Gonadotrophins – luteinizing hormone and follicle stimulating hormone

LH and FSH are secreted from the gonadotrophs, which make up 10–15% of cells in the anterior pituitary. The glycoproteins LH and FSH are composed of a common α-subunit and individualized β–subunit. Variation of the carbohydrate post-translational modification (i.e. the 'glyco-'part;) leads to substantial subtle variation (microheterogeneity).

Effects and mechanism of action

LH and FSH regulate gonadal function in males (testosterone biosynthesis and spermatogenesis in the testis) and females (oestrogen and progesterone biosynthesis in the ovary, and the menstrual cycle). Both hormones act through cell-surface G-protein–coupled receptors linked to cAMP second messenger signalling.

Regulation of production

The production of gonadotrophins is stimulated by the hypothalamic 10-amino acid hormone, GnRH, which binds to its G-protein–coupled receptor on the cell surface of the gonadotroph and is linked to cAMP second messenger signalling. Factors such as stress and prolactin act negatively (see Figure 1). Like the hypothalamic–anterior pituitary axes regulating the adrenal cortex and thyroid, hormones secreted by the testis and ovary(steroid sex hormones and inhibins) exert negative feedback on the production of both GnRH and gonadotrophins (see , Figures 2).

Clinical disorders

Excess gonadotrophins

Increased levels of both gonadotrophins almost always reflect loss of negative feedback from the testis or ovary. Usually, primary testicular or ovarian failure yields serum LH and FSH levels several fold higher than the upper limit of normal. The commonest cause of this gonadotrophin overactivity is physiological after the menopause when ovarian depletion of ova ends cyclical hormone production in women. Excess gonadotrophin secondary to increased GnRH stimulation is rare. In contrast, inappropriately timed rather than excessive production causes central precocious puberty. A pituitary adenoma secreting functional LH or FSH is incredibly rare. Commonly, however, non-functioning pituitary adenomas may stain by

immunohistochemistry for the α-subunit, perhaps giving an indication of the developmental lineage, but little else.

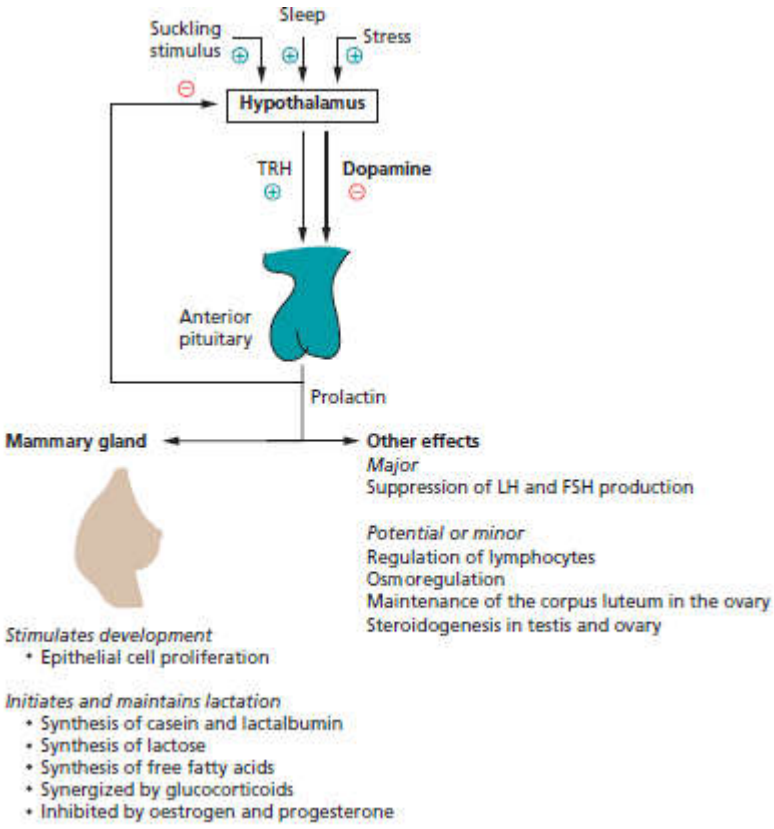

Figure 1 Summary of the regulation and effects of prolactin. For the influences on the hypothalamus, the + and – symbols reflect their net effect on prolactin secretion. The bold arrow for dopamine reflects its predominance as a regulatory factor compared to thyrotrophin releasing hormone (TRH). LH, luteinizing hormone; FSH, follicle stimulating hormone.

Deficiency of the gonadotrophins

During childhood, it is normal for the gonadotrophins to be low and relatively unresponsive to GnRH; however, continued gonadotroph inactivity will delay. This can be tested by GnRH stimulation when serum LH and FSH are measured 30 and 60 min later. A normal response is a two- to three-fold increase from basal serum levels. After puberty, loss of gonadotrophins causes secondary hypogonadism. In women, this is very common at some stage of the reproductive years as cyclical gonadotrophin secretion is very vulnerable to ‘stress’, such as major exercise (e.g. marathon running), excessive dieting or, most commonly, emotional anxiety of relatively minor proportions. A rise in prolactin levels is also sufficient to suppress LH and FSH production . Several syndromes from mutations in any one of a number of genes also

result in loss of gonadotrophins because of absent GnRH. **Kallman syndrome** is a combination of absent GnRH-secreting neurones and lack of smell (anosmia). Clinically, it is important to realize that, in the face of significant hypogonadal symptoms and signs, and low levels of sex hormones, gonadotrophins within the normal range are inappropriately low. In women, where significant fluctuation of gonadotrophins accompanies the normal menstrual cycle, this can be more difficult to identify. It tends to manifest as amenorrhoea with low or undetectable serum oestrogen. In both sexes the disorder is described as 'hypogonadotrophic hypogonadism' (Box 5.8; see Chapter 7).

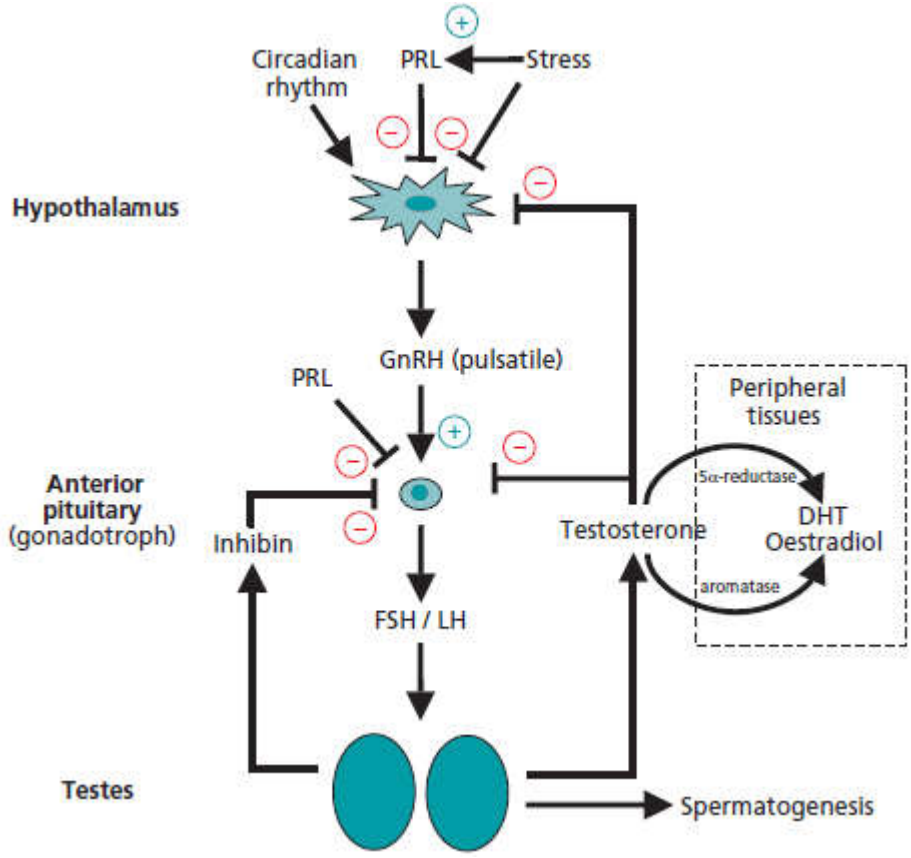

Figure 2. The hypothalamic–anterior pituitary–testicular axis. Negative feedback at the gonadotroph and hypothalamus is complex and involves: 5α- dihydrotestosterone (DHT) and testosterone on luteinizing hormone (LH); and inhibin, testosterone and oestrogen on folliclestimulating hormone (FSH). Prolactin (PRL) exerts a negative influence on gonadotrophin release, probably via altering gonadotrophin-releasing hormone (GnRH) pulsatility and action. Stress inhibits GnRH release and action at least in part by stimulating PRL.

Amenorrhoea

Ovarian hormone disruption causes loss of ovulatory cycles and, consequently, absence of periods. Amenorrhoea can be classified as either primary (periods never started) or secondary (periods started but now absent for >6 months); this distinction becomes arbitrary when the same pathology underlies both. Clinically, in determining the cause, the first task is to assess whether oestrogen is present or absent.

Precocious puberty

Precocity may result from either the normal process, driven by GnRH pulses, occurring abnormally early (central or true), or aetiology extrinsic to the hypothalamic–anterior pituitary–gonadal axis that results in premature sex steroid biosynthesis. Precocity may be caused by oestrogen in boys and androgen in girls, leading to inappropriate feminization or virilization respectively (contra-sexualprecocity). The goal is to treat the underlying cause and avoid significant disruption of psychosocial development or the attainment of predicted final height. It needs to focus on the individual cause. For true precocity, continuous GnRH can be used to suppress the pituitary gonadotrophins. For isolated premature breast development (‘thelarche’), reassurance is appropriate