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# DECREASED ANDROGEN PRODUCTION IN THE TESTES OF THYROIDECTOMIZED RATS[1]

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**Ching-Fong Liao, Ru-Shiow Tsai, Yien-Shing Chow and John Yu-Lin Yu** (1991) Decreased androgen production th the testes of thyroidectomized rats. *Bull. Inst. Zool., Academia Sinica* **30**(3): 139-148. The testicular androgen production of thyroidectomized (Tx) rats in response to human chorionic gonadotropin (hCG) stimulation was studied *in vitro* with decapsulated testes and dispersed testicular interstitial cells. The effects of the thyroidectomy were more severe in immature rats than in adult rats resulting in a greater decrease in overall body weight, weight of testes, adrenal glands, ventral prostate glands and seminal vesicles, and changes in serum levels of thyrotropin (TSH) and androgen in the younger animals. Decreased androgen secretion from hCG stimulation by the testes was noted in both immature and adult Tx rats. The androgen production, on the basis of an equal number of testicular interstitial cells, in the adult Tx rats were less sensitive to hCG stimulation than the euthyroid controls. The cellular androgen production was dependent on the cell concentration and incubation time. Under various incubation conditions, the Tx group always showed less androgen production as compared to the euthyroid control. The results of this study imply that decreased cellular androgen production in hypothyroid rats may lead to decreased serum androgen levels.

**Key words:** Androgen, Gonadotropin, Testis, Thyroidectomy.

Our previous studies showed that in male rats a thyroidectomy resulted in decreased levels of serum testosterone (Jea *et al.*, 1981) but not luteinizing hormone (LH) (Jea *et al.*, 1981, Liao and Wan, 1983). These results suggest that the responsiveness of testes to LH stimulation decreased in the thyroidectomized (Tx) rats. Kalland *et al.* (1978) reported that testis response to LH stimulation did not change in hypothyroid rats, and the administration of a single dose of hCG could not differentiate the testosterone synthesis by hypothyroid rats from the euthyroid control. Nevertheless, it has been shown that serum cholesterol and its carrying proteins, high- and low-density lipoproteins, are elevated in hypothyroid rats (Dory and Roheim, 1981). A specific binding site for a high-density lipoprotein has been identified in the Leydig cells and the availability of cholesterol and lipoproteins could

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influence the testicular steroidogenesis (Quinn *et al.*, 1981). Therefore, the increased cholesterol available for testosterone synthesis *in vivo* may mask the reduced testicular response of hypothyroid rats. In this study, we examined the testicular response to hCG stimulation *in vitro* in isolated testes and dispersed testicular interstitial cells.

## MATERIALS AND METHODS

### Hormones and reagents

Rat pituitary hormone radioimmunoassay (RIA) kits were kindly supplied by the National Institute of Arthritis, Metabolism, and Digestive Diseases, Pituitary Distribution Program (Bethesda, MD). Steroids, human chorionic gonadotropin (hCG, 3,360 IU/mg), collagenase (Type IA), bovine serum albumin (BSA, Fraction V), heparin and trypan blue were obtained from Sigma Chemical Co. (St. Louis, MO). Hanks' Balanced Salt Solution (HBSS, powdered tissue culture medium without sodium bicarbonate), Medium 199 (powdered) culture medium with Hanks' salt and L-glutamine, without sodium bicarbonate) were purchased from Grand Island Biological Co. (Grand Island, NY). $^{125}I$ and $^{3}H$-testosterone (1, 2, 6, 7-$^{3}H$-testosterone) were obtained from New England Nuclear (Boston, MA). Diethyl ether (GR grade) for serum androgen extraction was obtained from Merck (E. Merck, Darmstadt, F.R.G.).

### Animals

Male Long-Evans rats, purchased from the National Laboratory Animal Resources, National Taiwan University Hospital, Taipei, were maintained in a temperature- and light- controlled room (22±1°C, 6:00-18:00 lighting). The rats were fed Purina Chow and tap water *ad libitum*. After a week's acclimation period, body-weight matched animals were thyroidectomized (Tx) or sham-operated under light ether anesthesia. Some immature rats were used in the whole testis incubation experiment. The other rats used in this study were all adults at the time of the operation.

### Response of whole testis to hCG stimulation

The rats were decapitated 8-10 weeks after undergoing the thyroidectomy. The testes were immediately removed, decapsulated and washed in a cold preincubation medium (1% BSA in HBSS, with 25 mM HEPES, sodium bicarbonate 0.35 g/l, penicillin 100,000 i.u./l, streptomycin sulfate 50 mg/l, heparin 2,550 USP K units/l, and aerated with 95% $O_2$ and 5% $CO_2$, pH 7.4), and each testis was then transferred to an individual 50 ml capped polyethylene tube (Falcon Ind. No. 2070) containing 5 ml incubation medium (substitution of HBSS in preincubation medium with Medium 199). The tube was placed horizontally in a 34°C water bath, parallel to the direction of the shaking motion which shook at 100 cycles per minute. After an hour of incubation, the medium was replaced with 5 ml of fresh medium containing 5 ng hCG. Thereafter, the incubation medium was aspirated and replaced with only fresh medium hourly for four or five hours, respectively, in different experiments. The aspirated medium was centrifuged at 1,500×g at 4°C for 10 minutes and the supernatant was then diluted to 1:200 with PBSG (0.1% gelatin in 0.01 M phosphate buffer, 0.15 M sodium chloride, pH 7.6) and stored at −20°C until RIA for androgen.

### Preparation of testicular interstitial cells (Enzymatic dispersion of testicular interstitial cells)

Collagenase dispersion of testicular interstitial cells was modified from the

procedure described by Moyle and Ramachandran (1973), Dufau and Catt (1975) and Yu *et al.* (1981). Four decapsulated testes were added to a 50 ml polypropylene tube containing 6 ml preincubation medium and 6 mg collagenase. The tube was laid horizontally in a 34°C water bath, parallel to the direction of the shaking. Fifteen minutes after shaking at 100 cycles/min, the digestion was stopped by adding 35 ml of cold preincubation medium and inverting the tube several times. The tube was allowed to stand for five minutes and was then filtered through a four-layer fine nylon mesh. Cells were collected by centrifugation at 4°C, 100×g for 10 minutes. The cell pellets were washed twice with preincubation medium and resuspended in incubation medium. Viability of the dispersed cells was assessed by trypan blue exclusion method. Nearly 100% of cells were viable and the sperm cells constituted less than 5% of the dispersed cells.

**Response of testicular interstitial cells to hCG stimulation**

The testicular interstitial cells from Tx and sham operated rats were prepared at the same time. Various concentrations of cells in 200 μl medium were pipetted into polyethylene tubes (10×75 mm), sealed with paraffin film, and preincubated for one hour at 34°C, shaken at 100 cycles/min. The supernatant was decanted after centrifugation of the tubes at 100×g for 10 minutes. Various concentrations of hCG in 200 μl fresh medium were then added to the tubes of cells. After several hours of incubation, 2 ml cold PBSG buffer was added to stop the incubation. The cells were discarded after centrifugation, and the supernatants were stored at −20°C until measurement of total androgen in the medium took place.

**Radioimmunoassay of androgen**

Radioimmunoassay (RIA) of the androgen produced *in vitro* was performed directly without pre-extraction (Yu *et al.*, 1984). Serum androgen extraction and quantitation were performed as previously reported (Roan and Yu, 1983), utilizing rabbit anti-testosterone antiserum produced in this laboratory (Wan *et al.*, 1978). The specific activity of the antiserum was tested by assessing the cross reactivity with other major steroids before being applied to the androgen RIA.

**Radioimmunoassay of TSH**

Serum TSH was measured by specific double-antibody RIA according to the previous report (Liao and Wan, 1983) except that NIAMDD-TSH-RP-1 was replaced by RP-2.

**Statistics**

Analysis of the RIA data followed the descriptions of Rodbard *et al.* (1970). Other statistical analyses are described in the Results section of this paper in accordance with the procedures of Sokal and Rohlf (1969).

## RESULTS

The specificity of the anti-testosterone antiserum used in androgen RIA is shown in Fig. 1. Only dihyroxytestosterone (DHT) cross-reacted with the antiserum. The other steroids showed less than 0.01% cross-reactivity. Thus we directly measured the incubation media and the ether-extracted serum samples without further purification, and the results are expressed as androgen instead of testosterone.

It has been shown that testicular androgen synthesis is age-dependent (Yu *et al.*, 1981). Therefore, we induced hypothyroidism in both immature and mature

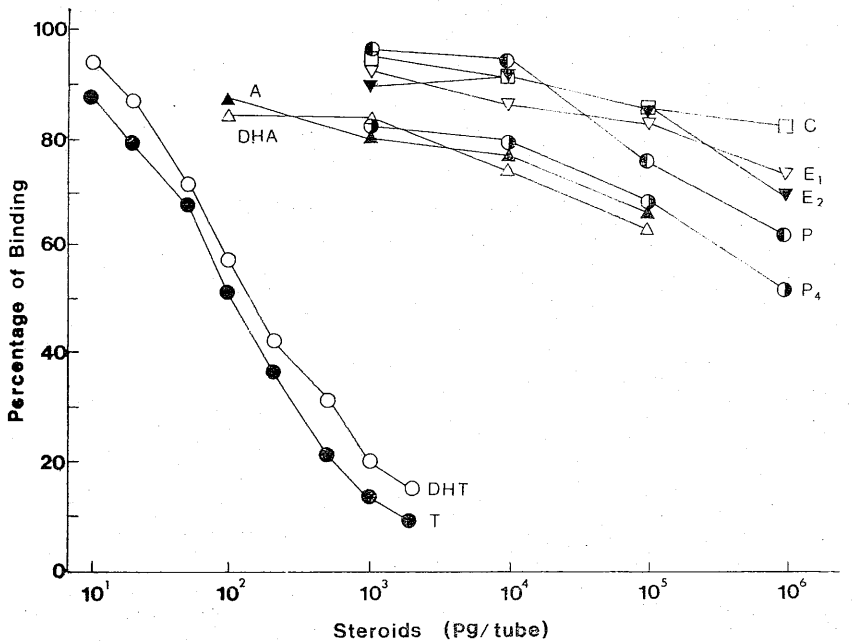


Fig. 1. Inhibition curves of various steroids on the binding of rabbit anti-testosterone serum and $^3$H-testosterone. Only DHT showed intense cross reactivity with the antiserum. A: 5$\beta$-Androstane-3$\beta$-ol-17-one; C: Corticosterone; DHA: dihydroisoandrosterone; DHT: dihydroxytestosterone; $E_1$: esterone; $E_2$: estradiol; P: pregnenolone; $P_4$: progesterone.

rats to examine the effect of age on testicular androgen production in hypothyroid rats.

The basic data on the rats used in the experiments are shown in Tables 1 and 2. Hypothyroidism induced in immature rats is more severe than in adult ones. Regardless of when the rats were subjected to thyroidectomy, we observed growth retardation and a decrease in the organ weights of testes, adrenal glands and accessory sex organs in the Tx rats. The serum androgen level decreased and the serum TSH level

Table 1
Body weight, organ weights and basal serum hormone levels in thyroidectomized (Tx) rats and sham operated (S) controls, with the thyroid operation performed before the rats have matured

| Treatment | Body Weight (g) | | Testis | Adrenal | Ventral Prostate | Seminal Vesicle | Serum Hormone (ng/ml) | |
|---|---|---|---|---|---|---|---|---|
| | Initial | Final | (g) | (mg) | (mg) | (mg) | TSH | Androgen |
| Tx | 63.6 ±0.9 | 209.7** ±7.9 | 2.7* ±0.2 | 17.1** ±0.7 | 86.4** ±10.5 | 145.3* ±16.7 | 12.36** ±1.02 | 1.21* ±0.29 |
| S | 63.6 ±0.9 (100%) | 373.1 ±8.1 (56%) | 3.5 ±0.12 (77%) | 41.6 ±2.3 (41%) | 138.7 ±11.7 (62%) | 218.7 ±13.3 (66%) | 1.40 ±0.15 (883%) | 2.50 ±0.23 (48%) |

The data are expressed as mean±SEM ($n$=7). The percentage in parenthesis represents the ratio of the means in the Tx group to the S group. * and ** represent the significant levels at $p<0.05$ and $p<0.01$ for the difference between two correspondent values of the Tx and S groups, respectively.

Table 2
Body weight, organ weights and basal serum hormone levels in thyroidectomized (Tx) rats and sham operated (S) controls, with the thyroid operation performed after the rats have matured

| Treatment | Body Weight (g) | | Testis | Adrenal | Ventral Prostate | Seminal Vesicle | Serum Hormone (ng/ml) | |
|---|---|---|---|---|---|---|---|---|
| | Initial | Final | (g) | (mg) | (mg) | (mg) | TSH | Androgen |
| Tx | 268.3 | 300.3** | 3.13* | 25.3** | 154.9** | 190.6* | 7.40** | 1.53* |
| | ±3.6 | ±4.0 | ±0.15 | ±0.9 | ±15.0 | ±12.6 | ±0.44 | ±0.14 |
| S | 268.34 | 414.4 | 3.95 | 50.2 | 233.5 | 293.2 | 1.48 | 2.50 |
| | ±4.1 | ±4.7 | ±0.12 | ±1.6 | ±15.3 | ±17.5 | ±0.13 | ±0.23 |
| | (100%) | (72%) | (84%) | (50%) | (66%) | (65%) | (500%) | (61%) |

The data are expressed as mean±SEM ($n$=15). The percentage in parenthesis represents the ratio of the means in the Tx group to the S group. * and ** represent the significant levels at $p<0.05$ and $p<0.01$ for the difference between two correspondent values of the Tx and S groups, respectively.

increased significantly as compared to the sham operated controls.

Fig. 2 plots the time course of hCG-stimulated androgen secretion by the whole decapsulated testes from Tx and sham operated rats. The basal secretion (control) was similar between the Tx and sham operated groups (Fig. 2A).

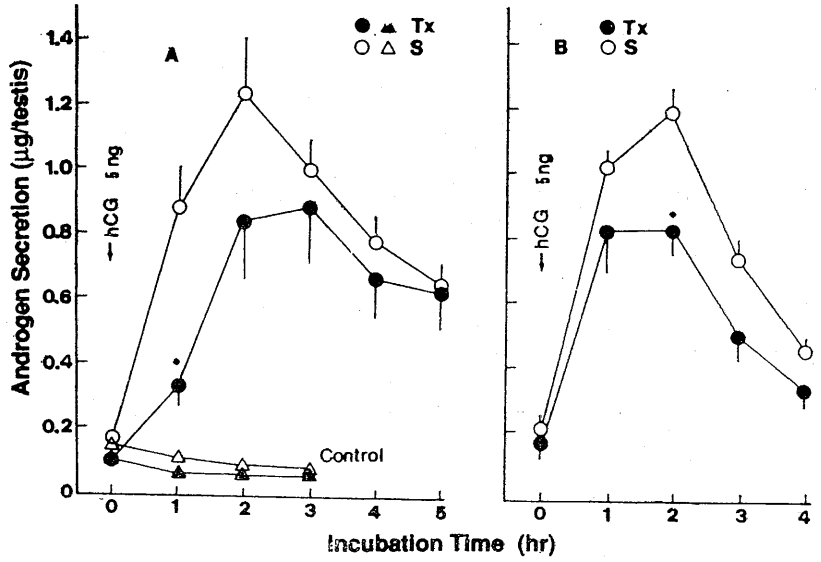


Fig. 2. The time course of androgen secretion by the whole testes from Tx and sham operated (S) rats after 5 ng of hCG stimulation. Decapsulated testes were prepared from the rats with the thyroidectomy performed either before (Fig. 2A) or after (Fig. 2B) sex maturation. After one hour of preincubation, fresh medium was added to hCG at hour 0. Thereafter, the medium was replaced with fresh medium hourly (see the Materials and Methods section for details). Each point and bar represent the mean and standard error of 6 (Fig. 2A) and 4 (Fig. 2B) incubation experiments. The area under the curve of the Tx group is 35% (Fig. 2A) and 30% (Fig. 2B) less than their respective sham operated control. The differences (** $p<0.01$, * $p<0.05$) for values were compared between Tx and S groups at the same incubation time.

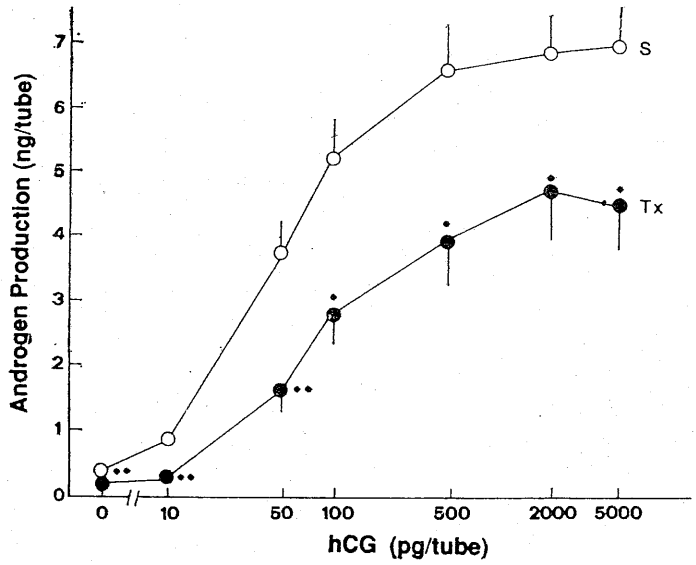


Fig. 3. Dose-response curve of hCG stimulation on androgen production by dispersed testicular cells from the Tx and sham operated (S) rats. Each incubation tube contained $3.6\times10^6$ cells in 0.2 ml medium and was incubated at 34°C with or without hCG stimulation for 3 hours. Each point and bar represent the mean and standard error of 8 incubation experiments. ** $p<0.01$, * $p<0.05$.

The thyroid glands were operated before (Fig. 2A) or after (Fig. 2B) sex maturation (around 60 days). Regardless of the age at which the rats were subjected to the thyroid operation, less androgen was secreted after the hCG stimulation from the Tx rats' testes than from the sham operated groups. However, the secretion patterns were somewhat different between the immature and adult Tx rats (Figs. 2A and 2B).

Hypothyroidism induced by the thyroidectomy performed on the immature rats was more severe than the same operation performed on the adult rats. However, hypothyroidism similarly resulted in reduced testicular androgen secretion in both of these groups. Consequently we used the young adult rats in the following experiments. Fig. 3 shows the dose-response relationship between hCG stimulation and androgen production by dispersed testicular cells from Tx and sham operated rats. The dose-response curves of these two groups are both sigmoid when expressed on a semi-log scale. The $EC_{50}$ for the euthyroid and Tx groups were 50 pg and 100 pg of hCG, respectively. A significant increase of androgen production was noted with 10 pg of hCG stimulation ($p<0.05$, paired $t$ test) in the euthyroid but not in the Tx group. The maximum response was achieved with 500 pg and 2,000 pg of hCG stimulation in the euthyroid and Tx groups, respectively. The Tx group produced less androgen than the sham operated control at all dose levels of hCG stimulation. At lower doses of hCG stimulation, the difference between these two groups was significant ($p<0.01$). With higher doses of hCG stimulation, the difference was still significant but became less prominent.

Fig. 4 shows the effect of the dispersed testicular cell concentration on the hCG-stimulated androgen production with 500 pg (Fig. 4A) and 100 pg (Fig. 4B) of hCG stimulation. The androgen production increased with increasing testicular cell

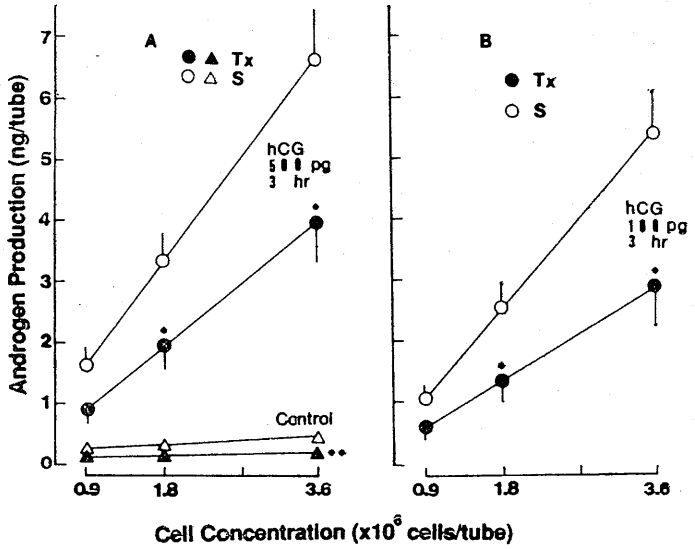


Fig. 4. Effect of cell concentraton on hCG-stimulated androgen production by dispersed testicular cells from the Tx and sham operated (S) rats. Three concentrations of testicular cells were incubated with 100 pg (Fig. 4B), 500 pg or without hCG (Fig. 4A) stimulation for three hours. Each value represents the mean and SEM of 7 incubation experiments. ** and * represents the significant levels at $p<0.01$, and $p<0.05$, respectively for the difference between two correspondent values of Tx versus S group.

concentrations in both the Tx and euthyroid groups. The difference in absolute values of androgen production between these two groups was more evident at higher cell concentrations. However, the androgen production in the Tx group remained around 56-60% (Fig. 4A) and 50-53% (Fig. 4B) of those in the euthyroid control. The basal androgen production of the Tx group was significantly lower than the sham operated control at the concentration of $3.6\times10^6$ cells/tube (Fig. 4A). At lower cell concentrations, the basal androgen productions of the Tx group were just around the detectable level when the incubation media were diluted and assayed as described in the Materials and Methods Section. The linearity between the cell concentrations and the hCG-stimulated androgen production was computed by analysis of variance with regression. The equality between the correspondent slopes of the regression lines was tested as described by Sokal and Rohlf (1969). The Tx group showed less responsiveness and less androgen production incremental change than the sham operated group as indicated by the lower slope. However, the slopes of the regression lines are similar with 500 or 100 pg hCG stimulation in the Tx group, and also in the control group.

Fig. 5 plots the time course of hCG-stimulated androgen production by dispersed testicular interstitial cells from Tx and sham operated rats. With 500 pg (Fig. 5A) and 100 pg of hCG stimulation (Fig. 5B), the androgen production increased with time in both the Tx and the sham operated groups. The difference between the two groups was more obvious during the first two hours when androgen productions in the Tx group were around 41-47% (Fig. 5A) and 28-32% (Fig. 5B), respectively, of those secreted by the euthyroid control.

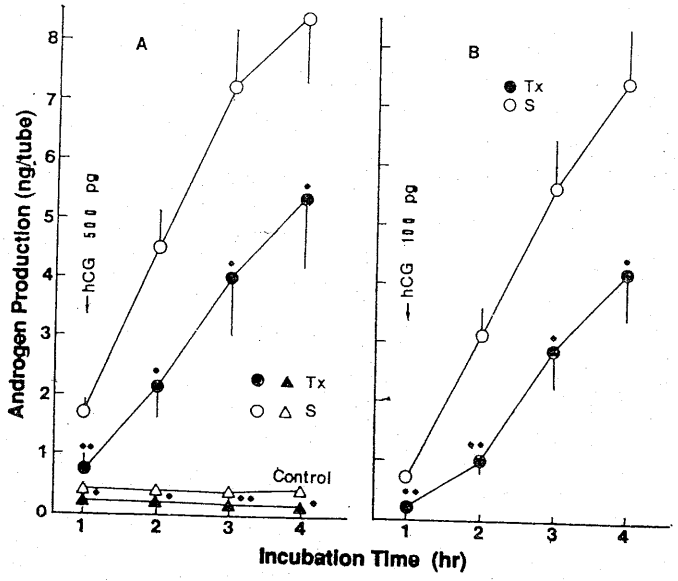


Fig. 5. Effect of incubation time on androgen production by the dispersed testicular cells from Tx and sham operated (S) rats. Each incubation tube contained $3.6\times10^6$ cells and was incubated with 100 pg (Fig. 5B), 500 pg or without (Fig. 5A) hCG stimulation for one to four hours. Each value represents the means±SEM of 6 incubation experiments. ** $p<$ 0.01, ** $p<0.05$.

With a longer incubation, the Tx group still produced less androgen but reached 55-64% (Fig. 5A) and 51-57% (Fig. 5B) of the control group.

## DISCUSSION

The present investigation clearly demonstrates that the hCG-stimulated androgen production by isolated testes or dispersed testicular cells decrease in Tx rats. Such testicular alterations may lead to lower serum androgen levels in hypothyroid rats.

Kalland *et al.* (1978) examined the serum testosterone levels and testis testosterone contents in $^{131}I$ or propylthiouracil induced hypothyroid rats after LH administration (30 $\mu$g/100 g BW, ip). They found no significant difference between euthyroid and hypothyroid rats. In contrast, our study detected a significant decrease of testicular androgen production in Tx rats under various experimental conditions (Figs. 2-5). This discrepancy may be due to the different testing systems, the modes of inducing hypothyroidism and the doses of hCG used.

In agreement with previous reports from Bruni *et al.* (1975) and our laboratory (Jea *et al.*, 1981), we found lower serum androgen levels in Tx rats. This finding is in contrast to others (Baksi, 1973; Kalland *et al.*, 1978; Kolena *et al.*, 1980). However, the weights of both ventral prostate and seminal vesicle decreased in hypothyroid rats (Wan and Chen, 1974; Bruni *et al.*, 1975; Amin and El-Sheikh, 1977; Kalland *et al.*, 1978; Jea *et al.*, 1981; Liao and Wan, 1983) and LRH (luteinizing hormone releasing hormone) administration resulted in a significantly higher rise of serum LH in hypothyroid rats (Kalland *et al.*, 1978; Liao and Wan, 1983). These findings support previous findings that serum androgen decreases in hypothyroid rats with resultant

decreases in target organ weights and less negative feedback for LH secretion.

The hCG-stimulated testicular steroidogenesis is a complex process, involving many steps; receptor binding, signal transduction by G proteins (Birnbaumer *et al.*, 1987), cAMP formation, and cAMP regulation of steroidogenesis (Voutilainen *et al.* 1986; Hales *et al.* 1987). Kolena *et al.* (1980) examined the gonadotropin receptors in testis homogenate from Tx rats. Their study showed that specific testicular binding of $^{125}$I-hCG and the affinity of gonadotropin receptors to hCG did not change after thyroidectomy. If their results can be applied to the hormone-receptor binding in the intact decapsulated testes and dispersed testicular cells, it is likely that the decreased testicular androgen production results from alterations in the post-receptor processes. It has been demonstrated that there are 2-3 distinct populations of Leydig cells in the mature rat testis which differ in hCG-stimulated testosterone production due to differential steroidogenic enzyme activities (Payne *et al.*, 1980a; O'Shaughnessy *et al.*, 1980; Payne *et al.*, 1980b). Those findings raise another possibility that hypothyroidism may affect the proportion of different populations of Leydig cells. The decreased testicular androgen production in Tx rats may reflect a decrease of the cell population with high responsiveness. To test these hypotheses, further investigation is needed.

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# 甲狀腺切除鼠之睾丸雄性素生成減少

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本實驗利用分離睾丸以及分散之睾丸精間細胞，在試管內研究甲狀腺切除鼠之睾丸對於人類絨毛性促素刺激所引起之雄性素生成反應。未成熟鼠經甲狀腺切除手術後，其甲狀腺功能低下之程度較成年之甲狀腺切除老鼠嚴重，此可由其體重、腎上腺、腹前列腺及儲精囊等器官重量，及血中甲促素與雄性素變化得知。未成熟與成年之甲狀腺切除老鼠，其睾丸受人類絨毛性促素刺激所分泌之雄性素都明顯下降。以相同數目之離體睾丸精間細胞研究雄性素生成能力，由劑量反應曲線可知，成年甲狀腺切除鼠與手術對照鼠相較，其睾丸精間細胞對人類絨毛性促素刺激的反應較不靈敏，雄性素生成較少。在各種不同的實驗條件下，例如改變性促素濃度或睾丸細胞濃度以及改變培養時間，發現甲狀腺切除鼠都比手術對照鼠生成較少之雄性素。本研究顯示甲狀腺切除鼠之睾丸雄性素生成減少，此變化可以導致其血中雄性素濃度降低。