Archival Report

Biological Psychiatry

Role of Serotonin Transporter Changes in Depressive Responses to Sex-Steroid Hormone Manipulation: A Positron Emission Tomography Study

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ABSTRACT

BACKGROUND: An adverse response to acute and pronounced changes in sex-hormone levels during, for example, the perimenopausal or postpartum period appears to heighten risk for major depression in women. The underlying risk mechanisms remain elusive but may include transiently compromised serotonergic brain signaling. Here, we modeled a biphasic ovarian sex hormone fluctuation using a gonadotropin-releasing hormone agonist (GnRHa) and evaluated if emergence of depressive symptoms was associated with change in cerebral serotonin transporter (SERT) binding following intervention.

METHODS: A double-blind, randomized, placebo-controlled study included 63 healthy female volunteers (mean age 24.3 ± 4.9 years) with regular menstrual cycles between 23 and 35 days. Participants were randomized to active (goserelin [GnRHa] 3.6 mg implant) or placebo intervention. Sixty women completed follow-up and entered the analyses. Primary outcome measures were changes from baseline in depressive symptoms assessed on the 17-item Hamilton Depression Rating Scale and SERT binding as imaged by [^{11}C]DASB positron emission tomography. Outcome measures were acquired at baseline in the follicular phase (cycle day 6.6 ± 2.2) and at follow-up (16.2 ± 2.6 days after intervention start).

RESULTS: Sex hormone manipulation with GnRHa significantly triggered subclinical depressive symptoms within-group ($p = .003$) and relative to placebo ($p = .02$), which were positively associated with net decreases in estradiol levels ($p = .02$) from baseline within the GnRHa group. Depressive symptoms were associated with increases in neocortical SERT binding in the GnRHa group relative to placebo ($p = .003$).

CONCLUSIONS: Our data imply both serotonergic signaling and estradiol in the mechanisms by which sex-steroid hormone fluctuations provoke depressive symptoms and thus provide a rationale for future preventive strategies in high-risk groups.

Keywords: [^{11}C]DASB-PET, Estradiol, Gonadotropin-releasing-hormone agonist, 5-HT, 5-HTT, Mood disorder

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The lifetime risk for major depression appears twice as high in women relative to men (1), even though this might be confounded by diagnostic criteria that tend not to appreciate the male experience of depressive symptoms (2). A broad spectrum of common mental disorders, including mood disorders, emerge primarily during or after puberty in both genders (3), suggesting that sex hormone changes play a role in the mechanisms by which these disorders manifest. Further, epidemiologic studies point to an increased risk for mood disorders in life phases of women where sex hormone levels fluctuate or decline rapidly from elevated levels such as during menopausal transition (4,5) or early postpartum (6,7), respectively.

Peripartum or postpartum depression (PPD) represents a severe public health problem, with a prevalence of 19% (7–9) and a peak incidence at days 10 to 19 postpartum (6). PPD affects not only the mother but also is associated with suboptimal outcomes of infant language and early cognitive development (10–12) and future mental health of the infant, e.g., depression at age 18 (13,14). Nonpathologic postpartum blues temporally coincides with the drop in placenta-produced steroid hormones (15), i.e., estradiol, and heightens the risk for PPD (16).

Menopausal transition is another female life phase where ovarian sex-steroid hormone levels fluctuate. Reproductive aging is a gradual process that can be described according to

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the Stages of Reproductive Aging Workshop criteria (17). The menopausal transition precedes the final menstrual period and is separated in an early and a late stage. The early stage is characterized by variations in cycle length ≥ 7 days in consecutive cycles. The late stage involves increased prevalence of anovulation corresponding to amenorrhea of ≥ 60 days and extreme fluctuations in hormonal levels including estradiol. It lasts around 1 to 3 years before the actual final menstrual period. Interestingly, the strongest risk factor for developing depressive symptoms across menopausal transition is fluctuation of estradiol around the women's own mean level (5). Notably, at the time the postmenopausal state is fully established and estradiol no longer fluctuates that risk decreases (4). Also, in PPD, sensitivity to estradiol fluctuations seemingly is central to risk (18,19); yet, very little is known as to how risk mechanisms associated with sex-hormone fluctuations work.

A large body of preclinical and clinical evidence supports crosstalk between estrogens, in particular estradiol, and key features of the serotonin system (20–22). In rodents and nonhuman primates, estrogen administration potentially increases serotonergic tone by increasing serotonin synthesis (23), decreasing degradation (24), and decreasing inhibitory feedback to serotonergic neurons in the dorsal raphe nucleus (25,26). However, this may be counterbalanced by an estradiol-induced increase in serotonin transporter (SERT) gene expression (27) and protein levels (28) predominantly in cortical projection areas (29). Nevertheless, the contribution from SERT responses across phases of sex-steroid hormone fluctuation and the timing of such serotonergic integration of ovarian steroid hormone information are far from clear and sparsely studied in humans.

We propose biphasic fluctuation in ovarian sex hormones induced by gonadotropin releasing hormone agonist (GnRHa) as a risk model for depression. Within this model, we evaluate if GnRHa triggers depressive symptoms in a manner dependent on net changes in estradiol levels and brain SERT binding as compared with placebo.

Pharmacologic intervention with continuous GnRHa induces a biphasic ovarian hormone response (30); after an initial stimulation of the hypothalamus-pituitary-gonadal (HPG) axis, pituitary GnRHa receptors desensitize, and consequently, ovarian sex-steroid production is suppressed to menopausal levels within about 10 to 14 days. The GnRHa model thus best matches the late menopausal transition stage (17) described above and reflects partly the physiological changes across the prepartum to postpartum transition where placenta-produced hormones including estradiol decline rapidly from the high levels established during pregnancy.

SERT is located presynaptically on cell bodies and terminals of serotonergic neurons. In the projection areas, e.g., cerebral cortex, it is the primary mechanism for clearing extracellular serotonin and thus regulates synaptic serotonin (31). SERT binding can be imaged in the living human brain with positron emission tomography (PET) using the radiotracer [^{11}C]DASB, which binds to SERT with high selectivity (32).

METHODS AND MATERIALS

Participants, Assessment Timing, and Intervention

Healthy women were recruited by internet advertisement, and if eligible, they were invited to a face-to-face screening by trained clinicians. Inclusion criteria were regular menstrual cycle between 23 and 35 days of length, no history of neurologic or psychiatric disorders (ICD-10 or DSM-IV Axis I diagnostic criteria for obsessive-compulsive disorder, anxiety, major depression, bipolar disorder/mania, or schizophrenia as assessed with the SCAN 2.1 interview), no premenstrual dysphoric disorder (premenstrual dysphoric disorder, DSM-IV criteria), no alcohol abuse or illegal drug use, and a normal neurologic and gynecologic examination. Screening included premenstrual symptoms questionnaire. To ensure a balanced recruitment with respect to high- and low-expressing variants of the SERT gene, candidate participants delivered saliva for genotyping of the serotonin transporter-linked polymorphic region (5-HTTLPR). Subsequently, they were placed on a standby list and reported their next first menstrual cycle day to the study coordinator.

Sixty-three healthy women were enrolled in this block randomized, placebo-controlled, and double-blinded intervention study. Block randomization was performed to balance the distribution of 5-HTTLPR genotype (LALA or not), described below. All participants (mean age 24.3 ± 4.9 years) had regular menstrual cycles (duration 23–35 days) and normal blood tests on cycle days 2 to 5, including follicle-stimulating hormone, thyroid-stimulating hormone, and androgen status. One participant did not receive intervention due to anovulation. One became pregnant and did not complete follow-up. Further, one baseline PET acquisition was lost due to a technical error. Consequently, datasets on 60 participants were available for analyses.

An overview of the timing of baseline, intervention, and follow-up relative to the menstrual cycle is provided in Figure 1.

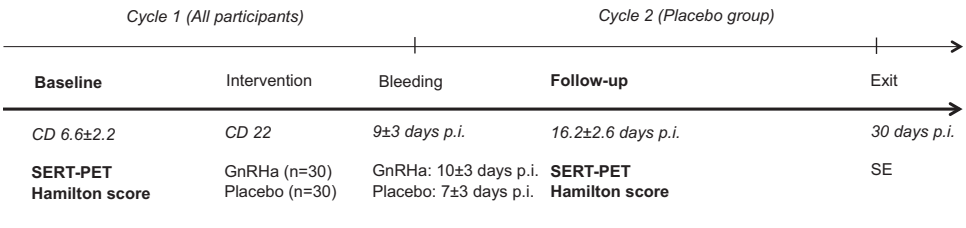

Figure 1. Timeline of study program. Baseline assessment was placed in the midfollicular phase of the menstrual cycle. Follow-up was scheduled to assure that the gonadotropin releasing hormone agonist (GnRHa) group had entered their early ovarian hormone suppression phase as well as secure that the placebos were again in their follicular phase in the follow-up cycle. Primary outcome measures were changes from baseline in depressive symptoms assessed on a 17-item Hamilton Depression Rating Scale (Hamilton score) and serotonin transporter (SERT) binding as imaged by [^{11}C]DASB positron emission tomography (PET). Side effects (SE) were scored on days 7, 12, and 30 postintervention (p.i.) and bleeding day was confirmed by telephone interview. CD, cycle day.