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Neuroendocrine Impairments in PCOS: Pathogenesis and Therapeutic Interventions

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ABSTRACT

Anovulatory infertility is primarily caused by the endocrine complication known as polycystic ovarian syndrome (PCOS). PCOS, which is characterized by hyperandrogenism, irregular periods, and polycystic ovaries, which is a multifaceted condition that is unlikely to have a single common cause. The brain is becoming a key candidate in both the ontogeny and pathophysiology of PCOS, despite the fact that it is still typically thought of as an ovarian disease. Impaired gonadal steroid hormone negative feedback to the GnRH neuronal network in the brain that controls fertility is a crucial pathogenic characteristic of PCOS. The primary characteristic of PCOS, androgen excess, is linked to this impairment. It is believed that hyperactivity of the neuroendocrine axis regulating fertility is caused by impaired steroid hormone feedback to GnRH neurons, creating a vicious cycle of excess androgen and reproductive failure. Due to the enormous complexity of researching the human brain, decades of clinical research have failed to identify the mechanisms behind this disability. We have only lately started to understand the function of the brain in the onset and evolution of PCOS, thanks to the creation of preclinical models of the condition. The research presented here shows how crucial the brain is to PCOS ontogeny and pathophysiology and emphasizes the need for a deeper comprehension of the underlying mechanisms.

KEYWORDS: PCOS, Neuroendocrine, Brain, Ovary, and Androgen.

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1. INTRODUCTION

Polycystic ovarian syndrome (PCOS) is the leading cause of anovulatory infertility [1]. Because PCOS varies in its clinical presentation, current diagnostic criteria remain a subject of discussion. The latest National Institutes of Health (NIH) consensus guidelines require hyperandrogenism and oligo-or amenorrhea for a PCOS diagnosis, provided other causes of hyperandrogenism, like congenital adrenal hyperplasia, are ruled out [2]. Six to ten percent of reproductive-aged women experience Cushing's syndrome or androgen-secreting tumors. Under the broader Rotterdam criteria, which require at least two of the three primary symptoms, 19% of women of reproductive age receive a PCOS diagnosis [3]. PCOS frequently occurs alongside other health conditions, such as obesity, insulin resistance, cardiovascular disease, reproductive organ cancers, and depression [4]. Therefore, PCOS is recognized as a significant condition impacting women before, during, and after their reproductive years. Despite its high prevalence, the exact origins and progression of PCOS remain poorly understood. This complex disorder affects multiple body systems, including the brain, fat tissue, heart, and reproductive organs. Extensive laboratory and clinical research involving human patients and animal models points to a mixture of genetic, epigenetic, prenatal, and lifestyle factors as the likely underlying causes. Multiple literatures have also examined insights gained from animal models of PCOS. The goal of this review is to synthesize data regarding the less understood contribution of central brain circuits to the development and symptoms of the disease. The brain not only controls the neuroendocrine axis responsible for ovarian function but also reacts strongly to metabolic and peripheral gonadal hormones. This review will first go over the preclinical models that are currently available for studying central brain circuits and the prevailing theories on the aetiology of the disease. Next, it will examine the evidence that is currently available to correlate brain alterations to the PCOS phenotype and its related comorbidities [4]. In this review, we have merged the pathological alterations that take

place during neuroendocrine crosstalk and the therapeutic interventions that may take a major role in the management of PCOS and associated disorders.

2. PATHOGENESIS ASSOCIATED WITH THE NEUROENDOCRINE IMPAIRMENT IN PCOS

Although ovarian dysfunction is a hallmark of PCOS, an increasing volume of clinical and laboratory evidence indicates that PCOS could stem from changes in the neural pathways governing reproduction. The ability to reproduce is fundamentally directed by the GnRH neural system. A small group of GnRH neurons distributed throughout the rostral forebrain, alongside their incoming nerve fibers and adjacent glial cells, transmits crucial endocrine, metabolic, circadian, and stress inputs to the reproductive axis. GnRH neurons send long projections to the median eminence, where the portal vasculature receives a pulsatile release of GnRH peptide. This causes the gonadotropes to produce the hormones LH and FSH in a pulsatile manner in anterior pituitary gland [5]. Which gonadotropin hormone is preferentially released depends in part on the frequency of GnRH pulses; quicker frequencies promote LH production, whereas Lower frequencies encourage the secretion of FSH. The key ovarian processes, specifically folliculogenesis and steroidogenesis, are regulated by the activity-dependent pattern of LH and FSH release throughout the ovarian cycle. The pituitary gland and hypothalamus get vital feedback from ovarian gonadal steroid hormones, including estrogens, androgens, and progestogens, which in turn create a balanced regulatory loop that regulates the discharge of GnRH, LH, and FSH [6]. For much of the reproductive cycle, progesterone alongside estradiol decrease the activity of GnRH neurons by negative feedback mechanisms. Throughout the mid-follicular stage, rising estradiol concentrations promote a shift toward positive feedback, which raises GnRH and LH levels and starts the onset of ovulation. When PCOS interferes with this conventional homeostatic feedback system between the central nervous system and the ovaries, the hypothalamic-pituitary-gonadal axis becomes hyperactive and the ovary's neuroendocrine regulation is changed. Elevated LH pulse rates are a frequent clinical hallmark of PCOS, clearly indicating neuroendocrine dysfunction. This trait is often associated with greater LH pulse amplitude, raised blood LH levels, and an elevated FSH-to-LH ratio. One of the effects of this accelerated LH pulsation in the ovary is increased androgen generation within theca cells, which leads to an overproduction of androgens. Reduced levels of FSH prevent follicular growth, which leads to a buildup of fluid-filled, cystic follicles and anovulation. Thus, such an imbalance in the secretion of gonadotropins is responsible for increased androgen synthesis, ovulation, along with the multi-cystic appearance of the ovaries that gives polycystic ovary syndrome its name [7].

2.1. Pre clinicals models of PCOS

It should come as no surprise that studying how the brain influences the development and resulting consequences of PCOS in women is exceedingly challenging, and we continue to rely on animal subjects that closely mirror the disorder to investigate specific neurological pathways. Just like the human condition, researchers can reproduce elements of the PCOS profile in animal test subjects [8]. These options include introducing environmental variables like high-fat diets, an excess of soy, or transgenic modifications like amplifying the expression of plasminogen activator inhibitor-1 or nerve growth factor in the ovary (Dissen et al., 2009). Nevertheless, the standard approaches for modeling PCOS expose females to significant androgen levels. However, in the most popular models of PCOS, females are exposed to excessive androgen amounts. Differences in androgen administration consist of injecting both aromatizable and non-aromatizable androgens directly before and after birth, alongside pharmaceutical treatments that stop the biological transition of testosterone into estradiol. A PCOS-like phenotype is caused by a rise in female peri- and prenatal androgen across every mammal researched so far, such as rats, mice, sheep, and nonhuman primates. Early androgen exposure can result in PCOS-related comorbidities and postpubertal reproductive and metabolic symptoms in the majority of animals, which are similar to the clinical manifestation. But following PNA, a range of PCOS symptoms appear, most likely due to species differences as well as exposure duration and time [9]. The rhesus macaque may either present a condition resembling PCOS on its own or in response to PNA treatment. This includes the metabolic traits of the condition as well as the emergence of the main PCOS reproductive signs, such as hyperandrogenism and improper ovarian function. Since primates are the most genetically similar to humans of all the mammalian species used to research PCOS, changes in the reproductive system of this model are most likely to mirror PCOS in the clinic [9]. **Fig. 1** shows the impaired steroid hormone feedback during PCOS.

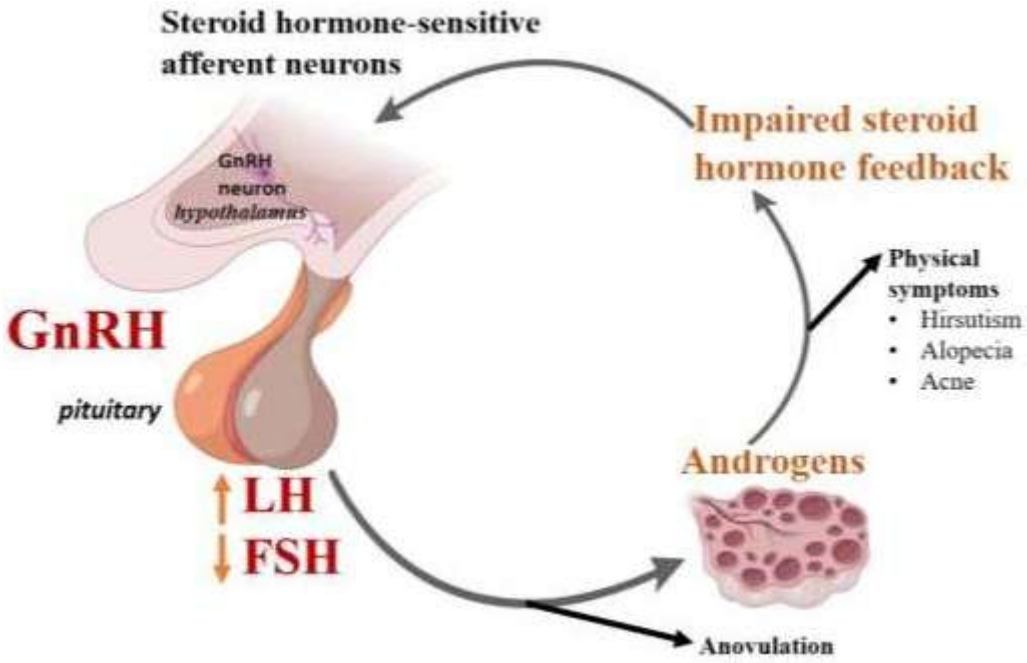

Fig. 1: Schematic representation of the neuroendocrine feedback loop in hyperandrogenic anovulation. Dysregulation begins with altered gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus, leading to a disproportionate release of luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH) by the anterior pituitary. This elevated LH/FSH ratio stimulates the ovaries to overproduce androgens. The resulting hyperandrogenemia directly contributes to local ovarian dysfunction (anovulation) and systemic physical symptoms, including hirsutism, alopecia, and acne. Crucially, these elevated androgen levels cause impaired steroid hormone feedback at the level of steroid hormone-sensitive afferent neurons in the hypothalamus, perpetuating the abnormal GnRH pulsatility and maintaining the cyclical pathology of the disorder.

2.2. Neuroendocrine Pathology

A rising corpus of both clinical and experimental research indicates how PCOS could be triggered by changes within the neural circuits that control fertility, despite the fact that PCOS remains characterized by ovarian failure. The GnRH neural pathway ultimately bears responsibility for controlling reproductive function. The reproductive axis receives crucial endocrine, metabolic, circadian, and tension-related cues from GnRH neurons, a small population of neurons dispersed throughout the anterior forebrain, in addition to input from their connected nerve pathways and adjacent supportive glial cells. Extended nerve fibers originating from GnRH neurons reach the median eminence, at which point the GnRH peptide becomes pulsatiley discharged into the portal blood vessels [11]. The gonadotropes within the frontal lobe of the pituitary gland produce the FSH and LH hormones in a pulsatile manner as a result. The rate of GnRH pulsation dictates the specific gonadotropin that is primarily released; higher rates encourage the synthesis of LH, whereas slower frequencies encourage the secretion of FSH. The activity-dependent pattern of LH and FSH release during the reproductive cycle controls the fundamental dual processes within the ovaries, namely folliculogenesis and steroidogenesis [11]. Ovarian sex steroid hormones, such as estrogen, progestogen, and androgen hormones, deliver crucial signals toward the cerebrum and the pituitary gland, which in turn establishes a balancing feedback mechanism governing the secretion of GnRH, LH, as well as FSH. Progesterone along with estradiol cause this hypothalamic-pituitary-gonadal axis to become hyperactive and the ovary's neuroendocrine regulation to be disrupted by reducing GnRH neuron activity during most of the ovarian cycle through negative feedback [12]. Elevated rates of LH pulsation present a typical medical sign of PCOS and is an obvious indication of impaired neuroendocrine function. This trait frequently gets linked to higher LH pulse volume, raised blood concentrations of LH, alongside an elevated proportion of FSH to LH. One of the results of a higher LH pulsation rate within the ovaries involves increased androgen production by theca cells, which leads to a surplus of androgens. Depleted FSH amounts prevent follicular growth, which leads to anovulation and a build-up of liquid-filled, cystic follicles. Therefore, an irregularity in the release of gonadotropins is the source of increased androgen synthesis, lack of ovulation, and the polycystic look of the ovaries from which the condition gets its name. GnRH neuron hyperactivity is indicated by persistently high LH pulse rates, which is probably connected to a rise in upstream GnRH pulse frequency [13]. Placing a cannula in the portal blood vessels of sheep reveals the matching rhythmic synthesis of GnRH from the median eminence alongside LH from the

front of the pituitary, but it is not currently feasible to measure in humans. Although the exact mechanism causing elevated LH pulsation rates in PCOS remains still unknown, higher levels of androgens act peripherally to trigger numerous observable signs of PCOS, as well as centrally to force higher GnRH/LH pulsation rates and subsequent reproductive impairment [14]. Increased LH pulse frequency does not seem to be a direct result of acute testosterone treatment. Giving an androgen receptor (AR) blocker did fail to reinstate standard LH production within PCOS-affected individuals, and downloading from Neuroendocrine Impairments of PCOS had no effect on LH release in female PCOS patients. Rather, it remains believed that androgens boost the frequency of GnRH/LH pulses by preventing the brain from receiving negative feedback from progesterone and estradiol to suppress the production of GnRH/LH. Female patients with PCOS suffer a much smaller decrease in the rate and size of LH pulses when exposed to external estradiol and progesterone injection, according to important research done at Marshall and Berga's labs [15]. Because long-term treatment with an AR antagonist restores the ability of progesterone and estradiol to regulate LH production in women with PCOS, it appears that androgen excess maintains this weak negative feedback. These clinical findings indicate that androgen excess disrupts steroid hormone feedback, which leads to a vicious cycle of androgen excess and impaired neuroendocrine regulation of reproductive function. As a result, the frequency of the LH pulse is probably increased, which increases the ovaries' synthesis of androgen (**Fig. 1**). Understanding the pathophysiology of insufficient steroid hormone feedback is essential to treating PCOS and breaking this vicious cycle [16].

2.3. Role of neurotransmitter in PCOS

A consistently elevated LH pulse rate suggests overactivity of GnRH neurons, which probably indicates an increased rate of upstream GnRH pulses. While currently impossible to measure directly in humans, studies using cannulas in the portal blood vessels of sheep demonstrate that the pulsatile release of GnRH from the median eminence aligns with LH release from the anterior pituitary [17]. High androgen levels act within the brain to accelerate GnRH and LH pulse rates, leading to subsequent reproductive problems. This occurs alongside their peripheral effects, which produce many noticeable PCOS symptoms. However, the precise mechanism behind the rapid LH pulsing in PCOS remains undetermined [18]. Because brief exposure to testosterone does not appear to directly trigger faster LH pulses, when patients with PCOS get medications that block androgen receptors, their LH secretion fails to normalize. Moreover, LH release in these patients is not influenced by short-term blockade. Instead, androgens likely accelerate GnRH and LH pulses by preventing progesterone and estradiol from exerting the necessary negative feedback on the brain to reduce hormone release. Pivotal studies show that females with PCOS and adolescents with elevated androgens display a notably smaller reduction in LH pulse speed and size after receiving external estradiol and progesterone compared to healthy individuals. Similarly, patients with PCOS require greater quantities of progesterone and estradiol to suppress LH release to the same extent as unaffected women [19]. This diminished negative feedback appears to be sustained by excess androgens, as extended treatment with an AR antagonist restores the ability of progesterone and estradiol to suppress LH production. According to this clinical research, excess androgens initiate a detrimental cycle of further androgen overproduction and defective neuroendocrine control over reproduction by interfering with steroid feedback. This interference likely causes a rise in LH pulse frequency, which subsequently increases the ovarian synthesis of androgens. Comprehending the physiological basis of this inadequate steroid feedback is crucial for treating PCOS and halting this continuous cycle [20].

2.4. Negative Feedback of Progesterone in PCOS

Since recorded serum levels for these hormones are similar to those of healthy control women, disrupted negative feedback from estradiol and progesterone in PCOS begins during adolescence and does not stem from diminished synthesis of estradiol and progesterone by the ovaries. This implies that the activation of steroid hormones in the brain is the cause of the issue. In fact, women with PCOS show decreased hypothalamic sensitivity to steroid hormones. However, since these ground-breaking research, little therapeutic progress has been achieved in understanding the involvement of the brain in PCOS pathophysiology due to the difficulty of studying the human brain [21]. Animal models have been essential to expanding our knowledge of PCOS etiology, despite the views of certain medical experts. Only lately have we discovered changes within particular neural pathways potentially responsible for disturbed hormonal control of reproduction in clinical PCOS and begin to suggest targeted therapeutics for managing this widespread condition, thanks to the application of laboratory animal models for PCOS. Animal models: crucial resources for understanding the brain's function in PCOS The majority of PCOS animal models are created through generating a hyperandrogenic state, usually by giving an estrogen in the late stages of pregnancy or the early postnatal period. PCOS models have been developed using rats, lambs, and nonhuman primates [22]. Mouse models of PCOS are especially useful for researching brain function because their genomes are easily altered. This makes it possible to employ easily accessible and developing transgenic technology. Because DHT treatment eliminates the confusing effects of testosterone aromatization to estradiol and clarifies the AR-mediated pathways implicated in PCOS pathogenesis, it is frequently utilized to create PCOS mice models. The primary neuroendocrine characteristics of PCOS in adulthood are displayed by mice prenatally exposed to androgens (the PNA model), which gets created through DHT administration in the final stages of gestation. These characteristics include

elevated internal testosterone concentrations, higher frequency of LH pulses, disrupted negative feedback from estradiol and progesterone, changed ovarian structure, and a lack of ovulation [23].

The PNA animal model is similar to patients with lean PCOS, while mice subjected to chronic DHT after birth, which was developed with a continuous DHT release implant over 90 days starting at three weeks old, mimics the fertility and metabolic traits associated with PCOS, such as the presence of ovarian cysts, failure to ovulate, and excess weight. Considerable research using this paradigm has shown the brain's critical role in regulating this development of PCOS since targeted neural ablation of the androgen receptor eliminates the majority of PCOS characteristics caused by postnatal DHT. Even though LH secretion appears to be unaltered, this paradigm may not be ideal for studying faulty steroid hormone feedback [24].

Many of the fertility and metabolic characteristics seen in PCOS, such as elevated bloodstream levels of androgens and LH, cyst-like changes in the ovaries alongside anovulation, greater body weight and fat mass, and diminished glucose tolerance, can be replicated in mice treated with letrozole, which is created by giving the aromatase inhibitor letrozole after puberty [25].

2.5. Role of androgen in developing female brain

The majority of PCOS animal models are created by generating hyperandrogenism, which is frequently achieved by giving an estrogen in the late stages of pregnancy or the early postnatal period. It goes without saying that no preclinical model of PCOS is flawless and that animal models cannot accurately duplicate human diseases. Nonetheless, the main neuroendocrine characteristics of people with PCOS are present in a number of animal models of hyperandrogenism-induced PCOS. PCOS models have been developed in rats, lambs, and nonhuman primates thus far. Mouse models of PCOS are especially useful for researching brain function because their genomes are easily altered. This makes it possible to employ transgenic technologies that are readily available and developing [26].

Because it avoids the confusing effects of testosterone aromatization to estradiol and allows for clarification of the AR-mediated processes linked with PCOS pathogenesis, DHT treatment is frequently employed to generate PCOSousem models. The major neuroendocrine characteristics of PCOS in adulthood, such as elevated endogenous testosterone levels, increased LH pulse frequency, the prenatally androgenized (PNA) mouse model demonstrates abnormal ovarian structure, a lack of ovulation, and disrupted negative feedback of estradiol and progesterone. This model is created by late prenatal DHT exposure [27, 28].

2.6. Alteration of extrahypothalamic circuits in PCOS

Even though little direct steroid hormone feedback happens at the GnRH neurons themselves through estrogen receptor b, these cells do not possess essential steroid receptors such as the androgen receptor (AR), progesterone receptor (PR), or estrogen receptor a (ERa). Therefore, most important steroid feedback to GnRH neurons happens indirectly through the afferent steroid-sensitive GnRH network. While the specific neuronal populations involved remain still unknown, several brain regions, such as the arcuate nucleus (ARN), periventricular nucleus (PeN), and anteroventral periventricular nucleus (AVPV), are associated with mediating the regulatory negative feedback of estrogens and progesterone [29]. Studies involving mice, rats, and sheep demonstrate that the ARN is a crucial site for estrogen and progesterone negative feedback. This regulatory mechanism can occur in PCOS. Evaluating steroid hormone-receptor expression within the PNA mouse model of PCOS reveals that PR levels are markedly reduced across the ARN, AVPV, and PeN. This animal's postgonadectomy rise in LH cannot be significantly reduced by exogenous progesterone injection, aligning with the observed reduction in PR levels. Reduced PR expression in the ARN is also seen within sheep treated prenatally with testosterone, another model exhibiting connected steroid feedback mechanisms. Furthermore, the hypothalamic PR mRNA within prenatally androgenized rats was found in one study [30]. Interestingly, neural ERa levels remain virtually unchanged in prenatally androgenized mouse and rat models. The regulatory feedback pathways for progesterone alongside estradiol are impaired during PCOS, according to clinical and preclinical research. It is unclear exactly what causes estrogen-specific negative feedback impairments and their impact on the underlying pathology of PCOS. Yet, genetically suppressing ERa within kisspeptin neurons, a vital neuronal subset for reproduction within the GnRH network, generates traits similar to PCOS, indicating that inadequate estrogen feedback contributes to the underlying mechanics of PCOS [31]. Nevertheless, animal models suggest that the disruption of progesterone negative feedback seen in human PCOS is probably due to decreased PR levels in the hypothalamus. Furthermore, researchers have recently identified the exact hypothalamic neuronal types that become insensitive to progesterone. The incoming GnRH neural network's reduced sensitivity to steroid hormones is one obvious reason [32].

2.7. Kisspeptin and kisspeptin/neurokinin B/dynorphin neurons

Endocrinology shows a timing mismatch between kisspeptin and LH pulses compared to eumenorrheic PCOS patients, offering some of the initial clinical proof of dysregulation in the kisspeptin GnRH/LH network. Kisspeptin, a potent and recognized controller of GnRH neuron activity that remains essential to the beginning of puberty and fertility, is dysregulated in patients. In rodents, two distinct groups of kisspeptin neurons are found within the AVPV/PeN and the ARN, whereas in humans, these groups are located within the preoptic area and the fundibular nucleus [33]. This long-elusive GnRH pulse generator has recently been found to

represent the ARN kisspeptin population, sometimes referred to as kisspeptin/neurokinin B/dynorphin (KNDy) neurons, while the AVPV/PeN kisspeptin community is primarily in charge of GnRH/LH surge creation. Kisspeptin neurons, which are heavily involved with steroid hormone signaling to GnRH neurons, express PR, ERa, and AR. It is thought that defective steroid hormone responses and excessive GnRH/LH secretion in PCOS are at least partially driven by anomalies in the kisspeptin signaling system [34] since kisspeptin has a significant stimulatory impact on GnRH/LH release. While most clinical studies conclude that women with PCOS exhibit elevated plasma/serum kiss peptin levels, several studies have found no difference in kiss peptin levels. The finding that nonobese PCOS patients have higher kisspeptin levels than obese PCOS patients may help to explain why kisspeptin levels vary among clinical investigations. It's interesting to note that individuals with oligomenorrhea but not eumeorrhea appear to have PCOS, whereas those with both conditions had greater kisspeptin levels. Due to contradictory observations regarding alterations, or the absence of such changes, within the kisspeptin signaling cascade (Table 1) [36], data from preclinical PCOS models has not yet shed considerable light on impairment within the kisspeptin-GnRH/LH system. There have been reports of increased, decreased, or unaltered kisspeptin neurons or kisspeptin mRNA expression in the ARN. Despite occasional reports of a decline, most studies in the AVPV have demonstrated that the quantity of kisspeptin neurons or kisspeptin mRNA expression is stead. Contradictory results have been reported even within the same rat model, which may be partly explained by species differences and PCOS modeling techniques. Ewes given testosterone during pregnancy exhibit compromised steroid hormone feedback in a model. The soma size of KNDy neurons grows, the concentration of shared KNDy connections decreases, and the KNDy signals directed to GnRH neurons decrease. Interestingly, even while PR expression within the ARN drops in this framework, the quantity of kisspeptin-positive neurons located in the ARN, as well as their overlap with PR, stays stable. This implies the fact that progesterone sensitivity is not inherently lost by kisspeptin neurons. However, in sheep given testosterone during pregnancy, there are fewer synaptic connections reaching the soma of kisspeptin cells within the AVPV and ARN, suggesting that presynaptic neurons may have altered kisspeptin neuron regulation [37].

Table 1: Changes involved during Kisspeptin-GnRH signalling pathway in PCOS rodent models [36].

Model	**ARN**	**AVPV**
Mouse	↑No of kisspeptin neurons ↑No change in kiss1 or Kiss 1R mRNA	↓No. of kisspeptin neurons No change in kiss1or kiss 1R mRNA No change in number of kisspeptin neurons or kiss1 mRNA
Sheep	No change in no of ↑kisspeptin neurons. ↑Kisspeptin neuron soma size Inputs to ↓kisspeptin neurons (unidentified)	No change in no. of kisspeptin neurons No change in kisspeptin neuron soma size ↓Inputs to kisspeptin neurons (both reciprocal and unidentified)
Chronic postnatal DHT Rat	↓No of kisspeptin neurons No change in kisspeptin neurons	Decrease in number of kisspeptin neurons
Letrozole Mouse	↓No. of kisspeptin neurons	↓No of kisspeptin neurons
Rat	Kiss1 mRNA increased in the posterior hypothalamic block containing the ARN	↓No change in kiss1 mRNA in the anterior hypothalamic block containing the AVPV

2.8. Integration of basic and clinical research

Campbell RE, Ruddenklau A. It describes the endocrine deficits linked to polycystic ovarian syndrome [38]. According to Fauser et al. (2012), anti-androgen receptor drugs are commonly used to treat hyperandrogenism, the main feature of PCOS. Future research must concentrate on identifying the 20 critical times that treatment is most effective as well as the effective targets of androgen-receptor medications. Both scientific and clinical evidence supports the hypothesis that androgens interfere with the neuroendocrine reproductive axis through modifications to central brain pathways. A fresh and focused approach to lowering the frequency of LH pulsing in females diagnosed with PCOS may be provided by medications that target neuronal traits found during laboratory studies to be possible causes for the overproduction of GnRH and LH.

The neuropeptide kisspeptin, which has been recognized as a key central controller for reproduction, is able to elevate LH

pulse frequency when given to adult males, whether used by itself or alongside medications targeting neurokinin B and dynorphin receptors. Despite the lack of data presently existing on the use of this method in patients with PCOS, robust findings demonstrate that applying targeted kisspeptin antagonists lowers the frequency of LH pulses in mice [40].

3. TREATMENT TARGETING NEUROENDOCRINE IMPAIRMENT IN PCOS

3.1. Targeting NKB signalling in PCOS

In an initial randomly assigned, double-blind, placebo-controlled, phase 2 study, women with PCOS were examined for a specific neurokinin 3 receptor antagonist, MLE4901. Patients taking 80 mg per day of MLE4901 saw meaningful drops in the area under the curve of LH levels (by 52%, 95% confidence interval [CI] between 30 and 67%), LH pulses measured over 8 hours (dropping by 3.6 pulses per hour, 95% CI 2.0 to 5.1), and overall testosterone levels (decreasing by 29%, 95% CI 14% to 41%). Interestingly, inhibiting the NK3 receptor with MLE4901 was previously tested over 12 weeks in a mouse model of PCOS that exhibited metabolic traits like increased triglycerides, severe weight gain, and high blood sugar. The reproductive traits did not change after treatment, but the metabolic indices did, with a reduction in body weight and obesity [41].

The postnatal anogenized model that was used, which does not exhibit overactivity of arcuate KNDy neurons, may help to explain this. It may therefore not completely rule out an effect on reproductive phenotype in other PCOS-like mouse models. Fezolinetant is now in phase III development to treat postmenopausal women's vasomotor symptoms, but it could additionally serve as an effective therapy for hyperandrogenism in women experiencing PCOS. In a randomized, double-blind, multi-center Phase II trial lasting 12 weeks, 73 female participants with PCOS, identified using the Rotterdam criteria, received fezolinetant doses of either 60 mg or 180 mg. Following a 12-week treatment period, the participants showed a dose-dependent decrease in serum testosterone concentrations ranging from 14% to 33% [42]. KNDy neurons contain dynorphin, which attaches to their kappa opioid receptors through an autocrine or paracrine mechanism, stopping the release of kisspeptin onto GnRH neurons. Even with elevated β-endorphin concentrations in the peripheral blood, researchers propose that a reduction in hypothalamic opioid inhibitory action [44]. Therefore, it makes sense to believe that a central action opioids agonist could lower GnRH pulsatility and offer potential therapeutic benefits for PCOS. Peripherally restricted kappa receptor agonists (PRKA), which retain the ability to penetrate the hypothalamus through the median eminence, were recently administered to a mouse model of PCOS. Consequently, KNDy activity was inhibited, which lowered the levels of LH but testosterone and restored ovarian cyclicity [45].

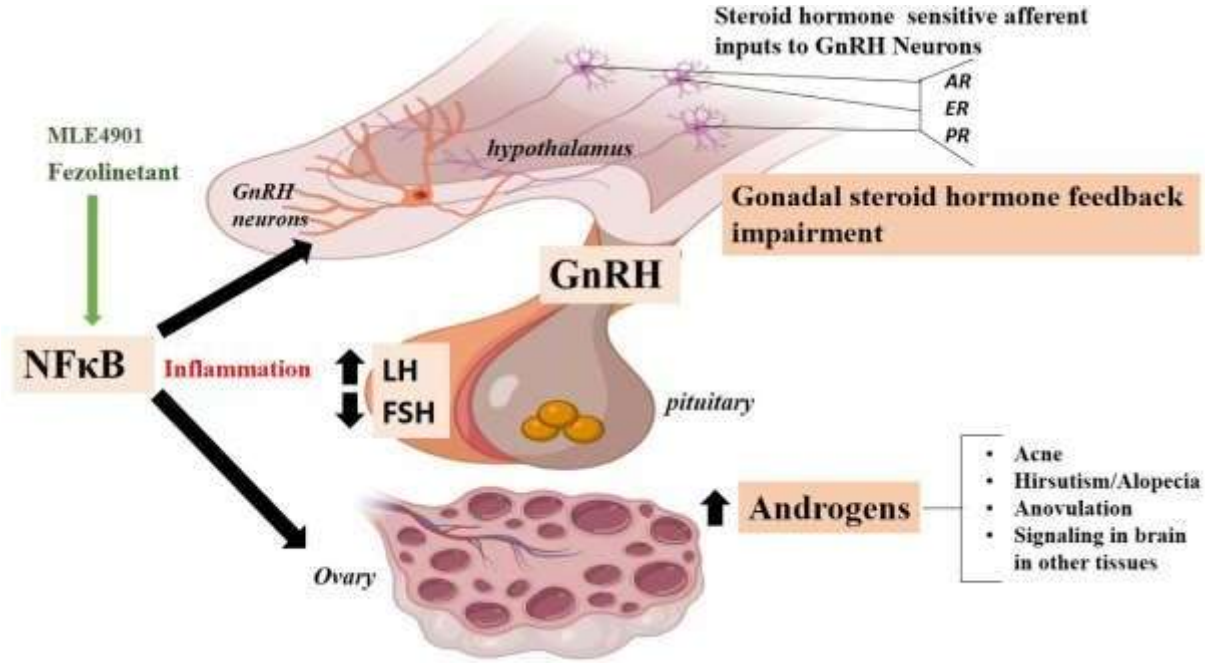

Fig. 2: NF-κB mediated neuroinflammation in the pathophysiology of hyperandrogenic anovulation and potential therapeutic intervention. This model illustrates how inflammation, acting through the NF-κB signaling pathway, directly hyperstimulates hypothalamic GnRH neurons and disrupts normal ovarian function. This inflammatory drive increases GnRH pulsatility, prompting the anterior pituitary to secrete elevated levels of luteinizing hormone (LH) relative to follicle-stimulating hormone (FSH). The resulting LH/FSH imbalance drives ovarian hyperandrogenism, producing characteristic clinical phenotypes including acne, hirsutism, alopecia, and anovulation. The systemic androgen excess further perpetuates the cycle by impairing normal gonadal steroid hormone feedback at the hypothalamic level, specifically affecting afferent neurons expressing androgen, estrogen, and progesterone receptors (AR, ER, PR).

Pharmacological agents such as MLE4901 and Fezolinetant are shown to block this NF-κB-driven inflammatory cascade, highlighting a potential mechanism to disrupt the pathological feedback loop and restore neuroendocrine homeostasis.

3.2. Dynorphin

KNDy neurons include dynorphin, which 0attaches to their kappa opioid receptors through an autocrine or paracrine mechanism, stopping the release of kisspeptin onto GnRH neurons. Even with elevated β-endorphin concentrations in the peripheral blood, researchers propose that a reduction in hypothalamic opioid inhibitory action [44]. Therefore, it seems sense to believe that a central action opioid agonist could lower GnRH pulsatility and provide potential therapeutic benefits for PCOS. Peripherally restricted kappa receptor agonists (PRKA), which retain the ability to reach the hypothalamus via the median eminence, were recently administered to a mouse model of PCOS. Consequently, KNDy activity was inhibited, which lowered the levels of LH and testosterone and restored ovarian cyclicity [45].

3.3. Gamma aminobutyric acid (GABA)

It's interesting to note that exposure to androgens during pregnancy enhances GABAergic connections to GnRH neurons. While GABA generally functions as an inhibitory neurotransmitter, DHT enhances GABA-mediated activation of GnRH neurons, and GABA excites these same GnRH neurons due to elevated intracellular chloride level [46]. Although GABA concentrations in the peripheral bloodstream are reduced, the levels within the central cerebrospinal fluid are elevated in patients with PCOS. Consequently, a higher frequency of PCOS64 has been associated with anti-epileptic medications and other treatments that increase GABA. Ovarian granulosa cells (GCs) secrete AMH, also known as anti-Müllerian hormone, which regulates follicle selection. It belongs to the growth factor transforming β (TGF-β) superfamily [47]. Female patients with PCOS had serum AMH and AMHR2 levels that were 2-4 times greater than those of controls. These levels are associated with abnormal GC functioning, follicular arrest, and slow follicular growth [48]. Androgens increase GC FSH receptors (FSHR), and developing follicles in PCOS express more AMH due to increased FSH activity. Anovulatory and hyper-androgenic women with PCOS showed greater levels of AMH than normo-androgenic women. NK3R antagonism caused AMH levels to drop in PCOS-affected women during the course of twelve weeks. It would be beneficial to change the KNDy signaling pathway to reduce AMH levels by decreasing GnRH pulsatility. AMH receptor antagonists may be beneficial in PCOS, despite the lack of data at this time. The current research describing AMHR2's signaling pathways may serve as the foundation for future AMH antagonists.

4. FUTURE PROSPECTIVE AND LIMITATIONS

The poor progesterone negative feedback has been linked to androgen activity for nearly 20 years. Marshall and colleagues [49] found that extended inhibition of AR pathways using flutamide restores normal negative feedback for both progesterone and estradiol in PCOS patients. There is data suggesting that an androgen-driven inhibition of PR gene transcription is responsible for defective negative feedback from progesterone as well as decreased progesterone receptor synthesis within ARN GABAergic neurons, and possibly additional unknown cell groups. AR-directed androgen activity disrupts the negative feedback of progesterone on GnRH neurons, particularly the feedback regulated through GABA neurons, according to early electrophysiological research in mice [50]. Results from in vivo studies indicate that this disruption could result from inhibiting estradiol-stimulated PR transcription, given that short-term testosterone treatment in female rats lowers PR mRNA in the preoptic mediobasal region of the hypothalamus and stops the rise in PR mRNA levels normally caused by estradiol [51]. The AR likely controls this outcome as blocking the AR stops the reduction. The precise method through which the AR assembly prevents PR gene transcription is yet understood, however it does not seem to involve direct ER complex disruption. According to one explanation, upon AR assembly being activated, the PR gene undergoes epigenetic changes that lower the sensitivity to progesterone within ARN GABAergic neurons, impede the negative feedback loop of progesterone, and inhibit PR production [52]. These recent explored pathways can be a cornerstone for newer therapeutic approaches for the treatment of PCOS.

5. CONCLUSION

The vicious loop of high androgen levels driving neuroendocrine issues and fertility struggles in PCOS is thought to be at least partly caused by defective gonadal steroid feedback loops. Lowered sensitivity to progesterone within a distinct group of ARN GABAergic neurons could be the origin of improper negative feedback from progesterone seen in a PCOS-type syndrome, according to recent research utilizing animal models of the disorder. This reduction in sensitivity to progesterone is most probably the result of AR-driven regulation over PR gene transcription, while the precise process is still understood. Moreover, it is unclear whether the enhanced input to GnRH neurons from GABAergic neurons in the arcuate nucleus is related to this lack of progesterone responsiveness. Although we now have a better grasp of the pathophysiology of faulty feedback of steroid hormones in PCOS, numerous uncertainties persist. Understanding the precise pathways by which androgen excess promotes androgen blockade ameliorates PCOS pathogenesis, as well as the developmental time course of androgen effects in the female brain, will be essential to effectively treating, curing, and potentially preventing this common disorder. Only by carefully utilizing preclinical

models will we be able to address these problems and develop targeted, mechanism-based treatments for women with PCOS.

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