Clinical Experimental Obst. & Gynecology
Vol. I nn. 2-3-4, October 1974 pp. 97-100

Effect of testosterone propionate administration on pituitary response to synthetic Gn RH (gonadotropins releasing hormone)

by

L. DE CECCO, P. MASTRURZO, G. L. CAPITANIO, G. FOGLIA, P. L. VENTURINI, T. BARRECA, E. ROLANDI and A. POLLERI

It is widely accepted that testosterone has an effect on the incretion of gonadotropins by the pituitary and that a feed-back mechanism is involved ([1]). The data available indicate that the androgen administration induces a decrease of LH and, at certain doses also of FSH levels in serum ([1]). It has also been demonstrated that upon administration of daily doses of testosterone propionate ranging between 5 and 50 mg the fall of gonadotropins is dose related ([2]). These finding have leed to assume that the operating feed-back is a negative one.

It has also been demonstrated that an other steroid, involved in the regulation of gonadotropin secretion, 17-β-estradiol, exerts a similar negative feed-back on gonadotropins incretion ([1]). Other data indicate that in the woman estradiol administration at certain doses exerts a positive feed-back on gonadotropins incretion ([3]).

A variety of information is available poiting out that the feed-back mechanisms involved in gonadotropins regulation by androgens depend on steroid receptors located in the hypothalamus and in the pituitary. Since a few years, stereotactic implants of testosterone in the hypothalamus have proved to be effective in decreasing gonadotropins serum levels in laboratory animals ([4]). On the other hand, implants of testosterone in the animals' pituitary induce the regression of castration histological aspects and modify gonadotropins content in the gland, indicating that the pituitary is a direct target of a testosterone effect ([5]). Moreover, the pretreatment of laboratory animals with testosterone has been found to decrease the effect of a subsequent administration of gonadotropins releasing hormone (GnRH) ([6, 7]). All the above mentioned findings seem to poit out a direct pituitary effect of testosterone, the androgen being able to diminish the hypophyseal sensitivity to hypothalamic stimuli.

With the aim to gather data on the effects of high serum levels of testosterone on pituitary sensitivity to GnRH in man, we have studied the effect of testosterone administration on pituitary stimulation by GnRH.

MATERIALS AND METHODS

Four men aged between 23 and 31 and in good health were studied. Preliminary clinical and laboratory examination ruled out any endocrine disorder.

Gonadotropins were determined in serum by the radioimmunoassay described by

From the Obstetrical and Gynaecological Clinic of the University of Genoa.
Scientific Institute of Internal Medicine, Chair of Medical Pathology.

Midgley ([8, 9]). The reagent for the determinations were supplied by Serono Immunochemicals, Rome. Serum testosterone was also determined by a radioimmunoassay, according to Collins ([10]). Details of the technique and about the statistical evaluation of the data have been supplied elsewhere ([11]).

GnRH was a synthetic preparation of the decapeptide ([12]), obtained by Serono Immunochemicals, Rome. The dose used in the present research was 100 µg, administered by rapid intravenous injection.

Testosterone was administered as its propionate, by intramuscular injection at the dose of 50 mg.

The study of each case consisted of the daily determination of serum levels of gonadotropins and of testosterone during a four days period. On the fifth day GnRH was administered and LH, FSH and testosterone determined in serum. Gonadotropins were determined 10 and 5 minutes before GnRH administration and 5, 19, 20, 30, 45, 60, 90, 120 minutes thereafter.

Testosterone was determined on the serum samples collected at the end of the observation period.

On the following four days testosterone propionate was administered and daily determinations of gonadotropins and testosterone levels in serum were performed. On the fifth day of testosterone treatment a second dose of GnRH was administered and the gonadotropins response was followed in the same way as in the previous test.

RESULTS

Gonadotropins serum pattern showed a marked decrease of both LH and FSH during treatment with testosterone. The minimal levels were reached between the second and the fourth day of testosterone administration. Testosterone serum levels were followed during the observation period and showed a rapid increase after exhogenous administration of the hormone.

GnRH administration before the treatment with testosterone induced a peak of LH in all cases. FSH response was more variable: in two cases hormone levels did not change significantly.

When GnRH was administered during testosterone treatment, LH response was comparable in all cases to the one obtained after the precocious stimulation of the pituitary. Owing to the very low basal levels of the tropin, the height of the peak obtained is more elevated. FSH response was absent in three of the four cases (Fig. 1).

DISCUSSION

Decrease of serum gonadotropins after testosterone administration has been already observed by others ([1, 2]). Lee and Coll. ([2]) have demonstrated a dose related decrease slope. Our data are in good agreement with those reported by these Authors.

Testosterone effect upon the pituitary response to GnRH has been considered inhibitory in nature, as the already remembered experiments on rats and dogs seem to indicate ([6, 7]). On the basis of these results, Debeljuk and Coll. ([13]) state that endogenous testosterone potentiates the effect of exogenous estradiol in inhibiting pituitary response to GnRH. In castrated rats, however, et a time when endogenous testosterone had disappeared, estradiol showed a stimulatory effect, indicating that testosterone was necessary to ist pituitary inhibitory action. In dogs, Jones and Boyne ([7]) found that estradiol has a greater inhibitory effect than testosterone alone. The fact that these animals were intact, has perhaps the same meaning than the above mentioned findings on rats.

Clinical Experimental Obst. & Gynecology Vol. I nn. 2-3-4, October 1974 pp. 97-100

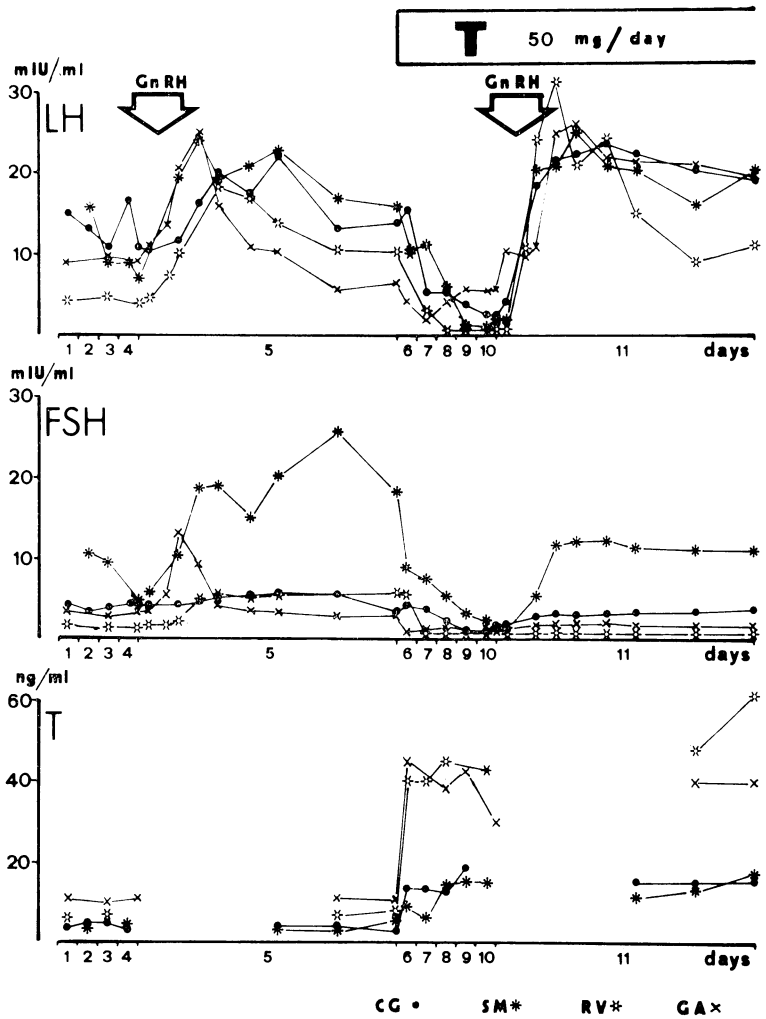

FIG. 1 - Serum levels of gonadotropins (LH, FSH) and of testosterone (T) in basal conditions, under the effects of GnRH, testosterone and testosterone plus GnRH.

Our data indicate that testosterone serum levels that display an inhibitory effect on gonadotropins release by the pituitary, demonstrated by their decrease in blood, do not have an inhibitory effect on the action of exhogenous GnRH on LH. These findings suggest that in these conditions pituitary is still stimulable and that, perhaps, the main effect of circulating testosterone is at the hypothalamic level. It might be argued however that the GnRH dose employed in these studies indice at the pituitary level concentrations far above the physiological ones ([14]), but the same remark can be easily made also for the experimental conditions above remembered ([6, 7]). GnRH effect on FSH release seems however impaired. It is well knonw that GnRH effect is chiefly displayed on LH release ([15]). Incidentally this was the reason why the 100 μg dose was selected in this

study, aimed to test the effect of testosterone on the release of *both* gonadotropins. It is interesting to stress that GnRH was ineffective to obtain a significant peak in testosterone treated subjects that were responsive before steroid administration.

These findings suggest that testosterone interferes with pituitary sensitivity to GnRH, in that FSH secretion is concerned.

Lee and Coll. ([2]) were interested also to investigate whether testosterone had a stimulating effect on LH and FSH release for certain doses. Their search was unsuccessful, indicating that no positive feed-back was involved. Our data do not show a potentiating effect of testosterone on GnRH action. Nevertheless, it must be remarked that the absolute peak height in our cases was more elevated after testosterone administration than before, owing to the very low basal levels.

SUMMARY

Pharmacological doses of testosterone propionate (50 mg daily) do not inhibit synthetic GnRH effect on LH release, in four normal adult male subjects. FSH release seems to be impaired. No stimulatory effect of testosterone has been observed.

BIBLIOGRAPHY

1. Burger H. G., Baker H. W. G., Hudson B. and Pincus Taft H.: *Gonadotropic and gonadal function in the normal adult man.* In Gonadotropins, Saxena BB, Beling C. G. and Gandy H. M. Eds. Wiley-Interscience, New York, 1971, p. 569. - 2. Lee P. A., Jaffe R. B., Midgley A. R. jr., Kohen F. and Niswender G. D.: *J. Clin. Endocr. Metab.* 35, 636, 1972. - 3. Knobil E., Diersche D. J., Yamaji T., Karsch F. J., Hotchkiss J. and Weick R. F.: *Role of Estrogen in the positive and negative Feed-back control of LH secretion during the menstrual cycle of the resus Monkey.* In: Gonadotropins, Saxena B. B., Beling C. G. and Gandy HM Eds., Wiley-Interscience, New York, 1971, p. 72. - 4. Bogdanove E. M.: *Vit. and Horm.* 22, 205, 1964. - 5. Kingsley T. R. and Bogdanove E. M.: *Endocrinology*, 93, 1398, 1973. - 6. Debeljuk L., Arimura A. and Schally A. V.: *Endocrinology* 90, 1578, 1972. - 7. Jones G. E. and Boyns A. R.: *J. Endocrinology*, 59, XV, 1973. - 8. Midgley A. R. jr.: *Endocrinology* 79, 10, 1966. - 9. Midgley A. R. jr.: *J. Clin. Endocr. Metab.* 27, 295, 1967. - 10. Collins W. P.: *J. Steroid Biochem* 3, 333, 1972. - 11. Rolandi E., Capitanio G. L., Indiveri F., Azzolini A. De Cecco L.: *Boll. Soc. It. Biol. Sper.*: in press. - 12. Matsuo H., Baba Y., Nair R. M. G., Arimura A. and Schally A. V.: *Biochem. Bioph. Res. Comm.* 43, 1334, 1971. - 13. Debeljuk L., Arimura A. and Schally A. V.: *Proc. Soc. Exp. Biol. Med.* 143, 1164, 1973. - 14. Fink G.: *Morphology and function of Hypothalamus and anterior Pituitary. Proc. 1st International symposium on physiologic pathology of human reproduction*, Bologna, 1974, in press. - 15. Schally A. V., Kastin A. J. and Arimura A.: *Fertil. Ster.* 22, 703, 1971.