Oleic acid antagonizes the action of high fructose high fat diet on insulin secretion and adipose tissue β-arrestin signaling

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Running title: Oleic acid and insulin resistance

Abstract

Insulin resistance is a metabolic disorder associated with a wide array of cardiovascular complications. This study aimed to investigate the effect of oleic acid on a dietary model of insulin resistance in mice using high fructose high fat diet (HFrHFD) focusing on the role of β-arrestin signaling in the adipose tissue. Insulin resistance was induced by feeding mice high fructose high fat diet (HFrHFD) for 16 weeks. Oleic acid (40 mg/kg/day) was orally administered for 4 weeks starting at week 13. At the end of experiment, survival curve, body weights (BW), fasting blood glucose, serum insulin and insulin resistance (IR) were measured. Furthermore, adipose tissue levels of β-arrestin2, phosphatidyl inositol 4,5 bisphosphate (PIP2), diacyl glycerol (DAG) and phospho serine 473 of protein kinase B (pS473 Akt) were measured. Results showed that, oleic acid significantly increased survival percentage, BW and fasting blood glucose level compared to HFrHFD fed mice. On the other hand, oleic acid significantly reduced serum insulin level while slightly reduced IR compared to HFrHFD fed mice. In addition, oleic acid significantly increased β-arrestin2, PIP2 and pS473 Akt levels while significantly decreased DAG level in the adipose tissue. In conclusion, although oleic acid significantly improved survival curve and β-arrestin signaling in the adipose tissue, it worsened fasting blood glucose level in HFrHFD fed mice. An effect that may be attributed to reduced insulin secretion without comparable improvement in insulin resistance

Keywords: Oleic acid, Insulin resistance, β-arrestin, Adipose tissue

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1. INTRODUCTION

Insulin resistance is a condition associated with impaired insulin signaling and glucose disposal (**Weyer *et al.*, 2001; Ormazabal *et al.*, 2018**). Untreated insulin resistance usually progresses into type 2 diabetes (T2D) (**Nickerson and Dutta, 2012**).

The main triggers of insulin resistance are sedentary life style and high calorie diets including high fat and high carbohydrate diets (**Lai *et al.*, 2014**). Saturated fatty acids through activation of diacylglycerol (DAG)/protein kinase c (PKC) promote serine phosphorylation and degradation of insulin receptor substrate 1 (IRS1) (**Coll *et***

al., **2006**). Also, β-oxidation of saturated fatty acids contributes to reactive oxygen species (ROS) production (**Dai Ly *et al.*, 2017**).

Chronic fructose consumption induces downregulation of insulin receptors, decreases insulin induced phosphorylation of IRS1/2 and increases triglycerides (TG) production leading to insulin resistance (**Jornayvaz and Shulman, 2012**).

G-protein coupled receptor 40 (GPR40) and 120 (GPR120), also known as free fatty acid receptor 1 (FFAR1) and 4 (FFAR4) respectively, affect both insulin secretion and insulin action (**Araki *et al.*, 2012; Stone *et al.*, 2014**). FFAR1 is highly expressed in the pancreatic β-cells while FFAR4 is highly expressed in the liver, skeletal muscles and adipose tissue (**Steneberg *et al.*, 2005; Oh and Walenta, 2014**). FFARs are coupled to Gαq proteins which can activate phospholipase C (PLC) to mediate cleavage of phosphatidyl inositol 4,5 bisphosphate (PIP2) into DAG and inositol triphosphate (IP3) (**Yamada *et al.*, 2016**). IP3 stimulates calcium release from intracellular storage sites into the cytoplasm to promote insulin secretion (**Yamada *et al.*, 2016**). On the other hand, DAG through its action on PKC mediates insulin resistance (**Jornayvaz and Shulman, 2012**).

β-Arrestins are GPCRs desensitizing proteins (**Miller and Lefkowitz, 2001**). Recently, β-arrestins have been found to activate signaling pathways independent of G-proteins (**Barki-Harrington and Rockman, 2008**). Other studies showed that β-arrestins are critical for insulin signaling. β-Arrestin2, a subtype of β-arrestins, forms a complex with IRS-1, Src and protein kinase B (Akt) to enhance insulin signaling (**Luan *et al.*, 2009**). Moreover, insulin resistance has been found to be associated with severe down-regulation of β-arrestin2 in liver and skeletal muscles (**Luan *et al.*, 2009**).

Oleic acid is a monounsaturated omega-9 fatty acid. It occurs naturally in various animal and vegetable oils with high abundance in olive oil (**Orsavova *et al.*, 2015**). Oleic acid can bind and activate both types of FFA receptors FFAR1 and FFAR4 (**Kim *et al.*, 2016; Schnell *et al.*, 2007**). The effect of oleic acid on insulin resistance is highly controversial, some studies support its insulin sensitizing action (**Perdomo *et al.*, 2015**) while others showed detrimental effect (**Rosa and Rosa., 2004**) .

This study aimed to investigate the effect of 4 weeks treatment with oleic acid (40mg/kg/day, orally) on insulin resistance induced by feeding mice HFrHFD for 16 weeks focusing on the role of β-arrestin signaling in the adipose tissue.

Materials and Methods

1. Animals:

Adult male swiss albino mice (weighting 20±5 g) were purchased from Faculty of Veterinary Medicine, Zagazig University, Egypt, housed in cages with wood shave bedding in the animal care unit of the Faculty of Pharmacy, Zagazig University. The animals were kept in well-ventilated cages at room temperature (28-30'C), 12 hr light/12 dark. Animals were kept for two weeks prior to experiment initiation for acclimatization. During this period, they

were fed standard pellet chow diet and allowed free access to tap water. All procedures were conducted in accordance with the accepted principles for care and use of laboratory animals and were approved by the animal ethics committee of Faculty of Pharmacy, Zagazig University (Protocol # P1/6/2017).

2.Drugs and Chemicals:

Oleic acid was purchased from Carbosynth Co., USA. Dimethyl sulfoxide (DMSO) was purchased from Sigma-Aldrich Co. USA. All chemicals used in this study were of analytical grade.

3. Experimental Design and induction of insulin resistance:

After the acclimatization period, mice were randomly distributed into three experimental groups (n=10 each). Group 1 (standard chow diet, SCD): mice were fed SCD for 16 weeks. Groups 2 and 3 (high-fructose/high-fat diet, HFrHFD): mice were fed HFrHFD composed of 155 g of chow diet, 200 g of beef tallow, 170 g of fructose, 320 g sweetened condensed milk, 100 g corn glutin (60% protein), 25 g of salt mixture, and 30 g of water per kilogram of diet and received fructose (20% w/v) in drinking water for 16 weeks **(Panchal *et al.*, 2011)**. All nutritional parameters of this diet meet or exceed the guidelines of National Research Council, Canada, for rats and mice. Group 2 (HFrHFD): mice received only the vehicle. Group 3 (Oleic acid): mice received oleic acid (40mg/kg/day, orally). Oleic acid was dissolved in a mixture of DMSO, Tween 80 and water (1:1:8) (100μl/40 g body weight). Oleic acid was administered for 4 weeks

starting from week 13 of feeding. Oleic acid dose was selected based on previous publication **(Gonçalves de Albuquerque *et al.*, 2012)**.

4. Survival curve calculations:

Mice deaths were recorded and given numerical value 1 for each death condition during the last 4 weeks of the experiment. Mice which survived the last 4 weeks until the end of experiment were given numerical value 0 for each mice. Survival curve was blotted and survival percentage was calculated.

5. Measurement of body weight and tibial length

At the end of experiment and before euthanization, fasted mice body weights and tibial length of one of the hind limbs were measured.

6. Collection of blood and adipose tissue samples:

At the end of experiment, mice were euthanized by decapitation and trunk blood was collected form the site of decapitation. Epididymal visceral adipose tissue was harvested and immediately frozen in liquid nitrogen, then stored at -80'C till analysis.

7. Measurement of blood glucose level

Blood glucose level was measured in a blood drop obtained from a mouse tail tip using an automated glucometer (GM100, Bionime GmbH, Berneck, Switzerland).

8. Enzyme linked immunosorbent assay (ELISA):

Serum insulin, adipose tissue levels of β-arrestin2, PIP2, DAG and phosphoserine 473 of Akt were measured by ELISA technique using kits supplied by CUSABIO,

Huston, USA (Cat. No. CSB-E05071m); Nova lifetech limited (Mongkok, Hong Kong, Cat. No. CELI-66111m); BlueGene Biotech (Shanghai, China, Cat. No. E03D0010); LifeSpan BioSciences (WA, USA, Cat. No. LS-F18999); Abcam (Cambridge, UK, Cat No. ab176635), respectively. All procedures were performed as per the manufacturer's instructions.

9. Calculation of insulin resistance (IR):

Insulin resistance index was calculated using homeostatic model assessment of insulin resistance HOMA-IR **(Matthews et al., 1985),** according to the following equation:

HOMA-IR = Fasting glucose level (mg/dl) x fasting insulin level (IU/ml)/405.

10. Statistical analysis:

Data are expressed as mean ± standard error of the mean (SEM.). Statistical analysis was performed using unpaired student's t-test and one-way ANOVA followed by Tukey's post Hoc test. Comparison of survival curves was performed using Log-Rank (Mantel-Cox) test. P-values <0.05 are considered significant. All tests were performed using Graph Pad Prism software version 5 (Graph Pad Software, Inc., CA, USA).

Results:

3.1. Oleic acid increased survival percentage and body weights in HFrHFD fed mice:

Feeding mice HFrHFD for 16 weeks significantly decreased survival percentage (-30%, Fig.1A), body weights (BW) (27.5±1.2 vs 34±1.1 g, Fig.1B), BW/tibial length (TL) (14.8±0.6 vs 18.9±0.6 g/cm, Fig.1D) and BW gain % (25.8±3.6 vs 40.5±2.1, Fig.1E) compared to SCD fed mice. On the other hand, oleic acid (40 mg/kg/day) oral administration for 4 weeks starting at week 13 of feeding significantly increased survival percentage (30%, Fig.1A), BW (25%, Fig.1B), BW/TL (24%, Fig. 1B) and BW gain % (55%, Fig.1E) compared to HFrHFD fed mice.

3.2. Oleic acid increased fasting blood glucose and decreased serum insulin levels:

Feeding mice HFrHFD for 16 weeks significantly increased serum insulin level (58.9±2.3 vs 31.4±2.06 IU/ml, Fig.2B) and IR (0.013±0.001 vs 0.006±0.0004, Fig.2C) compared to SCD fed mice. On the other hand, oleic acid (40 mg/kg/day) oral administration for 4 weeks starting at week 13 of feeding significantly increased fasting blood glucose level (135.7±5.4 vs 91.3±3.5 mg/dl, Fig.2A)), decreased serum insulin level (37.6±0.94 vs 58.9±2.3 IU/ml, Fig.2B) and slightly decreased IR (P=0.06) (0.011±0.0008 vs 0.013±0.001, Fig.2C) compared to HFrHFD fed mice.

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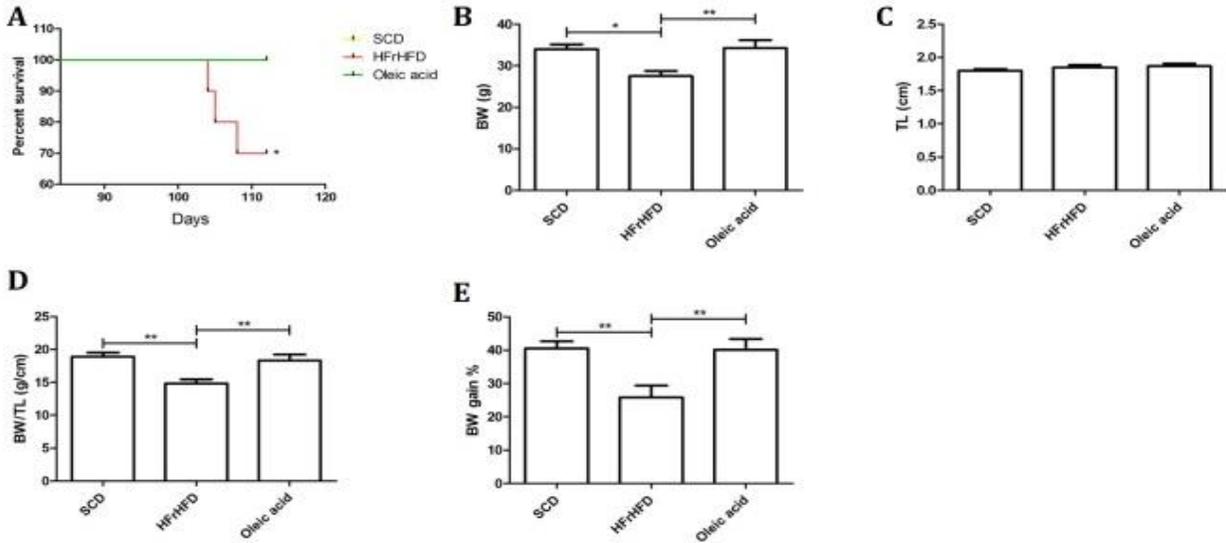ISSN (on-line) 2356_9786

Fig.1: Effect of oleic acid on survival curve and body weights. (A): *Graphical presentation of the percentage of survival in the last 4 weeks of experiment;* ***(B, C and D)*** *Graphical presentations of the body weights (BW), tibial length (TL) and BW/TL at the end of experiment;* ***(E)*** *Graphical presentation of BW gain %. SCD: Mice were fed standard show diet for 16 weeks and received vehicle orally (DMSO, Tween 80 and water (1:1:8) (100µl/40 g body weight) for 4 weeks starting at week 13. HFrHFD: Mice were fed high fructose high fat diet for 16 weeks and received the same vehicle orally for the same duration mentioned above. Oleic acid: Mice were fed HFrHFD for 16 weeks and received oleic acid (40 mg/kg/day, orally) dissolved in the same vehicle and for the same duration mentioned above. Statistical analysis of figure (A) was performed using Log-Rank (Mantel-Cox) test. Statistical analysis of figures (B, D and E) was performed using one way ANOVA followed by tukey's post-test; values are represented as mean±S.E.M. n=10. *P<0.05, **P<0.01.*
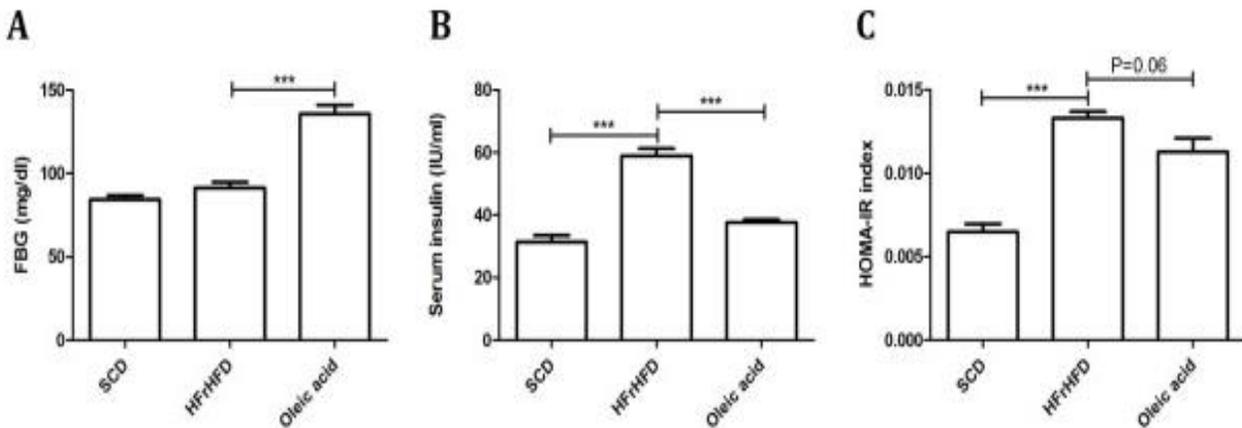

Fig.2: Effect of oleic acid on glycemic changes. (A): *Quantitative analysis of fasting blood glucose level (FBG);* ***(B)*** *Quantitative analysis of fasting serum insulin level;* ***(C)*** *Graphical presentation of insulin resistance calculated by using homeostasis model assessment of insulin resistance (HOMA-IR). SCD: Mice were fed standard show diet for 16 weeks and received vehicle orally (DMSO, Tween 80 and water (1:1:8) (100µl/40 g body weight) for 4 weeks starting at week 13. HFrHFD: Mice were fed high fructose high fat diet for 16 weeks and received the same vehicle orally for the same duration mentioned above. Oleic acid: Mice were fed HFrHFD for 16 weeks and received oleic acid (40 mg/kg/day, orally) dissolved in the same vehicle and for the same duration mentioned above. Statistical analysis was performed using one way ANOVA followed by tukey's post-test; values are represented as mean±S.E.M. n= 4-6. ***P<0.001. P=0.06: comparing oleic acid group with HFrHFD group using unpaired Student's t-test*

. *3.3. Oleic acid enhanced β-arrestin signaling in adipose tissue*

Feeding mice HFrHFD for 16 weeks significantly decreased adipose tissue levels of β-arrestin2 (43.3±8.8 vs 251.3±21.4 ng/mg, Fig.3A), PIP2 (2.6±0.12 vs 4.7±0.16 ng/mg, Fig.3B) and pS473 Akt (5.9±0.4 vs 25.4±1 µg/mg, Fig, 3D), while significantly increased DAG (26±1.1 vs 7.6±0.5 ng/mg, Fig.3C) compared to SCD fed mice. On the other hand, oleic acid (40 mg/kg/day) oral administration for 4 weeks starting at week 13 of feeding significantly increased adipose tissue levels of β-arrestin2 (151.3±18.8 vs 43.3±8.8 ng/mg, Fig.3A), PIP2 (4.8±0.24 vs 2.6±0.12 ng/mg, Fig.3B) and pS473 Akt (18.5±1.76 vs 5.9±0.4 µg/mg, Fig, 3D), while significantly decreased DAG (8±0.4 vs 26±1.1 ng/mg, Fig.3C) compared to HFrHFD fed mice.
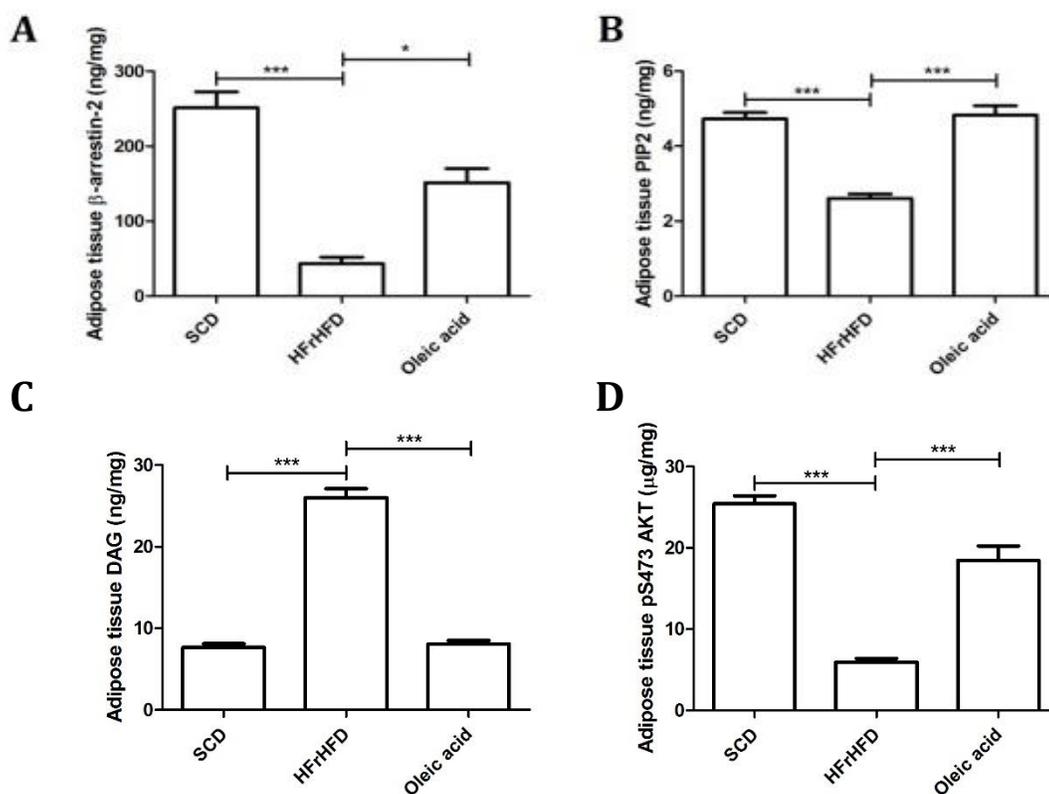

Fig.3: Effect of oleic acid on adipose tissue β-arrestin signaling. *(A) Quantitative analysis of β-arrestin2 expression; (B) Quantitative analysis of Phosphatidylinositol 4,5-bisphosphate (PIP2); (C): Quantitative analysis of Diacyl glycerol (DAG); (D) Quantitative analysis of Phospho serine 473 AKT (pAKT). SCD: Mice were fed standard show diet for 16 weeks and received vehicle orally (DMSO, Tween 80 and water (1:1:8) (100µl/40 g body weight) for 4 weeks starting at week 13. HFrHFD: Mice were fed high fructose high fat diet for 16 weeks and received the same vehicle orally for the same duration mentioned above. Oleic acid: Mice were fed HFrHFD for 16 weeks and received oleic acid (40 mg/kg/day, orally) dissolved in the same vehicle and for the same duration mentioned above. Statistical analysis was performed using one way ANOVA followed by tukey's post-test; values are represented as mean ± S.E.M. n= 3-4. *P<0.05, ***P<0.001.*

Discussion:

Insulin resistance and type 2 diabetes (T2D) are growing health problems in both developed and developing countries. Oleic acid is a monounsaturated omega-9 fatty acid (**Orsavova et al., 2015**). Its effect on glucose homeostasis and FFARs is controversial and not completely clarified. In this study, we investigated the effect of oleic acid on a dietary model of insulin resistance in mice focusing on the role of adipose tissue β-arrestin signaling.

Insulin resistance was induced by feeding mice HFrHFD for 16 weeks following the model designed by Panchal et al. (**Panchal et al., 2011**). In accordance with Panchal et al study, the current work showed significant reduction in the body weight in HFrHFD fed mice compared to SCD fed mice. Panchal et al showed that mice fed HFrHFD for 16 weeks exhibited significant reductions in food (25%) and water (60%) intake compared to SCD fed mice. This may explain the significant reduction observed in the body weights of HFrHFD fed mice. Moreover, Panchal et al reported significant pathological changes in the heart, liver and kidneys of HFrHFD fed mice, which may contribute to the decrease in survival percentage in mice fed HFrHFD in the current study. Also, HFrHFD fed mice showed significant increase in serum insulin level and IR compared to SCD fed mice. Both saturated fatty acids and fructose can induce down regulation of insulin receptors and deactivation of IRS-1 leading to insulin resistance (**Jornayvaz and Shulman, 2012**).

Although, IR significantly increased in HFrHFD fed mice, no significant changes were observed in blood glucose level compared to SCD fed mice. The same result was previously reported by Panchal et al study. It is well established that hyperinsulinemia associated with insulin resistance can maintain normoglycemia for a long period before being converted to overt type 2 diabetes (**Weyer et al., 2001; Ormazabal et al., 2018**).

FFAR 1 and 4 are G-αqPCRs which upon activation by circulating FFAs can mediate PIP2 degradation by phospholipase C into DAG and IP3 (**Yamada et al., 2016**). IP3 increases intracellular calcium level which stimulates insulin secretion from pancreatic β-cells (**Yamada et al., 2016**). On the other hand, DAG activates PKC which deactivates the IRS-1 leading to insulin resistance in peripheral tissues (**Jornayvaz and Shulman, 2012**). Therefore circulating FFAs can mediate both hyperinsulinemia and insulin resistance as evidenced in our experiment.

β-Arrestins are GPCRs desensitizing proteins (**Miller and Lefkowitz, 2001**). Recent study, showed severe down regulation of β-arrestin2 protein in insulin resistance (**Luan et al., 2009**). Moreover, it has been found that β-arrestins form a complex with Akt and Src proteins to enhance insulin signaling (**Luan et al., 2009**). In accordance with these studies, our results showed significant decreases in adipose tissue β-arrestin2, PIP2 and Akt active form (pS473) in HFrHFD fed mice compared to SCD fed mice. Also, adipose tissue DAG level significantly increased in HFrHFD fed mice.
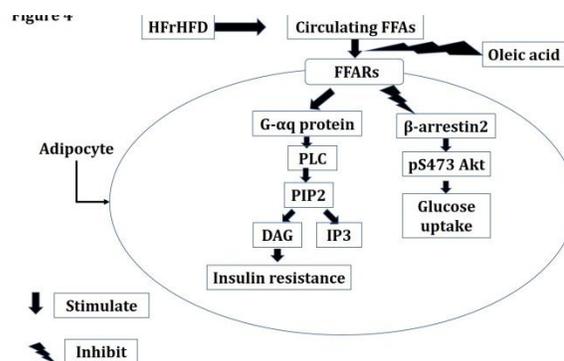
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β-Arrestins enhance both the activity and production of phosphatidyl inositol 3 kinase (PI3K) and PIP2 (**Li and Woulfe, 2006; Nelson et al., 2008**). PI3K phosphorylates PIP2 into PIP3 which subsequently phosphorylates Akt at serine 473 position leading to increased Akt activity (**Huang *et al.*, 2018**). Activated Akt promotes glycogen synthesis and glucose uptake in peripheral tissues including liver, skeletal muscles and adipose tissue (**Honka *et al.*, 2018**). Therefore reduced Akt activity as observed in the current study contributes to insulin resistance in HFrHFD fed mice.

Oleic acid is a monounsaturated omega-9 fatty acid (**Orsavova *et al.*, 2015**). It acts as a ligand to FFARs (**Schnell *et al.*, 2007; Kim *et al.*, 2016**). However, its exact effect on FFARs down-stream signals is not completely clarified. Furthermore, its effect on insulin resistance is controversial (**Rosa and Rosa, 2004; Perdomo *et al.*, 2015**). In our study, oleic acid administration for 4 weeks in HFrHFD fed mice significantly increased survival rate and fasting blood glucose level while significantly decreased serum insulin and slightly decreased IR. It seems that, oleic acid antagonized the effect of circulating FFAs on insulin secretion and to a lesser extent on insulin resistance. However, the improvement in insulin resistance was not sufficient to compensate for the reduction in insulin secretion leading to fasting hyperglycemia.

In the same context, oleic acid significantly increased β-arrestin2, PIP2 and pS473 Akt levels in the adipose tissue compared to HFrHFD fed mice. While, it significantly decreased DAG level compared

to HFrHFD fed mice. Although oleic acid antagonized the effect of HFrHFD on β-arrestin signaling in the adipose tissue, it was not sufficient to prevent fasting hyperglycemia. An interpretation of this finding, is that adipose tissue levels of both β-arrestin2 and pS473 Akt did not return to their normal levels in SCD fed mice. To our knowledge, this is the first time to study the effect of oleic acid on β-arrestin signaling in the adipose tissue of HFrHFD fed mice.

In conclusion, oleic acid antagonizes the action of HFrHFD on insulin secretion and adipose tissue β-arrestin signaling. Oleic acid elevates fasting blood glucose level. Oleic acid is not a suitable choice as insulin sensitizer.

Scheme showing the effect of high fructose high fat diet (HFrHFD) and oleic acid on insulin resistance and adipose tissue β-arrestin signaling. **FFAs:** Free fatty acids; **FFARs:** Free fatty acid receptors; **PLC:** Phospholipase C; **PIP2:** Phosphatidyl inositol 4,5 bisphosphate; **DAG:** Diacyl glycerol; **IP3:** Inositol triphosphate; **pS473 Akt:** phosphor serine 473 of protein kinase B.

Conflicts of interests

Authors declare no conflicts of interest.

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يقاوم حمض الأوليك تأثير الحمية الغذائية عالية الفركتوز عالية الدهن على افراز الإنسولين و اشارات البيتا اريستين في النسيج الدهني

رحاب م .ا .س .منصور، إسلام أ .ع .ا .ح .ابراهيم، حسن م .الفيومي، أحمد فهمي

تعتبر مقاومة الإنسولين اضطراب في التمثيل الغذائي و ترتبط بمجموعة و اسعة من مضاعفات القلب و الأوعية الدموية

يهدف هذا البحث إلى دراسة تأثير حمض الأوليك على مقاومة الإنسولين المستحثة في الفئران باستخدام الحمية الغذائية عاليه الفركتوز عالية الدهن و التركيز على دور اشارات البيتا ارستين في النسيج الدهني. تم احداث مقاومة الإنسولين عن طريق إطعام الفئران حمية غذائية عالية الفركتوز عالية الدهن لمده ستة عشرة أسبوعا

تم اعطاء حمض الأوليك بجرعة ٤٠ مجم لكل كجم يوميا عن طريق الفم لمده أربعة أسابيع ابتداء من الأسبوع الثالث عشر

بعد الانتهاء من التجربة تم قياس معدلات الحياه، وزن الجسم مقسوما على طول عظمة الساق، تركيز الجلوكوز الصائم في الدم، تركيز الإنسولين في مصل الدم و مقاومة الإنسولين

علاوة على ذلك تم قياس مستويات بروتين البيتا ارستين و الفوسفاتيديل اينوزيتول ٥،٤ ثنائي الفوسفات، الجلسرين ثنائي الأسيل و الفوسفو سيرين ٤٧٣ من بروتين الكيناز بي في النسيج الدهني

أظهرت النتائج أن حمض الأوليك رفع معدلات الحياه، وزن الجسم مقسوما على طول عظمة الساق و مستوى الجلوكوز الصائم في الدم مقارنة بفئران الحمية الغذائية عالية الفركتوز عالية الدهن

من ناحية اخرى فقد انخفض بشكل كبير مستوى الانسولين بينما انخفض بشكل طفيف مقاومة الإنسولين مقارنه بفئران الحمية الغذائيةعالية الفركتوز عالية الدهن

أضف إلى ذلك رفع حمض الأوليك بشكل ملحوظ مستويات بروتين البيتا ارستين، الفوسفاتيديل اينوزيتول ٥،٤ ثنائي الفوسفات و الفوسفو سيرين ٤٧٣ من بروتين الكيناز بي و خفض بشكل ملحوظ مستوى الجلسرين ثنائي الأسيل في النسيج الدهني

من ذلك نستنتج أن على الرغم من تحسين حمض الأوليك بشكل كبير لمعدلات الحياة و إشارات البيتا ارستين في النسيج الدهني فقد أضر بمستوى الجلوكوز الصائم في الدم في فئران الحمية الغذائية عالية الفركتوز عالية الدهن

هذا التأثير قد يعذى إلى انخفاض افراز الإنسولين دون تحسن مماثل في مقاومة الإنسولين