Reproductive Hormonal Changes during Pre- and Post-Pubertal Stages in Male Wister Rats

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Abstract:

The present study has been conducted to investigate the reproductive hormonal changes at pre- and post-pubertal stages of male Wister rats. Fifty male Wister rats (25 immature and 25 mature) were used in the present study. At pre-pubertal stage, 5 male rats of 25, 30, 35, 40, and 45 days old, and at post-pubertal stage, 5 male rats of 55, 60, 65, 70, and 75 days old were anasthetized and blood samples were obtained from abdominal vein for assessment of activin-A, inhibin-B, FSH, LH, testosterone, and estrogen. The results demonstrated significant increase of serum activin-A concentration at 30 and 40 day periods. Throughout the post-pubertal stage, activin-A concentration gradually decreased. Serum inhibin-B concentrations gradually decreased at the pre-pubertal stage. Post-pubertal stage registered gradual increase. At 25, 30, and 35 day periods, serum FSH level registered no significant changes, whereas 40 day period recorded significant increase then decreased at 45 day period. Throughout the post-pubertal period, the level of FSH concentrations continued in graduall decrease. At 25, 30, 35, and 40 day periods, serum LH and testosterone levels showed no significant differences, whereas 45 day period recorded significant increase. Postpubertal stages showed gradual significant increase. Serum estradiol concentration decreased gradually at the pre-pubertal stage and continued in decrement at the post-pubertal stage. It can be concluded that serum inhibin-B has positive correlation with testosterone concentration at pre- and post-pubertal stages, and positive correlation with FSH and LH concentrations at pre-pubertal but negative partial correlation at post-pubertal stage.

Key words: Inhibin, Activin, FSH, LH, Estradiol, testosterone

Introduction:

The first wave of spermatogenesis in the male encompasses the proliferation and differentiation of germ cells and Sertoli cells is regulated by a complex interaction between hormones, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), androgens and locally produced factors including activins and inhibins (1). Inhibin is the principal negative modulator of FSH synthesis and secretion, whereas activins promote the opposite (2). There are changes with age in the responsiveness of the pituitary gland to the actions of inhibin, the clearance of inhibin and the testicular secretion and circulating concentrations of inhibins (3).

Early puberty is characterized by a positive correlation between inhibin B and LH/testosterone, but no correlation to FSH. Late puberty is characterized by a negative correlation between inhibin B and FSH (which is maintained in adult men), a diminishing negative correlation between inhibin B and LH, and no correlation between inhibin B and testosterone (4). The circulating level of FSH is, in turn, regulated by a complex mechanism mediated by interactions between inhibins and activins (5). Accumulating evidence indicates that modulation of FSH secretion is, in addition to the endocrine action, resulted from autocrine/paracrine activities of these proteins (6).

The gonadotropin control of testicular inhibin B secretion by the primate testes involves opposing stimulatory and inhibitory actions of FSH and LH, respectively. FSH is posited to act directly on the Sertoli cell, The action of LH, on the other hand, appears to be mediated by a paracrine action of testosterone from the Leydig cell to regulate inhibin βB gene expression by the Sertoli cell (7). In the adult, serum inhibin B shows a clear diurnal variation closely related to that of testosterone (8).

The testes of prepubertal males synthesize and secrete significant amounts of inhibin and the pattern of secretion of inhibin changes during sexual development although there appears to be substantial differences between species. For example, circulating concentrations of inhibin during sexual maturation have been found to increase in male monkeys (9) and boys (10) but to decrease in male rats (11), bulls (12) and rams (13).

The testosterone and/or other factors from the testis are essential for the maintenance of *Inhba* gene expression in mouse (14). On the other hand Serum inhibin B concentrations in postpubertal men were closely related to the presence of germ cells from pachytene spermatocytes to early spermatids (15). On the other hand, the oestradiol is important for the long-term maintenance of spermatogenesis, particularly the production of round spermatids

and formation of the acrosomal granule, suggesting a role for oestrogen in the differentiation of spermatocytes (16).

The present study aims to investigate the sequential changes of male reproductive hormones (inhibins, activins, FSH, LH, testosterone and oestradiol) during pre- and post-pubertal stages in male rats, to try gain insight in to the roles of these hormones in normal testicular development and reproduction. This could assist future studies in experimentally manipulated animals that exhibit perturbed or altered testis function.

Materials and Methods

Animals:

Fifty male Wistar rats, were breed at the animal house of the college of veterinary medicine, Al-Qadisiya University. Animals were reared under controlled conditions (12L:12D cycles at 22±2 C°) and fed on standard laboratory food (19% protein ratio and 3000 kilocalories energy) and drinking water *ad libitum*. The studu has been performed in two stages: at pre-pubertal stage, 5 males of 25 days old (weighted 34±0.89g), 30 days old (weighted 46±0.93g), 35 days old (weighted 58±0.91g), 40 days old (weighted 71±1.15g), and 45 days old (weighted 89±1.10g), and at post-pubrtal stage, 5 males of 55 days old (weighted 102±9.84g), 60 days old (weighted 111±1.22g), 65 days old (weighted 127±1.74g),70 days old (weighted 138±1.55g) and 75 days old (weighted 150±1.64g) were sacrificed after general anesthesia by combination of Xylazine and Ketamine (10mg and 90mg/kg, *ip*, respectively). Blood samples were obtained from abdominal vein for assessment of FSH, LH, estrogen, testosterone, activin A, and inhibin B.

Hormonal assays in blood serum by ELISA technique:

A) Assessment of Activin-A concentrations (pg/ml) :

According to the manufacturer instructions (ABO Switzerland), activin-A (pg/ml), inhibin-B (ng/L), FSH (IU/L), LH (ng/L), testosterone (nmole/L), and estradiol (ng/L) concentrations have been assessed:

Statistical analysis:

Results were expressed as mean ± standard error. Comparisons were performed using one way analysis of variance (ANOVA1) and newman- keuls to test all groups unpaired values. Differences were considered to be significant at the level of $P<0.05$. All statistical analysis were carried out using the GraphPad Prism (SAS Institute, Inc., USA).

Results

Reproductive hormones profile:

Activin –A: Serum activin-A concentration registered significant increase ($P<0.05$) at 30 day and 40 day of prepubertal period in comparison with the closed previous period for each stage, respectively. Throughout the postpubertal period, the concentration of activin-A showed graduall decrease especially at the 70 day stage which reached to the significant level ($P<0.05$), whereas other stages of this period showed no significant changes ($P>0.05$) when each stage compared with its closed previous stage, respectively (figure1).

Inhibin-B: Serum concentrations of inhibin-B illustrated in figure (1) showed gradual decrease at the prepubertal stage which reach the significant significancy ($P<0.05$) at 30 day, 35 day, and 40 day stages, whereas 45 day stage registered significant increase ($P<0.05$). each stage was compared with its closed previous stage. Postpubertal period registered further gradual increase especialy at 65 day and 70 day stages which reach the significant levels ($P<0.05$), in comparison with its closed previous period, respectively.

Follicle stimulating hormone FSH: Serum FSH concentration, at prepubertal periods, registered no significant changes ($P>0.05$) in comparison between 25 day, 30 day, and 35 day stages, whereas 40 day stage recorded significant increase ($P<0.05$) compared with 35 day stage then significantly decreased ($P<0.05$) at 45 day stages. Throughout the postpubertal period, the concentration of FSH concentrations continued in graduall decrease especially at the 60 day and 70 day stages which reached the significant level ($P<0.05$), whereas other stages of this period showed no significant changes ($P>0.05$) when each stage compared with its closed previous stage, respectively (figure 1).

Luteinizing hormone LH: At prepubertal stages (25 day, 30 day, 34 day, and 40 day), serum LH concentrations showed no significant differences when compared with each other, whereas 45 day stage recorded significant increase ($P<0.05$) in comparison with 40 day stage. Postpubertal stages showed gradual significant increase ($P<0.05$) started from 55 day stage to 70 day stage, when each stage compared with its closly previous one, whereas 75 day stage showed no significant difference ($P>0.05$) when compared with 70 day stage (figure 1).

Testosterone: As in LH concentrations, same picture was shown for testosterone concentrations at prepubertal stages (25 day, 30 day, 34 day, and 40 day), which revealed no significant differences when compared with each other, while 45 day stage recorded significant increase ($P<0.05$) in comparison with 40 day stage. Postpubertal stages showed gradual significant increase ($P<0.05$) started from 55 day stage to 70 day stage (figure 1).

Estrogen: Serum estrogen concentration, at prepubertal periods, registered no significant changes (P>0.05) in comparison between 25 day, 30 day, and between 35 day and 40 day stages, whereas 35 day stage recorded significant decrease (P<0.05) compared with 30 day stage and 45 day recorded significant decrease (P<0.05) compared with 40 day stage. Postpubertal period started with significant decrease (P<0.05) at 55 day stage compared with 45 stage of prepubertal period, and continued in significant decrement (P<0.05) at 60 day stage, whereas 65 day, 70 day, and 75 day stages showed no significant changes (P>0.05) when compared with each others (figure 1).

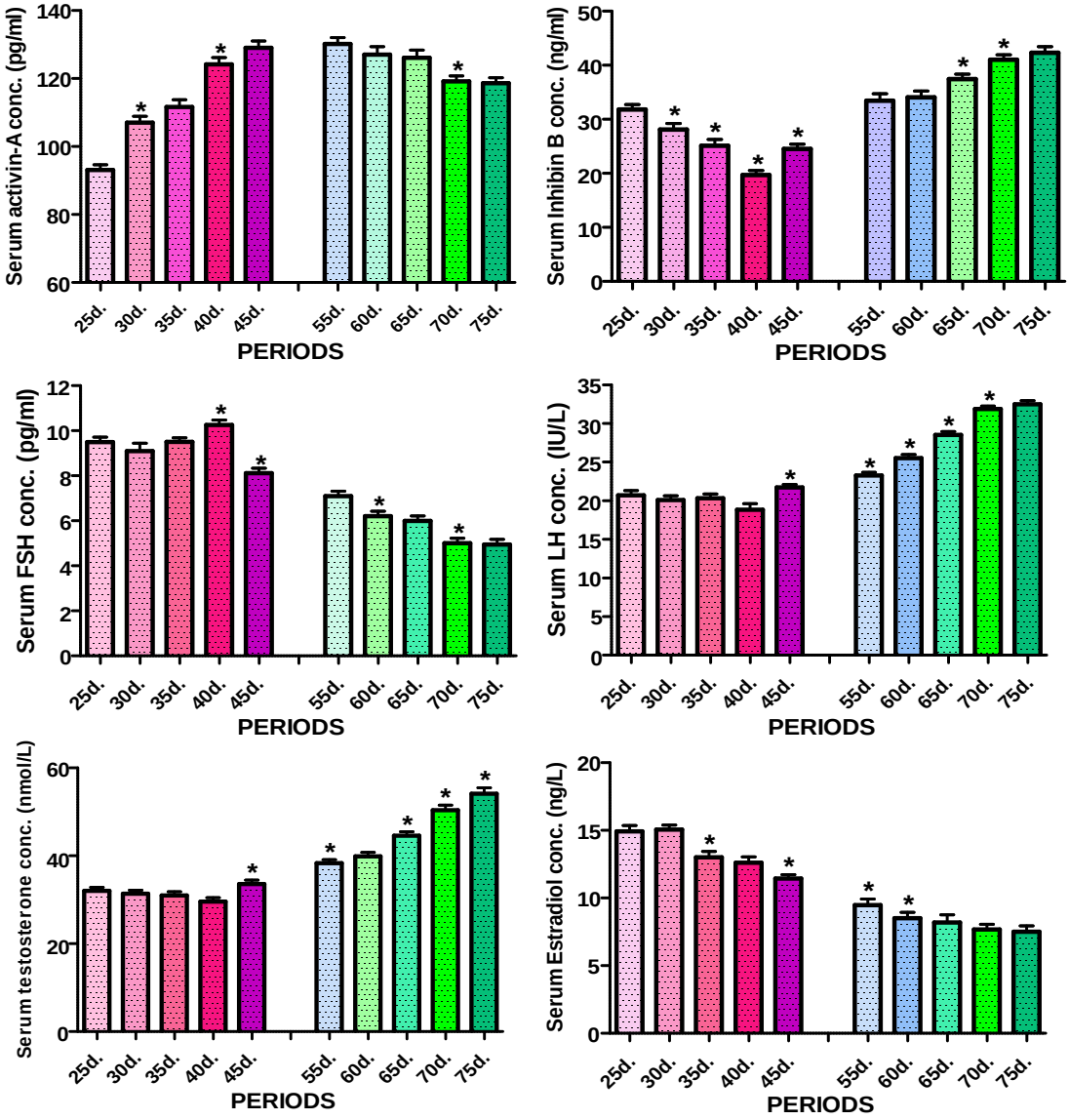

Figure (1): Serum activin-A (pg/ml), inhibin-B (ng/L), FSH (IU/L), LH (ng/L), testosterone (nmole/L), and estradiol (ng/L) concentrations at prepubertal (25, 30, 35, 40, and 45 day) and postpubertal (55, 60, 65, 70, and 75 day) stages of male rats life.
-Values represents Mean±SE
- Stars represents significant difference in comparison with the closed previos period (P<0.05).

Discussion

The present study reported that the levels of serum inhibin B, testosterone, increased progressively throughout puberty. In pre-pubertal stage, positive correlation has been observed between inhibin-B and FSH, LH, and testosterone. However, at this stage, each hormone correlated strongly with age, and at puberty a negative partial correlation for inhibin-B with FSH and LH. This result was in agreement with other studies (10;17;18) whom showed that inhibin was observed to increase progressively through post-pubertal development in primates and the correlation of inhibin-B to FSH, LH, and testosterone changed during post-pubertal development. The positive correlation of inhibin-B to testosterone levels observed early in puberty. Literatures suggest that the serum inhibin-B levels have been shown to reflect Sertoli cell function in adult men (19).

Present findings showed correlation between LH and inhibin-B concentrations particularly during post-pubertal stage. This fact was in agreement with that speculated about the mechanism of the LH effect on inhibin production which may be indirect, through the action of testosterone or other Leydig cell factors either directly on the Sertoli cells or via the peritubular cells (20). However, destruction of Leydig cells leading to testosterone depletion results in increased inhibin levels in adult rats (21). It has been reported that the correlation in adult men between serum inhibin-B levels and spermatogenesis may be due to the fact that inhibin B in adult men is possibly a joint product of Sertoli cells and germ cells, including the stages from pachytene spermatocytes to early spermatids (4), also in adult rat testis, inhibin secretion has been shown to be stimulated by the presence of late spermatids, as high testicular levels of testosterone seem to facilitate spermatogenesis in the absence of FSH. Therefore, the positive correlation between inhibin-B and LH (and testosterone) early in puberty may be due to an effect of testosterone on the initiation of spermatogenesis and, via the presence of late spermatides, the stimulation of inhibin-B secretion by Sertoli cells (22).

On the other hand, as serum inhibin-B concentrations decreased, serum FSH concentration increased particularly during post-pubertal stage. These changes was in correlation with the increment of activin-A. The decrement of inhibin-B decreased the compitition between inhibin-B and activin-A on activin receptors in the pituitary gland, therefore freely activin binding to its receptors may increase FSH secretion, as it has been reported that inhibin inhibits and activin stimulats FSH secretion in the pituitary gland (23). Serum inhibin-B levels reflect the functional state of the seminiferous epithelium and are involved in the feedback of the pituitary-gonadal axis (24) . Inhibin-B is involved in the negative feedback regulation of FSH secretion and has been shown to be a serum marker of

spermatogenesis in adult men (4). Hermans *et al.* (25) showed that testicular inhibin plays a role in the control of plasma FSH levels in the rat until 50 days of age. In the adult, serum inhibin-B shows a clear diurnal variation closely related to that of testosterone (8).

Serum levels of testosterone increased with age progression in paralel status with the increase of LH concentration, as Leydig cell testosterone was the primary feedback factor for LH. These changes also was in paralel with the decrease of serum FSH concentrations, as testosterone was known to be capable of FSH suppression (26). On the other hand, FSH is known to increase inhibin subunit mRNA level and to stimulate inhibin secretion (27), because serum concentrations of FSH and immunoreactive inhibin decline in the male rat from weaning through adulthood and plays a major role in the induction and maintenance of spermatogenesis (28).

However, when spermatogenesis is normal (29), FSH biosynthesis is also regulated at the transcriptional level by gonadal steroids, glucocorticoids and GnRH, and these actions are modulated by activin signaling. For example, in the present study it has been shown that testosterone and activin-A synergistically stimulate FSH secretion, as FSH-β transcription, and the stimulation by androgen or activin alone is dependent on the presence of an intact Smad binding element or androgen response element (respectively) within the FSHβ promoter (30;31;32), and FSH levels are also affected by GnRH, estradiol, and testosterone (33). Fujisawa *et al.* (34) found that the inhibin-B concentrations showed a significant negative correlation with serum FSH concentrations. Based on that inhibin-B has been shown to be an important factor related to testicular hormonal function, and several reports have been made indicating correlations between inhibin-B and FSH, LH or testosterone (35).

The early postnatal increase in inhibin-B level is presumably due to the activation of the hypothalamic-pituitary-testicular axis (36). Intriguingly, the early postnatal rise of inhibin B is better correlated with LH and testosterone than with FSH, raising the possibility that Sertoli cell proliferation in neonatal life depends more on LH/testosterone than on FSH (37). This leading to that FSH secretion is controlled both by inhibin and testosterone. This can be explained as declining testosterone causes an increase in FSH levels which in turn could stimulate the Sertoli cells to further increases in inhibin levels, as it has been reported that Sertoli cells are responsible for the secretion of inhibin under the control of FSH (38).

The high levels of inhibin-B, FSH, LH, and testosterone during the pre-pubertal stage may attributed to the rapid changes in the sensitivity to testosterone and probably to inhibin, which has been reported in the male rat around 5 week of age (39), when the hypothalamic-pituitary-gonadal axis is transiently activated (37). Serum inhibin-B concentrations decreased

more gradually and remained measurable during post-pubertal stage, also there was a brief increase in the gonadotropins (FSH and LH) during the last periods of the pre-pubertal stage, followed by an increase to basal levels until the onset of puberty. Testosterone also increased in the serum increased again following the elevation of gonadotropins during the post-pubertal stage. These changes was in agreement with that reported by Chada *et al.* (40). During post-pubertal stage, serum levels of inhibin B were inversely proportional to levels of FSH but not LH or testosterone, where FSH levels are the lowest during the period of Sertoli cell proliferation and increase after Sertoli cell maturation, with the negative relationship to inhibin established shortly after birth (41), and this in agreement with our study.

Our results recorded that the highest levels of activin-A were at 45 and 55 day periods which showed gradual increase during pre-pubertal stage and gradual decrease during post-pubertal stage. Based on that the inhibin was found to stimulate testosterone production and antagonise the testosterone suppressive effects of activin-A (42). On the other hand, the gradual decrease of estradiol concentrations during post-pubertal stage are in agreement with a number of studies that refered to estradiol concentrations are typically higher in the testicular vein and lymph than in the general circulation. However, blood estrogen concentrations are low in the male, therefore, it can be presumed that estrogens from Leydig cell synthesis would provide limited endocrine activity in the reproductive tract, as it has been shown that the estrogen not only has important functions in the adult male reproductive tract, but that estrogen and its α-receptor are essential for normal fertility (43). Other studies have shown that estrogen, even in the presence of maintenance levels of testosterone, produces harmful effects on the epididymis and reduces fertilizing ability of epididymal sperm (44), also FSH stimulates the granulosa cell aromatase system that catalyzes the conversion of androgens into estrogens (45).

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التغيرات في تراكيز الهورمونات التكاثريةفي مرحلتي قبل وبعد البلوغ لذكور جرذان الوستر

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الخلاصة:

أجريت الدراسة الحالية بهدف التحري عن التغيرات في هرمونات التكاثر في مرحلتي قبل وبعد البلوغ لذكور جرذان الوستر. أستخدم في الدراسة خمسون ذكراً من سلالة الوستر (25 غير بالغة و 25 بالغة). تم تخدير خمسة حيوانات من كل مرحلة من مراحل قبل البلوغ (بعمر 25 و 30 و 35 و 40 و 45 يوماً) ومراحل بعد البلوغ (بعمر 55 و 60 و 65 و 70 و 75 يوماً) وأخذت منها عينات دم من الوريد البطني لغرض قياس تراكيز الأكتفين أي والانهبين بي والهرمون محفز الجريب والهرمون اللوتيني (المصفر) والتستوستيرون والاسترادايول في المصل. سجلت الدراسة زيادة معنوية في تركيز الاكتفين أي بعمر 30 و40 يوماً. خلال مراحل بعد البلوغ، انخفض تركيز الاكتفين أي تدريجياً. إنخفض تركيز الانهبين بي تدريجياً خلال مراحل قبل البلوغ بينما ارتفع تدريجياً خلال مراحل بعد البلوغ. لم يختلف تركيز الهرمون محفز الجريب معنوياً بعمر 25 و 30 و 35 يوماً بينما سجل التركيز ارتفاعاً معنوياً بعمر 40 يوماً ثم انخفض بعمر 45 يوماً. سجلت تراكيز الهرمون اللوتيني والتستوستيرون عدم وجود فروقات معنوية في الأيام 25 و 30 و 35 و 40 بينما ارتفع معنوياً بعمر 45 يوماً وقد استمر الارتفاع المعنوي التدريجي خلال مراحل بعد البلوغ. أظهرت تراكيز الاسترادايول انخفاضاً تدريجياً خلال مراحل قبل البلوغ واستمر الانخفاض خلال مراحل بعد البلوغ. يمكن الاستنتاج أن التغيرات في تركيز الانهبين بي في مصل الدم له علاقة ايجابية مع تركيز التستوستيرون خلال مراحل قبل وبعد البلوغ مع وجود علاقة ايجابية مع تركيز الهرمون محفز الجريب والهرمون اللوتيني خلال مراحل قبل البلوغ وسلبية خلال مراحل بعد البلوغ.