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Fluoxetine-Induced Decrements in Sexual Responses of Female Rats and Hamsters Are Reversed by 3 α ,5 α -THP

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Abstract

Introduction—Sexual dysfunction, as a result of selective-serotonin reuptake inhibitor (SSRI) treatment among women, is relatively common and is a factor in medication compliance. The mechanisms that underlie these side-effects of SSRIs are not well-understood. SSRIs can alter activity of catabolic enzymes that are involved in progesterone's conversion to 5 α -pregnan-3 α -ol-20-one (3 α ,5 α -THP). 3 α ,5 α -THP plays a key role in female reproductive physiology and behavior.

Aims—This study aimed to determine whether 3 α ,5 α -THP, in the midbrain ventral tegmental area (VTA) may be a potential mechanism for fluoxetine's reduction in sexual responding of female rodents. We hypothesized that if fluoxetine induces decrements in sexual responding in part through actions of 3 α ,5 α -THP, then fluoxetine will inhibit sexual receptivity concomitant with reducing 3 α ,5 α -THP levels, effects which can be reversed by 3 α ,5 α -THP administration.

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Methods—Experiment 1 investigated effects of acute systemic fluoxetine [20 mg/kg intraperitoneal (IP)] and/or 3 α ,5 α -THP [500 μ g, subcutaneous (SC)] administration on sexual responding of ovariectomized, hormone-primed rats. Experiment 2 examined effects of 3 α ,5 α -THP administration to the midbrain VTA (100 ng) on fluoxetine-induced decrements in lordosis of ovariectomized, hormone-primed rats and hamsters.

Main Outcome Measures—Sexual responding was determined in rats and hamsters. For rats, the percentage of times that the lordosis response occurred following mounting by a sexually-vigorous male (lordosis quotients) was utilized. For hamsters, lateral displacement, the pelvic movement that females will make to facilitate intromissions by a male hamster, was utilized.

Results—Fluoxetine significantly reduced lordosis, and this was reversed SC 3 α ,5 α -THP. Intra-VTA 3 α ,5 α -THP attenuated fluoxetine's detrimental effects on lordosis quotients and lateral displacement of rats and hamsters, respectively.

Conclusions—Thus, fluoxetine's effects to disrupt female sexual responses may involve its effects on progesterogens in the midbrain VTA.

Keywords

Lordosis; Sexual Function; SSRI; Anti-depressant; Neurosteroids; Fluoxetine-Associated Sexual Dysfunction

Introduction

The use of selective serotonin reuptake inhibitors (SSRIs) as therapeutics has expanded beyond the treatment of major depressive disorder. In addition to depression, SSRIs are now commonly used to treat premenstrual and post-partum disorders, anxiety disorders, eating disorders, and obsessive-compulsive disorder [1–3]. Although SSRIs are effective in the treatment of many neuropsychiatric diseases, one of the well-known side-effects of this class of therapeutics is sexual dysfunction, and this is one of the primary reasons for discontinuation of SSRI therapy [4–9]. Lack of desire, arousal, and/or pleasure during sexual activity significantly impairs quality of life and relationship satisfaction among women [10–12]. Notably, the disorders that are most commonly treated with SSRIs tend to be more prevalent among women than men [13]. Given the common use of SSRIs as therapeutics, it is important to understand the mechanisms by which they have both their beneficial effects and their negative side-effects.

Sexual dysfunction is a common side-effect of SSRIs, and it has been reported that over 1/3 of women using SSRIs therapeutically experience sexual dysfunction of some kind [14]. According to the DSM-IV-TR, sexual dysfunction from pharmacotherapies, such as SSRIs, involve disturbances in all components of the sexual response cycle and these symptoms typically develop within 2–4 weeks of the beginning of treatment [15,16]. For example, among women, sexual dysfunction that has been reported following SSRI treatments are reduced libido and anorgasmia or delayed orgasm, which are the most commonly reported side-effects among women [16–20]. There are reports of sexual dysfunctions among women with treatment with all SSRIs (fluoxetine, paroxetine, sertraline, etc.) that may differ modestly depending on the SSRI and dosing [15]. There is also evidence of disruption in reproductive physiology and behavior in animal models. For example, fluoxetine administration disrupts estrous cyclicity and lordosis of female rats when administered chronically [21]. Female hamsters in behavioral estrus have reduced lateral displacement movements, which is a measure of sensitivity to reproductively-relevant stimuli, following administration of an acute fluoxetine regimen [22]. Furthermore, there are modest effects of fluoxetine to reduce the time female rats spend near a sexually-experienced male in a male

preference test, depending upon dosing regimen [23]. Some of these effects may be due, in part, to disruptions in central actions of ovarian hormones, such as progesterone. Ovarian progesterone is an important steroid regulating sexual behavior [24]. In rodents, its actions in ventromedial hypothalamus (VMH) are essential for normative expression of lordosis (the reflexive posture female rats and hamsters demonstrate in order to allow copulation to occur) [25–28]. Despite the relatively high incidence of SSRI-related sexual dysfunction among women, there has been little research into the possible mechanisms by which these effects might occur.

Reproduction-related behavior (i.e., lordosis, social interaction, proceptivity) of female rodents is also mediated, in part, by actions of progesterone's metabolite, 3 α -hydroxy-5 α -pregnan-20-one (3 α ,5 α -THP), in the midbrain ventral tegmental area (VTA) [29–31]. The conversion of progesterone to 3 α ,5 α -THP occurs via actions of the 5 α -reductase and 3 α -hydroxysteroid dehydrogenase enzymes (3 α -HSD) [31]. While progesterone can have classic actions via intracellular progesterin receptors to mediate lordosis in the VMH [25–28], in the VTA there are virtually no functional progesterin receptors. Progesterone-mediated lordosis is known to occur via 3 α ,5 α -THP's actions at neurotransmitter targets, such as GABA and dopamine [29,32,33].

Genes for factors that mediate neurosteroidogenesis, such as steroidogenic acute regulatory protein (STARD1) and P450scc (CYP11A1), which are rate-limiting factors in the transport of cholesterol across mitochondrial membranes and its subsequent conversion to pregnanolone, are localized to brain regions important for sexual function of rodents [30,34–36]. Lordosis of female rodents is a hormonally-mediated sexual response, which is modulated in part by activity of these factors involved in gonadal steroid metabolism. In support, progesterone administration to mice deficient in the 5 α -reductase enzyme, exhibit deficits in social behavior and reduced brain levels of 3 α ,5 α -THP, compared with their wildtype littermates [37]. Blocking progesterone's conversion to 3 α ,5 α -THP, either systemically or in the VTA, decreases lordosis of female rats, mice, and hamsters, concomitant with reducing levels of 3 α ,5 α -THP in the VTA [29,38]. In contrast, enhancing activity of 5 α -reductase and 3 β -hydroxysteroid dehydrogenase facilitates lordosis of rats and hamsters and increases 3 α ,5 α -THP levels in the VTA [39–42]. Together, these data suggest that reproductive behavior of female rodents is modulated, in part, by actions of 3 α ,5 α -THP in the midbrain VTA.

Aims

This study aimed to determine whether the progesterone metabolite, and neurosteroid 3 α ,5 α -THP may be a potential mechanism for fluoxetine's reduction in sexual responding of female rodents. We hypothesized that fluoxetine's effects on sexual receptivity of rodents may be influenced by 3 α ,5 α -THP levels in the VTA. The present study investigated whether administration of 3 α ,5 α -THP systemically, or to the midbrain VTA, could mitigate fluoxetine-induced decrements in lordosis and proceptive behaviors of rats and lateral displacement responses of hamsters. Rats and hamsters, in the present study, were ovariectomized and primed with estrogen and progesterone regimen that produce circulating levels of these steroids akin to levels during behavioral estrus. In this study, an acute regimen of fluoxetine and 3 α ,5 α -THP was utilized to address whether actions of 3 α ,5 α -THP in the midbrain VTA are necessary for sexual responding of rats and hamsters. A cross-species approach using rats and hamsters was utilized so that these mechanistic questions could be ascertained in two different animal models that differ in their reliance on progestogens for lordosis. For instance, rats are less reliant on progestogens' actions for lordosis than are hamsters. Specifically, rats will assume a lordosis posture when mounted by a male with estrogen-priming alone [35]. Hamsters will only assume lordosis when they

have physiological estrogen and progestogen levels in the VMH and VTA [39]. Furthermore, the characteristics of the lordosis posture and proceptivity among rats and hamsters differ. Lordosis of rats is characterized by its refractory nature and proceptivity has a motor component (i.e., hopping and darting). For hamsters, lordosis is sustained for many minutes at a time. The pelvic adjustments that hamsters make when in lordosis to facilitate intromission by the male during mating can be considered a proceptive behavior in this species. Thus, the approach of investigating effects of fluoxetine on lordosis and/or proceptive behaviors of rats and hamsters, and whether this was due to actions of 3 α ,5 α -THP, was utilized in the present study.

Materials and Methods

These methods were pre-approved by the Institutional Animal Care and Use Committee at the University at Albany-SUNY.

Animals and Housing

Adult (55–65 days of age), female rats (N = 76) and hamsters (N = 26) were bred in the Social Sciences Laboratory Animal Care Facility from stock obtained from Taconic Farms (Germantown, NY, USA) and Charles River Laboratories (Kingston, NY, USA), respectively. Female rats and hamsters utilized in this study were sexually-naïve. Animals were group-housed in solid bottom, plastic cages (38 × 33 × 17) in separate temperature- (22°C) and humidity- (60%) controlled rooms on a reversed light dark cycle. All animals had free access to water and chow in home cages.

Surgery

Rats were ovariectomized only (N = 27) or were ovariectomized and received concurrent stereotaxic placement of bilateral guide cannulae over the VTA (N = 49; from bregma, anterior/posterior [AP] = −5.3, medial/lateral = ±0.4, dorsal/ventral = −7.0) [43], under xylazine [12 mg/kg intraperitoneal (IP)] and ketamine (80 mg/kg IP) anesthesia. Cannulae consisted of 23-gauge thin wall guide tubing and 30-gauge removable inserts made to extend 3 mm beyond the end of the guide cannulae. After surgery, rats were monitored daily for weight loss, loss of righting response, failure to respond to flank stimulus, and deficiencies in hindlimb withdrawal. There were no animals that exhibited any loss of the aforementioned functions. Results of rats that received systemic and intra- VTA administration of 3 α ,5 α -THP were similar. Hence, in order to reduce the number of hamsters utilized in the present experiment, we did not conduct an experiment administering systemic 3 α ,5 α -THP to hamsters.

Hamsters were ovariectomized concurrent with stereotaxic placement of bilateral guide cannulae aimed over the VTA (from bregma: AP = −2.8, ML = ±0.3; DV = −7.8) [44], under sodium pentobarbital (75 mg/kg IP or to effect). Cannulae were as described above. Animals were monitored for loss of functions as mentioned above; no animals exhibited loss of any of these functions.

Baseline Hormonal Milieu

Rats and hamsters received systemic estradiol benzoate [EB; 10 μ g subcutaneous (SC)] at hour 0 and progesterone (500 μ g) at hour 44; behavioral testing began at hour 48. This hormone-priming regimen has been shown previously to induce maximal sexual receptivity in rats and hamsters [39].

Drug/Hormone Regimen

Animals were administered either vehicle (saline) or fluoxetine immediately after baseline testing. The fluoxetine regimen for rats was 20 mg/kg (IP), 30 minutes prior to testing in the first post-test, as per a previous study [45]. For hamsters, fluoxetine was administered at 10 mg/kg (IP), followed 30 minutes later by testing in the first post-test, based upon a previous study [22]. In this previous study, effects of fluoxetine on lateral displacement of hamsters were observed 60 minutes after its administration.

Animals were also administered 3 α ,5 α -THP or vehicle either SC (rats in Experiment 1) or intra- VTA (rats and hamsters in Experiments 2 and 3, respectively). The concentration of 3 α ,5 α -THP was 500 μ g (SC) or 100 ng (intra-VTA), followed 30 minutes later by testing. These drug regimen have been shown previously to enhance sexual behavior of rats and hamsters [29,45].

Behavioral Testing

Sexual Behavior of Rats in a Standard Mating Task—Lordosis was used as a main index of sexual behavior of rats. Proceptive and aggressive responses of female rats toward male rats during the test were also recorded. For this test, experimental rats were placed in a mating chamber (50 $\times$ 25 $\times$ 30) with a sexually-experienced male. The percentage of times rats exhibited lordosis in response to mounting/intromissions of the male (lordosis quotient) and the intensity of the lordosis response (mean lordosis rating; scored 0–3 for each mount) were recorded for the first 10 mounts/ intromissions that the female rats received, which occurred in less than 10 minutes. Lordosis ratings were based upon those described by Hardy and Debold where 0 equals no lordosis and 3 equals a maximal lordosis response [46]. In the present study, there were no male rats that ejaculated during the tests. The percentage of times rats engaged in proceptive and aggressive-like behaviors in response to mounting were also recorded (proceptivity and aggression quotients, respectively). Proceptive behavior was defined as the female rat hopping/darting in front of the male and/or showing an “ear wiggling” response (due to rapid head movements of rat). Aggression-like behavior was defined as the female kicking or boxing (a defensive upright posture [47]) in direct response to an attempted mount/intromission by the male.

Sexual Behavior of Hamsters—The measure of sexual behavior for hamsters in the present study was lateral displacement. Lateral displacement of hamsters was quantified as previously described [22]. Briefly, hamsters were brought into lordosis via exposure to a stimulus male or manual flank stimulation. Lordosis of hamsters is characterized by the movement of the perineum such that it is perpendicular to the surface of the testing chamber, followed by tonic immobility, which allows the experimenter to observe any movements of the perineum directly. Each probe from a calibrated set of 17 von Frey aesthesiometric probes was applied to the perineum in descending order of force. Probes were applied in a pulsatile manner in a sequential order to the right and left inner zones ($\pm$ 2 mm from the ano-vaginal midline) and the right and left outer zones ($\pm$ 7 mm) until lateral movement stopped. The magnitude of lateral movement of the perineum in response to such stimulation was measured (in mm) by a ruler aligned under the perineal region of the subject using the ano-vaginal midline as a reference point. When there was no lateral movement in response to two consecutive probes, testing was concluded. A typical length of the test was under 10 minutes. Scores of lateral displacement were summed for the right and left sides to yield a total lateral displacement score for the inner and outer zones based upon all the probes that hamsters received.

Procedure

Rats were pre-tested in the standard mating task and hamsters were pre-tested for lateral displacement at hour 48 after EB- and progesterone-priming. Immediately following the pre-test, animals were administered either fluoxetine or vehicle and were tested 30 minutes later (post-test 1). Immediately following post-test 1 (which lasted approximately 10 minutes), animals were administered 3 α ,5 α -THP or vehicle (either systemically or to the VTA) and tested again for 30 minutes later (post-test 2; See Figure 1). Upon completion of testing, tissues are collected and infusion sites are assessed for congruency with a hit to the VTA (Figure 2A). We have previously demonstrated via histological analysis on fixed (Figure 2B) and fresh (Figure 2C) tissue that infusions to the VTA robustly alter sexual behavior of rodents whereas infusions to nearby missed sites do not.

Statistical Analyses

This study was a mixed within/between design and was analyzed with analyses of variance (anova) with one within (test-time) and two between (fluoxetine condition, 3 α ,5 α -THP condition) factors. These analyses indicated that there was a significant effect of test-time in each experiment, as well as the other between factors at post-test 1 and 2, but not during the pre-test before animals received experimental manipulations. Hence, the results below are focused on describing the interactions of these factors. The alpha level for statistical significance was $P < 0.05$. *Post hoc* analyses (Fisher's least significant difference test) were utilized as appropriate to determine differences between groups.

Main Outcome Measures

The main outcome measures utilized in this study to determine the effects of manipulations were those typically used to determine sexual responding in rodents. For rats, the percentage of times that the lordosis response occurred following mounting by a sexually-vigorous male (lordosis quotients) was utilized. For hamsters, a measure of lateral displacement, or the movement that females will make to facilitate intromissions by a male hamster, was utilized.

Results

Experiment 1: Systemic 3 α ,5 α -THP Attenuates Fluoxetine-Induced Alterations in Lordosis, Proceptivity, and Aggressive-Like Behavior of Rats

As has been observed previously in ovariectomized, estrogen-primed rats [45], fluoxetine significantly reduced lordosis quotients [$F(2,69) = 33.72$, $P < 0.05$, Figure 3] and ratings [$F(2,69) = 7.96$, $P < 0.05$] during post-test 1 of ovariectomized estrogen and progesterone-primed rats. Systemic 3 α ,5 α -THP increased lordosis quotients of fluoxetine-administered rats, but not those administered vehicle, during post-test 2 [$F(2,69) = 6.67$, $P < 0.05$]. Lordosis ratings of fluoxetine-administered rats were also increased following 3 α ,5 α -THP; however these effects did not reach statistical significance [$F(2,69) = 2.74$, $P = 0.07$, Table 1].

Fluoxetine significantly reduced proceptivity quotients [$F(2,69) = 4.49$, $P < 0.05$] and increased aggression quotients [$F(2,69) = 8.70$, $P < 0.05$] during post-test 2 (Table 1). Aggression quotients during post-test 2 of rats administered fluoxetine were significantly reduced by 3 α ,5 α -THP [$F(2,69) = 5.30$, $P < 0.05$, Table 1].

Experiment 2: Intra-VTA 3 α ,5 α -THP Attenuates Fluoxetine-Induced Changes in Lordosis, Proceptivity, and Aggressive-Like Behavior of Rats

Infusions of 3 α ,5 α -THP to the VTA increased lordosis quotients [$F(2,135) = 23.30$, $P < 0.05$, Figure 4] and lordosis ratings [$F(2,135) = 24.92$, $P < 0.05$] of fluoxetine-administered

rats, but not those administered vehicle. $3\alpha,5\alpha$ -THP to the VTA of fluoxetine-, but not vehicle-, administered rats significantly increased proceptivity quotients [$F(2,135) = 3.20$, $P < 0.05$] and significantly decreased aggression quotients [$F(2,135) = 10.95$, $P < 0.05$] during post-test 2 (Table 2).

Experiment 3: Intra-VTA Administration of $3\alpha,5\alpha$ -THP Attenuates Effects of Systemic Administration of Fluoxetine on Lateral Displacement of Hamsters

As has been shown previously among hamsters in behavioural estrus [22], systemic fluoxetine significantly reduced inner [$F(2,66) = 8.10$, $P < 0.05$, Figure 5] and outer [$F(2,66) = 4.03$, $P < 0.05$, Table 3] lateral displacement scores during post-test 1 of ovariectomized, estrogen and progesterone-primed hamsters. Infusions of $3\alpha,5\alpha$ -THP to the VTA increased inner lateral displacement scores of fluoxetine-administered hamsters, but not those administered vehicle during post-test 2 [$F(2,66) = 3.43$, $P < 0.05$, Figure 5]. Total outer lateral displacement scores of fluoxetine-administered hamsters were also increased following $3\alpha,5\alpha$ -THP administration, although this effect was not statistically significant (Table 3).

Discussion

Results of the present study supported our hypothesis that $3\alpha,5\alpha$ -THP to the midbrain VTA would reverse decrements in lordosis, and lateral displacement, of an acute fluoxetine regimen to rats and hamsters, respectively. Fluoxetine-administered rats that received SC or intra-VTA administration of $3\alpha,5\alpha$ -THP had lordosis quotients that were similar to those seen at baseline testing. However, this was not seen in fluoxetine-administered rodents administered vehicle. A similar pattern was observed for the quality of the lordosis response (lordosis ratings) and proceptive behaviors. Among fluoxetine-administered hamsters, a similar pattern of significantly higher lateral displacement scores following $3\alpha,5\alpha$ -THP, but not vehicle, administration directly to the midbrain VTA, was observed. These data suggest that actions of $3\alpha,5\alpha$ -THP in the midbrain VTA can mitigate inhibitory effects of fluoxetine on lordosis, proceptive behaviors, and lateral displacement of female rodents.

The present data confirm previous findings from our lab and others that a systemic fluoxetine regimen can disrupt reproductive physiology and behavior in rodent models. In male rats, acute or chronic fluoxetine administration disrupts sexual behaviors, including time between mounts, latency to first intromission, number of intromissions, and latency to, and frequency of, ejaculation [47,48]. Female rats treated with a low dosage of fluoxetine (2 mg/kg) for 6 weeks have significantly lower circulating levels of estrogen (E_2) compared with intact or ovariectomized, E_2 -primed rats [49]. Chronic fluoxetine regimens (1–3 weeks) also disrupt estrous cyclicity and progestin levels of female rodents [21,22]. These fluoxetine regimens result in concomitant deficits in reproductive behavior, such as reduced or eliminated lordosis behavior or lateral displacement [21,22,45,50,51]. The current results reveal that fluoxetine can rapidly decrease both lordosis and lateral displacement responses in rats and hamsters, respectively. The slightly more robust effects of fluoxetine in rats compared with hamsters, might be due, in part, to differences in metabolism [52]. Furthermore, fluoxetine not only altered lordosis in this and previous studies, but also measures of proceptive behaviors in both species. In support, the effects of fluoxetine were not statistically significantly different in Experiment 1 for proceptive behavior, perhaps due to a low number of rats per group. Yet, a similar pattern for acute fluoxetine to reduce proceptive behavior of estrogen- and progesterone-primed rats was observed. Indeed, these data are of interest given that SSRIs can have effects on several components of the sexual responses cycle, including sexual desire/libido. However, it should be noted that decreases in proceptive behavior occurred concomitantly with an increase in aggressive-like behavior, a competing behavior, as has been discussed in other reports [53]. Hence, it is important to

temper our interpretation of these data in terms of the relevance to decreased libido in women.

Previous reports on the effect of SSRIs on reproductive physiology and behavior have primarily examined effects using a chronic dosing regimen. The present data suggest that fluoxetine can have rapid effects (within 30 minutes) to alter lordosis and lateral displacement of female rats and hamsters, respectively. Although the therapeutic effects of SSRIs are thought to occur primarily via actions on the serotonin system, the rapidity of the effects that we observed on sexual behavior suggests that another mechanism may underlie some of these effects. One possible mechanism by which SSRIs may influence reproductive physiology and behavior is by altering progesterin concentrations. Indeed, some SSRIs, including fluoxetine, alter activity of the 3 α -HSD enzyme in vitro [54]. Rats administered systemic fluoxetine chronically had significantly decreased lordosis responses and midbrain 3 α ,5 α -THP levels [45]. Interestingly, when fluoxetine was administered directly to the midbrain VTA acutely, lordosis was enhanced and 3 α ,5 α -THP levels in the midbrain were increased [41]. The present results confirm our previous data that a systemic fluoxetine regimen produces deficits in lordosis and lateral displacement of rats and hamsters, respectively [22,45], and extend them to suggest that increasing 3 α ,5 α -THP concentrations directly in the midbrain VTA can attenuate these effects. However, it should be noted that changes observed after acute treatment with fluoxetine may not reflect changes following chronic treatment. That differences were observed for systemic and intra-VTA fluoxetine on lordosis and midbrain 3 α ,5 α -THP levels support our hypothesis that 3 α ,5 α -THP in the midbrain VTA may be a target for these effects. Further, these data underscore the importance of considering the regimen utilized and the brain areas investigated when considering the effects and mechanisms of SSRIs. Thus, fluoxetine may have site-specific effects on 3 α ,5 α -THP by altering enzyme activity, but this need further investigation.

There are a number of ways in which 3 α ,5 α -THP can influence neuroendocrine functions. These include effects on hypothalamic secretion of gonadotropin-releasing hormone (GnRH) and thereby release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which when culminating in an LH surge, can trigger ovulation. Progesterone, from ovaries and/or the brain, act through cognate progesterin receptors and postsynaptic GABA_A receptors on GnRH neurons, in the hypothalamus to mediate E₂-induced release of GnRH for the LH surge [55–57]. E₂ induces *de novo* progesterone synthesis in the medial basal hypothalamus and thereby the LH surge through the release of GnRH [58,59]. Inhibiting biosynthesis of progesterone in the hypothalamus blocks the LH surge [60]. Infusions of 3 α ,5 α -THP that activate hypothalamic GABA_A receptors suppress ovulation [60]. Moreover, E₂ enhances 3 α ,5 α -THP biosynthesis in the anterior pituitary of ovariectomized rodents [61], and a 3 α ,5 α -THP precursor produced by the pituitary, 3 α -hydroxy-4-pregnen-20-one (3 α HP), can inhibit GnRH-stimulated FSH secretion [62,63]. Neurosteroids regulate gonadotropin secretion, which can in turn regulate neurosteroid production. Indeed, LH increases expression of neuronal StAR and, thereby, pregnenolone concentrations [64]. Pheromone-stimulated release of GnRH, ovulation, and preference of female rats for odors of male rats may be mediated in part by neurosteroids [65]. As such, there are a number of ways through which fluoxetine's effects on 3 α ,5 α -THP may alter sexual function.

Although these are intriguing data that provide insight into a putative mechanism by which SSRIs may alter reproductive behavior, there are some caveats that need to be considered. First, the rodent models used in the present study address questions regarding sexual ability but not necessarily sexual arousal and desire [66,67]. Clinical reports suggest that problems with sexual function among women involve, at least in part, issues with arousal and desire rather than ability [15]. However, modest effects of fluoxetine to reduce time spent by a female rat near the male rat in a preference test have been reported [23]. Second, given that

there was no direct measurement of progesterone levels in the present studies, we cannot definitively say that the sexual dysfunction induced by fluoxetine was due to decreased progesterone. However, our previous studies have shown that this regimen of systemic fluoxetine to rats significantly reduces 3 α ,5 α -THP levels in the midbrain [45]. Further, the ability of 3 α ,5 α -THP administration to the midbrain to reinstate lordosis and lateral displacement of rats and hamsters, respectively, strongly supports our hypothesis that fluoxetine-induced sexual dysfunction was due, at least in part, to altered progesterone levels in the midbrain VTA.

In summary, these data suggest that a modest regimen of fluoxetine is sufficient to elicit disruptions in sexual responding of female rats and hamsters. Further, increasing concentrations of 3 α ,5 α -THP in the midbrain VTA can attenuate these fluoxetine-induced deficits. Given the prevalence of SSRI-induced sexual dysfunction among women, and the significance of this on quality of life, expanding our understanding of the underlying mechanisms by which sexual dysfunction occurs is vital to the area of women's health.

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Figure 1.
Schematic of when rats and hamsters were tested and administered vehicle or fluoxetine and vehicle or 3 α ,5 α -THP.

Figure 2. Depicts schematic representation of the ventral tegmental area (VTA; Panel A) of rats, histological verification of cannula placement (Panel B) of rats, and verification of cannula placement in fresh, nonfixed rat brain (Panel C).

Figure 3.

Lordosis quotients ($\pm$ SEM) of rats administered vehicle intraperitoneal (IP) and vehicle subcutaneous (SC) ($N = 6$), vehicle IP and 3 α ,5 α -THP SC ($N = 7$), Fluoxetine IP and vehicle SC ($N = 8$), or fluoxetine IP and 3 α ,5 α -THP SC ($N = 6$). *Indicates significantly different effect of fluoxetine, compared with vehicle, during post-test 1. **Indicates a significant effect of 3 α ,5 α -THP, compared with vehicle, in conjunction with fluoxetine during post-test 2.

Figure 4.

Lordosis quotients (±SEM) of rats administered vehicle intraperitoneal (IP) and vehicle intra-VTA (N = 12), vehicle IP and 3α,5α-THP intra-VTA (N = 12), fluoxetine IP and vehicle intra-VTA (N = 13), or fluoxetine IP and 3α,5α-THP intra-VTA (N = 12).

*Indicates significantly different effect of fluoxetine, compared with vehicle, during post-test 1. **Indicates a significant effect of 3α,5α-THP, compared with vehicle, in conjunction with fluoxetine during post-test 2.

Figure 5.

Total inner lateral displacement ($\pm$ SEM) of hamsters administered vehicle intraperitoneal (IP) and vehicle intra-VTA (N = 7), vehicle IP and 3 α ,5 α -THP intra-VTA (N = 7), fluoxetine IP and vehicle intra-VTA (N = 6), or fluoxetine IP and 3 α ,5 α -THP intra-VTA (N = 6). *Indicates significantly different effect of fluoxetine, compared with vehicle, during post-test 1. **Indicates a significant effect of 3 α ,5 α -THP, compared with vehicle, in conjunction with fluoxetine during post-test 2.

Table 1

Lordosis ratings, proceptivity quotients, and aggression quotients ($\pm$ SEM) of rats administered veh IP and veh SC (n = 6), veh IP and 3 α ,5 α -THP SC (n = 7), fluox IP and veh SC (n = 8), or fluox IP and THP SC (n = 6)

Condition	n	Lordosis ratings		Proceptivity quotients		Aggression quotients	
		Pre-test	Post-test 1	Post-test 2	Pre-test	Post-test 1	Post-test 2
Veh IP + veh SC	6	2.5 $\pm$ 0.3	2.6 $\pm$ 0.2	2.0 $\pm$ 0.4	32.7 $\pm$ 12.4	8.3 $\pm$ 8.3	22.7 $\pm$ 12.1
Fluox IP + veh SC	8	2.6 $\pm$ 0.1	1.0 $\pm$ 0.1 *	1.0 $\pm$ 0.1	46.9 $\pm$ 5.5	0 $\pm$ 0 *	32.5 $\pm$ 4.5
Veh IP + THP SC	7	2.8 $\pm$ 0.1	2.6 $\pm$ 0.2	2.5 $\pm$ 0.1	37.3 $\pm$ 7.8	30.4 $\pm$ 13.9	4.9 $\pm$ 2.3
Fluox IP + THP SC	6	2.6 $\pm$ 0.1	2.4 $\pm$ 0.1	2.4 $\pm$ 0.1	27.0 $\pm$ 8.5	15.5 $\pm$ 9.7 *	18.3 $\pm$ 6.5 **

* Indicates significantly different effect of fluox, compared with veh, during post-test 1.

** Indicates a significant effect of THP, compared with veh, to decrease aggression quotients, of fluox-administered rats during post-test 2.

IP = intraperitoneal; fluox = fluoxetine; SC = subcutaneous; THP = 3 α ,5 α -THP; veh = vehicle.

Table 2

Lordosis ratings, proceptivity quotients, and aggression quotients ($\pm$ SEM) of rats administered veh IP and veh intra-VTA (n = 12), veh IP and 3 α ,5 α -THP intra-VTA (n = 12), fluox IP and veh intra-VTA (n = 13), or fluox IP and THP intra-VTA (n = 12)

Condition	n	Lordosis ratings			Proceptivity quotients			Aggression quotients		
		Pre-test	Post-test 1	Post-test 2	Pre-test	Post-test 1	Post-test 2	Pre-test	Post-test 1	Post-test 2
Veh IP + veh VTA	12	2.8 ± 0.1	2.7 ± 0.1	2.8 ± 0.1	67.2 ± 5.4	60.0 ± 4.8	44.7 ± 5.3	0 ± 0	0 ± 0	0 ± 0
Fluox IP + veh VTA	13	2.6 ± 0.1	1.2 ± 0.2 *	1.2 ± 0.1	48.5 ± 4.6	8.0 ± 8.0 *	3.1 ± 3.1	1.0 ± 1.0	49.7 ± 5.4 *	30.2 ± 4.7
Veh IP + THP VTA	12	2.8 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	57.7 ± 6.2	75.1 ± 20.5	54.7 ± 4.4	0 ± 0	1.7 ± 1.1	0 ± 0
Fluox IP + THP VTA	12	2.8 ± 0.1	0.7 ± 0.1 *	2.7 ± 0.1 **	60.0 ± 6.0	0 ± 0 *	48.8 ± 7.5 **	0 ± 0	57.4 ± 6.6 *	0 ± 0 **

* Indicates significantly different effect of fluox, compared with vehicle, during post-test 1.

** Indicates a significant effect of THP, compared with veh, to increase lordosis ratings and proceptivity quotients, and decrease aggression quotients, of fluox-administered rats during post-test 2.

IP = intraperitoneal; fluox = fluoxetine; THP = 3 α ,5 α -THP; veh = vehicle; VTA = ventral tegmental area.

Table 3

Total outer lateral displacement scores ($\pm$ SEM) of hamsters administered vehicle intraperitoneal (IP) and vehicle intra-VTA (N = 7), vehicle IP and 3 α ,5 α -THP intra-VTA (N = 7), fluoxetine IP and vehicle intra-VTA (N = 6), or fluoxetine IP and 3 α ,5 α -THP intra-VTA (N = 6)

Condition	N	Outer scores		
		Pre-test	Post-test 1	Post-test 2
Veh IP + veh VTA	7	24.3 $\pm$ 2.2	25.9 $\pm$ 2.6	24.3 $\pm$ 0.4
Fluox IP + veh VTA	6	29.3 $\pm$ 2.2	19.8 $\pm$ 0.8 *	20.7 $\pm$ 2.1
Veh IP + THP VTA	7	25.0 $\pm$ 2.0	23.7 $\pm$ 1.2	27.0 $\pm$ 2.2
Fluox IP + THP VTA	6	25.0 $\pm$ 1.5	18.8 $\pm$ 1.7 *	30.0 $\pm$ 2.5

* Indicates significantly different effect of fluox, compared with veh, during post-test 1.

IP = intraperitoneal; fluox = fluoxetine; THP = 3 α ,5 α -THP; veh = vehicle; VTA = ventral tegmental area.