonalcoholic fatty liver disease (NAFLD) and in disease progression from steatosis to nonalcoholic steatohepatitis. In this study, we have characterized effects of an α_2-adrenoceptor agonist, dexmedetomidine (DEX), which can alleviate IR in hepatocytes in high-fat diet (HFD)-induced NAFLD mice. The NAFLD mice received a daily intraperitoneal administration of DEX (100 $\mu g \cdot kg^{-1}$) after 16 days exhibited lower body weight, fewer and smaller fat droplets in the liver, markedly reduced the plasma triglyceride levels, accompanied by improvement of liver damage. This inhibition of lipid accumulation activity in obese mice was associated with a robust reduction in the mRNA and protein expression of the lipogenic enzyme stearyl-coenzyme A desaturase 1 (SCD1), which was probably mediated by the inhibition of C/EBP β, PPAR γ and C/EBP α through suppressing α_{2A}-adrenoceptor (α_{2A}-AR) via negative feedback. Additionally, DEX can also improve IR and inflammation by inhibiting the mitogen-activated protein kinases (MAPK) and nuclear factor kappa beta (NFκB) signaling pathway in vivo. Our findings implicate that DEX may act as a potential anti-steatotic drug which ameliorates obesity-associated fatty liver and improves IR and inflammation, probably by suppressing the expression of SCD1 and the inhibition of MAPK/NFκB pathway and suggest the potential adjuvant use for the treatment of NAFLD.

KEYWORDS
DEX, NAFLD, SCD1, α_{2A}-AR

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; C/EBP, CCAAT enhancer binding protein; DEX, Dexmedetomidine; H&E, hematoxylin and eosin; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; IpGTT, Intraperitoneal Glucose Tolerance Test; IpITT, Intraperitoneal Insulin Tolerance Test; IR, insulin resistance; MAPK, mitogen-activated protein kinases; NAFLD, Nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NFκB, nuclear factor kappa beta; ORO, Oil Red O; PPAR γ, peroxisome proliferators-activated receptor γ; SCD1, stearyl-coenzyme A desaturase 1; T-CHO, total cholesterol; α_{2A}-AR, α_{2A}-adrenoceptor.

1 | INTRODUCTION

NAFLD has significantly increased in prevalence in parallel with increasing obesity and is now the most common cause of chronic liver disease in the worldwide.[1] NAFLD begins with accumulation of triacylglycerols in the liver (steatosis), and is defined by hepatic fatty infiltration amounting to greater than 5% by liver weight or the presence of over 5% of hepatocytes loaded with large fat vacuoles.[2,3] This disease is heterogeneous and represents a spectrum of diseases ranging from simple steatosis to more severe forms of liver injury including nonalcoholic steatohepatitis, fibrosis, and hepatocellular carcinoma.[4-6] Current management of NAFLD[7] is largely focused on lifestyle interventions through diet and exercise to try and achieve weight loss and to ameliorate underlying metabolic and cardiovascular risk factors.[8-10] Although many pharmacological interventions, including antidiabetic agents, antidyslipidemic drugs, antihypertensive drugs, antiobesity drugs, and several other treatment targets, to limit the development and progression of NAFLD have been tested,[7] none are to date specifically licensed for the treatment of NAFLD and efforts to control complications arising from the condition are far from satisfactory. Thus, better understanding of hepatocytic lipid accumulation and inflammation might provide a new therapeutic strategy for NAFLD prevention and treatment.

NAFLD is closely associated with IR and type 2 diabetes,[11] IR is implicated both in pathogenesis of NAFLD and in disease progression from steatosis to NASH.[12] Thus, modulation of IR represents a potential strategy for NAFLD treatment. It has been recently reported that DEX can alleviate IR in hepatocytes[13] by reducing endoplasmic reticulum stress and protect against hepatic lipid peroxidation and histological damage in sepsis and IR animal models.[14-16] In addition, studies have found that DEX can maintain postoperative blood glucose stability[17] and reduce blood glucose level in diabetic patients by inhibiting systemic inflammation. These all suggest that DEX may play a protective role in body metabolic homeostasis. Based on these findings, we speculated that DEX can act against HFD-induced obesity and NAFLD and the underlying molecular mechanism deserves further study.

DEX is a highly selective α_2-adrenoceptor (α_2-AR) and imidazoline receptor agonist,[18] has been widely used for sedation and analgesia in anesthesia as well as antihypertensive, anxiolytic, and anti-delirium in the intensive care unit.[19-21] DEX can exert its effects via activation of three α_2-adrenoreceptor subtypes. α2A and α_{2C}-adrenoreceptor (α_{2A}-AR and α_{2C}-AR) located in presynaptic membrane, and regulate the release of neurotransmitter (norepinephrine) in the central nervous system (CNS), cause transient hypertension, hyperglycemia, and tachycardia, which form a negative feedback loop to reduce the release of norepinephrine by inhibiting α_{2A}-AR.[22] Studies have been reported that stimulation of α_{2A}-AR can activate cyclic AMP-response element-binding protein (CREB)[23]; depletion of CREB inhibits the expression of C/EBP α, C/EBP β, and PPAR γ.[24] Besides, SCD1 is one of the down-stream genes of PPAR γ[25] and the transcription of PPAR γ can be activated by C/EBP β and C/EBP α.[26]

In this study, we demonstrated that DEX ameliorates HFD-induced NAFLD by targeting SCD1 via negative feedback in obesity mice, explore the signaling pathway involved and to identify a novel function of DEX on limiting fat accumulation in liver.

2 | MATERIALS AND METHODS

2.1 | Animals and treatments

All experimental procedures and the protocols with animals were approved by the Animal Care and Use Committee of the Chongqing Medical University and followed the National Institute of Health guidelines on the care and use of animals. The experiments were performed on 6- to 8-week-old male C57BL/6J. The mice were purchased from the Experimental Animal Center of Chongqing Medical University (Chongqing, China) and group-housed (5 mice per cage) 12-hour light/12-hour dark cycles, fed with normal diet (ND) and HFD (60% kcal in fat, beginning at age 8 week) and provided water ad libitum. IpGTT and IpITT were performed at 22–23 weeks of age to evaluate the whole-body metabolic state and insulin sensitivity, and then mice fed with HFD were assigned randomly to either the treatment group or control group based on bodyweight. DEX (Jiangsu Hengrui pharmaceutical co. LTD, China) was dissolved in saline which as a Vehicle at a terminal concentration of 20 $ng{\cdot}\mu L^{-1}$ and injected intraperitoneally (i.p.) at a dose of 100 μg per kg body weight ($\mu g{\cdot}kg^{-1}$), the rationale for DEX dosage and concentration selections were mainly referred to some other previous research reports.[27-30] Animals received a daily i.p. injection of Vehicle or DEX for 16 consecutive days. Ten mice per group were used for the experiment. Food intake (in grams) and body weight (in grams) were monitored daily (Figure 1A).

2.2 | Biochemical analysis in plasma

The following metabolites and metabolic hormones were measured in plasma: aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (T-CHO) and high-density lipoprotein cholesterol (HDL-C) assay kits were obtained from Jiancheng Institute of Biotechnology (Nanjing, China). Plasma insulin assay kit was purchased from CUSABIO (Wuhan, China) according to the manufacturer's instructions.

2.3 | Histological analysis of tissues

Liver samples were fixed in 4% paraformaldehyde and embedded in paraffin for histological assessments with hematoxylin and eosin (H&E) staining. Cryostat frozen sections were stained with

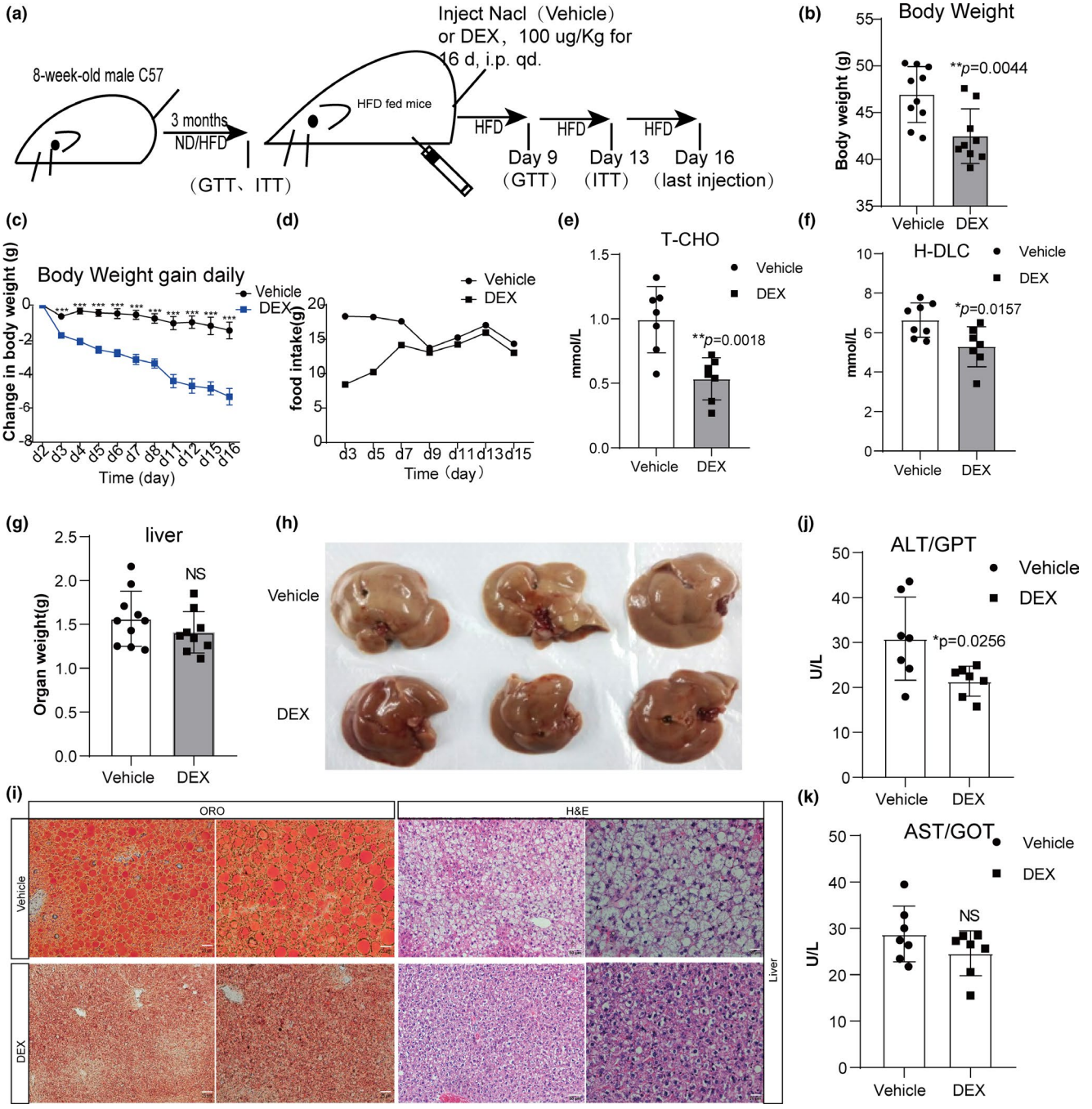

FIGURE 1 DEX protects mice against HFD-induced NAFLD. (A) Schematic shows the DEX and Vehicle injection strategy used in this study. In short, the mice were group-housed (5 mice per cage) and fed with HFD (beginning at age 8 week). IpGTT and IpITT were carried out after 14 weeks of ND or HFD feeding. At 22–23 weeks of age, HFD fed mice were assigned randomly to treatment and control group based on bodyweight. DEX was dissolved in saline which as a Vehicle at a terminal concentration of 20 ng μL^{-1} and injected intraperitoneally (i.p.) at a dose of 100 μg per kg body weight (μg kg^{-1}). Animals received a daily i.p. injection of Vehicle or DEX for 16 consecutive days. Ten mice per group were used for the experiment. Food intake and body weight were monitored daily ($n = 10$ per group). (B) Body weight of mice when sacrificed ($n = 10$ per group); (C) Changes in body weight daily while injection; (D) food intake once every 2 days while injection; (E) plasma total cholesterol (T-CHO) concentrations when sacrificed ($n = 7$ per group); (F) plasma high-density lipoprotein cholesterol (H-DLC) concentrations when sacrificed ($n = 7$ per group); (G) and (H) liver weight and appearance when sacrificed, Representative images are shown; (I) H&E and ORO staining of liver when sacrificed, Scale bars, 50 μm and 20 μm; (J) and (K) plasma ALT and AST activities were analyzed 24 h after the last injection ($n = 7$ per group). Data were analyzed by unpaired two-tailed Student's *t*-test. Values are expressed as the mean ± SD
*$P < .05$; ** $P < .01$; *** $P < .001$

Oil Red O (ORO) staining for analysis of lipids and fat depots in the liver.

2.4 | RNA isolation and RT-QPCR analysis

Total RNA was extracted using Trizol Reagent (Invitrogen, USA) and quantified using a spectrophotometer to ensure ratios of absorbance at 260 to 280 nm of 1.8–2.0. RNA was reversed-transcribed to generate cDNA using the Revert Aid first-strand cDNA synthesis kit (Thermo Scientific, USA) as per manufacturer's instructions. And then analyzed using the Power SYBR green PCR master mix (Applied Biosystems, Carlsbad, CA) with the ABI Prism 7500 qPCR machine (Applied Biosystems). Standard curves were constructed for each gene to confirm amplification efficiency. Quantification was calculated using the comparative cycle threshold ($2^{-\Delta\Delta Ct}$) method.

2.5 | Protein extraction and western blot analysis

Tissue homogenate or cells lysate in lysis buffer containing 10% SDS and 1 M Tris–HCl (pH6.8) supplemented with a cocktail of protease inhibitors (cOmplete Tablets) and phosphatase inhibitors (Roche, Germany). Lysates were then quantitated and equal amounts of protein were subjected to SDS-PAGE and immunoblotted with antibodies against HSP 90, SCD1, p-P65/P65, p-P38/P38, p-JNK/JNK, PPAR γ, C/EBP α, C/EBP β, FASN, ACC. Antibodies against HSP 90, p-P65/P65, p-P38/P38, p-JNK/JNK, and PPAR γ were from Cell Signaling Technology (Beverly, MA, USA), antibodies against C/EBP α was from Santa Cruz Biotechnology (Santa Cruz, CA, USA), antibodies against SCD1, FASN, and ACC were from proteintech (Wuhan, China), and antibodies against C/EBP β was from the Department of Biological Chemistry, Johns Hopkins University School of Medicine.

2.6 | Intraperitoneal glucose and insulin tolerance test (IPGTT/IPITT)

For the glucose tolerance test (GTT), mice were fasted for 14 h, weighed and basal blood samples taken from the tail tip, followed by intraperitoneal glucose injection with a 25% glucose solution (1 mg/g body weight), and tail blood glucose levels were taken at 30, 60, 90, and 120 min. For the insulin tolerance test (ITT), mice fasted for 4 h, weighed and basal blood samples taken from the tail tip, followed by intraperitoneal human insulin injection (Novo Nordisk) (0.75mU/g body weight), and tail blood glucose levels taken at 15, 30, 45, and 60 min.

2.7 | Cell culture

Human hepatic carcinoma cell line HepG2 cells were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco, USA) containing 10% (vol/vol) fetal bovine serum (FBS; Biological Industries, Israel), 1% penicillin-streptomycin (Beyotime, China) at 37°C with humidified air and 5% CO_2. Primary hepatocytes were isolated from C57BL/6J mice and cultured in Dulbecco's modified Eagle medium-low sugar (DMEM; Gibco, USA) with 10% fetal bovine serum (FBS; Biological Industries, Israel) for 2 to 4 h, after cells have attached, keep cells in serum-free medium to maintain their morphology.

2.8 | Statistical analysis

All the data in the graphs were expressed as mean ± standard deviations (SD). The statistical analysis was performed using GraphPad Prism version 8.0.1 (GraphPad Software). The significance of differences within and between groups was primarily evaluated using two-way analysis of variance [ANOVA; factors: treatment (Vehicle/DEX) or time] and the appropriate post hoc test for multiple comparisons. Comparisons between groups were made by unpaired two-tailed Student's *t*-test, where $p < .05$ was considered as statistically significant.

2.9 | Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[31] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[32]

3 | Results

3.1 | DEX protects mice against HFD-induced obesity and NAFLD

To investigate the effects of DEX on HFD-induced obesity and NAFLD, the obese mice fed HFD for 14 weeks were treated intraperitoneally with DEX or Vehicle. The changes in body weight and food intake were monitored daily. Interestingly, the treatment with DEX significantly reduced the body weight while food intake was less during the initial 7 days posttreatment but there was no significant difference after 7 days treatment (Figure 1B-D). Furthermore, the DEX group displayed lower levels of both total cholesterol (T-CHO) (Figure 1E) and high-density lipoprotein cholesterol (HDL-C) (Figure 1F) concentrations than controls. Consistent with these data, H&E histological and ORO staining (Figure 1I) showed that fat accumulation also decreased dramatically in livers of DEX-treated mice, accompany with decreasing liver weight (Figure 1G) and less pale liver(Figure 1H) comparing with Vehicle mice.

Furthermore, DEX-treated mice had significantly lower serum alanine transaminase (ALT) and aspartate transaminase (AST) activities (Figure 1J and K), indicating that DEX ameliorated liver injury in HFD-induced NAFLD. These findings indicate that DEX may play a protective role in HFD-induced obesity and NAFLD.

3.2 | DEX protects against HFD-induced hepatic glucose intolerance and improves insulin sensitivity

To assess whether fatty liver model is successful and to evaluate the whole-body metabolic state and insulin sensitivity before DEX treatment,IpGTT and IpITT were carried out after 14 weeks of ND or HFD feeding. The results showed significantly impaired glucose tolerance and markedly blunted insulin responsiveness in HFD-fed mice relative to ND-fed mice (Figure 2A and B). To test whether hepatic glucose metabolism could be modulated by DEX, IpGTT and IpITT were performed on mice at day 9 and day 13 after DEX treatment. We found that glucose intolerance (Figure 2C) and insulin resistance (Figure 2D) were improved with DEX treatment compared with Vehicle. Furthermore, DEX-treated mice had significantly lower random blood glucose levels compared with Vehicle (Figure 2E), suggests that DEX increased whole-body insulin sensitivity. In addition, we detected lipid infiltration in the liver using ORO staining prior and after DEX treatment, the liver exhibited fewer and smaller fat droplets in the liver after DEX treatment (Figure 2F). These findings suggest that DEX can protect against HFD-induced hepatic glucose intolerance and improves insulin sensitivity.

3.3 | DEX impedes SCD1, C/EBP α, C/EBP β, AND PPAR γ

To identify the molecular mechanisms underlying the anti-steatotic role of DEX, the expression of key lipid metabolism genes were screened, including FA synthesis, TG synthesis, FA oxidation, and lipid uptake genes in liver. The data revealed that the mRNA expression of stearoyl-Coenzyme A desaturase 1 (SCD1), which catalyzes saturated fatty acids to form monounsaturated fatty acids was dramatically decreased in DEX-treated mice (Figure 3A). The protein level of SCD1 also decreased in DEX-treated mice compared to Vehicle mice (Figure 3B and D). These data suggest that DEX decrease lipogenic genes expression especially downregulate the expression of SCD1 in vivo. Then we detected the protein level of C/EBP β, C/EBP α, and PPAR γ, all of them were significantly decreased in DEX-treated mice compared to Vehicle mice (Figure 3C and D).

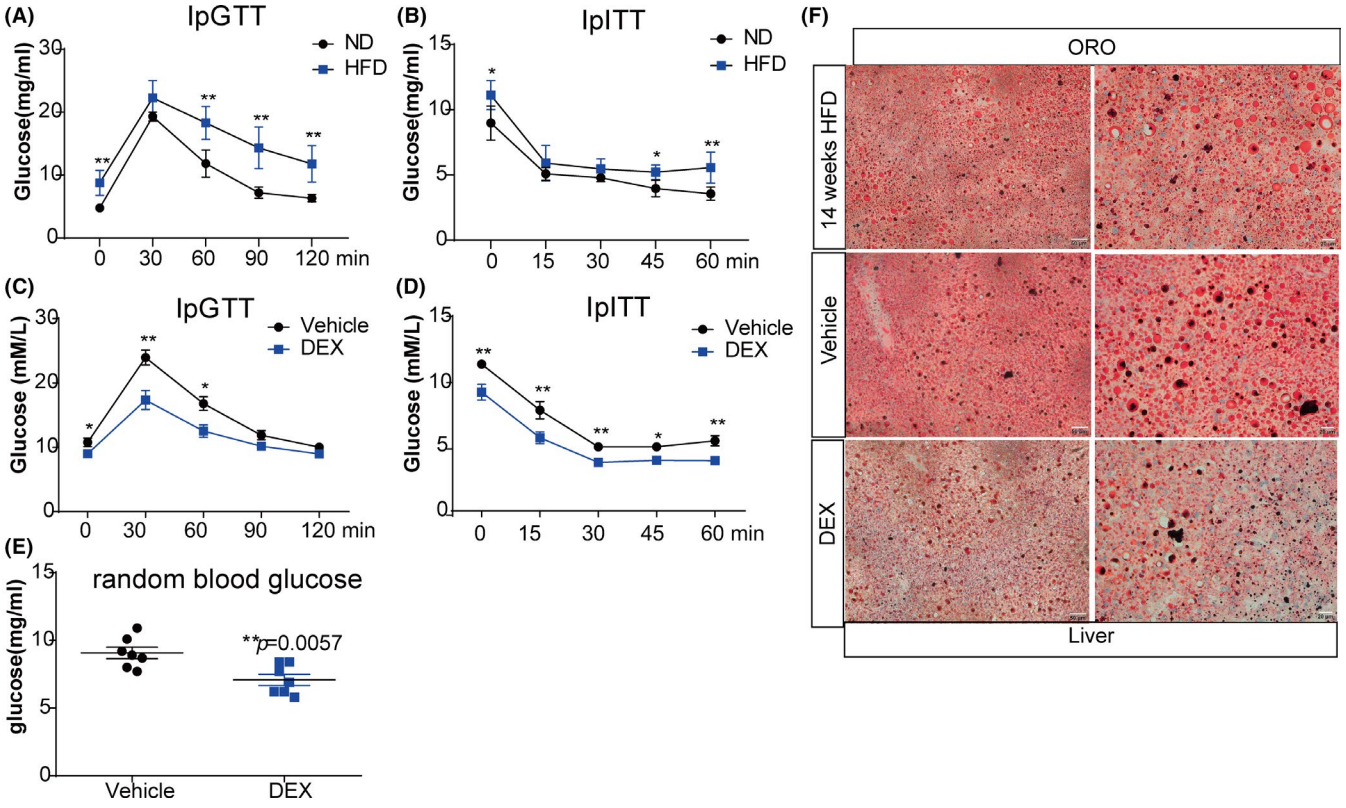

FIGURE 2 DEX protects against HFD-induced glucose intolerance and improves insulin sensitivity. (A) and (B) IpGTT and IpITT were performed at 22–23 weeks of age among ND and HFD fed mice ($n = 6$ per group); (C) and (D) IpGTT and IpITT assays were conducted among DEX and Vehicle-injected mice ($n = 10$ per group); (C) For the IpGTT, mice began fasting at 7 PM on day 8 for 14 h, then weighed and basal blood samples taken from the tail tip at 9 AM on day 9, followed by intraperitoneal glucose injection with a 25% glucose solution (1 mg/g body weight), and tail blood glucose levels were taken at 30, 60, 90, and 120 min; (D) For the ITT, mice began fasting at 9 AM on day 12 for 4 h, weighed and basal blood samples taken from the tail tip at 1 PM, followed by intraperitoneal human insulin injection (Novo Nordisk) (0.75mU/g body weight), and tail blood glucose levels taken at 15, 30, 45, and 60 min. (E) random plasma glucose of DEX- and Vehicle-treated mice after 14 days of injection ($n = 7$ per group); (F) ORO staining of liver prior and after DEX treatment, Scale bars, 50 μm and 20 μm. Values are expressed as the mean ± SD. *$P < .05$; ** $P < .01$; *** $P < .001$

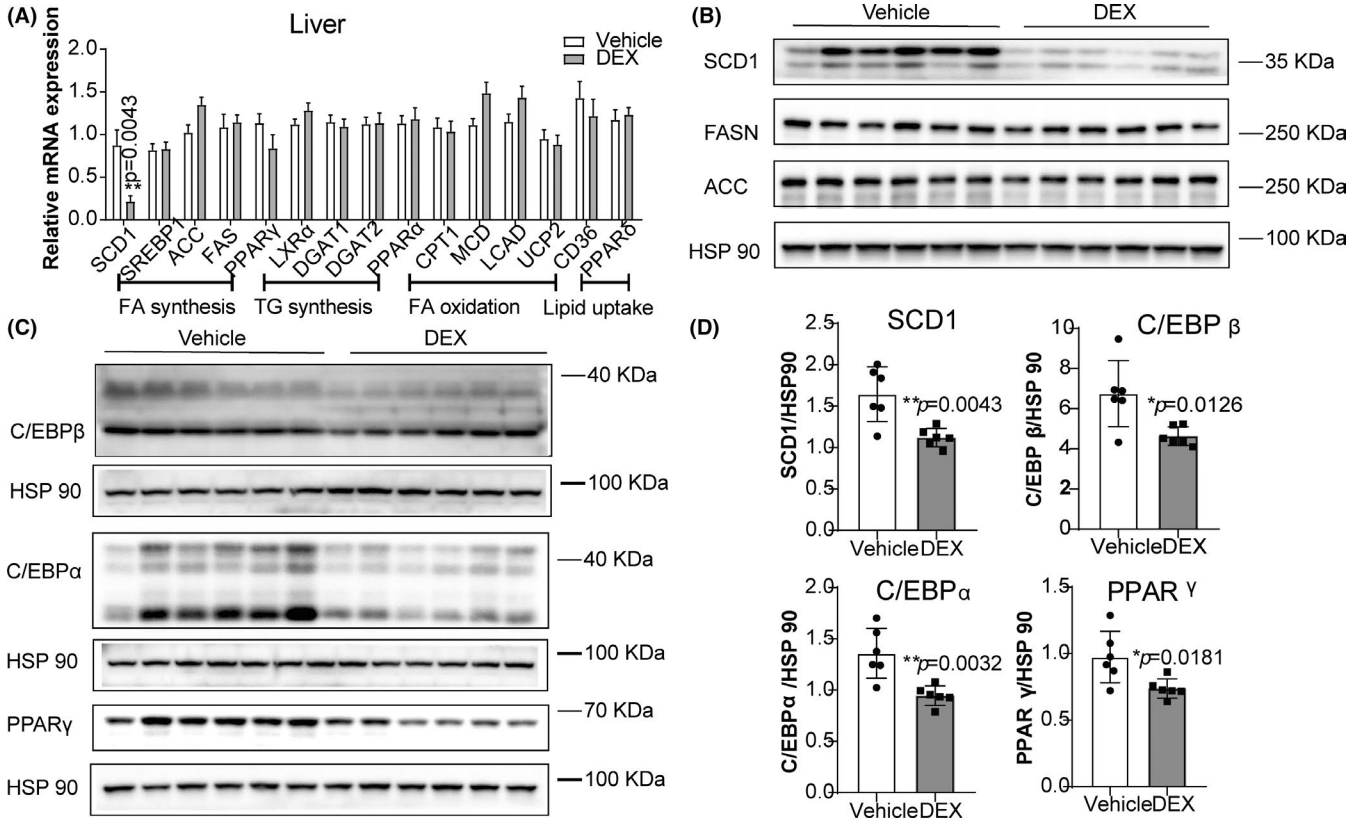

FIGURE 3 DEX impedes SCD1, C/EBP α, C/EBP β and PPAR γ gene expression in Liver. (A) RT-qPCR analysis of key lipid metabolism genes in liver from DEX- or Vehicle-treated mice ($n = 8$ per group); (B) Western blot analysis of key lipid synthesis proteins in liver from DEX- or Vehicle-treated mice ($n = 6$ per group), (C) Western blot analysis of C/EBP β, C/EBP α ,and PPAR γ in liver from DEX- or Vehicle-treated mice, respectively ($n = 6$ per group); (D) Quantitative analysis of the expression of SCD1, C/EBP β, C/EBP α, and PPAR γ in liver from DEX- and Vehicle-treated mice, respectively ($n = 6$ per group); Data were analyzed by unpaired two-tailed Student's *t*-test. Values are expressed as the mean ± SD. *$P < .05$; ** $P < .01$; *** $P < .001$

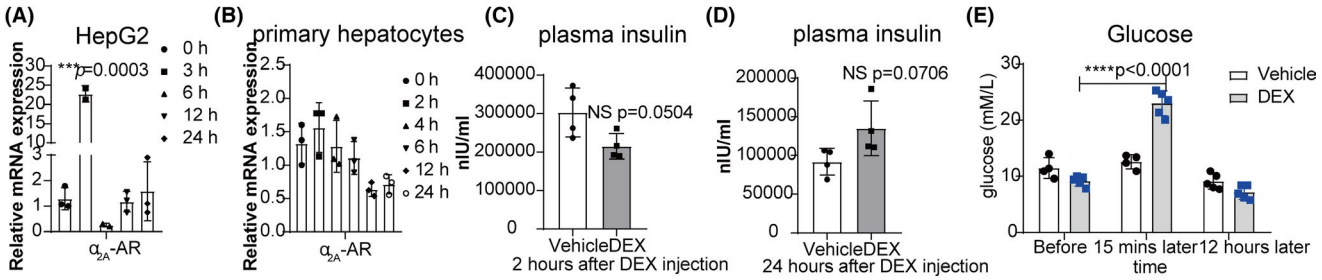

FIGURE 4 DEX impedes SCD1 gene expression through suppressing α_{2A}-AR via negative feedback. (A and B) RT-qPCR analysis of the expression of α_{2A}-AR in HepG2 cells and primary hepatocytes across DEX treatments ($n = 3$ per group); (C) ELISA assay analysis of plasma insulin levels in DEX and control mice 2 h after injection ($n = 4$ per group) and (D) 24 h after injection ($n = 4$ per group), (E) plasma glucose levels in mice after 15 min injection and 12 h injection after 16 days treated with DEX compared with the control ($n = 5$ per group). Data were analyzed by unpaired two-tailed Student's *t*-test. Values are expressed as the mean ± SD. *$P < .05$; ** $P < .01$; *** $P < .001$

3.4 | DEX impedes SCD1 gene expression through suppressing α_{2A}-AR via negative feedback

The expression of α_{2A}-AR was detected in HepG2 cells and primary hepatocytes, it turns out that the expression of α_{2A}-AR was first increased and subsequently a negative feedback loop to decrease gradually in a time-dependent manner across DEX treatment (Figure 4A and B). The results show that the negative feedback loop to inhibit α_{2A}-AR after treating with DEX may be the critical factor for the suppression of SCD1 in liver.

Besides, as a rate-limiting enzyme that catalyzes the synthesis of monounsaturated fatty acids, SCD1 could also be regulated by many factors in liver, including dietary, and hormonal factors. Studies have revealed that insulin up-regulate SCD1 expression through PI3K and

mTOR pathways,[33,34] another report showed that DEX can reduce insulin release through α_{2A}-AR[35] as well. Hence, we sought to identify whether DEX could regulate plasma insulin release and then influence the expression of SCD1. The level of plasma insulin in DEX group was indeed decreased 2 h later after injection (Figure 4C) while increased after 24 h treatment (Figure 4D), and this phenomenon was positive correlation with the changes in plasma glucose (Figure 4E) and α_{2A}-AR expression. Thus, these results further suggest that treatment with DEX decrease the expression of SCD1 probably through suppressing α_{2A}-AR via negative feedback.

3.5 | DEX also protects mice against HFD-Induced inflammation

To investigate the effects of DEX on HFD-induced inflammation, several key molecules closely related with inflammation in MAPK and NFκB signaling pathways were detected. We found that the phosphorylation of important events, JNK, P38, and P65 were significantly decreased in liver with DEX treatment (Figure 5A-D). These data all suggest that DEX may improve HFD-induced inflammation by inhibiting the MAPK/NFκB signaling pathway in vivo.

4 | DISCUSSION

NAFLD usually begins with an aberrant triglyceride (TG) and T-CHO accumulation in hepatocytes due to metabolic imbalances such as increased de novo lipogenesis.[36,37] High levels of plasma TG, T-CHO, and saturated fatty acids contribute to metabolic syndrome-associated inflammation and the secretion of pro-inflammatory cytokines.[38] It has been reported that DEX had protective effects in the hippocampus, spinal cord, heart, liver, and kidney[39,40] in normal rats through the antioxidative and anti-inflammatory effects. In our study, the protective effect of DEX was also observed in HFD-induced NAFLD. Body weight, plasma TG, and HDL-C were reduced significantly. Meanwhile, the lipid accumulation was decreased dramatically after treatment with DEX.

DEX is a highly selective α_2-adrenoceptor (α_2-AR) and imidazoline receptor agonist,[18] has been widely used for sedation and analgesia in anesthesia as well as antihypertensive, anxiolytic, and anti-delirium.[19-21] DEX may lead to the temporary less food intake as a sedation during the initial 7 days posttreatment, after this kind of calming effect gradually reduce and disappear, namely, the mice developed a tolerance to the sedative effects of DEX, food intake will not different between Vehicle- and DEX-treated groups, the body weight continues to decline may be due to the inhibition of liver fatty acid synthesis by DEX, which resulted in a decrease in lipid synthesis.

SCD1 is a key enzyme for de novo lipogenesis of TG in liver.[41-43] Dysregulation of SCD1 has been implicated in NAFLD, hyperlipidemia and obesity.[44] Studies have shown that SCD1 deficiency in mice reduced liver TG accumulation, increased fatty acid oxidation, and reduced TG de novo synthesis.[45,46] Interestingly, DEX specifically suppressed the mRNA and protein levels of SCD1 in our study, so we speculated that DEX suppressed lipid accumulation mainly due to the suppressed de novo lipogenesis.

SCD1 is one of the downstream effectors of PPAR γ,[25] the transcription of PPAR γ can be activated by C/EBP β and C/EBP α,[26] and the protein level of C/EBP β, C/EBP α, and PPAR γ were significantly suppressed by DEX intervention in our study. DEX mediates the physiological and pharmacological actions mainly via the activation of α_{2A}-ARs and the modulation of catecholamine (norepinephrine and epinephrine) release.[22] Norepinephrine, which activates ARs on target tissues, causes transient hyperglycemia, vasoconstriction, and hypertension[47] related to the sympathetic system. In the central nervous system, α_{2A}-ARs are predominantly located presynaptically[48] and modulate the release of

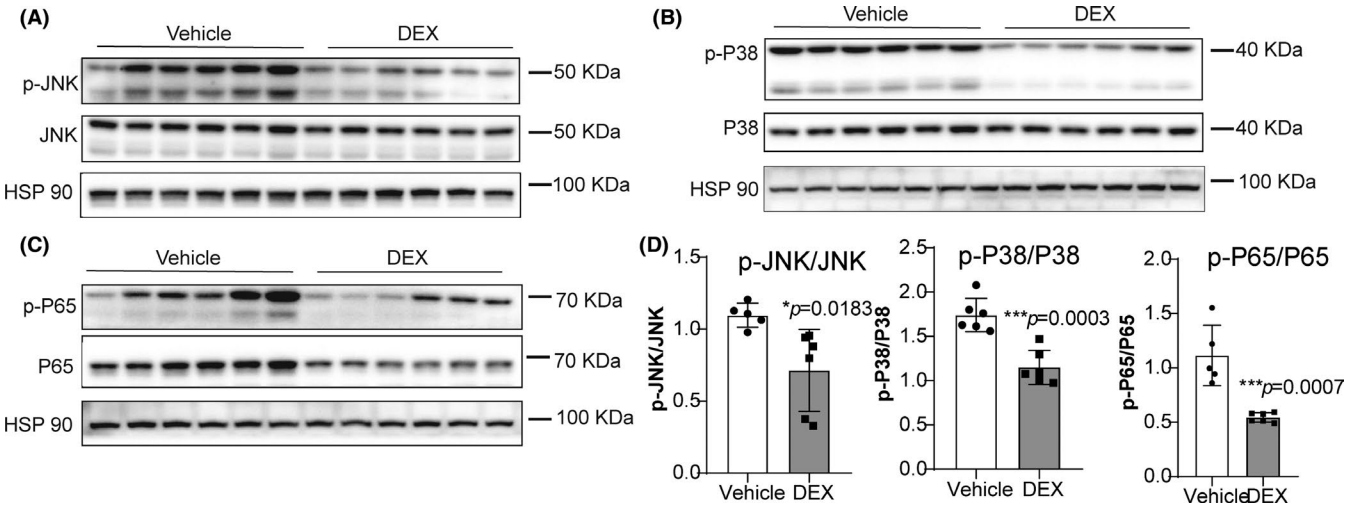

FIGURE 5 DEX protects mice against HFD-induced inflammation. (A, B and C) Western blot analysis of p-JNK, p-P38, p-P65 and JNK, P38, P65 in liver from DEX- or Vehicle-treated mice respectively ($n = 6$ per group); (D) Quantitative analysis of the ratio of p-JNK, p-P38, and p-P65 compared to JNK, P38 and P65 in liver from DEX- and Vehicle-treated mice ($n = 6$ per group). Data were analyzed by unpaired two-tailed Student's *t*-test. Values are expressed as the mean ± SD. *$P < .05$; ** $P < .01$; *** $P < .001$

catecholamines through a negative feedback mechanism. Notably, norepinephrine was found to induce hepatocellular dysfunction and modulate the responsiveness of macrophages to pro-inflammatory mediators through the activation of the α_2-AR.[49] On the other hand, epinephrine impairs glucose tolerance by inhibiting insulin secretion and augmenting hepatic glucose output via stimulation of both gluconeogenesis and glycogenolysis.[50] In our study, we found that DEX treatment activates the α_{2A}-AR, and subsequently a negative feedback loop to represents transient high plasma glucose while the levels of plasma insulin decreased and then increased 24 h after DEX injection. The decreased level of SCD1 in DEX-treated mice may attribute to the suppression of C/EBP β, PPAR γ, and C/EBP α and act as a systemic effect.

The intracellular concentration of SCD1 fluctuates in a wide range in response to complex and often competing hormonal and nutritional factors, such as insulin, leptin, and growth hormone as well.[51] Insulin is a powerful activator of SCD1 transcription and has been shown to induce SCD1 expression,[34] in this study, the suppression of SCD1 probably partly ascribe to the reduction in plasma insulin levels in plasma.

Studies have shown that DEX regulates inflammation through activate or deactivate ERK, JNK, and P38 MAPK pathways.[52-54] Our results showed that treatment with DEX significantly decreased the phosphorylation of JNK, P38, and P65 in liver. These results suggest that treatment with DEX decreased the expression of SCD1 and improved inflammatory state probably through MAPK and NFκB signaling pathways.

In summary, our results showed that DEX could improve HFD-induced NAFLD, and the suppression of lipid accumulation was associated with down regulation of SCD1 in liver. The mechanism in regulating lipid metabolism, insulin sensitivity, and inflammation may due to suppressing the expression of C/EBP β, PPAR γ, and C/EBP α and a negative feedback loop to inhibit α_{2A}-AR and the level of insulin in plasma through MAPK and NFκB singling pathway. DEX can be considered to be a potential adjuvant use for the treatment of NAFLD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

Tao made substantial contributions to perform experiments and analyze data. Guo, Xu, Wang, Xie, Chen, and Ma performed some experiments and analyzed some data. Tao and Li were involved mainly in drafting the manuscript and revising it critically for important intellectual content. Li gave final approval of the version to be published. Li contributed funding support.

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DATA AVAILABILITY STATEMENT

All data generated and analyzed in the study are available from the corresponding author upon reasonable request.

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