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Original Research Article

Postnatal Exposure to High Altitude Hypoxia Induces Developmental Changes in Rat Testis

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ABSTRACT

Introduction: Recently, there are great concerns regarding effects of high altitude hypoxia on postnatal rat testicular development which intern may affects spermatogenesis. The purpose of this study was to elucidate the effect of high altitude hypoxia on plasma hormonal levels and haematocrit values.
Method: This study was carried out at two different altitudes in the southern Saudi Arabia. Sixty neonate's wistar rats were divided into two groups; control group (24) rats and hypoxic group (36) rats. Control Rats subdivided into six subgroups while hypoxic rats were subdivided into six groups. Blood samples were taken directly from the eye orbital vein. Hormonal levels and haematocrit values were measured on days 7, 14, 21, 28, 35 and 45.
Result: Testosterone secretion in hypoxic rats compared to control showed marked reduction after postnatal day 21. Whereas, levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) measured at weeks 4, 5 and 6 of high altitude (HA) rats were decreased significantly as compared to their corresponding levels measured at low altitude (LA). This study showed a weekly gradual increase in serum levels of this hormone during the first 6 weeks of postnatal development of control rats. While, the value of cortisol obtained in any week was significantly higher than its value of the preceding week. Moreover, significant reductions in Haematocrit (Hct) percentages were reported from week 2 to 6 in HA rats more than in LA rats.
Conclusion: that postnatal exposure to high altitude hypoxia adversely affects testicular hormones level and Haematocrit values.

Keywords: high altitude, hypoxia, postnatal, serum, haematocrit.

INTRODUCTION

Spermatogenesis is mainly regulated by Follicle stimulating hormone (FSH) which binds to receptors in Sertoli cells and regulates spermatogenesis through Sertoli cell function, [1] it has a major role in the proliferation of Sertoli cells [2,3] and it controls the secretion of Sertoli cell products such as transferrin, androgen binding protein, Müllerian inhibiting substance, stem cell factor (SCF) and inhibin B. [1,4] Immature Sertoli cells secrete both α- and β-subunits of Inhibin B. [5] In humans, expression of inhibin β-subunit changes at puberty; however, Sertoli cells continue to secrete inhibin α-subunit in adulthood. This developmental change makes inhibin B a good marker for germinal epithelial function. [6] LH stimulates the secretion of testosterone, which has

paracrine and autocrine effect as it binds to nuclear androgen receptors. [7] FSH plasma levels in rats decrease after birth to the lowest point around postnatal day 5-15. [8,] Then FSH levels start to increase again reaching a peak on postnatal day 25-45. [9-12] After that, plasma levels of FSH fall reaching a plateau from postnatal day 50 onwards. Unlike FSH, postnatal period show a less marked changes in the plasma levels of LH; but have a tendency to increase as the rat matures. [9,10] In humans, plasma levels of FSH and LH increase after birth and reach a peak during the first three months. [13,14,6] Whereas, levels of these hormones decline to a level at which they remain during childhood. During puberty plasma levels of LH and FSH increase. [15] The plasma level of testosterone follows the pattern of LH, which indicate that the immature testis responds to LH stimulation. [14,16]

MATERIALS AND METHODS

Experimental design

Sixty wistar rats were used in the present study were divided into two groups; control group (24) rats and hypoxic group (36) rats. Rats of the control group will further subdivided into six subgroups of four each. Rats of the hypoxic group will subdivided into six groups of six each. Rats in their corresponding group were anesthetized using Phenobarbital (65 mg/kg). Then blood sample was taken directly from the eye orbital vein to assess the levels of testosterone were measured on days 7, 14, 21, 28, 35 and 45.

Serum collection and biochemical measurements

Rats from both areas (HA and LA) were maintained in the same polypropylene cages. They were housed in 6 groups of 4 rats per cage (50´26´16 cm) and fed the same standard diet. At the end of each period of HA exposure or LA, all rats in their corresponding group were anesthetized using Phenobarbital (65 mg/kg). A blood sample was taken directly from the eye orbital vein and hematocrit was determined by centrifugation of a capillary tube with heparinized blood in a micro-hematocrit centrifuge. After that, another blood sample was collected directly from the heart with the aid of 3 ml syringe and placed in 5 ml plain tubes where they were allowed to clot at room temperature. Then, the samples were centrifuged at 4000 RPM for 10 min to collect serum for testosterone level measurements, cortisol, FSH and LH using ELISA kits.

RESULTS

Changes in Haematocrit

Changes in Hct levels in the blood of all groups of rats at both LA and HA areas are presented in (Text- figure 2 and table 2). Significant increases in Hct percentages were seen from week 2 to 6 in both LA and HA areas. Low baseline levels of Hct were noted in the blood of rats in both LA (31.33%±1.36) and HA (24.67%±1.36) areas. Baseline Hct level measured at HA rats was significantly lower than its corresponding baseline levels measured at LA. The percentages of decrease in this baseline Hct level were 21.05%. However, At both LA and HA area, the measured Hct percentages showed significant changes between weeks 3,4 and 5 but the levels of these Hct values were significantly higher than those measured at baseline, and significantly lower than those measured in week 6. However, as compared to baseline levels, the maximum increases in the levels of Hct percentages were seen by the end of week 6 at both LA (48.0%±0.632) and HA (57.15±. 725) areas. However, the data showed that the percentage of increase in Hct level at the end of weeks 6 in the blood of HA rats as compared to that measured in LA rats was 18.75%.

Hormonal assay

Changes in testosterone levels: Text-Figure 3 and table 3 show the changes in the levels of serum testosterone in both LA and HA rats at different time intervals of development. There was a significant decrease ($P<0.0001$) in testosterone baseline levels of 2 weeks in rats exposed to HA

environment (4.79±0.086) as compared to its corresponding levels measure on week 2 at LA area (5.23±0.20) resulting in a decrease of about 8.9 %. However, a gradual increase of testosterone levels on weeks 3 and 4 was followed by a gradual decrease in its levels on weeks 5 and 6 observed in both LA and HA rats. However, the statistical analysis showed that the peak increases in testosterone levels in both LA and HA areas occurred on week 4 (5.965±0.488 versus 5.142±0.098) ng/ml, respectively) and the least decrease in its levels, in both LA and HA areas, were seen by the end of week 6 (2.824±0.33 versus 1.709±0.133 ng/ml). When compared to the maximum value of testosterone levels on week 4 in each area, the percentages of decreases in testosterone levels on week 6 at both LA and HA areas were 52.5% and 66.7% respectively. However, all levels of testosterone measured in both HA areas over all periods of study were significantly lower than those of the corresponding levels measured at LA. As compared to their corresponding time intervals at LA area, the percentages of decreases in testosterone levels at weeks 3, 4, 5 and 6 were 17.4%, 14 %, 25.9% and 40%, respectively.

Changes in FSH levels

As shown in Text-figure 4 and table 4, baseline levels and weekly changes in FSH hormones were measured in the serum of rats at both LA and HA. The data showed no significant changes (P=0.06832) in the baseline levels of FSH at week 2 between LA (0.968±0.08 ng/ml) and HA (1.072±0.15 ng/ml) rats. On week 3, and as compared to FSH levels in week 2, only rats of LA area showed a significant increase (P<0.0001) in FSH levels (48.3%)whereas no significant change (P=0.9849) were encountered in the levels of this hormone in week 3 of HA rats (1.146±. 063 ng/ml versus 1.072±0.15 ng/ml). However, from week 4 to 6, there was a steady increase in the levels of this hormone with the maximum encountered in week 6 in both areas. The levels of FSH measured by the end of week 6 at both LA and HA areas were 5.533±0.19 ng/ml and 3.298±0.12 ng/ml resulting in about 471% and 207.6% of increases as compared to their corresponding levels measured by the end of week 2, thus showing the increase in FSH levels was greater at LA area. However, the data of this analysis showed that levels of FSH measured at weeks 4, 5 and 6 of HA rats were decreased significantly (P<0.0001) as compared to their corresponding levels measured at LA. The percentages of decreases in FSH levels in the serum of these rats were 18.4%, 23.9% and 40.4%, respectively.

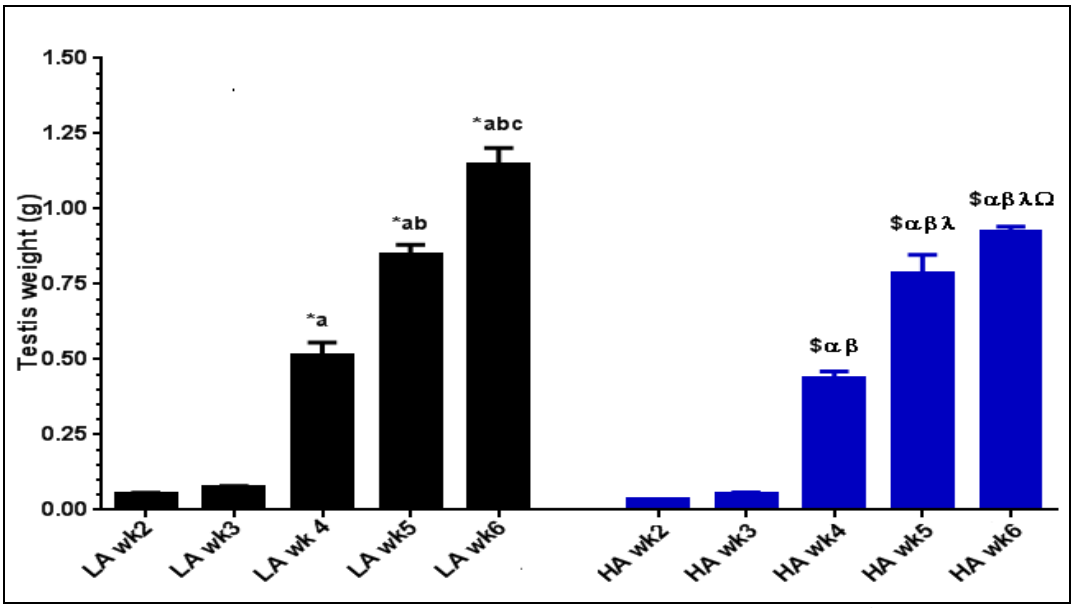
Changes in LH levels

The changes in the levels of LH in the sera of LA and HA rats are shown in figure 5 and table 5. Similar to FSH and testosterone, baseline serum levels of LH were not significantly different (P<0.0001) when the LA and HA rats compared against each other by the end of week 2 (1.22±0.25 versus1.13±0.34). However, a gradual increase in the levels of LH was seen starting from week 3 to week 6 at both LA and HA areas; each measured value was significantly higher than the measured value of the preceding week (P<0.05). The maximum increase in the levels of FSH in both areas were observed by the end of week 6, with 53.8% and 31.8% increase of this hormone occurred in both LA and HA rats respectively as compared to baselines values obtained by the end of week 2. However, in spite of the increases in the levels of LH at HA area, serum levels of these hormones were significantly lower than their corresponding levels obtained at the same time intervals in the sera of LA rats. The percentages of decreases in the levels of this hormone in the sera of HA rats at week 3, 4, 5 and 6 were 42.2%, 29.1%, 24%and 38.9%, respectively.

Changes in Cortisol levels

The changes in levels of cortisol in the sera of rats at both LA and HA areas are shown in figure 6. The data showed a weekly gradual increase in the serum levels of this hormone during the first 6 weeks of rat's developments in both areas. However, the value of cortisol obtained each week

was significantly higher than its value obtained the week before and all values obtained at HA area at all periods of study were significantly higher than those obtained in LA rats. In both LA and HA areas, the maximum increase in cortisol levels were detected at the end of week 6; 129.7±23.08 and 269.2±19.37 respectively. Thus, as compared to baseline levels on week 2, the percentages in increase in cortisol levels in these areas were 240% and 557.8% when compared to their corresponding values obtained from LA rats at weeks 2, 3,4,5 and 6; cortisol was significantly increased by 64%, 70.7, 43.1%, 115.2% and 108.5%.



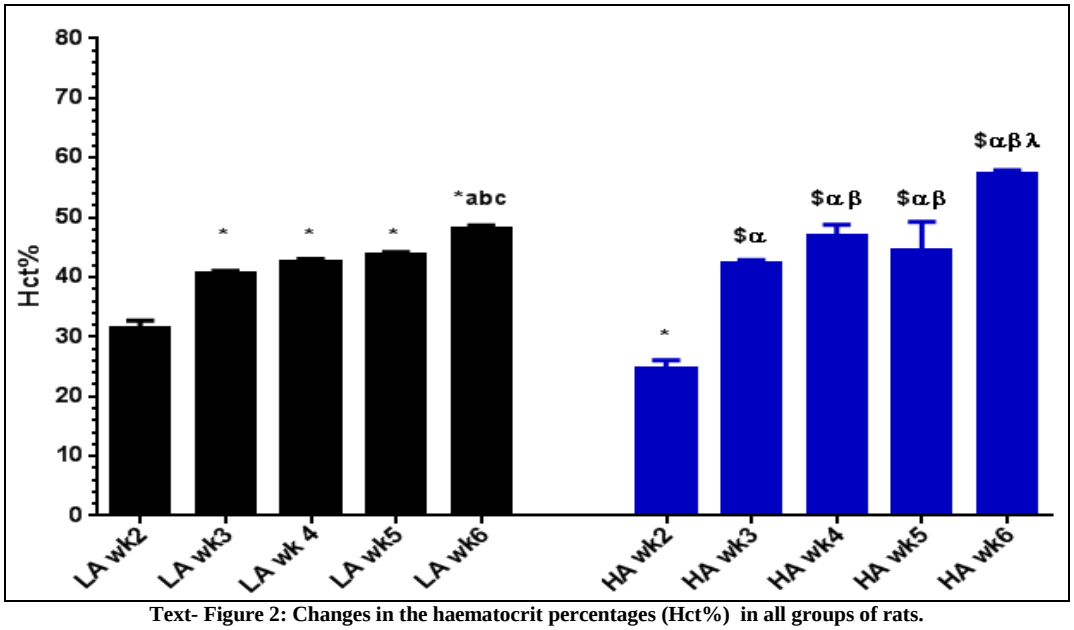
Text- Figure 1: Changes in the average right testis weight levels in all groups of rats.

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P <0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: Significantly different when compared to same corresponding age group in the LA area.

Table 1: Changes in the average weight of the right testicle in all groups of rats

Group	Week 2	Week 3	Week 4	Week 5	Week 6
LA	0.052±0.005	0.074±0.005	$0.511\pm0.044^{*a}$	$0.850\pm0.0310^{*ab}$	$1.148\pm0.0543^{*abc}$
HA	0.0338±0.002	0.0544±0.004	$0.0433\pm0.0221^{\$\alpha\beta}$	$0.0666\pm0.294^{\$\alpha\beta\lambda}$	$0.924\pm0.0181^{\$\alpha\beta\lambda\Omega}$

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: Significantly different when compared to same corresponding age group in the LA area.



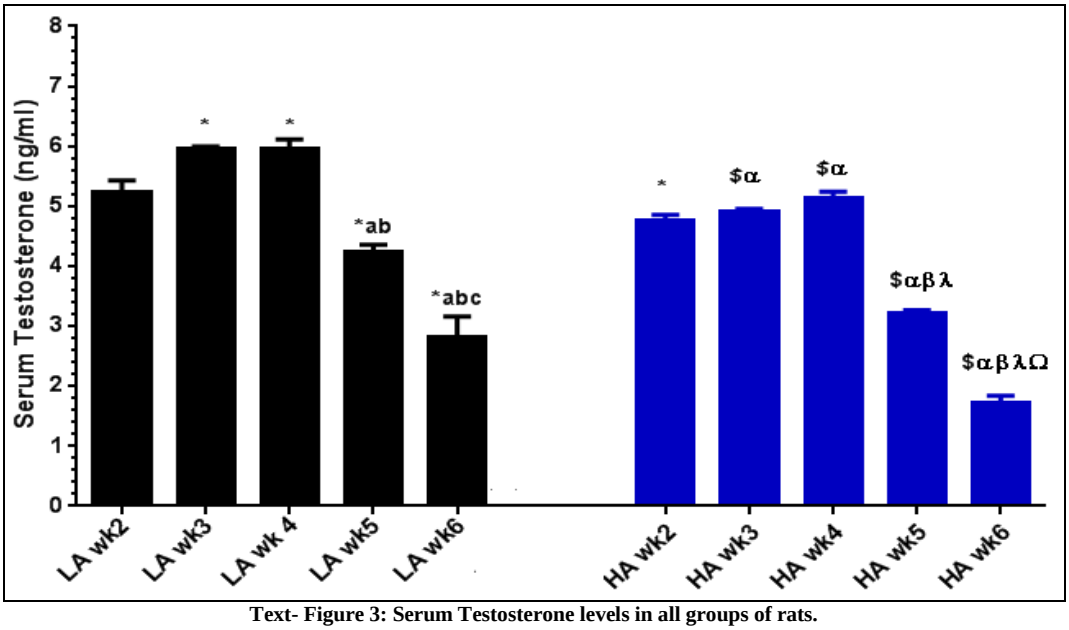
Text- Figure 2: Changes in the haematocrit percentages (Hct%) in all groups of rats.

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P <0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: Significantly different when compared to same corresponding age group in the LA area.

Table 2: Changes in the haematocrit percentages (Hct%) in all groups of rats.

Group	Week 2	Week 3	Week 4	Week 5	Week 6
LA	0.31.33±1.366	40.50±0.547*	42.50±0. 0.547 *	43.67±0.516*	48.00±0.6325^{*abc}
HA	.67±1.366*	42.33±0.516$^{\$\alpha}$	46.83±1.94$^{\$\alpha\beta}$	44.50±4.76$^{\$\alpha\beta}$	57.17±0.752$^{\$\alpha\beta\lambda}$

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P <0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: Significantly different when compared to same corresponding age group in the LA area.



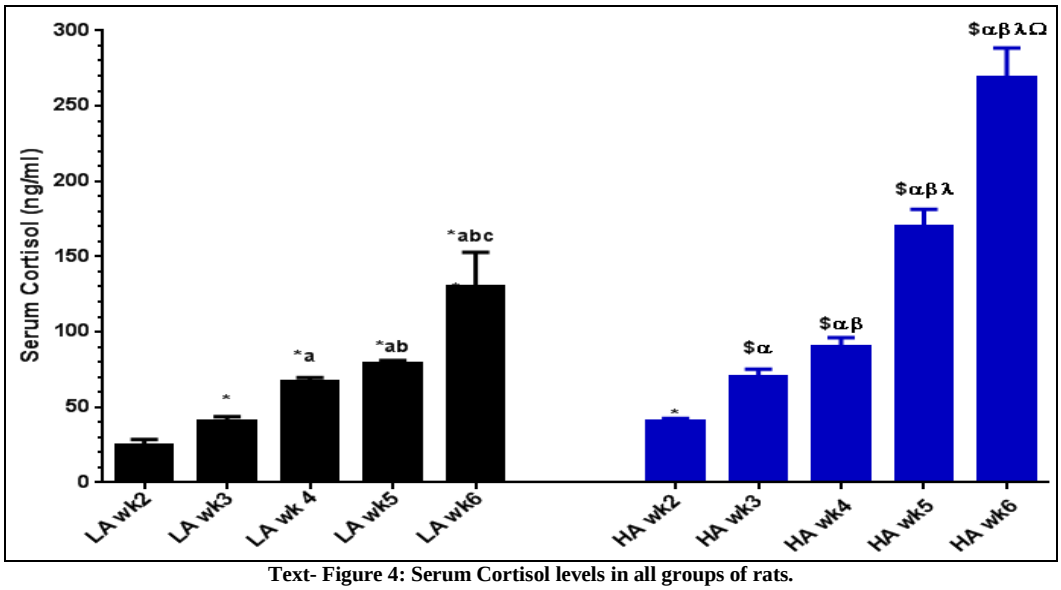
Text- Figure 3: Serum Testosterone levels in all groups of rats.

Table 3: Serum Testosterone levels in all groups of rats

Group	Week 2	Week 3	Week 4	Week 5	Week 6
LA	5.230±0.201	5.94±0.0487*	5.96±0.149 *	4.23±0.121 *ab	2.82±0.334 *abc
HA	4.76±0.086*	4.91±0.045 $α	5.14±0.097 $α	3.22±0.045 $αβλ	1.70±0.133 $αβλΩ

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: significantly different when compared to same corresponding age group in the LA area.

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different 5.

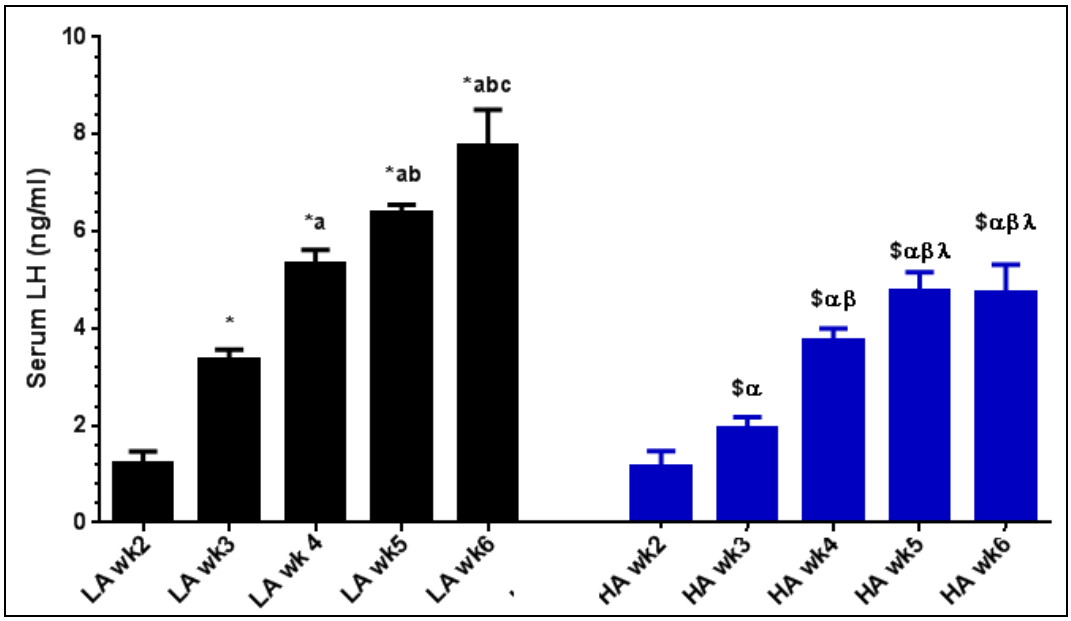


Text- Figure 4: Serum Cortisol levels in all groups of rats.

Table 4: Serum Cortisol levels in all groups of rats.

Group	Week 2	Week 3	Week 4	Week 5	Week 6
LA	24.94±3.62	40.99±2.66*	67.12±2.68^{*a}	79.14±1.85^{*ab}	129.7±23.08^{*abc}
HA	40.92±1.55*	69.98±5.34$^{\$\alpha}$	90.24±5.90$^{\$\alpha\beta}$	170.0±11.36$^{\$\alpha\beta\lambda}$	269±19.37$^{\$\alpha\beta\lambda\Omega}$

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared α: Significantly different when compared to HA different when compared to same corresponding age group in the LA area. to HA wk5. $: significantly different when compared to same corresponding age group in the LA area. wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: significantly



Text- Figure 5: Serum LH levels in all groups of rats.

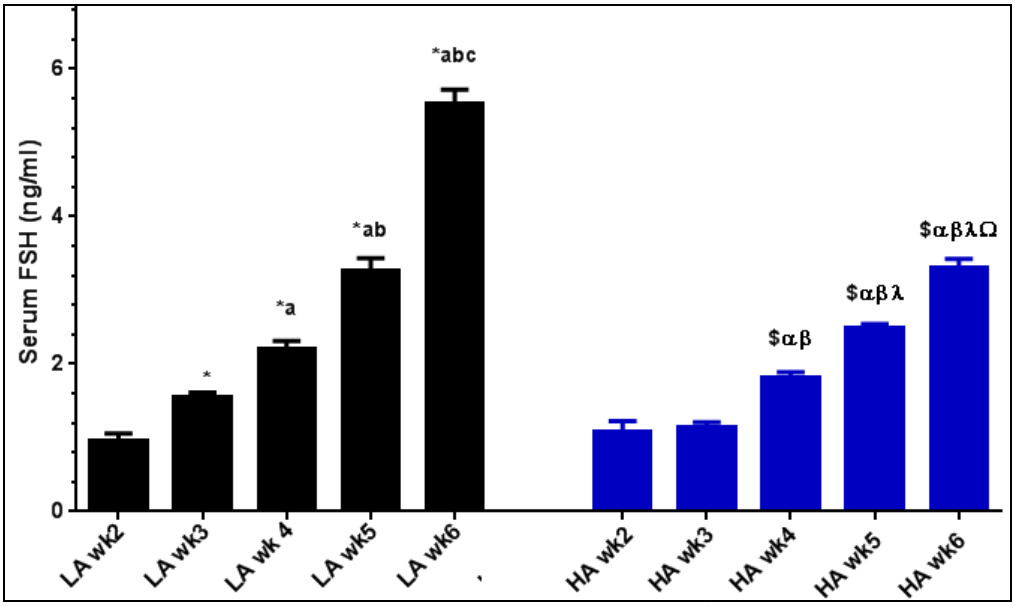
Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: significantly different when compared to same corresponding age group in the LA area.

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly

different when compared to HA wk5. $: significantly different when compared to same corresponding age group in the LA area.

Table 5: Levels of LH in all groups of rats

Group	Week 2	Week 3	Week 4	Week 5	Week 6
LA	1.21±0.251	3.35±0.211*	5.33±0.287^{*a}	6.37±0.177^{*bc}	7.75±0.753^{*abc}
HA	1.13±0.342	1.93±0.238$^{\$\alpha}$	3.74±0.253$^{\$\alpha\beta}$	4.78±0.374$^{\$\alpha\beta\lambda.}$	4.73±0.581$^{\$\alpha\beta\lambda.}$



Text- Figure 6: Serum FSH levels in all groups of rats.

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: significantly different when compared to same corresponding age group in the LA area.

Table 6: Levels of LH in all groups of rats

Group	Week 2	Week 3	Week 4	Week 5	Week 6
LA	0.968±0.089	1.55±0.063*	2.20±0.109^{*a}	3.27±0.164^{*bc}	5.53±0.191^{*abc}
HA	1.07±0.153	1.14±0.063	1.80±0.081$^{\$\alpha\beta}$	2.48±0.055$^{\$\alpha\beta\lambda.}$	3.29±0.123$^{\$\alpha\beta\lambda.}$

Values are expressed as Mean ± SD for 6 rats in each group. Values were considered significantly different at P < 0.05.*: Significantly different when compared to LA wk2. a: Significantly different when compared to LA wk3. b: Significantly different when compared to LA wk4 c: Significantly different when compared to LA wk 5. α: Significantly different when compared to HA wk2 β: significantly different when compared to HA wk3. λ: significantly different when compared to HA wk4. Ω: Significantly different when compared to HA wk5. $: significantly different when compared to same corresponding age group in the LA area.

DISCUSSION

Haematocrit

Significant increases in Hct percentages were seen from week 2 to 6 in

both LA and HA areas. Low baseline levels of Hct were noted in the blood of rats at both LA and HA areas. The ANOVA analysis showed that the baseline Hct level measured at HA rats was significantly lower than its corresponding baseline levels measured at LA, this may be due to the reason that new blood cell are found in the circulation after 4 to 5 days from the stimulation of the kidney by hypoxia. [17]

The percentages of decrease in this baseline Hct level were 21.05%. However, in both LA and HA area, the measured Hct percentages showed significantly changes between weeks 3,4 and 5 but the levels of these Hct values were significantly higher than those measured at baseline, and significantly lower than those measured at week 6. However, the data showed that there was an increase in Hct level at the end of weeks 6 in the blood of HA rats as compared to that of the LA rats; this is probably because hypoxia is the main stimulus for the release of hormone erythropoietin from the kidney, and this hormone acts on the erythropoietin sensitive committed stem cells in the bone marrow to stimulate red blood cell production. [17]

Cortisol

Cortisol is the primary stress hormone; stress causes increase in plasma cortisol levels that in short run are life-saving, but in the long run are definitely harmful and disruptive. [18] This study showed a weekly gradual increase in the serum levels of this hormone during the first 6 weeks of rat's developments in both areas. However, the value of cortisol obtained in any week was significantly higher than its value of the preceding week. Moreover all values obtained at HA area at all periods of study were significantly higher than those obtained in LA rats. Our results indicate that hypoxia increases the levels of plasma cortisol and this may be the cause of the structural changes in testes in all weeks of postnatal development.

Reproductive hormones

The plasma testosterone concentration in control rats was maintained at a low level from birth to postnatal day 21, and began to increase after postnatal day 28.This confirms the findings of [19] in which it was shown that the concentration of testosterone in plasma increases on week four and thereafter till maturity. The trend of plasma testosterone level is said to be due to apoptosis of the fetal-type Leydig cells and the differentiation of adult-type Leydig cells during the neonatal period. [20,21,7] In this investigation, testosterone secretion in hypoxic rats was inhibited on postnatal day 7, stimulated between postnatal day 7 and 21, and followed by suppression after postnatal day 21.Interestingly, in hypoxic rats after postnatal day 21, the plasma testosterone level dramatically declined to the baseline, but increased rapidly after postnatal day 28 in the controls. One of the possible explanations for this difference might be that the hypoxia arrested differentiation of adult-type Leydig cells within critical period for neonatal development through the hypoxia induced-hypothyroidism. The critical role of thyroid hormone is to initiate the onset of mesenchymal cell differentiation into adult Leydig cells; this has been proposed by. [22] It was demonstrated that neonatal hypothyroidism arrested the differentiation of adult-type Leydig cells, [23,24] and also induced a chronic reduction in the circulating gonadotropins. [25] Testosterone seems to have an important role in high altitude adaptation owing to its identity as an erythropoietin hormone which acts directly on bone marrow at the level of polychromatophilic erythroblasts. [26] Thus, an early rise in testosterone in hypoxia and its role as a vasodilatation agent is consistent with its possible role in early vascular changes in the hypoxic testes, as well as being a likely activator of the erythropoietin response in hypoxia, acting both as a local paracrine hormone and as an endocrine signal toward bone marrow cells. [27] In the testes, LH stimulates testosterone secretion. FSH is important in the initiation and maintenance of spermatogenesis by stimulating Sertoli cells. [28] In this study, it

was shown that on week 3, and as compared to FSH and LH levels of week 2, only rats of LA area showed a significant increase in FSH and LH levels. This may explain how hypoxia inhibits spermatogenesis, especially in the first three weeks of postnatal development. Control mechanisms for FSH secretion seem to be influenced not only by testosterone and its metabolic derivative estradiol, but also by activin and inhibin produced by Sertoli cells. [29] Hypoxia induces a decrease in testicular function by early direct effects on spermatogenesis and later, by affecting hypophysis-gonad hormonal axis. [30]

Abbreviations

FSH, follicle stimulating hormone; **LH,** luteinizing hormone; **HA,** high altitude; **LA** low altitude **Hct,** heamatocrit; **SCF**, stem cell factor; **RPM,** round per minute.

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Competing Interests

The authors have declared that no competing interest exists.

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