7. LH-RH AGONISTS: INHIBITION OF TESTICULAR FUNCTIONS AND POSSIBLE CLINICAL APPLICATIONS


While discovery of the structure of LH-RH (Matsumo et al., 1971) and the relative ease of synthesis of the decapeptide and its analogues has led to a rapid increase in our knowledge of the control of LH and FSH secretion, the use of these gonadotropin-releasing peptides in the treatment of oligospermia and male infertility has had limited success (Schwarzstein, 1976). It thus has become important to analyze in detail the effects of such treatment with LH-RH agonists in experimental animals in an attempt to gain a better understanding of the mechanisms involved and to improve clinical treatment.

In this chapter, we discuss the inhibitory effect of two LH-RH agonists, [D-Leu\textsuperscript{6}, des-Gly-NH\textsubscript{2}\textsuperscript{10}]LH-RH ethylamide and [D-ALa\textsuperscript{6}, des-Gly-NH\textsubscript{2}\textsuperscript{10}]LH-RH ethylamide, on testicular gonadotropin receptors, steroidogenesis, and spermatogenesis in the adult male rat. In addition, the inhibitory effects of single intranasal administration of another LH-RH agonist, [D-Ser(TBU\textsubscript{6}) des-Gly-NH\textsubscript{2}\textsuperscript{10}] LH-RH ethylamide on androgen formation in normal adult men is also described. Such data suggest the possible clinical use of LH-RH agonists in the treatment of androgen-dependent pathologies such as prostatic carcinoma and benign prostatic hyperplasia, and as a new approach in male contraception.

1. INHIBITION OF TESTICULAR GONADOTROPIN RECEPTORS BY SHORT-TERM TREATMENT WITH LH-RH AGONISTS

Following our first report that single injection or daily treatment for one week with a relatively large dose (1.8 \(\mu\)g) of the potent LH-RH agonist [D-Leu\textsuperscript{6},des-Gly-NH\textsubscript{2}\textsuperscript{10}] LH-RH ethylamide led to a marked reduction in testicular weight, LH receptor levels, and plasma testosterone concentration (Auclair et al., 1977a and b), the effect of lower and more physiological doses of the LH-RH agonist was studied. Groups of rats were injected with saline or increasing doses (0.008, 0.04, 0.2, 1.0, or 5.0 \(\mu\)g) of [D-Leu\textsuperscript{6}, des-Gly-NH\textsubscript{2}\textsuperscript{10}] LH-RH ethylamide once (0800 hours) or three times a day (0800, 1600, and 2400 hours). The last injection was at 0800 hours on day 7 and the rats were decapitated 24 h later.

There was a significant loss of testicular LH/hCG receptors in animals treated with as little as 8 ng of the LH-RH agonist (30\%) with a maximal effect (80\%) occurring between 40 and 200 ng (Fig. 1a). Interestingly, the desensitizing effect of the LH-RH agonist was more apparent in animals injected once rather than three times a day. Figure 1b shows that a similar inhibitory effect was seen on testicular PRL receptor levels, a maximal effect being observed at 200 ng of the LH-RH agonist. Since treatment with doses of 40 ng or higher of the LH-RH agonist led to a reduction in testis weight, it is important to mention that a similar inhibitory pattern was observed when LH and PRL receptor levels were expressed per gram testis.

Although the total number of FSH receptors decreased after treatment with [D-Leu\textsuperscript{6}, des-Gly-NH\textsubscript{2}\textsuperscript{10}] LH-RH ethylamide, this effect was not significant when expressed per gram testis. It could also be seen that plasma testosterone levels as well as testis and seminal vesicle weight were reduced after treatment with doses of 40 ng or higher of the LH-RH agonist.

Before performing long-term studies on the effect of treatment with the LH-RH agonist, we next investigated the time course of changes in LH receptor levels after a single injection of increasing

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2. INHIBITION OF TESTICULAR STEROIDOGENESIS BY SHORT-TERM TREATMENT WITH LH-RH AGONISTS

The above-mentioned studies have shown that treatment of adult male rats with LH-RH or its agonistic analogues leads to a marked loss of testicular LH receptors accompanied by decreased testis, ventral prostate, and seminal vesicle weight as well as lowered plasma testosterone concentration (Auclair et al., 1977a and b, 1978; Labrie et al., 1978).

Studies performed with rat Leydig cells desensitized by human chorionic gonadotropin (hCG) treatment have shown that the hCG-induced desensitization process was accompanied by a defect of 17.20-desmolase activity (Cigorraga et al., 1978). Moreover, it could be clearly seen that the extent and nature of the block in the androgen biosynthetic pathway are highly dependent upon the dose of hCG used. In order to analyze the steroidogenic pathway during desensitization induced by LH-RH agonist treatment, we have studied the time course of the effect of daily administration of 1 μg of [D-Ala6, des-Gly-NH210] LH-RH ethylamide on testicular and plasma levels of steroid intermediates. Changes in testicular LH, prolactin, and FSH receptor levels have been correlated with changes in steroidogenesis.

A transient increase in the ratio of progesterone to pregnenolone was observed up to day 2, while the ratio of 17-OH-progesterone to progesterone decreased rapidly after LH-RH agonist treatment, thus suggesting a rapid inhibition of 17-hydroxylase activity (Fig. 3). The progressive and dramatic fall in testicular androstenedione and testosterone levels after treatment with the LH-RH agonist is well illustrated in Fig. 4. An approximately 25% inhibition of the concentration of these two steroids is already seen at 24 h with a progressive decrease to 5%–15% of control at day 4. The inhibitory effect on 5α-dihydrotestosterone levels is, however, of