Effects of Estradiol and Progesterone Administration on Human Serotonin 2A Receptor Binding: A PET Study

Eydie L. Moses, Wayne C. Drevets, Gwenn Smith, Chester A. Mathis, Brinda N. Kalro, Meryl A. Butters, Mark P. Leondires, Phil J. Greer, Brian Lopresti, Tammy L. Loucks, and Sarah L. Berga

Background: *Preclinical studies demonstrate that 17β-estradiol (E_2) increases serotonin-2A receptor (5-HT_{2A}R) density in rat frontal cortex.*

Methods: *We investigated the impact of hormone replacement therapy on 5-HT_{2A}R binding potential (BP) using positron emission tomography and [^{18}F]altanserin in five postmenopausal women. Subjects were imaged at baseline, following 8 to 14 weeks of transdermal E_2, 0.1 mg/d, and following 2 to 6 weeks of E_2 plus micronized progesterone (P) 100 mg* per os *twice daily. Regional BPs in the anterior cingulate cortex, dorsolateral prefrontal cortex, and lateral orbitofrontal cortex were calculated by Logan analysis.*

Results: *There was a main effect of time ($p = .017$) for 5-HT_{2A}R BP, which increased 21.2% ± 2.6% following combined E_2 and P administration relative to baseline. This effect was evident in all cerebral cortex regions examined.*

Conclusions: *5-HT_{2A}R BP increased in widespread areas of the cerebral cortex following combined E_2 + P administration.* Biol Psychiatry 2000;48:854–860 © *2000 Society of Biological Psychiatry*

Key Words: Estradiol, progesterone, PET, neurotrophin, behavior, 5-HT_{2A}

Introduction

Ovarian hormones exert prominent effects on the central serotonergic receptor systems of experimental animals (Osterlund and Hurd 1998; Pecins-Thompson and Bethea 1998; Rubinow et al 1998). For example, E_2 administration increases serotonin-2A receptor (5-HT_{2A}R) density in the anterior cingulate, olfactory, and frontal cortices of ovariectomized rats (Cyr et al 1998; Sumner and Fink 1995). Progesterone (P) promotes comparable 5-HT_{2A}R increases but prevents E_2-related 5-HT_{2A}R increases when the two hormones are initiated concurrently (Biegon et al 1983). The 5-HT_{2A}R system has been implicated in the pathophysiology of depression (Yates et al 1990), suicide (Arango et al 1997), schizophrenia (Jakab and Goldman-Rakic 1998), and Alzheimer's disease (Crow et al 1986), so it is conceivable that the effects of ovarian hormones on cognitive and emotional behavior (Anderson et al 1987; Coble and Day 1988; Phillips and Sherwin 1992; Tang et al 1996) may be partly mediated via indirect effects on 5-HT_{2A}R binding.

Our study investigates changes in 5-HT_{2A}R binding potential (BP) following E_2 and P administration, using the selective 5-HT_{2A}R radioligand [^{18}F]altanserin and positron emission tomography (PET; Lemaire et al 1991; Sadzot et al 1995) in healthy postmenopausal women. Based on the cortical regions where E_2 administration was associated with increased 5-HT_{2A}R density in rats (Cyr et al 1998; Sumner and Fink 1995), we tested the hypothesis that the 5-HT_{2A}R BP would increase in areas of the frontal and cingulate cortices during E_2 and P administration.

Methods and Materials

Five postmenopausal women provided informed consent as approved by the University of Pittsburgh Biomedical Institutional Review Board. Subject characteristics are listed in Table 1. Inclusion criteria were age over 45 years, laboratory confirmation of postmenopausal status (amenorrhea for 12 months unless menopause is surgical and laboratory confirmation of follicle-stimulating hormone [FSH] $>$ 20 IU/L and E_2 $<$ 40 pg/mL), normal gynecologic exam, PAP smear, and mammogram. Exclusion criteria were contraindications for magnetic resonance imaging (MRI), presence of psychiatric or medical conditions, and use of psychotropic medications in the past 3 months. Three women who were taking hormone replacement therapy (HRT) at study entry discontinued HRT for 3 months at which time laboratory data confirmed menopause. The MRI scans (Signa 1.5 tesla scanner, GE Medical Systems, Milwaukee) performed before PET scanning ruled out focal abnormalities (e.g. stroke,

From the Departments of Ob/Gyn/ReproSci (BNK, TLL, SLB), Psychiatry (ELM, WCD, GS, MAB, SLB), and Radiology (WCD, CAM, PJG, BL), University of Pittsburgh, Magee-Women's Research Institute, Pittsburgh, Pennsylvania; NICHD/NIH/ERRB, National Institutes of Health, Bethesda, Maryland (MPL); and Psychiatry Research and Neuroscience Research Center, North Shore–Long Island Jewish Health Care System, Glen Oaks, New York (GS).

Address reprint requests to Eydie Moses, M.D., NIMH Clinical Research Fellow, Magee-Women's Hospital, Department of OB-GYN/RS, 300 Halket Street, Pittsburgh PA 15213-3180.

Received February 15, 2000; revised June 19, 2000; accepted June 21, 2000.

0006-3223/00/$20.00
PII S0006-3223(00)00967-7

Table 1. Subject Characteristics

Subject	Age	Education (years)	Years menopause	Type of menopause	Body mass index (kg/m^2)	Estradiol (pg/mL)	Progesterone (nmol/L)	FSH (IU/L)
1[a]	52.2	13	2	Natural	25.8	—	—	—
2	56.3	12	2	Surgical	33.0	<10	1.5	51.6
3	47.1	13	1.3	Surgical	31.5	38	1.5	67.5
4	52.6	14	12	Surgical	24.9	17	0.9	97.0
5	52.0	17	4	Natural	23.5	17	0.9	69.7
Mean ± SD	52.0 ± 3.3	14 ± 2.2	4.3 ± 4.5	NA	27.7 ± 4.2	NA	1.2 ± 0.35	71.5 ± 18.8

FSH, follicle-stimulating hormone.
[a]Missing laboratory data prevent us from confirming menopause in subject 1; nevertheless, this subject had symptoms consistent with menopause for 2 years before study entry.

tumor) and provided an anatomic reference for region-of-interest (ROI) analysis.

For each subject, [^{15}O]water and [^{18}F]altanserin PET scans were performed at baseline (PET 1), following 8 to 14 weeks of transdermal 17β-estradiol, Climara 0.1 mg/d (PET 2), and following 2 to 6 weeks of E_2 plus micronized P, Prometrium 100 mg *per os* twice daily (PET 3). Laboratory confirmation of E_2 and P levels was obtained at each scan to confirm adherence to the protocol and achievement of hormone concentrations within the reproductive range. Serum levels of E_2 and P were measured by radioimmunoassay (RIA; Coat-A-Count, DPC, Los Angeles, CA) as previously described (Berga et al 1997). Each specimen was measured in duplicate, and all samples were run in the same assay.

The procedures for [^{18}F]altanserin arterial blood sampling, image acquisition, and analysis were described previously (Smith et al 1998). Briefly, after arterial and venous cannulation, emission and transmission PET images were acquired using a Siemens/CTI HR+ (63 contiguous slices over 15.2 cm; full width half maximum resolution = 5 ± 0.5 mm transverse and 4.5 ± 0.5 mm axially; Brix et al 1997). Cerebral blood flow data were obtained in a 3-min dynamic scan following bolus injection of 12-mCi of [^{15}O]water (Quarles et al 1993). 5-HT_{2A}R BP data were obtained in a 90-min dynamic scan following bolus injection of 10-mCi high specific activity [^{18}F]altanserin.

The PET studies acquired on 3 days were aligned to each other and then to the MRI scan using automated image registration (Woods et al 1993). The ROIs (Figure 1) were defined to approximate prefrontal cortical regions where E_2 sensitivity was demonstrated in rodents and where human brain mapping studies showed activation during emotional processing (lateral orbitofrontal cortex and pregenual anterior cingulate cortex) or language and visuospatial processing (dorsolateral prefrontal cortex and dorsal anterior cingulate gyrus; reviewed in Drevets and Raichle 1998). Control ROIs were defined in hippocampus, because 5-HT_{2A}R density did not significantly change following E_2 administration in the rat dentate gyrus (Sumner and Fink 1995), and the occipital and lateral temporal cortex, which were not examined in preclinical studies.

Decay-corrected time-radioactivity concentrations were obtained for each ROI, and the right and left regions were summed. The plasma input function was corrected for the fraction of unmetabolized [^{18}F]altanserin. The volume of distribution for each ROI (DV_{ROI}) was determined by Logan graphical analysis (Logan et al 1994), as previously described (Smith et al 1998). The DV in the cerebellum ($DV_{cerebellum}$) represented the concentration of free and nonspecifically bound [^{18}F]altanserin due to the relatively low concentration of 5-HT_{2A}R in this region (Pazos et al 1987). The BP was calculated as ([$DV_{ROI}/DV_{cerebellum}$] − 1) to minimize the influence of plasma and tissue nonspecific binding (Mintun et al 1984). The BP relates to the free receptor concentration according to the formula

$$\frac{DV_{ROI}}{DV_{cerebellum}} - 1 = \frac{(B_{max} - L)}{K_d}\left(\frac{1}{1 + NS}\right) \text{ (Logan et al 1994),}$$

where B_{max} = receptor density, L = concentration of endogenous neurotransmitter bound to receptor, K_d = dissociation constant, and NS = ratio of kinetic constants for nonspecific binding.

Cerebral blood flow was assessed using a one tissue compartmental model (K1, k2, delay), in which K1 (mL/min/100 mL) was used to quantitate cerebral blood flow (Quarles et al 1993). Cognitive, psychiatric, and quality-of-life assessments (Table 2) were administered within one day of each scan. The effects of E_2 and P on 5-HT_{2A}R were statistically assessed by repeated-measures analysis of variance (ANOVA) using the Huynh–Feldt correction. The Tukey honestly significant difference was applied post hoc to examine the significance of specific contrasts in which the ANOVA showed significant differences.

Results

Baseline serum E_2, P, and FSH concentrations confirmed menopause (Table 1). E_2 concentrations (mean ± SD) increased to and remained at the targeted postreplacement levels at PET 2 (73.3 ± 36.2 pg/mL) and PET 3 (76.0 ± 32.9 pg/mL). (The mean E_2 concentration across a normal menstrual cycle is 110 pg/mL.) The concentrations of P were negligible at PET 2 (1.3 ± 0.46 nmol/L) and increased to the reproductive range following replacement at PET 3 (67.7 ± 67.7 nmol/L). The wide P and E_2 concentration ranges resulted from variable timing of blood draws with respect to peak and trough levels of the administered hormone. Whereas the variability was greater with Prometrium (because of the oral route of administration and its short half-life), it was narrower for

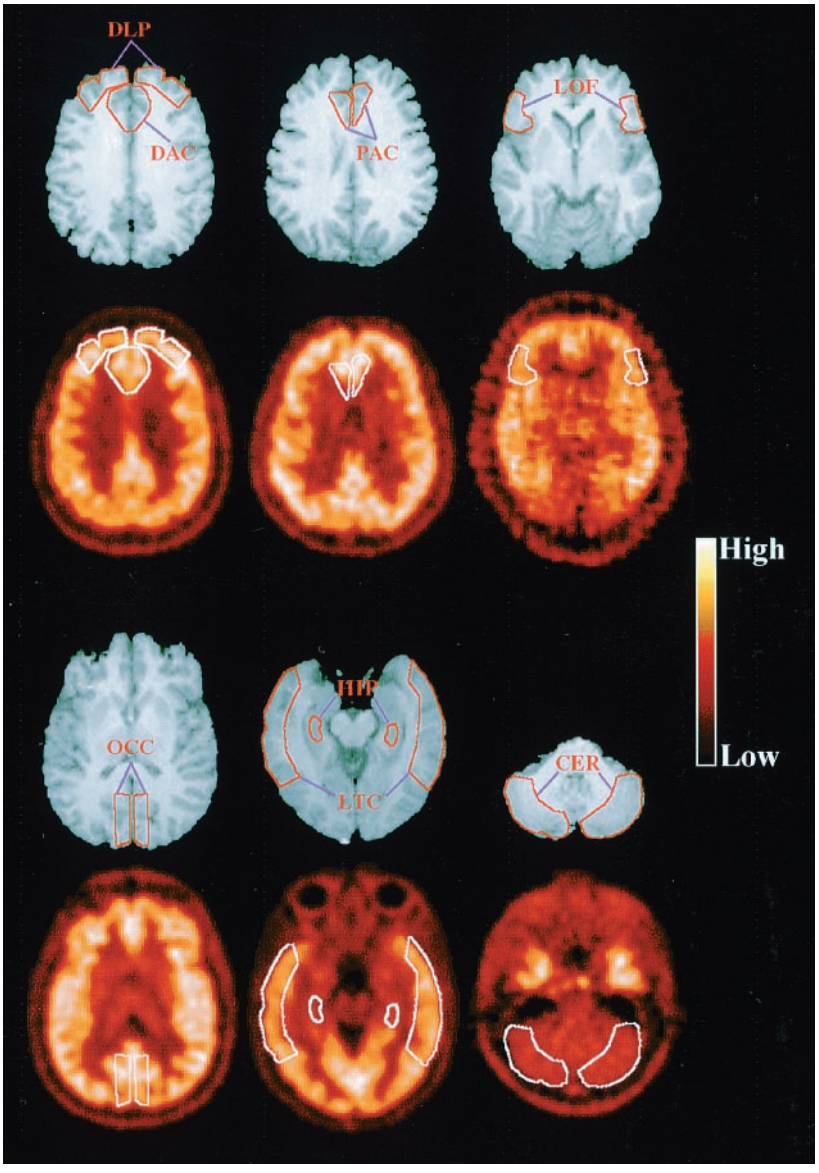

Figure 1. Representative horizontal magnetic resonance imaging sections through each of the regions of interest (ROIs; first and third rows). The coregistered baseline [^{18}F]altanserin positron emission tomography (PET) scans for the same horizontal slices and subjects are shown below, in images generated post hoc by summing dynamic PET frames from 45 to 90 min. Color scale indicates radioactive counts per pixel. The dorsal anterior cingulate cortex (DAC) ROI was defined on the anterior cingulate gyri in the four planes situated immediately dorsal to the dorsum of the corpus callosum. The dorsolateral prefrontal cortex (DLP) ROI was defined on the middle and superior frontal gyri in three planes immediately dorsal to the dorsum of the corpus callosum. The pregenual anterior cingulate cortex (PAC) ROI was defined on the anterior cingulate cortex situated immediately rostral to the genu of the corpus callosum in three planes. The lateral orbitofrontal cortex (LOF) ROI was defined on the inferior frontal gyrus on one plane at the level of the third ventricle. The occipital cortex (OCC) was defined on the lingular and cuneate gyri at the level of the third ventricle. The lateral temporal cortex (LTC) ROI was defined on the middle temporal gyrus on one plane. The hippocampus (HIP) sampled the head of the hippocampus posterior to the alveus and temporal horn of the lateral ventricle in up to five planes and beyond 2 × full width half maximum from the insula, LTC, and fusiform gyrus. The cerebellar cortex (CER) ROI was defined on the CER at the level of the fourth ventricle (Talairach and Tournoux 1988).

Climara (because transdermal administration provides uniform release over 7 days).

Cerebral blood flow data for four subjects (technical problems precluded use of the cerebral blood flow image from one subject) showed no significant changes across scans (Table 3).

There was a main effect of time [$F(2,8) = 9.90$, $p = .017$] for 5-HT$_{2A}$R BP in the primary ROIs (Figure 2 and Table 4). There was no significant time-by-region interaction. Post hoc analysis showed that the 21.2% ± 2.6% (mean of all four *a priori* regions ± SD) BP increase between PET 1 and PET 3 was significant ($p = .0055$). The mean increase in BP between PET 1 and PET 2 and between PET 2 and PET 3 did not reach significance (mean ± SD increases in BP were 10.5% ± 3.6% and 10.6% ± 4.2%, respectively; $0.1 < p < .2$). Post hoc, exploratory analysis of control regions also showed a similar main effect of time [$F(2,8) = 5.28$, $p = .034$] with the 5-HT$_{2A}$R BP increasing between PET 1 and PET 3 ($p = .029$), and no significant time by region interaction.

Baseline cognitive, psychiatric, and quality-of-life assessments were in the expected range for healthy subjects (Table 2). There were post-HRT tendencies for improvement in the spatial working memory task, the anxiety subscale of the Hopkins Symptom Checklist-90, and the Menopause Specific Quality of Life Questionnaire (Hilditch et al 1996).

Table 2. Cognitive, Psychiatric, and Quality-of-Life Scores before and after Estradiol (E_2) and Progesterone (P)

Measure		Sample Means ± SDs		
		Baseline	Post-E_2	Post-E_2 + P
1. Spatial working memory task (CANTAB)[a]	No. errors	49 ± 29	28 ± 8.9	24 ± 6.2[b]
2. Rivermead Paragraph Recall Test[a]	Immediate recall	13 ± 2.6	14 ± 2.9	13 ± 3.5
	Percent retention	98 ± 11	90 ± 13	101 ± 15
3. California Verbal Learning Test[a]	Immediate recall	67 ± 7.5	64 ± 7.9	72 ± 5.2
	Percent retention	96 ± 4.3	97 ± 6.3	98 ± 3.1
4. Brief Visuospatial Memory Test[a]	Immediate recall	25 ± 5.4	27 ± 5.5	29 ± 1.5
	Percent retention	97 ± 5.6	98 ± 4.6	100 ± 7.8
5. Beck Depression Inventory Scale		1.5 ± 1.3	0.5 ± 1.0	0.8 ± 1.0
6. Hopkins Symptom Checklist-90	Global severity index	39 ± 6.4	34 ± 5.2	35 ± 5.5
	Anxiety subscale	48 ± 9	39 ± 8.3	39 ± 3.5
	Depression subscale	39 ± 6.0	37 ± 6.0	36 ± 4.0
7. Medical Outcomes Study[c]	Physical subscale	52 ± 3.9	54 ± 2.2	54 ± 2.5
	Mental subscale	58 ± 6.5	60 ± 1.9	58 ± 3.4
8. Menopause quality of life scale[d]	Total score	3.1 ± 1.4	1.7 ± 1.3	1.2 ± 0.3

$n = 4$. One subject underwent a unique battery of tests and so was not included in these results. CANTAB, Cambridge Neuropsychological Automated Test Battery (Sahakian et al 1992).

[a]Alternate forms of tests were administered at different time points.

[b]$n = 3$. Missing data point was a result of technical difficulties.

[c]Medical Outcomes Study Short Form-36 Women's Health Questionnaire.

[d]The Menopause Specific Quality of Life Questionnaire, where score represents total score of vasomotor, psychomotor, physical, and sexual subdomains (Hilditch et al 1996).

Discussion

These data demonstrate that E_2 plus P administration significantly increases cerebral cortical 5-HT_{2A}R BP in humans. These changes were several fold greater than the test–retest variability for [^{18}F]-altanserin that was determined over 2 to 16 days in corresponding regions (Smith et al 1998). It is unlikely these BP changes were confounded by ligand delivery because cerebral blood flow did not increase between PET 1 and PET 3 (Table 3). Although the sample size was small, the finding that BP increased in all five subjects in all ROIs examined is compelling.

We used BP to quantitate receptor specific binding because this term presumably excludes the effects of free and nonspecifically bound [^{18}F]altanserin from PET measures of regional 5-HT_{2A}R concentration. It is nonetheless noteworthy that although the magnitude of the BP_{ROI} elevation between PET 1 and PET 2 was similar to that seen between PET 2 and PET 3, the DV_{ROI} values increased between PET 1 and PET 2, but not between PET 2 and PET 3 (Table 4). This observation raised the possibility that E_2 administration increased 5-HT_{2A}R to a level that plateaued and that P administration did not further elevate 5-HT_{2A}R binding. This issue does not detract from the statistically significant result that HRT increased 5-HT_{2A}R BP between PET 1 and PET 3. It does, however, highlight the inability of our study design to differentiate the relative contributions of E_2 and P to the change in 5-HT_{2A}R binding or to delineate the time-course of E_2 and P effects on 5-HT_{2A}R binding.

The mechanism by which ovarian hormone replacement leads to the observed 5-HT_{2A}R BP increases is unclear. A classic genomic E_2 mechanism has been suggested whereby E_2 bound to the intracellular estrogen receptor translocates into the cell nucleus and directly promotes DNA expression. Cyr et al (1998; and personal communication) reported that rodent CNS 5-HT_{2A}R density increased in parallel with 5-HT_{2A}R mRNA expression following E_2 administration in the dorsal raphe nucleus, frontal cortex, anterior cingulate cortex, and striatum. In contrast, Sumner and Fink (1995) found that E_2-mediated 5-HT_{2A}R increases in frontal regions were not associated with corresponding changes in 5-HT_{2A}R mRNA, suggesting that alternative mechanisms (such as transynaptic stimulation of 5-HT_{2A}R gene transcription, posttranslational 5-HT_{2A}R processing effects, or putative membrane

Table 3. Cerebral Blood Flow (CBF) before and after Estradiol (E_2) and Progesterone (P) Administration in *A Priori* Regions of Interest and Cerebellum ($n = 4$)

Region of interest	Mean CBF ± SD (mL/min/100 mL)		
	Baseline	Post-E_2	Post-E_2 + P
LOF	0.45 ± 0.039	0.46 ± 0.061	0.44 ± 0.030
DLP	0.44 ± 0.037	0.44 ± 0.040	0.41 ± 0.023
PAC	0.49 ± 0.050	0.47 ± 0.056	0.44 ± 0.026
DAC	0.46 ± 0.036	0.45 ± 0.072	0.43 ± 0.029
CER	0.49 ± 0.057	0.47 ± 0.078	0.44 ± 0.042

Technical problems prevented use of data from one subject. LOF, lateral orbitofrontal cortex; DLP, dorsolateral prefrontal cortex; PAC, pregenual anterior cingulate cortex; DAC, dorsal anterior cingulate cortex; CER, cerebellar cortex.

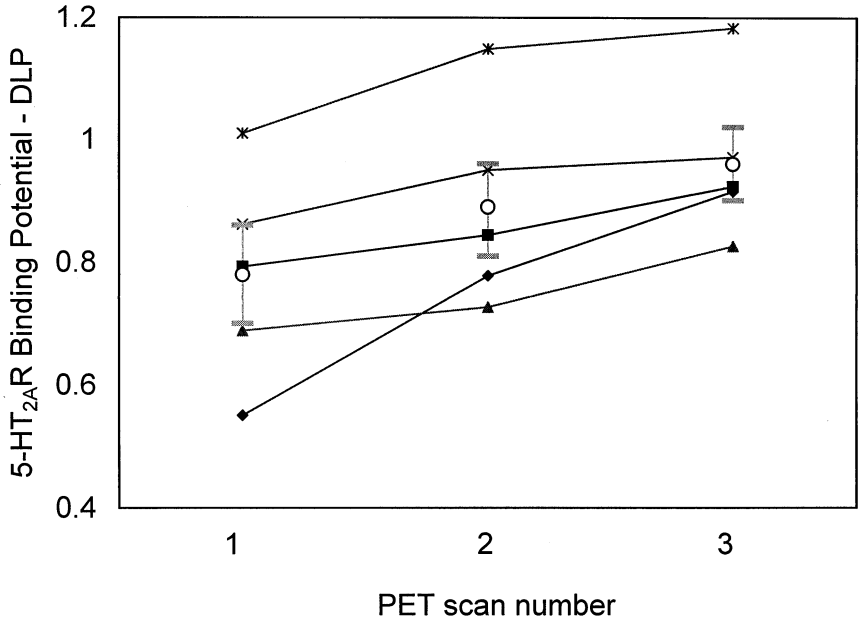

Figure 2. 5-HT_{2A} receptor (5-HT_{2A}R) binding potential (BP) in the dorsolateral prefrontal cortex (DLP) for the five subjects at three time points: baseline (positron emission tomography [PET] 1), postestradiol (PET 2), and postestradiol plus progesterone (PET 3) administration. Icons represent the BP value measured in a single PET scan, for each subject, at the designated time point. The mean is shown by the circle with SEM bars.

estrogen-receptor-mediated enhancement of second messenger systems) may also or alternatively account for the effects of E_2 on 5-HT_{2A}R .

The widespread distribution of 5-HT_{2A}R BP increases may also reflect ovarian-hormone-mediated neurotrophic effects. Administration of E_2 promotes neuronal outgrowth (Toran-Allerand 1996), increases expression of neurotrophin receptor trkA and brain derived neurotrophic factor (BDNF) mRNA expression, mitogen-activated protein kinase and cAMP response element binding protein (Gibbs 1998; McEwen and Alves 1999). Because 5-HT_{2A}Rs are present on nearly all cortical pyramidal cells and interneurons (Jakab and Goldman-Rakic 1998), the proliferation of neuritic processes induced by these neurotrophic effects would likely be associated with upregulation of 5-HT_{2A}R expression.

Nonetheless, the effect of HRT on 5-HT_{2A}R is not global in rats. Administration of E_2 did not change 5-HT_{2A}R density in regions including the claustrum, dentate gyrus, locus coeruleus, and medial preoptic area (Sumner and Fink 1995). Because of the spatial resolution limitations of PET, we could not assess the effects of HRT

Table 4. 5-HT_{2A} Receptor Binding Potential (BP) before and after Estradiol (E_2) and Progesterone (P) Administration in All Regions of Interest (ROIs)

	Mean DV ± SD			Mean BP ± SD			Mean % ΔBP (E_2 + P vs. baseline) ± SD
	Baseline	Post-E_2	Post-E_2 + P	Baseline	Post-E_2	Post-E_2 + P	
A Priori ROIs							
LOF	2.51 ± 0.37	2.73 ± 0.21	2.74 ± 0.13	0.84 ± 0.15	0.89 ± 0.23	1.01 ± 0.15	20 ± 18[a]
DLP	2.43 ± 0.41	2.75 ± 0.38	2.68 ± 0.15	0.78 ± 0.17	0.89 ± 0.17	0.96 ± 0.13	25 ± 24[a]
PAC	2.68 ± 0.64	2.98 ± 0.61	2.89 ± 0.45	0.94 ± 0.24	1.03 ± 0.15	1.10 ± 0.19	19 ± 16[a]
DAC	2.55 ± 0.36	2.83 ± 0.37	2.81 ± 0.18	0.87 ± 0.12	0.95 ± 0.15	1.06 ± 0.11	22 ± 14[a]
CER[b]	1.36 ± 0.18	1.46 ± 0.22	1.37 ± 0.13	0	0	0	0
Control ROIs							
LTC	2.64 ± 0.64	2.89 ± 0.56	2.88 ± 0.38	0.92 ± 0.27	0.98 ± 0.23	1.11 ± 0.20	26 ± 35[c]
OCC	2.71 ± 0.47	2.95 ± 0.29	2.90 ± 0.11	0.99 ± 0.15	1.04 ± 0.18	1.13 ± 0.15	14 ± 18[c]
HIP[d]	1.74 ± 0.12	1.97 ± 0.14	1.78 ± 0.13	0.24 ± 0.20	0.29 ± 0.23	0.29 ± 0.20	27 ± 23[c]

DV, volume of distribution; LOF, lateral orbitofrontal cortex; DLP, dorsolateral prefrontal cortex; PAC, pregenual anterior cingulate cortex; DAC, dorsal anterior cingulate cortex; CER, cerebellar cortex; LTC, lateral temporal cortex; OCC, occipital cortex; HIP, hippocampus.

[a]There was a main effect of time [$F(2,8) = 9.90$, $p = .017$] for 5-HT_{2A} receptor BP in the *a priori* ROIs. There was no significant effect of region or time-by-region interaction. Post hoc analysis showed that the increase between baseline and post-E_2 + P scans was significant ($p = .0055$).

[b]The change in cerebellar DV across time was not significant [$F(2,8) = 2.49$, $p = .14$].

[c]Post hoc analysis of control ROIs showed a similar main effect of time [$F(2,8) = 5.28$, $p = .034$] for 5-HT_{2A} receptor BP with a significant increase between baseline and post-E_2 + P scans ($p = .029$).

[d]Data from one subject were excluded in the calculation of HIP BP because of poor model fit to the time activity data (Logan et al 1994).

on 5-HT_{2A}R in these regions. Although we attempted to measure hippocampal 5-HT_{2A}R BP, we could not specifically resolve the dentate gyrus. Furthermore, our hippocampal measures were affected by spilling-in of radioactive counts from the perirhinal, entorrhinal, parahippocampal cortices, and amygdala (Links et al 1996).

The cognitive and emotional assessments used to detect clinical correlations with the imaging data had limited sensitivity because of the small sample size. In addition, GABAergic P metabolites may have influenced these behavioral measures at the third time point. The extent to which changes in 5-HT_{2A}R binding may be involved in mediating the effects of gonadal steroids on behavior, via either specific serotonin receptor changes or neurotrophic effects, remains unclear.

This study was supported by National Institute of Health Grant Nos. MH16804, MH01713, MH/HD50748, MH01621, MH49936, MH57078, and MH52247 (Intervention Research Center for Late-Life Mood Disorders); National Center for Research Resources Grant No. RR-00056 to the University of Pittsburgh School of Medicine General Clinical Research Center; and the Functional Imaging Research Program of the Department of Radiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

The authors thank Michelle Zmuda, Carolyn Cidis Meltzer, M.D., and the PET facility staff for technical assistance; Florence Hall for assisting with recruitment; and Julie Price, Ph.D., Cristy Matan, B.S., Robert Sembrat, B.S., Tyrone Holliman, and Clara Gautier, Ph.D., for assistance with data analysis.

References

Anderson E, Hamburger S, Liu J, Rebar R (1987): Characteristics of menopausal women seeking assistance. *Am J Obstet Gynecol* 156:428–433.

Arango V, Underwood MD, Mann JJ (1997): Postmortem findings in suicide victims. Implications for in vivo imaging studies. *Ann N Y Acad Sci* 836:269–287.

Berga SL, Daniels TL, Giles DE (1997): Women with functional hypothalamic amenorrhea but not other forms of anovulation display amplified cortisol concentrations. *Fertil Steril* 67: 1024–1030.

Biegon A, Reches A, Snyder L, McEwen BS (1983): Serotonergic and noradrenergic receptors in the rat brain: Modulation by chronic exposure to ovarian hormones. *Life Sci* 32:2015–2021.

Brix G, Zaers J, Adam L-E, Belleman ME, Ostertag H, Trojan H (1997): Performance evaluation of a whole-body PET scanner using the NEMA protocol. *J Nucl Med* 38:1614–1623.

Coble PA, Day NL (1988): The epidemiology of mental and emotional disorders during pregnancy and the postpartum period. In: Cohen RL, editor. *Psychiatric Consultation in Childbirth Settings.* New York: Plenum Press, 37–47.

Crow T, Ferrier I, Johnson J (1986): The selectivity of the reduction of serotonin S2 receptors in Alzheimer-type dementia. *Neurobiol Aging* 7:3–7.

Cyr M, Bosse R, Di Paolo T (1998): Gonadal hormones modulate 5-HT2A receptors: Emphasis on the rat frontal cortex. *Neuroscience* 83:829–836.

Drevets WC, Raichle ME (1998): Reciprocal suppression of regional cerebral blood flow during emotional versus higher cognitive processes: Implication for interaction between emotion and cognition. *Cogn Emotion* 12:353–385.

Gibbs RB (1998): Levels of trkA and BDNF mRNA, but not NGF mRNA, fluctuate across the estrous cycle and increase in response to acute hormone replacement. *Brain Res* 787: 259–268.

Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, et al (1996): A menopause-specific quality of life questionnaire: Development and psychometric properties. *Maturitas* 24:161–175.

Jakab RL, Goldman-Rakic PS (1998): 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: Possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. *Proc Natl Acad Sci U S A* 95:735–740.

Lemaire C, Cantineau, Plenevaux A, Christiaens L (1991): Fluorine-18-Altanserin. A radioligand for the study of serotonin receptors with PET: Radiolabeling and in vivo biologic behavior in rats. *J Nucl Med* 32:2266–2272.

Links JM, Zubieta JK, Meltzer CC, Stumpf MJ, Frost JJ (1996): Influence of spatially heterogeneous background activity on "hot object" quantification in brain emission computed tomography. *J Comput Assist Tomogr* 20:680–687.

Logan J, Volkow N, Fowler J, Wang G-J, Dewey SL, MacGregor R, et al (1994): Effects of blood flow on [11C]raclopride binding in the brain: model simulations and kinetic analysis of PET data. *J Cereb Blood Flow Metab* 14:995–1010.

McEwen BS, Alves SE (1999): Estrogen actions in the central nervous system. *Endocr Rev* 20:279–307.

Mintun MA, Raichle ME, Kilbourn MR, Wooten GF, Welch MJ (1984): A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann Neurol* 15:217–227.

Osterlund MK, Hurd YL (1998): Acute 17β-estradiol treatment down-regulates serotonin 5HT1A receptor mRNA expression in the limbic system of female rats. *Mol Brain Res* 55:169–172.

Pazos A, Probst A, Palacios JM (1987): Serotonin receptors in the human brain. IV. Autographic mapping of serotonin-2 receptors. *Neuroscience*21:123–139.

Pecins-Thompson M, Bethea CL (1998): Regulation of serotonin re-uptake transporter mRNA expression by ovarian steroids in rhesus macaques. *Mol Brain Res* 53:120–129.

Phillips SM, Sherwin B (1992): Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 17:485–495.

Quarles RP, Mintun MA, Larson KB, Markham J, MacLeod AM, Raichle ME (1993): Measurement of regional cerebral blood flow with positron emission tomography: A comparison of [15O]water to [11C]butanol with distributed-parameter and compartmental models *J Cereb Blood Flow Metab* 13:733–747.

Rubinow DR, Schmidt PJ, Roca CA (1998): Estrogen-serotonin interactions: Implications for affective regulation. *Biol Psychiatry* 44:839–850.

Sadzot B, Lemaire C, Maquet P, Salmon E, Plenevaux A, Degueldre C, et al (1995): Serotonin 5HT2 receptor imaging in the human brain using positron emission tomography and a new radioligand, [18F]altanserin: Results in young normal controls. *J Cerebr Blood Flow Metab* 15:787–797.

Sahakian BJ, Owen AM (1992): Computerized assessment in neuropsychiatry using CANTAB: Discussion paper. *J R Soc Med* 85:399–402.

Smith GS, Price JC, Lopresti BJ, Huang Y, Simpson N, Holt D, et al (1998): Test-retest variability of Serotonin 5-HT2A receptor binding measured with positron emission tomography and [18F]Altanserin in the human brain. *Synapse* 30: 380–392.

Sumner BE, Fink G (1995): Estrogen increases the density of 5-HT2A receptors in cerebral cortex and nucleus accumbens in the female rat. *J Steroid Biochem Mol Biol* 54:15–20.

Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain 3-Dimensional Proportional System: An Approach to Cerebral Imaging.* New York: Thieme.

Tang MX, Jaocbs D, Stern Y, Marder K, Schofield, Gurland B (1996): Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet* 348:429–432.

Toran-Allerand CD (1996): Mechanisms of estrogen action during neural development: Mediation by interactions with neurotrophins and their receptors? *J Steroid Biochem Mol Biol* 56:169–178.

Woods RP, Mazziotta JC, Cherry SR (1993): MRI-PET registration with automated algorithm *J Comput Assist Tomogr* 17:536–546.

Yates M, Leake A, Candy JM, Fairbairn AF, McKeith IG, Ferrier IN (1990): 5HT2 receptor changes in major depression. *Biol Psychiatry* 27:489–496.