oestrogen formation in pre- and postmenopausal patients like luteinising hormone-releasing hormone (LH-RH) agonists and aromatase inhibitors, respectively, became available for the treatment of advanced breast and endometrial cancers. The first generation of aromatase inhibitors were not specific and, therefore, toxic. Today, a number of potent and very selective aromatase inhibitors are available. There is renewed interest in anti-oestrogens, now called selective oestrogen receptor modulators (SERMs), without uterine side-effects, being anti-oestrogenic in the breast but oestrogenic in the bone and cardiovascular system. New hormonal developments for after 2000 are pure anti-oestrogens, antiprogestins, somatostatin analogues and LH-RH antagonists.

References

1. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment with illustrative cases. *Lancet* 1896, **ii**, 104–107.
2. Knauer E. Die Ovarientransplantation. *Experimentelle Studie Arch Gynaek* 1900, **60**, 322.
3. Murray WS. Ovarian secretion and tumor incidence. *Science* 1927, **66**, 600–601.
4. Allen E, Doisy EA. An ovarian hormone. Preliminary report on its localization, extraction and partial purification and action in test animals. *JAMA* 1923, **81**, 819–821.
5. Greene HSN. Uterine adenomata in rabbits. *J Exp Med* 1941, **73**, 273–292.
6. Meissner WA, Sommers SC, Sherman G. Endometrial hyperplasia, endometrial carcinoma and endometriosis produced experimentally by estrogen. *Cancer* 1957, **10**, 500–509.
7. Geist SH, Walter RI, Salmon UF. Are estrogens carcinogenic in the human female Atypical endometrial proliferation in a patient treated with oestrogens? *Am J Obstet Gynecol* 1941, **42**, 242–248.
8. Gusberg SB. Precursors of corpus carcinoma — estrogens and adenomatous hyperplasia. *Am J Obstet Gynecol* 1947, **54**, 905–907.
9. Jensen EI, Ostergaard E. Clinical studies concerning the relationship of estrogens to the development of cancer of the corpus uteri. *Am J Obstet Gynecol* 1954, **67**, 1094–1102.
10. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. *New Engl J Med* 1975, **293**, 1164–1167.
11. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. *New Engl J Med* 1975, **293**, 1167–1170.
12. Kelly RM, Baker WH. Progesterone for endometrial cancer. *New Engl J Med* 1961, **246**, 216–220.
13. Dockerty MB, Massey E. Malignant lesions of the uterus associated with estrogen-producing ovarian tumors. *Am J Obstet Gynecol* 1951, **61**, 147–150.
14. Lilienfeld AM, Johnson EA. The age distribution in female breast and genital cancers. *Cancer* 1955, **8**, 875–881.
15. MacDonald PC, Grodin JM, Siiteri PK. The origin of postmenopausal oestrogens. *Proc Int Congr Endocrinol* 1969, **184**, 770.
16. Siiteri PK, MacDonald PC. Role of extraglandular estrogen in human endocrinology. In *Handbook of Physiology, vol. 2. Female Reproductive System*. Am Physiol Soc, 1973.
17. Miller WR, Forrest APM. Oestradiol synthesis by a human breast carcinoma. *Lancet* 1974, **ii**, 866–868.
18. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, *et al*. A prospective study of endogenous estrogens and breast cancer in psotmenopausal women. *J Natl Cancer Inst* 1995, **87**, 190–197.
19. Jensen EV. *Proc Intl Congr Biochem, Vienna 1958*. London, Pergamon Press, 1960.
20. Toft D, Gorski J. A receptor molecule for estrogens: isolation from the rat uterus and preliminary characterisation. *Proc Natl Acad Sci USA* 1966, **55**, 1574–1581.

Molecular mechanisms of oestrogen — the gynaecologists' viewpoint

A. Vashisht *, J.W.W. Studd

Chelsea and Westminster Hospital, London SW10 9NH, UK

The use of oestrogen as a hormone replacement therapy (HRT) for postmenopausal women is increasing. There are known benefits of relief of climacteric-related mood and vasomotor symptoms and there is protection against osteoporosis and cardiovascular disease. The applications of oestrogen are limited by the need for a progestagen in non-hysterectomised women, and by women's dislike of uterine bleeding, and fear of breast cancer. Molecular biology perhaps holds the key for widening the clinical use of HRT. By studying the molecular actions of oestrogen, compounds are being developed that will mimic its action while avoiding the unwanted effects associated with conventional therapy.

Nuclear hormone receptors are transcription factors that can initiate or amplify the transcription of genes that are hormonally responsive. The oestrogen receptor (ER) protein consists of 595 amino acids, and is separated into six functional domains. Each domain is responsible for different functions: binding hormones, binding hormone response elements, or containing transcription activation functions, to initiate gene transcription.

* Corresponding author.
E-mail address: a.vashisht@ic.ac.uk (A. Vashisht).

0959-8049/00/$ - see front matter
PII: S0959-8049(00)00205-7

A second oestrogen receptor, ERβ, was discovered in 1996. It exhibits separate oestrogen binding affinities from the ERα receptor, and the two receptors are expressed in different amounts in different tissues.

Oestrogens are rapidly absorbed by the gastrointestinal tract, skin, mucous membranes and after parenteral injection. On arrival at a tissue, oestrogen diffuses into a cell and binds to a nuclear receptor. Heat shock proteins dissociate, inducing a configurational change in structure. The receptor dimerises. If the cell has a receptor molecule present, and has a DNA sequence responsive to the oestrogen, then the tissue will produce a response. The rate of transcription of target genes will be affected. For example, in the uterus and breast, there is increased cellular proliferation.

Numerous studies show a cardiovascular morbidity and mortality reduction in response to oestrogen therapy. Oestrogen decreases serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and increases high-density lipoprotein (HDL) cholesterol and triglyceride [1]. This occurs as a result of ER-mediated effects on the hepatic expression of apoprotein genes. Similarly coagulation proteins are regulated by oestrogen: plasma fibrinogen, protein S and antithrombin III are all reduced.

Oestrogen increases vasodilation. This effect is manifested over a few minutes and is a non-genomic response. Increased levels of nitric oxide are achieved. It is postulated that some form of oestrogen receptor is activated that has a direct effect on nitric oxide synthase. Oestrogen also inhibits the response of blood vessels to injury, and inhibits atherosclerotic plaque build-up. These effects occur as a result of altered gene expression, and consequently take longer to become established.

Oestrogen exerts both genomic and non-genomic effects on the central nervous system (CNS). Oestrogen receptors have been located in the hypothalamus, cortex, pituitary and limbic system [2]. Here, oestrogens effect changes in the production of a variety of neurotransmitters and neuropeptides. They may also affect the number of neurotransmitter and neuropeptide receptors, amplifying signal transduction.

Oestrogen increases noradrenaline activity by decreasing its uptake and by decreasing monoamine oxidase. Similarly, levels of serotonin are increased. This is important in elevating mood. Acetylcholine synthesis is increased by oestrogen-mediated upregulation of choline acetyl-transferase, which may play an role in improved memory function. It has also been implicated in the aetiology of Alzheimer's disease.

The menopause causes an increase in bone turnover, with resorption outpacing formation. The consequent loss of bone leads to a weakening of bone architecture, and a susceptibility to fracture. Oestrogen is known to slow this task, and may have an anabolic effect on bone. ERs have been identified in osteoblasts. ERs have been found on osteoclasts, although there is no evidence of changes in cell response on exposure to oestrogens. It might be that osteoclasts receive signals from activated osteoblasts to mediate their activity. Oestrogen also inhibits locally acting cytokines such as interleukin (IL)-1 and IL-6, which promote osteoclast activity.

Type I anti-oestrogens are analogues of tamoxifen; type II are the pure anti-oestrogens. Both competitively inhibit the binding of oestradiol to the ER. Type I anti-oestrogens appear to form a receptor complex that is incompletely converted to the fully active form and is, thus, only partially active in initiating gene activation. Another postulated mechanism is that the anti-oestrogen-ER complex, unable to bind to the oestrogen-response-element, will instead bind to an anti-oestrogen-response-element (AERE) in the promoter region, and hence initiate gene transcription via a separate route [3]. Type II anti-oestrogens bind to newly synthesised ERs in the cytoplasm, preventing their transport to the nucleus. This complex is then destroyed, preventing oestrogen-dependent function. They have been proposed as drugs that might be useful in treating oestrogen-dependent tumours. Selective oestrogen receptor modulators (SERMs) have been developed that have oestrogenic effects on the bone and cardiovascular system, and anti-oestrogenic effects on breast and uterine tissue.

Oestrogens have a wide range of activity. One oestrogen has different effects in different tissues and two oestrogens can have similar effects in one tissue, but opposite effects in another. The distribution and localisation of different receptors, the activation of different hormone-binding domains, and hence the interaction of transcription factors and coactivators determines an agonist, antagonist or mixed response. The goal of attaining the 'ideal oestrogen' is becoming an increasing reality.

References

1. The Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA* 1995, **273**, 199–208.
2. Sherwin B. Hormones, mood and cognitive functioning in postmenopausal women. *Obst and Gynaecol* 1996, **87**, 20S–26S.
3. Yang NN, Venugopalan M, Hardikar S, Glasebrook A. Identification of an estrogen response element activated by metabolites of 17β-estradiol and raloxifene. *Science* 1996, **273**, 1222–1225.