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Follicle-Stimulating Hormone (Follitropin)

As many people know, the vast complexities and intricacies involved in the functioning of the human body are great, and one component that lends greatly to our complex physiology are hormones. Endocrinology is the study of endocrine glands that secrete these hormones into the blood, which in turn, bind to receptor molecules on target cells and effectively induce a cellular response. One such hormone of interest is the follicle-stimulating hormone (FSH), or Follitropin. FSH functions primarily in gamete preparation, in males FSH initiates spermatogenesis, the secretion of androgen-binding proteins (STP), and inhibin by Sertoli cells of the testes to convert androgen to estrogen, another hormone of interest. In females, FSH initiates follicle growth in the ovaries, the conversion of androgens to estrogen and the synthesis of inhibin through the induction of aromatase (P450arom), (Norris, Table 10-1, pg 319).

FSH is a category I tropic, glycoprotein hormone that originates in the pars distalis region of the adenohypophysis of the pituitary gland, and shares its categorization and area of origin with Thyrotropin (TSH), which is another hormone of interest by the class, (Norris, Fig. 4-3 pg 97). FSH is categorized due to its chemical structure and deemed tropic because falls into a group of peptide and protein hormones that regulate endocrine activities of the thyroid, adrenal cortex, gonads and liver, (Norris, pg 6). As with TSH and Luteinizing hormone (LH), FSH consists of a α-subunit and β-subunit.
Each of these tropic glycoprotein hormones (GpHs) has identical α-subunits, but specific β-subunits to each hormone that are responsible for their biological activity. Each subunit of FSH is, “synthesized as a separate prosubunit. Each prosubunit is coded by a different gene and modified posttranslationally…and then coupled to form a heterodimer,” (Norris, pg 111). The α-subunit of FSH contains 89 amino acids, and 115 amino acids make up the β-subunit, with a total molecular weight of 32 kilodaltons, (Wikipedia). Because the α-subunit is produced at greater levels than the β-subunit, and the β-subunit is responsible for its biological activity, transcription of the FSH-β-subunit gene (FSHB) is considered the rate limiting step in FSH’s production, essentially dictating the amount of FSH synthesized, (Bernard, et. al.). The story of FSH’s synthesis begins in the gonadotropic cells found in the pars distalis of the anterior pituitary, and is regulated by multiple members of the Hypothalamus-pituitary-gonad (HPG) axis.

In general terms the reproductive system, to which FSH is a major player, is controlled by the HPG axis, several environmental factors, and the hypothalamus-pituitary-thyroid (HPT) and hypothalamus-pituitary-adrenal (HPA) axes, (Norris, pg 317). The HPG axis is a complex series of influencing and feedback interactions between the hypothalamus, the pituitary gland found in the brain, and the gonads. Gonadotropin-releasing hormone (GnRH), which is synthesized and secreted by the hypothalamus, is the major player in FSH regulation. Although very complicated and not entirely understood, research has shown that GnRH induces FSHB expression by activating, “several mitogen-activated protein kinase (MAPK) cascades in gonadotropes, including the extracellular signal-regulated kinases 1 and 2 (ERK1/2),” (Bernard, et. al.). Three other major regulators of FSH are activins, inhibins and follistatins. Activins, “stimulate
intracellular signaling that culminates in enhanced expression of the FSHB subunit and subsequent dimeric hormone secretion,” (Bernard, et. al.). Inhibins, which are structurally related to activins, suppress FSH synthesis and release by antagonizing activins. This competitive antagonist action is accomplished by inhibin binding to activin receptors on gonadotropes, and essentially out competing activin for receptor binging sites. Increasing the effect of inhibins is the presence of betaglycan (TGFBR3), a coreceptor that increases inhibins affinity for the activin receptors. Follistatins are different structurally from activins and inhibins and suppress FSH production by binding to activins with a high affinity that prevents receptor binding. Once synthesized, as with many hormones, FSH is released into the blood where it travels to target cells such as Sertoli cells of males and follicular (granulosa) cells of females. Although the half life of FSH is not extremely lengthy at 220 minutes (~3.5 hrs), apart from triiodothyronine (T3) and thyroxine (T4) it is longer than most, (Norris, pg 49).

Once FSH reaches it target cell it binds to the follicle-stimulating hormone receptor (FSHR) located on the target cell membrane. The FSHR is a G protein-coupled receptor (GPCR) that includes seven membrane-spanning domains, an intracellular domain and an extracellular domain, consisting of 695 amino acids total and has a molecular weight of 76 kilodaltons, (Wikipedia). The FSHR protein coded for by this gene belongs to superfamily 1, or the class A, depending on the classification system of GPCRs, and over 70 organisms have orthologs with human gene FSHR, (NCBI). A few other hormones that utilize GPCRs are calcitonin, oxytocin, serotonin, and TSH. The C-terminal end of the FSHR is located intracellular and is rich in serine and threonine, which when phosphorylated increases affinity of scaffolding proteins. The seven
transmembrane-spanning domains are $\alpha$-helices containing cysteine residues that build disulfide bonds to stabilize the receptors structure, and a conserved asparagine-arginine-tyrosine triplet motif that aids conformational change during signal transmission. The N-terminal end of the FSHR is located extracellular, is glycosylated, has eleven leucine-rich repeats, and contains two subdomains. The hormone-binding subdomain is responsible for the binding affinity to the hormone, and the signal-specificity subdomain containing a sulfated tyrosine in a hinged loop is required for hormone activity, (2Wikipedia). Once bound to its receptor, FSH initiates a number of signal transductions that lead various responses specific to each cell.

One of many signal transductions initiated by FSH in Sertoli cells is the activation of the transcription factor cyclic adenosine monophosphate (cAMP) regulatory element binding protein (CREB) which leads to the production of factors necessary for germ cells as they mature into spermatozoa, (Norris, pg 54). Once FSH is bound to FSHR, the conformational change causes the receptor coupled $G_s$ proteins to interact with adenylate cyclase (AC) and in turn increase intracellular levels of cAMP. Many factors can be activated by cAMP including protein kinase A (PKA) that can regulate the expression of multiple transcription factors including CREB. FSH also causes a $Ca^{2+}$ influx mediated by cAMP and PKA that can activate CaM kinases and calmodulin, which have many effects including the phosphorylation of CREB. During puberty, FSH activates the MAPK cascade and ERKs that are also capable of activating transcription factors such as CREB, (Walker, Cheng). Another signal transduction is the activation of protein kinase B (PKB) in follicular cells that play a key role in the proliferation, differentiation, and mRNA translation of granulosa cells. Once bound, FSH again activates AC with $G_s$
proteins increasing cAMP production, which activates type I PKA. PKA promotes the
dephosphorylation of GRB2-associated-binding protein 2 (GAB2) on tyrosine 452 (Y^{452}),
and phosphorylation of GAB2 on serine 159 (S^{159}), and insulin receptor substrate-1 (IRS-1) on Y^{989}. Phosphorylation of IRS-1 on Y^{989} provides the binding site for the p85 regulatory subunit of phosphoinositide 3-kinase (P13K) to allosterically activate the p110 catalytic subunit, resulting in phosphorylation-dependent activation of PKB at threonine 308 (T^{308}) and S^{473} promoting differentiation and proliferation of granulosa cells, (Choi, et. al.). These examples are just a couple of the many signal transduction pathways FSH initiates when bound to FSHR.

Although modulations to the signal transductions of FSH are possible, there are few, if any medicines currently on the market that directly alter these pathways. Most medicines that affect FSH are fertility drugs for women that do so by either regulating FSH through control of GnRH, or act as an FSH analog. The drug Buserelin acetate is a GnRH agonist that binds to GnRH receptors (GnRHR) stimulating them and effectively increasing the levels of FSH. Conversely, Cetrorelix acetate acts in an antagonistic fashion, binding to GnRHRs and blocking them, reducing the levels of FSH. In addition, Follitropin alfa is a FSH analog that acts in the same fashion as FSH that in essence, increases the levels of FSH and thereby aiding in granulosa cell development, (Bourn Hall). There are only few drugs that effect FSH levels in males, which typically consist of recombinant FSH used to treat infertility. Although FSH plays important roles in other physiologic processes such as menopause, infertility issues supply a greater source of revenue for pharmaceutical companies.
In conclusion, FSH as with all hormones, play sometimes subtle but substantial roles in the physiology of vertebrates, through complex factors of regulation, synthesis, reception, and signal transduction. Moreover, the depth to understanding the vast interactions and affects between these hormones has only begun.

References


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