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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

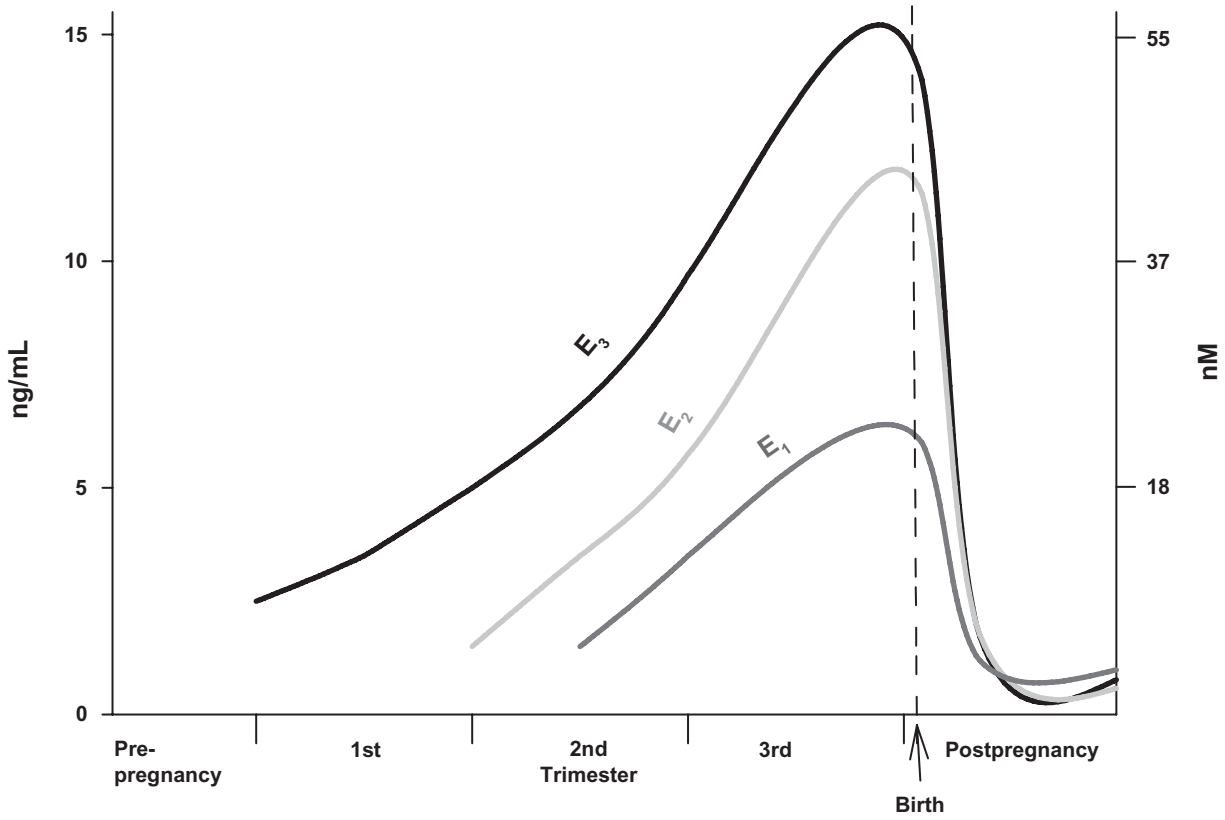

Figure 1 Hormone level changes in predominant physiological estrogens in the nonpregnant state versus the trimesters of pregnancy.
Note: The levels of the estrogens estrone, estradiol, and estriol (E_1, E_2, and E_3, respectively) drop rapidly to nonpregnant levels at parturition. Graphed from published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

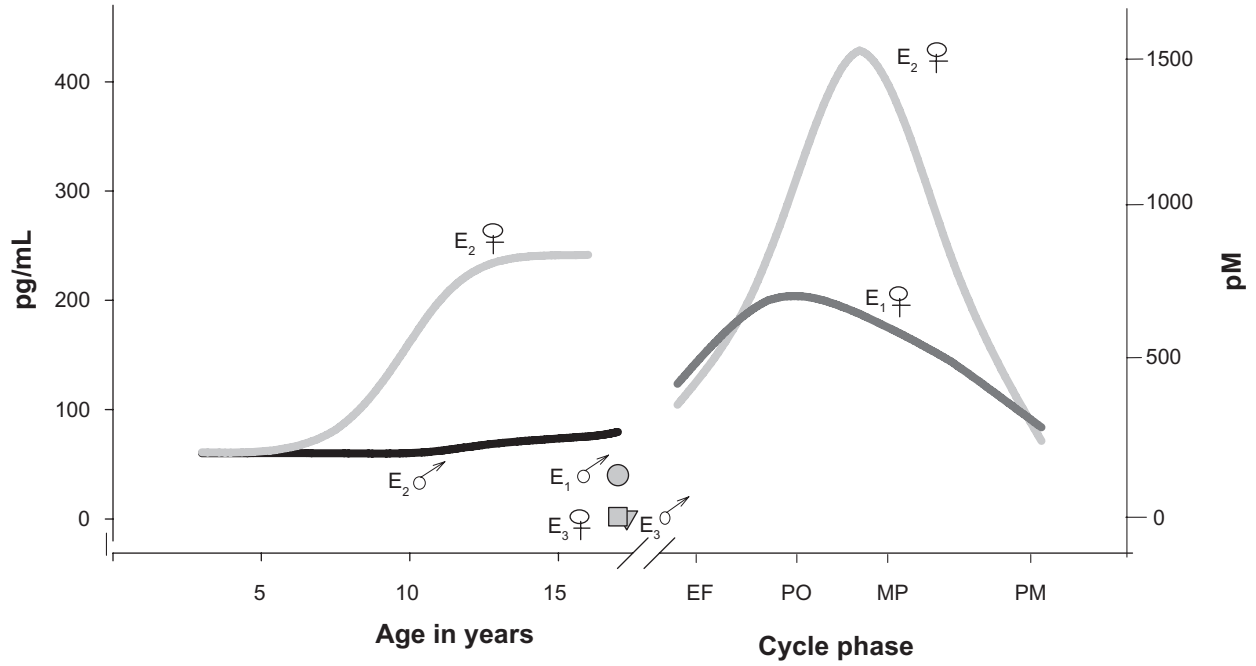

Figure 2 Hormone level changes in predominant physiological estrogens with increasing age in females compared to males, and during menstrual cycle phases. **Note:** These levels are depicted on scales three orders of magnitude lower than those used in Figure 1. The levels of the estrogens estrone, estradiol, 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]

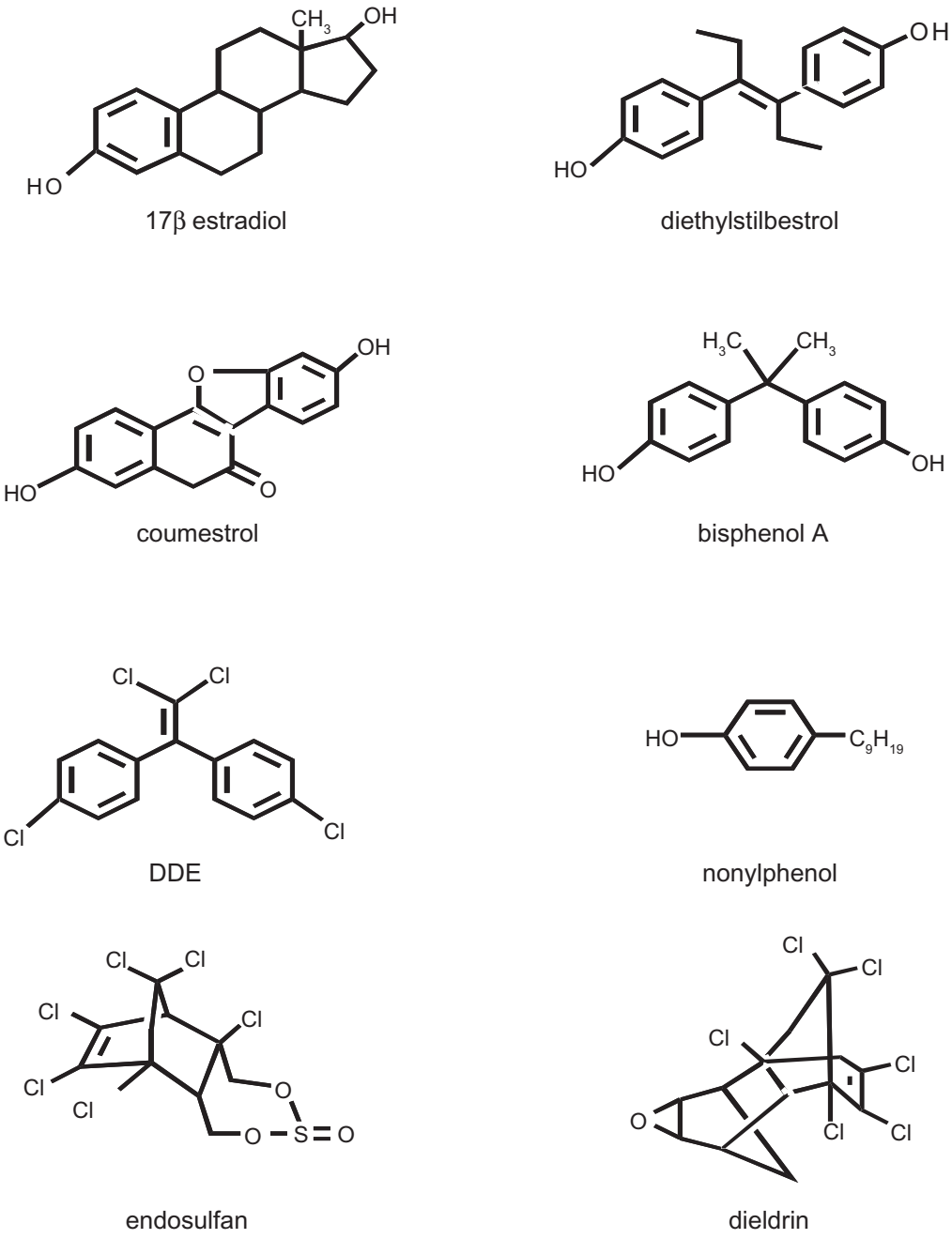

Figure 3 Structurally diverse xenoestrogens compared to the predominant physiological estrogen, E_2.
Note: Diethylstilbestrol is a pharmaceutical estrogen. Coumestrol is a plant estrogen. Bisphenol A is a monomer from which polycarbonate plastics are polymerized. Nonylphenol is an industrial surfactant. 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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References

1. Micevych P, Dominguez R. Membrane estradiol signaling in the brain. *Front Neuroendocrinol*. 2009;30:315–327.
2. Pfaff D. Hormone-driven mechanisms in the central nervous system facilitate the analysis of mammalian behaviours. *J Endocrinol*. 2005; 184:447–453.
3. Mora S, Dussaubat N, Diaz-Veliz G. Effects of the estrous cycle and ovarian hormones on behavioral indices of anxiety in female rats. *Psychoneuroendocrinology*. 1996;21:609–620.
4. Sell SL, Scalzitti JM, Thomas ML, Cunningham KA. Influence of ovarian hormones and estrous cycle on the behavioral response to cocaine in female rats. *J Pharmacol Exp Ther*. 2000;293:879–886.
5. Walf AA, Frye CA. The use of the elevated plus maze as an assay of anxiety-related behavior in rodents. *Nat Protocols*. 2007;2:322–328.
6. Belcher SM, Ma X, Le HH. Blockade of estrogen receptor signaling inhibits growth and migration of medulloblastoma. *Endocr*. 2009;150: 1112–1121.
7. Jackson LR, Robinson TE, Becker JB. Sex differences and hormonal influences on acquisition of cocaine self-administration in rats. *Neuropsychopharmacology*. 2006;31:129–138.
8. Fahrbach SE, Meisel RL, Pfaff DW. Preoptic implants of estradiol increase wheel running but not the open field activity of female rats. *Physiol Behav*. 1985;35:985–992.
9. Walf AA, Frye CA. A review and update of mechanisms of estrogen in the hippocampus and amygdala for anxiety and depression behavior. *Neuropsychopharmacology*. 2006;31:1097–1111.
10. Belcher SM. Rapid signaling mechanisms of estrogens in the developing cerebellum. *Brain Res Rev*. 2008;57:481–492.
11. Shughrue PJ, Lane MV, Merchenthaler I. Comparative distribution of estrogen receptor-α and -β mRNA in the rat central nervous system. *J Comp Neurol*. 1997;388:507–525.
12. Qiu J, Ronnekleiv OK, Kelly MJ. Modulation of hypothalamic neuronal activity through a novel G-protein-coupled estrogen membrane receptor. *Steroids*. 2008;73:985–991.
13. Brailoiu E, Dun SL, Brailoiu GC, et al. Distribution and characterization of estrogen receptor G protein-coupled receptor 30 in the rat central nervous system. *J Endocrinol*. 2007;193:311–321.
14. Hazell GG, Yao ST, Roper JA, Prossnitz ER, O'Carroll AM, Lolait SJ. Localisation of GPR30, a novel G protein-coupled oestrogen receptor, suggests multiple functions in rodent brain and peripheral tissues. *J Endocrinol*. 2009;202:223–236.
15. Staley JK, Sanacora G, Tamagnan G, et al. Sex differences in diencephalon serotonin transporter availability in major depression. *Biol Psychiatry*. 2006;59:40–47.
16. Halbreich U, Kahn LS. Role of estrogen in the aetiology and treatment of mood disorders. *CNS Drugs*. 2001;15:797–817.
17. Felthous AR, Robinson DB. Oral contraceptive medication in prevention of psychotic exacerbations associated with phases of the menstrual cycle. *J Prev Psychiatry*. 1981;1:5–14.
18. Parker WH, Shoupe D, Broder MS, Liu Z, Farquhar C, Berek JS. Elective oophorectomy in the gynecological patient: when is it desirable? *Curr Opin Obstet Gynecol*. 2007;19:350–354.
19. Dluzen DE, Mickley KR. Gender differences in modulatory effects of tamoxifen upon the nigrostriatal dopaminergic system. *Pharmacol Biochem Behav*. 2005;80:27–33.
20. Foltynie T, Lewis SG, Goldberg TE, et al. The BDNF Val66Met polymorphism has a gender specific influence on planning ability in Parkinson's disease. *J Neurol*. 2005;252:833–838.
21. Benedetti MD, Maraganore DM, Bower JH, et al. Hysterectomy, menopause, and estrogen use preceding Parkinson's disease: an exploratory case-control study. *Mov Disord*. 2001;16:830–837.
22. Quinn PO. Treating adolescent girls and women with ADHD: gender-specific issues. *J Clin Psychol*. 2005;61:579–587.
23. Kurlan R. The pathogenesis of Tourette's syndrome. A possible role for hormonal and excitatory neurotransmitter influences in brain development. *Arch Neurol*. 1992;49:874–876.
24. Yoon DY, Rippel CA, Kobets AJ, et al. Dopaminergic polymorphisms in Tourette syndrome: Association with the DAT gene (SLC6A3). *Am J Med Genet B Neuropsychiatr Genet*. 2007;144:605–610.
25. Compton J, van AT, Murphy D. Mood, cognition and Alzheimer's disease. *Best Pract Res Clin Obstet Gynaecol*. 2002;16:357–370.
26. Markowitz JS, DeVane CL, Pestreich LK, Patrick KS, Muniz R. A comprehensive in vitro screening of d-, l-, and dl-threo-methylphenidate: an exploratory study. *J Child Adolesc Psychopharmacol*. 2006;16: 687–698.

27. Osterlund MK, Overstreet DH, Hurd YL. The flinders sensitive line rats, a genetic model of depression, show abnormal serotonin receptor mRNA expression in the brain that is reversed by 17β-estradiol. *Brain Res Mol Brain Res*. 1999;74:158–166.
28. Nutt DJ. Relationship of neurotransmitters to the symptoms of major depressive disorder. *J Clin Psychiatry*. 2008;69 Suppl E1:4–7.
29. Doornbos B, Fokkema DS, Molhoek M, Tanke MA, Postema F, Korf J. Abrupt rather than gradual hormonal changes induce postpartum blues-like behavior in rats. *Life Sci*. 2009;84:69–74.
30. Williams CL. Estrogen effects on cognition across the lifespan. *Horm Behav*. 1998;34:80–84.
31. Moses-Kolko EL, Berga SL, Kalro B, Sit DK, Wisner KL. Transdermal estradiol for postpartum depression: a promising treatment option. *Clin Obstet Gynecol*. 2009;52:516–529.
32. Loucks TL, Berga SL. Does postmenopausal estrogen use confer neuroprotection? *Semin Reprod Med*. 2009;27:260–274.
33. Prior JC. Ovarian aging and the perimenopausal transition: the paradox of endogenous ovarian hyperstimulation. *Endocrine*. 2005; 26:297–300.
34. Yonkers KA, Brown C, Pearlstein TB, Foegh M, Sampson-Landers C, Rapkin A. Efficacy of a New Low-Dose Oral Contraceptive With Drospirenone in Premenstrual Dysphoric Disorder. *Obstet Gynecol*. 2005;106:492–501.
35. Almeida OP, Barclay L. Sex hormones and their impact on dementia and depression: a clinical perspective. *Expert Opin Pharmacother*. 2001; 2:527–535.
36. Stein D, Hanukoglu A, Blank S, Elizur A. Cyclic psychosis associated with the menstrual cycle. *Br J Psychiatry*. 1993;163:824–828.
37. Steiner M, Dunn E, Born L. Hormones and mood: from menarche to menopause and beyond. *J Affect Disord*. 2003;74:67–83.
38. Taylor M. Psychological consequences of surgical menopause. *J Reprod Med*. 2001;46:317–324.
39. Oinonen KA, Mazmanian D. Does body fat protect against negative moods in women? *Med Hypotheses*. 2001;57:387–388.
40. Dreher JC, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Menstrual cycle phase modulates reward-related neural function in women. *Proc Natl Acad Sci U S A*. 2007;104:2465–2470.
41. Sell SL, Thomas ML, Cunningham KA. Influence of estrous cycle and estradiol on behavioral sensitization to cocaine in female rats. *Drug Alcohol Depend*. 2002;67:281–290.
42. Elman I, Karlsgodt KH, Gastfriend DR. Gender differences in cocaine craving among non-treatment-seeking individuals with cocaine dependence. *Am J Drug Alcohol Abuse*. 2001;27:193–202.
43. Soares CN, Poitras JR, Prouty J. Effect of reproductive hormones and selective estrogen receptor modulators on mood during menopause. *Drugs Aging*. 2003;20:85–100.
44. Coromina SM, Rodie JU, de Montagut LM, Sanchez AM. The use of oral contraceptives as a prevention of recurrent premenstrual psychosis. *Psychiatry Res*. 2009;170:290–291.
45. Benmansour S, Piotrowski JP, Altamirano AV, Frazer A. Impact of ovarian hormones on the modulation of the serotonin transporter by fluvoxamine. *Neuropsychopharmacology*. 2009;34:555–564.
46. Bender CM, Sereika SM, Berga SL, et al. Cognitive impairment associated with adjuvant therapy in breast cancer. *Psychooncology*. 2006;15:422–430.
47. Shively CA, Bethea CL. Cognition, mood disorders, and sex hormones. *ILAR J*. 2004;45:189–199.
48. Klier CM, Muzik M, Dervic K, et al. The role of estrogen and progesterone in depression after birth. *J Psychiatr Res*. 2007;41:273–279.
49. Genazzani AR, Spinetti A, Gallo R, Bernardi F. Menopause and the central nervous system: intervention options. *Maturitas*. 1999;31:103–110.
50. Grigoriadis S, Kennedy SH. Role of estrogen in the treatment of depression. *Am J Ther*. 2002;9:503–509.
51. Epperson CN, Wisner KL, Yamamoto B. Gonadal steroids in the treatment of mood disorders. *Psychosom Med*. 1999;61:676–697.
52. Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Effects of gonadal steroids in women with a history of postpartum depression. *Am J Psychiatry*. 2000;157:924–930.
53. Morrison MF, Kallan MJ, Ten HT, Katz I, Tweedy K, Battistini M. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol Psychiatry*. 2004;55:406–412.
54. Huttner RP, Shepherd JE. Gonadal steroids, selective serotonin reuptake inhibitors, and mood disorders in women. *Med Clin North Am*. 2003;87:1065–1076.
55. Miller KJ. The other side of estrogen replacement therapy: outcome study results of mood improvement in estrogen users and nonusers. *Curr Psychiatry Rep*. 2003;5:439–444.
56. Klaiber EL, Broverman DM, Vogel W, Kobayashi Y. Estrogen therapy for severe persistent depressions in women. *Arch Gen Psychiatry*. 1979;36:550–554.
57. Watson CS, Jeng YJ, Kochukov MY. Nongenomic actions of estradiol compared with estrone and estriol in pituitary tumor cell signaling and proliferation. *FASEB J*. 2008;22:3328–3336.
58. Alyea RA, Watson CS. Nongenomic mechanisms of physiological estrogen-mediated dopamine efflux. *BMC Neurosci*. 2009;10:59.
59. Lebrun CE, van der Schouw YT, De Jong FH, Pols HA, Grobbee DE, Lamberts SW. Endogenous oestrogens are related to cognition in healthy elderly women. *Clin Endocrinol (Oxf)*. 2005;63:50–55.
60. Almeida OP, Lautenschlager N, Vasikaram S, Leedman P, Flicker L. Association between physiological serum concentration of estrogen and the mental health of community-dwelling postmenopausal women age 70 years and over. *Am J Geriatr Psychiatry*. 2005;13:142–149.
61. Barha CK, Galea LA. Influence of different estrogens on neuroplasticity and cognition in the hippocampus. *Biochim Biophys Acta*. 2010; S0304–4165(10):00011–00015.
62. Newby D, Aitken DA, Howatson AG, Connor JM. Placental synthesis of oestriol in Down's syndrome pregnancies. *Placenta*. 2000;21:263–267.
63. Vanson A, Arnold AP, Schlinger BA. 3 β-hydroxysteroid dehydrogenase/isomerase and aromatase activity in primary cultures of developing zebra finch telencephalon: dehydroepiandrosterone as substrate for synthesis of androstenedione and estrogens. *Gen Comp Endocrinol*. 1996;102:342–350.
64. Reddy VV. Estriol synthesis in rat brain and pituitary. *Brain Res*. 1979;175:165–168.
65. Deslypere JP, Verdonck L, Vermeulen A. Fat tissue: a steroid reservoir and site of steroid metabolism. *J Clin Endocrinol Metab*. 1985;61:564–570.
66. Richardson TA, Robinson RD. Menopause and depression: a review of psychologic function and sex steroid neurobiology during the menopause(1). *Prim Care Update Ob Gyns*. 2000;7:215–223.
67. Moffatt CA, Rissman EF, Shupnik MA, Blaustein JD. Induction of progestin receptors by estradiol in the forebrain of estrogen receptor-α gene-disrupted mice. *J Neurosci*. 1998;18:9556–9563.
68. Dannies PS. Control of prolactin production by estrogen. In: Litwack G, ed. *Biochemical Actions of Hormones*. 12 ed. Orlando: Academic Press, Inc.; 1985;289–310.
69. Sobrinho LG. Prolactin, psychological stress and environment in humans: adaptation and maladaptation. *Pituitary*. 2003;6:35–39.
70. Bression D, Brandi AM. In vitro and in vivo antagonistic regulation by estradiol and progesterone of the rat pituitary domperidone binding sites: correlation with ovarian steroid regulation of the dopaminergic inhibition of prolactin secretion in vitro. *Endocr*. 1985;116:1905.
71. Arbogast LA, Voogt JL. Hyperprolactinemia increases and hypoprolactinemia decreases tyrosine hydroxylase messenger ribonucleic acid levels in the arcuate nuclei, but not the substantia nigra or zona incerta. *Endocr*. 1991;128:997–1005.
72. van Amelsvoort TA, Abel KM, Robertson DM, et al. Prolactin response to d-fenfluramine in postmenopausal women on and off ERT: comparison with young women. *Psychoneuroendocrinology*. 2001;26:493–502.

73. Adams AB. Human breast cancer: concerted role of diet, prolactin and adrenal C19-delta 5 steroids in tumorigenesis. *Int J Cancer*. 1992;50:854–858.
74. Nevalainen MT, Valve EM, Ingleton PM, Nurmi M, Martikainen PM, Harkonen PL. Prolactin and prolactin receptors are expressed and functioning in human prostate. *J Clin Invest*. 1997;99:618–627.
75. Clevenger CV, Furth PA, Hankinson SE, Schuler LA. The role of prolactin in mammary carcinoma. *Endocr Rev*. 2003;24:1–27.
76. Gutzman JH, Miller KK, Schuler LA. Endogenous human prolactin and not exogenous human prolactin induces estrogen receptor α and prolactin receptor expression and increases estrogen responsiveness in breast cancer cells. *J Steroid Biochem Mol Biol*. 2004;88:69–77.
77. Rose-Hellekant TA, Arendt LM, Schroeder MD, Gilchrist K, Sandgren EP, Schuler LA. Prolactin induces ERα-positive and ERα-negative mammary cancer in transgenic mice. *Oncogene*. 2003;22:4664–4674.
78. Gorski J, Wendell D, Gregg D, Chun TY. Estrogens and the genetic control of tumor growth. [Review] [23 refs]. *Prog Clin Bio Res*. 1997;396:233–243.
79. Lee KC, Lee KW. Nuclear receptors, coactivators and chromatin: new approaches, new insights. *Trends Endocrinol Metab*. 2001;12: 191–197.
80. Tsai MJ, O'Malley BW. Molecular mechanisms of action of steroid/thyroid receptor superfamily members. [Review]. *Ann Rev Biochem*. 1994;63:451–486.
81. Evans RM. The steroid and thyroid hormone receptor superfamily [Review]. *Science*. 1988;240:889–895.
82. Bulayeva NN, Gametchu B, Watson CS. Quantitative measurement of estrogen-induced ERK 1 and 2 activation via multiple membrane-initiated signaling pathways. *Steroids*. 2004;69:181–192.
83. Campbell CH, Bulayeva N, Brown DB, Gametchu B, Watson CS. Regulation of the membrane estrogen receptor-a: role of cell density, serum, cell passage number, and estradiol. *FASEB J*. 2002; 16:1917–1927.
84. Clarke CH, Norfleet AM, Clarke MSF., Watson CS, Cunningham KA, Thomas ML. Peri-membrane localization of the estrogen receptor-a protein in neuronal processes of cultured hippocampal neurons. *Neuroendocrinology*. 2000;71:34–42.
85. Norfleet AM, Clarke C, Gametchu B, Watson CS. Antibodies to the estrogen receptor-a modulate prolactin release from rat pituitary tumor cells through plasma membrane estrogen receptors. *FASEB J*. 2000;14:157–165.
86. Norfleet AM, Thomas ML, Gametchu B, Watson CS. Estrogen receptor-a detected on the plasma membrane of aldehyde-fixed GH3/B6/F10 rat pituitary cells by enzyme-linked immunocytochemistry. *Endocr*. 1999;140:3805–3814.
87. Pappas TC, Gametchu B, Yannariello-Brown J, Collins TJ, Watson CS. Membrane estrogen receptors in GH3/B6 cells are associated with rapid estrogen-induced release of prolactin. *Endocrine*. 1994;2:813–822.
88. Pappas TC, Gametchu B, Watson CS. Membrane estrogen receptor-enriched GH_3/B6 cells have an enhanced non-genomic response to estrogen. *Endocrine*. 1995;3:743–749.
89. Pappas TC, Gametchu B, Watson CS. Membrane estrogen receptors identified by multiple antibody labeling and impeded-ligand binding. *FASEB J*. 1995;9:404–410.
90. Szego CM. Cytostructural correlates of hormone action: new common ground in receptor-mediated signal propagation for steroid and peptide agonists. *Endocrine*. 1994;2:1079–1093.
91. Watson CS. *The Identities of Membrane Steroid Receptors .... and Other Proteins Mediating Nongenomic Steroid Action*. Boston: Kluwer Academic Publishers, 2003.
92. Watson CS, Gametchu B. Proteins of multiple classes participate in nongenomic steroid actions. *Exp Biol Med*. 2003;228:1272–1281.
93. Watson CS, Gametchu B. Membrane-initiated steroid actions and the proteins that mediate them. *Proc Soc Exp Biol Med*. 1999;220:9–19.
94. Watson CS. Signaling themes shared between peptide and steroid hormones at the plasma membrane [Review] STKE E1. *Science's Signal Transduction Knowledge Environment*. [serial online] 1999.
95. Ikeda Y, Nagai A, Ikeda MA, Hayashi S. Sexually dimorphic and estrogen-dependent expression of estrogen receptor β in the ventromedial hypothalamus during rat postnatal development. *Endocr*. 2003;144:5098–5104.
96. Morissette M, Le SM, D'Astous M, et al. Contribution of estrogen receptors α and β to the effects of estradiol in the brain. *J Steroid Biochem Mol Biol*. 2008;108:327–338.
97. Waters EM, Mitterling K, Spencer JL, Mazid S, McEwen BS, Milner TA. Estrogen receptor α and β specific agonists regulate expression of synaptic proteins in rat hippocampus. *Brain Res*. 2009; 1290:1–11.
98. Gonzales KL, Tetel MJ, Wagner CK. Estrogen receptor (ER) β modulates ERα responses to estrogens in the developing rat ventromedial nucleus of the hypothalamus. *Endocr*. 2008;149:4615–4621.
99. Le SM, Di PT. Influence of oestrogenic compounds on monoamine transporters in rat striatum. *J Neuroendocrinol*. 2006;18:25–32.
100. D'Astous M, Mendez P, Morissette M, Garcia-Segura LM, Di PT. Implication of the phosphatidylinositol-3 kinase/protein kinase B signaling pathway in the neuroprotective effect of estradiol in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mice. *Mol Pharmacol*. 2006;69:1492–1498.
101. Lacreuse A, Wilson ME, Herndon JG. No effect of different estrogen receptor ligands on cognition in adult female monkeys. *Physiol Behav*. 2009;96:448–456.
102. Walf AA, Koonce CJ, Frye CA. Estradiol or diarylpropionitrile administration to wild type, but not estrogen receptor β knockout, mice enhances performance in the object recognition and object placement tasks. *Neurobiol Learn Mem*. 2008;89:513–521.
103. Alyea RA, Laurence SE, Kim SH, Katzenellenbogen BS, Katzenellenbogen JA, Watson CS. The roles of membrane estrogen receptor subtypes in modulating dopamine transporters in PC-12 cells. *J Neurochem*. 2008;106:1525–1533.
104. Koldzic-Zivanovic N, Seitz PK, Watson CS, Cunningham KA, Thomas ML. Intracellular signaling involved in estrogen regulation of serotonin reuptake. *Mol Cell Endocrinol*. 2004;226:33–42.
105. Watson CS, Pappas TC, Gametchu B. The other estrogen receptor in the plasma membrane: implications for the actions of environmental estrogens. *Environ Health Perspect*. 1995;103 Suppl 7:41–50.
106. Filardo EJ, Quinn JA, Bland KI, Frackelton AR. Estrogen-induced activation of Erk-1 and Erk-2 requires the G protein-coupled receptor homolog, GPR30, and occurs via trans-activation of the epidermal growth factor receptor through release of HB-EGF. *Mol Endocrinol*. 2000;14:1649–1660.
107. Filardo EJ, Quinn JA, Frackelton AR, Bland KI. Estrogen action via the G protein-coupled receptor, GPR30: Stimulation of adenylyl cyclase and cAMP-mediated attenuation of the epidermal growth factor receptor-to-MAPK signaling axis. *Mol Endocrinol*. 2002;16:70–84.
108. Revankar CM, Cimino DF, Sklar LA, Arterburn JB, Prossnitz ER. A transmembrane intracellular estrogen receptor mediates rapid cell signaling. *Science*. 2005;307:1625–1630.
109. Xu H, Qin S, Carrasco GA, et al. Extra-nuclear estrogen receptor GPR30 regulates serotonin function in rat hypothalamus. *Neuroscience*. 2009;158:1599–1607.
110. Watson CS, Alyea RA, Hawkins BE, Thomas ML, Cunningham KA, Jakubas AA. Estradiol effects on the dopamine transporter – protein levels, subcellular location, and function. *J Mol Signal*. 2006;1:5.
111. Bologa CG, Revankar CM, Young SM, et al. Virtual and biomolecular screening converge on a selective agonist for GPR30. *Nat Chem Biol*. 2006;2:207–212.
112. Ariazi EA, Brailoiu E, Yerrum S, et al. The G protein-coupled receptor GPR30 inhibits proliferation of estrogen receptor-positive breast cancer cells. *Cancer Res*. 2010;70:1184–1194.

113. Thase ME, Haight BR, Richard N, et al. Remission rates following antidepressant therapy with bupropion or selective serotonin reuptake inhibitors: a meta-analysis of original data from 7 randomized controlled trials. *J Clin Psychiatry*. 2005;66:974–981.
114. Bannon MJ. The dopamine transporter: role in neurotoxicity and human disease. *Toxicol Appl Pharmacol*. 2005;204:355–360.
115. Torres GE, Gainetdinov RR, Caron MG. Plasma membrane monoamine transporters: structure, regulation and function. *Nat Rev Neurosci*. 2003;4:13–25.
116. Giros B, Caron MG. Molecular characterization of the dopamine transporter. *Trends Pharmacol Sci*. 1993;14:43–49.
117. Blakely RD, Bauman AL. Biogenic amine transporters: regulation in flux. *Curr Opin Neurobiol*. 2000;10:328–336.
118. Yamashita A, Singh SK, Kawate T, Jin Y, Gouaux E. Crystal structure of a bacterial homologue of Na^+/Cl^- dependent neurotransmitter transporters. *Nature*. 2005;437:215–223.
119. Pifl C, Drobny H, Reither H, Hornykiewicz O, Singer EA. Mechanism of the dopamine-releasing actions of amphetamine and cocaine: plasmalemmal dopamine transporter versus vesicular monoamine transporter. *Mol Pharmacol*. 1995;47:368–373.
120. Sandoval V, Riddle EL, Ugarte YV, Hanson GR, Fleckenstein AE. Methamphetamine-induced rapid and reversible changes in dopamine transporter function: an in vitro model. *J Neurosci*. 2001;21:1413–1419.
121. Kokoshka JM, Vaughan RA, Hanson GR, Fleckenstein AE. Nature of methamphetamine-induced rapid and reversible changes in dopamine transporters. *Eur J Pharmacol*. 1998;361:269–275.
122. Holton KL, Loder MK, Melikian HE. Nonclassical, distinct endocytic signals dictate constitutive and PKC-regulated neurotransmitter transporter internalization – on line in press. *Nat Neurosci*. 2005;8:881–888.
123. Jayanthi LD, Samuvel DJ, Blakely RD, Ramamoorthy S. Evidence for biphasic effects of protein kinase C on serotonin transporter function, endocytosis, and phosphorylation. *Mol Pharmacol*. 2005;67:2077–2087.
124. Ramamoorthy S, Blakely RD. Phosphorylation and sequestration of serotonin transporters differentially modulated by psychostimulants. *Science*. 1999;285:763–766.
125. Melikian HE. Neurotransmitter transporter trafficking: endocytosis, recycling, and regulation. *Pharmacol Ther*. 2004;104:17–27.
126. Gulley JM, Doolen S, Zahniser NR. Brief, repeated exposure to substrates down-regulates dopamine transporter function in Xenopus oocytes in vitro and rat dorsal striatum in vivo. *J Neurochem*. 2002;83:400–411.
127. Prasad HC, Steiner JA, Sutcliffe JS, Blakely RD. Enhanced activity of human serotonin transporter variants associated with autism. *Philos Trans R Soc Lond B Biol Sci*. 2009;364:163–173.
128. Eriksen J, Rasmussen SG, Rasmussen TN, et al. Visualization of dopamine transporter trafficking in live neurons by use of fluorescent cocaine analogs. *J Neurosci*. 2009;29:6794–6808.
129. Jeng YJ, Kochukov MY, Watson CS. Membrane estrogen receptor-α-mediated nongenomic actions of phytoestrogens in GH3/B6/F10 pituitary tumor cells. *J Mol Signal*. 2009;4:2.
130. Jeng YJ, Watson CS. Proliferative and anti-proliferative effects of dietary levels of phytoestrogens in rat pituitary GH3/B6/F10 cells – the involvement of rapidly activated kinases and caspases. *BMC Cancer*. 2009;9:334.
131. Watson CS. Signaling themes shared between peptide and steroid hormones at the plasma membrane. *Sci STKE*. 1999;1999:E1.
132. Foster JD, Adkins SD, Lever JR, Vaughan RA. Phorbol ester induced trafficking-independent regulation and enhanced phosphorylation of the dopamine transporter associated with membrane rafts and cholesterol. *J Neurochem*. 2008;105:1683–1699.
133. Gorentla BK, Moritz AE, Foster JD, Vaughan RA. Proline-directed phosphorylation of the dopamine transporter N-terminal domain. *Biochem*. 2009;48:1067–1076.
134. Price DA, Sorkin A, Zahniser NR. Cyclin-dependent kinase 5 inhibitors: inhibition of dopamine transporter activity. *Mol Pharmacol*. 2009;76:812–823.
135. Eshleman AJ, Henningsen RA, Neve KA, Janowsky A. Release of dopamine via the human transporter. *Mol Pharmacol*. 1994;45:312–316.
136. Holton KL, Loder MK, Melikian HE. Nonclassical, distinct endocytic signals dictate constitutive and PKC-regulated neurotransmitter transporter internalization. *Nat Neurosci*. 2005;8:881–888.
137. Torres GE, Carneiro A, Seamans K, et al. Oligomerization and trafficking of the human dopamine transporter. Mutational analysis identifies critical domains important for the functional expression of the transporter. *J Biol Chem*. 2003;278:2731–2739.
138. Chambliss KL, Yuhanna IS, Mineo C, et al. Estrogen receptor α and endothelial nitric oxide synthase are organized into a functional signaling module in caveolae. *Circ Res*. 2000;87:E44–E52.
139. Li L, Haynes MP, Bender JR. Plasma membrane localization and function of the estrogen receptor α variant (ER46) in human endothelial cells. *Proc Natl Acad Sci U S A*. 2003;100:4807–4812.
140. Zivadinovic D, Watson CS. Membrane estrogen receptor-α levels predict estrogen-induced ERK1/2 activation in MCF-7 cells. *Breast Cancer Res*. 2005;7:R130–R144.
141. Smart EJ, Ying YS, Anderson RG. Hormonal regulation of caveolae internalization. *J Cell Biol*. 1995;131:929–938.
142. Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. *Am J Psychiatry*. 2001;158:1492–1499.
143. Munro CA, McCaul ME, Wong DF, et al. Sex differences in striatal dopamine release in healthy adults. *Biol Psychiatry*. 2006;59:966–974.
144. Evans SM. The role of estradiol and progesterone in modulating the subjective effects of stimulants in humans 1. *Exp Clin Psychopharmacol*. 2007;15:418–426.
145. White TL, Justice AJ, de WH. Differential subjective effects of D-amphetamine by gender, hormone levels and menstrual cycle phase 1. *Pharmacol Biochem Behav*. 2002;73:729–741.
146. Fog JU, Khoshbouei H, Holy M, et al. Calmodulin Kinase II Interacts with the Dopamine Transporter C Terminus to Regulate Amphetamine-Induced Reverse Transport. *Neuron*. 2006;51:417–429.
147. Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. *Annual Review of Pharmacology and Toxicology*. 2007;47:681–698.
148. Alyea RA, Watson CS. Differential regulation of dopamine transporter function and location by low concentrations of environmental estrogens and 17β-estradiol. *Environ Health Perspect*. 2009;117:778–783.
149. Furman CA, Chen R, Guptaroy B, Zhang M, Holz RW, Gnegy M. Dopamine and amphetamine rapidly increase dopamine transporter trafficking to the surface: live-cell imaging using total internal reflection fluorescence microscopy. *J Neurosci*. 2009;29:3328–3336.
150. Boudanova E, Navaroli DM, Melikian HE. Amphetamine-induced decreases in dopamine transporter surface expression are protein kinase C-independent. *Neuropharmacology*. 2008;54:605–612.
151. Belcher SM, Le HH, Spurling L, Wong JK. Rapid estrogenic regulation of extracellular signal- regulated kinase 1/2 signaling in cerebellar granule cells involves a G protein- and protein kinase A-dependent mechanism and intracellular activation of protein phosphatase 2A. *Endocr*. 2005;146:5397–5406.
152. Foster JD, Cervinski MA, Gorentla BK, Vaughan RA. Regulation of the dopamine transporter by phosphorylation. *Handb Exp Pharmacol*. 2006;197–214.
153. Zahniser NR, Sorkin A. Trafficking of dopamine transporters in psychostimulant actions. *Semin Cell Dev Biol*. 2009;20:411–417.
154. Bulayeva NN, Watson CS. Xenoestrogen-induced ERK 1 and 2 activation via multiple membrane-initiated signaling pathways. *Environ Health Perspect*. 2004;112:1481–1487.
155. Narita SI, Goldblum RM, Watson CS, et al. Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators PMCID:17366818. *Env Health Perspect*. 2007;115:48–52.
156. Watson CS, Alyea RA, Jeng YJ, Kochukov MY. Nongenomic actions of low concentration estrogens and xenoestrogens on multiple tissues PMCID:17601655. *Mol Cell Endocrinol*. 2007;274:1–7.

157. Wozniak AL, Bulayeva NN, Watson CS. Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-α-mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. *Environ Health Perspect*. 2005;113: 431–439.
158. Alonso-Magdalena P, Morimoto S, Ripoll C, Fuentes E, Nadal A. The estrogenic effect of bisphenol A disrupts pancreatic β-cell function in vivo and induces insulin resistance. *Environ Health Perspect*. 2006;114:106–112.
159. Midoro-Horiuti T, Tiwari R, Watson CS, Goldblum RM. Maternal bisphenol a exposure promotes the development of experimental asthma in mouse pups. *Environ Health Perspect*. 2010;118:273–277.
160. McKinlay R, Plant JA, Bell JN, Voulvoulis N. Calculating human exposure to endocrine disrupting pesticides via agricultural and non-agricultural exposure routes. *Sci Total Environ*. 2008;398:1–12.
161. Hotchkiss AK, Rider CV, Blystone CR, et al. Fifteen years after "Wingspread" – environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go. *Toxicol Sci*. 2008;105:235–259.
162. Colborn T. Neurodevelopment and endocrine disruption. *Environ Health Perspect*. 2004;112:944–949.
163. Nadal A, Alonso-Magdalena P, Soriano S, Quesada I, Ropero AB. The pancreatic β-cell as a target of estrogens and xenoestrogens: Implications for blood glucose homeostasis and diabetes. *Mol Cell Endocrinol*. 2009;304:63–68.
164. Krishnan AV, Stathis P, Permuth SF, Tokes L, Feldman D. Bisphenol A: an estrogenic substance is released from polycarbonate flasks during autoclaving. *Endocr*. 1993;132:2279–2286.
165. Milligan SR, Balasubramanian AV, Kalita JC. Relative potency of xenobiotic estrogens in an acute in vivo mammalian assay. *Environ Health Perspect*. 1998;106:23–26.
166. vom Saal FS, Cooke PS, Buchanan DL, et al. A physiologically based approach to the study of bisphenol A and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior. *Toxicol Ind Health*. 1998;14:239–260.
167. Rudel RA, Camann DE, Spengler JD, Korn LR, Brody JG. Phthalates, alkylphenols, pesticides, polybrominated diphenyl ethers, and other endocrine-disrupting compounds in indoor air and dust. *Environ Sci Technol*. 2003;37:4543–4553.
168. Herbst AL. Behavior of estrogen-associated female genital tract cancer and its relation to neoplasia following intrauterine exposure to diethylstilbestrol (DES). *Gynecol Oncol*. 2000;76:147–156.
169. Lakshmana MK, Raju TR. Endosulfan induces small but significant changes in the levels of noradrenaline, dopamine and serotonin in the developing rat brain and deficits in the operant learning performance. *Toxicology*. 1994;91:139–150.
170. Bornman MS, Pretorius E, Marx J, Smit E, van der Merwe CF. Ultrastructural effects of DDT, DDD, and DDE on neural cells of the chicken embryo model. *Environ Toxicol*. 2007;22:328–336.
171. Kitazawa M, Anantharam V, Kanthasamy AG. Dieldrin-induced oxidative stress and neurochemical changes contribute to apoptopic cell death in dopaminergic cells. *Free Radic Biol Med*. 2001;31: 1473–1485.
172. Naqvi SM, Vaishnavi C. Bioaccumulative potential and toxicity of endosulfan insecticide to non-target animals. *Comp Biochem Physiol C*. 1993;105:347–361.
173. Otaka H, Yasuhara A, Morita M. Determination of bisphenol A and 4-nonylphenol in human milk using alkaline digestion and cleanup by solid-phase extraction. *Anal Sci*. 2003;19:1663–1666.
174. Sajiki J, Takahashi K, Yonekubo J. Sensitive method for the determination of bisphenol-A in serum using two systems of high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl*. 1999;736:255–261.
175. Myers JP, vom Saal FS, Akingbemi BT, et al. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. *Environ Health Perspect*. 2009;117:309–315.
176. Alonso-Magdalena P, Laribi O, Ropero AB, et al. Low doses of bisphenol A and diethylstilbestrol impair Ca2+ signals in pancreatic α-cells through a nonclassical membrane estrogen receptor within intact islets of Langerhans. *Environ Health Perspect*. 2005;113: 969–977.
177. Bulayeva NN, Watson CS. Xenoestrogen-induced ERK-1 and ERK-2 activation via multiple membrane-initiated signaling pathways. *Environ Health Perspect*. 2004;112:1481–1487.
178. Zsarnovszky A, Le HH, Wang HS, Belcher SM. Ontogeny of rapid estrogen-mediated extracellular signal-regulated kinase signaling in the rat cerebellar cortex: potent nongenomic agonist and endocrine disrupting activity of the xenoestrogen bisphenol A. *Endocr*. 2005;146:5388–5396.
179. Midoro-Horiuti T, Tiwari R, Watson CS, Goldblum RM. Maternal bisphenol A exposure promotes the development of experimental asthma in mouse pups. *Environ Health Perspect*. 2010;118:273–277.
180. Della SD, Farabollini F, Dessi-Fulgheri F, Fusani L. Environmental-like exposure to low levels of estrogen affects sexual behavior and physiology of female rats. *Endocrinology*. 2008;149:5592–5598.
181. MacLusky NJ, Hajszan T, Leranth C. The environmental estrogen bisphenol a inhibits estradiol-induced hippocampal synaptogenesis. *Environ Health Perspect*. 2005;113:675–679.
182. Palanza P, Gioiosa L, vom Saal FS, Parmigiani S. Effects of developmental exposure to bisphenol A on brain and behavior in mice. *Environ Res*. 2008;108:150–157.
183. Zhou R, Zhang Z, Zhu Y, Chen L, Sokabe M, Chen L. Deficits in development of synaptic plasticity in rat dorsal striatum following prenatal and neonatal exposure to low-dose bisphenol A. *Neuroscience*. 2009;159:161–171.
184. Xu X, Liu Y, Sadamatsu M, et al. Perinatal bisphenol A affects the behavior and SRC-1 expression of male pups but does not influence on the thyroid hormone receptors and its responsive gene. *Neurosci Res*. 2007;58:149–155.
185. Fujimoto T, Kubo K, Aou S. Prenatal exposure to bisphenol A impairs sexual differentiation of exploratory behavior and increases depression-like behavior in rats. *Brain Res*. 2006;1068:49–55.
186. Negishi T, Kawasaki K, Suzaki S, et al. Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. *Environ Health Perspect*. 2004;112:1159–1164.
187. Watson CS, Bulayeva NN, Wozniak AL, Alyea RA. Xenoestrogens are potent activators of nongenomic estrogenic responses. *Steroids*. 2007;72:124–134.
188. Suzuki T, Mizuo K, Nakazawa H, et al. Prenatal and neonatal exposure to bisphenol-a enhances the central dopamine d1 receptor-mediated action in mice: enhancement of the methamphetamine-induced abuse state. *Neuroscience*. 2003;117:639–644.
189. Miyatake M, Miyagawa K, Mizuo K, Narita M, Suzuki T. Dynamic changes in dopaminergic neurotransmission induced by a low concentration of bisphenol-A in neurones and astrocytes. *J Neuroendocrinol*. 2006;18:434–444.
190. Whitten PL, Patisaul HB. Cross-species and interassay comparisons of phytoestrogen action [Review]. *Environ Health Perspect*. 2001;109:5–20.
191. Adlercreutz H, Yamada T, Wahala K, Watanabe S. Maternal and neonatal phytoestrogens in Japanese women during birth. *Am J Obstet Gynecol*. 1999;180:737–743.
192. Adlercreutz H, Gorbach SL, Goldin BR, Woods MN, Dwyer JT, Hamalainen E. Estrogen metabolism and excretion in oriental and caucasian women. *J Natl Cancer Inst*. 1994;86:1076–1082.
193. Adlercreutz H. Phytoestrogens: epidemiology and a possible role in cancer protection. [Review]. *Environ Health Perspect*. 1995;103 Suppl 7: 103–112.
194. Kumar P, Padi SS, Naidu PS, Kumar A. Effect of resveratrol on 3-nitropropionic acid-induced biochemical and behavioural changes: possible neuroprotective mechanisms. *Behav Pharmacol*. 2006;17: 485–492.

195. Sonmez U, Sonmez A, Erbil G, Tekmen I, Baykara B. Neuroprotective effects of resveratrol against traumatic brain injury in immature rats. *Neurosci Lett*. 2007;420:133–137.
196. Zhao L, Brinton RD. WHI and WHIMS follow-up and human studies of soy isoflavones on cognition. *Expert Rev Neurother*. 2007; 7:1549–1564.
197. Whitten PL, Patisaul HB, Young LJ. Neurobehavioral actions of coumestrol and related isoflavonoids in rodents. *Neurotoxicol Teratol*. 2002;24:47–54.
198. Kuiper GG, Lemmen JG, Carlsson B, et al. Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor β. *Endocr*. 1998;139:4252–4263.
199. Harris DM, Besselink E, Henning SM, Go VLW, Heber D. Phytoestrogens Induce Differential Estrogen Receptor α- or β-Mediated Responses in Transfected Breast Cancer Cells. *Experimental Biology and Medicine*. 2005;230:558–568.
200. Lephart ED, West TW, Weber KS, et al. Neurobehavioral effects of dietary soy phytoestrogens. *Neurotoxicol Teratol*. 2002;24:5–16.
201. Lund TD, Lephart ED. Dietary soy phytoestrogens produce anxiolytic effects in the elevated plus-maze. *Brain Res*. 2001;913:180–184.
202. Fernandez SP, Nguyen M, Yow TT, et al. The flavonoid glycosides, myricitrin, gossypin and naringin exert anxiolytic action in mice. *Neurochem Res*. 2009;34:1867–1875.
203. Garey J, Morgan MA, Frohlich J, McEwen BS, Pfaff DW. Effects of the phytoestrogen coumestrol on locomotor and fear-related behaviors in female mice. *Horm Behav*. 2001;40:65–76.
204. Paech K, Webb P, Kuiper GGJM, et al. Differential ligand activation of estrogen receptors ERa and ERb at AP1 sites. *Science*. 1997;227: 1508–1510.
205. Hall JM, McDonnell DP. The estrogen receptor β-isoform (ERβ) of the human estrogen receptor modulates ERα transcriptional activity and is a key regulator of the cellular response to estrogens and antiestrogens. *Endocr*. 1999;140:5566–5578.
206. Lee YB, Lee HJ, Sohn HS. Soy isoflavones and cognitive function. *J Nutr Biochem*. 2005;16:641–649.
207. Sheehan DM. No-threshold dose-response curves for nongenotoxic chemicals: findings and applications for risk assessment. *Environ Res*. 2006;100:93–99.
208. Kochukov MY, Jeng YJ, Watson CS. Alkylphenol xenoestrogens with varying carbon chain lengths differentially and potently activate signaling and functional responses in $GH_3/B_6/F10$ somatomammotropes. *Env Health Perspect*. 2009;117:723–730.
209. Sheffler DJ, Conn PJ. Allosteric potentiators of metabotropic glutamate receptor subtype 1a differentially modulate independent signaling pathways in baby hamster kidney cells. *Neuropharmacology*. 2008;55:419–427.
210. Lipsett MB. Estrogen use and cancer risk. *J Am Med Assoc*. 1977;237: 1112–1115.
211. Crandall CJ, Guan M, Laughlin GA, et al. Increases in Serum Estrone Sulfate Level Are Associated with Increased Mammographic Density during Menopausal Hormone Therapy. *Cancer Epidemiol Biomarkers Prev*. 2008;17:1674–1681.
212. File SE, Heard JE, Rymer J. Trough oestradiol levels associated with cognitive impairment in post-menopausal women after 10 years of oestradiol implants. *Psychopharmacology (Berl)*. 2002;161:107–112.
213. Maki PM. A systematic review of clinical trials of hormone therapy on cognitive function: effects of age at initiation and progestin use. *Ann N Y Acad Sci*. 2005;1052:182–197.
214. Prentice RL, Langer R, Stefanick ML, et al. Combined postmenopausal hormone therapy and cardiovascular disease: toward resolving the discrepancy between observational studies and the Women's Health Initiative clinical trial. *Am J Epidemiol*. 2005;162:404–414.
215. Krieger N, Lowy I, Aronowitz R, et al. Hormone replacement therapy, cancer, controversies, and women's health: historical, epidemiological, biological, clinical, and advocacy perspectives. *J Epidemiol Community Health*. 2005;59:740–748.
216. Barrett-Connor E, Laughlin GA. Endogenous and exogenous estrogen, cognitive function, and dementia in postmenopausal women: evidence from epidemiologic studies and clinical trials. *Semin Reprod Med*. 2009;27:275–282.
217. Laughlin GA, Kritz-Silverstein D, Barrett-Connor E. Endogenous oestrogens predict 4-year decline in verbal fluency in postmenopausal women: the Rancho Bernardo Study. *Clin Endocrinol (Oxf)*. 2010;72:99–106.
218. Henderson VW. Aging, estrogens, and episodic memory in women. *Cogn Behav Neurol*. 2009;22:205–214.
219. Sherwin BB. Estrogen and cognitive functioning in women. *Endocr Rev*. 2003;24:133–151.
220. Sherwin BB, Henry JF. Brain aging modulates the neuroprotective effects of estrogen on selective aspects of cognition in women: a critical review. *Front Neuroendocrinol*. 2008;29:88–113.
221. Knuuti J, Kalliokoski R, Janatuinen T, et al. Effect of estradiol-drospirenone hormone treatment on myocardial perfusion reserve in postmenopausal women with angina pectoris. *Am J Cardiol*. 2007;99:1648–1652.
222. Simpkins JW, Green PS, Gridley KE, Singh M, de Fiebre NC, Rajakumar G. Role of estrogen replacement therapy in memory enhancement and the prevention of neuronal loss associated with Alzheimer's disease. *Am J Med*. 1997;103:19S–25S.
223. Haynes LE, Lendon CL, Barber DJ, Mitchell IJ. 17 β-oestradiol attenuates dexamethasone-induced lethal and sublethal neuronal damage in the striatum and hippocampus. *Neuroscience*. 2003;120:799–806.
224. Arvin M, Fedorkova L, Disshon KA, Dluzen DE, Leipheimer RE. Estrogen modulates responses of striatal dopamine neurons to MPP(+): evaluations using in vitro and in vivo techniques. *Brain Res*. 2000;872:160–171.
225. vom Saal FS, Hughes C. An extensive new literature concenring low-dose effects of bisphenol A shows the need for a new risk assessment. *Environ Health Perspect*. 2005;113:926–933.
226. Greenspan FS, Gardner DG. Appendix: Normal Hormone Reference Ranges. In: Greenspan FS, Gardner DG, editors. *Basic and Clinical Endocrinology*. 7th ed. New York: Lange Medical Books, McGraw Hill; 2004;925–926.
227. Katzenellenbogen BS, Bhardwaj B, Fang H, et al. Hormone binding and transcription activation by estrogen receptors: analyses using mammalian and yeast systems. *J Steroid Biochem Mol Biol*. 1993;47: 39–48.