Review article

The role of gonadotrophin releasing hormone in the investigation and treatment of hypogonadism

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Introduction

Normal progression through puberty and maintenance of fertility depends on the integral functioning of the hormonal circuit linking the hypothalamus, pituitary and gonads shown in Figure 1. The hypothalamic factor – gonadotrophin-releasing hormone (Gn-RH) was isolated and its structure determined in 1971 (Schally *et al.*, 1971). This releasing hormone acts on cells within the anterior pituitary and stimulates their secretion of the gonadotrophins, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Gonadotrophin-releasing hormone is given for therapeutic as well as for diagnostic purposes and there is now considerable clinical experience of its use. This article discusses the clinical use of Gn-RH in the investigation and treatment of infertility and delayed puberty and the clinical application of the development of long-acting synthetic analogues.

Hormonal changes of normal puberty

The first recognised hormonal change preceding puberty is an increase in the adrenal output of androgenic steroids (Ducharme *et al.*, 1976; Sizonenko & Paunier, 1975). The hormonal stimulus causing the increase in adrenal androgen production has not been identified but there is evidence for a shift in emphasis of the adrenal enzymes, resulting in greater production of androgens (Kelnar & Brook, 1983). The increase in plasma dehydroepiandrosterone occurs before LH and FSH begin to rise and adrenal androgens may be important for the 'maturing' of the hypothalamus. As puberty progresses the hypothalamus seems to become less sensitive to the

inhibitory feedback effects of sex-steroids and so the release of Gn-RH and consequently FSH and LH is not inhibited until higher plasma concentrations of sex-steroids are reached. An early manifestation of this change is the incremental development of pulsatile release of LH with maximal activity at about 0300 h (Boyar *et al.*, 1972). In healthy pre-pubertal children the gonadotrophins are present at low plasma concentrations but both FSH and LH will rise in response to Gn-RH. At puberty the LH response becomes greater than that of FSH (Roth *et al.*, 1972). The pre-pubertal plasma levels of LH and FSH respond to variations in the low plasma levels of sex steroids but this regulatory influence appears not to become dominant until puberty.

The pulses of gonadotrophins occur in response to hypothalamic pulses of Gn-RH. Once established the pulses of FSH and LH occur with a frequency of 2–4 per 6 h in men. In women they occur more closely to hourly intervals during the follicular phase of the menstrual cycle, a pulse rhythm described as circhoral by Knobil (1980), but during the luteal phase the frequency and amplitude of the pulses and the mean plasma level of LH reduces, probably due to the influence of progesterone (Soules *et al.*, 1984).

Hypothalamic hypogonadism

Many of the patients who lack hypothalamic Gn-RH will present with delayed puberty or sometimes later with infertility. There may be a congenital inability to detect smells, sometimes with additional midline defects such as cleft palate, a condition known as Kallmann's syndrome (Kallmann *et al.*, 1944). These individuals will have persistently low or undetectable plasma levels of LH and FSH and there will not be any increase in plasma levels in response to the standard

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Figure 1 (a) Female; (b) Male. The hypothalamus releases pulses of gonadotrophin-releasing hormone (Gn-RH) which stimulate the pituitary to release pulses of the gonadotrophins: luteinising hormone (LH) and follicle stimulating hormone (FSH) (LH in the male was previously termed interstitial-cell-stimulating hormone ICSH). FSH stimulates the maturation of gonadal germ cells. In the female FSH is predominant during the follicular phase of the cycle and stimulates the production of oestrogens. During the luteal phase in females LH is predominant and stimulates the production of progesterone. In the male, LH stimulates the production of testosterone. The pituitary production of LH and FSH lessen as the levels of gonadal steroids and inhibin rise. The LH surge predisposing to ovulation is dependent on the prior rise in plasma levels of oestrogens but with a fall in oestrogen levels just preceding the release of LH.

test doses of 100 µg i.v. of Gn-RH. The frequency and amplitude of the hypothalamic pulses of Gn-RH can also be reduced by illness, resulting in delayed puberty. Delayed development of the pulses of Gn-RH is also thought to be the explanation for the delayed menarche occurring in marathon runners and ballet dancers (Warren, 1980), and a reversion to the pre-pubertal pattern is found in anorexia nervosa and secondary amenorrhoea with low body weight syndromes.

Investigation of hypogonadism

It is difficult to distinguish between simple delay of puberty, due to slow development of the gonadotrophic axis, and lack of gonadotrophins due to pituitary or hypothalamic disease states. A test with a single bolus of Gn-RH will not reliably separate the two groups (Roth *et al.*, 1972), although it has been reported that the ratio of FSH to LH is increased in those with hypothalamic hypogonadism (Crowley *et al.*, 1980). A poor response may occur in both delayed puberty and hypothalamic hypogonadism, the magnitude and pattern of response being related to the degree of prior exposure to Gn-RH. Following exposure to Gn-RH, further provocation tests with boluses of Gn-RH show that the LH response becomes more marked whereas the FSH response shows little enhancement (Roth *et al.*, 1972). This alteration in FSH and LH response resembles the normal physiological pattern at puberty.

Hypogonadism due to intrinsic pituitary failure is demonstrated by complete lack of gonadotrophin response despite repetitive infusions of Gn-RH (Snyder *et al.*, 1979). Investigation of patients with delayed puberty and hypothalamic hypogonadism has also been explored by continuous infusion of Gn-RH. The normal post-pubertal response to a 4 h continuous infusion of Gn-RH is biphasic (Bremner & Paulsen, 1974). There is an initial surge of LH response which begins to decline at 40 min but then increases again at 90 min and the new raised level is sustained for the remainder of the 4 h. Bremner and colleagues (1977) reported that the typical response for pre-pubertal children, hypothalamic-hypogonadal patients and patients with anorexia nervosa is monophasic; the initial response with FSH is relatively greater than LH and the expected second phase of the response is lacking. The second phase can be provoked in patients with hypothalamic hypogonadism after only 4 days of repeated exposure to Gn-RH (Bremner *et al.*, 1977) or more quickly after treatment with agonist analogues of Gn-RH (Crowley & McArthur, 1980). The biphasic response to agonist analogues in postpubertal normal subjects has a more prolonged first phase compared with natural Gn-RH and the second phase occurs at 24 h.

Whilst the pituitary of females is receiving pulsatile stimulation by the hypothalamic Gn-RH it should be capable of making a positive response and release LH following the administration of oestrogens (Knobil, 1980). This capability will be absent if the stimulation by Gn-RH has not begun or has ceased. In general, amenorrhoeic patients who have absent or impaired responses to Gn-RH will not respond to clomiphene (Ginsburg *et al.*, 1975) or oestrogens. Amenorrhoeic patients who do respond to administration of oestradiol by an increased pituitary secretion of LH will still have pulsatile rhythms of LH secretion (El Sheikh *et al.*, 1983) and hence, presumably, pulses of Gn-RH secretion.

If gonadotrophins are lacking or reduced the ovary or testis will remain underdeveloped. Consequently the hormonal response to an administered stimulus to the gonad will be less than that of gonadal tissue from a normal person and an interval is needed during which the response to successive doses of the stimulus will increase. Both ovarian and testicular tissues are able to up-regulate and down-regulate their receptors for the gonadotrophins (Conti *et al.*, 1976).

In conclusion, Gn-RH will provide a valuable contribution in the assessment of hypogonadal patients but often further tests are necessary and continued stimulation by Gn-RH may be needed to clarify the diagnosis.

Treatment of infertility by Gn-RH

It had always been expected that the isolation and subsequent synthesis and availability of Gn-RH would allow clinicians to help patients with delayed puberty and infertility. Gn-RH has however proved difficult and unpredictable in clinical use. Continuous infusion of Gn-RH to normal subjects for prolonged periods will raise plasma levels of LH and FSH but this response begins to attenuate after about 5 h and is lost after a few days. However a pulsatile infusion of Gn-RH results in an increase in FSH and LH levels that is sustained (this was studied in rhesus monkeys for 7 weeks (Belchetz *et al.*, 1978)). The use of pulsatile prolonged infusions of Gn-RH allows the patient with hypothalamic deficiency to synthesize and release FSH and LH. The increasing response to repeated Gn-RH in the early stages of treatment contrasts with the diminishing and eventual loss of response to sustained excess of Gn-RH and indicates that the pituitary gonadotrophs are able both to up-regulate and down-regulate their cell-membrane concentrations of Gn-RH receptors, according to relative lack or excess of Gn-RH. This has been demonstrated in rat tissue (Clayton *et al.*, 1979) and probably occurs in physiological circumstances during the normal ovarian cycle.

Early regimens for induction of LH and FSH used large doses of Gn-RH varying from 0.5 mg daily (Nillius *et al.*, 1975) to 2 mg daily (Hammond *et al.*, 1979). More recently, good results have been reported with 20 µg Gn-RH given intravenously every 90 minutes (Leyendecker *et al.*, 1980). Most investigators are now giving doses of 5–20 µg per bolus, usually subcutaneously but occasionally intravenously, and at intervals of between 1 and 2 h.

Both male and female patients with infertility due to hypothalamic Gn-RH deficiency can now be offered this treatment with a reasonable expectation that they will become fertile. Men with low sperm counts require continuous treatment for periods of 1 to 9 months before achieving sperm counts of sufficient number and maturity (Hoffman & Crowley, 1982). The gonadal steroid feedback to the pituitary is still operating so that inhibition prevents any excess of FSH and LH release and there have been no reports of multiple births nor any serious problems with this form of management of infertility. The normal surge in FSH release at the time of ovulation still occurs. If pulsed Gn-RH leads to sustained high levels of FSH and LH then there is down-regulation of the gonadal receptors and hence reduced responsiveness of the gonadal tissue. Moreover, in rodents, Gn-RH receptors have been reported in gonadal tissue and Gn-RH appears to have a direct modifying action on gonadal function (Hsueh & Erickson, 1979). Gn-RH receptors were not found in human gonadal tissue by Clayton & Huhtaniemi (1982).

Induction of puberty by Gn-RH

Gonadotrophin releasing hormone infusions have been used for the induction of puberty. Jacobson and colleagues (1979) gave 40 µg hourly s.c. overnight for 10 nights in an attempt to mimic the early hormonal changes of puberty and showed that this treatment was feasible. Hoffman and colleagues (1982) gave 25 µg per kg s.c. 2 hourly and found clear clinical and biochemical evidence of puberty developing within 2–4 weeks of therapy in four of five patients. A more

recent report describes successful use of only 2 pg given 16 times per day i.v. but 21 weeks treatment was needed before spermatogenesis was detected (Dellemarre-Van de Waal & Schoemaker, 1983).

Further applications of Gn-RH and its analogues

Long-acting analogues of Gn-RH have an effect similar to that of continuous infusion of Gn-RH and lead to loss of FSH and LH release from the pituitary. Lack of FSH and LH results in falling plasma levels of sex steroids. These changes have already been exploited therapeutically and in the treatment of hormone dependent malignancy Gn-RH manipulation is likely to become an important means of treatment. One hindrance to its acceptability by the patient is that analogues need to be given parenterally or taken intranasally. The decline in plasma levels of sex steroids by this means is a more acceptable treatment for disseminated hormone dependent malignancies than other current treatments. It has been shown to have therapeutic benefit in breast malignancy (Klijn & De Jong, 1982) and carcinoma of the prostate (Waxman *et al.*, 1983).

Interfering with the menstrual cycle by Gn-RH provides a means of contraception which appears to be remarkably free of side effects (Berquist *et al.*, 1979). Women took the hormone intra-nasally with completely successful suppression of the menstrual cycle. In the longer term however, the lack of oestrogen and possibly a relative dominance of effect of adrenal androgens may cause side effects.

Gonadotrophin secretion in post-menopausal women can be reduced by Gn-RH but this does not necessarily mean that menopausal symptoms will be reduced (Casper & Yen, 1981). The premature secretion of gonadotrophins found in precocious puberty has been successfully suppressed by a long-acting analogue of Gn-RH (Comite *et al.*, 1981).

These examples illustrate that Gn-RH has potential benefits over and above the treatment of infertility and delayed puberty. Its introduction is a significant scientific advance.

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