Maturitas 104 (2017) 29–35

Contents lists available at ScienceDirect

Maturitas

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

27-Hydroxycholesterol, an endogenous selective estrogen receptor modulator

Sisi He[a], Erik R. Nelson[a,b,c,*]

[a] Department of Molecular and Integrative Physiology, University of Illinois at Urbana-Champaign, Urbana, IL, USA
[b] University of Illinois Cancer Center, Chicago, IL, USA
[c] Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA

ARTICLE INFO

Keywords:
Cholesterol
27-hydroxycholesterol
Estrogen receptor
Estrogen
Selective estrogen receptor modulator

ABSTRACT

Estrogen receptors (ERs) mediate the actions of the steroidal estrogens, and are important for the regulation of several physiological and pathophysiological processes, including reproduction, bone physiology, cardiovascular physiology and breast cancer. The unique pharmacology of the ERs allows for certain ligands, such as tamoxifen, to elicit tissue- and context-specific responses, ligands now referred to as selective estrogen receptor modulators (SERMs). Recently, the cholesterol metabolite 27-hydroxychoelsterol (27HC) has been defined as an endogenous SERM, with activities in atherosclerosis, osteoporosis, breast and prostate cancers, and neural degenerative diseases. Since 27HC concentrations closely mirror those of cholesterol, it is possible that 27HC mediates many of the biological effects of cholesterol. This paper provides an overview of ER pharmacology and summarizes the work to date implicating 27HC in various diseases. Wherever possible, we highlight clinical data in support of a role for 27HC in the diseases discussed.

1. Introduction

Originally characterized for their roles in female reproduction, it is now appreciated that estrogens and their cognate receptors (estrogen receptors; ERs) play important modulatory roles in several different physiological systems including development, the cardiovascular system, brain function, immune system, and bone [1]. Estrogens are chemically related compounds derived from androgen precursors but containing a defining aromatic and hydroxyl group at the 17 position (Fig. 1). 17β-estradiol is the main physiologic hormone, but it is speculated that estriol, estetrol and estrone may play important roles during pregnancy and post-menopause [2–4].

Interestingly, recent work has identified oxysterols such as 27-hydroxycholesterol (27HC) and 25-hydroxycholesterol as being able to bind and modulate the activity of ERs [5–7]. The differential effects of 27HC across tissues was reminiscent of findings from Tamoxifen, and thus has led to the classification of 27HC as an endogenous Selective Estrogen Receptor Modulator (SERM) [6,8,9].

The objective of this review is to summarize our current understanding of ER-pharmacology and highlight recent reports of 27HC as SERM in physiology and pathophysiology. Given 27HC levels are correlated with those of cholesterol [10], and the prevalence of hypercholesterolemia (39.7% of U.S. population) [11], it is important to consider the roles of this major cholesterol metabolite in the etiology of diseases.

2. Estrogen receptors

Two mammalian estrogen receptors have been described: ERα and ERβ. ERα, originally cloned from the MCF7 breast cancer cell line, is widely expressed throughout many tissues [12,13]. ERβ was originally cloned from rat prostate and has a distribution largely restricted to the ovary, lung and prostate, although there are reports of its activity in other cell types [13,14]. Both ERα and ERβ are members of the nuclear receptor superfamily. As such, they share the same general structure, containing an N-terminal domain, DNA-binding domain, hinge region, ligand-binding domain, and C-terminal F region. Two activation function domains (AF1 & AF2), which regulate the transcriptional activity of ERs, are located within the N-terminal domain and ligand-binding domain respectively. ERα and ERβ share a high degree of sequence homology in the DNA-binding domain (more than 95% amino acid identity) and ligand-binding domain (~55% amino acid identity). However, the N-terminal domain of ERβ is shorter than that of ERα, and the sequence homology between the two isoforms is only ~15% [15,16].

Upon ligand binding, the ERs are thought to dissociate from a

* Corresponding author at: University of Illinois at Urbana-Champaign. 407 S Goodwin Ave (MC-114), Urbana, IL, 61801, USA.
E-mail address: enels@illinois.edu (E.R. Nelson).

http://dx.doi.org/10.1016/j.maturitas.2017.07.014
Received 4 July 2017; Received in revised form 26 July 2017; Accepted 28 July 2017

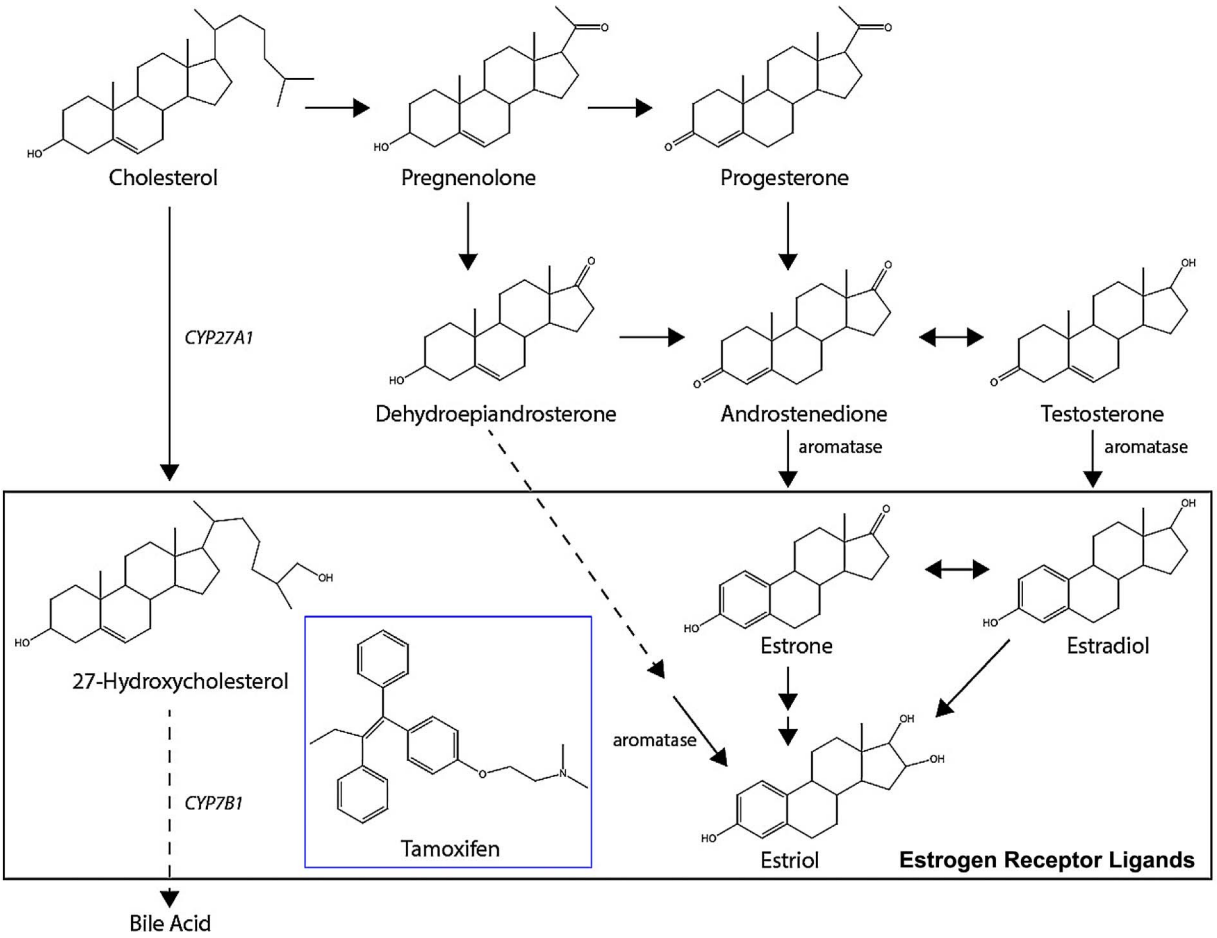

Fig. 1. Chemical structures and biosynthesis pathways for endogenous estrogens and the endogenous selective estrogen receptor modulator (SERM) 27-hydroxycholesterol (27HC). Tamoxifen, a synthetic SERM is shown for comparison. 27HC is a primary metabolite of cholesterol, hydroxylated by the actions of CYP27A1, and is further metabolized by CYP7B1. Estrogens are formed when they are aromatized by the enzyme aromatase (CYP19) from precursor androgens.

complex of heat-shock proteins and subsequently dimerize to form either homo or heterodimers. Through the two zinc fingers on each receptor, the ligand-bound ER-dimers then bind to DNA at specific estrogen response elements (EREs) located in the regulatory regions of target genes where they act as a hub for a large transcriptional complex including co-activators and co-repressors, ultimately resulting in altered gene transcription [16]. The ligand-bound ER-dimers can also alter transcription indirectly by interacting with other transcription factors such as AP1, C/EBPβ and Sp1 [17].

The above transcriptional regulating cascade upon ER activation is described as 'genomic' or 'classical' ER signaling. In addition, ERs can regulate different signal transduction cascades in a 'non-genomic' and 'rapid' manner. Such membrane-initiated cascades were studied utilizing one of the following two approaches: (1) Estradiol conjugated to form large dendromeric structures that prevents the ligand from entering the nucleus. (2) Mice harboring a mutant ERα that fails to bind DNA but should retain its non-genomic actions (non-classical ER knock-in, NERKI). Although both approaches suggest the potential importance of non-classical ER signaling, it should be noted that they do not always agree [18,19], and this continues to be an emerging field. *In vitro* studies in support of non-classical ER signaling indicate that ERs can interact with and modulate the activities of MAPK, adaptor protein Shc, caveolins, c-Src protein kinase complex and the regulatory subunit of phosphoinositide-3 kinase (p85) [20,21].

In addition to ERα and ERβ, there is growing evidence that estrogens can bind to and activate the G-protein associated receptor GPER (also known as GPR30) [22–24]. Curiously, GPER knockout mice did not manifest a reproductive phenotype. However, GPER has been implicated in obesity, insulin resistance, cardiovascular dysfunction, and breast cancer progression [25]. As many of these studies have relied on the GPER knockout mouse model, the physiological relevance of this receptor in mediating the actions of estrogens remains controversial. Unless otherwise specified, the remainder of this review will focus primarily on the nuclear ERs.

3. Estrogen receptor ligands; pharmacological concept of selective estrogen receptor modulators

As described above, estrogens comprise the natural ligands for ERs, with 17β-estradiol being a potent agonist. It was traditionally thought that the binding of ER agonists would induce a conformational change in the receptors, conferring the ability for coactivators to bind; while ER antagonists would compete for binding. However, the complex pharmacology of the ERs was first revealed with tamoxifen, originally described as an ER antagonist. Indeed, it behaved as an ER antagonist in breast cancer. Conversely, and quite the opposite of what would be expected for an ER antagonist, tamoxifen exhibited estrogenic activity in bone, protecting against bone loss in postmenopausal women [26]. Tamoxifen has also been shown to behave as an ER agonist in the uterus, promoting hypertrophy [27]. Thus, tamoxifen was behaving as both an ER agonist and an antagonist depending on the tissue context, and therefore reclassified as a Selective Estrogen Receptor Modulator (SERM). This unique pharmacology of the ERs offers a rare advantage for drug development as at least in theory it would be possible to develop ligands with tissue selective agonist and antagonist activities. SERMs that are currently on the market in USA include tamoxifen