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Estrogen Receptors in the Male

R. B. DICKSON AND C. R. CLARK

Estrogens in the male are secreted by the testes and derived extragonadally from the aromatization of certain androgens. In some brain regions critical for the control of gonadotropin secretion and behavior, androgens may be aromatized to estrogens within the cells that are regulated. Estrogen may have other physiological roles on the testes to control testosterone secretion and on accessory sex glands to promote both fibromuscular growth and secretion. High doses of estrogen given for treatment of prostatic cancer or modulation of reproductive function not only reduce testosterone secretion but also interact with the liver, changing the secretion of various plasma proteins and causing several undesirable side effects. The hypothalamus, pituitary, testes, accessory sex glands, and liver all contain an apparently identical protein, the estrogen receptor, which may mediate the actions of estrogen.

Key Words: Estrogen; Receptors; Male; Aromatase; Feminization; Steroidogenesis.

INTRODUCTION

The study of male sexuality has traditionally centered on androgens. In recent years, however, it has become apparent that estrogens also play a crucial role in the development, physiology, and behavior of the male. Estrogens in the male have actions on the sex organs, central nervous system, adrenals, liver, and other organs [19, 44, 51, 71].

To determine if a tissue is a direct target of estrogen, one criterion which must be satisfied is the identification of macromolecules with "receptorlike" properties which can mediate the effect(s) of estrogen on that tissue. The following five criteria are frequently used to establish whether an estrogen binding site can be termed a receptor [31]. First, the binding should be reversible and of high affinity; the levels of estrogen are low and responses may be transient. Second, since there should be a limited number of receptors per cell, binding should be saturable. Third, binding should be specific for the hormone and related hormone analogues. Fourth, binding should be confined to those organs that show a response to the hormone. Finally, hormone binding should be in some way functionally linked to the initiation of a response. Of all the criteria, assigning a functional role to a receptorlike macromolecule has proven to be notoriously difficult. Therefore, the term "receptor" is used rather loosely to label those macromolecules which satisfy the first three of the above hormone binding criteria.

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MECHANISM OF ACTION OF ESTROGENS

The uterus of the female rat has been used extensively as a model target tissue in the study of the mechanism of estrogen action. The uterus has been a useful model system for other estrogen target tissues, including those in the male. A model for the mechanism of action of estrogens in the male is proposed (Fig. 1). Cells of estrogen-responsive tissues are exposed to estrogen principally through the circulatory system, although in tissues where estrogen is derived from the local aromatization of testosterone, estrogen may be formed locally. Estrogens circulate in two states: bound to plasma "transport proteins" and unbound [30]. Transport proteins (i.e., sex hormone-binding globulin, α_1 -acid glycoprotein, and albumin) are synthesized in the liver, and this synthesis is under partial estrogenic control [66]. Bound estrogen is in equilibrium with the much smaller pool of unbound, the portion which is immediately available for tissue interactions. Estrogen enters all cells by a process that is currently not understood.

Target tissues contain receptors, enzymes of estrogen metabolism, and nonreceptor binding proteins that modulate estrogen-receptor complex formation [15, 16, 19, 30]. Within estrogen target cells, estrogen is specifically bound with a high affinity to a cytoplasmic receptor protein. A change in conformation of the estrogen-receptor com-

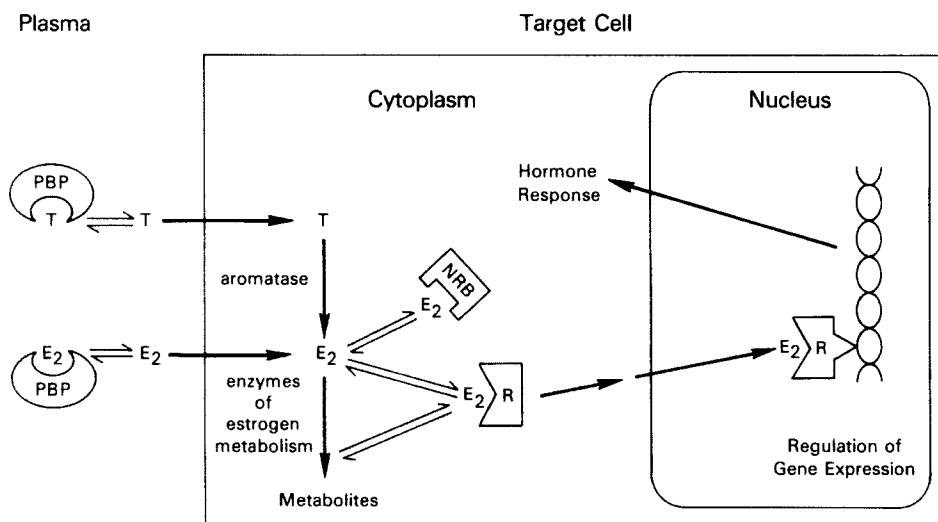


FIGURE 1. Mechanism of action of estrogens in the male: a model. Plasma estradiol (E₂) and testosterone (T) circulate either bound to plasma proteins (PBP) or unbound. Unbound steroids enter all cells to a certain extent by a process that is not currently understood. T may be converted to E₂ if the aromatizing enzyme complex aromatase is present. Estrogen may be further metabolized, bound to nonreceptor binders (NRB) or bound to cytoplasmic receptor proteins (R) exclusively within estrogen target cells. Estrogen receptor complex (E₂R) formation triggers a process which results in an activated complex with a high affinity for chromatin. The activated E₂R is translocated to the nucleus with a resultant regulation of gene expression.

plex occurs, triggering a process that results in an activated complex with a high affinity for chromatin. The activated estrogen-receptor complex is "translocated" into the nucleus [30]. Where on the chromatin the estrogen-receptor complexes bind and how they modulate cell function is currently under intensive investigation. Steroids may modulate gene expression in a manner similar to enzyme induction in bacteria. Steroid receptors may bind to tissue-specific promoter (or repressor) control sites in the chromatin and facilitate the transcription of RNA. Estrogen-stimulated messenger RNA is translated and processed to yield specific steroid-induced protein(s) [57].

SOURCES OF ESTROGENS IN THE MALE

In the male, the free estrogens, estrone and estradiol, enter the blood both as a result of direct secretion from the testis and extragonadal conversion from androgenic precursors (Fig. 2). In the testes of men, testosterone is converted to estradiol and androstenedione to estrone [39], releasing estradiol (97.2–892.0 pg/ml) and estrone (30.0–234.8 pg/ml) into spermatogenic venous blood [40]. The conversion of androstenedione to estrone is the main source of estrone entering the body [38]. Extragonadal conversion or aromatization of androgen provides the other source of estrogen (25%–50% [23, 35]) in the male. The major site of androgen secretion is the testis, although the adrenal cortex also secretes smaller amounts of C₁₉ steroids—dehydroepiandrosterone, androstenedione, and 11 β -hydroxyandrosterone [7]. In many species, aromatase activ-

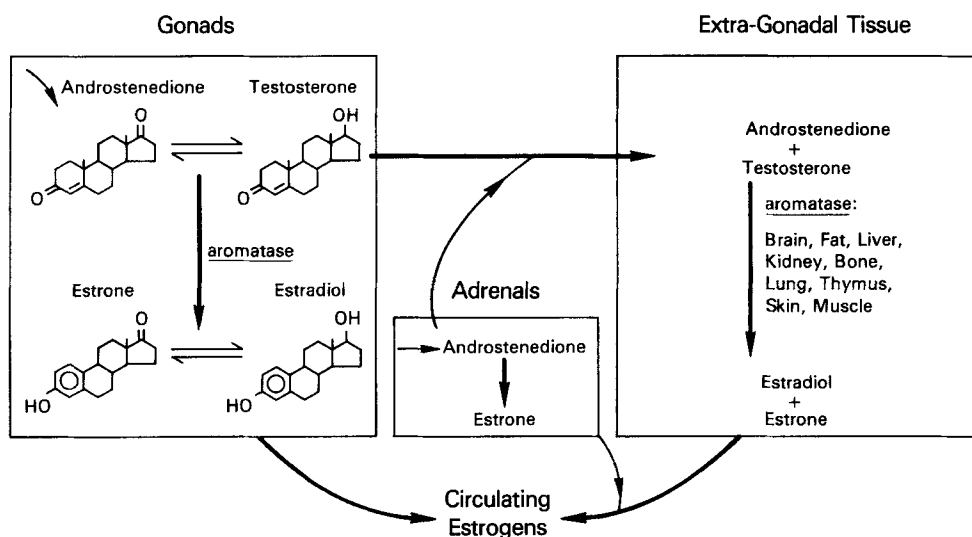


FIGURE 2. Physiologic sources of estrogen in the male. Gonadal androgens are converted by the enzyme complex aromatase to estrogens. Both androgens and estrogens are released into the general circulation. Androgens may, in addition, be aromatized to estrogens in extragonadal tissues. These estrogens may have local actions prior to their release into the general circulation. The adrenals normally contribute relatively minor amounts of androgens and estrogens to the circulatory pools.

ity has been detected in nonneural and neural tissues, specifically in the hypothalamus and limbic system [10, 54] (Fig. 2). In most areas of the brain, the extent of *in vitro* aromatization is low—in the range of 1% or less of substrate metabolized. However, the potency of estrogen for biological actions is very high—often 10–100-fold higher than that of the parent androgen. Some actions of androgen on the brain may be carried out via conversion to estrogen at the cellular level [53].

Superphysiologic elevations in the level of plasma estrogens, for example as a consequence of pharmacologic administration in the treatment of prostatic cancer, or resulting from abnormal biosynthesis by a testicular or adrenal tumor, can lead to marked changes in male physiology. Environmental influences can also result in increased levels of estrogens in the blood. A variety of chemicals including certain carcinogens, e.g., DMBA [49] and polychlorinated biphenyls [6], appear to be estrogenic. Some plants, notably marijuana [55], contain estrogenic or antiandrogenic substances, and various herbicides and insecticides, e.g., DDT [6] and Kepone [8], are estrogenic or influence the hepatic metabolism of estrogens. Each of these modes of estrogenization can lead to some degree of feminization of men and other mammalian males. A spectrum of changes can occur: reduction in testosterone synthesis, impotence, regression of testes and secondary sex organs, loss of pubic and axillary hair, changes in the levels of various hepatic enzymes and plasma proteins, thromboembolism, and gynecomastia. Tumors of the pituitary gland and many other target organs for estrogen have also been reported. Whether some of these diverse changes are the result of direct or indirect (i.e., by reduction in the levels of testosterone) effects of estrogens remains to be determined [19, 21, 24, 44, 51, 71].

CENTRAL NERVOUS SYSTEM

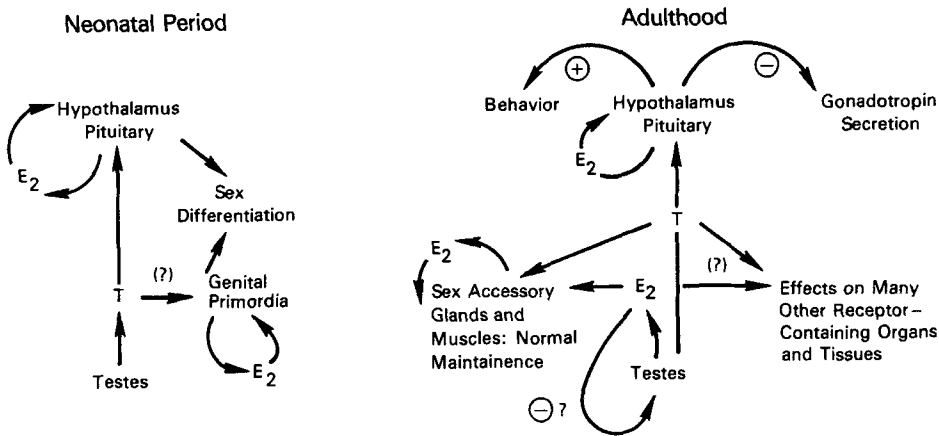
The strongest evidence for a physiologic role of estrogens in the male is in the central nervous system. Estrogens are critical during development and maturation of the brain and in adulthood to allow normal expression of sexual and aggressive behaviors and to regulate gonadotropin secretion (Fig. 3). Implantation, lesion, and morphological studies implicate the hypothalamus, amygdala, and pituitary as important sites of action of estrogen in the central nervous system (CNS).

Estrogen Receptors

Most of the actions of estradiol on the developing and adult male CNS appear to be the result of an interaction of estradiol with specific intracellular proteins that translocate hormone into the nuclear compartment of the cell and alter genomic activity. Although receptors have been identified within the brain and pituitary for the other major classes of steroid hormone, i.e., androgens, progestins, glucocorticoids, and mineralocorticoids [42], the estrogen receptors have the most extensively studied role in behavior and neuroendocrine function.

The ability of the male pituitary and hypothalamus–preoptic area to retain and concentrate estradiol was demonstrated using systemically injected ^3H -estradiol [20]. Pre-treatment with unlabelled estradiol diminished the uptake of ^3H -estradiol, and the

A. Physiological



B. Pharmacologic, High Doses of Estrogen in Adulthood

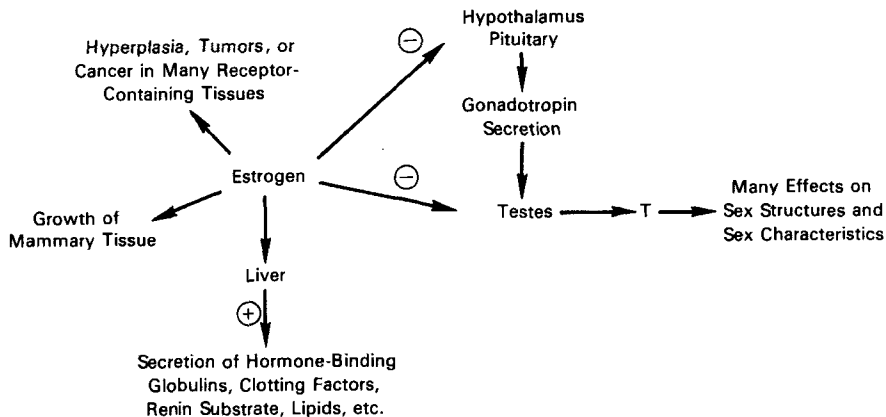


FIGURE 3. Proposed role of estrogen in the male. A. Physiologic estrogen (E₂) derived from testosterone (T) may play a critical role during development both in the differentiation of the central nervous system and the genital primordia. In adulthood, E₂ has important actions in modulating behavior and regulating the secretion of gonadotropins and testosterone. Effects may be observed in sex-accessory glands, testes, and on other E₂-receptor-containing tissues. B. Exposure of the adult male to pharmacologic levels of estrogen can result in an abolition or severe reduction in testosterone secretion with widespread physiologic consequences. Pharmacologic estrogen may also have undesirable direct effects on liver and other tissues. Under certain circumstances the formation of tumors can occur in some receptor-containing tissues.

radioactivity in the tissues was identified as being primarily unchanged ^3H -estradiol. Autoradiographic studies of the distribution of radioactivity among cells in the male and female rat brain following injection of ^3H -estradiol have revealed no sex differences in neurons which concentrate estradiol [58]. The highest labeling of cells in the male and female rat and other vertebrate species is to be found in the preoptic area, prepiriform cortex, olfactory tubercle, septum, cingulate gyrus, amygdala, and ventromedial hypothalamus.

Binding of ^3H -estradiol to soluble receptors from male rat pituitary and various brain regions has been described by a number of laboratories. Like those in the uterus, neural estrogen receptors have a sedimentation coefficient in low ionic strength sucrose density gradients of approximately 8S; they have a high affinity (K_A of 10^{10} M), and they are highly specific for estrogens [56]. There are up to 30-fold more receptors in the pituitary than in the hypothalamus. Sex differences in the physicochemical properties of estrogen receptors within the pituitary and brain have not been found [33]. That the 8S cytoplasmic molecules are precursors for 6S nuclear binding sites may be inferred from studies in which injected estradiol increases nuclear binding sites for several hours and reduces the cytosol binding sites for up to 15 hr. Receptor depletion is followed by replenishment of cytosol receptor levels, which is only partially sensitive to cycloheximide, an inhibitor of protein synthesis [30, 31].

Role of Estrogen Receptors in the Male Central Nervous System

Sexual Differentiation

In rodents, estradiol formed by aromatization of testosterone is the principal active steroid involved in sexual differentiation of the brain (Fig. 3) [45]. Increases in the levels of the estrogen receptor coincide with the critical period of neural development [4]. These receptors appear to be at least partially occupied in neonatal male but not female rats by endogenous hormone [70]. Endogenous estrogen in the female is prevented from reaching the fetal CNS by the presence of high levels of a serum estrogen-binding protein, α -fetoprotein [2]. This molecule has a stereospecific, high affinity for estradiol and is present, in progressively diminishing concentrations in the rat, from late gestation through the first 4 weeks of postnatal life [59]. The neonatal male brain has the ability to aromatize androgen to estrogen, and the masculinizing effects of testosterone are attenuated both by aromatase inhibitors and antiestrogens. The masculinizing effects of testosterone given to castrated newborn hamsters are blocked [13] by pentobarbitol and SKF 525A, inhibitors of microsomal oxidation that decrease the conversion of testosterone to estradiol. "Defeminization" of lordosis in response to neonatal testosterone propionate may be blocked with CI-628, a potent nonsteroidal estrogen antagonist [47]. In addition, the administration of estradiol during the critical neonatal period mimics the effect of androgen in blocking ovulation in the adult female and masculinizing neural differentiation in the neonatally castrated male. Moreover, neonatal treatment of female rats with the nonaromatizable androgen 5α -dihydrotestosterone is ineffective in altering the normal female pattern of neural development [26].

Sexual differentiation of neuroendocrine and behavioral function in species other than rodents, men in particular, is poorly understood. It is not known how widely the

situation in rodents can be generalized to other species [40]. One of the most informative disorders involving the process of sexual differentiation is the androgen insensitivity syndrome in humans, mice, and rats. In primates and rodents the primary defect responsible for this syndrome is the virtual absence of androgen receptors. Hence there is a complete failure of masculine development of the Wolffian ducts, urogenital sinus, and external genitalia [46]. With respect to neuroendocrine and behavioral function, the brains of androgen-insensitive rats are essentially masculine in character, suggesting the importance of aromatization of testosterone to estradiol in this species [63]. However, in humans there is no evidence for masculine tendencies in gender role behavior [3].

Gonadotropin Secretion

Gonadotropin secretion in the male is partially modulated through negative feedback inhibition by circulating androgens (Fig. 3). Castration elevates plasma gonadotropins, whereas the exogenous administration of testosterone results in their suppression. In the male rat, testosterone or one of its 5α -reduced metabolites is the active steroid in the regulation of gonadotropin secretion. Hence, exogenously administered 5α -dihydrotestosterone and other 5α -reduced androgens suppress luteinizing hormone (LH) and follicle stimulating hormone (FSH) in castrated rats in a time course similar to testosterone. Estrogen also suppresses gonadotropin secretion but at a much faster rate than testosterone [69].

The obligatory role of testosterone and/or one of its 5α -reduced metabolites in the regulation of LH release is suggested by the elevated levels of LH and FSH that follow administration of the nonsteroidal antiandrogen Sch-16423 [12], or its parent compound, flutamide [65]. That the action of testosterone on gonadotropin secretion does not require its aromatization to estradiol is suggested by the inability of the aromatase inhibitor 1,4,6-androstatriene-3,17-dione to block testosterone-mediated suppression of LH secretion in castrated rats [37]. Estrogen, both in vivo [29] and in vitro [60], can also directly interfere with Leydig cell function, inhibiting biosynthesis of testosterone (Fig. 3).

In man, in contrast to the male rat, estrogen appears to play a crucial role in the regulation of gonadotropin secretion. A recent study [41] employed men in whom a daily dose of testosterone (1 mg) or estradiol (45 μ g) was infused for 7 days. Plasma LH was measured in these individuals every 20 min for 8 hr before and on the 4th day of infusion. This infusion rate of testosterone suppressed LH by 39%, whereas estradiol suppressed plasma LH by 22%. Estradiol administration reduced the amplitude of LH secretory spikes, whereas testosterone reduced their frequency [61]. Treatment of normal and androgen insensitive men with the antiestrogen clomiphene citrate elevated LH [34]. A pure androgen effect on LH secretion has also been established. Treatment of men with the nonaromatizable androgens 5α -dihydrotestosterone or fluoxymesterone (a synthetic androgen) suppressed LH secretion [62]. Androgen-insensitive men have elevated levels of LH, possibly the result of impaired negative feedback of androgens [22]. Both estrogen and androgen play separate yet important roles in the regulation of gonadotropin secretion in the human male.

STEROIDOGENIC TISSUES: TESTES AND ADRENALS

Administration of estrogen to men and other species of mammalian males rapidly reduces the synthesis of testosterone by the testes [43, 44, 51, 71] (Fig. 3). This probably occurs by a blockade of the 17–20 desmolase reaction [29, 60], either as a direct effect on the testes or as an indirect effect on pituitary LH levels [11]. In hypophysectomized rats, as little as 0.01 μg of diethylstilbestrol given in vivo partially blocked the ability of testicular tissue to respond in vitro to gonadotropin stimulation; 0.2 μg of diethylstilbestrol given in vivo to hypophysectomized rats lowered basal production of testosterone by testicular tissue in vitro [27]. Estrogen implanted near the epididymis of one testicle caused the local testicle to atrophy but had no effect on the contralateral testicle, on plasma levels of FSH or testosterone, or on fertility in rats [36]. Direct estrogen–testes interaction can lead to impaired testicular function.

^3H -estrogen is concentrated in the testes of adult rats or men, suggesting the presence of a receptor [43]. A cytosol receptor for estrogen appears at puberty in rat Leydig cells and is capable of rapid translocation from cytoplasm to nucleus after in vivo estrogen administration [1, 14, 50, 68]. Nuclear receptors for estrogen in the testes have been very difficult to study in the rat because of the very high levels of nonspecific binding of estrogen [14]. Only low levels of nuclear estrogen receptors have been reported in human testes, possibly as a result of the lack of studies using purified Leydig cells [52]. Following stimulation of rats with gonadotropin, the cytoplasmic estrogen receptor in the testes is rapidly depleted as enhanced estrogen biosynthesis occurs [48]. Thus, the receptor system may be able to interact with locally produced estrogens. The testicular receptor for estrogens may be part of a “short loop” feedback system that could mediate an estrogenic control over androgen (and estrogen) synthesis [27].

Estrogen receptors are also found in the adrenal glands of rats [9, 20, 67] and it is possible that steroidogenesis could also be regulated by estrogen in this tissue. Estrogen treatment of men and rodents increases 17 α -hydroxylase [28] and adrenal steroid output [64]. Prolonged exposure of rodents to estrogen can lead to estrogen-dependent testicular interstitial cell tumors (usually classed as benign), and estrogen treatment of humans and rodents is sometimes associated with adrenal hyperplasia or tumors [21, 24].

ACCESSORY SEX ORGANS

Estrogen administration has marked, castrationlike effects on accessory sex organs in man and other mammalian species; prostate, seminal vesicle, and other secondary sex structures regress (Fig. 3). This potent effect of estrogens may be attributed to a reduction in testosterone synthesis as described above. In contrast, when low doses of estrogen are given to the castrated rodent, a number of growth-promoting effects are seen. The fibromuscular portions of the anterior prostate, seminal vesicle, and coagulating gland grow after in vivo estrogenization, and the prostate gland shows fibromuscular hyperplasia after in vitro estrogenization [43, 44]. There may be a physiological role of estrogen in the normal growth and maintenance of these smooth muscles. Low doses of estrogen synergize with androgen in promotion of secretion by sex accessory organs; thus, estrogen may also have a physiological role in the epithelia. Pharmacologic doses of estrogen in men and other mammalian males can block andro-

gen-stimulated secretion by seminal vesicle and prostate and also induce squamous metaplasia or hyperplasia. The periurethral region and the ducts of the anterior region of the human prostate appear to be the most sensitive to estrogen. Estrogens can also potentiate the action of androgens in promotion of secretion by bull seminal vesicle, on fructose concentration in mouse seminal vesicle, and on the weight of rat seminal vesicle and anterior prostate. Estrogen effects on secondary sex structures are complex; synergism with and antagonism of androgen action occur, with estrogen sensitivity being dependent on organ tissue type and region [43, 44, 52].

Benign prostatic hyperplasia and prostatic cancer are usually associated with old age, a time when plasma estrogen levels have increased relative to plasma androgen levels. Chronic elevations in the level of plasma estrogens may contribute to the development of benign prostatic hyperplasia in the periurethral portion and prostatic cancer in the peripheral portion [43, 44, 52].

In rodents, high levels of estrogen receptors exist in the fibromuscular portion of the prostate and seminal vesicle and lower levels occur in the epithelia of these organs and in the epididymis and the ductus deferens. Their properties appear to be similar to those of the estrogen receptors found in the CNS and other tissues. Prolonged tissue and nuclear retention of ^3H -estradiol after injection indicates that nuclear translocation of the receptors can occur [5, 43, 52, 68]. In men, nuclear and cytoplasmic estrogen receptors occur in the epididymis, seminal vesicle, and the peripheral portion of the prostate—lower levels were also observed in the periurethral prostate. The synthetic estrogen ^3H -R2858 was used to detect estrogen receptors in the presence of contaminating plasma SHBG [52].

The levator ani, a striated sex accessory muscle, is also estrogen sensitive and contains translocatable estrogen receptors, at least in rodents [17]. Estrogens and aromatizable androgens increase the activity of glucose-6-phosphate dehydrogenase and stimulate growth [32]. The effect on enzyme induction is blocked by antiestrogens but not antiandrogens, suggesting that androgens are locally converted to estrogens for their effect on muscle metabolism. This mode of action of aromatizable androgens and estrogens is probably not a general one on all skeletal muscles since estrogen cannot mimic the general androgen myotropic response of myoblast cells *in vitro* [32].

Autoradiography following ^3H -diethylstilbestrol injections in pregnant mice has localized estrogen receptors in the urogenital primordia of the fetal male. The nuclear concentration of ^3H -estrogen in the mesenchyme surrounding the genital tracts, urogenital sinus, and rectum and in the gubernaculum testes suggests the possibility of a role for estrogen in the sex differentiation of these primordia [67]. As in the neonatal brain, testosterone may be converted locally to estradiol for developmental effects.

LIVER

The liver is a likely mediator in the development of some side effects of estrogen administered to modulate reproductive function. The liver is the primary site of metabolic transformation and degradation of estrogens, but in addition estrogens influence liver function (Fig. 3). Among the estrogen-sensitive, liver synthesized plasma components are the steroid and thyroid hormone-binding globulins, clotting factors and

inhibitors, prebetalipoproteins, triglycerides, haptoglobin, and renin substrate. The bile flow rate and cholesterol to bile acid ratio are also estrogen sensitive [19, 44, 51, 66]. Changes in the levels of these liver synthesized components may contribute to the development of disease states. In men given estrogens for prostatic cancer, thromboembolism and heart disease are side effects [19]. Some of the pathological consequences of estrogen administration in women for contraception are increases in thrombosis, atherosclerosis, hypertension, heart attacks, gall bladder disease, and benign hepatomas [19, 21, 51, 66].

Demonstration of the classical estrogen receptor in the rat liver has been more difficult than for most tissues. In rats, high levels of the estrogen receptor can be measured, but only after puberty, coincident with development of the capacity for renin substrate induction. Unlike many other target tissues for estrogen, the maintenance of the hepatic receptor in adult male or female rats requires an intact pituitary gland [19]. A hepatic estrogen receptor also exists in humans [18].

The estrogen receptor, partially purified from liver cytosol of male and female rats, appears to be identical to the classical estrogen receptors in rat uterus and brain. Adult male rat liver has an additional, unusual binding protein for androgens and estrogens and some of their metabolites [19]. The high rate of hepatic metabolism of estrogen limits its intracellular concentrations and necessitates high estrogen doses before translocation of receptors and the changes in liver function occur [19]. Hepatic metabolism is more efficient in deactivating estradiol than 17α -ethinyl estradiol, and this allows increased receptor interactions and changes in liver function with the synthetic estrogen [15, 16]. The identity of hepatic nuclear-bound estrogen has been determined after exposure of isolated rat liver cells to radioactive estradiol or 17α -ethinyl estradiol. In addition to nuclear-bound parent estrogens, their 2-hydroxylated metabolites have also been identified [15, 19]. Since these metabolites are chemically reactive, potentially toxic compounds, their production may be related to the development of some of the hepatic side effects of estrogen, for example, hepatoma or reduced bile flow [19].

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