HIGHLIGHT

Oestrogens – essential for reproduction in males, too

Jens P Berg

Hormone Laboratory, Aker University Hospital, Trondheimsveien 235, N-0514 Oslo, Norway

Both sexes produce oestrogens, but little is known about the physiological role of the 'female' hormone in males. A recent report by Hess *et al.* (1) shows that oestrogen receptor activation is necessary for normal male fertility, and indicates that the effects of oestradiol are important for reproduction in males and females.

Oestrogens bind to and activate an intracellular receptor which is a ligand-activated transcription factor belonging to the steroid hormone receptor superfamily. The first oestrogen receptor (ER) was cloned and sequenced in 1986, and was denoted ER α (2), after the identification of an additional receptor (ER β) ten years later (3). In 1993 a knock-out mouse model lacking a functional ER α was created (ERKO mice) (4, 5). The phenotype of both male and female ERKO mice initially appeared normal and excluded a role for ER α in the fetal development of genitalia. That adult female mice had hypoplastic uteri, did not develop corpora lutea and were infertile, came as no surprise. However, adult male mice also became infertile with atrophy of the testes and dysmorphic seminiferous tubules. Sperm from the mice were abnormal, and the sperm concentration in the epididymis was low (6). In a case report of a man with dysfunctional oestrogen receptor, the sperm count was normal but viability of the sperm was low (7). A low level of the hormone caused by aromatase deficiency was seen in a 24-year-old man with increased testicular volume (8), whereas a 38-year-old man with the same deficiency had small testicles and severe oligozoospermia (9). Testicles of male ER α knock-out mice developed normally until puberty, after which they started to degenerate. A transient increase in weight occurred between 32 and 81 days of age when the rete testis became dilated and the efferent ductules were swollen with increased luminal area. This was caused by an increased secretion of fluid by the testis or a defective removal of the fluid secreted. After 185 days of age the observed atrophy and decreased weight of the testes appeared to result from long-standing increased luminal fluid pressure.

The efferent ductules conduct sperm from the testis to the epididymis (reviewed in (10)). They are the first site of epithelial ER expression in the developing male reproductive organ in mice, and both male rat and marmoset monkey show a pronounced immun-expression of ER α in the efferent ductules (11, 12). The concentration of oestrogens in fluid from the testes is

high and comparable to the serum 17 β -oestradiol level in females of reproductive age. Interestingly, spermatids express aromatase and may convert androgens to oestrogens. The number of spermatozoa in transit to the epididymis may determine the oestrogenic stimulation of the cells lining the efferent ductules. These cells have a well-developed apparatus for the reabsorption of fluid, and more than 90% of the fluid continuously secreted by the seminiferous epithelium of the testes is reabsorbed in the efferent ductules. By occluding the ductal system at different levels Hess *et al.* (1) demonstrated that the apparent increase in luminal pressure in mice lacking ER α was caused by a defect in the reabsorption of testicular fluid in the efferent ductules and not by an increased testicular fluid secretion. Experiments with cultured pieces of epididymis corroborated these findings. Thus, ER α seems to be important for fluid reabsorption and normal adult function of the efferent ductules. However, wild-type efferent ductules treated with the antioestrogen ICI 182,780 *in vitro* did not swell like the ductules from the ER α knock-out mice. The presence and effects of ER β in efferent ductules and the epididymis may explain this discrepancy (13).

The study by Hess *et al.* (1) shows that oestrogens have an important physiological role in male reproduction. It suggests that defects in the oestrogen action should be taken into consideration in the evaluation of male infertility, although only one patient with ER α deficiency has been reported. The finding is also important for research on a possible association between declining male reproductive health and exposure to environmental oestrogens (14).

References

- 1 Hess RA, Bunick D, Lee K-H, Bahr J, Taylor JA, Korach KS & Lubahn DB. A role for oestrogens in the male reproductive system. *Nature* 1997 **390** 509–512.
- 2 Green S, Walter P, Kumar V, Krust A, Bornert JM, Argos P & Chambon P. Human oestrogen receptor cDNA: sequence, expression and homology to v-erb-A. *Nature* 1986 **320** 134–139.
- 3 Kuiper GGJM, Enmark E, Peltö-Huikko M, Nilsson S & Gustafsson J-Å. Cloning of a novel estrogen receptor expressed in rat prostate and ovary. *Proceedings of the National Academy of Sciences of the USA* 1996 **93** 5925–5930.
- 4 Lubahn DB, Moyer JS, Golding TS, Couse JE, Korach KS & Smithies O. Alteration of reproductive function but not prenatal sexual development after insertional disruption of the mouse estrogen receptor gene. *Proceedings of the National Academy of Sciences of the USA* 1993 **90** 11162–11166.

- 5 Korach KS. Insights from the study of animals lacking functional estrogen receptor. *Science* 1994 **266** 1524–1527.
- 6 Eddy EM, Washburn TF, Bunch DO, Goulding EH, Gladen BC, Lubahn DB & Korach KS. Targeted disruption of the estrogen receptor gene in male mice causes alteration of spermatogenesis and infertility. *Endocrinology* 1996 **137** 4796–4805.
- 7 Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B *et al.* Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. *New England Journal of Medicine* 1994 **331** 1056–1061.
- 8 Morishima A, Grumbach MM, Simpson ER, Fisher C & Qin K. Aromatase deficiency in male and female siblings caused by a novel mutation and the physiological role of estrogens. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 3689–3698.
- 9 Carani C, Qin K, Simoni M, Faustini-Fustini M, Serpente S, Boyd J *et al.* Effect of testosterone and estradiol in a man with aromatase deficiency. *New England Journal of Medicine* 1997 **337** 91–95.
- 10 Ilio KY & Hess RA. Structure and function of the ductuli efferentes: a review. *Microscopy Research and Technique* 1994 **29** 432–467.
- 11 Cooke PS, Young P, Hess RA & Cunha GR. Estrogen receptor expression in developing epididymis, efferent ductules, and other male reproductive organs. *Endocrinology* 1991 **128** 2874–2879.
- 12 Fisher JS, Millar MR, Majdic G, Saunders PTK, Fraser HM & Sharpe RM. Immunolocalisation of oestrogen receptor- α within the testis and excurrent ducts of the rat and marmoset monkey from perinatal life to adulthood. *Journal of Endocrinology* 1997 **153** 485–495.
- 13 Hess RA, Gist DH, Bunick D, Lubahn DB, Farrell A, Bahr J, Cooke PS & Greene GL. Estrogen receptor (α and β) expression in the excurrent ducts of the adult male rat reproductive tract. *Journal of Andrology* 1997 **18** 602–611.
- 14 Sharpe RM & Skakkebaek NE. Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet* 1993 **341** 1392–1395.