Endocrine, *vol. 28, no. 3, 235–241, December 2005* 0969–711X/05/28:235–241/$30.00

Estrogen Action in Mood and Neurodegenerative Disorders

Estrogenic Compounds with Selective Properties—The Next Generation of Therapeutics

Marie K. Österlund,[1] Michael-Robin Witt,[1] and Jan-Åke Gustafsson[2]

[1]Karo Bio AB, Novum, S-141 57 Huddinge, Sweden; and [2]Department of Medical Nutrition and Biosciences, Karolinska Institutet, SE-141 57, Huddinge, Sweden

In this review, estrogenic effects in depression, anxiety, and neurodegenerative disorders are summarized. Moreover, preclinical findings from in vitro and animal models are discussed. There is a correlation between decreased estrogen levels (e.g., premenstrually, during the postpartum period, and perimenopausally) and increased anxiety and depressive symptoms. Several studies show beneficial effects of estrogen treatment in women with anxiety and depressive symptoms. Recent data indicate that the estrogen receptor (ER) β appears to be a major mediator of estrogenic effects in depression and anxiety. Additionally, both preclinical and clinical findings suggest that activation of estrogen receptors have an important role in neuroprotective and neurodegenerative processes in the mammalian central nervous system (CNS).

Key Words: Estrogen receptor; depression; anxiety; Alzheimer's disease; neuroprotection; affective disorders; 17β-estradiol.

Introduction

In 1996, Kuiper et al. described the discovery of a second estrogen receptor ERβ *(1)*. Since then, it has become apparent that ERβ has many important physiological roles; for instance, it is antiproliferative in the ventral prostate of rodents *(2)*, it is important in follicular development in the ovary *(3)*, and it is important for normal development of the CNS *(4–6)*. This review addresses some of the properties of ERβ in the CNS and how ERβ might be targeted pharmaceutically in attempts to treat diseases of the CNS.

The Role of Estrogen in Affective and Anxiety Disorders

Clinical Observations

For more than a century, gonadal hormones have been reported to affect mood and neuropsychiatric disorders. However, how and when these hormones act appears to be complex and is not fully understood. In psychotic disorders, such as schizophrenia, estrogens overall appear to have a protective role. For example, with respect to this particular disease, women have been shown to have a higher age of onset, a milder symptomatology, and a better outcome than men *(7–9)*. In the case of anxiety and affective disorders, the role of estrogens is more ambiguous. Major depression is nearly twice as common in women as in men, with a lifetime prevalence of 21% in women as compared to 12.7% in men and the lifetime prevalence for any anxiety disorder is reported to be 30.5% in women versus 19.2% in men *(10, 11)*. Evidence is accumulating that hormonal fluctuations and drastic drops in estrogen levels increase the risk for experiencing anxiety and depressive symptoms and that some women appear to be more vulnerable to these changes than others. Premenstrual dysphoric disorders are clearly linked to the radical fall in estrogen levels in the late-luteal premenstrual phase of the menstrual cycle and women with premenstrual dysphoric disorders show high comorbidity with other mood disorders *(12)*.

Another time-period when there is a strong connection between hormonal fluctuations, including a drastic estrogen drop, and mood symptoms is in the postpartum period *(13)*. Milder mood lability is very common within a few days after delivery, the postpartum "blues" *(14)*. Postpartum depression, a subtype of major depression, is more severe than the "blues" and affects approx 10% of child-bearing women with an onset within a month after delivery; within a year, up to 20% are affected *(13,15,16)*. Moreover, pregnancy and postpartum influences on anxiety have also been described *(17)*. Several items point toward the fact that there is a subgroup in the female population that is more vulnerable to normal hormonal fluctuations than others. As in premenstrual dysphoric disorders, mood disorders are more common in women who experience postpartum depressive symptoms, and these symptoms are more common in women with a history of mood disorder *(18,19)*. Furthermore, women who have experienced postpartum depression have an increased risk of relapse during the postpartum period of future pregnancies *(20,21)*.

Another female life event that includes declining estrogen levels is in the transition to menopause, which occurs

Received June 20, 2005; Accepted July 13, 2005.

Author to whom all correspondence and reprint requests should be addressed: Dr. Jan-Åke Gustafsson, Department of Medical Nutrition and Biosciences, Karolinska Institutet, SE-141 57 Huddinge, Sweden. E-mail: jan-ake.gustafsson@mednut.ki.se

at a median age of 51 yr *(22)*. Women are three to four times more likely than men to develop major depression during midlife (45–55 yr) *(23,24)* and perimenopausal women report high rates of depressive symptoms *(25–27)*. Moreover, a history of mood disorders, such as postpartum depression, premenstrual dysphoric disorders, and depression, increases the risk of experiencing depression or depressive symptoms during the perimenopause *(19,28)*.

A large, longitudinal population-based birth cohort study in northern Finland reported an interesting association between high age of onset of menarche and depression during early adulthood *(29)*. They found that women with delayed menarche had two- to threefold greater risk of depression at the age of 31 yr. The authors speculate that the longer exposure of higher estrogen levels in women with early menarche could have a protective effect for depression later in life.

Effects of Estrogen Treatment on Anxiety and Affective Disorders

Several studies on the effects of estrogen treatment on mood disorders have been conducted and the outcome of these studies is varying (for reviews see refs. *28* and *30*). There is a limited number of studies where preventing or treating postpartum depression with estrogens have been examined *(31–33)*. All of them reported significant positive effects with estrogens.

Estrogen replacement therapy (ERT) has been used for many decades for treating menopausal symptoms and a number of different studies have been performed in order to examine the effects of estrogens on anxiety and depressive symptoms in peri- and postmenopausal women. As study designs, population groups, treatments, and diagnostic analyses are very heterogeneous among the different studies, it is difficult to obtain a conclusive answer of whether and when estrogens could be an effective treatment. Some of the methodological shortcomings consist in the inclusion of women of various ages and with different degrees of mood disturbances. Moreover, some studies are based on hormone replacement therapy (HRT) where estrogen treatment is combined with progestins, which may have opposite effects to those of estrogens. Some studies show lack of efficacy on depressive symptoms with ERT *(34–36)*. However, it appears that ERT most likely improves well-being and mood in non-depressed subjects *(37–40)*. Most of the studies also find improved ratings with estrogens for milder forms of depression. However, ERT appears to be less effective in major depression, although some studies have also shown significant effects of estrogen in this disease category in perimenopausal women *(41,42)*.

After the report in June 2002 *(43)* of increased risks for breast cancer and cardiovascular disease in women treated with estrogen and progestin in the Women's Health Initiative Study, many women abruptly discontinued HRT. A smaller study found that women with a long history of depression who had been in remission, began to have reemergence of their depressive symptoms shortly after they stopped hormone therapy *(44)*. Altogether, many studies show positive effects of estrogens on well-being, depressive symptoms, and anxiety. However, the findings in the Women's Health Initiative Study indicate the need for safer estrogen therapy, separating the many beneficial effects from the undesired side effects.

ERβ-Selective Estrogen Receptor Agonists—The Next Generation of Chemotherapeutics in Affective and Anxiety Disorders?

As mentioned above, a second estrogen receptor ERβ was discovered in the mid-1990s *(1)*. The major natural estrogen 17β-estradiol binds both receptor subtypes, ERα and ERβ, with a similar high affinity. Although the tissue distribution of the two ERs to some degree overlaps, their distribution patterns are in general distinct *(45–47)*. During the recent decade intense research has been conducted to define the respective physiological roles of the two ER subtypes. This has been performed by analyzing the anatomical distribution of the ERs, studying ERα and ERβ knockout mice, and using ER-subtype selective ligands. Many of the undesired side effects of estrogen therapy, such as proliferative effects in uterus and mammary gland, appear to be mediated through ERα *(48,49)*, rendering ERβ a very attractive drug target.

Recently, several articles have been published indicating that ERβ plays an important role in depression and anxiety. In a study by Walf and co-workers *(50)*, vehicle, 17β-estradiol, or ER subtype selective agonists were administered acutely to female ovariectomized rats prior to behavioral testing. 17β-Estradiol and the ERβ-selective agonist diarylpropionitrile (DPN) *(51)*, but not the ERα-selective agonist propyl pyrazole triol (PPT) *(52)*, showed antidepressant-like effects (reduced immobility) in the forced swim test, an animal model of depression. Moreover, another study has shown that 17β-estradiol has antidepressant-like effects in different strains of mice in the forced swim test, but not in mice lacking the ERβ *(53)*. Taken together, this indicates that ERβ is the major ER subtype in mediating the antidepressant effects of estrogens. Estrogens have been shown to regulate several components of the serotonergic system *(54–58)*, promoting serotonergic neurotransmission. The serotonergic system is strongly implied in the etiology of depression and is the target for the majority of the antidepressant drugs available today. Estrogen has been shown to regulate the expression of the rate-limiting enzyme in serotonin synthesis, tryptophan hydroxylase (TPH) *(54,56)*. A recent publication *(59)* showed that the estrogenic effect on the expression levels of TPH1 is very likely to be mediated by ERβ. Estrogen increased TPH1 expression in the dorsal raphe nuclei (DRN) of wild-type and ERα knockout mice but not of ERβ knockout mice. Moreover, ERβ and TPH were shown to be co-localized in the serotonergic cells

in the DRN. In line with this study, another publication *(60)* also found co-localization of ERβ and TPH in the mouse DRN (>90% of the ERβ expressing cells). Furthermore, *in situ* hybridization histochemistry technology revealed a significant reduction of TPH (the probe was designed from the TPH1 sequence) mRNA in the DRN of the ERβ knockout mice as compared to the wild-type mice, whereas the TPH mRNA levels where not affected in the ERα knockout mice.

A novel tryptophan hydroxylase isoform (TPH2) was identified a few years ago *(61)* and found to be highly expressed in the central nervous system. A recent publication regarding estrogen regulation of this gene observed no significant changes in TPH2 mRNA levels in mouse DRN after 4 d (once daily) of 17β-estradiol dosing *(62)*. However, in experiments from our own laboratory, significant dose-dependent upregulation of TPH2 mRNA in mouse DRN was found after 2 d (once daily) of 17β-estradiol dosing (unpublished results). In addition, Sanchez and co-workers found an upregulation of both TPH1 and TPH2 mRNA in DRN of macaqes after 1 mo of estradiol, or estradiol and progesterone treatment *(63)*. New tools have opened new possibilities and future tasks in this area will be to delineate the ER subtype-selective mechanisms in neurotransmitter systems relevant for affective disorders and to correlate them with results obtained in behavior models.

ERβ has also been proposed to mediate the anxiolytic effects of estrogens. There are two studies that have shown behavior consistent with increased anxiety in female mice lacking a functional ERβ *(64,65)*. This behavior was also associated with a reduced threshold for the induction of synaptic plasticity (measured by electrophysiology) in the basolateral amygdala (a region relevant for anxiety) *(64)*. In addition, the serotonergic system was altered in the amygdala of the ERβ knockout mice, i.e., a significant increase in 5-HT_{1A} receptor immunoreactivity was found. Also in the study by Imwalle et al. *(65)*, changes in monoamine systems were found in ERβ knockout mice. A reduced level of both serotonin and dopamine was observed in discrete areas of the brain of ERβ knockout mice. Furthermore, in rats, the ERβ-selective agonist DPN has been shown to have anxiolytic properties *(49)*. Ovariectomized rats treated with DPN showed significantly reduced anxiety-related behavior in the elevated plus maze and the open field test. The effects were blocked by co-administering the nonselective ER antagonist tamoxifen; thus, the anxiolytic effects of DPN appear to be ERβ-specific. In contrast, the ERα-selective agonist PPT increased anxiogenic behavior. Anxiolytic effects of DPN were also observed in gonadectomized male rats; thus, the anxiolytic properties of the ERβ agonist are not gender specific.

Although the number of studies published on ER subtype-selective effects related to depression and anxiety are limited, so far, all the results point in one direction: ERβ is the major mediator of these effects.

The Role of Estrogen in Neuroprotection and Neurodegeneration

The preclinical evidence linking estrogen to both neuroprotective and antineurodegenerative effects in the mammalian brain is overwhelming *(66)*. A number of clinical studies suggest an involvement of the sex hormones in the etiology of major neurodegenerative disorders such as Alzheimer's disease (AD) *(67)*, multiple sclerosis *(68)*, and Parkinson's disease *(69)*. There is also a strong gender dependence observed in the epidemiology of these disorders *(70)*. Additionally, there is evidence that estrogen as well as androgen may have beneficial effects on neurodegeneration following stroke as well as following experimental spinal cord injury *(71,72)*. In view of the lack of available therapies for any of these disorders and the wealth of preclinical, clinical, as well as epidemiological data on the neuroprotective effects of estrogens, either in form of postmenopausal ERT or, in conjunction with progestin, in HRT, the estrogen signaling system is an attractive target for drug discovery of compounds with neuroprotective properties (for reviews see refs. *73* and *74*).

Preclinical Findings

The trophic effects of estrogen on neuronal growth and differentiation are developmentally regulated and are believed to be most prominent in the growing phases of the CNS. However, trophic effects on, for example, neurite outgrowth and differentiation reappear following the cessation of estrogen trophic support such as after ovariectomy *(75)*.

The traditional and well-described mechanisms of action of estrogen in the mammalian brain are thought to occur through the activation of target gene expression following the binding of 17β-estradiol to the two prominent estrogen receptor subtypes in the brain. Although the repression or induction of target gene expression through ligand-activated ERα or ERβ requires minutes to manifest, the neuroprotective effects of 17β-estradiol in vitro can be observed immediately, suggesting a "non-genomic" mode of action via plasma membrane–bound receptors and activation of the MAPK/ERK pathways *(76)*. Recently, a putative, plasma membrane–bound, 17α-estradiol binding ER receptor, ER-X, has been postulated *(77,78)*. In a series of in vitro experiments, 17α-estradiol and 17β-estradiol have been shown to be equally neuroprotective, suggesting that activation of the ER-X receptor could be particularly relevant for neuroprotection and perhaps AD. Indeed, there is evidence that the neuroprotective effects of estrogens might be dependent on the structural properties of the ligand rather than on the specific ER receptor subtype activated. The structure–activity relationship between a series of steroids and their neuroprotective properties suggests that it is the phenolic A ring of the steroid core structure and not the binding properties *per se* that determine the neuroprotectant profile *(79)*. Furthermore, the estrogen receptor antagonist ICI 182,780

has been shown to be neuroprotective in vitro and the selective estrogen modulator (SERM) tamoxifen has been shown to be neuroprotective against stroke *(80,81)*.

Owing to the multifactorial nature of both neuroprotective and neurodegenerative processes, any form of activation of the estrogen system through (a) genomic ER receptor activation, (b) non-genomic ER-receptor–mediated effects, or (c) non-genomic, non-ER–mediated effects, may contribute to the final outcome *(82)*.

All of these three ER activation mechanisms have been implicated in the mechanism of action of antioxidative, antiapoptotic and anti-inflammatory properties of ER ligands.

Antioxidative Properties

Oxidative stress, an imbalance between the endogenous antioxidant defense and reactive oxygen species (ROS) leading to protein and DNA damage, lipid peroxidation, and, ultimately, neuronal death, has been implicated in the neurodegenerative processes of AD *(83,84)*. The CNS is rich in unsaturated fatty acids, which are particularly susceptible to ROS attack. Estrogen has been shown to have direct antioxidant properties in hippocampal neurons in vitro *(85)* and blocks the generation of hydrogen peroxide directly. The modulation of calcium influx through L-type calcium channels *(86,87)* might inhibit the activation of calcium-dependent phospholipases and lead to a reduction of free-radical generation from the arachidonic acid pathway *(88)*. Clinically, substantial gender differences in the degree of lipid peroxidation have been shown in patients with traumatic brain injury (TBI) *(89)*. Furthermore, since ROS play a role in the pathophysiology of spinal cord injury (SCI), a relatively common disease (30 cases/million), for which no pharmacotherapeutic approach exists, estrogens could be of particular relevance in case of this affection *(90)*.

Antiapoptotic Properties

Estrogen has been shown to reduce apoptosis in cortical neurons in primary culture, as well as to attenuate the apoptotic cell death in an animal stroke model in vivo *(91,92)*. The latter finding is presumed to be due to an ERα-mediated upregulation of the antiapoptotic protein BcL-2, that is, a classical, genomic, receptor-mediated mechanism *(93)*. In contrast, the antiapoptotic effects of estrogen in hydrogen peroxide–induced apoptosis in endothelial cells and the glutamate-induced apoptotic cell death in neurons were reported to be estrogen receptor independent *(85)*. Furthermore, estrogen has been shown to attenuate ethanol-induced apoptosis of neurons in vitro as well as in vivo, and this neuroprotective activity is correlated with the attenuation of protein kinase C ε isozyme (PKC ε) activity *(94)*. These effects illustrate how estrogen may give a biological effect through different mechanisms.

Anti-inflammatory Properties

Estrogen attenuates the inflammatory component of neurodegeneration through the reduction of neuroinflammatory mediators, in particular the IL-1 β–mediated cycooxygenase-2 pathway *(95,96)*. Furthermore, 17β-estradiol, acting through ERα, protects against the development and reduces the severity of experimental allergic encephalitis (an animal model for multiple sclerosis) through a reduction of T-cell activation *(97)*. The nuclear factor NFκB mediates both inflammatory as well as immune responses and can have both neuroprotective as well as neurotoxic effects, depending on the experimental setting *(98,99)*. Following oxidative stress, the activation, subsequent translocation into the nucleus, and the formation of NFκB–DNA complexes mediate hypoxic injury *(100)*. Some of the neuroprotective effects of estrogen might be mediated through the inhibition of NFκB translocation by upregulation of the IκBα protein, which inhibits NFκB translocation to the nucleus and DNA binding. However, an inhibition of inflammatory gene expression in macrophages, independent of IκBα protein regulation, has recently been described *(101)*. Furthermore, estrogen has been shown to block toxin-induced NFκB translocation in glial cells *(102)*. The neuroprotective effects of estrogen have been shown to be both ER-receptor dependent *(103)* and ER-receptor independent *(104)*. One important aspect of the antiinflammatory properties of estrogen is the attenuation of the inflammatory response to beta-amyloid peptide, of potential clinical relevance in AD *(70)*. Additionally, estrogens have been shown to reduce the generation of amyloid peptides in neurons *(105)* in vitro as well as to increase the uptake of amyloid beta protein into microglial cells derived from human tissue *(106–108)*.

Clinical Findings

17β-Estradiol, in a number of studies, has been shown to have positive effects on cognition in healthy postmenopausal women. Kugaya et al. *(109)* have shown that treatment with 17β-estradiol improves verbal fluency and divided attention, and Duka et al. *(110)* have shown that memory and non-verbal reasoning are improved. 17β-Estradiol also improves verbal memory *(111)*.

In line with the findings with 17β-estradiol, estradiol valerate has been shown to improve verbal memory and abstract verbal reasoning *(74,112,113)*. More recent studies have shown that estradiol valerate enhances subjective well being and benefits sleep and selected cognitive abilities, including concentration and attention *(114)*.

Thus, although there are a number of studies which suggest that estrogen may have positive effects on cognition, there are also studies implying that the opposite may be true, that is, that estrogen is detrimental to cognition, as shown in the Women's Health Initiative (WHI) and Women's Health Initiative Memory Study (WHMS) *(43,115–118)*. Although these investigations have provided invaluable insight into the consequences of use of conjugated equine estrogen (CEE) for postmenopausal women's health, a number of factors limit generalizations from these studies on the use of estrogens in the treatment of age-related diseases such as demen-

tia. Most problematic is the rather high age (average of 63 yr) in the Prempro group as well as a probable, underlying cardiovascular disease and high occurrence of obesity in this group, possibly masking the potentially beneficial effects of estrogen treatment *(82,119)*.

Treatment with oral CEE, Prempro, for a period of 5 yr or more, increased the risk for coronary heart disease, stroke, breast cancer, and dementia in older women *(116,118)*. Similarly, extended therapy with Premarin increases the risk of stroke *(115)*. It should be noted, however, that Prempro and Premarin are commonly used hormone replacement therapies *(120)* consisting of estrone and a number of unidentified hormones *(121,122)*, while the main hormone in menstruating women is 17β-estradiol, which is released cyclically in pre-menopause as opposed to the high-steady-state hormone levels achieved during Prempro and Permarin treatment.

There are a few studies suggesting that there may be cognitive benefits of estrogen treatment in women with Alzheimer's disease. Honjo et al. *(123)* have shown that CEEs reduce cognitive impairment in women with senile dementia. Asthana et al. *(124,125)* have shown that 17β-estradiol treatment enhances selective attention and verbal and visual memory in women with Alzheimer's disease. Interestingly, all clinical studies using 17β-estradiol or estradiol valerate have shown positive cognitive effects, whereas studies using CEEs showed no benefit or contradictory results. The same trend is apparent when looking at the therapeutic potential of estrogen treatment in postmenopausal women with dementia in that it is the treatment with 17β-estradiol and not the treatment with CEEs that shows conclusive or strong beneficial effects *(126)*.

The differences in the findings in the clinical studies can be explained by a number of factors: (a) *Co-administration of progestin* (medroxiprogesterone is a component of Prempro). Although it is unknown if the synthetic forms of progestin have the same biological effects as progesterone, it cannot be excluded that these compounds may interfere with the beneficial cognitive effects achieved with estrogen alone. (b) *Levels of sex hormone binding globulin (SHBG)*. High levels of SHBG, which are found in Alzheimer's patients, may reduce the bioavailable, free form of estradiol. (c) *Route of HRT administration*. It has been shown that high doses of transdermal estradiol but not oral conjugated estrogen enhanced cognitive function in postmenopausal women. (d) *Timing of HRT*. It has been suggested that there is a critical time frame shortly after the start of menopause, during which initiation of HRT exerts its most beneficial effects *(127)* and beyond which the positive cognitive effects are lost.

Taking all these factors into account, the WHI findings should stimulate the development of hormonal treatments that more faithfully resemble the biological processes in women.

In conclusion, the vast amount of data from basic research, the multiple modes of neuroprotective action mediated by the ER system, the large number of positive data seen in a variety of in vivo as well as in vitro models of neurodegeneration and neuroprotection in conjunction with the beneficial effects observed in most of the clinical studies suggest that the ER system in the CNS will be a priority target for the development of pharmacological agents for the treatment of neurodegenerative disorders, also in the future.

Conclusion

Taken together, estrogens show many positive effects in mood disorders and neurodegeneration and neuroprotection. However, the estrogenic therapy available today is blunt and targets all ERs, thereby also generating undesired side effects. The estrogenic drugs of tomorrow will most likely have more selective properties, e.g., be ER-isoform-specific. Neuropsychiatric disorders occur in high frequency and result in personal suffering and high costs for society. There is an urgent need for new therapies with alternative mechanistic routes for these diseases.

References

1. Kuiper, G. G., Enmark, E., Pelto-Huikko, M., Nilsson, S., and Gustafsson, J.-A. (1996). *Proc. Natl. Acad. Sci. USA* **93(12),** 5925–5930.
2. Imamov, O., Morani, A., Shim, G. J., Omoto, Y., Thulin-Andersson, C., Warner, M., and Gustafsson, J.-A. (2004). *Proc. Natl. Acad. Sci. USA* **101(25),** 9375–9380.
3. Cheng, G., Weihua, Z., Makinen, S., et al. (2002). *Biol. Reprod.* **66(1),** 77–84.
4. Wang, L., Andersson, S., Warner, M., and Gustafsson, J.-A. (2001). *Proc. Natl. Acad. Sci. USA* **98(5),** 2792–2796.
5. Wang, L., Andersson, S., Warner, M., and Gustafsson, J.-A. (2002). *Sci.* STKE **2002(138),** PE29.
6. Wang, L., Andersson, S., Warner, M., and Gustafsson, J.-A. (2003). *Proc. Natl. Acad. Sci. USA* **100(2),** 703–708.
7. Riecher-Rossler, A. and Hafner, H. (1993). *Eur. Arch. Psychiatry Clin. Neurosci.* **242(6),** 323–328.
8. Seeman, M. V. (1996). *J. Psychiatry Neurosci.* **21(2),** 123–127.
9. Grigoriadis, S. and Seeman, M. V. (2002). *Can. J. Psychiatry* **47(5),** 437–442.
10. Weissman, M. M., Bland, R., Joyce, P. R., Newman, S., Wells, J. E., and Wittchen, H. U. (1993). *J. Affect. Disord.* **29(2–3),** 77–84.
11. Kessler, R. C., McGonagle, K. A., Zhao, S., et al. (1994). *Arch. Gen. Psychiatry* **51(1),** 8–19.
12. Yonkers, K. A. (1997). *J. Clin. Psychiatry* **58(Suppl. 15),** 19–25.
13. Hendrick, V., Altshuler, L. L., and Suri, R. (1998). *Psychosomatics* **39(2),** 93–101.
14. Gale, S. and Harlow, B. L. (2003). *J. Psychosom. Obstet. Gynaecol.* **24(4),** 257–266.
15. Campbell, S. B. and Cohn, J. F. (1991). *J. Abnorm. Psychol.* **100(4),** 594–599.
16. Robinson, G. E. and Stewart, D. E. (1986). *CMAJ* **134(1),** 31–37.
17. Pigott, T. A. (1999). *J. Clin. Psychiatry* **60(Suppl. 18),** 4–15.
18. Kumar, R. and Robson, K. M. (1984). *Br. J. Psychiatry* **144,** 35–47.
19. Payne, J. L. (2003). *Int. Rev. Psychiatry* **15(3),** 280–290.
20. Cox, J. L., Murray, D., and Chapman, G. (1993). *Br. J. Psychiatry* **163,** 27–31.
21. Cooper, P. J., Campbell, E. A., Day, A., Kennerley, H., and Bond, A. (1988). *Br. J. Psychiatry* **152,** 799–806.

22. McKinlay, S. M., Brambilla, D. J., and Posner, J. G. (1992). *Maturitas* **14(2),** 103–115.
23. Kessler, R. C., McGonagle, K. A., Swartz, M., Blazer, D. G., and Nelson, C. B. (1993). *J. Affect. Disord.* **29(2–3),** 85–96.
24. Schmidt, P. J., Roca, C. A., Bloch, M., and Rubinow, D. R. (1997). *Semin. Reprod. Endocrinol.* **15(1),** 91–100.
25. Hay, A. G., Bancroft, J., and Johnstone, E. C. (1994). *Br. J. Psychiatry* **164(4),** 513–516.
26. Stewart, D. E., Boydell, K., Derzko, C., and Marshall, V. (1992). *Int. J. Psychiatry Med.* **22(3),** 213–220.
27. Schmidt, P. J., Haq, N., and Rubinow, D. R. (2004). *Am. J. Psychiatry* **161(12),** 2238–2244.
28. Grigoriadis, S. and Kennedy, S. H. (2002). *Am. J. Ther.* **9(6),** 503–509.
29. Herva, A., Jokelainen, J., Pouta, A., et al. (2004). *J. Psychosom. Res.* **57(4),** 359–362.
30. Epperson, C. N., Wisner, K. L., and Yamamoto, B. (1999). *Psychosom. Med.* **61(5),** 676–697.
31. Gregoire, A. J., Kumar, R., Everitt, B., Henderson, A. F., and Studd, J. W. (1996). *Lancet* **347(9006),** 930–933.
32. Ahokas, A., Kaukoranta, J., Wahlbeck, K., and Aito, M. (2001). *J. Clin. Psychiatry* **62(5),** 332–336.
33. Sichel, D. A., Cohen, L. S., Robertson, L. M., Ruttenberg, A., and Rosenbaum, J. F. (1995). *Biol. Psychiatry* **38(12),** 814–818.
34. Strickler, R. C., Borth, R., Cecutti, A., et al. (1977). *Psychol. Med.* **7(4),** 631–639.
35. Morrison, M. F., Kallan, M. J., Ten Have, T., Katz, I., Tweedy, K., and Battistini, M. (2004). *Biol. Psychiatry* **55(4),** 406–412.
36. Hays, J., Ockene, J. K., Brunner, R. L., et al. (2003). *N. Engl. J. Med.* **348(19),** 1839–1854.
37. Whooley, M. A., Grady, D., and Cauley, J. A. (2000). *J. Gen. Intern. Med.* **15(8),** 535–541.
38. Palinkas, L. A. and Barrett-Connor, E. (1992). *Obstet. Gynecol.* **80(1),** 30–36.
39. Hlatky, M. A., Boothroyd, D., Vittinghoff, E., Sharp, P., and Whooley, M. A. (2002). *JAMA* **287(5),** 591–597.
40. Schiff, R., Bulpitt, C. J., Wesnes, K. A. and Rajkumar, C. (2005). *Psychoneuroendocrinology* **30(4),** 309–315.
41. Schmidt, P. J., Nieman, L., Danaceau, M. A., et al. (2000). *Am. J. Obstet. Gynecol.* **183(2),** 414–420.
42. Soares, C. N., Almeida, O. P., Joffe, H., and Cohen, L. S. (2001). *Arch. Gen. Psychiatry* **58(6),** 529–534.
43. Rossouw, J. E., Anderson, G. L., Prentice, R. L., et al. (2002). *JAMA* **288(3),** 321–333.
44. Stewart, D. E., Rolfe, D. E., and Robertson, E. (2004). *Psychosomatics* **45(5),** 445–447.
45. Couse, J. F., Lindzey, J., Grandien, K., Gustafsson, J.-A., and Korach, K. S. (1997). *Endocrinology* **138(11),** 4613–4621.
46. Kuiper, G., Carlsson, G., Grandien, B., et al. (1997). *Endocrinology* **138(3),** 863–870.
47. Osterlund, M. K., Gustafsson, J.-A., Keller, E., and Hurd, Y. L. (2000). *J. Clin. Endocrinol. Metab.* **85(10),** 3840–3846.
48. Harris, H. A., Katzenellenbogen, J. A., and Katzenellenbogen, B. S. (2002). *Endocrinology* **143(11),** 4172–4177.
49. Lund, T. D., Rovis, T., Chung, W. C., and Handa, R. J. (2005). *Endocrinology* **146(2),** 797–807.
50. Walf, A. A., Rhodes, M. E., and Frye, C. A. (2004). *Pharmacol. Biochem. Behav.* **78(3),** 523–529.
51. Meyers, M. J., Sun, J., Carlson, K. E., Marriner, G. A., Katzenellenbogen, B. S., and Katzenellenbogen, J. A. (2001). *J. Med. Chem.* **44(24),** 4230–4251.
52. Stauffer, S. R., Coletta, C. J., Tedesco, R., et al. (2000). *J. Med. Chem.* **43(26),** 4934–4947.
53. Rocha, B. A., Fleischer, R., Schaeffer, J. M., Rohrer, S. P., and Hickey, G. J. (2005). *Psychopharmacology (Berl.)* **179(3),** 637–643.
54. Bethea, C. L., Mirkes, S. J., Shively, C. A., and Adams, M. R. (2000). *Biol. Psychiatry* **47(6),** 562–576.
55. Fink, G., Sumner, B. E., Rosie, R., Grace, O., and Quinn, J. P. (1996). *Cell. Mol. Neurobiol.* **16(3),** 325–344.
56. Lu, N. Z., Shlaes, T. A., Gundlah, C., Dziennis, S. E., Lyle, R. E., and Bethea, C. L. (1999). *Endocrine* **11(3),** 257–267.
57. Osterlund, M. K., Halldin, C., and Hurd, Y. L. (2000). *Synapse* **35(1),** 39–44.
58. Osterlund, M. K. and Hurd, Y. L. (1998). *Brain Res. Mol. Brain Res.* **55(1),** 169–172.
59. Gundlah, C., Alves, S. E., Clark, J. A., Pai, L. Y., Schaeffer, J. M., and Rohrer, S. P. (2005). *Biol. Psychiatry* **57(8),** 938–942.
60. Nomura, M., Akama, K. T., Alves, S. E., et al. (2005). *Neuroscience* **130(2),** 445–456.
61. Walther, D. J., Peter, J. U., Bashammakh, S., et al. (2003). *Science* **299(5603),** 76.
62. Clark, J. A., Pai, L. Y., Flick, R. B., and Rohrer, S. P. (2005). *Biol. Psychiatry* **57(8),** 943–946.
63. Sanchez, R. L., Reddy, A. P., Centeno, M. L., Henderson, J. A., and Bethea, C. L. (2005). *Brain Res. Mol. Brain Res.* **135(1–2),** 194–203.
64. Krezel, W., Dupont, S., Krust, A., Chambon, P., and Chapman, P. F. (2001). *Proc. Natl. Acad. Sci. USA* **98(21),** 12278–12282.
65. Imwalle, D. B., Gustafsson, J.-A., and Rissman, E. F. (2005). *Physiol. Behav.* **84(1),** 157–163.
66. Lee, S. J. and McEwen, B. S. (2001). *Ann. Rev. Pharmacol. Toxicol.* **41,** 569–591.
67. Selkoe, D. J. and Schenk, D. (2003). *Ann. Rev. Pharmacol. Toxicol.* **43,** 545–584.
68. Roth, M. P., Clayton, J., Patois, E., and Alperovitch, A. (1994). *Neuroepidemiology* **13,** 211–215.
69. Saunders-Pullman, R., Gordon-Elliott, J., Parides, M., Fahn, S., Saunders, H. R., and Bressman, S. (1999). *Neurology* **52(7),** 1417–1421.
70. Atwood, C. S. (2005). *Cell. Mol. Life Sci.* **62(3),** 255–256.
71. Alkayed, N. J., Harukuni, I., Kimes, A. S., London, E. D., Traystman, R. J., and Hurn, P. D. (1998). *Stroke* **29(1),** 159–165; discussion 166.
72. Culmsee, C., Vedder, H., Ravati, A., et al. (1999). *J. Cereb. Blood Flow Metab.* **19(11),** 1263–1269.
73. McEwen, B. (2002). *Recent Prog. Horm. Res.* **57,** 357–384.
74. Sherwin, B. B. (2003). *J. Mol. Neurosci.* **20(3),** 385–393.
75. Matsumoto, A. and Arai, Y. (1981). *J. Comp. Neurol.* **197(2),** 197–205.
76. Singh, M., Setalo, G. Jr., Guan, X., Warren, M., and Toran-Allerand, C. D. (1999). *J. Neurosci.* **19(4),** 1179–1188.
77. Toran-Allerand, C. D. (2004). *Endocrinology* **145(3),** 1069–1074.
78. Toran-Allerand, C. D., Guan, X., MacLusky, N. J., et al. (2002). *J. Neurosci.* **22(19),** 8391–8401.
79. Green, P. S., Yang, S. H., and Simpkins, J. W. (2000). *Novartis Found Symp.* **230,** 202–213.
80. Marin, R., Guerra, B., Morales, A., Diaz, M., and Alonso, R. (2003). *Ann. NY Acad. Sci.* **1007,** 108–116.
81. Krishnan, K., Campbell, S., Abdel-Rahman, F., Whaley, S., and Stone, W. L. (2003). *Curr. Drug Targets* **4(1),** 45–54.
82. Simpkins, J. W., Yang, S. H., Wen, Y., and Singh, M. (2005). *Cell. Mol. Life Sci.* **62(3),** 271–280.
83. Behl, C. and Moosmann, B. (2002). *Biol. Chem.* **383(3–4),** 521–536.
84. Rao, A. V. and Balachandran, B. (2002). *Nutr. Neurosci.* **5(5),** 291–309.
85. Behl, C., Widmann, M., Trapp, T., and Holsboer, F. (1995). *Biochem. Biophys. Res. Commun.* **216(2),** 473–482.
86. Chaban, V. V., Mayer, E. A., Ennes, H. S., and Micevych, P. E. (2003). *Neuroscience* **118(4),** 941–948.

87. Mermelstein, P. G., Becker, J. B., and Surmeier, D. J. (1996). *J. Neurosci.* **16(2),** 595–604.
88. Lewen, A., Matz, P., and Chan, P. H. (2000). *J. Neurotrauma* **17(10),** 871–890.
89. Bayir, H., Marion, D. W., Puccio, A. M., et al. (2004). *J. Neurotrauma* **21(1),** 1–8.
90. Sekhon, L. H. and Fehlings, M. G. (2001). *Spine* **26(24 Suppl.),** S2–12.
91. Singer, C. A., Figueroa-Masot, X. A., Batchelor, R. H., and Dorsa, D. M. (1999). *J. Neurosci.* **19(7),** 2455–2463.
92. Jover, T., Tanaka, H., Calderone, A., et al. (2002). *J. Neurosci.* **22(6),** 2115–2124.
93. Koski, C. L., Hila, S., and Hoffman, G. E. (2004). *Endocrinology* **145(1),** 95–103.
94. Jung, Y. S., Lee, B. K., Park, H. S., et al. (2005). *Neuroreport* **16(7),** 741–744.
95. Ospina, J. A., Brevig, H. N., Krause, D. N., and Duckles, S. P. (2004). *Am. J. Physiol. Heart Circ. Physiol.* **286(5),** H2010–H2019.
96. Vegeto, E., Belcredito, S., Etteri, S., et al. (2003). *Proc. Natl. Acad. Sci. USA* **100(16),** 9614–9619.
97. Polanczyk, M., Zamora, A., Subramanian, S., et al. (2003). *Am. J. Pathol.* **163(4),** 1599–1605.
98. Fridmacher, V., Kaltschmidt, B., Goudeau, B., et al. (2003). *J. Neurosci.* **23(28),** 9403–9408.
99. Castagne, V., Lefevre, K., and Clarke, P. G. (2001). *Neuroscience* **108(3),** 517–526.
100. O'Neill, L. A. and Kaltschmidt, C. (1997). *Trends Neurosci.* **20,** 252–258.
101. Ghisletti, S., Meda, C., Maggi, A., and Vegeto, E. (2005). *Mol. Cell. Biol.* **25(8),** 2957–2968.
102. Dodel, R. C., Du, Y., Bales, K. R., Gao, F., and Paul, S. M. (1999). *J. Neurochem.* **73(4),** 1453–1460.
103. Harnish, D. C., Scicchitano, M. S., Adelman, S. J., Lyttle, C. R., and Karathanasis, S. K. (2000). *Endocrinology* **141,** 3403–3411.
104. Speir, E., Yu, Z. X., Takeda, K., Ferrans, V. J., and Cannon, R. O. 3rd (2000). *Circulation* **102(24),** 2990–2996.
105. Jaffe, A. B., Toran-Allerand, C. D., Greengard, P., and Gandy, S. E. (1994). *J. Biol. Chem.* **269(18),** 13,065–13,068.
106. Greenfield, J. P., Leung, L. W., Cai, D., et al. (2002). *J. Biol. Chem.* **277(14),** 12128–12136.
107. Li, R., Shen, Y., Yang, L. B., Lue, L. F., Finch, C., and Rogers, J. (2000). *J. Neurochem.* **75(4),** 1447–1454.
108. Xu, H., Gouras, G. K., Greenfield, J. P., et al. (1998). *Nat. Med.* **4(4),** 447–451.
109. Kugaya, A., Epperson, C. N., Zoghbi, S., et al. (2003). *Am. J. Psychiatry* **160(8),** 1522–1524.
110. Duka, T., Tasker, R., and McGowan, J. F. (2000). *Psychopharmacology (Berl.)* **149(2),** 129–139.
111. Hogervorst, E., Boshuisen, M., Riedel, W., Willeken, C., and Jolles, J. (1999). *Psychoneuroendocrinology* **24(1),** 43–68.
112. Sherwin, B. B. (1988). *Psychoneuroendocrinology* **13(4),** 345–357.
113. Phillips, S. M. and Sherwin, B. B. (1992). *Psychoneuroendocrinology* **17(5),** 485–495.
114. Saletu, B. (2003). *Climacteric* **6(Suppl. 2),** 37–45.
115. Anderson, G. L., Limacher, M., Assaf, A. R., et al. (2004). *JAMA* **291(14),** 1701–1712.
116. Lacey, J. V. Jr., Mink, P. J., Lubin, J. H., et al. (2002). *JAMA* **288(3),** 334–341.
117. Rapp, S. R., Espeland, M. A., Shumaker, S. A., et al. (2003). *JAMA* **289(20),** 2663–2672.
118. Shumaker, S. A., Legault, C., Rapp, S. R., et al. (2003). *JAMA* **289(20),** 2651–2662.
119. Wise, P. M., Dubal, D. B., Rau, S. W., Brown, C. M., and Suzuki, S. (2005). *Endocr. Rev.* **26,** 308–312.
120. Hersh, A. L., Stefanick, M. L., and Stafford, R. S. (2004). *JAMA* **291(1),** 47–53.
121. Bhavnani, B. R. (2003). *J. Steroid Biochem. Mol. Biol.* **85 (2–5),** 473–482.
122. Bhavnani, B. R., Nisker, J. A., Martin, J., Aletebi, F., Watson, L., and Milne, J. K. (2000). *J. Soc. Gynecol. Investig.* **7(3),** 175–183.
123. Honjo, H., Ogino, Y., Tanaka, K., Urabe, M., Kashiwagi, T., and Ishihara, S. (1993). *J. Jap. Mneop. Soc.* **1,** 167–171.
124. Asthana, S., Craft, S., Baker, L. D., et al. (1999). *Psychoneuroendocrinology* **24(6),** 657–677.
125. Asthana, S., Baker, L. D., Craft, S., et al. (2001). *Neurology* **57(4),** 605–612.
126. Gleason, C. E., Cholerton, B., Carlsson, C. M., Johnson, S. C., and Asthana, S. (2005). *Cell. Mol. Life Sci.* **62(3),** 299–312.
127. Resnick, S. M. and Maki, P. M. (2001). *Ann. NY Acad. Sci.* **949,** 203–214.