Mammalian Follicle-Stimulating Hormone Secretion

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Mammalian reproduction is mainly driven and regulated by the hypothalamic-pituitary-gonadal (HPG) axis. Follicle-stimulating hormone (FSH), which is synthesized and secreted by the anterior pituitary gland, is a key regulator that ultimately affects animal fertility. As a dimeric glycoprotein hormone, the biological specificity of FSH is mainly determined by the β subunit. As research techniques are being continuously innovated, studies are exploring the underlying molecular mechanism regulating the secretion of mammalian FSH.

pituitary follicle-stimulating hormone gonadotropin-releasing hormone signal transduction animal reproduction

1. Introduction

Follicle-stimulating hormone (FSH) is a glycoprotein hormone synthesized and secreted by the pituitary gland. The pituitary gland, as one of the endocrine organs of the animal, plays a crucial and pivotal role in different physiological processes of mammals due to the secretion of various hormones. In addition to FSH, the other hormones secreted by the pituitary gland are growth hormone (GH), prolactin, adrenocorticotropic hormone, melanocyte-stimulating hormone, thyroid-stimulating hormone (TSH) and luteinizing hormone (LH) [1]. Among these hormones, FSH, as one of the important gonadotropins involved in mammalian reproductive development, is secreted into the blood after synthesis by the gonadotroph cells (a type of basophilic cell) in the anterior pituitary gland (adenohypophysis). Then, it acts on the corresponding target organs of the mammals, namely the testes and ovaries, to exert its biological functions through the peripheral blood circulation [2]. Since FSH is a key regulator in the hypothalamic-pituitary-gonadal (HPG) axis, it plays an indispensable role in mammalian reproductive activities.

Some reproductive disorders are associated with the disruption of FSH secretion, and/or its signaling pathways. For instance, it has been observed that the concentration of FSH was lower in polycystic ovarian syndrome (PCOS) than in the controls [3]. In women with PCOS, it can promote follicular development by injecting an appropriate amount of exogenous FSH to supplement the low concentration of FSH caused by insufficient endogenous secretion [4][5]. The lack of FSH and FSHR may also cause difficulty in spermatogenesis and infertility in men [6]. Some preliminary data suggest a beneficial effect on live birth and pregnancy of gonadotrophin treatment for men with idiopathic male factor subfertility [7][8].

In view of the non-negligible role of FSH in mammalian reproductive development, it is very meaningful to learn about how to regulate the synthesis and secretion of FSH. In this review, we summarize the classical molecular characteristics and signaling pathways involved in the regulation of mammalian FSH secretion.

2. Function and Structure of FSH

FSH and luteinizing hormone (LH) synergistically regulate animal reproduction through specific G protein-coupled receptors (GPCRs) under physiological conditions, and they can also regulate steroid hormone production, cell metabolism and growth and other physiological activities, thereby exerting specific biological effects on the hypothalamus, pituitary, ovary, testis and other target tissues [9][10][11][12]. The formation and maturation of ovarian follicles, the proliferation of follicular granulosa cells, the synthesis of sertoli cells and leydig cells, and the development of seminiferous epithelium all require the cooperation of gonadotropins. FSH plays different functions in female animals and male animals.

In female animals, FSH stimulates the growth and development of follicles, and increases the oxygen uptake of parietal granulosa cells to promote related protein synthesis [13]. Especially in the late stage of follicle formation, FSH induces granulosa cells to express a large number of luteinizing hormone receptors and their own proliferation and induces an increase in the expression of epidermal growth factor receptor (EGFR) to promote the occurrence of ovulation under the synergistic effect of LH [14][15]. In addition, FSH treatment up-regulated the synthesis of related hormones, including progesterone [16]. The clinical manifestation that FSH-deficient women become infertile due to blocked follicle production also implies the essential role of FSH [17]. FSH can also promote differentiation of the follicular inner membrane cells, thereby promoting the proliferation of granulosa cells and the secretion of follicular fluid [18].

In male animals, FSH promotes seminiferous epithelial development and spermatogenesis [19]. Congenital FSH deficiency caused by the *FSHB* mutation could directly lead to abnormal sperm and even infertility [6]. With the emergence of recombinant FSH, more and more FSH preparations or biosimilar drugs are used in the treatment of male infertility, while the use of different FSH preparations achieved similar results in stimulating spermatogenesis in males and eventually inducing physiological pregnancy [20]. In addition, FSH has a direct effect on germ cells, such as supporting cells and spermatogonial stem cells in the testis [21][22]. The development of testes and the synthesis of testosterone are also inseparable from the participation of FSH [23].

Due to in-depth studies of FSH functions, new FSH functions are gradually being recognized in addition to the traditional physiological functions. For example, FSH may regulate the endocrine function of the rat pancreas via the FSHR [24]. FSH has also been gradually confirmed to play a potential role in bone [25], fat [26], prostate tumors [27] and other tissues. However, the detailed mechanism still needs further analysis.

FSH is a heterodimeric glycoprotein consisting of two noncovalently bound and dissociable subunits, α and β [28], and its molecular structure is similar to that of LH. For this type of glycoprotein hormone, the α-subunit is common, but the β-subunit has hormone specificity. Therefore, the β-subunit determines the biological specificity of

gonadotropins, and the transcriptional differences of genes encoding the β-subunit will directly affect the synthesis and secretion of hormones [29]. It is well known that *FSHB* is highly expressed in the pituitary gland, but an increasing number of studies have found that it is also expressed in many tissues other than the pituitary gland. In 2010, Chu et al. [24] confirmed that *Fshb* and its receptor FSHR can be expressed in the rat pancreas. In addition, FSHR has also been identified in the female reproductive tract and developing placenta, and a low-level expression of *FSHB* has been detected in the following various nonovarian tissues: gravida, maternal decidua, placenta and myometrium [30]. This also means that FSH has many unknown functions to be explored, not just limited to the HPG axis.

3. Conclusions and Prospects

The normal reproductive function and reproductive ability of animals depend on the precise regulation of various reproductive hormones, including FSH. Therefore, it may help us better understand the physiological and pathological processes, such as spermatogenesis, ovulation, the menstrual cycle, puberty, and even reproductive system diseases, if the molecular mechanisms that regulate the synthesis of gonadotropins can be determined. In recent decades, we have clarified the molecular mechanism of the overall regulation of FSH secretion. Every step of FSH synthesis and secretion is strictly controlled by the signals that mediate initial synthesis to the signals required to successfully perform biological functions. Therefore, the regulation of FSH secretion is a highly complex and multilevel network. GnRHR differentially activates a number of different signal transduction pathways in response to changing GnRH pulse frequencies. Various signaling pathways will also interweave and interfere with each other. All of these phenomena further increase the complexity of the molecular mechanism regulating FSH secretion. There are still more kinds of apparent genetic modifications that play unknown functions, although we have clarified the regulation of the FSH molecular basis and signaling pathways. Additionally, more comprehensive studies are needed to decipher the intertwined potential molecular mechanisms that regulate the synthesis and secretion of FSH in different physiological systems. These studies will help us have a clearer understanding of the internal processes regulating animal reproduction, improve the artificial regulatory system of animal reproductive processes, and even provide deeper theoretical support for the exploration and development of potential therapeutic targets and effective therapies related to reproductive diseases or other diseases affected by FSH.

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