Journal of Steroid Biochemistry & Molecular Biology 137 (2013) 27–49

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

The structural biology of oestrogen metabolism

Mark P. Thomas, Barry V.L. Potter*

Department of Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath, BA2 7AY, UK

ARTICLE INFO

Article history:
Received 11 September 2012
Received in revised form
10 December 2012
Accepted 12 December 2012

Keywords:
Oestrogen
Protein structure
Reaction mechanism
Aromatase
Sulfatase
Sulfotransferase
17β-Hydroxysteroid dehydrogenase

ABSTRACT

Many enzymes catalyse reactions that have an oestrogen as a substrate and/or a product. The reactions catalysed include aromatisation, oxidation, reduction, sulfonation, desulfonation, hydroxylation and methoxylation. The enzymes that catalyse these reactions must all recognise and bind oestrogen but, despite this, they have diverse structures. This review looks at each of these enzymes in turn, describing the structure and discussing the mechanism of the catalysed reaction. Since oestrogen has a role in many disease states inhibition of the enzymes of oestrogen metabolism may have an impact on the state or progression of the disease and inhibitors of these enzymes are briefly discussed.

This article is part of a Special Issue entitled 'CSR 2013'.

Contents

1. Introduction

Estrogens have many roles in the body including, but not limited to, in reproduction and the menstrual cycle [1–5], many breast cancers [6], the development of osteoarthritis [7], the prevention of heart disease [8], neuroprotection during cerebral ischaemia [9] and in multiple sclerosis [10], appetite and eating behaviour [11], fat metabolism [12], schizophrenia [13], autoimmunity [14], and auditory and visual processing [15]. Estrogens exert their effects in several ways [16–18]. In the 'classic genome response' oestrogen binds to specific intracellular oestrogen receptors (ERα and ERβ) that, subsequent to oestrogen binding, dimerise and translocate to the nucleus, where they modulate the transcription of target genes that contain oestrogen-responsive elements in their promoters.

Abbreviations: 17β-HSD, 17β-hydroxysteroid dehydrogenase; COMT, catechol-*O*-methyl transferase; DHEA(S), dehydroepiandrosterone (sulfate); DHETNA, O5′-[9-(3,17β-dihydroxy-1,3,5(10)-estratrien-16β-yl)-nonanoyl]adenosine; DNC, 3,5-dinitrocatechol; E1(S), estrone (sulfate); E2(S), estradiol (sulfate); E3, estriol; E4, estetrol; ER, estrogen receptor; E2B, 3-(((8*R*,9*S*,13*S*,14*S*,16*R*,17*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-16-yl)methyl)benzamide; FAD/FMN, flavin adenine dinucleotide/flavin mononucleotide; FG, formylglycine; HFG(S), hydroxyformylglycine (sulfate); mb-COMT, membrane-bound COMT; $NADP^+$, nicotinamide adenine dinucleotide phosphate (oxidised); NADPH, nicotinamide adenine dinucleotide phosphate (reduced); PAP, 3′-phosphoadenosine-5′-phosphate; PAPS, 3′-phosphoadenosine-5′-phosphosulfate; s-COMT, soluble COMT; SAM, S-adenosyl methionine; SDR, short-chain dehydrogenase/reductase.

* Corresponding author. Tel.: +44 0 1225 386639; fax: +44 0 1225 386114.
E-mail addresses: m.thomas@bath.ac.uk (M.P. Thomas), b.v.l.potter@bath.ac.uk (B.V.L. Potter).

0960-0760/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jsbmb.2012.12.014

However, these same oestrogen receptors have also been shown (a) to bind to other transcription factors thus influencing the expression of genes that do not contain oestrogen-responsive elements in their promoters, and (b) to engage signal transduction pathways (that may include, but are not limited to, the activation of protein kinases), thus modulating cellular responses to oestrogen. Signal transduction pathways can also be activated by oestrogen binding to cell surface membrane bound receptors [16–18].

The three most common estrogens are estrone (E1), estradiol (E2) and estriol (E3). A fourth oestrogen is estetrol (E4). Estradiol is the most potent. Estrone and estradiol are synthesised by the aromatisation of androstenedione and testosterone, respectively (Fig. 1). They can also be interconverted by the action of 17β-hydroxysteroid dehydrogenases (17β-HSDs). Estriol is synthesised from estrone via a 16α-hydroxyestrone intermediate. Although, in some tissues, estrogens can be made on demand, oestrogen can be stored in the form of estrone sulfate. This is synthesised from estrone by the action of oestrogen sulfotransferase with estrone being regenerated by the steroid sulfatase-catalysed hydrolysis of estrone sulfate. A review of many aspects of human steroidogenesis is available [19]. Estrogens are eliminated from the body mainly as the sulfated and glucuronidated derivatives [20, and references therein]. The first step in synthesising these conjugates is the generation of the hydroxylated derivatives. Hydroxylation occurs primarily at the 2-, 4- and 16-positions. The hydroxyl group can then be sulfated, glucuronidated or methylated.

Because there is little published work on estetrol it is discussed only briefly here. It is synthesised in the foetal liver, but its function is presently unknown. Several possible biosynthetic routes have been proposed starting from various androgens, estrogens, and their 3-sulfated derivatives, with the hydroxylations occurring in various different orders and, in the case of the androgens, the aromatisation occurring either before or after the hydroxylations. Evidence suggests that estetrol is made through multiple biosynthetic routes. See [21–29] for details. Estetrol will not be discussed further herein.

Given the role of estrogens in preventing, causing and exacerbating disease a good knowledge of how estrogens are synthesised and metabolised may help in the understanding and treatment of disease. This review looks in turn at each of the enzymes involved in oestrogen metabolism in terms of their structure and reaction mechanism, before a final section compares the various enzymes. Inhibition of the enzymes of oestrogen metabolism impacts on the amount of oestrogen in the body and this has been the subject of

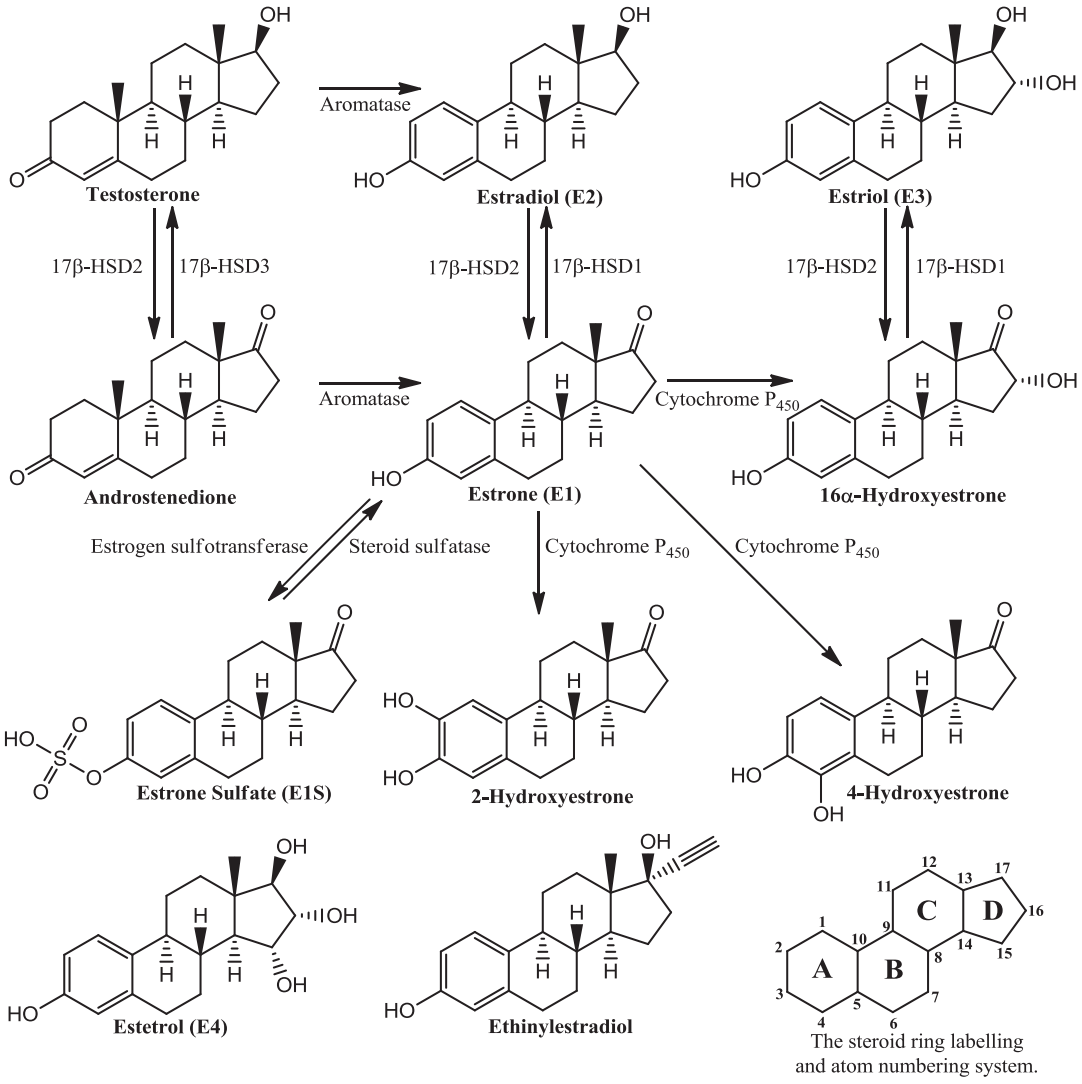

Fig. 1. Pathways of oestrogen metabolism. Not all pathways are shown. There are tissue-specific variations in synthetic pathways: see [19]. The A-ring hydroxylated compounds are converted to the methoxy compounds by catechol *O*-methyltransferases. The structures of estetrol and ethinylestradiol are shown, as is the steroid ring labelling and atom numbering system.