PULSATILE GONADOTROPHIN RELEASING HORMONE - A NEW MODE OF HORMONE THERAPY

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INTRODUCTION

The Nobel prize was awarded to two eminent peptide chemists in 1979 for their pioneering work on the neuropeptides including gonadotrophin releasing hormone (GnRH, also known as luteinizing hormone release hormone or LHRH) (1,2). When synthesized in 1971 it was widely believed that GnRH would alleviate a variety of disorders of reproduction. This hope was however shortlived and by 1978 (3,4) many authors had concluded that this substance was of no value diagnostically or therapeutically.

In retrospect this conclusion was reached because the neuropeptide was ineffective when given by the conventional means of once to three times per day. This realization came from studies of the menstrual cycle of the rhesus monkey (Macaca mulatta) in which it was apparent that the normal pulsatile secretion of the gonadotrophins was mediated by hypothalamic secretion of GnRH (5). These hourly pulses were attributed to intermittent discharges of GnRH into the pituitary portal plexus. The efficacy of α adrenergic receptor blockade in arresting pulsatile secretion (6) and the subsequent demonstration by Carmel et al (7) that immunoreactive GnRH concentrations in blood from the pituitary stalk increased at approximately hourly intervals supported this proposition. It had been suggested that the arcuate nuclei are the source of hypothalamic GnRH; this was confirmed by the destruction of these bilateral nuclei using a parallel array of six radiofrequency electrodes (8). The ensuing precipitous decline in gonadotrophins was permanent and no response occurred to an estradiol challenge. If the monkey was given GnRH by continuous infusion there was a brisk but transient increase in gonadotrophins despite continuation of the infusion. By contrast if the GnRH was given in a pulsatile fashion, i.e. 1 µg/min for 6 min once hourly, pre-lesion levels of gonadotrophins were restored (9). Changing the mode of administration to continuous infusion once having restored these levels led to abolition of this response. This occurred irrespective of the dose used (0.1 - 10 µg/min).

It appears that the pre-pubertal female monkey might be analagous to the lesioned adult. The above regime was therefore applied to two such animals. Within a few days a gonadotrophin response was observed and by 10 days changes were apparent in the sex skin of buttocks although there was no immediate increase in plasma estradiol. Subsequently these animals had LH and FSH surges, increments in estradiol and progesterone and menstruation indistinguishable from the normal adult monkey (10).

INDUCTION OF TESTICULAR MATURATION

Based upon the above results it was hypothesized that puberty in the male primate was initiated by the arcuate nuclei commencing to secrete GnRH and that the pituitary and testis were subservient. Accordingly an immature male rhesus monkey was prepared by inserting a right atrial catheter through the internal jugular vein. The distal end was passed subcutaneously to a metal platform fixed to the vertex of the skull. At this point the catheter entered a flexible protective tube which passed to the roof of the cage where blood could be drawn off or GnRH could be infused (11). When given 1 µg of GnRH for 5 min hourly for 60 days the following changes were noted : a 10-fold increment in testicular size (2 to 20 ml, Prader orchidometer), a 50-fold increment in plasma testosterone (^{125}I-T RIA) and the development of full spermatogenesis shown histologically (12). Thus the hypothesis was upheld in this one study. When repeated in three immature male baboons (Papio hamadryas) a similar but delayed response occurred.

The opportunity to address this question in pre-pubertal boys was made available by children referred with cryptorchidism. Previously attempts had been made to induce testicular descent with intranasal GnRH (13). To apply the principles derived from the sub-human primate studies a delivery system was developed. This consisted of a Graseby-Dynamics MS16 syringe driver which was modified by the incorporation of an integrated circuit which interrupted the continuous mode of operation to one in which the drug was delivered subcutaneously via a scalp vein needle from a 2 ml syringe over 3 min every 60-90 min. The GnRH solution was replenished daily and the peak concentrations achieved in the peripheral blood were about 120 pg/ml at 10-15 min after activation of the syringe driver. Twenty-two boys (22 months-12½ years) whose testes were in the line of descent but were not retractile were treated. Initially 10-60 µg of GnRH/day was administered; an absent or slow response led to the use of 100 µg/day. This regime resulted in testicular descent in 70% of boys within 1-19 weeks (mean = 6) and was accompanied by increased gonadotrophins (follicle stimulating hormone [FSH] < 2 to 8 U/L, luteinizing hormone [LH] < 2 to 10 U/L), testosterone (< 1 to 30 nmol/L, normal ranges for men 3-19, 4-15 and 15-46 respectively) and testicular size (1 to 4 ml). Penile and scrotal development were conspicuous and some children manifested behavioural changes. Testicular growth ceased when the regime was stopped

once a satisfactory clinical response had been obtained. Nonetheless it demonstrates that in man, as well, puberty may be induced precociously with GnRH and that it is dependent upon hypothalamic activation.

One of nature's metabolic errors provided the opportunity to test this hypothesis in another clinical setting - Kallmann's syndrome. This 28 year old anosmic man was eunuchoid with small testes, low gonadotrophins and testosterone. Such patients have a congenital deficiency of GnRH and as a result are azoospermic. Initial treatment with GnRH 10 µg qid, s.c., elicited no clinical response but during a GnRH infusion test (1 µg/min for 240 min) FSH increased steadily. After GnRH had been given in a pulsatile fashion the FSH response to a 4 hr infusion of GnRH increased further but was later exceeded by the LH response. The LH increment also became biphasic, typical of the normal adult male. Testicular size increased from 5 to 20 ml and the sperm count reached 2 x 10^6/ml.

It has been possible to effect testicular development in three species by the simple expedient of pulsatile GnRH administration. This suggests that in the male there is within the arcuate nucleus region, the mechanism for initiating sexual maturation.

INDUCTION OF OVULATION

The lesioned female rhesus monkey also had its clinical counterpart in the form of an anosmic woman who was anovulatory. This 25 year old woman was the female equivalent of the man with Kallmann's syndrome. She had only six menstrual periods between her menarche at the age of 19 years and when she presented with a history of primary infertility at the age of 25 years. Her prolactin, FSH and LH were in the normal range but plasma estradiol was low. When given GnRH in the pulsatile mode her basal body temperature fell then rose on day 15 after which it remained elevated, consistent with pregnancy. She ovulated, conceived and was subsequently delivered of a normal boy.

A 27 year old woman who had been amenorrhoeic since stopping the contraceptive pill two years previously presented with primary infertility. Her biochemical parameters of pituitary and ovarian function were low (LH 3 U/L, Follicular phase 3-13, FSH 4 U/L, Follicular phase 5-20) Her basal urinary estriol was 0.04 µmol/24 hr (post-menstrual range 0.024-0.080). Thirty days after initiating pulsatile GnRH she showed a rise in plasma LH (11 U/L) and estriol (0.18 µmol/24 hr). This was followed by menstruation 14 days later. Evidence of ovulation and menstruation occurred for the subsequent three months but ceased when the regime was interrupted for social reasons. She was again amenorrhoeic until the regime was re-instituted six months later when ovulation and menstruation recurred.

Thus women appear to respond in a fashion similar to that seen in the rhesus monkey suggesting that the principles elucidated from the monkey studies are relevant to man. As in the male it appears that the onset of puberty in girls is dependent upon activation of the arcuate nuclei.

CONCLUSION

Pulsatile administration of exogenous GnRH can duplicate the function of the primate hypothalamus in both sexes of three primate species. As well it can induce precocious puberty in both sexes suggesting that sexual maturation is triggered by hypothalamic secretion of GnRH. The regimes devised in the rhesus monkey have been successfully applied to several clinical problems. Other disorders such as the Stein-Leventhal syndrome may well respond to this approach which offers the facility of manipulating the ratio of LH to FSH. The efficacy of intermittent or pulsatile delivery of this hormone may well be relevant to other hormone systems or drugs.

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