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Experimental Research Article

Pancreatic HB9 protein expression is affected by long-term high-fat diet in female rat dams

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ABSTRACT

Introduction: Maternal high-fat feeding has been identified as a risk factor for metabolic disorders involving abnormal glucose homeostasis and reduced whole-body insulin sensitivity. Recognizing factors like HB9, which play a role in the development of pancreatic β-cells and the release of insulin, is crucial for preventing disruptions in glucose metabolism.

Methods: Twenty female Wistar rats were randomly divided into normal (N) and high-fat (HF) groups, each receiving their specific diets during the pre-pregnancy, pregnancy, and lactation periods (10 weeks). At the end of lactation, the animals' body weight, food consumption, and calorie intake were measured. Additionally, fasting plasma levels of glucose, insulin, and corticosterone were assessed, and the homeostatic model assessment of β-cell function (HOMA-β) was calculated. Pancreatic tissue was collected to evaluate HB9 protein levels, while the adrenal glands were separated and weighed.

Results: The HF group showed significant increases in adrenal gland weight, plasma corticosterone levels, and pancreatic HB9 protein expression compared to the N group. Despite this, there were no significant variations in plasma glucose and insulin concentrations, HOMA-β index, or body weight among the study groups. Whereas, the HF group consumed less food.

Conclusion: Chronic intake of high-fat foods can act as a psychophysical stressor, triggering the hypothalamic-pituitary-adrenal (HPA) axis and resulting in elevated plasma corticosterone levels in female rat dams. This rise in corticosterone may lead to an upsurge in HB9 protein expression, potentially preventing disturbances in glucose regulation.

Keywords:
Chronic high-fat diet
HB9 protein expression
Pancreas

Introduction

A long-term consumption of a high-fat diet, especially during pregnancy and lactation, could be a metabolic health-threatening factor for both mother and her children (Gawlińska et al., 2021; Li et al., 2017; Saengnipanthkul et al., 2021). Therefore, considering the globally prevalence of metabolic disorders (Barnett et al., 2022; Fenichel 2017; Gosadi 2016; Ji et al., 2014), the high-

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fat content in modern food sources (Khalil et al., 2023; Wali et al., 2020; Wali et al., 2023), and given that the mother is also highly inclined to eat this type of food during her pregnancy and breastfeeding, it is essential to explore the factors and mechanisms contributing to the prevalence of metabolic disorders linked to a high-fat diet during this crucial time.

Experimental models have demonstrated that maternal high-fat feeding not only affects the mother's metabolic health but also leads to altered glucose metabolism and insulin sensitivity in the offspring, which can persist into adulthood (Li et al., 2017; Mendes-da-Silva et al., 2014). Accordingly, the long-term consumption of a high-fat diet in pregnant (Elsakr et al., 2021; Satokar et al., 2022) and non-pregnant conditions (Mosser et al., 2015) can result in reduced sensitivity to insulin, glucose intolerance, as well as β-cells dysfunction. Evidence suggests that sustained exposure to free fatty acids derived from a high-fat diet can lead to lipotoxic damage in the pancreatic islets, which in turn suppresses the synthesis and release of insulin (Oh et al., 2018; Sharma and Alonso 2014; Ye et al., 2019; Acosta-Montaño and García-González 2018).

It has also been shown that a high-fat diet can affect the activity of the hypothalamic-pituitary-adrenal (HPA) axis and the plasma levels of glucocorticoids. This may lead to changes in the function of beta cells and insulin secretion, as well as alterations in the plasma levels of insulin and glucose (Acosta-Montaño and García-González 2018). In this regard, after a glucose load, a decreased insulin secretion and a lower plasma insulin level may occur, which ultimately causes insufficient maintenance of normal plasma glucose levels.

It is revealed that the high-fat diet could change the expression of HB9, which is a transcription factor encoded by the homeobox gene HLXB9, that predominantly expresses in the pancreas of humans and rodents (Leotta et al., 2014). This gene is essential for the formation, differentiation, and function of pancreatic beta cells (O'Dowd and Stocker 2013; Sadeghimahalli et al., 2021). HB9 regulates insulin secretion by inhibiting two target genes that negatively control insulin expression and secretion, leading to an increase in insulin release and biosynthesis (Sahoo et al., 2015; Shi et al., 2013). In this respect, this is worth noting that the expression of proteins, like HB9, that regulate the function of beta cells and insulin secretion, can be changed by a high-fat diet for various reasons, including changes in corticosterone (Busceti et al., 2019; Janssen 2022) and free fatty acids (Armoni et al., 2005; Lam et al., 2003) levels.

Considering the earlier discussions regarding the link between maternal high-fat food consumption and the incidence of metabolic disorders, and the curial role of HB9 protein in preserving beta cell function and glucose homeostasis, it is likely that the expression of this protein varies when a high-fat diet is consumed during pre-pregnancy, pregnancy, and lactation periods, potentially impacting glucose homeostasis. Therefore, this study was conducted to investigate this hypothesis and clarify the potential role of HB9 protein in glucose homeostasis under these dietary conditions.

Material and methods

Animals and study design

In a 10-week study, 16 female Wistar rats were randomly split into two groups: Group N, which was fed a normal diet, and Group HF, which was given a high-fat diet. The animals of each group used their respective diets during the pre-pregnancy (4 weeks), pregnancy, and lactation periods. The high-fat food contained 65% by weight of standard pellets mixed with 35% by weight of animal butter (58.2% of energy from fat). In normal food (4.75% of energy from fat), saturated fatty acids make up 18.53% while unsaturated fatty acids constitute 81.37%. Throughout the study, all animals had unrestricted access to food and water and were housed in a controlled environment with a temperature of 22±2°C and a 12-hour light/dark cycle.

At the end of lactation (10-week), the animals' weight, food consumption, and calorie intake were measured. Subsequently, fasting blood samples were taken to determine the concentrations of plasma corticosterone and insulin. The amount of the homeostasis model assessment of β-cell function (HOMA-β) was calculated, using HOMA-β formula [HOMA-β= 20×fasting insulin (μU/mL)/ fasting glucose (mM) - 3.5] (Izadi et al., 2022), to evaluate the secretory function of beta cells. Following the dissection of the animals, the pancreatic tissue was extracted to measure the level of HB9 protein; moreover, the adrenal glands were isolated and weighed.

The animals' body weight and food consumption were measured using a digital scale (FWE Company, Japan, with a sensitivity of 1 gram) at the end of the 10-week research. Also, the level of kilocalories consumed by

each animal was calculated by multiplying the weight of food consumed by the energy available in each gram of food. The authors ensured ethical considerations in animal studies, and the study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (ethical code IR.SBMU.MSP.REC.1398.173).

Blood sampling

Blood sampling was conducted at the end of the 10-week research period, between 8:00 to 9:00 am, under overnight fasting conditions (16 h). The rats were anesthetized with intraperitoneal injection of sodium pentobarbital (60 mg/kg) (Sigma, USA), then decapitated to collect their trunk blood in a microtube containing heparin (5000 IU/ml, Caspian Tamin, Tehran, Iran) (10 microliters per 1 milliliter of blood). The collected blood was centrifuged at a speed of 3000 rpm for 10 minutes at 4°C, then the plasma was separated and frozen at -80°C.

Assays

Plasma concentrations of insulin and corticosterone were evaluated with the rat insulin ELISA kit (detection limit: 0.07 mg/l) from Mercodia, Sweden, and the corticosterone ELISA kit (detection limit: 1.631 nmol/l) from DRG Instruments GmbH, Marburg, Germany, respectively. The concentration of plasma glucose was measured utilizing the glucose oxidase method (detection limit: 5 mg/dl) from Pars Azmoon, Tehran, Iran.

Western blot

Western blotting was employed to assess the levels of pancreatic HB9 protein. After completing the experimental process, the anaesthetized rats in all groups (n=3/group) were decapitated, and their pancreatic tissue was extracted. After being frozen in an Azot tank, the samples were preserved at -80 °C to assess the HB9 protein level. The pancreatic tissues were homogenized in lysis buffer and then centrifuged to eliminate cell debris. The supernatant was then gathered and analyzed for total protein concentration using the Bradford method (Kruger 2009).

The proteins were applied to polyacrylamide gels with 12% sodium dodecyl sulfate (SDS) and subjected to electrophoresis before being transferred to a polyvinylidene fluoride membrane.

Overnight treatment of the membranes at 4°C was conducted using a rabbit polyclonal anti-HB9/HLXB9 antibody (Abcam, Cambridge, MA, Cat. No. ab92606). The following day, the membranes were treated with a secondary antibody, horseradish peroxidase-conjugated goat anti-rabbit IgG from Santa Cruz Biotechnology Inc. (Dallas, TX) for 90 minutes at room temperature. Visualization was achieved using the ECL advance kit from Amersham Bioscience (Piscataway, NJ). Results were quantified by conducting a densitometry scan of the films, and the data analysis was carried out using Image J software (Sadeghimahalli et al., 2021).

Statistical analysis

The data were presented as mean ± SEM (standard error of mean), and the results were analyzed using GraphPad Prism 6 statistical software. The Kolmogorov-Smirnov test was conducted to determine the normality of data distribution. To compare different diets in the groups, the unpaired t-test was used. The limit of significance of differences was set at $P \leq 0.05$ in all cases.

Results

The study findings revealed that mothers who ingested high-fat food in HF group, plasma corticosterone levels ($P<0.0001$) ($t_{14}=8.712$) (Figure 1a), exhibited higher adrenal gland weight per body weight ($P<0.0001$) ($t_{14}=5.501$) (Figure 1b), and pancreatic HB9 protein expression ($P<0.05$) ($t_{4}=4.438$) (Figure 2) than those in the N group. The HF group showed no variance in body weight ($P=0.2970$) ($t_{14}=1.083$) (Figure 3a). Whereas, this group consumed less food ($P<0.05$) ($t_{14}=2.840$) (Figure 3b), compared to the N group. There was also no variation in calorie intake ($P=0.5197$) ($t_{14}=0.660$) (Figure 3c) between groups. Additionally, HF animals did not display significant differences in fasting plasma glucose ($P=0.5922$) ($t_{14}=0.5483$) (Figure 4a), insulin levels ($P=0.5721$) ($t_{14}=0.5785$) (Figure 4b), or HOMA-β ($P=0.7430$) ($t_{14}=0.3344$) (Figure 4c) between the HF animals and the N group.

Discussion

Our results indicated that mothers who consumed high-fat food had higher pancreatic HB9 protein level, plasma corticosterone concentration, along percentage of adrenal gland weight/body weight compared to the N group. According to available reports, the expression of HB9 protein in the islets of Langerhans is critical for the development of the pancreas in humans and rodents,

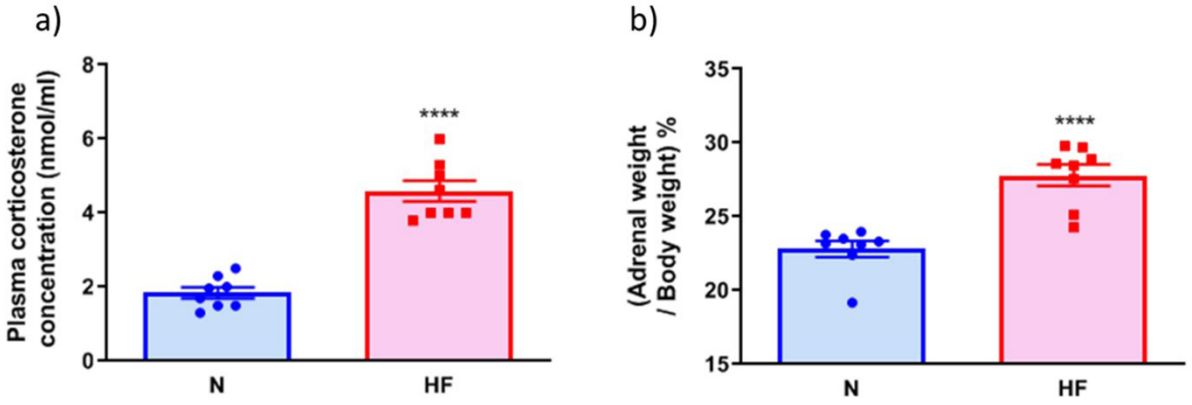

FIGURE 1. The effect of high-fat diet on adrenal gland weight/body weight (%) (a) and plasma corticosterone concentration (b) in dams at the end of lactation. Each column denotes mean ± SEM (n = 8); N: Normal group, HF: High-fat group; * (P <0.05) **** (P <0.0001) showed a significant difference compared to the N group.

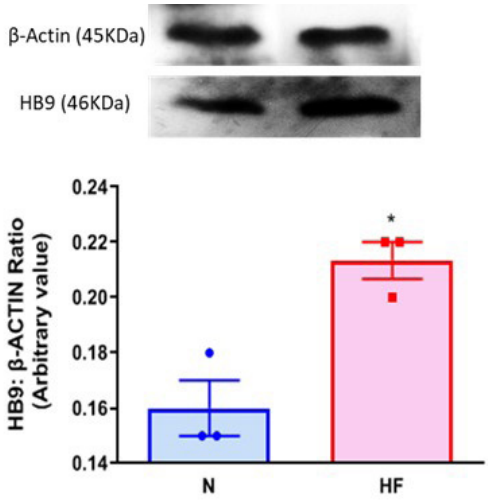

FIGURE 2. The effect of a high-fat diet on pancreatic HB9 protein amount in dams at the end of lactation. Each column denotes mean ± SEM (n = 3); N: Normal group, HF: High-fat group; *(P<0.05) showed a significant difference compared to the control group.

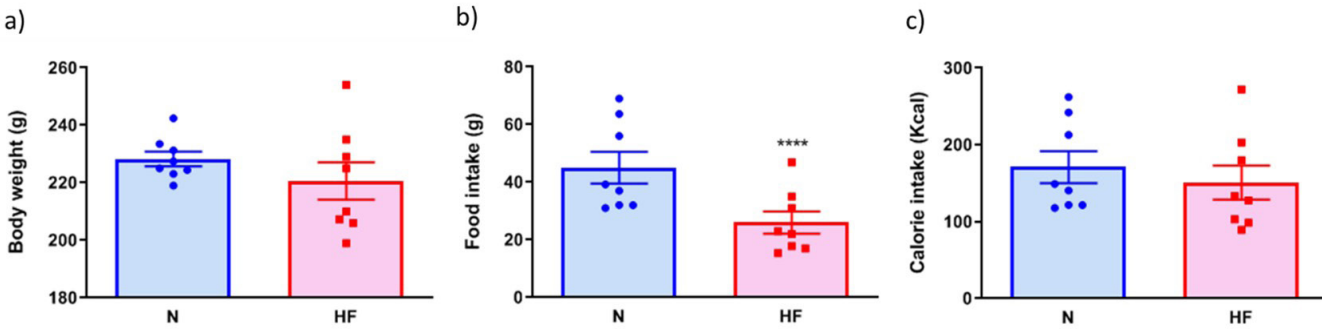

FIGURE 3. The effect of a high-fat diet on body weight (a), food intake (b), and calorie intake (c) in dams at the end of lactation. Each column denotes mean ± SEM (n = 8); N: Normal group, HF: High-fat group. * (P <0.05) showed a significant difference compared to the control group.

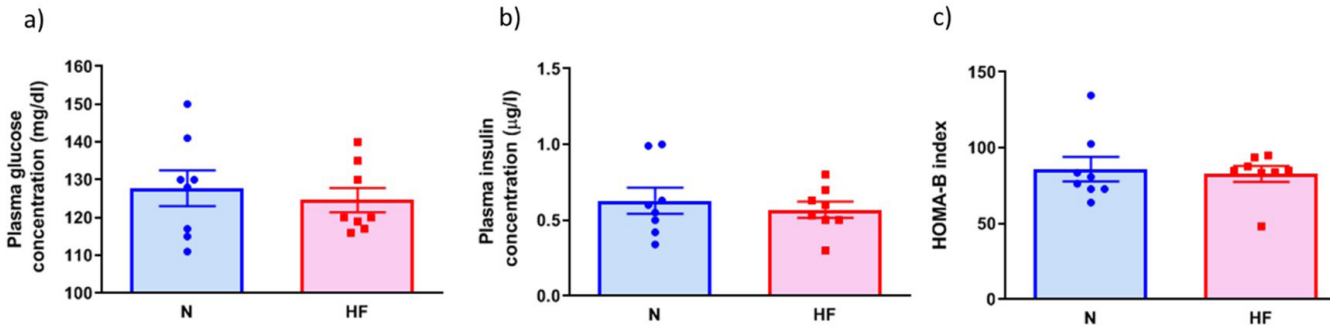

FIGURE 4. The effect of a high-fat diet on plasma glucose (a) and insulin (b) concentrations, also on HOMA-β index (c) in dams at the end of lactation. Each column denotes mean ± SEM (n = 8); N: Normal group, HF: High-fat group.

resulting in normal beta-cell function. Any change in its expression can disrupt insulin secretion from the islets (Harrison et al., 1999a; Kaneto and Matsuoka 2015). In this regard, investigations on Hlxb9-deficient mice have highlighted the restricted expression of HB9 to beta cells, which was accompanied by small islets of Langerhans with reduced numbers of insulin-producing β-cells and low levels of the glucose transporter Glut2 (Harrison et al., 1999b). Studies on diet-induced obese C57BL/6J mice have shown alterations in pancreatic islet structure, metabolism, and gene expression when exposed to a HF diet. These alterations include changes in islet morphology, insulin secretion, and gene expression profiles in high-fat-fed mice compared to those on a normal diet (Roat et al., 2014). Reports on the effects of a high-fat diet on HB9 expression are limited; nonetheless, according to the above-mentioned findings and the results of the present study, there is a possibility that a high-fat diet has an effect on HB9 expression. The presence of free fatty acids in a HF diet and increased plasma corticosterone levels, as occurred in the present study, can both lead to elevated levels of free fatty acids in plasma, which can affect the expression of transcription factors, including HB9. Regarding the fatty acids in the high-fat diet could alter the corticosterone circadian rhythm (Teeple et al., 2023), which may lead in turn to changes in gene expression (Paula et al., 2020), the increase in HPA axis activity is likely linked to modifications in HB9 protein expression. That might be accomplished by means of epigenetic modifications (Beaudry and Riddell 2012; Sadeghimahalli et al., 2021). We did not analyze the corticosterone circadian cycle, but the plasma corticosterone level among HF group animals increased significantly, which might be due to the influence of high-fat food as a psychophysical stressor (Benite-Ribeiro et al., 2015; Desai et al., 2014; Namvar et al., 2016). Thus, the heightened corticosterone levels in the HF group might have resulted in enhanced HB9 protein expression in pancreatic tissue (Fine et al., 2018; Udagawa et al., 2023).

In this study, the HF animals exhibited no significant differences in fasting plasma glucose and insulin levels, nor in HOMA-β when compared to the N group. On the other hand, it has been reported that a high-fat diet, rich in saturated fats, can lead to increased plasma glucose levels and decreased insulin sensitivity, which possibly compromises the body's ability to respond to insulin and raises the risk of type 2 diabetes as a consequence (von Frankenberg et al., 2017). It is noteworthy that the elevated levels of glucocorticoids can inhibit insulin secretion in a concentration-dependent manner. On the other hand, as they participate in tissue metabolism and stimulate lipolysis and protein degradation, they can provide the necessary substrates for insulin secretion by enhancing the levels of FFAs and amino acids (Lambillotte et al., 1997). Thus, in the current study, the dual role of glucocorticoids in insulin secretion could have contributed to the lack of change in insulin plasma levels observed in the animals of the HF group. Additionally, it is possible that the elevated HB9 expression observed in the HF group of the current study plays a role in maintaining beta cell function, which helps to stabilize insulin plasma levels and prevent a rise in glucose plasma concentration (Harrison et al., 1999a; Kaneto and Matsuoka 2015).

Although the high-fat diet of this study was high in

calories, the animals fed a high-fat diet did not exhibit a significant difference in body weight. However, they did show a reduction in food consumption compared to the control group, which aligns with the results of the Namvar study (Namvar et al., 2016). In contrast, several studies have reported different results regarding the effect of a high-fat diet on food and calorie intake as well as body weight (Bhandari et al., 2011; Lasker et al., 2019; Marques et al., 2016). Variations in the results observed in distinct studies could be a result of either the duration or the type of high-fat food consumed. The similarity in calorie intake between the HF group animals and the control group could be the result of lower food consumption observed in the HF group. It seems that a self-regulation mechanism has occurred to maintain calorie intake and body weight in the HF group.

In this regard, some evidence indicates that elevated corticosterone levels may decrease food intake by modifying the gene expression of orexigenic (like ghrelin) or anorexigenic (such as proopiomelanocortin) peptides in the hypothalamus (Ans et al., 2018). This relationship is intricate and can be affected by both the fat content and the length of the diet (de Moura e Dias et al., 2021; Higa et al., 2014; Wang et al., 2020). As a result, other studies have also observed contrasting outcomes. For example, in a study, the animals who fed a cafeteria diet showed a disrupted self-regulation mechanism, which led to an increase in food consumption (Higa et al., 2014). Moreover, some studies have reported that oxytocin mRNA expression in the hypothalamus increases following high-fat diet consumption, which could be involved in reducing food intake in the HF group (Manti et al., 2018; Sullivan et al., 2012).

Conclusion

Long-term consumption of high-fat foods before and during pregnancy, as well as during lactation, can stimulate the HPA axis and elevate corticosterone levels in the dams. This increase may promote HB9 protein expression, which could help prevent disruptions in glucose regulation. Nonetheless, continued adherence to this dietary habit threatens glucose homeostasis, emphasizing the importance of conducting more research.

Limitations and future suggestions

Considering the limitations of this study, the following suggestions are proposed: Evaluating the hypothalamic factors that influence anorexia and orexia affecting the food intake. Analyzing plasma and pancreatic fatty acid levels. Exploring potential epigenetic modifications of the HB9 gene. Performing HB9-specific knockout or inhibitor experiments to clarify the role of this protein in regulating glucose metabolism.

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Conflict of interest

The authors affirm that they have no competing interests.

Ethics approval

This article was reviewed by the Department of Physiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. The authors upheld ethical standards in animal research, and the study received approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences under ethical code IR.SBMU.MSP.REC.1398.173.

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