IRAK inhibitor can improve insulin sensitivity in insulin-resistant mice fed with a high-fat diet

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Abstract

Background: Obesity and the inflammation associated with it, play a key role in the development of insulin resistance through the release of inflammatory cytokines and free fatty acids and the stimulation of toll-like receptors (TLR). Interleukin-1 receptor-associated kinase (IRAK), which mediates the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, is an important molecule in TLR signaling. The NF-κB pathway can reduce insulin efficacy by increasing the expression of proinflammatory cytokines. There is no safe inhibitor for the NF-κB pathway, and for this reason, the upper mediator of this pathway was selected for investigation.

Objectives: To determine the effects of an IRAK inhibitor on insulin resistance and serum biochemical factors in high-fat-fed insulin-resistant mice.

Methods: Insulin resistance was developed in C57BL/6J mice by 12 weeks of a high-fat diet. Subsequently, the IRAK inhibitor 1-(2-(4-morpholinyl)ethyl)-2-(3-nitrobenzoylamino)benzimidazole (IRAKi)/or pioglitazone, or both, were administered for a further 2 weeks. After 12 h fasting, blood and tissue samples were collected, insulin and glucose levels were assayed, and the homeostatic model assessment was used to quantify insulin resistance (HOMA-IR).

Results: The IRAKi decreased blood glucose levels significantly (253 ± 14.3 mg/dL vs 390.1 ± 16.6 mg/dL) and increased insulin sensitivity compared with untreated controls. However, we did not find a synergistic effect of IRAKi with pioglitazone in increasing insulin sensitivity.

Conclusion: IRAKis can increase insulin sensitivity and their efficacy is comparable to pioglitazone. However, combined administration of pioglitazone and IRAKi had no synergistic effect compared with monotherapy.

Keywords: adipose tissue; diabetes mellitus; inflammation; insulin resistance; mice, inbred C57BL; thiazolidinediones

Type 2 diabetes mellitus is a complicated metabolic disorder that affects 9% of the adult population and causes the death of more than 1.5 million people annually worldwide. Its worldwide prevalence is estimated to exceed 350 million by 2030 [1, 2]. In Iran, the prevalence of impaired fasting glucose is 17% and type 2 diabetes is 8% [3]. Type 2 diabetes is caused by increased liver glucose synthesis, insufficient insulin secretion, and insulin resistance [4]. In insulin resistance, the main insulin-sensitive tissues, such as skeletal muscles, the liver, and adipose tissue, lose their ability to respond adequately to insulin. The precise molecular mechanism of insulin resistance remains unknown; nevertheless, obesity-induced elevation of plasma free fatty acid levels and altered expression of the genes involved in inflammation...
and metabolism of glucose and lipids have been proposed [2–5]. Insulin sensitivity is described as the concentration of insulin required to induce half of the maximum insulin effect, and insulin resistance is defined as a reduction of the response to the metabolic effects of insulin. Insulin resistance plays a pivotal role in the pathophysiology of type 2 diabetes, obesity, high blood pressure, coronary artery disease, dyslipidemia, and other disorders, which are collectively called metabolic syndrome [6].

Obesity, especially visceral obesity, increases the release of nonesterified fatty acids, glycerol, hormones, proinflammatory cytokines, and other factors that contribute to insulin resistance [7]. Insulin resistance and obesity-induced inflammation contribute substantially to the development of diseases such as atherosclerosis, nonalcoholic fatty liver, hypertension, hyperlipidemia, polycystic ovarian disease, and type 2 diabetes [8]. Adiponectin is an anti-inflammatory adipocytokine produced almost exclusively by adipose tissue. Adiponectin gene expression is downregulated by tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), but upregulated by agonists of gamma peroxisomal activator receptor (PPAR-γ) such as thiazolidinedione [9]. PPAR-γ is a nuclear transcription factor that improves insulin sensitivity by modifying glucose metabolism and reducing inflammation [10]. Adiponectin affects the metabolism of glucose and lipids via phosphorylation and activation of the mitogen-activated protein kinase pathway, thus boosting insulin sensitivity [9].

Inflammatory cytokines, including TNF-α, IL-6, and interleukin 1 (IL-1), contribute to insulin resistance. These cytokines reduce insulin sensitivity by activating Jun N-terminal kinases (JNK), IκB kinase (IKK), and suppressors of cytokine signaling (SOCS) pathways, and by decreasing the amount of adiponectin secretion [11–13]. Members of the Toll-like receptor (TLR) family cause inflammation by activating nuclear factor κB (NF-κB) pathways, and this effect is mediated by myeloid differentiation primary response protein 88 (MYD88) and interleukin-1 receptor-associated kinase (IRAK) [14]. There are 4 IRAKs coded in the human genome (IRAK-1, IRAK-2, IRAK-3, and IRAK-4). The nonphosphorylated form of IRAK is bound to MYD88 through its death domain. After being isolated from MYD88 upon phosphorylation, it binds with TRAF6 to activate the NF-κB pathway [15].

Activation of the NF-κB pathway increases the levels of IL-6 and TNF-α, leading to an increase in insulin resistance. Adipose tissue contributes to insulin resistance by producing cytokines and proinflammatory chemokines. Therefore, it is expected that inflammatory inhibitors may be used to increase drug efficacy in obese diabetic patients taking pioglitazone, a thiazolidinedione, and PPAR-γ agonist, which is used in the treatment of type 2 diabetes mellitus. Among these inflammatory inhibitor drugs are IRAKi inhibitors, the use of which has not yet been reported in diabetic patients. Therefore, the effect of an IRAKi inhibitor on the efficacy of pioglitazone in improving insulin resistance and expression of IL-6 and adiponectin genes was investigated in mice. We selected C57BL/6J mice for the present study because this strain is especially suitable for the study of insulin resistance factors [16].

**Methods**

**Experiments using mice**

All animal experiments were approved by the Ethics Committee of Kerman University of Medical Sciences (ethics approval code: IR.KMU.REC.1396.1359). Mice were purchased from the Pasteur Institute, Tehran, Iran, and after a quarantine period, they were maintained under a 12-h light/darkness regime at 25 °C in the animal house of the KU School of Medicine. In the present study, obesity and insulin resistance were induced in 48 male C57BL/6J mice [17]. The mice were then divided without selection into 6 groups each consisting of 8 and maintained under standard conditions for 2 weeks to acclimate them to the new environment. To make 1 kg of a high-fat diet, we mixed 365 g of powdered food (regular mouse feed from Javaneh Khorasan Co., Iran, described following), 310 g of bovine fat, 250 g of casein, 60 g of vitamins and minerals each (Golbar Navid Bahar Co., Iran), 10 g of cholesterol, 3 g of methionine, and 2 g of colic acid, such that the composition is 45% carbohydrate, 20% protein, 23% fat, 1% cholesterol, 5% fiber, and about 5% methionine, lysine, calcium, phosphorous, sodium chloride, and other minerals and from which 58.8% calories are from fat, 27.5% from carbohydrates, and 14.7% from proteins [18]. The resulting dough was molded into standard pellets using a meat grinder. After the food was dried at room temperature, it was kept in a refrigerator.

The weights of the mice were measured, and the mice were treated with the following regimen for 14 weeks (Figure 1).

**Group 1**: A standard diet group, which was fed with Regular Mouse Feed composed of 65% carbohydrate, 21% protein, 5% fiber, 2%–3% fat, and about 5% methionine, lysine, calcium, phosphorous, sodium chloride, and other minerals, in which 72.2% of calories were from carbohydrates, 22.1% from...
protein, and 5.7% from fat (Javaneh Khorasan Co., Iran).

Group 2: A control group, which was fed with the high-fat diet.

Group 3: A sham group, which was fed with the high-fat diet for 12 weeks and was then injected intraperitoneally with dimethylsulfoxide (DMSO) 10 μg/kg in 100 μL sterile phosphate-buffered saline (PBS) each day for 2 weeks.

Group 4: A pioglitazone group, which was fed with the high-fat diet for 12 weeks and was then administered 10 mg/kg pioglitazone by intragastric gavage daily for 2 weeks [19].

Group 5: An IRAKi group, which was fed with the high-fat diet for 12 weeks and was then injected intraperitoneally with 10 mg/kg/day of (IRAK 1/4 inhibitor, catalog No. I5409; Sigma-Aldrich; IUPAC synonym 1-(2-(4-morpholinyl)ethyl)-2-(3-nitrobenzoylamino) benzimidazole; PubChem Substance ID 329815384 (IRAKi) dissolved in DMSO at 1 μg/μL and injected intraperitoneally in 100 μL PBS [20].

Group 6: A dual treatment group was fed with the high-fat diet for 12 weeks, and for a further 2 weeks they were administered 10 mg/kg/day of pioglitazone by intragastric gavage in addition to 10 mg/kg/day of the IRAK 1/4 inhibitor, which was dissolved in DMSO at 1 μg/μL and injected intraperitoneally in 100 μL PBS [19, 20].

The weight of mice was measured at the beginning of each week and at the end of the experiment. We did not see any behavioral changes in the mice throughout the study period.

At the end of the treatment, mice were anesthetized using ether after 12 h of overnight fasting (AVMA Guidelines for the Euthanasia of Animals, 2013 Edition). After anesthesia, blood samples were collected by exsanguination from the heart of the mice at 8 AM effecting human killing. Visceral fat samples were resected and immediately placed in liquid nitrogen to minimize degradation of mRNA before molecular analysis. Serum and tissue samples were stored at −75 °C for further investigation.

**Measurement of biochemical parameters**

Mouse blood samples were centrifuged to prepare serum samples for analysis. The levels of fasting glucose, triglyceride, and cholesterol were determined by enzymatic assay kits using glucose oxidase, glycerol oxidase, and cholesterol.
All kits were used according to the manufacturer’s instructions (Darman Kav Co., Iran).

Insulin concentrations were measured by enzyme-linked immunosorbent assay (ELISA; Mercodia, Sweden) according to the manufacturer’s protocol. HOMA-IR was calculated using the following equation [21]:

\[
\text{Glucose (mmol/L)} \times \text{insulin (μU/mL)} / 22.5.
\]

Measurement of IL-6 expression

The level of IL-6 expression was determined in adipose cells by real-time quantitative PCR. To achieve this, the total RNA was extracted according to the kit protocol using an RNA extraction kit (Total RNA purification kit, Yekta Tajhiz Azma, Iran). The purity of extracted RNA was determined by calculating the 260/280 nm absorbance ratio, and the quality was evaluated by electrophoresis on agarose gel and observing the 28s and 18s ribosomal RNA bands. Using a cDNA Synthesis Kit (Yekta Tajhiz Azma), complementary DNAs (cDNA) were synthesized according to the kit’s protocol and used for further investigation. Real-time PCR was performed using a real-time PCR kit (SYBER Green qPCR MasterMix 2×, Yekta Tajhiz Azma). PCR was performed at initial denaturation and enzyme activation (94 °C for 3 min), denaturation (95 °C for 5 s), annealing (62 °C for 10 s), and extension (72 °C for 15 s). After plotting the standard curves of the target (IL-6) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) reference genes, and calculating and comparing the performance of PCR, the 2^−ΔΔCT equation was used to compare gene expression in different groups [22]. The primer sequences are presented in Table 1.

| Direction       | GAPDH                  | IL-6                    |
|-----------------|------------------------|-------------------------|
| Forward primer  | CCCATCACCATCTCCAGGAGC  | CCTCTGGTCTTCTGAGTACC    |
| Reverse primer  | CCAGTGAGCTTCGCTTCAGC   | ACTCCTCTGTGACTCCAGC     |

GAPDH, glyceraldehyde 3-phosphate dehydrogenase (reference); IL-6, interleukin 6 (target).

Statistical analysis

All data were analyzed using IBM SPSS Statistics for Windows (version 22), and presented as mean ± SE (standard errors of the mean). A one-way analysis of variance (ANOVA) followed by a Tukey post hoc test was used to compare the means between groups. Differences with \( P < 0.05 \) were considered significant.

Results

Weight changes in mice

The weights of the mice were measured at the beginning of each week. Weight gain was calculated by subtracting initial weight from the final weight. Weight gain in the standard diet group was significantly less than it was in the control group; thus, the weights of mice increased after the high-fat diet. There was no significant difference in weight gain between the high-fat diet group and other treated groups in this study, which shows the IRAKi and pioglitazone have no effect on the weight of mice.

Mice were fed with the high-fat diet or standard diet for 12 weeks and then they were treated with the IRAKi, pioglitazone (Pio), or a combination of both (IRAIki+Pio) for a further 2 weeks (Figure 2).

Metabolic profile

The mean fasting blood glucose level in the pioglitazone group (260.8 ± 22.6 mg/dL), the IRAKi group (253 ± 14.3 mg/dL), and the IRAKi + pioglitazone group (261.9 ± 15.4 mg/dL) significantly decreased compared with the control group (390.1 ± 16.6 mg/dL). However, the mean blood glucose in the sham group (372.1 ± 40.2 mg/dL) did not show a significant difference compared with the control group. The levels of triglyceride and cholesterol of the treated groups did not change significantly compared with the control group (Figure 3).

Fasting serum insulin

The fasting blood insulin levels in the pioglitazone group (12.7 ± 0.7 mU/L), the IRAKi group (14.1 ± 0.3 mU/L), and the IRAKi + pioglitazone group (13.4 ± 0.3 mU/L) significantly
IRAK inhibitor increases insulin sensitivity

Real-time qPCR showed that IRAK inhibitor reduced the IL-6 gene transcription in the adipose tissue of insulin-resistant mice by about 5-fold compared with the high-fat-diet group. IRAK inhibitor had a greater effect on the decrease of IL-6 gene expression than pioglitazone or pioglitazone + IRAKi combination (Figure 6).

HOMA-IR index

The HOMA-IR index, as an insulin sensitivity index, in the pioglitazone group (8.3 ± 1.1), the IRAKi group (8.8 ± 0.5), and in the IRAKi + pioglitazone group (8.6 ± 0.5) significantly decreased in comparison with the control group (21.2 ± 3). Reduction in this index is evidence of an increase in insulin sensitivity (Figure 5).

decreased compared with the control group (21.6 ± 2.4 mU/L). However, there was no significant difference in fasting blood insulin in the sham group (18.9 ± 2.3 mU/L) compared with the control group (Figure 4).

IL-6 gene transcription

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Discussion

Treatment with pioglitazone or the IRAKi or a combination of both can reduce blood glucose, blood insulin, and HOMA-IR in insulin-resistant mice. A decrease of HOMA-IR is an indicator of an increase in insulin sensitivity [23]. Thiazolidinediones (rosiglitazone and pioglitazone) are high-affinity ligands of PPAR-γ, which are currently used to treat type 2 diabetes even though their consumption poses complications [24]. Pioglitazone is preferred as the use of rosiglitazone leads to complications such as cardiovascular threats and the atherogenic lipid profile [25]. Thus, pioglitazone was used in this study, and as expected, it caused an increase in insulin sensitivity.

Proinflammatory cytokines and inflammation impair insulin signaling and insulin action in the main insulin-sensitive organs. These cytokines induce phosphorylation of serine and threonine residues instead of tyrosine in insulin receptor substrates, and, through this mechanism, interfere with insulin receptor actions. IRAK is a key factor in this pathway [26], and thereby, IRAKi inhibitors can inhibit this pathway and reduce the effect of inflammation on insulin action, whereas deletion of the IRAK1 gene decreases insulin resistance in the muscle [26]. From our previous study, we concluded that IRAKi inhibitors can increase blood adiponectin levels, and because adiponectin is an insulin-sensitizing factor, the adiponectin-inducing effect of the IRAKi is a probable mechanism for the decrease in HOMA-IR [27, 28].

The level of IL-6 gene expression in the fat tissue of the IRAK group and the IRAK + pioglitazone group showed a statistically significant decrease of 80% and 70%, respectively. Inflammation signaling through IRAK induces the NF-κB, which in turn activates IL-6 gene expression [26, 29, 30]. Therefore, it is not surprising that IRAKi can reduce the transcription of IL-6.

A study by Myiazaki et al. [31] found that patients with type 2 diabetes had increased insulin sensitivity throughout the body after oral consumption of pioglitazone. This study highlights the importance of the IRAK-mediated inflammation pathway for insulin resistance. Increased levels of IRAK1 expression were associated with inflammation of adipose tissue in obese patients, and given that obesity accompanies diabetes, the level of IRAK1 expression and proinflammatory cytokines increases compared with the healthy individuals [32].

Therefore, it seems that inflammation, either from the IRAK or from the cyclooxygenase pathway, plays an important role in the promotion of insulin resistance. Notably, the effect of concomitant consumption of IRAK inhibitors and other anti-inflammatory drugs should be investigated in the development of insulin sensitivity.

The short duration of the treatment is a limitation in this study. Because there was no difference in the results of the sham group and the high-fat-diet group, to reduce the number of mice used, there is no need to use the sham group in future studies.
Conclusion

IRAKi can decrease insulin resistance in insulin-resistant mice and improve fasting glucose status. The effects of the IRAKi are comparable to pioglitazone, even though they do not have any synergistic effect. IRAKi can decrease IL-6, and NF-κB suppression is a probable mechanism for the IRAKi effect. IRAKi may be a candidate to control diabetes. It may be possible to reduce insulin resistance in diabetic patients by IRAK inhibition if safe drugs can be found.

Author contributions. HF contributed substantially to the study design. MA and AR made substantial contributions to acquiring the data and all data were analyzed by HF. MA and AR drafted the manuscript, and HF and MA critically revised it; all authors approved the final version submitted for publication and take responsibility for the statements made in the published article.

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Data sharing statement. The data sets generated and analyzed during the present study are included in this published article. Further details are available for noncommercial purposes from the corresponding author on reasonable request.

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