Importance of estrogens in human males’ fertility and bone pathophysiology

Carmela Asteria
Institute of Endocrine Sciences, Ospedale Maggiore IRCCS, University of Milan, Italy

Since estrogens play a crucial role in several processes such as embryo implantation and fetal development it has been thought that mutation of the estrogen-receptor (ER) gene would be lethal. This hypothesis was supported by the fact that no mutations of the ER gene leading to estrogen insensitivity had been observed in mammalians. In contrast, conditions of resistance to other hormones (tri-iodothyronine, vitamin D, cortisol, androgens), which also act via receptors belonging to the nuclear receptor superfamily, have been reported with increasing frequency.

However, this notion changed in 1994 when Korach (1) created a mutant mouse line without a functional ER, obtained by the gene knock-out technique (ER knock-out; ERKO). These animals provided an attractive experimental model which could be used to gain a better understanding of the role of estrogens in a variety of tissues during early developmental stages. The main finding was that crosses of the heterozygous ERKO mice resulted in live birth offspring containing the expected Mendelian distribution of the three possible genotypes. This result suggested that, in contrast to what was previously thought, disruption of the ER was not crucial for survival. Furthermore, the homozygous ERKO mice showed no bias in sex ratio, indicating that sex determination was not affected by the absence of the estrogen receptor. As far as the phenotype was concerned, both sexes of the homozygous ERKO mice were infertile, as demonstrated by mating studies, and exhibited a variety of changes, some of which were associated with the gonads, mammary glands, reproductive tracts and skeletal tissues. In particular, homozygous mutant female mice showed the presence of hypoplastic reproductive tract structures, hemorrhagic cystic ovaries with no functional corpora lutea and no uterine response to estrogen treatment. The mammary glands were undeveloped with only vestigial ducts present at the nipples. Of particular relevance was the observation that the bone density of the ERKO male and female mice was 20 to 25% lower than in wild-type mice, suggesting a direct role for estrogen in bone physiology.

An unexpected finding was the infertility of the sexually mature male adult ERKO mice, despite the presence of anatomically normal reproductive apparatus. In order to assess the essential role for ER-mediated processes in the regulation of male reproduction, further studies on ERKO male mice were recently carried out by Eddy and colleagues (2). These authors demonstrated that the absence of ER was detrimental to spermatogenesis, sperm function and mating performance. Although the findings in ERKO mice were exciting, their relevance to human physiology appeared to be questionable, due to the species differences in genetic background. Nevertheless, the first case report of estrogen resistance in man due to mutation in the ER gene (3) provided the evidence that the ERKO mouse could be an acceptable model for the evaluation of a variety of estrogen responses and accompanying mechanisms related to human population. In the above report, the patient was a 28-year-old white man, fully masculinized, who had osteoporosis, unfused epiphyses and continuing linear growth in adulthood. He also had elevated serum estrogen, steroid and gonadotropin levels and no target-tissue responses to estrogen therapy. Genetic analysis showed that the patient was homozygous for a mutation in the second exon (R157X) of the ER gene, generating a premature stop codon. Similar to the observations in the ERKO mice, these findings suggested that estrogens in human males have a pivotal role in bone maturation and mineralization and are also important for complete epiphyseal closure. Therefore, normal androgen levels alone, as in this case, are not sufficient to promote skeletal maturation and retain bone mass, in contrast with the idea that androgens are important for the maintenance of bone mass in men. Data on the fertility of this patient were not available.

Other insights into the relevance of estrogen action in men arise from the recent description of aromatase deficiency in male and female siblings due to mutation in exon 9 of the P450 aromatase gene (CYP 19) (4). In the female sibling this condition led to an autosomal recessive form of female pseudohermaphroditism, as a consequence of impaired or absent conversion of fetal and maternal androgens to estrogens by the placental syncytiotrophoblast. This observation supports the contention that estrogen synthesis in the blastocyst, fetus and placenta is not fundamental for normal fetal development and reinforces the concept that placental estrogens are not essential for the physiology of pregnancy, but are important in preventing virilization in female fetuses and in the mother. The 24-year-old
male sibling, who grew normally during childhood, showed tall stature, delayed bone age and osteopenia, similar to the observations reported in the male patient with a mutation in the ER gene and in the ERKO male mice. Together, these findings confirm that estrogens are essential in males for skeletal maturation and proportion (but not linear growth), for the maintenance of bone mass and for the control of bone turnover. The patient also presented with normal male secondary sex characteristics, macroorchidism and elevated plasma follicle-stimulating hormone, luteinizing hormone and androgen levels associated with very low estradiol and estrone concentrations. This latter observation gives prominence to the fact that estrogens are also important regulators of gonadotropin secretion in the male. In addition, hyperinsulinism and an abnormal plasma lipid profile were detected, suggesting that estrogen deficiency in men may cause impairment of glucose tolerance and lipid metabolism. Finally, the psychosexual orientation of both brother and sister was appropriate for their phenotypic sex, indicating that estrogens in humans do not have the critical effects on sex differentiation of the brain described in nonprimate mammals (5).

In conclusion, the data obtained by studies performed in humans and in the ERKO mice are consistent with an important role for estrogens in male pathophysiology where they exert relevant effects on skeletal maturation and mineralization, epiphyseal fusion, lipid metabolism, glucose tolerance and fertility. As a consequence, ER or aromatase defects leading to estrogen insensitivity or deficiency respectively, should be suspected in male patients with infertility, especially when this condition is associated with tall stature and osteoporosis. Finally, it has been clearly demonstrated that estrogens are not crucial to survival and do not affect either sex determination or the psychosexual behavior in humans.

References