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POTENTIAL ADMINISTRATION OF LIPOIC ACID AND COENZYME Q AGAINST ADIPOGENSIS: TARGET FOR WEIGHT REDUCTION

[1,5]Maryam A. AL-Ghamdi, [1,2]Hani Choudhry, [1,3]Huda A. AL-Doghather, [1,3,5] Etimad H. Huwait, [1,3,5] Taha A Kumosani and [1,4,5,6]Said S Moselhy

[1]Department of Biochemistry, Faculty of Science, King Abdulaziz University (POBox.80203), Jeddah , Saudi Arabia.[2]Department of Biochemistry, Faculty of Science, Center of Innovation in Personalized Medicine, King Fahd Center for Medical Research, King Abdulaziz University, Jeddah, Saudi Arabia. [3]Production of bioproducts for industerial purposes Research Group , King Fahd Medical Research Center,KAU.[4] Bioactive Natural Products Research Group.[5]Experimental Biochemistry Unit, king Fahd Medical Research Center, KAU.[6] Department of Biochemistry, Faculty of Science, Ain Shams University.

Corresponding author E-mail: moselhy6@hotmail.com

Abstract

Background: Body overweight and obesity were considered as a risk factor for many systemic diseases as diabetic hypertension, cardiovascular diseases, and some cancers. The lipoic acid and Co Q are considered as coenzymes needed for enhancement metabolic rate. The goal of this study is to evaluate the anti-obese effect of lipoic acid alone or combined with Co-Q in rats.
Materials and Methods: Ninety male albino rats (100–150g) were used in this study, divided into six groups (15 each). Group I: Normal rats fed normal diet. Group II: Rats fed high fat diet (HFD). Group III: Rats fed HFD were given lipoic acid (10 µg/kg b w /day) intra-gastric by stomach tube. Group IV: Rats fed HFD were given Co-Q (10 µg /kg b.w/day) intra-gastric. Group V: Rats fed HFD were given lipoic acid (50 mg/kg b w /day) and Co-Q (10 µg /kg b. w/day). Group VI: Rats were given orlistat intra-gastric (10 mg/kg b w/day) as positive control for 6 weeks. Serum was subjected for determination of lipid profile, liver function tests atherogenic factor and lipoprotein lipase.
Results: It was found that treatment with lipoic acid or Co-Q or combined showed increase in the activity of lipoprotein lipase ($P < 0.001$) and reduction of atherogenic effect and obesity index ($P < 0.001$). The effect of combined gives good results than orlistat or individual treatment.
Conclusion: lipoic acid combined with Co-Q increase fat oxidation and prevent fat accumulation. The consumption of lipoic acid daily promotes fat oxidation and prevents its accumulation in visceral tissues. Further studies should be carried out to examine the mechanistic signals of these nutrients that helps in weight management.

Key words: lipolysis, obesity, *lipoic acid*, Co-Q

Introduction

Obesity is defined as accumulation of excess fats in body due to imbalance between energy intake and expenditure. Obesity is considered as one of the risky health problems and the major cause of chronic disease [Buttener etal., 2007]. The etiological factors contributing in obesity include lifestyles, high fat and carbohydrate diet, low fibers intake, exercise, psychological and genetic factors [Van Heek etal.,1997]. The medical problems of weight gain include diabetes, high blood pressure hyperlidemia, hypercholesterolemia and some cancers. The ant obese products include herbal, chemicals, hormones which have adverse effects. Flavonoids and saponin showed promising effects to reduce body weight by different mechanisms [Warden and Fisler, 2008]. Dietary triacylglycerol needs emulsification with bile acids and co lipase before hydrolyzed with pancreatic lipase. The action of lipase is the release of monoacylglycerol and free fatty acids which are absorbed as mixed micelles. Inhibition of this lipolysis decreases the absorption of triglycerides and reduces calorie intake. Weight control management as Orlistat act via inhibition of lipses decreases the dietary fat absorption from the GIT to prevent weight gain and to stimulate loss of weight [Shi and Burn, 2004]. These drugs have serious side effects including deficiency of essential nutrients as polyunsaturated fatty acids and fat soluble vitamins, peptic ulcer, vomiting and nausea. Lipoic acid is one of the important β-complex vitamin needed as coenzyme for pyruvate dehydrogenase enzyme [Barnstorm,1988]. The second action explanation is that it activates metabolism in neurons which increase energy production. This indicated that the thermogenesis effect by lipoic acid is mediated by β-adrenergic stimulation and reduction in energy expenditure [Weibel etal.,1987]. Several studies revealed that supplementation of essential trace elements was effective in treatment of some disease [Li etal., 2007]. One of the essential elements is Coenz-Q which has important biological activity in living cell as in respiratory chain to increase oxidative phosphorylation [Sharma et al., 2005S]. It was reported that Co-Q administration improves glucose tolerance in experimental diabetic animals [Szallasi and Blumberg,1999]. The metabolic role of Co-Q is attributed to its role as potentiate in the interaction with insulin receptor and improved action [Westerterp etal.,2005]. The rational of this work

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is to explore a novel natural lipase inhibitor with more potent and low contraindications. In the present study, lipoic acid alone or combined with Coenz-Q will be tested as antiobese and hypolipidemic action in rats fed high fat diet.

Materials and Methods

Animals

Ninety male albino rats (100–150g) used in this study were obtained from King Fahad Medical Research Center (KFMRC), housed in a standard condition in a temperature-controlled room. Food and water will be given *ad libidum*. The experimental protocols were approved by the Animal Ethics Committee and proceeded according to the guidelines of the Committee at King Abdulaziz University. Rats were divided into six groups (15 each). Group I: Normal rats fed normal diet (10 calories as fat). Group II: Rats fed high fat diet (HFD). Group III: Rats fed HFD were given lipoic acid (10 µg /kg b.w /day) intragastric by stomach tube. Group IV: Rats fed HFD were given Coenz-Q (10 µg /kg/day) intragastric by stomach tube. Group V: Rats fed HFD were given lipoic acid (10 µg /kgb.w /day) and Coenz-Q (10 µg /kg/day). Group VI: Rats were given orlistat intragastric (10 mg/kg b.w/day) as positive control. High-Fat Diet (HFD) contains 58% fat, 25% protein and 17% carbohydrate, lard (13%), cholesterol (1%), vitamin, and minerals (0.6%) as a percentage of total kcal ad libitum, respectively, was administered every day. The doses of lipoic acid and Co-Q were given for 6 weeks; rats were anesthetized with thiopental and blood was collected for serum separation by centrifugation at 4000 rpm for 10 minutes.

Measuring of weight gain, food intake, food efficiency and obesity index

Food intake was measured daily and body weight measured weekly and food efficiency ratio calculated as weight gain (g)/food intake (g). Obesity index measured by Lee index as weight (g)/length (cm) $x10^3$

Assay of serum lipoprotein lipase activity

The enzyme activity was measured using a commercially available triglyceride lipase assay kit (Biorad, England), a porcine co-lipase which is necessary for lipase activity. The reaction mixture of test sample contains 3% DMSO (10 µl), serum (50 µl), pH was incubated for 10 minutes at pH 8.4. Then substrate (25 µL) was added and the reactions were incubated at 37°C for 30 min. Each sample was tested in triplicate and the 580nm optical density [Kawda etal.,1986].

Histopathological examination

Liver tissues were collected after animal sacrifice, fixed in 10% formalin and embedded in paraffin. Sections of about 5-µm thick were prepared and stained haematoxylin daily.

Results

Food consumption in rats fed HFD and treated with lipoic acid or Co-Q or combined for 10 weeks. Food intake of all groups was the same at the start of experiment; however, 4week dependence on HFD resulted in a slight increase in food intake. Following 4week treatment with lipoic acid, or combined with Co-Q resulted in low food intake (P<0.001 and <0.01) respectively when compared to the HFD group. However, Co-Q alone does not exert any change in food intake. Consequently, the body weight in animals fed HFD was statistically significantly higher than normal diet (P<0.001). Lipoic acid combined with Co-Q decreased body weight compared with untreated and rats treated with Orlistat as positive control. The HFD rats showed significantly higher organ weight (liver and kidney).

Effect of lipoic acid or Coenz-Q or combined on lipid profile

Results in fig.1 showed that rats fed on HFD resulted in a marked increase in the levels of serum lipids (total cholesterol, triglycerides, LDL-c, VLDL-c) (P < 0.001) for each and decreased level of HDL-c (P < 0.001) compared with normal group receiving the normal diet. However, treatment with lipoic acid or Co-Q or combined for 10 weeks reversed the hyperlipedimic effect significantly by lowering total cholesterol, triglycerides, LDL-c, VLDL-c (P < 0.001) and elevation HDL-c (p<0.001). Similar results were obtained with the standard drug orlistate. Further, there was a significant increase in the atherogenic index in rats fed on HFD and reduction in the atherogenic index (Table 2).

Effect of lipoic acid or Co-Q or combined on Liver Enzymes

The liver enzyme activities (ALT, AST, ALP and GGT) were significantly elevated in rats fed on high fat diet group allied with a significant increase of liver weight. Treatment with lipoic acid or Co-Q or combined showed a

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hepato-protective effect as indicated by decreased levels of these enzymes. Further, the combined effect is better than individual treatment and orlistat (P<0.01).

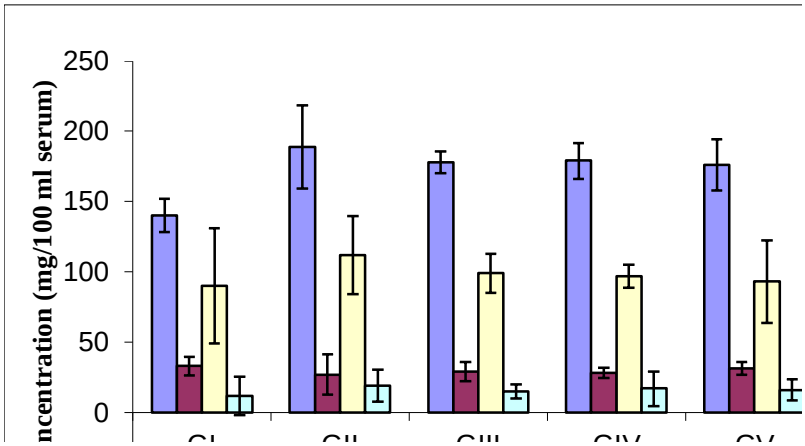

Figure 1: Serum lipid profile in different groups (Mean± SD)

Table 1: The activity of liver function tests in different studied groups (Mean ±SD).

Animal groups	(GpI) Control	(GpII) HFD	(GpIII) HFD+Lipo A	(GpIV) HFD+Co-Q	(GpV) HFD+Lip+CoQ	(GpVI) HFD+Oril
AST(U/L) Mean ±SD	23.5±2.3	60.9±5.0[a,b]	44.7±2.5[a,b]	37.7±2.6[a,b]	26.4±3.3	23.6±3.2
ALT (U/L) Mean ±SD	20.6±2.1	76.9±1.1[a,b]	59.6±2.2[a,b]	42.8±2.5[a]	30.8±3[a]	31 .8±4.0[a,b]
ALP (U/L) Mean ±SD	120.7±13.2	220.9±16.8 a,b	175.8±20.0 a,b	140.9±13 a,b	127.9±6.5	103.9±2.6
GGT (U/L) Mean ±SD	41.8±8	79.3±10[a,b]	68.7±12[a,b]	55.6±13 .	49.8±9	50.8±7.1

a: P < 0.05 vs control, b: *p* < 0.05 vs lipoic acid, c: p < 0.05 vs Liopoic acid +Co Q

Results in table 2 showed that rats fed on HFD resulted in a marked reduction in the activity of serum lipoprotein lipase (*P* < 0.001) and elevation atherogenic effect and obesity index (*P* < 0.001) for each compared with normal rats receiving the normal diet. However, treatment with lipoic acid or Co-Q or combined showed increased the activity of lipoprotein lipase (*P* < 0.001) and reduction of atherogenic effect and obesity index (*P* < 0.001). The effect of combined gives better results than orlistat or individual treatment (Table 2).

Table 2: The effect of lipoic acid and Co-Q on lipoprotein lipase activity, atherogenic index and obesity index of different groups.

	Lipoprotein lipase activity (U/L)	atherogenic index	obesity index
Control Group	41.4±6.5	1.1±0.3	213.9±11.2
HFD group	29.7±4.9	2.1±0.2	249±12.9[a]
HFD+lipoic acid	36.2±3.2	1.7±0.23	227.8±21.8[a]
HFD+Co-Q	35.8±5.1	1.9±0.54	229±19.7[a]
HFD+Lipoic+Co-Q	38.6±4.2	1.4±0.34	227±18[.8a]
HFD+Orilstate	37.7±5.1	1.47±0.12	229±21.l9[a]

a: P < 0.05 vs control, b: *p* < 0.05 vs lipoic acid, c: p < 0.05 vs Liopoic acid +Co Q

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Histological examination of liver of normal showed no cellular degeneration and necrosis (fig 2a). Rat Liver fed on HFD showed marked fatty deposition and foamy degeneration of hepatocytes (fig2b). Rat liver fed HFD and treated with lipoic acid (fig 2c) or Co-Q (fig2d) or combined (fig 4f) showed hepatocytes with decreased deposition of fats with mild infiltration and congestion. Rat liver section of treated with orlistat showed normal hepatocytes and central vein but some degree of swelling (fig 4f).

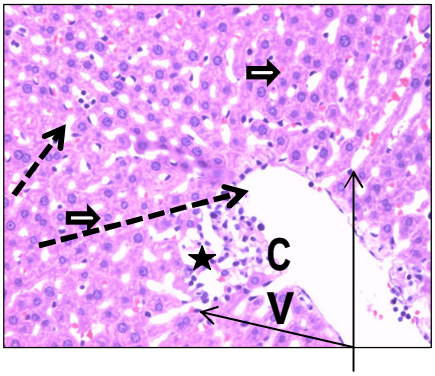

Figure 2a

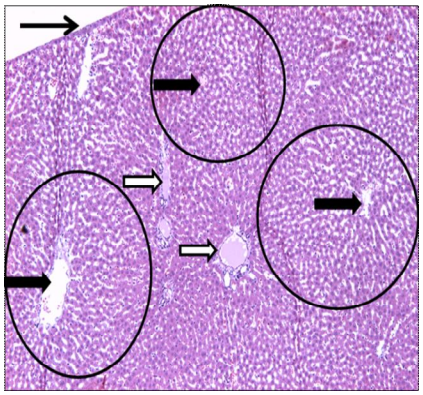

Figure 2b

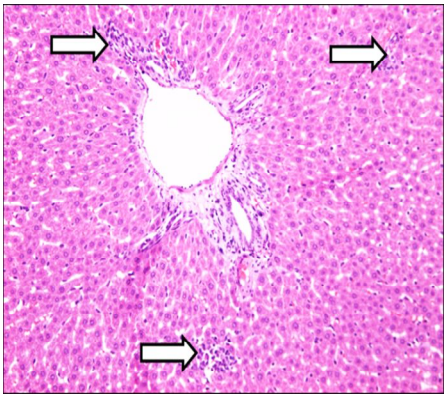

Figure 2c

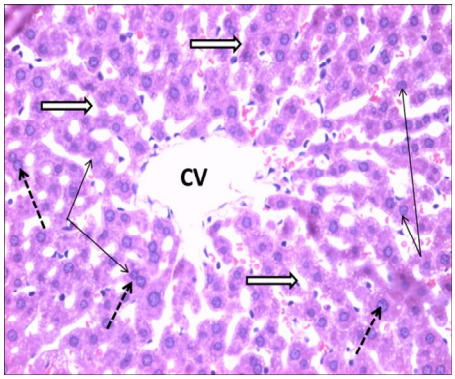

Figure2d

Discussion

The effort of researches for development of ant obesity drugs have been continually conducted. Pancreatic lipase has been validated as one of the important targets in the lipid metabolic process [Watanabe etal., 1988]. High-fat diets used in experimental research contain about 30 to 50% of calories derived from fat. Diets of 50 kcal% fat are used to induce obesity in animals since animals tend to gain more weight, therefore helping researchers to examine effect of compounds in shorter period. Insulin resistance is the major factor that leads to the metabolic syndrome, which comprises obesity, dyslipidemia, hypertension, and hyperglycemia [Watanabe etal., 1987]. Previous studies showed that a high fat diet can lead to visceral obesity in rodent animal models [19]. Dietary Co-Q plays an important role in improving metabolic disorders and hyperglycemia by providing beneficial effects in the insulin action [Belza etal., 2009]. Co-Q improves insulin receptors; enhances their affinity to the hormone, [Sahin etal.,2007]. It has been shown that a HFD results in significant increase in body weight, food intake. Supplementation of lipoic acid or Co-Q or combined reduced body weight and food and intake compared with rats fed HFD. Lipoic acid supplementation increases energy expenditure at least in energy balance [Anderson etal., 2004].

It was reported that utilization of these co-factors have no side effects. However, previous laboratory animal study indicated that capsiacin possesses hypocholesterolemic activity in rats [Kim and Lindman, 2010]. Still, no evidences are available for antiobesity potential. This study has been designed to demonstrate the effect of lipoic acid or Co-Q or combined in high fat diet-induced obesity compared with oristste as positive control.

There was a significant increase in food intake of animals between different groups. There was a significant increase in body weight of rats fed HFD compared with the control group. This reflects that an increase in body weight is dependent on food intake. Treatment of HFD rats with lipoic acid or Co-Q or combined caused a significant

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reduction of body weights compared to untreated. It was suggested that lipoic acid or Co-Q or combined are capable of preventing body weight gain by maintaining the body weight. In the present study, the levels of total cholesterol and LDL-c, TG and VLDL-c were significantly elevated and the level of HDL-c was reduced in rats feed with HFD. Supplementation with lipoic acid or Co-Q or combined showed reversed effect compared with untreated. Lipoic acid showed more potentials than orlistat. Similar results were obtained where treatment with lipoic acid elevates serum HDL-c level and decreases levels of total cholesterol, LDL-c, TG and VLDL-c. Thus, lipoic acid combined with Co-Q possess cardio protective potential by lowering bad cholesterol [Shin etal., 2009]. Obesity index and atherogenic index are taken as markers for cardiovascular disorders; higher value increased risk of developing cardiovascular disease [Tanaka etal., 2008]. Rats fed on HFD resulted in the increased obesity index and atherogenic index. Treatment with lipoic acid or Co-Q or combined significantly attenuated the obesity index and atherogenic index and thus provides cardio protection. The decreased obesity index atherogenic index by lipoic acid or Co-Q or combined supports the cardio protection of these nutrients.

Lipoprotein lipase is a clearing factor to prevent the accumulation of chylomicron and TG in blood. Rats fed on HFD showed a reduction in the activity of this enzyme compared with control. Treatment with lipoic acid or Co-Q or combined enhance the activity to reach normal, but the combined give good results. In order to supplement the results, the histopathological studies were also performed.

Our results showed that rats fed HFD play a role in the pathogenesis of fatty liver or hepatic steatosis associated with obesity. Elevated levels of liver enzymes (ALT, AST, ALP and GGT) are markers of hepatocellular damage and correlate with increased liver weight [Dougkan etal., 2009]. It was found that HFD causes hepatocellular damage, as shown by the marked elevation of serum enzymes (ALT, AST, ALP and GGT) activities and treatment with lipoic acid or Co-Q or combined normalize these elevations. This is supported by histopathological examination that showed liver exaggerated with hepatic steatosis in rats fed HFD. However, treatment with lipoic acid or Co-Q or combined prevent genesis of fatty liver and inhibit infiltration caused by HFD compared with orlistat.

However, supplementation with lipoic acid or Co-Q or combined reverses all the parameters, thus suggesting its weight reducing potential. In summary, the present study showed lipoic acid increased fat oxidation. The consumption of lipoic acid daily promotes fat oxidation and prevents its accumulation in visceral tissues.

Conclusion

It can be concluded that the lipoic acid combined with Co-Q may be important for weight management with no side effects. Further studies will be carried out to examine the mechanistic signals of these nutrients that help in weight management.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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