

## The Study of Effects of Clomipramine on Pituitary Gonadal Axis in Mature Big Male Rat

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**Introduction and aim:** the prevalence of obsessive-compulsive disorders and depression increase prescription and consumption of serotonin reuptake medications. Therefore, the aim of this study is to investigate the side effects of clomipramine on testosterone, LH, FSH. 40 mature big male rats were divided into groups of control, sham, and experimental 1,2,3. these groups received 2.5, 5, 10 mg/kg doses of clomipramine medicine by gavage method for 21 days. at the end, after drawing blood samples was used in order to measure serum concentration of LH, FSH and testosterone hormones, by radioimmunoassay. Data were analyzed by SPSS software (version of 18) and Duncan test. Results indicated a significant increase in concentration of LH and there was a significant decrease in the testosterone concentration in experimental group 3 in the level of ( $p < 0.001$ ) than other groups. no significant difference was also observed in the concentration of FSH. Clomipramine decreases testosterone secretion. Therefore, the use of this medicine is not recommended in the ages of pregnancy.

**Key words:** Clomipramine-LH-FSH-Testosterone-mature male big rats.

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Obsessive-compulsive disorder disease is one of the most common disorders and sometimes, is extremely disabling. Limitation of facilities of psychotherapy in most of the country regions as well as relatively high cost of sessions of psychotherapy make psychotherapy in the form of the way of selective treatment for such sick people<sup>1</sup>. Recently, the use of anti-depression medicines such as clomipramine has been common by the increase

of depression among societies that are: many of the persons who use of these medicines may be in the ages of pregnancy. Some of environmental mechanism and also central mechanism such as some of the neurotransmitters like serotonin, dopamine and noradrenaline play many roles in appearance of sexual behavior<sup>2-3</sup>.

Studies have shown that selective serotonin reuptake inhibitors are the most effective available medicine for obsessive-compulsive disorder treatment<sup>4</sup>.

Clomipramine (Anafranil) is one of the tricyclic medicines derived from dibenzazepine. This medicine is anti-obsession and anti-depression

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and was used in order to treat these disorders<sup>5</sup>.

Studies have shown that clomipramine has more effects in inhibiting of absorption of serotonin and blocks of dopaminereceptors compared to other tricyclic anti-depressions<sup>6</sup> leading to prolactin release, increase and no orgasm through 5-ht2 mediums<sup>7-8</sup>. in some recent studies have shown that inhibitors of dopamine and serotonin have an effect on asteroid hormones of Gonads<sup>9</sup>. In some studies, it is identified that anti-depression medicines have harmful effect on sexual performance and make problems in erection<sup>10</sup> (induction) and decrease the level of total cholesterol which is prefabricate of spermatic androgen in leydig cells<sup>11</sup>. Therefore, the aim of this present research is to investigate the effects of clomipramine medicine on hormonal axis of Pituitary Gonad.

## MATERIALS AND METHODS

In this research, 40 mature big male wistar rats obtained from Razi vaccine and serum research center in Shiraz. All animals were kept in the temperature of 22±2 centigrade degree with free access to food and water and standard condition of 12 h lightness and 12 h darkness. in order to acquire of adaptation to the ecompered tonvironment, all the experiments performed 2 weeks after inhabitation of rats. Classification of the animals was done as follows : (control group, sham group (receptor of medicine solvent (water) experimental groups 1,2,3 which received doses of 2.5,5,10 mg/kg of clomipramine. Rats orally treated with clomipramine for 21 days. at the end of the experiment, rats anaesthetized with diethyl ether and after drawing blood, their blood samples gathered into sterile plastic tube and coagulated in the room temperature for 20 minutes. Then, samples were centrifuged 15 minutes in speed of 3000 Rpm and its serum was separated. They were kept in order to evaluate the activation of LH, FSH and testosterone in the temperature of -20 centigrade degree. Then, the evaluation of mentioned hormones was done with the use of Radioimmunoassay and results were analyzed by help of SPSS software, version 18 and variance analysis tests (One way Anova) and Duncan test. ( $p < 0.05$ )

## Findings

The results of this research have shown

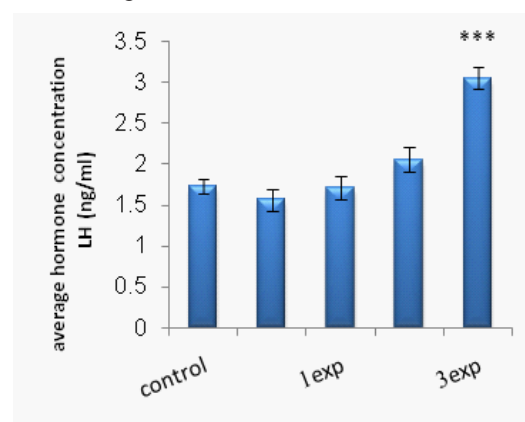
that LH concentration in experimental group 3 (receptor group of maximum dose of clomipramine 10 mg/kg indicate that significant increase compered to other groups. ( $p < 0.00$ ) (chart 1) but no significant difference in other groups was observed. Moreover, on the one hand, a significant difference was not observed serum concentration of FSH hormone among investigated groups. (chart 2).

At the end of the experiment, testosterone serum concentration showed a significant decrease in the level of ( $p < 0.001$ ) than other groups in experimental group 3 (receptor group of maximum of clomipramine dose (10 mg/kg). (chart3)

## RESULTS AND DISCUSSION

In this research, LH concentration in experimental group 3 show a significant increase compered to other groups, but there wasn't a significant difference in the average of FSH concentration in mentioned groups. in experimental group 3, testosterone concentration has a significant decrease to other groups.

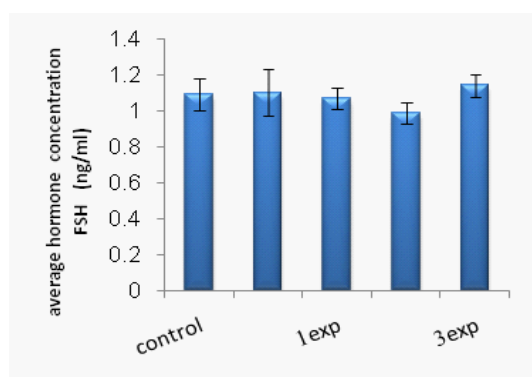
In normal situation, testosterone increase makes negative feedback mechanism run via the effect on Hypothalamus and frontal (anterior) pituitary. Finally this action make genadotropines decrease<sup>12-13</sup>. in conducted studies on the medicines which are selective serotonin reuptake inhibitors (such as clomipramine). it is stated that these medicines lead to spermary activation decrease for testosterone secretion through LH receptor decrease in leydig cells<sup>11</sup>. Additionally, the consumption of serotonin uptake inhibitor medicines causes the rate



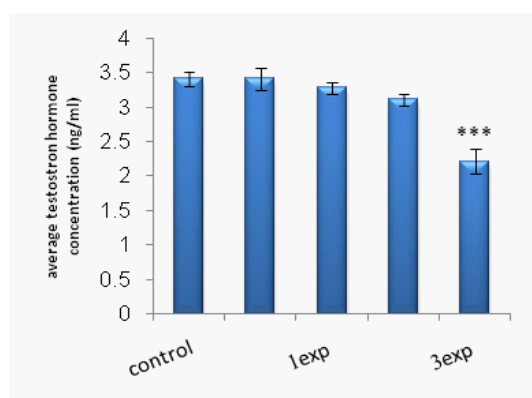
**Chart 1.** Points have shown as Mean ± S.E  
\*\*\* is sign of significant difference in the level of ( $P \leq 0.001$  toward control group)

of total cholesterol to decrease<sup>11</sup>. This action is the prefabrication of spermatogenic androgen production in Leydig. Consequently, inhibitive effect of androgens on androgen receptor and through LH receptor decrease lead to make negative feedback mechanism. So, LH concentration increase according to this mechanism. In one research, it is known that serotonin uptake inhibitor medicines cause serotonin levels to increase and serotonin increase makes enzyme activation interfering in the production of the spermatogenic steroid inhibition. This action causes testosterone decrease which is consistent with the present research. It is claimed that some of the serotonin uptake inhibitor medicines increase the production of melatonin<sup>14</sup> and melatonin decreases the production of STAR protein that inhibits the conversion of cholesterol to pregnenolone and makes disorders in the function of enzymes of

steroid production. Research has shown that serotonin uptake inhibitor medicines cause ACTH to decrease by histamine decrease<sup>15</sup>. Therefore, when ACTH decreases, the activation of cells of the adrenal cortex decreases to make steroids, and the most important stage of ACTH stimulation for secretion of the adrenal cortex, weakens. It means that the activation of protein kinase A is weakened in order to the conversion of cholesterol to pregnenolone. Regarding testosterone decrease through the procedure of negative feedback, GnRH secretion from the hypothalamus and consequently, LH secretion from the anterior pituitary increases that is consistent with this research<sup>16</sup>. In some of the studies, it has been shown that the feedback mechanism of FSH versus are not applied just for spermatogenic steroids but also inhibin, activin and follistatin with central effect on GnRH production, play a role in FSH concentration adjustment. It is probably that the inexistence of the significant increase of FSH<sup>17</sup> arises from adjustment effects of these factors. The studies have shown that FSH concentration of blood changes less than LH. The findings of other researchers show that prolactin causes the conversion of cholesterol to pregnenolone through nitric oxide increase. It has also stated that some of the medicines of this group cause the levels of cortisol to increase.<sup>18</sup> Cortisol decreases the numbers of LH receptors in Leydig and causes some of the existing enzymes in the production of steroids to inhibit. There is a possibility that clomipramine causes testosterone production to decrease by increasing the cortisol.



**Chart 2.** Points have shown as Mean  $\pm$  S.E



**Chart 3.** Points have shown as Mean  $\pm$  S.E \*\*\* is sign of significant difference in the level of ( $P < 0.001$ ) toward control group

## CONCLUSION

Generally speaking, consumption of clomipramine in high rates makes testosterone concentration decrease, therefore, we would do necessary caution in order to its consumption in the ages of pregnancy.

It is suggested that clomipramine consumption is done with the medicines that activate steroid production. So, the side effects originated from it are decreased.

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