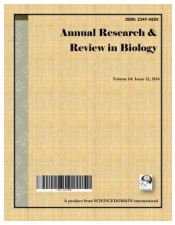

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Immune Modulation of Interleukin-1α by Noradrenaline and Cortisol in Women with PCOS (Psychoneuroimmunology Aspect)

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background & Objectives: Polycystic ovary syndrome (PCOS) is a common complex condition in women associated with reproductive, metabolic and psychological features. Evidences from studies on women with PCOS and on an experimental rat PCO model suggest that the sympathetic regulatory drive to the ovary may be unbalanced (hyperactivity). The sympathetic nervous system (SAS) and the hypothalamic-pituitary-adrenal (HPA) axis (cortisol) are the major integrative and regulatory components of different immune responses. The aims of this study were 1) to determine serum cytokines 2) The study of pattern four cytokines in PCO patients 3) Cross-talk between two super systems: SAS & Immune systems.
Methods: In this study, 171 women were divided into two groups: PCO (n=85) and control (n=86 non-PCOS). All women were between 20-40years old ages and their body mass index (BMI) was below 28. Serum cytokines: IL-17, IL-1α, IL-1β and TNFα concentrations in women with polycystic ovary syndrome (PCOS) were determined in both groups.
Results: The results showed that IL-17 in serum of patients with PCOS significantly lower than the control group ($p<0.001$). Interleukin 1 (alpha and beta) increased in the PCO group than the control

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group: Interleukin 1α ($p<0.001$) and IL-beta ($p=0.017$).
Discussion: The results of this study indicate that overactivity of sympathetic nervous system (SNS) in women with PCO impairs 1) three cytokines pattern and 2) the increased sympathetic outflow may be related to hormonal and metabolic features of this syndrome.
Conclusion: The activation of SNS during an immune response might be aimed to localize the inflammatory response. The results of this study confirm low-grade chronic inflammation in PCOS.

Keywords: Polycystic ovary syndrome (PCOS); chronic inflammation; Interleukins; sympathetic nervous system (SNS); noradrenaline; cortisol.

1. INTRODUCTION

Polycystic ovary syndrome (PCOS), the most common female endocrine disorder, is a complex and heterogenic disease with unknown etiology. PCOS is characterized by reproductive disturbances including chronic anovulation, hyperandrogenism and polycystic ovaries [1]. PCOS, one of the most common causes of female infertility, its prevalence among infertile women is 15-20% [2]. Clinically, PCOS has reproductive, psychological and metabolic features, the latter predisposing to cardiovascular disease (CVD) [3]. Although physical symptoms of PCOS are increasingly recognized by practicing clinicians, little attention has focused on psychological correlates of this frequent endocrine disorder. Emotional disturbances such as depression and chronic stress are associated with certain physiological changes such as increased immune system activity and pro-inflammatory markers, which increase one's risk for eventual development of chronic disorders such as cardiovascular disease, diabetes, and cancer [4]. Some evidence suggests strong associations between depression and other proinflammatory cytokines such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1β (IL-1β) [5]. Prospective studies employing pharmaceutical treatment illustrate the relationship between mood and inflammation. For example, antidepressants have been shown to inhibit pro-inflammatory cytokine production both *In vitro* and *In vivo* [6]. Women with PCOS have chronic low-level inflammation [7] and recent evidence has been focused on a condition of low-grade chronic inflammation as a potential cause of the long-term consequence of the syndrome [8]. Low-grade chronic inflammation seems to play an essential role in insulin resistance and its metabolic consequences [9] and may also play a role in the pathogenesis of PCOS [10]. Normal reproductive functioning in healthy, fertile women exists due to the presence of unique immunologic barriers, and also due to harmonic functioning of immunoregulatory by neuro-immunologic mechanisms. It is believed that cytokines produced by activated lymphocytes, monocytes and macrophages, such as interleukin-1, interleukin-6, gamma-interferon and others, affect the processes of fertilization, development and implantation of the fertile egg in the uterus, and this may be a reason for habitual miscarriage and infertility [11]. In female reproductive function neuropeptides, growth factors and cytokines are expressed in reproductive organs and tissues, where they interact with afferent endocrine messages to modulate cell proliferation and differentiation, local hormone secretion and vascular function. These events regulate complex processes such as gonadotropin plasticity, ovulation, implantation and parturition [12]. During female reproductive life, the role of the cytokine cascade and regulation of the expression of cytokine genes in the processes of fertilization is very complex. Studies show Low-grade chronic inflammation is reflected by minor but significant increases in circulating levels of known inflammatory and acute phase proteins such as interleukin (IL)-1, IL-6, tumor necrosis factor-(TNF) and serum C-reactive protein (CRP). One of the most prominent mediators of inflammation is the interleukin-1 (IL-1) family that consists of three different cytokines, the proinflammatory cytokines IL1α, IL1β and the physiological antagonist IL1 receptor antagonist (IL-1RA) [13]. IL-1α and IL-1β are produced by monocytes, macrophages, neutrophils and epithelial cells, and affect nearly every cell type [13,14]. Interleukin-1 (IL1) is a multifunctional cytokine and it has highly inflammatory features in reproductive biology and is believed to affect the processes of fertilization and implantation [14]. While human granulosa and cumulus cells synthesize IL1RA, expression of paracrine-acting IL-1 in the ovary could be involved in multiple steps leading to ovulation and, thereby, influence ovarian physiology [15]. The interactions among mood, behavior, and inflammation often manifest in a cluster of symptoms referred to as “sickness behavior” including depressed mood, anhedonia,

fatigue, psychomotor retardation, decreased appetite, social withdrawal, sleep disturbances, cognitive dysfunction, and increase sensitivity to pain [16,17]. These symptoms generally are exacerbated when inflammation increases. The relations among these symptoms and inflammation are so robust that even exogenous administration of pro-inflammatory cytokines reliably produces sickness behavior symptoms [18]. Possibly due to chronically elevated inflammatory markers, PCOS women exhibit some sickness behavior symptoms, including fatigue, depressed mood, social withdrawal [19] and sleep disturbances [20]. Based on the immune studies and on the role of inflammatory processes in the pathogenesis of PCOS, we hypothesized that neuroimmune-endocine events are related to overactivity of the sympathetic nervous system that trigger cascade of intra ovary in PCO. There is now sufficient data to conclude that immune modulation by psychosocial stressors and/or interventions can lead to actual health changes.

2. METHODS

This study was carried out at February 2012-April 2013. Totally 85 PCO patients (case group) and 86 health women (control group) participated in this study. The diagnosis of PCOS was made according to the joint criteria of the European Society of Human Reproduction and Embryology and the American Society of Reproductive Medicine (ESHRE/ASRM) [21]. Data were collected from clinical and anthropometric variables, including hirsutism score, body mass index (BMI) and a demographic questionnaire inquiring about age, education, occupation, and duration of illness. This study was approved by the Ethics Committee of Tehran University of Medical Sciences. The study objectives were explained to the patients before they entered the study, and an informed consent was obtained from all.

2.1 Statistical Analysis

The quantitative variables were presented with mean and standard deviation and were compared between study groups with t test. The qualitative variables were presented with count and percentage and were compared between study groups with chi square test. According to departure from normal distribution, the median was used for presenting inflammatory cytokines, and for comparing of those variables between two study groups Mann-Whitney nonparametric test was used. Multinomial linear regression model was used to deleting the confounding effect. In this analysis, age (year), BMI (kg/m2), occupation, irregular menstrual, hirsutism and painful menstrual were including in the model as confounder. Suffering from PCO was independent variable and each inflammatory cytokines separately were including in the model as dependent variable. The data were analyzed in IBM SPSS 19 (SPSS Inc, Chicago Ill). P value less than 0.05 considered as significant level.

3. RESULTS

The mean age of women the control group had an average of 2 years longer than patients in PCO group (P = 0.001). The two groups did not differ in height (P = 0.070), whereas weight in PCOS group was more than control group (P < 0.001) and BMI in PCO group was higher than the control group (P = 0.001). Duration of marriage and infertility also pregnancy and delivery count were not significant difference between two groups (Table 1). Education level of two groups was not statistically difference (P = 0.864). But occupation rate in PCO group was higher than control (P = 0.002). The symptom of PCO was significantly higher in PCO patients (Table 2).

IL-17 in PCOS group was significantly lower than control group (P < 0.001). Both IL-1-α (P <0.001) and IL-1-β (P = 0.017) were significantly higher in PCOS than control group (Table 3).

Multinomial linear regression model was used to clarify relationship between PCOS and each inflammatory cytokines. Occupation (β = 60.4, SEβ = 29.4, P = 0.042) was significantly related with TNF-α (R2 = 0.069). Age (β = -3.3, SEβ = 1.4, P = 0.020) and having PCO (β = -58.8, SEβ = 16.8, P = 0.001) were significantly related with IL-17 (R2 = 0.139). Having PCO (β = 387.3, SEβ = 32.2, P < 0.001) was just one variables that had significantly relationship with IL-1-α (R2 = 0.592). Painful menstural (β = -18.8, SEβ = 6.5, P = 0.005) and having PCO (β = 17.2, SEβ = 6.5, P = 0.009) were significantly related with IL-1-β (R2 = 0.090).

4. DISCUSSION

Cytokines and other humoral mediators of inflammation are potent activators of the central stress response, constituting the afferent limb of a feedback loop through which the immune/inflammatory system and the CNS

communicate [22]. Some of the activating effects of cytokines on the HPA axis may be exerted indirectly by stimulation of the central catecholaminergic pathways.

Conversely, activation of the HPA axis has profound inhibitory effects on the inflammatory/immune response because virtually all the components of the immune response are inhibited by cortisol. Alterations of leukocyte traffic and function, decreases in production of cytokines and mediators of inflammation, and inhibition of the latter's effects on target tissues are among the main immunosuppressive effects of glucocorticoids [23,24].

The mammalian ovary has a rich sympathetic nerve supply with norepinephrine as the major sympathetic neurotransmitter [25]. In human, the ovary has a functional sympathetic innervation coupled to steroid secretion. The value for the concentration of norepinephrine in the ovary was similar to others previously reported and 10 times higher than rat ovarian tissue; this neurotransmitter is coupled to a steroidogenic response [26]. The immune system regulates CNS and interferes with steroidogenesis at the level of the adrenals, testes, and ovaries [27]. This study follows previous studies in the field of overactivity of the sympathetic system in patients with PCO and investigation of sympathoexcitation and cytokinins.

Cytokines and other inflammatory mediators can signal the brain, and the importance of this Neuroimmune-endocrine cross-talk becomes evident in the case of autoimmune and inflammatory diseases. Interleukin-1 (IL-1) has been shown by many investigators to be a potent activator of the HPA axis.

Adrenal steroidogenesis is under the control of the HPA axis. Furthermore, metabolic factors including insulin and obesity-related signals may play a role in the regulation of both enzymes involved in the steroidogenetic pathways, as well as in the regulation of the HPA axis [28]. Smagin et al. [29] in 1996 showed that noradrenergic terminals in the hypothalamus play a role in the IL-l-induced activation of the HPA axis. Hypothalamic noradrenaline (NA) release parallels the increases in plasma corticosterone induced by IL-1.

Noradrenergic innervation of the hypothalamus participates in adrenocortical responses to interleukin-1, and it is possible that noradrenergic terminals in the hypothalamus play a role in the IL-l-induced activation of the HPA axis [30]. There is evidence that the immune-HPA axis circuit is not the only one involving immune components and neuroendocrine mechanisms and that the immune system interacts at several levels with mechanisms integrated by the CNS.

The operation of a complex network of immune-neuroendocrine interactions contributes to immunoregulation and to the homeostatic adjustments necessary during diseases that involve the immune system, cathecolamines and glucocorticoids (stress hormones) are immune madulators and the role of cytokines as modulators of glucocorticoids receptors (GR) has received scarce attention. One of the effects of immune stimulation was elevation of glucocorticoid blood levels [31].

Besedovsky et al. [32] in 1986 originally used conditioned media from immune cells stimulated in vitro, which contain several immune-derived substances including lymphokines and monokines. The first pure lympho-monokine natural or recombinant found to stimulate ACTH and glucocorticoid release by mechanisms integrated at hypothalamic levels was IL-1. Milutinovic's hypothesize in 2011 is that modulation of glucocorticoid receptor (GR) expression and function may underlie possible PCOS-related impairment of feedback inhibition of HPA axis activity and imply that PCOS is associated with increased GR protein concentration and HPA axis sensitivity to dexamethasone [33]. IL-1 has been shown to up-regulate GR mRNA expression in hypothalamic CRH secreting cells [34]. Then up-regulation of GR can be the reason of normal rate of cortisol in women with PCO.

Essentially, PCOS is a chronic condition with manifestations that begins most commonly in adolescence with oligomenorrhea / amenorrhea and transition into problems including infertility, metabolic complications and even cancer over time [35].

It has become increasingly clear that PCOS is an important metabolic disorder, as women with PCO may have significant insulin resistance, glucose intolerance, obesity, and dyslipidemia [36]. Therefore, it is not surprising that the risk of serious metabolic disorders such as type2 diabetes, metabolic syndrome, and subsequent cardiovascular disease [37] are significantly increased in women with PCOS.

Table 1. Comparison of quantitative factors between groups

Quantitative factors	PCOs (n = 85)		Control (n = 86)		P-value t test
	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	27.1	4.4	29.5	5.1	0.001
Duration of marriage (year)	6.52	3.42	6.88	4.01	0.537
Duration of infertility (year)	4.84	3.22	4.33	3.96	0.365
Body mass index (kg/m^2)	27.39	3.94	25.41	3.76	0.001
Pregnancy (count)	0.41	0.75	0.40	0.69	0.863
Delivery (count)	0.23	0.45	0.19	0.42	0.499

Table 2. Comparison of qualitative factors between groups

Qualitative factors		PCOS		Control		P-value chi square
		N	%	N	%	
Education (years)	less than 12	30	35.29%	27	31.40%	0.864
	12	43	50.59%	46	53.49%	
	more than 12	12	14.12%	13	15.12%	
Occupation	housewife	2	2.35%	14	16.28%	0.002
	occupied	83	97.65%	72	83.72%	
Abortion	no	76	89.41%	72	83.72%	0.275
	yes	9	10.59%	14	16.28%	
Infertility type	primary	59	69.41%	59	68.60%	0.909
	secondary	26	30.59%	27	31.40%	
Menstrual state	regular	27	31.76%	71	82.56%	<0.001
	irregular	58	68.24%	15	17.44%	
Hirsutism	no	37	43.53%	68	79.07%	<0.001
	yes	48	56.47%	18	20.93%	
Painful menstrual	no	11	12.94%	23	26.74%	0.024
	yes	74	87.06%	63	73.26%	

Table 3. Comparison of inflammatory cytokines between two groups

Interlukins	PCOs (n = 85)			Control (n = 86)			P-value Mann-Whitney
	Mean	Standard deviation	Median	Mean	Standard deviation	Median	
IL-17 (pg/ml)	5.80	6.90	3.50	59.92	121.11	16.30	<0.001
TNF-α (pg/ml)	10.91	26.42	1.90	45.60	172.48	6.20	0.119
IL-1-α (pg/ml)	401.40	228.61	293.25	19.32	37.89	8.00	<0.001
IL1-β (pg/ml)	17.38	40.56	5.90	11.55	23.65	3.05	0.017

Many of the common features of PCOS, such as central obesity, hyperinsulinaemia and obstructive sleep apnoea, are associated with chronic sympathetic overactivity.

This is suggestive of possible involvement of sympathoexcitation in the pathogenesis of this condition [38]. The higher sympathetic tone is confirmed within PCOS, chronic inflammatory and/or psycho-emotional distress provoke a series of neuroimmunoendocrine interactions such as increased tissue and plasma levels of proinflammatory cytokines and neurotrophins, vegetodystonia, misbalance of neurotransmitters, hormones and immunity markers, activation of the HPA axis, insulin resistance, and atherosclerosis [38].

Our works in 2011 confirmed overactivity in sympathetic nervous system in rat modeling of PCOS [39,40] and in women with PCO [38]. Research over the past decade shows proinflammatory cytokine interleukin-1 (IL-1) produced during psychological and immunological stress plays a significant role in the neuroendocrine and stress responses [41].

Specifically, production of brain IL-1 is an important link in stress-induced activation of the HPA axis and secretion of glucocorticoids. Furthermore, IL-1 signaling and the resultant glucocorticoid secretion mediate the development of depressive symptoms associated with exposure to acute and chronic stressors, at least partly via suppression of hippocampal neurogenesis [42].

Kolbus et al. [14] in 2007 have shown that a common polymorphism of the interleukin-1alpha but not interleukin-1beta gene is associated with the presence of PCOS and with clinical parameters of women affected by this condition. IL-1β stimulates basal progesterone secretion by human granulosa and theca cells [43] and small and large follicles [44] *In vitro* and also IL-1β induce and increase levels of progesterone and PGF2-α in equine granulosa and cumulus cells which demonstrated that IL-1 is involved in equine oocyte *In vitro* maturation [45]. When stimulated by gonadotropins, IL-1β inhibits both LH/hCG and FSH stimulated progesterone and estradiol secretion by follicular theca and granulosa cells, affecting cAMP production, suggesting a follicle-stage dependent regulatory role of IL-1 on ovarian follicles [46].

Atsumi et al. [47] in 2014 have redefined inflammation as local activation of the inflammation amplifier, which causes an accumulation of various immune cells followed by deregulation of local homeostasis. The inflammation amplifier is activated by the stimulation of cytokines, such as TNF-α, IL-17, and noradrenaline, resulting in the subsequent expression of various target genes for chemokines.

Then, the significant decreasing of IL17 can be because of the regulatory role of noradrenaline. In this study, increasing of IL1α and β can obtain from a special relationship with noradrenaline and cortisol in women with PCOS. These results can indicate that 1) the increase in IL-1β ($p < 0.01$) could be due to lack of ovulation (anovulation) in women with PCOS. One of the genetic factors that have been associated with PCOS is IL-1β, particularly synergy with psychogenic and neurogenic stressors are described. It has proactive effects on mood states. 2) Study of Kolbus et al. [14] in 2007 showed that a common polymorphism of the interleukin-1alpha gene is associated with the presence of PCOS. Increasing of IL1 α could be due to sympathoexitation in these patients [48]. Although crosstalk between these two systems is clear, the role of NE in mediating inflammatory responses is less clear, with evidence of both pro- and anti-inflammatory effects. 3) Regulation of IL-17 by adrenal hormones caused a significant reduction of this cytokine in the serum of patients [49]. 3) PCO is a chronic condition and recent studies show that PCO as chronic low-grade subclinical inflammation has been increasingly recognized as an interposer in the endocrine, metabolic and reproductive disturbances [50]. 4) In addition, this study shows that an abnormal lymphocyte subset distribution was observed in PCOS, possibly associated with an impaired cytokine pattern that can play a major role in the immunopathogenesis of PCO. IL1 extremely is high in PCO patients which; confirm the high activity of HPA axis and sympathetic overactivity. Then noradrenaline exerts anti-inflammatory and neuroprotective effects *In vitro* and *In vivo* and can regulates IL17 activity in PCO. 5) Immune-modulatory role of cortisol and noradrenaline in HPA axis and reproductive health of women. 6) SNS may thus offer a new therapeutic target in PCO and can be a novel biological target for the treatment of it [38].

5. CONCLUSION

This study shows that an abnormal lymphocyte subset distribution was observed in PCOS, possibly associated with an impaired cytokine pattern that can play a major role in the immune-pathogenesis of PCOS.

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COMPETING INTERESTS

The authors report no conflict of interest.

REFERENCES

1. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet. 2007;370:685-697.
2. Badawy A, Elnashar A. Treatment options for polycystic ovary syndrome. Int J Womens Health. 2011;3:25-35

3. Burchall G, Linden MD, Teede H, Piva TJ. Hemostatic abnormalities and relationships to metabolic and hormonal status in polycystic ovarian syndrome. Trends Cardiovasc Med. 2011;21:6-14.
4. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: Inflammation and the pathogenesis of depression. Trends Immunol. 2006;27:24-31
5. Anisman H, Ravindran AV, Griffiths J, Merali Z. Endocrine and cytokine correlates of major depression and dysthymia with typical or atypical features. Mol Psychiatry. 1999;4:182-188
6. Kenis G, Maes M. Effects of antidepressants on the production of cytokines. Int J Neuropsychopharmacol. 2002;5:401-412
7. Diamanti-Kandarakis E, Paterakis T, Alexandraki K, Piperi C, Aessopos A, Katsikis I, Katsilambros N, Kreatsas G, Panidis D. Indices of low-grade chronic inflammation in polycystic ovary syndrome and the beneficial effect of metformin. Hum. Reprod. 2006;21:1426–1431
8. Repaci A, Gambineri A, Pasquali R. The role of low-grade inflammation in the polycystic ovary syndrome. Mol Cell Endocrinol. 2011;335:30-41
9. Fernandez-Real JM, Ricart W. Insulin resistance and chronic cardiovascular inflammatory syndrome. Endocr Rev. 2003;24:278-301
10. Escobar-Morreale HF, Luque-Ramirez M, San Millan JL. The molecular-genetic basis of functional hyperandrogenism and the polycystic ovary syndrome. Endocr Rev. 2005;26:251-82.
11. Sukhikh GT, Vanko LV. Interrelationships between immune and reproductive systems in human. Russ. J. Immunol. 1999;4:312–314.
12. Reis FM, Cobellis L, Luisi S, Driul L, Florio P, Faletti A, Petraglia F. Paracrine/ autocrine control of female reproduction. Gynecol Endocrinol. 2000;14:464-75.
13. Dinarello CA. Interleukin-1, interleukin-1 receptors and interleukin-1 receptor antagonist. Int. Rev. Immunol. 1998;16: 457-499.
14. Kolbus A, Walch K, Nagele F, Wenzl R, Unfried G, Huber CJ. Interleukin-1 alpha but not interleukin-1 beta gene polymorphism is associated with polycystic ovary syndrome. Journal of Reproductive Immunology. 2007;73:188-193.
15. Gerard N, Caillaud M, Martoriati A, Goudet G, Lalmanach AC. The interleukin-1 system and female reproduction. J. Endocrinol. 2004;180:203-212.
16. Dantzer R. Cytokine-induced sickness behavior: Where do we stand? Brain Behav Immun. 2001;15:7-24.
17. Kent S, Bluthe RM, Kelley KW, Dantzer R. Sickness behavior as a new target for drug development. Trends Pharmacol. 1992; 13:24-28.
18. Yirmiya R, Weidenfeld J, Pollak Y, Morag M, Morag A, Avitsur R, et al. Cytokines, “depression due to a general medical condition,” and antidepressant drugs. Adv Exp Med Biol. 1999;461:283-316.
19. Mansson M, Holte J, Landin-Wilhelmsen K, Dahlgren E, Johansson A, Landen M. Women with polycystic ovary syndrome are often depressed or anxious-a case control study. Psychoneuroendocrinology. 2008;33:1132-1138.
20. Zangeneh FZ, Naghizadeh MM, Abdollahi A, Bagheri M. Synchrony between ovarian function & sleep in polycystic ovary syndrome patients. Open Journal of Obstetrics and Gynecology. 2014;4:725-731.
21. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19:41-7.
22. Chrousos GP. The hypothalamic–pituitary– adrenal axis and immune mediated inflammation. N Engl J Med. 1995;332:1351-62.
23. Elenkov IJ, Webster EL, Torpy DJ, Chrousos GP. Stress, corticotropin-releasing hormone, glucocorticoids, and the immune/inflammatory response: Acute and chronic effects. Ann NY Acad Sci. 1999;876:1-11 (discussion 11-3).
24. Guzmán C, Hernández-Bello I, Morales-Montor J. Regulation of Steroidogenesis in Reproductive, Adrenal and Neural Tissues by Cytokines. The Open Neuroendocrinology Journal. 2010;3:161-169.
25. Burden HW. In: Catecholamines as hormone regulator. Ben-Jonathan N, Bahr JM, Weiner RI. (eds.). Serono Symposia Publications. Raven: New York; 1985.
26. Lara HE, Porcile A, Espinoza J, Romero C, Luza SM, Fuhrer J, Miranda C, Roblero L.

Release of norepinephrine from human ovary. Endocrine J. 2001;15;187-192.

27. Bornstein SR. Rutkowski H, Vrezas I. Cytokines and steroidogenesis. Molecular and Cellular Endocrinology. 2004;215(1-2): 135-141.
28. Dunn AJ, Chuluyan H. The role of cyclo-oxygenase and lipoxygenase in the interleukin-l-induced activation of the HPA axis: Dependence on the route of injection. Life Sci. 1992;51:219-225.
29. Smagin GN, Swiergiel AH, Dunn A. Peripheral administration of interleukin-1 increases extracellular concentrations of norepinephrine in rat hypothalamus: comparison with plasma corticosterone. Psychoneuroendocrinology. 1996;21:83-93.
30. Chuluyan H, Saphier D, Rohn W, Dunn AJ. Noradrenergic innervation of the hypothalamus participates in the adrenocortical responses to interleukin-1. Neuroendocrinology. 1992;56:106-111.
31. Besedovsky HO, del Rey A, Sorkin E. Lymphokine-containing supernatants from Con Astimulated cells increase corticosterone blood levels. J Immun. 1981;126:385-387.
32. Besedovsky HO, Del Rey A, Sorkin E, Lotz W, Schwulera U. Lymphoid cells produce an immunoregulatory glucocorticoid increasing factor (GIF) acting through the pituitary gland. Clin Exp Immun. 1986;59: 622-28.
33. Milutinović DV, Macut D, Božić I, Nestorov J, Damjanović S, Matić G. Hypothalamic-pituitary-adrenocortical axis hypersensitivity and glucocorticoid receptor expression and function in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes. 2011;119:636-43.
34. Angeli A, Masera RG, Sartori ML, Fortunati N, Racca S, Dovio A, Staurenghi A, Frairia R. Modulation by cytokines of glucocorticoid action. Ann N Y Acad Sci. 1999;876:210-20.
35. Mallappa Saroja CS, Hanji Chandrashekar S. Polycystic ovaries: Review of medical information on the internet for patients. Arch Gynecol Obstet. 2010;281:839-843.
36. DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril. 2005;83:1454-1460.
37. Solomon CG. Reducing cardiovascular risk in type 2 diabetes. N Engl J Med. 2003; 348:457-459.
38. Lansdown A, Rees DA. The sympathetic nervous system in polycystic ovary syndrome: A novel therapeutic target? Clin Endocrinol (Oxf). 2012;77:791-801.
39. Zangeneh FZ, Mohammadi A, Ejtemaeimehr Sh, Naghizadeh MM, Fatemeh A. The role of opioid system and its interaction with sympathetic nervous system in the processing of polycystic ovary syndrome modeling in rat. Arch Gynecol Obstet. 2011;283:885-92.
40. Zangeneh FZ, Abdollahi A, Tavassoli P, Naghizadeh MM. The effect of cold stress on polycystic ovary syndrome in rat: Before and during modeling. Arch Gynecol Obstet. 2011;284:651-7.
41. Gądek-Michalska A, Bugajski J. Interleukin-1 (IL-1) in stress-induced activation of limbic-hypothalamic-pituitary adrenal axis. Pharmacol Rep. 2010;62: 969-82.
42. Goshen I, Yirmiya R. Interleukin-1 (IL-1): A central regulator of stress responses. Front Neuroendocrinol. 2009;30:30-45.
43. Chen HF, Shew JY, Chao KH, Chang LJ, Ho HN, Yang YS. Luteinizing hormone up-regulates the expression of interleukin-1 beta mRNA in human granulosa-luteal cells. Am J Reprod Immunol. 2000;43: 125-33.
44. Baratta M, Basini G, Bussolati S, Tamanini C. Effects of interleukin-1 beta fragment (163-171) on progesterone and estradiol-17 beta release by bovine granulosa cells from different size follicles. Regul Pept. 1996;67:187-94.
45. Caillaud M, Gerard N. *In vivo* and *In vitro* effects of interleukin-1beta on equine oocyte maturation and on steroidogenesis and prostaglandin synthesis in granulosa and cumulus cells. Reprod Fertil Dev. 2009;21:265-73.
46. Kohen P, Castro A, Caballero-Campo P. Interleukin-1beta (IL-1beta) is a modulator of human luteal cell steroidogenesis: Localization of the IL type I system in the corpus luteum. J Clin Endocrinol Metab. 1999;84:4239-45.
47. Atsumi T, Singh R, Sabharwal L, Bando H, Meng J, Arima Y, Yamada M, Harada M, Jiang JJ, Kamimura D, Ogura H, Hirano T, Murakami M. Inflammation amplifier, a new paradigm in cancer biology. Cancer Res. 2014;74:8-14.

48. Mu Y, Liu J, Wang B, Wen Q, Wang J, Yan J, Zhou S, Ma X, Cao Y. Interleukin 1 beta (IL-1β) promoter C [-511] T polymorphism but not C [+3953] T polymorphism is associated with polycystic ovary syndrome. Endocrine. 2010;37:71-5.
49. Bosmann M, Meta F, Ruemmler R, Haggadone MD, Sarma JV, Zetoune FS, Ward PA. Regulation of IL-17 family members by adrenal hormones during experimental sepsis in mice. Am J Pathol. 2013;182:1124-30.
50. Ojeda-Ojeda M, Murri M, Insenser M, Escobar-Morreale HF. Mediators of low-grade chronic inflammation in polycystic ovary syndrome (PCOS). Curr Pharm Des. 2013;19:5775-91.

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