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ESTRADIOL BLOCKS PITUITARY CAPACITY FOR FSH RELEASE IN FEMALE HYPOGONADOTROPIC HYPOGONADISM

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In contrast to women with some estrogen production, severely hypo-estrogenic women with hypothalamic amenorrhea fail to show an increased LH response to GnRH after treatment with estradiol. The reason for this difference is unclear. We performed a double stimulation GnRH test with 25 ug GnRH per bolus, before and after a 5-day treatment with increasing doses of estradiol valerate, in 28 hypogonadotropic women, to measure pituitary capacity in this condition. Before the test, hormonal treatment had been discontinued for at least three months. Out of 11 patients with primary amenorrhea, six had hypogonadotropic hypogonadism (HH). Ten out of 17 seconday amenorrhea patients had more than 30% of ideal body weight weight loss.
The maximal responses of LH and FSH to the second, and to the third and fourth bolus of GnRH were exprssed as a percentage of the first maximal response. Arbitrarily, a change of more than 20% was considered to be significant.
The GnRH self-priming effect (bolus 2) was seen in all women. After E_2,pituitary capacity for LH and FSH was increased in all subjects with estrogenic activity of their own. The LH response was diminished in 5 patients with HH and in 3 with severe weight loss, and the FSH response was diminished in all who were severely hypo-estrogenic. Again (bolus 4) self-priming of GnRH was present, but in all women with HH the FSH response was severely depressed, while even the most hypogonadal women with secondary amenorrhea exhibited a positive FSH response. These results suggest that the interaction of estrogens and GnRH with the pituitary in HH is different from other forms of hypothalamic amenorrhea. At present, we are investigating whether this test is usefull for the differentiation of hypothalamic hypogonadotropic hypogonadism from constitutional delayed puberty in girls.

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MODULATION BY COMBINED PRETREATMENT WITH GnRH AND ESTRADIOL BENZOATE AND/OR CLOMIPHENE CITRATE OF THE SECRETION OF LH AND FSH BY THE PITUITARY GLAND OF THE LONG-TERM OVARIECTOMIZED RAT. AN IN-VITRO STUDY.

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Using long-term ovariectomized (OVX) rats, we investigated in a perifusion system the effect of estradiol benzoate (EB), alone or in combination with clomiphene citrate (Cl) on the secretion of LH and FSH by isolated rat anterior pituitary tissue. In a first series of experiments pituitary glands of OVX rats which had been pretreated in vivo with GnRH during 6 days (GnRH was continuously delivered by sc implanted osmotic minipumps at the rate of either 25, 50, 100, 250 or 500 ng/h), and with EB (3 µg/sc injection) during 3 days, were superfused with medium containing no GnRH (for assessment of the autonomous (i.e. non-GnRH-stimulated) release of LH and FSH), and subsequently with medium containing GnRH at the maximally stimulating concentration of 1 µg/ml.

We observed that EB enhanced the rate of autonomous LH- and FSH secretion (positive effect of estrogen), regardless the in-vivo rate of GnRH infusion. The effect of EB on the GnRH-stimulated component of LH/FSH secretion, however, was GnRH-dependent: if the in-vivo GnRH infusion rate had been lower than about 150 ng/h (which rate establishes GnRH concentrations in the plasma which are within the physiological range), the GnRH-induced LH/FSH-responses were increased by estradiol. With higher GnRH infusion rates, however, the LH/FSH responses were decreased by estradiol (negative effect of estrogen). Moreover, after discontinuation of the GnRH-treatment the negative effect of estradiol changed rapidly into the positive effect.

In a second series of experiments OVX rats were treated with clomiphene citrate (100µg/sc injection) during 3 days. Cl, given either alone or in combination with EB, enhanced the autonomous and GnRH-induced LH/FSH-responses: Cl 'behaved' like an estrogen-agonist. However, unlike EB, Cl, when given to OVX rats which had been pretreated with GnRH, 250 ng/h during 6 days, did not decrease the gonadotropin responses to GnRH: there was a positive effect of Cl on the secretion of FSH and no effect at all on the secretion of LH. When given to OVX rats, treated with GnRH and EB, Cl appeared to neutralize the negative effect of EB on the secretion of both LH and FSH.

Our data show that the effect of estradiol on the autonomous secretion of LH and FSH by the pituitary gland of the OVX rat is always positive and independent of GnRH. The (positive) effect of EB on the GnRH-stimulated component of LH/FSH secretion, on the other hand, can be down-regulated by GnRH and may become negative. The data further show that clomiphene has definite estrogenic properties, but the (positive) effect of Cl on the GnRH-stimulated component of LH/FSH secretion can not be down-regulated by GnRH.