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Ferulic acid, a natural polyphenol, alleviates insulin resistance and hypertension in fructose fed rats: Effect on endothelial-dependent relaxation

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ABSTRACT

Ferulic acid (FER) is a polyphenolic compound contained in various types of fruits. It has a substantial therapeutic effect inhibitory activity against aldose reductase (AR) inhibition. In this study, we examined the effect of FER on fructose-fed rats in comparison to a standard AR inhibitor, zopolrestat (ZOP). We determined the protective role of FER against metabolic syndrome by examining serum insulin/Glucose levels, triglycerides (TGs), cholesterol and advanced glycation end product (AGE) in rats supplied with 10% fructose drinking water. In addition, blood pressure, vascular reactivity of isolated thoracic aortas and acetylcholine-induced NO were all evaluated to estimate the cardiovascular complications of metabolic syndrome (MetS) associated with fructose feeding. Animals were randomly divided into four groups: control, (+10% fructose, Fru), zopolrestat-treated fructose fed (Fru-zop) and ferulic acid-treated fructose fed rats (Fru-Fer). After 12 weeks of FER treatment, we found significant reduction in both hyperinsulinemia and elevated diastolic blood pressure associated with fructose-fed to levels comparable to those achieved with ZOP. Both FER and ZOP significantly augmented the impaired relaxation associated with fructose-fed, whereas neither showed any significant effect on the developed vasoconstriction. Isolated aortas from fructose-fed rats incubated with either FER or ZOP, reinstated normal relaxation response to acetylcholine (ACh). Furthermore, isolated aortas showed attenuated nitric oxide (NO) production following the addition of (ACh), while both FER and ZOP restored normal induction of NO. Taken together, the current study shows that, FER alleviated insulin resistance and hypertension associated with metabolic syndrome compared to the standard AR inhibitor (ZOP). This potential protective effect is at least mediated by restoring endothelial relaxation.

1. Introduction

Insulin resistance (IR) is a status in which insulin is unable to achieve its required biologic effects at its circulating levels [1]. Insulin resistance, hypertension and hyperglycaemia are the main causative factors of metabolic syndrome (MetS), which enhances the risk of cardiovascular diseases [2]. In hyperglycaemia, a surplus of glucose is reduced to sorbitol in the polyol pathway and further to fructose via a key enzyme called aldose reductase [3]. The reduction of glucose depletes an important cofactor of aldose reductase (AR) activity, called the reduced nicotinamide adenine dinucleotide phosphate (NADPH). Activation of the polyol pathway triggers metabolic abnormalities in tissues accumulated with sorbitol, including alterations in vascular structure and function [4]. Endothelial dysfunction also has been strongly connected with IR and subsequently vascular disorders [5]. Endothelial dysfunction—particularly impaired endothelium relaxation—is characterised by attenuated vascular reactivity to acetylcholine, in which the vasoactive action of nitric oxide (NO) in inhibited causing endothelium contraction [6].

FER is a natural polyphenol existed in various fruits and vegetables such as tomatoes, sweet corn and rice bran. It has antioxidant

Abbreviations: AGEs, advanced glycation end product; ANOVA, analysis of variance; CMC, carboxymethyl cellulose; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; PE, phenylephrine; Ach, acetyl choline.

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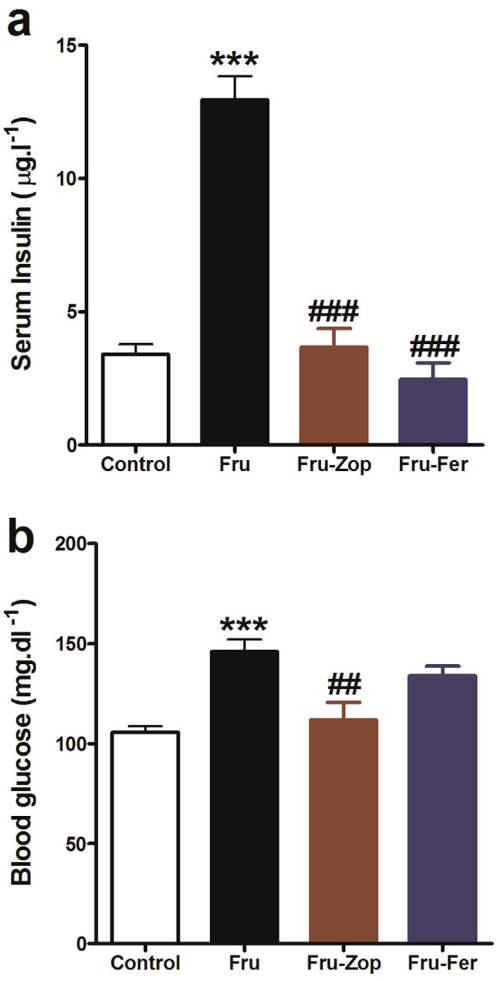

Fig. 1. The Effect of ferulic acid or zopolrestat on the serum insulin and blood glucose levels in fructose-fed rats. Ferulic acid and Zopolrestat (Fer, 20 and Zop, 25 mg/kg/d respectively) were administered daily for 6 weeks as suspension in 0.5% carboxy methyl cellulose (CMC) after 6 weeks of inducing MetS. Control group received CMC as a vehicle. Blood was collected and serum was analysed for glucose (A) and insulin (B). Symbols indicate mean ± SEM for N = 6–8; $^{***}P < 0.001$, compared with the corresponding control group values; $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ compared with the corresponding (+10% fructose, Fru) group values using One Way ANOVA and Newman Keuls *post hoc* test.

[7], hypotensive [8], and anti-inflammatory properties [9]. Previous literature attributed some of ferulic acid effects to its reported inhibitory effect on aldose reductase [10].

Likewise, ZOP is a novel, carboxylic acid with a potent aldose reductase inhibitory activity. It showed a significant effectiveness in the treatment of microvascular complications of diabetes [11,12]. In diabetic rats, ZOP has been shown to modulate sorbitol, fructose and myo-inositol levels in the sciatic nerve, lenses, retinas and kidneys. Furthermpre, ZOP adjusted renal plasma flow in galactosemic rats [13].

This study aimed to examine the potential protective role of ferulic acid on hypertension and insulin resistance associated with metabolic syndrome compared to a standard AR inhibitor, zopolrestat and also to identify the possible mechanisms underlying this effect. This will identify a new therapeutic strategy for limiting metabolic syndrome components like insulin resistance and hypertension.

2. Methods and materials

2.1. Animals

Male albino rats weighing 120–130 g from Zagazig University, Zagazig, Egypt were maintained in clear polypropylene cages in stable environmental conditions and equal light–dark cycles (3–4 rats per cage). Rats had free access to a commercially available rodent-pellet diet and purified water. The animal procedures conformed to guidelines from the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. Experimental protocol was approved by the Zagazig Ethical Committee for Animal Handling.

2.2. Study protocol

Animals were randomly divided into four experimental groups (8 rats/group) as follows: control, (+10% fructose), zopolrestat-treated metabolic syndrome (MetS-zop) and ferulic acid-treated-metabolic syndrome (MetS-Fer). Metabolic syndrome was induced by adding 10% fructose to the drinking water. Insulin resistance was determined by a constant hyperinsulinemia (6–8 µIU/ml) 6 weeks post-fructose drinking. Then, ZOP and FER (25 and 20 mg/kg/day, respectively) were administered daily by oral gavage for another 6 weeks as a suspension in 0.5% carboxymethyl cellulose (CMC), whereas the control and (+10% fructose) groups received only CMC as a vehicle. Fructose delivering occurred for 12 weeks which was sufficient to develop metabolic syndrome determined by a state of insulin resistance and vascular complications based upon the results of recent work from our laboratories [14]. The selected dose of zopolrestat was shown to inhibit aldose reductase [15,16]. The dose of ferulic acid was selected according to the median inhibiting concentration of aldose reductase as well as the previously reported effect of ferulic acid on blood pressure [8,10]. Blood pressure was recorded 12 h after final treatment. Rats were slightly anaesthetised with ether. Blood was then collected from the retro-orbital plexus and centrifuged for 20 min at 3000× *g*, 4 °C. The serum was analysed for glucose, insulin, triglycerides (TGs), total cholesterol, LDL cholesterol and advanced glycation end products (AGEs). After that, the descending thoracic aorta was isolated and placed in cold Krebs–Henseleit buffer (KHB) that contained NaCl 118.1, KCl 4.69, KH_2PO_4 1.2, $NaHCO_3$ 25.0, glucose 11.7, $MgSO_4$ 0.5 and $CaCl_2$ 2.5 mM. The aorta was then

Table 1
Effect of daily oral administration of ferulic acid (20 mg/kg) or zopolrestat (25 mg/kg) on the body weight, triglycerides, total cholesterol, LDL-cholesterol and advanced glycation end products (AGE) in rats with fructose-fed rats.

Treatment	Body weight (g)	Triglycerides (mg/dl)	Total cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	AGEs (fluorescent units)
Control	129.7 ± 16.5	52.1 ± 8.5	63.9 ± 7.4	26.9 ± 4.9	102.5 ± 3.9
+ Fructose (10%)	181.5 ± 9.9**	88.7 ± 6.1*	85.8 ± 5.1*	35.2 ± 5.3	135.0 ± 10.4*
+ Fructose (10%)-zopolrestat	191.7 ± 8.4	80.5 ± 8.5	102.3 ± 5.8	33.0 ± 6.6	120.7 ± 7.5
+ Fructose (10%)-ferulic acid	199.6 ± 6.1	68.0 ± 7.4	72.82 ± 8.4	26.9 ± 4.9	119.0 ± 6.2

Values are expressed as the mean ± SEM; N = 8 animals; $^{*}P < 0.05$, $^{**}P < 0.01$, compared with the corresponding control group values using One Way ANOVA and Dunnett's *post hoc* test.