Biochemistry of Aromatase: Significance to Female Reproductive Physiology

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Abstract

The formation of estrogens in mammals via aromatase involves the relatively unique capacity to form an aromatic ring de novo in contrast to most other aromatic substances (essential amino acids) which are obtained only in the diet. The reaction is the only example of a cytochrome P-450 system which resides in both the mitochondrial and microsomal fractions of the cell. It occurs widely throughout the body in diverse tissues and functions via both de novo synthesis and transformation of prehormones (androstenedione and testosterone). It is found widely in animal species in both the brain and gonads even in phylogenetically primitive species.

Placental aromatase appears to be associated with the evolution of viviparity and an extended gestational period in utero. Follicular aromatase which is dependent upon follicle-stimulating hormone stimulation appears to be essential for oogenesis, ovulation, and normal luteal functions while central nervous system aromatase serves to determine sexual behavior and the neurohormonal link to the hypothalamus and pituitary for ovarian cyclicity.

While estrogens are the key to pituitary, breast, and endometrial growth and development, this hormone is one of the few examples of an endogenous steroid that has been implicated as a carcinogen or a stimulant for carcinogenesis.

Aromatase and Estrogen Biosynthesis

The enzymatic pathway for biosynthesis of the aromatic estrogens remained a mystery for many years after they were first discovered. Aromatic compounds are not usually synthesized in higher vertebrate species, and substances like the aromatic amino acid phenylalanine must be obtained via the diet. Phenylalanine is in turn used as a building block for the hormones epinephrine and thyroxin. The preformed cyclic substances quinice acid and hexahydrobenzoic acid obtained from the diet can be aromatized by gut microorganisms or liver enzymes, and for a long time it was believed that the aromatic ring of estrogens was similarly derived (5). This was found not to be the case when aromatase was described in some detail in human placental microsomes with a requirement for reduced pyridine nucleotide and oxygen (12). Unlike many other mixed-function cytochrome P-450 oxidases, this reaction is not readily inhibited by carbon monoxide, probably due to the high affinity of the enzyme for its major substrate, androstenedione (8, 9).

Aromatase has also been described in brain, ovary, testis, adrenal, fetal liver, skin, fat, breast, and bone marrow and, at least in the brain, ovary, and placenta, the enzyme is present in many different vertebrate species (3, 5). In the ovary, aromatase is the final step in a multienzyme system that synthesizes estrogen from acetate and cholesterol while, in most other tissues, aromatase acts upon preformed plasma precursor androgens secreted by the adrenal or gonad (16). For many species, the source of the androgen substrate for placental aromatase is the fetal adrenal (14).

Aromatase is unique in that it resides in both the microsomal and mitochondrial fractions of cells and as far as can be determined is the same type of enzyme in both cellular subfractions (4). While the existence of more than one form of aromatase has been suggested for differently substituted androgen substrates, a clear resolution of this has not yet been achieved (11). Similarly, the detailed mechanisms for the enzymatic transformation of androgens to estrogens involving molecular oxygen, removal of an angular methyl group, and introduction of extra double bonds are not precisely established (5, 13).

The estrogen synthesized by the aromatase may be secreted to function in a typical hormonal fashion and/or may be used locally by the tissue in which the estrogen is produced (7). The primary estrogenic products of aromatase are estrone derived from androstenedione, 17β-estradiol from testosterone, estril from 16α-hydroxytestosterone, and 16α-hydroxyestrone from 16α-hydroxyandrostenedione. Various substituted C19 steroids can also be aromatized as long as their conformation and ring substituents do not hinder the reaction (5, 13).

Estrogen Metabolism

The primary biologically active estrogen, 17β-estradiol, can be produced by aromatase from testosterone or converted from estrone (derived from androstenedione aromatization) via a 17β-ol oxidoreductase. The estrogen molecule can be modified by substitutions on at least 12 of its 18-carbon skeleton. For the most part, metabolism of estradiol reduces or abolishes its biological activities, but in some instances it is believed that an oxygen function at carbon atoms 2, 4, or 16 may confer special properties of biological importance (17).

Significance of Aromatase in Reproductive Function

In the evolution from unicellular to multicellular organisms, cells have become limited to highly specialized functions. This specialization results in the enzymatic production of substances (hormones) that coordinate and regulate differentiated cells in the shared economy of a multicellular organism. It also allows coordination of behavior between 2 separate organisms when interaction is required for reproduction and/or survival. Aromatase in the specialized cells of the ovary, hypothala-
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mus, and placenta clearly serves such a role in reproduction for mammalian and other vertebrates. While aromatase is present in many diverse tissues, such as skin, fat, bone marrow, liver, adrenal, and testes, its biological role in such sites is not as well understood.

Throughout evolution, the role of aromatase via its estrogen products appears to be centered on reproductive functions: oogenesis, egg processing, sexual behavior, neuroendocrine synchronization, mammary development, and accommodation to viviparity. Even the so-called “metabolic” functions of estrogens in mammals appear to be left over from phylogenetically more primitive reproductive mechanisms in the evolution from oviparity to viviparity. The estrogenic hormone has been adapted to many diverse functions as reproduction evolved.

**Ovarian Aromatase.** This aromatase produces the bulk of systemic estrogens for general reproductive functions. These estrogens also act locally. Follicles that produce estrogens have sequestered pituitary follicle-stimulating hormone which in turn stimulates the aromatase reaction. Such follicles can undergo normal development and ovulation and contain eggs that readily resume meiosis when released. In the absence of an active local aromatase (i.e., no follicle-stimulating hormone), the follicles and oocytes become atretic and regress without ovulating. If aromatase is present, the estrogen and follicle-stimulating hormone can further develop the follicular cells for normal luteal function after ovulation takes place (6, 7).

The systemic estrogen produced by ovarian aromatase modulates central nervous system and pituitary functions for the ovarian cycle and in spontaneously ovulating mammals triggers the release of the ovulatory surge of luteinizing hormone. Ovarian estrogen is the major component of negative and positive feedback for pituitary release of gonadotrophic hormones (6, 7).

The most primitive vertebrate reproductive “tract” consists of a genital pore that merely discharges eggs outside the body, but in evolution the oviduct became a conduit and a way station for processing eggs (15). Such specialized functions as oviduct contractility and protein secretion are under estrogenic control. In the mammalian oviduct and uterus, the specialized epithelial cells of the tube, the endometrial lining, the muscle layers, and rich blood supply are all developed by estrogenic stimulation.

In birds, reptiles, and amphibians, estrogen stimulates the production of phosphoproteins and lipoproteins by the liver for incorporation into the yolk of the growing oocyte (18). While this function is missing in most mammals, estrogens still stimulate the production by liver of lipoproteins and other products which have more generalized metabolic functions. It is likely that these “metabolic” effects of estrogen are a carry-over from a reproductive mechanism.

**Brain Aromatase.** This aromatase is present in every vertebrate species tested except the most primitive cyclostomes and is represented in homologous areas of the brain throughout phylogeny (3). In some species (telecots), aromatase is more active in the brain than in the gonad. There is a functional sexual dimorphism of the hypothalamus in several mammalian species which specifies male (tonic) or female (cyclic) reproductive hormonal patterns and sexual behavior. The male pattern is developed in the rodent in the first 10 days of life when testicular androgen is converted to estrogen by hypothalamic aromatase. In addition, brain aromatase controls both male and female adult sexual behavior in some species. The presence of brain aromatase in so many animal species, including phylogenetically primitive ones, has led us to speculate that it played an important role in the evolution of reproductive cycles and behavior (3).

**Placental Aromatase.** This aromatase is present in many mammalian species with a gestational period longer than 60 days. It is suggested that the estrogen produced by the placenta provides a backup and then a replacement of ovarian estrogen to ensure continued hormone during the longer gestation period of some viviparous species including the human (14, 15).

**Breast Development.** This development evolved with mammalian viviparity, and estrogen was again recruited as the basic hormone for this “reproductive target tissue.” In the breast as in most other estrogenic target organs, the estrogen provides the initial growth and development but also prepares the tissue for subsequent effects by other hormones such as progesterone and prolactin. Aromatase is present in breast tissue and breast fat and may play some role in local tissue function (10).

**Aromatase and Cancer**

Estrogens have a phenolic ring structure in common with the carcinogenic hydrocarbons, and this has been invoked to explain the association of estrogen effects with cancer in target tissues. Although excess exogenous estrogens or estrogens produced by the ovary unopposed by progesterone have been common features in experimental or clinical examples of endometrial and breast cancer, estrogen produced by extraglandular aromatase in the absence of active ovarian function has also been considered a possible factor in carcinogenesis (16).

Estradiol and estrone have been shown to bind covalently to DNA during incubations with liver microsomal preparations, a property shared by diethylstilbestrol and carcinogenic aromatic hydrocarbons (1, 2). Whether estrogen is directly carcinogenic or renders the tissue more susceptible to other carcinogenic influences is still uncertain. A key issue is whether control of cancer can be accomplished by aromatase inhibition of estrogen production or whether it would be more profitable to try to influence the effects of estrogen at its site of action.

**References**


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