National Academy of Clinical Biochemistry Symposium: Introduction

The National Academy of Clinical Biochemistry recently held its annual meeting symposium in Chicago, IL, July 17–18, 1992, on the topic, "Molecular Endocrinology; Current Concepts in Receptors, Growth Factors and Signal Transduction Mechanisms." In this issue of *Clinical Chemistry*, we are publishing seven representative papers from the symposium. These cover a range of diverse molecular endocrinology topics, including the cellular mechanisms associated with the activation of steroid receptors at the transcriptional level, the molecular basis for protein hormone synthesis and secretion, and the role of oncogenes and growth factors in the regulation of gene expression and cell programming. The field of molecular endocrinology is rapidly evolving as studies dwell on the identity of the genetic programming that controls both the synthesis of hormones and and the mechanism of hormon action. These representative papers are a sampling of the complexity of these studies, studies critical to our understanding of both normal physiology and of the endocrine basis of disease.

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Tissue-Specific Promoters Regulate Aromatase Cytochrome P450 Expression

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In humans, estrogen biosynthesis occurs in several tissue sites, including ovary, placenta, adipose, and brain. Recent work from our laboratory indicates that tissue-specific expression of aromatase cytochrome P450 (P450arom), the enzyme responsible for estrogen biosynthesis, is determined, in part, by the use of tissue-specific promoters. Thus, the expression of P450arom in human ovary appears to utilize a promoter proximal to the translation start site. This promoter is not utilized in placenta; instead, the promoter used to drive aromatase expression in placenta is ≥40 kb upstream from the translational start site. In addition, a minor promoter used in the expression of a small proportion of placental transcripts is 9 kb upstream from the start of translation. Transcripts from these promoters are also expressed in other fetal tissues, including placenta-related cells such as JEG-3 choriocarcinoma cells and hydatidiform moles and other fetal tissues such as fetal liver. In adipose tissue, on the other hand, expression of P450arom may be achieved by yet another, adipose-specific promoter. The various 5′-untranslated exons unique for expression driven by each of these promoters are spliced into a common intron/exon boundary upstream from the translational start site. This means that the protein expressed in each of the various tissue-specific sites of estrogen biosynthesis is identical.

Indexing Terms: *estrogen biosynthesis · genes · ovary · placenta · adipose tissue · brain*

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The conversion of androgens to estrogens is catalyzed by an enzyme complex known as aromatase, whose activity results in aromatization of the A ring of androgens, to form the phenolic A ring characteristic of estrogens with concomitant loss of the C-19 angular methyl group. This enzyme complex is localized to the endoplasmic reticulum of cells in which it is expressed and consists of two components. The first is a form of cytochrome P450 known as aromatase cytochrome P450 (P450arom) (*1*, *2*), the product of the *CYP19* gene (*3*). This heme protein is responsible for binding the C_{19} steroid substrate and catalyzing the concerted series of reactions leading to formation of the phenolic A ring. The second component is a flavoprotein, NADPH cytochrome P450 reductase, which is a ubiquitous protein in the endoplasmic reticulum of most cell types that is responsible for transferring reducing equivalents from NADPH to any microsomal cytochrome P450 species with which it comes into contact. The aromatase reaction utilizes 3 moles of O_2 and 3 moles of NADPH for every mole of C_{19} steroid metabolized (*4*) (Figure 1). There is general agreement that the first two oxygen molecules are utilized in the oxidation of the C-19 angular methyl group. A growing consensus of opinion considers that the third oxygen attack is also on the C-19 methyl group, resulting in its loss as formic acid. Concomitant with this, aromatization of the A ring takes place with loss of the 2β-hydrogen and a resulting rearrangement to form the phenolic A ring characteristic of estrogens (*5*). That this complex series of reactions takes place at a single catalytic site was confirmed by expression of a full-length cDNA encoding human P450arom in COS-1 monkey kidney tumor cells (*6*). Addition of androstenedione,