Effects of oxymatrine on inhibiting hepatic endoplasmic reticulum stress signaling pathway and reducing insulin resistance in high-fat diet rats

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Abstract: Objective: To observe the effects of oxymatrine on endoplasmic reticulum (ER) stress signaling pathway molecules ATF4, ATF6, IRE1α, and fibroblast growth factor 21 (FGF21) as well as insulin resistance in high-fat diet rats. Methods: A total of 64 adult male SD rats were randomly divided into 8 groups. They were normal control group (CON), oxymatrine group (OM), high-fat diet group (HFD), high-fat diet + pioglitazone group (HFD+PZ), high-fat diet + low-dose oxymatrine (50 mg/kg) group (HFD+OM-L), high-fat diet + medium-dose oxymatrine (100 mg/kg) group (HFD+OM-M), and high-fat diet + high-dose oxymatrine (150 mg/kg) group (HFD+OM-H) and high-fat diet + low-dose oxymatrine + pioglitazone group (HFD+OM+PZ), with 8 rats in each dose group. After 10-week intervention, the rats were abstained from food except water for 12 hours, they were weighed and then killed after being collected blood from abdominal aorta. The serum of rats in each group was separated for immediate measurement of fasting plasma glucose (FPG), fasting insulin (FINS), total cholesterol (TC) and triglyceride (TG). The homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated. Meanwhile, the liver of rats was separated to measure the ATF4, ATF6, IRE1α and FGF21 mRNA levels and their protein expression levels. The mechanism of oxymatrine on above endoplasmic reticulum stress pathway on insulin resistance pathway was also investigated. Results: Compared with CON, there was no significant difference in serum TG, TC, and FPG levels and HOMA-IR (P>0.05); at the same time, there was no difference in liver ATF4, AFT6, IRE1α and FGF21 mRNA and protein levels (P>0.05) in OM. Compared with CON, serum TG, TC, and FPG levels as well as HOMA-IR increased obviously in HFD (P<0.05); meanwhile, ATF4, ATF6, IRE1α mRNA levels and their protein expression levels apparently up-regulated, while FGF21 mRNA level and its protein level down-regulated (P<0.05). Compared with HFD, serum TG, TC, and FPG levels as well as HOMA-IR decreased obviously, while ATF4, ATF6, IRE1α mRNA levels and their protein expression levels in the liver apparently down-regulated, and FGF21 mRNA level apparently up-regulated (P<0.05) in HFD+OM; no difference was found among different doses of oxymatrine (P>0.05) in HFD+OM. Compared with CON, serum TG, TC, and FPG levels as well as HOMA-IR increased obviously in HFD (P<0.05); meanwhile, ATF4, ATF6, IRE1α mRNA levels and their protein expression levels apparently up-regulated, while FGF21 mRNA level and its protein level down-regulated (P<0.05). Compared with HFD, serum TG, TC, and FPG levels as well as HOMA-IR decreased obviously, while ATF4, ATF6, IRE1α mRNA levels and their protein expression levels in the liver apparently down-regulated, and FGF21 mRNA level apparently up-regulated (P<0.05) in HFD+OM; no difference was found among different doses of oxymatrine (P>0.05). Compared with HFD, serum TG, TC, and FPG levels as well as HOMA-IR decreased obviously, meanwhile, ATF4, ATF6, IRE1α mRNA levels and their protein expression levels in the liver were down regulated, and FGF21 mRNA level apparently up-regulated (P<0.05) in HFD+OM; there was no difference in serum TG, TC, and FPG levels as well as the decrease of HOMA-IR (P>0.05), meanwhile, no difference was found in ATF4, ATF6, IRE1α and FGF21 mRNA levels and their protein expression levels in HFD+OM (P>0.05). Conclusion: Oxymatrine can not only down-regulate ATF4, ATF6, and IRE1α mRNA levels and their protein levels, but also up-regulate FGF21 mRNA level and its protein level, besides it plays an important role in regulating the metabolism of glucose and insulin resistance in rats with hyperlipidemia.

Keywords: Hyperlipidemia, fibroblast growth factor, endoplasmic reticulum stress, blood glucose

Introduction

Diabetes is a group of clinical syndromes, which is caused by a combined impact of environmental factors and genetic factors, with clinical manifestations of glucose metabolism disorders and body fluid imbalance. Type 2 diabetes (T2DM), the main type of diabetes, is extremely
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Harmful to human health with high disability rate and mortality [1]. Islet β cells damage and insulin resistance (IR) are the main pathogeneses of type 2 diabetes. IR is a syndrome that the insulin is less capable of prompting the glucose uptake and utilization efficiency because of various causes, so that the body compensates for excessive secretion of insulin to maintain a stable blood glucose, thus leading to hyperinsulinemia. IR often presents before the onset of diabetic symptoms, mainly manifesting as obesity, dyslipidemia, impaired glucose tolerance, atherosclerosis and so forth.

Endoplasmic reticulum (ER) is an essential cell organelle for the protein synthesis and transport in animals. It is quite sensitive to a variety of stimuli. The increased demand for protein folding, external stimuli or other factors can cause the imbalance between ER protein folding load and protein folding ability, resulting in misfolded protein or accumulation of unfolded protein in the ER cavity and leading to endoplasmic reticulum stress (ERS) [2, 3]. In order to relieve ERS, ER will activate the protein folding ability, stagnate the translation of the majority of proteins, and accelerate protein degradation, that is, the unfolded protein response (UPR). In eukaryotes, UPR is mainly mediated by three kinds of transmembrane proteins, they are inositol-requiring enzyme 1 (IRE1), RNA-dependent protein kinase R-like ER kinase (PERK) and activating transcription factor 6 (ATF6), forming three essential branches. When in normal physiological state, the above three unactivated proteins are all combined with the intracavitary binding immunoglobulin protein (Bip). When stress occurs, Bip is dissociated and used as a molecular partner of ER protein, to help the folding of unfolded or misfolded proteins in the endoplasmic reticulum cavity; while IRE1, PERK and ATF6 are activated after deviating from Bip and participate in the signal transduction of UPR.

ERS, an important mechanism of inducing T2DM and IR, is closely associated with obesity, IR and diabetes [4, 5]. Growing studies have found that liver-derived hormones are involved in the metabolism of blood glucose and fat. FGF21, an atypical member of the FGF family, expresses predominantly in the liver; it is a hormone-like cytokine secreted by the liver, and also expresses a little in islet β cells and adipose tissues [6, 7]. The main function of FGF21 is to regulate the metabolism of glycolipids [8]. It is confirmed by both clinical and animal experiments that the level of FGF21 is significantly higher in T2DM. Besides, its level has a positive correlation with the levels of triglyceride (TG), insulin, low density lipoprotein and other indexes [9-11]. Meanwhile, studies have confirmed that the level of FGF21 increases with the increase of ERS [12, 13].

ERS is closely related to IR: insulin stimulates target cell by binding the receptor to trigger cascade signal transduction, promotes target cells (fat, skeletal muscle, liver, etc.) for glucose uptake, and accelerates its oxidation use in cells; promotes the synthesis of glycogen, inhibits glycogen decomposition, and inhibits glycogen dysplasia to lower blood glucose. There are two main signaling pathways: one is that the protein kinase B (PKB) is activated by the signaling pathway of the insulin receptor substrate and phosphatidylinositol-3-kinase, to regulate the metabolism of three major substances; the other is that cell proliferation and growth are activated by mitogen-activated protein kinase.

At present, the main therapies of T2DM include diet control, weight loss by exercising and drugs (insulin and oral hypoglycemic drugs). However, there are different degrees of side effects and adverse reactions in a variety of oral hypoglycemic drugs that serve as first-line medications. Oxymatrine is one of the main alkaloids of leguminous plants Sophora flavescens with an effect of lowering blood glucose, but its mechanism is not clear at present [14]. Whether oxymatrine can inhibit the hepatic ERS and FGF21 to play a role in hypoglycemic action is not clear. The aim of this study is to investigate the effects of oxymatrine on the ERS pathways and FGF21 in liver of rats with T2DM, and to explore its possible hypoglycemic mechanism.

Materials and methods

Animal feeding

The healthy adult male Sprague Dawley (SD) rats, weighing 250-300 g, were provided by the Animal Center of Xuzhou Medical University. They were placed at 24°C ± 2°C and maintained a circadian rhythm of 12 h/12 h with free food and water intake. All the experimental animals had 7 days to adapt to the envi-
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Environment before the experiment. All animal experiments were approved by the Experimental Animal Ethics Committee of Xuzhou Medical University.

Related reagents

The oxymatrine was produced by Shanghai Bo Yan Biological Technology Co., Ltd. (CAS: 16837-52-8). Pioglitazone was purchased from Nos-0130 Sigma (USA). Iodinated insulin radioimmunoassay kit was purchased from Beijing North Institute of Biological Technology.

Animal models and experimental grouping design

High-fat diet modeling: After one week adapting to the environment, the SD rats were fed with high-fat diet (10% of flour, 33% of bean pulp, 20% of bean flour, 30% of lard oil, 2% of fish protein concentrate, 2% of wheat bran, 3% of bone meal; heat composition: 20.1% of carbohydrate, 59.8% of fat and 20.1% of protein, with 501 kcal per 100 g). Eight weeks later, the weight of the rats significantly increased to 360 g or more.

Oxymatrine intervention: SD rats were given intragastric treatment of 50 mg/kg of oxymatrine once time for 8 weeks in oxymatrine group. High-fat diet + oxymatrine group had the same way as the high fat diet T2DM modeling. After the modeling finished, SD rats was given intragastric treatment of 50 mg/kg, 100 mg/kg, 150 mg/kg of oxymatrine respectively, once a day for 8 weeks.

High-fat diet + pioglitazone intervention: After the above modeling finished, SD rats was given intragastric treatment of 4.5 mg/kg of pioglitazone, once a day for 8 weeks. This group was set as the positive control group.

Experimental grouping design: The rats were divided into 8 groups, they were normal control group (CON), oxymatrine group (OM), high-fat diet group (HFD), high-fat diet + pioglitazone group (HFD+PZ), high-fat diet + low-dose oxymatrine group (HFD+OM-L), high-fat diet + medium-dose oxymatrine group (HFD+OM-M), high-fat diet + high-dose oxymatrine group (HFD+OM-H) and high-fat diet + pioglitazone group (HFD+OM+PZ), with 8 rats in each group.

Observing indexes and corresponding experimental methods

Blood samples were collected 8 weeks after the rats were treated with intragastric oxymatrine and pioglitazone. Rats in each group were fasted for 12 hours with free access to water. After that, chloral hydrate anesthesia (0.3 ml/kg) was performed on rats by intraperitoneal injection, and 6 ml blood was collected from abdominal aorta and injected into the centrifuge tubes with corresponding number, centrifuging for 10 min at a speed of 3000 r/min to separate the serum. The blood glucose was measured immediately, and then the serum specimens were stored in cryogenic refrigerator at -70°C until used.

Glucose oxidase method was used to detect FPG. Enzyme method was adopted to detect TC and TG. And radioimmunoassay was used for the detection of fasting insulin (FINS).

Calculate insulin resistance index: HOMA-IR= FPG*FINS/22.5.

Real-time PCR was used to detect the expression of FGF21 mRNA in liver. Three livers of rats from each group were used for Real-time PCR. Total RNA was taken out after homogenate. After reverse transcription, fluorescent PCR was used for gene amplification. The primer sequences were as follows:

FGF-21 primer, upstream 5’-CACCGCAGTCCA-GAAAGTC-3’, downstream 5’-CAAAGTGAGGCG-ATCCATA-3’; ATF4 primer, upstream 5’-GCTTTC-GCTTCCATTTCTCTCTC G-3’, downstream 5’-TTGG-CGAGAGAATCTGCC TT-3’; ATF6 primer, upstream 5’-CACACGGTTTTGCTGTCTCAG, downstream 3’: ACCCATTTCATTGTCAGCG; internal reference GAPDH primer, upstream 5’-TGCTGAGTATGCTGGAAGT-3’, downstream 5’-TGCTGAGTATGCTGGAAGT-3’.

$\Delta\Delta$CT value of every gene was calculated to gain gene’s relative expression in every group.

Statistical analysis

The statistics analyses of the data obtained from the above experiments were performed with SPSS 16.0 statistical software. All measurement data were expressed as mean ± standard deviation. One-way analysis of variance was used for comparison of multiple gr-
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Oxymatrine could reduce blood glucose and blood lipids levels, pioglitazone exerted no synergistic effect with oxymatrine

After 8 weeks’ intervention, compared with CON, the body mass, serum TG, TC and FPG levels were significantly higher in HFD (P<0.05). Compared with HFD, serum TG, TC and FPG levels were significantly lower in HFD+PZ (P<0.05); serum TG, TC and FPG levels as well as HOMA-IR were obviously decreased in HFD+OM (P<0.05) and there was no difference among different doses of oxymatrine (P>0.05); serum TG, TC and FPG levels as well as HOMA-IR was remarkably decreased in HFD+PZ+OM (P<0.05). Compared with HFD+OM, no difference was found in decrease of body mass index, serum TG, TC and FPG levels in HFD+PZ+OM (P>0.05) (Figure 1).

Figure 1. Comparison of body mass and serum biochemical indexes of rats in each group. Compared with CON group, *P<0.05; compared with HFD group, #P<0.05. Normal control group (CON), oxymatrine group (OM), high-fat diet group (HFD), high-fat diet + pioglitazone group (HFD+PZ), high-fat diet + low-dose oxymatrine group (HFD+OM-L), high-fat diet + medium-dose oxymatrine group (HFD+OM-M), high-fat diet + high-dose oxymatrine group (HFD+OM-H) and high-fat diet + low-dose oxymatrine + pioglitazone group (HFD+OM+PZ).
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Oxymatrine could reduce HOMA-IR in HFD, pioglitazone exerted no synergistic effect with oxymatrine

After 8 weeks’ intervention, compared with CON, FINS level and HOMA-IR were significantly higher in HFD (P<0.05). Compared with HFD, FINS level and HOMA-IR were obviously lower in HFD+PZ (P<0.05); FINS level and HOMA-IR were obviously lower in HFD+OM (P<0.05) and no difference was found among different doses of oxymatrine (P>0.05); FINS level and HOMA-IR were significantly reduced in HFD+PZ+OM (P<0.05). Compared with HFD+OM, there was no difference in down-regulation of FGF21 mRNA level and its protein level in HFD+PZ+OM (P>0.05) (Figure 2C-E).

Effects of oxymatrine on liver cell organelles in rats with high fat diet

Rich hepatocytes, mitochondria, rough ER, and free ribosomes remained in CON. In HFD, there were lipid droplets in the cytoplasm of hepatocytes, and most of the mitochondrial cristae were fused with partial membrane, which was ambiguous or absent, with broken and irregularly arranged cristae; besides, the particles on rough ER were fused, fuzzy or with degranulation and the free ribosomes were slightly reduced. In HFD+PZ, there were a large number of mitochondrial densification and electron density increase, the mitochondrial cristae and membrane were visible. In HFD+OM-L, it showed large and obvious nucleoli and slightly irregular nuclear profile; most of the mitochondrial cristae were fused with a small part of membrane, which was

Figure 2. Comparison of FINS, HOMA-IR and FGF21 of rats in each group. Compared with CON group, *P<0.05; compared with HFD group, #P<0.05. Normal control group (CON), oxymatrine group (OM), high-fat diet group (HFD), high-fat diet + pioglitazone group (HFD+PZ), high-fat diet + low-dose oxymatrine group (HFD+OM-L), high-fat diet + medium-dose oxymatrine group (HFD+OM-M), high-fat diet + high-dose oxymatrine group (HFD+OM-H) and high-fat diet + low-dose oxymatrine + pioglitazone group (HFD+OM+PZ).
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ambiguous or absent, the particles on rough ER were with obvious degranulation and free ribosomes were reduced. In HFD+OM-M, most of the mitochondrial cristae were moderate fused with partial membrane, which was ambiguous or absent; the particles on rough ER were fused or with degranulation, along with reduced free ribosomes. In HFD+OM-H: partial mitochondrial cristae were fused with membrane and gone with absence; rough ER was with degranulation, and slightly reduced free ribosomes. See Figure 3.

Effects of oxymatrine on ATF4, ATF6, IRE1α mRNA levels and their protein levels in liver tissues of high-fat diet rats

After 8 weeks’ intervention, compared with CON, ATF4, ATF6, IRE1α mRNA levels and their protein levels in liver tissues were significantly higher in HFD (P<0.05). Compared with HFD, ATF4, ATF6, IRE1α mRNA levels and their protein levels in liver tissues in HFD+PZ were obviously increased (P<0.05); while ATF4, ATF6, IRE1α mRNA levels and their protein levels in liver tissues in HFD+OM were remarkably decreased (P<0.05); no difference was found among different doses of oxymatrine (P>0.05). Compared with HFD, ATF4, ATF6, IRE1α mRNA levels and their protein levels in liver tissues in HFD+PZ+OM were obviously decreased (P<0.05). Compared with HFD+OM, there was no difference in down-regulation of ATF4, ATF6, IRE1α mRNA levels and their protein levels in HFD+PZ+OM (P>0.05) (Figure 4).

Effects of oxymatrine on PI3K and IRS-1mRNA levels in liver tissues of high-fat diet rats

After 8 weeks’ intervention, compared with CON, PI3K and IRS-1mRNA levels in liver tissues were significantly higher in HFD (P<0.05). Compared with HFD, PI3K and IRS-1mRNA levels in liver tissues were obviously increased in HFD+PZ (P<0.05); PI3K and IRS-1mRNA levels in liver tissues were significantly lower in HFD+OM (P<0.05) and no difference was found among different doses of oxymatrine (P>0.05). Compared with HFD+OM, there was no difference in down-regulation of PI3K and IRS-1mRNA levels in HFD+PZ+OM (P>0.05) (Figure 5A and 5B).
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Discussion

Oxymatrine is an alkaloid extracted from Sophora alopecuroides, a traditional Chinese herbal medicine, with biological activities such as antivirus, anti-inflammatory, anti-allergic, anti-tumor, cardiotonic, anti-hypertension, anti-asthma, etc. [15, 16]. It has been proven that oxymatrine can reduce blood glucose and blood lipids, and improve IR in high-fat diet rats as well, but its specific mechanism has not been fully elucidated yet [13]. The results of this study also confirmed that giving oxymatrine to rats could significantly reduce their body mass, blood glucose and blood lipids levels and improve IR.

Previous studies found that FGF21 had potential benefits for diabetic patients, and could lower the blood glucose and increase the sensitivity of insulin [17, 18]. However, some researchers also revealed that in adult diabetic patients, FGF21 level was significantly increased, and its biological function was impaired.

Figure 4. Comparison of ATF4, ATF6, IRE1α mRNA levels and their protein levels in liver tissues of rats in each group. Compared with CON group, *P<0.05; compared with HFD group, #P<0.05. Normal control group (CON), oxymatrine group (OM), high-fat diet group (HFD), high-fat diet + pioglitazone group (HFD+PZ), high-fat diet + low-dose oxymatrine group (HFD+OM-L), high-fat diet + medium-dose oxymatrine group (HFD+OM-M), high-fat diet + high-dose oxymatrine group (HFD+OM-H) and high-fat diet + low-dose oxymatrine + pioglitazone group (HFD+OM+PZ).
FGF21 could be used as an independent factor to predict the occurrence of diabetes and was able to reflect the IR index in liver [19]. In this study, it also confirmed that FGF21 level significantly increased in liver of diabetic rats. At the same time, some animal experiments also found that in diabetic models, the function that FGF21 increased adiponectin products through ERK1/2 phosphorylation was impaired [20]. In high-fat fed APOE gene knockout mice, the content of hepatic FGF receptor 1-3 obviously reduced [21]. Therefore, it can be speculated that in diabetes, FGF21 resistance may associate with the compensatory increase of FGF21.

ER is a vital organelle in eukaryotic cells, for protein synthesis and modification, meanwhile, it participates in carbohydrates and lipid metabolism. Excessive accumulation of lipid, disorders of intracellular energy flow and nutrient utilization resulted from obesity will induce ERS, which activates the IRE1-α-JNK signaling pathway, leading to the dysfunction of insulin receptor and its substrate, and this is an important cause of IR [22, 23]. Islet β cells are very sensitive to ERS, persistent IR will lead to continuous synthesis and secretion of insulin, then cause the compensatory expansion of ER in islet β cells and the increasing synthesis of protein, resulting in the accumulation of immature protein in ER, then further aggravated ERS, eventually generated the failure of β cells and caused type 2 diabetes mellitus [24, 25]. At the same time, studies have described that PPARα was activated when ERS occurred, which led to the initiation of the unfolded protein reaction, causing the cascade reaction of PERK-Eif2α-ATF4; ATF4 could result in the upregulated expression of FGF21 by binding directly to the sequences AARE1 and AARE2 [26-30].

Animal experiment findings have demonstrated that, compared with normal-diet rats, the activations of PERK phosphorylation and c-Jun N-terminal kinase (JNK) in adipose tissues increased significantly in 16-week high-diet rat [31]. At the same time, the activations of IRE1-α, ATF-6 and XBP-1n adipose tissues exposed to high-carbohydrate-fat diet also increased significantly [32]. IRE1α activation activates JNK, which directly phosphorylates serine residues of IRS1, blocking the insulin signaling pathway and promoting IR. When patients are overweight, adipose tissue is an essential part where inflammatory cytokine generates and inflammation occurs. The in vivo experiment proved that ERS played a crucial part in inflammatory response induced by high-fat diet.
PERK could promote diglyceride to form phospholipid acid in the role of lipid kinase, which had an antagonistic effect on insulin [33]. UPR could also activate NF-κB inflammatory pathway mediated by IRE1α and ATF-6, inducing the expression of inflammatory genes and thus leading to IR [34].

In this study, it revealed that the expressions of ATF4, ATF6, IRE1α and FGF21 mRNA were up-regulated in high-fat diet rats, the signaling pathways of hepatic ERS were activated, and the down-regulated FGF21 induced by ATF4, ATF-6 and IRS1 was involved in the development of diabetes in rats. The increased expression of FGF21 in the liver tissues of oxymatrine was inhibited ATF4, ATF-6 and IRS1, accompanied by the decrease of blood glucose and blood lipid in rats. Through inhibiting the signaling pathways of hepatic ERS, oxymatrine may inhibit the expression of ATF4, ATF-6 and IRS1; in turn, the combination of ATF4, ATF-6, IRS1 and FGF21 reduced, resulting in the inhibition of the expression of FGF21, so that IR of rats was improved. At present, with the advantages of high efficiency, low toxicity and low cost, oxymatrine has been widely used in clinic. This experiment provides valuable experimental basis for clinical treatment of diabetes, which is in favor of further popularization.

Pioglitazone is a commonly used lipid lowering drug, this study indeed pointed out serum-lipid levels in OM+PZ obviously decreased in comparison of those in HFD; this indicated in terms of serum-lipid levels, oxymatrine combined with pioglitazone had better effects on high-fat diet rats, which owned remark descend range than oxymatrine or pioglitazone alone. However, there was no better effect of oxymatrine combined with pioglitazone than oxymatrine alone. That may be because the receptors for both drugs were the same, so the combination of the two drugs cannot enhance the curative effects.

There still exist some shortcomings in this experiment. ERS involves many transcription factors and metabolic enzymes, in the next step we can carry out comprehensive in-depth exploration on the mechanism of oxymatrine using genetic screening method, to provide a more solid experimental basis for clinical practice.

In summary, this study confirms that oxymatrine can inhibit the expression of FGF21, reduce blood glucose in high-fat diet rats, and improve IR by regulating the signaling pathways of hepatic ERS. It provides a new insight for the clinical treatment of diabetes.

Disclosure of conflict of interest

None.

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