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Aromatase Inhibitors

Paul E. Goss and Caroline C. Reid

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1. INTRODUCTION

There are two biological subtypes of human breast carcinoma: those that are hormone-dependent and those that are hormone-independent. Estrogen is thought to be the primary mitogen for the hormone-dependent subtype, but the exact mechanism(s) by which it promotes and stimulates growth has not been fully established. In both the adjuvant and metastatic setting estrogen deprivation is beneficial in a proportion of patients. To this end, hypophysectomy and adrenalectomy have been performed in postmenopausal women while ovarian ablation (surgical or radiation-induced) remains a treatment in premenopausal women (1). These irreversible procedures have significant morbidity and do not address estrogen biosynthesis occurring in extraglandular or peripheral tissues (2,3).

Currently there are three medical approaches to estrogen deprivation of breast tumors. One is to block estrogen receptors (ER) with antagonists such as tamoxifen. A second is to inhibit gonadotrophins by continuous administration of gonadotrophin-releasing hormone (GnRH) or one of its analogues (4). The third is to decrease circulating estrogens by inhibiting their biosynthesis. The
target of such inhibition is the aromatase enzyme, which catalyzes the final step in estrogen production in humans (5,6).

In this chapter, estrogen synthesis with respect to therapeutic inhibition is examined in detail. Particular emphasis has been placed on the aromatase (estrogen synthetase) enzyme complex, which is responsible for the final step in the estrogen biosynthetic pathway. Firstly, the aromatase P450 gene, CYP19, and tissue-specific estrogen production regulated by alternate CYP19 promoter usage is described. The potential both for estrogen production within the breast to promote carcinogenesis, as well as for intratumoral estrogen synthesis to enhance breast-tumor growth, are then discussed. Subsequently, aromatase enzyme inhibitors, which have recently become available for the treatment, and possible prevention, of breast cancer in women, are introduced according to current classifications. Cell culture and in vivo models used for preclinical evaluation of aromatase inhibitors are described providing a background to their clinical development. Nonpharmacologic aromatase inhibitors are reviewed and targets of inhibition of the aromatase pathway other than enzyme inhibitors are proposed. The clinical experience and future potential of aromatase inhibitors are described in more detail in the next chapter.

2. AROMATASE AND ESTROGEN SYNTHESIS

2.1. The Aromatase Enzyme Complex

The initial step in estrogen biosynthesis is the cleavage of the cholesterol side chain to yield pregnenolone, a process catalyzed by the enzyme desmolase. A subsequent multi-step process culminates with the conversion of the androgens to estrogens by aromatase (estrogen synthetase) (Fig. 1). This enzymatic process is the rate-limiting step in estrogen biosynthesis and ultimately results in the conversion of C19 steroids, such as testosterone and androstenedione, into the C18 steroids, estradiol and estrone, respectively. Located in the endoplasmic reticulum, aromatase is an enzyme complex composed of two proteins: aromatase cytochrome P450 (aromatase P450) and reduced nicotinamide adenine dinucleotide diphosphate (NADPH)-cytochrome P450 reductase. Aromatase P450 binds androgen substrates and, in the presence of molecular oxygen and NADPH, catalyzes a series of slow steps to produce 2-beta-hydroxy-19-aldehydes, which then collapse rapidly and nonenzymatically to estrogens. NADPH-cytochrome P450 reductase, a ubiquitous flavoprotein component of the endoplasmic reticulum in most cells, transfers reducing equivalents from NADPH to aromatase P450. For every mole of C19 steroid metabolized, the aromatase reaction utilizes three moles of oxygen and three moles of NADPH (7). The principal source of substrate presented to the aromatase enzyme complex in breast tissue is circulating androstenedione. As a result, the primary product of aromatization in the breast is estrone. Estrone may be converted locally to estra-