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20. Steroids in Male Reproduction
THE ROLE OF TESTOSTERONE AND OTHER HORMONES IN REGULATION OF LH

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SUMMARY

Although many data suggest a role for oestrogen in the negative feedback for LH in the rodent, more recent studies indicate that testosterone or 5α-dihydrotestosterone is also important. Nonaromatizable androgens decrease LH, and in several diseases LH is high when plasma testosterone is low, even though plasma oestradiol is normal. Testosterone and oestradiol modulate the response to GnRH differently. In recent studies in men using an inhibitor of aromatization, a role for both testosterone and oestradiol was demonstrated. Finally, there are data to suggest that a tubular factor and excessive secretion of glucocorticoids or prolactin can affect LH release.

Plasma LH concentrations are regulated by secretions from the testis. However, the relative importance of these secretions and the nature of the proximal regulatory hormones at central nervous system sites remain in question. Additionally, during the past 5 years, analyses of several clinical problems have suggested that there are other fine-tuning mechanisms whose importance must still be assessed.

The negative feedback relationship seemed quite straightforward when it was shown that castration increased LH and that administration of testosterone decreased it [1, 2]. Two groups of investigators found that administration of testosterone or its 5α-reduced metabolite, dihydrotestosterone, decreased the frequency of the pulses of LH [2, 3]. Fluoxymesterone, a synthetic androgen, acted as did testosterone [2].

Naftolin, Ryan and their coworkers have extensively discussed the possibility that oestradiol is the proximate hormone acting at LH receptors [4]. The evidence for this is derived from many sources. The testis is responsible for about 80% of plasma oestradiol, either by direct secretion [5] or peripheral aromatization of testosterone [6]. The hypothalamus can aromatize C_{19}-steroids to oestrogens [4] and contains oestrogen receptors [7]. In the rodent, oestradiol given during the neonatal period promoted a male pattern of gonadotropin secretion and behavior. And clomiphene, an antioestrogen but not an antiandrogen, suppressed the LH response to GnRH [8, 9]. Thus, they have made an impressive argument for the role of oestrogen in the regulation of LH secretion.

However, in the 3 years since Naftolin's summary of the role of oestrogens, the evidence that androgens are major modulators of responses in the central nervous system has become convincing. Androgen target cells have been located in the hypothalamus with a distribution different from that for oestradiol [10] and the androgen receptors have been characterized [7, 11]. Nonaromatizable androgens decreased LH secretion, and did so by a different mechanism than did oestradiol [2, 3]. Santen[3] showed that oestradiol reduced the height of the LH pulses in normal men, whereas testosterone reduced the frequency of these pulses.

In contrast to the effect of oestrogen in the rodent, nonaromatizable androgens maintain male pattern behavior in the monkey [12] and in man.

There are a series of clinical conditions that support the importance of testosterone or its immediate metabolite, dihydrotestosterone, for LH regulation. In testicular feminization, where testosterone action does not occur, LH levels are high in spite of normal plasma oestrogen levels [13, 14]. Nevertheless, LH may be lowered by administration of oestrogen [2]. Thus, at the concentrations of testosterone and oestradiol found in normal males, LH release seems to depend critically on androgen. In ageing men, the decrease in plasma free testosterone is accompanied by an increase in LH, even though plasma oestradiol remains unchanged [15, 16]. In Klinefelter's syndrome, the plasma LH is increased in response to low plasma testosterone levels in spite of increased oestrogen production rates [17] and plasma oestrogen concentrations [18].

Recent experimental studies [19] have shown that both testosterone and oestradiol are regulatory hormones in the normal state. An inhibitor of aromatase, Δ^1-testololactone, was given to normal men, and it was noted that plasma oestradiol decreased and LH increased, However, when testosterone was infused into men receiving Δ^1-testololactone, oestradiol remained unchanged, plasma testosterone increased and LH fell. Thus, within the physiologic range, both testosterone and oestradiol exerted effects on plasma LH.

In a careful series of experiments [20], the role of testosterone in LH regulation in the rhesus was clarified. Immediately after castration, silastic capsules containing either testosterone or oestradiol were implanted. The LH levels remained at precastration levels. When the oestradiol-containing capsules were

withdrawn, LH levels were maintained. However, when testosterone replacement was withdrawn, LH increased. An additional point of interest was that the testosterone in the capsules was supplemented with single daily injections of testosterone to stimulate the clinical variation. In an earlier study from the same laboratory [21], maintenance of an unchanging plasma testosterone level permitted plasma LH to rise.

To summarize the evidence, then, it is probable that oestradiol and testosterone (or some nonestrogenic metabolite) are the primary controls of LH secretion.

Inhibin has been suggested as a specific regulator of FSH secretion, and the data supporting this have been summarized [22]. However, there are also some findings that suggest that a tubular factor influences LH secretion [22]. In a clinical study, LH was correlated with plasma testosterone only in men with severe tubular damage [23]. In normal men, there was no correlation suggesting additional regulatory mechanism. An experimental counterpart of this is the effect of local testicular radiation in the rat. Both LH and FSH increased, although plasma testosterone and oestradiol were unchanged [24], suggesting that tubular damage affected gonadotropin release by a mechanism other than steroid hormone feedback.

It also seems probable that glucocorticoids can alter LH synthesis of release. A comprehensive study of the testis–pituitary axis in Cushing's syndrome [25] disclosed that plasma testosterone and plasma LH were low and the response to GnRH was decreased. These aberrations disappeared with cure of Cushing's syndrome.

Prolactin, too, may have an effect within the central nervous system. In women with hyperprolactinemia, plasma gonadotropins tend to be low in spite of decreased plasma oestrogens. Similarly, in men with high plasma prolactin concentrations, testosterone and LH levels were low [26]. After a decrease in prolactin in response to bromocriptine, both testosterone and LH increased, showing that it was prolactin and not the pituitary adenoma itself that was responsible for the effect.

There are many studies of the effect of GnRH on LH and FSH secretion in man and many other species. There is general agreement that GnRH is required for LH and FSH synthesis and release. What has not been established is the modifications of response to GnRH that are imposed on the pituitary by the steroid hormones. In order to dissociate steroid effects on the pituitary from those on the hypothalamus, the actions of oestradiol and testosterone on the response to GnRH were tested in the stalk-sectioned castrate male rat [27]. At a given dose of oestradiol and a high dose of GnRH, the effect of GnRH was potentiated. Testosterone at certain doses depressed the response to GnRH. The important point of the study was that the effect of the steroid hormones was related to both the quantity of steroid and the dose of GnRH.

From several other studies, the effect of a given dose of GnRH may also be dependent on duration of treatment with steroid and the pattern of the steroid plasma concentration (steady state vs diurnal variations). In man [2], oestradiol infusion at twice the daily production rate suppressed the response to GnRH, whereas testosterone given at a similar ratio was without effect. It does not seem likely that it will be possible in men to dissect the effects of the steroid hormones in the dynamic situation of changing responses at pituitary and hypothalamus, as well as the effects of small variations in steroid hormone levels.

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