Effect of Estrogen-Serotonin Interactions on Mood and Cognition

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Both the neurotransmitter serotonin and the ovarian steroid estrogen have been implicated in the modulation of mood and cognition. Although significant functional interactions between estrogen and serotonin are acknowledged, the nature of their relationship has not been fully elucidated. Research using ovariectomized animals has identified estrogen-induced changes in serotonin transmission, binding, and metabolism in brain regions implicated in the regulation of affect and cognition. Studies in humans, particularly of menopausal women undergoing estrogen treatment, have provided some support for these findings and identified instances in which change in mood or cognition is accompanied by alterations in serotonin function and hormonal status. However, it is apparent that further research is required to understand the neural processes involved in the interplay between estrogen and serotonin. By reviewing animal and human data regarding estrogen and serotonin’s effects on mood and cognition, the authors aim to better define their relationship and highlight areas for further research.

Key Words: estrogen, serotonin, mood, cognition

In recent years, a number of laboratories have focused on estrogen’s role in nonreproductive behavior, such as the modulation of cognition and mood. Research in animals has demonstrated that estrogen can act as a neuroprotectant during brain injury, can regulate cellular events through involvement in second messenger systems, and has a broad distribution of receptors throughout the brain (see the review in McEwen, 2001). Studies in humans have suggested improved mood and possibly cognition. The mechanism of estrogen’s effects is still being elucidated, but the hormone is known to modulate a number of neurotransmitters implicated in the regulation of cognition and affect, including acetylcholine, serotonin, dopamine, and norepinephrine. Many researchers have postulated a unique and significant relationship between estrogen and serotonin (Archer, 1999; Bethea, Gundlah, & Mirkes, 2000; Bethea, Pecins-Thompson, Schutzer, Gundlah, & Lu, 1998; Huttner & Shepherd, 2003; Joffe & Cohen, 1998; Rubinow, Schmidt, & Roca, 1998). Given that serotonin has been most frequently implicated in the regulation of mood, is a prime target for the pharmacologic treatment of depression, and has a recognized influence on cognition, we have chosen to examine estrogen-serotonin interactions to facilitate our understanding of estrogen’s effects on these nonreproductive behaviors. This analysis is important in the delineation of current knowledge in basic neuroscience but is also critical in understanding the impact of ovarian hormones on women’s health.

Activational effects (as opposed to organizational or developmental effects) of gonadal steroids have been implicated in sex differences and in fluctuations in mood and cognition across the female reproductive life cycle (Halbreich, Lemus, Lieberman, Parry, & Schiavi, 1990; McEwen, Alves, Bulloch, & Weiland, 1998). Across the menstrual cycle and during major hormonal changes across life, such as during pregnancy, after childbirth, and during menopause, there are significant changes in mood as well as cognitive processing that suggest an estrogenic influence in both domains (Buckwalter, Buckwalter, Bluestein, & Stanczyk, 2001; Burt & Stein, 2002; Sherwin, 2003). Elucidating the effects of cyclic and dramatic hormonal fluctuation is essential in identifying issues specific to women’s health and quality of life.

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In addition, the Women’s Health Initiative (WHI), a recent large randomized trial of a common oral estrogen plus progestin regimen, has engendered some apprehension of the use of hormone therapy (HT) during menopause with the controversial finding that long-term HT could increase the risk of dementia (Shumaker et al., 2003). The older age of the population tested, the type of estrogen used (conjugated equine estrogen), and other aspects of the study have since been criticized as biasing the WHI results, but such findings highlight the importance of understanding estrogen’s effects on the central nervous system to better inform the use of HT in menopausal women.

Many studies of estrogen’s effects in the brain have been conducted in rodents and nonhuman primates, but there is a growing neuroscientific literature that explores its ability to modulate nonreproductive behavior in humans. An examination of the accordance or divergence between animal and human studies is an important step in understanding estrogen’s impact on mood and cognition. In addition, by identifying strengths and weaknesses in study design and measures used, as well as highlighting potential areas for research, we endeavor to guide future investigation in this area.

After an overview of serotonin and estrogen’s individual effects on mood and cognition, we will discuss data on their interactive effects. Physiological and behavioral data from animals involving brain regions important to affect and cognition are followed by a discussion of research on premenopausal women, menopausal women, and hormone-related mood disorders.

**OVERVIEW OF SEROTONIN REGULATION OF MOOD AND COGNITION**

**Serotonin and Mood**

Serotonin neuronal cell bodies are located in the raphe nuclei of the midbrain and have diverse projections throughout the brain, including regions implicated in emotion regulation and cognition such as the hippocampus, limbic system, and frontal cortex (Meneses, 1999). Various serotonin receptors including the 5-HT₁A, 5-HT₂A, 5-HT₂C, 5-HT₅A, and 5-HT₄ are associated with emotion regulation through pathways in limbic structures such as the amygdala, cingulate gyrus, and hippocampus (Barnes & Sharp, 1999). For example, 5-HT₂C antagonists are anxiolytic, and 5-HT₄ receptors have been associated with cognitive function through their modulation of acetylcholine release in the cortex and hippocampus (Barnes & Sharp, 1999).

In humans, memory has repeatedly been shown to be impaired by tryptophan (TRP) depletion, a manipulation that results in rapid reduction of brain TRP and serotonin levels (McAllister-Williams, Massey, & Rugg, 2002; Park et al., 1994; Schmitt et al., 2000). Other studies have found response inhibition, decision making, and processing of reward cues to be disrupted by TRP depletion (Murphy, Smith, Cowen, Robbins, & Sahakian, 2002; Park et al., 1994; Rogers et al., 1999; Rogers et al., 2003). Thus, it is hypothesized that cognitive processing mediated by temporal lobe memory structures and the orbitofrontal cortex is most affected by TRP depletion. In addition, Alzheimer’s disease is associated with reduction in brain serotonin as well as acetylcholine, and serotonergic drugs have been shown to improve cognition in Alzheimer’s patients, although it is possible that cognitive improvement is secondary to enhancement of mood or other effect (Meneses, 1999). Similarly, serotonergic drugs have resulted in improved cognition in depressed patients. For example, when comparing memory performance in depressed patients’ pretreatment and posttreatment with either an SSRI (fluoxetine) or selective noradrenergic tricyclic (desipramine), memory was significantly improved with the SSRI (Levkovitz, Caftori, Avital, & Richter-Levin, 2002). However, both treatments were equally effective in treating depression, suggesting serotonin’s distinct effects on memory as well as the overlap between its cognitive and affective influence (Levkovitz et al., 2002).
OVERVIEW OF ESTROGEN MODULATION OF COGNITION AND MOOD

17β-estradiol is the most potent of the female sex hormones known collectively as estrogens. The only estrogen receptors (ERs) in the brain that have been cloned, ERα and ERβ, are classical nuclear receptors that act by altering gene expression and are thus said to have genomic actions. These actions are likely to have a slower time course and longer duration than nongenomic actions, which do not directly affect gene transcription. According to a small number of postmortem studies, ERα mRNA is most common in the amygdala, hypothalamus, and cortex with some evident in the hippocampus, whereas ERβ mRNA is abundant in the cortex, hippocampus, entorhinal cortex, and certain thalamic nuclei (Ostlund, Keller, & Hurd, 2003). Similarly, in rats and mice, mRNA and protein of both ERs are found throughout the brain, including cortical and limbic regions important for affect and cognition (Merchenthaler, Lane, Numan, & Dellovade, 2004; Mitra et al., 2003; Shughrue, Lane, & Merchenthaler, 1997; Shughrue & Merchenthaler, 2001; Simerly, Chang, Muramatsu, & Swanson, 1990). Interestingly, animal studies suggest that the amygdala, a structure involved in emotion and memory, has one of the highest densities of ERs in the brain (Merchenthaler et al., 2004; Mitra et al., 2003; Shughrue et al., 1997; Shughrue & Merchenthaler, 2001). Although recent studies suggest nongenomic estrogen actions through membrane (instead of nuclear) receptors in the brain, these receptors have yet to be purified or cloned (Beyer, Pawlak, & Karolczak, 2003).

Estrogen and Cognition

Neuroprotective role. Through gene transcription (e.g., of antiapoptotic genes or neurotrophic factors) as well as its direct molecular interaction with signal transduction pathways and its ability to scavenge free radicals, estrogen has protective functions relevant to illnesses such as stroke, Alzheimer’s disease, and Parkinson’s disease (Behl, 2002; Dhandapani & Brann, 2002). In vitro evidence shows that estrogen protects cultured cells from various neurotoxic insults and suggests that estrogen promotes neurogenesis through promoting transcription of nerve growth factor and structural proteins in neurons (Behl, 2002). In vivo evidence is also supportive of estrogen’s protective role and has suggested that the ERs may differ in their importance for neuroprotection. For example, when ERα knockout, ERβ knockout, and wild-type mice were ovariectomized and implanted with physiological levels of estradiol or vehicle and compared with regard to recovery following ischemia, there were differences between the knockout mice (Dubal et al., 2001). ERα knockouts and animals not treated with estradiol showed increased damage compared to those treated with estradiol, which suggests that ERα is a required receptor for neuroprotective effects following brain injury (Dubal et al., 2001).

Estrogen effects in brain regions critical to cognitive function. Because of estrogen’s neuroprotective properties, multiple animal and human studies have investigated its influence on cognition. In female rats, the density of dendritic spines on pyramidal cells in the CA1 region of the hippocampus, a structure critical for learning and memory, is known to fluctuate across the 5-day estrous cycle (Shors, Chua, & Falduto, 2001; Woolley, Gould, Frankfurt, & McEwen, 1990; Woolley & McEwen, 1992). In addition, ovariectomy decreases dendritic spine density in these cells, whereas treatment with estradiol can prevent or reverse this decrease, possibly through an NMDA receptor–mediated mechanism (Gould, Woolley, Frankfurt, & McEwen, 1990; Segal & Murphy, 2001; Woolley & McEwen, 1993, 1994). Although it is unclear how these morphological changes affect cognition or behavior, a recent study in mice showed that estradiol treatment resulted in maturation of CA1 dendritic spines and improved spatial episodic memory (Li et al., 2004).

The rat estrous cycle has also been found to modulate dendritic spine density in the medial nucleus of the amygdala, although this effect is less studied (Rasia-Filho, Fabian, Rigoti, & Achaval, 2004). Similarly, ovariectomized rhesus monkeys treated with estrogen showed increased spine density in the prefrontal cortex but not primary visual cortex (Tang et al., 2004). In support of estrogen’s cognitive effects through these morphological changes, another study found that cyclic estrogen replacement improved performance on a prefrontal cortex–dependent task in aged rhesus monkeys (Rapp, Morrison, & Roberts, 2003).

Estrogen and cognitive task performance. In both humans and animals, estrogen is thought to improve certain forms of learning but to interfere with others (Fitch & Bimonte, 2002; Kimura & Hampson, 1994; Sherwin, 2003). For example, studies in women have found that increased estrogen during normal hormonal fluctuations interferes with spatial processing in the mental rotation task while it enhances verbal memory (Hausmann, Slabbe-Koom, Van Goosen, Cohen-Kenten, & Gunturkun, 2000; Maki, Rich, & Rosenbaum, 2002; Rosenberg & Park, 2002). Similarly, when comparing gonadectomized, estradiol- or vehicle-treated mice that were either ERα knockout or wild type, only the wild-type females treated with estradiol were unable to learn spatial discrimination in the Morris water maze,
although their cue discrimination was intact (Fugger, Cunningham, Rissman, & Foster, 1998).

Because of estrogen’s neuroprotective functions and ability to improve certain cognitive processes, the efficacy of HT (progesterone is usually added to estrogen therapy [ET] regimens to prevent endometrial hyperplasia) for hindering age-related decline in menopausal women has been widely investigated in randomized and observational studies. Reviews and meta-analyses suggest a positive, albeit modest, effect of HT on verbal memory, attention, and reasoning and associate it with a decreased risk of dementia (e.g., Hogervorst, Williams, Budge, Riedel, & Jolles, 2000; Rice & Morse, 2003). However, most reports also cite methodological problems with many studies and highlight difficulties in comparing results across the different cognitive tests, types of hormone treatments, and routes of administration that have been used. Some meta-analyses suggest that mainly hormone treatments, and routes of administration that may be interneurons (Alves, Weiland, Hayashi, & MacKinnon, 1980; Vitale & Chiocchio, 1993). As discussed above, serotonin and estrogen have overlapping spheres of influence beyond reproduction, extending to mood and cognition.

**ANIMAL STUDIES**

**Estrogen and Serotonin Interactions**

Interactions between estrogen and serotonin have long been acknowledged with regard to reproductive behaviors. Serotonin modulates sexual behavior, with data suggesting inhibition or facilitation based on which receptor subtypes are activated (Meston & Gorzalka, 1992). The preovulatory surge in luteinizing hormone (LH), caused by positive feedback exerted by estrogen, is thought to be mediated by serotonin (Morello & Taleisnik, 1985; Vitale, Villar, Chiocchio, & Tramezzani, 1987). In the presence of estrogen, serotonin elicits LH secretion and ovulation, whereas it can have the opposite effect in estrogen’s absence (Coen, Franklin, Laynes, & MacKinnon, 1980; Vitale & Chiocchio, 1993). As discussed above, serotonin and estrogen have overlapping spheres of influence beyond reproduction, extending to mood and cognition.

**Estrogen Receptor and Serotonin Neuron Colocalization.** Animal studies provide the most direct connections between estrogen and serotonin physiology (see also reviews in Bethea et al., 1998; Bethea et al., 2000; Bethea, Lu, Gundlah, & Streicher, 2002; Rubinow et al., 1998), but findings have differed based on the animal studied. For instance, studies in macaques have shown the existence of ERβ mRNA and protein in serotonin neurons (Gundlah, Lu, Mirkes, & Bethea, 2001). Immunocytochemical localization in the mouse and rat brain also found ERβ-labeled (and some ERα-labeled) cells in neurons of the raphe nuclei, although ERα-labeled cells are not necessarily the same as serotonin-releasing cells and may be interneurons (Alves, Weiland, Hayashi, & McEwen, 1998; Mitra et al., 2003). Another study did find that at least some serotonergic neurons of the dorsal
Table 1: Summary of Animal Studies Involving Ovariectomy: Effect of Estrogen Treatment on the Serotonin System

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Effect</th>
<th>Treatment</th>
<th>Animal</th>
<th>Examples of Regions Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT turnover*</td>
<td>↑</td>
<td>Acute</td>
<td>Rat</td>
<td>Dorsal raphe, amygdala</td>
</tr>
<tr>
<td>5-HT synthesis/releaseβ</td>
<td>↓</td>
<td>Chronic</td>
<td>Rat/macaque</td>
<td>Dorsal raphe</td>
</tr>
<tr>
<td>Serotonin transporter bindingα</td>
<td>↑</td>
<td>Acute/chronic</td>
<td>Rat/macaque</td>
<td>Basolateral amygdala, frontal cortex, some thalamic nuclei</td>
</tr>
<tr>
<td>Monoamine oxidase activity/mRNAβ</td>
<td>↓</td>
<td>Acute/chronic</td>
<td>Rat/macaque</td>
<td>Amygdala, dorsal raphe</td>
</tr>
<tr>
<td>5-HT2A binding/mRNAε</td>
<td>↑</td>
<td>Acute/chronic</td>
<td>Rat</td>
<td>Cortex, dorsal raphe</td>
</tr>
<tr>
<td>5-HT1A binding/mRNAβ</td>
<td>↓</td>
<td>Acute/chronic</td>
<td>Rat/macaque</td>
<td>Cortex, limbic areas, dorsal raphe</td>
</tr>
</tbody>
</table>

c. Fink, Summer, McQueen, Wilson, and Rosie (1998); Lu, Eshleman, Janowsky, and Bethea (2003); Summer et al. (1999).
e. Cyr, Bosse, and Di Paolo (1998); Fink and Summer (1996); Fink, Summer, Rosie, Wilson, and McQueen (1999); Summer and Fink (1993, 1995); Summer et al. (1999).

Ovariectomy express ERβ in rats (H. Lu, Ozawa, Nishi, Ito, & Kawata, 2001), supporting the general assumption that ERβ is more closely associated with regulating the serotonin system than ERα (Merchenthaler et al., 2004).

Ovariectomy and estrogen treatment studies. Few studies have investigated estrogen-serotonin interactions in intact animals. Correlational research on the estrous cycle has found conflicting results regarding the relationship between concentrations of estrogen and serotonin in various regions of the brain (Fludder & Tonge, 1975; Greengrass & Tonge, 1971; Gundlah, Simon, & Auerbach, 1998; S. Maswood, Truitt, Hotema, Caldarola-Pastuszka, & Uphouse, 1999), perhaps because of the confound of other hormones, such as progesterone. Studies that evaluate the ability of estrogen to regulate serotonin through ovariectomy followed by estrogen treatment have found less ambiguous results (see Table 1), although it cannot be presumed that these effects take place in normally cycling animals.

In general, acute estradiol administration in ovariectomized rats increases serotonin and its metabolite 5-HIAA in various brain regions, including the dorsal raphe, striatum, medial preoptic nuclei, and ventromedial and cortical amygdaloid nuclei, suggesting increased 5-HT turnover in these areas (Di Paolo, Diagle, Picard, & Barden, 1983; Johnson & Crowley, 1983; Morissette, Levesque, Belanger, & Di Paolo, 1990; Munaro, 1978; Tonge & Greengrass, 1971). Chronic estradiol or estradiol and progesterone administration were also found to increase 5-HT levels and accumulation rate (estimated by administering the monoamine oxidase inhibitor pargyline shortly before death) in the dorsal raphe of ovariectomized rats (Cones, Davis, & Goy, 1981). This possible stimulation of 5-HT synthesis is supported by a primate study that found that estrogen administration induces gene expression of TRP hydroxylase (the rate-limiting enzyme in serotonin synthesis) in ovariectomized macaques (Pecins-Thompson, Brown, Kohama, & Bethea, 1996).

In addition to estrogen’s involvement in serotonin synthesis, studies have established a relationship between estrogen and the serotonin transporter (SERT), which is responsible for reuptake. Studies in rats by Fink, Summer, McQueen, Wilson, and Rosie (1998) have shown that acute estradiol administration following ovariectomy increases SERT mRNA in the dorsal raphe nucleus and the density of SERT sites (tested through paroxetine binding) in regions such as the basolateral amygdala and lateral septum of the limbic system. Tamoxifen, an ERβ antagonist, blocked estradiol’s increase of SERT mRNA and binding, which suggests ERβ involvement in this process (Summer et al., 1999).

Depending on the measure used (mRNA or binding) or treatment schedule (chronic or acute), there often appear to be conflicting results regarding estrogen effects. Two studies of recovered ovariectomized rats and macaques have suggested a decrease in SERT mRNA in the midbrain raphe nuclei after chronic estradiol treatment (Pecins-Thompson, Brown, & Bethea, 1998; Zhou et al., 2002). However, a decrease in mRNA does not necessarily reflect a decrease in function because SERT protein is available as long as it binds 5-HT but is phosphorylated when inactive (Ramamoorthy & Blakely, 1999). Considering the evidence that estradiol promotes serotonin synthesis and release, it is possible that chronic estradiol treatment eventually results in downregulation of SERT due to the greater availability of 5-HT (N. Z. Lu, Eshleman, Janowsky, & Bethea, 2003). Further research is necessary to determine at which point estrogen exerts direct or indirect influence.

Although facilitation of serotonin release seems at odds with facilitation of its reuptake, the data suggest that estrogen has an overall stimulatory effect on seroto-
nucleus and 5-HT2A receptor binding in the frontal cortex is also well studied. In contrast to the 5-HT2A receptor, several studies have found that acute and chronic estradiol treatment of ovariectomized rats decreased levels of 5-HT1A receptor mRNA and binding in regions such as the amygdala, hippocampus, and cortex (Biegon & McEwen, 1982; Biegon, Reches, Snyder, & McEwen, 1983; Osterlund, Haldin, & Hurd, 2000; Osterlund & Hurd, 1998). Similarly, in ovariectomized macaques, 5-HT1A mRNA in the dorsal raphe (which would affect autoreceptors) was found to decrease with estrogen or progesterone treatment (Pecins-Thompson & Bethea, 1999). In another study, however, ovariectomized rats orally treated with estradiol did not differ on 5-HT1A binding or mRNA in the hippocampus, prefrontal cortex, cingulate cortex, and the dorsal raphe nucleus (Landry & Di Paolo, 2005). The use of oral treatment and the resulting difference in hormone metabolism may explain the disparate finding in this case, which underscores the importance of routes of administration in both animal and human studies.

Functional effects of estrogen on the serotonin system and serotonin-mediated effects. Although studying mRNA levels is useful in understanding estrogen’s effects on gene transcription, changes in receptor function are possible apart from (or as a later consequence of) changes in mRNA or binding and form a critical area for further research. Several studies have investigated estrogen-agonist effects in this context (Table 2). Studies of 5-HT1A receptor function have suggested that, through unidentified mechanisms, estrogen causes sensitization of postsynaptic 5-HT1A receptors in the hippocampus (Clarke & Goldfarb, 1989; Clarke & Maayani, 1990) but desensitization of presynaptic 5-HT1A receptors in the dorsal raphe (Lakoski, 1988). Another study found that estrogen facilitated 5-HT1A-mediated acetylcholine release in the frontal cortex, suggesting that estrogen effects on cognition may be through its agonistic effects on 5-HT1A receptors (Matsuda, Hirano, & Watanabe, 2002). Although there is evidence that acute estrogen administration can cause a rapid, short-term decrease in 5-HT1A receptor activity in the frontal cortex and hippocampus (Mize & Alper, 2000; Mize, Poisner, & Alper, 2001), the time course of the effects (resensitization within 3 hours) and the use of supraphysiological levels of estradiol (Mize et al., 2001) make the application of these findings to normal function uncertain.

Based on several studies in rats, there is a well-known association between estrogen and hippocampal morphology (Gould et al., 1990; Segal & Murphy, 2001; Woolley & McEwen, 1993, 1994). Serotonin may also play a role in estrogen’s effects in the hippocampus and on cognition, but research in this area is sparse. One recent study found that estrogen administration exclusively to the median raphe resulted in increased dendritic spine density in the CA1 region of the dorsal hippocampus, which showed that serotonin could mediate...
estrogen’s effects (Prange-Kiel, Rune, & Leranth, 2004). However, another study found that estrogen administration was able to increase spine density in the absence of serotonergic transmission (Alves et al., 2002). In a contrasting situation, adult neurogenesis in the rat hippocampus was shown to require serotonin but to involve estrogen, suggesting that serotonin mediates estrogen’s actions (Banasr, Hery, Brezun, & Daszuta, 2001). The pathways through which estrogen and serotonin exert their effects on hippocampal morphology appear to be linked, although each has an independent effect.

Summary of physiological data. Most studies involving ovariectomy followed by controlled estradiol administration (usually through injection or implant) have found associations between estrogen and serotonin function in brain regions related to mood and cognition. However, measurements of levels of serotonin and its metabolites across the estrous cycle have yielded contradictory and inconclusive results, challenging the relevance of these data to intact animals. The majority of papers evaluate binding or mRNA of serotonin receptors, SERT, or other related proteins. Analysis of receptor function, such as the finding that estrogen can enhance postsynaptic 5-HT_{1A} responses relevant to cognition or prevent autoinhibition through presynaptic 5-HT_{1A} receptors (Beck, Clarke, & Goldfarb, 1989; Clarke & Maayani, 1990; Lakoski, 1988; Matsuda et al., 2002), provides more detailed information about estrogen’s effects and should be useful in understanding how estrogen influences mood and cognition. Although the functions of ERα and ERβ are not always delineated, ERβ appears to be more involved in serotonin regulation, such as in its effect on SERT and 5-HT_{2A} (Sumner et al., 1999).

Behavioral Data

Understanding how these physiological interactions affect behavior is necessary to distinguish the impact of estrogen-serotonin interactions. Several animal studies have tested estrogen’s ability to modulate behaviors that are known to be serotonin dependent, but few have provided evidence of interactive effects on mood or cognition. For example, female rats have more pronounced serotonin behavioral syndrome (symptoms include tremor, hindlimb abduction, and forepaw treading) in response to serotonin pharmacological challenges than do male rats, although this may be more of an effect of testosterone in males than of female gonadal hormones (Biegon, Segal, & Samuel, 1979; Carlsson, Svensson, Eriksson, & Carlsson, 1985; Fischette, Biegon, & McEwen, 1984). In contrast, a behavioral study of chronic estradiol treatment in ovariectomized rats found that estradiol decreased the hyperphagia caused by 8-OH-DPAT (a 5-HT_{1A} agonist), suggesting a decrease in presynaptic receptor activation (N. Maswood & Uphouse, 1997), which is consistent with a previous electrophysiological study (Lakoski, 1988).

A study of transgenic mice succeeded in showing a relationship between estrogen, serotonin receptor function, affective influence, and changes in electrophysiology when comparing ERα knockouts, ERβ knockouts, and wild-type mice (Krezel, Dupont, Krust, Chambron, & Chapman, 2001). In females, there was increased anxiety in ERβ mutants according to the open field test and elevated plus maze, whereas the rotarod test of motor function showed no differences (Krezel et al., 2001). According to electrophysiological stimulation of the amygdala and hippocampus, these mice also showed reduced threshold for induction of synaptic plasticity in the basolateral amygdala (Krezel et al., 2001). In addition, there was a local increase in 5-HT_{1A} receptor expression in the medial amygdala but not in an adjacent control region (Krezel et al., 2001). These findings suggest that ERβ dysfunction results in changes in emotional behavior, increased amygdala sensitivity, and increased 5-HT_{1A} receptor expression in the amygdala.
Although various tests of memory have been used to examine animal cognition, few studies have attempted to link estrogen and serotonin effects. As mentioned previously, estrogen has been shown to interfere with spatial learning in the mental rotation task in humans and the Morris water maze in animals, possibly through the ERα receptor (Frye, 1995; Fugger et al., 1998; Hausmann et al., 2000; Maki et al., 2002; Rosenberg & Park, 2002). A study of working and reference memory found a possible relationship between estrogen, serotonin, and performance (Heikkinen, Puolivali, Liu, Rissanen, & Tanila, 2002). Ovariectomized mice implanted with estradiol pellets had increased performance on radial arm and T-maze, and intact and male mice also showed improved radial arm performance with estrogen treatment (Heikkinen et al., 2002). In addition, hippocampal choline acetyltransferase (ChAT, necessary for the synthesis of acetylcholine) and 5-HIAA levels were decreased in ovariectomized mice (Heikkinen et al., 2002). However, there was no significant relationship between neurochemical measures and learning, so the study only showed improved cognition only with estrogen treatment and correlations between hippocampal 5-HT, 5-HIAA, and ChAT and estrogen (Heikkinen et al., 2002).

Few behavioral studies have attempted to link estrogen and serotonin effects on mood and cognition. However, several studies support findings from physiological experiments as well as human studies investigating estrogen and serotonin. Estrogen treatment resulted in improved memory performance along with changes in serotonin regulation (Heikkinen et al., 2002), which is consistent with previous studies finding increased serotonin turnover with estrogen treatment (Di Paolo et al., 1983; Johnson & Crowley, 1983; Morissette et al., 1990; Munaro, 1978) and modest improvements in cognition in humans (Hogervorst et al., 2000). Behavioral response consistent with decreased 5-HT1A autoreceptor activation was also found (N. Maswood & Uphouse, 1997), as in a previous electrophysiological study (Lakoski, 1988). Anxiety symptoms increased in ERβ knockout mice, along with amygdala response and 5-HT1A receptor expression (Krezel et al., 2001). This maintains ERβ involvement in serotonin regulation and supports its importance in emotional processing. On the other hand, ERα may be more important in estrogen’s effects on cognition (Fugger et al., 1998). Sex differences in behavioral response to serotonin were also identified, although estrogen’s effects cannot be isolated (Biegon et al., 1979; Carlsson et al., 1985; Fischette et al., 1984).

**HUMAN STUDIES**

**Healthy Premenopausal Women: Sex Differences and Menstrual Fluctuation**

Human sex differences relating to serotonin as well as changes in serotonin function across the menstrual cycle have shown how estrogen-serotonin interactions found in animal studies may relate to humans. For example, in a positron emission tomography (PET) study involving 8 men and 7 women who had undergone TRP depletion, the rate of serotonin synthesis in women was more affected by TRP depletion than in men (Nishizawa et al., 1997). The baseline rate of synthesis throughout the brain was significantly higher in men than in women, and although TRP depletion decreased the rate of serotonin synthesis in all participants, the effect on women was significantly greater (Nishizawa et al., 1997). Another study of 20 women found that TRP depletion resulted in significant worsening of mood, although data from men had shown no significant change (Ellenbogen, Young, Dean, Palmour, & Benkelfat, 1996). This suggests that women are also more susceptible to the mood effects of TRP depletion than men. However, as with the animal studies on serotonin behavioral syndrome, it is impossible to isolate estrogen’s influence.

As previously discussed, negative mood and exacerbation of psychiatric illness has been associated with phases of declining or low ovarian hormones across the menstrual cycle (Collins et al., 1985; Hendrick et al., 1996). However, a relationship to serotonin activity has been more difficult to establish. Several studies have indirectly tested the effects of menstrual cycle phase on serotonin function, but these have generally relied on peripheral measures of serotonin function and had few participants, methodological problems, and conflicting findings.

Although two platelet studies found decreased serotonin uptake and content during phases of high estrogen (D’Andrea, Hasselmark, Cananzi, & Alleci, 1995; Tam, Chan, & Lee, 1985), a phase lag or other indirect relationship is likely between serotonin activity and hormonal changes, rendering the data uninterpretable. Plasma serotonin measures have not yielded more definitive results, perhaps because platelet-poor plasma levels of serotonin are low and difficult to measure. Although one study suggested that serotonin activity is greater during phases of higher estrogen levels (Hindberg & Naesh, 1992), another study found platelet-poor plasma serotonin levels to be lowest during the estrogen peak at ovulation (Blum et al., 1992).

Most human studies have had to use peripheral measures and have had inconclusive findings, but it is gener-
ally agreed that decreased levels of estrogen result in decreased serotonin activity as suggested in animal studies. In an experiment more directly related to central nervous system serotonin function, prolactin (PRL) release from the anterior pituitary in response to fenfluramine, a 5-HT–releasing agent, was used as a marker of central 5-HT responsiveness across the menstrual cycle (O’Keane, O’Hanlon, Webb, & Dinan, 1991). In this placebo-controlled study, fenfluramine elicited the greatest PRL response at midcycle during the highest estrogen levels and least response in the early follicular phase during least estrogen (O’Keane et al., 1991). It is possible that estrogen has effects on PRL unrelated to serotonin, but basal PRL levels were unchanged across the cycle (O’Keane et al., 1991). A blunted PRL response to fenfluramine is a marker for depression and may also relate to increased menstrual and premenstrual negative mood (O’Keane et al., 1991).

Studies in healthy premenopausal women have provided some conflicting results about the relationship between estrogen and serotonin. As with correlational estrous cycle studies (Fludder & Tonge, 1975; Greengrass & Tonge, 1971; Gundlah et al., 1998; S. Maswood et al., 1999), most menstrual cycle studies have also had inconsistent findings, particularly because they are required to use indirect measurements of central serotonin function (Blum et al., 1992; D’Andrea et al., 1995; Hindberg & Naesh, 1992; Tam et al., 1985). Some results are similar to animal data, however. Women were found to be more sensitive to TRP depletion than were men (Ellenbogen et al., 1996; Nishizawa et al., 1997), just as female rats are more sensitive to serotonin behavioral syndrome than are males (Biegon et al., 1979; Carlsson et al., 1985; Fischette et al., 1984). Although some studies have attempted to relate menstrual mood fluctuations with serotonin activity (Tam et al., 1985), little research has focused on how serotonin may influence the cognitive changes observed across the menstrual cycle (Hausmann et al., 2000; Maki et al., 2002; Rosenberg & Park, 2002).

**Menopause and HT**

The effect of estrogen-serotonin interactions on mood and cognition in humans is most evident in studies of menopause and hormone treatment. Estrogen appears to be useful in treating perimenopausal (Schmidt et al., 2000; Soares et al., 2001) but not postmenopausal (Morrison et al., 2004) depression, and there is evidence that ET enhances cognition in women undergoing surgical menopause (Sherwin, 1990) and can protect against dementia when used early in the menopause transition (Zandi et al., 2002). As previously mentioned, reviews and meta-analyses suggest a small positive effect of HT on verbal memory, attention, and reasoning (Hogervorst et al., 2000; LeBlanc et al., 2001; Rice & Morse, 2003). Several studies have suggested that the improvements in mood and cognition resulting from HT are also affecting the serotonin system, although there are inconsistencies (see Table 3).

For example, PRL and cortisol response to the 5-HT 2A/2C agonist meta-chlorophenylpiperazine (m-CPP) were blunted in menopausal women compared to premenopausal women but increased following ET (Halbreich et al., 1995). However, the effect was not significant after controlling for basal PRL secretion, suggesting that estrogen-induced PRL secretion unrelated to serotonergic activity was involved. In addition, a study of leuprolide-induced ovarian suppression and “addback” hormone treatment found m-CPP-stimulated PRL secretion in response to progesterone but not estrogen treatment, highlighting the importance of studying estrogen and progesterone effects independently (Schmidt, Raju, Danaceau, Murphy, & Berlin, 2002). In response to fenfluramine challenge, however, PRL response was blunted in postmenopausal women compared to young women and postmenopausal women on long-term ET, supporting estrogen effects (van Amelsvoort et al., 2001). In another study, urinary 5-HIAA excretion increased in women after 4 weeks of transdermal and oral ET, suggesting greater serotonin turnover (Lippert, Filshie, Muck, Seeger, & Zwirner, 1996). In a double-blind crossover study of ET in surgically menopausal women, improved mood and increased platelet imipramine binding were found compared to placebo (Sherwin & Suranyi-Cadotte, 1990), although a similar study found no change in platelet paroxetine binding (Wihlback et al., 2001).

As in animal studies, a relationship between 5-HT 2A binding and estrogen treatment is also apparent. Although a study of platelet binding showed no effects of HT despite improved mood effects (Wihlback et al., 2001), PET studies have found increased cortical binding similar to that in rat studies (Cyr et al., 1998; Fink & Sumner, 1996; Sumner & Fink, 1995; Sumner et al., 1999). In one study, 10 women underwent PET measurement of 5-HT 2A binding before and after ET via transdermal patch (Kugaya et al., 2003). Receptor binding was significantly increased in the right prefrontal cortex, inferior frontal gyrus, medial frontal gyrus, and anterior cingulate, and receptor upregulation in the inferior frontal gyrus correlated with the change in plasma estradiol (Kugaya et al., 2003). In addition, verbal fluency and trail-making test performance were significantly improved by estrogen, although the improvements did not correlate with receptor changes (Kugaya et al., 2003). A similar study investigated 5-HT 2A binding before and after use of a transdermal ET patch as well as a transdermal estrogen plus progesterone patch (Moses-
As in the other study, estrogen treatment resulted in increased binding potential in cortical regions such as the superior frontal gyrus, ventrolateral prefrontal cortex, inferior parietal lobe, and temporal pole (Moses-Kolko et al., 2003). A greater number of regions were affected following use of the estrogen plus progesterone patch, suggesting synergistic effects of the 2 hormone treatments (Moses-Kolko et al., 2003).

Studies of ET and HT effects on postmenopausal women suggest increased serotonin activity, improved mood, and improved cognitive performance (Halbreich et al., 1995; Hogervorst et al., 2000; LeBlanc et al., 2001; Lippert et al., 1996; Rice & Morse, 2003; Sherwin & Suranyi-Cadotte, 1990; van Amelsvoort et al., 2001). However, the links between them are not frequently studied, and there are only a few cases in which changes in serotonin activity are found coincident with mood or cognitive changes (Kugaya et al., 2003; Sherwin & Suranyi-Cadotte, 1990). PET studies confirm the finding in animals that estrogen treatment results in increased 5-HT2A receptor binding in frontal cortical regions (Kugaya et al., 2003; Moses-Kolko et al., 2003), although the mechanism and implication of the change are yet unknown.

### Hormone-Related Mood Disorders and Depression

Although studies of ET and HT in menopausal women have found the most data regarding interactions with serotonin and effects on mood and cognition, most research on estrogen-serotonin interactions in women has focused on depression and hormone-related mood disorders. Reproductive events, such as certain phases of the menstrual cycle, hormone withdrawal in the postpartum period, and the perimenopausal transition, are often associated with depression in women, and SSRIs are often the most effective treatments used in these situations (Altshuler, 2002; Rapkin et al., 2002). Patients with premenstrual dysphoric disorder (PMDD), postpartum depression, and perimenopausal depression respond well to SSRIs, and there is some evidence to suggest that estrogen treatment is also effective (Ahokas et al., 2001; Ditkoff, Crary, Cristo, & Lobo, 1991; Epperson, Wisner, & Yamamoto, 1999; Gregoire et al., 1996; Halbreich & Kahn, 2001; Sherwin, 1988). Others suggest that the inclusion of estrogen in a treatment strategy may improve efficacy of traditional antidepressant medications such as SSRIs (Birkhauser, 2002; Huttner & Shepherd, 2003; Sloan & Kornstein, 2003). Although one study supports this hypothesis (Schneider, Small, & Clary, 2001), the data were confounded by a differential placebo response between those receiving and those not taking HT. In addition, another study found no significant difference in fluoxetine efficacy in women on and off HT (Amsterdam et al., 1999).

Nevertheless, there is evidence to suggest that estrogen-serotonin interactions are involved in hormone-related mood disorders such as PMDD and perimenopausal depression (for review, see Rubinow et al., 1998). Joffe and Cohen (1998) proposed that even depression that is not directly related to extreme hormonal change is significantly affected by estrogen-serotonin interactions, perhaps by a preexisting vulnerability that is exacerbated by cyclic hormonal fluctuations. Similarly, some suggest that PMDD is an extreme example of how variations in serotonin transmission across the menstrual cycle can have marked effect on women who are prone to depression (Bancroft, 1995), although others propose that the disorder is a manifestation of dysregulation caused by hypersensitivity and impaired adaptation to hormonal change, probably

### Table 3: Human Studies of Postmenopausal Women: Effect of Estrogen Treatment on Serotonin Function

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Paradigm</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Amelsvoort et al. (2001)</td>
<td>33</td>
<td>Fenfluramine challenge</td>
<td>Blunted PRL response in nonusers compared to users and young women</td>
</tr>
<tr>
<td>Lippert, Fishie, Muck, Seeger, and Zwirner (1996)</td>
<td>35</td>
<td>5-HIAA excretion</td>
<td>Increased urinary excretion after ET</td>
</tr>
<tr>
<td>Sherwin and Suranyi-Cadotte (1990)</td>
<td>31*</td>
<td>Platelet imipramine binding</td>
<td>Increased binding compared to placebo</td>
</tr>
<tr>
<td>Wihlbck et al. (2001)</td>
<td>23</td>
<td>Platelet paroxetine binding</td>
<td>No changes despite improved mood</td>
</tr>
<tr>
<td>Halbreich et al. (1995)</td>
<td>33</td>
<td>m-CPP challenge</td>
<td>Increased basal PRL and cortisol levels</td>
</tr>
<tr>
<td>Wihlbck et al. (2001)</td>
<td>23</td>
<td>Platelet LSD binding</td>
<td>No changes despite improved mood</td>
</tr>
<tr>
<td>Moses-Kolko et al. (2003)</td>
<td>5</td>
<td>Altanserin binding through PET</td>
<td>Increased cortical binding</td>
</tr>
<tr>
<td>Kugaya et al. (2003)</td>
<td>10</td>
<td>Altanserin binding through PET</td>
<td>Increased prefrontal cortical binding</td>
</tr>
</tbody>
</table>

**NOTE:** PRL = prolactin; ET = estrogen therapy; SERT = serotonin transporter; m-CPP = meta-chlorophenylpiperazine; PET = positron emission tomography; LSD = lysergic acid diethylamide.

* Participants were surgically menopausal.
relating to a genetic vulnerability (Halbreich, 2003). This hypothesis may also apply to other hormone-related mood disorders, considering that women who experience mood symptoms during a particular hormonal event are more likely to develop symptoms relating to other hormonal fluctuations throughout the life cycle (Freeman, Sammel, Rinaudo, & Sheng, 2004; Gregori, Masand, & Yohai, 2000; Stewart & Boydell, 1993; Sugawara et al., 1997).

The superior efficacy of SSRIs is not limited to treatment for hormone-related mood disorders such as PMDD. In a double-blind trial involving 101 depressed men and women, the SSRI fluoxetine was found to be more effective than maprotiline in treating women younger than 44 years, whereas men showed no difference in response (Martenyi, Dossenbach, Mraz, & Metcalfe, 2001). In women older than 44 years, who are more likely to be peri- or postmenopausal, there was also no difference in response to the drugs (Martenyi et al., 2001). Similarly, a randomized double-blind study of 235 male and 400 female chronic depressed patients found that premenopausal women had better response with the SSRI sertraline and slower response with the tricyclic imipramine, men had better response with imipramine, and postmenopausal women had similar response to either medication (Kornstein et al., 2000). It should be noted, however, that male and female groups differed on age and severity of symptoms (Kornstein et al., 2000), and it is possible that the SSRI worked better in premenopausal women because some had PMDD or, because male and female depression symptoms are often different, a depressive subtype better treated by SSRIs.

A great deal of human literature has focused on estrogen-serotonin interactions in relation to mood disorders in women. Such research is essential given the evidence of a significant sex difference in the incidence of major depression (Angst et al., 2002; Kessler et al., 1993; Weissman et al., 1996) as well as the increased likelihood of depression during periods of hormonal fluctuation (Burt & Stein, 2002; Rapkin et al., 2002). Data suggest that SSRIs are the most effective antidepressant treatment in premenopausal women (Eriksson, Hedberg, Andersch, & Sundblad, 1995; Kornstein et al., 2000; Martenyi et al., 2001), whereas other evidence indicates estrogen’s potential as monotherapy for hormone-related mood disorders (Epperson et al., 1999). Although the relationship between hormone fluctuation, depression, and serotonin is unclear, many have proposed a vulnerability model, whereby those with a genetic predisposition are more likely to be affected by hormonal fluctuation, which can lead to central nervous system dysregulation (Bancroft, 1995; Halbreich, 2003; Joffe & Cohen, 1998).

CONCLUSION

Although animal data provide more direct information about estrogen-serotonin interactions, human data support the idea of estrogen’s facilitatory effect on serotonin and certain specific consequences such as increasing cortical 5-HT2A binding. In addition, estrogen is an effective treatment for certain hormone-related mood disorders and may ameliorate cognitive deficits in menopause. A large amount of literature focuses on how estrogen and serotonin interact in the treatment of mood disorders, but there is much less evidence regarding their interactive effects on cognition. Given the numerous brain regions in which estrogen and serotonin interact, more research in that area may prove useful in understanding how estrogen and serotonin exert their effects on cognition.

Considering the broad range of effects estrogen has on multiple neurotransmitter systems and neuronal architecture, it is possible that estrogen’s considerable effects on serotonin are not critical to estrogen’s role in modulating cognitive function. ERα has been associated with estrogen effects on spatial processing, whereas ERβ is more closely associated with serotonin regulation and has been linked to depression-like neural response and change in emotional behavior in mice. However, the abundance of ERβ binding sites in the cortex and hippocampus would suggest that ERβ would be involved in cognition. Also, estrogen-serotonin interactions in the hippocampus have been identified with regard to electrophysiology, spine density, and cell proliferation.

Many physiological links between estrogen and serotonin have been identified in regions relevant to mood and cognition according to animal studies and human imaging studies, but more research is necessary to understand their joint effects. In some cases, there is a correlation between estrogen and serotonin activity and a change in mood or cognition, but causation is unclear. Further research in humans using short-term hormone replacement therapy and manipulation of serotonin transmission (e.g., through TRP depletion) could help uncover the causal links. In addition, investigation is necessary of the supposed vulnerability in some women, which allows serotonin dysregulation during hormonal fluctuation. Genetic vulnerabilities for depression in the serotonin system have already been identified (Lesch, 2001) and may relate to the differential response across women to hormonal fluctuation. Noninvasive techniques such as functional magnetic resonance imaging would be valuable in investigating effects on emotional processing and cognition in conjunction with these types of studies and would provide more information on which regions of the brain are involved.
Information is also lacking with regard to the physiological connections between estrogen and serotonin. For example, although nongenomic, short-term actions of estrogen have been identified, the suspected membrane receptors have yet to be discovered. Estrogen can enhance 5-HT1A-mediated response in the hippocampus and cortex but decrease autoinhibition caused by presynaptic 5-HT1A receptors. Future animal studies should focus on understanding at which points estrogen exerts its effects to discover the underlying mechanisms of its actions.

Most studies providing consistent and interpretable findings about estrogen’s effects on the serotonin system were done in ovariecotomized animals and postmenopausal women. There have been few estrous cycle studies, and many studies of the normal menstrual cycle have used imperfect designs. The greater degree of control and ability to eliminate confounding variables, such as progestrone level, are obvious advantages of studying ovariecotomized animals and menopausal women. Thus, estrogen-serotonin interactions in intact animals and healthy premenopausal women are largely unknown. It is possible that the effects of normal hormonal fluctuation are very different from the effects of hormone withdrawal plus treatment, and further investigation is necessary.

In conclusion, there is substantial evidence for estrogen-serotonin interactions in brain regions involved in mood and cognition, and estrogen appears to facilitate serotonergic transmission through several mechanisms. Furthermore, investigation of depression and hormone-related mood disorders in women suggests a unique relationship between estrogen and the serotonin system with regard to mood, although the details of this relationship require further investigation. The pathways through which estrogen and serotonin influence cognition overlap in some cases, but their interactive effects on cognition await additional exploration.

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