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REVIEW

Estrogens of multiple classes and their role in mental health disease mechanisms

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Abstract: Gender and sex hormones can influence a variety of mental health states, including mood, cognitive development and function, and vulnerability to neurodegenerative diseases and brain damage. Functions of neuronal cells may be altered by estrogens depending upon the availability of different physiological estrogenic ligands; these ligands and their effects vary with life stages, the genetic or postgenetic regulation of receptor levels in specific tissues, or the intercession of competing nonphysiological ligands (either intentional or unintentional, beneficial to health or not). Here we review evidence for how different estrogens (physiological and environmental/dietary), acting via different estrogen receptor subtypes residing in alternative subcellular locations, influence brain functions and behavior. We also discuss the families of receptors and transporters for monoamine neurotransmitters and how they may interact with the estrogenic signaling pathways.

Keywords: estrogen receptor α, estrogen receptor β, GPR30, GPER, xenoestrogens, phytoestrogens, transporters, brain function, neurotransmitter receptors

Estrogens, or the immediate downstream products that they induce, have long been known to alter reproductive behaviors. Prime examples are sexual receptivity and maternal behavior.[1,2] However, estrogens can also modify nonreproductive behaviors and cellular responses including mood, affect, anxiety, fear, locomotor activity,[3–5] tumor susceptibility,[6] and vulnerability to addictive drugs.[7] In some cases these estrogenic influences on behavior have been localized to specific brain areas. For example, estrogens alter locomotor activity via actions in the medial preoptic area,[8] while anxiety and conditioned fear appear to be controlled by the amygdala,[9] and developmental and tumor growth effects have been documented in the cerebellum.[10] Each of these brain regions expresses both α and β subtypes of estrogen receptors (ERs),[11] although their balance varies between locations. Other, more novel ER candidates found in multiple brain areas[12–14] are also beginning to be examined.

Life stage-specific, fluctuating levels of several physiological estrogens, and their relationship to diseases and vulnerabilities in women

There are major sex-based differences in diseases in which neurotransmitters, and their transporters and receptors, play a role. For example, depression is more prevalent in women,[15] especially during periods of fluctuating estrogen levels.[16,17] Diseases involving the dopamine transporter (DAT) such as Parkinson's, Alzheimer's, Tourette's, and attention-deficit hyperactivity disorder (ADHD), worsen in women after menopause,[18]

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or are different in premenopausal versus postmenopausal females,[19–25] suggesting a protective effect of estrogens, or altered vulnerabilities. Receptors and transporters for other catecholamines [notably the serotonin transporter (SERT) and the norepinephrine transporter (NET)] may also be involved in these sex-biased diseases.[26–28]

Because estrogen actions can alter the function of these machineries for neurotransmission, it is important to review the fluctuations in hormone levels that affect women. Levels of the most prominent physiological estrogens rise dramatically during pregnancy (see Figure 1), and return to prepregnancy levels very rapidly after parturition; this abrupt change can be correlated with the onset of postpartum depression.[29] Levels of these hormones also vary widely between the sexes, and between women's cycle stages and life stages (Figure 2). These changes are a likely basis for age- or pregnancy status-specific disease biases in women.[30–32] Ovarian hormones fluctuate in perimenopause, followed eventually by chronically lower levels[33] that can be correlated with the onset of mood disorders and reward circuit-based or other behavioral disturbances. Likewise, pubertal and menstrual cycle-based fluctuations can also lead to phase-dependent mood disorders.[34–40] Females are more vulnerable to cocaine use disorders than males,[4,7,41,42] and depressive states associated with drug addiction vulnerability or lack of recovery success can coincide with the rise and decline of estrogens.[43] Crises in schizophrenia/bipolar disorders can sometimes be directly correlated to menstrual cycle-related hormonal fluctuations.[17,44] Estradiol (E_2) can rapidly reverse the effects of selective serotonin reuptake inhibitors (SSRIs) used to treat depression.[45] Estrogens may also be involved in cognitive function and attention.[46,47] These observations suggest that dramatic fluctuations in estrogens or their downstream effectors are key to our understanding of these life stage-specific disease biases in women.

Is there evidence that treatment with estrogens can alleviate some of these conditions and diseases caused by deficits or dramatic decreases in estrogens? Although it has been proposed that a more rapid decline in E_2 is associated with postpartum depression, some recent evidence does not fully support this notion.[48] However, treatment with estrogens can relieve some cases of postpartum depression,[31,49–51] and

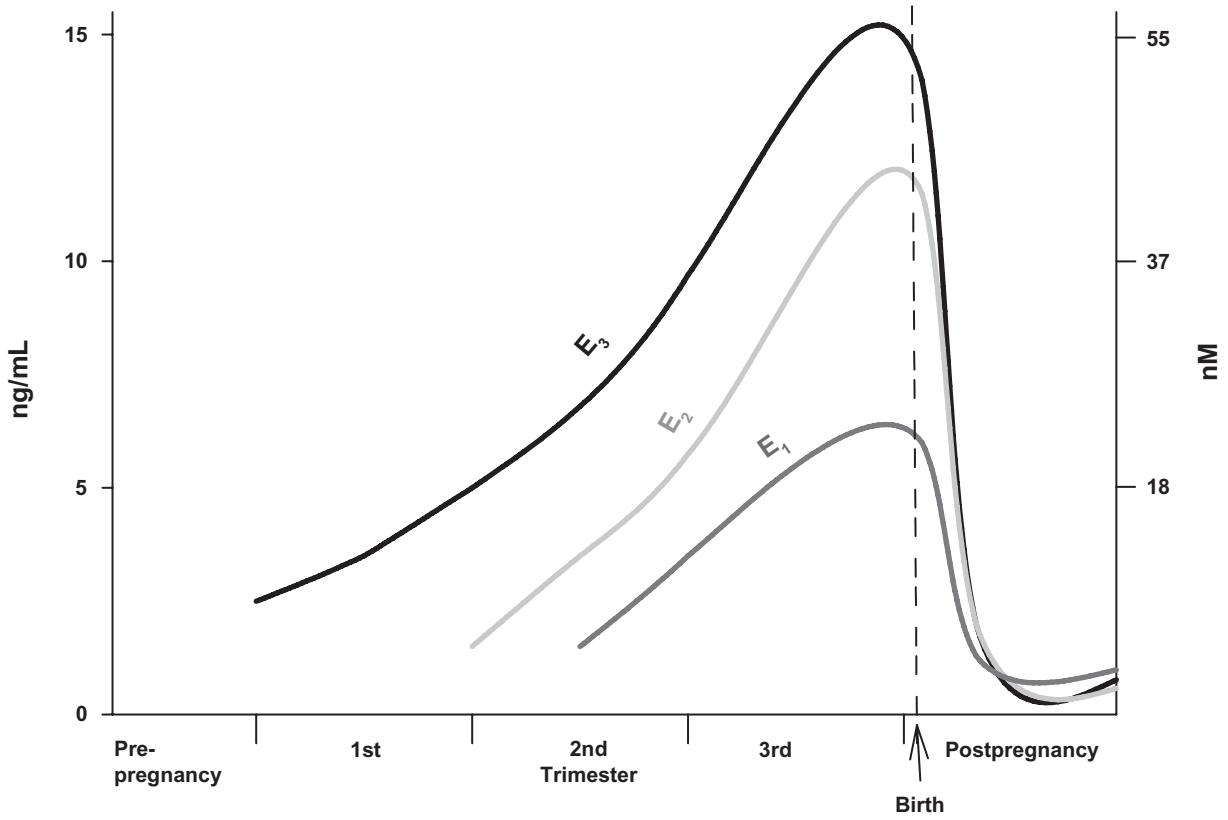

Figure 1 Hormone level changes in predominant physiological estrogens in the nonpregnant state versus the trimesters of pregnancy.
Note: The levels of the estrogens estrone, estradiol, and estriol (E_1, E_2, and E_3, respectively) drop rapidly to nonpregnant levels at parturition. Graphed from published data tables.[226]

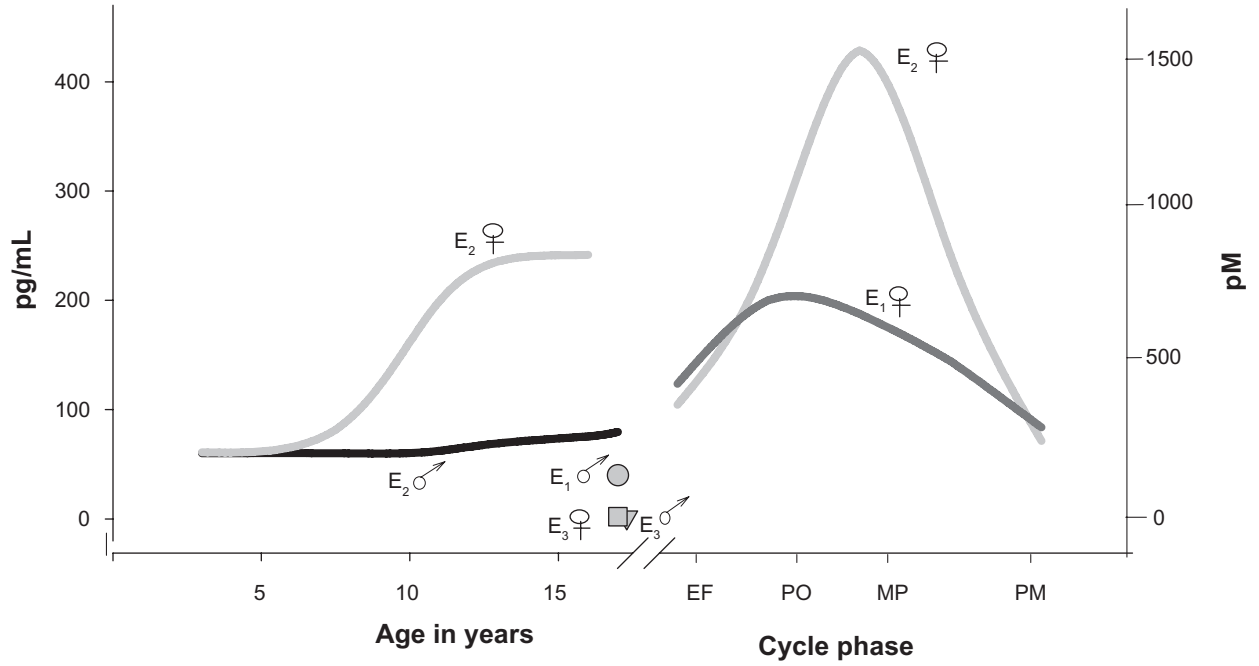

Figure 2 Hormone level changes in predominant physiological estrogens with increasing age in females compared to males, and during menstrual cycle phases. **Note:** These levels are depicted on scales three orders of magnitude lower than those used in Figure 1. The levels of the estrogens estrone, estradiol, and estriol (E_1, E_2, and E_3, respectively) are shown for females (♀) and males (♂). The cycle phases depicted are early follicular (EF), pre-ovulatory (PO), midcyle peak (MP), luteal (L), and postmenopausal (PMlevels). Graphed from published data tables.[226]

some experimental designs that simulate pre- and postpartum estrogen levels also support this conclusion.[52] Yet E_2 therapy in humans can be ineffective in reversing mood depression or other purportedly estrogen-influenced diseases.[50,52–56] One explanation for these discrepancies could be the involvement of other prominent estrogen metabolites [eg, estrone (E_1) and estriol (E_3); see Figures 1 and 2] that have not been studied nearly as extensively for these activities. They can have potent nongenomic actions,[57,58] in contrast to their previously determined minor role in genomic responses as "weak" estrogens. A few studies have looked at the effects of E_1 or E_3 on behavior,[59–61] but most have focused on treatments with E_2, with substrates for several estrogens (DHEA), or mixtures of estrogens such as Premarin®, making it difficult to interpret effects of individual estrogens in those preparations.

The primary physiological estrogens (E_1, E_2, and E_3) are predominantly synthesized in the ovaries, though they can also be synthesized in placenta (especially E_3),[62] brain,[63,64] and fat cells.[65] The levels of these hormones are therefore affected by the quantity and state of such non ovarian tissues. In addition, reports that only large doses of estrogens can improve mood disorders[66] may suggest the involvement of metabolites of the administered compound (usually E_2); these would be present in smaller amounts and could only accumulate to active levels after a large dose of the precursor estrogen is given.

Effects mediated by peptide hormones downstream of estrogens

Besides direct actions of estrogens on behavior, there are also indirect effects that cause synthesis of other receptors,[67] or synthesis and secretion of peptide hormones which act downstream. A classic example of such indirect action is production and secretion of the hormone prolactin (PRL). In the pituitary, estrogens facilitate both synthesis and regulated secretion of PRL.[68] PRL and its receptors are widely distributed throughout the body. Most actions elicited by this hormone are directly or indirectly related to reproductive processes (such as lactation). However, behavioral changes that facilitate reproductive success also result. Behavioral hallmarks associated with high PRL levels are diverse, and can be elicited in both pregnancy and pseudopregnancy (when PRL levels rise without a pregnancy). These include maternal behavior (including aggressiveness associated with protectiveness and territoriality) and sexual dysfunction (which may prevent a subsequent pregnancy during a critical infant developmental period). PRL overstimulation can also be correlated with depression, changed affect, and abnormal responses to stress.[69] As dopamine of hypothalamic origin provides D_2 dopamine receptor-mediated inhibitory control over PRL secretion,[70] and PRL and/or estrogens may also affect dopamine[71] and serotonin signaling,[72] there is clear interplay

among these factors. Low dopamine levels (associated with depression) also relieve dopamine's suppressive effect on PRL secretion in the pituitary, thus perhaps compounding adverse effects on mood. Estrogen-induced cell proliferation is also part of the normal response of the pituitary and many other reproduction-related tissues.[73,74] Estrogen exposures at the wrong levels or of inappropriate types can cause disregulated proliferation, and even produce tumors of those tissues,[75–77] including the pituitary;[78] behavioral issues are compounded if these tumors are prolactinomas.

Models for cellular mechanisms of estrogen action

The vast majority of studies on the mechanisms of estrogen (and other steroid) actions over the past 40–50 years focused on nuclear transcription (genomic) effects.[79–81] However, more recent evidence (including our own)[82–89] also supports nongenomic steroid actions initiated at the level of the cell membrane.[90–93] While we are beginning to understand the various ways in which E_2 acts via membrane receptor-initiated pathways, we still know very little about nongenomic responses to other prominent physiological estrogens (such as E_1 and E_3) or xenoestrogens (see below), and still less about other metabolites of these compounds. Membrane-initiated signaling pathways include complex webs of interacting signals that can converge to ramp a particular function up or down, and can have either immediate mechanistic consequences due to rapid signaling, or later downstream consequences after the accumulation of signaling cascade intermediates, or phosphorylation of transcription factors.[94] Multiple individual pathways must thus be tested to comprehensively understand functional control via such regulatory mechanisms, and their effects on women's health.

Which receptors mediate these responses?

Many areas of the brain express both ERα and ERβ,[95] although the receptors and their functions can vary during different stages of development. Various approaches have been used to detect selective actions of these subtypes[96] the most recent and convincing of which are ERα versus ERβ-selective ligands (PPT versus DPN, respectively) or knockdowns/knockouts of the ERs. DPN selectively regulates AMPA receptor subunits GluR2/3 in the hipopocampus[97] and also opposes ERα induction of progesterone receptors in the ventromedial nucleus.[98] ERβ can modulate DATs and D_2 receptors in rats.[99] ERα is thought to participate in striatal dopamine neuroprotection.[100] However, the neuroprotective effects of estrogens are usually seen at much higher than physiological concentrations, and therefore may also act via nonreceptor-mediated mechanisms, such as changing fluidity of membranes surrounding the receptors, in which steroids dissolve readily at these high concentrations. Few studies have as yet been aimed at examining α- versus β-selective behavior; though some have been inconclusive,[101] others have shown ERβ-specific effects on object recognition and placement tasks.[102]

In our own studies we examined nongenomic effects of estrogens on the stimulation of dopamine efflux in PC12 cells;[103] we showed that plasma membrane versions of ERs (mERα and mERβ) and the newly renamed GPER (formerly called GPR30) are all involved in nongenomic estrogenic effects.[85–89,104,105] GPER is a membrane ER of a different receptor family[106–108] that works by activating matrix metalloproteinase that in turn cleaves active epidermal growth factor (EGF) from a tethered heparin-bound EGF membrane protein precursor, triggering subsequent action via the EGF receptor. A family of GPER-related receptors was identified in a wide variety of tissues and species, including humans; multiple reports indicate that GPER is present in the brain,[12–14,109] though knowledge of its behavioral effects is still pending. We determined that GPER RNA and protein are expressed in PC12 cells,[58,103,110] where a recently developed GPER-selective ligand[111] appears to have inhibitory effects on ERα-stimulated dopamine efflux via the DAT, similar to GPER's inhibitory effects in other tissues.[109,112]

Signaling from both the cell surface and from the nucleus – fitting estrogenic actions into the big picture

Ligands first encountered at a cell's surface generally initiate cellular responses to a changing environment. Other classes of plasma membrane receptors have long been associated with membrane-initiated rapid signaling cascades; ERs that employ these signaling mechanisms are relatively new considerations. Such events can set into motion coordinated actions eventually leading to one of three main cell fates: proliferation, differentiation, or death. To direct the cell toward one of these decisions, multiple signaling pathways must funnel into a final common pathway signal, such as those involving mitogen-activated protein kinases (MAPKs). These enzymatic "signal receiving stations" sum many inputs from multiple signaling cascades to result in a tally of active MAPKs (with ERKs, JNKs, and p38 subtypes). Thus many stimuli can

reconcile to a final decision for a major cellular response. Acting via their membrane receptors, steroids are only one class of input signals to the MAPK "signal integrator". Estrogenic signals combine with those from other pathways, originating either from the cell surface or from intracellular locations.

The integration of these signal inputs is complex. Not all estrogens elicit identical responses (in level or timing) along these pathways.[82] Also, as each tissue may contain a different repertoire of signaling machineries, the complex mixture of patterns leading to pivotal cellular fate decisions will likely also be tissue-specific. Fluctuating endogenous metabolites, along with introduced pharmaceutical estrogens or other nonphysiological estrogen mimetics (see below) can all contribute to a different final tally with distinct kinetics, and so lead to alternative final cellular responses. Therefore, discovering the spectrum of responses within the complex signaling web particular to each part of the brain will be an important goal for understanding the impact of estrogens on women's behavioral health.

The cell biology and biochemistry of transporter function, and their regulation by estrogens

Many drugs currently used to treat behavioral disorders target the DAT and/or the SERT.[113,114] Transporters of this family are recognized as the predominant mechanism for maintaining adequate synaptic levels of the corresponding neurotransmitters. For instance, in DAT or SERT knockout mice the synthetic machinery for producing new neurotransmitters cannot compensate for the loss of neurotransmitter reuptake via these transporters.[115] Transporters in this family (DAT, SERT, and NET) all have 12 transmembrane regions, with both the N- and C-termini located within the cytoplasm, and a proposed structure-based mechanism for opening and closing extracellular versus cytoplasmic substrate (neurotransmitter) gates.[116–118] Various therapeutic drugs and the addictive drugs cocaine, methamphetamine, and amphetamine bind to the DAT and inhibit or reverse its activity[119–121] via mechanisms now beginning to be understood at the cellular and molecular levels. Some evidence also suggests that agents that cause DAT and SERT phosphorylation may regulate their removal from the plasma membrane and sequestration to an intracellular compartment.[122–126] Protein kinases PKC and PKG and the p38 MAPK[127] probably[128] mediate these effects by modifying a C-terminal pentapeptide sequence that is homologous across the DAT, SERT, and NET proteins.

It is also possible that many different kinases controlled by estrogens regulate neurotransmitter transporters. We recently determined that E_2 can rapidly alter several signaling pathways in PC12 cells to cause efflux of dopamine via the DAT;[58] PKC and MEK (the enzyme upstream of the MAPK-ERKs) are activated by E_2. E_2 also increases intracellular calcium levels via release from stores. In addition, from our work in the pituitary field, and the work of others, we know that multiple estrogens induce activation of MAPKs.[129,130] The estrogenic activation of other kinases likely to act on DAT's N-terminal tail have yet to be investigated;[93,131] these include PKA, PKG, the subtypes of PKC (α, βI, and II, γ), calmodulin kinase II (CamKII)[132,133] and Cdk5.[134] Such modifiers of phosphorylation and activity states could affect DAT in a variety of ways, including reversing the direction of transport,[120,121,135,136] and/or degradation or removal of the transporter from the membrane.[115,123,125,137] Specific phosphatases are also now being investigated for their role in maintaining a balance of phosphorylation at specific serines, threonines, and tyrosines at the cytosolic accessible regulatory tails of transporters;[133] the part played by estrogens in these processes is largely unknown.

Both neurotransmitter transporters and receptors can be found in the same specialized membrane compartment as ERs – the cholesterol-rich microdomains or caveolae.[138–140] Many kinases and phosphatases also reside here.[132,138,140,141] However, nonraft or caveolar plasma membrane populations of these groups of proteins also exist, and the regulated movement between compartments is not yet understood. ER-induced kinase and phosphatase effects on neurotransporters and neurotransmitter receptors could be either direct or indirect (via intervening enzymes in signaling cascades), so mERs may or may not need to interact directly with these parts of the neurotransmission machinery in the same membrane compartment.

There are also sex differences in the expression levels and localization of DAT; females express higher DAT levels in the striatum than men,[142] although men experience higher amplification of amphetamine-stimulated striatal dopamine release,[143] perhaps because of their lower baseline levels due to lower endogenous estrogen levels. Sex steroid levels in females also correlate with different behavioral/neurochemical responses to drugs.[144] The euphoric effects of psychoactive drugs are greatest during the follicular phase of the menstrual cycle, when the highest E_2 levels occur (see Figure 2).[145]

New parallels between the actions of estrogens and drugs of abuse on the DAT have recently been identified. Both amphetamines[118,146,147] and estrogens[58,103,148] can induce reversal of the DAT to cause dopamine efflux. Other coincident actions include DAT trafficking caused by amphetamines and some estrogens (though sometimes in different directions),[149,150] and the dependence of efflux caused by both compounds on PKC

actions and release of intracellular calcium stores. However, outcomes can depend upon whether transporter expression is under the control of endogenous or transfection-driven expression.[128] Interactions between CamKIIα and DAT's cytoplasmic C-terminus are thought to bring about phosphorylation of nearby N-terminal tail serines to cause amphetamine-induced efflux.[146] It will be interesting to see if CamKIIα is similarly involved in estrogen-induced dopamine efflux.

Currently, we only know that DAT function is differentially regulated by different physiological and nonphysiological estrogens.[58,148] Functional and structural homologies of the transporters suggest that similar estrogenic mechanisms could affect all transporters in this family (DAT, SERT, and NET). Estrogens are already implicated in control of SERT and NET function and related disease etiologies.[47,104] So while it is now well recognized that these transporters can be regulated by acute and selective responses via kinases and phosphatases, and that estrogens can activate kinases and phosphatases,[140,151] it is unknown if estrogens will be one of the initial triggers of phosphoregulation of cellular neurotransmitter machineries, as has been shown for other targets.[152,153]

Xenoestrogens (nonphysiological estrogens) and their role in women's mental health

Estrogenic toxins or environmental estrogens (see examples in Figure 3) are capable of mimicking the effects of endogenous estrogens, but usually not perfectly. Thus they can initiate more, less, different, and/or mistimed estrogenic actions that can lead to disruptions of estrogenic signaling, as shown in several recent studies.[151,154–159] Common human exposure levels have been associated with a variety of reproductive, neurological, and other impairments.[160–163] Bisphenol A (BPA), a monomer of polycarbonate plastics, is found in beverage bottles, canned food liners, and epoxy dental sealants.[164–166] Nonylphenol (NP) and structurally related alkylphenols are surfactant manufacturing byproducts and also found in detergents, cleaning materials, and pesticides.[167] Diethylstilbestrol (DES) is a potent pharmaceutical estrogen that was prescribed to prevent miscarriages in the 1950s to 1970s; unfortunately, although not really preventive for miscarriage, DES frequently caused multiple reproductive tract abnormalities in offspring, and cancers in some.[168] DDE, endosulfan, and dieldrin are estrogenic pesticides that have been associated with neurological impairments.[169–172] Besides manufacturing exposures, these compounds break down slowly, so persistent deposits are found in the soil and water, where plants and animals, and thus food supplies become exposed, subsequently passing these exposures on to humans and their infants.[173,174] Because many of these xenoestrogenic compounds bioaccumulate in fat tissues, resulting in prolonged and escalating human exposures, the exposure levels causing deleterious health effects are actively debated. Other discrepancies between reports arise from the insensitivity of some animal models to the effects of xenoestrogens.[175] However, toxicities to cellular signaling functions can occur at much lower concentrations than the maximum currently allowed by law.[155,157,176–179] We also know that some pharmaceutical estrogens become environmental contaminants because of pervasive human use (eg, ethinylestradiol in birth control pills). The known behavioral effects of these compounds at environmentally relevant concentrations are still relatively few, due to limited data. However, BPA is now known to adversely affect some sociosexual behaviors,[180–182] locomotion,[183] spatial learning/memory,[184] and fear/anxiety[185,186] at relatively low doses.

Like E_2, xenoestrogens can increase dopamine efflux by changing the amount or function of DAT in the cell membrane.[187] Xenoestrogens could further exacerbate the effects of physiological estrogens on transporters via these mechanisms, perhaps with behavioral consequences. In rodent models, prenatal and neonatal exposure to BPA leads to enhanced sensitivity to the rewarding effects of methamphetamine[188] and morphine.[189] It remains to be seen if there are associations between human xenoestrogen exposure during specific developmental stages and an increased vulnerability to drug addictions later in life, with possible gender differences. Developmental effects of xenoestrogen exposure have recently been shown in rodents in diseases of the immune system such as asthma[179] and in cerebellar neurons.[178]

Phytoestrogens (derived from plant sources) are another type of nonphysiological or xenoestrogen. Many are important constituents of Asian diets, which contain approximately 10-fold higher concentrations of many phytoestrogens than Western diets.[190,191] Phytoestrogen-rich diets are thought to be one reason why women in cultures who eat them have less dramatic symptoms of menopause (such as hot flashes, osteoporosis, rise in heart disease), presumably due to the ability of phytoestrogens to replace some of the beneficial effects of estrogens.[192] These cultures also have lower incidences of estrogen exposure-related cancers,[193] suggesting that some phytoestrogens may oppose the carcinogenic effects of physiological estrogens and some xenoestrogens. Finally, phytoestrogens may protect against brain damage and aging,[194,195] although studies are still few and conflicting.[196]

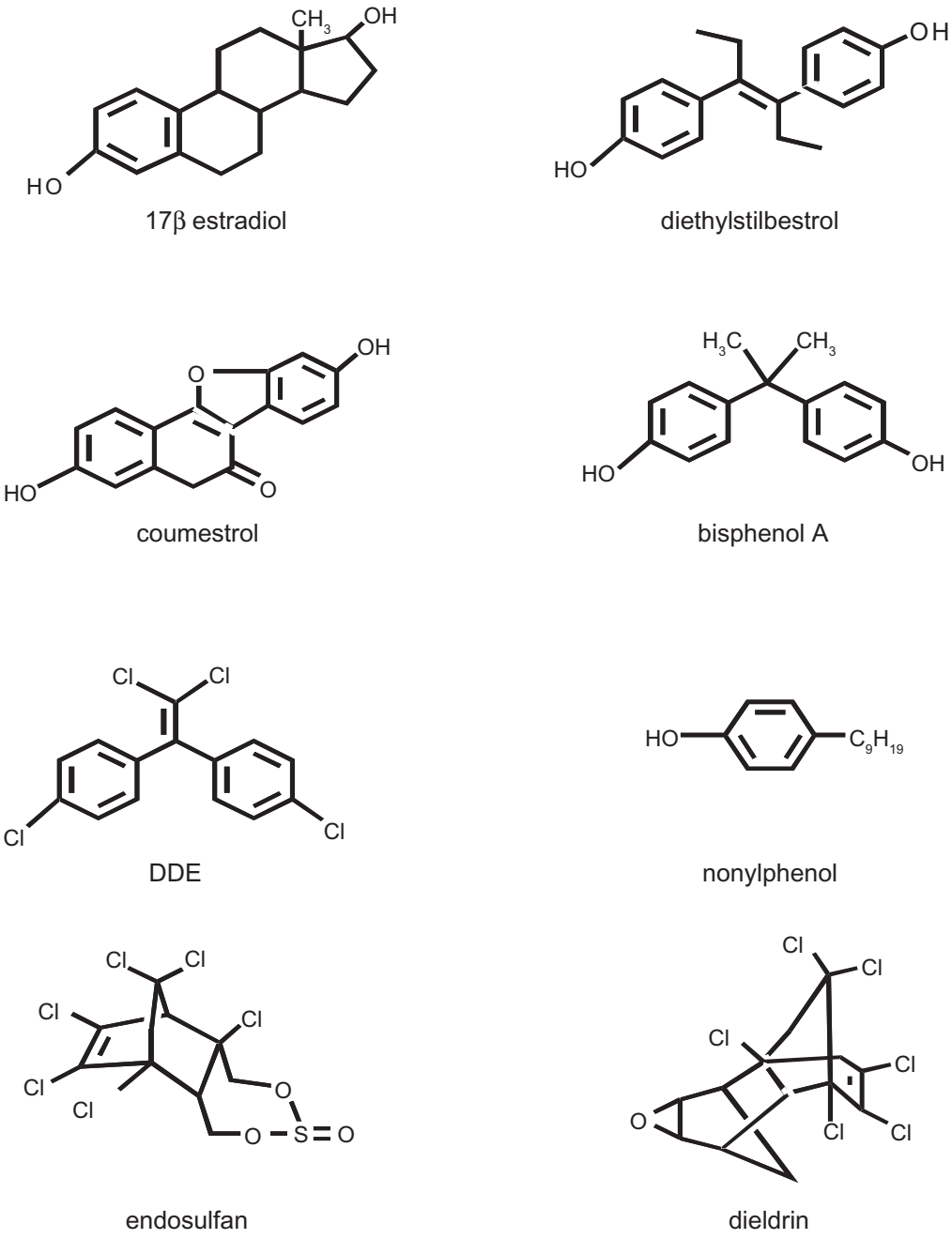

Figure 3 Structurally diverse xenoestrogens compared to the predominant physiological estrogen, E_2.
Note: Diethylstilbestrol is a pharmaceutical estrogen. Coumestrol is a plant estrogen. Bisphenol A is a monomer from which polycarbonate plastics are polymerized. Nonylphenol is an industrial surfactant. DDE (a metabolite of DDT), endosulfan, and dieldrin are pesticides. Though some are structurally less similar to estradiol, the most important receptor contact points for ERs α and β are maintained in these chemicals.[227]

Unlike E_2, which binds to both ER subtypes with relatively equal affinity, some phytoestrogens bind with higher affinity to ERβ (measured on nuclear version of the receptors), and therefore could affect behaviors quite selectively if the affinities for the membrane versions of ERβ are the same. Because membrane receptors are in a different chemical environment (lipid) and therefore expected to assume alternate protein conformations, it is not surprising that they have different potencies for estrogenic effects initiated there, compared to transcriptional effects initiated in the nucleus. Phytoestrogens and many other xenoestrogens show a much higher potency in nongenomic responses, therefore we expect their binding affinities could be higher for mERs. It is probably not correct to just "adopt" the literature on nuclear measurements of binding affinity to fit the membrane receptor. Though we would like to measure the binding affinities for membrane steroid receptors directly,

these data are very difficult to interpret because binding of a lipophilic ligand to a receptor lodged in a lipid membrane is subject to very high levels of nonspecific binding. However, if binding to the nuclear receptor has any relevance for predicting binding affinities for the membrane forms of the receptors, there are several examples which might predict higher activities via ERβ. For example, the plant estrogens coumestrol and several isoflavonoids bind more tightly to ERβ.[190,197–199]

Phytoestrogens have been implicated in memory and learning,[196,200] and can have anxiolytic effects.[200–202] Some phytoestrogenic compounds can also antagonize the effects of E_2; for example, while coumestrol by itself does not affect locomotor activity, it can antagonize the effects of E_2.[203] Besides its higher affinity for ERβ, coumestrol might act by triggering ERβ-mediated compensatory inhibition in the face of ERα activity in both genomic[204,205] and nongenomic activation systems. The latter recent result demonstrated that estrogenic effects on the DAT (reversal of the transporter to cause efflux) are mainly mediated via ERα, but that an ERβ-selective synthetic ligand is inhibitory in the presence of ERα activity.[103] Phytoestrogens can also act as agonists directly via ERβ in the brain[206] and at the cellular level,[103] in the absence of any ERα stimulation.

Estrogen replacement therapeutic strategies: pros and cons

It is very important to obtain low dose, wide dose, and temporal response information about compounds that mimic estrogens, to determine if and when they are safe for use as therapeutics. Many previous researchers have examined the actions of only very high concentrations of nonphysiological estrogens, under the mistaken assumption that dose-response relationships are always monotonic and entirely predictable, and that the effects of lower and noneffective doses could be extrapolated downwards. We now know that such extrapolations are incorrect,[207] and that estrogenic actions via nongenomic responses are nonmonotoic.[157,178] We have also learned that the temporal phasing of estrogenic and xenoestrogenic responses is different,[177,208] suggesting that combinations of these compounds with one another might disrupt normal regulation by causing sustained responses, or cancelling each other out,[148] rather than demonstrating the oscillating signals caused by endogenous estrogens. Thus the actions of multiple different estrogens and their pathways are complex.[154,209] To understand the breadth of possible disease vulnerabilities influenced by variant endogenous and exogenous hormone levels we need to establish the principles of individual and combinatorial action of estrogenic compounds for each brain region, tissue type, and developmental stage.

To treat diseases associated with loss or imbalance of physiological estrogens (due to menopause, surgery, pregnancy, parturition, or cycle disturbances), or perhaps to counteract the effects of harmful nonphysiological estrogens, it is important to design estrogen replacement or augmentation strategies that deliver the most effective estrogens, over the lowest possible effective doses, with the most effective scheduling and fewest side effects. Currently, E_2 and equine urine estrogen mixtures (Premarin®) are the most frequently used replacement therapies. While there are numerous suggestions in the clinical literature that replacing lost estrogens can be beneficial (to bones and skin, in specific cognitive and mood states, and perhaps for the cardiovascular system), there are also risks involved. Long term use of replacement estrogens can increase the risk of some cancers, notably those of the breast and uterus,[210] complicate diagnostic procedures such as breast imaging,[211] or exacerbate some cardiovascular problems.[32] Though some studies have linked replacement estrogens to a decline in specific cognitive functions and increased heart disease,[212–215] or have concluded that estrogens do not help prevent disease,[216,217] these effects may also depend upon the dose, the use of the most appropriate estrogen metabolites, how long estrogen withdrawal occurred before replacement,[218–220] or whether progestins are coadministered.[221] Most of these parameters have yet to be systematically studied and agreed upon.

Protective effects of some estrogens against ischemic, glucocorticoid-induced, or other induced brain injury have been touted;[222–224] however, such studies have been focused on very high doses of estrogens that, while acceptable for acute therapies to prevent death, are unacceptable for chronic therapeutic use because of the cancer risk. Therefore, we clearly do not yet understand how different estrogens and their metabolites at various doses and schedules may interact, especially given the nonmonotonic dose-response patterns that are becoming recognized as typical of nongenomic steroid actions.[225] It is thus critical to know the lowest effective dose ranges of specific estrogens that regulate given functions such as neurotransmitter transporter and receptor activity. It remains to be proven conclusively if some phytoestrogens or E_2 metabolites could act therapeutically to either restore estrogenic effects on transporters when endogenous estrogens are absent (such as to control hot flashes), or to act preventatively as inhibitory estrogens in scenarios where estrogenic overstimulation results in cancers.

Summary

There are important differences between males and females in a number of functional responses and vulnerabilities to behavioral disorders. Signaling mechanisms, both genomic and nongenomic, operating via several different ER proteins residing in different subcellular compartments, are beginning to be found responsible for diverse actions of estrogens involved in these functions. Complex signaling cascades and receptor systems can be influenced by multiple physiological estrogens, as well as some nonphysiological (dietary, pharmaceutical) and contaminant (environmental) estrogens. Such influences could have profound effects on the functioning of the brain and nervous system. Elucidating the underlying cellular mechanisms via which variant estrogens and their receptors act will provide explanations of how we might intervene medically to address severely imbalanced estrogens that cause disease, or enlighten our choices among commercial products or foods/dietary supplements that contain estrogens. These considerations should also inform future decisions about hormone replacements, analogs, and antagonists that could alleviate life stage-specific effects of estrogens or their withdrawal. An enhanced focus on the relatively new area of nongenomic estrogenic effects may allow entirely new understandings and approaches to treatment of these maladies, and perhaps change current treatment standards. One such change could be the preservation of ovaries in women undergoing hysterectomies, potentially justified because of the multiple beneficial estrogens that they provide.[18] Hopefully, among these new understandings and opportunities will be ones that improve the diagnosis and treatment of mental state diseases for women.

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