so-called preputial sac which may be of importance for lubrication during intercourse.

References

II.1.5 Endocrine Regulation
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Summary
Pulsatile secretion of luteinizing hormone releasing hormone (LHRH) by the hypothalamus stimulates the production and secretion of the gonadotrophins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland. These gonadotrophins circulate in the blood to reach the testis. LH stimulates the secretion of testosterone and oestradiol by the interstitial cells of Leydig. Very high concentrations of testosterone surround the seminiferous tubules and these are required for spermatogenesis. Testosterone in blood induces puberty and virilization, and exerts feedback inhibition of LHRH and LH secretion, after aromatization and 5-alpha reduction at the hypothalamo–pituitary level. FSH binds to Sertoli cells, stimulating the production and secretion of enzymes and substances that support spermatogenesis. Depending on the intensity of spermatogenesis, the Sertoli cells secrete inhibin B into the blood, which exerts feedback inhibition of FSH secretion by the pituitary. Optimal spermatogenesis depends on adequate functioning of all aspects of the hypothalamo–pituitary–testicular axis, but can be deregulated by many internal and external factors.

II.1.5.1 Hypothalamic–Pituitary–Testicular Axis
II.1.5.1.1 Luteinizing Hormone Releasing Hormone (LHRH)
Maleness depends on the effects of androgens, mainly testosterone, which is needed for pubertal development (Hammond et al. 1979), body composition, growth, sexual function and spermatogenesis (Dufau 1988). The hypothalamic neurons produce and secrete a releasing factor called gonadotrophin releasing factor or hormone (GnRH), more commonly referred to as luteinizing hormone releasing hormone (LHRH). GnRH results in a preferred release of LH, and it seems to play a less determinant role in the secretion of follicle-stimulating hormone (FSH). However, a specific FSH-releasing hormone has not been detected (Schally et al. 1971), and the deficient secretion of GnRH results in failure to release both LH and FSH. The secretion of GnRH is not continuous, but rather pulsatile (Crowley et al. 1991). The so-called pulse generator (Kaufman et al. 1985; Knobil 1990) initiates pulsatility, which is inherent of the neuroendocrine cells of the hypothalamus (Knobil 1980; Marshall and Kelch 1986). It is under feedback control of testosterone (Matsumoto and Bremner 1984; Plant and Dubey 1984) which is converted to oestradiol by the aromatase of the hypothalamic cells. GnRH pulsatility is also influenced by neurotransmitters and endorphins (Veldhuis et al. 1984). It can be depressed in the case of extreme stress or physical exertion (MacConnie et al. 1986; Opstad 1992), serious disease conditions (Aitken et al. 1985), depression, malnutrition (Warren 1983) and abuse of “recreational drugs” (Kesner et al. 1986; Vescovi et al. 1992). The GnRH is transported through the portal veins along the pituitary stalk to the anterior lobe of the pituitary gland where it binds to the receptors on the gonadotropes. In physiological circumstances the GnRH–receptor complex is internalized and the GnRH receptor is upregulated (Clayton 1989). Continuous or high GnRH concentrations result in profound gonadotropes desensitization (Schumeyer et al. 1984; Matsumoto et al. 1991), involving receptor downregulation (Belchetz et al. 1978; Conn and Crowley 1991). Figure II.1.19 represents a simplified summary of the hormonal regulation of testicular function and spermatogenesis.
II.1.5.1.2
Luteinizing Hormone (LH)

The pituitary gonadotrophic hormones are LH and FSH, which are two structurally related glycoproteins. They are dimeric molecules composed of two dissimilar, noncovalently linked subunits: the alpha- and the beta-subunit (Nilsson et al. 1986). The alpha-subunit is common to both gonadotrophins, and shared with other hormones namely human chorionic gonadotrophin (hCG) and thyroid stimulating hormone or thyrotrophin (TSH). The specific activity of LH and FSH is determined by the beta-subunit. The secretion of LH closely follows the stimulation pattern by GnRH and is clearly pulsatile (Spratt et al. 1988), whereas this is much less clear for the secretion of FSH. The mean time interval between pulses of LH in eugonadal men is approximately 120 min. The amplitude of the LH pulses is determined by a complex interaction of several factors including the intrinsic responsiveness and the number of gonadotropes, the GnRH pulse frequency, the size of the bolus of GnRH secreted into the portal circulation along the pituitary stalk, and the time elapsed since the previous GnRH bolus. The amplitude of LH pulses in eugonadal men is highly variable within and between subjects. A remarkable diurnal variability of LH secretion is seen in pubertal boys, with strikingly higher amplitude pulses during night-time (Boyar et al. 1972). In adult men, diurnal variability is less pronounced and differs between subjects (Fehm et al. 1991).

In response to the LH stimulation, secretion of testosterone by the Leydig cells also presents a pulsatile pattern, but pulsatility is less distinct in peripheral blood (Veldhuis et al. 1987). Testosterone and oestradiol are co-secreted episodically (Winters and Troen 1986). The intra-testicular variability of the testosterone concentration is very large (Comhaire and Vermeulen 1976) and it follows the LH rhythmic secretion closely. The possible importance of the latter is unknown, but it has been speculated to serve as a kind of “pace maker” influencing the timing of the subsequent steps in spermatogenesis. A pulsatile pattern of LH secretion is not necessary for sustained testosterone secretion, since men with hypogonadotrophic hypogonadism can perfectly well be treated with injections of hCG, which cause prolonged and uninterrupted stimulation of the Leydig cells and normal male development. On the other hand, the absence of pulsatility may influence spermatogenesis, as treatment of hypogonadotrophic men with pulsatile administration of GnRH may result in better spermatogenesis than non-pulsatile treatment with gonadotrophins in some cases (Hoffman and Crowley 1982; Christiansen et al. 2002).

The secretion of LH is regulated by the feedback action of testosterone, influencing the pulse frequency of GnRH secretion (Bridges et al. 1993). Testosterone is aromatized into oestradiol by the hypothalamic neurosecretory cells, which reduces the amplitude of GnRH pulses (Santen 1975; Winters and Troen 1985). In certain models, the 5-alpha-reduced dihydrotestosterone
exerts feedback on the secretion of LH at the pituitary level, further influencing the LH secretion (Santer 1975; Canovatchel et al. 1994).

### II.1.5.1.3 Follicle-Stimulating Hormone (FSH)

The pattern of secretion of FSH is less clearly pulsatile (Veldhuis et al. 1989) and FSH has a relatively long half-life. FSH binds to its receptors on the cells of Sertoli and, in synergy with testosterone, it stimulates these to produce substances that are secreted into the seminiferous tubules. These are necessary for initiating and sustaining spermatogenesis (Verhoeven 1992) (see Chap. I.3.14) in a normal qualitative and quantitative manner. Once spermatogenesis has been initiated during puberty, it can be maintained by high concentrations of testosterone alone, but sperm production will not reach a normal quantity. The Sertoli cells also secrete inhibin B (Anderson and Sharpe 2000), a glycoprotein that specifically inhibits the secretion of FSH at the pituitary level (Ying 1988; Hancock et al. 1992). Inhibin B is also implicated in the paracrine regulation of spermatogenesis and may reduce sperm production. It is debated whether FSH secretion is governed, at least in part (Hayes et al. 2001b), by feedback action of testosterone (Hayes et al. 2001a) or rather by oestradiol. The concentration of inhibin B in serum also reflects the level of spermatogenesis and its quantity. It is reduced in cases with incomplete or absent spermatogenesis (Pierik et al. 2003), and is inversely correlated with sperm concentration (Mahmoud et al. 1998).

### II.1.5.1.4 Prolactin and Melatonin

The role of prolactin in endocrine regulation is complex (Bartke 1977). High concentrations of prolactin inhibit the secretion of GnRH and LH (Winters and Troen 1984) causing hypoandrogenism, whereas lower concentrations may strengthen the effect of LH on the Leydig cells through interaction with the LH receptor and androgen metabolism (Magrini et al. 1976).

Long-term melatonin administration does not alter pituitary gonadal hormone secretion in normal men. Sleep parameters are influenced by melatonin, whereas the mean nocturnal LH, FSH, testosterone and inhibin B integrated values do not change (Luboshitzky et al. 2000).

### References


