Journal of Steroid Biochemistry & Molecular Biology 127 (2011) 44–50

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

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

Review

Endocrine disruption via estrogen receptors that participate in nongenomic signaling pathways☆

Cheryl S. Watson*, Yow-Jiun Jeng, Jutatip Guptarak

Department of Biochemistry & Molecular Biology, University of Texas Medical Branch, Galveston, TX 77555-0645, USA

ARTICLE INFO

Article history:
Received 8 July 2010
Received in revised form 27 January 2011
Accepted 30 January 2011

Keywords:
Estrogens
Nonmonotonic
Nongenomic
Receptors
Xenoestrogens
Women's health

ABSTRACT

When inappropriate (non-physiologic) estrogens affect organisms at critical times of estrogen sensitivity, disruption of normal endocrine functions can result. Non-physiologic estrogen mimetics (environmental, dietary, and pharmaceutical) can signal rapidly and potently via the membrane versions of estrogen receptors, as can physiologic estrogens. Both physiologic and non-physiologic estrogens activate multiple signaling pathways, leading to altered cellular functions (e.g. peptide release, cell proliferation or death, transport). Xenoestrogens' mimicry of physiologic estrogens is imperfect. When superimposed, xenoestrogens can alter endogenous estrogens' signaling and thereby disrupt normal signaling pathways, leading to malfunctions in many tissue types. Though these xenoestrogen actions occur rapidly via nongenomic signaling pathways, they can be sustained with continuing ligand stimulation, combinations of ligands, and signaling that perpetuates downstream, eventually also impinging on genomic regulation by controlling the activation state of transcription factors. Because via these pathways estrogens and xenoestrogens cause nonmonotonic stimulation patterns, they must be carefully tested for activity and toxicity over wide dose ranges. Nongenomic actions of xenoestrogens in combination with each other, and with physiologic estrogens, are still largely unexplored from these mechanistic perspectives.

Contents

Abbreviations: Ab, antibody; DAT, dopamine transporter; DES, diethylstilbestrol; E2, estradiol; E3, estriol; E1, estrone; ERK, extracellular-regulated kinase; ERR, estrogen receptor-related receptor; ER, estrogen receptor; GPER, G protein-coupled estrogen receptor; MAPK, mitogen-activated protein kinase; MEK, kinase activators of ERK; mER, membrane estrogen receptor; SERMs, selective estrogen receptor modulators; SmERMs, selective membrane estrogen receptor modulators.

☆ Article from the Special issue on Endocrine disruptors.

* Corresponding author at: Department of Biochemistry & Molecular Biology University of Texas Medical Branch, 301 University Blvd., Galveston, TX 77555-0645, USA. Tel.: +1 409 772 2382; fax: +1 409 772 2382.

E-mail addresses: cswatson@utmb.edu (C.S. Watson), yjeng@utmb.edu (Y.-J. Jeng), juguptat@utmb.edu (J. Guptarak).

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doi:10.1016/j.jsbmb.2011.01.015

1. Introduction

Estrogens are triple-edged swords. If women have too little of them they can experience problems such as reproductive failure, bone loss, hot flashes, skin changes, and some cardiovascular system vulnerabilities and cognitive declines [1]. Too much of them can result in cancers such as for the breast, uterus, colon, and pituitary [2], or other malfunctions such as blood clots [3] and nausea/eating disorders [4,5]. Exposure to the wrong estrogens (xenoestrogenic mimetics) could result in endocrine disruption of functions normally mediated by physiologic estrogens [6]. There are many different types of estrogens to consider as candidates for estrogenic or estro-disruptive cellular actions. Since many tissues of males also have estrogen receptors, they will also respond to both physiologic estrogens and xenoestrogens. Some of these actions in both males and females could be of the organizational (nonreversible) types that occur during development [7].

Compounds that have estrogenic effects can act in several ways. Acting through an estrogen receptor (ER) in the cell nucleus, they can directly change the expression of genes via binding to DNA response elements, or binding to other transcription factors that bind to response elements [8]. Acting via an ER at the surface of the cell, they can rapidly initiate cascades of chemical signals (specific ions, lipids, cyclic nucleotides, etc.) which then percolate through a series of kinases and phosphatases to control their eventual targets by adjusting their phosphorylation levels [9,10]. While these membrane-initiated actions generally happen rapidly, they may take some time to travel to the functional end of the pathways or to build up levels of products that change function. They may also be sustained by repeated reactivation and perpetuation down signaling cascades. Post-translational modifications brought on by nongenomic signaling can have a variety and multiplicity of downstream effects on functional molecules. Of these (and other) possible estrogen-induced mechanisms, only the genomic pathway has yet been extensively examined, and xenoestrogens are very weak via that mechanism. Data are beginning to emerge indicating that xenoestrogens may be much more potent via the non-nuclear (nongenomic, membrane-initiated) mechanisms.

2. Different kinds of ERs, their different subcellular distribution, and association with different cellular signaling mechanisms

Historically, genomic (directly transcriptional) responses to steroids acting via their nuclear receptor mediators have been the most studied and thoroughly described with respect to signaling partners, modulators, and biochemical products (RNAs and proteins) [11]. Though very rapid responses to estrogens have been observed for decades [12–14], only recently have separate nongenomic receptor-mediated signaling mechanisms been assigned to them. A variety of ERs (α, β, and GPER) have been linked to nongenomic estrogenic responses, including some ERα splice variants [15,16]. Though ERs α and β are highly homologous in sequence and structure [17], the GPER (formerly known as GPR30) is of an entirely different receptor class homologous to other seven transmembrane G protein-coupled receptors [18]. Another class of so-called orphan (without clear ligand assignments) receptors, the estrogen receptor-related (ERR) receptors, has so far not been implicated in rapid responses and nongenomic signaling. It is still unclear why such a variety of ERs would be necessary to mediate the effects of estrogens. However, there are quite a few different estrogens (see Section 3) and this may offer one reason, as we learn more about selectivity of some ligands for certain receptor forms [19]. However, it is interesting that when more than one ER is present in the same tissue or cell type for either genomic or nongenomic responses, ERα tends to be the driver of responses, while ERβ and GPER, when in the presence of ERα, tend to antagonize its responses [20–22].

Among the unique correlations of rapid nongenomic actions with a receptor is one linking recognition of a specific receptor epitope (see Fig. 1) to a rapid nongenomic response time-frame. The hinge region epitope for the H151 antibody (Ab) has very interesting properties [23]. When this receptor region is blocked by Ab binding in live unpermeabilized cells (meaning that the Ab can only see the membrane form of receptor), rapid responses to estrogens in those cells are blocked [24]; however, when that same Ab is applied to cells after estrogens are administered, recognition of the epitope by the Ab is blocked for several minutes [25]. In addition, an Ab applied to a very nearby epitope (epitope R3/4; also recognized by Ab ER75 [26]), in the absence of estrogens, triggers the same estrogenic response (prolactin release) as does the E_2 ligand [24,25]. This is an interesting connection between membrane receptor specific subtype (ERα) recognition and a rapid functional response. Perhaps careful testing of the many Abs now available for different ER subtype epitopes can make some parallel connections and uncover some new therapeutic uses for such Abs.

3. So many different kinds of estrogens

3.1. Other physiological estrogens

Besides the most often studied estrogen – cycle-dominant estradiol (E_2) – there are other prominent physiologic estrogens with significant impact at different life stages, such as E_1 (estrone, elevated postmenopausally) and E_3 (estriol, elevated during pregnancy). There are also many modified physiologic estrogens or metabolites, such as catechol estrogens, methoxy estrogens, sulfated estrogens, etc. [27,28]. These other physiologic estrogens have long been labeled weak estrogens because they were tested exclusively via the genomic signaling pathway. Now we find that some of them (that have so far been tested) are actually quite potent via the nongenomic signaling pathway [29–32]. Their ability to act potently may relate to actions at particular life stages of women in which these hormones are quite prominent. In pregnancy E_3 levels climb steadily until at parturition they are the predominant estrogen available in the circulation; abnormally low amounts of E_3 are associated with fetal risk for diseases like Down's syndrome [33] and eclampsia [34]. In peri- and post-menopause, the levels of E_1 rise until they become a dominant hormonal influence [35]. It is at such times that lifelong exposures to some estrogens begin to cause tumors in a variety of estrogen target organs with high receptor numbers (the most sensitive). It is interesting that at this same time, signaling may switch from hormones that are predominantly known for their potent genomic actions (E_2) to those that act potently via only the nongenomic pathway (E_1 and E_3). Is this a protective mechanism at a tumor-prone time? Are the high levels of E_3 present at the end of pregnancy also protective—against eventual estrogen-induced tumor induction in exposed fetuses or pregnant women?

3.2. Environmental estrogens

There are also many different classes of environmental (toxic contaminant) estrogens. Products containing these compounds litter our landfills and leach into our land and water sources (plastics, industrial surfactants, and pesticides). Some xenoestrogens such as pesticides (e.g. dieldrin, endosulfan) and plastics monomers such as bisphenol A (BPA) have known disease associations [36]. Though the mechanisms are not well understood, BPA has become a frequent topic of news reports and regulatory agency debates because