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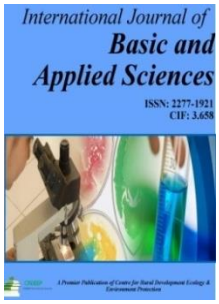

Review Paper

Hormones of HPG-axis and their Active Role during Chronic Stress and PCOS Induction: A Review

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ABSTRACT

Polycystic Ovary Syndrome (PCOS) is an endocrine disorder occurring in women of reproductive age. In recent times, PCOS manifestations in the non-obese/lean individuals have raised the concern to negate the classic belief of obesity along with genetic polymorphisms, food associated with glycated end products (AGE) etc., as the primary factors of disease prognosis and has paved the way to explore several other factors responsible for the occurrence mainly stress. Stress is a body's non-specific response to any external demand where the response may be physical or psychological. A study has reported 91.9% of PCOS patients have been found to have experienced psychological distress, and a similar result has been given by another study elsewhere, which reported the *psychological score status >8 among the patients using General Health Questionnaire (GHQ)-28. The review explores our understanding of the psychological chronic stress, its impact along the HPG-axis and related hormones and their inception in PCOS induction.*

Introduction

Polycystic Ovary Syndrome (PCOS) is the most common endocrine disorder in women of reproductive age associated with hyperandrogenism, polycystic ovaries, elevated levels of luteinizing hormone (LH), irregular menstrual cycle, along with decreased follicular stimulating hormone (FSH), decreased estrogen, hyperinsulinemia, insulin resistance, and high risk of type 2 diabetes [Paris et al. (2020); Vaidya et al. (2020); Hoeger et al. (2021)]. As of 2017 report by the World Health Organization (WHO) and Indian Council of Medical Research (ICMR), 4% to 8% of the world's women population and around 12.2% of the Indian women population have been suffering from the syndrome [Krishnan and Muthusami (2017)]. A recent study reports published in 2020 have shown the elevation in the prevalence of the cases worldwide up to 4% to 26% [Rao et al. & Deswal et al. (2020)]. A number of possible causative factors have been enlisted for the disposition of PCOS such as obesity, genetic polymorphisms, food associated with glycated end products (AGE), stress etc., [Sam (2007); Alvarez-Basco et al. (2006); Yildiz et al. (2008); Amato and Simpson (2004); Prapas et al. (2009); Crespo et al. (2018); Diamanti-Kandarakis et al. (2012); Zangeneh et al. (2012)]. In recent times, a PCOS manifestation in the non-obese/lean individuals have raised the concern to think over the classic belief of obesity as the primary factor of disease prognosis and has paved the way to explore several other factors responsible for the occurrence. Several recent studies have shown the correlation of PCOS with the psychologically stressed condition of the patients. [Zangeneh et al. (2012); Sayyah-Melli et al. (2015); Damone et al. (2019)]. Stress is a body's non-specific response to any external demand where the response may be physical or psychological [Fink (2010)]. The agents that cause stress are termed as stressors. Pain, extreme cold, extreme heat etc., lay under the physical stressors, whereas psychological feelings like depression, anxiety, fear etc., lay under

psychological stressors. Psychological stress is a non-physical, mental suffering caused out of fear, anxiety, and depression [Fink (2010)]. A study has reported 91.9% of PCOS patients are under psychological distress, identifying it as a prognostic marker of PCOS [Zangeneh et al. (2012)], whereas studies elsewhere have reported the anxiety and depression being significantly most common psychological distress condition found to occur in the patients, [Sayyah-Melli et al. (2015); damone et al. (2019)] and a similar finding elsewhere has been shown the close association of psychological distress with the clinical symptoms of PCOS [Zafari-Zangeneh et al. (2012)], where the psychological score status among the patients using GHQ-28 was found to be >8 in the study [Sundararaman and Sridhar (2008)]. The disease is primarily known to manifest the manipulations occurring in the HPG-axis. Hypothalamus is responsible for the production of gonadotropin releasing hormone (GnRH) [Millar et al. (2004)], which in turn stimulates the production of luteinizing hormone (LH) and follicular stimulating hormone (FSH) from the anterior pituitary [Meethal et al. (2009)] where they help in the regulation of menstrual cycle with the production of estrogen [Meethal and Atwood (2005)]. Estrogen further inhibits the GnRH production from the hypothalamus by feedback mechanism [Meethal and Atwood (2005)]. The current review focuses on the manifestations of PCOS at the backdrop of stress and its hormonal interplay around HPG-axis.

a) Glucocorticoids:

Under psychological stress conditions, the hypothalamus release the corticotrophin-releasing hormone (CRH) to stimulate the anterior pituitary to release adrenocorticotropic hormone (ACTH). The released ACTH in circulation will stimulate the adrenal gland to release the glucocorticoids [Cruz-Topete and Cidlowski (2015)] as a part of Hypothalamus-Pituitary-Adrenal (HPA) axis.

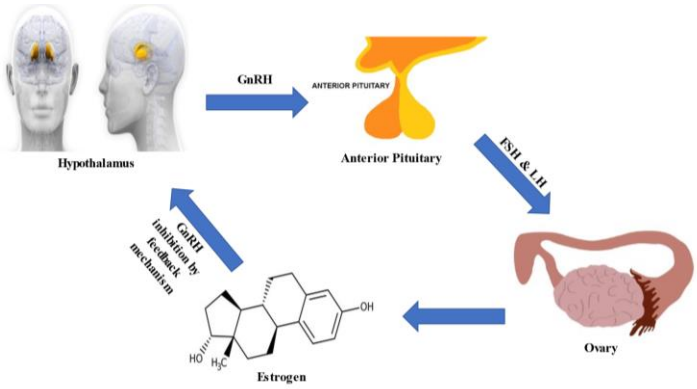

Fig. 1: Diagram representing the mode of action of HPG-axis**.**

This entire axis' activity under stress is initiated by the gene CRH spanning 2 exons showing maximum expression in placenta, fat tissue and brain respectively [Perng et al. (2020); Tache et al. (2018); Fagerberg et al. (2014)]. Previously, the association of CRH with psychiatric disorders like anxiety and depression have been reported in studies elsewhere [Binder and Nemeroff (2010); Claes (2004); Holsboer and Ising (2008)].

Glucocorticoids are the suppressors of GnRH expression wherein the effect of elevated glucocorticoids is shown to reduce GnRH activity with inhibition of FSH and LH and modulating the gametogenesis in testes/ovaries [Whirledge and Cidlowski (2010)] through GnRH pulse suppression and reduction in GnRH production via interaction between glucocorticoid receptor (GR) and Octamer transcription factor-1 (Oct-1). In humans, Cortisol is the primary glucocorticoid, but in rodents it is Corticosterone [Koning et al. (2019)]. The enzyme 17-hydroxylase encoded by the gene CYP17A1, is required for the glucocorticoid/cortisol production [DeVore and Scott (2012)] with the gene spanning 8 exons with its maximum expression in adrenal tissue and a very small quantities of expression can be seen in testis and kidney respectively [Fagerberg et al. (2014)]. In females, cortisol is shown to regulate the function of the aromatase enzyme for the elevation of subcutaneous adiposity along with the production of estrogen from C19 steroids [Wickenheisser et al. (2000)]. Hyperinsulinemia is shown to cause over expression of androgen from the ovaries by acting on ovarian stromal and thecal androstenedione and testosterone synthesis [Barbieri and Hornstein (1988)].

Inturn, in one of the study it has shown that the elevated cortisol can lead to the condition with the induction of metallothionein and Zip14 expressions leading to the disruption of zinc metabolism by decreasing the normal zinc concentration in the body [Morais et al. (2019)].The hyperinsulinemia due to insulin resistance has been shown to contribute in disrupting GnRH and LH pulsatile secretion in a study on obese rat models by knocking out the GnRH specific insulin receptors where it has shown the higher pulse of GnRH in normal models as the peripheral insulin level increases [DiVall et al. (2015)].

b) Catecholamine:

Dopamine, Epinephrine and Nor-Epinephrine are the primary molecules responsible for 'fight-flight-fright' response. During psychological stress, these hormones help in increasing the blood glucose by glycogenolysis to increase glycogen production and decreased insulin production. Catecholamines are organic compounds, composed of a benzene ring with two hydroxyl groups next to each other, referred to as catechol, and a side-chain containing an amine group. Catecholamines are mainly produced by the sympathetic unit of autonomic nervous system for any stress response [Paravati et al. (2018)]. The fall in dopamine concentration under stress is shown to elevate LH leading to the possible manifestation of PCO phenotype [Virsaladze et al. (2006)]. The dual nature of dopamine on insulin secretion based on its concentrations has been deduced elsewhere, where, under the high concentration of glucose, with normal concentration of dopamine (10^{-8}M) in circulation is shown to stimulate the production of insulin through the Dopamine D2 receptors in pancreas, while the higher concentrations of dopamine (10^{-7}M–10^{-4}M) is shown to inhibit the insulin production independent of the glucose concentration [Shankar et al. (2006)]. The possible role of dopamine in ovarian physiology and pathology has been demonstrated in a study showing a higher concentration of dopamine in the follicular fluid of PCOS patients compared to healthy individuals along with exhibiting a fourfold increase in dopamine-induced reactive oxygen species (ROS) in granulosa cells compared to granulosa cells of healthy individuals [Saller et al. (2014)]. The Dopamine acts as the principal precursor for other two physiologically active members of the catecholamine family i.e., Epinephrine and Nor-Epinephrine. The importance of nor-epinephrin in ovarian physiology and in ovulation has been well established in a study showing the contribution of nor-epinephrin in the microenvironment of the preovulatory follicle and has noticed the significantly decreased levels of nor-epinephrin in the follicular fluid and the granulosa cells of PCOS patients [Saller et al. (2012)]. The role of nor-epinephrin in GnRH production has been demonstrated in a study on immortalized hypothalamic neurons (GT1-7), which has showed the nor-epinephrin's dosage dependent GnRH production. Study has shown, a concentration of 10^{-8}M has no significant difference in GnRH production, whereas 10^{-7}M and 10^{-6}M of nor-epinephrin significantly increase the production of GnRH with a significant elevation in Ca^{2+}ion concentration leading to the depolarization of membrane and calcium movement through voltage sensitive Ca^{2+} channel and release the GnRH [Uemura et al. (1997)]. A negative effect has been shown on the insulin production by nor-epinephrin, where it shows to inhibit the insulin production by three major ways, firstly by the activation of K^{+} channel and prevents the Ca^{2+} out flow by which prevents insulin release, second, inhibition of adenylyl cyclase that prevents the insulin release by cyclic AMP and lastly the distal effect, where downstream increase in Ca^{2+} prevents the exocytosis. All these three have shown to mediated through pertussis toxin (PTX)-sensitive heterotrimeric Gi and Go proteins [Straub and Sharp (2012)].

Table 1: Table explaining the role of Stress hormones in GnRH, LH and insulin regulation and representing the role along reproductive axis.

Hormone Family	Hormone	GnRH & LH regulation	Role in Reproduction	Insulin regulation
Glucocorticoids	**Cortisol**	Reduces GnRH activity and inhibit LH [Whirledge and Cidlowski(2010)].	Modulate gametogenesis [Whirledge and Cidlowski(2010)]..	Causes Insulin resistance and Hyperinsulinemia [Morais et al. (2019)].
Catecholamines	**Dopamine**	Upregulate LH in less concentration and suppress in higher concentration [Virsaladze et al. (2006); Chaudhari et al. (2018)].	Decrease dopamine levels with increased glutamate concentrations in PCOS patients relative to healthy controls has been observed [Chaudhari et al. (2018)].	Stimulates Glucose-induced insulin secretion in low concentrations and suppress insulin secretion at higher concentrations [Shankar et al. (2006)].
	Epinephrine	Central epinephrine has the stimulatory effect on LH production [Terry et al. (1982)].	It is observed that the PCOS patients had higher plasma epinephrine concentrations than the control group [Hashim et al. (2015); Ek et al. (2002)].	Epinephrine stimulates insulin secretion through β-adrenergic receptors, but it blocks insulin stimulators through α-adrenergic receptors and block insulin production in a dominant action [Hiatt et al. (1978)].
		Stimulates GnRH in a	Play an important role in Ovarian physiology and	Prevents insulin

	Norepinephrine	dose dependent manner [Uemura et al. (1997)].	ovulation. Significantly decreased levels of nor-epinephrine is observed in the follicular fluid of PCOS patients [Saller et al. (2012)].	production by preventing Ca^{2+} discharge and inhibiting adenylyl cyclase in β-cells [Straub and Sharp (2012)].
Growth Hormone	**Growth Hormone**	No direct effect on GnRH, elevated GH suppress LH [Chandrashekar and Bartke (1998)].	Growth hormone has a pro-gonadal effect in physiological concentrations, but it is anti-gonadal in pharmacological concentrations and pathophysiological in high concentrations [Hull and Harvey (2001)].	Chronic elevation in GH causes insulin resistance by acting upon PI 3-Kinase [Takano et al. (2001)].
Prolactin	**Prolactin**	Elevated prolactin suppresses GnRH pulse [Levine and Muneyyirci-Delale (2018)].	Plays a vital role in ovarian steroidogenesis. Hyperprolactinemia can harm oocyte maturation, follicular growth and prevents ovulation [Ghumman (2015)].	Pathophysiological elevation of prolactin plays a potential role in the risk of type 2 diabetes [Wang et a. (2016); Park et al. (2011)].

The epinephrine, another physiologically active member of catecholamine family has also shown its role in the reproductive axis. Studies have demonstrated the importance of epinephrine in LH surge where it has shown that the inhibition of central epinephrine synthesis will block the estrogen and progesterone stimulated LH surge, whereas the adrenal epinephrin blockage has shown to have no significant effect on the LH surge, suggesting the stimulatory effect of central epinephrine on LH [Terry et al. (1982)]. In a study, the plasma epinephrine in PCOS patients compared with control individuals was found to be significantly high and has showed the positive correlation between plasma epinephrine to BMI and waist to hip ratio in the study [Hashim et al. (2015)]. A similar study elsewhere has showed a twofold elevation in the catecholamine induced lipolysis in PCOS women due to changes at post receptor levels [Ek et al. (2002)]. As it is well known that the dysregulated insulin can interrupt with ovarian functions, epinephrine has shown a dual activity in insulin production. Despite of the fact that epinephrine stimulates the insulin production, its dominant effect is shown to be the inhibition of insulin production. A study has demonstrated the stimulatory effect of epinephrine through β-adrenergic receptor by blocking the α-adrenergic receptor using KCl and showing the role of epinephrine in stimulating insulin secretion through β-adrenergic receptor, whereas blocking the α-adrenergic receptor for the other stimulators for insulin by which inhibiting insulin secretion [Hiatt et al. (1978)].

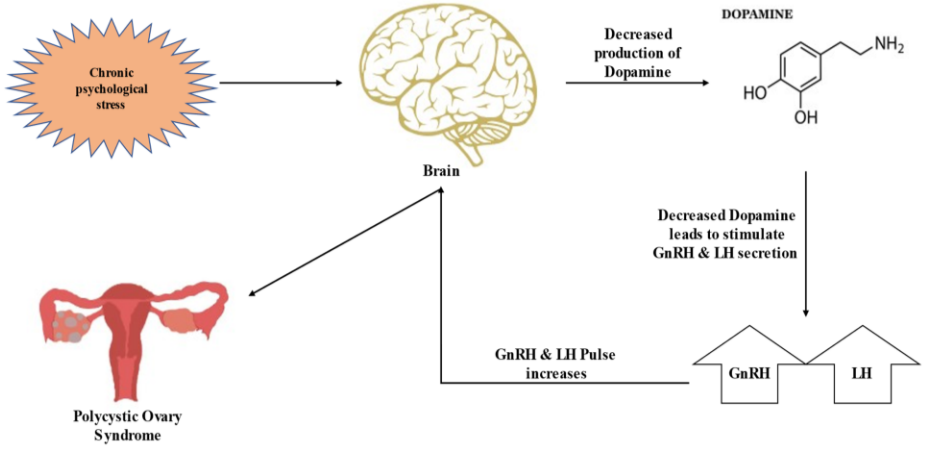

Fig. 2: Diagram representing the possible rout of induction of PCOS by decreased dopamine due to chronic stress.

c) Growth hormone (GH)

Growth hormone, a peptide hormone necessary for an individual's proper growth and development is expressed in a cluster of growth hormone (GH), chorionic somatomammotropin (CSH) and growth hormone like gene (GH2) [Owerbach et al. (1978)] with the gene spanning 5 exons showing maximum expression in placenta [Fagerberg et al. (2014)]. Psychological stress is shown to regulate the production of growth hormone in patients under emotional stress and have shown an elevation of GH from 1.9 ng/ml ±0.56 ng/ml to 6.4 ng/ml ±2.50ng/ml in the subjects under psychological conflicts [Kurokawa et al. (1977)]. Suppression of LH and prolactin (Hypoprolactinemia) in the male rats treated with GH has been demonstrated with an elevation in GH concentration significantly decreasing the LH and prolactin surge [Chandrashekar and Bartke (1998)]. A review has highlighted the role of GH in female reproductive axis and is shown to have progonadal effect of GH at physiological concentration and highlighted the anti-gonadal effect under pharmacological concentrations, with pathophysiological under high concentrations [Hull and Harvey (2001)]. The chronic elevation in GH is shown to be a potential causative criterion in insulin resistance, the phenomenon has been explained elsewhere with a demonstration of the effect of chronic elevation of GH in 3T3-L1 adipocytes, where it uncouples the insulin stimulated Phosphoinositide 3-kinase (PI 3-Kinase) and the downstream signal, including glucose transporter and protein kinase B (Akt) activation through an unknown gene expression mechanism [Takano et al. (2001)].

d) Prolactin

Prolactin, a reproductive inhibitor along the reproductive axis has shown to be inhibiting the production of GnRH in suppressing the production of FSH and LH with impairing gonadal steroidogenesis in both the sex [Levine and Muneyyirci-Delale (2018)]. PRL, the gene responsible for prolactin production spans 7 exons showing maximum expression in placenta, endometrium and minimum across testis and appendix [Fagerberg et al. (2014)]. In humans, escalation in circulating prolactin has shown to cause hyperprolactinemia resulting in anovulation due to impaired gonadotropin pulsatility and imbalanced estrogen positive feedback to LH [Matsuzaki et al. (1994)]. Study has shown the interference of prolactin with proper follicular growth preventing ovulation by inhibiting progesterone and causing premature carpus luteum disruption [Ghumman (2015)]. The importance of circulating high prolactin concentration has been deduced in a study showing the reduced risk of type 2 diabetes, whereas under pathologically higher concentration i.e., hyperprolactinemia is shown to cause the risk of insulin resistance and type 2 diabetes [Wang et al. (2016)]. A similar study has been reported elsewhere showing the exacerbated effect of high doses of prolactin on hepatic and whole-body insulin resistance in diabetic mouse model [Park et al. (2011)], highlighting it as a crucial molecule in ovarian activity and a common feature in PCOS.

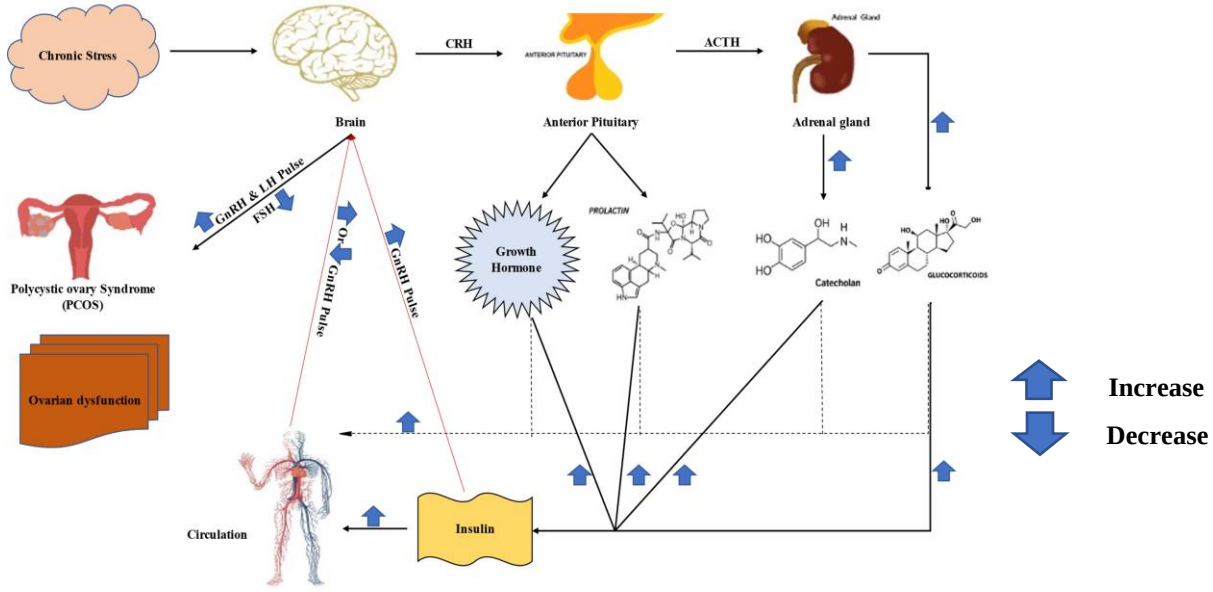

Fig. 3: Diagram representing the possible rout of PCOS induction and reproductive dysfunction from chronic stress.

Discussion and Future Perspectives

Polycystic ovary syndrome (PCOS) is emerging as a major female endocrine disorder drawing the attention due to its nature of causing irregular menstrual cycle and affecting fertility. The disease primarily occurs due to the manipulations occurring in the Hypothalamus-Pituitary-Gonadal (HPG) axis. The primary hormones that lay under this axis includes GnRH, LH, FSH and estrogen in female. The disease has been reviewed detailing dysregulation of the pulsatile secretion of GnRH leading to the decreased FSH concentration along with increased LH resulting in elevated androgen with decreased estrogen. Of the several factors leading to these criterion, psychological stress, which has been one of the vital study factors which has been reviewed to influence the onset of the condition [Zangeneh et al. (2012); Virsaladze et al (2006)]. Studies have identified the

insulin as the key regulator of the disease PCOS. The secretion and metabolism of insulin is strictly altered by these stress hormones whose physiological concentrations altered under the stress/chronic stress. Studies elsewhere have described the expression of insulin by the cells of the central nervous system besides the pancreas [Gray et al. (2014)], but it is not yet reported that what is the effect of these stress hormones on the brain insulin concentrations. A few other studies elsewhere have highlighted the potential activity of corticosteroids and glucocorticoids in causing epigenetic modifications of genes in the brain [Hunter (2012); Intabli et al. (2019)], but the epigenetic modifications with respect to the GnRH gene or some other genes that are regulating the GnRH is not well interpreted.

The future findings in the current area are required to look over the effect of stress hormones on the possible epigenetic modifications in the genes that lay along the HPA and HPG axis, regulating ovarian function that may cause polycystic ovary syndrome. The primary challenge to address the PCOS manifestations is the availability of the clinical samples for the studies. A study on rat model published in 2016 has demonstrated the formation of cystic ovaries in female rats under the imbalance in the hormones of Hypothalamus-Pituitary-Gonadal (HPG) axis, increased androgen levels, insulin, reactive oxygen species (ROS) etc., with respect to the time period of stress [Divyashree and Yajurvedi (2016)] and another study elsewhere has reported the effect of insulin in brain on the GnRH expression by knocking out the GnRH specific insulin receptors [DiVall et al. (2015)]. The current review has tried to explore the role of stress related hormones along Hypothalamus-Pituitary-Gonadal (HPG)-axis, their active role in inducing PCOS under psychological stress conditions and the potent animal model system the research could benefit in answering the questions putforth by this enigmatic syndrome.

Conclusion and recommendation

The current review has tried to explore the role of stress related hormones along Hypothalamus-Pituitary-Gonadal (HPG)-axis, their active role in inducing PCOS under psychological stress conditions and the potent animal model system the research could benefit in answering the questions put forth by this enigmatic syndrome.

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