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Impact of Stress on Hormonal Imbalance in Rats with Alimentary Obesity

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Abstract

Obesity is a multifaceted chronic disease that poses a significant health risk due to its association with cardiovascular and metabolic disorders. Among the various factors contributing to obesity, adipokines—hormones secreted by adipose tissue—such as leptin, adiponectin, and visfatin play a key role in regulating metabolic processes. This study investigated the effect of chronic emotional stress on the secretion of these adipokines in the blood serum of obese rats. The analysis showed that stress-induced decreases in leptin levels may lead to eating disorders, whereas visfatin levels are influenced by factors beyond adipose tissue mass. The findings suggest that chronic stress, combined with obesity, may accelerate the onset of insulin resistance, and further complicate metabolic health.

Keywords: Obesity, Leptin, Stress, Adiponectin, Visfatin

Introduction

Chronic stress, along with factors such as genetic predisposition, lack of physical activity, and unhealthy eating habits, is recognized as one of the main contributors to the development of obesity [1, 2]. It is well-documented that stress triggers an excessive release of cortisol, a hormone that plays a critical role in helping the body adapt to stress but also stimulates increased appetite [3, 4]. When stress becomes persistent, it can set off a harmful cycle that eventually leads to obesity [5, 6].

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Obesity is increasingly regarded as a complex, chronic disease that poses significant health risks, particularly due to its links to cardiovascular and metabolic complications [7, 8]. A crucial factor in the progression of obesity is the action of adipokines—hormones produced by adipose (fat) tissue. Among these, leptin, adiponectin, and visfatin are of particular importance [9, 10].

Leptin plays a central role in regulating body weight and energy metabolism [11]. Often referred to as the "hunger-suppressing hormone," leptin helps control appetite by inhibiting the production of neuropeptide Y, a molecule that triggers hunger signals in the brain [12, 13]. On the other hand, adiponectin serves a protective function by improving insulin sensitivity and offering cardiovascular protection [14].

The role of visfatin is still under investigation, with some studies suggesting that it is involved in the development of cardiovascular diseases and metabolic disturbances in

obese individuals [15-17]. Since visfatin mimics the action of insulin, it is believed to play a part in the onset of insulin resistance, type 2 diabetes, and its associated complications [18]. Although adipokines are known to contribute to the early stages of vascular and metabolic problems, conclusive evidence of their exact role is still lacking [19].

This study aims to explore the effects of chronic emotional stress on the levels of key adipokines—leptin, adiponectin, and visfatin—measured in the blood serum of rats with alimentary obesity.

Materials and Methods

To induce obesity, a fat supplement was added to the standard vivarium diet over 3 months. Each rat was given 3 grams of pork fat daily, starting from an initial weight of 200 grams. Chronic emotional stress was induced through immobilization, where the rats were confined to narrow enclosures for one hour daily for 10 consecutive days [20, 21]. The animals were then divided into four experimental groups, each consisting of 10 rats:

- Group 1 (control): Rats maintained on a standard vivarium diet, representing the normal physiological state.
- Group 2 (stress): Healthy rats subjected to immobilization stress without any dietary modification.
- Group 3 (obesity + stress): Rats with induced obesity were also subjected to immobilization stress.
- Group 4 (obesity): Rats with alimentary obesity but not subjected to stress.

At the end of the experiment, all rats were euthanized by decapitation, and peripheral blood samples were collected. To evaluate stress exposure, serum corticosterone levels (a cortisol analog in humans) were measured using enzyme-linked immunosorbent assay (ELISA) on a BioTekELx80 analyzer (USA), and the weight of the adrenal glands was recorded.

Given that chronic stress induces free radical oxidation, the markers of the "lipid peroxidation - antioxidant protection" system (LP–AOP) were also assessed [22]. Malonic dialdehyde (MDA), the primary product of lipid peroxidation, was quantified using its reaction with 2′-thiobarbituric acid [23]. The activity of superoxide dismutase (SOD), an antioxidant enzyme, was measured based on its inhibition of quercetin oxidation [24]. Catalase activity, which helps neutralize hydrogen peroxide, was measured spectrophotometrically based on the formation of a colored complex with molybdenum salts [25]. These parameters were analyzed using the BioTekELx80 IFA analyzer (USA).

To confirm the obesity model, body weight was monitored throughout the study. After decapitation, the animals were dissected, and the weight of internal organs was measured. The percentage of visceral adipose tissue was calculated [26].

Serum analyses included measurements of total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), glucose, amylase, and lipase activity, using a BS-200 biochemical analyzer (China) and reagents from Randox (Great Britain) and Diasens (Belarus) [27]. The content of total phospholipids in liver tissue was determined through the detection of inorganic phosphorus released during phospholipid hydrolysis [28]. Adipose tissue hormones—leptin, adiponectin, and visfatin—were assessed using enzyme immunoassay on a Chem Well analyzer (USA) with DRG test systems (Germany) [29].

Data analysis was performed using Statistica 12.0 software (USA). The normality of distribution was tested using the Shapiro-Wilk test. For group comparisons, either the Student's t-test for independent samples or the nonparametric Mann–Whitney test was used. All results are expressed as mean ± standard error of the mean (SEM), with statistical significance set at $P < 0.05$.

Results and Discussion

The analysis revealed that the adrenal gland mass in the rats of groups 2 and 3 was significantly higher than in the control group, with increases of 2.5 and 2 times, respectively. This hypertrophy likely represents a compensatory response, where the adrenal glands are under functional stress due to chronic exposure to stress [30]. Additionally, in these groups, the serum levels of corticosterone, which serves as a key stress hormone in rats and functions similarly to cortisol in humans, showed a significant reduction compared to the control **(Table 1)**.

The findings presented in **Table 1** suggest a depletion of the stress regulatory mechanisms, a phenomenon that aligns with observations in other studies [31, 32]. Regarding the lipid peroxidation and antioxidant protection system (LP-AOP), a significant increase in malondialdehyde (MDA) levels was observed in the

serum of rats from all experimental groups when compared to the control group ($P \leq 0.05$). This indicates enhanced oxidative stress in response to chronic stress. Furthermore, a decrease in the activity of the antioxidant enzymes superoxide dismutase (SOD) and catalase was noted in rats subjected to prolonged emotional stress, as well as in rats from group 3, suggesting that the oxidative stress and the compromised antioxidant defenses were linked to both stress exposure and obesity **(Table 1)**.

Table 1. Changes in the levels of corticosterone, malondialdehyde, superoxide dismutase, and catalase activity in the blood serum of obese rats under chronic stress

Experimental groups	Corticosterone (nmol/L)	MDA (nmol/L)	SOD (U/mL)	Catalase (mcat/L)
Group 1 (n = 10)	0.170 ± 0.04	10.580 ± 0.868	3.463 ± 0.236	8.303 ± 0.711
Group 2 (n = 10)	0.050 ± 0.03*	15.339 ± 0.397*	1.771 ± 0.092*	4.761 ± 0.237*
Group 3 (n = 10)	0.071 ± 0.03*	19.642 ± 0.396*	1.360 ± 0.080*	1.752 ± 0.177*
Group 4 (n = 10)	0.016 ± 0.03	14.287 ± 0.966*	3.309 ± 0.268	8.032 ± 0.819

* – significant differences from the control ($P < 0.05$)

The observed changes may be influenced by the development of metabolic acidosis, reduced oxygen transport, and decreased synthesis of key macroregion compounds [33]. Additionally, the reduced effectiveness of the antioxidant protection (AOP) system might be linked to factors like lower levels of antioxidants, inhibited anti-peroxide enzymes, or disruptions in hydrogen supply caused by metabolic toxins or other mechanisms [34, 35].

In rats with experimentally induced obesity, there was an 18.8% increase in body weight compared to the control group. Additionally, the kidneys showed a 26.0% increase in weight, the spleen grew by 33.0%, and visceral fat expanded by 80.0%. A notable ($P < 0.05$) decrease in liver phospholipids was observed, with a 47.0% reduction relative to the control group. The total cholesterol (TC) levels in the obese group were 1.930 ± 0.174 mmol/L, representing a 30.0% rise over the control group's 1.468 ± 0.172 mmol/L. These findings suggest a deficiency in phospholipids due to impaired liver metabolic function in obesity [36, 37].

Biochemical analysis of blood parameters revealed significant increases in TC levels in group 3 (obesity + stress), rising from 0.98 ± 0.07 mmol/L in the control group to 1.58 ± 0.07 mmol/L. The low-density lipoprotein (LDL) level rose from 0.1 ± 0.02 mmol/L to 0.16 ± 0.02 mmol/L, while the high-density lipoprotein (HDL) increased from 0.5 ± 0.055 mmol/L to 0.8 ± 0.060 mmol/L ($P \leq 0.05$). These changes are likely driven by glucocorticoids, which promote lipid production in hepatocytes by enhancing fatty acid synthase gene expression [38]. Glucose levels in this group also rose significantly, from 3.6 ± 0.18 mmol/L in the control to 4.9 ± 0.20 mmol/L.

In terms of enzymatic activity, blood levels of lipase and amylase were elevated in both the stress-only group (group 2) and the combined obesity and stress group (group 3) ($P < 0.05$), as shown in **Table 2**. This increase suggests the onset of inflammation in pancreatic tissue [39]. Pancreatitis is commonly caused by the activation of pancreatic enzymes, which are often released due to stress-induced regurgitation into the pancreatic ducts from the duodenum, possibly containing bile [40, 41].

Table 2. Changes in the lipase and amylase activity in the blood serum under stable emotional stress of rats with alimentary obesity

Parameter	Group 1 (n = 10)	Group 2 (n = 10)	Group 3 (n = 10)	Group 4 (n = 10)
Amylase (U/L)	973.8 ± 33.1	1470.6 ± 129.4*	1789.2 ± 148.5*	1076.5 ± 21.3
Lipase (U/L)	23.8 ± 0.5	155.3 ± 14.2*	211.2 ± 59.2*	21.3 ± 2.6

*$P < 0.05$

The analysis of adipose tissue hormone levels revealed a significant decrease in serum leptin levels in rats from groups 2 and 3. In contrast, group 4 showed a slight increase in leptin ($P \geq 0.05$) **(Figure 1a)**. This increase in group 4 can be attributed to the growth in adipose tissue volume, leading to greater secretion of this hormone [42, 43]. Across all experimental groups, a consistent trend of decreased adiponectin levels in the blood was observed **(Figure 1b)**. Additionally, a weak negative correlation was found between adiponectin levels and glucose levels in group 3. This suggests that chronic stress in combination with alimentary obesity may accelerate the

onset of insulin resistance, as reduced adiponectin levels are closely linked to decreased insulin sensitivity [44]. This hypothesis warrants further investigation through more focused and comprehensive studies.

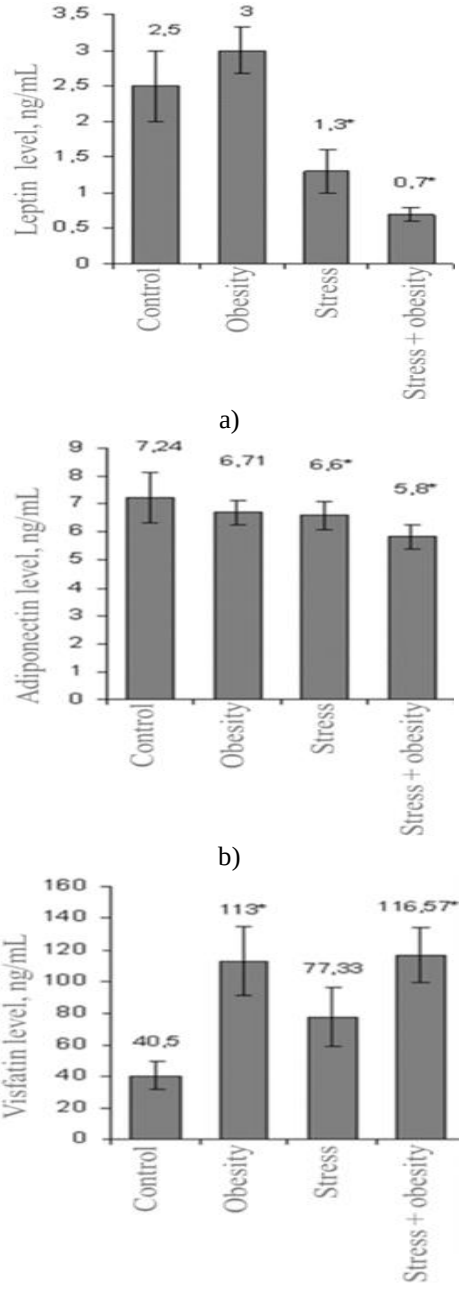

Figure 1. Changes in the hormone levels of leptin a), adiponectin, b) and vistafatin, c) in the blood serum of rats with alimentary obesity under chronic emotional stress (n = 10 for each group); *reliable differences from control (P < 0.05)

An interesting finding was the increase in visfatin levels across all experimental groups, with the most pronounced increase observed in the rats subjected to both stress and obesity (P < 0.05) **(Figure 1c)**. This can likely be attributed to the increased volume of adipose tissue [45]. Similar results were observed in cases of chronic asthma, where visfatin levels in the serum were elevated, potentially due to more intricate biochemical reactions in its metabolism [46]. Furthermore, a positive correlation between corticosterone and visfatin was noted in group 3, suggesting that stress might stimulate the visfatin gene expression via glucocorticoids, contributing to its secretion from adipose tissue [47-50].

Conclusion

In summary, the findings point to the possibility that a reduction in leptin levels during chronic stress could disrupt eating patterns. Regarding adiponectin, it appears that stress combined with obesity may accelerate the onset of insulin resistance. Visfatin secretion, while influenced by adipose tissue quantity, may be regulated by a more complex mechanism involving glucocorticoid-induced upregulation of the visfatin gene.

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