

REVIEW ARTICLE

SHORT REVIEW OF PATHOPHYSIOLOGY OF
CATECHOL ESTROGEN

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INTRODUCTION

In women of reproductive age, the primary source of circulating estrogens is the ovaries. There are three forms of estrogen circulating in our bloodstream: estradiol, estrone and estriol. The normal ratio of these three types of estrogens ideally should be 10–20%, 10–20%, and 60–80% respectively. The estrogen that accounts for most of the tissue stimulation is called estradiol. Estrone is a little bit less potent with estriol being the weakest.¹ Brain converts estrone and estradiol to 2- and 4-hydroxylated derivatives known as catechol estrogens.²

As shown in Figure-1, catechol estrogens are generated by the actions of genes encoded by CYP1A1, CYP1A2 (which catalyse 2-hydroxylation of estrogens) and CYP1B1, which is an estrogen 4-hydroxylase. Catechol estrogens also yield potent genotoxic molecules implicated in carcinogenesis. 4-hydroxyoestrogens can be oxidised to quinone intermediates that react with purine bases of DNA, resulting in depurinating adduct that generate highly mutagenic apurinic sites. Quinines derived from the 2-hydroxyoestrogens produce stable DNA adducts and are presumed to be less genotoxic.³ Catechol estrogens are biologically active metabolites of oestrogen which are synthesised by estrogen 2- and 4-hydroxylase in the liver, brain, and other organs.⁴

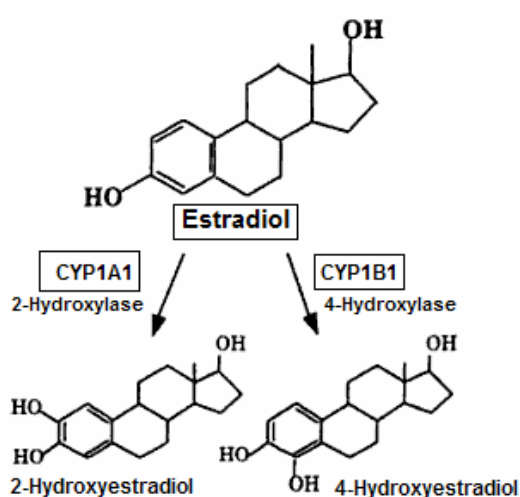


Figure-1: Biosynthesis of the catechol estrogens

METABOLISM

Metabolism of estrogens occurs in several areas of the body, however the main ones are liver and gastrointestinal tissues. More than 50% of the metabolism and conjugation of estrogens takes place in the liver.⁵ In general, the hormone undergoes rapid hepatic biotransformation, with a plasma half-life measured in minutes. Estradiol is converted primarily by 17 β -hydroxysteroid dehydrogenase to estrone, which undergoes conversion by 16 α -hydroxylation and 17-keto reduction to estriol, the major urinary metabolite. A variety of sulphate and glucuronide conjugates also are excreted in the urine.^{6–8} The conjugated forms are water-soluble as well as they also do not bind to transport proteins and are readily excreted via bile, faeces and urine.⁹ Estrogen sulphates are excreted from the body at a slower rate, they have a higher chance to be hydrolysed in tissues and act as a source of biologically active estrogens.¹⁰ Another way oestrogen metabolism is accomplished is by the gastrointestinal system. Approximately 50% of the estrogen conjugates, which enter or are formed in the liver, are excreted in the bile, pass into the intestine, and are hydrolysed by intestinal bacteria. Following this hydrolysis reaction in the intestines the estrogens either are excreted in the faeces or they are reabsorbed into the portal circulation.¹¹

Lesser amounts of estrone or estradiol are oxidised to the 2-hydroxycatechols by CYP3A4 in the liver and by CYP1A in extrahepatic tissues or to 4-hydroxycatechols by CYP1B1 in extrahepatic sites, with the 2-hydroxycatechol being formed to a greater extent. The 2- and 4-hydroxycatechols are largely inactivated by catechol-O-methyl transferases (COMTs).⁸ Catechol-O-methyltransferase (COMT) a classical phase II enzyme, catalyses the transfer of methyl groups from S-adenosyl methionine, the enzyme cofactor, to hydroxyl groups of a number of catechol substrates, including the catechol oestrogens. Under normal circumstances, Catechol estrogens are, for the most part, promptly O-methylated by COMT to form 2- and 4-O-methylethers, which are then excreted.¹² However, smaller amounts may be converted by peroxidase-catalysed reactions to yield semiquinones or quinones that are capable of forming DNA adducts or of generating (via redox cycling) reactive oxygen species that could oxidise DNA bases.⁸

ROLE IN BREAST CANCER

Historically, the carcinogenic actions of estrogens were thought to be related to their trophic effects. An increase in cell proliferation would be expected to cause an increase in spontaneous errors associated with DNA replication, and estrogens would then enhance the growth of clones with mutations introduced by this or other mechanisms (e.g., chemical carcinogens). More recently, another mechanism has been proposed, that if catechol estrogens, especially the 4-hydroxycatechols, are converted to semiquinones or quinones prior to 'inactivation' by COMT, these products, or reactive oxygen species generated during subsequent biotransformations, may cause direct chemical damage to DNA bases. In this regard, CYP1B1, which has specific estrogen-4-hydroxylase activity, is present in tissues such as uterus, breast, ovary, and prostate, which often give rise to hormone-responsive cancers.^{8,13} Endogenous estrogens can become carcinogenic via formation of catechol estrogen quinones, which react with DNA to form specific depurinating estrogen-DNA adducts. The mutations resulting from these adducts can lead to cell transformation and the initiation of breast cancer.¹⁴

Breast cancer is the leading cause of death for women. Caucasian women have a higher risk of developing breast cancer than African-American, Asian, or Hispanic women. Abundant evidence indicates that estrogens, including estrone (E1) and β -estradiol (E2), play a key role in the pathogenesis and progression of breast cancer. Epidemiologic studies have indicated that breast cancer risk is higher in women with early menarche and late menopause, i.e., those who have longer exposure to sex hormones. An increased risk of breast cancer was also associated with increased circulating levels of the precursors and metabolites of estradiol. The mechanism of estrogen carcinogenesis has been mainly explained by enhancing receptor-mediated cell proliferation. Estrogen metabolites have indirect and direct genotoxicity. Hydroxylation is an important elimination step for estrogens to generate catechol estrogens. The 4-hydroxyoestrogen generates free radicals from reductive-oxidative cycling with the corresponding semiquinone/quinone forms, thus causing DNA damage. In contrast to 4-hydroxyoestrogen, 2-hydroxyoestrogen is not carcinogenic and has a potent inhibitory effect on the growth of tumour cells and on angiogenesis.¹⁵

ROLE IN UTERINE CANCER

More recently, the estrogens E2 and 17-ethinylestradiol, as well as the catechol estrogens 2-hydroxyestradiol and 4-hydroxyestradiol, have been

demonstrated to induce uterine adenocarcinoma in the CD-1 mouse model. Data from these rodent models strongly suggest that estrogens play a direct role in inducing endometrial cancers and are consistent with the hypothesis that estrogens act through a genotoxic mechanism in the neonatal uterus to initiate carcinogenesis. Alternatively, the administered estrogens may act through an estrogen receptor-mediated mechanism to trigger developmental changes in the neonatal uterine epithelium and stroma that predispose to adenocarcinoma in the adult animals.¹⁶

2-Hydroxylated metabolites of estrogen have been shown to have antiangiogenic effects and inhibit tumour cell proliferation, whereas 4-hydroxylated metabolites have been implicated in carcinogenesis. Their findings are consistent with the hypothesis that increased estrogen 2-hydroxylation is associated with decreased endometrial cancer risk, but replication of these results is required before any firm conclusions can be reached.¹⁷

ROLE IN NEUROENDOCRINE REGULATION

Catechol estrogens have been identified and measured in rat brain and various endocrine tissues with the use of a sensitive radioenzymatic assay. The specificity of this assay was confirmed by thin-layer chromatography and mass spectral analysis of the reaction products. The concentration of catechol estrogens in the hypothalamus and pituitary are at least ten times higher than reported previously for the parent estrogens. Catechol estrogens have potent endocrine effects and, because of their normal occurrence in the hypothalamic-pituitary axis, they have an important role in neuroendocrine regulation.¹⁸

The brain is capable of 2-hydroxylation and consequently forms catechol estrogens from estrone and estradiol. These serve as links between ovarian steroids and catecholamines in the modulation of neuronal activity. It has been suggested that the increased availability of estrogen and estradiol for binding and hypothalamic sites would facilitate formation of catechol estrogens, which, in turn may induce LHRH release through two possible mechanisms:

- Competitive inhibition of catecholamine-metabolising enzyme, Catechol-O-methyltransferase, with subsequent increase in the norepinephrine effect for facilitating LHRH release;
- Reduction of the negative feedback action of estradiol on LHRH neurons by effective competition by catechol estrogens for estrogen receptors.¹⁹

2- and 4-hydroxylated steroid exerts its physiological effects on the cyclic secretion of LH and perhaps even FSH and prolactin. Catechol estradiol competes with estradiol for estrogen-binding sites in the anterior pituitary gland and hypothalamus. In addition, the catechol estrogens compete for dopamine binding sites on anterior pituitary membranes.²

ROLE IN NEPHROCARCINOGENICITY

Catechol estrogen formed within the liver and brain is transported to kidney. In the kidney they cause oestrogen-mediated nephrocarcinogenicity by forming insoluble polymers within renal tubules. Insoluble polymers provide a constant irritant that might well be the proliferative stimulus for renal carcinoma. Indeed, it has been noted that estrogen-induced renal tumours are sometime initiated at sites of deliberate physical injury to the tissue.²⁰

CONCLUSION

The possibility of developing cancer is probably the major concern for the use of estrogens and oral contraceptives. These studies established that estrogens can induce tumours of the breast, uterus, testis, bone, kidney, and several other tissues in various animal species. Estrogen-induced carcinogenesis involves enhanced cell proliferation (promotion) and genotoxic effects (initiation). Estrogens and their metabolites contribute to tumour initiation, induced by estradiol and its metabolites (2- and 4-hydroxyestradiol). It indicates that catechol estrogens play a role in tumour initiation through oxidative DNA damage, whereas estrogens themselves induce tumour promotion and progression by enhancing cell proliferation. Further studies at ultra structural and functional level could reveal the mechanism by which catechol estrogen changes pathphysiology of various organs.

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