Endocrinology & Metabolic Syndrome

Shalaby, et al., Endocrinol Metab Synd 2015, 4:1
DOI: 10.4172/2161-1017.1000159

Research Article Open Access

Sex Differences in Some Physiological Effects of Cold Season or Short-Term Cold Exposure in Adult Albino Rat

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Abstract

Background: Cold exposure is a permanent part of human life. Response to cold varies according to different factors and individual differences. The main factors potentially differentiating thermoregulation in men and women are the properties of female physiology, anthropometric characteristics, body composition, social behavior and physical working capacity.

Aim of the study: Detecting the effect of short term cold exposure or cold season on body weight, food consumption, and levels of TSH, T_3, T_4, insulin, glucagon, adrenaline, cortisol, testosterone, progesterone and estrogen.

Material and methods: This study was carried out on 96 adult albino rats of local strain, half of them were males and the other half were females. The animals were divided equally into two control groups (males and females), and four experimental groups (two males and two females). Each group was divided into two equal sub-groups (one for morning experiment where blood samples were collected at 7:00 a.m to 8:00 a.m., and one for night experiment where blood samples were collected at 700 p.m to 8:00 p.m.). Blood samples were taken at the end of experimental period (7 days) for determination of TSH, T_3, T_4, insulin, glucagon, adrenaline, cortisol, testosterone, and progesterone and estrogen levels.

Results: Exposure of the body to cold produced the physiological responses according to the degree of cooling. The more severe the exposure to cold, the more marked were the effects that can be observed in body heat balance. Thyroid hormones increased through release of hypothalamus to TRH which led to release of TSH from the pituitary gland. Cortisol increased through stimulation of HPA axis. Adrenaline increased through stimulation of sympathetic nervous system and led to vasoconstriction and increased the release of fatty acids from adipose tissue to be used as energy substrates for heat production. Increased activity of the sympathetic nervous system during cold exposure led to decreased insulin secretion to increase blood glucose level which was used as a fuel for heat production. Activation of HPA was associated with increased progesterone hormone which has a role in thermogenesis. The increased needs for heat production in cold situations to keep body temperature constant led to increased food consumption, and the body weight showed no changes. This was because energy intake was used for heat production. Conclusion: Exposure to 4°C for 60 minutes for seven days cause significant increase in cortisol, adrenaline, estrogen, progesterone, insulin, T_3 and TSH, while testosterone significantly decreased. Also, exposure to 15-17°C for seven days caused significant increase in cortisol, adrenaline, estrogen and progesterone, while testosterone hormone significantly decreased. No significant changes occurred in T_4 and glucagon.

Keywords: Cold exposure; Sex difference; Physiological and biochemical effects of cold

Introduction

During the cold season, cold exposure is a permanent part of human life in circumpolar countries and occasionally also in the temperate zone as well. In some occupations, like in the mining industry, construction work, agriculture, forestry or seafaring, cold exposure may be considerable. There is also considerable cold exposure during indoor work, e.g. in the food industry. Evidently, circumpolar residents are exposed to cold in significant amounts in their everyday life [1].

Sexual dimorphism of body composition and physiological processes could result in differences in the male and female responses to cold [2]. Some of the differences in temperature regulation observed between men and women may be attributed to anthropomorphic characteristics. Compared to men, women tend to be of smaller stature, with resultant larger surface area-to-body mass ratio and lower total thermal mass. These contribute to a more rapid heat loss and decrease in core temperature when exposed to cold stress [3].

The main factors potentially differentiating thermoregulation in men and women are the properties of female physiology (e.g. sex hormones, body water regulation, exercise capacity, etc.), anthropometric characteristics (e.g. body mass and size), body composition (i.e. muscle and body fat content), and social behavior (e.g. daily physical activity). In conclusion, there are no substantial sex differences in the effectiveness of thermoregulation, except those that resulted from differences in body size and composition and physical working capacity. However, women show sex hormone-related fluctuations in body temperature and some thermoregulatory processes during the menstrual cycle and in the period of menopause. The mechanisms and site of female sex hormone action on thermoregulation are not fully understood and require further studies. The data are at some points confusing and, to say the least, incomplete [4].

The present study aimed to study the effects of cold season and short-term exposure on several hormonal parameters, i.e. TSH, T_3, T_4,

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Received December 23, 2014; **Accepted** February 09, 2015; **Published** February 16, 2015

Citation: Shalaby A, Eliwa KAA, Hassan AM, El-Fiky M (2015) Sex Differences in Some Physiological Effects of Cold Season or Short-Term Cold Exposure in Adult Albino Rat. Endocrinol Metab Synd 4: 159. doi: 10.4172/2161-1017.1000159

insulin, glucagon, adrenaline, cortisol, testosterone, progesterone and estrogen.

Materials and Methods

Materials

Ninety-six adult albino rats of local strain, 70 days old, weighing 100-110 g, were chosen as an animal model for this study. Half of the rats were males and the other half was females. The rats were obtained from one of animal houses in Cairo at Al-Azhar University. All rats were kept under observation for two weeks prior to the experiments to permit the animals to adjust to the environments. The animals were housed in standard suitable cages (20 × 32 × 20 cm for every 4 rats) in controlled temperature room (23°C ± 1°C) with normal light and dark cycle. They were maintained on a standard diet of commercial rat chow and tap water.

Methods

Experimental Procedure: The animals were divided into six equal groups as follows:

A- Control groups:

1. Group I: Male rats which were kept at room temperature of 23°C ± 1°C for seven days.
2. Group II: Female rats which were kept at room temperature of 23°C ± 1°C for seven days. B- Experimental groups:
3. Group III: Male rats which were kept in air-conditioned room at a temperature of 15-17°C for seven days.
4. Group IV: Female rats which were kept in air-conditioned room at a temperature of 15-17°C for seven days.
5. Group V: Male rats which were exposed to temperature of 4°C for 60 minutes daily for seven days.
6. Group VI: Female rats which were exposed to temperature of 4°C for 60 minutes daily for seven days.

Each group was divided into two equal sub-groups:

Sub-group **(a)** was for morning experiment where blood samples were collected at 7:00 a.m to 8:00 a.m.

Sub-group **(b)** was for night experiment where blood samples were collected at700 p.m to 8:00 p.m.

Food consumption was measured daily during the exprimental period (7 days). Body weight was measured at the beginning and at the end of the experiment.

Blood sampling: At the end of experimental period (7 days), blood samples were collected from the retro-orbital venous plexus by using heparinized capillary tubes (about 0.75-1.0 mm internal diameter) inserted in the medial canthus. The collected blood samples were kept in dry graduated plastic centrifuge tubes until coagulated. Blood samples were centrifuged at 4000 rpm for about 10 minutes to separate the serum. The serum was sucked out into Eppendorf tubes and all specimens of sera were stored at -20°C until used for the determination of:

- TSH [5]
- T3 [6]
- T4 [6]
- Insulin [7]
- Glucagon [8]
- Adrenaline [9]
- Cortisol [10]
- Testosterone [11,12]
- Progesterone [13]
- Estrogen [14]

These hormones were measured by ELISA.

Statistical analysis: One way ANOVA (Analysis Of Variance) test was used to do the following:

- Calculation of the descriptive statistics in studied groups (means ± standard deviations).
- Detection of any significant difference between different groups and between different samples.
- Performing multiple comparisons between each group and another and each sample and another by using the "Post Hoc LSD" multiple comparison tests.

The computer program SPSS version "17" was used to perform ANOVA test.

Results

Changes in body weight and food consumption (Figure 1): No significant difference in BW of experimental male – morning groups with corresponding controls at the beginning of the experiment. However, BW showed significant difference in experimental male – morning and night groups with corresponding controls at the end of the experiment. Experimental female – morning and night groups with corresponding controls at the beginning of the experiment showed no significant difference at the beginning and at the end of the experiment. However, BW showed significant difference between experimental female – night groups with corresponding controls at the end of experiment. In comparison between morning groups with corresponding night groups in males and females, there was no significant difference in food consumption between any of these groups. There were significant differences in experimental groups with corresponding controls.

Changes in thyroid hormones levels (Figure 2):T3: In comparison between morning groups with corresponding night groups in males and females, there was no significant difference in T3 level between any of groups. There were significant differences in experimental short-term cold exposure groups with corresponding controls. However, there were no significant differences in comparing experimental cold weather groups with corresponding controls. In comparison between female with corresponding male groups there was no significant difference in T_3 level between any of these groups.

T_4: In comparison between morning groups with corresponding night groups in males and females, there was no significant difference in T_4 level between any of these groups. There were no significant differences in comparing experimental groups with corresponding controls. In comparison between female with corresponding male groups there was no significant difference in T_4 level between any of these groups.

TSH: In comparison between morning groups with corresponding night groups in males and females, there was no significant difference

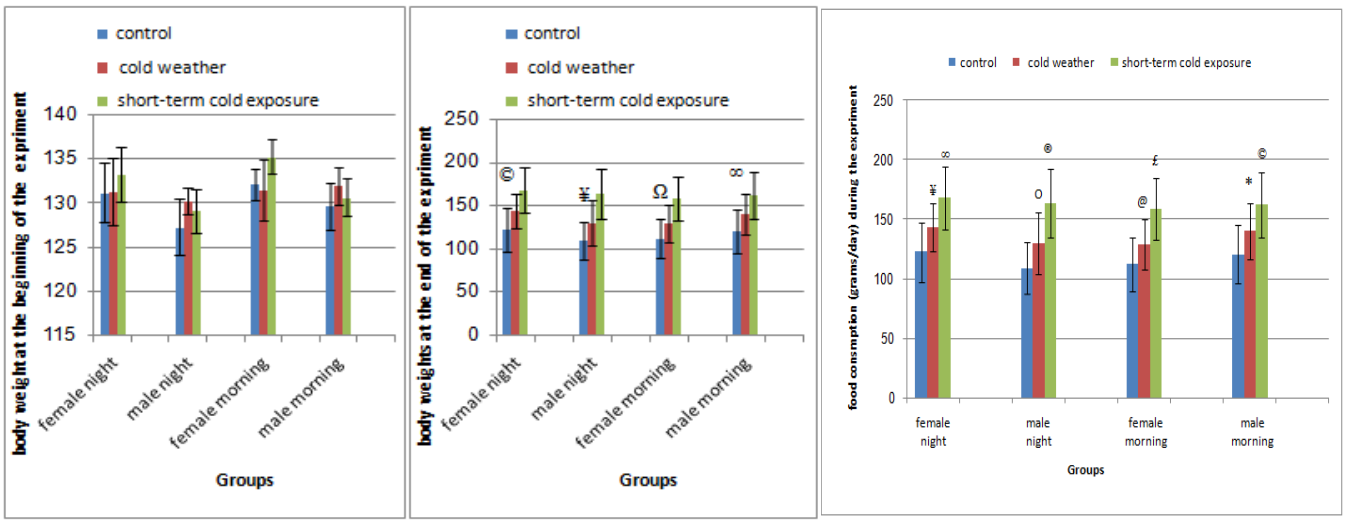

Figure 1: Changes in body weight and food consumption (Mean ± SD).
(¥)=Significant change on comparing female control and exposed to cold weather at night.
(∞)=Significant change on comparing female control and exposed to short-term cold at night.
(O)=Significant change on comparing male control and exposed to cold weather at night.
(®)=Significant change on comparing male control and exposed to short-term cold at night.
(@)=Significant change on comparing female control and exposed to cold weather at morning.
(£)=Significant change on comparing female control and exposed to short-term cold at morning.
(*)=Significant change on comparing male control and exposed to cold weather at morning.
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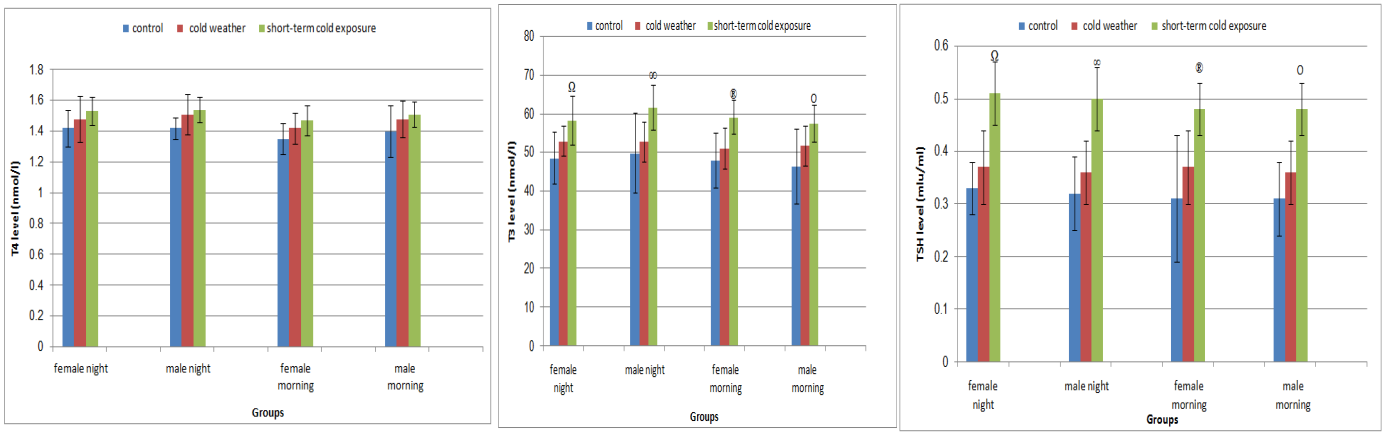

Figure 2: Changes in thyroid hormone levels.
(Ω)=Significant change on comparing female control and exposed to short-term cold at night.
(∞)=Significant change on comparing male exposed to short term cold at night with male exposed to cold weather at night.
(®)=Significant change on comparing female control and exposed to short-term cold at morning.
(O)=Significant change on comparing male control and exposed to short-term cold at morning.

in TSH level between any of groups. There were significant differences in comparing experimental cold weather groups with corresponding controls. However, there were no significant differences in comparing experimental cold weather groups with corresponding controls and in comparison between female with corresponding male groups.

Changes in insulin and glucagon levels (Figure 3): Insulin: There were significant differences in comparing experimental – short-term cold exposure groups with corresponding controls. There were no significant differences in comparing experimental - cold weather– groups with corresponding controls. In comparison between morning groups and corresponding night groups in males and females, there were no significant differences in insulin level between any of these groups. b-Glucagon: There were no significant differences in glucagon level between experimental groups and their corresponding controls. In comparison between morning groups with corresponding night groups in males and females, there was no significant difference in glucagon level.

Changes in cortisol and adrenaline levels (Figure 4(: Cortisol: There were significant differences in comparing experimental groups with corresponding controls. In comparison between morning groups with corresponding night groups in males and females, there was no significant difference in cortisol level between any of these groups. In comparison between female with corresponding male groups, there was no significant difference in cortisol level between any of these

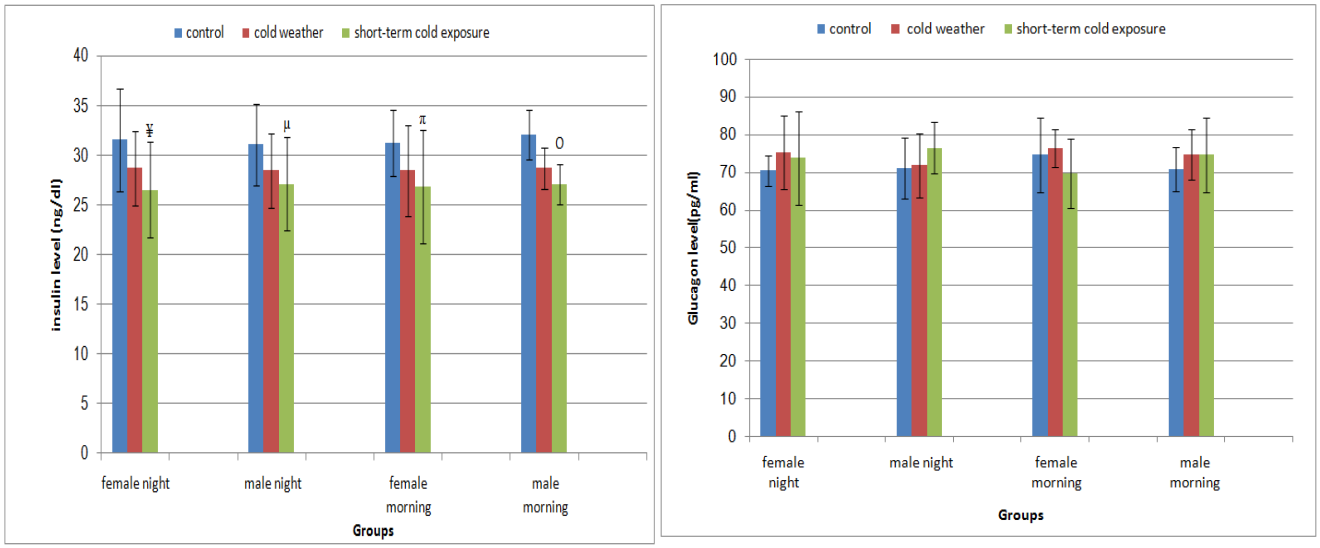

Figure 3: Changes in insulin and glucagon levels (Mean ± SD).
(¥)=Significant change on comparing female control and exposed to short-term cold at night.
(μ)=Significant change on comparing male control and exposed to short-term cold at night.
(π)=Significant change on comparing female control and exposed to short-term cold at morning.
(O)=Significant change on comparing male control and exposed to short-term cold at morning.

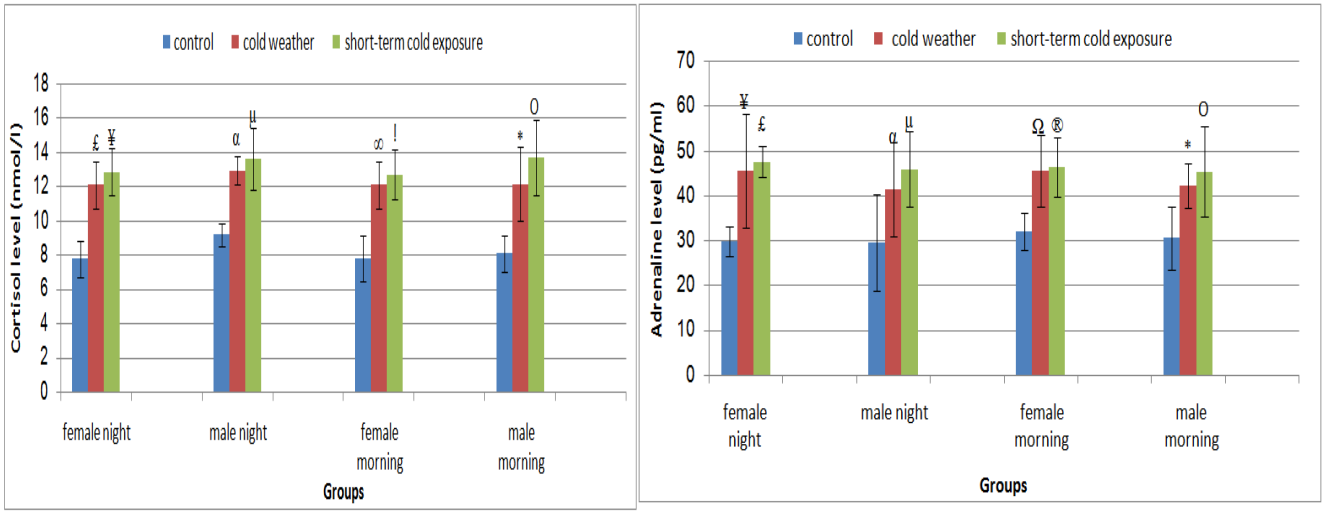

Figure 4: Changes in cortisol and adrenaline levels (Mean ± SD).
(£)=Significant change on comparing female control and exposed to cold weather at night.
(¥)=Significant change on comparing female control and exposed to short-term cold at night.
(α)=Significant change on comparing male control and exposed to cold weather at night.
(μ)=Significant change on comparing male control and exposed to short-term cold at night
(∞)=Significant change on comparing female control and exposed to cold weather at morning.
(!)=Significant change on comparing female control and exposed to short-term cold at morning.
(*)=Significant change on comparing male control and exposed to cold weather at morning.
(O)=Significant change on comparing male control and exposed to short-term cold at morning.

groups. Adrenaline: In comparison between morning groups with corresponding night groups in males and females, there were no significant difference (in adrenaline level between any of these groups. In comparison between female with corresponding male groups, there were no significant differences in adrenaline level between any of these groups.

Changes in sex hormones levels (Figure 5): E2: In comparison between morning groups with corresponding night groups, there was no significant difference in E2 level between any of these groups. There were significant differences in comparing experimental groups with corresponding control groups. Progesterone: In comparison between morning groups with corresponding night groups, there was no significant difference in progesterone level between any of the groups. There were significant differences in comparing experimental groups with corresponding control groups. Testosterone: In comparison

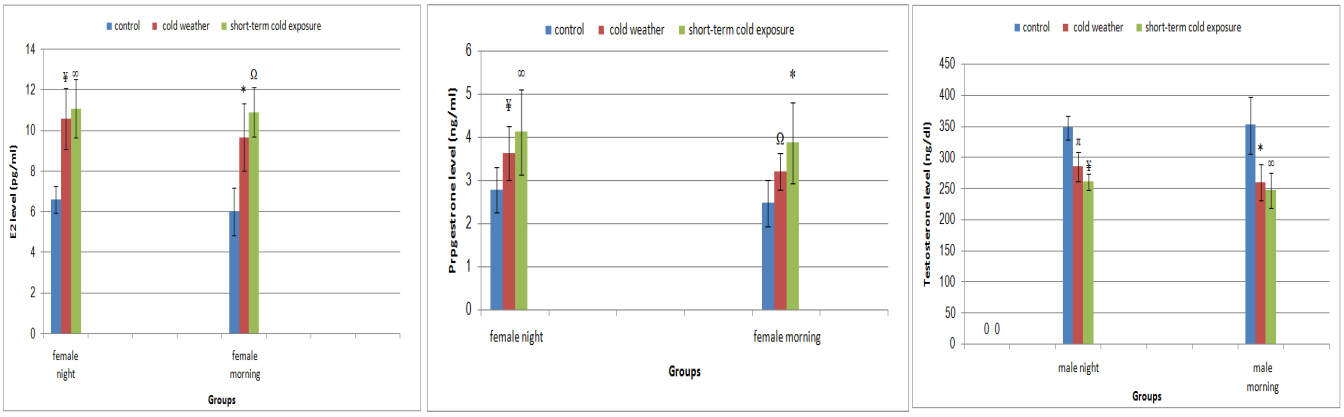

Figure 5: Changes in E2, Progesterone and Testosterone levels (Mean ± SD).
(¥)=Significant Changes on Comparing Female control and exposed to cold weather at night.
(∞)=Significant Changes on Comparing Female control and exposed to short term cold at night.
(*)=Significant Changes on Comparing Female control and exposed to cold weather at morning.
(Ω)=Significant Changes on Comparing Female control and exposed to short term cold at morning.

between morning groups with corresponding night groups, there was no significant difference in testosterone level between any of these groups. There were significant differences in comparing experimental groups with corresponding control groups.

Discussion

Thermoregulation is a complex system involving physical, chemical, and behavioral processes that allow the maintenance of body temperatures within a restricted range under conditions of variable internal or external heat loads [4]. When ambient temperature decreases below a thermoneutral temperature, the physiological heat producing mechanisms and the mechanisms that minimize the heat loss from the body become activated [15].

Chemical heat production is seen in the brown fat, Brown Adipose Tissue, (BAT). Brown fat can liberate its chemical energy directly in the form of heat. This process requires Uncoupling Proteins (UCP) which can be activated by thyroid hormones, catecholamines and the sympathetic nervous system [16,17]. Increase in noradrenaline concentration in the blood during cold exposure increases the production of cyclic AMP (cAMP), lipolysis and Free Fatty Acids (FFA). FFAs open the mitochondrial proton channel protein. Protons enter the mitochondria and inhibit ATP synthesis (uncoupling). This way, energy is transformed into heat instead of ATP [18,19].

The more severe the exposure to cold, the more marked are the effects that can be observed in body heat balance. Genes to cold tolerance, cold climate genes, promote adaptation to cold conditions and increase thermogenesis [20]. Marked individual differences have been found in the physiological responses to cold. The individual ability to protect against cold is affected by the shape and mass of the body, the amount of subcutaneous fat, physical fitness, age, sex, as well as some illnesses and medications [21]. These individual factors can also modulate the development of cold acclimatization. Habituation to cold usually produces reduced thermal discomfort and changes in circulatory as well as endocrine responses [22].

In the present study, there was a significant increase of T_3 and TSH level in comparing experimental short-term cold exposure groups with corresponding controls. These results were compatible with the findings of O´Malley [23] who found that exposure to ambient temperature of 4°C for 30–120 minutes increases serum T_3 concentrations. Maurya [24] found that exposure to cold leads to increase of serum T_3 levels. Rondeel [25] mentioned that thyroid hormone secretion is quickly activated by cold exposures. This may be due to activation of the thyroid gland which can be mediated via neuronal reflexes from the hypothalamus in mid brain. Hypothalamus increases TRH secretion which activates TSH and thyroid hormone release. Thyroid hormones exert their major effects on obligatory thermogenesis and resting metabolic rate, and seem to stimulate almost all reactions in the intermediary metabolism leading to heat production [26]. Thyroid hormones, particularly T_3, stimulate a general increase in metabolism by increasing the activity of the enzyme Na^+/K^+ ATPase (the sodium pump) in the plasma membrane, decreasing the efficiency of oxidative phosphorylation (via changes in the properties of the inner mitochondrial membrane), and possibly increasing calcium ion cycling. T_3 serves to increase heat production by two independent mechanisms: First, they work in conjunction with the sympathetic nervous system to stimulate heat production in brown adipose tissue. Second, they cause a generalized increase in the metabolic rate of all tissues by stimulating Na^+/K^+ ATPase-mediated ion transport across the plasma membrane [27]. Small mammals, like the mouse and rat, have a relatively high rate of heat loss, and at 4°C, the Resting Metabolic Rate (RMR) needs to double to maintain body temperature. Cunningham [28] and Quiroz [29] reported that thyroid hormones stimulated mRNA expression of UCP in skeletal muscles and the heart, and to a much lesser extent in spleen, lung or liver.

There were no significant differences in T_4 level in comparing experimental short-term cold exposure groups with corresponding controls. This may be due to peripheral deiodination of T_4 to T_3 in response to cold exposure [30].

There was no significant differences in T_3, T_4 and TSH levels in comparing experimental cold weather groups with corresponding controls. Weeke and Gundersen [31] found that core cooling in a thermoneutral environment had no effect on circulating thyroid hormone or TSH levels. This was also in agreement with Young et al. [32] who stated that, in short –term exposure to cold (cold air at 10°C) for 120 min, there are no changes in the serum levels of thyroid hormones indicating that cold stimulus is not enough to stimulate the secretion of these hormones. This may be due to that catecholamine thermogenesis in the adults obviates TSH and thyroid response [33].

In the present study, there was significant decrease of insulin level in comparing experimental – short-term cold exposure groups with corresponding controls. Galbo [34] and Seitz [35] found that cold

exposure inhibits insulin secretion. This decreasing in insulin secretion may be due to increased sympathetic nervous activity, and the decrease in insulin level may be compensated by increased sensitivity of tissues to insulin.

In the present study, there was no significant change in insulin level in comparing experimental-cold weather with corresponding controls. Koska et al. [36] stated that cold weather has no effect on insulin secretion indicating that cold stimulus is not enough to stimulate sympathetic nervous system to the degree that decreases secretion of insulin hormone in cold weather.

In the present study, there was no significant change in glucagon level in comparing experimental groups and their corresponding controls. This may be due to the increase of blood cortisol level in all experimental groups. Cortisol reduces glucose metabolism in most cells except the brain [37]. Also, Maurya et al. [24] found that glucose increases in cold exposure. So, there is more glucose in the blood which suppresses **glucagon** secretion. Seitz et al. [35] and Cannon and Nedergaard [38] stated that plasma glucagon level increases during cold exposure.

In the present study, there was significant increase of cortisol level in comparing experimental groups with corresponding controls. This may be due stimulation of the sympathetic nervous system. This was in agreement with *Pääkkönen and Leppäuto* [39] who mentioned that, in a short-term exposure to cold, increased secretion of cortisol has a positive effect by increasing the blood glucose level and FFA levels as well as vascular tone. Ohno et al. [40] Gerra et al. [41] and Wittert et al. [42] reported that the cold exposure has to be severe enough to increase plasma corticotropin level (>30 min, 4°C). Cortisol hormone stimulates catabolic processes and suppresses utilization of glucose and other substrates. They play a key role in glycogen synthesis, gluconeogenesis, including stimulation of glucogenic amino acid release. In adipocytes, they stimulate lipolysis and reduce the number of glucose transporters. Cortisol hormone acts in concert with catecholamines and many other hormones including those involved in rapid reaction to external temperature changes. Most effects of cortisol hormone consist in their regulation of the expression of various genes through interaction with glucocorticoid receptors and their binding to Glucocorticoid Responsive Elements (GRE) in the DNA of regulated genes [43].

In the present study, there was significant increase of adrenaline level in comparing experimental groups with corresponding controls. These results were in agreement with the findings of Wagner et al. [44] who reported that plasma adrenaline level increased in response to cold exposure. This also was in agreement with Thomas et al. [45] who found that the cold exposure has to be severe or combined with a stressful task to increase plasma adrenaline.

In the present study, there was significant decrease of testosterone level in comparing experimental groups with corresponding control groups. These results were in agreement with the findings of Weeke and Gundersen [31], O'Malley et al. [23] and Leppäluoto et al. [46] who mentioned that testosterone is potentially thermogenic hormone due to its ability to increase the metabolism, but its secretion is suppressed during cold exposure. The decreased testosterone level may be due to that stressors generally induce depression of hypothalamo-pituitary-testis system, mediated by activated hypothalamo-pituitary-adrenocortical system, resulting in fall in plasma LH and testosterone levels. CRH induces the release of endogenous opioids from hypothalamus, which along with corticosteroids suppresses the secretion of hypothalamic Gonadotrophin Releasing Hormone (GNRH). Suppression in secretion of GNRH causes reduced secretion of LH and FSH from pituitary, which in turn causes decrease in testosterone level. They suggested that increase in plasma level of glucocorticoids act via glucocorticoid receptors on testicular interstitial cells to suppress the testicular response to gonadotropins. There is a negative relationship between cortisol and testosterone [47].

There was significant increase of E_2 level in comparing experimental groups with corresponding control groups. These results were in agreement with Stephenson and Kolka [48] who mentioned that the role of the reproductive hormones on thermoregulation in women has been well documented. Estrogens may also influence hormones involved in substrate metabolism or those that could affect the thermogenic response to cold.

In the present study, there was a significant increase of progestrone level in comparing experimental groups with corresponding control groups. Like cortisol, progestrone is released in response to Adrenocorticotropin Hormone (ACTH) In comparison between morning groups with corresponding night groups in males and females, there were no significant differences between any of these groups. Female with corresponding male groups showed no significant difference between any of these groups. These results were in agreement with Kaciuba-Uscilko and Grucza [4] who reported that there are no substantial sex differences in the effectiveness of thermoregulation, except those that resulted from differences in body size and composition and physical working capacity.

In the present study, there was significant increase in food consumption in comparing experimental groups with corresponding control groups. There was significant increase in body weight in comparing control groups at the beginning and at the end of the experiment, and there was significant increase in body weight in comparing control groups at the beginning and at the end of the experiment. This may be due to the increased of the energy expenditure in the cold exposure which led to increase of heat production to protect the rat from hypothermia in cold conditions. The increased energy expenditure stimulates appetite and causes enhanced energy intake, i.e. diet-induced thermogenesis, which is probably facultative and adaptive and due to brown adipose tissue activity [49]. The unchanged body weight may be due to that energy intake is the same as the energy expenditure in which energy intake is used mainly for thermoregulation [24].

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