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Follicle Stimulating Hormone

Regulation of Secretion and Molecular Mechanisms of Action

With 132 Figures

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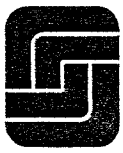

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Cell-Cell Interactions that Influence FSH Regulation of Testis Function

JOHN N. NORTON, CATHERINE TANANIS ANTHONY, AND MICHAEL K. SKINNER

Follicle stimulating hormone (FSH) is a gonadotropin secreted from the pituitary that influences the function and differentiation of the testicular Sertoli cell (Sc). This influence of FSH on Sc is mediated through activation of adenylate cyclase, followed by elevation of cAMP levels, stimulation of cAMP-dependent protein kinase, and regulation of gene expression (1–5). FSH promotes and regulates Sc function and differentiation throughout pubertal development; however, the role of FSH in the adult animal is unclear and remains to be fully elucidated.

Under endocrine, paracrine, and/or autocrine regulation, several testicular somatic cells influence testis function and the maintenance of spermatogenesis. Although FSH is an endocrine agent, FSH is speculated to promote paracrine interactions in the testis. For example, spent media from FSH-stimulated Sc has been shown to stimulate testosterone secretion from Leydig cells (6). In addition, local cell-cell interactions may also influence the actions of FSH on Sc. The focus of this chapter is a review of testicular cell-cell interactions that influence FSH actions, with emphasis on peritubular cell-Sc communication and the paracrine factor PModS.

Cell-Cell Interactions and FSH Action

Leydig Cell-Sc Interactions

Leydig cells are responsible for androgen production (7) that subsequently acts on the seminiferous tubule and maintains the process of spermatogenesis (8). Sc contain and express the androgen receptor gene (9); however, in vitro studies have demonstrated that androgens alone have less of an effect on Sc function than FSH (10). Androgens have generally been shown to have little

influence on the actions of FSH on Sc. The role androgens have in the regulation of Sc functions requires further investigation. A nonsteroidal Leydig cell product that may influence Sc function is the proopiomelanocortin (POMC)-derived peptides. Adrenocorticotropin (ACTH) and α-melanocyte stimulating hormone (α-MSH) elevate cAMP levels in Sc (11, 12), but functional effects are small. Leydig cells also produce β-endorphin (β-END), which may interact with receptors on Sc to decrease cAMP levels in FSH-stimulated Sc (13). The POMC peptides, however, require high concentrations to elicit responses in Sc cultures, and the effects are less dramatic than those seen with FSH. Further investigation of regulatory agents, such as the POMC-derived β-END is needed to elucidate the importance of Leydig cell products and their potential influence on the regulation of FSH actions on Sc.

Germinal Cell-Sc Interactions

Several important interactions exist between germinal cells and Sc. Co-culture of these cells has been shown to influence several functional parameters of Sc, such as increased androgen binding protein (ABP) production and inhibition of estradiol production (14, 15). Similar effects on Sc functions have been observed with germinal cell-conditioned medium (16). Secretory products of germinal cells may be important for regulation of FSH action on Sc. For example, nerve growth factor (NGF) has been demonstrated to be produced by germinal cells (17), and Sc express the NGF receptor (NGF-R) gene under androgen influence (18). Further investigation of germinal cell-Sc interactions requires the identification and characterization of germinal cell regulatory agents, such as NGF, that may influence FSH actions on Sc.

Peritubular Cell-Sc Interactions

Growth factors are postulated to mediate numerous regulatory interactions between peritubular cells and Sc. For example, both cell types produce TGFα and TGFβ (19, 20). Receptors for TGFα are speculated to be present on Sc (21), and lactate production by Sc may be influenced by TGFβ (22); thus, growth factors such as TGFα and TGFβ may influence FSH regulation of Sc functions. An additional interaction between these cell types is mediated through a nonmitogenic paracrine factor, PModS. This protein is produced by peritubular cells under androgen stimulation (23) and has been shown to influence Sc function in vitro to a greater extent than any individual regulatory agent previously examined, including FSH (24, 25). PModS has been purified into two potentially related forms with $M_r \approx 56{,}000$ and $M_r \approx 59{,}000$ (24), and both forms of PModS have equivalent biological activities in vitro (24, 25).

Interactions Between PModS and FSH

The effects of FSH on Sc are dependent upon the stage of pubertal development. Utilizing transferrin (Trf) secretion as a marker of Sc function, the effects of PModS on Sc function and differentiation were investigated at various stages of pubertal development. PModS alone was found to increase Trf secretion from Sc isolated and cultured from 10-day-old rats (prepubertal). Simultaneous treatment with FSH greatly enhanced the response to PModS, suggesting a potential synergism between PModS and FSH in prepubertal-age animals. In 20-day-old rats (pubertal), FSH treatment of cultured Sc resulted in approximately a 2-fold elevation of Trf secretion above control cells, while treatment with PModS resulted in an approximately 4-fold elevation of Trf secretion (25). In contrast to prepubertal Sc, no synergism on Trf secretion was demonstrated in 20-day-old Sc with the combined treatment of FSH and PModS. FSH treatment of 35-day-old Sc (late puberty) demonstrated no influence on Trf secretion. In contrast, PModS treatment of 35-day-old Sc resulted in a significant elevation of Trf secretion in long-term cultures. Further investigations are needed to examine the importance of PModS in the adult testis, as well as potential interactions between PModS and FSH.

The physiological effects of FSH are mediated by elevation of cAMP levels in Sc, and agents that elevate cAMP levels or cAMP analogs have been shown to mimic FSH actions. Following activation of many functional processes in Sc, FSH induces a refractory response that leads to a reduction in the number of FSH receptors (FSH-R) (26) and decreased activity of adenylate cyclase (27). In addition, gene expression for a high-affinity cAMP phosphodiesterase is induced by FSH (28). A cAMP inhibitory pathway that is activated by such agents as adenosine, acetylcholine, and β-END is also present in Sc (13, 29). Although no regulatory agent has been shown to regulate other second-messenger systems in Sc, potential interactions between second-messenger systems exist. For example, it has been shown that phosphatidylinositol hydrolysis in Sc leads to a reduction of FSH-induced cAMP levels (30).

The mechanism of action for PModS is unknown, but PModS treatment of cultured Sc leads to an increase in cellular cGMP levels (25) with no obvious change in cellular cAMP levels, phospholipid turnover, or calcium fluxes. Treatment of Sc with agents that activate guanylate cyclase or cGMP analogs, however, do not mimic the effects seen with PModS. Sc treated with a combination of FSH and a crude PModS preparation resulted in no change in PModS-stimulated cGMP levels, but the presence of crude PModS partially inhibited the FSH-induced cAMP response. Further investigation of the mechanism of action for PModS is needed to elucidate potential interactions between PModS and FSH on a pharmacological level.

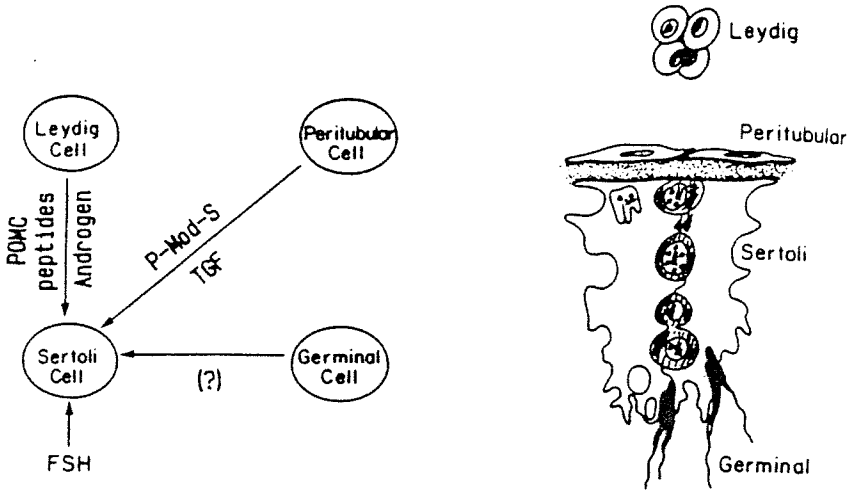

FIGURE 19.1. Current postulated cell-cell interactions of the testis that regulate FSH actions.

Summary

Interactions between the different cell types of the testis are important for normal reproductive function in the male and are speculated to be mediated by regulatory agents, such as PModS. Future identification of additional paracrine/autocrine agents will provide a better understanding of the testis cell biology. Of interest will be whether FSH stimulates the secretion of Sc products that act as paracrine agents. The paracrine factor PModS has been shown to have dramatic effects on Sc function and differentiation in culture. The speculation is made that PModS may be a differentiation factor for Sc similar to FSH. Although both FSH and PModS have been demonstrated to be important for control and maintenance of Sc function and differentiation in vitro, there is a need to examine the proposed cell-cell interactions in vivo to assess the physiological relevance of PModS and postulated interactions with FSH. The concept that FSH and androgen are the primary regulators of testis function needs to be reevaluated with a consideration of the influence of local cell-cell interactions. Data imply that these local interactions may influence the ability of FSH to regulate testis function (Figure 19.1).

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