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PHARMACOLOGY OF SEROTONIN AND FEMALE SEXUAL BEHAVIOR

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Abstract

In this review, first a historical perspective of serotonin's (5-HT) involvement in female sexual behavior is presented. Then an overview of studies implicating 5-HT is presented. The effect of drugs that increase or decrease CNS levels of 5-HT is reviewed. Evidence is presented that drugs which increase 5-HT have negative effects on female sexual behavior while a decrease in 5-HT is associated with facilitation of sexual behavior. Studies with compounds that act on 5-HT_1, 5-HT_2 or 5-HT_3 receptors are discussed. Most evidence indicates that 5-HT_{1A} receptor agonists inhibit sexual behavior while 5-HT_2 or 5-HT_3 receptors may exert a positive influence. There is substantial evidence to support a role for 5-HT in the modulation of female consummatory sexual behavior, but studies on the role of 5-HT in other elements of female sexual behavior (e.g. desire, motivation, sexual appetite) are few. Future studies should be directed at determining if these additional components of female sexual behavior are also modulated by 5-HT.

Keywords

review; sexual receptivity; proceptivity; SSRIs; sexual motivation; 5-HT receptors

1.0 Introduction and Overview

A contribution of serotonin (5-HT) to the modulation of female sexual behavior has been appreciated since the early 1960s when a variety of compounds with effects on the 5-HT system were found to reduce female rodent sexual receptivity (for reviews, see (Mendelson, 1992; Uphouse, 2000; Uphouse and Guptarak, 2010). 5-HT cell bodies are located in a diffuse cluster of neurons in the midbrain and brainstem (Steinbusch, 1981). Among the rostral group are the dorsal raphe nucleus (DRN), medial raphe nucleus (MRN) and the caudal linear nucleus that provide a majority of the ascending 5-HT innervation of the brain, including those areas important in the control of female sexual behavior (Azmitia and Segal, 1978; Hornung, 2003). The caudal grouping, located in the pons and medulla, is the major source of 5-HT to the spinal cord (Hornung, 2003)

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Although findings were not always consistent, the bulk of evidence supported the hypothesis that compounds that increased 5-HT reduced female sexual behavior and compounds that decreased 5-HT facilitated sexual behavior. This early view of 5-HT as a negative regulatory of rodent female sexual behavior has been reinforced by studies in humans that have implicated serotonergic compounds in the treatment of human sexual dysfunction (Moll and Brown, 2011) and by studies of genetic polymorphisms of the 5-HT system that are associated with low sexual desire in humans (Burri et al., 2012). In addition, alterations in 5-HT functioning are thought to contribute to the sexual dysfunction that occurs following treatment with antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (Clayton et al., 2006; Clayton, 2002; Gelenberg et al., 2000; Gregorian et al., 2002; Montgomery et al., 2002).

Between 1950 and 1990, a variety of drugs that impacted 5-HT at every level from synthesis to degradation to receptor action were examined. Although most investigators accepted the assumption that any means of increasing 5-HT function would reduce female sexual behavior, such assumptions were based on a belief that 5-HT, as well as other chemical messengers, acted on a single neurotransmitter receptor. The existence of at least two serotonin receptors had been indicated as early as 1957 (Hannon and Hoyer, 2008), but it was not until Peroutka and Snyder's report (Peroutka and Snyder, 1979) for the existence of two different central nervous system CNS 5-HT receptors (5-HT_1 and 5-HT_2) that the concept of multiple CNS 5-HT receptors received major acceptance. Thereafter, the search was on to determine which of these receptors might be responsible for 5-HT's behavioral effects and the study of female sexual behavior was no exception. When the first relatively selective 5-HT_{1A} receptor agonist, 8-OH-DPAT (8-hydroxy-2-(di-N-propylamino) tetralin), became available, several investigators reported that systemic treatment with the drug inhibited female rat lordosis behavior (Ahlenius et al., 1986; Fernandez-Guasti et al., 1987; Mendelson and Gorzalka, 1986a). These studies led to suggestions that 5-HT_1 receptors, activated by 8-OH-DPAT, were responsible for pharmacological effects of 5-HT on female lordosis behavior. However, as more and more 5-HT receptors were identified (Hoyer and Martin, 1997; Zifa and Fillion, 1992), it became obvious that 5-HT's modulation of sexual behavior was more complex than originally anticipated. There were reports that some pharmacological compounds increased rather than decreased female rat lordosis behavior (Hunter et al., 1985; Wilson and Hunter, 1985) and evidence accumulated that 5-HT could both inhibit and facilitate the behavior (Mendelson and Gorzalka, 1985; Wilson and Hunter, 1985). Moreover, a member of the 5-HT_1 family, the 5-HT_{1A} receptor, was found to reside not only on targets of 5-HT terminals but also on soma and dendrites of 5-HT neurons in the DRN where they reduced firing of 5-HT neurons and thereby reduced release of 5-HT (Romero and Artigas, 1997; Sprouse and Aghajanian, 1987). Such findings challenged the singular view that 5-HT_1 receptors, as negative regulators of female sexual behavior, were solely responsible for the effects of 5-HT.

In animal studies of 5-HT and female sexual behavior, emphasis was on the lordosis response, a posture made by the female to enable the male to achieve intromission. The lordosis reflex is a supraspinal reflex that is initiated by somatosensory stimuli especially from the female's rump. During mating, somatosensory information reaches the spinal cord and travels in the anteriolateral column to the medulla where it integrates with relevant

motor output (Kow and Pfaff, 1998). Higher brain areas are required to mediate the hormonal control of the reflex. In particular, the ventromedial nucleus (VMN) of the hypothalamus is critical for this hormonal control and communicates with the dorsal and lateral portions of the periacqueductal gray (PAG) of the midbrain (Flanagan-Cato, 2011; Kow and Pfaff, 1998). This VMN-PAG information is thought to be critical to estrogen's ability to facilitate the reflex and to coordinate the behavior with the female's ability to procreate. Other brain areas contribute to the fine-tuning of the reflex by coordinating the behavior to environmental events that influence successful reproduction (Kow and Pfaff, 1998; Pfaff et al., 2008). The PAG relays hormonal information from the VMN to brainstem areas that control the motor output and lead to the arching of the back that characterizes the reflex (Kow and Pfaff, 1998).

However, female rodent sexual behavior is not a single behavioral response but a repertoire of behaviors that can be divided into appetitive (grooming, excitement, motor activation), precopulatory (proceptivity, solicitation), and consummatory (receptivity, lordosis) activities that vary in their hormonal control and neuronal circuitry (Erskine, 1989; Pfaus et al., 1999). Solicitation/appetitive behavior allows the female to obtain proximity to the male. Proceptive behaviors engage the male's attention on the female while receptive behavior includes the actual act of copulation. Although subprimate female sexual behavior differs from human sexual behavior in its dependence on female gonadal hormones, many aspects of female sexual behavior have similarity across species (Agmo et al., 2004; Pfaus et al., 2001) so that rodent models of sexual behavior have provided valuable insight regarding the effects of serotonergic drugs. Nevertheless, there have been few attempts to differentiate the role 5-HT plays on the various components of female sexual behavior. This is a particularly important omission since low sexual desire/motivation is one of the most frequent complaints in human females that experience hypoactive sexual desire disorder (HSDD) or after antidepressant treatment (Clayton, 2002; Segraves, 2007; Shifren et al., 2008) but has been the least studied in animal models. Therefore, a greater understanding of 5-HT's role in appetitive/precopulatory behaviors is badly needed.

In the following review, the effects of drugs which alter 5-HT function are overviewed with an aim toward pointing the way to future studies that may further delineate 5-HT's relatively complex role in the modulation of different components of female sexual activity. A historical and current overview of drugs that alter levels of serotonin and/or activate 5-HT receptors is presented. Thereafter, the implications and limitations of these studies to our understanding of 5-HT's role in female sexual behavior is discussed.

2.0 Compounds that alter total or synaptic levels of 5-HT

In most early studies, the lordosis reflex was examined after peripheral administration of pharmacological compounds that varied in their mode of action from blocking 5-HT synthesis/degradation to altering release of 5-HT from nerve terminals. Drugs, such as the monoamine oxidase inhibitor, pargyline (*N*-methyl-*N*-(2-propynyl)benzylamine monohydrochloride), which lead to an increase in 5-HT were among the first group of compounds reported to decrease lordosis behavior after either systemic or intrahypothalamic administration (Allen et al., 1993; Luine and Paden, 1982; Meyerson, 1964). Consistent with

these findings, 5-HT releasing agents, such as fenfluramine [(+)-N-ethyl-α-methyl-m-[trifluoromethyl]phenethylamine hydrochloride] (Pettibone and Williams, 1984), reduced lordosis behavior (Everitt et al., 1975; Michanek and Meyerson, 1977); and negative effects on lordosis behavior were found following treatment with the 5-HT precursor, 5-hydroxytryptophan (Sietnieks and Meyerson, 1982).

Depletion of 5-HT with vesicular monoamine inhibitors such as reserpine [(3β,16β,17α, 18β,20α)-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]yohimban-16-carboxylic acid methyl ester] (Meyerson, 1966) or tetrabenazine (9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-3-isobutyl-2H-benzo[a]quinolizin-2-one) (Ahlenius et al., 1972; Meyerson, 1966) or with the 5-HT synthesis inhibitor, parachlorophenylanine (1-[(2s,6r,11s)-8-hydroxy-3,6,11-trimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-11-yl]octan-3-one), (Ahlenius et al., 1972; Meyerson and Lewander, 1970), increased lordosis. A particularly significant observation was the finding that the 5-HT neurotoxin, 5,7, dihydroxytryptamine, increased lordosis behavior (Luine et al., 1983; Moreines et al., 1988) and that this effect was reversed over time as reinnervation with 5-HT terminals occurred (Frankfurt et al., 1985).

Reinforcing the putative negative role of 5-HT in regulation of lordosis behavior, a variety of relatively nonselective monoamine reuptake inhibitors such as desmethylimipramine (10-11-dihydro-*N*-methyl-5*H*-dibenz(*Z*)-[*b*,*f*]azepine-5-propanamine hydrochloride); imipramine [3-(10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyldimethylamine hydrochloride] and amitriptyline [3-(10,11-dihydro-5H-dibenzo[a,d]cyclopenten-5-ylidine)propyldimethylamine hydrochloride] were reported to reduce lordosis behavior (Meyerson, 1966). Although the effects of these drugs were consistent with an inhibitory role of 5-HT on lordosis behavior, the fact that these compounds blocked reuptake of multiple amine transporters made causal interpretations difficult. In more recent studies, emphasis has been directed toward the category of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) because these compounds produce the greatest amount of sexual dysfunction in women (Montgomery et al., 2002; Segraves, 2007; Strohmaier et al., 2011). A summary of these studies with drugs affecting synaptic serotonin is shown in Table 1.

In animal studies, fluoxetine [Prozac®; (±)-N-methyl-γ-[4-(trifluoromethyl) phenoxy]benzenepropanamine hydrochloride] has been the most investigated of the SSRIs and has been routinely reported to reduce lordosis behavior in female rats or to reduce lateral displacement (a measure of sexual receptivity) in hamsters (Adams et al., 2012; Frye et al., 2003; Frye and Rhodes, 2010; Guptarak et al., 2010). In female rats, the reduction of lordosis behavior exhibits dose-dependency, the IC_{50} of which varies with hormonal priming, rat strain and testing condition (Adams et al., 2012; Guptarak et al., 2010; Miryala et al., 2013). Ovariectomized Fischer rats treated with estradiol benzoate and progesterone were less sensitive to the lordosis-inhibiting effect of fluoxetine than were rats hormonally primed only with estradiol benzoate (Guptarak et al., 2010); and pretesting for lordosis behavior immediately prior to injection with fluoxetine amplified the effect of the SSRI (Adams et al., 2012). Although the act of mating is reinforcing for the female, mating has both positive and negative effects (Camacho et al., 2009). For example, when placed in a

novel environment with an unfamiliar male, females show an elevated corticosterone response (Hennessy et al., 2008). Fluoxetine also increases corticosterone (Van de Kar et al., 1985) so that mating before injection may have amplified this response.

Since acute fluoxetine has anxiogenic properties (Birkett et al., 2011; Ravinder et al., 2012; Robert et al., 2011) and progesterone is recognized as a potent anxiolytic (Bitran et al., 1993; Frye, 2007; Picazo and Fernandez-Guasti, 1995), these findings suggest that stress could amplify the effects of fluoxetine on lordosis behavior and that progesterone may reduce this effect. An additional connection between a potential protective effect of progesterone against the lordosis-inhibiting effect of fluoxetine has been provided by Frye and colleagues (Frye, 2007; Frye et al., 1998; Frye and Rhodes, 2010) who reported that the progesterone metabolite, allopregnanolone (3α-hydroxy-5β-pregnan-20-one; 3α,5β-THP), whether delivered systemically or intracranially into the ventral tegmental area, attenuated the effects of systemic treatment with fluoxetine.

In sharp contrast to the robust inhibitory effects of fluoxetine on lordosis behavior of Fischer female rats, higher doses of the SSRI were required to reduce lordosis behavior in hormonally-primed, ovariectomized or naturally cycling Sprague-Dawley females (Miryala et al., 2013). The strain difference reported for the acute treatment is consistent with a similar strain difference in subchronic effects of fluoxetine on lordosis behavior and estrous cyclicity (Maswood et al., 2008; Sarkar et al., 2008b; Uphouse et al., 2006). Daily treatment of Fischer females with 10 mg/kg fluoxetine reduced lordosis behavior and estrous cyclicity within the first 5 days of treatment (Uphouse et al., 2006) while the effects in Sprague-Dawley females were considerably more modest and less consistent (Maswood et al., 2008). Although not examined in Sprague-Dawley females, it is interesting to note that fluoxetine-treated Fischer females had lower circulating progesterone than their vehicle controls (Uphouse et al., 2006). Given progesterone's potential to attenuate sexual side effects of fluoxetine, examination of progesterone levels in humans exhibiting antidepressant-induced sexual dysfunction could be valuable.

Strain differences may account for fluoxetine's failure to disrupt the estrous cycle of Wistar rats even though reductions in lordosis behavior and proceptivity were present but only following long-term treatment (Matuszczyk et al., 1998). In hormonally-primed ovariectomized rats of this strain, 21–28 days of treatment with fluoxetine (10 mg/kg) were required before disruptions in lordosis behavior were observed (Matuszczyk et al., 1998). Thus, it might be assumed that repeated treatment with fluoxetine could amplify effects of fluoxetine on lordosis behavior. However, this possibility is inconsistent with the finding that, relative to the acute effects, the lordosis-inhibiting effects of fluoxetine were reduced, not increased, after Fischer females were treated for 10 days with the SSRI (Sarkar et al., 2008a). Because Matuszczyk et al. (Matuszczyk et al., 1998) tested the rats at least weekly, the repeated mating, and not just exposure to male pheromones/odors, may have increased the effect of fluoxetine because daily exposure to soiled bedding from the male reduced the effect of fluoxetine in naturally cycling Fischer female rats (Sarkar et al., 2008b).

In contrast to effects of fluoxetine, the SSRI, paroxetine [(−)-trans-4R-(4′-fluorophenyl)-3S-[(3′,4′-methylenedioxyphenoxy) methyl] piperidine hydrochloride hemihydrate] has not

been reported to robustly reduce lordosis behavior. Following daily treatment with paroxetine, treated rats showed a decline in lordosis behavior at only a single time point (after 7 days of treatment) and this was present only in rats with suboptimal hormonal priming (e.g. 5 μg estradiol benzoate alone) (Snoeren et al., 2011b). The lack of an effect of paroxetine is a surprising outcome because the incidence of sexual dysfunction after paroxetine treatment in humans is equal to or greater than that reported for fluoxetine (Outhoff, 2010) and both compounds are effective blockers of 5-HT reuptake (Haenisch and Bonisch, 2010; Hyttel, 1994; Owens et al., 1997). However, experiments with paroxetine have primarily been performed in a pacing paradigm where females control the sexual interaction (Erskine, 1989) while studies with fluoxetine have predominantly been conducted in a shorter-duration paradigm where the female does not control interaction with the male. Because paced mating is more rewarding and less stressful than mating under conditions where the female is not in control (Parada et al., 2012; Paredes and Vazquez, 1999), this difference in testing could be a significant factor in comparisons of the effects of SSRIs on lordosis behavior.

Few investigators have examined the effects of SSRIs on appetitive/precopulatory female sexual behaviors. In the no-contact, partner preference paradigm, females choose between spending time in the vicinity of a sexual (intact male) or a social (castrate male or ovariectomized female) stimulus (Clark et al., 2004). An increase in time spent near the sexual incentive is thought to reflect an increase in the female's sexual motivation/arousal. In a variation of this procedure, the time the female spends investigating (sniffing, licking or chewing) the wire mesh that prevents access to the male is also assumed to reflect the female's sexual motivation (Adams et al., 2012; Hawcock et al., 2010).

In the first report in which the female's preference for spending time with the male was examined after fluoxetine treatment, the antidepressant produced a transient decline (significant only after 7 days of treatment) in male preference (Matuszczyk et al., 1998). However, such reductions in partner preference were not reported for hormonally-primed ovariectomized Fischer females after either acute or 10 days of fluoxetine treatment (Adams et al., 2012; Sarkar et al., 2008a). Nevertheless, after acute treatment, time near the female was increased, investigation time was reduced, and measures of general excitement (e.g. crossings and grooming) were reduced, consistent with a negative effect of fluoxetine on sexual motivation (Adams et al., 2012). However, fluoxetine also appeared to reduce general locomotor activity and this may have confounded measures of sexual motivation. In contrast, acute paroxetine did not alter the female's preference for spending time near the male, but after 20 days of paroxetine treatment, time near the male was reduced (Kaspersen and Agmo, 2012).

In the pacing paradigm, the female is allowed to control the frequency of interaction with the male by "escaping" the male's compartment into a chamber to which only the female has access (Clark et al., 2009; Erskine, 1989; Paredes and Vazquez, 1999; Pfaus et al., 1999). In this paradigm, it is assumed that sexual motivation is correlated with a faster return to interact with the male. When treated acutely with fluoxetine, females left the male's chamber and remained away from the male for most of the testing period (Adams et al.,

2012). In contrast, there were no significant effects of paroxetine on time spent with the male in the pacing paradigm (Snoeren et al., 2011b).

While lordosis behavior is clearly reduced following treatments that increase 5-HT, the limited study of SSRIs (or other drugs which increase 5-HT) on appetitive/precopulatory measures of female sexual activity makes it difficult to draw major conclusions about 5-HT's role in these behaviors. Most antidepressants can produce sexual dysfunction in human females, but SSRIs are associated with the highest incidence; and the most prevalent complaint following SSRI treatment is related to low sexual desire and satisfaction (Montgomery et al., 2002; Schweitzer et al., 2009; Segraves, 2007). Thus, additional studies of the appetitive/precopulatory effects of agents that alter 5-HT levels are needed. Nevertheless, the relatively small, if any, effects of antidepressant drugs, such as buproprion [(±)-l-(3-chlorophenyl)-2-[(l,l-dimethylethyl)amino]-l-propanone hydrochloride] or mirtazepine (1,2,3,4,10,14b-hexahydro-2-methylpyrazino [2,1-a] pyrido [2,3-c] benzazepine) with low or absent effects on 5-HT reuptake, on sexual behavior of humans or animals (Gregorian et al., 2002; Kanaly and Berman, 2002; Lopez et al., 2007; Meston and Frohlich, 2001; Moll and Brown, 2011; Segraves, 2007; Serretti and Chiesa, 2009) provide some support for the hypothesis that global elevations in 5-HT negatively impact female sexual behavior.

3.0 Drugs acting at 5-HT receptors

Prior to recognition of the many 5-HT receptor families, a variety of drugs with putative 5-HT receptor action were investigated. Some drugs, such as methiothepin (1-[10,11-dihydro-8-(methylthio)dibenzo(*Z*)[*b*,*f*]thiepin-10-yl]-4-methylpiperazine maleate), ketanserin [3-(2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl)-2,4(1H,3H)-quinazolinedione (+)tartrate salt], ritanserin (6-[2-[4-(bis(4-fluorophenyl)methylene]-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-) and cyproheptadine [4-(dibenzo[1,2-a:1′,2′-e] [7]annulen-11-ylidene)-1-methylpiperidine] reduced lordosis behavior (Mendelson and Gorzalka, 1986c; Sietnieks, 1985). Others such as methysergide ([8β(S)]-9,10-didehydro-N-[1-(hydroxymethyl)propyl]1,6-dimethylergoline-8-carboxamide) increased lordosis behavior (Franck and Ward, 1981; Hunter et al., 1985). Other drugs had effects that varied depending on the dose of the drug used (Mendelson, 1992). With the discovery of the many serotonin receptors and further identification of the agonist/antagonist actions of these earlier drugs at select 5-HT receptors, studies with these drugs paved the way for current understandings that, dependent on both the receptor subtype and the brain region affected, 5-HT can have both positive and negative effects on female sexual behavior.

Seven families, each with subclasses, of 5-HT receptors are currently recognized (Hannon and Hoyer, 2008). Of these, the 5-HT_1, 5-HT_2, 5-HT_3 and 5-HT_7 families have been examined for their role in female sexual behavior. Two members of the 5-HT_1 family (5-HT_{1A} and 5-HT_{1B}) and two members of the 5-HT_2 family (5-HT_{2A} and 5-HT_{2C}) have received the most investigation. With the development of drugs that exhibit relative selectivity for these receptors, insight into the role that different 5-HT receptors play in female sexual behavior has begun to emerge.

3.1 5-HT$_{1A}$ Receptors

Primarily because it was the target of one of the first relatively selective 5-HT receptor agonists to be developed, there is more information about effects of 5-HT$_{1A}$ receptor agonists on female sexual behavior (especially lordosis behavior) than for other 5-HT receptors (see Table 2 for a summary of studies). 5-HT$_{1A}$ receptors are G-protein coupled primarily to inhibition of adenylate cyclase and/or lead to opening of a K^+ channel (Artigas, 2013; Hannon and Hoyer, 2008), are present on soma and dendrites of 5-HT neurons (where they reduce firing of 5-HT neurons) as well as on soma and dendrites of neurons that are postsynaptic to 5-HT terminals (Blier et al., 1998; Sprouse and Aghajanian, 1987, 1986).

Systemic treatment with 5-HT$_{1A}$ receptor agonists reduces lordosis behavior in rats (Ahlenius et al., 1989; Fernandez-Guasti et al., 1987; Kishitake and Yamanouchi, 2003; Mendelson and Gorzalka, 1986a, b; Snoeren et al., 2011b) and hamsters (Hebert et al., 1995) and reduces sexual behavior and solicitation in female marmoset monkeys (Aubert et al., 2012; Snoeren et al., 2011b). However, both species and rat strain differences may exist. In the female ferret, the 5-HT$_{1A}$ receptor agonist, 8-OH-DPAT, does not reduce, but facilitates, receptivity (Paredes et al., 1994), and in a comparison of two commonly used rat strains, Fischer and Sprague-Dawley, lordosis behavior was reduced at a lower dose of 8-OH-DPAT in Sprague-Dawley than in Fischer females (Uphouse et al., 2002).

The most effective intracranial site for 5-HT$_{1A}$ receptor agonist's effects on lordosismay be the mediobasal hypothalamus (MBH), a brain area containing the VMN that is recognized to be critical for estradiol-facilitated female rat sexual receptivity (Blaustein, 2008). Infusion of several 5-HT$_{1A}$ receptor agonists [8-OH-DPAT, buspirone ([±)-l-(3-chlorophenyl)-2-[(l,l-dimethylethyl)amino]-l-propanone hydrochloride], 5-OH-DPAC [5-hydroxy-(3-di-n-propylamino)chroman] and 5-MEO-DPAC [5-methoxy-(3-di-n-propylamino)chroman] into this brain region rapidly inhibited lordosis behavior (Gonzalez et al., 1997; Uphouse et al., 1992b; Uphouse et al., 1993). When 8-OH-DPAT was used as the agonist, a variety of nonselective 5-HT$_{1A}$ receptor antagonists, propanolol [(±)-1-isopropylamino-3-(1-naphthyloxy)-2-propanol hydrochloride] and pindolol [1-(1*H*-indol-4-yloxy)-3-(isopropylamino)-2-propanol], as well as the selective 5-HT$_{1A}$ receptor antagonist, WAY100635 [N-[2[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]N-(2 pyridinyl) cyclohexane-carboxamide trihydrochloride], prevented the effects of 8-OH-DPAT following infusion into the MBH (Uphouse et al., 1996a; Uphouse and Wolf, 2004).

However, the MBH is not the only site relevant to the effects of 5-HT$_{1A}$ receptor agonists on lordosis behavior. Infusion of 8-OH-DPAT into the vicinity of 5-HT cell bodies in the DRN (but not directly into the DRN) or MRN or into the PAG inhibited lordosis behavior but only at higher concentrations than required to reduce lordosis behavior in the MBH (Uphouse et al., 1992a; Uphouse et al., 1994). The fact that 8-OH-DPAT was more effective near, but not directly in the DRN, may suggest that the drug's effect was mediated by 5-HT$_{1A}$ receptors located on non 5-HT neurons of the DRN rather than on 5-HT cell bodies (Uphouse et al., 1992a).

In the medial preoptic area (mPOA), a brain area that several authors have argued contributes significantly to sexual motivation (Guarraci and Clark, 2006; Kato and Sakuma,

2000; Martinez and Petrulis, 2013), infusion of 8-OH-DPAT (at relatively high concentrations) reduced lordosis behavior but less efficiently than following MBH infusions (Uphouse and Caldarola-Pastuszka, 1993). Proceptivity, however, was reduced and the female's resistance to the male's attempt to mount was increased. This may reflect a role for 5-HT_{1A} receptors in the mPOA in female sexual motivation. In Syrian hamsters, a significant reduction in lordosis duration was also seen following infusion of 8-OH-DPAT into the mPOA-anterior hypothalamus (mPOA-AH) (Caldwell and Albers, 2002).

Therefore, drugs acting on 5-HT_{1A} receptors may influence female precopulatory as well as copulatory behaviors. Consistent with this is a recent report that systemic treatment with 8-OH-DPAT reduced proceptivity and also reduced the time females spent in the male's compartment in a pacing paradigm (Snoeren et al., 2010; Snoeren et al., 2011a; Snoeren et al., 2011b). Because both effects were attenuated by the 5-HT_{1A} receptor antagonist, WAY100635 (Snoeren et al., 2010; Snoeren et al., 2011b), a 5-HT_{1A} receptor-mediated effect was implicated. Therefore, the collective findings indicate that 5-HT_{1A} receptor agonists may negatively affect both consummatory and appetitive/precopulatory effects of female sexual behavior and most evidence is consistent with a location of the relevant receptors that is postsynaptic to 5-HT neurons. While MBH 5-HT_{1A} receptors may be especially relevant for consummatory responses, other brain areas may be involved in the appetitive/precopulatory effects of 5-HT_{1A} receptor agonists.

Activation of somatodendritic 5-HT_{1A} receptors at 5-HT neurons reduces firing of these neurons and, thereby, reduces release of 5-HT in terminal areas (Adell et al., 1993; Hjorth and Sharp, 1991). If an elevation of synaptic 5-HT is inhibitory to female sexual behavior, activation of somatodendritic 5-HT_{1A} receptors might be expected to increase sexual behavior. Data consistent with this expectation were reported by Mendelson and Gorzalka following subcutaneous treatment with low doses of the 5-HT_{1A} receptor agonists, ipsapirone [2-[4-[4-(2-pyrimidinyl)-1-piperazin-yl]butyl]-1,2-benzisothiazol-3(2*H*)-one-1,1-dioxide- monohydrochloride] or gepirone (2′-methyl-4′-(5-methyl-[1,2,4]oxadiazol-3-yl)-biphenyl-4-carboxylic acid [4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide), given to suboptimally hormonally primed ovariectomized rats (Mendelson and Gorzalka, 1986b). Because somatodendritic 5-HT_{1A} autoreceptors are thought to be more sensitive to 5-HT_{1A} receptor agonists than are those receptors located postsynaptic to 5-HT terminals (Beer et al., 1990; Kennett et al., 1987), the low doses of these agonists were assumed to provide activation of 5-HT_{1A} autoreceptors without substantial activation of the postsynaptic sites. However, more definitive tests of this possibility have not been performed. Moreover, most evidence indicates that 5-HT, by acting on 5-HT_{1A} receptors that exist in areas terminal to 5-HT neurons, are responsible for 5-HT_{1A} receptor agonists on lordosis behavior and that these receptors may not be tonically active in preventing the emergence of the behavior (Uphouse, 2000; Uphouse and Wolf, 2004). However, in rats with low sexual receptivity, both the neutral 5-HT_{1A} receptor antagonist, WAY100635, and the partial agonist/antagonist, WAY100135 [chiral N-t-butyl-3-(1-(4-(2-methoxy) phenyl)piperazinyl)-1-phenylpropionamide dihydrochloride, quarter hydrate], increased lordosis responding (Kishitake and Yamanouchi, 2004; Uphouse et al., 1996a). Moreover, when women with HSDD were treated with gepirone-extended release tablets, there was a significant reversal

of HSDD in 63% of the patients (Fabre et al., 2011). Thus, it remains possible that some populations of 5-HT_{1A} receptors may be responsive to 5-HT_{1A} receptor active drugs in a way that positively affects female sexual behavior.

The majority of data that have implicated 5-HT_{1A} receptors in the negative modulation of female sexual behavior have used the 5-HT_{1A} receptor agonist, 8-OH-DPAT, that is now known to also act as an agonist at 5-HT_7 receptors (Barnes and Sharp, 1999; Cornfield et al., 1991). In contrast to the large number of studies that implicate 5-HT_{1A} receptors in modulation of female sexual behavior, there have been only 2 reports that specifically evaluated 5-HT_7 receptor active compounds (Siddiqui et al., 2007; Siddiqui and Shaharyar, 2007). These investigators reported that hormonally-primed, ovariectomized female rats, treated with 5-HT, 8-OH-DPAT or 5-CT (5-carboxyamidetryptamine, a non-selective 5-HT receptor agonist with 5-HT_7 receptor agonist properties), showed a decline in lordosis behavior and that both the 5-HT_{1A} receptor antagonist, WAY100135, and the 5-HT_7 receptor antagonist, SB 269970-A [2-(2-(4-methyl-piperidin-l-yl)-pyrrolidine-1-sulfonyl)-phenol (Thomas and Hagan, 2004)] antagonized the respective agonists (Siddiqui et al., 2007). Facilitation of the behavior in suboptimally hormonally-primed females was seen after treatment with either WAY100135 or SB 269970-A so it is currently impossible to exclude a role for 5-HT_7 receptors. However, evidence that the sexual behavioral effects of 8-OH-DPAT are blocked by both pindolol and WAY100635 (Uphouse et al., 1996a; Uphouse and Wolf, 2004), which have modest if any effect on 5-HT_7 receptors (Hannon and Hoyer, 2008; Lovenberg et al., 1993), enhances confidence in the conclusion that 5-HT_{1A} receptor agonists that have been studied reduce female sexual activity by interaction with 5-HT_{1A} receptors.

Based on the presence of inhibition after intracranial infusion to sites postsynaptic to 5-HT terminals and the comparatively smaller effects in the DRN, postsynaptic sites are likely to be responsible for effects of 5-HT_{1A} receptor agonists. In addition, since 8-OH-DPAT inhibits sexual behavior in rats that are missing the serotonin transporter (Olivier et al., 2011; Snoeren et al., 2010), the drug's ability to produce inhibition does not appear to be dependent on changes in reuptake of 5-HT. However, in a recent study with marmoset monkeys, 16 weeks of treatment with 8-OH-DPAT was reported to increase mRNA for the serotonin transporter in the DRN (Aubert et al., 2013). Interestingly, 5-HT_{1A} receptor mRNA was increased in the medial prefrontal cortex; and 5-HT_7 mRNA was increased in the CA1 region of the hippocampus (Aubert et al., 2013). These findings illustrate the potential for chronic 5-HT_{1A} receptor activation to lead to alterations in gene expression in brain areas that are important for female sexual receptivity and motivation.

3.2 5-$HT_{1B/1D}$ receptors

5-$HT_{1B/1D}$ receptors are negatively coupled to cAMP and are located on terminals of 5-HT and non 5-HT neurons where they function as terminal autoreceptors and heteroceptors, respectively (Daws et al., 2000; Engel et al., 1986; Hannon and Hoyer, 2008; Maura et al., 1986; Riad et al., 2000) and reduce release of neurotransmitter from nerve terminals (Daws et al., 2000; Hjorth et al., 2000; Hjorth and Tao, 1991). 5-HT_{1B} receptors are the most prominent such terminal autoreceptors in rats while, in humans, 5-HT_{1D} receptors are the

dominant such receptor (Kriegebaum et al., 2010; Kroeze et al., 2012). Both 5-HT_{1B} and 5-HT_{1D} receptors may be located on neuronal terminals and have similar, though not identical, pharmacology (Hannon and Hoyer, 2008; Kroeze et al., 2012). Although agents are emerging that differentiate the two receptors, most pharmacological agents that have been used to study female sexual behavior do not discriminate well between the two receptors and the notation 5-$HT_{1B/1D}$ will be used in most of the following discussion.

If high levels of extracellular 5-HT reduce female sexual behavior, 5-$HT_{1B/1D}$ receptor agonists would be expected to facilitate sexual behavior by reducing depolarization-dependent 5-HT release while 5-$HT_{1B/1D}$ receptor antagonists would be expected to reduce the behavior. There have been few tests of this hypothesis. Focus on 5-$HT_{1B/1D}$ receptors was initially based on findings with drugs that, while now known to affect several 5-HT receptors, were thought to have relatively selective agonist action at 5-$HT_{1B/1D}$ receptors. For example, TFMPP [1-[m-trifluoromethylphenyl]piperazine] and mCPP [1-(m-chlorophenyl) piperazine] enhanced lordosis behavior (Aiello-Zaldivar et al., 1992; Mendelson, 1992; Mendelson and Gorzalka, 1990) or reduced 5-HT_{1A} receptor-mediated lordosis inhibition (Wolf et al., 1998b). These earlier studies were influential in implicating 5-$HT_{1B/1D}$ receptors in female rat lordosis behavior. However, studies with more selective compounds have not offered convincing evidence for robust effects of 5-$HT_{1B/1D}$ receptor-acting drugs (Kaspersen and Agmo, 2012).

MBH infusion with the 5-$HT_{1B/1D}$ receptor antagonist, GR 127935 N-[4-methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1,2,4-oxadiazol-3--yl)-1,1′-biphenyl-4-carboxamide hydrochloride (Liao et al., 2000), inhibited lordosis behavior in rats made sexually receptive with estradiol benzoate priming but was considerably less evident in rats hormonally primed with estradiol benzoate and progesterone (Uphouse et al., 2009). Interestingly, the effect of the 5-$HT_{1B/1D}$ receptor antagonist appeared to result from an amplification of infusion stress on lordosis behavior (Uphouse et al., 2009). After infusion with the 5-$HT_{1B/1D}$ receptor agonist, CP 93129 [1,4-dihydro-3-(1,2,3,6-tetrahydro-4- 27 pyridinyl)-5H-pyrrol[3,2-bi]pyridin-5-one-dihydrochloride] (Uphouse et al., 2010), rats primed only with estradiol benzoate showed lordosis inhibition, but in contrast to a transient decline in lordosis behavior following infusion with the antagonist, effects of CP 93129 were long lasting. An explanation for similarity in effects of the agonist and antagonist is not clear but may result from a partial agonist effect of GR 127935 (Beer et al., 1998; de Groote et al., 2003).

Only a single study of a 5-$HT_{1B/1D}$ receptor compound has been reported for appetitive/precopulatory behavior. Kaspersen and Agmo (Kaspersen and Agmo, 2012) examined the 5-$HT_{1B/1D}$ receptor antagonist, GR 125743 [*N*-[4-methoxy-3-(4-methylpiperazin-1-yl)phenyl]-3-methyl-4-(pyridin-4-yl)benzamide], in both the partner preference and in the pacing paradigms and found no effect on any component of female sexual behavior.

Given the few studies that have been performed with 5-$HT_{1B/1D}$ receptor selective compounds, it is premature to draw conclusions as to how such drugs might ultimately be found to influence female sexual activity. However, the lack of effect of these drugs in rats hormonally primed with estradiol benzoate and progesterone coupled with the amplification

of the effects of stress by the receptor antagonist allows for interesting speculation. Since progesterone also reduces extracellular 5-HT in the MBH (Farmer et al., 1996; Maswood et al., 1999) and since activation of 5-$HT_{1B/1D}$ receptors reduces depolarization-dependent release of 5-HT, effects of 5-$HT_{1B/1D}$ receptor active drugs might be apparent only under conditions of high 5-HT release.

3.3 5-HT_2 receptors

Two 5-HT_2 receptors, 5-HT_{2A} and 5-HT_{2C}, have been implicated in 5-HT's modulation of female sexual behavior. Like 5-HT_{1A} receptors, members of the 5-HT_2 receptor family can activate multiple signaling pathways but with the phospholipase C second messenger pathways being the most consistently observed (Raymond et al., 2001). Most 5-HT_2 receptor active drugs that have been used in the study of female sexual behavior have some affinity for both 5-HT_{2A} and 5-HT_{2C} receptors. Inhibition of lordosis behavior by drugs, such as mianserin [1,2,3,4,10,14b-hexahydro-2-methyl-dibenzo[*c*,*f*]pyrazino[1,2-*a*]azepine hydrochloride], mesulergine [*N*′-[(8-α1,6-dimethylergolin-8-yl]-*N*,*N*--dimethylsulfamide hydrochloride], pirenpinone [3-[2-[4-(4-fluorobenzoyl)-1-piperidinyl]ethyl]-2-methyl-4H-pyrido-[1,2-a] pyrimidin-4-one], cinanserin [*N*-[2-[[3-(dimethylamino)propyl]thio-]phenyl]-3-phenyl-2-propenamide hydrochloride] and ketanserin, with antagonist action at 5-HT_2 receptors, initially led to assumptions that 5-HT_2 receptors might facilitate lordosis behavior (Hunter et al., 1985; Mendelson and Gorzalka, 1986c; Sietnieks, 1985; Wilson and Hunter, 1985). Although these drugs are not selective for 5-HT_2 receptors and fail to differentiate between the 5-HT_{2A} and 5-HT_{2C} receptors, the fact that they all shared 5-HT_2 receptor antagonist activity was influential in pointing toward a facilitating role for 5-HT_2 receptors (See Table 3)

Of the above 5-HT_2 receptor antagonists, ketanserin is the most selective in showing higher affinity for 5-HT_2 than other 5-HT receptors and exhibits higher affinity for the 5-HT_{2A} than for the 5-HT_{2C} receptor (Hoyer et al., 2002). Systemic treatment with ketanserin has been unequivocably associated with a decline in lordosis behavior (Hunter et al., 1985; Mendelson and Gorzalka, 1986c). Interestingly, the SSRI, fluoxetine also acts as a 5-HT_2 receptor antagonist (Jenck et al., 1993; Palvimaki et al., 1996) so that 5-HT_2 receptor effects may contribute to this antidepressant's ability to reduce lordosis behavior.

When ketanserin was infused into the MBH, ketanserin inhibited lordosis behavior (Uphouse et al., 1996b) and effects were reversed by the relatively selective 5-$HT_{2A/2C}$ receptor agonist, DOI [(+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane HCl] (Wolf et al., 1998a). DOI has high affinity for 5-HT_{2A} and 5-HT_{2C} receptors but little affinity at other 5-HT receptors (Hoyer et al., 1994; Zifa and Fillion, 1992). The 5-$HT_{2B/2C}$ receptor antagonist, SB206553 [N-3-pyridinyl-3,5-dihydro-5-methyl-benzo(1,2-b:4,5-b′)dipyrrole-(2 H)carboxamide], with considerably higher affinity for 5-HT_{2C} than for 5-HT_{2A} receptors (Kennett et al., 1996), had no effect on lordosis behavior after peripheral administration but reduced lordosis following MBH infusion (Wolf et al., 1999). In contrast, the 5-HT_{2A} receptor antagonist, MDL 100907 [(R)-2,3-dimethoxyphenyl)-1-[2-(4-piperdine)-methanol] which has higher affinity for the 5-HT_{2A} than the 5-HT_{2C} receptor (Herth et al., 2009), had

little effect following MBH infusion (Wolf et al., 1999) and led to the suggestion of 5-HT_{2C} receptor involvement in 5-HT's facilitation of lordosis behavior.

Consistent with a putative facilitative role for 5-$HT_{2A/2C}$ receptors in lordosis behavior, MBH infusion of DOI increased lordosis behavior in rats with low sexual receptivity and the facilitation was reversed by ketanserin (Wolf et al., 1998a). Since both DOI and ketanserin have been reported to have higher affinity for 5-HT_{2A} than for 5-HT_{2C} receptors, these findings might implicate 5-HT_{2A} receptors in the lordosis facilitation. However, infusion of the 5-HT receptor antagonist, MDL 100907 (which has considerably higher affinity for 5-HT_{2A} than for 5-HT_{2C} receptors) was less effective in attenuating the facilitative effects of DOI than was the 5-$HT_{2B/2C}$ receptor antagonist, SB 206553 (Wolf et al., 1999).

In contrast to findings in the MBH, in the mPOA, 5-HT_{2A} rather than 5-HT_{2C} receptors were implicated in the facilitation of lordosis behavior (Gonzalez et al., 1997). In this brain area, both DOI and mCPP facilitated sexual behavior and ketanserin blocked lordosis behavior which was interpreted as evidence of 5-HT_{2A} receptors in the facilitation. Comparable facilitative effects were not found in the MBH. Consistent with a role for 5-$HT_{2A/2C}$ receptors in the mPOA, DOI infusion into the mPOA-AH of Syrian hamsters increased lordosis duration (Caldwell and Albers, 2002). Thus, dependent on the brain area, both 5-HT_{2A} and 5-HT_{2C} receptors may have the potential to influence lordosis behavior.

Few reports of 5-HT_{2A2C} receptor active agents are available for precopulatory/appetitive behaviors. In one experiment where DOI was administered subcutaneously, DOI increased proceptivity, but not receptivity, in sexually receptive females (Rossler et al., 2006). There have been 3 reports of 5-$HT_{2A/2C}$ receptor agents in either the partner preference or pacing paradigms. Kaspersen and Agmo (Kaspersen and Agmo, 2012) examined effects of SB 206553 in both paradigms and reported no effect with the exception of a small decline in the number of proceptive behaviors. This contrasts with the report that SB 206553 reduced the time females spent in the male's compartment(Uphouse et al., 2005) and with the report by Nedergaard et al. (Nedergaard et al., 2004) who compared the effects of DOI and MK-212 [6-chloro-2-(1-piperazinyl)pyrazine hydrochloride] as examples of preferential 5-HT_{2A} and 5-HT_{2C} receptor agonists, respectively. In the pacing paradigm, DOI reduced the female's post-ejaculatory return latencies, interpreted as an increase in sexual motivation; and MK-212 increased the female's latency to approach to the male, interpreted as a decline in sexual motivation (Nedergaard et al., 2004). However, the authors noted the possibility that MK-212 may have increased anxiety and thereby influenced the female's approach behavior.

Therefore, both 5-HT_{2A} and 5-HT_{2C} receptors probably contribute to the facilitative effects of 5-HT_2 receptor compounds but additional experiments will be required to determine if the brain areas and/or elements of female sexual behavior that are affected are specific to one or both receptors.

3.4 5-HT_3 receptors

Unlike other 5-HT receptors, 5-HT_3 receptors are cation-selective, ligand –gated ion channels (Barnes et al., 2009). There have been only a few studies of 5-HT_3 receptor

compounds and female sexual behavior (Tanco et al., 1994; Uphouse et al., 2011). Systemic treatment with 5-HT_3 receptor active drugs had little effect on lordosis behavior (Tanco et al., 1994, 1993). However, a significant decline in lordosis behavior occurred when the 5-HT_3 receptor antagonist, tropisetron [(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1*H*-indole-3-carboxylic acid ester monohydrochloride], was infused into the MBH of hormonally primed ovariectomized rats, but not in naturally cycling proestrous rats (Maswood et al., 1997, 1998; Uphouse et al., 2011). Tropisetron's inhibition was reduced by the 5-HT_3 receptor agonist, mCPBG (m-chlorophenylbiguanide). However, DOI also attenuated the effects of tropisetron; and mCPBG reduced the inhibitory effects of 8-OH-DPAT (Maswood et al., 1998). Therefore, the specificity of these effects for 5-HT_3 receptors remains unclear. However, a variety of sexually active neurosteroids (Rupprecht, 2003) and SSRIs, such as fluoxetine, (Choi et al., 2003; Davies, 2012; Fan, 1994) are able to modulate 5-HT_3 receptor function; and 5-HT_3 receptor active drugs influence a variety of physiological events such as pain and nausea (Costall and Naylor, 2004) that could indirectly influence female sexual satisfaction. Moreover, activation of 5-HT_3 receptors may increase the sensitivity of peripheral sensory fibers (McKenna et al., 1991) and thereby facilitate somatosensory modulation of lordosis behavior. Consequently, at this time, it would be premature to draw conclusions about 5-HT_3 receptor-active compounds and female sexual behavior.

3.5 Summary of 5-HT Receptor Effects and Receptor Cross Talk

Over the past 20 years, studies with drug effects at 5-HT_{1A} and 5-HT_2 receptors have yielded a relatively consistent profile indicating that 5-HT_{1A} receptor agonists facilitate lordosis behavior while antagonists of 5-HT_2 receptors inhibit the behavior. The effect of these drugs on behaviors other than lordosis has received minimal investigation. Similarly, the study of drugs that act on other 5-HT receptors has lagged behind, in part due to the absence of drugs with relative selectivity. However, the endogenous ligand 5-HT does not affect a single receptor but has the potential to activate all receptors within the area of release. Understanding how activation of a single 5-HT receptor affects sexual behavior is likely to be an oversimplification of the effect of the neurotransmitter. For example, while infusion of 5-HT_{1A} receptors agonists into the VMN reliably reduced lordosis behavior, the behavior was unaffected by simultaneous infusion with a 5-HT_{1A} receptors agonist and either a 5-HT_2 or 5-HT_3 receptor agonist (Maswood et al., 1998). Therefore, additional studies with combinations of 5-HT receptor active drugs are needed.

In this regard, flibanserin [a 5-HT_{1A} receptor agonist and 5-HT_{2A} receptor antagonist; (3-[2-[4-[4-(trifluoromethyl)phenyl]piperazin-1-yl]ethyl]-1H-benzimidazol-2-one) has been reported to increase sexual desire in women with HSDD (Borsini et al., 2002; DeRogatis et al., 2012; Katz et al., 2013; Kennedy, 2010; Stahl et al., 2011; Thorp et al., 2012) and to reduce microdialysate levels of 5-HT in several brain regions (Allers et al., 2010; Invernizzi et al., 2003). These effects of flibanserin have been attributed to its action at 5-HT_{1A} receptors because the decrease in 5-HT was attenuated by WAY100635 (Invernizzi et al., 2003). Consistent with the drug's effect on extracellular 5-HT, long-term (but not acute) treatment with flibanserin increased solicitous behavior in rats (Gelez et al., 2013) and increased both social and sexual behaviors in female marmoset monkeys (Aubert et al.,

2012). These effects, while attributed to 5-HT_{1A} receptor activation, are clearly distinct from those of drugs such as the 5-HT_{1A} receptor agonist, 8-OH-DPAT (Aubert et al., 2012). Therefore, it is increasingly important to focus on the similarity and differences between drugs such as flibanserin and those with more restricted receptor action.

Flibanserin and 8-OH-DPAT might be expected to have similar effects on sexual behavior because both have 5-HT_{1A} receptor agonist action. However, flibanserin alters a variety of other sexually-related neurotransmitters such a norepinephrine (Aubert et al., 2012) and has a greater effect on postsynaptic than on somatodendritic 5-HT_{1A} receptors (Borsini et al., 1995a; Borsini et al., 1995b; Marazziti et al., 2002) while 8-OH-DPAT acts at both somatodendritic and postsynaptic 5-HT_{1A} receptors. Moreover, flibanserin and 8-OH-DPAT may differ in the intracellular signaling cascades initiated (Borsini et al., 1995a; Borsini et al., 1995b). In addition, flibanserin's 5-HT_{2A} receptor antagonism (Aubert et al., 2012) could be an important factor in flibanserin's apparent prosexual effects. However, the SSRI, fluoxetine, also acts as a5-HT_2 receptor antagonist, in vitro, (Jenck et al., 1993; Palvimaki et al., 1996) and 5-HT_2 receptor antagonists are generally associated with a decrease rather than facilitation of sexual behavior (Uphouse, 2000) (see section 3.3). Nevertheless, fluoxetine has a higher affinity for 5-HT_{2C} than for 5-HT_{2A} receptors (Boothman et al., 2006; Chen et al., 1995) so that the differential effect on these two receptor subtypes could be important in the divergent effects of flibanserin and fluoxetine on female sexual behavior. Moreover, fluoxetine's 5-HT_3 receptor antagonism (Choi et al., 2003; Davies, 2012; Fan, 1994) could contribute to its sexual behavioral effects. Importantly, though, while effects of flibanserin on extracellular 5-HT and 5-HT receptors are rapid, prosexual effects do not occur for several weeks (Allers et al., 2010; Stahl et al., 2011). The long delay required for the increase in sexual activity may reflect well-known desensitization of 5-HT_{1A} receptors after agonist activation and of 5-HT_{2A} receptors following either agonist or antagonist treatment (Gray and Roth, 2001; Kreiss and Lucki, 1992).

The above discussion illustrates the potential importance of 5-HT receptor cross talk in the actions of pharmacological compounds. Since most commonly prescribed pharmacological compounds exert multiple effects on the 5-HT system, greater emphasis on the global effects of 5-HT manipulation and female sexual behavior is needed.

4.0 Summary and Conclusions

There is little doubt that pharmacological manipulations leading to alterations in the serotonergic system can influence female sexual behavior in a variety of species, including humans. Recent attempts to identify 5-HT system relevant genetic polymorphisms (Kroeze et al., 2012; Sghendo and Mifsud, 2011) and their association with female HSDD and/or after treatment with 5-HT system altering drugs (Bishop et al., 2009; Bishop et al., 2006; Burri et al., 2012; Serretti et al., 2007) may begin to offer a profile about which components of the 5-HT system are especially important in female sexual behavior. However, in spite of a considerable amount of data, there are still many limitations to our current knowledge.

It remains unclear what component(s) of the relatively complex repertoire of female sexual behaviors are affected and which brain regions contribute to the various behavioral

components. Since, in research with animal models, the lordosis reflex has received major emphasis (see Table 4 for a summary), there is more information about this behavior than for other components of female sexual behavior. For this behavior, 5-HT in the MBH is a particularly critical site for the negative effects of 5-HT receptor-active agents. However, these studies offer only a partial snapshot of the role 5-HT plays in female sexual behavior. The contribution of 5-HT to female sexual motivation/satisfaction has received limited study in animal models but is a major focus for humans with HSDD and/or for women who experience sexual side effects of antidepressant drugs. The absence of a thorough investigation of 5-HT active compounds in animals models of female sexual motivation is, therefore, an important limitation on understanding 5-HT's role in female sexual behavior. As a consequence, the neural location(s) and 5-HT receptor(s) that contribute to female sexual motivation remain largely unexplored.

An additional limitation is the relatively low efficacy of compounds such as SSRIs, which regularly lead to sexual dysfunction in humans, to reduce measures of sexual motivation in those few animal studies that have been reported. Therefore, additional effort is needed to identify the best model(s) for studying female HSDD and/or SSRI-induced sexual dysfunction.

In addition, it is not known how different 5-HT receptors interact to modulate sexual behaviors or which transduction pathways are involved in 5-HT's effects. Because 5-HT receptors show unique, but often overlapping CNS distributions, activation of the same receptor subtype has the potential to increase or decrease female sexual behavior depending on (a) the brain region affected, (b) the receptor's microenvironment, (c) and the organism's state at the time of drug administration. In particular, female gonadal hormones influence the number and/or functioning of 5-HT receptors that have been implicated in female sexual behavior (Fink et al., 1996; Mize and Alper, 2000, 2002; Mize et al., 2001; Mize et al., 2003; Sumner and Fink, 1997). In fact, virtually all aspects of 5-HT synthesis and metabolism are modified by estradiol (Bethea et al., 2002; Clark et al., 2012; Lu et al., 2003; Smith et al., 2004) and/or progesterone (Farmer et al., 1996; Maswood et al., 1995; Renner et al., 1987). Not surprisingly, therefore, the type and timing of hormonal treatment can have robust effects on the sexual behavioral response to 5-HT drugs (Guptarak et al., 2010; Jackson and Etgen, 2001; Jackson and Uphouse, 1998, 1996; Trevino et al., 1999; Truitt et al., 2003).

In addition, because 5-HT receptors can utilize multiple signaling pathways (Hannon and Hoyer, 2008; Hoyer et al., 2002; Raymond et al., 2001) and since G-protein coupled receptors can activate different pathways often dependent on the levels of the neurotransmitter (Hazell et al., 2012), it remains unclear what signaling pathways mediate the effects of 5-HT receptors on female sexual behavior and if the same or distinct pathways are involved in 5-HT's effect on different components of the female sexual behavior repertoire. Moreover, in most studies, investigators have focused on individual 5-HT receptors while endogenous 5-HT can simultaneously activate all 5-HT receptors within the release environment. Interactions that occur among 5-HT receptors and/or their signaling cascades may amplify or even attenuate the effects of activation of individual 5-HT

receptors. Few investigators have addressed the relevance of such interactions to female sexual behavior.

Therefore, in spite of its rich history, the study of 5-HT pharmacology and female sexual behavior remains in its infancy. Given the large number of 5-HT active drugs that are prescribed for disorders of high prevalence in women, it is essential that studies of 5-HT and female sexual behavior continue with an increased emphasis on closing the gaps in our current understanding.

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Highlights

1. A historical view of serotonin's (5-HT) involvement in female sexual behavior is presented.
2. The effect of drugs that increase or decrease CNS levels of 5-HT is reviewed.
3. Studies with compounds that act on 5-HT_1, 5-HT_2 or 5-HT_3 receptors are overviewed.
4. Limitations of current understanding about 5-HT's role in female sexual behavior is discussed.

Table 1

Summary of Studies with Drugs that Alter Synaptic Levels of 5-HT

Drug	Mode of Action	Route and Duration	Synaptic 5-HT	Behavior Examined	Behavioral Effect	References
Drugs That Decrease Synaptic 5-HT						
Reserpine	VMI[a]	peripheral-acute	decrease	lordosis	increase	(Mendelson, 1992)
Tetrabenazine	VMI	peripheral-acute	decrease	lordosis	increase	(Mendelson, 1992)
PCPA[b]	5-HT synthesis inhibitor	peripheral-acute	decrease	lordosis	increase	(Mendelson, 1992; Meyerson and Lewander, 1970)
5,7-DHT[c]	5-HT neurotoxin	ic[d]- hypothalamus- acute	decrease	lordosis	increase	(Luine et al., 1983)
Drugs That Increase Synaptic 5-HT						
pargyline	MAOI[e]	peripheral-acute	increase	lordosis	decrease	(Luine and Paden, 1982; Mendelson, 1992) (Luine and Paden, 1982)
pargyline	MAOI	ic-hypothalamus- acute	increase	lordosis	decrease	(Allen et al., 1993; Mendelson, 1992)
fenfluramine	5-HT releasing agent	peripheral-acute	increase	lordosis	decrease	(Mendelson, 1992)
5-HTP[f]	5-HT precursor	peripheral-acute	increase	lordosis	decrease	(Mendelson, 1992)
desmethyl- imipramine	Monoamine reuptake inhibitor	peripheral-acute	increase	lordosis	decrease	(Meyerson, 1966)
imipramine	Monoamine reuptake inhibitor	peripheral-acute	increase	lordosis	decrease	(Meyerson, 1966)
amitriptyline	Monoamine reuptake inhibitor	peripheral-acute	increase	lordosis	decrease	(Meyerson, 1966)
fluoxetine	SSRI; 5-HT reuptake inhibitor	peripheral-acute	increase	lordosis	decrease	(Frye et al., 2003; Guptarak et al., 2010)
fluoxetine	SSRI; 5-HT reuptake inhibitor	peripheral- repeated	increase	lordosis	minor effect	(Adams et al., 2012; Matuszczyk et al., 1998; Sarkar et al., 2008)
paroxetine	SSRI; 5-HT reuptake inhibitor	peripheral- repeated	increase	lordosis	minor effect	(Snoeren et al., 2011b)
fluoxetine	SSRI; 5-HT reuptake inhibitor	peripheral-acute	increase	male preference	no effect	(Sarkar et al., 2008)
paroxetine	SSRI; 5-HT reuptake inhibitor	peripheral-acute	increase	male preference	no effect	(Kaspersen and Agmo, 2012)
paroxetine	SSRI; 5-HT reuptake inhibitor	peripheral- repeated	increase	male preference	transient decline	(Snoeren et al., 2011)
fluoxetine	SSRI; 5-HT reuptake inhibitor	peripheral- repeated	increase	male preference	transient decline	(Matuszczyk et al., 1998)
paroxetine	5-HT reuptake inhibitor	peripheral- repeated	increase	male preference	decrease	(Kaspersen and Agmo, 2012)
fluoxetine	5-HT reuptake inhibitor	peripheral-acute	increase	pacing time with male	decrease	(Adams et al., 2012)
paroxetine	5-HT reuptake inhibitor	peripheral- repeated	increase	pacing time with male	no effect	(Snoeren et al., 2011)
fluoxetine	5-HT reuptake inhibitor	peripheral-acute	increase	investigation of male	decrease	(Adams et al., 2012)

Drug	Mode of Action	Route and Duration	Synaptic 5-HT	Behavior Examined	Behavioral Effect	References
Fluoxetine	SSRI; 5-HT reuptake inhibitor	peripheral- repeated	increase	estrous cycle	blocked cycle	(Uphouse et al., 2006)
Fluoxetine	SSRI; 5-HT reuptake inhibitor	peripheral- repeated	increase	estrous cycle	no effect	(Maswood et al., 2008; Matuszczyk et al., 1998)

[a] VMI-vesicular monoamine inhibitor;

[b] PCPA-parachlorophenylanine;

[c] 5,7-DHT-5,7-dihydroxytryptamine;

[d] ic-intracranial;

[e] MAOI-monoamine oxidase inhibitor;

[f] 5-HTP-5-hydroytryptophan

Table 2

Summary of Studies with 5-HT_{1A} Receptor Active Drugs on Sexual Behavior

Drug	Receptor	Action	Route	Behavior Examined	Effect	References
8-OH-DPAT	5-HT_{1A}	agonist	peripheral	lordosis	decrease	(Fernandez-Guasti et al., 1987; Hebert et al., 1995; Snoeren et al., 2010; Snoeren et al., 2009; Snoeren et al., 2011b)
ipsapirone	5-HT_{1A}	agonist	peripheral- hi dose	lordosis	decrease	(Mendelson and Gorzalka, 1986)
ipsapirone	5-HT_{1A}	agonist	peripheral- low dose	lordosis	increase	(Mendelson and Gorzalka, 1986)
gepirone	5-HT_{1A}	agonist	peripheral- hi dose	lordosis	decrease	(Mendelson and Gorzalka, 1986)
gepirone	5-HT_{1A}	agonist	peripheral- low dose	lordosis	increase	(Mendelson and Gorzalka, 1986)
buspirone	5-HT_{1A}	agonist	peripheral- hi dose	lordosis	decrease	(Mendelson and Gorzalka, 1986)
buspirone	5-HT_{1A}	agonist	peripheral- low dose	lordosis	increase	(Mendelson and Gorzalka, 1986)
WAY 100635	5-HT_{1A}	antagonist	peripheral	lordosis	increase	(Kishitake and Yamanouchi, 2004)
8-OH-DPAT	5-HT_{1A}	agonist	ic-hypothalamus	lordosis	decrease	(Gonzalez et al., 1997; Uphouse et al., 1992b)
WAY 100135	5-HT_{1A}	antagonist	ic[a]-hypothalamus	lordosis	increase	(Uphouse et al., 1996a)
8-OH-DPAT	5-HT_{1A}	agonist	ic-PAG[b]	lordosis	decrease	(Uphouse et al., 1992a)
8-OH-DPAT	5-HT_{1A}	agonist	ic-POA[c]	lordosis	modest decrease	(Gonzalez et al., 1997; Uphouse and Caldarola- Pastuszka, 1993; Uphouse et al., 1992b)
8-OH-DPAT	5-HT_{1A}	agonist	ic-POA-AH[d]	lordosis- hamsters	decrease	(Caldwell and Albers, 2002)
8-OH-DPAT	5-HT_{1A}	agonist	ic-DRN[e]	lordosis	no effect	(Uphouse et al., 1992a)
8-OH-DPAT	5-HT_{1A}	agonist	ic-MRN[f]	lordosis	decrease	(Uphouse et al., 1994)
buspirone	5-HT_{1A}	agonist	ic-hypothalamus	lordosis	decrease	(Uphouse et al., 1992b)
5-OH-DPAC	5-HT_{1A}	agonist	ic-hypothalamus	lordosis	decrease	(Uphouse et al., 1993)
5-MEO-DPAC	5-HT_{1A}	agonist	ic-hypothalamus	lordosis	decrease	(Uphouse et al., 1993)
8-OH-DPAT	5-HT_{1A}	agonist	peripheral	pacing time with male	decrease	(Snoeren et al., 2010)

[a] ic-intracranial;

[b] PAG-periaqueductal gray;

[c] POA-preoptic area;

[d] AH-anterior hypothalamus;

[e] DRN-dorsal raphe;

[f] MRN-median raph

Table 3

Summary of Studies with 5-$HT_{2A/2C}$ Receptor Active Drugs on Sexual Behavior

Drug	Receptor	Action	Route	Behavior Examined	Effect	References
ketanserin	5-$HT_{2A/2C}$	antagonist	peripheral	lordosis	decrease	(Hunter et al., 1985; Mendelson and Gorzalka, 1986; Uphouse et al., 1996b)
DOI	5-$HT_{2A/2C}$	agonist	peripheral	lordosis	no effect	(Rossler et al., 2006)
SB206553	5-$HT_{2B/2C}$	antagonist	peripheral	lordosis	no effect	(Wolf et al., 1999)
ketanserin	5-$HT_{2A/2C}$	antagonist	ic[a]-hypothalamus	lordosis	decrease	(Uphouse et al., 1996a; Uphouse et al., 1996b)
DOI	5-$HT_{2A/2C}$	agonist	ic-hypothalamus	lordosis	increase	(Wolf et al., 1998)
SB206553	5-$HT_{2B/2C}$	antagonist	ic-hypothalamus	lordosis	decrease	(Wolf et al., 1999)
MDL 100907	5-HT_{2A}	antagonist	ic-hypothalamus	lordosis	no effect	(Wolf et al., 1999)
DOI	5-$HT_{2A/2C}$	agonist	ic-preoptic area	lordosis	increase	(Gonzalez et al., 1997)
DOI	5-$HT_{2A/2C}$	agonist	peripheral	proceptivity	increase	(Rossler et al., 2006)
SB 206553	5-$HT_{2A/2C}$	antagonist	peripheral	male preference	no effect	(Kaspersen and Agmo, 2012)
SB 206553	5-$HT_{2A/2C}$	antagonist	peripheral	pacing time with male	no effect	(Kaspersen and Agmo, 2012)
SB 206553	5-$HT_{2A/2C}$	antagonist	peripheral	pacing time with male	decrease	(Uphouse et al., 2005)
DOI	5-$HT_{2A/2C}$	agonist	peripheral	pacing post- ejaculatory return	decrease	(Nedergaard et al., 2004)
MK-212	5-HT_{2C}	agonist	Peripheral	pacing post- ejaculatory return	increase	(Nedergaard et al., 2004)

[a] ic-intracranial

TABLE 4

OVERALL SUMMARY OF 5-HT AND LORDOSIS BEHAVIOR

COMPONENT OF 5-HT SYSTEM	EFFECT ON LORDOSIS
HIGH 5-HT	DISRUPTIVE
LOW 5-HT	FACILITATIVE
5-HT_{1A} RECEPTORS	DISRUPTIVE
5-HT_{2} RECEPTORS	FACILITATIVE
$5\text{-HT}_{1B/1D}$ RECEPTORS	FACILITATIVE??
5-HT_{3} RECEPTORS	FACILITATIVE??
5-HT_{7} RECEPTORS	DISRUPTIVE??

?? data are not yet clear and/or insufficient for conclusions