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LH AND FSH RESPONSES TO GnRH IN HEALTH AND DISEASE

R. J. DASH, R. SIALY and N. S. RAO
Department of Endocrinology, Postgraduate Institute of Medicine Education and Research, Chandigarh, India

Summary—LH and FSH responses to intravenous bolus GnRH were evaluated in healthy men and women and in patients with various hypothalmo–pituitary disorders. Higher LH FSH responses to GnRH were recorded. In prepubertal girls FSH responses were higher than those of LH; however, while FSH responses remained unaltered through pubertal development stages 2–5, there was a progressive increase in LH response during that period. GnRH test was marginally useful in diagnosis of delayed puberty but more so in hypogonadotropic hypogonadism and true precocious puberty. In experimental hyperprolactinemia, GnRH induced a near normal LH response but caused an exaggerated FSH response, which was normalized after clomiphene treatment. GnRH test was found to be useful to assess pituitary reserve of gonadotropins in a variety of clinical situations involving hypothalamo–pituitary gonadal axis.

INTRODUCTION

GnRH, a decapeptide characterized in the laboratories of A. V. Schally and Roger Guillemin [1, 2] has now been commercially made available. Histidine and trytophan at 2 and 3 positions are critical for receptor activation and glycine at positions 6 and 10 are critical for maintaining the structural conformation and particular binding characteristics [3, 4]. Inactivation occurs by proteolytic cleavage of the bond between glycine and leucine at 6 and 7, amino acid substitutions at 2 or 3 positions result in antagonistic action while those at 6 or 10 in super-agonistic action [4].

Simulation of LH and FSH secretions occur on intravenous or nasal administration of GnRH [5]. GnRH receptors have been localized on the pituitary gonadotropes [6], a single cell population that produces and secretes both LH and FSH [7]. No significant side effects have been noted with intravenous GnRH or nasal GnRH administration. However, the absolute amounts in increments of LH and FSH vary in different laboratories, depending on the nature of immunoassay and the reagents employed.

LH, FSH RESPONSES TO GnRH IN NORMAL MEN AND WOMEN

A linear-log dose–relationship has been demonstrated for LH response to intravenous GnRH in adult men over a range of 1–3000 μg and perhaps the same range in early follicular phases of normally menstruating women [8]. In general, the responses are higher in females than in males (Fig. 1), and in cycling females, increasing response in late follicular phase with maximal responses around and mid-cycle and comparatively higher responses in the luteal phase [9]. Woolsen *et al.*[10] showed that the slope of the LH response to GnRH was steeper in the luteal phase than in the follicular phase. Progressive rise in estradiol in the follicular phase with the consequent priming effect on the gonadotropes accounts for higher response in late follicular phase, around mid-cycle and later perhaps as a carry out effect in luteal phase.

EFFECT OF AGE ON LH, FSH RESPONSES TO GnRH

Age related LH and FSH responses to 50 μg bolus GnRH were studied in a group of female subjects from the 1st to 8th decades. The gonadotropin response varies with age of the subject (Fig. 2). In prepubertal girls, the LH response to GnRH was minimal but the FSH response was higher; the increment being about three times the basal value. However, while the FSH response remained unchanged through pubertal stages 2–5, the LH response showed a progressive increase. In the peri-

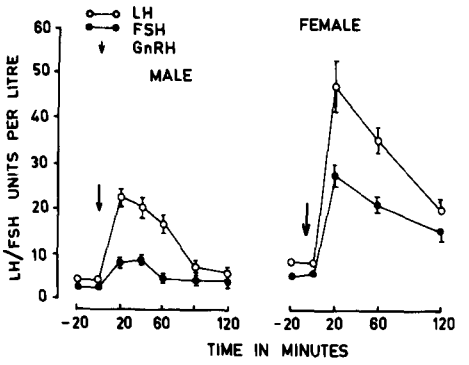

Fig. 1. LH and FSH responses to GnRH in adult males (n = 10) and cycling females (n = 10) in the follicular phase. Note higher mean responses in females.

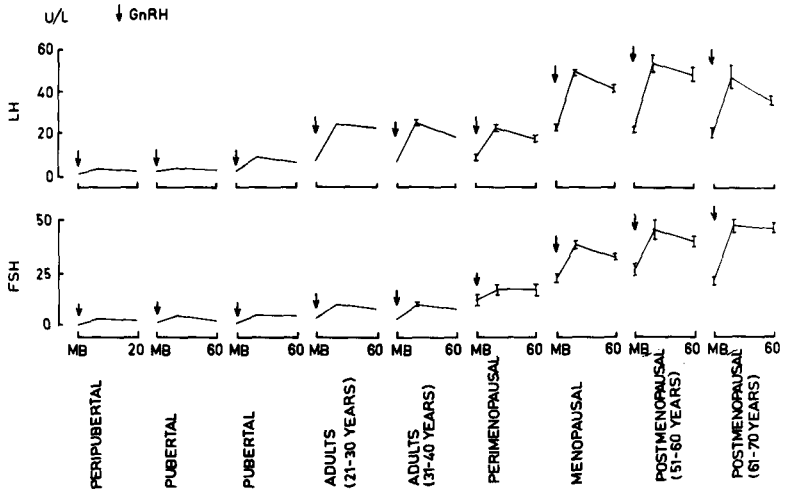

Fig. 2. LH and FSH responses to GnRH in females at different stages of sexual maturation and menopause.

menopausal period, age 51–45, the LH response was similar to that in the adults but the FSH response was comparable to that in menopause and postmenopausal subjects, age 50 and above. Bolus GnRH administration during menopause and postmenopause elicited a substantial rise in LH and FSH, though the magnitudes of the responses were lower than those at other stages of female sexual maturation.

CIRCADIAN VARIATIONS IN LH AND FSH RESPONSES TO GnRH

We studied circadian variations, if any, in the LH and FSH responses to GnRH in adult men, using a bolus GnRH at 0600, 1200, 1800 and 2400h at weekly intervals. There was no significant change in peak, and LH and FSH responses to the GnRH bolus [11].

We have employed GnRH test in the following circumstances mainly to evaluate (a) responsiveness of the pituitary gonadotropes and (b) to study LH, FSH reserve in various pituitary dysfunction.

DELAYED PUBERTY AND PRECOCIOUS PUBERTY

Differentiation between the constitutional delay in growth and development from that of idiopathic hypogonadotropic hypogonadism in boys still remains an enigma. It has been generally recommended that evaluation of such patients be undertaken if no evidence of sexual maturation occur by age 14 in boys and age 13 in girls [12]. In over 95% of boys the testicular volume will exceed 12 ml by age 14 as assessed using Prader's orchidometer [13]. Use of GnRH bolus generally results in increments of LH and to a lesser extent of FSH over the circulating

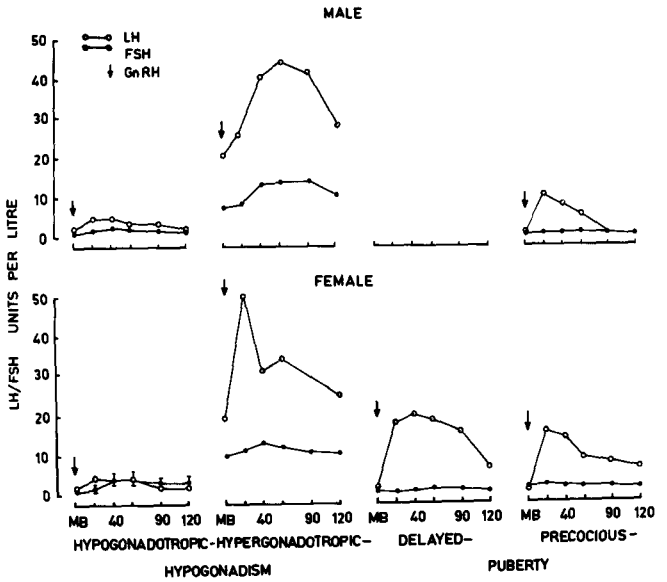

Fig. 3. LH and FSH responses to GnRH in disorders of puberty.

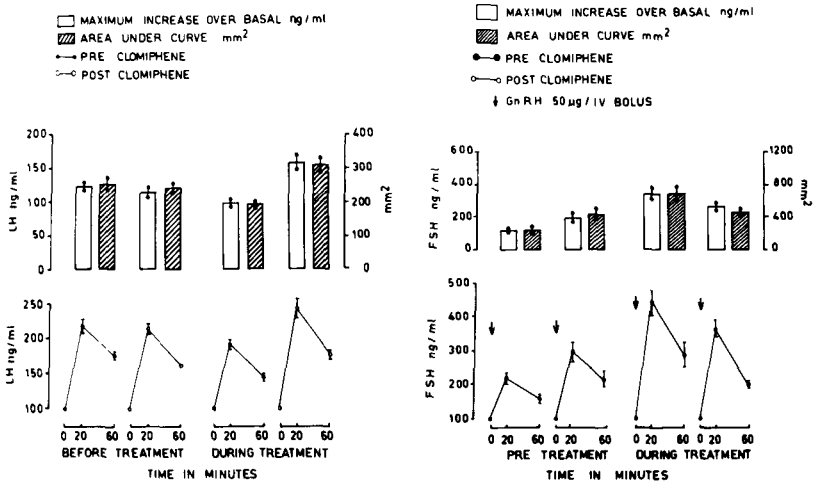

Fig. 4. LH and FSH responses to GnRH before and after clomiphene, before and during sulpiride-hyperprolactinemia in rhesus monkeys. Note the lowering of FSH responses to GnRH after clomiphene during sulpiride-hyperprolactinemia.

basal values in boys with delayed puberty but not in those with idiopathic hypogonadotropic hypogonadism. Compared to normal prepubertal boys, those with delay in the onset of puberty often have higher levels of basal gonadotropins and a greater cumulative response ratio, to a single injection of 25 μg GnRH [14]. We have further found a useful guide in prolactin (PRL) response studies using chloropromazine (CPZ) as a distinctive value in this clinical condition. With androgenic exposure a significant PRL response to CPZ occurs in subjects with delayed puberty while none so in hypogonadotropic hypogonadism [15]. In true precocious puberty we noted a near normal LH and FSH response in the postpubertal range (Fig. 3).

MENSTRUAL CYCLE DISORDERS

There are innumerable publications on GnRH test evaluating patients with menstrual cycle disorders. Various schemes for the diagnostic evaluation of amenorrhoea have been proposed and currently available test evaluated [16]. The approaches in general, are investigator/clinician oriented depending on the modes of therapy available at a particular center. After a thorough assessment of patient's history, physical examination, analysis of the reasons for referral and baseline investigation, only a small percentage of patients with amenorrhoea require GnRH test. Hyperprolactinemia accounts for 30% of patients with secondary amenorrhoea and infertility with or without galactorrhoea [17]. We like others [18, 19] have noted basal prolactin measurements to be of immense value in diagnosis of pituitary microadenoma, in whom dynamic tests employing TRH, chloropromazine as well as the LH and FSH response to GnRH are of limited or negligent value. Some hyperprolactinemic secondary amenorrhoea patients with low circulating gonadotropins and absent response to GnRH require exogenous gonadrotropin therapy along with bromocryptine for induction of ovulation. We noted that in female rhesus monkeys rendered hyperprolactinemic with sulpiride, clomiphene citrate administration (2.5 mg/kg body weight daily) could induce ovulation in 4 of the 8 animals [20]. During sulpiride-hyperprolactinemia GnRH induced an exaggerated FSH but near normal LH response (contrary to reports of decreased LH and FSH response in some hyperprolactinemic females). In these monkeys clomiphene normalizes the gonadotropin responses to GnRH, perhaps by its estrogen like effect (Fig. 4).

GnRH test is of no value in diagnosis of primary amenorrhoea except for a minority of patients where GnRH deficiency is considered a cause. Such patients would benefit from GnRH therapy employing its super analogues. Similarly GnRH test is of no value in evaluating patients of premature menopause and Savage syndrome (resistant ovary syndrome) where basal gonadotropins are evaluated. Distinction between the two could be made by studying ovarian morphology. It would thus be apparent that the usefulness of GnRH is extremely limited in menstrual cycle disorders.

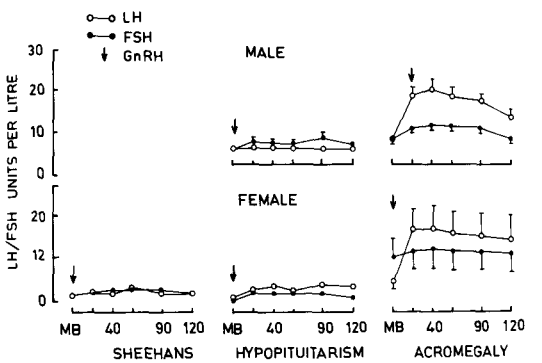

Fig. 5. LH and FSH responses to GnRH in pituitary disorders.

HYPOTHALAMIC AND PITUITARY DISORDERS

LH, FSH response studies following GnRH are very useful in distinguishing hypothalamic from pituitary causes accounting gonadal dysfunction [21]. We have extensively used GnRH test to study pituitary reserve of LH and FSH in acromegaly, postpartum pituitary necrosis (Sheehan's syndrome) and in assessing the hypothalamo-pituitary–gonadal axis in patients with Bardet–Biedl syndrome. The gonadotropin response to GnRH in acromegalics were considered normal. In 50% of acromegalics GnRH also induced a rise in GH. In patients with post-partum pituitary necrosis LH and FSH responses to GNRH bolus were lower than those in control subjects (Fig. 5). In 5 patients with Bardet–Biedl syndrome gonadotropin responses to GnRH were highly variable, varying from subnormal to highly exaggerated response [22].

Introduction of GnRH commercially provided a dynamic study tool for assessing the physiology and pathologic conditions involving the hypothalamo-pituitary gonadal relationship. As discussed, values of this dynamic test in various clinical conditions are very useful.

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