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Effect of Trazodone HCL on levels of Gonadotropin Hormone, Testosterone and Histological Changes of testis in Adult Rat

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ABSTRACT

Background: Considering the importance of Trazodone as a serotonin antagonist reuptake inhibitor in treating nervous diseases, its side effects on the endocrine axis are extremely important.
Objective: In this research the effect of Trazodone on the concentration of testosterone, FSH and LH levels and spermatogenesis were studied.
Materials and Methods: 40 male wistar rats were divided to 5 groups of 8. The control group received no treatment and the sham group was given distilled water as a solvent. The experimental groups were administrated 30, 60 and 90 mg/kg of the drug orally for 28 days. Blood serum samples were taken at 29th day and concentrations of testosterone, FSH and LH were measured by RIA method. In addition, the testes were separated at the 29th day and histological changes were studied among experimental, control and sham groups. The results were evaluated by ANOVA using SPSS software.
Results: The results showed that 90mg/kg of Trazodone reduced serum testosterone level while it increased FSH and LH levels ($p \leq 0/05$). Histological investigation of the testes showed a decline on spermatogenesis chain in 90 mg/kg dose.
Conclusion: According to our findings, Trazodone decreases the concentration of testosterone level and the number of spermatogenic cells and increases FSH and LH levels at high doses. Also, it can probably weaken the function of reproduction activity.
KEY WORD: Trazodone, Reproduction, Rat

INTRODUCTION

So far a certain mechanism hasn't been describe for the cause of depression. Most researchers believe that the disease caused by following the change in the rate of major neurotransmitters in the brain that the most important of them are dopamine, serotonin and norepinephrine. Therefore, the drugs that cause the balance of the level of these neurotransmitters are effective in depression treatment. Trazodone is a serotonin reuptake inhibitor and antagonist of 5HT2C and 5HT2A receptors, and is located in the group of antidepressants (1). This drug is derived from Triazolopyridine. Trazodone is rapidly absorbed after oral administration and its half-time is between 5- 9 hours (2). Trazodone is metabolized in the liver by CYP3A4 cytochrome to an active metabolite called Chlorphenirpiperazine (3). This drug is used to treat depression and insomnia. The level of dosage for the treatment of depression is 250- 600 mg per day and the proper dose for the treatment of insomnia is 25- 100 mg before sleep (4). Of the side effects of drug can be noted to Priapism, Impotence, abnormal ejaculation and early menarche in women (5). The drug is useful as an antihistamine for allergic patients due to its antagonist properties of H1 receptor (6). Treatment with serotonin reuptake inhibitors such as trazodone may lead to sexual dysfunction in 70% of patients (7). Antidepressants due to damage to sperm DNA are one of the causes of sterility in men (8). With the increasing prevalence of depression among communities, the use of antidepressants such as Trazodone became very common. In the present study, the effect of trazodone on the pituitary- gonad hormone axis and testicular issue was studied to provide suitable solution about configuration, development or restriction of its consumption by using obtained results.

MATERIALS AND METHODS

This experimental study was conducted in a laboratory environment and 40 adult male wistar rats in the weight range of 180- 220 gr were used. All animals were in the standard lighting conditions of 12 hours of lights and 12 hours of dark and in the temperature of 22˚ C, and had indefinitely access to food and water. Animals were

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randomly divided into 5 groups of 8 in the control, sham and experimental groups. The animals of the control group received no pharmacological and non-pharmacological treatments. The sham group had received daily a drug solvent meal that is 1 mL of distilled water orally. A meal of trazodone drug with doses of 30, 60 and 90 mg/kg were fed daily to the experimental groups for 28 days. After 28 days, the animals weighed, then are anesthetized by ether and blood samples were taken from their hearts. Approximately 5 mL of blood from each rat was collected in test tubes. Blood samples were centrifuged for 15 minutes at a speed of 3000 rpm to separate the serum from the clot. Then the samples were kept at a temperature of -20˚ C for the measurement of the serum concentrations of LH, FSH and Testosterone. Hormone measurement was performed by using radioimmunoassay method (RIA). After opening the animals abdomen and scrotum, both testes of all groups were exited and the tissue sections of them prepared and were stained with hematoxylin- eosin colors. Then by using scaled slide for measuring, changes of sperm density in seminiferous tubes, changes in the number of interstitial cells, sertoli and spermatogenic chain between experimental, sham and control groups in histological studies were determined. Mean and standard deviation were expressed as mean ± standard error. For statistical analysis of the result between experimental and control groups, the ANOVA statistical test using SPSS software was used. $P \leq 0.05$ was the border of statistical inference to assess significant differences between the mean of the experimental and control groups.

RESULTS

The result showed that of testosterone at the end of day 28 had a significant decrease in the drug receiving group to the rate of 90 mg/kg in compared to control group. The serum concentrations of LH and FSH at the end of 28 days showed significant increase in the drug receiving group to the rate of 90 mg/kg in compared to control group. By reducing the serum concentrations of testosterone in the drug receiving group to the rate of 90 mg/kg, decrease in sperm density in seminiferous tubes and the number of spermatogonia, primary spermatocytes and spermatid cells was observed (table 1) (figure 2). The number of Sertoli cells in the experimental group than the control group showed no significant difference (table 2). The number of Leydig cells in the experimental group than the control group decreased after the period of 28 days (table 2) (figure 4).

Table 1- mean (± standard deviation) of the number of sperm lineage cells in the seminiferous tube after oral administration of the trazodone drug

Groups	Amount of drug Mg/kg	The number of spermatogonia	The number of spermatocytes	The number of spermatid
control	-	47/2±/26	57/3±/31	152/2±/31
Sham	-	48/5±/41	56/6±/28	154/2±/43
Experimental1	30	45/01±/34	55/7±/4	152/1±/32
Experimental2	60	43/4±/44	52/6±/3	150/3±/42
Experimental3	90	*41/1±/25	*46/4±/32	146/3±/34*

*sign indicates a significant difference between control and experimental groups

Table 2- mean (± standard deviation) of the number of Leydig and Sertoli cells in the seminiferous tube after oral administration of the trazodone drug

Groups	Amount of drug Mg/kg	The number of Sertoli	The number of Leydig
control	-	14/8±/26	17/4±/21
Sham	-	14/7±/26	17/4±/22
Experimental1	30	14/5±/34	16/1±/27
Experimental2	60	14±/31	14/1±/32
Experimental3	90	14/5±/22	12/3±/32*

*sign indicates a significant difference between control and experimental groups

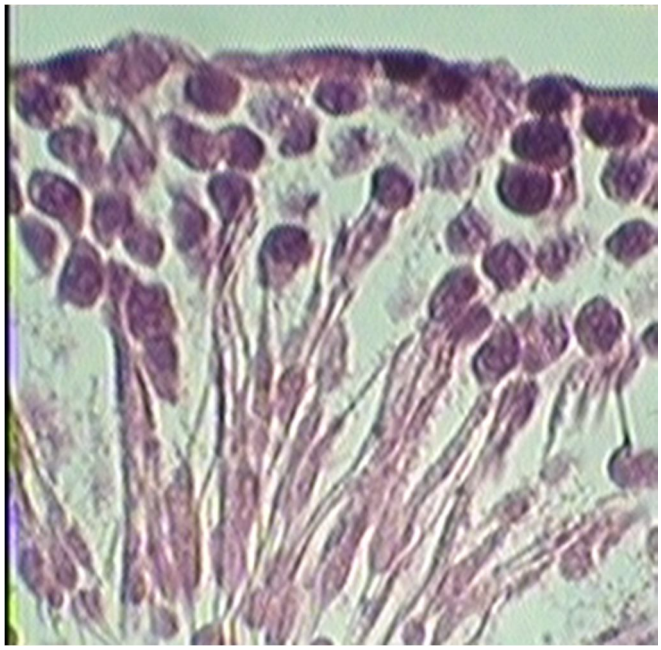

Figure 1- photomicrograph of Spermatogonia, Primary Spermatocyte, Spermatid and Sperm cells in the controlled group.

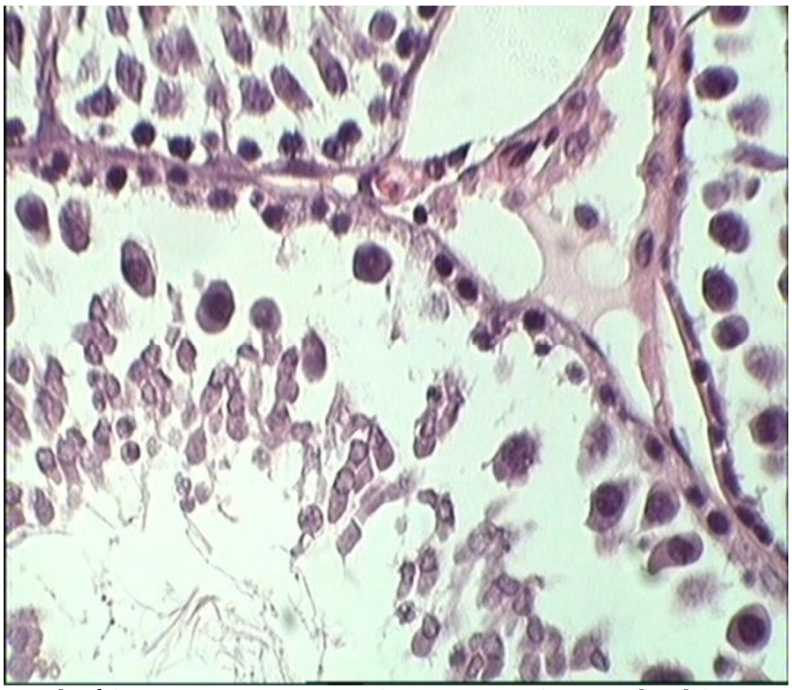

Figure 2- photomicrograph of Spermatogonia, Primary Spermatocyte, Spermatid and Sperm cells in the group that treated with the maximum amount of drug.

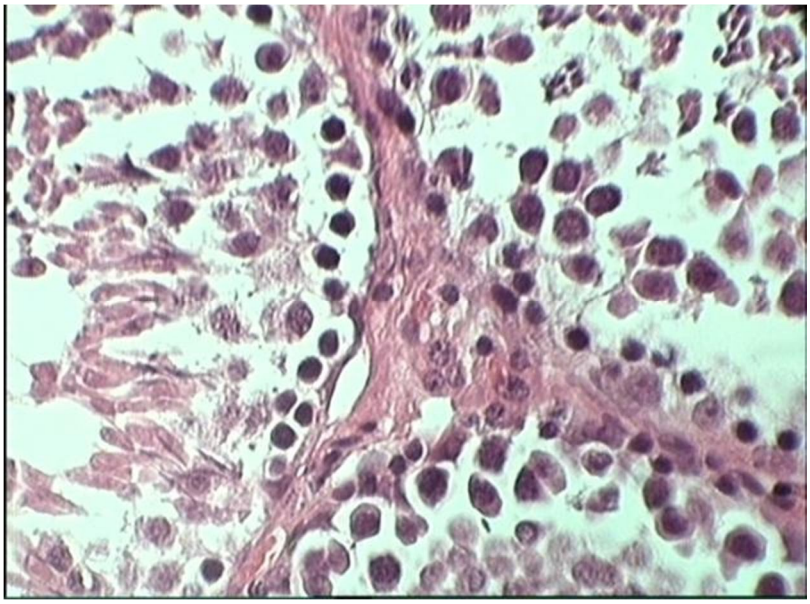

Figure 3- photomicrograph of interstitial cells in the control group.

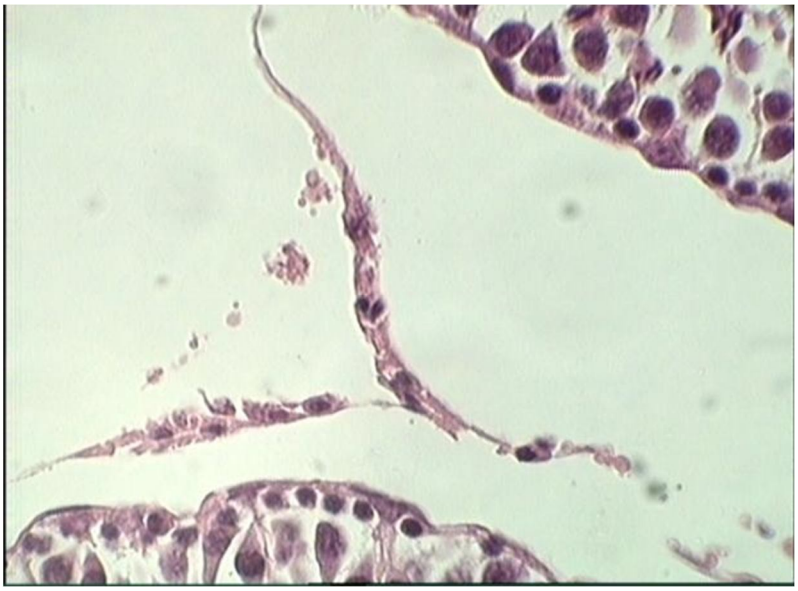

Figure 4- photomicrograph of interstitial cells in the group that treated with the maximum amount of drug.

DISCUSSION

Due to the reduction in testosterone levels in the drug receiving group to the rate of 90 mg/kg, it seems that trazodone by inhibiting of serotonin reuptake causes increase in the level of these neurotransmitters and increase in serotonin causes inhibition of the activity of interfering enzymes in the production way of the testes steroids and will be followed by decreased testosterone (9 and 10). Trazodone causes ACTH reduction by reducing histamine. Thus, with reducing the ACTH, activity of cortical cells of the adrenal glands to produce steroids decreases and the most important step of stimulation of ACTH to regulate the secretion of cortical of the adrenal glands hence activation of A Kinase Protein for conversion of cholesterol to pregnenolone are weakened (11). According to testosterone reduction by the way of negative feedback, GNRH secretion of hypothalamic and subsequently LH and FSH secretion of the anterior pituitary are increased (12). Testosterone is an inhibitor factor of the activity of Monoamine oxidase enzyme which is involved in dopamine catabolism and reduction in this enzyme, increases the levels of dopamine (13 and 14). Probably by reduction in testosterone, this inhibitory effect on the activity of the enzyme decreases and the concentration of dopamine is also reduced. Dopamine by affecting the brain arcuate nucleus

prevents the production of gonadotropin hormones and dopamine reduction causes increase in gonadotropins (16 and 15). The obtained results from the present study show the increased level of LH and FSH and the testosterone reduction in experimental group that received 90 mg/kg drug at the end of 28 days than the control group. In this study, sperm density in the seminiferous tubes of the experimental group that received 90 mg/kg drug than the control group was reduced. Studies have shown that testosterone is a survival factor in spermatogenesis and especially in the final stages of Spermatozoa evolution and evolution of their natural form, existing of testosterone is vital (17 and 18). Any decrease in this hormone, sperms density and process of spermatogenesis are reduced, although further studies are needed. In general, we can say that one of the side effects of trazodone drug is the reduction in the process of steroidogenic in the testicular issue. High dose Trazodone causes to reduce in serum concentrations of testosterone and probably interfere with reproduction activity. It recommends that its use in the patients with impairment in production of sex hormones should perform with caution. To reduce the side effects of Trazodone in these patients, concurrent use of it with drugs that activate the production of steroids is recommended.

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