

Electromagnetic Fields Ameliorate Insulin Resistance and Hepatic Steatosis by Modulating Redox Homeostasis and SREBP-1c Expression in db/db Mice

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Purpose: The prevalence of nonalcoholic fatty liver disease (NAFLD), which has recently become known as metabolic-associated fatty liver disease (MAFLD), has risen. However, pharmacotherapies for this disease have not been approved. Electromagnetic fields (EMFs) have excellent bioeffects on multiple diseases. However, the effects of EMFs on NAFLD are unknown. This study investigated the bioeffects of EMF exposure on insulin resistance, liver redox homeostasis and hepatic steatosis in db/db mice.

Methods: Animals were sacrificed after EMF exposure for 8 weeks. The fasting blood glucose and insulin levels in the serum were tested. The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by a formula. The levels of MDA, GSSG and GSH, biomarkers of redox, were assessed. The activities of CAT, SOD and GSH-Px were assessed. The body and liver weights were measured. Hepatic lipid accumulation was observed by Oil Red O staining. Hepatic CAT, GR, GSH-Px, SOD1, SOD2 and SREBP-1 expression was determined by Western blotting.

Results: EMF exposure ameliorated insulin resistance and oxidative stress in the liver by downregulating the MDA and GSSG levels, increasing the reduced GSH levels, and promoting the GSH-Px levels in db/db mice. In addition, liver weight and triglyceride (TG) levels were reduced by EMF exposure. Simultaneously, EMF exposure improved hepatic steatosis by downregulating the protein expression of SREBP-1c.

Conclusion: The present findings suggest that EMF exposure has positive effects in the treatment of NAFLD.

Keywords: nonalcoholic fatty liver disease, electromagnetic fields, hepatic steatosis, oxidative stress, insulin resistance

Introduction

The prevalence of Nonalcoholic fatty liver disease (NAFLD), which has recently become known as metabolic-associated fatty liver disease (MAFLD), has risen, but its pathophysiology remains unknown.^{1,2} To date, the response rates of several phase 2B and phase 3 clinical trials for treating NAFLD appear modest.² Thus, no pharmacotherapies have been approved by the Food and Drug Administration (FDA).^{3,4} Aberrant redox signalling affects the pathophysiology of NAFLD, which is becoming increasingly understood.^{5,6} Oxidative stress can reduce insulin sensitivity and increase hepatic triglyceride (TG) content.^{7,8} Hepatic insulin

resistance can result in hepatic steatosis by causing lipid metabolism disorders, which further lead to systemic IR.⁹ Excessive hepatic lipid accumulation further exacerbates IR.⁵ Thus, re-establishing systemic redox homeostasis plays an important role in treating NAFLD.⁸ Unfortunately, intervention in redox systems remains a clinical challenge because of side effects that negatively impact adherence to treatment.¹⁰ Re-establishing redox homeostasis requires new methods.

Recent literature has reported that static magnetic fields combined with electric fields can promote insulin sensitivity by modulating redox homeostasis for the treatment of T2DM.¹¹ Electromagnetic fields (EMFs) include both electric and magnetic fields, so we reasoned that EMFs may improve IR and oxidative stress in NAFLD. However, evidence supporting the bioeffect of EMFs in insulin sensitivity is scarce. The findings regarding the potential biological effects of EMFs on redox homeostasis contradictory, with some investigations showing that EMFs induces oxidative stress and others showing no effects.^{12–15} These investigations utilized different parameters of EMFs, lacked measurements of insulin sensitivity and utilized no animal models of NAFLD. Thus, the bioeffect of EMFs on insulin resistance and oxidative stress has not been systematically assessed in NAFLD.

Here, we investigated the bioeffects of EMFs in db/db mice, which can recapitulate human NAFLD. Finally, we found that EMFs could improve IR and ameliorate hepatic oxidative distress and lipid accumulation in db/db mice. Therefore, we hypothesized that EMFs might attenuate the hepatic damage associated with NAFLD by modulating redox homeostasis. Thus, EMFs could be a novel treatment for NAFLD.

Methods and Materials

Animals and Experimental Design

Diabetic leptin receptor-mutant mice (db/db mice) were obtained from the Model Animal Research Centre of Nanjing University. The animals were housed in SPF conditions with 12-hour alternating light/dark cycles, and a constant temperature was maintained (22 °C). The animals were fed ad libitum. The animal experiments were approved by the Institutional Animal Care and Use Committee at Air Force Medical University and carried out according to the Guide for the Care and Use of

Laboratory Animals published by the National Institutes of Health (NIH).

Eight female C57BL/KsJ mice (18.07 ± 1.54 g) were used as controls. Sixteen female C57BL/6J db/db mice (29.73 ± 2.27 g) were equally and randomly divided into the db/db group and db/db + EMF group. The db/db + EMF group was exposed to electromagnetic fields (2 h/d, 1.6 mT). These parameters were in accordance with other published studies.^{16,17} The control and db/db groups were placed in identical cages with no EMF. Eight weeks after EMF exposure, all the mice were fasted overnight, and then, the fasting blood glucose levels were analysed. Liver tissues were harvested and stored at -80 °C before evaluation. Whole blood samples were centrifuged, and serum was collected for biochemical assays.

Electromagnetic Exposure System

The EMF stimulators used in this study were described as previously reported.^{17,18} In brief, there were four parts: LabVIEW software, a multifunction data acquisition device (NI USB-6211), a power amplifier (XP9900S, Huamei, China) and Helmholtz coils. The waveform consisted of a pulse burst repeated at 15 Hz. The coils were 20 cm in diameter. Two copper enamelled round coils were placed 10 cm apart in parallel rows. A gaussmeter (Model 455, Lake Shore Cryotronics, USA) was used to accurately further confirm the distribution of the electromagnetic field intensity. In this study, the reference electromagnetic fields were set to 0 mT, and the intensity of the electromagnetic fields between coils was determined to be approximately 1.6 mT (mean \pm SD, RMS). The background magnetic fields were determined to be 50 ± 2 μ T. A schematic representation of the EMF exposure system and output waveform is shown in Figure 1.

Biochemical Analysis

Fasting blood glucose was analysed with a commercial blood glucose meter (OMRON Health Medical Co., Ltd., Japan), and serum insulin was measured using a mouse insulin ELISA kit (Cusabio Biotech Co., Ltd., Wuhan, China). The homeostatic model assessment of insulin resistance (HOMA-IR) index was calculated by the following formula:

$$\text{HOMA-IR} = \text{fasting insulin (m U/L)} \times \text{fasting glucose (nmol/L)} / 22.5.^9$$

Hepatic TG content, malondialdehyde (MDA), reduced glutathione (GSH), glutathione disulphide (GSSG), glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide

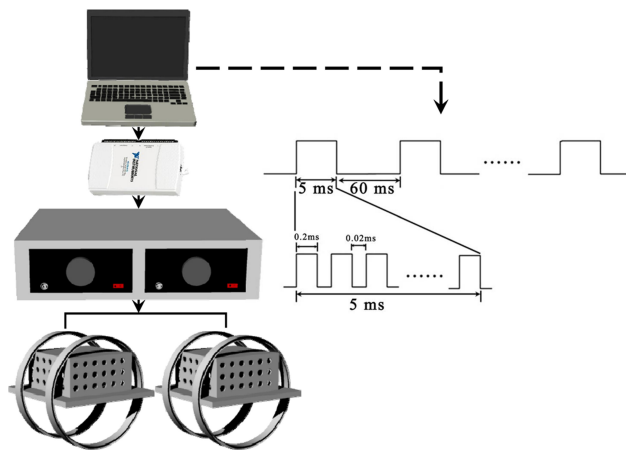


Figure 1 Schematic representation of EMF exposure system and output waveform. The exposure waveform comprises a pulsed burst (burst width, 5 ms; pulse width, 0.2 ms; pulse wait, 0.02 ms; burst wait, 60 ms; pulse rise, 0.3 μ s; pulse fall, 2.0 μ s) repeated at 15 Hz.

dismutase (SOD) assay kits were all purchased from Nanjing Jiancheng Bioengineering Institute (product numbers: A110-2-1, A003-1-2, A006-2-1, A061-1-1, A005-1-1, A007-2-1 and A001-3-2, respectively). The experimental procedures were performed according to the manufacturer's instructions.¹⁹

Histological Analysis

Oil Red O reagent (Sigma-Aldrich Co., St. Louis, USA) were used to stain frozen liver slices to examine lipid accumulation within hepatocytes. Stained sections were detected with a light microscope and measured using Fiji software (ImageJ, NIH, USA).

Western Blot

Western blotting was used to examine protein expression, and the procedure was the same as that previously reported.^{19,20} In brief, HRP-conjugated goat anti-rabbit secondary antibodies (1:3000 diluted in TBST) were used. The protein bands were visualized by an ECL chemiluminescence reagent (Thermo Scientific, Rockford, IL, USA) following the manufacturer's guidelines, and semi-quantitative analysis was performed using Quantity One Software. β -Actin (1:2000, Bioworld Technology, Inc., Nanjing, China) was used as the internal control for normalization. The BCA Protein Assay Kit was purchased from Thermo Scientific (IL, USA). SREBP-1c antibody was purchased from Santa Cruz Biotechnology (1:1000, CA, USA). CAT antibody was purchased from Proteintech Group, Inc. (1:1000, Wuhan, China). Glutathione reductase (GR) and GSH-Px antibodies were purchased from Bioworld Technology, Inc. (1:1000, Nanjing, China).

SOD1 and SOD2 antibodies were purchased from Abcam Biotechnology (1:1000, Cambridge, UK).

Statistical Analysis

All the data are expressed as the mean \pm standard deviation (SD), and one-way ANOVA with an LSD *t*-test was used to determine the difference between two groups. Statistical analysis was performed with SPSS 16.0, and $P < 0.05$ was considered statistically significant.

Results

EMF Exposure Improved Insulin Resistance in db/db Mice

EMF exposure significantly improved fasting blood glucose and serum insulin in db/db mice ($P < 0.05$, Figure 2A and B). In the db/db mice, EMF exposure reduced the HOMA-IR by more than 50% compared with control (Figure 2C).

EMF Exposure Modulated Hepatic Redox in db/db Mice

EMF exposure significantly elevated the reduced GSH level and lowered the MDA and GSSG levels in the db/db mice ($P < 0.05$, Figure 3A–C). In addition, EMF exposure increased the GSH-Px level ($P < 0.05$) but did not change the CAT and SOD levels (Figure 3D–F). The expression of the CAT, GR, SOD1 and SOD2 proteins was not changed by EMF exposure, whereas the overexpression of GSH-Px was observed to be significant ($P < 0.05$, Figure 3G).

EMF Exposure Ameliorated Hepatic Lipid Accumulation in db/db Mice

Body weight (Figure 4A) was not changed, but liver weight (Figure 4B) was significantly decreased by EMF exposure ($P < 0.05$). In addition, EMF exposure significantly reduced the liver TG content (Figure 4C). EMF exposure remarkably reduced the area of lipid droplets ($P < 0.05$, Figure 4D and E). The expression of the SREBP-1c protein was also significantly downregulated by EMF downregulated ($P < 0.05$, Figure 4F).

Discussion

NAFLD has become the most common form of chronic liver disease in the world and affects patients' quality of life.²¹ The continuously growing prevalence of NAFLD is closely associated with T2DM, which is of great

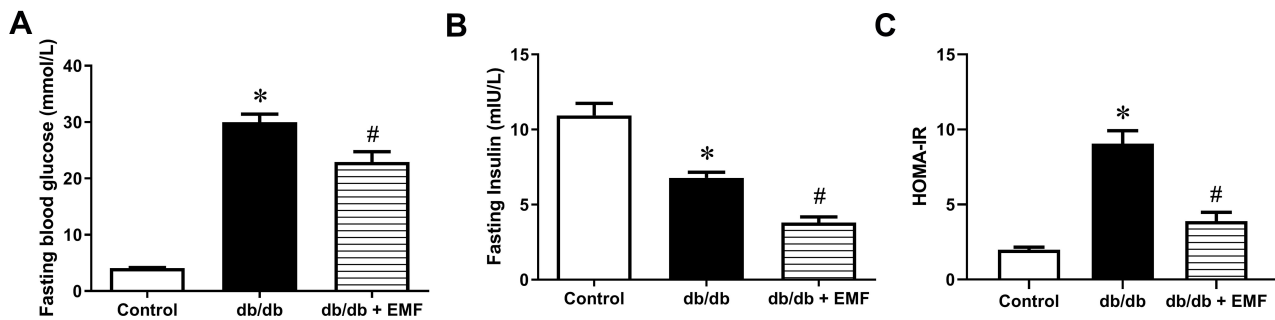


Figure 2 Effect of EMF on IR in db/db mice. (A) Data of fasting blood glucose. (B) Data of fasting blood insulin. (C) Results of HOMA-IR. * $P < 0.05$, compared with control; # $P < 0.05$, compared with db/db group.

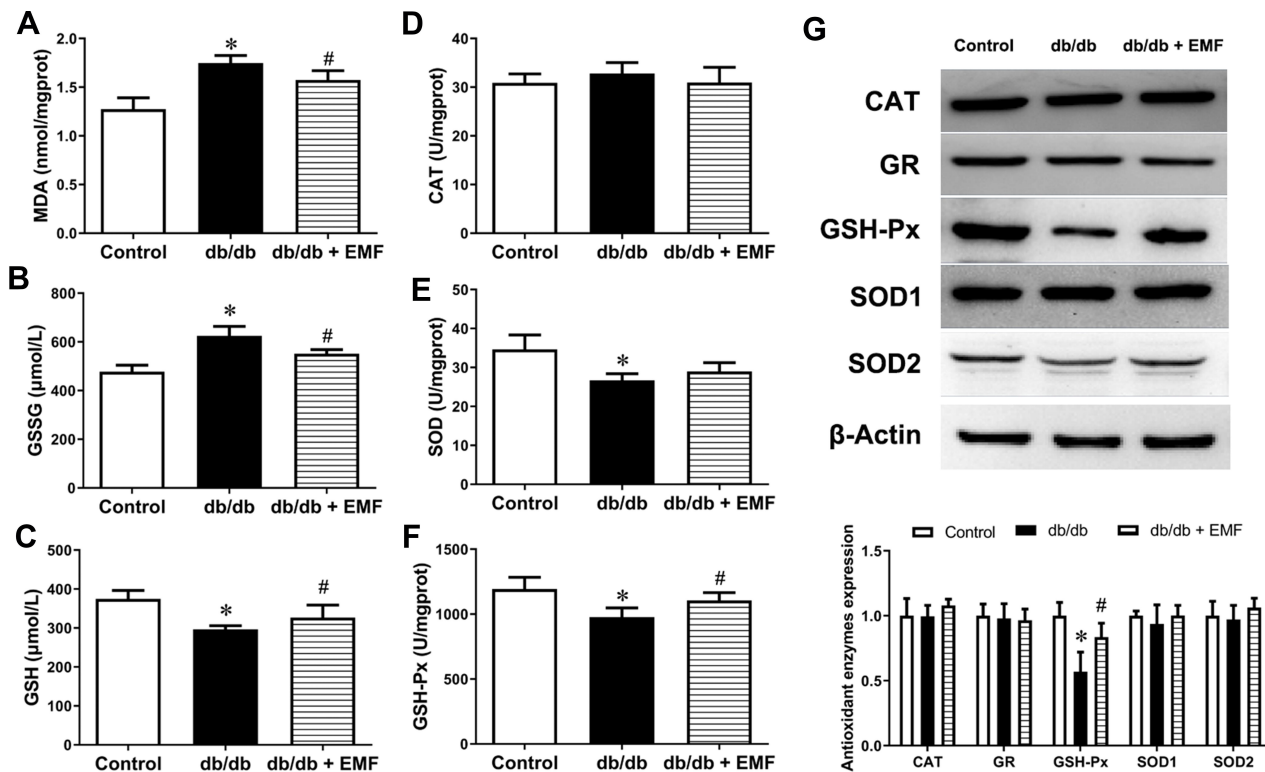


Figure 3 Effects of EMF exposure on redox homeostasis. (A) Liver MDA content. (B) Liver GSSG content. (C) Liver GSH content. (D) Activity/unit of CAT. (E) Activity/unit of SOD. (F) Activity/unit of GSH-Px. (G) Original recording and quantification of Western blotting. Values are all expressed as mean \pm SD. * $P < 0.05$, compared with control; # $P < 0.05$, compared with db/db group.

concern.²² To date, the pathogenesis of NAFLD has not been completely clarified, and there is no available treatment.^{1,3} Studies have shown that oxidative stress, as a key mechanism, has an impact on the progression of NAFLD by causing abnormal lipid metabolism.^{23–25} Accordingly, antioxidant therapy has become a potential treatment for NAFLD. Although very little is known, the biological responses caused by EMFs are allegedly mediated by the induction of interactions between quantum spin-state and paramagnetic radicals, which then regulate endogenous redox reactions.^{11,26,27} Accordingly, the

present study explored the bioeffects of EMF exposure on redox homeostasis in a NAFLD animal model. We found that EMF exposure was associated with attenuated hepatic steatosis in db/db mice by improving insulin resistance and reducing oxidative stress.

Insulin resistance is defined as insensitivity to insulin and inability to dispose of blood glucose properly. Compared with wild-type mice, the db/db mice exhibited high blood glucose and a high index of HOMA-IR. This indicated that the db/db mice suffered from severe insulin resistance. Eight weeks of EMF treatment lowered fasting

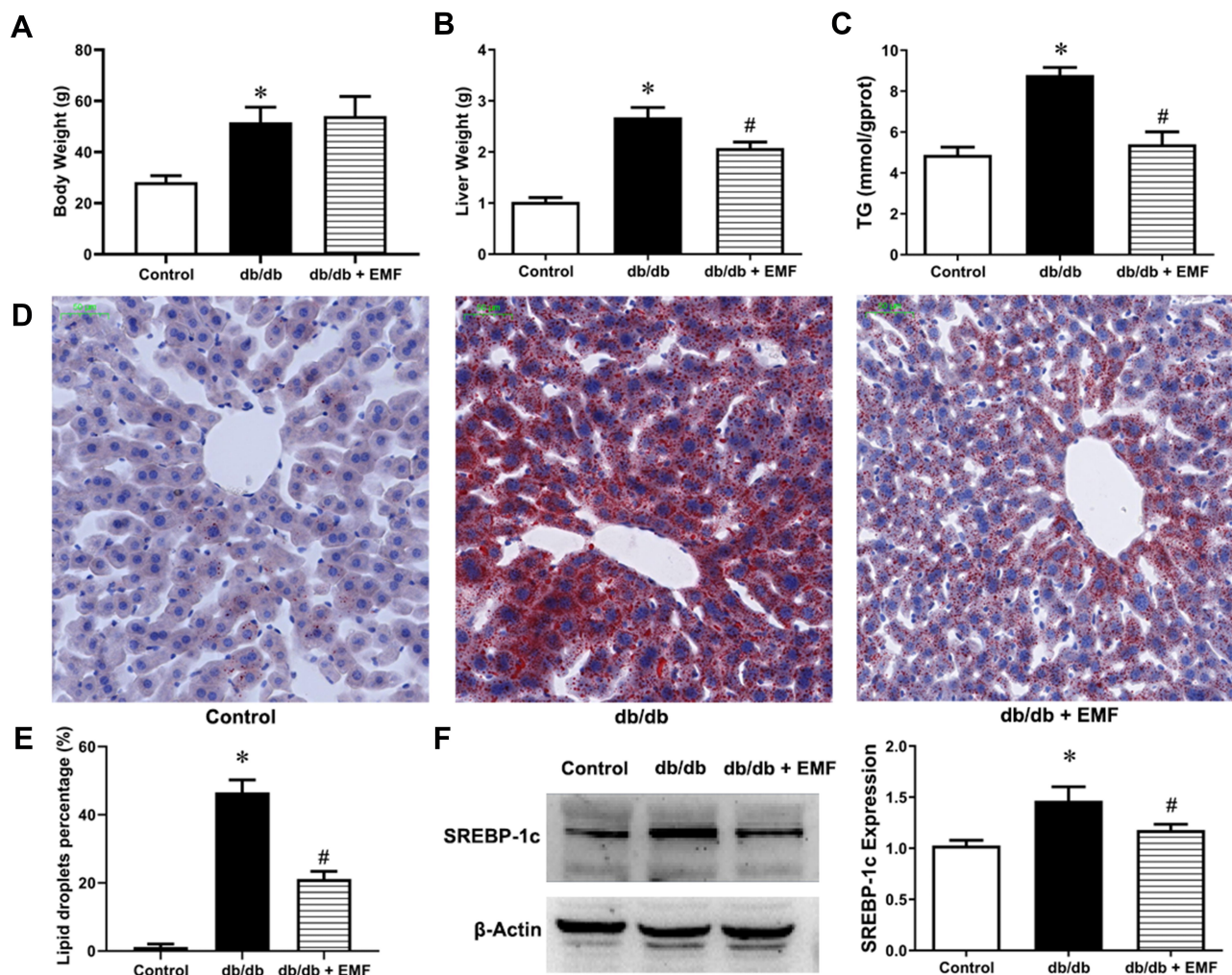


Figure 4 Effects of EMF exposure on liver and SREBP-1c expression. (A) Weight of body. (B) Weight of liver. (C) Liver triglyceride content. (D) Oil Red O staining ($\times 20$). (E) Percentage of lipid droplets. (F) Liver SREBP-1c expression. Values are all expressed as mean \pm SD. * $P < 0.05$, compared with control; # $P < 0.05$, compared with db/db group.

blood glucose, fasting serum insulin and the HOMA-IR index. These results suggested that EMFs could effectively improve impaired insulin sensitivity. These findings are similar to the results of a prior study.¹¹ Studies have reported that redox imbalance deviating from oxidation contributes to the development of insulin resistance.^{28,29} MDA, as an indicator of oxidative stress, is an index of lipid peroxidation.³⁰ We found that liver the MDA content increased sharply in db/db mice, which suggests hepatic oxidative stress injury. After treating db/db mice with EMFs, the MDA and GSSG levels were obviously decreased. In addition, EMF exposure strikingly increased the hepatic GSH levels, leading to a considerably reduced redox status in db/db mice. Moreover, adjusting the redox environment can alter insulin sensitivity and glycogen synthesis.^{29,31} Taken together, our results suggested that

EMFs exert an insulin-sensitizing effect in part by regulating the systemic GSH/GSSG redox status.

To further explore the mechanisms of oxidative stress regulation through EMFs, a series of antioxidant enzyme activities were assessed. GSH, as a cellular reductant controller, is able to counteract oxidative damage by scavenging free radicals against oxidative damage.³² GSH-Px enhances the interaction between GSH and H_2O_2 to counteract peroxide.³³ GSH-Px can transform GSH (reduced form of glutathione) as a cosubstrate into GSSG (oxidized form of glutathione). GSH-Px can remove hydrogen peroxide and scavenge lipid hydroperoxides to avoid peroxide damage.^{30,34} Subsequently, GR catalyses GSSG conversion into GSH. Low GSH levels weaken the antioxidant status and lead to lipid peroxidation enhancement.³⁵ A case report showed that GSH-Px activity was

significantly reduced, while the concentration of plasma MDA was obviously elevated in IR patients compared with controls.³⁶ Recent studies have shown that increasing the activity of GSH-Px can inhibit oxidative stress in NAFLD rats with abdominal obesity.³⁷ In our study, the activity/unit of CAT and SOD and the expression of CAT, SOD and GR were not altered. However, both the activity/unit and expression of GSH-Px increased obviously. Presumably, EMF exposure could improve hepatic oxidative stress in db/db mice by elevating the activity/unit and expression of GSH-Px and then promoting the antioxidant ability of enzymes.

Another important characteristic of NAFLD is excess lipid accumulation in hepatocytes. To date, recent studies have already shown that de novo lipogenesis strongly induces excess storage of TG in the liver, causing hepatic steatosis in NAFLD patients.^{38,39} Traditionally, it has been believed that abnormal hepatic lipid deposition causes mitochondrial dysfunction, which generates ROS and can result in oxidative stress.^{39,40} With increasing visceral adipose tissue mass, the risk of IR and metabolism disorders increases. Therefore, eliminating the abnormal accumulation of hepatic lipids might provide a way to treat metabolic disorders. This has been confirmed by several studies. Treating high-fat diet-fed mice with a mixture of Chinese herbal extracts can moderate IR, hyperlipidaemia and visceral obesity.⁴¹ Furthermore, daily intake of whey protein with a multimode exercise training programme can reduce fasting blood glucose and improve insulin sensitivity in overweight/obese people.⁴² We also focused on changes in the liver, the most important metabolic organ in the body, to determine the further beneficial bioeffects of EMFs on NAFLD. According to the liver weight, TG content and frozen sections stained with Oil Red O, the 8 weeks of EMF exposure obviously reduced the liver weight of db/db mice by alleviating lipid accumulation in hepatocytes. Prior research found that EMFs function similarly to physiological stress and can alter the lipid profile in the brain.⁴³ The EMFs can also alter the lipid metabolism of soil nematodes.⁴⁴ This study obtained analogous findings with the induction of positive effects on hepatic lipid accumulation by EMFs.

To explore the potential mechanism by which lipid metabolism is regulated by EMFs, we investigated sterol regulatory element binding protein-1c (SREBP-1c), which is a key transcription factor. An especially high level of SREBP-1c expression has been observed in fatty livers of obese, IR and hyperinsulinaemia animal models.^{45,46} We

assessed the protein expression level of SREBP-1c because of the significant alleviation of hepatic lipid accumulation in db/db mice by EMFs. The results revealed that SREBP-1c expression could be downregulated significantly by EMFs. SREBP-1c expression is decreased by Meretrix oligopeptides to relieve the NAFLD induced by a high-fat diet.⁴⁷ Xyloketal B can reduce SREBP-1c in NAFLD and decrease hepatic lipid accumulation.²³ By inhibiting SREBP-1c expression in NAFLD, crude triterpenoid saponins from *Ilex latifolia* can also attenuate hepatic lipid accumulation.⁴⁸ Therefore, the present study suggested that SREBP-1c expression was potentially downregulated and that abnormal liver lipid deposition could be reduced in db/db mice exposed to EMFs.

As with the majority of studies, the design of the current study was subject to the following limitations. (1) Although EMFs have been proven to be safe for orthopaedic applications, we need data to prove that EMFs are not harmful to the liver of wild-type mice. (2) Our research data assumed that EMF-mediated modification of SREBP-1c expression would continue, and we would need to clarify a plausible mechanism.

Conclusion

In conclusion, EMF exposure could increase antioxidant enzyme activity to improve IR and ameliorate lipid accumulation by downregulating SREBP-1c expression. Ameliorating the abnormal accumulation of lipids in the liver also improved impaired insulin sensitivity. Although further pathological mechanisms of NAFLD need to be elucidated and there is still no FDA-approved drug for NAFLD, this investigation provides a possible new solution for exploring NAFLD prevention and treatment.

Disclosure

The authors report no conflicts of interest in this work.

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