Alterations in neuroendocrine levels and gut microbiota contributing to potential psychiatric disorder prevalence in PCOS: a Review

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Abstract

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder in women, affecting up to 15% of women in the reproductive age. [35]-[36] PCOS is a heterogeneous disorder, meaning that there are many different factors that may play a role in the manifestations of this disease, and multiple systems throughout the body can be affected. Studies have shown that PCOS can be linked to multiple psychiatric disorders. The prevalence of anxiety and depression are significantly higher in females with PCOS compared to females without PCOS. [35]-[36] Currently, there are several theories discussing the possible causes of the connection between PCOS and psychiatric disorders. Certain causes such as the overactive hypothalamic-pituitary-adrenal axis (HPA axis) or the hypothalamic-pituitary-ovarian axis (HPO axis) found in PCOS could be linked to an altered hormonal profile that manifests as anxiety and depression. Another theory speculates that the altered levels of neurotransmitters and the gut-brain axis dictate the severity and frequency of psychiatric disorders in PCOS. Dietary supplements such as vitamin D and selenium paired with a probiotic have shown to improve neurotransmitter levels as well as significantly reduce the effects of mental distress and manifestations of PCOS symptoms. This approach introduces the possibility of gut nutrient deficiencies in PCOS causing psychiatric disorders. In this review, I will examine different theories on association between PCOS and psychiatric disorders. [35]-[36]

Introduction

Polycystic ovarian syndrome (PCOS) affects a large population of women worldwide. It is estimated that 6% to 12%15% of women of reproductive age are affected by PCOS, and it is a complex condition that has severe consequences if left undiagnosed or unmanaged.[35]-[36] PCOS is often diagnosed following criteria set by National Institute of Health (NIH). The NIH states that PCOS is diagnosed if two out of the following symptoms are presented: irregular menses, polycystic ovaries, and hyperandrogenism. [34]-[35]-[36] PCOS usually manifests before or during the first menstrual cycle, although patients are not usually diagnosed until after it occurs.[35]

PCOS is highly associated with multiple gynecologic, metabolic, and endocrine dysfunction that leads to clinical manifestations of hirsutism, infertility, and insulin resistance. [35]-[36] Due to such nature, it is important for health care providers to evaluate and treat all commonly associated comorbidities in PCOS patients. While mental disorders are known to be a manifestation of PCOS, they often go undiagnosed. Psychiatric disorder prevalence is associated with chemical imbalance, but may be a result of altered hormones, neurotransmitter

dysfunction, and even diet.[10]-[11]-[20]-[21] It is important to consider that it is crucial to look for the presentation of these disorders in PCOS.

There are many commonly observed psychiatric disorders associated with PCOS, including depression, generalized anxiety, social phobia, attention deficit hyperactivity disorder (ADHD), and obsessive-compulsive disorder (OCD).[32] The higher prevalence of these disorders in PCOS could be linked to neuroendocrine dysfunction.[32] The gonadotropin releasing hormone (GnRH) is a hormone that controls production of luteinizing hormone (LH) and follicle stimulating hormone (FSH). The frequency at which GnRH is released in the hypothalamus is abnormal in PCOS. GnRH can moderate how much LH and FSH are produced by how quickly it is being released at varying intervals. LH and FSH are hormones that play crucial roles in regulating the gonadal and follicular regions of the body. In PCOS, there is hyperactivity of the GnRH pulse generator, leading to high levels of LH and FSH and altered neuroendocrine system. When the neuroendocrine system is altered, many psychiatric changes may be observed. In the case of PCOS, the dysregulation caused by the disrupted GnRH pulse frequency and the consequent axis may lead to psychiatric disorders originating from hormones produced by these axes, LH and FSH.

Recently, there has been a shift in evaluating PCOS. It is now considered a multisystemic condition rather than just gynecologic and endocrine condition.[21] The impact of input into the gastrointestinal (GI) tract as well as short-term appetite and food intake can be regulated by the hypothalamus, and PCOS can directly affect this process. The GI tract is in fact an important endocrine organ that is the source of a variety of hormones that regulate metabolism throughout the body. Additionally, the GI tract is a peripheral secretor of neurotransmitters that are found across multiple brain regions. The multiple involvement of the GI function and its role in neurotransmitter secretion supports its direct role in brain function. Therefore, an altered gut-brain axis in PCOS may contribute to the development of GI disorders as well as psychiatric disorders through abnormal gut microbiota and dysregulated gut hormones.[19]-[21]-[24]

In this paper, I will be discussing potential biological causes of an increased prevalence of neuropsychiatric disorders associated with PCOS. More specifically, the gut-brain axis, HPA/O axis, and the hormone imbalances in PCOS. This is an area that is lacking in research, as many previously published articles are focused on the psychosocial aspect of PCOS that causes psychiatric disorders. By reviewing the existing literature on the topics covered in this paper, I was able to generate a comprehensive review that expands on the existing resources about this topic.

The HPA and HPO axes in PCOS

The two main hormonal axes altered in PCOS are the Hypothalamic-Pituitary-Adrenal (HPA) axis and the Hypothalamic-Pituitary-Ovarian (HPO) axis. Within each axis, there are multiple organs involved in multidirectional communication, thus have interconnected functions. Due to this nature, the brain regions within the HPA and HPO can be affected by PCOS-induced

dysfunctions of other organ within the axes (Figure 1). Both the HPA and HPO axes begin in the hypothalamus. This part of the brain controls vital aspects of both the autonomic nervous system and the actions of the pituitary gland which sits below it. The hypothalamus controls functions such as sleep, blood pressure, temperature, hunger, and thirst via secretion of a variety of hormones. These hormones include growth hormone releasing hormone (GHRH), corticotropin releasing hormone (CRH), thyrotropin releasing hormone (TRH), dopamine, and GnRH.

In the case of the HPO axis, GnRH is the primary hormone involved in signaling the pituitary gland.[9]-[25] The pituitary gland receives the GnRH signals from the hypothalamus and then produces hormones itself. The amount and type of hormone the pituitary gland secretes is directly dependent on the pulsatile frequency of the GnRH from the hypothalamus.[26] The two types of hormones that can be released include LH and FSH, which are used to signal to the ovaries. When the level of LH increases, it triggers the ovaries to ovulate and to release eggs. When FSH level rises, it aids in the development of eggs in the ovaries as well as increases the estrogen levels in the body. [36] This signaling mechanism also works in the opposite direction. The hormone levels secreted in the ovaries can provide feedback back to the hypothalamus and pituitary gland to modulate their functions. In PCOS, the excess in androgen production is linked to LH hypersecretion and impaired hypothalamic-pituitary feedback.[36] Women with PCOS have increased LH pulse frequency, LH pulse amplitude, and increased LH/FSH ratios. Because of this, estrogen is dysregulated, and is sometimes underproduced in PCOS. Estrogen moderates many aspects of the HPO axis and is even suggested to have an antipsychotic effect. A decrease in estrogen could possibly lead to a higher risk of developing psychosis and psychotic disorders alongside other neuropsychiatric disorders. Along with this, studies show that women with psychotic disorders exhibit PCOS like symptoms such as menstrual irregularity.[11] The increase in reproductive hormones does not only affect the levels of estrogen, but also greatly increases the androgen production in the body. This androgen excess and a distorted HPO axis leads to the classic phenotype of enlarged ovaries with a string-of-pearl morphology and theca interstitial hyperplasia (the common pathological symptoms of the ovaries in PCOS).[36] The effect that hyperandrogenism has upon the body is not limited to the ovaries. Hyperandrogenemia can affect hair loss, acne, unwanted hair growth, and even changes in mental health. Studies have shown that hyperandrogenemia is associated with higher depression scores in older women with PCOS. Additionally, the study showed that women with PCOS and anxiety have higher free testosterone levels compared to women with PCOS and no anxiety.[8]

While the HPO axis is related to the overproduction of androgens like testosterone, the HPA axis plays a role in controlling other androgenic hormones that can be observed affecting mental health as well. Dehydroepiandrosterone (DHEA) is a HPA hormone that is produced in the adrenal gland. Similarly to GnRH, DHEA is a precursor hormone and can be converted to androgens. The adrenal cortex synthesizes dehydroepiandrosterone sulfate (DHEAS) from DHEA.[3] This conversion begins the process of creating androgens in the HPA axis. High levels

of DHEAS are the main cause of PCOS-like symptoms such as hyperandrogenism and even inhibited estrogen levels. Due to this, DHEA is prevalent in the development and manifestations of PCOS, as well as in neuropsychiatric disorders. As previously discussed, high androgens can cause serious psychological effects that usually cause changes in preexisting psychiatric disorders.[3] Balikci et. al. shows a significant correlation between the anxiety scores and the serum levels of DHEA. This supports the theory that anxiety symptoms result from increased DHEA and the hyperandrogenism it causes in patients with PCOS.[3] Most of the time, our important decisions, feelings, and actions stem from the level of stress that we are experiencing. You might wonder how it biologically occurs, and how it is related to PCOS. This can be answered by many things which have been discussed in this paper already: neurons, what you eat, and your unique hormonal makeup. When considering this interaction, we must also accept that the HPA axis is essential in most stress, but the hypothalamus and pituitary glands aren't the only sections of the brain involved in this process. At the start of the stress response the amygdala, the gray matter in charge of processing fearful stimuli, stimulates brain stem neurons. This inhibits the parasympathetic nervous system, excites the sympathetic nervous system, and releases epinephrine and norepinephrine throughout the body (Which will be later discussed in the neurotransmitter section). Understanding this interaction helps us grasp how the brain works harmoniously to react to stressful stimuli. At the same time, the amygdala also excites a group of neurons in the paraventricular nucleus (PVN), which is in the hypothalamus. These PVN neurons send messages to the base of the hypothalamus and increase the production of CRH. As previously discussed, CRH causes the pituitary gland to release ACTH and then acts in the adrenal glands to increase glucocorticoid (i.e., Cortisol) secretion. PCOS patients that have an overactive HPA axis have increased cortisol turnover. The influx of cortisol may increase anxiety and stress response.[25]

The typical emotional response to the sudden increase in glucocorticoids and sympathetic nervous system activity is what is known as a "fight or flight" response. This is useful when looking at it from a survival standpoint, since these biological processes help an animal maintain energy, be more alert, and prepare the body for physical exertion. This commonly means that there is a sharp increase in blood pressure and heart rate, which is extremely beneficial for running away from danger. Unfortunately, this response is what is seen in patients with anxiety, but in a chronic manner. Furthermore, this form of chronic anxiety leads to oligomenorrhea, amenorrhea, and even hyperandrogenism. In that case, if the adrenal regulation of glucocorticoids is abnormal, could PCOS be caused by that? The possibility is quite likely, given that so many of these symptoms are analogous with PCOS symptoms.[37]

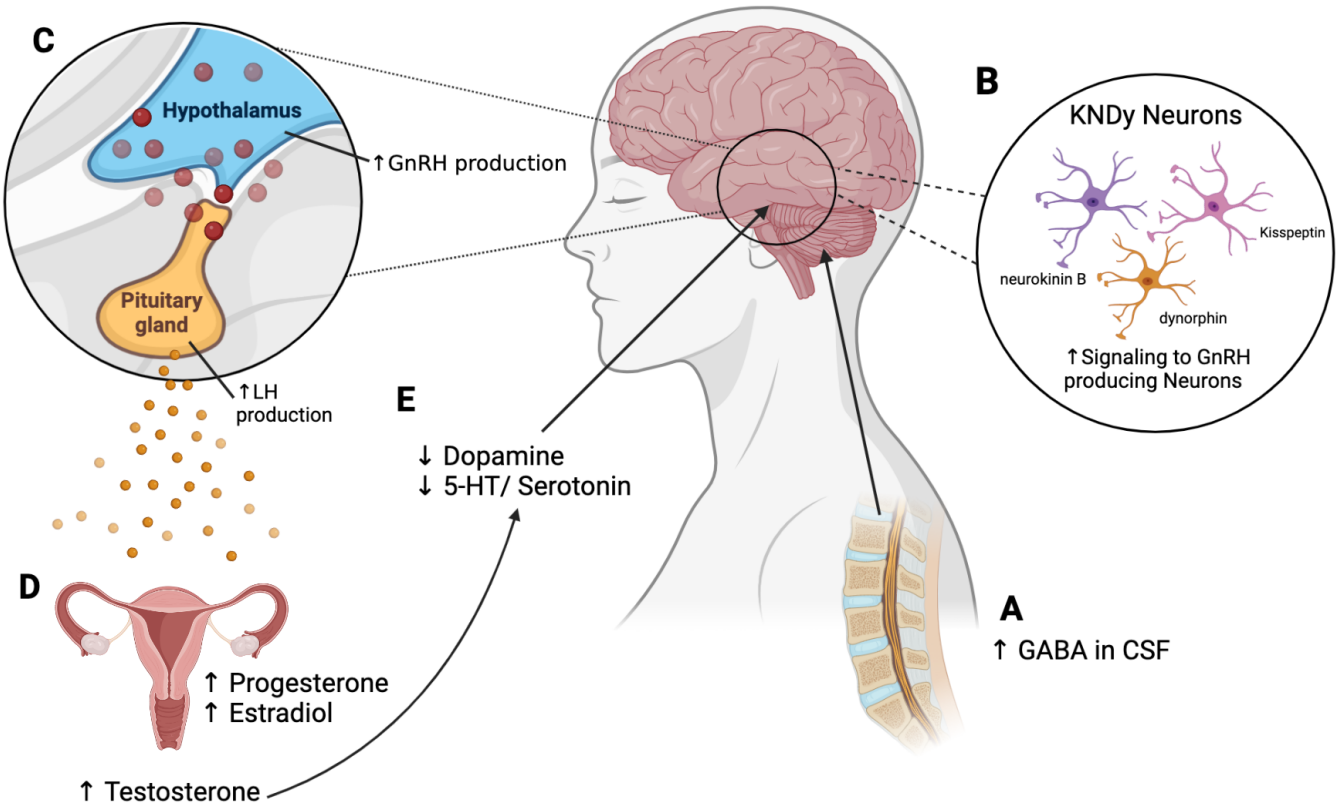

Figure 1. Neurotransmitter and Neuropeptide Relationships with the HPO Axis in Polycystic Ovarian Syndrome. (A) PCOS patients sometimes have higher levels of GABA found in CSF. These high levels cause dysfunctional GABAergic neurons which can regulate anxiety and fear. (B) The high levels of GABA being secreted cause the dysfunction of KNDy neurons which are commonly found centrally in the brain. The altered signaling of these neurons causes the hypothalamus to start producing more GnRH. (C) The increase of GnRH increases secretion of LH. (D) Increased LH upregulates the production of progesterone, estradiol, and testosterone. (E) The abnormal increase in testosterone decreases dopamine and serotonin levels in the bloodstream and the brain.[25]-[34]-[36]

Neurotransmitter differences in PCOS associated with neuropsychiatric disorders

Neurotransmitters are chemicals of the nervous system that act as the body's messengers. They are essential to the functioning of the body, and when atypical can cause pathological concerns. If the neurotransmitter physiology in the brain is dysregulated, it may have a strong psychological impact. This phenomenon is something commonly observed in PCOS patients with neuropsychiatric disorders.[34] The arcuate nucleus of the hypothalamus, also known as the ARC, is composed of multiple types of neurons and regulates hunger, metabolism, and the onset of puberty. Neurons in the ARC secrete neuropeptides named kisspeptin, neurokinin B, and dynorphin. As seen in Figure 1, this group of neurons is called the KNDy neurons after what they secrete. The KNDy neurons are what activate the GnRH pulse generator in the hypothalamus. The KNDy neurons are activated by hormonal inputs alongside the deactivation of inhibitory inputs. This process of neuronal activation is what initiates the increased GnRH secretion from the hypothalamus. The whole process is slow, since neuropeptides are a larger class of neurotransmitters, so this acts as the upstream regulator of the GnRH pathway. [25]-[34]-[36] In PCOS the signaling of the GnRH pathway is dysregulated. Researchers speculate that this may be caused by abnormal levels of neuropeptides secreted by KNDy neurons. Studies show that in cases of abnormal KNDy neuropeptide production, there is a possible psychological impact since dynorphin, kisspeptin, and neurokinin B all function as regulators of behavior and mood neuroendocrine processes. [25]-[34]-[36] Neuropeptides aren't the only group of neurotransmitters that could be important in the development of PCOS and neuropsychiatric disorders. Monoamine neurotransmitters are also important substances in the central nervous system and are involved in many physiological activities. Some examples of well-known monoamine neurotransmitters are serotonin (5-HT), norepinephrine (NE), and dopamine (DA). These neurotransmitters assist in things like learning, emotion, and memory. Furthermore, they aid in the GnRH release pathway, so disturbed monoamine neurotransmitters may lead to PCOS symptoms. In addition to this, a decrease in monoamine neurotransmitters, specifically NE, 5-HT, and DA, play a crucial role in the development of neuropsychiatric disorders. Studies done have shown NE and epinephrine to be significantly decreased in the hypothalamus and pituitary glands of PCOS models. This is a significant finding that could show a deeper link between neurotransmitters and psychiatric disease in PCOS. Low NE and epinephrine can result in mental symptoms of anxiety, depression, and chronic stress.[21] DA is a neurotransmitter that plays a role in the brain's pleasure and reward system. It is a major suppressor of the GnRH release pathway; therefore, it is usually lowered in PCOS patients. Low DA is characterized by increased fatigue, stress, and depressive mood. Similarly, newer studies suggest that 5-HT plays a role in the GnRH regulation pathway. It works both to stimulate and suppress the GnRH pathway, yet studies show that 5-HT is decreased in the hypothalamus and pituitary of PCOS models. This may be due to the high testosterone levels. 5-HT may be related

to the development of major depressive disorder, as many antidepressants work by increasing the reuptake of serotonin.[21]

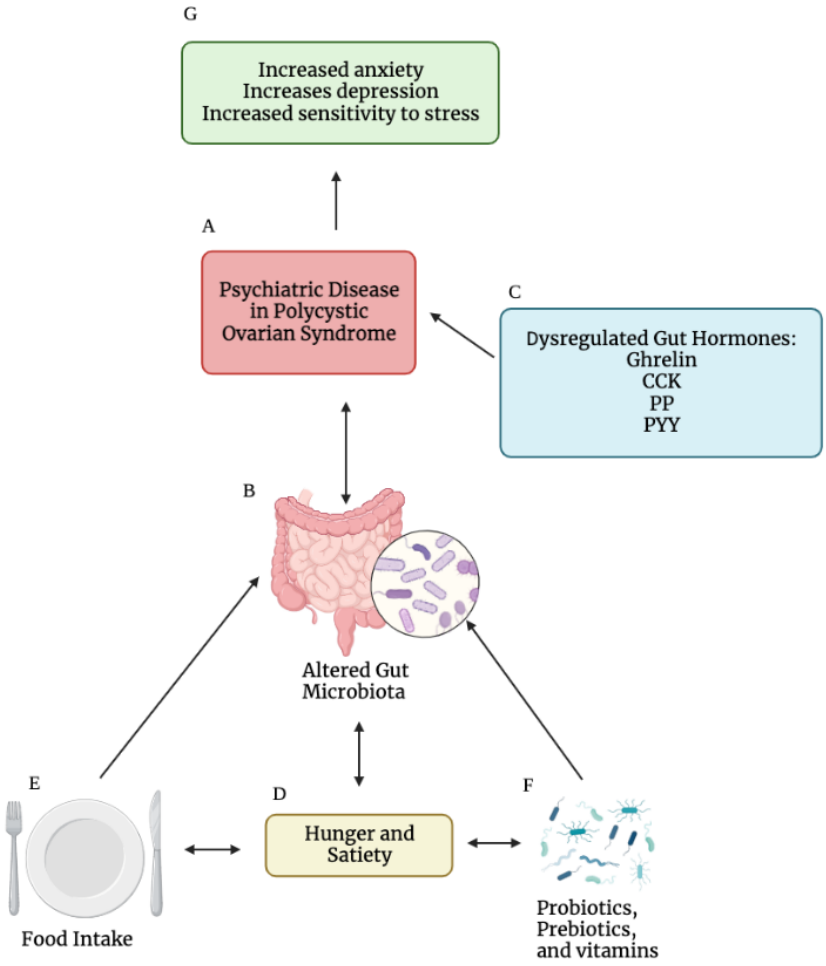

Figure 2. Gut Brain Connection in PCOS. (A) PCOS is central to this figure because it shows how the disease interacts with the gastrointestinal tract. (B) Gut Bacteria levels can be abnormal in PCOS and can contribute to PCOS. (C) These hormones can cause PCOS and PCOS-like symptoms. (D) Hunger and satiety affect the voluntary intake of nutrients into the body. (E) The type and amount of food consumed by a person. (F) microbiota and dietary supplements added to a diet. Impact preexisting microbiota in the gut. (G) The result of PCOS being unmanaged and the development of psychiatric disease.[26]-[31]

Gut-Brain Pathways in PCOS

One of the most complicated and fascinating connections in the body is between the gastrointestinal tract and the brain. Not only does this pathway contribute to our lives through our metabolism, but it has been shown to be linked to crucial aspects of underlying health changes, hormones, and emotion. Though the notion of the gut-brain axis has been around for a significant amount of time, scientists have only recently been honing in on the possibilities this may hold for new advances in healthcare. One of the newer areas of research that has stemmed from these recent discoveries is the impact that the gut has on the prevalence and severity of PCOS and its symptoms.

In the short term, food intake as well as appetite can be regulated through the hypothalamus alongside certain GI tract signals. This mechanism is only possible because the majority of gut neuropeptides are regulated through the hypothalamus. In the case of many patients with neuropsychiatric disorders, a change in diet may even prove to help balance their symptoms; this is only possible because of how involved the hypothalamus is in affecting mood through hormones. Some research shows that alternatively, neuropsychiatric disorders may arise as a result of the diet not being composed of enough nutrients. Though commonly overlooked in a typical ‘western’ diet, the specific vitamins that are consumed aid in a plethora of body systems.[26]-[31] When there is a deficiency of vitamins the immune system, nervous system, and even skeletal system can become impaired which can lead to serious diseases. In addition to this, new studies show that PCOS symptoms and depression may be linked to a deficiency of vitamin D. The aim of this study was to assess different biological parameters that can be linked to an increase in stress, hormonal dysfunction, and neuropsychiatric changes with the co-administration of vitamin D and probiotics. What these researchers found was that after 12 weeks, the women with PCOS showed significantly better mental health parameters, hormonal tests, and hirsutism prevalence.[26]-[31] This experiment was tried with selenium and probiotics; the researchers got very similar results. This is a significant finding since PCOS had not been previously studied in such a way that focused on specific vitamin intake. Besides that, it is intriguing because it targeted the gut brain axis in a specific way: through the gut microbiome. The administration of probiotics supports a very widespread biological idea that the specific microorganisms lining and living in the digestive tract play a role in digestion and metabolism. Through many modern studies on this phenomenon, it has been figured out that the gut microbiota are important influencers of the gut-brain axis and neurotransmitter secretory neurons. As discussed previously, GABA is an influential neurotransmitter that, when altered, can increase the occurrence or severity of psychiatric disorders. Certain strains of gut bacteria that have been shown to alter GABA concentration in CSF have been found in higher

concentrations in PCOS patients. This expands the possibility of psychiatric disorders in PCOS being caused by a link between the GI tract and the brain.[34]

Similarly, to the other topics discussed in this paper, the hormones that play a role in the gut may affect mood and prevalence of neuropsychiatric disorders. As seen in Figure 2, ghrelin levels are increased, cholecystokinin (CCK) levels are decreased, and PYY levels are decreased in women with PCOS. These abnormal hormone levels are most likely due to the close link between the brain regions of the hypothalamus and pituitary gland. Because they are dysfunctional in PCOS they affect these neuropeptides as a result. Three members of the NPY family (a group of biologically active peptides) are NPY, PPY, and pancreatic polypeptide (PP). These peptides are expressed by specific levels in the gut-brain axis, starting in the endocrine cells in the GI tract.[19]-[21]-[23] These peptides are useful in the communication of information for the gut-brain axis because there are a series of five receptor types found along signaling pathways in the axis. Furthermore, these gut hormones are crucial in the neurological processes of energy homeostasis, mood, anxiety, and stress tolerance. Some of these hormones are released peripherally, through the intestines, but the others are prevalent within the brain. Specifically, NPY is the most abundant neuropeptide in the brain. It is found throughout multiple brain regions including (but not limited to) the hypothalamus, hippocampus, amygdala, basal ganglia, cerebral cortex, and medulla. Its ubiquity throughout the brain is what allows this neuropeptide to strongly impact neuropsychological factors and symptoms. [19]-[21]-[23] Animal experiments have been done to prove this link, and they confirm that NPY is involved in stress, and can have an anti-anxiety effect. The neuropeptides in this section all act in various, but similar ways to alter the mood. Another factor to consider in patients with PCOS is the relation between commonly known hormones such as ghrelin, and their roles in regulating the neuropeptides in the gut. Ghrelin is primarily known to many as the ‘hunger hormone’. [19]-[21]-[23] While this is not entirely false, ghrelin acts in a variety of ways that have little to do with the actual feeling of hunger. The hypothalamus has been established as the main source of ghrelin in the central nervous system, which once again links this hormone back to the hypothalamic-pituitary axis. Researchers have found that ghrelin frequently works to excite neurotransmitter secretors and gene expression throughout the entire brain. One of the links they found was between ghrelin and CRH, a critical hormone in the HPA axis. Ghrelin has also recently interested researchers due to its potential role in the cholinergic-dopaminergic reward link, a pathway designed for neurotransmitters to control motivation, goal setting, and rewarding behavior. In this way, ghrelin may affect dopamine producing neurons and its receptors. The other neuropeptides may have an effect on neurotransmitter secreting neurons, but researchers are still unsure. It has been observed that PYY and PP both act to decrease depressive behavior in patients suffering with a psychiatric disorder, and CCK has been found to increase anxiety-like behavior when at abnormal levels. [19]-[21]-[23]

Conclusion

It is essential to understand that each system discussed in this paper is interconnected to the point where even the tiniest alteration could influence the other systems drastically. Because PCOS is multisystemic it is important to observe it in such a way that nothing is isolated in its explanation. For example, neurotransmitters such as DA and NE may act as mood regulators in the brain, but can contribute to feelings of hunger and satiety as neuropeptides do in the gut-brain connection. Ultimately these connections need to be understood to advance the care and research of PCOS. It is important for healthcare providers to be aware of the psychiatric risks PCOS patients have: onset of or exacerbated anxiety or depression, bipolar disorder, borderline personality disorder, as well as other mood disorders to be more specific. This article highlights the central multisystemic aspects of PCOS and its connection to psychiatric health from a biological standpoint. Future research must be continued to broaden our understanding of the matter, specifically for neurotransmitters and the gut brain axis. This research is important beyond the scientific aspect because patients need to be aware of the full risks that come along with PCOS. Increased awareness may also lead to new treatment options and prevention education amongst vulnerable groups.

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