Nutrition and Food Sciences Research Vol 5, No 2, Apr-Jun 2018, pages:3-10

Original Article

The Effect of Peripheral Injection of Leptin on Biomarkers of Aging in Calorie Restricted Rats

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Received: November 2017 **Accepted:** February 2018

ABSTRACT

Background and Objectives: Calorie restriction (CR) is one of the proven methods of extending lifespan and slowing aging. Leptin is a nutritionally regulated adipokine that has been proposed as a possible key signal in the adaptive responses relevant to CR. Under CR, plasma leptin levels decrease, thus it was hypothesized that leptin administration may counteract CR-induced weight loss. Therefore, the effect of leptin administration on modulating CR-induced alterations in some biomarkers of aging was investigated in a rat model.

Materials and Methods: Fifty male Wistar rats were fed either ad libitum (AL) or 40% calorie restricted diet for 11 weeks. Then each group randomly assigned to receive 0.5 mg/kg/day intravenous leptin or saline, for 3 days. Fasting blood glucose, insulin, and leptin levels as well as body temperature were measured at the end of the treatment.

Results: After CR, all variables including body weight, BMI, body temperature, serum levels of glucose, insulin and leptin decreased significantly compared to the AL group. After 3 days of leptin treatment, no statistically significant differences were observed in body weight, BMI, serum glucose and insulin levels compared to the saline treatment. Body temperature did not change after leptin administration in CR subgroups, but it was significantly higher in AL-leptin compared to AL-saline group.

Conclusions: Based on these findings, administration of recombinant leptin was not effective in modulating the alterations of aging biomarkers induced by calorie restriction.

Keywords: Aging, Body temperature, Calorie restriction, Insulin, Leptin

Introduction

Today gerontology is one of the largest study areas in the world. Increased life expectancy along with healthcare expenditures allocated for these growing part of the population has raised this issue as a prominent topic in global health (1). Elucidating the mechanisms that affect longevity, will be a major step in understanding the age dependency of chronic human diseases and will help to improve the quality of life in old age (2).

Among different methods examined for extending lifespan and slowing aging, calorie restriction (CR) is the only method that demonstrated the most consistent results by many laboratories, using various dietary techniques and animal models (3-7). It seems the effect of CR is secondary to the hormonal, physiological, and biochemical adaptations (8). In fact, CR has a unique ability to modulate two basic life processes; the biological aging processes and the pathological processes (9).The consistent positive effects of CR on health and longevity among different studies, create interests to recognize the involved mechanisms and develop CR mimetic pharmaceuticals, because even if results from these studies could eventually substantiate CR as an

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[DOI: 10.29252/nfsr.5.2.3]

effective pro-longevity strategy for humans, the utility of this intervention would be hampered because of the degree and length of restrictions required. As an alternative strategy, new research has focused on the development of CR mimetics. The objective of this strategy is to identify compounds that mimic CR effects by targeting metabolic and stress response pathways affected by CR, but without actually restricting caloric intake (10).

From an evolutionary point of view, metabolic and neuroendocrine systems are being used during food deprivation to increase the chance of survival. In this way, the total energy consumption is changed from fat and carbohydrates to fat exclusively (11).These aspects, point to the presence of a signaling molecule related to adipocytes regulates neuroendocrine system and energy consumption. Role of leptin as a mediator affects energy homeostasis and appetite via both peripheral and central routs is considered in this regard (12) .As serum leptin decreases due to calorie restriction (13), it was hypothesized that leptin administration may counteract calorie restriction-induced weight loss.

On the other hand, among different biomarkers attributed to aging, lower body temperature and insulin levels have been shown to have a key role (3, 14). There is little information about the effects of leptin administration on aging biomarkers in CR. Therefore, the present study was conducted to investigate the potential role of leptin administration on modulating CR-induced alterations in weight as well as some biomarkers of aging in a rat model.

Materials and Methods

Fifty male Wistar rats (five weeks old) were used based on the experimental studies on rodents, the most positive effects of calorie restriction on life span will happen when this intervention begin at the earliest stage of life (15). The animals were kept separately in plastic cages (plexiglass) (20*20*30), with temperature range of 22-26°*C* and 12-h light/dark cycle schedule and free access to tap water. Wistar rats were fed ad libitum with AIN-93G purified diets of laboratory rodents for one week (adaption phase) (16, 17). The mean amount of daily food consumed by rats was measured at the end of this period. Then rats were classified according to their body weight and temperature, and randomly assigned to two groups; the basic group that had ad libitum food intake (AL) and 40% calorie restriction group (CR). No significant difference between the two groups was shown by independent sample T-test ($p=0.92$ for weight and $p=0.73$ for body temperature). Diet composition in the two groups (nearly isocaloric at 3.6 kcal/g) is shown in Table 1.

Table 1. Composition of the AIN-93G and AIN-93M Diet Formulated for Calorie Restriction Studies

Ingredient	AIN-93G		AIN-93M	
	AL	CR	AL	CR
Corn Starch	529.48	210.52	620.7	400
Casein	200	333.28	140	233.3
Sucrose	100	100	100	100
Soybean oil	70	116.73	40	66.7
Cellulose	50	67.8	50	67.8
Mineral Mix*	35	58.3	35	58.3
Vitamin Mix**	10	16.7	10	16.7
L-Cystine	3	5	1.8	3
Choline Chloride	2.5	4.2	2.5	4.2
Butyl Hydroquinone	.014	.025	.008	.013

†Diet composition is shown as g/kg. Diets are nearly isocaloric at 3.6 kcal/g.
AL= ad libitum-fed; CR = calorie restriction

***Mineral mix:** Calcium carbonate, anhydrous, 40.04% Ca; Potassium phosphate, monobasic, 22.76% P, 28.73% K; Potassium citrate, tri-potassium, monohydrate, 36.16% K; Sodium chloride, 39.34% Na, 60.66% Cl; Potassium sulfate, 44.87% K; 18.39% S ; Magnesium oxide, 60.32% Mg ; Ferrie citrate, 16.5% Fe; Zinc carbonate, 52.14% Zn; Manganous carbonate, 47.79% Mn; Cupric carbonate, 57.47% Cu; Potassium iodate, 59.3% I; Sodium selenate, anhydrous, 41.79% Se; Ammonium paramolybdate, 4 hydrate, 54.34% Mo

** **Vitamin Mix:** Nicotinic acid, Pantothenate, Pyridoxine, Thiamin, Riboflavin, Folie acid, Vitamin K, D-Biotin, Vitamin B-12, Vitamin A, Vitamin D3, Vitamin E

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For administrating 40% restriction in the CR group, the mean daily intake of AL group was measured and with eliminating 40% of its weight, considered as CR group's diet. The minimum period required to demonstrate the effects of energy restriction is 2- 3 month (15). So in the current study, calorie restriction was applied for 11 weeks. During this phase, the reduction of caloric intake by 40% of ad libitum consumption was considered for the CR group by a regular weekly monitoring - while maintaining adequate nutrient intake. Depending on puberty age of rats, diet was formulated based on AIN-93G purified diets in the first 4 weeks and AIN-93M purified diets for later weeks. After 11 weeks of CR, 8 rats in each group were selected randomly. Then after 12 hours of fasting, anesthetized and scarified for blood collection. Serum was isolated by centrifugation and stored at -20^{o}C. The remaining animals in each group were randomly divided to two groups to receive recombinant leptin (R & D Systems, Sigma) or placebo (0.01 M phosphate-buffered saline, pH: 7.2), intravenously (IV) at doses of 0.5 mg/kg/d for 3 days. Injections were administered in two equal doses (7:00 and 19:00). After these 3 days, blood samples were taken (Figure 1). Weekly measurement of weight was done. Rectal probe thermometry was used every 15 days to measure body core temperature. Each rat was held at the base of its tail as the probe was inserted ~2.5 cm into the rectum. The probe was removed after the animal's temperature stabilized 30–60 sec later. The thermostat was accurate to 0.1°C. Serum glucose was measured by enzymatic methods. Insulin and leptin were measured using rat ELISA kits (Biovendor & IBL Company respectively).

Before starting the study, we considered 3 extra rats in each group for preventing potential losses to follow-up. After randomization in the first phase, these rats were labeled and kept on the same protocol. During the second phase, we had two losses in the CR group because of some water supply problems that were replaced with reserved ones.

Data were analyzed using the SPSS version 15. The Shapiro-Wilk test was used for ensuring normal distribution of all quantitative data. Related p value for all variables was more than 0.05. Independent sample T-test was used to compare variables before treatment phase (leptin or saline) in both dietary groups and also used to compare variation of variables within CR and AL groups after leptin or saline treatment. Two-way ANOVA was used to compare variables between different groups (4: leptin and saline subgroups) as well as the percentage of their variation at the end of the study. The results are presented as mean ± standard deviation (SD). The p values of ≤0.05 were considered as statistically significant.

This study was approved by the animal experimentation ethics committee of the Tehran University of Medical Science (Code Number: 132/8682).

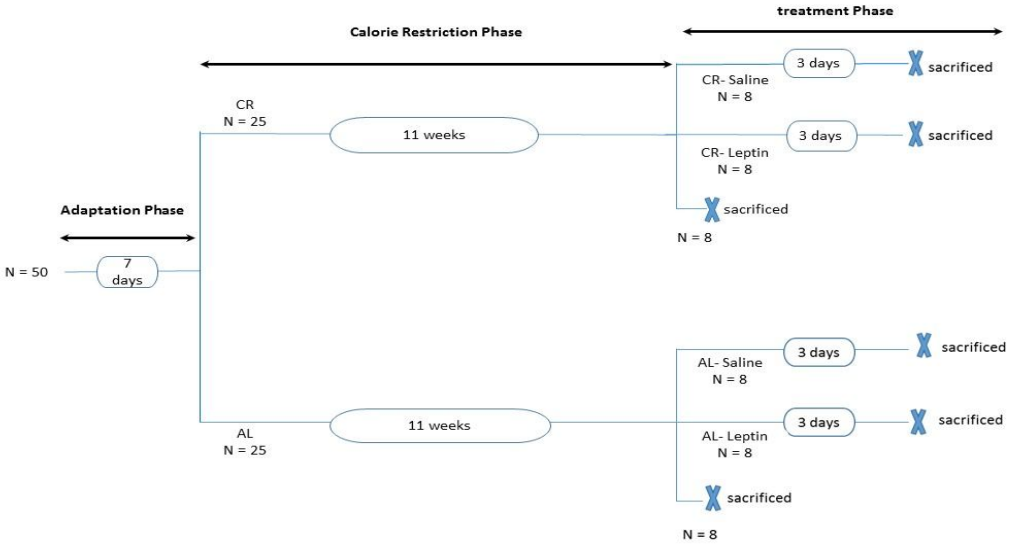

Figure 1. Study Flowchart

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Results

Body weight and BMI were significantly lower in the CR compared to AL group (216.31 ± 5.75 vs 302.21 ± 16.71 gr and 0.52 ± 0.03 vs 0.65 ± 0.03 gr/cm2). Also, body temperature (p=0.001), serum levels of glucose (p=0.035), insulin (p=0.021) and leptin (p<0.001) were significantly reduced in the CR group (table 2).

Changes in variables after the second phase of the study in different groups are given in Table 3.

After 3 days of leptin administration, none of the variables, including body weight, BMI, body temperature, serum levels of glucose and insulin were significantly different between leptin treatment and control groups. Body temperature did not change after leptin injection in the CR-leptin compared to CR-saline group (36.53 ± 0.22 vs 36.63 ± 0.18 ºC, p=0.34); but it was significantly higher in AL-leptin compared to AL-saline group (37.23 ± 0.17 vs 36.97 ± 0.1 ºC, p=0.02).

After the injection phase, statistically significant differences were observed between CR and AL groups in body weight (P<0.001), BMI (P<0.001), body temperature (P<0.001), and serum levels of glucose (P=0.001) and insulin (P=0.047), regardless of the type of treatment (saline or leptin). But no meaningful differences were observed between the two injection groups, regardless of the type of diet. Data analysis between four groups with two-way ANOVA showed interaction effect of diet and injection on these markers were not significant, apart from body temperature. The combined effect of diet and leptin injection on body temperature was significant (p=0.007).

Table **2.** Body weight, BMI, body temperature, and serum levels of glucose, insulin and leptin after CR

Variables	n	AL† (mean ± SD)	CR‡ (mean ± SD)	P value
Weight (g)	25	302.21 ± 16.71	216.31 ± 5.75	0.0004
Body temperature (ºC)	25	37.04 ± 0.39	36.5 ± 0.32	0.001
Glucose (mg/dL)	8	111.83 ± 25.21	79.8 ± 15.35	0.035
Insulin (ng/mL)	8	2.32 ± 0.47	1.33 ± 0.19	0.021
Leptin (ng/mL)	8	4.8 ± 0.87	1.32 ± 0.33	0.001

†AL = ad libitum fed group
‡ CR = calorie restricted group

Table 3. Body Weight, BMI, Body Temperature, Serum Glucose, Insulin and Leptin after Leptin Administration in CR and AL group

Variables	CR			AL		
	CR-leptin†	CR-saline‡	P value	AL-leptin§	AL-saline؏	P value
Weight (g)	221.56 ± 2.3	224.8 ± 4.64	0.1	315.12 ± 8.2	313.25 ± 11.5	0.71
Body temperature (ºC)	36.53 ± 0.22	36.63 ± 0.18	0.34	37.23 ± 0.17	36.97 ± 0.1	0.02*
Glucose (mg/dL)	97.3 ± 13.34	91.8 ± 9.02	0.42	122.6 ± 22.34	118.5 ± 9.46	0.74
Insulin (ng/mL)	1.37 ± 0.45	1.46 ± 0.6	0.85	1.74 ± 0.64	2.33 ± 0.96	0.27

† CR-leptin = calorie restricted group with leptin injection
‡CR-saline = calorie restricted group with saline injection
§ AL-leptin = ad libitum fed group with leptin injection
؏ AL-saline = ad libitum fed group with saline injection
* p < 0.05

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Discussion

As expected, no significant changes were observed in weight. It was maybe due to low administered doses, short duration and also the method of injection. Leptin affects food intake, body weight and energy expenditure centrally, so central injection needs to be in very little doses of leptin compared with peripheral methods (18, 19). For example Halaas *et al.* reported subcutaneous administration of leptin for 14 days to wasted mice led to weight loss with dose dependent patterns while chronic intracerebroventricular (ICV) injection of leptin for 4 weeks with 3ng/hr or more resulted in reduction and complete depletion of visible fat tissue. In that study, peripheral administration of leptin to obese mice, resulted in weight reductions, but their sensitivity to leptin were less than the wasted mice (20). Based on animal studies, plasma leptin level is positively related to fat mass and leptin injection reduces food intake and fat content in healthy models (21). In current study, there were no meaningful changes in body weight; consequently, the BMI did not change significantly.

Peripheral injection of leptin was expected to cause reductions in serum insulin levels. Although insulin levels in the leptin treatment groups (CR-leptin and AL-leptin) were less than the saline groups, this change was not significant. This result is consistent with Ahima *et al.*'s findings, as they observed exogenous leptin could not alter insulin levels of starved mice compared to saline group (18). Merrison *et al.* also showed that intracerebro-ventricular (ICV) injection of leptin for 8 days in ewe lambs which were on calorie restricted diet for 14 weeks, did not affect the insulin levels (22). In other studies, leptin administration without calorie restriction caused a dose-dependent decrease in plasma insulin levels compared to saline group (23). In another study by Ramsay *et al*, a bolus injection of 200 µg/kg and 500 µg/kg leptin to carotid artery of pigs could acutely decrease insulin levels (24). Maybe the amount of increase in leptin levels is an important parameter in manifestation of its effects. In addition, it seems that the leptin injection method plays an important role in changes of insulin level. Muzumdar *et al.* compared the effect of short term ICV vs IV leptin administration on insulin signaling. They could show leptin affects insulin levels mainly through central mechanisms (25). Park *et al*. also supported this finding by a long term intervention. They reported that 3ng/hour of ICV leptin injection to normal and diabetic rats for 4 weeks reduced insulin levels and enhanced insulin sensitivity (26). Overall, it seems that the effect of leptin administration on serum insulin levels depends on dosage, duration and method of treatment (central or peripheral).

There were very few studies on the effect of leptin on glucose levels and homeostasis after calorie restriction. In the current study, serum glucose levels were not statistically different between leptin and saline treatment groups in CR and AL. Some studies (without calorie restriction) reported that both central and peripheral leptin injection can enhance glucose uptake by skeletal muscles (27-29), although others did not support these findings (30-32). In fact, some studies reported leptin can affect glucose homeostasis without any changes in serum glucose levels (26, 33, 34). Leptin affects glucose metabolism through possible mechanisms such as increasing insulin sensitivity and suppressing hepatic glucose production. CNS, especially hypothalamus, is also involved (26, 33, 35). On the other hand, leptin affects glucose metabolism and insulin sensitivity by both weight and fat mass changes through dependent and independent mechanisms (36, 37). The unchanged serum glucose levels in the present study may be partly due to dosage and duration of leptin administration. Although it may be related to unchanged weight and insulin levels, too.

Body temperature has been emphasized as a main component of energy homeostasis in experimental studies (13). The effect of CR on decreasing body temperature is widely accepted. Moreover, there is a reverse relationship between body temperature and lifespan (38). In fact, even a small decline in body temperature can increase lifespan significantly; regardless of energy intake status. Therefore, it seems that lower body temperature during CR, may be one of the mediating mechanisms for increasing longevity (13). After leptin administration, changes in body temperature were not different between CR subgroups in the current study but were significantly higher in the AL-leptin group compared to control group. This finding has been supported by other studies. Central (39) and peripheral leptin administration (40) in rats, induced significant changes in body temperature. No changes were

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found in body temperature in the CR group This may be explained by down regulation of leptin receptors on TRH-TSH axis; because in energy restriction, as it is a life threatening situation for organisms, neuroendocrine and metabolic systems involved, maximize the survival through consuming the least amount of energy (41). However, no definitive conclusion could be made because thyroid hormones were not measured before and after the leptin treatment in the current study. Legradi showed that intracerebroventricular injection of leptin to fasting mice prevents the reduction of T3 and T4 levels and production of pro TRH messenger RNA (42). It is important to notice that the above study was done on the basis of short term fasting; so it could not have important effects on leptin receptors. While our study was designed for relatively long term calorie restriction; which gives enough time for the above-mentioned modifications. Rosenbaum *et al.* reported in models received subcutaneous leptin for 5 weeks after 10% weight loss; changes of thyroid hormones were frustrated by administration of substitute leptin doses (43). With respect to the similarity in design between Rosenbaum and our study, and the fact that thyroid hormones are the main factors in body temperature regulation and basic metabolic rate; similar findings would be probable with increasing duration and doses of treatment and also measuring thyroid hormones. Campfield *et al.* expressed the role of leptin in direct regulation of TRH promoter function (44). In fact, with more stimulation of leptin receptors on TRH-TSH axis, release of T3 and T4 hormones will increase which leads to higher basal metabolism (40, 44, 45).

The main limitation of our study was short term treatment of leptin. Maybe, with increased intervention time or higher doses of leptin, expected changes in study variables would be more apparent.

Conclusion

According to our results, administration of recombinant leptin to calorie restricted rats, at the doses and schedule that had been studied, was not effective in modulating the alterations of aging biomarkers induced by calorie restriction and leptin is not a key signal in the adaptive responses induced by calorie restriction in our model. Further studies are needed to assess the effect of longer and different doses of leptin administration on aging biomarkers in chronic CR models.

Acknowledgement

The authors would like to thank Research Deputy of Tehran University of Medical Sciences for funding this research. We also thanks Mrs Friba Fatehi and Mrs Mahnaz Zareyi, the laboratory technicians for their assistance in performing laboratory tests.

Financial disclosure

The authors declare that there is no conflict of interest.

Funding/Support

This research was approved and funded by research deputy of Tehran University of Medical Sciences with the grant number 132/8682.

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