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ALPHA1-ADRENERGIC RECEPTOR BLOCKING ACTION OF CARVEDILOL CONTRIBUTES TO TACKLING DEXAMETHASONE-INDUCED INSULIN RESISTANCE AND TO A LESSER EXTENT HEPATIC DAMAGE

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Insulin resistance is a well-established risk factor for serious health problems, including type 2 diabetes, cardiovascular disease, and stroke. Carvedilol has been documented to improve insulin sensitivity, ameliorate hyperlipidemia, and reduce the risk of diabetes. This study aimed to explore the role of α1-adrenergic receptors (α1ARs) in mediating the insulin-sensitizing effect of carvedilol in dexamethasone-treated rats. Insulin resistance was induced by subcutaneous injection of dexamethasone (10 mg/kg) for 7 days in rats. Five groups were used: control; dexamethasone; carvedilol (10 mg/kg); phenylephrine (1 mg/kg); carvedilol and phenylephrine. Serum glucose, insulin, and lipid profiles, as well as hepatic glycogen content, diacylglycerol level, protein kinase B activity, collagen type I, histopathological changes, and β-arrestin2 immunohistochemistry, were measured. The results demonstrated that blocking of α1- and β-ARs by carvedilol mitigated dexamethasone-induced insulin resistance and hepatic damage. Moreover, pre-injection of phenylephrine attenuated the insulin-sensitizing effect of carvedilol and, to a lesser extent, hepatic damage. In conclusion, the α1-blocking action of carvedilol contributes to its insulin-sensitizing effect as well as to its beneficial effect on the lipid profile. On the other hand, the hepatoprotective effect of carvedilol in dexamethasone-treated rats is less dependent on the α1AR

Keywords: *α1-adrenergic receptors; Carvedilol; Dexamethasone; Insulin resistance; Phenylephrine*

INTRODUCTION

Insulin resistance can be described as a reduced physiological reaction to the stimulation of insulin in target tissues, such as the liver, muscle, and adipose tissue, leading to impaired glucose disposal and hyperinsulinemia[1]. Impaired glucose tolerance (IGT) is a worldwide public health problem. According to a recent study, it has been predicted that approximately 10.6% of adults globally exhibit IGT. This percentage is expected to be increased to 11.4% of all adults by 2045[2].

Insulin resistance can be classified as acquired, hereditary, or mixed. Glucocorticoids are considered the main iatrogenic cause of insulin resistance and type 2 diabetes[1]. Glucocorticoids also result in hyperlipidemia and visceral adiposity that contribute to the insulin resistance; direct potential actions of glucocorticoids on the liver, muscle, and other tissues also play a role. Moreover, glucocorticoids can decrease insulin receptor substrate (IRS-1 and IRS-2) protein levels in fat cells, as well as insulin receptor and IRS-1 phosphorylation in the liver[3].

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Adrenergic receptors (ARs) belong to the G-protein-coupled receptor (GPCR) superfamily. It is worth mentioning that α1-adrenergic receptors (α1ARs) are commonly associated with the heterotrimeric Gαq/11 family of G-proteins, which activates phospholipase Cβ1 (PLCβ1). This activation triggers the breakdown of phosphatidylinositol 4,5-bisphosphate in the cell membrane, culminating in the release of inositol triphosphate (IP3) and diacylglycerol (DAG) into the cytosol. Then, DAG activates the protein kinase C (PKC) enzyme. Some PKC isoforms have the ability to interfere with insulin signaling by phosphorylating serine residues on IRS-1 and the insulin receptor[4].

The recruitment of regulatory proteins, β-arrestin1 and β-arrestin2, is facilitated by the phosphorylation of activated β-ARs through G protein-coupled receptor kinases (GRKs). β-Arrestin2, a GPCR desensitizing and scaffolding protein, has been discovered to play a crucial role in insulin signaling by mediating the interaction between IRS-1, Src, and Akt to enhance serine 473 phosphorylation of the latter. Furthermore, β-arrestin-2 can inhibit the insulin desensitizing effect of the DAG/PKC pathway by activating DAG kinase which mediates degradation of DAG into phosphatidic acid. Noteworthy, It has been documented that β-arrestin2 is downregulated during insulin resistance[5].

Carvedilol is a third-generation vasodilatory antihypertensive agent. It selectively blocks α1ARs and non-selectively antagonizes β1ARs and β2ARs. As well, it has been classified as a β-arrestin biased agonist. Furthermore, earlier studies reported antioxidant, anti-inflammatory, antiproliferative, and antiarrhythmic properties to be involved in its beneficial effects. In addition, carvedilol was documented to ameliorate insulin resistance and hyperlipidemia and decrease the risk of diabetes. These effects have been proved to be dependent on β-arrestin signaling at least in part[6].

The primary objective of the present study was to investigate the role of α1AR in mediating the insulin-sensitizing effect of carvedilol in dexamethasone-treated rats. To clarify the role of α1AR, the glycemic effects of phenylephrine alone and in combination with carvedilol were investigated. Furthermore, we recorded the changes in hepatic β-arrestin2 levels in response to the used treatments.

MATERIALS AND METHODS

Ethics statement

All procedures were conducted in accordance with both national and international criteria for the ethical treatment and utilization of laboratory animals. These methods were also approved by the Institutional Animal Care and Use Committee at Zagazig University (ZU-IACUC), with the assigned permission number: ZU-IACUC/3/ F/210/2019.

Animals

The study utilized adult male Wistar albino rats with an average weight of 180 ± 20 g, and an age of 8 weeks. These rats were obtained from the Faculty of Veterinary Medicine, Zagazig University. They were maintained in plastic cages with wood shavings bedding within the animal care section of the Faculty of Pharmacy, Zagazig University. The animals were maintained in a controlled environment with a temperature of (23 ± 2 ◦C), humidity of (60% ± 10%), and a 12-hour light/dark cycle. The rats had a period of acclimatization lasting a minimum of two weeks before the commencement of the studies. During this time, the rats were provided with unrestricted access to a regular pellet chow diet and tap water.

Drugs and Chemicals

Carvedilol was procured from Multi-Apex Pharma Company (Cairo, Egypt); dexamethasone sodium phosphate was obtained from EIPICO Co. (10th of Ramadan City, Egypt); tween 80 from El-Nasr Pharmaceutical Chemicals (Cairo, Egypt); phenylephrine and dimethyl sulfoxide (DMSO) from Sigma-Aldrich (St. Louis, MO, USA). All 3 drugs (dexamethasone, carvedilol, and phenylephrine) were obtained as raw powders from their mentioned sources and then dissolved in the vehicle before administration.

Experimental design

Following a period of acclimatization, a total of nine rats were randomly assigned to each of the five experimental groups. In group

1 (Control group), rats were intraperitoneally injected (i.p.) with vehicle (a mixture of DMSO, Tween 80, and sterile water in a volume ratio of 1:1:8) for 7 days. Rats in groups 2 to 5 were administered dexamethasone at a dosage of (10 mg/kg/day) via subcutaneous injection[7]. All drugs were dissolved in the vehicle, and both carvedilol and phenylephrine were administered two hours before dexamethasone administration for 7 days[8]. In group 2 (DEXA group), rats were subcutaneously injected with dexamethasone (10 mg/kg/day)[9]. In group 3 (CARV group), carvedilol (10 mg/kg/day; i.p.)[10]. In group 4 (PHEN group), phenylephrine (1 mg/kg/day; i.p.)[11]. In group 5 (PHEN+CARV group), phenylephrine (1 mg/kg/day; i.p.) then after 30 minutes carvedilol (10 mg/kg/day; i.p.). The injection volume utilized in all groups was 500 µL per 200 g of body weight. The administration of drugs and vehicle was carried out as depicted in the schematic representation in **Fig. 1**.

Blood and tissue sampling

Rats were subjected to euthanasia through decapitation upon the end of the study, namely at 12 PM on the 8th day. Subsequently, trunk blood was taken from the site of decapitation. The collection of serum samples was conducted using the process of centrifugation (4000 rpm, 4◦C, 15 min) and then preserved at a temperature of -80◦C for subsequent analyses. Additionally, liver specimens were obtained. The liver samples were partitioned into two segments. One segment was preserved in formalin for the purpose of histological evaluation, while the other segment was rapidly frozen in liquid nitrogen and maintained at a temperature of -80◦C for further biochemical analysis.

Measurement of body weight, waist circumference, tibial length, and liver weight

Prior to euthanasia, rats had an overnight fasting period, and their body weights were recorded; also, waist circumference and tibial lengths were measured. Shortly following the euthanasia, the liver was subjected to dissection and subsequent measurement of its weight.

Measurement of fasting blood glucose, total cholesterol, high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG)

Fasting blood glucose (FBG), total cholesterol, high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were measured using commercially available quantitative enzymatic colorimetric assay kits obtained from Biomed diagnostics (Badr city, Egypt, Cat. No. GLU 109250, Cat. No. CHO 104090, Cat. No. HDL 114100, and Cat. No. TG 117100, respectively).

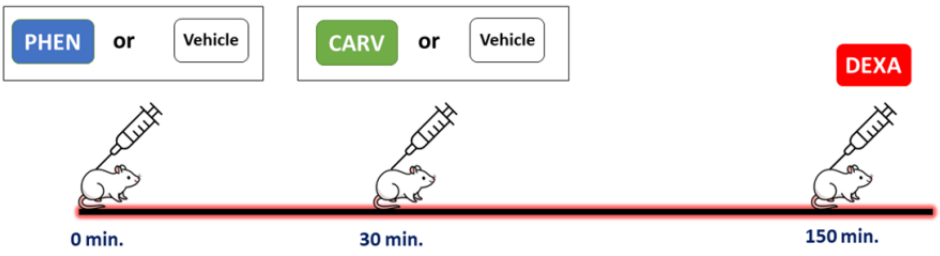

Fig. 1: Schematic presentation of experiment timeline illustrating vehicle and drugs administration for 7 days [intraperitoneal injection of phenylephrine (PHEN) 1 mg/kg/day in groups 4 and 5, carvedilol (CARV) 10 mg/kg/day in groups 3 and 5 and subcutaneous injection of dexamethasone (DEXA) 10 mg/kg/day in groups 2 to 5].

Measurement of fasting serum insulin and liver glycogen content and calculation of Insulin Resistance (IR) index

Serum insulin was measured by enzyme-linked immunosorbent assay (ELISA) using kits supplied by CUSABIO (Houston, TX, USA, Cat. No. CSB-E05071m). Liver glycogen content was measured by competitive ELISA technique using kits supplied by MyBioSource (San Diego, USA, Cat. No. MBS731185). Insulin resistance index was calculated according to the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) using the following formula[12]: HOMA-IR = (insulin * glucose) / 405; for fasting serum glucose concentration in mg/dl and fasting serum insulin concentration in mU/L.

Measurement of diacylglycerol (DAG), Protein kinase B (PKB/AKT) kinase activity and collagen type I

Diacylglycerol (DAG), Akt kinase activity, and collagen type I were measured by enzyme-linked immunosorbent assay (ELISA) using kits supplied by MyBioSource, Inc. (San Diego, CA 92195-3308 USA, Cat. No. MBS750727), Creative Diagnostics (45-1 Ramsey Road, Shirley, NY 11967, USA, Cat. No. DEIABL547), and CUSABIO (Houston, TX, USA, Cat. No. CSB-E08084r), respectively.

Histopathological examination

Liver specimens were dissected, preserved in a solution of 10% formalin, dried in gradient ethanol, treated with xylene to enhance transparency, embedded in paraffin blocks, sliced into sections with 5 μm thickness using a rotary microtome, and stained with hematoxylin and eosin (H&E) for the assessment of structural changes of the liver. Other sections were stained with Masson trichrome stain for collagen deposition and determination of fibrosis area using a light microscope.

Quantification of fibrotic area utilizing Masson trichrome stain

The quantification of the collagen fiber staining area, expressed as a percentage of the total area (% blue area) was performed on liver sections using ImageJ v.1.51d (NIH & LOCI, Wisconsin University, USA). Briefly, regions with high expression of collagen fibers were chosen, delineated using a blue binary color scheme, and subsequently quantified in relation to a standardized measurement framework.

Immunohistochemical examination of liver β-arrestin2

The avidin-biotin-peroxidase technique was used for immunohistochemical analysis. The procedure was performed as previously described[13]. The immunohistochemistry staining of β-arrestin2 was observed as a brownish discoloration within the cytoplasm of the cells. The monoclonal antibody used in this study was specific to β-arrestin2 (β-arrestin 2 (C16D9) Rabbit mAb, Cat No. #3857, Cell Signaling, Danvers, USA). The sections were subjected to morphometric analysis after being stained with β-arrestin2 antibodies. The area percentage of immunological reactivity to β-arrestin2 was quantified in liver slices of three rats per group using ImageJ v.1.51d (NIH & LOCI, University of Wisconsin, USA) at a magnification of 100X. In summary, regions exhibiting positive staining (characterized by a brown color) were chosen, delineated using a red binary mask, and quantified in relation to a standardized measurement framework.

Pooling of samples

The samples from each group were randomly combined into three pools[14]. Based on the final survival count of animals, it can be observed that each pool consists of one, two, or three samples.

Statistical analysis

The mean and standard error of the mean (SEM) are utilized as statistical measures to describe the entirety of the data. The group means were compared using a one-way analysis of variance (ANOVA) followed by a Bonferroni post-hoc test for selected pairings. The statistical analysis was conducted using GraphPad Prism v. 5 (GraphPad Software, Inc., La Jolla, CA, USA). The log-rank (Mantel-Cox) test was utilized to compare survival curves. A significance level of $p < 0.05$ (two-tailed) was employed to determine statistical significance for all tests.

RESULTS AND DISCUSSION

Results

Effect of Carvedilol, Phenylephrine and their combination on body weight and waist circumference in dexamethasone-treated rats

In **Table. 1**, dexamethasone group exhibited a significant decrease in body weight/tibial length compared to control group, but the administration of carvedilol alone or phenylephrine alone significantly increased body weight/tibial length compared to phenylephrine + carvedilol group. Furthermore, phenylephrine group significantly increased waist circumference/tibial length compared to dexamethasone group. In addition, phenylephrine + carvedilol group exhibited a significant decrease in waist circumference/tibial length compared to both dexamethasone and phenylephrine groups. On the other hand, carvedilol administration significantly decreased waist circumference/tibial length compared to phenylephrine group. Moreover, dexamethasone administration resulted in a significant increase in liver weight/tibial length compared to control group. However, phenylephrine treatment significantly increased liver weight/tibial length compared to both dexamethasone and phenylephrine + carvedilol groups. In addition, dexamethasone administration resulted in a significant decrease in BMI compared to control group.

Carvedilol improved glucose homeostasis and the hepatic insulin signaling in dexamethasone-treated rats

As depicted in **Fig. 2**, dexamethasone administration resulted in a significant increase in FBG level compared to control group. In addition, dexamethasone administration significantly increased fasting serum insulin level compared to control group. However, carvedilol group, phenylephrine group, and phenylephrine + carvedilol group significantly decreased fasting serum insulin levels compared to dexamethasone group. Furthermore, dexamethasone administration resulted in a significant increase in HOMA-IR index compared to control group. Nevertheless, carvedilol group and phenylephrine + carvedilol group significantly reduced HOMA-IR index compared to dexamethasone group. Additionally, treating rats with carvedilol resulted in a significant decrease in HOMA-IR index compared to phenylephrine group. Moreover, dexamethasone administration resulted in a significant decrease in liver glycogen content compared to control group. Noteworthy, carvedilol group and phenylephrine + carvedilol group significantly increased liver glycogen content compared to dexamethasone group.

Table 1: Changes in the body weight, waist circumference and liver weight normalized to tibial length and the body mass index (BMI).

		Body weight/TL (g/cm)	Waist circum./TL	Liver weight/TL (g/cm)	BMI (g/cm^2)
	Control	**63.81 ± 1.86**	**4.48 ± 0.08**	**2.27 ± 0.09**	**0.6 ± 0.02**
DEXA Groups	**DEXA**	**48.58 ± 1.2[a]**	**4.34 ± 0.1**	**3.17 ± 0.12[a]**	**0.5 ± 0.03[a]**
	CARV	**50.52 ± 0.93**	**4.11 ± 0.08**	**3.56 ± 0.12**	**0.44 ± 0.01**
	PHEN	**53.33 ± 3.4**	**4.84 ± 0.09[c]**	**3.83 ± 0.26**	**0.5 ± 0.01**
	PHEN+CARV	**40.97 ± 1.44[c]**	**3.78 ± 0.07[b]**	**2.99 ± 0.11**	**0.44 ± 0.01**

TL: tibial length.

Statistical analysis was performed using one way ANOVA followed by Bonferroni post-test for selected pairs. Values are expressed as mean ± S.E.M. n = 9 for the control and CARV groups. n = 7 for the DEXA group. n = 4 for the PHEN and PHEN+CARVgroups. a $P < 0.05$ vs Control group, b $P < 0.05$ vs DEXA group and c $P < 0.05$ vs CARV group.

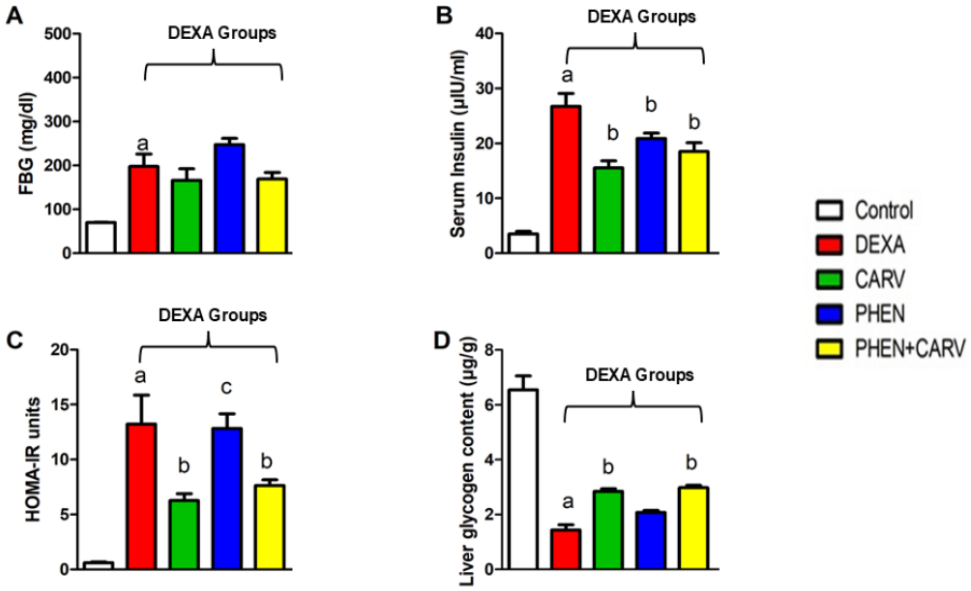

Fig. 2: Changes in the fasting blood glucose (FBG), fasting serum insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index and liver glycogen content. Graphical presentation of the fasting blood glucose (FBG) (A), fasting serum insulin (B), HOMA-IR index (C) and liver glycogen content (D). Control: vehicle. DEXA: dexamethasone (10 mg/kg/day, S.C.). CARV: carvedilol (10 mg/kg/day, I.P.). PHEN: phenylephrine (1 mg/kg/day, I.P.). PHEN+CARV: phenylephrine thereafter carvedilol 30 min later. Rats in groups 2 to 5 were administered dexamethasone (10 mg/kg/day, S.C.). All drugs were dissolved in vehicle (DMSO: Tween 80: sterile water in a volume ratio of 1:1:8) and injected 2 hours before dexamethasone administration for 7 days. n = 9 for the control and CARV groups. n = 7 for the DEXA group. n = 4 for the PHEN and PHEN+CARV groups. One way ANOVA and Bonferroni post-test for selected pairs were used in statistical analysis. Showed values represent mean ± S.E.M. a $P < 0.05$ vs Control group, b $P < 0.05$ vs DEXA group and c $P < 0.05$ vs CARV group.

Carvedilol slightly improved the lipid profile in dexamethasone-treated rats

In **Table. 2**, dexamethasone administration resulted in a significant increase in total cholesterol level compared to control group. Nonetheless, phenylephrine + carvedilol group significantly reduced total cholesterol level compared to both dexamethasone and phenylephrine groups. Moreover, dexamethasone administration resulted in a significant increase in HDL-C level compared to control group. Also, dexamethasone administration resulted in significant increases in triglycerides and VLDL-C levels compared to control group. Also, administration of carvedilol alone or phenylephrine alone exhibited significant decreases in triglycerides and VLDL-C levels compared to phenylephrine + carvedilol group.

The administration of Carvedilol and Phenylephrine resulted in a reduction in liver damage generated by dexamethasone

In **Fig. 3** and supplementary **Fig. 3**, the hepatic portal triad of control group showed intact bile duct, hepatocytes with homogenous eosinophilic cytoplasm and vesicular nucleus, and congested portal vein. Dexamethasone treatment resulted in a markedly dilated central vein, hepatocytes with massively vacuolated cytoplasm, and pyknotic darkly stained nuclei; others are binucleated, and sinusoids are obscured, reflecting hepatic apoptosis and damage. Use of carvedilol and phenylephrine separately or in combination significantly decreased the dexamethasone-induced hepatic damage and histopathological alterations. Both the carvedilol and phenylephrine groups had a limited presence of occluded blood capillaries and vacuolated hepatocytes.

Table 2: Changes in the serum lipid profile.

		Total cholesterol (mg/dl)	HDL-C (mg/dl)	Triglycerides (mg/dl)	VLDL-C (mg/dl)
	Control	**56 ± 2.95**	**31.44 ± 3.18**	**53.56 ± 4.24**	**10.71 ± 0.84**
DEXA Groups	**DEXA**	**178.7 ± 27.61[a]**	**69.14 ± 9.88[a]**	**351.3 ± 88.75[a]**	**70.27 ± 17.75[a]**
	CARV	**142.6 ± 11.8**	**75.89 ± 6.87**	**168.4 ± 20.32**	**33.68 ± 4.06**
	PHEN	**189.8 ± 47.18**	**69.67 ± 7.21**	**206.7 ± 62.15**	**41.33 ± 12.43**
	PHEN+CARV	**86 ± 16.41[b]**	**48.33 ± 1.45**	**493.7 ± 167.9[c]**	**98.73 ± 33.58[c]**

*HDL:*High-density lipoprotein-cholesterol, *VLDL-C*: Very low-density lipoprotein-cholesterol
Statistical analysis was performed using one way ANOVA followed by Bonferroni post-test for selected pairs. Values are expressed as mean ± S.E.M. n = 9 for the control and CARV groups. n = 7 for the DEXA group. n = 4 for the PHEN and PHEN+CARV groups. a $P < 0.05$ vs Control group, b $P < 0.05$ vs DEXA group and c $P < 0.05$ vs CARV group.

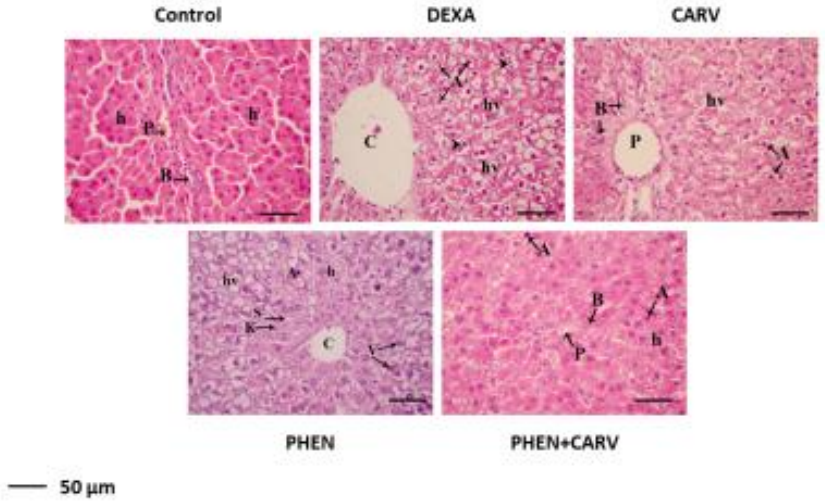

Fig. 3: Histopathological alterations in the liver tissues stained with Hematoxylin and Eosin (H&E) stain (X 400). Representative photomicrographs of hepatocytes. h, hv, A, V, f: Normal, massively vacuolated cytoplasm, pyknotic darkly stained nuclei, vesicular nuclei and excessive fatty vacuolations within hepatocytes, respectively; B: bile duct; P: portal vein; C: central vein; S: sinusoids; K: Kupffer cells; Control: vehicle. DEXA: dexamethasone (10 mg/kg/day, S.C.). CARV: carvedilol (10 mg/kg/day, I.P.). PHEN: phenylephrine (1 mg/kg/day, I.P.). PHEN+CARV: phenylephrine thereafter carvedilol 30 min later. Rats in groups 2 to 5 were administered dexamethasone (10 mg/kg/day, S.C.). All drugs were dissolved in vehicle (DMSO: Tween 80: sterile water in a volume ratio of 1:1:8) and injected 2 hours before dexamethasone administration for 7 days.

Carvedilol and Phenylephrine showed distinct effects on the hepatic levels of β-arrestin2 in dexamethasone-treated rats

As depicted in **Fig. 4**, dexamethasone administration resulted in a significant decrease in hepatic levels of β-arrestin2 compared to control group. In contrast, carvedilol group and phenylephrine group resulted in significant increases in hepatic levels of β-arrestin2 compared to dexamethasone group. Additionally, treatment with carvedilol alone or phenylephrine alone exhibited significant increases in hepatic levels of β-arrestin2 compared to phenylephrine + carvedilol group.

Carvedilol markedly reduced hepatic fibrosis in dexamethasone-treated rats

As in **Fig. 5**, dexamethasone administration resulted in a significant increase in the hepatic levels of DAG compared to control group. However, carvedilol group, phenylephrine group, and phenylephrine + carvedilol group significantly reduced the hepatic levels of DAG compared to dexamethasone group. In the same context, dexamethasone administration resulted in a significant increase in hepatic Akt kinase activity compared to control group. However, carvedilol group, phenylephrine group, and phenylephrine + carvedilol group resulted in significant decreases in hepatic Akt kinase activity compared to dexamethasone group. Also, carvedilol administration exhibited a significant decrease in hepatic Akt kinase activity compared to phenylephrine group. Furthermore, dexamethasone administration resulted in a significant increase in hepatic collagen type I level compared to control group. Nevertheless, carvedilol group, phenylephrine group, and phenylephrine + carvedilol group resulted in significant decreases in hepatic collagen type I levels compared to dexamethasone group. In addition, dexamethasone administration resulted in a significant increase in hepatic fibrosis area % compared to control group. Noteworthy, carvedilol group, phenylephrine group, and phenylephrine + carvedilol group showed significant decreases in hepatic fibrosis area % compared to dexamethasone group. Moreover, phenylephrine + carvedilol group showed a significant decrease in hepatic fibrosis area % compared to phenylephrine group.

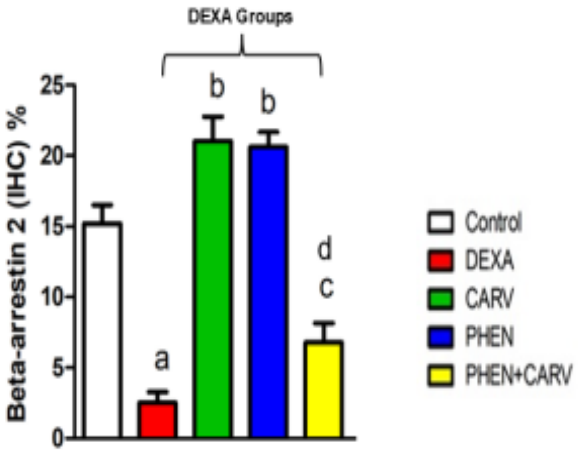

Fig. 4A

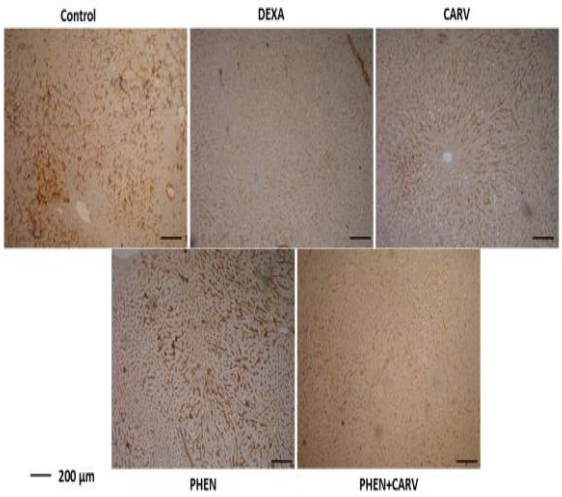

Fig. 4B

Fig. 4: Changes in the hepatic β-arrestin-2 level. Graphical presentation of the hepatic β-arrestin-2 level percentage (A), Representative photomicrographs of immuno-stained hepatocytes (X 100) (B). Control: vehicle. DEXA: dexamethasone (10 mg/kg/day, S.C.). CARV: carvedilol (10 mg/kg/day, I.P.). PHEN: phenylephrine (1 mg/kg/day, I.P.). PHEN+CARV: phenylephrine thereafter carvedilol 30 min later. Rats in groups 2 to 5 were administered dexamethasone (10 mg/kg/day, S.C.). All drugs were dissolved in vehicle (DMSO: Tween 80: sterile water in a volume ratio of 1:1:8) and injected 2 hours before dexamethasone administration for 7 days. n = 9 for the control and CARV groups. n = 7 for the DEXA group. n = 4 for the PHEN and PHEN+CARV groups. One way ANOVA and Bonferroni post-test for selected pairs were used in statistical analysis. Showed values represent mean ± S.E.M. a $P < 0.05$ vs Control group, b $P < 0.05$ vs DEXA group, c $P < 0.05$ vs CARV group and d $P < 0.05$ vs PHEN group.

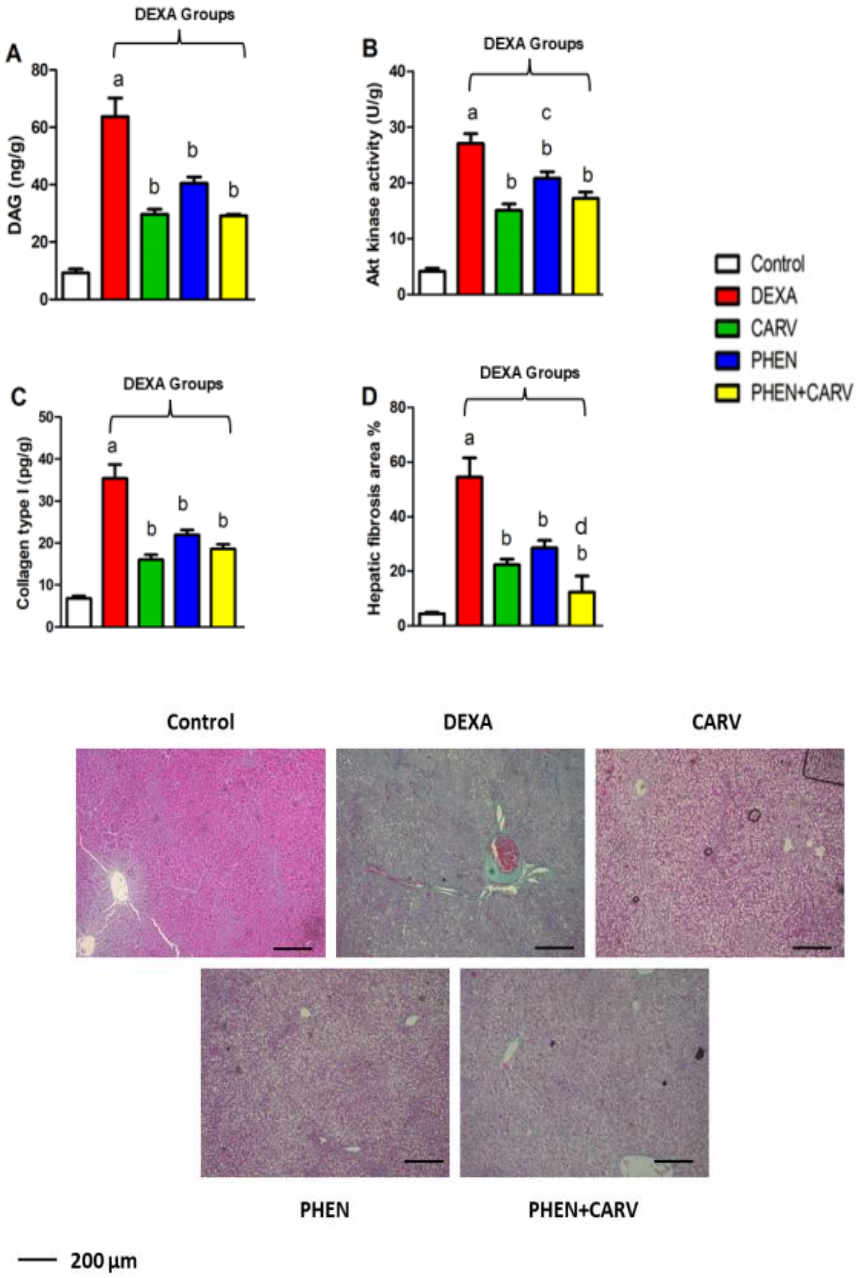

Fig. 5: Changes in the hepatic levels of DAG, hepatic Akt kinase activity,hepatic levels of collagen type I, and hepatic fibrosis area % and. Graphical presentation of the hepatic levels of DAG (A), hepatic Akt kinase activity (B), hepatic levels of collagen type I (C), and hepatic fibrosis area percentage (D), and Representative photomicrographs of hepatocytes stained with Masson trichrome (X 100) (E). Control: vehicle. DEXA: dexamethasone (10 mg/kg/day, S.C.). CARV: carvedilol (10 mg/kg/day, I.P.). PHEN: phenylephrine (1 mg/kg/day, I.P.). PHEN+CARV: phenylephrine thereafter carvedilol 30 min later. Rats in groups 2 to 5 were administered dexamethasone (10 mg/kg/day, S.C.). All drugs were dissolved in vehicle (DMSO: Tween 80: sterile water in a volume ratio of 1:1:8) and injected 2 hours before dexamethasone administration for 7 days. n = 9 for the control and CARV groups. n = 7 for the DEXA group. n = 4 for the PHEN and PHEN+CARV groups. One way ANOVA and Bonferroni post-test for selected pairs were used in statistical analysis. Showed values represent mean ± S.E.M. a $P < 0.05$ vs Control group, b $P < 0.05$ vs DEXA group, c $P < 0.05$ vs CARV group and d $P < 0.05$ vs PHEN group.

Discussion

Dexamethasone is a commonly used anti-inflammatory and immunosuppressive drug. Upon using large doses, it can result in severe complications, such as insulin resistance and pancreatic β-cell dysfunction leading to hyperglycemia in 20-50% of patients without a previous history of diabetes and aggravate hyperglycemia in diabetic patients[15]. Carvedilol is a widely clinically used antihypertensive medication. Notably, previous reports showed beneficial effects for carvedilol on glucose homeostasis in hypertensive diabetic patients[16]. This study aimed to investigate the role of α1AR in mediating the insulin-sensitizing effect of carvedilol in dexamethasone-treated rats.

In the current study, the subcutaneous administration of dexamethasone at a dosage of 10 mg/kg/day for 7 days resulted in insulin resistance and hyperglycemia[9]. The intervention led to marked decreases in body weight and body mass index (BMI) compared to control group. These effects may be due to the ablation of the anabolic effects of insulin[17]. Noteworthy, dexamethasone significantly induced hepatomegaly compared to control group. This effect may be attributed to triglycerides accumulation and deposition secondary to rapid mobilization of depot fat in the liver[18].

In the same context, dexamethasone-treated rats showed significant increases in insulin intolerance, FBG, serum insulin, and HOMA-IR index compared to control group, reflecting reduced insulin sensitivity. The insulin desensitizing effect of dexamethasone has been found to be mediated by inhibition of glucose uptake and intracellular glucose oxidation secondary to increased lipolysis and lipid oxidation. Furthermore, the observed hyperinsulinemia may be due to a compensatory and temporary increase in insulin secretion as a response to acute insulin resistance and hyperglycemia[19].

In harmony with previous findings, dexamethasone-treated rats showed significant increases in serum total cholesterol, HDL-C, TG, and VLDL-C compared to control group. It is well documented that long term administration of dexamethasone induces adverse effects, such as adiposity, hepatic fat deposition, and dyslipidemia[20]. The observed increases in TG and cholesterol may be attributed to reduced activity of lecithin-cholesterol acyltransferase (LCAT) and lipoprotein lipase in the liver leading to low degradation of lipoprotein, TG, and cholesterol[7]. In the same context, corticosteroids may stimulate hepatic production of nascent HDL-C[21].

Notably, dexamethasone-treated rats showed a significant decrease in liver glycogen content compared to control group. In harmony with our finding, it has been previously reported that the high-dose administration of dexamethasone causes hepatic glycogen degeneration and an elevated glycophagy process leading to reduced hepatic glycogen[22].

On the other hand, dexamethasone-treated rats showed a significant increase in hepatic DAG level compared to control group. Repeated dexamethasone administration causes a significant increase in phosphoinositide-specific phospholipase C enzyme (PI-PLC) expression, which in turn causes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol 1,4,5-trisphosphate (IP3) and DAG[23].

Moreover, in line with these biochemical alterations, the histopathological analysis of liver tissue in rats treated with dexamethasone, using the H&E staining method, demonstrated extensive hepatocellular injury. This was evident through the presence of significantly enlarged cytoplasm filled with vacuoles, as well as the presence of condensed and deeply stained nuclei when compared to the control group. In a previous study, rats were administered dexamethasone at doses ranging from 4 to 16 mg/kg for a duration of 6 days, resulting in the observation of comparable histological changes[9].

Interestingly, dexamethasone-treated rats showed a significant decrease in hepatic levels of β-arrestin2 compared to control group. The genes of β-arrestin1 and β-arrestin2 are affected by glucocorticoids and can be considered as target genes in this context. Glucocorticoids have been observed to elicit the upregulation of β-arrestin-1 and the downregulation of β-arrestin-2 expression in several cell types, primarily through direct transcriptional modulation[24]. Notably, decreased β-arrestin-2 hepatic level may

contribute to hepatocellular damage and increased systemic insulin resistance[25].

On the other hand, dexamethasone-treated rats showed significant increases in hepatic collagen type I level, fibrosis area, and Akt kinase activity in comparison to control group. This finding suggests that dexamethasone upregulates connective tissue growth factor (CTGF) expression, which has a potent effect on fibroblast proliferation and extracellular matrix molecules deposition like collagen type I and fibronectin, causing fibrosis. Furthermore, it has been observed that increased Akt kinase activity is linked to enhanced fibroblast migration, as well as elevated expression of fibronectin and collagen type 1. These factors play a significant role in promoting collagen deposition and fibrosis[26].

Carvedilol is a drug belonging to the third generation of non-selective β- and α1-blockers. It exhibits β-arrestin biased agonistic properties, as well as anti-inflammatory and antioxidant actions[27]. The administration of carvedilol markedly increased the survival rate when compared to the group receiving dexamethasone, indicating potent protective effects against dexamethasone-induced derangements. However, carvedilol did not show significant changes in the body weights, waist circumference, body mass index, and liver weight in comparison to the group treated with dexamethasone alone.

Moreover, treatment with carvedilol resulted in a significant enhancement in the insulin sensitivity in dexamethasone-treated rats as evidenced by significant reductions in serum insulin and HOMA-IR index in addition to slight reductions in insulin intolerance and fasting blood glucose level. The insulin-sensitizing effect of carvedilol was previously reported and may be attributed to several factors, such as induction of peripheral vasodilation by blocking the α1ARs leading to increased blood flow to peripheral organs and enhanced glucose uptake[28], suppressing the hepatic glucose overproduction and enhancing the muscular insulin signaling pathway[29]. The latter effects may be attributed to its unique biased agonistic activity on β-arrestin2 signaling[30]. β-Arrestin2 can reduce hepatic insulin resistance by activating DAG kinase which mediates degradation of DAG into phosphatidic acid. Diacylglycerol (DAG) is a key mediator of lipid-induced insulin resistance. DAG activates protein kinase C ε (PKCε), which phosphorylates and inhibits the activity of IRS-1[31]. Supporting our interpretation, previous studies have found that β-arrestin2 is severely downregulated in the liver and skeletal muscles of insulin-resistant mice[32]. In harmony with these changes, the present study showed that carvedilol treatment significantly elevated the hepatic levels of β-arrestin2 and glycogen, and significantly reduced hepatic DAG level when compared to the group treated with dexamethasone.

In contrast, carvedilol showed marked but not statistically significant improvement in the lipid profile compared to the dexamethasone group as evidenced by reduction in the serum total cholesterol, TG, and VLDL-C and increase in HDL-C. Blockade of α1ARs by carvedilol may contribute to these effects by relaxing the peripheral vessels and facilitating the uptake of lipids by skeletal muscles. Blockade of α1ARs in the liver diminishes TG efflux and cholesterol synthesis. Also, carvedilol may increase HDL-C level by increasing serum paraoxonase 1 (PON1), which is exclusively found in HDL-C structure, and by increasing ApoA1 level, a major lipoprotein in HDL-C[33].

Noteworthy, treatment with carvedilol significantly decreased hepatic fibrosis and histopathological alterations when compared to the group treated with dexamethasone alone, as evidenced by significant decreases in the hepatic levels of collagen type 1, Akt kinase activity, and hepatic fibrosis area in addition to marked improvement in the hepatocellular tissue integrity. In accordance with our findings, previous studies have shown that carvedilol can reduce the activation and proliferation of hepatic stellate cells (HSCs), Transforming growth factor-β1 (TGF-β1) expression, hydroxyproline production, and collagen synthesis and deposition[34].

Despite that carvedilol significantly increased the hepatic levels of β-arrestin2, it significantly decreased the hepatic Akt kinase activity. A previous study has shown that in some situations β-arrestin2 may decrease, not increase, the Akt kinase activity[35]. This may interpret our findings and may show for the first time, according to our knowledge, that carvedilol can reduce hepatic fibrosis by

enhancing the inhibitory effect of β-arrestin2 on Akt kinase activity.

Phenylephrine is a selective α1AR agonist. Treatment with phenylephrine caused a significant reduction in the survival rate compared to both dexamethasone and carvedilol groups. Although administration of phenylephrine significantly increased waist circumference and liver weights, it did not show significant changes in the body weights and BMI compared to the dexamethasone group. Additionally, treatment with phenylephrine did not improve the insulin sensitivity in dexamethasone-treated rats, as evidenced by non-significant changes in the insulin tolerance, FBG, and HOMA-IR index despite that it caused a significant reduction in the serum insulin level. In accordance with our findings, earlier studies reported that the stimulation of α1AR contributes to increased peripheral vascular resistance, thus causing a decreased blood supply and decreased glucose uptake at peripheral tissue sites. Also, activation of α1AR in human and rodent livers has been found to increase gluconeogenesis and glycogenolysis[36]. In the same context, no notable differences were detected in the lipid profile and hepatic glycogen level in comparison to the group treated with dexamethasone. Notably, previous studies showed that phenylephrine treatment may be correlated with elevated hepatic VLDL-TG secretion and therefore elevated serum VLDL-TG levels[37].

In contrast, treatment with phenylephrine markedly reduced hepatic DAG level, hepatic damage, and histopathological changes compared to dexamethasone group; however, this change was not associated with improved systemic insulin sensitivity. In line with our previous findings, the decrease in hepatic DAG level is usually associated with decreased activity of the PKC/NF-κB/TNFα pathway leading to reduced liver injury[38]. Noteworthy, treatment with phenylephrine significantly increased hepatic β-arrestin2 levels compared to the dexamethasone group. The latter effect may mediate the observed reduction in hepatic DAG level as explained before[39]. Also, the improvement in hepatic tissue integrity may be attributed to the increase in hepatic β-arrestin2 level, which mediates cytoprotective effects.

Consistent with our previous findings, treatment with phenylephrine significantly decreased hepatic fibrosis compared to the dexamethasone group as evidenced by significant reductions in the hepatic levels of collagen type 1, Akt kinase activity, and fibrosis area. In accordance with our findings, it has been found that induction of the PI3K/Akt/mTOR signaling pathway has a critical role in the pathogenesis of liver fibrosis[40].

Therefore, it can be estimated that the inability of phenylephrine to improve insulin sensitivity is attributed to its vasoconstrictor effect, which reduces blood flow to peripheral organs such as skeletal muscles, leading to decreased glucose uptake. On the other hand, the phenylephrine-mediated hepatoprotective effects are attributed to its ability to increase hepatic β-arrestin2 level and its cytoprotective downstream signals. The same point may indicate that the insulin-sensitizing effect of carvedilol should be, at least in part, mediated by vasodilation and increased blood flow to peripheral organs.

To illustrate the α1AR role in mediating the insulin-sensitizing properties of carvedilol, we used carvedilol in combination with phenylephrine. Concurrent administration of phenylephrine and carvedilol in dexamethasone-treated rats significantly decreased the survival rate compared to the carvedilol group. This finding reflects the crucial role of the α1AR blockade in mediating the protective effects of carvedilol against the dexamethasone-induced derangements. In addition, concurrent administration of phenylephrine and carvedilol in dexamethasone-treated rats significantly decreased the body weights compared to the carvedilol group without significant differences in the waist circumference, BMI, and liver weights. The interpretation of this point is not clear and beyond the aim of the current study.

Notably, the combined treatment with both phenylephrine and carvedilol slightly but not significantly decreased the insulin-sensitizing effect compared to the carvedilol group. This finding confirms that the antagonism between the two drugs on the α1AR reduces the insulin-sensitizing effect of carvedilol and confirms the role of α1AR

blockade in mediating these effects, at least in part.

In the same context, combined use of phenylephrine and carvedilol significantly increased the serum levels of TG and VLDL-C compared to the carvedilol group but decreased the serum total cholesterol and HDL-C levels. Also, this finding validates the possible involvement of α1AR blockade in mediating the beneficial effects of carvedilol on lipid profile. Moreover, and in harmony with their combined effect on glucose homeostasis, concomitant use of both drugs showed antagonism on the hepatic glycogen and DAG levels despite that they significantly reduced the hepatic β-arrestin2 level compared to either carvedilol or phenylephrine separate groups. Similarly, combined use of phenylephrine and carvedilol showed antagonism on the hepatic levels of collagen type 1, Akt kinase activity, and fibrosis area. These data provide confirmation of the involvement of α1AR in the mediation of these effects, at least in part.

Conclusion

Carvedilol mediates insulin-sensitizing and hepatoprotective effects in dexamethasone-treated rats. The α1AR blockade effect of carvedilol contributes to its insulin-sensitizing action as well as to its beneficial effect on the lipid profile. On the other hand, the hepatoprotective effect of carvedilol in dexamethasone-treated rats is less dependent on the α1AR.

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يساهم تأثير دواء (كارفيديلول) على مستقبلات ألفا ١ الأدرينالية في معالجة مقاومة الأنسولين وبدرجة أقل تلف الكبد الناجمين عن معالجة الجرذان بدواء (ديكساميثازون)

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لقد ثبت أن مقاومة الأنسولين تزيد من خطر الإصابة بمشاكل صحية خطيرة، بما في ذلك مرض السكري من النوع ٢ وأمراض القلب والسكتة الدماغية. وقد ثبت أن دواء (كارفيديلول) يحسن من مقاومة الأنسولين وزيادة الدهون في الدم ويقلل من خطر الإصابة بمرض السكري. وتهدف هذه الدراسة إلى التحقق من دور مستقبلات ألفا ١ الأدرينالية في التوسط في قدرة دواء (كارفيديلول) على تحسين حساسية الأنسولين في الجرذان المعالجة بدواء (ديكساميثازون). وقد أشارت النتائج إلى أن حجب مستقبلات ألفا ١ وبيتا الأدرينالية بواسطة دواء (كارفيديلول) قلل من مقاومة الأنسولين وتلف الكبد الناجمين عن المعالجة بدواء (ديكساميثازون). كذلك أدى الحقن المسبق لدواء (فينيليفرين) إلى تقليل تأثير دواء (كارفيديلول) المحسن لحساسية الأنسولين.

ومما سبق نستنتج أن، قدرة دواء (كارفيديلول) على تثبيط مستقبلات ألفا ١ الأدرينالية يساهم في تأثيره لزيادة حساسية الأنسولين بالإضافة إلى تأثيره المفيد على مستويات الدهون في الدم. من ناحية أخرى، فإن التأثير الوقائي من تلف الكبد لدواء (كارفيديلول) في الجرذان المعالجة بدواء (ديكساميثازون) أقل اعتمادًا على مستقبلات ألفا ١ الأدرينالية.