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THE EFFECTS OF OPIUM ADDICTION ON THYROID AND SEX HORMONES IN DIABETIC AND NON-DIABETIC MALE AND FEMALE RATS

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Abstract

Objective. Opium is a narcotic drug that is commonly abused. The prescription of pharmaceutical derivatives of opium is limited due to their possible harmful effects on the body's metabolism and tolerability by patients. The aim of the present study was to evaluate the effects of chronic opium consumption on some sexual and thyroid hormones in diabetic and non-diabetic male and female rats.

Material and Methods. This experimental study was conducted on 56 Wistar rats. The animals were divided into diabetic addicted (DA), diabetic non-addicted (DNA), non-diabetic addicted (NDA) and non-diabetic non-addicted (NDNA) groups of male and female rats. Peripheral blood samples were collected to measure the thyroid and sex hormone levels. Student's t-test was used to compare the mean values of the hormones between two groups.

Results. T3 serum level in male addicted groups significantly increased in comparison with non-addicted ones in both diabetic and non-diabetic groups. The testosterone level of male rats decreased due to the consumption of opium while it was significantly increased in diabetic and NDNA female rats in comparison with non-addicts. In DNA female animals, the mean level of 17-hydroxyprogesterone increased significantly compared with non-diabetic groups, however, it decreased in addicted females (diabetic and non-diabetic) in comparison with non-addicts. The level of DHEA-S increased significantly in diabetic and NDA male rats as compared with the non-addicted group.

Conclusion. Opium affects the endocrine system in a sex-dependent manner, and opium could have different effects in diabetic and non-diabetic conditions.

Key words: opium, addiction, diabetes, sex hormones, thyroid hormones.

INTRODUCTION

Opium is a milky extract obtained from the opium poppy or *Papaver somniferum* (1). It has been used in traditional medicine as a palliative drug and for the treatment of some diseases. Some therapeutic compounds obtained from opium include morphine, noscapine, codeine and papaverine which are composed of 8-17%, 1-10%, 0.7-5%, and 0.5-1.5% of opium, respectively (1–3). Opium is the second most commonly abused drug in Asian countries after tobacco (4).

Today, narcotic drug consumption has turned into a serious threat in many countries. In addition, the effects of opioids on the body and endocrine system confined their chronic consumption as analgesics (5–7). Attachment of opioids to their hypothalamic receptors alters the serum level of numerous hormones. These opioid-receptor complexes can change the release process of stimulators and inhibitors of the hypothalamus (5). The gonadotropin-releasing hormone (GnRH) is secreted from the hypothalamus and affects the pituitary gland which regulates the sex hormones: luteinizing-hormone (LH) and follicle stimulating hormone (FSH). These two hormones have feedback effects on the hypothalamus (8,9). Previous animal studies have confirmed the reducing effects of opioids on testosterone, which occur via changes in the secretion of LH. LH regulates the serum level of progesterone and testosterone through attaching to its receptors on those tissues producing these sex hormones (10). The consumption of morphine and its derivatives can increase the level of corticosterone and progesterone (11,12). The above-mentioned effects of the opioids lead to oligomenorrhea and amenorrhea in

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women, lower libido in men, and cause infertility in both sexes, which consequently reduces their life quality (13–15). Moreover, the thyroid function is dependent upon hypothalamus and pituitary. Studies on triiodothyronine (T3) and thyroxine (T4) have shown different results on opium and morphine effects (5,11,12).

One of the reasons for prevalent opium abuse in Asia is that the public and even the medical personnel believe that opium consumption has a positive and regulatory effect on blood glucose and lipids in diabetic individuals as well as some therapeutic properties against certain diseases (16,17). Diabetes mellitus is one of the most prevalent metabolic disorders with remarkable consequences. In this disease, the metabolism-affecting hormones are influenced and, as a result, the metabolic regulation of the body is disrupted. The acute and chronic effects of morphine on the secretion of the hormones and the metabolic pathways are different. Studies conducted on non-diabetic rats have indicated that the blood glucose level will be increased due to opium consumption and this might be as a result of the narcotic drugs effects on the levels of glucose-regulating hormones (16,18).

Regarding the known effects of opium and its derivatives, it could be presumed that if diabetic individuals are consuming opium, it will have interfering effects on their endocrine system. Despite numerous studies having examined different effects of opium derivatives on hormones and metabolic pathways, the number of studies on opium itself is limited. Based on our knowledge, the effects of opium on the endocrine system under diabetic conditions on males and females have not been studied yet.

Due to the wide variety of sexual and thyroid disorders among opium addicts (5,19), the aim of this study was to examine the effects of the chronic consumption of opium on thyroid and some sex hormones in male and female diabetic and non-diabetic rats.

MATERIALS AND METHODS

The required opium was supplied from Anti-Narcotics Department of Kerman Police (Iran). Based on the official information, the origin of opium was Helmand, Afghanistan. The GC mass-spectrometry test showed that the opium includes more than 30% alkaloids and the rest consisted of non-alkaloid organic and non-organic substances such as water (13%). Most opium alkaloids were morphine (16%), codeine (5.5%), thebaine (4.4%) and papaverine (3.2%) (3). Streptozocin was purchased from the Pfizer Company (AG, Zurich, Switzerland). The glucose oxidase kit was attained from the Pars Azmoon Company (Tehran, Iran). Radioimmunoassay kits (Kavoshyar Company, Iran) were purchased to measure the serum level of testosterone, dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone, T3, and T4. All other materials were supplied from standard sources.

In the present experimental study, 56 Wistar rats, approximately 6-7 months of age, 28 males and 28 females (250 to 300 gram), were randomly divided into 8 groups including diabetic addicted (DA), diabetic non-addicted (DNA), non-diabetic addicted (NDA) and non-diabetic non-addicted (NDNA) in both sexes. The Ethics Committee of Rafsanjan University of Medical Sciences approved the study procedure. All of the animals were maintained on a 12-hour light-dark cycle and unlimited access to food and water. All processes related to the maintenance of animals were done based on "Guide for the care and use of laboratory animals" (NIH Publication, No. 85-23: 1985). To induce diabetes, streptozocin (solved in sodium citrate buffer; pH=4.4) was intravenously administered into the tail vein at a single dose of 60 mg per kilogram of the body weight. After 3 days, blood was collected from the orbit cavity of anesthetized rats by thin heparinized tubes. The serum level of glucose was determined by the glucose oxidase method and animals with glucose level higher than 250 mg/dL were considered as diabetic (20).

The DA and NDA groups were treated with opium for 8 consecutive days. Based on the following schedule, a double dose of opium was intraperitoneally administered to the addicted groups at 8 AM and 8 PM every day, as previously described (3). Briefly, the administration of opium was 30, 60, 90, 120 and 150 mg/kg in the first, second, third, fourth and fifth until the eighth day of treatment. The control groups received normal saline as a vehicle. The withdrawal symptoms in addicted rats appeared after 5 days of opium administration. The first symptom was wet-dog shakes followed by head shakes, irritability, salivation, hyperactivity, writhing, and ptosis (21). On the ninth day, three hours after the last administration of opium (150 mg/kg), approximately 20 cc cotton impregnated with diethyl ether (Merck, Germany) was placed in a one-liter desiccator (buccal), subsequently, 2 minutes after transferring the rats to the desiccator, the animals were anesthetized and blood samples were collected from orbit cavity. Then, blood samples were transferred to laboratory to measure testosterone, DHEA-S, 17-hydroxyprogesterone, T4, and T3.

The data were expressed in mean ± SEM

Table 1. Comparison of hormone levels between diabetic addicted (case) and diabetic non-addicted (control) male and female rats. Data from seven animals in each group

Hormones	Groups					
	Male, (mean ± SEM)			Female, (mean ± SEM)		
	Diabetic Addicted (Case)	Diabetic non-Addicted (Control)	P-Value	Diabetic Addicted (Case)	Diabetic non-Addicted (Control)	P-Value
T3 (ng/dL)	1.171±0.058	0.832±0.047	**0.001***	1.452±0.173	1.358±0.034	0.612
T4 (µg/dL)	29.4±2.96	29.771±1.854	0.917	35.114±2.084	40.714±5.922	0.4
17OH-Progesterone (ng/mL)	0.2±0.025	0.257±0.037	0.234	0.968±0.230	3.984±0.846	**0.011***
Testosterone (ng/mL)	0.3±0.095	0.394±0.089	0.524	0.395±0.077	0.218±0.078	0.134
DHEA-S (ng/mL)	0.557±0.183	0.085±0.025	**0.042***	0.072±0.016	0.245±0.064	**0.023**

Mean serum level of T3 was significantly increased in male diabetic addicted rats compared to male diabetic non-addicted rats (P=0.001). The mean level of 17-hydroxyprogesterone was decreased in male and female diabetic addicted rats as compared to diabetic non-addicted group, which was significant in females (P=0.011). The mean level of DHEA-S in male diabetic addicted rats had a significant increase in comparison with the diabetic non-addicted group (P=0.042), while, a significant decrease was observed in female rats (P=0.023). *Significance at 0.05 levels.

Table 2. Comparison of hormone levels between diabetic addicted (case) and diabetic non-addicted (control) male and female rats. Data from seven animals in each group

Hormones	Groups					
	Diabetic Addicted (Case), (mean ± SEM)			Diabetic Non-addicted (Control), (mean ± SEM)		
	Male	Female	P-Value	Male	Female	P-Value
T3 (ng/dL)	1.171±0.058	1.452±0.173	0.151	0.832±0.047	1.358±0.034	**< 0.001***
T4 (µg/dL)	29.4±2.96	35.114±2.084	0.141	29.771±1.854	40.714±5.922	0. 12
17OH-Progesterone (ng/mL)	0.2±0.025	0.968±0.230	**0.016***	0.257±0.037	3.984±0.846	**0.005***
Testosterone (ng/mL)	0.3±0.095	0.395±0.077	0.492	0.394±0.089	0.218±0.078	0.164
DHEA-S (ng/mL)	0.557±0.183	0.072±0.016	**0.039***	0.085±0.025	0.245±0.064	**0.039***

As Table 2 shows, in male diabetic non-addicted rats, the mean levels of T3 were significantly lower than in females (P<0.001). The mean level of 17-hydroxyprogesterone was significantly higher in female than in male diabetic addicted rats (P=0.016). However, the mean level of DHEA-S was significantly lower in female diabetic addicted compared to male rats (P=0.039). The mean levels of 17-hydroxyprogesterone and DHEA-S in male diabetic non-addicted were significantly lower in comparison with females (P=0.005 and P=0.039, respectively). *Significance at 0.05 levels.

for all hormone serum levels. The student's t-test/ Mann-Whitney U-test were used to compare the mean values between the two groups. Statistical analyses were performed using SPSS software version 18.0 for Windows.

Values < 0.05 were considered statistically significant.

RESULTS

Effects of opium on the serum level of thyroid hormones

The results of the opium effects on thyroid hormones in male and female rats are presented in Table 1. The mean serum level of T3 was significantly increased in male DA rats compared to male DNA rats (P=0.001). In both sexes, no significant differences were observed in the mean serum levels of T4 between DA and DNA groups (P>0.05 for both comparisons) (Table 1).

As shown in Table 2, the mean levels of T3 and T4 in female DA rats were higher than in males. In male DNA rats, the mean levels of T3 and T4 were lower than in females, this difference in T3 serum level was significant (P<0.001) (Table 2).

The results demonstrated that in male NDA rats, the mean level of T3 had a significant increase in comparison with control group (P=0.002). Furthermore, the mean levels of T3 and T4 were increased in female NDA rats in comparison with control group (P>0.05 for both comparisons) (Table 3).

Among male NDA rats, the mean levels of T3 and T4 were lower than in female rats (P>0.05 for both). In male NDNA rats, the mean levels of T3 and T4 were lower than in females. This difference in T3 level was significant (P<0.001) (Table 4).

Regarding the mean serum levels of T3 and T4, no significant differences were found between the DA and NDA groups in both sexes (P>0.05) (Table 5). Moreover, no significant differences were observed between male and female DNA and NDNA groups (P>0.05) (Table 6).

Effects of opium on the serum level of sex hormones

The mean level of 17-hydroxyprogesterone was decreased in male and female DA rats as compared to DNA group, which was significant in females (P=0.011). Comparison of the male and female DA with DNA rats demonstrated a respective decrease and increase in the level of testosterone (P>0.05 for both comparisons).

Table 3. Comparison of hormone levels between non-diabetic addicted (case) and non-diabetic Non-addicted (control) male and female rats. Data from seven animals in each group

Hormones	Groups					
	Male, (mean ± SEM)			Female, (mean ± SEM)		
	Non-diabetic Addicted (Case)	Non-diabetic Non-addicted (Control)	P-Value	Non-diabetic Addicted (Case)	Non-diabetic Non-addicted (Control)	P-Value
T3 (ng/dL)	1.337±0.111	0.872±0.044	**0.002***	1.561±0.132	1.334±0.041	0.128
T4 (µg/dL)	29.191±2.928	29.557±1.834	0.917	34.220±2.432	32.714±6.625	0.835
17OH-Progesterone (ng/mL)	0.217±0.022	0.251±0.034	0.421	0.734±0.072	1.417±0.091	**< 0.001***
Testosterone (ng/mL)	0.261±0.034	0.351±0.037	0.104	0.617±0.041	0.242±0.029	**< 0.001***
DHEA-S (ng/mL)	0. 480±0.081	0.107±0.034	**0.001***	0.224±0.077	0.248±0.044	0.790

The Table 3 illustrates that in male non-diabetic addicted rats, the mean level of T3 had a significant increase in comparison with control group (P=0.002). However, the mean level of DHEA-S showed a significant decrease in non-diabetic addicted compared to non-diabetic non-addicted (P=0.001). Comparison of female non-diabetic non-addicted with non-diabetic addicted group, the mean levels of 17-hydroxyprogesterone and testosterone were significantly decreased and increased, respectively (P<0.001 for both comparisons). *Significance at 0.05 levels.

Table 4. Comparison of hormone levels between non-diabetic addicted (case) and non-diabetic non-addicted (control) male and female rats. Data from seven animals in each group

Hormones	Groups					
	Non-diabetic Addicted (Case), (mean ± SEM)			Non-diabetic Non-addicted (Control), (mean ± SEM)		
	Male	Female	P-Value	Male	Female	P-Value
T3 (ng/dL)	1.337±0.111	1.561±0.132	0.221	0.872±0.044	1.334±0.041	**< 0.001***
T4 (µg/dL)	29.191±2.928	34.220±2.432	0.211	29.557±1.834	32.714±6.625	0.654
17OH-Progesterone (ng/mL)	0.217±0.022	0.734±0.072	**< 0.001***	0.251±0.034	1.417±0.091	**< 0.001***
Testosterone (ng/mL)	0.261±0.034	0.617±0.041	**< 0.001***	0.351±0.037	0.242±0.029	**0.041***
DHEA-S (ng/mL)	0. 480±0.081	0.224±0.077	**0.042***	0.107±0.034	0.248±0.044	**0.028***

The Table 4 shows that in male non-diabetic non-addicted rats, the mean level of T3 was significantly lower than in females (P<0.001). The male non-diabetic addicted rats demonstrated a lower mean level of 17-hydroxyprogesterone and testosterone as compared to female non-diabetic addicted rats (P<0.001 for both comparisons), however, the mean level of DHEA-S was higher (P=0.042). The mean levels of 17-hydroxyprogesterone and DHEA-S were significantly lower in male than in females non-diabetic non-addicted, while testosterone was higher (P≤0.0001, P=0.028 and P=0.041, respectively). *Significance at 0.05 levels.

Table 5. Comparison of hormone levels between diabetic addicted and non-diabetic addicted male and female rats. Data from seven animals in each group

Hormones	Groups					
	Male, (mean ± SEM)			Female, (mean ± SEM)		
	Diabetic addicted	Non-diabetic addicted	P-Value	Diabetic addicted	Non-diabetic addicted	P-Value
T3 (ng/dL)	1.171±0.058	1.337±0.111	0.213	1.452±0.173	1.561±0.132	0.628
T4 (µg/dL)	29.4±2.96	29.191±2.928	0.961	35.114±2.084	34.220±2.432	0.785
17OH-Progesterone (ng/mL)	0.2±0.025	0.217±0.022	0.629	0.968±0.230	0.734±0.072	0.364
Testosterone (ng/mL)	0.3±0.095	0.261±0.034	0.651	0.395±0.077	0.617±0.041	**0.027***
DHEA-S (ng/mL)	0.557±0.183	0. 480±0.081	0.708	0.072±0.016	0.224±0.077	0.1

The Table 5 illustrates that the mean level of testosterone was significantly reduced in female diabetic addicted rats compared to non-diabetic addicted ones (P=0.027). However, the mean levels of T3, T4, 17-hydroxyprogesterone, testosterone, and DHEA-S did not show any significant difference between male diabetic addicted and non-diabetic addicted animals (P>0.05). *Significance at 0.05 levels.

Table 6. Comparison of hormone levels between diabetic and non-diabetic male and female rats. Data from seven animals in each group

Hormones	Groups					
	Male, (mean ± SEM)			Female, (mean ± SEM)		
	Diabetic	Non-diabetic	P-Value	Diabetic	Non-diabetic	P-Value
T3 (ng/dL)	0.832±0.047	0.872±0.044	0.549	1.358±0.034	1.334±0.041	0.66
T4 (µg/dL)	29.771±1.854	29.557±1.834	0.936	40.714±5.922	32.714±6.625	0.386
17OH-Progesterone (ng/mL)	0.257±0.037	0.251±0.034	0.912	3.984±0.846	1.417±0.091	**0.023***
Testosterone (ng/mL)	0.394±0.089	0.351±0.037	0.666	0.218±0.078	0.242±0.029	0.778
DHEA-S (ng/mL)	0.085±0.025	0.107±0.034	0.626	0.245±0.064	0.248±0.044	0.971

The Table 6 illustrates that the mean level of 17-hydroxyprogesterone was significantly increased in female diabetic non-addicted rats as compared to non-diabetic non-addicted group (P=0.023). In male rats, no significant differences were found in measured hormones (P>0.05). * Significance at 0.05 levels.

However, this difference was not significant. The mean level of DHEA-S in male DA rats had a significant increase in comparison with the DNA group (P=0.042), while a significant decrease was observed in female rats (P=0.023) (Table 1).

The mean level of 17-hydroxyprogesterone was significantly higher in female than in male DA rats (P=0.016). However, the mean level of DHEA-S was significantly lower in female DA compared to male rats (P=0.039). The mean levels of 17-hydroxyprogesterone and DHEA-S in male DNA were significantly lower in comparison with females (P=0.005 and P=0.039, respectively) (Table 2).

In male NDA rats, the mean levels of 17-hydroxyprogesterone and testosterone declined as compared to NDNA group (P>0.05 for both comparisons), whereas the level of DHEA-S showed a significant increase (P=0.001). Comparison of female NDNA with NDA group revealed the mean levels of 17-hydroxyprogesterone and testosterone were significantly decreased and increased, respectively (P<0.001 for both comparisons) (Table 3).

The male NDA rats demonstrated a lower mean level of 17-hydroxyprogesterone and testosterone as compared to female NDA rats (P<0.001 for both comparisons), however, the mean level of DHEA-S was higher (P=0.042). The mean levels of 17-hydroxyprogesterone and DHEA-S were significantly lower in male than in female NDNA, while testosterone was higher (P<0.001, P=0.028 and P=0.041, respectively) (Table 4).

The mean levels of 17-hydroxyprogesterone, testosterone, and DHEA-S did not show any significant difference between male DA and NDA animals (P>0.05). The mean level of testosterone was significantly reduced in female DA rats compared to NDA ones (P=0.027) (Table 5).

In both sexes, no significant differences were observed in the mean levels of testosterone and DHEA-S between DNA and NDNA groups (P>0.05). The mean level of 17-hydroxyprogesterone was significantly increased in female DNA rats as compared to NDNA group (P=0.023). In male rats, no significant differences were found in measured hormones (P>0.05) (Table 6).

DISCUSSION

In the present study, the opium showed significant effects on various hormones of the male and female rats in diabetic and non-diabetic conditions. Numerous studies have been conducted regarding the effects of opium and its derivatives on thyroid and sex hormones (5,8). To the best of authors' knowledge, until now there has been no study undertaken on the effects of opium on sexual and thyroid hormones of females and males in diabetic condition.

The serum T3 level in male DA and NDA rats was significantly higher than in DNA and NDNA groups, and it was more significant in diabetic rats. A recent study concerning the effects of opium on thyroid hormones in opium-addicted individuals confirms the current results (5). In two other reports about the effect of heroin as an opioid derivative, T3 and T4 mean values were increased in men (22, 23). On the contrary, the mean level of T4 had no significant change in the present study. Results of another study on rats demonstrated that opium consumption contributed to a significant decrease in T4 and no significant change in T3 mean level (24). These findings are inconsistent with the present results. In humans, it has been found that chronic consumption of methadone, a synthetic opioid, has no significant changes on T3 and TSH mean levels (19). Also, a study conducted by Moshtaghi-Kashanian *et al.* showed that TSH level significantly decreased in opium and cigarette addicted men (25).

The effect of opium on the level of thyroid hormones could be explained as follows: based on the two studies measuring the T3 uptake, the results showed a significant increase in T3 level and a significant reduction in T3 uptake in addicted individuals as compared with non-addicts. Concerning the reduction in T3 uptake and the reverse association of T3 uptake with thyroid binding globulin (TBG), it could be concluded that the opium consumption probably increases TBG level (26, 27). The increase of the T3 level might lead to negative feedback on the pituitary gland and inhibit the secretion of TSH as reported by Moshtaghi *et al.* (25). Also, another possible mechanism is the direct interference of opium in activating the conversion process of T4 to T3. Indeed, there is no exact mechanism to explain how opium alters the thyroid hormones levels in males and females differently in diabetic condition.

Narcotic drugs have a substantial inhibiting effect on sexual behaviors (28). The effects of opium and its derivatives on sex hormones have been verified with changes in sexual behaviors of males and females (8,13,14). Consumption of opium and its derivatives leads to hypogonadism as well as a change in the values of the pituitary hormones. The most common sexual disorders related to opium addiction include oligomenorrhea and amenorrhea in women, lower libido in men and infertility in both sexes which might reduce

their life quality (13–15,29).

Few studies have evaluated the effects of opium on testosterone level in both sexes. The results of a retrospective study on short and long-term effects of different doses of opium on men have shown a reduction in testosterone level of diabetic and non-diabetic individuals which is consistent with the results of present study in males (30), although the difference was not significant in the present study. Moreover, in the present study, the testosterone level in DA and NDA females increased as compared with the non-addict ones. This change was significant in NDA group which implies that the effect of opium on testosterone level is sex-dependent and diabetes might influence these changes.

The Festa *et al*. study showed that opium reduces testosterone level in both male and female rats, which is in contrast to the present findings in females (31). Another survey on the effects of opium and its analogs on animal and human endocrine system reported that opium consumption reduces LH, testosterone, and estradiol while it increases prolactin, but it does not influence FSH values. Furthermore, women were more sensitive than men to the effects of opium while this was not observed in animals (28). In Moshtaghi *et al.*'s study on opium-addicted men, the results showed a significant reduction in TSH and FSH, an increase in prolactin, and serum levels of testosterone and LH remained unchanged (25). The plausible mechanism of opium and its derivatives effects on testosterone could be explained via their effect on LH as a stimulator of testosterone secretion through the inhibition of hypothalamic secretion of GnRH. Meanwhile, as testosterone reduction leads to a negative feedback in LH and increases its secretion, opium consumption might reduce LH secretion through an inhibitory effect on this feedback (28).

Based on our information, there was no document on the effects of opium on 17-hydroxyprogesterone up to now. The study findings revealed that addiction reduces the level of this hormone while diabetes increases it. Opium consumption in female DA group, not only prevented the diabetes-induced increase of this hormone, but it also reduced its level as compared with NDNA group. Further studies are required to clarify the mechanisms leading to these changes.

DHEA-S is the most abundant steroid hormone in the human circulatory system which plays a key role in the development of secondary sexual characteristics. The adrenocorticotropic hormone (ACTH) released from the pituitary stimulates the secretion of DHEA-S from the adrenal gland (32).

To the best of our knowledge, the impact of opium on DHEA-S has not been studied till now. Morphine was reported to diminish the level of DHEA-S precursor (DHEA) in female rats (33). Chronic consumption of opioids inhibits the secretion of ACTH. This might be explained by the concomitant release of Beta-endorphin and ACTH under all physiological conditions. The pathway is inhibited by negative feedback of exogenous narcotic substances (13). Regarding these findings, it was expected that after opium consumption, the ACTH and subsequently DHEA-S level would be decreased, however, this was observed significantly only for DA females.

In the present study, opium consumption led to a significant increase in DHEA-S in male DA and NDA rats. Also, the level of DHEA-S in male diabetic rats increased as compared with non-diabetic ones, which is in agreement with the findings of Yamauchi *et al.* (34). However, in the present study, this discrepancy was not significant. All DHEA-S of women are produced in the adrenal glands, whereas testis produces some levels of DHEA-S along with the adrenal glands in men (32), so it could be concluded that the difference between male and female groups is due to the probable opium effects on the testis.

Based on the fact that diabetes is a metabolic disorder that depends on its severity and the influence of diabetes progression, many parts of the body including reproductive and thyroid endocrine systems (35), it can be concluded that in this condition hormonal changes are various. As observed in Table 6, in the present study 17-hydroxyprogesterone in diabetic female animals increased significantly compared with non-diabetics. However, there were no changes in other measured hormones. This finding may be due to the fact that sexual hormones in females are prone to variation compared to males in different conditions (36).

The lack of financial resources limited the current study to measurement of sex hormone-binding globulin (SHBG) and pituitary hormones. However, since the downstream hormones play the functional role, we focused on the measured hormones. Further human research with a larger population is highly recommended to support the findings of this study. Also, further longitudinal studies are required to investigate the effects of opium with a focus on pituitary hormones.

In conclusion, according to the study findings, it could be deduced that the effects of opium on the endocrine system are sex-dependent and might have different effects in diabetic and non-diabetic conditions. Opium has a direct effect on target tissues and can alter signal pathways and cellular response. Concerning

the widespread effects of thyroid and sexual disorders induced by opium consumption, it is necessary to assess these hormones in those societies with high opium and its derivatives consumption rate. It is also critical to treat the opium-addicted individuals to inhibit the complications of hormonal disorders.

Conflict of interest

The authors declare that they have no conflict of interest.

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