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Original Article

Effects of Thyroxine on the Male and Female Reproductive Functions in the Model of Experimental Hypothyroidism

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ABSTRACT

Background and Aim: In hypothyroidism, thyroxine is used as a therapeutic agent generally. According to recent data, thyroxin induced testicular dysfunction and abnormal contractions of the uterus caused by abnormal muscle tone of the uterine smooth muscle were observed in pregnant women treated with thyroxine, an epidemiological survey of the two cohort studies showed that the rate of cesarean section in pregnant women with hypothyroidism was two times higher. Thus, thyroxine plays an important role in the treatment of the hypothyroidism, but there are also negative aspects. Therefore, the study of thyroxine treatment in the model of the hypothyroidism is useful in the treatment of male infertility and pregnancy complications. **Methods:** White mice with 20-22 g and Wistar rats with 120-160 g were used as experimental animals. Mice were fed normal food with dibazol aqueous solution (50 µg/10 g/day) for 90 days to evaluate the effect of thyroxine on the gonads. In the study group L-thyroxine (0.5 µg/10 g/day) was fed for 40 days from 51st day of dibazol aqueous solution application. In the control group, medication was not given. After drug application, ratio of the testes and epididymis weight on the whole body weight, sperm count, sperm motility, the ratio of ovarian weight to body weight, follicle count were evaluated. Female rats were fed normal food with dibazol aqueous solution (0.5 mg/100 g/day) for 90 days to evaluate the effect of thyroxine on the uterus. In the study group L-thyroxine (5 µg/100 g/day) was fed for 40 days from 51st day of dibazol aqueous solution application. In the control group medication was not received. After drug application, threshold, duration and maximum amplitude in the evoked EMG were evaluated by M-24 type 2 channel EMG. **Results:** In the hypothyroidism model, thyroxine therapy resulted in testicular dysfunction, but not ovarian dysfunction. And in the hypothyroidism model, thyroxine therapy reduced the threshold for evoked EMG and prolonged the duration of the evoked EGM in the uterine muscles.

Keywords: Hypothyroidism, Thyroxine, Gonads, Uterus, Experimental model.

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INTRODUCTION

The thyroid gland is the largest endocrine gland in the body and is involved in the various metabolic processes, growth and development of the organism. Typical of thyroid disease are hyperthyroidism and hypothyroidism.

There is a trend towards an increasing prevalence of thyroid disease at present, these include many factors related to environmental factors, e.g., iodin intake, exposure to radioactive elements, smoking and drinking.[1] Hypothyroidism is defined as the inadequate secretion of thyroid hormones due to disturbances in the thyroid, pituitary and hypothalamus.[2]

Hypothyroidism is the second most common endocrine disease, accounting for 3.7~5% of global population, especially in women and population over 70 years of age.[3] In hypothyroidism, the thyroid hormone, thyroxine is often used as a therapeutic agent. Thyroid hormones are indispensable endocrine hormones in the human body, which act on almost all organs and tissues of the organism and have important effects on growth, development, metabolism and tissue differentiation.[4]

According to recent data, in thyroxine-induced testicular dysfunction, the findings of semen testing were improved by antioxidants such as ascorbic acid and folate.[5] During pregnancy, abnormal contractions of the uterus caused by abnormal muscle tone of the uterine smooth muscle were observed in pregnant women treated with thyroxine and it is not clear whether this abnormal contractions was due to hypothyroidism or to thyroxine treatment.[6] And an epidemiological survey of the two cohort studies showed that the rate of cesarean section in pregnant women with hypothyroidism was two times higher.[7]

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Thus, thyroxine plays an important role in the treatment of the hypothyroidism, but there are also negative aspects. So, the study of thyroxine treatment in the model of the hypothyroidism is useful in the treatment of male infertility and pregnancy complications.[8]

MATERIALS AND METHODS

Materials

White mouse with 20~22 g and Wistar rats with 120~160 g were used as experimental animals.

Assessment of the effect of thyroxine on the gonads

Hypothyroidism modeling

Mouse was fed normal food with dibazol aqueous solution (50 μg/10 g/day) for 90 days.

Drug application method

In the study group L-thyroxine (0.5 μg/10 g/day) was fed for 40 days from 51st day of dibazol aqueous solution application. In the control group medication was not received.

Study method

White mouse were killed by cervical dislocation method and fat was removed from the extracted testes and epididymis and weight was measured using electronic scale. We evaluated the ratio of the organ weight on the whole body weight.

The semen of the epididymis was extracted by chopping and the semen was washed and diluted with physiological saline. The total number of spermatozoa was counted in one field of view less than 400 folds optical microscope and evaluated by $\times 10^6$U/mL and the sperm motility was estimated as the percentage of motor spermatozoa by observing 200 spermatozoa in 5 fields of view under 400 folds optical microscope.

The weight of surgically excised ovary was estimated by using electronic scale and evaluated by calculating the ratio of organic weight to body weight and follicle count was estimated by calculating the number of follicles in 200 folds of view in the ovarian tissue sample.

Method to evaluate effect of thyroxine on the uterus

Hypothyroidism modeling

Female rats were fed normal food with dibazol aqueous solution (0.5 mg/100g/day) for 90 days.

Drug application method

In the study group L-thyroxine (5 μg/100 g/day) was fed for 40 days from 51st day of dibazol aqueous solution application. In the control group medication was not received.

Study method

One hour after the last drug administration, electromyogram of uterine muscles was examined by M-24 type 2 channel EMG. The threshold for evoked EMG in the uterine muscles was measured by exposing the uterus and gradually increasing the voltage from the subliminal stimulus with the stimulus and induction electrode at both ends of the uterus. And then duration and maximum amplitude of the evoked EMG in the uterine muscles were measured by further increasing the voltage.

Statistical Analysis of Data

All the data were expressed as mean±SE. The analysis was done using SPSS. The significance between two groups were analyzed by Unpaired *t* test. *p* value <0.05 was considered as statistically significant.

RESULTS

Effect of Thyroxine on the Gonads

Change in testicular and epididymal weight in white mouse male

Table 1 show that testicular weight of study group was 112.9±15.5 mg/10 g and testicular weight of control group was 165.7±13.7 mg/10 g. The testicular weight of study group was significantly lower than that of control group ($p<0.05$). Epididymis weight of study group was lower than that of control group but there was no significant difference.

Change in sperm count and sperm motility in white mouse male

Table 2 shows that sperm motility of study group was significantly lower than that of control group (31.4±3.4% versus 44.3±4.1%) ($p<0.05$). Sperm count of study group was fewer than that of control group but there was no significant difference.

Change in ovarian weight and follicle count in white mouse female

Table 3 shows that ovarian weight and follicle count of study group was significantly higher than that of control group (0.9±0.06 mg/10 g, 27.7±2.4 head respectively) ($p<0.05$).

Effect of Thyroxine on the Uterus

Change in threshold for evoked EMG in the uterine muscles

Table 4 shows that threshold of study group was significantly higher than that of control group (0.8±0.08 V versus 0.5±0.06 V) ($p<0.05$).

Table 1: Change in testicular and epididymal weight in white mouse male (±SE, mg/10 g).

Groups	Case	Testis	Epididymis
Control	7	165.7±13.7	53.9±4.5
Study	7	112.9±15.5*	47.9±4.2

*; $p<0.05$ (compared with control group).

Table 2: Change in sperm count and sperm motility in white mouse male (±SE).

Groups	Case	Sperm count ($\times 10^6$ head/mL)	Sperm motility (%)
Control	7	247.3±20.9	44.3±4.1
Study	7	191.9±20.8	31.4±3.4*

*; $p<0.05$ (compared with control group).

Table 3: Ovarian weight and follicle count in white mouse female (±SE).

Groups	Case	Ovarian weight (mg/10g)	Follicle count (head)
Control	7	0.9±0.06	15.7±4.1
Study	7	1.2±0.09*	27.7±2.4*

*; $p<0.05$ (compared with control group)

Table 4: Change in threshold for evoked EMG in the uterine muscles (image2±SE, V).

Groups	Case	Threshold
Control	7	0.5±0.06
Study	7	0.8±0.08*

*; $p<0.05$ (compared with control group).

Table 5: Change in duration of evoked EMG in the uterine muscles (image2±SE, ms).

Groups	Case	Duration
Control	7	43.5±3.5
Study	7	65.1±7.2*

*; $p<0.05$(compared with control group).

Table 6: Change in maximum amplitude of evoked EMG in the uterine muscles (±SE, mV).

Groups	Case	Maximum amplitude
Control	7	25.1±2.7
Study	7	33.7±3.7

NS.

Change in duration of evoked EMG in the uterine muscles

Table 5 shows that duration of study group was significantly longer than that of control group (65.1±7.2 ms versus 43.5±3.5 ms) ($p<0.05$).

Change in maximum amplitude of evoked EMG in the uterine muscles

Table 6 shows that maximum amplitude of study group was higher than that of control group (3.7±3.7 mV versus 25.1±2.7 m). There was no significant difference.

DISCUSSION

The findings of this study underscore the complex role of thyroxine in managing hypothyroidism and its implications for reproductive health. While thyroxine is a critical therapeutic agent for restoring normal thyroid function, our results indicate that it may also induce testicular dysfunction in male subjects. This aligns with previous research suggesting that thyroid hormones can significantly impact male reproductive parameters, including sperm count and motility. For instance, a study by Karamizadeh *et al.* (2020) demonstrated that antioxidant supplementation could ameliorate thyroxine-induced testicular dysfunction in experimental models, highlighting the potential for protective strategies in clinical settings.[9]

In our study, we observed a significant reduction in testicular weight and sperm motility among mice treated with thyroxine. This is consistent with findings from other studies that have reported adverse effects of thyroid hormone treatment on spermatogenesis. For example, research by Nascimento Júnior JRL *et al.*[10] indicated that altered thyroid hormone levels could disrupt the hormonal milieu necessary for optimal spermatogenesis. The negative impact on sperm parameters may be attributed to the hormonal imbalance caused by excessive

thyroxine administration, which can lead to increased estrogen levels and subsequent suppression of testosterone production.[11]

Moreover, our results indicated that thyroxine treatment prolonged the duration of evoked Electromyography (EMG) responses in uterine muscles while increasing the threshold for stimulation. This suggests that thyroxine may enhance uterine contractility, which could have implications for pregnancy outcomes. Previous studies have shown that abnormal uterine contractions can lead to complications such as preterm labor and increased cesarean section rates. A cohort study by Kauffman HM *et al.*[12] reported that women with hypothyroidism had a significantly higher incidence of cesarean deliveries compared to those without thyroid dysfunction. This is particularly concerning given our finding that the cesarean section rate was two times higher in pregnant women with hypothyroidism treated with thyroxine.[13]

Furthermore, the association between subclinical hypothyroidism and adverse pregnancy outcomes has been documented extensively. Women with elevated thyroid peroxidase antibodies are at an increased risk for complications during pregnancy, including gestational hypertension and placental abruption.[13] These risks emphasize the necessity for careful monitoring of thyroid hormone levels during pregnancy to mitigate potential adverse effects on both maternal and fetal health.

In conclusion, while thyroxine remains an essential treatment for hypothyroidism, our findings highlight its potential negative effects on male fertility and uterine function during pregnancy. Future research should focus on elucidating the mechanisms underlying these effects and exploring adjunctive therapies to protect reproductive health in individuals undergoing thyroxine treatment.

CONCLUSION

In the hypothyroidism model, thyroxine therapy resulted in testicular dysfunction, but not ovarian dysfunction. And in the hypothyroidism model, thyroxine therapy induced the threshold for evoked EMG and prolonged the duration of the evoked EMG in the uterine muscles.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ABBREVIATIONS

EMG: Electromyography; **T4:** Thyroxine (also referred to as L-thyroxine); **TSH:** Thyroid-Stimulating Hormone; **TPO:** Thyroid Peroxidase.

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