Vol. 20, No. 1, Spring, 2024, 13-23 *Original Article*
DOI: 10.22055/IVJ.2023.418021.2640
Journal Homepage: http://www.ivj.ir/

Effects of betaine on histological and inflammatory changes of rat ovary caused by induction experimental polycystic ovary syndrome

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Received: 27.09.2023 Accepted: 20.11.2023

Abstract

Polycystic ovary syndrome (PCOS) is one of the most important endocrine disorders affecting about 5-10% of women in reproductive age. Betaine is a bioactive peptide that has an anti-inflammatory activity. The present study aimed to evaluate the effects of betaine on insulin resistance indices and inflammatory cytokines markers and histology alteration in rat ovary with experimental PCOS. This experimental study was performed on 48 female Wistar rats (170-200 g). PCOS was induced by administration of testosterone enanthate (1 mg/100g/day during 35 days). PCOS rats were treated with betaine (1% in drinking water) for 30 days. At the end of the experimental period, the insulin resistance markers (serum insulin and glucose concentrations the homeostasis model assessment of basal insulin resistance (HOMA-IR), serum estradiol (E2), progesterone (P4) and inflammatory cytokines were measured. The ovaries were also processed for histological study. PCOS induction resulted in insulin resistance, impaired E2, P4 production and elevation of tissue TNF-α, IL-1β levels. Moreover, a significant increase of ovarian cysts and atretic follicles and also a significant reduction in the early corpus luteum were observed in the ovarian tissue of the PCOS groups. Betaine treatment could reduce the inflammatory cytokines and improve steroid productions in PCOS rats. Betaine also restored normal Folliculogenesis by reducing atretic and cystic follicles. Our findings showed the beneficial effects of betaine in PCOS rats by improvement of folliculogenesis, suppression of inflammation in ovary.

Key words: Polycystic ovary syndrome, Ovary, Betaine, Folliculogenesis, Inflammation

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common hormonal disorders in women of reproductive age, which is caused by endocrine system disorders (Popovic et al, 2019). It is characterized by hyperinsulinemia, hyperandrogenism, hirsutism, amenorrhea, ovarian enlargement, ovulation disorders and infertility (Kokabiyan et al, 2022). One of the main symptoms of this disease is the

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occurrence of hormonal changes in gonadotrophs and sex hormones, which have a direct effect on the normal functions of ovary (Joham et al, 2022). In women with PCOS, an increase in the ratio of luteinizing hormone (LH) to follicle-stimulating hormone (FSH) leads to a lack of ovulation and increased synthesis and secretion of androgens. The increase in the activity of androgens leads to impaired ovarian steroidogenesis (Lo et al, 2017). Many studies have shown that several morphological changes occur in the ovaries of women with PCOS, including bilateral ovarian enlargement, hypertrophy, luteinization of the internal theca layer, and a decrease in the number of corpora lutea. These histological alterations lead to folliculogenesis disorders (Dunaif, 2012). Insulin resistance and compensatory hyperinsulinemia also increase the production of androgens (Misichronis et al, 2012). Hyperandrogenemia (HA) increases the severity of PCOS symptoms in patients with induction of follicular apoptosis, suppression of granulosa cells proliferation of, and finally, atresia of growing follicles (Ballester et al, 2007; Osibogun et al, 2020). Wang et al, (2019) has reported that insulin resistance and hyperinsulinemia contributors to the progression of metabolic dysfunction and the result in hyperandrogenism, leading to abnormal reproductive function in women with PCOS. There are growing concerns about the relationship between PCOS and systemic inflammation (Zaffari zangeneh et al, 2017). Some previous reports indicated the increased levels of inflammatory factors such as monocyte chemoattractant protein-1, C-reactive protein (CRP), interleukin-18, IL-6, IL-1β, and TNFα in women with PCOS (Kokabiyan et al, 2022). Zangeneh et al, (2017) also indicated that the median serum levels of IL-1α and IL-1β are higher in women with PCOS than those in healthy women (Shokri et al, 2019). The circulating malondialdehyde concentration in women with PCOS was increased in compared with controls groups (Murri et al, 2013).

Despite the prevalence of PCOS, its major causes are still unknown, and complete and accurate protocols to treat this reproductive disorder are not available. Various treatment methods have been suggested for polycystic ovary syndrome, such as lifestyle changes, surgery, and using chemical drugs such as clomiphene citrate and metformin (Marx et al, 2003). Due to the side effects of PCOS, it is crucial to identify and prepare an alternative compound. In the recent decades, the use of natural bioactive compounds has received more attention as an alternative treatment due to their effectiveness, fewer side effects, and easy availability (Hossain et al, 2020). Betaine (Trimethylglycine) is produced following the oxidation of choline in the inner membrane of mitochondria, mainly in the liver and kidneys. Abbasi Samie et al, (2020) has reported betaine treatment could ameliorate steroidogenesis impairment and the adverse effects of hyperglycemia on functions of mice granulosa cells under high glucose concentration condition. Du et al, (2018) have also shown that betaine supplementation enhances lipid metabolism and improves insulin resistance in mice fed a high-fat diet. Studies on the effects of betaine on ovaries are limited. Considering the pathogenesis of PCOS based on the induction of inflammatory pathways and insulin resistance, and taking into account the effects of betaine, especially its anti-inflammatory, it is possible that betaine can improve inflammatory pathways. Moreover, it may be effective on the improvement of histological changes and folliculogenesis of the ovary caused by the PCOS. Therefore, the present study was designed to investigate the impacts of betaine on insulin resistance indices, inflammatory cytokines, and ovarian histomorphometry in rats with PCOS.

Materials and Methods

In this experimental study, 48 mature female rats (170- 200 g) were purchased from laboratory animal center of Shahid Chamran university of Ahvaz, Iran. Animals were kept in the animal house under standard laboratory conditions of constant temperature (25±2˚ C) and humidity 45-60 % with a 12h: 12h cycle of light and dark. They had free access to a normal diet (Pars Feed Co, Iran) and water. All experimental assays were approved by the Ethics Committee of Shahid Chamran University of Ahvaz, Ahvaz, Iran, for animal and human experiments (EE/1401.2.24.126555/ scu.ac.ir). After a week of adaptation to the laboratory conditions, rats were randomly divided into 6 groups (n = 8 in each group).

G1: (Control): Rats were fed with standard rat chow; G2: (PCOS): PCOS was induced by subcutaneous injection of testosterone enanthate (1 mg/100 g dissolved in 0.2 ml sesame oil, daily for 35 days) (Beloosesky et al., 2010); G3:(PCOS+ Bet): PCOS rats received betaine (1% in drinking water for 30 days) (Nazari et al., 2017; Wang et al., 2010); G4: (PCOS+ Met): PCOS rats received metformin (100 mg/kg) for 30 days; G5: (Bet): The control rats received betaine (1% in drinking water for 30 days); G6: (Met): The control rats received metformin (100 mg/kg) for 30days.

The estrous cycle was determined daily by vaginal smear starting from 5th day after commencing the injection of testosterone. The vaginal opening was flushed about 5 times with pipette containing double deionized water (ddH2O) to obtain the epithelial cells. The final flush transferred onto glass slide and allowed to completely dry at room temperature. The smear was stained with crystal violet for 1 min and washed twice (one minute each time) in ddH2O and observed under light microscope (Olympus IX71, Japan) equipped with camera (Olympus E-30). The identification of leukocytes, nucleated epithelial and cornified epithelial cells, was used as markers of different stages of estrous including proestrus, estrous, metestrus, and diestrus, respectively.

After overnight fasting, the rats were anesthetized using ketamine 150 mg/kg and xylazine 15 mg/kg (Mendes Procopio et al., 2021) on day 30 after initiation of the treatment. Blood samples were collected from the rat by cardiac puncture. The blood was put into 2 ml tubes to clot and centrifuged at 5000 rpm for 10 min, and sera were stored at -20˚C for future use. Immediately after rat killing on day 30 of the experiment, both ovaries were removed and carefully cleaned of fat and adhering tissues. One ovary was stored at -70 °C for analysis of inflammatory factors and another was used for histological analysis.

For cytokine measurement, the ovary tissue (50 mg) was lysed in 200 µl lysis buffer (Tris-HCl 50mM, NaCl 150 mM, Triton X-100 0.1%, NaF 1mM) supplied with protease inhibitor cocktails (Sigma-Aldrich, MO, USA) for 30 min on ice. The protein concentration of cell lysate was quantified by Bradford protein assay. The supernatant was used for determination of TNF-α and IL-1β concentrations by species specific ELISA kit according to the manufacturer's protocols (BT laboratory assay China).

Serum glucose was measured using a commercial kit according to the manufacturer protocol (Man Co, Iran). Insulin concentration was measured using a species-specific ELISA kit (BT laboratory assay, China). The homeostasis model assessment of basal insulin resistance (HOMA-IR) was estimated using the following formula: Fasting Insulin (uU/mL) * Fasting Glucose (mmol/L/22.5).

Lower HOMA-IR values indicated greater insulin sensitivity, whereas higher HOMA-IR values indicated lower insulin sensitivity (insulin resistance) (Buettner et al, 2006).

The concentration of progesterone (P4) and estradiol (E2) was measured at the end

of the experiment by commercial ELISA kit according to the manufacturer's instructions (DiaMetra, Italy). All samples were run in one assay to avoid inter-assay variation. The limits of detection of P4 and E2 were 0.05 ng/ml and 5 pg/ml, respectively. The intra-assay coefficients of variation of both hormones were less than 5%. All assays were carried out in duplicate (Buettner et al, 2006).

The tissue samples were fixed in 10% buffered formalin immediately upon removal. Next, samples were dehydrated by passing through a graded series of ethanol, cleared in xylene and embedded in paraffin blocks. Then, 5-6-µm sections were prepared using routine paraffin embedding methods and the sections were stained by H&E and were studied histologically. The number of Primary, secondary, Graafian follicles, Corpus luteum, and follicular cysts were assayed in all animal ovaries according to Erickson's classification (Erickson et al, 2003).

Statistical analyses were performed using GraphPad Prism Software version 8 (GraphPad Software, Inc., San Diego, CA). The statistical significance between control group and other experimental groups was analyzed by one-way analysis of variance (ANOVA) with Tukey's post hoc test. Data are expressed as mean ± standard deviation (SD). Statistically significance difference between different experimental groups was represented as follows: *p<0.05, **p<0.01, *** p< 0.001, **** p<0.0001

Results

Effect of betaine supplementation on insulin resistance markers in PCOS rats

The results indicated a significant increase in blood glucose level in the PCOS group compared to the control group (p<0.0001) (Table 1). Treatment of PCOS animals with betaine (PCOS+ B) and metformin (PCOS+ M) for 30 days, significantly reduced blood glucose level compared to the untreated PCOS group (p<0.001), (p<0.01) (Table 1). The reduction of blood glucose level was not significantly different between (PCOS+ Bet) and (PCOS+ Met) animals. Betaine and metformin had no significant effects on blood glucose level in control group (Table 1). A significant increase in serum insulin level and HOMA-IR were observed in the PCOS group compared to the control group (p<0.001) (Table 1). The results of our study showed a significant decrease in serum insulin level and HOMA-IR index in the PCOS+ Bet and PCOS+ Met groups compared to untreated PCOS rats (p<0.01) (Table 1). There was no significant difference in serum insulin level and HOMA-IR index in PCOS groups treated with betaine (PCOS+ Bet) and metformin (PCOS+ Met) (Table 1). No obvious changes were observed in serum insulin level and HOMA-IR index in control groups treated with betaine and metformin (Table 1).

Table 1: Serum insulin and glucose levels and HOMA-IR in rats after treatment with betaine and metformin. Values are mean ± SD, n = 8 animals per group. Different letters in each column denote significant differences at p < 0.05.

Groups	HOMA-IR	Glucose mg/dl	Insulin ng/mL
Control	1.72 ± 0.31	94.95 ± 6.53	2.94 ± 0.41
PCOS	5.28 ± 1.40#	141.8 ± 7.98#	6.07 ± 1.36#
PCOS + Betaine	2.11 ± 0.26*	109.2 ± 8.41*	3.16 ± 0.20*
PCOS + Metformin	2.14 ± 0.29*	115.8 ± 6.10*	3.05 ± 0.50*
Betaine	1.58 ± 0.24	95.71± 5.69	2.69 ± 0.28
Metformin	1.51 ± 0.26	91.04 ± 2.05	2.72 ± 0.42

#: significant difference with the control group, *significant difference with the PCOS group

Effects of betaine on the ovarian inflammatory cytokines

As indicated in table 4, the tissue levels of TNFα and IL-1β of the PCOS groups were significantly higher than those of the healthy control group ($p<0.0001$) (Table 4). Treating the PCOS groups with betaine or metformin significantly reduced the tissue levels of TNFα and IL-1β compared to the untreated PCOS groups ($p<0.0001$) ($p<0.001$) (Table 4). Betaine and metformin treatment had no significant effects on the tissue levels of TNFα and IL-1β in the control group. No obvious change was observed between PCOS groups treated with betaine (PCOS+ Bet) and metformin (PCOS+ Met) (Table 4).

Table 4: Tissue levels of TNF-α and IL-1β in rats after treatment by betaine and metformin. Values are mean±SD, n = 8 animals per group. Different letters in each column denote significant differences (p<0.05)

Groups	TNF-α (pg/ mg protein)	IL-1β (pg/ mg protein)
Control	18.41 ± 8.03	22.76 ± 5.67
PCOS	136.3 ± 24.66#	117.5 ± 11.83#
PCOS + Betaine	63.57 ± 6.04*	63.85 ± 5.57*
PCOS + Metformin	68.38 ± 9.28*	72.99 ± 13.82*
Betaine	12.57± 1.11	13.80 ± 2.42
Metformin	18.66 ± 3.09	20.11 ± 8.31

#: significant difference with the control group, *significant difference with the PCOS group

Effects of betaine on hormonal changes in PCOS rats

As shown in Table 5, compared with the control animals, PCOS group exhibited a significant decrease in serum levels of E2 ($p<0.0001$) and P4 ($p<0.001$). Serum levels of E2 was significantly increased in PCOS group treated with betaine ($p<0.01$) and metformin ($p<0.05$) for 30 days, while serum levels of P4 in the (PCOS+ B) and (PCOS+ M) groups showed no significant changes compared to the PCOS group (Table 5). Treatment of healthy animals with betaine and metformin for 30 days, had no significant effects on serum levels of E2 and P4 (Table 5).

Table 5: Serum levels of estradiol and progesterone in PCOS rats after treatment with betaine and metformin. Values are mean ± SD, n = 8 animals per group. Different letters in each column denote significant differences (P<0.05)

Groups	Estradiol (ng/ml)	Progesterone (ng/ml)
Control	36.17 ± 2.70	310.7 ± 11.68
PCOS	15.83 ± 1.55#	214 ± 7#
PCOS + Betaine	26.97 ± 3.009*	246 ± 20.95
PCOS + Metformin	23.40 ± 3.16*	261.7 ± 12.50
Betaine	33.30± 2.39	320.7 ± 27.32
Metformin	33.67 ± 2.40	320.7 ± 17.79

#: significant difference with the control group, *significant difference with the PCOS group

Histological evaluation of ovaries in PCOS rats treated with betaine

The histological evaluation in control group showed numerous healthy follicles at various stages of development (Figure 1A). Most of these follicles revealed normal features such as intact oocyte and absence of pyknotic granulosa cells and absence of fragmented granulosa cells and cells debris in the antral cavity. Induction of PCOS by testosterone enanthate resulted in the formation of cystic follicles in PCOS group (Figure 1B) and increased numbers of antral atretic follicles in the ovary of PCOS animals. In comparison with the control group, counting the number of follicles in different stages in PCOS animals specified that the injection of testosterone enanthate decreased the number of primordial follicles, antral follicles, Graafian follicles, and corpus luteum, but increased the number of cystic follicles and degenerating corpus luteum (Figure 1B). Moreover, irregular ovarian structures were observed in PCOS group. Treatment of PCOS animals by betaine and metformin improved the histological features of the ovaries compared to untreated PCOS animals. The administration of betaine and metformin decreased the numbers of follicular cysts and significantly increased the number of antral follicles, Graafian follicles, and early corpus luteum. (Figure 1 C & D).

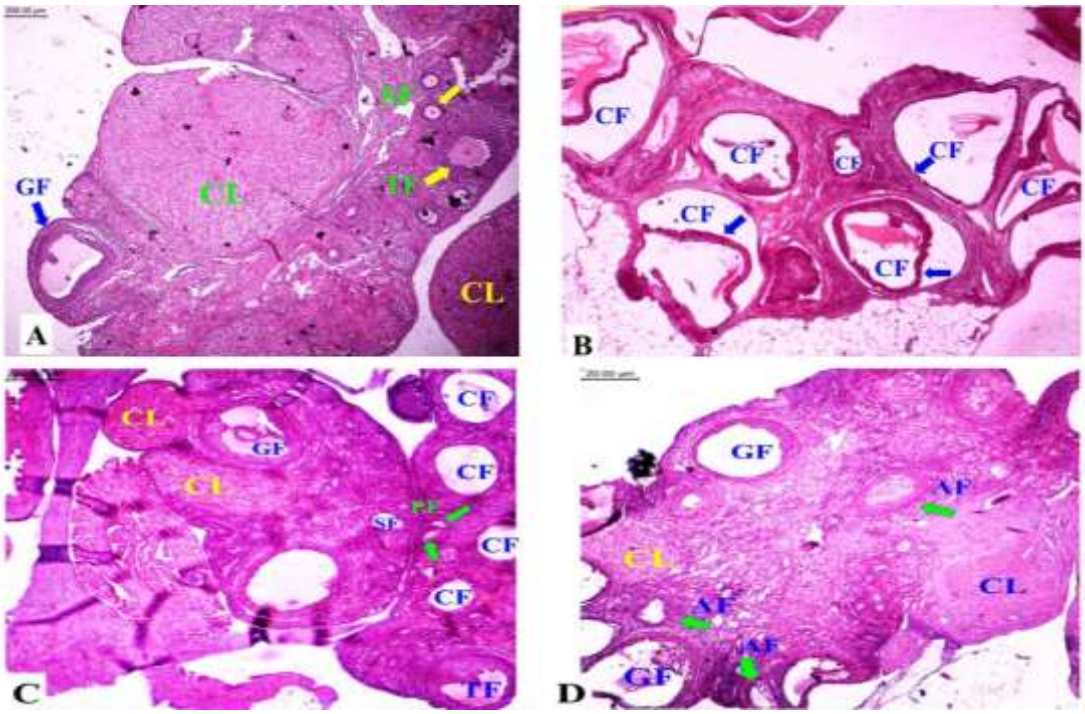

Figure 1: Photomicrograph of ovaries in different studied groups (H&E). (A): Ovarian section of control group with healthy growing follicles and corpus luteum (H&E, ×4), (B): In PCOS group, increased number of cystic follicles (CF), changes with decreased granulosa cells layer (blue arrow), separation of the granulosa cells layer from the basement membrane (blue arrow) and irregular ovarian structures were observed. (C and D): PCOS treated group with betaine (C) and metformin (D), that showed decreased cystic follicles (CF) and increased the number of antral follicles and growing early corpus luteum (CL). (SF): secondary follicle, (TF) tertiary follicle, (GF) graafian follicle, (CL) corpus luteum, (CF) cystic follicles

Discussion

In the present study, the therapeutic effects of betaine on hormonal alterations, insulin resistance markers ovarian tissue histology and inflammatory cytokines factors in the experimental model of PCOS in rats were investigated. Induction of PCOS resulted in a significant increase in ovarian tissue levels of inflammatory

cytokines (TNF- and IL1-), insulin resistance, formation of follicular follicles, and absence of ovulation, indicating progression of PCOS. Different hormones such as letrozole (Yu et al, 2021), estradiol valerate (Kokabiyan et al, 2022), dehydroepiandrosterone (Ikeda et al, 2014) and testosterone propionate (Beloosesky et al, 2004) are used to induce PCOS in experimental animals. In accordance with our results, Kalhori et al, (2013) have shown that testosterone enanthate treatment (1 mg/100 g body weight dissolved in sesame oil) for five weeks, led to the manifestation of human PCOS and caused the histological changes in the mouse ovary and significantly increased the percentage of cystic follicles. Previous studies have shown that the mechanism by which testosterone causes polycystic ovaries is by inhibiting the expression of molecules such as GDF9 in the oocyte, which causes the follicular growth to stop. It has also been reported that that testosterone strengthens primary follicles by stimulating Foxo3a phosphorylation and nuclear removal and increasing PI3-K/Akt pathway activation. As a result, it prevents the progress of primary to secondary follicles and stops the growth of pre-antral follicles (Yang et al, 2010).

In the present study, the rats with PCOS syndrome showed higher blood sugar, insulin, and HOMA-IR compared with the control group, which indicates the characteristic of insulin resistance. The cause of decreased insulin sensitivity in PCOS is still not well-known, though factors that compensate for insulin resistance have therapeutic effects (Kokabiyan et al, 2022). Holman et al., showed that continuous exposure to androgens due to the effect on glucose transport leads to insulin resistance, and increased testosterone levels may play a role in insulin resistance.

Betaine consumption could reduce blood glucose, insulin, and HOMA-IR and improve insulin resistance in PCOS rats. In accordance with our results, Grizales et al, (2018) demonstrated that betaine supplementation for 12 weeks could improve insulin sensitivity, hyperglycemia, and hepatic fat deposition in obese participants with prediabetes. Nazari et al., (2017) showed that betaine could improve insulin resistance in high-calorie diet-induced insulin resistance in rats by regulating some adipocytokine in adipose tissue.

The JNK pathway can directly phosphorylate serine 307 in IRS-1. Phosphorylation of serine 307 in IRS-1 is a critical mechanism that inhibits the insulin signaling pathway in physiological conditions. This negative signal is strongly stimulated by increasing JNK activity and leads to insulin resistance (Gual et al, 2005). Betaine can cause decreasing insulin resistance by reducing JNK activation (Zhao et al, 2018). AMPK acts as a key cellular energy sensor and a critical regulator of metabolic homeostasis. Activated AMPK enhances glucose uptake by stimulating glucose transporter type 4 (GLUT4). AMPK activation can occur independently of the AMP: ATP ratio through the action of the hormone adiponectin. Zhao et al, (2018) have shown that betaine increases the expression of the adiponectin gene and may thereby contribute to the increase in insulin sensitivity.

Several previous studies have shown that women with PCOS have low-grade chronic inflammation, which indicates the high activity of the pro-inflammatory cytokine such as IL-1β, TNF-α and IL6 (Popovic et al, 2019). The increase in the number of cytokines such as TNF-α and IL-1β indicates the presence of systemic and local inflammation in the body (Ciaraldi et al, 2013). Spaczynski et al, also showed that TNF-α induces the proliferation and differentiation of theca cells, resulting in androgen production and hyperandrogenemia.

Our results showed a significant increase in inflammatory markers such as IL-1 and TNF-α in the ovary of the PCOS group compared to the control group. These findings indicated that PCOS is a pro-inflammatory state (Dhindsa et al, 2004) and increased testosterone levels may lead to induce inflammation in the ovary of PCOS patients (Ikeda et al, 2014). Our results showed a significant decrease in tissue levels of IL-1β and TNF-α in PCOS groups treated with betaine compared to the control group. Betaine is a stable, non-toxic, natural nutrient with anti-inflammatory effects. It participates in reducing inflammation by reducing the secretion of pro-inflammatory cytokines. Mechanistically, betaine inhibits IL-1β production through different pathways, such as NF-κB, canonical NLRP3, and caspase-8/11 (Slow et al, 2008). In the present study, the production of estrogen and progesterone hormones was suppressed in the PCOS group compared to the control group. Consistent with our results, Cook et al, (2002) reported that serum estrogen levels were decreased in PCOS, while serum LH, FSH, and testosterone levels increased in PCOS patients. Also, Mu et al, showed that a decrease in plasma estrogen level by troglitazone in PCOS may be due to a reduction of aromatization. Previous findings demonstrated that hyperinsulinemia caused by PCOS increases the production of insulin growth factors I (IGF) and II in the liver, which leads to an increase in androgen production.

Our research showed a significant increase in serum estrogen levels in PCOS rats treated with betaine. Also, the serum levels of progesterone showed an increase in the group receiving betaine, although the level was insignificant. Several studies have shown that the occurrence of apoptosis in ovarian cells is associated with a decrease in steroidogenesis. Considering the role of betaine in reducing apoptosis, part of the effects of betaine in improving steroidogenesis can be attributed to the reduction of apoptosis caused by betaine consumption in granulosa cells. On the other hand, inflammatory factors such as IL-6 and TNF-α decrease steroidogenesis in ovarian cells (Amsterdam et al, 2003). Considering the role of betaine in reducing inflammation from different pathways, part of the effects of improving steroidogenesis may be due to the anti-inflammatory role of betaine. Abobakr et al, (2017) have shown that betaine treatment increases the steroidogenic acute regulatory protein (StAR) mRNA expression in the adrenal tissue of laying hens. StAR mRNA is a limiting step in the biosynthesis of steroid hormones that facilitates the translocation of cholesterol into the mitochondria. A recent study by Abbasi Samie et al, (2020) also showed that betaine ameliorates impaired steroidogenesis and apoptosis in mice granulosa cells induced by high glucose concentration. These findings revealed that betaine, by attenuation of apoptosis and inducing steroidogenesis in ovarian granulosa cells, have improving effects on ovarian function under insulin resistance and inflammatory conditions.

In the present study, the number of primordial follicles, graafian follicles, and corpus luteum decreased in PCOS rats, while the number of cystic follicles increased following PCOS induction. These findings confirmed the absence of ovulation in PCOS animals. These phenomena are probably caused by hyperandrogenism, which leads to the production of cystic follicles and a decrease in the number of normal follicles. Therefore, ovary tissue changes in our study may be due to hormonal disorders caused by testosterone. Ikeda et al, (2014) reported that dehydroepiandrosterone injection into immature female rats for 30 days reduces ovarian volume. This reduction can be due to ovarian atrophy, an increase in the number of atretic follicles, a decrease in the number of antral follicles, and the absence of the corpus luteum that occurs in PCOS rats. It seems that betaine can partially

improve the histological characteristics of ovaries and reduce the number of cysts in treated animals. Finally, it has been found that many of the beneficial effects of betaine were relatively similar to metformin. Our results demonstrated a significant decrease in blood glucose, insulin, and HOMA-IR in the metformin-treated PCOS group. Metformin can reduce hepatic glucose production and inhibit gluconeogenesis and adipogenesis. In the present study, metformin drugs in PCOS rats decreased the number of cystic and atretic follicles and the volume of ovaries. It has been reported that metformin can lead to weight loss and decrease the proliferation of ovarian theca cells caused by androgens in PCOS. Also, it can reduce ovarian volume and partially restore follicular dynamics (Mahamed et al, 2018).

The present study focused on the effects of betaine on some adverse features of PCOS induced by testosterone in rats. This study provided supporting evidence that betaine has sufficient anti-inflammatory properties. It showed beneficial effects on serum glucose and insulin, reproductive hormones as well as restoring regular ovulation in PCOS rats. Betaine could be a promising natural product to reduce PCOS symptoms. Our findings indicated that long-term treatment with betaine or higher doses might be a potential treatment in PCOS patients; however, more clinical studies are needed to confirm the therapeutic efficacy of betaine in these patients.

Acknowledgments

The authors express their gratitude to the Research Council of Shahid Chamran University of Ahvaz for its financial support.

Conflict of interest

The authors declare that they have no known conflict of interest.

Funding

This study was supported by a grant (no. SCU, VB1400.158) from the Shahid Chamran University of Ahvaz, Iran.

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Received: 27.09.2023
Accepted: 20.11.2023

DOI: 10.22055/IVJ.2023.418021.2640

اثرات بتائین بر تغییرات بافتی و التهابی تخمدان موش صحرایی ناشی از القای تجربی سندرم تخمدان پلی کیستیک

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تاریخ دریافت: ۱۴۰۲/۷/۵ تاریخ پذیرش: ۱۴۰۲/۸/۲۹

چکیده

سندرم تخمدان پلی‌کیستیک (PCOS) یکی از مهم‌ترین اختلالات غدد درون‌ریز است که حدود ۵ تا ۱۰ درصد از زنان در سنین باروری را تحت تأثیر قرار می‌دهد. بتائین یک پپتید فعال زیستی است که دارای فعالیت ضدالتهابی است. مطالعه حاضر با هدف بررسی اثرات بتائین بر شاخص‌های مقاومت به انسولین و نشان‌گرهای سایتوکین‌های التهابی و تغییرات بافت‌شناسی در تخمدان موش صحرایی با PCOSتجربی انجام شد. این مطالعه تجربی روی ۴۸ سر موش صحرایی ماده بالغ نژاد ویستار (۲۰۰-۱۷۰ گرم) انجام شد. سندرم تخمدان پلی‌کیستیک با تجویز تستوسترون انانتات (۱ میلی گرم/۱۰۰ گرم در روز در طی ۳۵ روز) القا گردید. موش‌های PCOS با بتائین (۱ درصد در آب آشامیدنی) به مدت ۳۰ روز تحت درمان قرار گرفتند. در پایان دوره آزمایشی، نشان‌گرهای مقاومت به انسولین (غلظت انسولین و گلوکز سرم، ارزیابی مدل هموستاز مقاومت به انسولین پایه (HOMA-IR)، استرادیول (E2)، پروژسترون (P4) سرم و سایتوکاین‌های التهابی اندازه‌گیری شد. تخمدان‌ها نیز برای مطالعه بافت‌شناسی پردازش شدند. القای PCOS منجر به مقاومت به انسولین، اختلال در تولید E2 و P4 و افزایش سطح TNF-α، IL-1β بافتی شد، همچنین افزایش قابل توجهی در کیست‌های تخمدان و فولیکول‌های آترتیک به همراه داشت. کاهش جسم زرد اولیه در بافت تخمدان گروه‌های PCOS مشاهده شد. درمان با بتائین، سیتوکین‌های التهابی را کاهش داده و تولید استروئیدها را در موش‌های PCOS بهبود بخشید. بتائین همچنین با کاهش فولیکول‌های آترتیک و کیستیک، فولیکولوژنز طبیعی را بازیابی کرد. یافته‌های این پژوهش نشان داد که بتائین در موش‌های PCOS با بهبود فولیکولوژنز و سرکوب التهاب در تخمدان می‌تواند اثرات سودمندی را اعمال کند.

کلمات کلیدی: سندرم تخمدان پلی‌کیستیک، تخمدان، بتایین، فولیکولوژنز، التهاب

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