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Animal Models for the Study of Female Sexual Dysfunction

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Abstract

Introduction—Significant progress has been made in elucidating the physiological and pharmacological mechanisms of female sexual function through preclinical animal research. The continued development of animal models is vital for the understanding and treatment of the many diverse disorders that occur in women.

Aim—To provide an updated review of the experimental models evaluating female sexual function that may be useful for clinical translation.

Methods—Review of English written, peer-reviewed literature, primarily from 2000 to 2012, that described studies on female sexual behavior related to motivation, arousal, physiological monitoring of genital function and urogenital pain.

Main Outcomes Measures—Analysis of supporting evidence for the suitability of the animal model to provide measurable indices related to desire, arousal, reward, orgasm, and pelvic pain.

Results—The development of female animal models has provided important insights in the peripheral and central processes regulating sexual function. Behavioral models of sexual desire, motivation, and reward are well developed. Central arousal and orgasmic responses are less well understood, compared with the physiological changes associated with genital arousal. Models of nociception are useful for replicating symptoms and identifying the neurobiological pathways involved. While in some cases translation to women correlates with the findings in animals, the requirement of circulating hormones for sexual receptivity in rodents and the multifactorial nature of women's sexual function requires better designed studies and careful analysis. The current models have studied sexual dysfunction or pelvic pain in isolation; combining these aspects would help to elucidate interactions of the pathophysiology of pain and sexual dysfunction.

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Conclusions—Basic research in animals has been vital for understanding the anatomy, neurobiology, and physiological mechanisms underlying sexual function and urogenital pain. These models are important for understanding the etiology of female sexual function and for future development of pharmacological treatments for sexual dysfunctions with or without pain.

Keywords

Copulatory Behavior; Desire; Arousal; Orgasm; Neural Pathways; Pain

Introduction

Research and understanding of sexual function in women has expanded over the last few decades, with new models and criteria defining sexual disorders [1–6]. This increased knowledge of the human condition helps not only with diagnosis and treatment, but makes it possible to refine existing animal models and design more relevant techniques for preclinical research and etiology. Female sexual behavior comprises desire (interest to engage in sexual activity), arousal (physiological changes include an increased sensitivity of erogenous zones, vaginal lubrication, genital vasodilatation, and cognitive awareness), and orgasm (rhythmic muscle contractions and an increase in sympathetic activity). Relaxation and a feeling of well-being or reward usually follows orgasm [7]. The various stages of the sex cycle are modulated by neural pathways and circulating levels of hormones that might facilitate sexual desire, arousal, and orgasm, or might lead to the downregulation or inhibition of sexual behavior (see Figure 1). Female sexual dysfunction has been categorized into various types based on the phases of the sex cycle. In women, the most prevalent are hypoactive sexual desire disorder, hypoactive arousal disorder, anorgasmia, and pain with vaginal intercourse [8–11].

Animal models used for studying sexual dysfunction in women must relate in a reliable and predictable way to the human condition. Past studies in rats, particularly, have provided considerable understanding of the pharmacology, neuroanatomy, and endocrine mechanisms of sexual function. Studies in other species have different advantages over rodents, for example, primates show more cognitive, complex behaviors without hormone priming, and may be more relevant to humans. Knockout mice allow for genetic traits to be studied and have helped document the importance of specific hormones (estrogen receptor alpha, oxytocin, GnRH, etc.) in specific brain regions that regulate female sexual behavior [12–16]. Other species, such as the Syrian hamster, have been valuable for understanding the role of hormones and brain pathways in social sexual behaviors [17–19]. Sexual arousal and hormonal regulation of sexual behavior have also been studied in birds [20] and monogamous prairie voles—these studies have been vital in elucidating the role of oxytocin and opioids in social bonding [21–23]. This review focuses on rodent animal models that correlate with clinical diagnoses and practices.

Behavioral Models of Sexual Desire and Motivation

There is no clear compartmental differentiation between desire, arousal, and reward in animal behavioral models, as these behaviors overlap and are dependent on each other.

However, some aspects of female behavior, cues, and preferences can indicate changes in certain aspects of motivation (desire), arousal, and reward. These behaviors were categorized into consummatory (ability to engage in copulation) and appetitive or proceptive (motivation or desire for sexual behavior) types of behavior [24–26]. Researchers have utilized their understanding of these specific behaviors to design effective techniques that represent various aspects of female sexual behavior. Care should be taken when interpreting any animal's behavior to consider whether the responses being measured are purely reflexive or motivationally driven, as well as the experimental conditions.

Copulatory Measures of Sexual Motivation or Desire

Female rats will display specific behaviors, such as ear wiggling, hopping, and darting, and will pace the number and frequency of approaches toward a male when they are sexually receptive [27–29]. This pacing of their preferred frequency of intromissions by the male has been useful to assess sexual motivation or sexual desire, and supports the importance of paced copulation in the female rat for reward. The proceptive behaviors can be recorded in multicompartmental pacing chambers, bilevel chambers, mazes, or choice boxes, and have been important in identifying the brain regions (medial preoptic area (MPOA), ventromedial hypothalamus (VMN), limbic regions, etc.) and neurotransmitters (such as the release of dopamine in anticipation of the rewards of sexual contact) important for the display of female sexual behavior [1,26,30–38].

One recent study examined proceptive behavior (hops/darts) and pacing behavior to examine the normal distribution of behaviors in female rats to see if individual differences exist. If individuals displayed high or low sexual motivation/behavior those females may mimic hyper- or hypoactive sexual desire and could be preselected and studied [39]. Three subgroups of females were observed, those that showed avoidance, a larger group that displayed normal approaches, and a group that displayed a high level of approaches to the male; the behaviors within each individual appeared to be stable over time. Some differences were observed between the avoiders and approachers with apomorphine treatment, which the authors suggest may be related to a difference in brain dopamine systems. Confirmation of this hypothesis and further studies on females that are avoiders is required to see if this is a good model of diminished sexual desire.

The relevance of monitoring female rat behavior is evident in a number of preclinical studies that have also demonstrated efficacy in measures of women's sexual function. Using the bilevel pacing chamber, investigators were able to show a dramatic increase in solicitations made by the female when treated with the melanocortin agonist, bremelanotide (PT-141) [40–42]. This drug also showed increased vaginal arousal in women viewing an erotic film and increased the ability of women with lifelong hypoactive sexual desire to initiate sex with their partners [43]. Acute or chronic administration of selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine or paroxetine) to female rats results in a reduction of lordosis behavior and sexual incentive motivation; SSRIs also reduce sexual behavior in women [44,45].

Another study used marmoset monkeys, in which mating occurs in stable male–female pairs, to examine sexual and social behavior with flibanserin (a 5-HT_{1A} agonist and 5-HT_{2A}

antagonist), or 8-OH-DPAT (a 5-HT_{1A} agonist) treatment. Many studies have previously shown that $5HT_{1A}$ receptor activation inhibits lordosis behavior in female rodents [46,47]. The study performed in monkeys showed that flibanserintreated females attracted more male sexual interest, and triggered increased grooming between partners. In contrast, 8-OH-DPAT-treated females showed an increased rejection of the male's sexual advances, a tendency for decreased male sexual interest, and increased aggression with their male partners. Flibanserin has been shown to increase solicitations and sexual receptivity in female rats [37,41,48]. Flibanserin improved sexual function in women with depression and hypoactive sexual desire disorder [49,50].

Motivation Utilizing Operant Response

In these studies, the rat is trained to complete a task, such as a lever press or nose poke, in order to receive a reward. The effort and attention made to obtain the reward is thought to provide a meaningful measure of the expression of desire or wanting. This paradigm has been used to train female rats to bar press for their preferred partner or subsequent to a mount or intromission.

A recent study conducted by Cummings and Becker was able to quantify female sexual motivation using the number of nose pokes in a two-chamber apparatus in which the female's strength of motivation to access and mate with a male was measured [51]. These studies have the advantage that female pacing and solicitation measures (hop/darts and ear wiggles) and strength of receptivity (lordosis) can be made simultaneously. During this first study, the authors found that hormonally primed female rats were significantly more motivated to obtain access to a sexually active male, approach the male after a shorter duration, and spend more time in direct contact with the male rat, compared with when they were not hormonally primed (not sexually receptive). This technique provides a new method to examine female sexual behavior; hopefully, further studies will confirm the relevance of this model to female sexual motivation.

Motivation and Reward Using Preference Testing

Animal models of a *choice paradigm* can measure solicitations, conditioned locomotion in anticipation of sex, time spent near a sexual incentive, choices made between two or more incentives, and are all used to measure sexual desire. Increase or decrease in the strength of the behaviors are measured and are based on the assumption that females with more desire will display more robust behaviors than animals with less desire [2,37,38,52–54].

Sexual preference paradigms—*Sexual preference paradigms* utilize preferences that are learned experiences paired with sexual reward, such as pacing behavior in females, or stimuli associated with sexual experience. These preferences are typically displayed prior to sexual interaction, allowing the female to focus their effort toward the sexual incentives. Some of these paradigms require differing degrees of training and consequently have only been used in a few studies [55,56].

This technique has also been used to study the brain sites in rats that are activated with olfactory stimulation paired with female-paced copulatory behavior. When females are

paired with almond-scented males in a paced testing paradigm, the females will subsequently select to solicit and receive ejaculations from an almond-scented male rather than an unscented male. This preference is not displayed when paired in a nonpaced behavioral paradigm [35,36]. The brain sites that were activated in rats were similar to those reported with arousal in women during brain imaging studies with visual sexual stimulation and orgasm [35,57–63]. The brain regions include cortex, striatum, nucleus accumbens, MPOA, ventral tegmental area, paraventricular nucleus, and medial amygdala; these brain regions are regulated by various neurotransmitters including serotonin, opioids, dopamine, norepinephrine, and oxytocin (see figure 7 in reference [37] for details).

Since sexual reward in female rats occurs when females are allowed to pace their copulations [27,64,65], these reward states can be measured using a *conditioned place preference paradigm*, where females show a strong distinct preference for an environment only if placed in the conditioned place preference box immediately after paced copulation [36,55,66]. Artificial vaginocervical stimulation (with glass rod or plunger at a force or frequency that mimics intromissions) provides a stimulus for reward and reproduction that mimics intromissions from the male [67,68]. For example, vaginocervical stimulation at 30-second intervals for 15 stimulations induced a reliable conditioned place preference in ovariectomized rats primed with estrogen and progesterone [67,69]. Other studies looked at clitoral stimulation alone—via a lubricated paintbrush or small cotton-tipped vibrator—and showed that conditioned place preference occurred if the stimulus frequency was 1 stimulation every 5 seconds for five trials [70,71]. Therefore, the pattern/frequency of the stimulus is important to produce changes in sexual motivation and conditioned place preference and does not occur if the stimulus is of a regular, nonpaced frequency. Both vaginocervical and clitoral stimuli induced robust conditioned place preference. However, clitoral-induced reward was also seen in ovariectomized females without hormone priming, indicating that clitoral induced sexual reward may be independent of the circulating levels of estrogen and progesterone. In female rodents, hormonal priming is required for lordosis, which allows clitoral stimuli from the male during mounting and intromission behavior. Systemic or central administration of naloxone can block pacing-related conditioned place preference [37,72,73]. Thus, activation of the opioid pathways is necessary for sexual reward.

Animal Models of Sexual Arousal

Central Arousal

Generalized arousal involves activation brain pathways (cortex, hypothalamus, and reticular formation) to increase heart rate, blood pressure, and blood flow, and provides the sensory alertness so that the motor system can respond through descending pathways from the brain to the spinal cord, peripheral nerves, and muscles. Thus, sexual arousal comprises some form of central arousal [74,75]. A few studies have examined the relationship between central arousal and sexual function [75–80]. Methamphetamine has been reported to increase sexual thoughts and behavior in women by increasing generalized arousal; when given to female rats, methamphetamine also increased the incidence of lordosis and increased sexual motivation [81].

Central and sexual arousal involves increased activity of particular brain pathways. Mapping the location of activated brain neurons using the immediate early gene, c-fos, has been reported after the female received various types of stimuli from the male, such as mounts only, intromissions or ejaculations [62,63,82–87]. These studies reported an increase in c-fos expression in various brain regions, including the MPOA, VMN, bed nucleus of the stria terminals, and medial amygdala, that are activated with female sexual behavior.

The cellular mechanisms regulating the activity of the MPOA, VMN, and brainstem reticular neurons, which are all known to be involved in female sexual behavior, have recently been examined using electrophysiology and patch clamp techniques [76,88–93]. These studies demonstrated, for example, that norepinephrine increases the excitability of VMN neurons; while histamine depolarizes VMN neurons via decrease in potassium current. Understanding the cellular mechanisms behind neuronal activation and deactivation may provide new insight to the excitatory and inhibitory processes of central arousal that may, one day, be used to understand new psychotherapies, such as mindfulness in the treatment of sexual dysfunction.

Genital Arousal

Autonomic (pelvic and hypogastric nerves) and somatic peripheral nerves (pudendal sensory nerve) mediate arousal and sensation of the genitals (see Figure 2) [2,94–97]. Genital arousal in females is associated with an increase in vaginal lubrication and blood flow to the vagina and clitoris, which facilitates clitoral erection and vaginal engorgement. Improved sexual function has been reported in women after sacral nerve stimulation (the nerve fibers of the pudendal and pelvic nerves are contained within S2-S4 in humans) [99,100]. Nerve stimulation studies in animal models may be useful in understanding the mechanisms of afferent nerve stimulation and their role in modulating sexual arousal and reducing pelvic pain. Animal models using rats and rabbits have been developed to mimic the physiological changes that occur with genital arousal [1,101–112]. Stimulation of the pelvic nerve increases vaginal and clitoral blood flow, vaginal length, clitoral intracavernosal pressure, and vaginal luminal pressure. Similar responses can be evoked by pudendal sensory nerve stimulation— the major sensory nerve innervating the clitoris and vagina [105]. Sensory input is then relayed through the dorsal horn and spinal interneurons to modify parasympathetic output, which leads to increased vaginal blood flow [94,95,105,113]. Stimulation of the MPOA also resulted in increased vaginal blood flow, indicating a possible pathway from brain arousal centers to induce genital arousal responses [104]. Interestingly, MPOA stimulation also evoked ejaculatory-like reflexes in males [114].

Evidence that clitoral erection is mediated by similar mechanisms as penile erection has been provided. The neuroanatomical pathways of the dorsal clitoral nerve are similar to the dorsal nerve of the penis, which forms part of the sensory branch of the pudendal nerve to regulate clitoral sensations and engorgement. In addition, evidence for endothelial and neuronal nitric oxide pathways have been documented [105,113,115–124]. However, in clinical studies, sildenafil did not improve sexual function or significantly increase clitoral engorgement in women with female sexual arousal disorder [125,126]. Phosphodiesterase type 5 inhibitors may be beneficial in women with sexual problems related to antidepressant

therapy, but appear to be less effective or ineffective in women with neurologically induced sexual dysfunction or sexual desire disorders [127].

In vitro smooth muscle preparations that examine contractile and relaxant effects of neurotransmitters or electrical field stimulation on vaginal or clitoral tissue have the potential of furthering our understanding of the peripheral mechanisms regulating sexual arousal responses and strength of muscle contractions that occur with orgasm [120,128–130]. Fewer studies have looked at cutaneous receptors and epithelial tissue [131]. Since genital stimulation and stimulation of erogenous skin can increase sexual arousal, this may be an opportunity for future research models.

Understanding the peripheral and spinal mechanisms mediating genital sensations and arousal is not only important for helping understand decreased genital arousal disorders, but is essential for development of treatments to aid women with persistent genital arousal that can cause severe distress in women [3,5].

Animal Models of Orgasm

Physiological responses that occur with orgasm in women include contractions of the pelvic floor, anal sphincter, and vagina, increases in respiration, blood pressure, and release of oxytocin [132–135]. The only animal model developed to mimic the physiological responses seen during orgasm is the urethrogenital reflex (UGR) [136,137]. Activation of the UGR, by brief distention of urethra or stimulation of pudendal nerve afferents in female rats, produces rhythmic contractions of the pudendal motor nerve, which regulates the pelvic floor and sphincter muscles, vagina, anal sphincter, and uterus. The sensory threshold required to evoke the UGR is reduced with infusion of intraurethral serotonin [137]. This model has been used to map the spinal and brain neurons and pathways activated with the UGR. The spinal pathways that innervate the genitalia and are activated with the UGR comprise a network that includes afferent inputs to the lumbar sacral dorsal horn, the dorsal gray commissure, and medial and lateral gray, specifically in regions that overlap with the sympathetic and parasympathetic preganglionic neurons of the hypogastric and pelvic nerves. In the brain, the nucleus paragigantocellularis, paraventricular nucleus of the hypothalamus, VMN, periaqueductal gray, MPOA, medial amygdala, bed nucleus of the stria terminalis, and cortex all have been shown to contain neurons whose activity is modulated by genital sensory stimulation [1,62,82]. These sites overlap with regions seen during functional MRI and PET scan mapping of the brain during orgasm in humans [57,59,138–140].

Models of Pain Associated with Potential Sexual Dysfunction

Genital pain can lead to sexual dysfunction by reducing desire, decreasing arousal, and increasing sexual inhibition. While pain with vaginal intercourse can arise from vaginal dryness, in which applied lubrications and estrogen cream can be helpful, the fear of pain associated with intercourse can lead to decreased sexual desire and arousal. Pain originating from the female reproductive organs is a major complaint during the fertile years [98,141]. Primary or secondary dysmenorrhea, pelvic inflammatory disease, or chronic pelvic pain,

are just a few examples, whose causes are still largely unknown. In postmenopausal women vaginal dryness, vaginal and vulvar irritation and pain are frequent complaints related to estrogen deficiency. In addition, hyperactive genital arousal or persistent or spontaneous orgasms can be painful, frustrating, and debilitating. The development of animal models to address many of these painful disorders is lacking. Several animal models of pain have been developed that employ nociceptive distension, inflammation, or endometriosis, and are reviewed below. These models are useful for replicating the symptoms and dissecting the neuroanatomical and pharmacological pathways involved in pain. However, animal models of pain may have limited value for studying treatment responses for translational purposes due to species differences in receptor systems and immunological reactions to pain, as well as the unknown cognitive experience of pain perception. One exception to this may be the spontaneous pain model development by Giamberardino and coworkers described below [142,143].

Mechanical Models of Pain

Vaginal

Vaginal hypersensitivity can be measured by distension of the vagina in female rats [144]. Under anesthesia, a lubricated balloon is inserted into the vagina, avoiding the cervix, and hyperalgesia develops over time. Subsequently, escape responses are measured at different distension volumes [144,145]. Berkley and coworkers have combined this distension paradigm in rats with ovariectomy, to propose a model for dyspareunia associated with ovarian function loss. This hypersensitivity was reversed by estrogen replacement.

Uterine

Uterine distension has been used to evoke uterine pain in rats [144]. In a similar fashion to the vaginal hypersensitivity technique, animals can be tested for the probability to produce an escape response to a noxious tail pinch with distension of one uterine horn.

Distension of the *uterine cervix* has also been applied in anesthetized rats, to mimic acute pain that women experience during labor. The perceived visceral pain is monitored via electromyographic (EMG) response in the rectus abdominis muscle, mean blood pressure, and heart rate changes in response to uterine cervical distension. Morphine and peripherally restricted kappa opioid receptor agonists attenuate these responses; but the presence of estrogen renders the morphine treatment ineffective [146,147]. The EMG activity induced by uterine cervix distension can be blocked by COX inhibitors (SC58238 and indomethacin), but the cardiovascular responses remain [148].

An ovarian ligament nociceptive technique was proposed, by the authors, to provide a humane mechanism to study the effectiveness of analgesics for acute ovarian pain [149]. Under anesthesia, the right ovary is accessed via laparoscopy, and a suture is placed around the ovarian ligament and exteriorized through the abdominal wall for stimulation. The noxious stimulus consists of pulling the ovary and ovarian ligament with a force transducer. The response to noxious stimulation is determined using the anesthetic minimum alveolar

concentration requirement (MAC) for sevoflurane (minimum concentration required to suppress the dog's purposeful movement after 1 minute of ovarian stimulation).

It is important to note that in the mechanical distension models, not all the manipulated animals show hypersensitive responses, and the amount of mechanical force necessary to evoke the nociception is probably beyond the range of any natural event. Thus, it is unclear how useful these models are in relation to the clinical situation [144,150]. However, they have the advantage of establishing a precise relationship between the noxious stimulus and the evoked responses, and have shown reversal with commonly used analgesics. The inflammatory and endometrial methods (see below) appear to mimic the clinical situations more closely, and are thus suitable to investigate and interpret the pain phenomena observed in clinical pain syndromes in patients.

Inflammatory Techniques

Vulvodynia

Repeated exposure of the vulva to *Candida albicans* in mice produces long-lasting (>3 weeks after resolution of infection/inflammation) localized mechanical allodynia and hyperinnervation of peptidergic nociceptor and sympathetic fibers [151,152]. Around 40% of the infected animals (*Candida* + fluconazole) were allodynic vs. 5.5% of the fluconazole controls (saline + fluconazole). The increased nerve innervation of the vagina was measured by comparing protein gene product 9.5, calcitonin gene-related peptide, and vesicular monoamine transporter 2 immunoreactivity in infected and noninfected mice. Long-lasting behavioral allodynia in a subset of mice was also observed after a single, extended *Candida* infection, as well as after repeated vulvar inflammation induced with zymosan, a mixture of fungal antigens. This model resembles provoked vestibulodynia in women, the most common form of vulvodynia, an idiopathic pain disorder associated with a history of recurrent candidiasis, which is characterized by vulvar allodynia and hyperinnervation [152,153].

Pelvic Visceral/Muscle Pain

Uterine inflammation

Uterine inflammation in female rodents can be initiated by injection of mustard oil into one uterine horn. This induces behaviors that mimic pelvic pain and referred muscle hyperalgesia in women with inflammatory conditions of their reproductive area. After 2–4 days, the majority of rats show spontaneous pain behavior (major episodes of movements/postures indicative of pelvic pain) and referred hyperalgesia (measured by vocalization) in the ipsilateral flank muscles, in response to stimulation [154,155]. The areas of referred muscle hyperalgesia are also the site of neurogenic plasma extravasation in the skin, which is the first experimental evidence of trophic changes in sites of referred pain from viscera, a well-known phenomenon in the clinical setting [156].

Ovariectomy

Ovariectomy has been used in mice and rats to produce a condition of visceral pain/hypersensitivity of the pelvic area, which has been proposed as a model of a hormonally dependent hyperalgesia resembling functional pain in women [157–160]. Ovariectomy also increases depression in rodents [158–160]. Ovariectomized mice and rats present a hyperalgesic state (a robust mechanical and thermal hyperalgesia in the abdominal and pelvic regions) of slow onset (4 weeks) and long duration, as well as visceral hypersensitivity. Hormone replacement with 17beta-estradiol prevents and reverses the development of hyperalgesia but does not stop the involution of the internal reproductive organs.

Experiments in mice have shown that spinal ERK 1/2 is involved in the estrogen-dependent chronic visceral hyperalgesia [161]. Ovariectomized mice show a significant increase in the activation of ERK 1/2 (the extracellular signal-regulated kinases 1 and 2, members of the MAPK [mitogen-activated protein kinases] family) in the lumbosacral spinal cord which followed the time course of the hyperalgesia. Estrogen replacement reversed both the development of the hyperalgesia and the enhanced activation of ERK 1/2, while intrathecal injections of the ERK 1/2 inhibitor, U0126, significantly attenuated the abdominal hyperalgesia (up to 24 hours after the injection) and reversed the enhanced expression of ERK 1/2 [161].

Endometriosis

Endometriosis can result in pain, related to secondary dysmenorrhea or a more generalized chronic pelvic pain syndrome; in addition, vaginal hyperalgesia can occur that results in sexual dysfunction [162]. In women, the intensity of painful symptoms is not related to the size or location of the lesions [163]. A number of nonhuman and rodent models of endometriosis have been developed to study subfertility; more recently, these techniques are being used to study pain [164]. For example, endometriosis can be induced in female rats by grafting pieces of autologous endometrium (from one uterine horn) in different locations of the abdominal cavity: on alternate cascade mesenteric arteries that supply the caudal small intestine, at the level of the ovary and inner surface of abdominal muscles. Two to three weeks later, fluid-filled cysts develop at the implantation sites. Estradiol is required for cyst maintenance, and the severity of vaginal hyperalgesia varies with the estrus cycle. Interestingly, the cysts develop their own sensory and sympathetic nerve supply, which may be useful for future vascular studies. Evidence has been provided for a role of local cannabinoids (CB1) in the expression of the hyperalgesia associated with the endometrial cysts [163]. Mouse studies of this endometrial model have been developed [165] allowing future studies to utilize the availability of the many transgenic mouse strains. When combined with an artificial ureteral calculosis, endometriosis in rats produces a notable enhancement of the poststone spontaneous pain behavior (increase in both “ureteral” and “uterine” typical behavior, monitored over several days at videotape recordings, and increase in pelvic muscle hyperalgesia) [142]. This combination model closely resembles the clinical condition of “viscero-visceral hyperalgesia” (i.e., increased spontaneous pelvic and urinary pain, as well as in referred pelvic muscle hyperalgesia) extensively documented in women

with endometriosis plus ureteral calculosis, and therefore is particularly suitable for studies understanding the pathophysiological mechanisms of this condition in women [143,166].

Summary

Many *in vivo* animal models of female sexual behavior (desire, arousal, motivation, and orgasm) and pelvic pain have been developed, some employing simple paradigms, such as monitoring proceptive behavior, or pelvic organ distension, others involving more complex learning paradigms or surgical interventions. Each model or technique has its advantages and limitations. Nevertheless, valuable information on the mechanisms, development, and occurrence of sexual function and dysfunction with or without pain have been gained that can be translated to women. New research understanding genital sensory inputs and their regulation in females should help aid our understanding and development of treatments for female sexual dysfunction that are not primarily based on the research conducted in males. More information on the etiology of women's sexual dysfunction disorders would aid development and application of the preclinical models.

Future Directions

Studies on gonadal steroid hormones have been conducted, but there remains a lack of studies in females examining other hormones, such as thyroid and stress hormones. Animal models for pathological and disease states are lacking, such as cancer, stroke, cardiovascular function, diabetes, and aging. The pelvic pain models should also be used to test the impact of pain on sexual dysfunction; effective pharmacologic treatments (classic and newer) for the pain should also be tested with respect to their effectiveness on the sexual dysfunction parameters. The study of comorbidities (e.g., bladder inflammation, fibromyalgia, and myofascial pain syndromes) related to pelvic pain that may lead to sexual dysfunction in females has yet to be fully explored. These types of techniques may mimic the clinical condition of extensive cooccurrence of several pain conditions in the urogenital area observed in patients [166–169].

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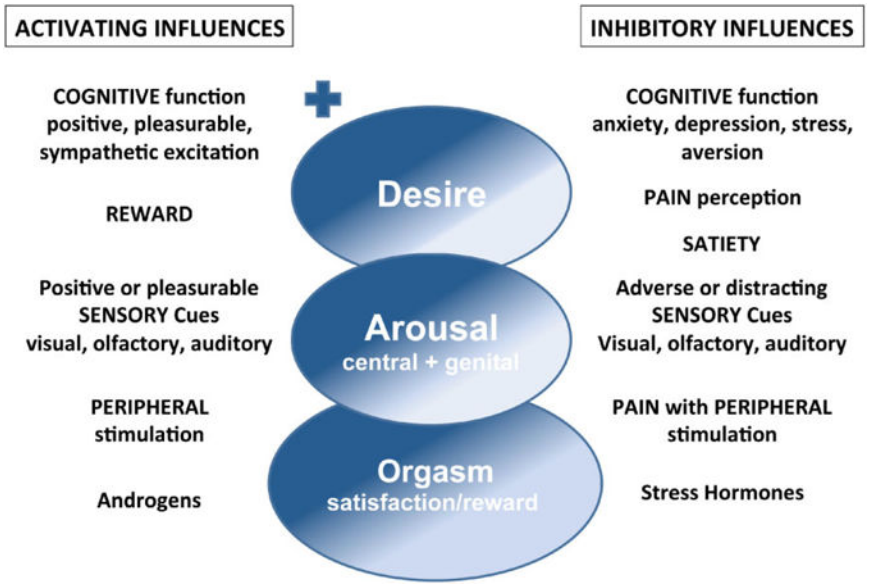

Figure 1.

Female sexual behavior comprises desire, arousal, orgasm, and reward. Multiple factors activate and inhibit each stage of the sex cycle. Cognitive activation of hypothalamic and limbic brain regions can result in increased desire and arousal; while activation of brain inhibitory sites (cortex, hypothalamus, limbic system, and midbrain) either by stress, anxiety, or postorgasm (with satiety) can lead to inhibition or cessation of sexual behavior. Sensory cues, such as pleasing visual sexual images or desirable odors (pheromones), can enhance desire and arousal. In contrast, frightening visual or auditory stimuli, or loss of attention or focus can inhibit sexual behavior. Peripheral stimulation may lead to localized genital arousal alone or may produce central arousal and desire depending of the integrity and balance of excitatory (dopamine, oxytocin, noradrenaline, and melanocortin) and inhibitory (opioids, serotonin and endocannabinoids) neurotransmission from the peripheral nerves through the spinal cord to the brain. Androgens (testosterone and estradiol), present at normal levels, act both peripherally and centrally to enhance sexual function, while stress hormones (e.g., cortisol) inhibit sexual interest. Hormones such as oxytocin and progesterone are released into the circulation with orgasm. Pain arising from the genitals or reproductive organs can lead to sexual dysfunction. Peripheral pain activates inhibitory central spinal and brain pathways that may lead to aversion to sexual activity or a decrease in desire and arousal. As a result, an increased focus on activating the excitatory pathways of arousal and reward is required for sexual activity. + indicates activation or facilitation, - indicates inhibition or reduction.

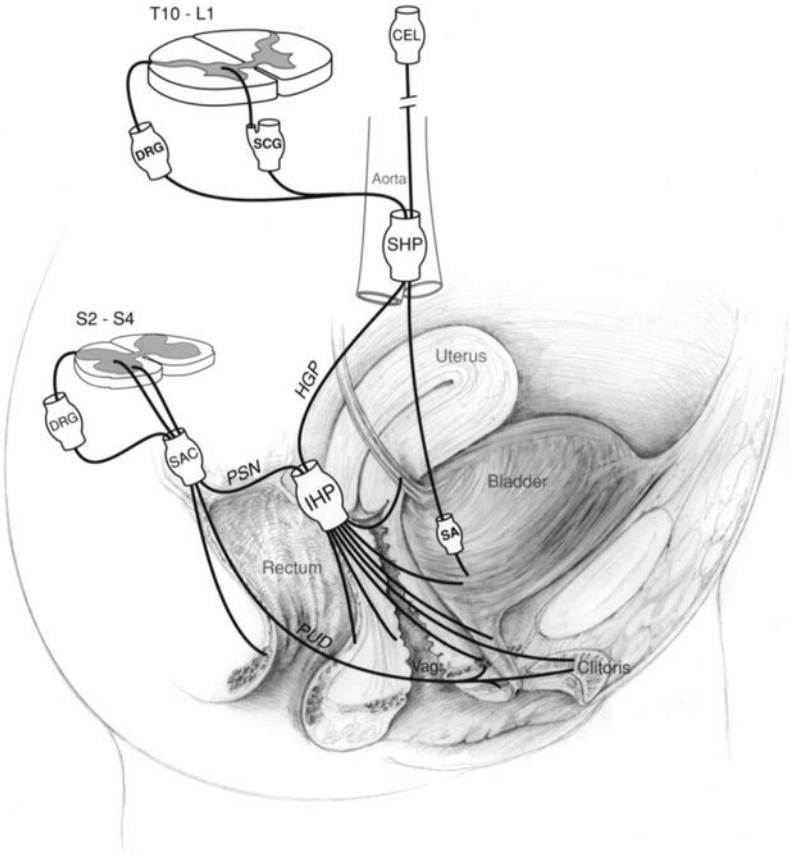

Figure 2.

Schematic drawing showing the innervation of the urogenital and rectal area in females. Although this diagram attempts to show the innervation in humans, much of the anatomical information is derived from animal data (see text). CEL, celiac plexus; DRG, dorsal root ganglion; HGP, hypogastric nerve; IHP, inferior hypogastric plexus; PSN, pelvic splanchnic nerve; PUD, pudendal nerve; SA, short adrenergic projections; SAC, sacral plexus; SCG, sympathetic chain ganglion; SHP, superior hypogastric plexus; vag, vagina. This figure has been reproduced with permission of the International Association for the Study of Pain^{R} (IASP) from reference [98]. The figure may not be reproduced for any other purpose without permission.