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Research Article

Amitriptyline Prescription Can Potentially Affect Pituitary-Gonadal Hormonal Axis in Female Mice

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Abstract

Amitriptyline (Ami) as a tricyclic antidepressant drug is widely used globally. Pituitary-gonadal hormonal axis with various hormones is affected by many antidepressant drugs. Thus in this experimental research, we aimed to assess the probable effects of Ami with various doses on serum levels of female sexual and gonadotropin hormones. 35 female mice (25 - 30 gr, 8 - 12 weeks old) were categorized into 5 groups (n = 7); control (received no treatments), sham (treated with 0.2 ml of distilled water), and three experimental groups (Ami 50, 75, and 100 mg/kg). Treatments were administrated orally for 4 weeks. A day following experiment, the animals were weighted and sacrificed by cervical dislocation. Thoracotomy procedure was applied and the blood was aspirated (1 ml) from right ventricle to measure blood serum levels of LH, FSH, estrogen and progesterone using ELISA assay. Animals treated with various doses of Ami represented significant ($p < 0.05$) decreased levels of estrogen (with the dose of 75 and 100 mg/kg Ami) and progesterone (with the doses of 100 mg/kg Ami). Also, serum levels of FSH (with the doses of 75 and 100 mg/kg Ami) showed increased trend significantly ($p < 0.05$). No significant ($p > 0.05$) differences were found in total animal body weight and serum levels of LH following Ami administration with whole doses. Ami is potentially able to reduce female sexual hormones (estrogen and progesterone) in mice with no effects on gonadotropin hormones. This fluctuation in sexual hormones probably can lead to disruption in female reproductive functions.

Keywords: Amitriptyline; Mice; Estrogen; Progesterone; FSH; LH

Introduction

Depression is a state of low mood and aversion of activity. This condition can affect thoughts, behaviors, motivation, feelings, sense of well-being, appetite and sleeping [1]. Depression prevalence varies from 3% (Japan) to 17% (United States). Studies revealed higher rates of depression in the Middle East, North Africa, South Asia and America than in other countries [2]. In North America, the probability of having a major depressive episode within any year-long period is 3 - 5% for males and 8 - 10% for females [3].

Ami is a tricyclic antidepressant for treatment of major depressive disorder and neurologic pain syndromes. Due to the presence

of side effects of Ami and its toxicity in overdose, thus Ami is generally considered a second-line therapy. Ami-associated sexual dysfunction seems to be mostly confined to males with depression and is expressed predominantly as erectile dysfunction and low libido disorder, with lesser frequency of ejaculatory and orgasmic problems. Besides, there is no comprehensive experimental study about the effects of Ami on female sexual hormones [4].

Sexual hormones, are steroid substances that interact with vertebrate steroid hormone receptors. Sexual hormones include the androgens, estrogens, and progestogens. Their effects are mediated by slow genomic mechanisms through nuclear receptors as well as membrane-associated receptors and signaling cascades. The polypeptide hormones luteinizing hormone, follicle-stimulating hormone and gonadotropin-releasing hormone are usually not regarded as sex hormones, although they play major sex-related roles [5].

Thus, the present study was designed to evaluate the possible effects of Ami on hypothalamic-pituitary-gonadal axis hormones (LH, FSH, estrogen, and progesterone) in female mice.

Materials and Methods

Laboratory animals

In this study, 35 adult female mice with the weight of 25 - 30 gr and the age of 12 - 18 weeks were prepared from the animal house. All standard living conditions were prepared for animals including: 12/12 hours photocycle, standard compressed food, and free access to water. Also, in order to prevent the secretion of interfering sexual hormones, the female animals were kept in standard environment with no presence of male mice.

Experimental groups

The animals were divided into five groups (7 mice in each) including: control group, sham, and three experimental Ami groups. The animals in control group received no experimental treatments. Mice in sham group were treated with 0.2 ml distilled water (as drug solvent). In whole experimental groups, the Ami was treated in various doses of 50, 75, and 100 mg/kg. All drugs and water administrations were applied orally and daily for 4 weeks.

Chemicals and laboratory kits

Dr. Abidi Pharmaceutical Company prepared the Ami tables with three doses of 50, 75, and 100 mg/kg of Ami. All biochemical analyses of sexual hormones were applied using ELISA kit (Abcam 108666, USA). Also animal weighting was conducted using laboratory scale (Precisa 125A; Switzerland).

Blood sampling

A day after the last day of experiment, all animals were weighted. Then, they were sacrificed by cervical dislocation. Thoracotomy procedure was applied and a syringe (5 cc) was inserted into the animal's heart (right ventricle). The blood was aspirated (1 cc) and incubated in room temperature for 15 min. After blood clot formation, the laboratory tubes were centrifuged (15 min, 3000 rpm) and the blood serum was aspirated and transferred into -196°C nitrogen container.

Statistical analysis

SPSS software (v. 16) was used for data analysis. One-way analysis of variance (ANOVA). The mean and standard deviation of data were calculated, and $P < 0.05$ was considered statistically significant.

Results

No significant changes ($p > 0.05$) were detected in animal body weight and serum levels of LH in all experimental Ami groups (50, 75, and 100 mg/kg) than control and sham groups. The animals in 75 and 100 mg/kg Ami groups showed a significant ($p < 0.05$) decrease in estrogen concentrations in comparison with the control group. Also, 100 mg/kg Ami animal group represented a significant ($p < 0.05$) reduction in serum progesterone concentration compared to the control group. Serum concentration of FSH was increased in both doses of 75 and 100 mg/kg Ami than control group (Figure 1 and table 1).

Discussion

Female sexual hormones (estrogen and progesterone) cause secondary sexual characteristics during puberty. Interfering factor, like antidepressant drugs, can change the serum concentration of sexual hormones leading to induction of impaired reproductive characteristics. Depression with genetic and environmental origins causes individual isolation, changes in diet, extensive biological alterations, and a wide range of somatic fluctuations in body. Today, various drugs are used to treat depression, one of which is Ami. Some studies have shown that administration of antidepressant drugs in males can lead to extensive changes in sexual hormones,

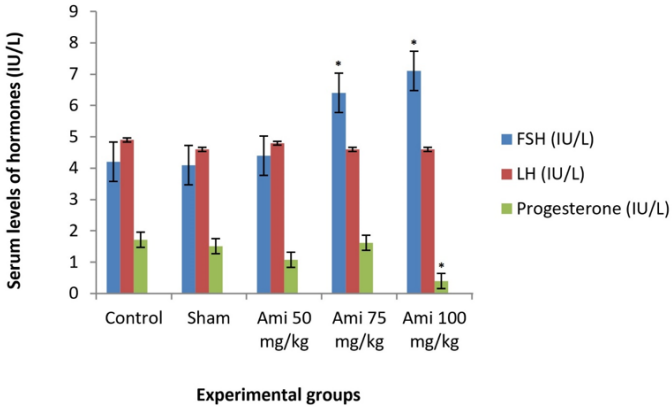

Figure 1: Serum levels of female sexual hormones in control, sham, and experimental groups (Ami 50, 75, 100 mg/kg). Concentration of hormones were presented as IU/L. Ami: Amitriptyline. *indicated significant changes compared to the control group.

Experimental Groups	Body weight (gr)	Serum levels of estrogen (IU/L)
Control	26.2 ± 4.7	398.2 ± 18.27
Sham	25 ± 1.5	390.4 ± 13.27
Ami 50 mg/kg	25.33 ± 0.4	367.6 ± 15.59
Ami 75 mg/kg	27.4 ± 0.3	328.5 ± 53.78 *
Ami 100 mg/kg	26.5 ± 0.5	163.2 ± 47.48 *

Table 1: Total body weight and serum levels of sterogen in control, sham, and experimetnal goups. Data were presented as mean ± SEM. *P < 0.05 compared to the control group. Ami: Amitriptyline.

but there are a few studies regarding the effects of these types of drugs on concentration of female sexual hormones. Thus, as we conducted in the present study, the changes of sexual hormones after 4 weeks of Ami administration and its potential effects on pituitary-gonadal axis in female mice were assessed biochemically [6].

Totally, in the present study it was found that the Ami can significantly lead to decreased levels of female sexual hormones including estrogen and progesterone in female mice. Besides, this antidepressant drug had no biological effect on LH serum level as a gonadotropin hormone and animals` weight, but had incremental effect on FSH levels. Thus, it was also revealed that the Ami with specific doses can lead to hormonal fluctuation in female mice; 75 and 100 mg/kg of Ami has decremental effects on serum levels of estrogen, 100 mg/kg of Ami had decremental effects on serum levels of progesterone, and 75 and 100 mg/kg of Ami had incremental impacts on serum level FSH.

Hansen FM and coworkers in an experimental study on isolated adipocytes from normal male and female rats assessed the probable effects of sexual hormones fluctuations on lipogenesis and lipolysis of fatty cells. They found that fatty acid synthesis and lipolysis processes are more obvious in female mice than males. It means that the cells of female mice are more sensitive to alteration of sexual hormones than males which is probably related to the estrous cycle in females. Finally, they concluded that adipocytes metabolism is influenced by sexual hormones which lead to changes of body weight in females [7]. This finding was not concluded by the results of our study. In the present study we considered the general biological features of female mice, thus; the estrous cycles of animals were ignored. Therefore, for precise observation of weight changes of animals following sexual hormones fluctuation, the estrous cycle must be considered. Also, another interfering factor returns to the simultaneous assessments of sexual hormones with hypophyseal gonadotropins. In this regard, Saadia assessed the body mass index (BMI) in polycystic ovarian syndrome (PCOS) women and concluded that BMI is not correlated to increased LH/FSH ratio, as we found in this animal study [8]. It is noteworthy that the obtained results from animal studies, such as our study, are different from the studies on human, like the study of Saadia. Thus, for better understanding of the effects of hypophyseal gonadotropin and sexual hormones on total body weight, experimental animal studies along with laboratory human assessments are recommended.

Secretory cycle of gonadotropins and sexual hormones in women begins with FSH by adenohypophysis. FSH with stimulating effects on granulosa cells available in ovarian follicles leads to cell proliferation and estrogen secretion. Eventually, with a gradual increase in estrogen secretion, the LH surge will be occurred according to the negative feedback mechanism among estrogen and LH. In normal condition, LH surge induce ovulation and corpus luteum formation. In this histological stage, the progesterone is secreted from corpus luteal cells. As mentioned earlier, the effect of antidepressants on serum levels of sex hormones is completely based on the dose-dependent manner. As we found, following inhibitory effects of Ami on hormones secreted from ovaries, the serum levels

of estrogen and progesterone were decreased in the present study. Also we know that, the LH levels depends on serum levels of estrogen based on the positive feedback mechanism. Since, there is no increased levels of estrogen, we also found no significant increased levels of LH in the animals treated with Ami. Besides, according to the negative feedback, the decreased levels of sexual hormones induced increased levels of FSH in animals of the present study. Thus, it is concluded that the antidepressant drugs like Ami, have inhibitory effects on sexual hormones of ovaries.

Conclusion

Oral administration of Ami in a dose-dependent manner (75 and 100 mg/kg) can decrease the levels of female sexual hormones including estrogen and progesterone. It is concluded that the Ami is effective of ovaries to inhibit the production and secretion of sexual hormones than adenohypophyseal hormones. Probably, in the first line of mechanism, the ovaries are affected by Ami, and then in a feedback mechanism the LH and FSH would be also affected. Also, following irregularities in sexual hormones secretion, detrimental function of female reproductive system is probable which needs more comprehensive researches.

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