Chapter 3
How are communication signals read in the male reproductive system?
Receptors for gonadotropins and androgens

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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 the production of a variety of signaling molecules and metabolites, thereby indirectly maintaining spermatogenesis. LH exerts its action on Leydig cells by stimulating their production of testosterone (T). T, or its more potent androgenic metabolite, 5α-dihydrotestosterone (5α-DHT), stimulates spermatogenesis in concert with FSH through effects on Sertoli cell function (Chapter 2). In addition, T and 5α-DHT have numerous extragonadal actions on the differentiation, growth and mature functions of accessory sex organs (e.g. prostate and seminal vesicle). Some actions of T, e.g. on bone, occur following its conversion to estradiol (E2). Besides gonadotropins and sex steroids, an array of other hormones and growth factors, present either in the circulation (e.g. prolactin, glucocorticoids, thyroid hormone; endocrine action) or originating from neighbouring cells (e.g. various growth factors, prostaglandins; paracrine and autocrine action) exert regulatory actions on the reproductive system. 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 briefly below the cellular mechanisms of action of the two main hormonal regulators of the male reproductive system, i.e. the gonadotropins LH and FSH, and the androgen T.

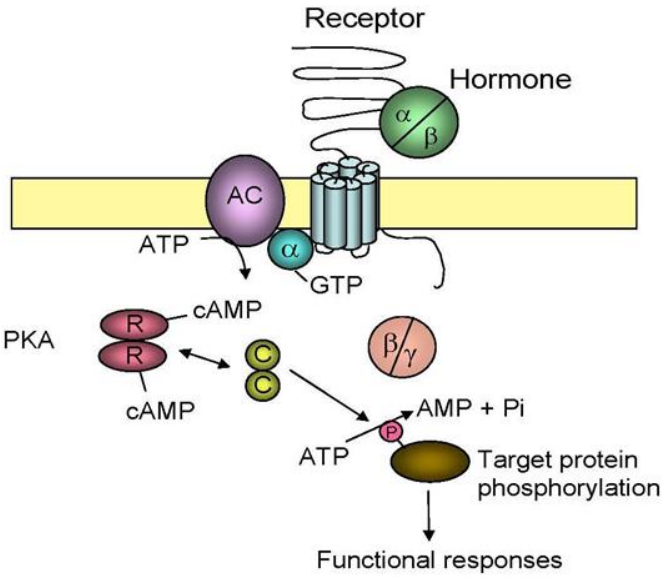

Figure 1. The mechanism of gonadotropin action. LH or FSH (Hormone) bind to the extracellular domain of their cognate receptor, i.e. LH- or FSH receptor. Both are 7-transmembrane domain G-protein associated receptors (GPCRs) and each has a long extracellular ligand-binding domain. Ligand binding induces association of guanidine trisphosphate (GTP) with the α-subunit of the heterotrimeric (alpha/beta/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 constitutes the most important functional response of target cells to gonadotropin stimulation.

Gonadotropins and Gonadotropin Receptors

FSH and LH are dimeric glycoprotein hormones secreted by the anterior pituitary gland under guidance of the hypothalamic gonadotropin-releasing hormone (GnRH). They bind to their cognate 7-times plasma membrane spanning G-protein coupled receptors (GPCR), located on the surface Sertoli and Leydig cells, respectively. The hormone-receptor contact triggers intracellularly the formation of "second messengers", of which, in the case of gonadotropin action, cyclic adenosine monophosphate (cAMP) is most important (Fig. 1). Besides the classical cAMP-mediated signalling, gonadotropins also activate other intra-cellular signalling cascades, such as calcium flux, protein kinase C, MAP kinase and PI3 kinase, but their importance in the overall gonadotropin action is still incompletely understood.

Testosterone and Androgen Receptor

Steroid hormones, including T, utilize a different principle of hormone action. Being small lipid-soluble molecules, steroids can enter their target cells through the plasma membrane. For this reason, steroid hormone receptors are located inside the cell, either in the cytoplasm or in the nucleus. Androgen receptor (AR) belongs, together with other steroid receptors, to the superfamily of ligand-activated transcription factors. Upon binding of testosterone or 5α-DHT in the cytoplasm, the ARs become dimerized, enter the cell nucleus and associate with specific DNA elements in the promoter regions of androgen target genes, thus acting as transcription factors. Another faster (within minutes) androgen action occurs through AR association with the plasma membrane and activation of intracellular kinase casades (e.g. MAPK, Akt, PKA, AMPK). The main events in the classical AR activation process are described in Fig. 2.

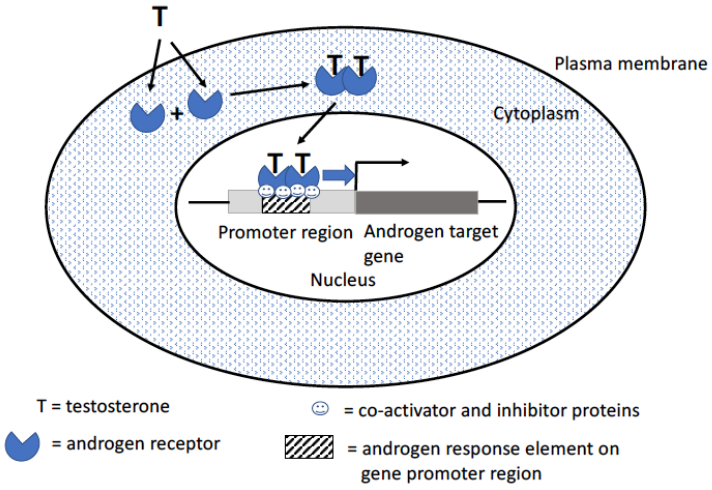

Figure 2. Mechanism of androgen action. Androgens (T) enter their target cell and bind to the cognate androgen receptor (AR), a ligand-activated transcription factor. After ligand binding AR becomes homodimerized and localized from cytosol to nucleus, where it recognizes and binds to a specific DNA motif, the androgen response element 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 involve 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.

Suggested reading

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