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EFFECT OF LOW GRADE INFLAMMATION IN THE DEVELOPMENT OF INSULIN RESISTANCE: A STUDY OF THE POSSIBLE EFFECTS OF ROSIGLITAZONE AND/OR ASPIRIN

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ABSTRACT:

The role of low grade inflammation in the development of insulin resistance and type 2 diabetes was investigated in rats fed with high fat diet (HFD). The possible effects of rosiglitazone and/or aspirin were studied in intact rats fed with HFD and on their isolated pancreas. Feeding rats with high fat diet for 8,14 and 16 weeks increased level of inflammatory markers e.g. fasting serum C-reactive protein (CRP) level and percentage of neutrophils. This was associated with impaired glucose tolerance. Rosiglitazone and aspirin caused a significant improvement in oral glucose tolerance (OGT) and lipid profile during prophylaxis and treatment. Insulin resistance and inflammation were reduced in prophylaxis only. Rosiglitazone and aspirin increased insulin release from isolated perfused pancreas of normal and HFD fed rats. Combination of the two drugs abolishes their individual effects on OGT, insulin resistance and insulin release. Inflammation is a pathogenic factor in induction of insulin resistance. Aspirin or rosiglitazone is effective anti-inflammatory, insulin sensitizer and insulinotropic drug. Combination of the two drugs abolishes their beneficial effects.

INTRODUCTION

Diabetes mellitus is a major emerging clinical and public health problem in Egypt. The "thrifty genotype" hypothesis may explain this observation[1]. Rural populations with more traditional lifestyles exhibit lower rates of diabetes risk factors and diabetes, whereas urban populations, and particularly those of a higher socioeconomic status, have higher rates of both risk factors and diabetes[2].

Elevated circulating inflammatory markers such as CRP and interleukin-6 predict the development of insulin resistance, and several drugs with anti-inflammatory properties lower both acute-phase reactants and glycemia and possibly decrease the risk of developing insulin resistance. It is not clear either inflammation induces insulin resistance or insulin resistance induces inflammation[3].

Rosiglitazone is an insulin sensitizer drug from the thiazolidinedione class. It acts by activating the peroxisome proliferator-activated receptor-γ (PPAR-γ). Recently, it has been found that rosiglitazone may have anti-inflammatory effects by lowering the nuclear factor kappa-B (NFκB) level [4]. The effect of rosiglitazone on beta cell functions remains controversial. Zawalich et al[5] mentioned that rosiglitazone had no effect on insulin secretion from isolated beta cells. However Juang et al[6] and Kim et al[7] showed that rosiglitazone stimulated insulin secretion from isolated beta cells.

Aspirin is a non-steroidal anti-inflammatory drug. It is an irreversible cyclo-oxygenase inhibitor. Aspirin improved both fasting and postprandial hyperglycemia in patients with type 2 diabetes, an effect that could be attributed to decreased basal rates of hepatic glucose production, enhanced peripheral insulin sensitivity, and decreased insulin clearance[8]. Recently, it has been found that aspirin- like compounds increase insulin secretion without affecting insulin sensitivity[9].

Aspirin is most commonly used in combination with rosiglitazone, because diabetes is usually associated with atherosclerosis and heart diseases[10]. It is important to study the possible types of interactions between the two drugs. Therefore, this work aims to investigate the role of inflammation in the development of insulin resistance using rosiglitazone and/or aspirin in-vitro and in-vivo in male rats fed with HFD and their isolated pancreas.

MATERIAL AND METHODS

A- Animals:

In all experiments performed, male adult albino rats, weighing 120-140g, obtained from the national research centre, Egypt were used. Standard diet, high fat diet and water were available ad libitum.

B- Induction of insulin resistance:

Insulin resistance was induced according to the method described by Tacikowski et al[11] with little modifications by feeding the rats with high fat diet (HFD) for 8, 14 and 16 weeks.

The HFD consists of the following components:

Casein (20 g%), L-cystine (0.3 g%), Maltodextrin (12.5 g%), corn starch (31.5 g%), Sucrose (6.88 g%), Soybean oil (2.5 g%), Lard (24.5 g%), Vitamins and minerals (1.82 g%)[12].

C- Experimental design:

1- *In vivo* study: After one week adaptation period, rats were randomly distributed into 2 main groups: Group 1: (Prophylaxis), rats were given drugs orally for 9 weeks starting one week before HFD administration. The rats were fed with HFD for 8 weeks concurrently with the drugs. Group 2: (Treatment), rats were fed with HFD for 10 weeks and then were given drugs orally for another 4 weeks along with HFD administration. Each group was subdivided into 5 subgroups, 14 rats in each subgroup, (control normal, control HFD, rosiglitazone (Galaxo-Welcome Co. England) in a dose of 0.8 mg/kg/day[13] orally, Aspirin (El-Nasr Pharmaceutical Chemical Co. Cairo Egypt) in a dose of 120 mg/kg/day[14] orally and aspirin + rosiglitazone in the same previous doses and by the same route. Aspirin and rosiglitazone were suspended in 10% gum acacia (El-Gumhoria Co. Egypt). Normal and HFD groups were given 10% gum acacia suspension by oral gavage.

2- *In vitro* study: Animals were divided into 2 main groups, one group fed with normal diet, the second group fed with HFD for 16 weeks before isolation of their pancreas. Each group was divided into 4

subgroups (one as a control, the others for drugs aspirin, rosiglitazone or both together).

D- Isolation and perfusion of pancreas:

The experiments were carried out on the isolated perfused rat pancreas according to the technique described by Grodsky et al[15]. Rats were fasted overnight and anaesthetized by intraperitonial injection of thiopental (50mg/kg body weight, EPICO Company, Egypt). Rats were dissected to remove, in one block, the pancreas with the adjacent proximal part of the duodenum, the spleen and the stomach, and attach cannulae to the celiac axis and portal vein in the perfusion system.

The perfusion medium is a Krebs-Ringer-bicarbonate solution with 6% hydroxyethylstarch (HAES) and 0.25% bovine serum albumin and supplemented with 3mM glucose (or 16.7mM glucose)(Adwic. Company Egypt), 10mM aspirin[16] or 4.5 µM rosiglitazone[17]. The pH of the final solution was always adjusted at 7.4 and checked using a pH meter. It was continuously gassed with a carbogen mixture of 95% O_2 and 5% CO_2 and the temperature was maintained constant at 37°C using a thermostat. The perfusion medium was introduced into the celiac artery at a flow rate of 1ml/min and the effluents were collected from the portal vein. The venous effluent was collected after a single passage through the pancreas preparation at different time intervals into pre-chilled tubes, then frozen and stored at -20°C until the assay of insulin.

E- Biochemical assays:

Serum glucose levels were measured by a glucose oxidase method according to the principle of Trinder[18]. The serum insulin levels were determined by the radioimmunoassay method according to the principle of Feldman and Roadbard[19]. Insulin resistance and beta cell function were calculated using the HOMA index model[20]. The serum free fatty acids (FFA) levels were measured according to the method of Ackman and Sipos[21]. The extraction of free fatty acids was done according to the method of Bligh and Dyer[22]. The serum triglycerides (TG), total cholesterol (TC) and HDLc levels were determined by the enzymatic colorimetric method described by Buccolo et al[23] and Naito et al[24]. Serum LDLc was calculated using the Friedwald formulae. Percentage of neutrophils was determined using the differential white blood cell count method according to the principle described by Hoffman et al[25]. Serum CRP levels were determined using the enzyme- linked immunosorbent assay method described by Helgeson et al[26].

Statistical analysis

The difference between values (mean±SEM) was tested for significance by ANOVA, Tukey test and by students t test for unpaired data[27] using SPSS program version 10. Results were considered significant at $P < 0.05$.

Graph Pad prism program version 5 was used to calculate the area under the oral glucose tolerance curves and insulin secretion time curves.

RESULTS

A- *In vivo* study:

1- The HFD group:

As shown in tables 1 and 2, feeding rats with high fat diet for 8 and 14 weeks caused a significant increase in body weights of animals, fasting serum glucose levels, serum TC, TG, LDLc, percentage of neutrophils, serum insulin, insulin resistance and serum CRP levels, while it caused a significant decrease in fasting serum HDLc levels, β-cell function and impaired glucose tolerance when compared with those of rats fed with normal diet.

2- The prophylaxis group:

a- The rosiglitazone group:

As shown in table 1, rosiglitazone caused no significant increase in body weights or a decrease in fasting serum HDLc, FFA and serum insulin levels while it caused a significant reduction in fasting serum glucose levels to the normal values, serum TC, TG , LDLc levels, percentage of neutrophils, serum CRP levels and a significant increase in insulin sensitivity, β-cell function and improved glucose tolerance when compared with those of rats fed with high fat diet for 8 weeks.

b- The aspirin group:

As shown in table 1, aspirin caused no significant increase in body weight, fasting serum TC, serum insulin and FFA level while it caused a significant decrease in fasting serum glucose level to the normal values, serum TG, LDLc, levels, percentage of neutrophils and serum CRP levels and a significant increase in insulin sensitivity, fasting serum HDLc levels, β-cell function and improved glucose tolerance when compared with those of rats fed with high fat diet for 8 weeks.

c- The aspirin+rosiglitazone group:

As shown in table 1, aspirin + rosiglitazone caused no significant increase in body weights, fasting serum TC, HDLc, LDLc, insulin resistance and FFA level while it caused a significant decrease in fasting serum glucose level to the normal values, serum TG level, percentage of neutrophils and serum CRP level and increased fasting serum insulin level, β-cell function and impaired glucose tolerance when compared with those of rats fed with high fat diet for 8 weeks.

3- The treatment group:

a- The rosiglitazone group:

As shown in table 2, Rosiglitazone caused no significant increase in body weight, while it caused a significant decrease in fasting serum glucose levels, serum TC, TG, LDLc level and a significant increase in fasting serum HDLc, FFA levels, β-cell function and improved glucose tolerance when compared with those of rats fed with high fat diet only for 14 weeks. The effect of rosiglitazone on fasting serum insulin, insulin resistance, percentage of neutrophils and serum CRP levels was not significant.

b- The aspirin group:

As shown in table 2, aspirin caused no significant increase in body weight while it caused a significant decrease in fasting serum glucose level, serum TC, TG, LDLc levels and a significant increase

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in fasting serum HDLc, β-cell function, the percentage of neutrophils and improved glucose tolerance when compared with those of rats fed with high fat diet only for 14 weeks. Also, the effect of aspirin on fasting serum insulin, insulin resistance, FFA and serum CRP level was not significant.

c- The aspirin+rosiglitazone group:

As shown in table 2, aspirin + rosiglitazone caused no significant increase in body weights while it caused a significant decrease in fasting serum glucose level to normal values, serum TC, TG and LDLc levels and a significant increase in fasting serum HDLc, serum insulin, β-cell function and impaired glucose tolerance when compared with those of rats fed with high fat diet only for 14 weeks. The effect of aspirin + rosiglitazone on insulin resistance, percentage of neutrophils, fasting serum FFA and CRP levels was not significant.

B- *In vitro* study:

1- Effect of glucose (16.7mM) on insulin release from isolated perfused pancreas of normal diet and HFD fed rats:

Feeding rats with HFD for 16 weeks caused a significant increase in insulin response to 16.7mM glucose when compared with that of normal rats.

2- Effect of aspirin (10mM) or rosiglitazone (4.5μM) or both together on insulin release from isolated perfused pancreas of normal rats:

Aspirin (10mM) increased significantly insulin release when introduced with 16.7mM glucose in the perfusion medium. Rosiglitazone (4.5μM) increased significantly insulin release when introduced with both 3mM and 16.7mM glucose in the perfusion medium. Aspirin (10mM) together with rosiglitazone (4.5μM) caused no significant increase in insulin release when introduced with 3mM and 16.7mM glucose in the perfusion medium.

3- Effect of aspirin (10mM) or rosiglitazone (4.5μM) or both together on insulin release from isolated perfused pancreas of rats fed with HFD:

Aspirin (10mM) increased significantly insulin release when introduced with 3mM glucose in the perfusion medium. Rosiglitazone (4.5μM) increased significantly insulin release when introduced with 16.7mM glucose in the perfusion medium. Aspirin (10mM) together with rosiglitazone (4.5μM) caused a significant increase in insulin release when introduced with 3 mM glucose in the perfusion medium.

Table 1. Biochemical changes caused by rosiglitazone, aspirin and their combination as a prophylactic treatment in rats fed on high fat diet:

Parameters \ Groups	Normal	HFD	Rosiglitazone	Aspirin	Aspirin+Rosiglitazone
Body weight(g)	169.4±6	258.7±10*	240.4±5	238.4±9	223.2±5
Blood glucose(mg/dl)	84.6±4	114.3±4*	87.5±3+	88.7±2+	76.2±7+
AUC of OGTT ($min.mg.dl^{-1}$)	13886±170	16788±394*	15502±374+	15780±446+	17350±1004+
Serum insulin(μU/ml)	2.9±0.2	2.8±0.2	2.6±0.1	2.3±0.2	4.4±0.5+
IR index	0.6±0.02	0.7±0.07	0.5±0.04+	0.4±0.05+	0.6±0.09
BCF	66.3±7.8	25.8±1.15*	49.2±0.8+	77±5.1+	117.1±7.7+
CRP(ng/ml)	4.84±0.2	6.6±0.5*	4.98±0.19+	3.94±0.05+	4.62±0.313+
Neutrophils %	7.2±0.8	17.7±1.6*	10.2±0.8+	6±0+	9±2.1+
TC(mg/dl)	52.3±1.6	67.5±7.8	44.7±4.38+	53.5±2.6	67±1.6
TG(mg/dl)	49.4±1.4	67.6±3.7*	31.1±2.5+	52±3.6+	47±5.5+
HDLc(mg/dl)	36.3±2	27.7±2.3*	29.4±1.5	38.6±1.8+	33±2.6+
LDLc(mg/dl)	6.12±0.68	26.3±4.76*	9.08±2.38+	4.5±0.08+	±2.1٢٤.٦
FFA(mmol/l)	52.12±3.25	46.8±2.54	49±3.4	57.3±4.8	52.7±5.5

Values expressed as mean ± SEM.
* Significantly different from rats fed with normal diet at $P<0.05$.
+ Significantly different from rats fed with high fat diet (HFD) for 8 weeks at $P<0.05$.
AUC of OGTT: area under the curve of oral glucose tolerance test. IR: insulin resistance. BCF: beta cell function.

Table 2. Biochemical changes caused by rosiglitazone, aspirin and their combination treatment in rats fed on high fat diet

Parameters \ Groups	Normal	HFD	Rosiglitazone	Aspirin	Aspirin+Rosiglitazone
Body weight(kg)	182±6.7	269.7±7*	272.7±14	254.8±11	275.7±10
Blood glucose(mg/dl)	84.6±4	130.3±5*	112±3&	90.1±2&	85.7±3&
AUC of OGTT min.mg.dl^{-1}	13886±170	23411±647*	19151±768&	17893±1614&	26038±505&
Serum insulin(μU/ml)	2.9±0.2	6.6±0.7*	5.7±0.2	6.5±0.2	10.5±0.7&
IR index	0.6±0.02	1.97±0.2*	1.36±0.07	1.3±0.07	2.5±0.14
BCF	66.3±7.8	37.1±1.6*	46.7±1&	147.7±3.5&	188.5±8.4&
CRP(ng/ml)	4.84±0.2	6.77±0.4*	5.97±0.2	6.66±0.2	7.1±0.27
Neutrophils %	7.2±0.8	41±5*	29.3±7.8	75±4.5&	58.6±9.7
TC(mg/dl)	52.3±1.6	80.4±4.8*	52.2±2.3&	53.3±4.6&	58.6±3.1&
TG(mg/dl)	49.4±1.4	96.6±7*	40.5±2.2&	64.4±6.2&	59.2±3.8&
HDLc(mg/dl)	36.3±2	26.9±1.7*	37.3±2.5&	32.6±0.6&	35.8±1.9&
LDLc(mg/dl)	6.12±0.68	48.5±2.6*	25±0.7&	20±0.7&	17.2±0.2&
FFA(mmol/l)	52.12±3.25	51.1±1.1	65.7±1.4&	56.8±7.1	49.65±5.8

Values expressed as mean ± SEM.-
* Significantly different from rats fed with normal diet at P<0.05.
& Significantly different from rats fed with high fat diet (HFD) for 14 weeks at P<0.05.
AUC of OGTT: area under the curve of oral glucose tolerance test. IR: insulin resistance. BCF: beta cell function.

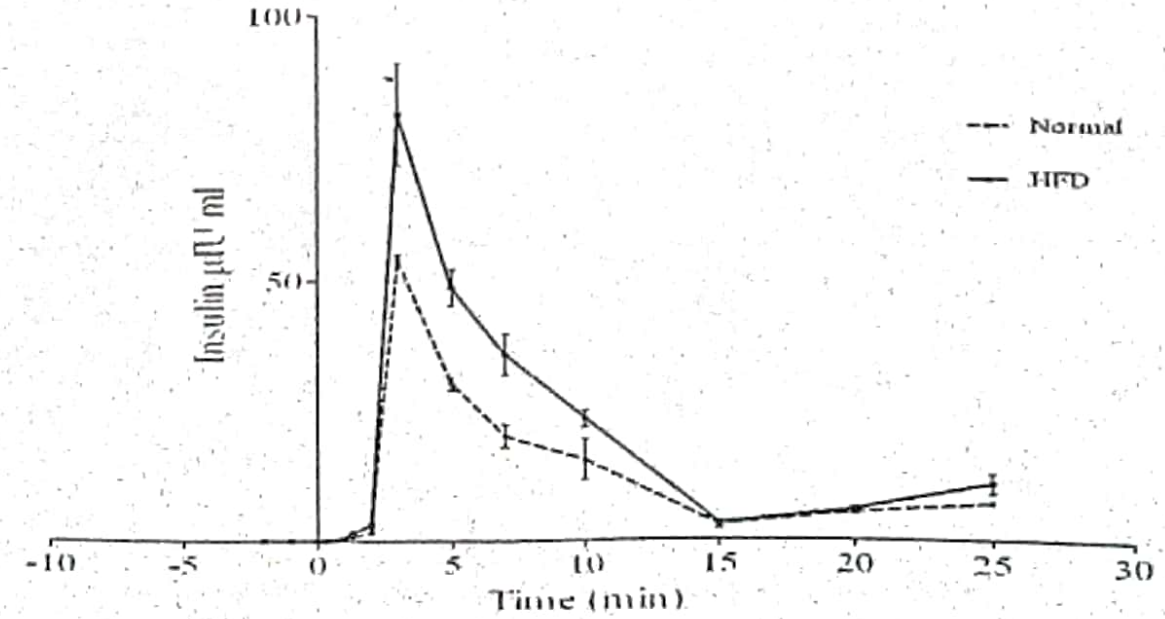

Fig.1. Effect of glucose (16.7 mM) on insulin release from isolated perfused pancreas of HFD and normal diet fed rats:
* Significantly different from the control normal group at P value < 0.05.

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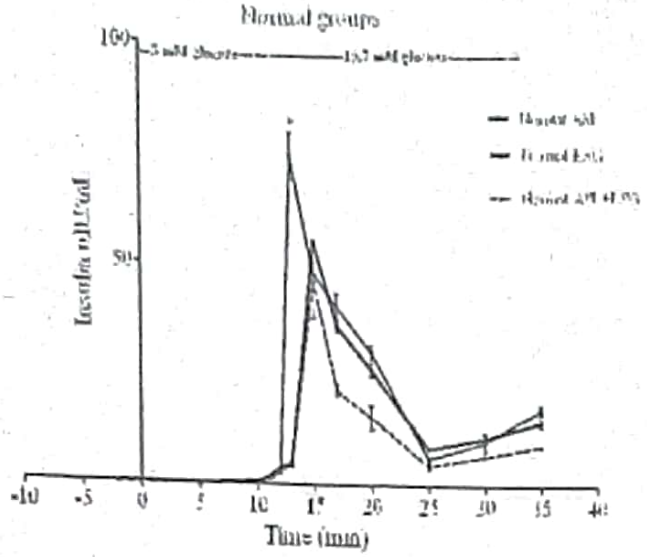

Fig.2a.

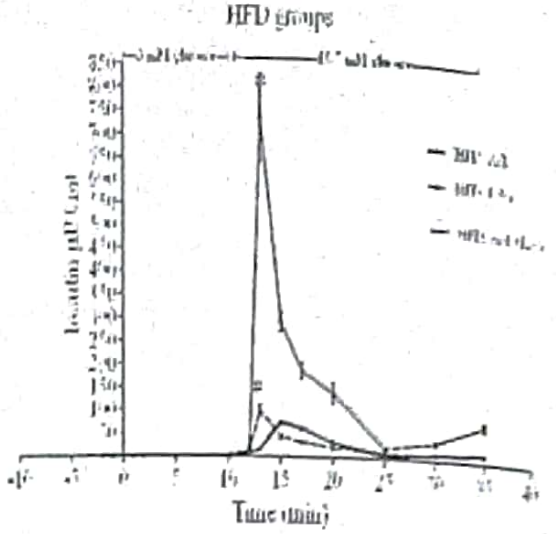

Fig.2b.

Fig.2. Effect of aspirin (10mM) or rosiglitazone (4.5 μM) or both together on insulin release from isolated perfused pancreas of normal and HFD fed rats:
* Significantly different from the control normal group at P value < 0.05.
# Significantly different from the control HFD group at P value < 0.05

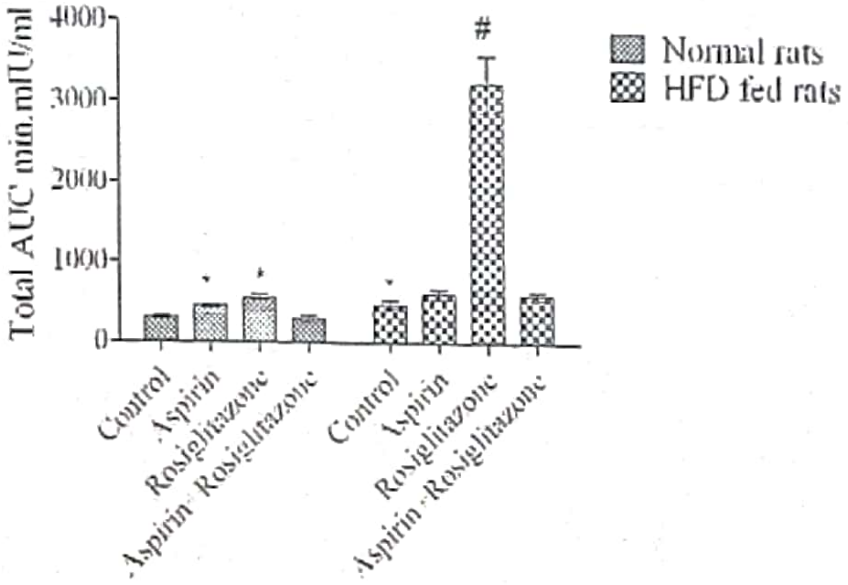

Fig.3. The calculated total area under the insulin secretion time curves.

* Significantly different from the control normal group at P value < 0.05.
# Significantly different from the control HFD group at P value < 0.05

DISCUSSION

In the present study, feeding rats with high fat diet for prolonged periods induced insulin resistance and impaired glucose tolerance. This was associated with increased levels of inflammatory markers e.g. fasting serum CRP levels and percentage of neutrophils. It seemed that inflammation preceded insulin resistance. Insulin resistance was correlated with inflammation. These results are in agreement with Tacikowski et al[11] who reported that feeding adult male Wistar rats with high fat diet for 9 weeks caused a significant increase in serum blood glucose level, serum insulin, insulin resistance, TC and serum TG levels. Moreover, Festa et al[28] indicated that serum CRP levels and white cell count were correlated with several components of insulin resistance syndrome. They also mentioned that, CRP is the most correlated parameter and there was a linear increase in CRP levels with the increase in the number of metabolic disorders.

Feeding rats with HFD for prolonged periods increased significantly insulin release from the pancreas at 16.7mM but not 3mM glucose concentration when compared with those of normal rats. Iguchi et al[29] reported that this effect may be attributed to reduced sex-determining region Y-box 6 (SOX6) mRNA levels within the beta cells, which was associated with increased ATP/ADP ratio, Ca2+ mobilization, proinsulin content, insulin gene expression and consequently glucose stimulated insulin secretion (GSIS). Moreover, Li et al[30] mentioned that this effect may be attributed to elevated pancreatic levels of urocortin 3 (Ucn3) mRNA, which increased GSIS. In

harmony to the previous postulations Latour et al[31] reported that HFD increased GSIS by acting on G-protein coupled receptor 40 (GPR40), which activates protein kinase C and calcium mobilization.

Rosiglitazone and aspirin when used in prophylaxis caused a significant improvement in OGT, lipid profile, insulin resistance and inflammation. However aspirin was more potent than rosiglitazone. Treatment with Rosiglitazone and aspirin showed significant improvement of OGT and lipid profile but it did not improve insulin resistance and inflammation. However, rosiglitazone was better than aspirin. These results are in agreement with Tacikowski et al[11] who reported that adult male wistar rats fed with high fat diet for 9 weeks and received rosiglitazone (10 micromol/kg b.w.) through a gastric tube showed a significant reduction in blood glucose level, serum insulin, TG, TC and insulin resistance. Moreover, Haffner et al [32] indicated that giving rosiglitazone for patients with type 2 diabetes for 26 weeks reduced significantly serum levels of CRP, matrix metalloproteinase-9 (MMP-9), WBC and non-significant reduction in serum IL-6 level. The change in each inflammatory marker from baseline to week 26 was significantly correlated with each of the other markers, as well as with the homeostasis model assessment estimate of insulin resistance.

The present study showed that rosiglitazone (4.5μM) caused a significant increase in insulin release from the isolated perfused pancreas of normal rats when included with 3mM and 16.7mM glucose in the perfusion medium. This is in accordance with Yang et al[15], Juang et al[10] and Kim et al(7), who reported that rosiglitazone may directly stimulate insulin release and insulin synthesis in pancreatic beta-cells. This effect may be attributed to the ability of rosiglitazone to up regulate expression of glucose transporter 2 (GLUT2) and glucokinase (GK) in beta cells(7). Also it may be due to the ability of rosiglitazone to activate phosphatidyl inositol 3 kinase (PI3K) within the beta cells[7].

In the present work, the inclusion of rosiglitazone (4.5μM) with glucose (16.7mM) caused a significant increase in insulin release from the isolated perfused pancreas of HFD fed rats. This is in accordance with Yang et al[15] who reported that rosiglitazone can activate PI3K pathway within the beta cell which is a similar mechanism by which HFD acts in the presence of low blood glucose level[33] so that there is no additional effect can be exerted by rosiglitazone on insulin release from the pancreas of HFD fed rats at low blood glucose levels. Moreover, Kim et al[7] reported that rosiglitazone can up regulate expression of GLUT2 and GK within the beta cells. Therefore, at high blood glucose levels, rosiglitazone can act through a pathway different from that of HFD and thereby, potentiates the effect of HFD.

Also, these results are in agreement with Hundal et al [8] who reported that type 2 diabetic patients given aspirin (7gm/day) for 2 weeks resulted in a 25% reduction in fasting plasma glucose, associated with a 15% reduction in total cholesterol and C-reactive protein, a 50% reduction in triglycerides and a 30% reduction in insulin clearance, despite no change in body weight. During a mixed-meal tolerance test, the areas under the curve for plasma glucose and fatty acid levels decreased by 20% and 50%, respectively. Aspirin treatment also resulted in a 20% reduction in basal rates of hepatic glucose production and 20% improvement in insulin-stimulated peripheral glucose uptake under matched plasma insulin concentrations during a hyperinsulinemic-euglycemic clamp. The curative effect of rosiglitazone and aspirin on fasting serum insulin, insulin resistance, percentage of neutrophiles and serum CRP levels was not significant. This may be due to that rosiglitazone and aspirin require prolonged periods of treatment to give their insulin sensitizing and anti-inflammatory effects as reported by Haffner et al[31] and Hundal et al[8].

Aspirin (10mM) increased insulin release from isolated perfused normal rat pancreas when introduced with glucose (16.7mM). This is in accordance with the results obtained by Fernandez-Real et al [9] who reported that Aspirin like compounds can increase insulin secretion from healthy obese subjects in a dose dependant manner.

The exact mechanism by which aspirin can increase insulin release is unknown. But this effect might be attributed to the ability of aspirin to induce rapid membrane depolarization by blocking KATP channels in a glucose concentration-dependent manner leading to Ca2+-entry through voltage-gated Ca2+ channels and insulin release [34]. Also, it may be due to the ability of aspirin to reduce NO production within the beta cells. NO can reduce GSIS by disruption of iron and sulfur containing enzymes within the mitochondria, such as aconitase and the electron transport chain complexes I and II [35-36]. This causes inhibition of glucose oxidation to CO2 and a fourfold reduction in the cellular levels of ATP(32). Another possible pathway for aspirin increased GSIS is by inhibiting cyclooxygenase-2 (COX-2) within the beta cells with concomitant reduction in prostaglandin E2 (PGE2) production. Prostaglandin E2 decreases cyclic adenosine monophosphate (cAMP) level inside beta cells causing reduction in insulin release [37-38].

In the present investigation, the inclusion of aspirin (10mM) with glucose (3mM) caused a significant increase in insulin release from the isolated perfused pancreas of HFD fed rats while it caused no significant increase when included with glucose (16.7mM) in the perfusion medium. Similarly, Li et al [33] reported that non steroidal anti-inflammatory drugs NSAID elevated the Ca2+ and increased insulin secretion in the presence of low, but not high glucose concentration. These effects may be due to HFD and high glucose concentration together increased the insulin release from beta cells to an extent that masked the effect of aspirin.

Aspirin and rosiglitazone combination when used in prophylaxis caused a significant deterioration in OGT, less improvement in the lipid profile and inflammation and no improvement in insulin resistance.

The curative effect of aspirin and rosiglitazone combination was significant in deteriorating OGT, less improvement in lipid profile while no improvement in

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insulin resistance and inflammation. The present investigation showed that aspirin (10mM) together with rosiglitazone (4.5μM) caused no significant increase in insulin release from the pancreas of normal rats when included with 3mM and 16.7mM glucose in the perfusion medium. Our in vitro results are in harmony with our results in the in vivo study, indicating that there is an interaction between aspirin and rosiglitazone.

On the other hand, aspirin (10mM) together with rosiglitazone (4.5μM) caused a significant increase in insulin release from the pancreas of HFD fed rats when included with 3mM but not with 16.7mM glucose. This indicates that this interaction did not involve the effect of aspirin on KATP channels but may be involved in the effect of rosiglitazone on PI3K activity, GLUT2 and GK expression within the beta cells.

In conclusion, inflammation is a pathogenic factor in induction of insulin resistance; aspirin and rosiglitazone are effective anti-inflammatory, insulin sensitizers and insulinotropic drugs. Aspirin and rosiglitazone antagonized the effect of each other on several parameters of insulin resistance when given in combination.

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تأثير الالتهاب المنخفض الحدة في حدوث مقاومة لتأثير الأنسولين: دراسة للتأثير المحتمل للروزيجليتازون أو الأسبرين أو كليهما معا.

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تم تصميم هذه الدراسة من أجل استقصاء دور الالتهاب المنخفض الدرجة في إحداث مقاومة لتأثير الأنسولين باستخدام الروزيجليتازون أو الأسبرين أو كلاهما معا داخل و خارج الجسم في الجرذان التي تم تغذيتها بغذاء عالي الدهون.

و قد حصلنا على النتائج التالية: أحدثت تغذية الجرذان بغذاء عالي الدهون زيادة في مقاومة الجسم لتأثير الأنسولين و خلل في تحمل الجسم للجلوكوز و ارتبط ذلك بزيادة مستوى مؤشرات الالتهاب (مستوى البروتين المتفاعل ج و كرات الدم البيضاء). تسبب استعمال الأسبرين و الروزيجليتازون منفصلين في تحسن تحمل الجسم للجلوكوز و مستوي الدهون في الدم في مجموعة الوقاية و العلاج. بينما أدى استعمالهما منفصلين إلى تقليل مقاومة الجسم لتأثير الأنسولين و مؤشرات الالتهاب فقط في مجموعة الوقاية، أما خارج الجسم فقد تسبب كلا منهما في زيادة إفراز الأنسولين من البنكرياس المفصول من الجرذان التي تغذت بغذاء عادي و تلك التي تم تغذيتها بغذاء عالي الدهون. أما عندما استخدمنا الأسبرين و الروزيجليتازون معا حدث خلل في تحمل الجسم للجلوكوز و قل التحسن الحادث في مستوي الدهون و مؤشرات الالتهاب و لم تتحسن مقاومة الجسم لتأثير الأنسولين في مجموعة الوقاية و العلاج، كما لم يزيد إفراز الأنسولين من البنكرياس المفصول خارج الجسم.

مما سبق يمكن أن نستنتج أن الالتهاب قد يؤثر في حدوث مقاومة الجسم لتأثير الأنسولين و أن للأسبرين وللروزيجليتازون عند استخدامهما منفصلين تأثير مضاد للالتهاب و محفز لإفراز و تأثير الأنسولين، أما عند استخدامهما معا فيضاد كلا منهما تأثير الأخر.