PRL ACTION ON E_2 OVARIAN SECRETION

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SUMMARY

5 amenorrhea hyperprolactinemic women in previous intermittent treatment with bromocryptine, received bromocryptine for three periods of 5, 4, 3 days; each treatment phase was followed by a ten days suspension.

During treatment and during suspension FSH, LH, PRL and E_2 were tested.

There was no significative variation of FSH and LH; PRL lowered during treatment and reached basal values during suspension.

Ovarian response (E_2) varies with PRL levels. There was a statistically significative negative correlation between PRL and 17-β-E_2.

Hyperprolactinemic syndrome is often associated with amenorrhea; nevertheless there is no evidence in literature of PRL activity on E_2 ovarian production. Several Authors ([1, 2, 3, 4]) could demonstrate a specific action of PRL both *in vivo* and *in vitro* on progesteron secretion.

Del Pozo, Schulz, L'Hermite ([5, 6, 7]) believe that hypo- and hyperprolactinemia farmacologically induced can interfere with progesteron secretion in luteal phase, while other Authors ([3, 9]) noted that in hyperprolactinemia there is no serum progesteron variation.

Recent demonstration ([10, 11, 12]) of specific PRL receptor in the ovary (in the teca and granulosa cells) allows to suppose that PRL can interact on ovarian steroidogenesis.

It has been observed ([13, 14, 15, 16, 17]) that in amenorrhea hyperprolactinemic syndrome there are serum mean LH-FSH levels in the normal range and low serum E_2 levels: this can suggest a PRL action on ovarian E_2 secretion and an associated disorder of negative feedback control of gonadotropin ([18]).

The aim of our investigation is to show PRL action on E_2 secretion, studying women affected by hyperprolactinemic amenorrhea.

MATERIAL AND METHODS

Our experimental design was arranged in order to evaluate if short term bromocryptine administration could cause, in amenorrhoic hyperprolactinemic women, an increase of E_2 ovarian secretion, and if a subsequent hyperprolactinemia could stop or reduce the E_2 secretion.

Five women with amenorrhea-galattorrhea syndrome were given bromocryptine 2.5 mg/die for five days, starting from the 5th day of their cycle; then a ten days suspension and a new four days treatment, at the same dosage, followed; then a new ten days pause came and after this a final three days administration, always at the same dose.

FHS, LH, PRL and E_2 were tested every day during the treatments, and every second day during the suspensions.

The five women involved in this study, aged between 23 and 31, had had amenorrhea galat-

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Table 1.

	PRL ng/ml 1st treat.	E_2 pg/ml	PRL ng/ml 2nd treat.	E_2 pg/ml	PRL ng/ml 3rd treat.	E_2 pg/ml
Basal levels	38 ±6	55±14	34 ±3.5	84±12	34 ±5	79±10
1st day of treat.	19 ±4	54±12	17 ±6	72± 9	18 ±5	70± 8
2nd » » »	10 ±3	70± 9	12 ±5	80± 8	12.5±4	86± 5
3rd » » »	8.5±2.4	89± 8.2	9.1±2	92± 7.5	9.7±1.5	90± 7
4th » » »	7.6±2.1	102± 7.6	7.1±1.2	110±10		
5th » » »	6.9±1	140±12				
2nd day after treat.	17 ±5	154±18	18.4±3.2	146±22	16 ±4	110±14
4th » » »	26 ±3.2	139±14	25.6±2.8	135±16	24 ±3	105± 9
6th » » »	31 ±2.9	116±10.5	32 ±3.4	120±14	30 ±4.5	94± 8.5
8th » » »	32 ±4	95±13	31 ±2	91±11	34 ±6	76±10
10th » » »	34 ±3.5	84±12	34 ±5	79±10	36 ±4	62± 9

Mean ± S.D. PRL, E_2, FSH, LH during 1st, 2nd and 3rd treatment.

torrhea for over 2 years, and had been treated for over three months with intermittent treatment (a 2 days suspension after the rise of basal temperature) so they all had ovulations and normal luteal phases in the three cycles before the study took place.

Computerized Axial Tomography could show that none of them had pituitary adenoma.

Prolactin was assayed by the radioimmunoassay double-antibody method ([19]) (kit obtained from Biodata, Serono - Rome). The sensitivity of the method is about 1.5 ng per milliliter. FSH and LH were measured by radioimmunodouble-antibody methods ([20, 21]) (Biodata, Serono-Rome) using as a reference preparation the second I.R.P.-H.M.G. and the LER 907. The sensitivity for both methods is about 1 mIU per milliliter. The assay of 17-β-estradiol ([22]) was performed by the RIA-PEH method (Biodata, Serono-Rome) after extraction with ethyl ether. Sensitivity for both methods is about 10 pg per milliliter.

RESULTS

PRL mean values were 38 ± 6 ng/ml in the 1st day of the first period of treatment; 6.9±1 ng/ml in the 5th day; and 34±3.5 ng/ml in the 10th day of suspension.

Similar values were found during the 2nd and 3rd period of treatment, and during the 2nd and 3rd pause (table 1). Mean FSH and LH values were nearly unchanged during 2nd and 3rd treatments and during the following suspensions. Both FSH (7.2±0.9 mIU/ml - 10.1±1.2 mIU/ml) and LH (6.2±0.6 mIU/ml - 9.2±1.2 mIU/ml) values showed a slight increase during the first (five days) period of treatment (fig. 1).

Basal E_2 mean values on 5th day of cycle, before treatment, are 55±14.5 pg/ml; they increase to 154±18 pg/ml two days after suspension, then decrease to 84±12 pg/ml ten days after suspension.

The following drug administration shows an increase of serum 17-β-E_2 levels (146 ± 22 pg/ml) two days after suspension and a reduction ten days after suspension (79±10 pg/ml).

Further bromocryptine administration induces a less evident increase of E_2 (110±14 pg/ml) two days after suspension with following decrease ten days after suspension (62±9 pg/ml) (tab. 1, fig. 1).

The increase of the mean values of E_2 observed during the 5 day treatment was 99 pg/ml; 62 pg/ml during the 4 day treatment and 31 pg/ml during the 3 day treatment, whereas the reduction of E_2 mean values during the hyper PRL state was 70 pg/ml (first period of suspension), 67 pg/ml (second period of

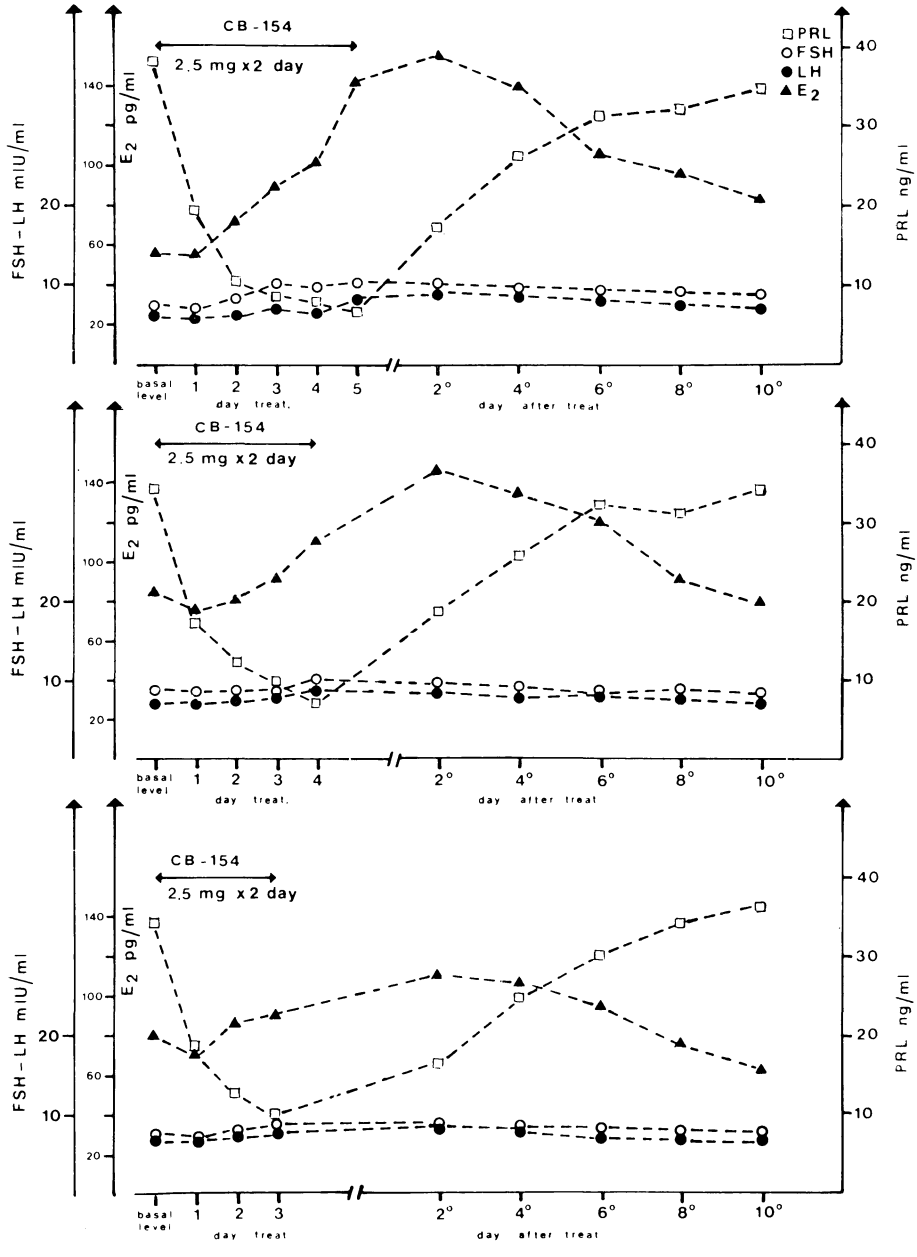

Fig. 1. — Mean values of PRL, FSH, LH, E_2 during 3 different bromocryptine (CB_{154}) treatments (Ist = 5 days, IInd = 4 days, IIIrd = 3 days).

suspension), and 58 pg/ml (third period of suspension) (table 1).

None of the so treated patients had menstruations in the 50 days following last cycle.

The statistical evaluation of results was performed by paired Student's test: there is no statistical significative correlation between 17-β-E_2 and FSH-LH; there is a highly statistically significative negative correlation between PRL and 17-β-E_2 ($P < 0.001$) during bromocryptine administration.

It has been shown a statistically significative difference between 17-β-E_2 of the first treatment and 17-β E_2 of the third treatment ($P < 0.001$).

CONCLUSIONS

There is not marked FSH and LH variation during bromocryptine treatment and its suspension. Gonadotropin mean values are similar to those observed in the first part of a normal ovulatory cycle. There are, nevertheless, two kinds of ovarian response to gonadotropins; the same FSH and LH values induce E_2 increase during bromocryptine administration but there is not E_2 increase during hyper PRL period. 17-β-E_2 decrease is likely correlated to the length of the treatment and thus to the PRL increase. The ovary reacts in different way at the same FSH and LH stimulation according to serum PRL levels. Again, it seems that E_2 ovarian production gradually increases when PRL plasma level is in the normal range, while pathologic values of PRL would induce gradual and constant E_2 reduction.

These results, occurring during each treatment, suggest that PRL acts directly on E_2 secretion (fig. 1). Our results may be explained by the difficulty of FSH and LH to induce in teca and granulosa cells aromatization necessary for E_2 synthesis, in presence of high serum PRL level ([23]) and by the existence of specific PRL receptors ([10, 11, 12]) in teca and granulosa cells.

It has been suggested that hyperprolactinemia can reduce LH spikes; but inhibiting action of PRL on ovarian aromatization is likely independent from LH plasma level ([23]). Only if we suppose a PRL action on E_2 secretion in presence of normal FSH and LH serum levels, it is possible to explain amenorrhea in hyperprolactinemic syndrome.

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