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 ERα (2), after the identification of an additional receptor (ERβ) ten years later (3). In 1993 a knock-out mouse model lacking a functional ERα was created (ERKO mice) (4, 5). The phenotype of both male and female ERKO mice initially appeared normal and excluded a role for ERα 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 ERα 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 immuno-expression of ERα in the efferent ductules (11, 12). The concentration of oestrogens in fluid from the testes is high and comparable to the serum 17β-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 ERα 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, ERα seems to be important for fluid reabsorption and normal adult function of the efferent ductules. However, wild-type efferent ductules treated with the anti-oestrogen ICI 182,780 in vitro did not swell like the ductules from the ERα knock-out mice. The presence and effects of ERβ 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 ERα 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