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How are communication signals read in the male reproductive system?

Receptors for gonadotropins and androgens

I. Huhtaniemi

The main regulatory signals of the male reproductive system are the two pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), that are essential for the maintenance of testicular sex hormone production and gametogenesis. FSH stimulates the prepubertal proliferation of Sertoli cells, and in adults it controls a variety of their metabolic functions that indirectly maintain spermatogenesis. LH exerts its action on Leydig cells by stimulating their production of testosterone. Testosterone or its more potent androgenic metabolite, 5α-dihydrotestosterone (5α-DHT), stimulates spermatogenesis in concert with FSH through effects on Sertoli cell metabolism. Testosterone and 5α-DHT also have extragonadal actions on the differentiation, growth and mature functions of accessory sex organs (e.g. prostate and seminal vesicle). Besides gonadotropins and sex steroids, an array of other hormones and growth factors, found either in the circulation (e.g. prolactin, glucocorticoids, thyroid hormone; endocrine action) or coming from neighbouring cells (e.g. various growth factors, prostaglandins; paracrine and autocrine action) exert regulatory actions on the reproductive system. However, there is apparently much redundancy in the para/autocrine regulation, and the physiological importance of any one single factor is difficult to demonstrate.

We describe here the cellular mechanisms of action of the two main hormonal regulators of the male reproductive system, i.e. the gonadotropins and the androgen testosterone.

Gonadotropin Receptors

FSH and LH are dimeric glycoprotein hormones secreted by the anterior pituitary gland. They bind to their cognate receptors that are located on cell membrane of Sertoli and Leydig cells, respectively. Because of protein structure of the gonadotropins they are not able to enter cells; therefore their contact with target cells has to occur through receptors residing on cell membranes. The contact triggers inside the target cell the formation of a "second messenger", that, in the case of gonadotropin action, is cyclic adenosine monophosphate (cAMP). The key events in the signalling mechanism are demonstrated in Figure 1. Besides the classical cAMP-mediated signalling, gonadotropins also activate other signalling mechanisms, such as calcium flux, protein kinase C, MAP kinase and PI3 kinase, but their importance in the overall gonadotropin action have not yet been elucidated.

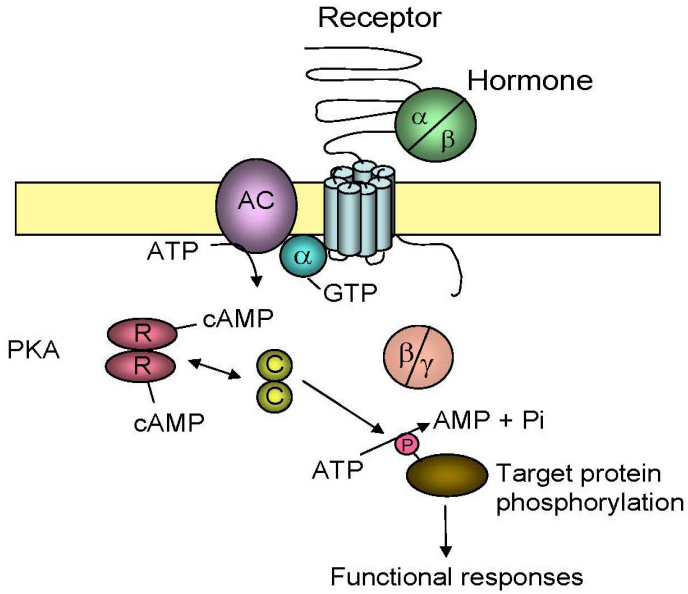

FIG. 1. **The mechanism of gonadotropin action.** LH or FSH (Hormone) bind to the extracellular domain of their cognate receptor, i.e. LH- or FSH receptor. Both are 7-transmembrane domain G-protein associated receptors (GPCRs) with long extracellular ligand-binding domain. Ligand binding induces association of guanidine trisphosphate (GTP) with the α-subunit of the heterotrimeric (alpha/betta/gamma) G-protein, thus activating the cell membrane associated adenylyl cyclase (AC) enzyme. The latter catalyzes the conversion of ATP to cyclic (c) AMP, which is the intracellular second messenger of gonadotropin action. cAMP binds to the regulatory subunit (R) of the tetrameric protein kinase A (PKA) enzyme. The liberated catalytic subunits (C) of PKA thereafter catalyze phosphorylation of target proteins (structural protein, enzymes, transcription factors), leading to alterations in their level of activation; this constitute the functional responses of target cells to gonadotropin action.

Androgens utilize a different principle of hormone action. Being small lipid-soluble molecules, steroid hormones can enter through the plasma

membrane into their target cells. For this reason, their receptors are located inside the cell, either in the cytoplasm or in the nucleus. Androgen receptor belongs, together with other steroid receptors, to the superfamily of ligand-activated transcription factors. Upon binding of testosterone or 5α-DHT, which may occur either in the cytoplasm or nucleus, the androgen receptor binds as homodimer to specific DNA elements of promoter regions of the androgen target genes, thus acting as transcription factors. The main events in this activation process are described in Figure 2.

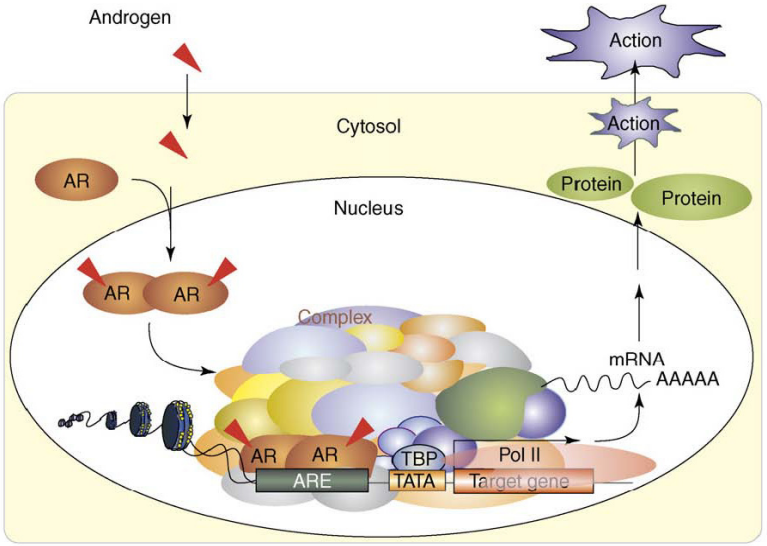

FIG. 2. **Mechanism of androgen action.** Androgens enter their target cell and bind to the cognate androgen receptor (AR), a ligand-activated transcription factor. After ligand binding AR will be homodimerized and localized from cytosol to nucleus, where it recognizes and binds to a specific DNA motif, the androgen response element (ARE) in the promoter region of androgen target genes. In addition, the binding of a number of co-regulators, forming the co-regulator complex, is required for androgen-bound AR to support ligand-dependent transcriptional control, which also iinvolve chromatin remodeling and histone modifications. The consequence is increased (sometimes decreased) transcription and translation of the androgen response genes, with subsequent functional alterations of the target cell. Abbreviations: TBP, TATA-box-binding protein; TATA, TATA box; Pol II, RNA polymerase II (from Kimura et al. 2007).

Suggested reading

Ascoli M, Fanelli F, Sgaloff DL. The lutropin/choriogonadotropin receptor, a 2002 perspective. Endocr Rev. 2002; 23: 141-74.

Heemers HV, Tindall DJ. Androgen receptor (AR) coregulators: a diversity of functions converging on and regulating the AR transcriptional complex. Endocr Rev. 2007; 28: 778-808.

Kimura S, Matsumoto T, Matsuyama R, Shiina H, Sato T, Takeyama K, Kato S. Androgen receptor function in folliculogenesis and its clinical implication in premature ovarian failure. Trends Endocrinol Metab. 2007; 18: 183-9.

Plant TM, Marshall GR. The functional significance of FSH in spermatogenesis and the control of its secretion in male primates. Endocr Rev. 2001; 22: 764-86.

Themmen APN, Huhtaniemi IT. Mutations of gonadotropins and gonadotropin receptors: elucidating the physiology and pathophysiology of pituitary-gonadal function. Endocr Rev. 2000; 21: 551-83.