

ORIGINAL ARTICLE

The Impact of High-Fat Diet-Induced Obesity on Erythropoietin (EPO) level in Rat Model

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ABSTRACT

Background: Obesity is a multifactorial disease that is associated with various metabolic syndromes. Erythropoietin (EPO), traditionally recognized for its role in red blood cell production, has been identified as a pleiotropic hormone with diverse physiological functions. The aim of this study was to investigate how high-fat diet obesity in rat model influenced the level of EPO in both serum and brain tissues.

Methods: Twenty adult male Wistar rats were randomly divided into two groups and weighed. The control group received a standard diet, while the experimental group was fed a high-fat diet (2.5% olive oil, 1% cholesterol, and 1% cholic acid as meals to the special rodent diet) for 30 days. Blood and brain tissue samples were collected at the end of the study. EPO level in serum and brain homogenates were measured using enzyme-linked immunosorbent assay (ELISA).

Results: The obese group showed significant weight gain compared to control. Serum EPO level in obese rats was significantly lower than the control group. In contrast, brain EPO level was higher in obese group than in the control group, though it was not significant. Furthermore, in the obese group, brain EPO concentration was significantly higher than the serum EPO level, while in control, brain EPO was lower than serum EPO, but without significant difference.

Conclusion: Our findings have important implications for understanding the dual role of EPO in peripheral and central metabolic regulation during obesity. Enhancing brain EPO signaling or increasing systemic EPO to appropriate levels might offer new therapeutic for obesity and related metabolic disorders.

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Introduction

Obesity is a global health challenge characterized by excessive accumulation of body fat, which impairs normal metabolic functions and increases

the risk of various chronic diseases (1, 2). According to the World Health Organization (WHO), the global prevalence of obesity has risen dramatically, with projections estimating nearly one in five

men and one in four women to be obese by 2025. Furthermore, overweight and obesity surge in children and adolescents aged 5 to 19 years (3). Obesity is one of the main causes of chronic non-communicable diseases and associated disabilities. It is linked to some disease such as hypertension, cardiovascular disorders, insulin resistance, and certain cancers (4-7).

In many developing countries, obesity often coexists with malnutrition and has wide-ranging social and psychological consequences (8). Multiple factors contribute to weight gain and obesity; while genetic factors play a role and behavioral and environmental effects are key drivers of the obesity epidemic (9-11). Body mass index (BMI) is closely correlated with an increased risk of developing some metabolic syndromes such as type 2 diabetes, hypertension, cardiovascular disease, dyslipidemia, glucose intolerance, insulin resistance, and some cancers. In chronic kidney disease (CKD), a strong association has been observed between BMI and the relative risk of disease progression (1, 2, 12). Given the impact of obesity on health, one key to developing effective treatments lies in the understanding of molecular regulators that control body weight and fat metabolism (13).

Erythropoietin (EPO) is a glycoprotein hormone primarily produced by the kidneys in response to hypoxia or anemia, stimulating the bone marrow to increase red blood cell production (14, 15). Oxygen pressure directly and low hemoglobin level indirectly stimulate EPO production. EPO is used to treat anemia, especially in chronic kidney disease (16, 17). Beyond its classical hematopoietic role, EPO and its receptor (EpoR) are expressed in various non-hematopoietic tissues, including the brain, skeletal muscle, and adipose tissue (18-21). A comprehensive review suggests that EPO significantly contributes to whole-body metabolic homeostasis through its effects on adipose tissue, skeletal muscle, and liver, independent of its classical role in erythropoiesis (22, 23). In addition, emerging evidence indicates that EPO influences glucose metabolism, fat oxidation, and energy balance. For instance, EPO administration has been shown to improve insulin sensitivity, reduce fat mass, and protect against weight gain in animal models (24, 25). The protective effect of EPO against diet-induced obesity has been studied before. The researchers employed gene electro-transfer to achieve supra-physiological EPO expression in skeletal muscles, resulting in approximately 100-fold increase in serum EPO level. The investigators observed that EPO-overexpressing mice fed a high-fat diet exhibited a remarkable 23% reduction in body weight compared to control,

primarily attributed to a 28% decrease in adipose tissue mass (24).

In one study, the effect of high-dose EPO (up to 1000 units per kg) on hematocrit level, body weight, body composition, glucose metabolism, food intake, and physical activity during a high-fat diet obesity suggested that the non-hematopoietic effects of EPO may only be partially responsible for the metabolic effects of EPO treatment (26). As mentioned earlier, the expression of multicellular EpoRs provides EPO activity beyond its known regulation of erythrocyte production. It was shown that EPO was expressed in the brain, astrocytes, and neurons too (27).

In the brain, EPO and EpoR are present in neurons and glial cells, particularly in regions critical for appetite and energy regulation such as the hypothalamus. EPO may regulate neuroendocrine functions by modulating the activity of pro-opiomelanocortin (POMC) neurons, which suppress appetite and increase energy expenditure. EPO treatment has been shown to enhance POMC expression anorexic neurons in the hypothalamus. Additionally, in the pituitary gland, EPO modulates the secretion of POMC-derived peptides, adrenocorticotrophic hormones, which regulate physiological and metabolic stress responses (26). It was shown that erythropoietin minimizes brain tissue damage after ischemia and has the potential to protect the brain from ischemic injury by modulating inflammatory responses and reducing neuronal damage (28). Despite these insights, little is known about how endogenous EPO level changes during obesity and whether alterations in brain and serum EPO contribute to metabolic regulation in this condition. Considering the increasing trend of obesity in communities, this study investigated how a high-fat diet-induced obesity model affected EPO concentrations in the serum and brain of male rats, aiming to clarify the potential role of EPO in obesity-related metabolic changes of rat model.

Materials and Methods

Experimental animals were used in accordance with the principles of the International Guidelines for Biochemical Research Involving Animals (29). This project was approved by the Ethics Committee of Babol University of Medical Sciences, Babol, Iran (IR.MUBABOL.HRI.REC.1400.089). Wistar rats were purchased from the Pasteur Institute in Tehran and bred in the animal house of Babol University of Medical Sciences, Babol, Iran. They were housed under controlled conditions (25±2°C, 50% humidity and 12 h light-dark cycle). Twenty adult male Wistar rats were randomly divided into two groups (n=10 each): control group was fed a

regular diet and experimental group received a high-fat diet for 30 days. The high-fat diet included 2.5% olive oil, 1% cholesterol, and 1% cholic acid added to standard rodent feed. Rats were weighed on days 1, 15, and 30.

After 30 days, blood samples were collected from the orbital sinus. Serum was separated by centrifugation at 3000 rpm for 10 minutes to determine the erythropoietin level. Then, rats were anesthetized through intraperitoneal injection of 10% ketamine (50 mg/Kg) and 2% xylazine (15 mg/Kg, Alfeslan, Nederland), and rats' brains were extracted, weighed and placed in phosphate saline buffer (PBS) at twice the brain weight. It was homogenized with a homogenizer (LABTRON, UK) at 12000 rpm for 20 seconds and mixture centrifuged at 15000 rpm for 20 minutes at 4°C. The supernatant was kept at -80°C for further work. Also, there were no exclusions (30).

Serum and brain erythropoietin levels were measured by ELISA using the erythropoietin ELISA kit (LEGEND MAX™ Rat Erythropoietin, USA). The standard erythropoietin solution was prepared at concentrations of 500, 250, 125, 62, 62, 32, 16, 8, 4, and 2 pg/mL according to the kit manufacturer's protocol. Absorbance was read at 450 nm with background correction at 570 nm.

Delta parameter (net absorption) was obtained from the following equation: $\Delta = OD_{450} - D_{570}$.

The adsorption graph was plotted against standard concentrations. Serum and brain erythropoietin concentrations were obtained using standard curves. For data analysis, the Kolmogorov-Smirnov test was used to check the normality of the final data distribution. Data were analyzed using one way ANOVA to compare EPO levels between groups. Differences were considered statistically significant at $p < 0.05$. All statistical analyses were performed using SPSS software (Version 20, Chicago, IL, USA).

Results

Rat weight was measured on days 1, 15, and 30. Both the control and high-fat diet groups showed weight gain during the 30-day period (Table 1). However, rats fed the high-fat diet experienced a significantly greater increase in body weight (approximately 119 g) compared to the control group (approximately 21 g) ($p = 0.000$), confirming the development of diet-induced obesity. Serum EPO concentration was measured by using the

standard erythropoietin curve. The serum EPO concentrations were significantly decreased in the high-fat diet (9.504 pg/mL) group compared to the control group (22.975 pg/mL) ($p = 0.007$), indicating that obesity suppresses circulating EPO levels. The concentration of EPO in the brain of the high-fat diet group (24.389 pg/mL) was higher than the control group (18.59 pg/mL), though this difference did not reach statistical significance ($p = 0.119$). This suggests a trend towards increased local brain EPO production in response to obesity. In obese rats, brain EPO concentration was significantly higher (24.389 pg/mL) than the serum level (9.504 pg/mL) ($p = 0.000$). Conversely, in controls, brain EPO was lower (18.59 pg/mL) than serum level (22.975 pg/mL) without statistical significance ($p = 0.273$).

Discussion

The diet ingredients have a pivotal role on cell function (31) and the prevalence of obesity (32). In this relation, EPO administration has been shown to improve insulin sensitivity, reduce fat mass, and protect against weight gain in animal models (24, 25). This study provided an insight into how obesity modulated EPO level differently in the serum and brain of rats. The significant reduction in serum EPO observed in obese rats may reflect altered renal production or increased EPO clearance, consistent with previous studies linking low circulating EPO to metabolic disturbances. Reduced serum EPO levels could contribute to impaired erythropoiesis or indicate systemic changes in oxygen sensing during obesity (21). Supporting our findings, Katz *et al.* investigated blood glucose level and body mass in rats overexpressing human EPO, which led to an elevated serum EPO level. Their results demonstrated that increased EPO reduced blood glucose across various models. Interestingly, obese rats in their study exhibited decreased EPO level associated with weight gain, consistent with our observations of reduced serum EPO level in obese rats. These findings suggested that obesity may suppress EPO production or increase its utilization (21).

A further research examined the effect of EPO administration on obesity and found no significant correlation between serum EPO level and annual weight change in 109 healthy individuals, although notable gender differences were observed. Specifically, non-hematopoietic endogenous EPO

Table 1: The average rat weight on the first, fifteenth, and thirtieth days.

Group	Average weight of rats			P value
	Day 1	Day 15	Day 30	
Control	196.6±3.8	212.1±6.1	227.8±5.9	0.077
High fat diet	194±3.2	244.2±4.9	313.1±7.3	0.000

level appeared to be associated with weight loss in men and weight gain in women, indicating a potential gender-specific role of EPO in body weight regulation (33). Additionally, Hojman *et al.* utilized the EPO overexpression model to investigate its protective effect against dietary obesity and to assess glucose sensitivity associated with enhanced fat metabolism in rat muscle. Their findings led to a substantial increase in serum EPO and hemoglobin levels, accompanied by a 23% reduction in weight and 28% decrease in adipose tissue over 12 weeks. These results emphasized the EPO's protective effects against diet-induced obesity through enhanced muscle fat metabolism (20).

Foskett *et al.* reported that subcutaneous EPO injections every 48 hours for five weeks caused weight and fat mass reduction, though lower doses (75 U/kg) had no this effect, highlighting the importance of dosage in EPO's anti-obesity effects (24). Conversely, in our study, after one month of high-fat diet feeding, obese rats showed significantly decreased serum EPO level (mean 18.98 U/kg), with no observed weight loss, suggesting that low EPO level may limit its efficacy in combating obesity. As reported earlier, EPO in the brain is expressed in astrocytes, and neurons and detectable in human cerebrospinal fluid (CSF). EPO receptors expression in the brain, especially in the embryonic stage, indicates a role in growth and tissue maintenance (4, 19, 34).

Obesity-related hypoventilation can cause hypoxia, which may influence EPO level in the central nervous system (CNS). Our findings showed higher brain EPO concentration relative to serum in rats fed a high-fat diet, while control rats had higher serum than brain EPO level. This suggests that in obese rats, the brain may increase local EPO synthesis as a protective response, potentially due to limited crossing of EPO across the blood-brain barrier (BBB). Supporting this, study in infants with CNS injury revealed elevated CSF and EPO levels without corresponding increases in serum, indicating that EPO production within the CNS was stimulated by hypoxia and that EPO did not readily cross the BBB under healthy conditions (35). Similarly, in traumatic brain injury, EPO concentration in ventricular CSF was correlated with cerebrovascular dysfunction, that further implied local CNS synthesis rather than peripheral transfer. These findings suggest that brain-derived EPO may serve neuroprotective functions in response to hypoxic or injury-related challenges (27).

EPO also plays a role in appetite regulation via hypothalamic neurons. Neurons in the arcuate nucleus, particularly POMC-producing cells,

suppress appetite when activated. Evidences indicate that EPO interacts with hypothalamic pathways; for example, EPO administration can induce POMC expression, while mice lacking EPO receptors tend to develop obesity due to impaired energy regulation (26). The elevated brain EPO level observed in obese rats might reflect a compensatory mechanism aimed at reducing appetite and increasing energy expenditure (35).

This study had several limitations that affected its power and general applicability. First, the small sample size limited both the statistical power and generalizability of the findings. Furthermore, the short duration of the high-fat diet intervention might not have been sufficient to capture long-term metabolic adaptations affecting EPO regulation. The exclusive use of male mice also precluded any analysis of potential sex-specific responses to obesity. Moreover, it was essential to focus on specific brain regions, such as the hypothalamus, which played an important role in appetite control and EPO signaling. Future research is needed to investigate the molecular mechanisms underlying the effect of obesity on EPO regulation in serum and brain.

Conclusion

Our findings suggested that obesity led to a decreased serum EPO level but an increased EPO level in CNS, possibly as a protective response to metabolic stress. The limited passage of EPO across the BBB means that brain EPO is likely produced locally, especially under hypoxic conditions associated with obesity. This differential regulation implies that EPO might have dual roles of supporting metabolic health and neuroprotection, and modulating appetite and energy balance. Understanding these mechanisms could contribute to developing novel therapeutic strategies for obesity and its related metabolic disorders, emphasizing the importance of further research into EPO's tissue-specific functions in obesity management.

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Authors' Contribution

MME performed the data analysis, interpreted the results, prepared the manuscript and supervised the study. RP performed the experiments, selected the candidates and designed the study. KSA collected the data and performed the biochemical experiments. HKA and SS performed the biochemical and physiological analysis, and approved the final manuscript version.

Conflict of Interest

The authors declared no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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