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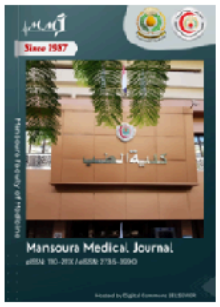


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# EXPERIMENTAL STUDY OF THE POSSIBLE EFFECT OF VALSARTAN ON INSULIN RESISTANCE IN FRUCTOSE- FED ALBINO RATS

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# EXPERIMENTAL STUDY OF THE POSSIBLE EFFECT OF VALSARTAN ON INSULIN RESISTANCE IN FRUCTOSE- FED ALBINO RATS

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## ABSTRACT

Insulin resistance (IR) is a consequence of high fructose fed diet in rats. The current study was carried out to declare if tumor necrosis factor-alpha (TNF-α) exerts a partial role in the development of IR in non-obese rat model; fructose fed rats (FFR) like that happens in obese rat models. We evaluate the influence of valsartan (a selective blocker of angiotensin receptor type-1) in comparison to metformin (a known insulin sensitizer) on enhancement of insulin sensitivity in FFR. Rats were divided into 2 equal groups (36 rats /group), one group received high fructose diet to induce insulin resistance and the other included standard diet fed rats. Each group is further divided into 3 equal subgroups, (standard diet+ saline), (FFR+ saline), (Standard diet + metformin), (FFR+ metformin), (standard diet+ valsartan) and (FFR+ valsartan). In all rats, body weight, fasting serum glucose, fasting serum insulin, insulin sensitivity test, fasting glucose insulin ratio (FGIR), serum TNF-α and serum malondialdehyde (MDA) were measured. Results revealed that administration of valsartan to FFR produced a comparable improvement of insulin resistance. In addition valsartan treatment in FFR produced significant decrease in serum TNF-α and MDA. It could be concluded that TNF-α and angiotensin II might regulate insulin sensitivity in non-obese FFR.

## INTRODUCTION

Insulin resistance occurs in a wide

variety of pathological states and is commonly associated with obesity, type-2 diabetes mellitus, accelerated atherosclerosis and hypertension [1,2]. Henriksen et al. [3], reported that angiotensin receptor blocker (ARB), irbesartan either acutely or chronically improves glucose tolerance in the obese Zucker rats, at least in part through enhancement of skeletal muscle glucose transport, and the effect of chronic Ang II receptor antagonism on skeletal muscle glucose uptake is associated with increase in GLUT4 protein expression. There have been some reports that Ang II upregulates TNF-α in many tissues including kidneys [4], cardiac fibroblasts[5] and monocytes [6]. Though the mechanisms of insulin resistance are not yet fully understood, many studies indicate that TNF-α plays a major role in the pathogenesis of obesity-induced insulin resistance, resulting from an interaction with insulin signaling pathway [7]. Though TNF-α was discovered as an inflammatory cytokine, it is now known that TNF-α is produced not only in macrophages and lymphocytes but also in adipocytes [8] and skeletal muscle cells [9] and that its expression increases in obesity-induced insulin resistant states. Therefore, the present work tried to answer the question does TNF-α play a similar role in non-obese insulin resistant FFR model? Furthermore, the present study was undertaken to investigate the effect of blocking the renin angiotensin system (RAS) by valsartan on the pathogenesis of insulin resistance.

## MATERIAL & METHODS

*Drugs used :*

- Valsartan; Diovan tablets (160mg/ tablet) supplied by Novartis Co.
- Metformin; Gluophage tablets (500 mg/ tablet), supplied by Cid Co.

• *Animals used :*

The present study was carried out on 72 healthy male albino rats. At the beginning of the study, the rats were aging 2 weeks; their body weights were monitored weekly. They were put under similar housing conditions. They were divided into 2 main equal groups (36 each), the first group fed standard diet and the second fed high fructose diet (table, 1) to induce hyperinsulinemia and insulin resistance according to Faure et a l [10]. Diets

(Standard and high fructose were given throughout the whole study (9 weeks). The rats of each group further divided into 3 equal sub-groups (12 rats each )as the following:

-Sub-group (1) : served as a control, received standard diet for 9 weeks and treated in the last 3 weeks of the experiment with intragastric 0.5ml of normal saline (the vehicle used to dissolve drugs).

-Sub-group (2) : Received high fructose diet and treated with saline (insulin resistant control).

-Sub-group (3) : Comprised rats that fed standard diet for 9 weeks and treated intragastrically with metformin in a dose of 200 mg/kg/day in the last 3 weeks of the experiment (10).

-Sub-group (4) : Consisted of rats fed high fructose diet for 9 weeks and after confirmation of being insulin resistant as determined from the results of fasting serum insulin (11), they treated intragastrically in the last 3 weeks with metformin as previously mentioned regimen.

-Sub-group (5) : Comprised rats fed standard diet and treated with valsartan in a dose of 30 mg/kg/day, intragastrically in the last 3 weeks of the experiment (12).

- Sub-group (6): FFR treated with valsartan as previously mentioned.

Diet composition according to Faure et al. [10] is shown in the following table ; (table 1):

| Component ingredient | Standard diet | High fructose |
|---|---|---|
| Glucose | 38 | 15.96 |
| Fructose | - | 33.64 |
| Wheat starch | 20 | 8.40 |
| Casein | 23 | 23 |
| Cellulose | 6 | 6 |
| Corn oil | 5 | 5 |
| Salt mixture | 7 | 7 |
| Vitamins | 1 | 1 |

All component ingredients were given in grams /100 grams of weight. The salt mixture is expressed in grams/kg, it include $CaHPo_4$ (30g), Kcl (100g), Nacl (100g), MgO (10.5g), Mg $So_4$ (50g), $Fe_2O_3$ (3g), $FeSo_4$ $7H_2O$ (5g). Retinol (53 mg), cholecalciferol (6.25mg), thiamine (2mg), riboflavin (1.5mg), niacin (7mg), pyridoxine (1mg), cyanocobalamine (5mg), menadione (1mg), nicotinic acid (10mg), O-choline (135mg), Folic acid (5mg) and biotin (30mg).

At the end of the experiment, insulin sensitivity test was performed according to Surwit et al. (13) in 6 rats from each group. Rats were fasted for 4 hours and injected intra -peritonealy (IP) with regular insulin in a dose of 1U/kg. Insulin was diluted in sterile saline for a final injected volume of 100μL; blood samples were collected for quantification of plasma glucose immediately before insulin injection (0 time) and after 15 minutes, 30 minutes and 90 minutes after IP insulin injection. Knifing decapitated the remaining 6 rats of each sub-group and collected blood samples were allowed to clot and then centrifuged. Serum was separated and stored at-70°C until time of assay of the following parameters:

- Fasting serum glucose using the enzymatic glucose oxidase method of Trinder (14).
- Fasting serum insulin according to Morgan and Lazarow by radioimmuno- assay using iodinated kits (11).
- Fasting glucose insulin ratio according to Silfen et al. (15) as they reported that a ratio $\geq 7$ is indicative of insulin sensitivity while a ratio <7 is indicative of insulin resistance.
- Serum malondialdehyde (MDA) as an indicator of oxidative stress according to Draper and Hadley (16).
- Serum tumor necrosis factor-alpha (TNF-α) according to Carti et al. (17) using a kit from immunotech (Acloulter Co.) by enzyme- linked immuno- sorbent assay method.

## STATISTICAL ANALYSIS

The results were compared using computer program (Stat.). The difference between two group means was analyzed using Student "t" test. P was statistically significant at value < 0.05.

## RESULTS

Animals fed high fructose diet showed non-significant change in body weight (BW) as compared to rats fed standard diet. Either valsartan or metformin treatment induced no significant change in BW (tab 2).

FFR developed significant insulin resistance as evidenced by impaired response (reduction in plasma glucose) to IP insulin administration and also from fasting serum insulin and FGIR (tab3, 4 &fig1, 2). Furthermore FFR showed significant increase in serum MDA and serum TNF-α levels but they showed no change in fasting serum glucose level. These findings are in comparison to rats fed standard diet (tab 5 & fig 3). Daily intragastric administration of either metformin (200 mg/kg/day) or valsartan (30 mg/kg/day) in the last 3 weeks of the experiment to FFR induced significant enhancement of insulin sensitivity and improvement of FGIR. In addition, these rats showed significant decrease in fasting serum insulin, serum MDA, serum TNF-α levels and no significant change in fasting serum glucose level. These results are in comparison to FFR untreated rats and rats fed standard diet. Furthermore administration of either metformin or valsartan as in the previous regimen to rats fed standard diet produced non-significant changes in all parameters as compared to that fed standard diet untreated group (tab3, 4,5 fig1, 2,3).

**Table (2) :** Effect of either metformin or valsartan treatment on body weight (BW) in standard and high fructose fed rats. Mean ± SEM

| | Animal groups | | | | | |
|---|---|---|---|---|---|---|
| | Standard diet for 9 weeks +saline (in the last 3 weeks) | High fructose diet (for 9 weeks) + saline (in the last 3 weeks) | Standard diet (9 weeks) + metformin (200mg/kg/day ) in the last 3 weeks intragastrically | High fructose diet (9 weeks) + metformin (200mg/kg/day intragastric in the last 3 weeks. | Standard diet (9 weeks) + valsartan (30 mg/kg/day intragastrically in the last 3 weeks | High fructose diet (9 weeks) + valsartan (30 mg/kg/day intragastrically in the last 3 weeks |
| BW | 315±3.3 | 318±4.1 | 316±5.1 | 316±3.9 | 320±6.3 | 318±5.6 |

P > 0.05 (Student "t" test).
SEM= standard error of mean.

**Table (3) :** Insulin sensitivity test in rats fed either standard diet (drug treated and untreated) or high fructose diet (drug treated and untreated). Mean ±SE M.:

| Time (minutes) | Plasma glucose (mg/dl) | | | | | |
|---|---|---|---|---|---|---|
| | Standard diet + saline (IG, 0.5ml in the last3 weeks) | High fructose diet + saline (IG, 0.5ml in the last 3 weeks) | Standard diet +IG metformin (200mg/kg/day in the last 3 weeks | High fructose +IG metformin (200mg/kg/day in the last 3 weeks) | Standard diet + IG valsartan (30 mg/kg/day in the last 3 weeks) | High fructose diet +IG valsartan (30 mg/kg/day in the last 3 weeks). |
| Immediate before IP injection of insulin | 88±0.5 | 90±0.7 | 86±0.4 | 89±0.4 | 90±0.4 | 92±0.6 |
| 15 | 72±0.1 | 86±0.4* | 70±0.1 | 73±0.3* | 70±0.2 | 72±0.1+ |
| 30' | 61±0.2 | 79±0.3* | 60±0.4 | 62±0.5* | 60±0.3 | 63±0.2+ |
| 90' | 54±0.3 | 77±0.4* | 56±0.5 | 55±0.3* | 58±0.1 | 57±0.2+ |

SEM = Standard error of mean.
Significant difference = P < 0.05.
* Significant difference between high fructose fed group and standard diet fed group.
* Significant difference between (high fructose fed + metformin) and (high fructose fed + saline).
+ Significant difference between (high fructose fed + valsartan) and (high fructose fed + saline).
IG= intragastric

**Table (4):** Fasting glucose insulin ratio (FGIR) in rats fed either standard diet or high fructose diet (drug treated and untreated), means ± SEM

| Parameter | Standard diet for 9 weeks and treated with saline in the last 3 weeks | FFR for 9 weeks and treated with intragastric saline in the last 3 weeks | Standard diet + metformin (200 mg/kg/day intragastric in the last 3 weeks) | FFR+ Metformin 200mg/kg/day , intragastric in the last 3 weeks | Standard diet + valsartan 30 mg/kg/day, intragastric In the last 3 weeks | FFR + valsartan 30mg/kg/day intragastric, in the last 3 weeks |
|---|---|---|---|---|---|---|
| Fasting serum glucose (mg/dl) | 98.3±1.1 | 100.2±1.7 | 96.5±1.4 | 99.1±3.2 | 99.2±2.4 | 101.1±0.7 |
| Fasting serum insulin (nu/dl) | 13.1±0.05 | 35.3±3.2▪ | 13.3±0.1 | 14.1±0.3 | 13.8±0.06 | 14.1±0.01 |
| FGIR | 7.5<br>IS | 2.8<br>IR | 7.3<br>IS | 7.03<br>IS | 7.1<br>IS | 7.17<br>IS |

▪ P value is significant (< .0.05) between high fructose fed group treated with saline and standard diet fed group treated with Saline
FFR = Fructose fed rats.
IS = Insulin sensitive (FGIR ≥ 7).
IR = insulin resistance (FGIR < 7).
SEM = Standard error of mean.

**Table (5):** Effect of administration of either metformin (200mg/kg/day) or valsartan (30mg/kg/day) in the last 3 weeks, intragastrically on fasting serum glucose, fasting serum insulin, serum MDA and serum TNF-α in FFR and in rats fed standard diet. Mean ± SEM.

| Parameter | Standard diet fed rats + saline treatment | FFR + saline treatment | Standard diet + Metformin | FFR+ Metformin | Standard diet + valsartan | FFR + valsartan |
|---|---|---|---|---|---|---|
| Fasting serum glucose (mg/dl) | 98.3± 1.1 | 100.2±1.7 | 96.5±1.4 | 99.1±3.2 | 99.3±2.4 | 101.1±0.7 |
| Fasting serum insulin (nu/dl) | 13.1±0.05 | 35.3±3.2▪ | 13.3±0.1 | 14±0.03* | 13.8±0.06 | 14.1±0.01◊ |
| Serum MDA (n mol/ml) | 4.7±0.03 | 18.3±1.1▪ | 4.9±0.02 | 9.3±0.3* | 5.1±0.1 | 10.2±0.1◊ |
| TNF-α (Pg/ml) | 0.93±0.001 | 4.1±0.05▪ | 0.96±0.003 | 0.98±0.03* | 0.97±0.02 | 1.4±0.001◊ |

SEM = Standard error of mean.
FFR = fructose fed rats.
▪ P value is significant (< .0.05) between (FFR treated with saline) & (standard diet fed rats treated with saline).
* P value significant (<0.05) between (FFR + metformin) and (FFR+ saline).
◊ Significant difference between (FFR + valsartan) and (FFR + saline).

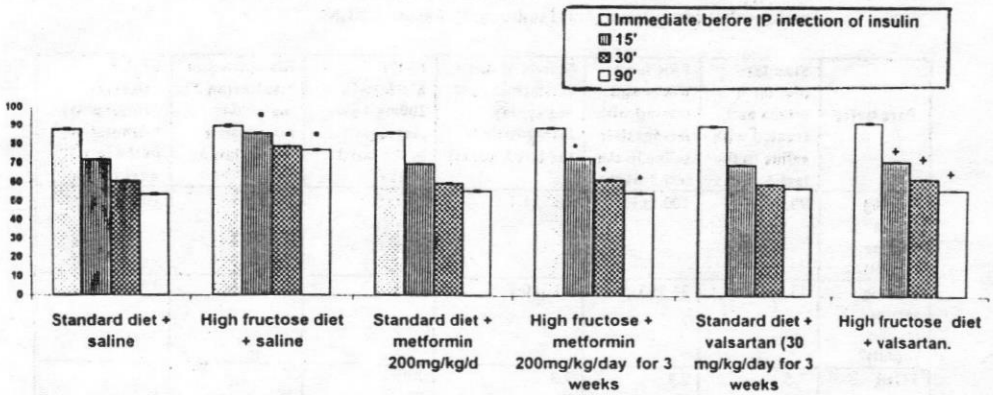


Fig (1): Insulin sensitivity test in rats fed either standard diet (drug treated and untreated) or high fructose diet (drug treated and untreated). Mean ±SE M. (n= 6 rats/group):

SEM = Standard error of mean.
Significant difference = P < 0.05.
• Significant difference between high fructose fed group and standard diet fed group.
* Significant difference between (high fructose fed + metformin) and (high fructose fed + saline).
+ Significant difference between (high fructose fed + valsartan) and (high fructose fed + saline).
IG= intragastric

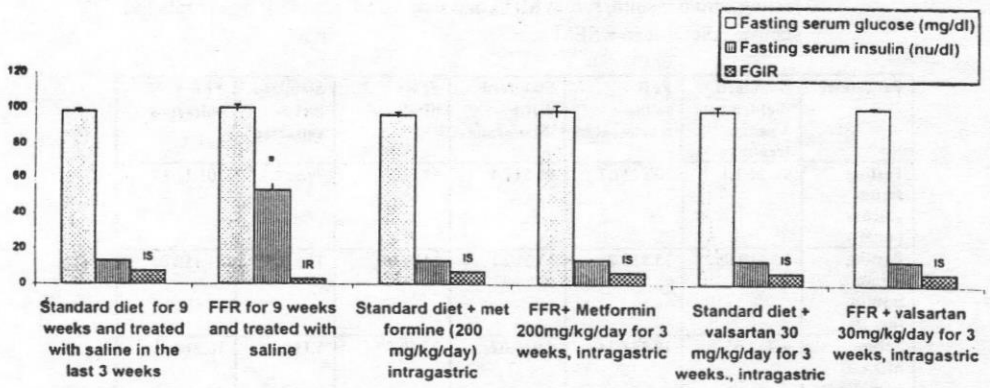


Fig (2): Fasting glucose insulin ratio (FGIR) in rats fed either standard diet or high fructose diet (drug treated and untreated), means ± SEM (n=6 rats/group).

• P value is significant (< .0.05) between high fructose fed group treated with saline and standard diet fed group treated with Saline
FFR = Fructose fed rats.
IS = Insulin sensitive (FGIR ≥ 7).
IR = insulin resistance (FGIR < 7).
SEM = Standard error of mean.

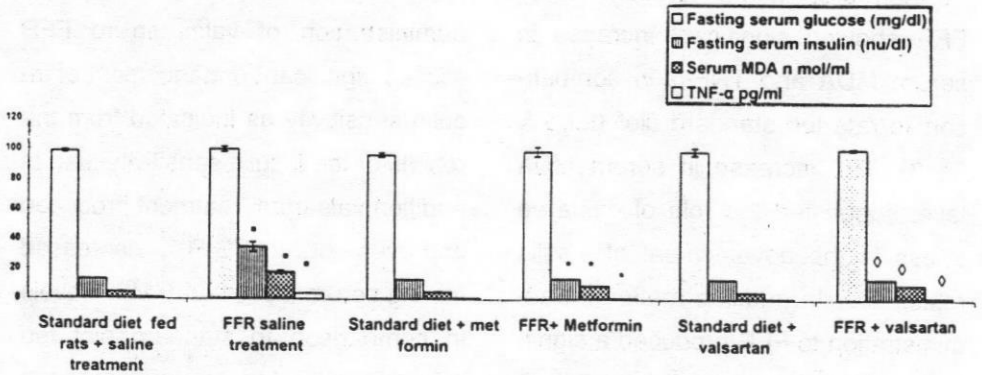


Fig (3): Effect of administration of either metformin (200mg/kg/day) or valsartan (30mg/kg/day) in the last 3 weeks, intragastrically on fasting serum glucose, fasting serum insulin, serum MDA and serum-α in FFR and in rats fed standard diet. Mean± SEM. (n= 6 rats/group):

SEM = Standard error of mean.
FFR = fructose fed rats.
• P value is significant (< .0.05) between (FFR treated with saline) & (standard diet fed rats treated with saline).
* P value significant (<0.05) between (FFR + metformin) and (FFR+ saline).
◊ Significant difference between (FFR + valsartan) and (FFR + saline).

## DISCUSSION

In the present study, the comparable effect of either administration of metformin or valsartan on insulin resistance induced by high fructose diet was examined. Insulin resistance was evaluated on the basis of FGIR and insulin sensitivity test [13,15]. This is in addition to fasting serum insulin where hyper- insulinemia has been used as an index of insulin resistance [15]. In the current study rats fed high fructose diet showed a significant insulin resistance as evidenced by impaired response to IP insulin injection in comparison to rats fed standard diet (table 3,4 & fig1, 2). These results are in consistent with previous studies [18,19,20,21]; as they concluded that high fructose diet induced insulin resistance in rats within 6 weeks due to post-receptor defects. These defects inhibited transport of insulin, which decreased the ability of insulin to stimulate glucose uptake to muscle and fat cells. In addition they reported that this insulin resistance was accompanied by increased fasting serum insulin but with production of non-significant change in fasting serum glucose, which is also in agreement with the results of the current work.

Furthermore, in the present study FFR showed significant increase in serum MDA and TNF-α in comparison to rats fed standard diet (tab5 & fig 3). The increase in serum MDA level suggested the role of oxidative stress in the development of insulin resistance. In addition metformin administration to FFR produced a significant enhancement of insulin sensitivity and elicited a significant decrease in serum MDA. These findings are in accord with Faure et al [10]. They documented that the improvement of insulin resistance elicited by metformin is due to its potential antioxidant effect, which is supportive to our work. Furthermore, in the present study metformin administration to FFR induced a significant decrease in serum TNF-α (tab.5 & fig 3). This reduction of TNF-α produced by metformin contributes to restoration of insulin sensitivity. This finding is supported by the study of Don-Dan et al. [22]. Metformin improved glucose uptake by the peripheral tissue due to increasing insulin binding to membrane receptors, activation of post-receptor metabolic pathways and also due to the beneficial effect on lipid metabolism [23,24,25].

In the present study intragastric administration of valsartan to FFR elicited significant enhancement of insulin sensitivity as indicated from the results of the insulin sensitivity test. In addition valsartan treatment produced improvement of FGIR , decreased fasting serum insulin and MDA levels in comparison to standard diet fed rats either treated or untreated (tab 3,4,5 & fig 1,2,3). Valsartan (angiotensin receptor blocker; ARB) inhibited the action of Ang II, which mediates oxidative stress that involved in the development of insulin resistance. Furthermore, valsartan decreased TNF-α, which inhibits insulin signaling linked to GLUT4 translocation to plasma membrane. This explanation is supported by other studies. Togashi et al. [26] demonstrated that blockade of AngII receptors decreased TNF-α expression in skeletal muscle of FFR and enhanced insulin sensitivity. Furthermore, it was reported that activation of the (RAS) is thought to be one of the factors up- regulating skeletal muscle TNF-α [27]. They concluded that blockade of AT1-receptors reduced local production of TNF-α in skeletal muscles of KK-Ay mice. Furthermore, Schiuchi et al. [28] and Van

et al. [29] found that AT1 receptors blockade increased insulin sensitivity in KK-Ay mice via stimulating insulin signaling cascade and consequent enhancement of GLUT4 translocation to plasma membrane. In consistent with the present study, Lau et al., Zhao et al., and Juan et al [30,31,32] demonstrated that oxidative stress plays an important role in AngII-mediated insulin resistance. It has been indicated that reactive oxygen species (ROS) play a pivotal role in the development of insulin resistance and that AngII is involved in the regulation of ROS production.

On the light of the present study, it could be concluded that, TNF-α and Ang II might regulate insulin sensitivity in non-obese normoglycemic rats as proved to exert such effect in obese hyperglycemic rats. In addition our results provide some information to understand the clinical relevance of the effect of angiotensin receptor blocker (ARB); valsartan on insulin sensitivity and the onset of diabetes, thereby preventing cardio- vascular events associated with insulin resistance in normoglycemic non-obese. We are in need to further human studies to support this observation.

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# الملخص العربى

# دراسة معملية للتأثير المحتمل لدواء الفالسرتان على حساسية الأنسولين فى الفئران البيضاء التى تغذت على كمية عاليه من سكر الفركتوز

**سوميه عبد اللطيف مقبل**

قسم الفارماكولوجيا الإكلينيكية _ طب المنصورة

أجرى هذا البحث لدراسة التأثير المحتمل لدواء الفالسرتان (قافل لمستقبلات الانجيوتنسين -١) على الاستجابة للأنسولين فى الفئران التى تعانى من مقاومة لمفعول الأنسولين الذى أحدثته التغذية على طعام عالى المحتوى من سكر الفركتوز.

كان من اهم اهداف هذا البحث هو محاولة التوصل لميكانيكية هذا الدواء من خلال تأثيره على معامل تحلل الأورام _الفا فى المصل وكذلك تأثيره على الشقوق الحره وذلك بالمقارنة مع دواء الميتفورمين .

استخدم لإجراء هذا البحث ٧٢ فأراً أبيضاً قسمت إلى مجوعتين رئيسيتين متساويتين ، الأولى غذيت بغذاء قياسى والثانية غذيت لمدة ٩ أسابيع (المدة الكلية للبحث) بغذاء يحتوى على كمية عالية من سكر الفركتوز لإحداث مقاومة لمفعول الأنسولين مع عدم التأثير على وزن الجسم أو مستوى السكر الصائم فى المصل ثم قسمت كل مجموعة رئيسية إلى ٣ تحت مجموعات متساوية (أجمالى٦ تحت مجموعات) كالتالى:

**الأولى** : ضابطة غذيت بطعام قياسى وعولجت يومياً بمحلول ملح عادى (٥ر مل) على مدى الثلاثة أسابيع الأخيرة من البحث.

**الثانية** : غذيت بغذاء عالى المحتوى من سكر الفركتوز وأعطيت محلول الملح العادى كما سبق .

**الثالثة** : غذاء قياسى وعولجت يومياً بدواء الميتفورمين عن طريق الفم بجرعة ٢٠٠مجم /كجم بنفس التوقيت و المدة السابقتين .

**الرابعة** : تعانى من مقاومة لمفعول الأنسولين وعولجت بدواء الميتفورمين كما سبق.

**الخامسة :** لاتعانى من مقاومة لمفعول الأنسولين ( غذاء قياسى) وعولجت يومياً عن طريق الفم بدواء الفالسرتان بجرعة ٣٠مجم/كجم على مدى الثلاثة أسابيع الأخيرة من الدراسة.

**السادسة :** تعانى من مقاومة لمفعول الأنسولين وعولجت مثل الخامسة .

وتم قياس مدى الحساسية لمفعول الأنسولين عن طريق اختبار تأثير حقن وحدة واحدة من الأنسولين المائى لكل كجم من وزن الجسم فى الغشاء البريتونى متبوعاً بقياس مستوى الجلوكوز فى البلازما مباشرة قبل حقن الأنسولين وبعد ١٥ دقيقة ، ٣٠ دقيقة، ٩٠ دقيقة من الحقن على التوالى. وكذلك تم تعيين نسبة الجلوكوز والأنسولين الصائم فى المصل وكذلك مستوى معامل تحلل الأورام _ ألفا ومستوى المالونديألديهيد (كعلامة للأكسدة) .

**ويمكن تلخيص نتائج هذا البحث فى النقاط الأتية :**

- تغذية الفئران بغذاء عالى المحتوى من سكر (الفركتوز) أدى إلى حدوث مقاومة لمفعول الأنسولين التى ظهرت فى صورة خلل ذو دلالة إحصائية فى الاستجابة لحقن الأنسولين فى الغشاء البريتونى وأيضاً فى مستوى الأنسولين الصائم فى المصل وكذلك على نسبة كل من الجلوكوز والأنسولين الصائم مع عدم التأثير على مستوى الجلوكوز الصائم فى المصل. كما صحب ذلك ارتفاع ذو دلالة إحصائية فى مستوى معامل تحلل الأورام _ ألفا ومستوى المالونديألديهيد فى المصل.

- عند أعطاء أى من دوائى الميتفورمين أو الفالسرتان للفئران التى تعانى من مقاومة لمفعول الأنسولين حدث تأثير إيجابي ومفيد على المقاومة لعمل الأنسولين وكذلك حدث نقص ذو دلالة إحصائية فى مستوى الأنسولين الصائم فى المصل ، معامل تحلل الأورام ألفا وكذلك المالونديألديهيد مع عدم حدوث تغيير فى مستوى الجلوكوز الصائم وذلك بالمقارنة مع الفئران التى تعانى من المقاومة ولم تعط هذه الأدوية.

وعلى ضوء هذه يمكن استنتاج أن لدواء الفالسرتان تأثير مقارب لدواء الميتفورمين على التحكم فى التأثير المقاوم لمفعول الأنسولين فى الفئران غير السمينه وذلك عن طريق انقاص مستوى معامل تحلل الأورام - ألفا وكذلك الشقوق الحره.