A Review of the Physiopathological Role of Follicle Stimulating Hormone (FSH) in Reproduction and in Vascularization of Tumors

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ABSTRACT

Follicle Stimulating Hormone (FSH) is a polypeptide hormone secreted by the cells of the anterior pituitary whose primary function is stimulation of ovarian follicle to grow and mature in females. Additionally, FSH stimulates the granulosa cells in the ovarian follicle to synthesize aromatase which converts androgen produced by the thecal cells to estradiol. Estradiol in the blood primes the hypothalamus to produce stronger pulses of Gonadotropin Releasing Hormone (GnRH) leading to secretion of Luteinizing hormone (LH). Then, LH causes ovulation and the development of corpus luteum. But, in the males, FSH stimulates the Sertoli cells to secrete Androgen Binding Protein (ABP) which concentrates local testosterone leading to stimulation of spermatogenesis. However, FSH has been identified in many angiogenic vasculature of many tumors. The review tries to bring out FSH in reproduction and pathology as well as reveal certain solutions which may be useful in infertility and oncogenic therapy.

Key words: Hormone, Follicle, androgen, Sertoli cells, Oncogenic Therapy

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INTRODUCTION

Follicle Stimulating Hormone (FSH) is a 35.5 kDa glycoprotein heterodimer, consisting of two polypeptide units, alpha and beta. Its structure is similar to those of Luteinizing Hormone (LH), Thyroid Stimulating Hormone (TSH) and Human Chorionic Gonadotropin (HCG) [1].

FSH is a glycoprotein dimer with alpha and beta subunits. The beta subunit is unique to FSH, while the alpha subunit is the same as in TSH, hCG, and LH. The alpha subunits of the glycoproteins LH, FSH, TSH, and hCG are identical and consist of about 96 amino acids while the beta subunits vary [2].

Both subunits are required for biological activity. FSH has a beta subunit of 111 amino acids (FSH β), which confers its specific biologic action, and is responsible for interaction with the Follicle Stimulating Hormone Receptor (FSHR) [3].

FSH possesses sugar which makes it useful in vascularization of tumor because tumors need nutrients and oxygen to survive. The sugar portion of the hormone is covalently bonded to asparagines and is composed of N-acetylgalactosamine, mannose, N-acetylglucosamine, galactose and sialic acid [4].

The gene for FSH is expressed in two cell types, most notably the basophils of the anterior pituitary. The gene for the FSH beta subunit is located on chromosome 11p13, and is expressed in gonadotropes of the pituitary cells, controlled by Gonadotropin releasing hormone (GnRH), inhibited by inhibin, and enhanced by activin [2, 5].

In humans, the gene for the alpha subunit is located at cytogenetic location 6q14.3 [2].

Gonadotropin Releasing Hormone (GnRH) or its agonist (Leuprolide) release occurs in a pulsatile manner, with low pulse frequencies stimulating more FSH production and high pulse frequencies stimulating more LH production [6]. Continuous use of GnRH suppresses the release of FSH and LH from the anterior pituitary which inhibits ovulation and estrogen production in females [7].

Follicle-stimulating hormone (FSH) is a gonadotropin, and a glycoprotein polypeptide hormone. It is synthesized and secreted by the gonadotropic cells of the anterior pituitary gland in response to gonadotropin-releasing hormone (GnRH) released by the hypothalamus. FSH is an important part of reproductive system. It is responsible for the growth of ovarian follicles [6].

FSH regulates the development, growth and pubertal maturation, reproductive processes of the body as well as angiogenesis of some tumors. Follicle stimulating hormone and luteinizing hormone (LH) work together in the reproductive system [7, 8].

During fetal development, GnRH producing neurons develop from the epithelium of the medial olfactory pit and then migrate to the hypothalamus. The anterior pituitary gland develops from Rathke's pouch, a portion of the oral cavity. During puberty, the hypothalamus secretes GnRH in a pulsatile manner, which stimulates the anterior pituitary to increase secretion of FSH and LH [9].

In the males, FSH stimulates spermatogenesis in the testes. However, it does not act directly on the spermatogenic cells as supposed; instead FSH along with testosterone stimulates the sustentacular cells (sertoli or supporting epithelial cells which lacks a specialist function.) to release Androgen Binding Protein

(ABP), which prompts the spermatogenic cells to bind and concentrate testosterone. Testosterone in turn, stimulates spermatogenesis. Thus FSH makes the cells to be receptive to testosterone's stimulatory effects [2, 10, 11].

Also, FSH stimulates Sertoli cell proliferation, which is the most significant contributor to testicular volume in children. The Sertoli cells produce an anti-mullerian hormone (AMH), which causes the involution of the Mullerian ducts, preventing the formation of female internal genitalia [12].

Furthermore, FSH induces Sertoli cells to secrete Androgen-binding proteins (ABPs), regulated by inhibin's negative feedback mechanism on the anterior pituitary. Specifically, activation of Sertoli cells by FSH sustains spermatogenesis and stimulates inhibin B secretion. FSH, along with testosterone, is necessary for maintaining normal sperm count and function. Studies have shown that FSH deprivation not only lowers sperm count but also affects the quality of the semen. In females, negative feedback from estrogen levels inhibits FSH secretion while in males, levels of inhibin B, secreted by the Sertoli cells in response to FSH, inhibit FSH secretion through negative feedback loops [9].

The hypothalamus secretes GnRH, which stimulates the anterior pituitary to release FSH and LH. In females, FSH receptors are located in the granulosa cells of the ovaries. In males, FSH receptors are found in the Sertoli cells of the testes. In both males and females, FSH stimulates the maturation of germ cells. FSH stimulates granulosa cells in the ovarian follicles to synthesize aromatase, which converts androgens produced by the thecal cells to estradiol [9, 13].

In females, FSH initiates follicular growth, specifically affecting granulosa cells. With the concomitant rise in inhibin B, FSH levels then decline in the late follicular phase. This seems to be critical in selecting only the most advanced follicle to proceed to ovulation. At the end of the luteal phase, there is a slight rise in FSH that seems to be of importance to start the next ovulatory cycle. Low frequency Gonadotropin-releasing Hormone (GnRH) pulses increase FSH mRNA levels in the rat [5] but is not directly correlated with an increase in circulating FSH [9].

Mechanism of Action of FSH

FSH stimulates the maturation of ovarian follicles. As a dominant follicle takes over and secretes estradiol and inhibin, FSH secretion is suppressed. When the dominant follicle produces enough estradiol to maintain levels of 200 to 300 pg/ml for 48 hours in humans. The hypothalamus responds with a surge of GnRH which stimulates the secretion LH [14].

In the primates, FSH stimulates the growth and recruitment of immature ovarian follicles in the ovary. In early (small) antral follicles, FSH is the major survival factor that rescues the small antral follicles (2–5 mm in diameter for humans) from apoptosis (programmed death of the somatic cells of the follicle and oocyte). In the luteal-follicle phase transition period the serum levels of progesterone and estrogen (primarily estradiol) decrease and no longer suppress the release of FSH, consequently FSH peaks. The cohort of small antral follicles is normally sufficient in number to produce enough Inhibin B to lower FSH serum levels [9].

In addition, there is evidence that gonadotropin surge-attenuating factor produced by small follicles during the first half of the follicle phase also exerts a negative feedback on

pulsatile luteinizing hormone (LH) secretion amplitude, thus allowing a more favorable environment for follicle growth and preventing premature luteinization [13].

In both human and most animal species, the release of estradiol from the dominant follicle inhibits the synthesis of FSH and increases the pulse of GnRH which favours the secretion of luteinizing hormone leading to ovulation and stoppage of further follicular growth. However, in the Mare, at about 40-90 days of gestation, accessory corpora lutea appear due to increased FSH secretion which is normal for this animal species in early pregnancy [15].

Measurement

In humans, Follicle stimulating hormone is typically measured in the early follicular phase of the menstrual cycle, typically day three to five, counted from last menstruation. At this time, the levels of estradiol (E2) and progesterone are at the lowest point of the menstrual cycle. FSH levels in this time is often called basal FSH levels, to distinguish from the increased levels when approaching ovulation.

In women, the most common reason for an FSH test is to diagnose disorders of the pituitary gland or disease involving the ovaries as well as a woman's transition to menopause.

In men FSH test is done to evaluate a low sperm count, assess hypogonadism or gonadal failure or assess testicular dysfunction.

In children FSH test is done to determine if a child is experiencing precocious puberty or delayed puberty.

FSH is measured in International Units (IU). For Human Urinary FSH, one IU is defined as the quantity of FSH that has an activity corresponding to 0.11388 mg of pure Human

Urinary FSH (WHO). For recombinant FSH, one IU corresponds to approximately 0.065 to 0.075 µg of a "fill-by-mass" product [16, 17].

Hyper-secretion of FSH

The most common reason for high serum FSH concentration is in a female who is undergoing or has recently undergone menopause. High levels of Follicle-Stimulating Hormone indicate that the normal restricting feedback from the gonad is absent, leading to an unrestricted pituitary FSH production. If high FSH levels occur during the reproductive years, it is abnormal. Conditions with high FSH levels include:

1. Premature Ovarian Failure

Premature ovarian failure occurs when ovarian failure and menopause occur before age 40. When this happens, FSH levels are elevated due to the lack of negative feedback from the ovaries. Although there may be multiple genetic causes, most cases are idiopathic [18].

2. Premature Ovarian Aging

3. Gonadal dysgenesis

4. Castration

5. Swyer syndrome or XY gonadal dysgenesis: this is a type of hypogonadism in a person whose karyotype is 46,XY. The person is externally female with streak gonads. If left untreated, the person will not experience puberty. Such gonads are typically surgically removed as they have a significant risk of developing tumors. Medical treatment for Swyer syndrome include: hormone replacement therapy.

6. Congenital adrenal hyperplasia (CAH).

7. Testicular failure.

8. Klinefelter syndrome (KS) also known as 47, XXY or XYY. This is the set of symptoms that result from two or more X chromosomes in males. Klinefelter syndrome is one of the most common chromosomal disorders, occurring in 1:500 to 1:1,000 live male births. The primary features are sterility and small testicles. Often symptoms may be subtle and many people do not realize they are affected. Sometimes symptoms are prominent and may include: weaker muscles, greater height, poor coordination, less body hair, breast growth and less interest in sex. Intelligence is usually normal. However, reading difficulties and problem with speech are more common. Klinefelter syndrome is not inherited.

While there is no cure, a number of treatments may help: physical therapy, speech and language therapy, counseling and adjustment of teaching methods may be useful. Testosterone replacement therapy may be used in those who have significantly lower levels. Enlarged breasts may be removed by surgery. About half of affected males have a chance of fathering children with the help of assisted reproductive technology [19].

Hypo-secretion of FSH

Diminished secretion of FSH can result in failure of gonadal function (hypogonadism). This condition is typically manifested in males as failure in production of normal numbers of sperm. In females, cessation of reproductive cycles is commonly observed [18].

Conditions with very low FSH secretions are:

1. Polycystic Ovarian syndrome
Recombinant polycystic ovarian syndrome with obesity, hirsutism and infertility.
2. Kallmann syndrome characterized by delayed or absence of puberty and an impaired sense of smell.
3. Hypothalamic suppression
4. Hypopituitarism
5. Hyperprolactinemia
6. Gonadotropin deficiency
7. Gonadal suppression therapy (GnRH antagonist and GnRH agonist which eventually leads to downregulation).

FSH Levels and Infertility

In males, if testicular size is normal and patients present with azoospermia or oligospermia, FSH levels can be used to determine whether the cause is a primary impairment of spermatogenesis or obstructive. In an obstructive cause of infertility, FSH levels remain normal, while a primary impairment of spermatogenesis will present with elevated FSH levels [20].

FSH use as Fertility Therapy

Several FSH preparations have been used to treat secondary hypogonadism in males. These preparations have been reasonably successful at inducing spermatogenesis and achieving paternity [21].

FSH is used commonly in infertility therapy, mainly for ovarian hyper-stimulation as part of In Vitro Fertilization (IVF). In some cases, it is also used for reversal of anovulation. FSH is available mixed with LH activity in various menotropins including more purified forms of urinary gonadotropins such as Menopur as well as without LH activity as recombinant FSH (Gonapure, Gonal F, Follistim, Follitropin alpha) [22].

FSH in Vascularization of Cancer

Gonadotrophins are mainly known to influence the body through the formation of gonadal steroids. However, receptors for luteinizing hormone (LH) and follicular-stimulating hormone (FSH) are present in a set of extra-gonadal tissues in humans and animals, but

their functional relevance is beginning to show in angiogenesis of tumor [23].

Selective expression of FSH receptor on the surface of blood vessels of prostate cancers has recently been reported. Measuring serum FSH preoperatively in patients with prostate cancer may provide clinically relevant information about extra prostatic spread of tumor [21].

The hypothalamo-pituitary-gonadal axis regulates the production of testosterone through luteinizing hormone (LH) and FSH secretion. FSH is a key hormone in reproduction. It stimulates sertoli cell proliferation in immature testes and maintains normal spermatogenesis in adults [11]. FSH binds to FSH receptor, which is expressed in both testicular sertoli cells and ovarian granulosa cells. FSH receptor is a member of the superfamily of receptors, which is characterized by the presence of seven trans-structures coupled to G-proteins. Although FSH receptor expression has been detected in prostate tissues, the direct biological function of FSH in prostate carcinogenesis and prostate cancer progression has not been well characterized [24, 25].

Recently, FSH receptor has been detected on the surface of blood vessels in a wide range of tumors, including prostate [26]. Although signal transduction through G-protein-coupled receptors is a major biochemical pathway involved in the regulation of cell proliferation by growth factors, the exact biological function of FSH signaling in tumor vessels remains unknown. FSH receptor expression by endothelial cells may be associated with the proliferation and invasiveness of cancerous cells. Blocking FSH and/or FSH receptor signaling may be a new strategy in the treatment of prostate cancer patients [25].

Pituitary adenomas can develop from any of the cell types in the pituitary. Pituitary adenomas

derived from gonadotropic cells are most often nonfunctioning or function within normal hormone levels and are diagnosed due to symptoms from mass effect rather than hormone secretions. However, in sporadic, these tumors can secrete excess FSH and/or LH and can cause ovarian hyperstimulation [22].

Elevated FSH receptor levels have been detected in the endothelia of tumor vasculature in a very wide range of solid tumors. FSH binding is thought to up-regulate neovascularization via at least two mechanisms – one in the Vascular Endothelial Growth Factor (VEGF) pathway, and the other VEGF independent – related to the development of umbilical vasculature when physiological. This presents possible use of FSH and FSH-receptor antagonists as an anti-tumor angiogenesis therapy [27].

Oncogenic Treatment Function of FSH

Gonadotropins play an important regulatory role on migration/invasion processes of breast cancer cells and mammary tumors of female rats. This set of actions is related to the recruitment of cytoskeletal controllers and to a broader set of genes involved in breast cancer progression [28].

Therefore, using drugs that decrease the circulating quantities of FSH and LH, such as gonadotropin-releasing hormone receptor antagonists (GnRH-R antagonists) may help in controlling cancer progression. Indeed, GnRH-R antagonists are commonly used in fertile women and in men to treat hormone-dependent tumors, but they are only thought to work through the secondary suppression of steroid synthesis [26].

DISCUSSION

LH synthesized enters the general circulation and functions in the ovary to cause ovulation and the development of the corpus luteum.

In the male, FSH synthesized in the anterior pituitary is released into the general circulation and functions in the gonads to stimulate the Sertoli cells to secrete Androgen Binding Protein (ABP) which concentrates local testosterone so that spermatogenesis can occur.

The role of FSH in angiogenesis of tumor is not well established but there is strong evidence that FSH receptors are found in vascular endothelia of some tumors. Consequently, it is postulated that GnRH or FSH antagonist may be used in the treatment of tumors.

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