Effect of Gonadal Hormones on Neurotransmitters Implicated in the Pathophysiology of Obsessive-Compulsive Disorder: A Critical Review

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Keywords

Obsessive-compulsive disorder · Female reproduction · Serotonin · Dopamine · Glutamate · Gonadal hormones

Abstract

Obsessive-compulsive disorder (OCD) is a relatively common neuropsychiatric disorder affecting between 1.6 and 3.2% of the population. A number of studies have previously reported increased incidence of OCD, or exacerbation of pre-existing symptoms in females during reproductive events. Since these periods are known to involve fluctuating levels of gonadal hormones, these steroids have been suggested to be involved in modulating the course of the disorder. However, to date, only a few studies have measured hormone levels and obsessive-compulsive (OC) symptoms concurrently; thus, direct evidence for this relationship is limited. In turn, investigations into neurotransmission in OC individuals have been more extensive, and have implicated the serotonergic, dopaminergic, and glutamatergic neurotransmitter systems in OCD pathology. There is evidence suggesting that reproductive hormones estrogens and progesterone can modulate neurotransmission in the aforementioned signaling pathways by regulating the expression of recep-

tors and channels, as well as the synthesis and release of the neurotransmitter itself. Overall, estrogen and progesterone appear to enhance serotonin signaling, which has been associated with improved OC symptoms. The effect of the gonadal hormones in dopaminergic and glutamatergic signaling is much more variable, highlighting the need for further research in this field. The existing evidence shows that gonadal hormones can have profound impacts on neurotransmission in the brain, leading to the conclusion that the hormonal fluctuations during reproductive events are a plausible factor contributing to the change in OCD course during these times.

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Introduction

Obsessive-compulsive disorder (OCD) is a debilitating neuropsychiatric disorder characterized by the presence of obsessions and compulsions. Obsessions are recurrent, persistent, and unwanted thoughts, urges, or images that cause anxiety. In response to these obsessions, the individual develops compulsions – repetitive behaviors, or mental acts that make a futile attempt to reduce

distress, or prevent some dreaded event. The specific obsessions and compulsions vary among individuals; however, they commonly revolve around themes of cleaning, symmetry, taboo thoughts, and harm. These behaviors consume significant amounts of time, and have debilitating consequences on social and occupational functioning [1]. OCD has a lifetime prevalence rate of 1.6–3.2%, making it a relatively common psychiatric disorder [2].

Although the exact etiology of OCD remains elusive at this point in time, there is strong speculation that both genetic and environmental factors are involved. Genetic variations in the receptor and enzyme components of the serotonergic, dopaminergic, and glutamatergic neurotransmitter systems, as well genetic variations in growth and transcription factors have been associated with OCD [3]. These gene variations may increase susceptibility of individuals to OCD at various life events.

It has been observed that in some cases, obsessive-compulsive (OC) symptoms worsen or first appear during reproductive milestones such as pregnancy, and the postpartum period [4–6]. A 2013 meta-analysis revealed that pregnant and postpartum women had a 45 and 138% increased risk of developing OCD, respectively [7]. It has been proposed that the hormonal changes associated with these reproductive events may be involved in modulating the course of OCD in these patients.

Existing literature provides only weak evidence to confirm the role of gonadal steroids in OCD pathology. To date, no study has concurrently measured hormone levels and OCD symptoms, making it difficult to derive sound conclusions about this relationship. To our knowledge, only 1 human study by Avgoustinaki et al. [8] measured both circulating levels of gonadal steroids and psychometric parameters to characterize the relationship between reproductive events and OC symptoms in a healthy population. In this study, researchers found only a marginally significant association between progesterone levels and scores on the 7-point scale of the Minnesota Multiphasic Personality Inventory [8].

Evidence from preclinical animal studies has suggested an inverse relationship between estradiol levels and OCD severity. Fernández-Guasti et al. [9] observed the effects of estradiol using the 8-hydroxy-2-(di-n-propyl-amino)-tetralin hydrobromide (8-OH-DPAT) model of OCD. Administration of 8-OH-DPAT decreases the number of times rats spontaneously choose different arms in a T maze (i.e., increases frequency of repetitive behaviors) [10]. Fernández-Guasti et al. [9] showed that administration of estradiol reduced the preservative effects of 8-OH-DPAT. In a different study, administration

Table 1. Keywords for database search

1	Serotonin	Dopamine	Glutamate	Oxytocin
2 AND (one of)	Estrogen Progesterone Oxytocin	Estrogen Progesterone Oxytocin	Estrogen Progesterone Oxytocin	OCD
3 AND (one of)	OCD Tryptophan hydroxylase MAO MAO-A SERT 5-HT receptor Synaptic proteins	OCD Tyrosine hydroxylase DA release DAT D1 D2 D3 D4 D5 Synaptic proteins	OCD Glutamate release NMDA AMPA mGlu EAAT Synaptic proteins	

of estradiol to prepubertal female rats decreased lever-pressing, while estradiol withdrawal, similar to the rapid decline in estradiol in postpartum, restored lever-pressing behaviors [11].

The regulation of OC symptoms by reproductive hormones is thought to be mediated by 3 neurotransmitter systems: the serotonergic, dopaminergic, and glutamatergic systems. Generally, impaired serotonergic signaling, and enhanced neurotransmission by dopamine and glutamate have been associated with worsened OCD [12, 13]. These neurotransmitter systems can be modified by hormones including estrogens, progesterone, and oxytocin, and are speculated to be the link between fluctuating hormone levels and altered OCD course during reproductive events.

In the currently existing literature, there appears to be a lack of high-quality evidence from prospective cohort studies assessing OC tendencies along the course of hormone level fluctuations in females. This research gap is partially justified by the difficulty in recruiting and retaining a large sample, and a general aversion to invasive procedures such as blood tests which are necessary for hormone level measurements. Nevertheless, collection of this type of data is necessary to better characterize the relationship between OC symptoms and hormonal changes during female reproductive milestones.

Since clinical studies reporting concurrent measurements of hormone levels and OC symptoms have been sparse, the significance of hormones in OCD course is not conclusively known at this point in time. However, based on the findings reported in the existing literature, this

does appear to be a relationship that warrants further investigation. In order to delineate the relationship between reproductive events and OCD, this article will summarize what is currently known about the effect of gonadal hormones on the neurotransmitter systems implicated in OCD pathology.

Methodology

The present study is a critical review of the literature, examining what is currently known about the effect of reproductive hormones on the neurotransmitter systems implicated in OCD. PubMed, PsychINFO, and OVID were searched for relevant literature. The combinations of keywords used for the searches are presented in Table 1. Reference lists were reviewed for other relevant publications. Articles published in English were retrieved, and no date restrictions were placed.

Neurotransmitter Systems in OCD

Serotonin

Serotonin in OCD

The serotonergic system was first implicated in the pathogenesis of OC symptoms by results from pharmacological studies. Early findings revealed that OC symptoms were alleviated with the administration of the tricyclic antidepressant clomipramine, which is a potent serotonin reuptake inhibitor (SRI) [12]. Other studies have shown that serotonin reuptake agonist metachlorophenyl-piperazine worsened OC symptoms in some patients [14]. This suggests that patients with OCD, or those demonstrating OC symptoms, might have a dysregulation inhibiting sustained serotonin release and/or signaling. Subsequent studies with selective SRIs (SSRIs) such as fluoxetine, paroxetine, sertraline, citalopram, and escitalopram showed comparable effects to treatment with clomipramine [15].

Later studies used more specific physiological measures to confirm the role of serotonin in OCD. The serotonin metabolite 5-hydroxyindoleacetic acid was found to be significantly higher in the cerebrospinal fluid (CSF) of patients with OC symptoms compared to healthy volunteers, suggesting increased brain serotonin turnover, although these results have not always been consistent [12, 16].

Other studies have used single-photon emission computed tomography to measure the availability of serotonin reuptake transporter (SERT) in small samples of OCD patients. Results from this research have been

Table 2. Effect of gonadal hormones on the serotonergic system and OCD symptoms

Hormone	Effect on serotonergic system	Overall effect	Theorized consequence on OCD
Estradiol	↑ TPH ↓ MAO-A ↓ 5-HT _{1A} ↓ 5-HT _{1B} ↑ 5-HT _{2A} ↑ synapse assembly ↑/↓ SERT	↑ serotonin signaling	improved OCD symptoms
Progesterone	↑ TPH ↓ MAO-A ↓ 5-HT _{1A} ↑ 5-HT _{2A}	↑ serotonin signaling	improved OCD symptoms

mixed, showing reduced, increased, and unchanged SERT availability in OCD patients [17–22].

Estradiol and Serotonin

Evidence from the literature points to 4 major effects of estradiol on the serotonergic system: increased serotonin synthesis, decreased serotonin breakdown, modulation of serotonin receptors, and increased synapse assembly [23, 24]. Estradiol does not appear to have a significant effect on the amount of serotonergic neurons in the central nervous system [25].

The ultimate effect of this neuromodulation by estradiol is an increase in serotonin release, and sustained serotonin neurotransmission, which is indicative of an overall protective effect against OCD. Effects of estradiol on the serotonergic system and the presumed implications for OCD are summarized in Table 2.

(1) Evidence for increased serotonin synthesis

Estradiol increases serotonin synthesis through an up-regulation of tryptophan hydroxylase (TPH) – the protein responsible for catalyzing the rate-limiting step in the serotonin synthesis pathway. Previous animal studies have demonstrated increased TPH mRNA levels in the dorsal raphe nuclei and trigeminal ganglia [26, 27]. Estradiol was later found to specifically increase TPH2 (an isoform exclusively expressed in the central nervous system) mRNA in the dorsal raphe nucleus in macaques and rats [28]. These associations are confirmed by evidence from

protein expression studies measuring TPH protein mass in ovariectomized (OVX) animals, unable to endogenously produce estradiol. It was found that OVX guinea pigs and macaques treated with estradiol for 28 days had significantly higher TPH protein mass than the untreated OVX controls [29, 30]. Although not examined in these studies, the increase in serotonin levels as seen in estradiol-treated animals should theoretically lead to the amelioration of OC symptoms. To our knowledge, there has been no investigation into hormone-regulated TPH expression in human subjects.

(2) Evidence for decreased serotonin breakdown

Estradiol decreases serotonin breakdown by inhibiting the activity of monoamine oxidase A (MAO-A) – the enzyme that degrades serotonin into the inactive 5-hydroxyindoleacetic acid metabolite [31]. Administration of estradiol to OVX rats over the course of 1–4 weeks resulted in a 30% decrease in MAO-A activity in the basomedial hypothalamus and corticomedial amygdala, as measured by a radiochemical assay [32]. Similar results were reported in estradiol-treated macaques and rats in various parts of the brain [30, 33, 34]. Despite the decrease in MAO-A after a month of estradiol treatment in the study by Smith et al. [30], the researchers interestingly noted that after 5 months of estradiol administration, MAO-A levels were no different from OVX controls. It was proposed that long-term estradiol treatment increases extracellular serotonin levels to concentrations high enough to induce a negative feedback loop to stimulate MAO-A production, and therefore serotonin metabolism in an effort to maintain homeostasis [30]. This is an important finding as it relates to the human menstrual cycle, where a woman is on a 28-day cycle of transient increases and drops in reproductive hormone levels rather than prolonged periods of stable steroid activity. Around day 22, estrogen levels drop significantly, and the subsequent days before menstruation have been associated with significant exacerbation of OC symptoms in as many as 49% of women in one study [35]. Women on birth control present an interesting case, as the pills are taken to stabilize hormone levels, which possibly leads to the inadvertent induction of feedback loops to regulate neurotransmitter levels, similar to the phenomenon observed by Smith et al. [30]. To our knowledge, there has been no investigation into the effect of hormonal contraceptives on OCD severity; however, they have been associated with other psychiatric disorders including depression [36].

To date, only a limited number of studies testing the relationship between estradiol and MAO activity have

been conducted in human subjects. A study by Sacher et al. [37] used carbon 11-labeled harmine positron emission tomography (PET) to measure MAO-A binding (a surrogate measure of MAO-A activity) in postpartum. Compared to controls, MAO-A distribution was found to be 43% higher in 4- to 6-day postpartum women, who may experience up to a 1,000-fold drop in estradiol levels during this time [37]. A methodologically similar study conducted in perimenopausal women, found MAO-A distribution to be 34 and 16% higher in perimenopausal women compared to women of reproductive age, and those undergoing menopause, respectively [38]. Perimenopause is associated with estradiol level fluctuations, with episodes of significant estradiol level decline, and as such is correlated with increased MAO-A density [38]. Increased MAO-A density associated with decreased estradiol may help explain the onset or worsening of OCD during reproductive events.

(3) Evidence for modulation of serotonin transporters and receptors

A substantial amount of evidence has also implicated estradiol in the modulation of a number of different serotonin transporters and receptors.

Estradiol administration has been shown to have variable effects on SERT – the protein involved in reuptake of serotonin from the synaptic cleft. In studies of acute estradiol exposure in rats, SERT proteins were shown to be upregulated in both the raphe nuclei and the hypothalamus [39, 40]. In contrast, chronic estradiol administration in macaques was associated with decreased levels of SERT in the raphe nuclei [41] and increased SERT activity in the basal ganglia and hypothalamic nuclei in several animal studies [30, 42]. Yet still, other studies found that treatment with estradiol in OVX macaques either increased or did not change SERT binding in various brain regions, and did not change SERT binding in rats [43].

Data from human studies have demonstrated a higher degree of consistency. A recent clinical investigation found that after a treatment period of 18 days, subjects treated with gonadotropin-releasing hormone, which is intended to model ovarian sex hormone fluctuation, demonstrated significantly higher depressive symptoms, which were positively associated with decreased estradiol levels, and increased neocortical SERT binding [44]. Other recent studies in transsexual and postmenopausal patient cohorts report an inverse association between estradiol levels and SERT activity – increasing estradiol results in a downregulation of SERT [45, 46].

Estradiol administration has generally been shown to downregulate expression of the 5-HT_{1A} and 5-HT_{1B} re-

ceptors in a region-specific manner. The 5-HT_{1A} and 5-HT_{1B} receptors are autoreceptors that have an inhibitory role over serotonergic transmission, and have been implicated in many anxiety disorders [31, 47]. The majority of research in OVX animals has consistently reported a downregulation of 5-HT_{1A} mRNA expression and/or protein binding in various brain regions [48, 49]. Estradiol has also been suggested to desensitize signaling via the 5-HT_{1A} receptor in the paraventricular nucleus [50]. Other studies have found no significant change in 5-HT_{1A} mRNA levels in the rat dorsal raphe nuclei, and instead only report a decrease in the 5-HT_{1B} autoreceptor subtype [51]. Levels of 5-HT_{1A} in estradiol-treated postmenopausal women also appeared unchanged [52].

In contrast, the 5-HT_{2A} receptor was shown to increase in density with the administration of estradiol. The 5-HT_{2A} receptors mediate serotonergic signaling, and are found on both pre- and postsynaptic neurons, as well as on other nonserotonergic neurons, for example those involved in dopamine signaling [53]. A study examining 5-HT_{2A} density after estradiol treatment in OVX rats, found a significant increase in the raphe nuclei and forebrain [54]. Binding to 5-HT_{2A} was also increased in the frontal cortex and striatum of estradiol-treated macaques [49]. In studies of human patients on hormone replacement therapy, PET scans revealed increased 5-HT_{2A} levels in the prefrontal cortex, anterior cingulate cortex (ACC), frontal gyrus, and cerebral regions [55, 56]. Another study found downregulation of 5-HT_{2A} receptors in long-term estradiol therapy users, and this was characterized as a compensatory mechanism for increased synaptic serotonin supposedly induced by estradiol [57]. The evidence suggests estradiol increases serotonin signaling through an upregulation of serotonin receptors and downregulation of autoreceptors which is hypothesized to improve OCD symptoms.

(4) Evidence for increased synapse assembly

A study by Bethea and Reddy [23] investigated the effects of estradiol and progesterone on the gene expression of proteins involved in the assembly of synapses. These effects were studied in serotonergic neurons of OVX rhesus macaques treated with placebo, estradiol, or an estradiol-progesterone combination. It was found that estradiol treatment increased expression of genes coding for synapse molecules such as ephrin receptor A4, cadherin 11, neurexin 3, integrin A8, and neural cell adhesion molecule, compared to placebo. The progesterone in the combination treatment appeared to suppress the estradiol-induced increase in gene expression [23].

Progesterone and Serotonin

Investigation into the effects of progesterone on serotonin neurotransmission has been more limited. Effects of progesterone on serotonin neurotransmission and its presumed effects on OCD symptoms are summarized in Table 2.

A study by Lu et al. [58] explored the effects of estradiol and progesterone on the TPH enzyme. It was found that in the hypothalamus of OVX rats, treatment with estradiol and progesterone resulted in levels of the TPH enzyme similar to those in rats treated with estradiol alone. However, treatment with estradiol and progesterone, but not estradiol alone, significantly increased serotonin levels. The authors suggest that this discrepancy is due to the absence of nuclear progesterone receptors in serotonergic neurons, thereby limiting progesterone's influence over TPH levels. Progesterone's effect on serotonin concentrations themselves is thought to be modulated by a nonnuclear receptor mechanism [58]. Other studies reported that progesterone alone was in fact sufficient to increase TPH protein levels in the dorsal raphe nuclei [28, 29]. Further conflicting results reported a decrease in serotonergic activity after the administration of progesterone in rats [59].

Progesterone has not been shown to significantly alter SERT expression, as no significant difference in SERT levels was detected between groups treated with estradiol and progesterone, and estradiol alone [41, 60]. On the other hand, there is evidence suggesting progesterone treatment significantly decreases MAO-A levels in various brain regions in animal models [61, 62]. Downregulation of the 5-HT_{1A} autoreceptor has also been reported after treatment with progesterone [60, 63]. In contrast, increasing progesterone dose in conjunction with estradiol treatment results in increased mRNA expression of 5-HT_{2A} in the ventral hippocampus [64]. Thus, like estradiol, progesterone appears to increase serotonin signaling, which may be neuroprotective against OCD.

Although numerous studies have demonstrated the effectiveness of SRIs as a primary treatment option for OCD, there appears to be a subset of OCD patients that are resistant to SRI treatment [65]. Furthermore, pharmacological challenge studies of the serotonin system, as well as studies measuring serotonin metabolite levels in the CSF have not always shown consistent results [66]. This points to the possibility of the involvement of other neurochemical systems in OCD pathology.

Fig. 1. Downstream interactions of the 3 neurotransmitter systems involved in OCD. In the event of low serotonin levels, possibly occurring as a consequence of low estradiol, the quantities of serotonin are insufficient to inhibit dopamine signaling via 5-HT_{2A} receptors. This results in increased dopaminergic tone, which has also been identified in some OCD patients. Increased dopaminergic signals from the substantia nigra pars compacta to the striatum, mediated by D1 receptors, increase GABA release from the striatum to the globus pallidus internal and substantia nigra reticulata, thus skewing the cortico-striato-thalamo-cortical loop towards the direct pathway.

Dopamine

Dopamine in OCD

The neurotransmitter dopamine has also been implicated in OCD pathology. Studies have demonstrated that administration of dopamine agonists leads to an exacerbation of OC symptoms, while dopamine blockers have been effectively used in treatment of some OCD spectrum disorders including Tourette's syndrome [12, 67]. Administration of the dopamine D2/D3 receptor agonist quinpirole has been shown to increase compulsive checking in rat models of OCD [68, 69].

Treatment with the SSRI fluvoxamine, increased D2 receptor binding, and was accompanied by an improvement in symptoms [70]. It was suggested that this modification of D2 receptor availability is a result of fluvoxamine's modulation of the serotonergic system. Serotonergic neurons projecting from the raphe nuclei are thought to modulate the cortico-striato-thalamo-cortical (CSTC) loop that is associated with OCD, in which dopamine is the dominant neurotransmitter [65]. When serotonin is released from a presynaptic neuron, it may bind to 5-HT_{2A} receptors on the somatodendritic surface of dopamine neurons. This interaction has an inhibitory effect on the dopamine neuron, which will reduce the release of dopamine into the synaptic cleft and consequently prevent further downstream dopamine signaling [71]. In the presence of an SSRI, there will be sustained serotonin signaling, resulting in a prolonged inhibitory effect

on the dopaminergic system. Conversely, in the absence of serotonin, or in the presence of a 5-HT_{2A} antagonist or 5-HT_{1A} autoreceptor agonist, the dopamine neuron may release its neurotransmitter to activate a dopamine signaling cascade (Fig. 1) [71]. As previously discussed, since OCD patients are thought to have impaired serotonin signaling, it is possible that this deficiency is leading to dopaminergic hyperactivity, characteristic of OCD [65].

When research revealed that there is some modulation of the dopaminergic system by serotonin, investigators proposed that concomitant use of SSRIs and dopaminergic antagonists may be an effective option for SSRI treatment-refractory patients [65, 71]. Indeed, co-administration of the 2 drugs appeared to be quite efficacious in a number of trials, including an open trial by Metin's group that showed a significant improvement in 95% of the patients treated with an SSRI and amisulpiride [72, 73].

A number of studies have also aimed to characterize dysregulations of the dopaminergic system in OCD patients through in vivo brain scans. Olver et al. [74, 75] used PET scans to assess binding of [¹¹C]-SCH23390, a dopamine D1 antagonist ligand, to the dopamine D1 receptor in untreated OCD patients. Receptor binding was found to be reduced in the caudate nucleus, putamen, and the ACC. This decreased D1 binding is thought to reflect a downregulation of D1 receptors as a compensatory mechanism for the increased dopaminergic drive from the substantia nigra pars compacta (SNc). This in-

Fig. 2. The cortico-striato-thalamo-cortical circuit in OCD. In OCD, increased glutamatergic signaling from the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) is thought to increase striatal inhibitory action on globus pallidus internal (GPi) and substantia nigra reticulata (SNr), ultimately reducing inhibition of the thalamus, which will continue increasing glutamate signaling to the OFC/ACC in a positive-feedback loop. Alternatively, a striatal defect decreases inhibition of globus pallidus external (GPe), which will increase subthalamic nucleus (STN) inhibition and decrease GPi/SNr excitation. In OCD, the balance between the direct and indirect pathways is skewed towards the former. Adapted from Pauls et al. [119].

creased dopaminergic activity from the SNc is thought to create an imbalance in the CSTC loop (Fig. 1, 2) [74]. It is suggested that in OCD there is increased stimulation of the ACC from the ventral tegmental area via D1 receptors [75]. Increased activation of the ACC has been previously shown to create a sense that something is ‘not right’ and may drive obsessions and compulsions in OCD patients [76]. Similar experiments have been performed to study D2 function, and demonstrated similar trends – reduced D2 receptor binding in the striatum [77, 78].

There has also been some investigation into the potential role of the dopamine transporter (DAT) in OCD. One study found higher DAT densities in the left basal ganglia of OCD patients, measured using [^{123}I] β -CIT binding ratios and single-photon emission computed tomography [79]. The researchers propose the increase in DAT density may be due to an inherent abnormality of the transporter itself, or may be a negative feedback mechanism in response to increased dopaminergic tone; the exact cause of this phenomenon is yet to be elucidated. In OCD patients treated with the SSRI citalopram, one study reported a 40% increase in DAT availability, which is thought to be a consequence of decreased synaptic dopamine levels due to the previously discussed serotonin-dopamine interactions [80].

Estradiol and Dopamine

Early studies have shown that neurotransmission by the dopaminergic system changes at various points of the menstrual cycle, suggesting a possible role of the gonadal hormones in modulating the neurosignaling pathway [81]. Existing literature suggests that estradiol modulates dopaminergic signaling through variations in tyrosine hydroxylase activity, dopamine release, and DAT and receptor expression [82]. This evidence is summarized in Table 3.

(1) Evidence for increased tyrosine hydroxylase activity

To date, only 2 studies investigating the effect of estrogens on tyrosine hydroxylase in OVX animals have been conducted. Estradiol was found to increase tyrosine hydroxylase immunoreactive neurons in the substantia nigra of rats, while in macaques, this effect was observed in the caudate nucleus and putamen [83, 84].

(2) Evidence for increased dopamine release

Estradiol has been found to increase dopamine release in the caudate-putamen and in the nucleus accumbens [85]. Estrogens are thought to be capable of interacting with dopaminergic neurons directly to downregulate D2 autoreceptors, as well as indirectly by inhibiting GABAergic neurons which have recurrent collaterals onto dopamine terminals [85]. In animal studies, ovariectomy

Table 3. Effect of gonadal hormones on the dopaminergic system and OCD symptoms

Hormone	Effect on dopaminergic system	Overall effect	Theorized consequence on OCD
Estradiol	↑ TH ↑ DA release ↑ D1 ↓ D3	↑ dopamine signaling	worsened OCD symptoms
	unclear effect on DAT and D2	↓ dopamine signaling	improved OCD symptoms
		unknown effect on dopamine signaling	unknown effect on OCD symptoms
Progesterone	↑ TH	↑ dopamine signaling	worsened OCD symptoms
	unclear effect on DA release, DAT and D2	unknown effect on dopamine signaling	unknown effect on OCD symptoms

was found to decrease dopamine release which was reversed with subsequent estradiol treatment [86, 87].

(3) Dopamine transporter

The expression of DAT fluctuates at the various stages of the menstrual cycle [81]. Ovariectomy in rats has been shown to decrease DAT density [88]. However, upon administration of estradiol treatment, these effects were shown to be corrected [89]. A study in postmenopausal women similarly found that estradiol replacement therapy produced an increase in DAT density in the left anterior putamen [90]. However, this effect seems to be region-specific as no such renewal of DAT levels was observed in the substantia nigra, amygdala, hypothalamus, midbrain, nucleus accumbens, ventral tegmental area, or in the striatum as reported by other animal studies [88, 91]. Yet still, conflicting evidence was reported by another study which found that ovariectomy increased DAT in the striatum, and subsequent estradiol treatment reduced levels back to normal [92].

(4) Dopamine receptors

Expression of D1 receptors in the striatum is thought to be modulated by gonadal hormones as evidenced by fluctuations in receptor density during the menstrual cycle [93]. Ovariectomy was associated with decreased D1 receptor density, but this effect was reversed with chronic estradiol treatment [94–97].

Evidence for the effect of estrogen on D2 receptors has been conflicting. One study reported increased D2 den-

sity in the nucleus accumbens and caudate nucleus of OVX rats, which was attenuated with estradiol treatment [43]. Estradiol has also been shown to induce a shift of D2 receptors from high- to low-affinity states [98]. Others have reported the opposite, with estradiol increasing D2 density in the striatum of OVX rats [81, 99]. In a human study, no changes in D2 receptor density were detected by PET scans at different phases of the menstrual cycle [100].

Although ovariectomy appeared to have no significant effects on D3 receptor binding, treatment with estradiol decreased receptor binding in the island of Calleja, the nucleus accumbens, and the anterior striatum [99]. The effect of the gonadal hormones on the D4 and D5 receptors has not been well characterized.

At this point in time, it is difficult to draw conclusions about estradiol's overall effect on dopaminergic signaling. Estradiol treatment in animal models appears to increase dopamine synthesis and release, which would suggest that periods of elevated estradiol could lead to worsening of OC symptoms. This is inconsistent with the current understanding of the serotonin-dopamine interactions, in which elevated serotonin, presumably occurring in relation to high estradiol levels, inhibits dopamine release. Further research is needed to better characterize these relationships in the context of OCD.

Progesterone and Dopamine

Studies examining modulation of dopaminergic activity by progesterone have been more limited in number. Effects of progesterone on dopamine neurotransmission are summarized in Table 3.

Physiological doses of progesterone were found to increase release of dopamine in the striatum of OVX rats [101, 102]. In contrast, in other studies, progesterone did not appear to have a significant effect on dopamine release in OVX rats that had not been pretreated with estradiol [103]. This suggested that estradiol is necessary in the mechanism of neuromodulation by progesterone. One study also found an increase in tyrosine hydroxylase immunoreactive neurons in the caudate nucleus and putamen after progesterone treatment of OVX macaques [84].

The dopamine receptors are also under the influence of progesterone. In the striatum and substantia nigra, DAT density increases with chronic progesterone treatment with a pharmacological dose [104]. Others reported no such effect in either rats treated with acute or chronic progesterone treatment [92, 105]. With regard to the D2

receptor, acute but not chronic progesterone treatment decreased binding density [106, 107].

As with the estrogen-dopamine relationship, the effects of progesterone on the dopaminergic system are variable with some components being upregulated, while others are inhibited. As such, it is difficult to draw conclusions about the role of this relationship in OCD. Dysregulated dopamine signaling can have additional consequences on signaling in the CSTC loop, leading to further dysregulation of the glutamate neurotransmitter system.

Glutamate

Glutamate in OCD

The first line of evidence suggesting the involvement of glutamate in OC etiology comes from examination of CSF samples. To date, 2 studies have been conducted to measure the levels of glutamate in the CSF of untreated OCD patients. Both have found significantly higher glutamate levels in the CSF of OCD patients compared to controls [108, 109]. Evidence from magnetic resonance spectroscopy studies used to measure glutamate brain concentrations in OCD patients showed elevated levels in the caudate nucleus and reduced levels in the ACC [110, 111]. However, a more recent study using 3T proton-magnetic resonance spectroscopy to quantify neurometabolite concentrations in the ACC, found no difference in concentration of glutamate plus glutamine in OCD patients compared to healthy controls [112].

The possibility of glutamatergic system involvement in OCD pathology has also spurred some interest in the effect of glutamate-modulating agents in the treatment of OCD [13]. Riluzole, which inhibits specific voltage-gated sodium channels, reduces glutamate release, in addition to enhancing glial uptake of extrasynaptic glutamate [113]. Riluzole has shown some positive clinical responses in refractory OCD patients [114]. However, in more controlled studies, results have shown only minimal benefits [115, 116].

Another drug target that has been explored for treatment of OC symptoms is the N-methyl-D-aspartate (NMDA) excitatory glutamate receptors. As described above, some studies have shown increased central nervous system glutamate concentrations in OCD patients; therefore, NMDA receptor antagonism has been proposed to dampen excess glutamate signaling. Memantine and ketamine, NMDA receptor blockers, have produced some positive results in small clinical trials [13].

Overall, investigations of glutamate involvement in OCD pathology have yielded interesting results that appear to be promising avenues for future research. How-

ever, to date, many of the findings have been far from conclusive; thus, the glutamatergic system is only speculated to be involved in OCD at this point in time [117].

The CSTC Circuit in OCD

It has been suggested that glutamate hyperactivity creates an imbalance in signaling in the CSTC circuitry, which has been implicated in OCD [118]. In a normally functioning CSTC circuit, glutamatergic signals from the OFC and the ACC excite the striatum. From this point, a balance of 2 pathways is possible: (1) direct pathway: striatal activation sends inhibitory γ -aminobutyric acid (GABA) signals to the globus pallidus internal (GPi) and the substantia nigra reticulata (SNr), which in turn decrease GABA output from the GPi and SNr to the thalamus, leading to excitatory glutamatergic output from the thalamus to the OFC and ACC; (2) indirect pathway: striatal activation inhibits the globus pallidus external, which decreases its inhibitory signals to the subthalamic nucleus (STN), which is now free to excite the GPi and SNr which will inhibit the thalamus and subsequent activation of the OFC and ACC [119]. These pathways are illustrated in Figure 2. It has been proposed that a skewing of the balance towards the direct pathway, which may be associated with glutamate hyperactivity, could lead to OC symptom development [118]. This ultimately results in increased stimulation of the OFC, which mediates exaggerated concerns about danger, hygiene, and harm, resulting in persistent attention to the perceived threat, followed by compulsions aimed to address the threat. Alternatively, it is speculated that a dysfunction of the striatum decreases inhibition of GPe, leading to increased inhibition of the STN, effectively decreasing excitation of the GPi/SNr similarly increasing excitatory output from the thalamus to the OFC [120]. In terms of the nature of the glutamatergic dysfunction, evidence points to postsynaptic dysfunction in glutamate signaling to explain the changes seen in the CSTC circuitry of OCD patients. Specifically, the glutamate transporter EAAT3/EAAC1, which is located on postsynaptic membranes is thought to be involved [118].

Estradiol and Glutamate

Estrogens are well known to modulate glutamatergic activity in the central nervous system. Studies in rats have suggested that estrogen demonstrates regionally specific effects on glutamate receptors in the brain. The literature suggests that estrogen exerts its effects on the glutamatergic system by modulating presynaptic glutamate release, and regulation of receptor and protein expression. These

Table 4. Effect of gonadal hormones on the glutamatergic system and OCD symptoms

Hormone	Effect on glutamatergic system	Overall effect	Theorized consequence on OCD
Estradiol	↑ glutamate release ↑ NMDA receptor ↑ mGluR1 ↑ synapse assembly unclear effect on AMPA receptor and EAAT	↑ glutamate signaling	worsened OCD symptoms
Progesterone	↑ EAAT3	↓ glutamate signaling	improved OCD symptoms

effects, as well as the presumed consequences for OCD symptoms are summarized in Table 4.

(1) Evidence for increased presynaptic glutamate release

Evidence demonstrates that estradiol increases glutamate release in the hippocampus. Studies applying estradiol to hippocampal brain slices noted increased excitatory postsynaptic potential slopes [121, 122]. A study by Schwarz et al. [123] found that estradiol also increases glutamate release in the hypothalamus, activating a signaling cascade that leads to dendritic spine formation, and creation of new synapses.

However, estrogen has also been shown to play a neuroprotective role against glutamate excitotoxicity, suggesting that it may also act to inhibit glutamatergic neurotransmission. Kuo et al. [124] found that administration of tamoxifen, an estrogen receptor (ER) modulator, inhibits Ca^{2+} entry into the presynaptic neuron, thereby inhibiting protein kinase C, which is needed for presynaptic glutamate exocytosis. Other possible mechanisms include activation of metabotropic glutamate receptors (mGluRs), and modulation of NMDARs in cases of increased intracellular Ca^{2+} concentrations [125].

(2) Evidence for glutamate receptor modulation

In OVX rats, it has been shown that estradiol treatment increases mRNA and protein expression levels of NMDA [126]. Estradiol has also been shown to increase NMDA receptors in the dentate gyrus of the hippocampus, while in the frontal cortex and caudate putamen, a decrease in NMDA receptors was observed. Conversely, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor density in the frontal cortex, caudate

putamen, and nucleus accumbens was observed to decrease with estradiol treatment [127]. However, a later study by Le Saux and Di Paolo [128] found that estradiol increases AMPA binding in the prefrontal cortex, cingulate cortex, and striatum, and that these effects are mediated by ER- α . The extracellular ER GPR30 is also suggested to be involved in modulation of AMPA, as a GPR30 agonist was shown to upregulate production of the GluR1 subunit of the AMPA receptor [129].

Estradiol has also been shown to modulate the activity of the mGluRs. In one study, treatment of hippocampal slices of OVX rats with estradiol benzoate resulted in increased mGluR1 protein expression. The downstream effect was an increase in NMDARs, suggesting that estradiol does not directly affect the NMDAR, but rather does so through an mGluR1-dependent mechanism [130].

(3) Evidence for glutamate transporter modulation

Investigations into the effect of estradiol on the EAATs have produced inconsistent results. Some studies found that treatment with estradiol enhanced EAAT activity in astrocytes [131, 132]. In contrast, 1 study reported a decrease in glutamate uptake, with another study still reporting no change in EAAT1 and EAAT2 levels in response to estradiol treatment [133, 134].

(4) Evidence for upregulation of synaptic proteins

Several studies in the literature have implicated estradiol in the formation of new glutamatergic synapses. Cultured hippocampal neurons exposed to acute estradiol treatment demonstrated an increase in vesicular glutamate transporter and NMDA subunits on the dendrites of the cells, suggesting an increase in synaptic density [135]. Subsequent inhibition of this phenomenon with ER antagonists and enhancement with ER agonists further confirmed the role of estradiol and its receptors in synapse formation [135]. It was found that estradiol upregulates a number of synaptic proteins in the hippocampus including GluR1 and Kalirin-7 [136, 137].

Based on our current understanding, excessive glutamate signaling in the CSTC loop may be involved in OCD. However, it is difficult to determine the role of estradiol in this signaling pathway as results from investigations have been inconsistent, suggesting estradiol both up- and downregulates different components of the glutamatergic neurotransmitter system.

Progesterone and Glutamate

The neuromodulatory effects of progesterone on glutamatergic signaling have been less well characterized. One study found that progesterone had no effect on spontaneous glutamate release, but appeared to inhibit dopa-

mine-evoked glutamate release [138]. The investigators speculate that progesterone blocks the sigma-1 receptors, which act synergistically with the dopamine D1 receptor to inhibit downstream signaling eventually inhibiting glutamate release.

Bethea and Reddy studied expression of a variety of glutamatergic synaptic proteins in the midbrain of OVX macaques after estradiol or estradiol and progesterone combination therapy. While estradiol and estradiol and progesterone treatments induced significant upregulation of several glutamatergic synaptic proteins, the effects of estradiol and progesterone combination treatment were not significantly different from those of estradiol alone. Progesterone is thought to induce only minor upregulation of the aforementioned proteins [139]. Another study to examine the effect of progesterone on NMDA also found no enhanced receptor binding effects [140]. In a study by Cyr et al. [127], progesterone treatment in OVX rats was found to decrease NMDA but not AMPA binding density in the frontal cortex, and had no effect in the hippocampus, dentate gyrus, striatum, and nucleus accumbens. Another study showed significantly enhanced EAAT3 activity after progesterone treatment performed in frog oocytes [141]. Mitrovic et al. [142] studied this association in cell cultures from rat brain and similarly found that EAAT affinity for glutamate was highest during proestrous and estrous periods, which are characterized by peak levels of both estradiol and progesterone. No acute effects of progesterone were observed in EAAT1 or EAAT2, leading the researchers to suggest that regulation is done through a genomic mechanism which usually takes a longer time to induce observable changes [142].

Oxytocin in OCD

There have been a few studies attempting to associate oxytocin directly with OC symptoms; however, results have been inconsistent. It has been previously reported that there are elevated oxytocin plasma levels in OCD patients [143, 144]. Since OC behaviors appear to be extreme versions of the behaviors induced by oxytocin, it is thought that the hormone may play a neuroregulatory role in OCD pathology [145]. Humble et al. [146] found a positive correlation between oxytocin levels and Y-BOCS scores amongst SRI-responsive patients (2013). Furthermore, treatment with the SRIs clomipramine and paroxetine modulated oxytocin levels, suggesting another antiobsessive function of SRIs. Other studies have reported no association between oxytocin and OCD [147, 148]. These results should be interpreted with caution as only small samples of patients were used.

Alternatively, oxytocin may be involved in OCD pathology through its neuromodulatory effects on other neurotransmitter systems. A study by Yoshida et al. [149] has suggested that oxytocin increases serotonin release. Evidence has led to the speculation that this is a result of direct activation of the oxytocin receptor found in serotonergic neurons, specifically in the raphe nuclei [149].

Hormonal Modulation of OC Symptoms

The neuromodulatory effects of estradiol have been investigated much more extensively compared to those of other reproductive hormones. Increased estradiol levels have been shown to increase serotonergic neurotransmission, which has been associated with an improvement in symptoms. Results from dopamine and glutamate signaling have been much more variable, as such making it difficult to draw an overall conclusion.

These results are also consistent with the clinical data. Vulink et al. [35] reported an exacerbation of OC symptoms in healthy controls beginning 4 days before the start of menstruation. Estradiol is known to decrease around the 22nd day of a 28-day cycle; thus, an exacerbation of OC symptoms after this time would be expected. During pregnancy, estradiol levels gradually increase over the course of the 9-month period. Interestingly, a study by Kaya et al. [150] found that the onset of pregnancy-related OCD was much more common in the first and second trimesters, which are characterized by comparatively lower estradiol levels than the third trimester. The early postpartum period is known to involve as much as a 1,000-fold drop in estradiol levels compared to the pregnant state [37]. Other studies have reported up to 50 and 25% of subjects experiencing worsening and onset in the postpartum period, respectively [151]. Women may be more prone to developing or experiencing a worsening of OC symptoms during this time of low neuroprotective estradiol levels.

Progesterone has been studied less thoroughly; however, it also generally appears to increase serotonin neurotransmission. Similarly to estradiol, progesterone levels also drop around the 22nd day of the menstrual cycle; thus, the results of Vulink et al. [35] may also be attributed to decreased progesterone levels. Additionally, progesterone levels increase during pregnancy, and plummet after delivery, and could therefore also be an impetus to pregnancy- or postpartum-related OCD.

Evidence for involvement of oxytocin in modulation of OC symptoms is currently inconclusive, and further

investigation is necessary to confirm its role. With some studies reporting high oxytocin plasma levels in individuals with OCD, it is possible that the increase in oxytocin during delivery and breastfeeding in the postpartum period may also contribute to development or worsening of OC symptoms.

Although not much is known about its role in OCD, the reproductive hormone testosterone has also been shown to increase during pregnancy [152, 153]. Testosterone, which is known to modulate neurotransmission, may be another hormone worth studying in pregnancy-related OCD. Maternal plasma testosterone levels, which differ depending on the sex of the offspring may have a differential impact on OCD severity [153].

As with most other psychiatric disorders, OCD appears to have a number of alternative factors that contribute to the illness. While the hormonal changes during female reproductive events are a plausible mechanism for changes in OCD course, they may only serve as a precipitating factor in individuals already predisposed to the condition. Furthermore, although this review examined

each neurotransmitter separately, it is important to keep in mind that the brain is an intricate system of signaling pathways that do not function independently and may all become dysregulated in the OCD pathological state (Fig. 1).

Conclusion

Current lines of evidence suggest a role for gonadal hormones in OCD pathology. Estrogen and progesterone have been shown to modulate serotonergic, dopaminergic, and glutamatergic neurotransmission, and these neurotransmitter systems have been shown to be dysregulated in OC patients. From this evidence, it can be inferred that hormones play an important role in influencing the course of OCD. Further investigation into this relationship is warranted. Future studies should prospectively evaluate OC symptom severity along the course of female reproductive events, with concurrent measurements of hormone levels.

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