Original Article

Exposure to Various Degrees and Durations of Hypobaric Hypoxia Causes a Reduction in Body Weight of Female Adult Rats

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Abstract

Background: Hypobaric hypoxia refers to a condition where there is a decreased oxygen partial pressure in the air due to low atmospheric pressure. It is known to affect the metabolism, leading to increased basal metabolic rate, alterations in appetite, and changes in cellular metabolism and energy homeostasis. The effects of hypoxia on metabolism and weight loss are influenced by genetic factors, gender, and the duration and severity of exposure to hypoxia. Currently, there are no reports which elucidate the impact of hypobaric hypoxia on female laboratory rats. **Objective:** The aim of this study was to observe the effect of varying degrees and durations of hypobaric hypoxia on the body weight of female rats. **Materials and Methods:** In this study, the body weight of 36 laboratory rats divided into six groups was taken at day 0, and then, the rats were exposed to hypobaric hypoxia in a specially designed hypoxia chamber and their body weights were recorded after 5 days and 10 days of hypoxia exposure. The change in body weight at 5 days and 10 days was compared to that of their body weight before the exposure to hypoxia. Data analysis was performed using IBM SPSS version 20. **Results:** Body weight was reduced in all rats subjected to varying degrees and duration of hypoxia. The percentage change in body weight was higher in moderate and severe hypoxia than in the mild hypoxia group. No significant difference was observed in rats exposed to varying degrees of hypoxia for 5 days as compared to those exposed for 10 days. **Conclusion:** Hypoxia may cause a reduction in body weight of female rats proportionate to the increasing severity of hypoxia and this reduction remains independent of the duration of exposure to hypoxia.

Keywords: *Body weight, female rats, hypobaric hypoxia, hypoxia*

Introduction

At higher altitudes, the air is less dense, resulting in a lower oxygen concentration per unit volume. This decreased oxygen availability can result in hypoxia, a condition in which organs and tissues in the body receive insufficient oxygen to meet their physiological requirements.[1] Hypobaric hypoxia refers to a condition characterized by reduced oxygen availability at lower atmospheric pressures. It influences several aspects of cell function, including growth, metabolism, and cell cycle.[2]

The effect of hypoxia extends across neurological, respiratory, and reproductive systems driven by cellular and subcellular alterations.[2,3] Hypobaric hypoxia can have significant physiological effects on living organisms, including humans, as the body must adapt to reduced oxygen availability to maintain normal function. These adaptations can include an increase in red blood cell production, changes in breathing patterns, and alterations in metabolic processes.[4]

Studies have shown that in response to hypoxia, there is a significant reduction in body weight.[5] This weight loss can be attributed to several factors, including dehydration in the hypobaric chamber, reduced appetite, dysfunctional digestive system, and malabsorption of nutrients.[3] A previously published study reported that hypobaric hypoxia can lead to increased glycolysis and reduced oxidative phosphorylation in skeletal muscle.[6,7] In addition, hypoxic training has been shown to regulate hepatic fatty acid metabolism in obese mice.[8,9] These findings suggest that hypobaric hypoxia may affect metabolic pathways such as oxidative phosphorylation and glycolysis, which could contribute to the observed changes in metabolic parameters.[6-9]

The effects of hypoxia on weight loss are also influenced by genetic factors and the

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duration and severity of exposure to hypoxia.[3] In addition, there are gender differences in the way hypoxia-mediated weight loss occurs. Studies have shown that women tend to have fewer body weight variations brought on by altitude than males.[10] Bai *et al*. have shown that exposure to hypobaric hypoxia produces a significant effect on the body weight of rats, resulting in negative body weight gain.[11] The underlying mechanisms are not fully understood, but changes in metabolic processes and hypoxia-induced stress may play a role. In the currently available studies, the exposure to hypoxia is often combined with an increase in physical activity like continuous hiking and trekking sessions to difficult terrains and exercise[12-19] or dietary modifications[15,18-23] often combined with decrease in ambient temperature at high altitude. Moreover, studies on hypoxia-mediated weight loss have focused on male rats, and there is a relative paucity of research specifically examining the effect of hypoxia on female rats. Understanding potential sex-specific differences in the response to hypoxia and the underlying mechanisms is an important area for future investigation. However, no such data are present that can correlate the effect of various degrees and durations of hypobaric hypoxia on the body weight of female rats. To date, the relationship between the duration and severity of hypoxia exposure and the extent of weight loss in female rats is also not well-defined. Determining the critical thresholds and understanding the dose-response relationship will provide valuable insights into the factors influencing weight loss under hypoxic conditions. Hence, through this study, we aimed to observe the effect of varying degrees and durations of hypobaric hypoxia on the body weight of female rats.

Materials and Methods

All the experiments were carried out using young female rats and adult female rats of (The Charles-Foster strain) following the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guideline after approval from the Institutional Animal Ethical Committee (IAEC), Banaras Hindu University (No. Dean/2021/IAEC/3028).

A total of 36 female rats (*Rattus norvegicus*) of Charles foster strain aged approximately 6 months old were used in this study. These rats were further divided into six groups, each corresponding to a different combination of degree (mild [670 mmHg], moderate [560 mmHg] and severe [450 mmHg]), and duration [5 days and 10 days] of hypoxia.

For exposure to different grades of hypobaric hypoxia, the rats were kept in a specially designed chamber for simulation of different environmental conditions (Patent application number 202311027550) for different time durations. The rats were maintained under a controlled temperature of 24°C ± 2°C and a light-dark cycle of 12 h with access to food and water *ad libitum*.

Their body weight was recorded at Day 0 and Day 5/Day 10 at all three degrees of hypoxia. The change in body weight at 5 days and 10 days was compared to that of their body weight before the exposure to hypoxia using the Wilcoxon Signed-rank test. Comparison between mild, moderate, and severe hypoxia groups was performed using Kruskal–Wallis one-way analysis of variance. The body weight of rats exposed to respective degrees of hypoxia was compared among 5-day and 10-day exposure groups using the Mann–Whitney *U*-test. Data analysis was performed using the statistical software IBM SPSS Statistics Version 20 (International Business Machine corporation , Armonk, New York, USA). "$P < 0.05$" was deemed statistically significant.

Results

The findings, as mentioned in Figures 1 and 2, indicate that exposure to hypoxia leads to a significant reduction in the body weight of female rats. The rats were exposed to either mild hypoxia (670 mmHg), moderate hypoxia (560 mmHg), or severe hypoxia (450 mmHg) for the duration of either 5 days or 10 days. The body weight of female rats declined after both 5 days and 10 days of exposure to hypoxia in a dose-dependent manner. When the percentage change in body weight was calculated, no significant percentage change in body weight was observed between 5 days of exposure to hypoxia and 10 days of exposure to hypoxia. When compared among the groups, the percentage change in body weight in response to hypoxia was higher in the moderate group and severe group than in the mild group; however, no significant change was observed between the moderate and severe groups. When all the groups were compared to each other, it was observed that the percentage change in body weight in the 10-day moderate hypoxia-treated group was significantly higher than the percentage change in body weight of the 5-day and 10-day mild hypoxia-treated groups. In addition, the percentage change in body weight in the 10-day severe hypoxia-treated group was significantly higher than in the 10-day mild hypoxia-treated group. The percentage change in body weight in the 5-day moderate and severe hypoxia-treated groups was significantly higher than the 10-day mild hypoxia-treated group. The maximum percent change in body weight was seen in the 10-day moderate hypoxia-treated group. These findings suggest that exposure to hypoxia negatively impacts weight gain in female rats.

Discussion

Hypobaric hypoxia is commonly experienced by individuals who live at high altitudes or engage in activities such as mountaineering, aviation, or space travel. It is well-documented that hypoxia impacts body weight at high altitudes through complex mechanisms involving changes in metabolism, energy expenditure, and appetite.[24] The effects of hypoxia on body weight may depend on factors of hypoxia exposure duration and severity, gender as well as individual physiological responses. In this study, we report the negative weight gain in female rats exposed to hypoxia. The percent change in body weight is greater among the moderate and severe hypoxia-treated groups in

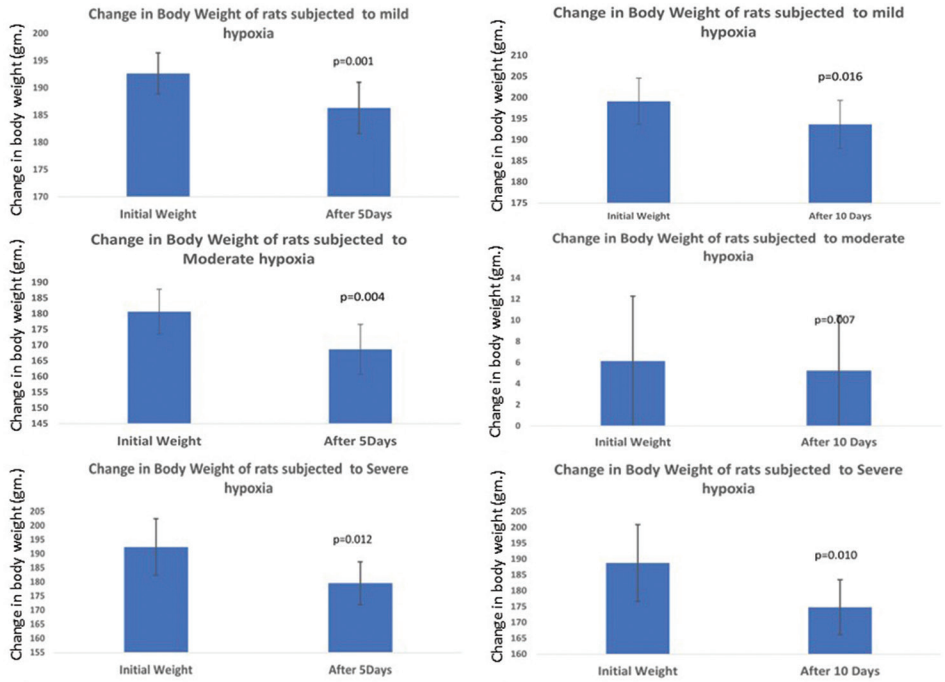

Figure 1: Graphical representation of change in body weight (in gm.) of female rats subjected to mild, moderate, and severe hypoxia after 5 days and 10 days compared to initial body weight

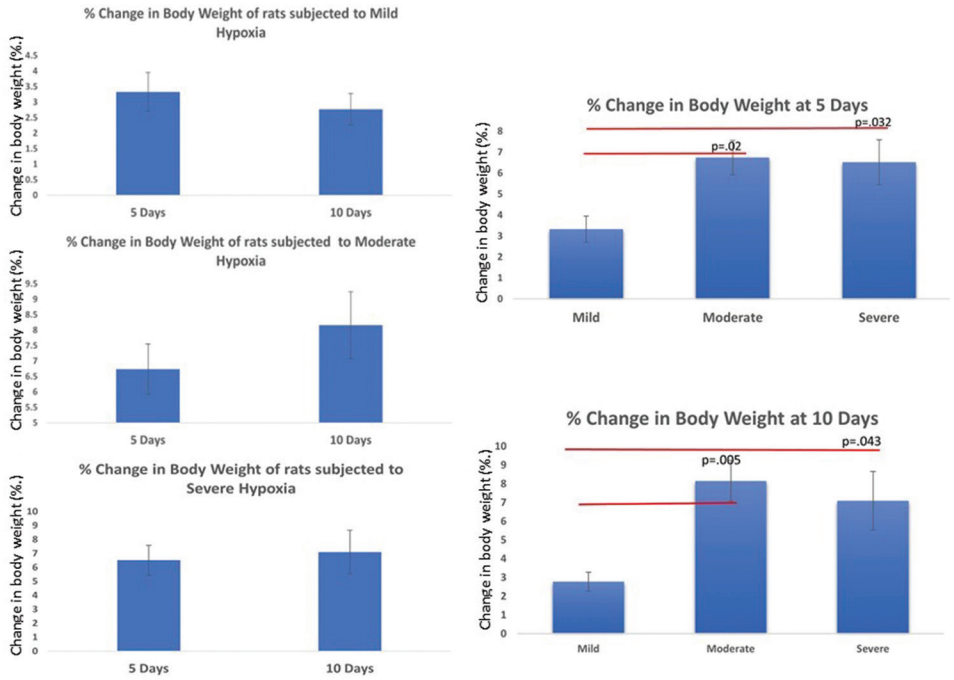

Figure 2: Graphical representations of percentage change in body weight of adult female rats subjected to mild, moderate, and severe hypoxia for 5 days compared to those subjected to mild, moderate, and severe hypoxia for 10 days

both 5 days and 10 days of exposure to hypoxia. However, not much change was observed between moderate-treated and severe hypoxia-treated groups. Maximum change in body weight was seen in moderate hypoxia-treated groups exposed to 10 days of hypoxia. These changes in body weight depend on hypoxia exposure duration and severity of hypoxia exposure, gender as well as individual physiological responses of rats.

One key factor involved in these metabolic changes is the activation of hypoxia-inducible factor (HIF). Hypoxia-induced HIF activation can be crucial for weight

loss due to its involvement in the regulation of metabolism and energy homeostasis.[25-27] HIF-α and HIF-β subunits are degraded by prolyl hydroxylases (PHDs) under conditions of normoxia, but under hypoxia, PHD activity is inhibited, promoting stabilization and accumulation of HIF-α.[26-29] Altitude-induced HIF-1α activation may upregulate leptin mRNA levels, improve leptin sensitivity, suppress appetite, and increase glucose metabolism and angiogenic genes, leading to increased energy expenditure and weight loss.[29-31] Hypobaric hypoxia significantly impacts cellular respiration, causing a shift from oxidative phosphorylation to glycolysis.[32] This adaptation enables cells to maintain ATP production even during conditions of low oxygen availability.[33] HIF activation leads to increased transcription of glycolysis-related genes and downregulation of oxidative phosphorylation genes. However, this shift may be less efficient and contribute to increased basal metabolic rate at high altitudes.[33,34] Moreover, the exposure to hypoxia also upregulates the expression of glucose transporter 1, facilitating glucose uptake, and supporting energy production through glycolysis.[35,36] This adaptation helps to maintain cellular energy balance and may contribute to the metabolic changes associated with weight loss in hypoxic conditions. Hypoxia has been found to have a suppressive effect on appetite. Previously published reports have indicated that hypoxia exposure can lead to a decrease in appetite and energy intake by regulating the production and release of appetite-regulating hormones, such as leptin and ghrelin.[37-40]

In addition, there is evidence of sexual dimorphism in the metabolic responses to altitude exposure, suggesting hormonal influences on HIF activity.[3,5] Males and females exhibit different metabolic adaptations to hypoxia, with males showing increased glucose utilization and potential weight loss. The specific hormonal factors underlying these sex-specific responses require further investigation. According to a study conducted by Bai *et al*., rats exposed to hypoxia for 3 weeks had a mean body weight that was 20.3% lower than rats exposed to normal oxygen levels.[11] We also observed similar results in female rats.

Rats have metabolic pathways and physiological responses that are similar to humans, making them a relevant model for studying the effects of hypoxia on body weight. Multiple studies have correlated hypoxia-mediated negative weight gain in male rats to the hormonal and physiological homeostasis of rats and humans. However, no such studies had been conducted on female rats. In this study, we have shown the effect of hypoxia on the body weight of female rats. This will pave the way for the investigation of the metabolic adaptations that occur in response to hypoxia, such as changes in energy expenditure, nutrient utilization, and hormonal regulation of appetite in females. We have compared the percent change in body weight at different doses and durations of hypobaric hypoxia, findings of which can be useful in studying hypoxia-related changes in females at high altitudes. In this study, we have not investigated the molecular mechanisms behind the weight loss in female rats. While reduced food intake and metabolic adaptations are commonly cited mechanisms for weight loss in hypoxia, other factors such as changes in water balance, muscle wasting, or alterations in gut microbiota may also contribute to the observed effects. It is important to consider and investigate these alternative mechanisms to gain a comprehensive understanding of the weight reduction observed in hypobaric hypoxia studies.

Conclusion

The study concludes that there is a significant decrease in the body weight of female rats exposed to hypobaric hypoxia. The findings of this study are significant to high-altitude acclimatization research because they provide a model to study the physiological and molecular mechanisms underlying weight loss in response to hypoxia, which is a common feature of high-altitude exposure. In addition, the findings can contribute to the development of targeted interventions and potential therapeutic strategies for managing weight loss or metabolic disorders associated with hypoxia in both animal models and human populations.

Ethical statement

The study was approved by the Institutional Animal Ethical Committee (IAEC), of Banaras Hindu University, Varanasi, U.P. India (No. Dean/2021/IAEC/3028).

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Conflicts of interest

There are no conflicts of interest.

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