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ROSIGLITAZONE AND PIOGLITAZONE PROTECT FROM INSULIN RESISTANCE-INDUCED HYPERTENSION INDEPENDENT OF THEIR INSULIN SENSITIZING ACTIVITY

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ABSREACT

Perixosome proliferator-activated receptor γ (PPARγ) is a key regulator of glucose homeostasis and adipogenesis. In the present study, we investigated the protective effect of PPARγ stimulation from the hypertension associated with insulin resistance. Insulin resistance (IR) was induced in rats by fructose (10%, in drinking water) and rats were left for 12 weeks for development of vascular dysfunction. Two PPARγ agonists were daily administered in the last 6 weeks of study, pioglitazone (10 mg.kg^{-1}), rosiglitazone (5 mg.kg^{-1}). The blood pressure (BP) was recorded and serum levels of glucose, insulin and lipids were measured. Rings of thoracic aorta were used to measure responses to phenylephrine (PE), KCl, acetylcholine (ACh), Ca^{2+} influx, reactive oxygen species (ROS) and nitric oxide (NO).

IR was associated with elevation in systolic and diastolic BP while, both PPARγ stimulants significantly reduced the elevation in diastolic BP. PPARγ stimulants decreased elevated serum insulin level in IR but serum insulin is not correlated with diastolic BP. IR increased vasoconstriction response of aorta to PE and KCl, decreased vasorelaxation response to ACh while PPARγ stimulants prevented the exaggerated response to PE and KCl but not affected response to ACh. IR increased KCl-induced Ca^{2+} influx while PPARγ stimulation restored normal Ca^{2+} influx. IR was accompanied with elevated levels of AGEs, triglycerides, total and LDL cholesterol while PPARγ stimulants normalized these levels.

In conclusion, PPARγ stimulation protects from the insulin resistance induced elevation in BP through a mechanism involving prevention of exaggerated vascular contractility.

INTRODUCTION

Insulin resistance (IR) denotes the inability of insulin to produce its usual biologic effects at circulating concentrations that are effective in normal subjects [1]. IR as well as hypertension and hyperglycemia are central components of metabolic syndrome, and have been associated with an increase in cardiovascular risk [2]. Some studies suggest a strong association between IR and endothelial dysfunction [3]. The intake of fructose is raised with an increased consumption of soft drinks and many beverages containing high fructose, Recent findings support that the increased consumption of fructose may be an important contributor to the metabolic syndrome, typically resulting in hyperinsulinemia, insulin resistance, hypertension, and hypertriacylglycerolaemia [4]. Thus, fructose has been implicated as a useful tool to induce insulin resistance in animals [5].

Peroxisome proliferators-activated receptors (PPARs) are ligand activated transcription factors belonging to the group of nuclear hormone receptors like vitamin D or steroid receptors [6], PPARs modulate genes that regulate lipid and glucose metabolism as well as gene expression in vascular cells [7]. Three receptors have been identified: PPAR γ, PPAR δ, and PPAR α, all with different tissue expression [8], PPARγ is expressed in endothelium and smooth muscle in the blood vessel wall [9]. The importance of PPARγ was originally recognized in adipogenesis and insulin sensitivity however little is known about its effect on the hypertension associated with insulin resistance. The beneficial impacts of PPARγ activation on endothelial cells, vascular smooth muscle cells, and macrophages suggest favorable effects on vascular disorders [10].

Thiazolidinediones (TZDs), also known as glitazones, are medications used for treatment and possibly the prevention of type 2 diabetes. TZDs, are potent agonists for the PPAR γ receptor, helped elucidate the important non-hypoglycemic effects of PPAR γ activation [11, 12]. It is also known that thiazolidinediones diminish vascular smooth muscle contractility in response to various vasoconstrictors. This has been demonstrated in different animal models [13, 14] due to the ability of glitazones to inhibit calcium currents into the smooth muscle cell [13, 15]. In addition to being most frequently used glitazones, pioglitazone and rosiglitazone, ligands for PPAR γ, improve insulin resistance in diabetic patients [16].

Therefore, the aim of the present work was to examine the potentially protective effect of PPAR-γ stimulants, pioglitazone and rosiglitazone against insulin resistance-induced hypertension and illustrate the mechanism of this protective effect.

MATERIALS AND METHODS

Animals

Adult male Wistar rats weighing 140–160 g (Zagazig University, Zagazig, Egypt) were housed in clear polypropylene cages (3-4 rats per cage) and kept on a light dark cycle of equal duration, under constant environmental conditions. Rats were fed commercially available rat normal pellet diet and water *ad libitum*. Experimental design and animal handling were according to the guidelines of the Ethical Committee of the Faculty of Pharmacy, Zagazig University, for Animal Use.

Study protocol

Animals were randomly divided into five experimental groups (8 animals each): control, insulin resistance, pioglitazone-treated insulin resistance (pioglitazone), rosiglitazone-treated insulin resistance (rosiglitazone). Insulin resistance was induced by adding fructose (10%) to the drinking water. Insulin resistance was confirmed by a stable hyperinsulinemia (6-8 μIU/ml) after 6 weeks of fructose drinking when insulin resistance rats are divided between groups. Then rats were received

pioglitazone (10 mg.kg^{-1}) or rosiglitazone (5 mg.kg^{-1}) treatment as suspension in 4% tween 80 by orogastric gavage for 6 weeks of study while control and diabetic groups receive 4% tween 80 as a vehicle. The dose of rosiglitazone (5 mg.kg^{-1}) [17] and pioglitazone (10 mg.kg^{-1}) [18,19] were chosen to be the most effective PPARγ receptor stimulating dose in previous literature.

At the end of the study and 12 h after the last injection, blood pressure was measured and rats were anesthetized with diethyl ether. Blood was collected from the retro-orbital plexus and centrifuged (3000×g, 4°C, 20 min) to separate serum that was analyzed for glucose, insulin, triglyceride (TGs), total cholesterol, HDL-cholesterol, LDL-cholesterol and advanced glycation end products (AGEs) Then, through opening the abdomen, descending thoracic aorta was carefully excised and placed in a Petri dish filled with cold Krebs–Henseleit buffer containing (in mM): 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. The aorta was cleaned of excess connective tissue and fat and cut into 4 rings of approximately 3 mm in length. For each animal, one aortic ring was suspended in an organ bath for studying vascular reactivity while the other three rings of aorta were used to study KCl-induced Ca^{2+} influx and basal intracellular level of reactive oxygen species (ROS) and nitric oxide (NO).

Serum analysis

Serum glucose was determined colorimetrically using a Randox reagent kit (Antrim, UK), according to the previously reported method [20]. The serum insulin level was assayed by sandwich ELISA (Millipore, Cairo, Egypt) that uses microtiter plate coated with mouse monoclonal anti-rat insulin antibodies. TGs were estimated colorimetrically using the glycerophosphate oxidase/p-aminophenazone method and total cholesterol was determined enzymatically with the cholesterol oxidase/p-aminophenazone method using Boehringer Mannheim colorimetric kit (Mannheim, Germany). Serum was mixed in a tube containing the precipitation reagent (phosphotungstic acid and magnesium chloride) to measure HDL-cholesterol content, and the clear supernatant was used for determination of its cholesterol content using the previous method. Finally, LDL-cholesterol was calculated according to the following Friedewald equation: total cholesterol−(HDL cholesterol+1/5 TGs) [21].

Serum AGEs was determined as previously described [22]. In brief, serum was diluted 1:15 in saline and the fluorescence intensity at (λex = 370 or 440 nm) was determined by LS45 fluorescence spectrophotometer (PerkinElmer®, Cairo, Egypt).

Blood pressure measurement

Blood pressure (BP) was measured indirectly in a conscious and slightly restrained rat by the tail cuff method. For these measurements, rats were conditioned to the restraint and the warming chamber for 10–20 min/day for at least 3 days before measurements. BP measurements were performed from 7:00 to 12:00 AM by the same investigator. After 5–10 min of stabilization in a warming chamber (35 °C), a typical run involved 10 repetitions of the automated inflation–deflation cycle. The mean of 6 readings within a 5–10 mmHg range was taken as the blood pressure.

Vascular reactivity

Thoracic aorta rings were suspended under 8 mN resting tension in individual 30 ml organ chambers containing Krebs–Henseleit buffer at 37°C and aerated with 95% oxygen, 5% carbon dioxide. Ring tension was determined by use of an isometric force transducer (Biegestab K30, Hugosachs Elektronik, March, Germany). Force displacement was recorded with a PowerLab Data Interface Module connected to a PC running Chart software (v4.2, ADI Instruments, Chalgrove, Oxon, UK). Rings were equilibrated for 60 min during which time, the bath solution was changed every 30 min. Before beginning the experiment, vessel viability was assessed by exposing arteries to KCl (80 mM). This was repeated until stable responses were achieved (usually two exposures). For studying the vasoconstrictor responsiveness of aorta, cumulative concentrations of phenylephrine (PE, 10^{-9} to 10^{-5} M) or KCl (10 to 100 mM) were added to the organ bath and the response was recorded. For studying the vasodilator responsiveness of aorta, rings were first precontracted with submaximal concentrations of PE (3×10^{-7} in case of diabetic group and 10^{-6} other groups). The submaximal concentration of PE was chosen to give similar precontraction in all studied groups. The cumulative concentrations of acetylcholine (ACh, 10^{-9} to 10^{-5} M) or sodium nitroprusside (SNP, 10^{-9} to 10^{-5} M) were then added to the organ bath and the response was recorded.

KCl-induced Ca^{2+} influx

The intracellular Ca^{2+} level following KCl stimulation were investigated with the fluorescence probes Calcium Green^{TM}-2 (Molecular Probes, Paisley, UK) according to the method described by [23] with some modification. The aorta rings were loaded for 30 min at 37°C with 5 mM of Calcium Green^{TM}-2 plus 0.1% Pluronic F-127 in Krebs–Henseleit buffer containing 25 mM HEPES. Aorta rings were washed twice and then cut and placed in a chamber especially designed for fluorescence measurement in aortic segments with the smooth muscle side up. One hundred ml of Krebs–Henseleit buffer containing HEPES were added quickly to the chamber. Calcium Green^{TM}-2 fluorescence was measured by LS45 PerkinElmer® Fluorescence spectrophotometer with remote fibre optic which allows measurement of tissue fluorescence in the used chamber. Readings (λem = 515 or 536 nm) were taken before and every 5 seconds after or KCl (100 mM) addition. The calcium ionophore was used as a positive control for Calcium Green^{TM}-2.

Basal levels of intracellular reactive oxygen species (ROS) and nitric oxide (NO)

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Determination of ROS was based on the methods of [24] with some modifications. Aortic rings loaded with 10 µM 2',7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) plus 0.1% Pluronic F-127 in Krebs–Henseleit buffer for 30 min at room temperature in the dark. Then, aortic rings were washed twice in kebs buffer, cut longitudinal and the fluorescence (DCF; 485nm excitation/515nm emission) of the smooth muscle side was measured by a remote fiber optic connected to LS45 PerkinElmer® Fluorescence spectrophotometer. NO determination is the same like ROS but using 4-amino-5-methylamino-2',7'-difluorofluorescein diacetate (DAF-FM).

Drugs and chemicals

The following drugs and chemicals were used Tween 80 (El-Nasr Chemical Co., Abou Zaabal, Cairo, Egypt), STZ, ACh, PE, SNP (Sigma-Aldrich, Dorset, UK). Both rosiglitazone and pioglitazone were gifts from (Amoun®, Egypt). Rosiglitazone and pioglitazone were administered orally as suspension using 4% Tween 80. ACh, PE and SNP were dissolved in distilled water.

Statistical analysis

All data are expressed as mean ± SEM. Statistical analysis was performed by the analysis of variance (ANOVA) followed by Newman-Keuls' post hoc test. The agonist maximum response (E_{max}) was calculated from concentration-response curve by non-linear regression analysis of the curve using computer based fitting program and used for comparison (Prism 4, Graphpad, CA, USA).

Table 1: Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of pioglitazone (10 mg.kg^{-1}) or rosiglitazone (5 mg.kg^{-1}) on serum levels of glucose, insulin, systolic and diastolic BP

Treatment	Glucose (mg.dl^{-1})	Insulin (µIU/ml)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Control	105.7 ± 2.985	3.4 ± 0.38	104.2 ± 1.7	84.4 ± 2.3
Insulin resistant	159.0 ± 8.6*	12.9 ± 0.37***	126.1 ± 2.8**	99.5 ± 1.6***
Pioglitazone	102.6 ± 12.7	6.4 ± 0.44###	103.1 ± 6.0##	85.9 ± 2.1###
Rosiglitazone	135.4 ± 8.8	6.0 ± 0.31###	116.7 ± 3.1	93.2 ± 1.9##

Values are expressed as the mean ± S.E. of mean, N=8 animals, *P<0.05, **P<0.01, ***P<0.001, compared with the corresponding control group values. ##P<0.001, ###P<0.001 compared with the corresponding insulin deficient group values, by One Way ANOVA and Newman Keuls *post hoc* test.

RESULTS

Serum parameters

High fructose intake as 10% in drinking water led to a significant elevation in blood glucose ($p<0.05$) and insulin ($p<0.001$) levels compared to control. The hyperinsulinemia in insulin resistance (IR) animals was significantly reduced by both PPARγ stimulants, rosiglitazone (5 mg kg^{-1}) and pioglitazone (10 mg.kg^{-1}) both at $p<0.001$ in the last 6 weeks while did not have a significant effect on blood glucose level (table 1).

IR animals have significantly higher serum levels of triglyceride ($p<0.05$) total cholesterol ($p<0.001$) and LDL-cholesterol ($p<0.05$) while serum level of HDL not change significantly compared to control (data not shown). The serum levels of triglyceride, cholesterol and LDL-cholesterol were significantly reduced by administration of both PPARγ stimulants, rosiglitazone ($p<0.001$) and pioglitazone ($p<0.05$, table 2).

The IR animals had a significantly higher level of serum AGEs ($p<0.001$) compared to control. However, PPARγ stimulants, rosiglitazone and pioglitazone administration significantly reduced it ($p<0.001$) compared with IR animals (table 2).

Blood pressure

IR animals had significant elevations in systolic ($p<0.01$), diastolic BP ($p<0.001$) compared with control. The elevation in diastolic BP was prevented by both PPARγ stimulants, rosiglitazone ($p<0.01$) and pioglitazone ($p<0.001$) while, pioglitazone administration prevented also the elevation in systolic BP ($p<0.01$, table 1). The diastolic BP was significantly correlated with serum insulin level in both control and insulin resistance animals ($r=0.74$, $p<0.01$) but not in PPARγ stimulants groups, rosiglitazone and pioglitazone.

Table 2: Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of pioglitazone (10mg.kg^{-1}) and rosiglitazone (5mg.kg^{-1}) on triglycerides, total cholesterol, LDL-cholesterol and advanced glycation end-products (AGEs)

Treatment	Triglycerides (mg.dl^{-1})	Total cholesterol (mg.dl^{-1})	LDL-Cholesterol (mg.dl^{-1})	AGEs (fluorescent units)
Control	70.2 ± 5.2	86.9 ± 5.9	26.9 ± 4.0	97.6 ± 5.9
Insulin resistant	105.7 ± 15.3*	106.7 ± 8.5***	42.0 ± 4.9*	171.9 ± 14.3***
Pioglitazone	56.8 ± 7.0#	81.5 ± 6.9#	26.3 ± 5.0#	105.2 ± 12.4###
Rosiglitazone	28.5 ± 4.6###	53.9 ± 6.2###	17.1 ± 2.1###	98.9 ± 3.6###

Values are expressed as the mean ± S.E. of mean, N=8 animals, [illegible] compared with the corresponding control group values, [illegible] ###P<0.001 compared with the corresponding insulin deficient group values, by One Way ANOVA and Newman Keuls *post hoc* test.

Vascular reactivity

Cumulative addition of PE (PE, 10^{-9} to 10^{-4} M) or KCl (10^{-2} to 10^{-1} M) to the organ bath resulted in concentration dependent contraction of aorta in all the groups (Fig. 1 and 2). IR induced by high fructose resulted in a large increase in aorta responsiveness to PE and KCl, reflected by a significant increase in apparent E_{max} ($p < 0.05$, $p<0.001$ respectively). Both rosiglitazone and pioglitazone administration reduced the isolated aorta responsiveness to PE ($p<0.05$) and KCl ($p<0.001$) (Fig. 1 and 2).

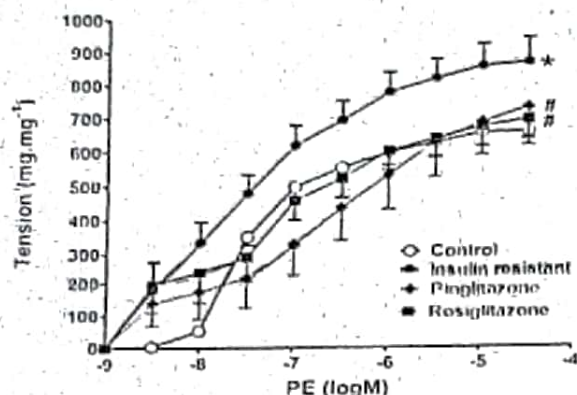

Fig. 1 : Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of rosiglitazone (5 mg.kg^{-1}) and pioglitazone (10 mg.kg^{-1}) on the maximal response (E_{max}) values of pheylephrine dose response curves. Values are expressed as the mean ± S.E. of mean: *P<0.05 compared with the corresponding control group values: #P<0.05, #P<0.05 compared with the corresponding insulin resistant group values: by One Way ANOVA and Newman-Keuls *post hoc* test.

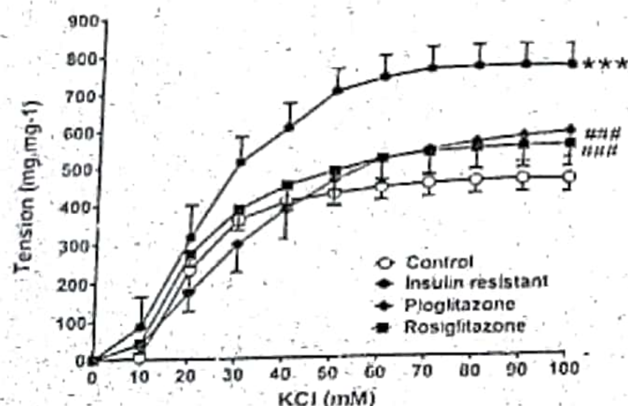

Fig. 2 : Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of rosiglitazone (5 mg.kg^{-1}) and pioglitazone (10 mg.kg^{-1}) on the maximal response (E_{max}) values of KCl dose response curves. Values are expressed as the mean ± S.E. of mean: ***P<0.001 compared with the corresponding control group values: ###P<0.001 compared with the corresponding insulin resistant group values: by One Way ANOVA and Newman-Keuls *post hoc* test.

Cumulative addition of ACh (10^{-9} to 10^{-5} M) to the organ bath resulted in concentration-related decreases in the tension of aortic artery rings precontracted with phenylephrine (Fig. 3). IR was associated with a large decrease in aorta responsiveness to ACh, reflected by a significant decrease in apparent E_{max} ($p < 0.001$; Fig. 3) while this impairment in response to ACh was not affected by any of the used PPARγ stimulants, rosiglitazone and pioglitazone (Fig. 3). On the other hand, neither diabetes nor rosiglitazone or pioglitazone treatment affects the aorta responsiveness to SNP (data not shown).

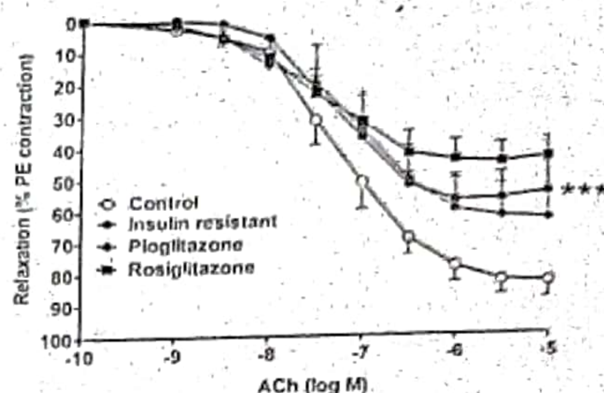

Fig. 3 : Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of rosiglitazone (5 mg.kg^{-1}) and pioglitazone (10 mg.kg^{-1}) on the maximal response (E_{max}) values of ACh dose response curves. Values are expressed as the mean ± S.E of mean: by One Way ANOVA and Newman-Keuls *post hoc* test.

KCl-induced Ca^{2+} influx

Addition of KCl (100 mM) to the fluorescence chamber increased the intracellular level of calcium in aorta isolated from animals in all groups. Aortae isolated from IR animals were characterized by a significant increase in the KCl-induced Ca^{2+} influx ($p<0001$) compared to control. On the other hand, rosiglitazone and pioglitazone administration significantly inhibited KCl-induced Ca^{2+} influx ($p<0.001$; Fig. 4).

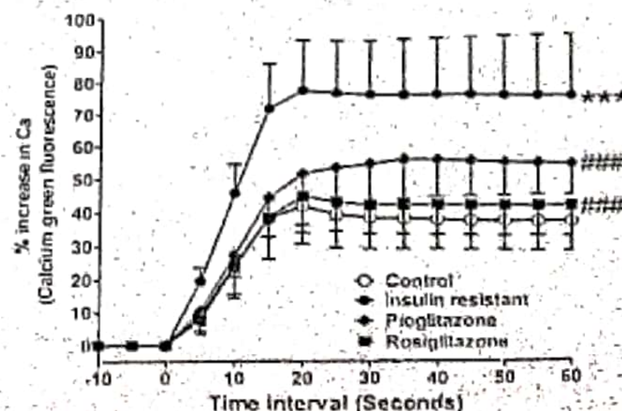

Fig. 4 : Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of rosiglitazone (5 mg.kg^{-1}) and pioglitazone (10 mg.kg^{-1}) on the maximal response (E_{max}) values of KCl stimulated increase in intracellular calcium. Values are expressed as the mean ± S.E of mean; ***P<0.001 compared with the corresponding control group values: ###P<0.001, ###P<0.001 compared with the corresponding insulin resistant group values; by One Way ANOVA and Newman-Keuls *post hoc* test.

Basal levels of intracellular ROS and NO

IR animals had significant elevations in basal levels of ROS ($p< 0.001$), NO ($p< 0.001$) compared with control. On the other hand, this elevation in basal levels

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of ROS and NO was prevented by both PPARγ stimulants, rosiglitazone ($p < 0.001$) and pioglitazone ($p < 0.001$)

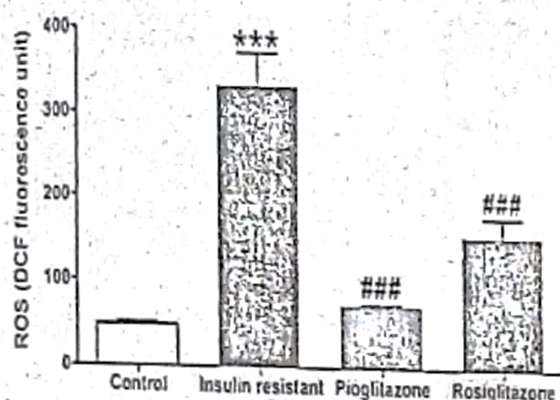

Fig. 5 : Effect of fructose- induced insulin resistance (10% in drinking water for 12 weeks) and daily oral administration of rosiglitazone (5 mg.kg^{-1}) and pioglitazone (10 mg.kg^{-1}) on ROS . Values are expressed as the mean ± S.E of mean: ***P<0.001 compared with the corresponding control group values. $^{###}$P<0.001, $^{###}$P<0.001 compared with the corresponding insulin resistant group values: by One Way ANOVA and Newman-Keuls *post hoc* test.

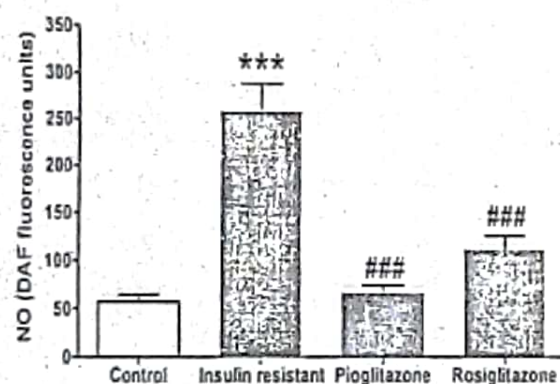

Fig. 6 : Effect of fructose- induced insulin resistance (10% in drinking water, for 12 weeks) and daily oral administration of rosiglitazone (5 mg.kg^{-1}) and pioglitazone (10 mg.kg^{-1}) on NO. Values are expressed as the mean ± S.E of mean: ***P<0.001 compared with the corresponding control group values: $^{###}$P<0.001, $^{###}$P<0.001 compared with the corresponding insulin resistant group values: by One Way ANOVA and Newman-Keuls *post hoc* test.

Control experiments

Neither the used PPARγ stimulants, rosiglitazone, pioglitazone nor the vehicle (4% Tween 80) administration had any effect on the previously mentioned parameters compared to control (data not shown).

DISCUSSION

The purpose of this study was to investigate the potentially protective effect of PPARγ ligands (rosiglitazone and pioglitazone) against insulin resistance (IR)-induced hypertension. We have shown for the first time that rosiglitazone and pioglitazone administration protects from IR-induced hypertension by a mechanism involving preventing exaggerated contractility-calcium influx signalling and independent of insulin sensitizing activity. These findings suggest a novel biological activity for the PPARγ ligands in the management of IR-induced vascular complications.

Previous studies demonstrated that high concentration of fructose (10% in drinking water) was the most suitable concentration for induction of insulin resistance and its associated vascular complication in rats [25]. In this study, fructose administration led to a significant insulin resistance (IR) as indicated by the elevation in serum insulin. The developed IR was accompanied by a significant elevation in systolic BP and diastolic BP. This elevation in BP could be a result of the vascular dysfunction in insulin resistance. The diastolic BP in control and IR groups of this study was significantly correlated with the serum insulin level. This is in harmony with the previous reports where high fructose loading enhanced the development of hypertension in normal [26] and diabetic rats [27]. In this study, we have shown an increased contraction of aorta in response to PE and KCl and decreased relaxation to ACh but not affected the response to SNP in insulin resistance. There is an increasing evidence that, insulin resistance has adverse effects on the reactivity of arteries and arterioles and promotes arterial hypertension and vascular occlusive diseases[28]. Thoracic aorta from fructose-fed rats showed exaggerated responses to PE and KCl [29, 30] while several studies have shown that fructose-fed rats exhibit impaired endothelium- dependent relaxation in response to ACh [31]. Similar findings concerning impairment of endothelium-dependent dilation in insulin resistance people have been derived from several regional circulations [32].

The impairment in vasoconstriction response could be due to increased extracellular calcium influx[33]. In the present study, KCl-induced Ca^{2+} influx was significantly increased in aortae isolated from IR. These data suggest an important role of Ca^{2+} influx in impaired vasoconstriction response in IR. On the other hand, the impairment in relaxation seems to be in the availability of NO, not in the response to NO. This is because: the relaxation to SNP (NO donor) is not affected. Inhibited endothelial nitric oxide sysnthase (eNOS) derived NO availability could be due to oxidative and nitrosative stress in IR. In this study, we reported excessive formation of reactive oxygen species (ROS) and inducible NOS derived (basal) NO. Also, we have shown previously impairment in pulmonary artery endothelial dependent relaxation which was mediated by stimulation of ROS generation and nitric oxide synthase uncoupling [23]. In addition, AGEs [34] and oxidized LDL-cholesterol [35] has been reported to inhibit NO production. In the present work, IR was associated with both increases in AGEs and dyslipidemia.

In the present work, both PPARγ ligands rosiglitazone and pioglitazone prevented the IR induced elevation in diastolic BP. This protective effect of PPARγ ligands rosiglitazone and pioglitazone seems to be due to a direct effect on vascular contractility and independent of insulin sensitization. We did not found any significant correlation between the diastolic and serum insulin level in rosiglitazone and pioglitazone groups despite, the strong significant correlation in control and IR groups. On the other hand, we have found that PPARγ stimulation by rosiglitazone and pioglitazone significantly inhibited the exaggerated response to vasoconstrictors PE and KCl but did not affect response to ACh. It has been reported previously that in vitro incubation with pioglitazone blunted the contractile response to norepinephrine and KCl and this effect is maintained after endothelial removal but lost in absence of calcium. In this study, both rosiglitazone and pioglitazone prevented the exaggerated Ca^{2+} influx associated with IR. This suggests an important role of Ca^{2+} signaling in the protective effect of PPARγ ligands rosiglitazone and pioglitazone from exaggerated vascular contractility.

The beneficial effect of rosiglitazone and pioglitazone on Ca^{2+} signaling could be related to either inhibition of AGEs or the associated dyslipidemia seen in this study. The inhibitory effects of PPARγ agonists on AGE formation may be ascribed to its antioxidative properties [16]. We have shown that both rosiglitazone and pioglitazone decreased ROS and basal NO generation. Moreover, previous study showed that pioglitazone decrease AGE/RAGE expression in the cerebral cortex of fructose-drinking rats [18]. On the other hand, rosiglitazone decreased triglyceride, total cholesterol and LDL-cholesterol levels in fructose-drinking rats [17].

In conclusion, PPARγ ligands (rosiglitazone and pioglitazone) prevents the development of hypertension in insulin resistance diabetic animals by a mechanism involving preventing exaggerated contractility-calcium influx signalling and independent of insulin sensitizing activity.

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وقاية مستحضرى الروزى جليتازون و البيوجليتازون من إرتفاع الضغط المصاحب لمرض مقاومة الإنسولين دونما الاعتماد على قدرتيهما علي تحسين الاستجابة للإنسولين

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تعتبر مستقبلات (PPARγ) هى المنظمة الرئيسية لعملية توازن الجلوكوز وتكون الشحم في الجسم. وتتناول هذه الدراسة التأثير الوقائى لتحفيز مستقبلات PPARγ من ارتفاع ضغط الدم مرتبطة بمقاومة الانسولين.

وتم احداث مقاومة الانسولين في الفئران عن طريق الفركتوز (10 ٪ ، في مياه الشرب) ، وتركت الفئران 12 أسبوعا من أجل إحداث خلل في الاوعية الدموية. هذا و تم تجريع الجرزان اثنان من محفزات مستقبلات PPARγ في الستة أسابيع الأخيرة من الدراسة و هما بيوجليتازوني و روزيجليتازون(10 و 5 مللىجرام لكل كيلوجرام) .ثم، تم تعيين ضغط الدم و تم قياس مستويات الانسولين والجلوكوز والدهون فى الدم. واستخدمت حلقات الأبهر الصدري لقياس إستجابة الأوعية الدموية للفينيليفرين ، كلوريد البوتاسيوم و الأستيل كولين وتدفق الكالسيوم وتكوين انواع الاكسجين التفاعلية (ريوس) واكسيد النيتريك.

إرتبطت مقاومة الانسولين بارتفاع في ضغط الدم الانقباضي والانبساطي، بينما ادى إستخدام أى من منشطات PPARγ إلى إنخفاض في ضغط الدم الانبساطي. أدى إستخدام منشطات PPARγ إلى تقليل الإرتفاع في مستوى الانسولين ولكنه غير مرتبط بضغط الدم الانبساطي. ارتبطت مقاومة الإنسولين بزيادة استجابة الأبهر للفينيليفرين و كلوريد البوتاسيوم و لكن بقلة استجابته للارتخاء بالأستيل كولين بينما أدى إستخدام منشطات PPARγ إلى منع زيادة استجابة الأبهر للفينيليفرين و كلوريد البوتاسيوم و لكنها لم تؤثر على قلة استجابته للارتخاء بالأستيل كولين. كما كانت مقاومة الإنسولين مرتبطة بزيادة تدفق الكالسيوم بواسطة كلوريد البوتاسيوم ولكنها عادت لمستواها الطبيعى مع إستخدام منشطات PPARγ. هذا و إرتبطت مقاومة الإنسولين بمستويات مرتفعة من المنتجات المتطورة نهاية الجلكزة والشحوم الثلاثية والكوليسترول في حين أدى إستخدام منشطات PPARγ إلى تطبيع هذه المستويات.

في الختام فإن استخدام منشطات PPARγ يحمي من إرتفاع ضغط الدم المصاحب لمقاومة الانسولين من خلال آلية تنطوي على الوقاية من المبالغة في انقباض الاوعية الدموية.