COMPARATIVE STUDY OF THE EFFECT OF PRAVASTATIN AND CAPTOPRIL ON THE CONTRACTILE RESPONSE OF ISOLATED AORTIC STRIP TO NORADRENALINE IN HIGH FRUCTOSE-FED ALBINO RATS.

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ABSTRACT

Insulin resistance is known to be a risk factor for the development of type II diabetes mellitus, cardiovascular diseases associated with dyslipidemia & obesity. The present work aimed at the investigation of the influence & possible mechanism of either pravastatin or captopril on contractile response of the isolated aortic strip to noradrenaline (NA) in rats with established insulin resistance induced by high fructose diet. Furthermore to our knowledge there is no study comparing the effect of pravastatin & captopril as regarding the biochemical changes associated with insulin resistance in rats. The present study was carried out on forty-eight male albino rats. Rats were divided into 2 main groups: Group (A); consisted of 12 an-

imals that received standard diet through the experiment (8 weeks) & treated with intragastric saline (the vehicle), starting from the last 2 weeks of experiment & served as normal control. Group (B); consisted of 36 animals, received high fructose diet (for 8 weeks) for induction of insulin resistance. This group was subdivided into 3 equal subgroups (12 rats / subgroup) as the following: subgroup (b1); served as insulin resistant control, treated with saline, subgroup (b2); insulin resistant rats treated with pravastatin in a dose of 20 mg/kg/day, intragastrically in the last 2 weeks of the experiment. subgroup (b3); received high fructose diet (insulin resistant) & treated with captopril in a dose of 2 mg/kg/day intragastrically in the last 2 weeks of the experiment.

Insulin sensitivity, fasting serum insulin, glucose, lipogarm (triglycerides (TG), cholesterol & low density lipoprotein (LDL)) & malondialdehyde (MDA) were assessed. Rats of high fructose diet developed a significant insulin resistance as assessed by calculating glucose-insulin ratio in fasting rats. Furthermore, these rats showed significant increase in insulin, TG, LDL & MDA, but no change in serum glucose & cholesterol level. Administration of pravastatin or captopril to insulin resistant rats produced a comparable beneficial effect on insulin resistance, dyslipidemia & restored fasting serum insulin & MDA to control level. In vitro study, isolated aortic strip from insulin resistant rats showed enhanced contractile response to NA compared with rats fed standard diet. Either pravastatin or captopril treatment of insulin resistant rats improved the contractile response to NA. Addition of either N-nitro-L-arginine (an inhibitor of nitric oxide synthesis) or indomethacin (an inhibitor of cyclooxygenase enzyme) induced partial block of the beneficial effect of pravastatin or captopril on the contractile response of the isolated strips from insulin resistant rats to NA; while the addition of both N-nitro- L-arginine & indomethacin

blocked the beneficial effect of both drugs. In conclusion, the present work, for the first time, demonstrated that pravastatin treatment as well as captopril has a comparable beneficial effect on the contractile response of isolated aortic strip from insulin resistant, hyperinsulinemic rats induced by high fructose diet. These action appear to be mediated through effects of pravastatin or captopril on nitric oxide production & inhibition of the oxidative stress

INTRODUCTION

Like other muscle cells, vascular smooth cells contract when the intracellular calcium concentration rises, and all vasoconstrictor substance act by increasing intracellular calcium (1). It is well known that vascular endothelium doesn't act just as a passive barrier keeping cells & proteins from escaping into the tissues but also acts as a source of several substances that control the contraction of underlying smooth muscle (2). Endothelial dysfunction, appears to be the initiating event in atherosclerosis and may play an important role in ischemic complications (3). Endothelial dysfunction of the coronary & peripheral circulation has been shown to predict coronary events (4). Dysfunction of

the endothelium predisposes to the increased vascular tone and impaired vasomotion and reactivity. Insulin resistance and hypertension are independent risk factors for atherosclerosis & both are capable of evoking dysfunction of endothelium (5). Insulin resistance is known to be risk factor for the development of type II diabetes mellitus and cardiovascular diseases associated with dyslipidemia and obesity (6). Abnormal functioning of the vascular smooth muscle cells has also been implicated as one of the mechanisms underlying vascular disease in diabetes. Many studies have demonstrated that vascular responsiveness to NA is altered in some way in experimental diabetes & this may be secondary to insulin resistance and its metabolic complications (7).

Pravastatin which is a (3-hydroxy-3methyl-glutary coenzyme A (HMG-CoA) reductase inhibitor, has been shown to reduce adverse cardiovascular events in patients suffering from coronary artery diseases with or without hypercholesterolemia (8). Moreover, few studies indicate that pravastatin posses additional beneficial vascular effect beyond that afforded by a mere reduction in cholesterol

level (9,10). In addition it has been shown that HMG-Co. A reductase inhibitor improved the defective endothelium-dependent vasodilation of atherosclerotic vessels in human or animals by lowering plasma cholesterol (11,12). Although the mechanism by which HMG-CoA reductase inhibitors preserve vascular function is primarily attributed to their inhibition of hepatic HMG-CoA reductase & subsequent lowering of plasma cholesterol levels, some studies have questioned the exclusive involvement of the decrease in plasma LDL levels in the effects of HMG-CoA reductase inhibitors (13, 14,15 & 16). Thus, it remains unclear how an early improvement in endothelial function might occur during treatment with HMG-CoA reductase inhibitor & how this affect vascular responsiveness to contracting agents such as NA.

Angiotensin-converting enzyme inhibitors ameliorate the deleterious effects of elevated renin & angiotensin II levels in patients with hypertension, congestive heart failure, and acute myocardial infarction. Endothelial cells can synthesize their own tissue-based components of the renin-angiotensin system (17). The con-

strictive effect of ACE via this locally generated angiotensin II & other endothelium derived constrictive factors are normally counter balanced by the primary endothelium-derived relaxing factor & nitric oxide (18,19). However when the endothelium is damaged, the coronary arteries & resistance vessels would lose the ability to fully vasodilate via this endothelium dependent pathway (20,21). Endothelium dysfunction may be one of the first steps in the development of overt atherosclerosis (22,23). There is considerable evidence that human coronary arteries exhibit endothelium-mediated coronary vasodilation which is important pathophysiologically as well as clinically, and this function, is impaired in patients with coronary disease (24,25). However, it remains unclear how ACEI, may affect vascular responsiveness to vasoconstricting agents in cases of insulin resistance per se not accompanied by hyperglycaemia, diabetes or atherosclerosis. The present study compared the effect & possible mechanisms of pravastatin and captopril treatment on the isolated aortic strip precontracted with NA in rats with established fructose diet-induced insulin resistance.

MATERIALS & METHODS

Drugs used :

- * Pravastatin : Lipostat tablets, 10mg supplied by squibb Co.
- * Captopril: Capoten tablets, 25 mg supplied by Squibb Co.
- * N-nitro-L-arginine its molecular weight is 219.2, obtained from Sigma Co.
- * Noradrenaline hydrochloride (NA): obtained from Sigma Co. molecular weight; 169.2.
- * Acetylcholine (A.ch): supplied by Sigma Co., molecular weight; 181.7.
- * Indomethacin; obtained from Sigma Co., molecular weight; 357.8.

Animals used :

Fourty -eight male albino rats were used throughout this study. At the beginning of the experiment, the rats were aged 2 weeks. Food intake was recorded daily & their weight was monitored weekly, they were put under similar housing conditions. They were divided into 2 main groups :

Group (A) : Twelve rats received standard diet throughout the experiment (8 weeks) & treated with intra-gastric saline daily (0.5ml).

Group (B) : Thirty six rats received high fructose diet for induction of insulin resistance (26) throughout the

experiment (8 weeks). This group was subdivided into 3 equal subgroups (12 rats / subgroup) as the following :-

- 1- subgroup (B1): (high fructose fed control), rats received a diet in which fructose composed 33-64% of total carbohydrates & treated with 0.5mg saline, intragastrically for 2 weeks before the end of the experiment (26).
- 2- Subgroup (B2): (insulin resistant + pravastatin treated) , received high fructose diet & after confirmation of being insulin resistant by insulin sensitivity assay (29), they received pravastatin treatment in a dose of 20mg/kg/day intragastric in the last 2 weeks (27) of the experiment.
- 3- Sub group (B3): (Insulin resistant + captopril treated)Received high fructose diet throughout the experiment (8 weeks) & after confirmation of being insulin resistant, they treated with captopril in a dose of 2mg/kg/day intragastrically for last 2 weeks (28).

** Aortic-strip preparation & protocol:-*

After 2 weeks of pravastatin or captopril treatment to insulin resistant rats, 6 rats from each group were killed by decapitation. A section of the thoracic aorta from arch to the diaphragm was removed & placed in ox-

ygenated modified krebs Henseleit solution (KHS) according to Tsuneo (30). The aorta was cleaned of loosely adhering fat & connective tissue & cut into helical strips 3mm in width & 20mm in length. The tissue was placed in a well oxygenated (95% O₂ & 5% Co₂) bath of 10ml KHS at 37°C. The presence of functional endothelial cells was confirmed by demonstrating relaxation to 10⁻⁵ M/ml A.ch. Aortic strips in which relaxation occurred were regarded as being tissues with functioning endothelium. For the contraction NA (10⁻⁵, 10⁻⁷, 10⁻⁹ M/ml/ bath) were added until maximum response was achieved.

Effects of either chronic pravastatin or captopril pretreatment on the contractile response induced by NA in aortic strips with established high fructose diet-induced insulin resistance was studied. N-nitro- L-arginine (10⁻⁴ M/ml/bath) and or indomethacin (10⁻⁷ M/ml /bath) were used to investigate their influence on NA-induced contractile response (30). At the end of the experiment the remaining 6 rats of each group were decapitated after 12 hours of starvation & blood was collected. Blood samples were allowed to clot & were centrifuged. Serum was separated & frozen at -70°C

until the time of assay of the following parameters:

- * Serum glucose, according to the enzymatic glucose oxidase method of Trinder (31).
- * Fasting serum insulin, according to Morgen & Lazarow (32), by radio immunoassay using iodinated kit, manufactured by diagnostic products Corporation.
- * Total serum cholesterol, using kits of biomerieux Co., according to Richmond (33)., LDL, according Burstein (34) using kits of biomerieux Co. & TG, according to Fassati and Prencipe (35) using TG kits of biomerieux .
- * Determination of malondialdehyde (MDA), according to Draper & Hadley (36).

Statistics :

Statistical analysis of the results were carried out according to pipkin (37), using student's "t" test. P is significant at < 0.05 .

RESULTS

General characteristics :

The general characteristics for the four experimental groups were showed in Tab.(1). Animals fed high fructose diet were hyperinsulinemic & insulin resistant as compared to rats

that kept on the standard diet ($P < 0.05$).

There were no difference between groups as regards body weight or serum glucose. On the other hand, administration of captopril or pravastatin to rats fed-high fructose diet induced significant decrease in insulin level and no changes in serum glucose & body weight.

Effects of pravastatin and captopril on MDA (nmol/m); fasting serum glucose (mM/L); fasting serum insulin (μ u/ml); serum cholestrol (mg/dl); LDL (mg/dl) & TG (mg/dl) in rats fed high fructose diet:

Rats which fed high fructose diet showed significant increase in MDA, fasting serum insulin, LDL & TG. On the other hand there was no change in cholesterol levels as shown in Tab (1&2).

Administration of pravastatin to rats with insulin resistance in daily dose of 20mg/kg/day orally for 2 weeks produced a significant decrease in fasting serum TG,LDL, insulin & MDA (96.1 ± 0.8 $P < 0.001$; 39.1 ± 0.2 , $P < 0.001$; 16.1 ± 1.1 , $P < 0.05$ & 8.8 ± 0.8 , $P < 0.05$ respectively), but it

produced no change in serum glucose & cholesterol levels as compared to insulin resistant rats untreated with pravastatin (118.3 ± 0.4 , $P > 0.05$ & 79.3 ± 1.5 , $P > 0.05$ respectively, Tab. 1&2).

Administration of captopril in a daily oral dose of 2mg/kg for 2 weeks to rats with insulin resistance induced a significant decrease in fasting serum TG, LDL, insulin & MDA (116.1 ± 0.8 , $P < 0.05$; 47.2 ± 0.9 , $P < 0.05$; 15.5 ± 0.3 , $P < 0.001$ & 3.6 ± 0.1 , $P < 0.001$ respectively), but it induced non-significant change in serum glucose & cholesterol as compared to insulin resistant rats untreated with captopril (115.9 ± 0.5 ; $P > 0.5$ & 81.9 ± 1.3 , $P > 0.5$ respectively, tab 1&2).

Contraction response to NA :

- * Exposure of aortic strips to NA (10^{-9} - 10^{-5} M) led to concentration-dependent rise in contractility in all the experimentally groups:

- In high fructose fed rats (insulin resistant) there was increased contractile response to NA as compared with control rats fed standard diet (Tab 3, fig. 1&2).
- Both Pravastatin and captopril treatment to insulin resistant rats in a dose of 20 mg/kg/day and 2mg/kg/day respectively for 2 weeks, ameliorates the increased contractile response of the aortic strip to NA (Tab. 3 & fig.3 , 4).
- In the presence of 10^{-4} M of N-nitro-L- arginine the effect of either pravastatin or captopril was partially blocked (Tab. 4 Fig. 5 &6).
- In the presence of 10^{-5} M indomethacin, the effect of pravastatin or captopril was partially blocked (Tab 5, fig. 7 & 8).
- In the presence of 10^{-4} M N-nitro-L-arginine plus 10^{-5} M indomethacin, the effect of pravastatin or captopril was blocked (Tab.6, Fig. 9 and 10).

Table (1): General characteristics of the rats in the four experimental groups. Mean $\pm$ SE.

Character	Group			
	standard diet control	High fructose fed control	Fructose fed+ pravastatin	Fructose fed +captopril
Body weight (grams)	315 $\pm$ 5	320 $\pm$ 7.2 P1>0.05	322 $\pm$ 7.2 P2>0.05	317 $\pm$ 7.1 P3>0.05
Glucose (mg/dl)	105 $\pm$ 0.1	110.5 $\pm$ 0.4 P1>0.05	118.3 $\pm$ 0.4 P2>0.05	115.9 $\pm$ 0.5 P3>0.05
Insulin (mU/dl)	14.8 $\pm$ 0.5	32.7 $\pm$ 0.3 P1<0.05	16.1 $\pm$ 1.1 P2<0.05	15.5 $\pm$ 0.3 P3<0.001
FGIR	7.9 $\pm$ 0.2 (IS)	3.37 $\pm$ 0.2 (IR)	7.34 $\pm$ 0.2 (IS)	7.47 $\pm$ 0.1 (IS)

» SE= Standard error.

» P1= Test of significance between rats fed high diet versus that fed standard diet.

» P2= Test of significance between rats fed high fructose and treated with pravastatin versus that fed high fructose diet.

» P3= Test of significance between rats fed high fructose diet and treated with captopril versus that fed high fructose diet.

» FGIR = Fasting glucose insulin ratio.

» IS = insulin sensitive (FGIR > 7)

» IR = Insulin resistance (FGIR $\geq$ 7=IS).Table (2): Effect of pravastatin (20mg/kg/day, intragstrically for 2 weeks) and captopril (2mg/kg/day, intragastrically for 2 weeks) on MDA, cholesterol, LDL & TG. (mean $\pm$ SE).

Serum parameters	Standard diet	High fructose fed diet	High fructose fed +pravastatin	High fructose fed+ captopril
Total serum MDA (nmol/ml)	4.7 $\pm$ 0.2	17.2 $\pm$ 1.1 P<0.001	8.8 $\pm$ 0.8 P2<0.05	3.6 $\pm$ 0.1 P3<0.001
Cholesterol (mg/ml)	81.5 $\pm$ 0.5	80.5 $\pm$ 0.8 P1:NS	79.3 $\pm$ 1.5 P2:NS	81.9 $\pm$ 1.3 P3:NS
LDL (mg/dl)	37.8 $\pm$ 0.8	52.3 $\pm$ 1.1 P1<0.05	39.1 $\pm$ 0.2 P2<0.001	47.2 $\pm$ 0.9 P3<0.05
TG(mg/dl)	95.2 $\pm$ 0.7	138.1 $\pm$ 2.1 P1<0.001	96.1 $\pm$ 0.8 P2<0.001	116.1 $\pm$ 0.8 P3<0.05

» SE= Standard error.

» P1= Test of significance between rats fed high fructose diet versus that fed standard diet.

» P2= Test of significance between rats fed high fructose diet treated with pravastatin versus control untreated..

» P3= Test of significance between rats fed high fructose and treated with captopril versus rats fed high fructose diet and non treated.

Table (3): Effect of pravastatin pretreatment (20mg/kg/day) and captopril (2mg/kg/day) intragastrically for 2 weeks on isolated aortic strip of insulin resistant rats precontracted with NA. Mean $\pm$ SE.

N=6	Contractile response to NA in standard diet fed rats			Contractile response to NA in fructose fed rats			Contractile response to NA in pravastatin treated rats			Contractile response in captopril pretreated rats		
	10^{-8} M/ml	10^{-6} M/ml	10^{-4} M/ml	10^{-8} M/ml	10^{-6} M/ml	10^{-4} M/ml	10^{-8} M/ml	10^{-6} M/ml	10^{-4} M/ml	10^{-8} M/ml	10^{-6} M/ml	10^{-4} M/ml
NA concentration in the water bath												
Aortic strip contractile response (mm).	340.1	6540.2	840.1	640.1*	1040.2*	1210.2*	3540.1**	740.1**	840.2**	3540.1**	740.1**	840.2**

* $p < 0.05$ compared with corresponding group in standard diet fed rats.

** $p < 0.05$ compared with corresponding group in high fructose fed rats.

Table (4): Effect of N-nitro-L-arginine (10^{-4} M/ml/bath) for 1 hour on the isolated aortic strip in insulin resistant rats, treated with pravastatin (20mg/kg/day) or captopril (2mg/kg/day) intragastric, for 2 weeks. Mean $\pm$ SE.

N-6	Pravastatin treated			captopril treated		
	Contractile response to NA before N-nitro-L-arginine (10^{-4} M / ml/bath)	Contractile to NA after N-nitro-L-arginine (10^{-4} M / ml/bath)	Contractile response to NA before N-nitro-L-arginine (10^{-4} M / ml/bath)	Contractile to NA after N-nitro-L-arginine (10^{-4} M / ml/bath)	Contractile to NA before N-nitro-L-arginine (10^{-4} M / ml/bath)	Contractile to NA after N-nitro-L-arginine (10^{-4} M / ml/bath)
Concentration of NA/bath	10^{-6} M/ml	10^{-6} M/ml	10^{-6} M/ml	10^{-6} M/ml	10^{-6} M/ml	10^{-6} M/ml
Contractile response (mm).	3.6 ± 0.2	7.1 ± 0.2	8.1 ± 0.1	3.5 ± 0.1	7.4 ± 0.1	8.9 ± 0.2
			$P1 < 0.05$		$P2 < 0.05$	$P3 < 0.05$
					$P1 > 0.05$	$P3 > 0.05$

* SE= Standard error, mm= millimeter

* P1= Test of significance after & before N-nitro-L-arginine in presence of NA in a concentration of 10^{-2} M/ml/bath.

* P2= Test of significance after & before N-nitro-L-arginine in presence of NA in a concentration of 10^{-7} M/ml/bath.

* P3= Test of significance after & before N-nitro-L-arginine in presence of NA in a concentration of 10^{-3} M/ml/bath.

Table (5) Effect of Indomethacin (10^{-7} M/ml/bath) for 1 hour on the isolated aortic strip in insulin resistant rats, treated with pravastatin (20mg/kg/day) or captopril (2mg/kg/day) intragastric, for 2 weeks Mean $\pm$ SE.

N=6	Pravastatin treated			captopril treated		
	Contractile response to NA before Indomethacin		Contractile to NA after Indomethacin	Contractile response to NA before Indomethacin		Contractile to NA after N-Indomethacin
Concentration of NA/bath	10^{-7} M/ml	10^{-7} M/ml	10^{-7} M/ml	10^{-7} M/ml	10^{-7} M/ml	10^{-7} M/ml
Contractile response (mm).	3.6 $\pm$ 0.2	7.1 $\pm$ 0.2	8.1 $\pm$ 0.1 P1<0.05	6.3 $\pm$ 0.1 P1<0.05	8.9 $\pm$ 0.1 P2<0.05	9.5 $\pm$ 0.2 P3<0.05
				3.5 $\pm$ 0.1	7 $\pm$ 0.1	5.9 $\pm$ 0.1 P1<0.05
						10.1 $\pm$ 0.2 P3<0.05

» SE= Standard error. mm= millimeter

» P1= Test of significance after & before indomethacin in presence of NA in a concentration of 10^{-7} M/ml/bath.

» P2= Test of significance after & before indomethacin in presence of NA in a concentration of 10^{-7} M/ml/bath.

» P3= Test of significance after & before indomethacin in presence of NA in a concentration of 10^{-5} M/ml/bath.

Table (6): Effect of combined addition of N-nitro-L- arginine 10^{-4} M/ml/bath and indomethacin 10^{-7} M/ml/bath) for 1 hour on isolated strip of insulin resistant treated with pravastatin (20mg/kg/day) or captopril (2mg/kg/day) orally for 2 weeks (Mean $\pm$ SE).

N=6	Pravastatin treated			captopril treated		
	Contractile response to NA before addition of N-nitro-L- arginine & indomethacin	Contractile response after addition of N-nitro-L- arginine & indomethacin		Contractile response to NA before addition of N-nitro-L- arginine & indomethacin	Contractile response after combined addition of N-nitro-L- arginine & indomethacin	
Concentration of NA/bath	10^{-8} M/ml	10^{-7} M/ml	10^{-4} M/ml	10^{-8} M/ml	10^{-7} M/ml	10^{-4} M/ml
Contractile response (m.m)	3.6 $\pm$ 0.2	7.1 $\pm$ 0.2	8.1 $\pm$ 0.1	3.7 $\pm$ 0.1	7.2 $\pm$ 0.1	8.3 $\pm$ 0.2
		6.1 $\pm$ 0.1 P1<0.05	10.0 $\pm$ 0.2 P2<0.05		6.5 $\pm$ 0.1 P1<0.05	10.7 $\pm$ 0.2 P2<0.05
			12.4 $\pm$ 0.2 P3<0.05			12.5 $\pm$ 0.2 P3<0.05

» SE= Standard error.

» P1= Test of significance after & before addition of both N-nitro-L-arginine & indomethacin in presence of NA in a concentration of 10^{-9} M/ml/bath.

» P2= Test of significance after & before combined addition of N-nitro-L-arginine & indomethacin in presence of N-nitro-L-arginine & indomethacin in presence of NA in a concentration of 10^{-7} M/ml/bath.

» P3= Test of significance after & before combined addition of N-nitro-L-arginine & indomethacin in presence of NA in a concentration of 10^{-4} M/ml/bath.

Fig. (1): Contractile response of isolated aortic strip of rat to NA (standard diet + saline pretreated).

Fig. (2): Contractile response of isolated aortic strip of rat to NA (high fructose diet, i.e. insulin resistant + saline pretreated).

Fig. (3): Contractile response of isolated aortic strip of rat to NA
(insulin resistant + pravastatin pretreated).

Fig. (4): Contractile response of isolated aortic strip of rat to NA
(insulin resistant + captopril pretreated).

Fig. (5): Contractile response of isolated aortic strip of rat to NA (insulin resistant + pravastatin pretreated + N-nitro-L-arginine).

Fig. (6): Contractile response of isolated aortic strip of rat to NA (insulin resistant + captopril pretreated + N-nitro-L-arginine).

Fig. (7): Contractile response of isolated aortic strip of rat to NA
(insulin resistant + Indomethacin, pravastatin pretreated).

Fig. (8): Contractile response of isolated aortic strip of rat to NA
(insulin resistant + captopril pretreated + indomethacin).

Fig. (9): Contractile response of isolated aortic strip of rat to NA
(high fructose diet, i.e. insulin resistant + N-nitro-L-arginine + Indomethacin, pravastatin pretreated).

Fig. (10): Contractile response of isolated aortic strip of rat to NA
(high fructose diet, i.e. insulin resistant + N-nitro-L-arginine + Indomethacin, captopril pretreated).

DISCUSSION

This is the first study in which the effects of pravastatin or captopril are examined on aortic strip of insulin-resistant hyperinsulinemic rats with high fructose diet.

In the current study rats fed high fructose diet for 6 weeks demonstrated insulin resistance in comparison with the control animals of similar weight & age fed standard diet. This finding was in accordance with previous study (38). This resistance was evidenced by insulin sensitivity assay using fasting glucose-insulin ratio (29). Although, high fructose diet produced a state of insulin resistance, it doesn't cause diabetes, hence the present study provides information on the ability of either pravastatin or captopril to influence an environmentally induced non-genetic form of insulin resistance in non-hyperglycaemic model. This model may resemble certain features of the non-diabetic human insulin resistance states of obesity & impaired glucose tolerance (39). The mechanism of insulin resistance induced by high fructose diet include both peripheral & hepatic insulin resistance (40). The cellular mechanism includes decreased insulin receptor binding & post-receptor defect (41).

In the present study rats fed high-fructose diet for 6 weeks showed a significant increase in fasting serum insulin, TG, LDL. On the other hand there was no change in fasting serum glucose & cholesterol level. These findings are consistent with Laakso (42). It has been proposed that insulin resistance elevates serum TG, through increasing the production of very low density lipoprotein (VLDL) & reducing the catabolism of (VLDL) due to low lipoprotein lipase activity. Furthermore, the rats with insulin resistance showed higher serum MDA. This is in accord with Lee (43), who reported that there was an increased oxidative stress in insulin resistance syndrome.

The results of the present study demonstrated that pravastatin treatment in rats with insulin-resistance induced a significant decrease in serum TG, LDL, insulin & MDA as compared to control rats with non-treated insulin resistant (mean $\pm$ SE: 96.1 $\pm$ 0.8; 39.1 $\pm$ 0.2; 16.1 $\pm$ 1.1, 8.8 $\pm$ 0.8 Vs 138.1 $\pm$ 2.1; $P < 0.001$; 52.3 $\pm$ 1.1, $P < 0.5$; 32.7 $\pm$ 1.3, $P < 0.05$ & 17.2 $\pm$ 1.8, $P < 0.001$ respectively). On the other hand pravastatin treatment induced no change in either serum glucose or cholesterol levels (Mean $\pm$ SE: 118.3 $\pm$

0.4 and 79.3 ± 1.5 VS 110.5 ± 0.4 & 80.5 ± 0.8 , P , 0.05 respectively). These findings are in accord with Tsuneok et al (7). They reported that HMG. Co A reductase inhibitor achieves its effects by a number of mechanisms, including primarily inhibition of hepatic cholesterol biosynthesis & depletion of critical intracellular pools of sterol & increased transcription of LDL & LDL- precursors. Furthermore, decreased production of VLDL with a parallel alteration of VLDL composition & increased removal of VLDL from plasma added to the mechanisms of HMG. Co A reductase inhibitor (44). The significant reduction of MDA produced by pravastatin administration to rats with insulin resistance could be explained by reduction of LDL & decreased its susceptibility to oxidation (9). The effect of pravastatin on insulin level can be explained by its influence on TG & non-esterified free fatty acids (NEFFA). It is well known that elevated NEFFA concentration & associated hypertriglyceridemia led to increased NEFFA utilization, inhibition of glucose oxidation, reduction of glucose uptake & impairment of insulin sensitivity. The later may then reactivates viscious cycle until possible development of impaired glucose toler-

ance as soon as a defect in insulin secretion occurs (45), so pravastatin cuts this cycle by decreasing TG & NEFFA levels.

Administration of captopril to rats with insulin resistance induced improvement in insulin sensitivity associated with a significant decrease in fasting serum TG, LDL, insulin & MDA, but it produced no change in serum glucose & cholesterol as compared to insulin resistant untreated rats (116.1 ± 0.8 ; 47.2 ± 0.9 ; 15.5 ± 0.3 , 3.6 ± 0.1 ; 115.9 ± 0.5 and 81.9 ± 1.3 respectively vs 138.1 ± 2.1 ; 52.3 ± 1.1 ; 32.7 ± 0.3 ; 17.2 ± 1.1 ; 110.5 ± 0.4 and 80.5 ± 0.8 , $P < 0.05$; < 0.05 ; < 0.001 ; < 0.001 ; > 0.05 & > 0.05 respectively). These findings are in accord with previous studies (46,47,48). They reported that in human & animal models of insulin resistance ACEI increased sensitivity to insulin. Most previous investigations have attributed the influence of ACEI on glucose disposal as a result of improvement of capillary blood flow & increased delivery of insulin & glucose to muscles. Other investigators indicated that improvement of insulin sensitivity may be via inhibition of endothelin-1 which has potent glycogenolytic effect on hepatocytes & may cause insulin re-

sistance in rat adipocyte (49). The decrease in serum MDA levels caused by captopril could be explained by the effect of ACE inhibitor on angiotensin II. Angiotensin II stimulates superoxide anion generation in vascular smooth muscle & therefore ACEIs by preventing the vascular actions of angiotensin II reduced superoxide anion generation within the vessel wall which manifested by decreased lipid peroxidation product, MDA (50).

In the present study, in vitro experiments, insulin resistance induced by high fructose diet produced increased contractility of isolated aortic strip to NA. This finding was in accord with other investigators (51). This result can be explained by increased plasma LDL which led to enhancement of NA- induced contraction, since it has been reported that oxidized LDL enhanced agonist-induced vasoconstriction in rabbit femoral artery via a direct interaction with vascular smooth muscle (52). In addition, it has been shown that LDL induces the expression of mRNA for insulin growth factor-1 receptor in cultured smooth muscle cells (53) & this might increase expression of $\alpha 1$ -adrenergic receptors. Also, Kabayashi & Kamato (51) reported that there

was up regulation of mRNA for the $\alpha 1B$ or $\alpha 1D$ adrenergic receptors secondary to hyperinsulinemia.

In the present study, pravastatin treatment in rats with insulin resistance induced improvement in the contractile response to NA. This result is in agreement with Dumont et al(10), as they found that pravastatin treatment has been restored endothelium dependent vasomotion. This may be direct effect of pravastatin on vessel wall specifically, the endothelium as a result of diminished oxidative stress (54&55). In the present study, pravastatin has also been proven to diminish serum levels of MDA (a marker of lipid peroxidation) which was supported by the previously mentioned studies. In addition statins have been proven to diminish plasma levels & production of endothelin -1 in vitro & in vivo, where as endothelin-1 is known to inhibit nitric oxide production (56,57). In the present study, the effect induced by pravastatin on the isolated aortic strip was partially blocked by addition of N-nitro-L-arginine to the bath. Also addition of indomethacin produced partial block to the effect of pravastatin. In the combined presence of N-nitro-L-arginine & indomethacin, the effect of pravastatin on contraction response of aortic strip was blocked.

These data reveal that pravastatin acts directly on the aortic strip via generation of nitric oxide & prostaglandins.

In the present work, captopril administration to rats with insulin resistance improve contractile response to NA. Furthermore, addition of N-nitro-L-arginine (an inhibitor of nitric oxide synthesis), blocked the beneficial effect of captopril on the contractile response of aortic strip from insulin resistant rats. In addition, pretreatment of isolated aortic strip with indomethacin blocked the effect of captopril partially. These data could be explained on the basis of the effect of ACE inhibitor (captopril) on angiotensin II production, bradykinin degradation, modulation of O₂ production & fibrinolytic activity (58,59, 60 & 61). Increased angiotensin II level appears to induce endothelin-1 activation which is recognized as being one of the most potent vasoconstrictors. Bradykinin degradation via the potent effect of ACE also increases vasoconstriction by diminishing the formation and or action of the endothelium derived relaxant nitric oxide. Furthermore angiotensin II has been shown to stimulate NADH-NADPH oxidases of smooth muscle cells which led to

increased generation of superoxide anions that then degrade nitric oxide. Fibrinolytic activity may also be impaired through generation of plasminogen activator inhibitor (PAI-1), these increased PAI-1 levels may further activates the endothelium. Inhibition of generation of angiotensin II will attenuate smooth muscle cells contraction & will also attenuate the generation of superoxide anions through stimulation of NADH/NADPH oxidase systems of smooth muscle cell. Conceivably, this may lead to less inactivation of nitric oxide. Furthermore, bradykinin- induced augmentation of nitric oxide release by endothelial cells(62).

In the present study, the effect induced by captopril on contractile response of isolated aortic strip was partially blocked by addition of N-nitro-L-arginine to the bath. Also addition of indomethacin produced partial block to the effect of the captopril. In the combined presence of the nitric oxide inhibitor (N-nitro-L-arginine) & the cyclooxygenase inhibitor (indomethacin), the effect of captopril was completely blocked. These data reveal that captopril act directly on vessel wall by generation of nitric oxide & prostaglandins.

Conclusions :

The present study compared the effect of pravastatin and captopril on the contractile response of isolated aortic strip of insulin resistant rats to NA. It was found that captopril & pravastatin improved the response to NA to a similar extent by increasing the bioavailability of nitric oxide & decreasing the oxidative stress.

On the light of this study, it could be concluded that captopril or pravastatin treatment has a comparable beneficial effect on vascular response in insulin resistant rats and accompanying metabolic changes. Furthermore both captopril & pravastatin may be useful in the treatment and / or preventing non-hyperglycaemic insulin resistance states such as obesity, impaired glucose tolerance as well as in the treatment of established NIDDM.

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دراسة مقارنة لتأثير كل من البرافاستاتين والكابتوبريل على إستجابة الشريط الأورطى المعزول للنورادرينالين فى الفئران البيضاء التى تغذت على كمية كبيرة من سكر الفركتوز.

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تعتبر المقاومة لمفعول الأنسولين واحدة من أهم العوامل المسببة للنوع الثانى من مرض البول السكرى وأمراض الجهاز الدورى المصاحبة للسمنة واضطرابات الدهون فى الدم.

يهدف هذا البحث لدراسة تأثير ميكانيكية كل من البرافاستاتين والكابتوبريل على إستجابة الشريط الأورطى المعزول للنورادرينالين وذلك فى الفئران المصابة بمقاومة لمفعول الأنسولين وأيضاً تهدف هذه الدراسة إلى المقارنة بين تأثير كل من البرافاستاتين والكابتوبريل على التغيرات البيوكيميائية المصاحبة لمقاومة فعول الأنسولين.

استخدام فى إجراء هذا البحث ٤٨ فأراً أبيضاً من الذكور، وقسمت إلى مجموعتين رئيسيتين، الأولى مجموعة ضابطة عادية، تكونت من ١٢ فأراً، تغذت بطعام لا يحتوى على نسبة عالية من سكر الفركتوز (غذاء قياسى) لمدة ٨ أسابيع أما المجموعة الثانية فعددها ٣٦ فأراً، تغذت على طعام يحتوى على نسبة عالية من سكر الفركتوز لنفس المدة السابقة وذلك لإحداث مقاومة لمفعول الانسولين. ثم قسمت هذه المجموعة إلى ٣ مجموعات فرعية متساوية كل منه ١٢ فأراً كالتالى:

المجموعة الفرعية الأولى:

ضابطة (تعانى من مقاومة لمفعول الأنسولين) - وأعطيت محلول ملح بالفم فى الأسبوعين الأخيرين من التجربة.

المجموعة الفرعية الثانية :

تعانى من مقاومة لمفعول الأنسولين وأعطيت دواء البرافاستاتين بالفم بجرعة ٢٠ مجم/كجم يومياً فى الأسبوعين الأخيرين من التجربة.

المجموعة الفرعية الثالثة :

تعانى من مقاومة لمفعول الأنسولين وأعطيت دواء الكابتوبريل بالفم بجرعة ٢ مجم/كجم يومياً فى الأسبوعين الأخيرين من التجربة.

وتم قياس حساسية الأنسولين، مستوى الأنسولين الجلوكونز، الدهون (التريجليسيريدات) الكوليستيرول والدهون المنخفضة الكثافة، بالإضافة إلى المالونديألددهيد.

ويمكن تلخيص نتائج هذا البحث كما يلى :

تغذية الفئران طعام يحتوى على نسبة عالية من سكر الفركتوز، أدى إلى إحداث مقاومة لمفعول الأنسولين، كما حدث زيادة ذات دلالة إحصائية فى مستوى الأنسولين الصائم فى المصل وكذلك فى مستوى الدهون منخفضة الكثافة والتريجليسيريدات وذلك دون تغير فى مستوى كل من السكر والكوليستيرول.

عند إعطاء أى من البرافاستاتين والكابتوبريل للفئران المقاومة لمفعول الأنسولين، حدث تأثير إيجابى ومفيد على المقاومة لمفعول الأنسولين وتحسن فى نسبة الدهون والمالونديألددهيد.

أما التجارب على الشريط الأورطى المعزل فكانت نتائجها كالتالى :

حدثت زيادة فى الاستجابة الانقباضية لمفعول النورادرينالين فى الفئران المقاومة لمفعول الانسولين عند مقارنتها بالمجموعة الضابطة العادية.

إعطاء الفئران المصابة بالمقاومة لمفعول الانسولين أى من الكابتوبريل أو البرافاستاتين لمدة أسبوعين قبل عزل الشريط الأورطى، أظهرت تحسناً فى الاستجابة الانقباضية للنورادرينالين.

إضافة أى من إن-نيترو-ال-أرجينين (مبطل لتكوين النيتريك أكسيد) أو الاندوميثاين (مبطل لمفعول أنزيم السيكلو أوكسيجيناز) لمدة ساعة إلى حمام الماء قبل إجراء التجربة، أحدثت إغلاقاً لمفعول كل من البرافاستاتين والكابتوبريل على الاستجابة الانقباضية للنورادرينالين.

وعلى ضوء هذه الدراسة وللمرة الأولى يمكن استخلاص أن إعطاء أى من الدوائين له تأثير متقارب ومفيد على الاستجابة الانقباضية للشريط الأورطى المعزول من الفئران المصابة بمقاومة لمفعول الأنسولين وهذا المفعول يعزى إلى تأثيرهم المضاد للأكسدة وتكوين النيتريك أكسيد.