Reversal of the Hypogonadotropic Hypogonadism of Obese Men by Administration of the Aromatase Inhibitor Testolactone

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Studies from this laboratory have shown that obese men have elevated serum estrogen levels and diminished levels of follicle-stimulating hormone (FSH) and free and total testosterone, all in proportion to their degree of obesity. The decreases in testosterone and FSH constitute a state of hypogonadotropic hypogonadism (HHG), and we have hypothesized that it results from feedback suppression of the pituitary by the elevated estrogen levels. We tested this hypothesis by lowering the serum estrogens of 6 health obese men (body mass index [BMI], 38 to 73) by administering the aromatase inhibitor testolactone (1 g daily for 6 weeks). Twenty-four–hour mean serum testosterone rose in every subject, from a mean of 290 ± 165 ng/dL to a mean of 403 ± 170 ($P < .0003$); 24-hour mean serum estradiol decreased in every subject, from a mean of 40 ± 10.8 pg/mL to a mean of 29 ± 6.7 ($P < .004$); and 24-hour mean serum luteinizing hormone (LH) increased in every subject, from a mean of 14.3 ± 4.1 mIU/mL to a mean of 19.3 ± 5.1 ($P < .004$). The rise in mean LH was due to an increase in the amplitude of the individual secretory pulses, especially at night. Twenty-four–hour mean serum estrone decreased nonsignificantly, from 48 ± 14 pg/mL to 39 ± 6.4, and 24-hour mean serum FSH increased nonsignificantly, from 13.5 ± 5.3 mIU/mL to 15.0 ± 5.4. The results are in accordance with the hypothesis, in that inhibition of estrogen biosynthesis (through administration of the aromatase inhibitor testolactone) results in alleviation of the HHG of our obese male subjects.

STUDIES FROM this laboratory have shown that obese men have elevated serum estrogen levels[1] and diminished levels of follicle-stimulating hormone (FSH) and free and total testosterone,[2]all in proportion to their degree of obesity. The decreases in testosterone and FSH constitute a state of hypogonadotropic hypogonadism (HHG),[3] and we have hypothesized that it results from feedback suppression of the pituitary by the elevated estrogen levels. We have undertaken to test the validity of this hypothesis by attempting to lower the elevated serum estrogen levels of obese men and observing whether the HHG then reverses. Three approaches to lowering the estrogen levels have suggested themselves: (1) Decreasing the adrenocortical secretion of androstenedione, which is the principal precursor of estrogens in males, via aromatization. This can be accomplished by administering a corticosteroid to suppress adrenocortical function. We performed such a study[3] and found that estrogen levels decreased and FSH levels increased, but testosterone levels did not change. We attributed the failure of the testosterone levels to rise despite the rise in gonadotropin levels to the reported direct testosterone-lowering effect of corticosteroid administration,[4] which presumably countered the expected testosterone-raising effect of lowering estrogen levels. (2) Inducing weight loss, on the assumption that if the hyperestrogenemia is due to the obesity, weight loss should reverse it. We also performed this study[5] and found a surprising result: the HHG largely resolved (FSH and testosterone levels rose nearly to normal), but serum estrogen levels did not decrease at all.[6] We attributed this to a continuous resupply of estrogen to the blood from the still considerable remaining fat depots, since our subjects started out massively obese and remained very obese even after losing 50 to 100 pounds. This explanation is supported by the finding of Stanik et al,[7] who studied the effect on serum estrogens of reducing weight from mild-to-moderate obesity to essentially normal weight and found that serum estrogen levels did fall to normal in their subjects. We hypothesize that the resolution of the HHG with weight loss in our subjects, despite the failure of the estrogen levels to fall, may be due to a second effect of weight loss, namely, an increase in the responsiveness of pituitary gonadotropin secretion to stimulation by gonadotropin-releasing hormone (GnRH). It is known that this responsiveness is decreased in obesity,[7] and it is also known that the analogously blunted response of growth hormone secretion to stimulation by growth hormone–releasing hormone in obesity is reversed by weight loss.[8] (3) Decreasing the peripheral transformation of androstenedione to estrogens by administering an inhibitor of the enzyme aromatase. It is the results of this third approach that we are reporting here.

MATERIALS AND METHODS

Six healthy obese men aged 20 to 43 years (mean ± SD, 35.5 ± 9.2 years), and with body mass indices (BMIs) ranging from 38 to 73 (49.3 ± 15.6), were studied with respect to their 24-hour mean serum levels of estrone, estradiol, testosterone, luteinizing hormone (LH), and FSH before and after a 6-week course of oral testolactone (Teslac, Bristol-Myers/Squibb, Princeton, NJ) 1 g/d. None of the men had any significant acute or chronic illness and none was taking any medication. The procedures for 24-hour sampling and for hormone analyses were as previously described from this laboratory[9]; briefly, an indwelling venous catheter was placed in an arm vein—a continuous slow infusion of normal saline was maintained over the 24-hour period, through a 3-way stopcock—samples of blood were withdrawn every 20 minutes and were allowed to clot, after which serum was separated—aliquots from each serum sample were pooled and the resulting 24-hour pool was analyzed for LH, FSH, testosterone, estrone, and estradiol to yield the 24-hour mean concentrations—each individual sample was also analyzed for LH, to determine the secretory profile. Differences between pre-and post-treatment 24-hour mean levels in the same individual were

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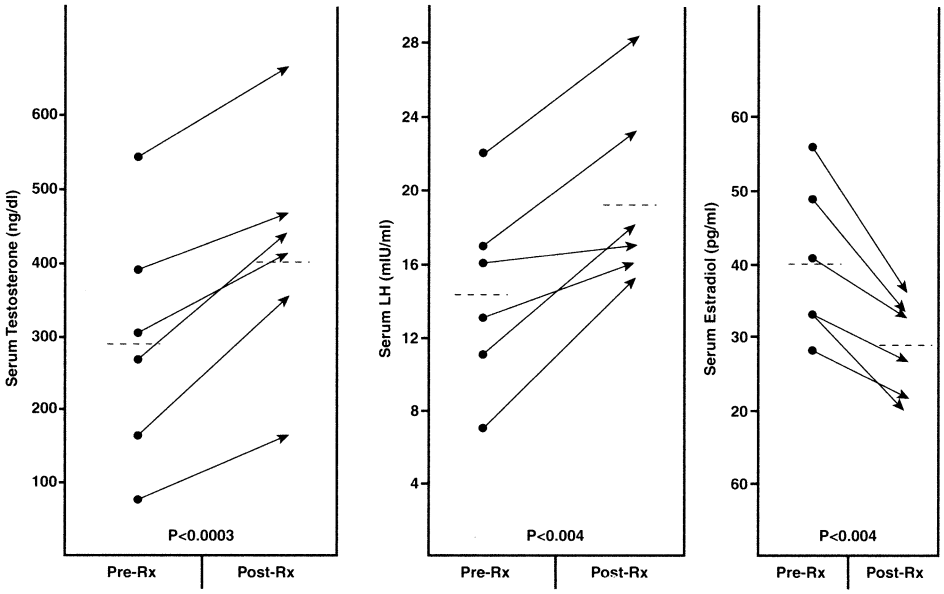

Fig 1. On treatment with testolactone, serum testoterone rose in every subject, from a mean of 290 ± 165 ng/dL to a mean of 403 ± 170 ($P < .003$); serum LH rose in every subject, from a mean of 14.3 ± 4.1 mIU/mL to a mean of 19.3 ± 5.1 ($P < .004$); and serum estradiol fell in every subject, from a mean of 40 ± 10.8 pg/mL to a mean of 29 ± 6.7 ($P < .004$).

tested for significance by the paired *t* test. The study protocol was approved by the medical center institutional review boards and informed consent was obtained from all subjects.

RESULTS

None of the subjects had a significant change in weight during the study and there were no side effects of the drug. Serum testosterone levels increased in every subject, from a pretreatment mean of 290 ± 165 ng/dL to a post-treatment mean of 403 ± 170 ($P < .0003$). Serum estradiol decreased in every subject, from a pretreatment mean of 40±10.8 pg/mL to a post-treatment mean of 29 ± 6.7 pg/mL ($P < .004$). Serum LH increased in every subject, from a pretreatment mean of 14.3 ± 4.1 mIU/mL to a post-treatment mean of 19.3 ± 5.1 ($P < .004$); the rise was due to an increase in the amplitude of the secretory pulses, especially at night. The results for these three 24-hour mean hormonal measurements are shown in Fig 1. Serum estrone fell in 4 subjects, rose slightly in 1, and remained unchanged in 1; the mean value decreased nonsignificantly from 48 ± 14 pg/mL to 39 ± 6.4. Serum FSH was measured in only 4 subjects: it rose slightly in 3 and fell slightly in 1; the mean value increased nonsignificantly from a pretreatment value of 13.5 ± 5.3 mIU/mL to a post-treatment value of 15.0 ± 5.4.

DISCUSSION

The results of treatment of these obese subjects with the aromatase inhibitor testolactone were essentially as expected: serum testosterone rose significantly, serum estrogen levels fell (significantly for estradiol, nonsignificantly for estrone), and serum gonadotropin levels rose (significantly for LH and nonsignificantly for FSH). (We measured only total testosterone and not free testosterone because the latter adds no significant independent information: studies from this laboratory have shown that the decrease of free testosterone in obese men is precisely proportional to the decrease in total testosterone[2] and the rise of free testosterone with weight loss in obese men is precisely proportional to the rise of total testosterone.[10]) It seems clear that the decrease in estrogen levels consequent to aromatase inhibition did indeed result in disappearance of the previous suppression of gonadotropin secretion and in resolution of the hypogonadotropic hypogonadism in these subjects. This strongly supports our starting hypothesis that HHG in obese men is at least partly due to feedback suppression of the pituitary by the elevated estrogen levels. However, in light of our earlier findings regarding the effect of weight loss on the HHG of obese men, namely, resolution of the HHG without a decrease in serum estrogen levels,[5] there is very likely an additional cause for their HHG, namely, their known diminished responsiveness of pituitary gonadotropin secretion to stimulation by GnRH.[8] It is known that the blunted growth hormone responsiveness is reversed by weight loss, and we plan to test directly whether the blunted gonadotropin responsiveness is reversible too.

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