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Prolonged Pulsatile LRH Treatment in Different Frequency Schedules in a Hypogonadotropic Male

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ABSTRACT

A 22 years old male patient with a pubertal arrest of unknown origin at stage P_4, G_3 received LRH in three different schedules, each lasting for four weeks.

1. 8 times per day 20 μg LRH iv
2. 16 times per day 20 μg LRH iv
3. 32 times per day 20 μg LRH iv. During the first period the low FSH levels increased into the normal adult range, while LH remained at the low level, a change also observed in early puberty. Testosterone increased to low normal adult values. In the second period LH as well as testosterone increased to normal adult values and in the third period LH, FSH as well as testosterone increased into the high normal range. There was no evidence of desensitization of the gonadotrophic cells during the third period.

From these data we suggest that: 1. LRH treatment in a frequency higher than physiologic, as observed in adult men, does not result necessarily in desensitization of the gonadotrophic cells and 2. the change in gonadotropin secretion in early puberty may be the result of an increased LRH stimulation in a frequency lower than observed in adults.

INTRODUCTION

Dierschke and co-workers (2) were the first to observe a pulsatile secretion pattern of LH in primates. In ovariectomized rhesus monkeys LH peaks occurred with a frequency of one every hour. When LRH was administered exogenously in the same frequency of 1 gift during 6 minutes every hour in ovariectomized rhesus monkeys in which gonadotropin secretion had been abolished by central lesions, LH and FSH levels returned to their original values (6). Plant (7) reported an episodic LH secretory pattern in intact male rhesus monkeys as well, although their pulse frequency was lower i.e. approximately 1 pulse every 4.5 hours.

In adult men LH peaks occur with a frequency of 1 pulse per 90–120 minutes (8), suggesting LRH stimulation in a pulsatile fashion in the human as well. In recent years

pulsatile LRH treatment has been used therapeutically in women to induce ovulation (5,9), in male infertility (19) and in children to induce puberty (1,4).
In this study we investigated the pituitary response to pulsatile LRH treatment in three different frequency schedules in a hypogonadotrophic male, who requested to be treated for induction of puberty by LRH.

CASE REPORT

The patient was a 22 years old Caucasian male. At the age of 14 years the secondary sexcharacteristics started to develop spontaneously. However after 2 years no progression of pubertal development occurred. At the age of 22 years he was referred to our clinic for LRH induction of puberty. No androgen treatment had ever been given. On physical examination the height was 180,4 cm, weigth 65 kg. Pubic hair was in stage 4 and genital development in stage 3 according to Tanner (11). Testicular volume assessed by the orchidometer method was 8 ml on both sides. Bone age according to Tanner and Whitehouse was 15.3 years (12). Haemoglobin, haematocrit, liver and kidney functions were normal. Endocrine evaluation: normal values were found for prolactin, thyroid hormone and cortisol. LRH (100 $\mu g/m^2$) iv elicited an impaired response for FSH particularly: LH baseline: 5.3 U/L, peak value 11.5 U/L; FSH baseline: 2.8 U/L, peak value 3.4 U/L.
Extended evaluation of gonadotropin secretion was performed by pulsatile administration of LRH for 7 days: 15 times per day 20 µg LRH/1.7 m^2 iv. On day 7 a LRH test was repeated. By this time FSH secretion had strikingly increased in contrast to LH secretion, which had remained the same level: LH baseline 5.4 U/L, peak value 11.6 U/L; FSH baseline 8,3 U/L, peak value 11.2 U/L. Basal testosterone level was 1.65 nmol/l and increased during LRH treatment to 5.6 nmol/l on day 7. We interpreted the results as evidence for appropiate gonadotrophic function.
Radiologic examination (X-sella, CT-scan) did not reveal any abnormality.

TREATMENT

LRH (HRF - Ayerst) was administered intravenously by a portable computarized infusion pump (Mill Hill). Treatment was started 11 weeks after evaluation of gonadotrophic function. Three different schedules, each during a period of 4 weeks were applied:

1. 8 times per day 20 µg LRH
2. 16 times per day 20 µg LRH
3. 32 times per day 20 µg LRH.

The pituitary response was investigated by determination of LH and FSH plasma levels during the first 14 days of each period daily, thereafter weekly including the last day of each period. Blood samples were obtained at the 09.00 a.m. pulse: just prior to and

30, 60 and 90 minutes after the LRH pulse.

On the day before treatment as well as on the last day of each treatment period blood was collected every 10 minutes for 6 hours from 09.00 a.m. till 03.00 p.m. Testosterone was determined from the 09.00 a.m. sample. Blood was heparinized and centrifuged at 3000 r.p.m. for 10 minutes. Plasma was frozen and stored at -20°C till assayed.

METHODS

LH, FSH and testosterone were determined as described previously (1).

Normal values for adult males are for LH 4-10 IU/L, for FSH 4-12 IU/L, for testosterone 8-35 nmol/l.

RESULTS

Baseline LH and FSH levels were low and barely showed any LH pulse. A pulse was defined as an increase from nadir to peak as great as or greater than 20% of the nadir value.

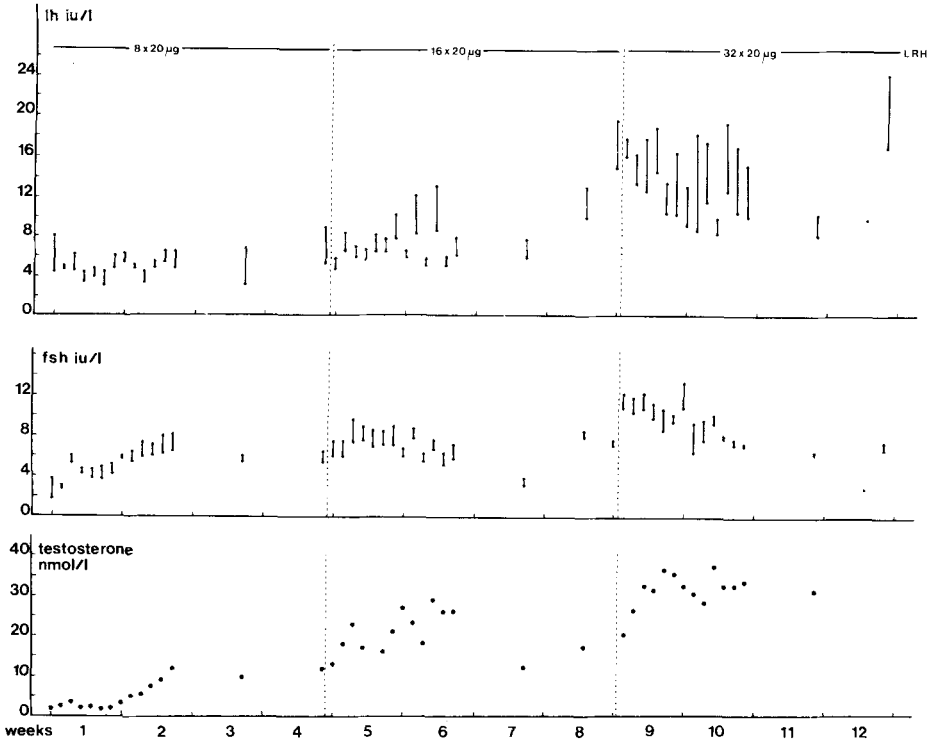

Figure 1: LH and FSH response to the 09.00 a.m. LRH dose. The lower end of the vertical bar represents the basal level before 09.00 a.m., the upper end represents the peak level after 09.00 a.m. Testosterone levels were determined from the 09.00 a.m. sample.

LRH treatment with 8 pulses per day of 20 µg elicited an increase of particularly FSH. LH levels remained approximately at the same level. Testosterone levels increased slowly into the low normal adult range (fig.1) Over the 6 hour period when blood was sampled at 10 minutes intervals at the end of the first treatment period, LH secretion showed 4 pulses more than could be explained by the LRH gifts (fig.2a). LH declined from 8.8 IU/L to 4.6 UI/L and FSH from 6.4 IU/L tot 5.1 IU/L between 09.00 a.m. and 10.30 a.m. After 10.30 a.m. LH and FSH remained at the same level.

16 LRH pulses of 20 µg per day elicited an increase of LH and a further increase of FSH as well as testosterone. All three hormones reached the normal adult range (fig.1). During the frequent sampling period at the end of the second treatment LH showed 5 pulses, of which one could not be explained by an exogenous LRH gifts.

At a treatment schedule of 32 times per day 20 µg LRH, LH, FSH and testosterone levels increased further to the high normal range (fig.1). All LRH pulses were followed by a LH peak (fig.2b).

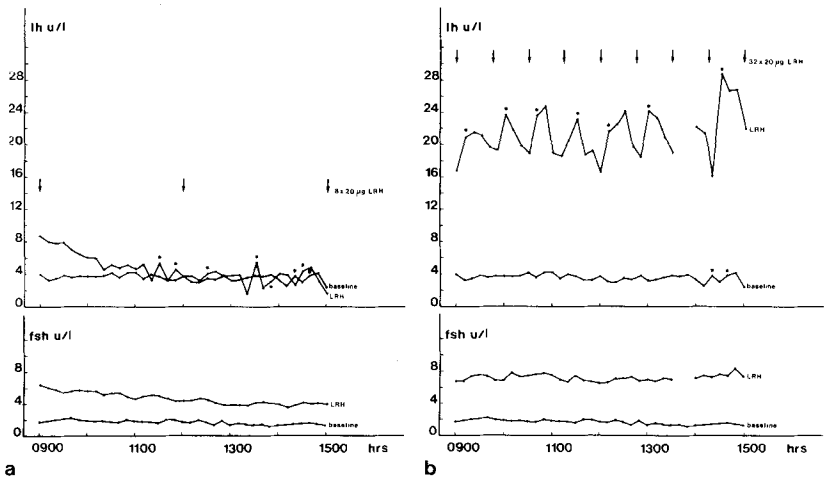

Figure 2a + b: LH and FSH levels determined at 10 minutes intervals from 09.00 a.m. till 15.00 p.m. Baseline levels as well as levels under LRH treatment are shown. Arrows point to exogenous LRH gifts, asteriks LH pulses.

During these 12 weeks of LRH treatment testicular volume increased from 8 to 12 ml at the left side and 15 ml at the right side. Length of the penis increased from 5.5 to 7.3 cm. After 5 weeks ejaculations occurred and after 11 weeks a semenanalysis demonstrated spermatozoa.

DISCUSSION

Wildt et al. (13) have reported that changes in the frequency of LRH stimulation have profound effects on gonadotropin plasma levels as well as on FSH to LH ratios in the female rhesus monkey. 2 LRH pulses per hour instead of the physiologic frequency of 1 pulse per hour, observed in ovariectomized monkeys, elicited a decrease of both gonadotropin levels.

This decline was most outspoken at the highest frequency of 5 LRH pulses per hour. When LRH administration was changed from 1 pulse per hour to 1 pulse per 3 hours in ovariectomized monkeys bearing hypothalamic lesions, FSH levels increased, while LH levels fell. They speculated that changes in the FSH to LH ratio, as observed during puberty as well as polycystic ovarian disease, may be the result of changes in the frequency of hypothalamic LRH release.

On 8 LRH pulses per day LH remained at the same low level, while FSH showed an increase in this patient. This changing pattern is also observed during the early stage of puberty (3). Therefore this observation may contribute to the notion that the first increase of gonadotropins during early puberty might be the result of increasing LRH stimulation in a frequency lower than the physiologic 1 pulse every 90 - 120 minutes, as observed in adult men (8).

During this treatment schedule more LH pulses were observed than could be explained by the exogenous LRH gifts. We suggest that it may be possible that these extra pulses are the result of endogenous LRH release.

The tendency of higher levels in the early morning as observed after the first treatment period, might be caused by nocturnal endogenous LRH release. On LRH treatment with 32 pulses per day, gonadotropin as well as the testosterone levels increased furtheron to high normal levels. No evidence of desensitization of the gonadotrophic cells was found in this patient. This is in contract to observations of Wildt et al. (13).

The reaction pattern of the human pituitary to LRH in different frequency schedules in the male has to be investigated to a wider extent.

REFERENCES

1. Delemarre-van de Waal, H.A. & Schoemaker, J.: Induction of puberty by prolonged pulsatile LRH administration. Acta Endocrinol 102:603-609, 1983.

2. Dierschke, D.J., Bhattacharya, A.N., Atkinson, L.E., Knobil, E.: Circhoral oscillations of plasma LH levels in the ovariectomized rhesus monkey. Endocrinology 487:850-853, 1970.

3. Faiman, C. & Winter, J.S.D.: Gonadotropins and sexhormone patterns in puberty: clinical data. In: Control of the onset of puberty (ed.M.M. Grumbach, G.D.Grave, F.E.Mayer),pp. 32-55. John Wiley & Sons, New York, 1974.

4. Hoffman, A.R. & Crowley, W.F.: Induction of puberty in men by long-term pulsatile administration of low dose gonadotropin releasing hormone. N Engl J Med 307:1237-1241, 1982.

5. Leyendecker, G, Struve, T., Plotz, E.J.: Induction of ovulation with intermittent (pulsatile) administration of LH-RH in women with hypothalamic and hyperprolactinemic amenorrhea. Arch Gynecol 229:177-190, 1980.

6. Nakai, Y, Plant, T, Hess, D.L., Keogh, E.J., Knobil, E.: On the sites of the negative and positive feedback actions of estradiol in the control of gonadotropin secretion in the rhesus monkey. Endocrinology 102:1008-1014, 1978.

7. Plant, T.M.: Time courses of concentrations of circulating gonadotropin, prolactin, testosterone and cortisol in adult male rhesus monkeys (Macaca mulatta) throughout the 24h light-dark cycle. Biol Reprod 25:244-252, 1981.

8. Santen, R.J. & Bardin, C.W.: Episodic luteinizing hormone secretion in man. J Clin Invest 52:2627-2628, 1973.

9. Schoemaker, J., Simons A.H.M., van Osnabrugge, G.J.C., Lugtenburg, C., van Kessel, H: Pregnancy after prolonged pulsatile administration of luteinizing hormone - releasing hormone in a patient with clomiphene-resistant secondary amenorrhea. J Clin Endocrinol Metab 52:882-885, 1981.

10. Skarin, G., Nillius, S.J., Wibell, L., Wide, L.: Chronic pulsatile low dose GnRH therapy for induction of testosterone production and spermatogenesis in a man with secondary hypogonadotropic hypogonadism. J Clin Endocrinol Metab 55:723-726, 1982.

11. Tanner, J.M.: Growth at adolescence (second ed.) p.32. Blackwell Scientific Publications, Oxford, 1962.

12. Tanner, J.M., Whitehouse, R.H., Marshall, W.A., Healy, M.J.R., Goldstein, H.: Assessment of skeletal maturity and prediction of adult height (TW2 method). Academic Press, London, 1975.

13. Wildt, L., Häuster, A., Marshall, G., Hutchison, J.S., Plant, T.M., Belchetz, P.E., Knobil, E.: Frequency and amplitude of gonadotropin-releasing hormone stimulation and gonadotropin secretion in the rhesus monkey. Endocrinology 109:376-385, 1981.