Effect of Carbimazol-induced Hypothyroidism on Male Rat Reproductive System

Saadi M. Mahmood
Mohammed N.Taha
Gaida. A. K. Yahia
Dept. of Biology/College of Education for Pure Science(Ibn-Al Haitham)/
University of Baghdad

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Abstract

The present study is undertaken to evaluate the effects of hypothyroidism induced by carbimazol in male rat reproductive system. Rats were treated with carbimazol (80 and 160 mg/kg body weight) daily for two, four, six, and eight weeks, while control rats were given distilled water orally. The results of these experiments are:

1-Treatment with carbimazol produced increase in body weight of treated animals. This increase was not statistically significant even at high concentrations.

2-Decrease in testicular weight was observed during all administration points. This decrease was aggravated proportional to duration and dose ($p \leq 0.001$).

3-Results of most intervals showed significant decrease in epididymal-head weight, while no significant decrease was observed in epididymal-tail weight.

4-Carbimazol increased seminal vesicle weight, particularly after six ($P \leq 0.05$) and eight weeks for both doses.

5-Prostates were responsive to reduce thyroid hormones by increasing its weight in a dose-dependent manner.

Key words : Hypothyrodisim ,Carbimazol , Reproductive system ,Rat.

Introduction

The experimental evidence available indicated that eaten food which contains thiocyanate interfere with use of iodine by thyroid. These foods known as goitrogens such as: Broccoli, cabbage, Kale and soybean (1,2).

The use of thiourea derivatives such as carbimazol made the elucidation of hypothyroidism effect easier (3).Carbimazol is a common oral treatment widely prescribed for hyperthyroidism, The primary effect is to inhibit thyroid hormone synthesis by interfering with thyroid peroxidase-mediate thyroglobuline organification (4,5).

Many investigations attempted to present coherent pictures concerning the relationship between thyroid gland and reproductive functions (6). This has postulated that thyroid hormones play a significant role in male but not female reproductive tract development in human and rodents (7). Therefore, anattempt has been made to present a coherent picture concerning thyroid-gonad interrelationships using chemical- induced thyroid dysfunction biosynthesis in male rat and the relevance of reproductive effects observed for prediction of adverse effects in man.

Materials And Methods

Fifty two male rats (250-300g) obtained from the institute of embryo research and infertility treatments were used throughout this study. They were maintained under standard laboratory conditions, in a well ventilated room with 12h light: 12h darkness schedule at 20-30 C, and were given food and water *ad labium*.

Animals were divided into three groups:

Group I: Twenty rats were daily given orally low dose of carbimazol (80mg/kg body weight).

Group II: Twenty rats ware daily given orally high dose of carbimazol (160mg/kg body weight)

Group III: Twelve control rats were daily drenched distilled water orally.

Then, animals were killed after weighed under ether anesthesia, autopsied after two, four, six, and eight weeks of treatment. Testes, epididymies, prostate, and seminal vesicle were immediately dissected out, cleaned from adherent mesentery and blood vessels, and then their weights were calculated relative to body weight (8). Testes volume was calculated according to the following equation (9).

$V=2/3(abc) \times \pi$

Where a=testis length b=testis width c=testis thickness $\pi=3.1416$

Then testis was decapsulated and the tunica albuginea was weighted. Testicular tissue weight was obtained by subtracting the tunica weight from original testicular weight.

Results

One of the experiments performed was to determine whether hypothyroidism could affect the body weight by using carbimazol treatment. It can be seen that body weight gain in both control and treated groups, increased linearly with time and reached its maximum after eight weeks of treatment, but this increase was not statistically significant even at high concentration (table 1).

The degree to which hypothyroidism affect testicular weight in carbimazol treated rats can be shown in table (2). It can be seen from these data that the testicular weight of these animals were lower than those of control group during all administration points. The magnitude of this reduction was proportional to length, so that it's maximum value (-23.23) reached after eight weeks.

Table (3) shows that carbimazol caused inhibition of the volume of treated rat testis especially at the high concentration (160mg/kg); this decrease became significant after eight weeks for both concentrations. On the other hand, hypothyroidism was found to increase the

tunica albuginea weight of treated rats. These results summarized in table (4). It can be seen that this increase was more pronounced after four and eight weeks of treatment in a dose dependent-manner. The results here also showed significant increase ($p\leq0.05$) after eight weeks of treatment at high dose compared with low dose.

It is worth mentioning that the testicular tissue weight was decreased in all treated groups, but it did not show any significant changes except that of fourth and eighth weeks of treatment. This decrease was sensitive to the duration and dose, and reached minimum value (0.276±0.006) after eight weeks, see table (5).

Table (6) shows gradual increase of epididymal-head weight with age for both control and carbimazol treated rats. In spite of this, all values of carbimazol treated rats were lower than those of control and statistically significant in all time points except the end point. Despite a trend toward decreased epididymal tail weight in carbimazol treated rats compared with control, this was decreased at each time points were not significantly different between age-match controls and carbimazol rats (Table 7).

Carbimazol at high and low doses have increased the weight of seminal vesicle. After six weeks of treatment, high dose caused marked significant ($p\leq0.05$) increase compared with control and other treated groups, then after eight weeks this increase was highly significant ($p\leq0.001$). The relation between different concentrations of this agent and seminal vesicle weight is shown in table (8). Similarly, table (9) shows significant increase after six and eight weeks in rat prostate weight treated with carbimazol (160mg/kg) and reached highest value after eight weeks (0.393±0.017) while, the results of treated rats with low dose showed a significant ($p\leq0.01$) increase only in last period.

Discussion

Recently many investigations are now actively being pursued to understand the primary effects of thyroid hormones on male reproductive and fertility (10). Results of the present study indicated that carbimazol caused structural changes in male rat reproductive system. However, there are controversies about hypothyroidism effect on the body weight and strong evidence is still lacking to draw firm conclusion. Data obtained from this study showed no significant increase in the body weight of carbimazol treated rats despite losing appetite. The result was anticipated, since, the decrease in thyroid hormones secretion lead to decrease in basal metabolic rate (11).A similar situation has been reported by(12).

Alternatively, a different mechanism of hypothyroidism action can be suggested when (13) found that the seasonal loss of body weight observed in male mammals during sexual activity is correlated with elevated plasma testosterone level seems to be another reason for body weight gain.

To aid the investigation of hypothyroidism effect on male reproductive system, reproductive organs were employed. These effects on testis activity are less clear-cut. The results presented here, showed that carbimazol reduce testicular weight. This may be due to that all previous studies were performed on neonatal rats while, this study performed on adult rats. This inhibitory effect is not unexpected and it is in agreement with finding of other investigator (14, 15,16). There are two possible ways to explain this, firstly, impairment of spermatogenesis as a result of delaying germ cell maturation (14). Secondly, the decline in steroidogenic activity of leydig cells (15,17). The fact that testicular volume always related to testicular weight explained the significant decrease in testicular volume observed in this study.

The results also revealed that the absence of thyroid hormones decreased of epididymal weight. This observation is consistent with the suggestion that hypothyroidism induces epididymal hypofunction (18).One possible explanation of this finding is the decrease of testicular activity, this may cause decrease hormone support to epididymis which regulate growth and activity of this organ (19).

Surprisingly, carbimazol was found to have different effect on the accessory sex organs, increase seminal vesicle and prostate weight, since the growth of these organs was androgen-dependent (14,20).However,it can not be rolled out that adrenocoticotropic hormone (ACTH) increase in hypothyroidism (21) consequently, induce growth of prostate (22).
Finally, (23) reported that circulatory oestradiol in male mouse is positively correlated with adult prostate size and number of prostatic androgen receptors. It is apparent that hypothyroidism may cause oestrogen increase (24). If this is true, it is reasonable that there is another reason for prostate weight increase. Thus, further investigation is needed to understand how thyroid affect process such as spermatogenesis which could help uncovers the connection between thyroid and male infertility.

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Table (1): Body weight difference (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(grams)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	50.60±10.04 a	56.00±7.65 a	53.33±3.33 a	-5.40	+4.77	N.S.	N.S.	N.S.
4	84.50±10.50 b	80.50±12.10 ab	75.00±15.00 a	+11.24	+6.83	N.S.	N.S.	N.S.
6	97.00±16.96 bc	95.00±6.71 b	85.00±13.23 a	+12.37	+11.76	N.S.	N.S.	N.S.
8	120.00±6.71 c	117.00±12.90 b	88.30±10.14 a	+26.42	+23.90	N.S.	N.S.	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (2): Testes index (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.371±0.012 a	0.369±0.012 a	0.389±0.012 a	-4.63	-5.14	N.S.	N.S.	N.S.
4	0.342±0.019 ab	0.336±0.016 ab	0.393±0.016 a	-12.98	-14.50	0.05	0.05	N.S.
6	0.375±0.026 a	0.357±0.015 a	0.395±0.015 a	-5.06	-9.62	N.S.	N.S.	N.S.
8	0.315±0.018 b	0.304±0.007 b	0.396±0.015 a	-20.45	-23.23	0.01	0.001	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (3): Testes volume (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(cm^3)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	6.23±0.12 a	6.05±0.08 a	5.85±0.23 a	+6.50	+3.42	N.S.	N.S.	N.S.
4	6.03±0.17 ab	5.86±0.09 a	6.17±0.12 a	-2.27	-5.02	N.S.	N.S.	N.S.
6	6.05±0.11 ab	5.94±0.12 a	6.06±0.38 a	-0.17	-1.98	N.S.	N.S.	N.S.
8	5.64±0.17 b	5.43±0.27 b	6.35±0.13 a	-11.18	-14.49	0.01	0.001	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (4): Tunica albuginea index (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.0204±0.0029 a	0.0232±0.0014 a	0.0183±0.0006 a	+11.48	+7.17	N.S.	N.S.	N.S.
4	0.0228±0.0018 a	0.0244±0.0012 ab	0.0160±0.0001 a	+42.5	+52.5	0.01	0.01	N.S.
6	0.0218±0.0024 a	0.0220±0.0011 a	0.0203±0.0008 a	+7.31	+8.37	N.S.	N.S.	N.S.
8	0.0228±0.0011 a	0.0280±0.0014 b	0.0200±0.0017 a	+14.00	+40.00	N.S.	0.01	0.05

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (5): Testicular tissue weight (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.351±0.010 a	0.345±0.011 a	0.365±0.012 a	-3.86	-5.48	N.S.	N.S.	N.S.
4	0.319±0.018 ab	0.312±0.015 ab	0.373±0.016 a	-14.48	-16.35	0.05	0.01	N.S.
6	0.353±0.025 a	0.335±0.014 a	0.370±0.015 a	-4.59	-9.46	N.S.	N.S.	N.S.
8	0.292±0.017 b	0.276±0.006 b	0.376±0.013 a	-22.34	-26.60	0.001	0.001	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (6): Epididymal-head index (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.0558±0.0013 a	0.0554±0.0022 a	0.0763±0.0083 a	-26.87	-27.39	0.05	0.05	N.S.
4	0.0574±0.0059 ab	0.0620±0.0023 a	0.0863±0.0092 a	-33.49	-28.16	0.01	0.01	N.S.
6	0.0738±0.0093 b	0.0684±0.0054 a	0.0890±0.0066 a	-17.08	-23.15	N.S.	0.05	N.S.
8	0.0710±0.0066 ab	0.0710±0.0068 a	0.0833±0.0122 a	-14.77	-14.77	N.S.	N.S.	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (7): Epididymal-tail index (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks)	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.0688±0.0027 ab	0.0696±0.0016 ab	0.0776±0.0127 a	-11.34	-10.31	N.S.	N.S.	N.S.
4	0.0574±0.0059 a	0.0620±0.0023 a	0.0646±0.0185 a	-11.15	-4.02	N.S.	N.S.	N.S.
6	0.0804±0.0100 b	0.0868±0.0038 b	0.0860±0.0120 a	-6.51	+0.93	N.S.	N.S.	N.S.
8	0.0854±0.0015 b	0.0828±0.0048 b	0.0830±0.0108 a	+2.89	-0.24	N.S.	N.S.	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

Table (8): Seminal vesicles index (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg)and controls.

Duration (weeks)	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.089±0.003 a	0.088±0.005 a	0.086±0.005 a	+3.37	+2.27	N.S.	N.S.	N.S.
4	0.099±0.009 ab	0.094±0.002 ab	0.085±0.004 a	+14.14	+9.57	N.S.	N.S.	N.S.
6	0.092±0.005 a	0.111±0.003 b	0.089±0.012 a	+3.26	+19.82	N.S.	0.05	0.05
8	0.115±0.012 b	0.131±0.009 c	0.091±0.010 a	+20.87	+30.53	0.05	0.001	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the samecolumn.

Table (9): Prostate index (mean ± S.E.) of albino male rats treated with two doses of carbimazole (80 and 160 mg/kg) and controls.

Duration (weeks	Mean ± S.E.(w/w)			Treatment Efficiency (%)		Probability ≤		
	Carbimazole treated rats (mg/kg)		Controls					
	80	160		I	II	I	II	III
2	0.223±0.035 a	0.217±0.018 a	0.225±0.009 a	-0.90	-3.70	N.S.	N.S.	N.S.
4	0.291±0.010 b	0.273±0.021 b	0.285±0.030 a	+2.06	-4.40	N.S.	N.S.	N.S.
6	0.321±0.021 bc	0.363±0.015 c	0.273±0.031 a	+14.95	+24.79	N.S.	0.01	N.S.
8	0.349±0.017 c	0.393±0.017 c	0.253±0.012 a	+27.51	+35.60	0.01	0.001	N.S.

Treatment Efficiency I and II: Doses 80 and 160 mg/kg, respectively.
Probability I: Comparison between dose 80 mg/kg and controls.
Probability II: Comparison between dose 160 mg/kg and controls.
Probability III: Comparison between dose 80 mg/kg and dose 160 mg/kg.
Different letters: Significant difference between means of the same column.

تأثير نقص الدرقية المحث بوساطة الكاربيمازول في أعضاء الجهاز التكاثري في ذكور الجرذ

سعدي محمد محمود
محمد ناجي طه
غيداء عبد السلام كريم يحيى
قسم علوم الحياة / كلية التربية للعلوم الصرفة (ابن الهيثم) / جامعة بغداد

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الخلاصة

أجريت الدراسة الحالية للتحري عن تأثير نقص الدرقية المحث بوساطة الكاربيمازول في الجهاز التكاثري لذكور الجرذ، إذ استخدمت جرذ بالغة تتراوح أوزانها 300-250غم
جرعت ذكور الجرذان بعقار الكاربيمازول فموياًبأحدى جرعتي العقار 80,60 ملغم /كغم من وزن الجسم يومياً.وقد أجريت عليها الاختبارات بعد مرور 8,6,4,2 أسابيع في حين جرعت مجموعة السيطرة بالماء المقطر وأوضحت النتائج ما يأتي:
1- تجريع الحيوانات بعقار الكاربيمازول أدى إلى حصول زيادة في وزن الجسم ولكن هذه الزيادة لم تكن معنوية حتى في التراكيز العالية.
2- لقد تم التحري عن تأثير نقص الدرقية في أوزان الأعضاء التكاثرية وقد لوحظ نقصان في وزن الخصى في جميع مراحل المعاملة مع تفاقم هذا النقصان بزيادة الوقت والجرعة ($P\leq0.001$).
3- أظهرت النتائج حصول انخفاض في وزن رأس البربخ ولكن هذا الانخفاض لم يكن معنوياً كذلك لأوزان الذيل
4- سبب الكاربيمازول زيادة في وزن الحويصلة المنوية ولاسيما بعد 6أسابيع ($P\leq0.05$)8 أسابيع لكلا الجرعتين.
أظهرت أوزان البروستات تحسساً لنقصان مستويات هرمونات الدرقية وذلك بزيادة اوزانها بشكل يتناسب مع مقدار الجرعة المستعملة.

الكلمات المفتاحية : نقص الدرقية – الكاربيمازول -الجهاز التكاثري - الجرذ