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EFFECT OF OBESTATIN AND TREADMILL EXERCISE ON LIPID PROFILE AND SERUM MALONDIALDEHYDE (MDA) LEVELS IN RAT MODEL

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ABSTRACT

Objective: The present study investigates the effect of intraperitoneally (IP)-administrated obestatin and short-term treadmill exercise on serum malondialdehyde (MDA) and lipid profile in rat model. Materials and Methods: Forty-five rats weighing 100 ± 5g were selected and divided into five experimental groups; Group-1/control was normally kept and did not receive obestatin-included solution or exercise. Group-2 (placebo) was treated with basal solution (50 ml distilled water). Group-3 was referred to as obestatin-group which was subjected to injection during the experiment with obestatin solution (10 µg obestatin/ rat). Group-4 was known as treadmill-group which was subjected to exercise protocol (15 days treadmill training), and group-5, known as obestatin and treadmill group (OT), was subjected to injection with obestatin and exercise protocol. The exercise-groups were trained for 3-weeks. Results: the treadmill-group was decreased total cholesterol (TC) concentration (67.67 mg/dl), in comparison with control and obestatin-group (79.00 and 78.33 mg/dl, respectively). Similarly with TC level, the triglyceride and HDL cholesterol (HDL-C) was decreased in treadmill-group (triglyceride: 70.66 mg/dl in compared with 87.67 mg/dl in control, and HDL-C: 46.10 mg/dl in compared with 57.33 mg/dl in control; P<0.05). Also, level of MDA was decreased in treadmill- and treadmill-obestatin groups. Conclusion: short-term treadmill exercise significantly reduced plasma lipid profile and MDA levels in rat model. Nevertheless, administration of obestatin had no significant effect on lipid profile and MDA. Furthermore, obestatin-administration in combination with treadmill-exercise did not have synergic effect on plasma lipids, MDA level and total protein in rats.

Key words: Animal model. Lipid profile. Obestatin. Oxidative stress. Treadmill training.

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RESUMO

Efeito do exercício de obestatina e tapete rolante no perfil lipídico e níveis de malondialdeído sérmio (mda) em modelo de rato

Objetivo: O presente estudo investiga o efeito da obestatina administrada por via intraperitoneal (IP), exercício em esteira de curta duração no malondialdeído sérico (MDA) e no perfil lipídico no modelo de ratos. Materiais e Métodos: Quarenta e cinco ratos pesando 100 ± 5g foram selecionados e divididos em cinco grupos experimentais; O grupo 1 / controle foi normalmente mantido e não recebeu solução ou exercício incluído na obestatina. O grupo 2 (placebo) foi tratado com solução basal (50 ml de água destilada). O grupo 3 foi referido como grupo de obestatina, que foi submetido a injeção durante o experimento com solução de obestatina (10 µg de obestatina / rato). O grupo 4 era conhecido como grupo de esteira que foi submetido ao protocolo de exercícios (treinamento de 15 dias em esteira) e o grupo 5, conhecido como grupo de obestatina e esteira (OT), foi submetido à injeção de obestatina e protocolo de exercício. Os grupos de exercícios foram treinados por 3 semanas. Resultados: o grupo da esteira apresentou diminuição da concentração de colesterol total (CT) (67,67 mg / dl), em comparação com o grupo controle e o grupo da obestatina (79,00 e 78,33 mg / dl, respectivamente). Da mesma forma que com o nível de CT, o triglicerídeo e o HDL-colesterol (HDL-C) diminuíram no grupo da esteira (triglicerídeo: 70,66 mg / dl em comparação com 87,67 mg / dl no controle e HDL-C: 46,10 mg / dl em comparação com 57,33 mg / dl no controle; P <0,05). Além disso, o nível de MDA diminuiu nos grupos de esteira e esteira-obestatina. Conclusão: o exercício em esteira de curta duração reduziu significativamente o perfil lipídico plasmático e os níveis de MDA no modelo de ratos. No entanto, a administração de obestatina não teve efeito significativo no perfil lipídico e no MDA. Além disso, a administração de obestatina em combinação com o exercício em esteira não teve efeito sinérgico nos lipídios plasmáticos, nível de MDA e proteína total em ratos.

Palavras-chave: Modelo animal. Perfil lipídico. Obestatina. Estresse oxidativo. Treinamento em esteira.

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INTRODUCTION

Obesity is one of the best known preventable causes of death in the world (Mokdad and collaborators, 2004). Obesity is significantly associated with oxidative stress (specifically MDA level) and lipid profiles (Haung and collaborators, 2015).

Nowadays, challenges of researchers is focused on appetite-regulatory peptides and their potential for solving this global health matter (Tiryaki-Sonmez and collaborators, 2013, 2015; Troke and collaborators, 2014).

In addition to these efforts, often the effect of running-exercises (treadmill) on weight losing and plasma levels of peripheral appetite-peptides is considered (Ghanbari-Niaki and collaborators, 2008; Tiryaki-Sonmez and collaborators, 2013).

In this regard, obestatin has a notable importance in experimental and clinical anti-obesity studies (Ghanbari-Niaki and collaborators, 2008; Tiryaki-Sonmez and collaborators, 2013; Zhang and collaborators, 2005).

Obestatin is a regulatory peptide encoded by the pre-proghrelin gene (Zhang and collaborators, 2005), and it can display effects opposite to those of ghrelin (Gesmundo and collaborators, 2013; Zhang and collaborators, 2005).

In biochemical aspect, obestatin is a ghrelin-related peptide with specific peptidic-structure (Broom and collaborators, 2009).

Initial studies on obestatin, show its positive correlation with body mass index (BMI) and glycaemia (Park and collaborators, 2007).

In the published studies, there is no direct evidence for effect of exogenous or endogenous-obestatin on lipid metabolism, whereas in Vicennati and collaborators (2007), authors have shown considerable effect of obestatin/ghrelin ratio in the pathophysiological parameters of obesity.

As well as, in a newly published study (*in vitro*) conducted by Carpene and collaborators (2018), it's stated that the obstatin in low dosage cannot directly affect lipolysis in human fat cells, whereas greater dosages of this peptide may alters glucose and lipid metabolism in cellular level.

It reported that peripheral obestatin was lower in obese individuals, when compared with lean individuals, and it showing a significant increase in the obese patients after dietary restrictions (Guo and collaborators, 2007).

It shows obestatin may stimulate hyperplasia and hypertrophy in adipose tissue, due to various pathways includes pre-adipocyte proliferation, adipocyte differentiation, and fatty acid uptake (Miegueu and collaborators, 2011). In other hand, obestatin is known as a regulatory peptide with anti-oxidative effect which documented in several studies (Erşahin and collaborators, 2013; Koyuncuoğlu and collaborators, 2017; Razzaghy-Azar and collaborators, 2016).

As well as, the plasma lipidemic-indices and oxidative indices (such as MDA) may affected with short-term treadmill exercise programs, and it's documented in studies on human (Diaz and collaborators, 2011; Ghanbari-Niaki and collaborators, 2013; Greene and collaborators, 2012) and rat (Badalzadeh and collaborators, 2014; Elahi and collaborators, 2016; Lee and collaborators, 2016).

With attention to obestatin potential effect in lipid metabolism (Miegueu and collaborators, 2011) and oxidative stress studies (Erşahin and collaborators, 2017; Koyuncuoğlu and collaborators, 2017; Razzaghy-Azar and collaborators, 2016) and efficiency of treadmill protocols on regulation of lipid profile and oxidative stress (Diaz and collaborators, 2011; Ghanbari-Niaki and collaborators, 2013; Greene and collaborators, 2012), the propose of present study was to investigate the possible effect of short-term treadmill exercise and exogenous obestatin-peptide (peripherally-administrated) on serum lipid profile and MDA level (an indicator of oxidative stress) in rat models.

MATERIALS AND METHODS

Forty-five male wistar rats weighing 100± 5g (6 months of age) were selected for the experiment following routine veterinary examinations. Animals were kept 1 week in 12h lighting/ 12h dark condition under room temperature (22^{oc}).

During the experiment, all animals were fed with standard and formulated diet recognized by laboratory animals enterprise Niroo-Sahand Co©, Tabriz.

Rats were divided into five experimental groups (each group or treatment: 9 rats), based on completely randomized design (CRD):

Group 1: *control* (C); This group was not treated with obestatin and without exercise protocol.

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Group 2: *placebo* which was treated with hormone-free (50 mL distilled water) at two times during the test and it was kept without exercise protocol.

Group 3: *obestatin group* which was subjected to intraperitoneal (IP)- injection at two times with obestatin (50 mL solution contained 10 µg obestatin/ rat). This group was kept under normal conditions without exercise protocol.

Group 4: *treadmill group* which was only subjected to treadmill exercise, according to Ghanbari-Niaki and collaborators (2011) (table 1).

Group 5: *Obestatin and treadmill (OT)* group which had obestatin administration (IP) at two times during the experiment with 50 mL solution containing 10 µg obestatin/ rat and they had treadmill exercise, according to Ghanbari-Niaki and collaborators (2011) (table 1).

Treadmill-Exercise protocol

In our initial research work, this protocol has been applied for studying effect of short-term exercise on serum peptides in trained-rats (Lotfi and collaborators, 2016).

In this experiment, the animals were adapted to the treadmill apparatus for four days (5-lines motorized-driven treadmill - designed by Technic-Azma Co., Tabriz).

The exercise (treadmill) groups were trained for three weeks using the same training protocol suggested by Ghanbari-Niaki and collaborators (2011) who designed to it as a short-term treadmill exercise. The animals were forced to run at 25m/min for 60 min, 5 days/week (table 1).

I.P-injection of obestatin

Lyophilized powder of obestatin (Cad no: O0266, Rat obestatin, Sigma-Aldrich Co., USA) was dissolved in distilled water, in according to Sigma (producer) brochure. The solution was injected intra-peripherally (I.P.) in 50 mL volume containing 10 µg obestatin for each animal. During three-week experimental period, this solution was injected twice, i.e. on the first day and on the seventh day.

Data collection

All the animals were weighed before and after the experimental treadmill exercise. In according to laboratory animal ethics, blood samples were taken from heart after anesthesia.

The The samples were centrifuged were centrifuged and the serum was analyzed for lipid profile and MDA by Elisa kit (Pars Azmoon Biochemical kits, Pars Azmoon Co., Tehran).

The serum lipid profile includes TC, triglyceride, and HDL-C, and MDA are assayed in serum.

The collected data was fed into SPSS V.16 for conducting the statistical analysis. The normality of collected data was analyzed by Kolmogorov–Smirnov test. ANOVA (analysis of variance) was applied to examine the significance differences among the groups of the study (P<0.05).

Then, tukey multiple comparison test (Olleveant, 1999) was used to detect the direction and location of significant difference among the five experimental groups.

Table1 - Treadmill exercise protocol*

Step (week of protocol)	Speed (meter/ min.)	Exercise duration (min./day)
1st	10	10-15
2nd	15-25	15-60
3rd	25	60

Legends: *includes three weeks with two day-offs in each week, designed by Ghanbari-Niaki and collaborators (2011).

RESULTS

The mean values (±SEM) of TC, triglyceride, and HDL-C, total protein, and MDA are presented in table 2, respectively. As presented in table 2, the TC concentration is decreased in comparison with control and *obestatin*-group, and there is no significant difference between *obestatin*-group and *OT*-group. Similarly with TC level, the triglyceride and HDL-C had decreased in *treadmill*-group (P<0.05).

Whereas MDA level is decreased in *treadmill-* and *treadmill-obestatin* groups. For total protein, there is not any significant difference between experimental groups, in other words, treadmill exercise and obestatin administration didn’t have any considerable effect on serum total protein.

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Table 2 - Effect of administration of obestatin and treadmill exercise on serum TC, triglyceride, HDL-C, total protein and MDA in Rat model

Groups	TC (mg/dl)	Triglyceride (mg/dl)	HDL-C (mg/dl)	Total protein (mg/dl)	MDA (nmol/ml)
Group 1 Control; intact	79.00^{a}	87.67 ^{a}	57.33 ^{a}	6.00	44.14^{a}
Group 2 placebo	80.33^{a}	86.00 ^{a}	56.00 ^{a}	5.96	43.01^{a}
Group 3 (obestatin-)	78.33^{a}	79.70 ^{a}	57.00 ^{a}	6.53	41.00^{a}
Group 4 (treadmill)	67.67 ^{b}	70.66 ^{b}	46.10 ^{b}	6.30	21.66^{b}
Group 5 (treadmill and obestatin)	77.00 ^{ab}	78.33 ^{ab}	49.00 ^{ab}	6.27	21.31^{b}
P value	0.0158	0.0454	0.0177	0.1852ns	0.0179
SEM	2.221	3.291	2.326	0.169	2.130

Legends: *Different letters ("a" and "b") show significant difference between mean of groups, and "ab" show not significant dfference (p<0.05). SEM: standard error of means.

DISCUSSION

In Tiryaki-Sonmez and collaborators (2013, 2015), Its aimed that continuous or regular exercise can has a dominant effect on appetite and lipid metabolism. As it is presented in table 2, the findings of the present study revealed that only treadmill exercise led to a significant decline in blood lipidemic indices (lipid profile) includes TC, triglyceride, and HDL-C which was not the case with the rats within other treatments.

Present study had shown that short-term exercise may decrease plasma lipidemic indices in rat model. Infusion of obestatin is not reduces lipidemic indices but may modulate the effect of exercise on these variables (group 5 in table 2, when compared with group 4).

In this regard, decreasing in blood lipid levels in present study (table 2) is in agreement with Greene and collaborators (2012) which reported that exercise and training alter Blood lipid and lipoproteins in human.

Also, our report on effect of treadmill exercise on TC was according to Coll-Risco and collaborators (2015) with states that strength exercise cause decreased TC in obese rats, whereas present study has a difference with their reports (2014) for HDL-C. In their reports HDL-C was increase in trained-animals but in our study it decreased along with other lipidemic indices. It suggested that this difference is occurred because of obesity condition in their study which destroy normal metabolism of lipids, and also differences in exercise protocol.

So that in Sertié and collaborators (2015), exercise training (similar training condition with present study), decreases all lipid measures in experimental rats. The possible mechanism is lipolysis and decreased adipocyte size with direct response to exercise, which is documented by Askew and Hecker (1976), and the group with both treadmill exercise and obestatin were not significantly different from the control group. In other words, the infusion of exogenous obestatin had no considerable impact on the plasma lipid level (table 2).

With attention to non-significant effect of administrated obestatin on lipidemic measures (table 2), it seems that obestatin is a peptide for only adjust plasma lipids (or lipid metabolism) in normal condition or in physiological concentrations, and also it not have direct hypo-effect. This idea is recognized in a review by Gargantini and collaborators (2013). They had suggests, obestatin display different function in adipocytes, and it regulate adipocyte function, and lipid metabolism. So, our findings for effect of obestatin on plasma lipids (table 2) are in agreement with Gargantini and collaborators (2013).

In present study, groups 4 and 5 had significantly low rate of serum MDA in compared with control (table 2).

This finding indicates that short-term treadmill training has reduced MDA level. This finding is in agreement with Cechetti and collaborators (2012) who concluded that Forced treadmill exercise can prevents oxidative stress in experimental rats, whereas Dehghan and collaborators (2014) had stated that exhaustive exercise with normal dietary regiment may has an oxidative effect in trained animals.

Our finding is based on the effect of short-term treadmill training on reducing MDA is in according to the findings of Tas and collaborators (2017), who show that moderate exercise can improve antioxidant activity in trained-rats.

The possible mechanism of this effect may be include the increased expressions and activities of key antioxidant enzymes (Brooks

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and collaborators, 2008; Huertas and collaborators, 2017), as well as, exercise induces the mobilization of non-enzymatic antioxidants to mitochondrial membranes and prevent their damage (oxidation) (Huertas and collaborators, 2017; Quiles and collaborators, 1999).

Argano and collaborators (2012) had shown that, the obestsatin regulate oxidative balance and promote phosphorylation, modulation of AMPK and pro-survival kinases in cellular level, more than having a strong antioxidant effect. In clinical condition, the obestatin may have a notable trapautic effects (Zhang and collaborators, 2017).

In present study, infusion of exogenous obestatin didn't alter MDA levels of serum (table 2), and it may show only regulatory effect of peptides (more than antioxidant effect).

CONCLUSION

The conclusion to be made based on the results of this study is that short-term treadmill exercise significantly reduced plasma lipids in rats.

Nevertheless, IP-injection of obestatin had no significant impact on plasma lipids. In general, it can be maintained that short-term treadmill exercises can have hypolipidemic effect.

Furthermore, administration of obestatin in combination with treadmill-exercise did not have notable impact on plasma lipids and total protein in animal model.

Moderate treadmill exercise may decrease malondialdehyde (MDA) as an index of lipid peroxidation.

It seems infusion of obestatin had no additive or synergy effects in short-term exercises for plasma total lipids, total protein and MDA level.

Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

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