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GABA Dysfunction and Its Consequences in Women with Polycystic Ovary Syndrome

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ABSTRACT

Background and Objective: The GABA system plays an important role in the development, maturation, and function of gonadotropin-releasing hormone (GnRH)-secreting neurons, as well as in the coordination of reproductive and metabolic signals. Considering the emerging evidence in this area, dysfunction of the GABA system may be involved in the development of polycystic ovary syndrome (PCOS). The aim of this study is to summarize the available evidence on dysfunction of the GABA system and its implications for women with PCOS.

Methods: This systematic review was conducted using the keywords Gamma-Aminobutyric Acid (GABA), GABAergic pathway, PCOS and their related MeSH and searching for English articles from 2000 to 2023 in WOS, Embase, Scopus and PubMed databases. Articles that conducted clinical research on the relationship between GABA supplementation or the GABA pathway and PCOS were identified as relevant articles. The quality of the studies was assessed using the Newcastle-Ottawa tool.

Findings: A total of 260 articles were found in the initial search, of which only 7 were selected. There is evidence that GABA and PCOS are associated, but the causal direction and underlying mechanism are unclear. Some studies have shown that PCOS alters the levels or function of GABA in the blood or brain, leading to psychological and physiological consequences. On the other hand, GABA dysfunction affects amino acid metabolism and GnRH hormone signaling, helping to improve PCOS symptoms.

Conclusion: Based on the results of this study, GABA may play an important role in the pathophysiology of PCOS by regulating GnRH neurons and GABA inputs to them. GABA is also a signaling molecule in various tissues and organs outside the brain, and GABA pathways may affect GnRH neuron function and PCOS development through different mechanisms.

Keywords: *Polycystic Ovary Syndrome, Gamma-Aminobutyric Acid.*

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Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder in women, affecting 10-12% of women of reproductive age. It can be associated with sex hormone imbalance, irregular ovulation, and polycystic ovaries, as well as a variety of metabolic and non-metabolic complications (1, 2).

The exact cause of PCOS is not yet fully understood, but evidence suggests that dysfunction of the hypothalamic-pituitary-ovarian (HPO) axis, which regulates reproductive and metabolic functions in women (3, 4), as well as alterations in the secretion of gonadotropin-releasing hormone (GnRH), may play a role in its pathogenesis (1, 5).

GnRH is a hormone secreted by the hypothalamus in the brain. It signals the pituitary gland, a small gland at the base of the brain, to produce two other hormones called luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH are essential for follicle maturation and ovulation. Disruptions in GnRH rhythms can lead to an imbalance of LH and FSH. High LH can overstimulate the ovaries and overproduce androgens (male sex hormones). Low FSH can also cause defective follicle maturation and irregular ovulation (6, 7). The GABAergic system plays an important role in regulating GnRH secretion. GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that helps regulate the activity of GnRH neurons in the hypothalamus. Disruptions in the GABAergic system can lead to increased or decreased GnRH secretion (8, 9). In fact, the hypothalamic-pituitary-gonadal (HPG) axis controls the reproductive system in women. This axis is influenced by various factors, including neurotransmitters, neuropeptides, and hormones (estrogen, progesterone, etc.). However, if these factors are disrupted or deficient, it may lead to endocrine reproductive disorders such as PCOS (6, 10).

Recent studies have shown that women with PCOS have altered levels of GABA and GABAR in cerebrospinal fluid, plasma, and brain regions compared with healthy controls (8, 9, 11). Animal models of PCOS have also shown that GABAergic modulation can affect ovarian function and hormonal profiles. In this regard, there is evidence that treatment with GABAergic drugs can help improve PCOS symptoms (12, 13). Evidence suggests that GABA treatment can have an effect on insulin resistance and, consequently, on metabolic parameters and body weight (14). Given that the treatment of PCOS is usually symptomatic, researchers are now trying to identify the pathways involved in the pathophysiology of this disorder in order to develop effective drugs. Drugs that affect the neuroendocrine pathway have been one of the options chosen in recent studies (15).

The aim of this review article is to summarize the available evidence on the precise mechanisms by which GABAergic dysfunction leads to PCOS or PCOS leads to GABAergic dysfunction.

Methods

This systematic review article was conducted after approval by the Ethics Committee of Shahid Beheshti University of Medical Sciences with the code IR.SBMU.ENDOCRINE.REC.1402.028 based on the SANRA checklist. The Web of Science, Embase, Scopus, and PubMed databases were systematically searched to identify studies in English from 2000 to 2023 that investigated the effect of GABAergic pathway or GABA supplementation on PCOS. The search was performed using the keywords polycystic ovary syndrome, GABA and GABAergic pathway, and their related MeSH. Similar search methods were used for all databases, focusing on titles, abstracts, and keywords, and included clinical studies published in journals and studies that examined the relationship between the GABAergic pathway or GABA supplementation and PCOS in women with PCOS according to standard criteria.

Review articles, letters to the editor, case reports, case series, guidelines, books, etc., studies conducted in populations other than PCOS, studies that used replicated data and overlapping populations, and animal and cell studies were excluded.

Two reviewers independently assessed the methodological quality of the identified studies. First, they screened the titles and abstracts of all articles based on their relevance to the research question and inclusion/exclusion criteria. In case of disagreement between reviewers, agreement was reached by consensus and consultation with a third reviewer. After the initial screening, the full text of the selected articles was prepared and assessed by the same two reviewers for final inclusion or exclusion.

The quality of the included studies was assessed using the Newcastle-Ottawa case control scale (NOS) tool. Then, the two reviewers assessed the quality of the included studies based on specified criteria, including selection criteria, blinding, randomization, outcome assessment methods, and data analysis. The tool consists of eight criteria, which are divided into three categories: selection of study groups, comparability of groups, and determination of exposure to the factor or outcome of interest respectively for case-control or cohort studies. For each criterion, a study is given one star if it meets its conditions. Data from all relevant studies were independently reviewed by two reviewers. Information on author description, year of publication, study design, study site, sample size (total and per group), sample type, and main results were then categorized and summarized (Tables 1 and 2).

Table 1. Quality assessment of articles based on the Newcastle-Ottawa case control scale (NOS) tool

Study	selection	Comparability	Result	Total result
Amino acid signatures in relation to polycystic ovary syndrome and increased risk of different metabolic disturbances	***	**	**	7
Gut microbiota alterations reveal potential gut–brain axis changes in polycystic ovary syndrome	****	**	***	9
Polycystic Ovary Syndrome and Risk of Five Common Psychiatric Disorders Among European Women: A Two Sample Mendelian Randomization Study	***	**	***	8
Sexual function and depression in polycystic ovary syndrome: Is it associated with inflammation and neuromodulators?	**	*	**	5
Decreased Serum Level of Gamma-amino Butyric Acid in Egyptian Infertile Females with Polycystic Ovary Syndrome is Correlated with Dyslipidemia, Total Testosterone and 25(OH) Vitamin D Levels	**	*	**	5
Increased cerebrospinal fluid levels of GABA, testosterone and estradiol in women with polycystic ovary syndrome	**	*	**	5
Novel role for anti-Müllerian hormone in the regulation of GnRH neuron excitability and hormone secretion	**	*	**	5

Table 2. Human study on GABAergic pathway dysfunction in women with PCOS

First author, year, (reference)	Title	Type of study	Population	Study result
Radwan (9), 2019	Decreased Serum Level of Gamma-amino Butyric Acid in Egyptian Infertile Females with Polycystic Ovary Syndrome is Correlated with Dyslipidemia, Total Testosterone and 25(OH) Vitamin D Levels	Clinical (Case-control)	Egyptian, 20-35 years old, 18 PCOS patients and 18 age-matched healthy women	The findings of this study suggest that impaired GABA levels in the peripheral circulation are an additional contributing factor to the manifestations of PCOS. GABA deficiency was associated with 25(OH) vitamin D deficiency, dyslipidemia, and total testosterone.
Liang, 2021 (16|)	Gut microbiota alterations reveal potential gut-brain axis changes in polycystic ovary syndrome	Clinical (Case-Control) Han Chinese Female Population	Female population 18-40 years (Total population 40, 20 controls and 20 PCOS)	Dietary analysis revealed that fiber and vitamin D intake were significantly reduced in PCOS. For the first time, our study discovered an increase in gamma-aminobutyric acid (GABA)-producing species in PCOS, including Parabacteroides distasonis, Bacteroides fragilis, and Escherichia coli, which were positively and significantly correlated with serum LH levels and LH:FSH ratio.
Kawwass, 2017 (17)	Increased cerebrospinal fluid levels of GABA, testosterone and estradiol in women with polycystic ovary syndrome	Clinical (Case-control)	Population 18-35 years old 12 women with polycystic ovary syndrome (PCOS) compared to 15 amenorrhea and ovulation (EW) women	Women with polycystic ovary syndrome showed higher CSF levels of GABA and E2, and possibly T, than amenorrhea cases.
Ye, 2022 (18)	Amino acid signatures in relation to polycystic ovary syndrome and increased risk of different metabolic disturbances	Clinical (cross-sectional), Chinese (Han) female population	Chinese (Han) female population, 20-35 years old (Total population: 380, 190 PCOS and 190 control) (Sample: Plasma)	Women with PCOS suffer from severe disruption of amino acid metabolism. The combination of alanine, valine, leucine, tyrosine, glutamic acid, cysteine, and glycine has shown potential to predict the risk of metabolic syndrome in women with PCOS. Increased levels of branched-chain amino acids, tyrosine, alanine, and lysine were correlated with insulin resistance in the PCOS group.

				Alterations in tyrosine, lysine, methionine, hydroxyarginine, 3-methylhistidine, GABA, methylhistidine, and glycine were associated with obesity in women with PCOS.
Cimino, 2016 (19)	Novel role for anti-Müllerian hormone in the regulation of GnRH neuron excitability and hormone secretion	Clinical (laboratory)	Human embryo (9^{th} week of pregnancy)	Increased LH pulsatility is an important pathophysiological feature in many cases of polycystic ovary syndrome (PCOS), the most common cause of female infertility, in which circulating AMH levels are also often elevated. AMH-dependent regulation of GnRH release may play a role in the pathophysiology of fertility and may have therapeutic potential for the treatment of PCOS.
Jin, 2021 (20)	Polycystic Ovary Syndrome and Risk of Five Common Psychiatric Disorders Among European Women: A Two Sample Mendelian Randomization Study	Clinical (Mendelian randomization)	Genetic variants from genome-wide association study data in European populations	In European populations, PCOS may be a risk factor for obsessive-compulsive disorder, but not anxiety disorder, bipolar disorder, major depressive disorder, or schizophrenia.
Aydogan Kirmizi, 2020 (21)	Sexual function and depression in polycystic ovary syndrome: Is it associated with inflammation and neuromodulators?	Clinical (Case-control)	The total population was 80 people aged 18-40 years, 20 fertile patients and 30 infertile patients diagnosed with PCOS and 30 healthy volunteers.	The study found that PCOS patients had higher levels of inflammatory and depressive markers than healthy controls. Depression severity was associated with lower levels of GABA and BDNF and higher levels of glutamate and inflammatory markers. Obesity and waist-to-hip ratio (WHR) were risk factors for sexual dysfunction, but no association was found between sexual function and inflammatory or depressive markers.

Results

260 articles were found, of which 165 duplicate articles were removed, leaving 92 articles, of which 84 articles included review articles, conference abstracts, book chapters, cell and animal studies, which were removed from the study, and finally 7 articles, all of which were clinically relevant, remained (Diagram 1).

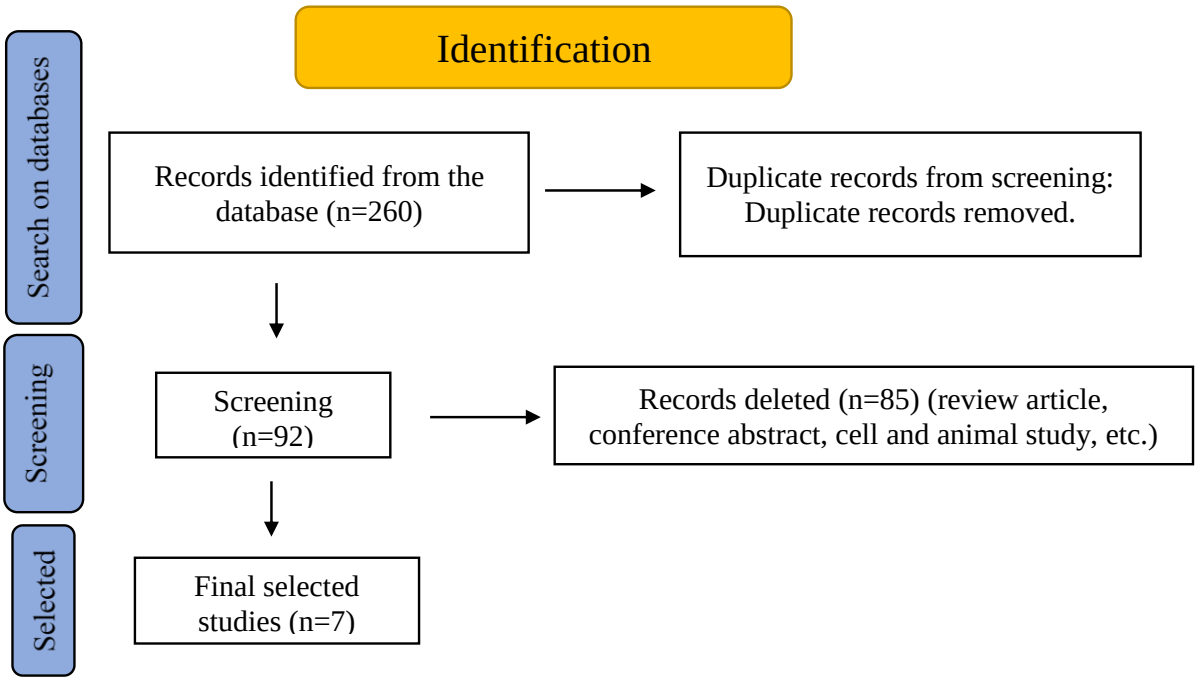

Diagram 1. Prism diagram

The clinical studies reviewed in this study included a population of 563 people, ranging in age from 18 to 40 years, and were mostly Chinese and European women. GABA is a brain chemical that is involved in many brain functions, such as emotion, stress, sleep, and hormone regulation. PCOS is a disorder that negatively affects hormones and fertility and is associated with impaired amino acid metabolism. There is evidence that GABA and PCOS are linked, but the pathway and cause of this link are not clear.

The first hypothesis is that PCOS causes GABA disruption. The main question is how can PCOS alter the levels or function of GABA, an important neurotransmitter, in the blood or brain?

It has been observed that women with PCOS who consume less dietary fiber and vitamin D have higher levels of certain gut bacteria that produce GABA. These bacteria are associated with certain ovarian hormones, called LH and the LH:FSH ratio (16). Results show that women with PCOS have lower blood GABA levels. Blood GABA levels are correlated with weight, vitamin D levels, and testosterone levels in the blood (9). In another study, results showed that women with PCOS have higher levels of GABA, estradiol, and possibly testosterone (17).

The second hypothesis is that GABA causes or exacerbates PCOS, the main question is how could GABA contribute to the symptoms or mechanism of PCOS or its infertility?

Studies have shown that women with PCOS have higher levels of some amino acids, which can be indicators of metabolic syndrome risk. High levels of some of these amino acids have been associated with insulin resistance, a common consequence of PCOS (18). GABA in the brain also reduces the secretion of GnRH/LH. GnRH/LH are hormones that stimulate the growth and release of eggs, and in women with PCOS, GnRH/LH secretion is higher, causing sex hormone abnormalities (22). AMH, on the other hand, increases the secretion of GnRH/LH. Women with PCOS also have higher levels of AMH in the blood. This suggests that AMH may be involved in the mechanism of PCOS infertility and may be a suitable therapeutic target (19) (Table 1). Dysfunction of the GABAergic system and its effect on various organs causes an increase in intestinal microbiota, and also causes disruption in the GnRH pathway, where an increase in GnRH causes symptoms of PCOS and a decrease in GnRH causes an increase in the hormone LH and a decrease in the hormone FSH. Moreover, dysfunction of the GABAergic system leads to dysfunction of the reproductive system and causes an increase in cysts in the ovaries (Figure 1).

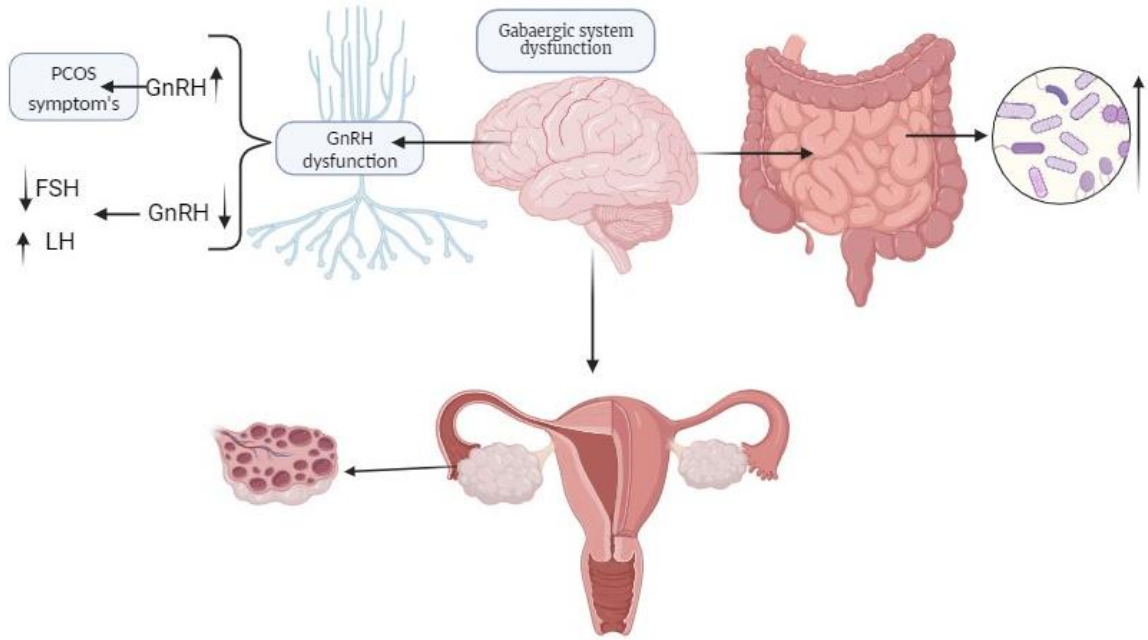

Figure 1. Dysfunction of the GABAergic system and its effect on various organs

Discussion

The results showed that there is evidence of a link between GABA and PCOS, but the direction and mechanism of this relationship are unclear. PCOS may alter the levels or function of GABA, which is an important neurotransmitter in the blood or brain. This may be due to factors such as diet, gut microbiota, vitamin D status, and sex hormone levels. Some studies have shown lower blood GABA levels in women with polycystic ovary syndrome who also had dyslipidemia and low vitamin D levels, compared with healthy women, while others have found higher levels. On the other hand, GABA may contribute to the development or exacerbation of PCOS symptoms or its pathophysiology. This may be due to factors such as amino acid metabolism, insulin resistance, and GnRH/LH secretion. Furthermore, higher levels of some amino acids can predict the risk of metabolic syndrome in women with PCOS. Moreover, GABA in the brain may reduce GnRH/LH secretion. In women with PCOS, GnRH/LH secretion is higher, causing an imbalance in sex hormones (9, 16-21).

Evidence suggests that the brain may play a role in the pathophysiology of PCOS (11). Unraveling this connection could provide valuable insights into how neurotransmitter abnormalities contribute to metabolic and reproductive abnormalities in individuals with PCOS. Research has shown that increased GABA signaling in the Arcuate Nucleus of the Hypothalamus (ARN) can stimulate the reproductive axis and contribute to reproductive dysfunction such as PCOS. Furthermore, GABA levels may be increased in the cerebrospinal fluid (CSF) of women with PCOS (12). Results from another study suggest that increased excitatory (glutamate) signaling and decreased inhibitory currents (serotonin, dopamine, GABA, and acetylcholine) may be responsible for the increased pulsatility of GnRH and LH, leading to an increased LH/FSH ratio in PCOS. It is also evident that the observed changes in brain neurotransmitter levels are mainly due to changes in their catabolism rates. Furthermore, the disturbed neurotransmitter profile in polycystic ovary syndrome may be a reason for the occurrence of low self-esteem, anxiety, frequent mood swings, and depression in PCOS women. Neurotransmitter modulation may act as a key feature in the development of PCOS pathology by increasing the risk of other comorbidities such as stress and mood (23).

In women with PCOS, abnormalities in GABA signaling pathways may potentially influence the onset or progression of PCOS symptoms. Research has shown that the hormonal imbalances characteristic of PCOS can affect neurotransmitter systems, including GABAergic pathways. Altered levels or activity of GABA receptors have been observed in animal models with features resembling PCOS, suggesting a possible link between impaired GABA function and aspects of this endocrine disorder. One study has suggested a potential link between aberrant GABA receptor expression and specific PCOS-related manifestations such as insulin resistance or abnormal ovarian function (24).

GABAergic activity on GnRH neurons, which can respond to GABA actions via GABAAR by stimulation, may be a contributing factor to the hyperactive GnRH/LH system observed in PCOS (12). Furthermore, GABA treatment has been shown protective effects in PCOS models, providing beneficial effects by reducing insulin resistance and improving reproductive function (25). In a study among 84 women with PCOS, melatonin and/or magnesium supplementation for 8 weeks improved their metabolism and hormones. Both melatonin and magnesium are involved in the production or utilization of GABA. Melatonin and magnesium supplementation reduced blood glucose levels, impaired blood sugar, cholesterol, bad cholesterol, male hormones, and increased good cholesterol and female hormones. Melatonin and magnesium supplementation also improved their sleep quality. The positive effects of melatonin and magnesium may be because they increase GABA transmission or because they have antioxidant or anti-inflammatory properties (26).

The cause-and-effect relationship between GABA dysfunction and PCOS is not clear. It is possible that both GABA dysfunction and PCOS are caused by something else, such as genetics or the environment. It is also possible that GABA dysfunction occurs before PCOS develops, or that it is caused by changes in how GnRH neurons work or how other parts of the body work. Perhaps PCOS causes or worsens GABA dysfunction by changing how sex hormones perform or how metabolism works. The temporal and causal relations between GABA dysfunction and PCOS may vary for different people or at different stages of the disease. More studies are needed to find out if GABA dysfunction is linked to PCOS.

Heterogeneity between studies in terms of study design and participant characteristics limited the ability to draw unified conclusions from the studies. Moreover, considering the importance of different PCOS phenotypes, the existing studies did not investigate the role of phenotypes in GABA pathway dysfunction, and it is recommended that future studies address this issue. One of the strengths of the study is that summarizing the existing evidence on this topic is an introduction to creating new hypotheses for future studies.

In addition to affecting GnRH neurons through GABA receptors, GABA may have an effective role in reproduction. That's because GABA is also synthesized and released in tissues outside the brain such as the intestine, pancreas, and placenta. As a result, the GABAergic pathway may be a therapeutic target for improving polycystic ovary syndrome in women.

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