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Effects of Estrogen and Progesterone on Catalepsy and Motor and Balance Impairment Classified as Haloperidol-induced Extrapyramidal Disorders

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ABSTRACT

Aims Various evidences have shown the effect of ovarian hormones on locomotor activities and catalepsy induced by a variety of stimuli. The aim of this study was to evaluate the effects of estrogen and progesterone on catalepsy and motor and balance impairment classified as haloperidol-induced extrapyramidal disorders.

Materials and Methods The current experimental study was performed on 96 female Wistar rats (180-200g). These rats were randomly divided into 16 groups (n=6). Prior to administration of haloperidol, the rats were pretreated with flutamide (10mg/kg, i.p.), estrogen (1mg/kg 17 β-estradiol, s.c.), and/or progesterone (1mg/kg, i.p.) for 1 day or 7 consecutive days. The effects of estrogen and progesterone on haloperidol-induced catalepsy and motor impairment were assessed by a bar test and a rotarod performance test, respectively. Data were analyzed by SPSS 22 software using ANCOVA and Tukey test.

Findings One to 7-day treatment with estrogen had a protective effect on haloperidol-induced extrapyramidal disorders such that it significantly improved catalepsy and motor impairment in the rats and restored and normalized their motor levels. However, the progesterone administration did not represent significant effects in improving extrapyramidal symptoms and a slight improvement was achieved. The co-administration of flutamide significantly reduced the protective effect of estrogen on catalepsy and motor balance impairment induced by haloperidol.

Conclusion The deficiency of ovarian hormones increases catalepsy; however, this disorder is more likely to occur due to estrogen insufficiency. Hence, progesterone plays a little role in it. Moreover, the anti-cataleptic effect of ovarian hormones is exerted through affecting androgenic receptors.

Keywords Parkinson's disease; Estrogen; Progesterone; Haloperidol; Catalepsy; Rotarod Test

CITATION LINKS

[1] Epidemiology of Parkinson's ... [2] Induction of Parkinson's disease model in rat by ... [3] Effect of chronic administration of buspirone and fluoxetine on inflammatory cytokines in ... [4] Effects of bilateral lesions in the striatum or nucleus accumbens on the cataleptogenic activity of neuroleptics ... [5] Effects of 5-HT in globus pallidus on haloperidol-induced catalepsy ... [6] Extrapyramidal side effects of clozapine and ... [7] Involvement of caudate nucleus, amygdala or reticular formation in neuroleptic and narcotic ... [8] Sex, genes, hormones and nigral neurodegeneration: Two different Parkinson's diseases in males ... [9] Sex differences in striatal dopamine release in healthy... [10] Influence of sex steroids and prolactin on haloperidol-induced ... [11] Pre-treatment with silymarin reduces brain myeloperoxidase activity and inflammatory cytokines in 6-OHDA hemi-parkinsonian ... [12] Effect of WR-1065 on 6-hydroxydopamine-induced catalepsy and IL-6 ... [13] An overview of hypoglycemia in the critically ... [14] Effects of WR1065 on 6-hydroxydopamine-induced motor ... [15] Short-term treatment with silymarin improved ... [16] Gender differences in Parkinson's ... [17] Sex differences in catalepsy: Evidence for hormone-dependent ... [18] Risk of Parkinson disease in women: Effect of reproductive ... [19] Estrogen as neuroprotectant of nigrostriatal dopaminergic ... [20] Effects of female sex steroids on Parkinson's disease in postmenopausal ... [21] Influences of estrogen and/or progesterone on some dopamine ... [22] Estrogenic induction of spermatogenesis in the hypogonadal (hpg) mouse: Role of ... [23] Effect of estrogen on androgen receptor dynamics in female rat ... [24] The effect of estrogen and androgen on androgen receptors and mRNA levels in uterine leiomyoma, myometrium and endometrium ...

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Introduction

Parkinson's disease is a degenerative progressive disease of the nerves, which occurs due to the destruction of dopaminergic neurons in the substantia nigra pars compacta and affects dopamine pathways in the nucleus core region. Generally, 1% of people over 50 years and at least 2% of people over 65 years suffer from this disease. One of the prevalent symptoms of this disease is catalepsy that refers to an inability to control and change muscle tightness and stiffness [1].

Human neurological defects can be simulated by standard methods in laboratory animals [2, 3]. Extrapyramidal symptoms of neuroleptic drugs are very similar to the symptoms of Parkinson's disease. This is why catalepsy induced by neuroleptic drugs can be considered for evaluating Parkinson's disease in laboratory models and the corpus striatum is regarded as the most important brain structure responsible for catalepsy induced by neuroleptic drugs [4]. Among standard methods of developing Parkinson's motor symptoms, administrating haloperidol, i.e. a neuroleptic drug, can be mentioned [5].

Haloperidol is an antipsychotic drug, which blocks dopaminergic receptors in the nigrostriatal pathway and leads to extrapyramidal motor disorders (a neuronal network in the brain associated with the motor system leading to non-motor movements) [6]. Studies conducted by electromyography (EMG) demonstrated that muscle stiffness developed in haloperidol-induced catalepsy had a similar quality to that found in Parkinson's disease [7].

It is estimated that more than 5 million people suffer from Parkinson's disease all over the world and its prevalence in men is 1.5 to 2 times more than that in women. Since the prevalence of this disease in men is higher than that in women, it seems that steroid hormones play a key role in the progression and treatment of this disease [7]. Some evidences have suggested that men and women choose different organizing methods in performing seemingly alike tasks. Methods of responding dopamine and the function of the dopamine system are not exception. Not only in animal studies but also in human studies, it was observed that the function of the dopaminergic system is different in men and women. The fact that the density of dopamine neuronal terminals in women is more than that in men confirms this. Additionally, it was observed that the transfer rates of dopamine in the corpus striata of healthy women and women with Parkinson's disease are respectively higher than these rates in healthy men and men with Parkinson's disease [8].

All these studies pointed out a relationship between Parkinson's disease and sex hormones. Epidemiological studies indicated that the onset of symptoms of this disease in women occurred later than men. This somehow confirms the neuroprotective effects of sex hormones, especially estrogen [9].

The neuroprotective effect of 17 β-estradiol was reported in animal models of Parkinson's disease. Although the neuroprotective effects of progesterone have less been studied, the beneficial effects of progesterone in the treatment of brain damage, ischemia, spinal cord injuries, diseases caused by neural demyelination, neuromuscular disorders, and epilepsy have been examined [10].

In this regard, the current study was conducted with the aim of assessing the effects of pretreatment and acute administration of estrogen and progesterone on haloperidol-induced extrapyramidal complications and comparing the effects of these two hormones in female rats.

Materials and Methods

Animals: The current experimental study was performed on 96 female Wistar rats (180-200g). All these rats were provided by an animal laboratory at Hamedan University of Medical Sciences. These animals were kept at 22±2°C on a 12-hour light/dark cycle with adequate ventilation. Throughout the course of this behavioral study, the animals had access to sufficient amounts of water and food. One to 2 hours before carrying out the experiment, the animals were transferred to the laboratory to adapt to the laboratory environment. In all behavioral studies, after giving animals 5 days to become familiar with the experimental environment and conditions, animals which do not have the required conditions for conducting tests are excluded. All the experiments were conducted under the supervision of the Ethics Committee at the Hamadan University of Medical Sciences.

The rats were randomly divided into 16 groups (n=6) and every 6 rats were placed in a standard cage:

1. Normal group (healthy intact animals)
2. Sham group (receiving a solvent): Due to the similarity of the results of sham group to the control group we demonstrated only one of them in the figures.
3. Estrogen receiving group (receiving estrogen intraperitoneally at a dose of 1mg/kg in healthy animals for 7 days)
4. Flutamide receiving group (receiving flutamide intraperitoneally at a dose of 10mg/kg in healthy animals for 7 days)
5. Progesterone receiving group (receiving progesterone intraperitoneally at a dose of 1mg/kg in healthy animals for 7 days)

6. Haloperidol receiving group (receiving haloperidol intraperitoneally at a dose of 1mg/kg)
7. Acute estrogen administration group (receiving estrogen intraperitoneally at a dose of 1mg/kg and 15 minutes before receiving haloperidol)
8. Estrogen pretreated group (receiving estrogen intraperitoneally at a dose of 1mg/kg for 7 days and receiving haloperidol after the last estrogen administration)
9. Acute progesterone administration group (receiving progesterone intraperitoneally at a dose of 1mg/kg and 15 minutes before receiving haloperidol)
10. Progesterone pretreated group (receiving progesterone intraperitoneally at a dose of 1mg/kg for 7 days and receiving haloperidol after the last administration of progesterone)
11. Acute flutamide administration group (receiving flutamide intraperitoneally 10mg/kg and 15 minutes before receiving haloperidol): Due to the similarity of the results of Acute flutamide administration group to the control group we demonstrated only one of them in the figures.
12. Flutamide pretreated group (receiving flutamide intraperitoneally at a dose of 10mg/kg for 7 days and receiving haloperidol after the last administration of flutamide): Due to the similarity of the results of Flutamide pretreated group to the control group we demonstrated only one of them in the figures.)
13. Co-administration of flutamide (10mg/kg) and estrogen (1mg/kg) for 7 days and, then, administration of haloperidol
14. Co-administration of flutamide (10mg/kg) and estrogen (1mg/kg) for 1 day and, then, administration of haloperidol
15. Co-administration of flutamide (10mg/kg) and progesterone (1mg/kg) for 7 days and, then, administration of haloperidol
16. Co-administration of flutamide (10mg/kg) and progesterone (1mg/kg) for 1 day and, then, administration of haloperidol

Drugs: To obtain desired concentrations, haloperidol, progesterone, estrogen, and flutamide were purchased (Sigma; United States). Haloperidol was dissolved in 0.9% normal saline and the rest of the drugs were dissolved in polyethylene glycol. All the solutions were prepared daily for administrations. Except for estrogen, which was administered intraperitoneally, the remaining administrations were done intraperitoneally.

Induction of extrapyramidal disorders and its evaluation: Extrapyramidal disorders were induced by administering the neuroleptic haloperidol drug (1mg/kg intraperitoneally).

Catalepsy evaluation: For measuring haloperidol-induced catalepsy, the standard bar test was used [11, 12]. In this method, two front legs of an animal are placed on a wooden bar with 0.9cm in diameter and 9cm in height from the ground and the length of time that the animal remained in a constant position was measured. The test is completed whenever the animal removes one of its front legs from the bar or moves its head curiously. The cut-off time of the test was considered 360 seconds. The test was performed at 5, 30, and 60 minutes after the administration of haloperidol.

Evaluation of Motor and balance impairment: To measure the motor balance condition, the standard rotarod performance test was applied [13, 14]. In this method, an animal was placed on a rotating rod at 10rpm and the length of time that the animal was able to stand and maintain its balance on the rotating rod. The cut off time was 720 seconds. The motor balance was evaluated at 5, 30 and 60 minutes after the administration of haloperidol [15].

Evaluation of haloperidol and progesterone on catalepsy: To evaluate the effect of haloperidol on catalepsy and balance, the animals were divided into 3 groups, the sham group (in which all stages of administration except taking the drug were conducted), the control group (in which the animals received normal saline at a dose of 1ml/kg), and the haloperidol receiving group (at a dose of 1mg/kg). The standard bar test was used to analyze catalepsy.

Evaluation of haloperidol and progesterone on motor and balance impairment: To evaluate the effect of haloperidol on catalepsy and balance, the animals were divided into 3 groups, i.e. the sham group (in which all stages of administration except taking the drug were conducted), the control group (in which the animals received normal saline at a dose of 1 ml/kg), and the haloperidol receiving group (at a dose of 1mg/kg). The standard rotarod performance test was used to analyze motor and balance impairment.

Evaluation of the co-administration of flutamide on anti-cataleptic effects of estrogen: To investigate the role of androgenic receptors in the protective effects of estrogen, flutamide, an antagonist of androgenic receptors, was used.

Data analysis: The results were expressed as Mean±SEM. To compare the differences between mean values, an analysis of covariance (ANCOVA) was used. In case of a significant difference, a Tukey test was applied. The SPSS 22 was used to analyze the data.

Findings

The Effect of Haloperidol and Progesterone on Catalepsy: The neuroleptic haloperidol drug significantly induced catalepsy compared to the

control and sham groups at all measurement times of 5, 30, and 60 minutes after the administrations of the drug (p<0.001; Diagram 1).

The acute administration of a single dose of progesterone (at a dose of 1mg/kg), 15 minutes before haloperidol at all times of the test (5, 30, and 60 minutes after the administration of haloperidol), did not have a significant effect on haloperidol-induced catalepsy (Diagram 1).

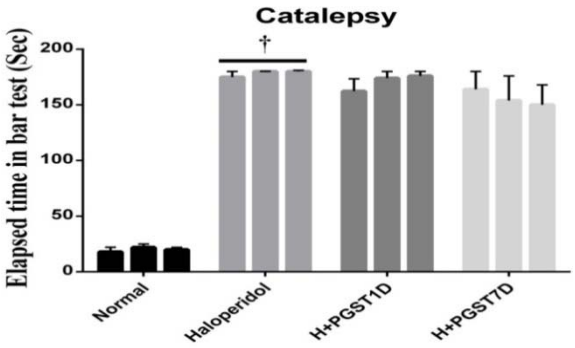

Diagram 1) The effect of pretreatment and acute treatment with progesterone on haloperidol (†P<0.001 in comparison with the normal group)

Catalepsy in the progesterone pretreated group at all measurement times of 5, 30, and 60 minutes after the administration of haloperidol did not significantly differ from that of the groups, which did not receive haloperidol and a slight improvement was just achieved.

The Effect of Haloperidol and Progesterone on Motor Balance Impairment:

Haloperidol significantly reduced motor and balance impairment compared to the control and sham groups at all measurement times of 5, 30, and 60 minutes after the administrations of the drug (p<0.001; Diagram 2).

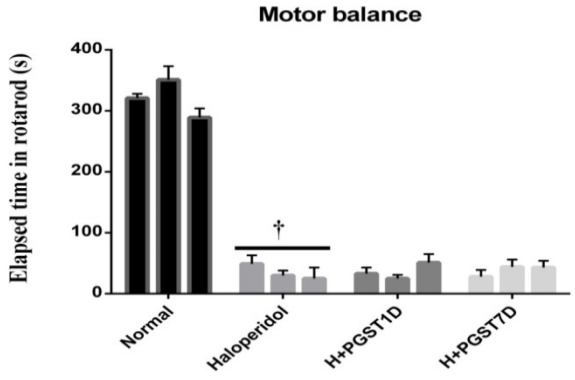

Diagram 2) The effect of pretreatment and acute treatment with progesterone on motor balance (†P<0.001 in comparison with the normal group)

The acute administration of a single dose of progesterone (at a dose of 1mg/kg), 15 minutes before haloperidol at all times of the test (5, 30, and 60 minutes), did not create a significant difference compared to the haloperidol receiving group. Balance impairment in the progesterone pretreated group at all measurement times of 5, 30, and 60 minutes after the administration of haloperidol did not significantly differ from that of the groups, which did not receive haloperidol.

Effect of the acute administration and pretreatment with estrogen on haloperidol-induced catalepsy: At all measurement times (5, 30, and 60 minutes after the administration of haloperidol), haloperidol-induced catalepsy was significantly reduced. This indicates the therapeutic effect of estrogen (Diagram 3). Furthermore, Catalepsy in the estrogen pretreated group at all measurement times of 5, 30, and 60 minutes after the administration of haloperidol significantly reduced compared to the haloperidol receiving group (Diagram 3).

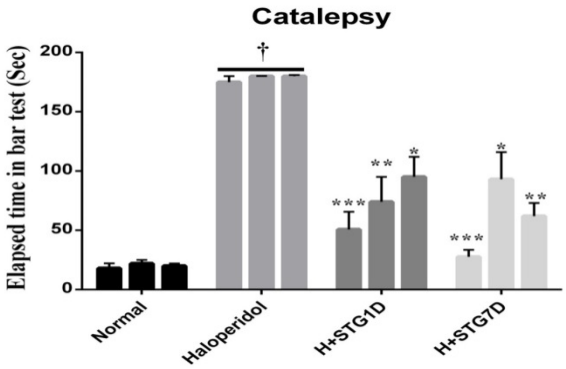

Diagram 3) The effect of pretreatment and acute treatment with estrogen on haloperidol-induced (†P<0.001 in comparison with the normal group, ***P<0.001 in comparison with the haloperidol group, **P<0.01 in comparison with the haloperidol group, and *P<0.05 in comparison with the haloperidol group)

Effect of the acute administration and pretreatment with estrogen on haloperidol-induced motor and balance impairment: The significant therapeutic effect of estrogen in increasing motor balance such that at all measurement times (5, 30, and 60 minutes), estrogen significantly improved haloperidol-induced motor impairment (Diagram 4). Moreover, motor and balance impairment in the estrogen pretreated group at all measurement times of 5, 30, and 60 minutes after the administration of haloperidol significantly increased compared to the haloperidol receiving group. However, this increase was not significant (Diagram 4). Flutamide was administered simultaneously with estrogen and intraperitoneally 15 minutes before that. The co-administration of flutamide significantly

reduced the effects of the acute administration of and pretreatment with estrogen for 7 days in reducing catalepsy compared to the estrogen receiving group ($p<0.05$) such that catalepsy increased in these groups. However, it was still significantly lower than the haloperidol group ($p<0.05$; Diagram 5).

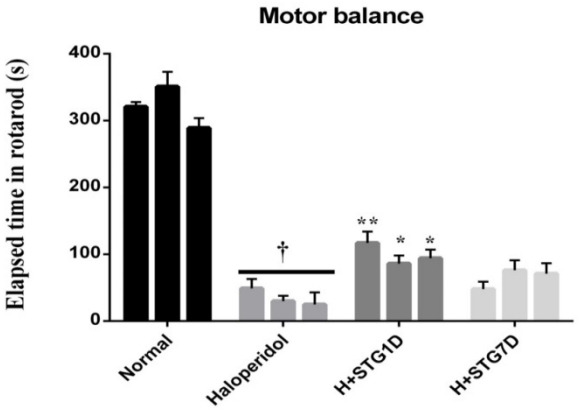

Diagram 4) The effect of pretreatment and acute treatment with estrogen on haloperidol-induced
†P<0.001 in comparison with the normal group, ** P<0.01 in comparison with the haloperidol group, and *P<0.05 in comparison with the haloperidol group

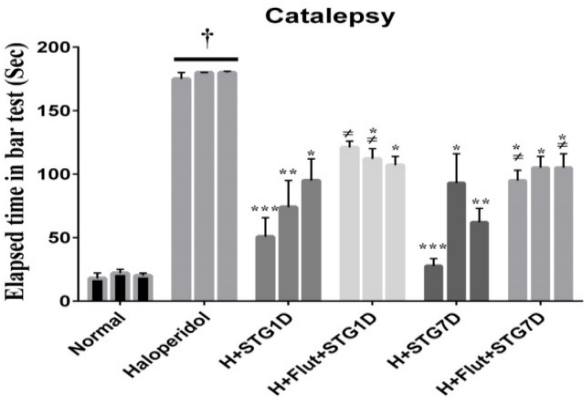

Diagram 5) The effect of the co-administration of flutamide on pretreatment and acute treatment with estrogen on haloperidol-induced catalepsy (†P<0.001 in comparison with the normal group, ***P<0.001 in comparison with the haloperidol group, **P<0.01 in comparison with the haloperidol group, *P<0.05 in comparison with the haloperidol group, and ≠ in comparison with the estrogen receiving group)

Effect of the co-administration of flutamide on anti-cataleptic effects of estrogen: The co-administration of flutamide significantly reduced the incremental effects of the acute administration and pretreatment of estrogen for 7 days in reducing motor and balance impairment such that motor and balance impairment was reduced in these groups. However, except for the first test of the acute administration ($p<0.05$), this reduction was not significant and it was still significantly higher than the haloperidol group (Diagram 6).

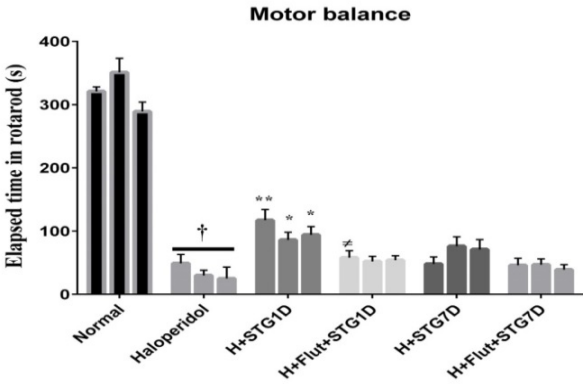

Diagram 6) The effect of co-administration of flutamide on pretreatment and acute treatment with estrogen on haloperidol-induced motor balance impairment (†P<0.001 in comparison with the normal group, **P<0.01 in comparison with the haloperidol group, *P<0.05 in comparison with the haloperidol group, and ≠ in comparison with the estrogen receiving group)

Discussion

Parkinson's disease is a degenerative progressive disease of nerves, which occurs due to the destruction of dopaminergic neurons in the substantia nigra pars compacta and affects dopamine pathways in the nucleus core region. Some common symptoms of this disease include tremor, bradykinesia, rigid muscles, impaired balance, and catalepsy [11].

Gender differences play an important role in the sensitivity and pathogens of many motor disorders such as Parkinson's disease [7].

Sexual dimorphisms developed during the evolution of the structure and function of the body systems have been affected by the coexistence of sex hormones and chromosomes [16]. Animal studies and clinical and epidemiological reports carried out on Parkinson's disease specified these differences in the performance of the dopaminergic system and the density of dopaminergic receptors in men and women [17]. The difference in the degradation of dopaminergic neurons in the nigrostriatal pathway also confirms the abovementioned findings. Since the difference in sex hormones is considered the main factor in gender differences, the difference in the function of the dopamine system in the nigrostriatal pathway and the destruction of neurons in this pathway are related to the difference in the effects of androgen, estrogen, and progesterone [7, 8].

In the present study, the effects of estrogen and progesterone in female rats were examined. The effects of estrogen were studied in the acute administration of and pretreatment with estrogen. In both ways of administration, estrogen was able to reduce the haloperidol-induced catalepsy. This finding is consistent with the results obtained in previous studies conducted on estrogen, which reported its protective effects on dopaminergic

neurons and in postmenopausal women with Parkinson's disease [18, 19].

The results of this study showed that the acute administration of estrogen compared to the pretreatment with estrogen increased the duration of staying on the rotarod to a great extent. In addition, assessing the time of staying on the bar in the bar test showed that there was no difference between the group pretreated with estrogen and the acute administration of estrogen group.

Progesterone was also assessed in this study. Like estrogen, the administration of progesterone was conducted in both acute and pretreatment procedures. The results of examining progesterone showed that this hormone had a slight effect on haloperidol-induced extrapyramidal disorders. This is in contrast with few studies carried out in the same field, which reported its protective effects [20, 21].

In the current study, the effectiveness of the acute administration of and pretreatment with progesterone was also evaluated and compared. Comparison of the results of the acute administration of progesterone and the progesterone pretreatment in the bar test and rotarod performance test did not show any significant differences between the acute administration of progesterone and the pretreatment with progesterone. This should be considered in the prevention and control of Parkinson's disease symptoms as well as neuroleptic-induced extrapyramidal disorders, such as haloperidol, in the users of these drugs.

To examine the role of androgenic receptors in the protective effects of estrogen in this study, flutamide, as an antagonist for these receptors, was simultaneously administered with estrogen. The results of this study showed that the co-administration of flutamide significantly reduced the protective effects of estrogen on haloperidol-induced catalepsy in both acute and pretreatment phases and catalepsy in these groups was significantly increased compared to the estrogen receiving group. However, it was still significantly lower than that in the haloperidol group. This indicated the role of androgenic receptors in the effects of estrogen in reducing catalepsy. This is while other receptors are also likely to be involved in this effect. Furthermore, flutamide completely prevented the protective effects of estrogen on motor balance in both therapeutic phases, which suggested that this effect is entirely induced by androgenic receptors.

The results of this study are in line with results of previous studies, which reported the effectiveness of estrogen and its derivatives through androgenic receptors [22]. Additionally, it was reported that estrogen increased the expression of androgenic receptors and testosterone binding sites and, consequently, promoted the androgenic effects in female rats [23, 24]. This is consistent with the findings of the present study.

The deficiency of ovarian hormones increases extrapyramidal disorders; however, it seems that this disorder is more likely to occur due to estrogen insufficiency. Hence, progesterone plays a little role in it. Moreover, the anti-cataleptic effect of ovarian hormones is somehow exerted through affecting androgenic receptors.

Further studies are needed to prove the positive effects of estrogen on haloperidol-induced extrapyramidal disorders and to demonstrate the mechanism of its effectiveness as well as to confirm the effects of progesterone. In addition, the effects of simultaneous administrations of these two hormones can be studied in future studies.

Conclusion

The deficiency of ovarian hormones increases catalepsy; however, this disorder is more likely to occur due to estrogen insufficiency. Hence, progesterone plays a little role in it. Moreover, the anti-cataleptic effect of ovarian hormones is exerted through affecting androgenic receptors.

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Ethical Permission: IR.UMSHA.REC.1395.536.

Conflict of Interests: All procedures performed in studies involving animal participants were in accordance with the ethical standards of the institutional Hamadan University of Medical Sciences and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Authors' Contribution: Sabahi M.M. (First author), Introduction author/ Original researcher or Assistant/ Discussion author (35%); Ami Ahmadi S. (Second author), Introduction author/ Methodologist/ Original researcher or Assistant/ Statistical analyst/ Discussion author (35%); Haddadi R. (Third author), Methodologist/ Statistical analyst/ Discussion author (30%)

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