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Evidence that serotonin affects female sexual functioning via peripheral mechanisms

P.F. Frohlich, C.M. Meston*

Department of Psychology, University of Texas at Austin, Austin, TX 78712, USA

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Abstract

A review of the literature indicates that serotonin is active in several peripheral mechanisms that are likely to affect female sexual functioning. Serotonin has been found in several regions of the female genital tract in both animals and humans. In the central nervous system (CNS), serotonin acts primarily as a neurotransmitter, but in the periphery, serotonin acts primarily as a vasoconstrictor and vasodilator. Since, in the periphery, the principal component of sexual arousal is vasocongestion of the genital tissue, it is likely that serotonin participates in producing normal sexual arousal. In addition, serotonin administration produces contraction of the smooth muscles of the genito-urinary system and is found in nerves innervating the sexual organs. Taken together, this evidence suggests that peripheral serotonergic activity may be involved in the normal sexual response cycle. In addition, exogenous substances that alter serotonin activity, such as selective serotonin uptake inhibitors (SSRIs) and the atypical antipsychotics, can produce sexual dysfunction. It is possible that sexual side effects seen with these drugs may result, at least in part, from their action on peripheral mechanisms.

Keywords: 5-HT; Sexual physiology; Antidepressants; Vascular; Female sexuality; Peripheral nervous system

Research examining the relationship between serotonin and sexual functioning has focused primarily on central nervous system (CNS) activity. Animal researchers typically inject compounds directly into the CNS, or into the periphery when known to cross the blood-brain barrier, and examine subsequent sexual responding. The goal has been to map relations between sexual activity and specific serotonin receptor activity and/or specific serotonin-rich brain regions (e.g., Refs. [58,77,124]). In humans, while such direct examination clearly, for ethical reasons, cannot be conducted, indirect research on the link between serotonin and sexual behavior has also focused primarily on centrally mediated events. For example, sexual side effects subsequent to antidepressant, anti-psychotic, or other serotonergic drugs have been discussed almost exclusively in terms of serotonin receptor subtype activation or inhibition in the CNS (e.g., Ref. [78]).

Clearly, serotonin may mediate some aspects of sexual functioning almost entirely within the CNS. For example, ample evidence suggests that hypothalmic serotonin activity can produce the lordosis response [58,77,124–130]. Given, however, that the vast majority of serotonin receptors are located in the periphery of the body, with only 5% located in the CNS [97], it is feasible that some aspects of sexual behavior are affected, at least in part, by activation of these peripheral receptors. This would be consistent with research on eating and drinking behaviors, which are also affected by serotonin, and which have been shown to be differently affected by central vs. peripheral manipulation (e.g., Refs. [12,41]). Moreover, a vast literature indicates that serotonin is involved in a wide variety of peripheral processes, including vascular and non-vascular smooth muscle contraction, autonomic and sensory neurotransmission, endocrine and exocrine secretion, and carotid body and cardiopulmonary reflexes. Although some or all of these processes may be expected to impact sexual functioning, to date, this literature has been geared exclusively toward understanding and treating pathologies such as vasospasm, hypertension, peripheral

* Corresponding author. Tel.: +1-512-232-4644; fax: +1-512-471-6175.

E-mail address: meston@psy.utexas.edu (C.M. Meston).

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vascular disease, and Carcinoid syndrome (complete description of serotonin's role in peripheral mechanisms is beyond the scope of this paper; for a thorough review of serotonin in the periphery, see Ref. [44]).

The purpose of this paper is to provide the first in-depth examination of the potential mechanisms by which peripheral serotonergic activity may impact female sexual functioning. A brief review of relevant female sexual anatomy and physiology is first presented, followed by a detailed discussion of the mechanisms by which peripheral serotonin may affect sexual functioning, and an overview of certain exogenous substances that affect both serotonin activity and sexual functioning. It should be noted at the outset that the majority of animal research and a disproportionate amount of human research relevant to the present review were performed using males. While it is certainly feasible that serotonin's role in the majority of peripheral processes is similar in males and females, it is also likely that some processes are dissimilar when generalizing results between sexes. Caution is clearly warranted.

1. Female sexual anatomy and physiology

The female genital tract consists of, externally, the mons veneris, clitoris, labia majora, labia minora, vestibule, orifice of the urethra, and the orifice of the vagina and, internally, Bartholin's gland, the bulbi vestibule, the vagina, uterus, uterine horn, fallopian tubes, and ovaries [53]. Normal sexual functioning is dependent upon genital muscles, rich sensory innervation, and an extensive vascular network. The genital muscles, also known as the pelvic floor muscles, include the bulbocavernosus and the ischiocavernosus muscles. The bulbocavernosus helps to maintain the structure of the pelvic viscera and serves as a vaginal sphincter while the ischiocavernosis acts to drive blood into the corpus cavernosum of the clitoris [115]. In women, orgasm involves contractions in the smooth muscles of the genital region, which are characterized by rhythmic, synchronized vaginal, anal [18], and uterine contractions [25,43]. The female genital tract is innervated by the pelvic splanchnic, hypogastric, and pudendal nerves [53]. The inner two-thirds of the vagina is innervated exclusively by pain receptors, but the outer third, in particular, between the vaginal wall and the bladder, is innervated by touch receptors [64]. The mons veneris, labia majora, labia minora, and the clitoris, by contrast, are innervated by touch receptors, pressure receptors, pain receptors, and other types of nerve endings [64,139]. The genital vascular network is supplied by the iliac artery, which branches into the uterine artery, the vaginal artery, and the pudendal artery. This vascular network becomes engorged with blood during intercourse resulting in vaginal lubrication [59] and possibly enabling orgasm [76]. Sexual arousal in women results in vasocongestion of the vagina, vulva, clitoris, uterus, and possibly the urethra [52] that is two to three times greater than when a woman is not sexually aroused [48,132] and can occur within 2 to 4 seconds of sexual stimulation [51] (for a more detailed description of female sexual anatomy and physiology, see Ref. [70]).

2. Serotonin and peripheral mechanisms

Serotonin is typically synthesized and stored in the tissue in which it is later used [44]. Animal and human studies suggest that certain areas within the female genital tract contain serotonin suggesting that serotonin is active in the genital region. In female dogs, serotonin was found in cells of the distal and middle urethra. The cells were in the greatest density in the central portion of the urethra and none were found in the bladder and lower urethra [55]. Nerve fibers innervating the vasculature of the rat oviduct and uterine horn have been shown to contain serotonin [7] while biopsies of human fallopian tubes and ovaries have not revealed cells containing serotonin [38].

Biopsies from human endometrium suggest that normal uterine cells do not contain serotonin [38]. In addition, the uterus is innervated by the hypogastric nerve and in the rat, 5-HT delivered via the uterine artery did not produce a response in the hypogastric nerve [15]. The rat hypogastric nerve also innervates the cervix [15] and serotonin has been found in the nerve fibers that innervate the cervical vasculature [7]. Cells containing serotonin have been found in human biopsies of the cervix [38].

The vaginal canal is innervated by the pelvic nerve and in the rat 5-HT delivered via the uterine artery produces an electrical response in the pelvic nerve branch [15]. To our knowledge, no one has reported the effects of serotonin on vaginal vasculature. While cells containing serotonin have been found in the rabbit vagina [42], very few have been detected in the canine vagina [55]. Serotonin cells have been found in the external genitalia of female animals. Specifically, they were found in the vaginal–vestibular junction and the clitoris of dogs [55] and in the vestibular epithelium of rabbits [42]. In humans, serotonin-containing cells have been found in biopsies of the vulva. They were most frequently found in the epithelium of Bartholin's glands, which are located on either side of the vaginal orifice [38].

These studies indicate that serotonin is present in the genital tissue of humans and animals although the specific genital region varies across species. The presence of serotonin in the genital region indicates that it is active in physiological processes in this region of the body and, hypothetically, in sexual physiology. If serotonin is active in sexual physiology, it would be expected that it affects peripheral systems that are active during the sexual response cycle. Specifically, serotonin may influence sex-

ual physiology through the vascular, muscular, endocrine, and peripheral nervous systems. Serotonergic activity in each of these systems will be reviewed and discussed in terms of how such activity may affect sexual physiology and sexual functioning.

2.1. Vascular mechanisms

One of peripheral serotonin's primary functions is the regulation of vascular tone and blood flow (for a thorough review of serotonin and vascular functioning, see Ref. [44]). In fact, the vasoconstricting effect of serotonin is the source of its name: a substance in the serum that produces vasoconstriction by increasing the tonus of vascular smooth muscle [101]. The majority of peripheral serotonin is stored in blood platelets. Indeed, much of the body's serotonin is synthesized in the enterochromaffin cells of the gastrointestinal tract and then released into the blood stream where it is taken up by blood platelets. Serotonin is taken into the blood platelets by an active transport mechanism when 5-HT levels are low and by passive diffusion when 5-HT levels are high [114]. While the majority of blood 5-HT is stored in blood platelets, some evidence suggests that the plasma also contains 5-HT. Blood plasma 5-HT has a high turnover and is unaffected by pharmacologic agents while platelet 5-HT has a slow turnover and is affected by pharmacologic agents [90]. It is estimated that 5-HT produced in the gastrointestinal tract has a half-life of 7 to 12 hours [35]. Serotonin that is not taken up by platelets is either metabolized in the liver by monoamine oxidase or by the pulmonary vascular endothelium [113].

Animal and human arteries, when exposed to serotonin, serotonin agonists, serotonin antagonists, and platelets can produce, depending on several factors, either vasoconstriction or vasodilation. Serotonin-induced vasoconstriction is mediated primarily by the 5-HT_{2A} receptor [31,47,65,104,141] (serotonin-induced vasoconstriction may be fairly complex; Koch et al. [63] found that serotonin-induced vasoconstriction did not seem to be mediated by the 5-HT_{2A} receptor). Evidence indicates that serotonin produces vasodilation by acting on 5-HT_1 receptors to stimulate the release of nitric oxide [23,71,107]. In addition, serotonin produces vasodilation by activating 5-HT_3 receptors [113].

Several other factors influence whether serotonin produces vasoconstriction or vasodilation. A particular artery may constrict or dilate when exposed to serotonin depending upon whether it was relaxed or constricted prior to serotonin exposure [141]. Serotonin may produce vasoconstriction or vasodilation depending upon the size and type of blood vessel. In general, larger arterioles tend to constrict when exposed to serotonin while smaller arterioles tend to dilate [5,6,23,63,107,135], although it is also feasible that serotonin acts differently on arterioles than on capillaries. It is unclear how serotonin may affect venules. In one study, serotonin had no affect on large venules between 115 and 196 μm [135], while in another study, human hand veins (size not reported) contracted when exposed to 5-HT as well as the 5-HT_1-like, 5-HT_2, and 5-HT_3 receptor agonists in vitro [17]. In rabbits, intravenous injections of 5-HT produced increased blood flow to the stomach, heart, and brain but not to the skin, lungs, and kidney. In rats, intraperitoneal injections produced greater blood flow in muscles, lungs, heart, and brain but not the skin and kidneys, although intravenous injections produced some increased blood flow to the skin [30].

Serotonin's differential vasoactive effect on small and large arterioles and venules could account for serotonin's effect on blood flow into various bodily regions. In addition, given the differences in structure and function of the male and female genitalia, it is possible that males and females differ in the relative proportion of different sizes and types of genital blood vessels. This could account for certain sex differences in sexual responses to specific serotonin receptor subtype activity noted in the animal literature (for review, see Ref. [78]). Of course, the latter notion is highly speculative given that anatomical evidence for differences between sizes and types of blood vessels between males and females has, to our knowledge, not yet been examined.

Serotonin may also act synergistically with other substances to affect vasoconstriction and dilation. For example, the neurotransmitter and neuromodulator, norepinephrine, and the endothelium-derived constriction factor, endothelin, both potentiate the contractile effects of serotonin [71,140,141]. In addition, serotonin receptors may become sensitized by exposure to vasoconstrictor agents such that previously silent serotonin receptors become active [142].

Thus, serotonin acts on 5-HT_1 and 5-HT_{2A} receptors to regulate vascular tone. Disruption to this delicate balance can lead to abnormalities in vascular tone. For example, some vascular diseases result in damage to the cells lining the blood vessels, known as the endothelium, and this process can be studied in laboratories by artificially removing the endothelium and examining how the blood vessels respond to stimulation. When the endothelium is intact, precontracted male rat aortic rings (i.e., sliced artery samples) dilated when exposed to 5-HT (via platelets); when the endothelium was removed, they contracted. Relaxed aortic rings with intact endothelium contracted slightly when exposed to 5-HT, while denuded endothelium markedly contracted [141]. Since nitric oxide is produced in the endothelium and serotonin acts on 5-HT_1 receptors to release nitric oxide and produce vasodilation, damage to the endothelium is likely to disrupt the process. When the endothelium is damaged, vasodilation processes may be disrupted while vasoconstriction processes may continue normally. In such a situation, the delicate balance of constriction and dilation would be disrupted such that serotonin administration would pro-

duce vasoconstriction only [113]. In summary, it is possible that during normal sexual arousal serotonin may help to regulate appropriate vasodilation and constriction. When serotonin mechanisms are abnormal, the sexual arousal response may be disrupted. For example, in both men and women, hypertension has been associated with sexual dysfunctions such as erectile dysfunction and difficulty achieving orgasm although it is not clear whether the sexual difficulties precede or are caused by the antihypertensive treatments [11,69].

2.2. Non-vascular smooth muscle contraction

In women, orgasm involves contractions in the smooth muscles of the genital region, which are characterized by rhythmic, synchronized vaginal, anal [18], and uterine contractions [25,43]. While, to our knowledge, serotonin has not been directly implicated in orgasmic function, serotonin is involved in smooth muscle contractions in the genito-urinary system (as well as in the gastro-intestinal tract and the trachea of the respiratory system). In the animal (rabbit, cat, pig) and human urinary system, 5-HT produces contractions of the bladder that are characterized by initial rapid contractions followed by tonic contractions. In cats, serotonin acts on 5-HT_3 receptors to produce rapid contractions and acts on 5-HT_2 receptors to produce tonic contractions. In humans, it has been shown that 5-HT_2 antagonists can block a portion of this contraction [26].

Serotonin administration produces contractions in the rat and human uterus [72,137]. The 5-HT_2 antagonists, LY53,857 and ketanserin, inhibits 5-HT induced contractions of the rat uterus in vitro [26,27]. Similarly, serotonin produced contractions in human myometrial smooth muscle harvested from women undergoing cesarean section and it was a more potent contractile agent than norepinephrine, prostaglandin F2α, and E2 [72]. It is feasible that serotonin may promote or facilitate orgasmic contractions although direct evidence supporting this is not, to our knowledge, currently available.

2.3. Endocrine functions

Evidence suggests that both central and peripheral serotonin affects the levels of some neuromodulators and hormones involved in the sexual response cycle although it is not clear whether its action is direct or indirect. While centrally administered 5-HT caused an increase in vasopressin release in male rats, this release was attenuated with xylamidine, a 5-HT_{2A} antagonist that does not cross the blood-brain barrier [94]. Similarly, in the male rat, peripheral administration of the 5-HT_{2A} agonist DOI produced increased adrenocortical secretion. Central administration produced a similar effect suggesting that adrenocortical secretions are mediated by both central and peripheral 5-HT_{2A} receptors [133]. It is possible that the effects found after peripheral administration resulted solely from DOI's central effects since the compound is able to cross the blood-brain barrier. Corticosterone secretions in male rats were increased by peripheral administration of the 5-HT_{2A} agonist DOI and this effect was attenuated by the peripheral 5-HT_{2A} antagonist, xylamidine [4]. Moreover, peripheral corticosterone administration produced increased receptive and proceptive behaviors in female rats and this effect was antagonized by the serotonin reuptake inhibitor and 5-HT_{2A} antagonist, nefazodone [54]. While no clear relationship has been found between vaginal pulse amplitude and estradiol, progesterone, prolactin, cortisol, luteinizing hormone, or testosterone, some evidence indicates that prolactin may be related to subjective sexual arousal [56,111].

Peripheral serotonin levels fluctuate during the menstrual cycle. During the midluteal, late luteal, and premenstrual phases, serotonin levels increase, and during the menstrual and follicular phases these levels decrease [100,121]. In platelet poor plasma (to obtain platelet poor plasma, blood samples were centrifuged at 4°C), serotonin levels were lowest during the ovulatory phase [16]. Serotonin may play a role in vaginal pulse amplitude changes throughout the menstrual cycle; vaginal pulse amplitude was highest and remained at a criterion level longest during the luteal phase of the menstrual cycle [111]. Thus, both serotonin and vaginal pulse amplitude seem to be highest during the luteal phase of the menstrual cycle although the implications of this similarity are unclear. To our knowledge, no one has specifically examined the effect of serotonin on vaginal pulse amplitude.

Women with premenstrual syndrome, which is characterized by several difficulties associated with central serotonin disregulation (headache, depression), have cyclical fluctuations in peripheral serotonin that differ from those seen in women without premenstrual syndrome. In women with premenstrual syndrome, as compared to women without premenstrual syndrome, peripheral serotonin levels, but not estradiol or progesterone levels, were lower throughout the cycle and did not show the typical increase during the luteal and premenstrual phases. In some premenstrual syndrome women, serotonin levels decreased slightly during these phases [100]. In addition, women reporting premenstrual dysphoria who were taking fluoxetine, a serotonin reuptake inhibitor, experienced changes in the length of their menstrual cycle (in some cases shortened and in some cases lengthened). This effect may be dose-dependent [116].

In summary, serotonin activity affects some neuromodulators and hormones and serotonin levels fluctuate during the menstrual cycle. The currently available evidence does not strongly suggest that serotonin affects sexual functioning through these mechanisms. Central to this conclusion is the fact that although some evidence suggests that sexual arousal increases during the luteal

and follicular menstrual phases (when 5-HT levels increase and then decrease, respectively), most research has failed to find a notable relation between sexual function and menstrual cycle changes (e.g., Ref. [111]).

2.4. Serotonin in the spinal cord and peripheral nerves

Serotonin receptors are also widely distributed in nerves of several systems likely to indirectly or directly affect sexual functioning. As discussed above, serotonin receptors are located in the nerves innervating the sexual organs [7,15]. Several studies indicate that tactile sensitivity affects sexual functioning [46,85,138] and serotonin may affect cutaneous free nerve endings and mechanoreceptors. The 5-HT_{2A} receptor was found on 32% of the axons in the glabrous (hairless) skin of the rat. Receptors were found in free nerve endings and in the Pacinian corpuscles and it was suggested that these receptors may be activated by 5-HT released from blood platelets and mast cells [24,103]. In the cat, serotonin excited cutaneous afferent fibers of slowly adapting pressure receptors, produced a weak response in free nerve cells and thermoreceptors, and produced no response in hair receptors [40].

Evidence suggests serotonin acts in nociception as a result of 5-HT activity in the spinal cord and in peripheral nerves. A previous review of 5-HT and nociception [102] suggests that serotonin stimulation to the spinal cord is complex in that it produces, depending on several factors, both hypoalgesia and hyperalgesia, while serotonin stimulation to peripheral nerves produces hyperalgesia. Indeed, when serotonin is injected subcutaneously, it produces behavior indicative of hyperalgesia and pain [60,119]. It is unlikely that hyperalgesia would facilitate sexual responsiveness and thus, it would be expected that serotonergic activity at peripheral nerves would be inhibited, if anything, during sexual activity. If this were the case, a disruption in the inhibition of peripheral nervous 5-HT could impair sexual functioning. To our knowledge, no studies have been published reporting altered peripheral nervous 5-HT in sexual pain disorder. It has been reported, however, that vaginal stimulation produces decreased pain sensitivity in humans [134] and rats [28], and that vaginal stimulation results in a significant increase in spinal 5-HT [117]. This is consistent with previous work indicating that spinal 5-HT produces hypoalgesia [102].

2.5. Acute vs. chronic affects of serotonin

It is important to distinguish between the acute and chronic effects of serotonin. While a single administration of a serotonin agonist or antagonist may activate or inhibit serotonin receptors, chronic administrations may produce a sensitization or desensitization of serotonin receptors or an increase or decrease in the number of receptors. Thus, chronic administration can alter the manner in which the body responds to serotonin. For example, in the rat, the 5-HT derivative isamide temporarily blocked 5-HT-induced uterine contractions in vitro. In subsequent administrations of 5-HT, the uterine 5-HT receptors were more sensitive resulting in greater contraction [61]. Multiple exposure to the 5-HT_{1A} agonist 8-OH-DPAT in vivo resulted in a reduced contraction response when the uterus was later exposed in vitro to 5-HT. No such downregulation was found with 5-HT in vivo overexposure, however, suggesting that selective 5-HT_{1A} agonism resulted in downregulation of the 5-HT_2 receptor [57].

3. Role of serotonin in sexual dysfunctions

Sexual difficulties often accompany certain disorders that are characterized by abnormalities in peripheral serotonin. It is possible that these sexual difficulties result, at least in part, from disregulation of peripheral serotonin. For example, depression, which has been traditionally viewed as a psychological disease, is characterized by changes in sexual functioning and evidence suggests that peripheral serotonin, as measured by platelet serotonin levels, is lower in depressed individuals as compared to non-depressed individuals [67,108,120]. In addition, platelet serotonin levels may be inversely related to severity of depression [73].

3.1. Selective serotonin uptake inhibitors (SSRIs) and sexual functioning

Given that genital vasocongestion is important to normal sexual arousal, and serotonin is a potent vasoactive substance in the peripheral tissues, it is feasible that changes in serotonin activity may impact sexual functioning. It is well established that sexual difficulties are a common side effect of antidepressant medications and it is possible that these sexual difficulties arise, at least in part, from the peripheral serotonergic properties of these medications. Antidepressants such as the monoamine oxidase inhibitors (MAOIs), tricyclics, and SSRIs all exert effects on serotonin and have all been found to induce sexual dysfunctions. The most typical sexual side effect of MAOIs and tricyclics is impaired orgasmic function [78]. The most common sexual side effects of SSRIs include, in both men and women, decreased sexual desire, and delayed or inhibited orgasm. Depending upon the study, between 2% and 75% of patients taking SSRIs, such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), and venlafaxine (Effexor), report sexual side effects [37,78,84,92,93,96]. Reports indicate that sexual dysfunctions induced by fluoxetine may be dose-dependent, for both men and women, such that higher doses are more likely to produce problems and that the problems may be alleviated by lowering the dose [14,92].

A previous literature review by Meston and Gorzalka [78] suggests that males are more likely than females to experience sexual side effects from antidepressants, such as

MAO inhibitors and tricyclics, although it is possible that men are simply more willing to report problems than women. Indeed, a study of 344 male and female outpatients, where the patients answered questions regarding their sexual functioning, revealed that sexual difficulties as a result of SSRIs were more severe for females than males. The women who reported sexual difficulties reported more severe loss of libido and greater difficulty achieving orgasm than did the men reporting sexual difficulties [84]. Women have higher levels of circulating plasma 5-HT, platelet 5-HT, and whole blood 5-HT but lower levels of 5-HIAA as compared to men suggesting that women do not metabolize serotonin as rapidly as men [90]. It is feasible that differences in serotonin metabolism contribute to more severe SSRI-induced sexual dysfunction in women.

One antidepressant, nefazodone, has a different mechanism of action as compared to typical SSRIs and seems to produce fewer sexual side effects [96,105]. Unlike the typical SSRIs, nefazodone is a 5-HT_2 receptor antagonist as well as a 5-HT reuptake inhibitor. As is the case with many typical SSRIs, chronic nefazodone use produces a reduction in the number of 5-HT_2 receptors. Although antagonists typically produce an upregulation of postsynaptic receptors, 5-HT activity at one receptor type can influence activity at another receptor type, which, given that nefazodone increases 5-HT activity at all but the 5-HT_2 receptors, could explain the fact that nefazodone appears to reduce the number of 5-HT_2 receptors. Because of its unique mechanism of action, chronic nefazodone use may produce an upregulation of 5-HT_{1A} receptors, which may account for its antidepressant quality [33]. It is not clear why nefazodone produces fewer sexual side effects compared to traditional SSRIs. A study examining diabetics revealed that antagonism of the 5-HT_2 receptor produced an increase in blood flow [110]. It is possible that nefazodone produces fewer sexual side effects because its 5-HT_2 receptor antagonist property serves to increase genital vasocongestion following sexual stimulation.

A previous review of the literature suggests that chronic antidepressant use alters serotonin activity centrally by altering receptor sensitivity, by decreasing the number of 5-HT_2 receptors and, although the evidence is inconsistent, by decreasing the number of 5-HT_1 receptors [78]. In the periphery, SSRIs block the uptake of 5-HT into the platelets [114] and mast cells [98,106] and impair the ability of the pulmonary vasculature to remove 5-HT from the blood [49,89,136]. Acutely, SSRIs produce an increase in blood 5-HT [91], and a decrease in platelet 5-HT in rats [20]. Chronically, fluoxetine-use also produces a decrease in platelet 5-HT [10,95,131], but unlike acute fluoxetine use, chronic fluoxetine use produces a decrease in whole blood 5-HT in both rats [89] and humans [123] indicating that 5-HT synthesis may be down-regulated.

Chronic SSRI-use may produce a decrease in platelet and plasma 5-HT, but it is not clear how this would affect sexual functioning. To our knowledge, no studies have been published reporting that SSRIs alter vascular functioning in previously healthy individuals. SSRIs have, however, been reported to exacerbate vascular disease [45,113]. It has been suggested that serotonin may be involved in the maintenance of the vascular endothelium [29], and if circulating 5-HT levels were altered, it is possible that normal maintenance of the vascular endothelium could be disrupted. One study that examined rats found that chronic serotonin administration produced a degeneration of the vascular endothelium [86]. When the vascular endothelium is damaged it is subject to exacerbated vasoconstriction [113]. Excessive vasoconstriction could prevent vasocongestion of the genital tissue thereby disrupting the processes of vaginal lubrication and possibly orgasm. It is feasible that chronic SSRI-use produces mild degradation of the vascular endothelium that is sufficient enough to reduce vasocongestion to the genital tissue but that is not severe enough to produce vascular problems likely to attract medical attention in otherwise healthy individuals.

It is also feasible that chronic SSRI-use produces a change in peripheral 5-HT receptor density and/or sensitivity in a manner similar to changes noted centrally [78]. If receptor density and/or sensitivity were altered, it would be expected that acute changes in 5-HT activity would produce a blunted or exacerbated effect compared to what is normally produced by increases or decreases in acute 5-HT activity. Sexual functioning could be affected by such changes. Adrenergic stimulation has been reported to produce an increased release of 5-HT from the enterochromaffin cells of the gastrointestinal tract [1,2,66,99] and in women, adrenergic activity facilitates sexual arousal [79–83]. It is feasible that increased adrenergic activity during sexual stimulation in women produces an acute increase in blood 5-HT. If platelet or endothelial 5-HT receptor density or sensitivity was altered, acute increases in circulating 5-HT could produce a transitory change in vascular functioning that could impair sexual functioning.

SSRIs could also act to alter 5-HT receptor density or sensitivity on peripheral nerves. As noted earlier, 5-HT is involved in nociception [102] and a change in the 5-HT receptor density or sensitivity could produce, depending upon the direction of effect, either hyperalgesia or hypoalgesia. Acute administration of the 5-HT reuptake inhibitors, zimeldine, fluoxetine, and fluvoxamine, produced hyperalgesia in mice and rats [32,36]. In contrast, anecdotal evidence suggests that chronic SSRI-use can produce vaginal anesthesia [34,62] and a study of several thousand patients prescribed SSRIs revealed an increased incidence of paresthesias, such as sensation disturbances and hypoesthesia as compared to those administered placebo [96]. As mentioned earlier, anesthesia from vaginal stimulation produces increased 5-HT activity in the spinal cord [28,117,134]. If SSRIs alter 5-HT receptor

density or sensitivity, SSRI-use may intensify analgesia from vaginal stimulation, which, in turn, may impair sexual functioning.

If SSRIs produce sexual side affects by impairing vasocongestion to the genital region, it would be expected that pharmacologic agents that increase blood flow to the genital region would improve sexual functioning. Indeed, several anecdotal reports and studies have found that sildenafil (a drug designed to treat erectile failure by increasing blood flow into the penile tissue) was successful in reversing SSRI-induced sexual dysfunction in both men and women [8,9,87,88,109]. Sildenafil acts to increase blood flow into the genital tissue by facilitating c-GMP activity that is initiated by nitric oxide [19] and preliminary evidence suggests that the SSRIs may cause sexual difficulties by inhibiting nitric oxide synthase [39,118].

3.2. Atypical anti-psychotics

Sexual side effects have also been reported with anti-psychotic medications. Most of the literature has focused on how these types of medications affect males, however. Typical side effects include decreased sexual desire and erectile and orgasm dysfunction [3,74]. When women were included in such studies, their sexual functioning was often not evaluated or it is often not clear whether only male or both male and female participants' sexual functioning was reported. For example, one study reported that patients receiving risperidone or haloperidol had erectile dysfunction and decreased libido; apparently, the female analog to erectile dysfunction, arousal dysfunction, was not evaluated and it is not clear whether decreased libido was measured in both men and women or in men only [74].

A study that included female subjects and evaluated their sexual functioning found increased rates of impaired orgasm but the anti-psychotics evaluated in this study were in a class of anti-psychotic drugs known as typical anti-psychotics that tend to act on dopamine receptors and not serotonin receptors [50]. Risperidone, which is in a newer class of anti-psychotics known as atypical anti-psychotics, acts on both dopamine receptors and serotonin receptors and has been found to produce sexual difficulties in men [74,122]. To our knowledge, no study has been published that has evaluated the affects of atypical anti-psychotics on female sexual functioning.

Several studies have demonstrated that some atypical anti-psychotic medications produce a downregulation of 5-HT_2 receptors in the brain [21,68] but it is also possible that these drugs produce sexual difficulties as a result of their action upon peripheral serotonin receptors. Risperidone has a high affinity for 5-HT_2 receptors [22] and, as mentioned above, the 5-HT_2 receptor is involved in peripheral processes likely to affect sexual functioning (e.g., vasoconstriction and tactile sensitivity). The mechanism by which atypical anti-psychotics produce sexual difficulties may be complicated, however. For example, olanzapine, which also acts on the 5-HT_2 receptor, produces fewer sexual side effects than does risperidone [13,122]. If risperidone causes sexual difficulties as a result of its action of peripheral 5-HT_2 receptors, it is possible that olanzapine produces fewer side effects because it has a lower affinity for the 5-HT_2 receptor compared to risperidone. In fact, however, olanzapine has a higher affinity for the 5-HT_2 receptors than does risperidone [75]. Alternatively, as some have argued, it is possible that atypical anti-psychotics produce sexual difficulties via dopaminergic mechanisms, adrenergic mechanisms, and/or central serotonergic mechanisms (e.g., Ref. [112]).

4. Summary and conclusions

The purpose of this paper was to review the existing literature to determine whether peripheral serotonin, independent from central serotonin, may affect female sexual functioning. The findings indicate that serotonin is active in several peripheral mechanisms that are likely to affect female sexual functioning. Serotonin has been found in several regions of the female genital tract in both animals and humans. In the CNS, serotonin acts primarily as a neurotransmitter but in the periphery, serotonin acts primarily as a vasoconstrictor and vasodilator. Since, in the periphery, the principal component of sexual arousal is vasocongestion of the genital tissue, it is feasible that serotonin participates in producing normal sexual arousal through its vasodilatory function. Of course, other peripheral substances that affect vasotone (such as adrenaline, noradrenaline, histamine, and/or angiotensin) may also play a role in enabling genital vasocongestion. Serotonin also acts on smooth muscles of the genito-urinary system and is found in nerves innervating the sexual organs. Taken together, this evidence suggests that peripheral serotonergic activity may be involved in the normal sexual response cycle and exogenous substances that alter serotonin activity, such as SSRIs and the atypical anti-psychotics, may produce sexual difficulties. Although these substances are designed to alter CNS physiology, they are typically ingested such that they interact with peripheral physiology as well. It is possible that sexual side effects seen with these drugs may result, at least in part, from their action on peripheral mechanisms.

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