We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



5

Paradigms for Preclinical Investigations of Female Sexual Function and Dysfunction (HSDD and FSAD)

Kelly A. Allers and Bernd Sommer
Boehringer Ingelheim Pharma GmbH & Co KG, Biberach an der Riss, Germany

1. Introduction

A prerequisite for successful discovery of treatment options for female sexual dysfunction is a deeper understanding of sexual function per se, e.g. which physiological systems are involved, and what goes wrong in a dysfunctional state.. The availability of animal models, which capture the physiological underpinnings of a disorder and have been shown to respond to existing clinical treatments are a major success factor in this endeavor. For example, the translational ability of penile erection models are extremely good, since they have high predictive value for drugs used to treat erectile dysfunction. Predictive validity of models of female sexual dysfunction is less well established. However, results from recent efforts to back-translate effects from drugs that have shown efficacy in clinical trials into laboratory animals provide promising starting points for a better disease understanding and model validation.

This chapter will briefly outline those models that have potential in helping understand female sexual function and dysfunction, followed by three examples (flibanserin, bremolantide, apomorphine) of how clinically efficacious compounds contributed to elucidate the physiology and pharmacology underlying both the natural and pathological states (Bechara et al. 2004; Caruso et al. 2004b; Clayton et al. 2010; Safarinejad 2008) of arousal and desire disorders, the major indications in terms of prevalence (Johannes et al. 2009).

Modeling a complex human behavior in the laboratory imparts many challenges. Only a few fundamental issues faced in the laboratory are similar in the clinic – ie. the necessity to define a 'normal' range of responses for a given function before attempting to assess a dysfunctional range. In the clinic, questionnaire based tools have been developed, that can define 'healthy' and 'dysfunctional' states of sexual behavior within human populations. Furthermore, the two behavioral domains 'desire' and 'arousal' become distinguishable when dysfunction is present (DeRogatis et al. 2011). This can principally be achieved in the lab too, since each species has a clear set of behaviors used to solicit sexual contact. Although it is not always easy to separate desire from arousal in rodents as these two components of the sexual response are temporally connected in a natural setting, they can be isolated and studied as distinct physiological pathways. However, in order to have translational relevance, such laboratory studies must address measures aligned with those used clinically. With this request a number of issues arise that are unique to working with

laboratory animals and are eloquently summarized by a quote from Professor Jim Pfaus, a well respected researcher in sexual function. 'Animals don't lie, but they don't talk, either'. There is no equivalent of a Female Sexual Function Index (Rosen et al. 2000) or clinical interview for laboratory rats. The interpretation of their behavior is the responsibility of a well-informed researcher who is devoted to understanding the motivations and actions of the animals. At first sight physiological studies appear easier to translate, a neuron fires or it doesn't, a neurotransmitter is released or it isn't, and usually standard statistical methods scan determine if a given effect is significant. However, whether these data are meaningful to the human situation again requires a careful interpretation of the study.

The preclinical testing of a drug candidate would ideally occur in a 'disease' model, i.e. a model that mimics some or all of the symptoms observed in the human disorder. Since a drug to treat sexual dysfunction should be expected to restore natural sexual behavior, NOT to promote increased sexual behavior in a healthy individual, the appropriate model should show some hyposexuality. However, manipulations that induce a state of hyposexuality in animals are not without disadvantage to research. On one hand, these models will allow the investigator to assess a drug's ability to restore natural behavior. On the other hand, whatever hormonal/pharmacological/behavioral manipulation that was used to induce hyposexuality becomes a confound that may bias the experiment. Careful interpretation of the data is required, and preferably a known predictive ability for clinical efficacy within the model can provide confidence in its usefulness.

With the abovementioned clinically efficacious compounds, substantial multidisciplinary investigation has ensued to elucidate the pharmacological mechanism of action of these drugs. This is just the boost that female sexual dysfunction research has needed, clinically efficacious drugs that can be used in back-translation to validate animal models, and the resources of the pharmaceutical industry to tenaciously investigate pharmacological mechanisms.

2. Measuring 'desire' in animal models

There is no single definition of desire. The DSM-IV-R defines the primary symptom of Hypoactive Sexual Desire Disorder as 'Deficient or absent sexual fantasies and desire for sexual activity'(American Psychiatric Association 2000), which suggests that sexual desire is the presence of fantasies and the desire for sexual activity….although this is clearly not a functional working definition. Perhaps Agmo's strategy in his recent review - to simply consult the dictionary - is more relevant (Agmo et al. 2004). The Merriam Webster dictionary suggests desire is: 1**:** conscious impulse toward something that promises enjoyment or satisfaction in its attainment, 2*a*: longing, craving *b* **:** sexual urge or appetite, 3**:** a usually formal request or petition for some action (http://www.merriam-webster.com/dictionary). With this definition paradigms that assess the different components can be obtained. We can assess whether an animal is motivated to seek a partner for sexual activity and whether this activity was enjoyed using paradigms that allow the female rat to choose place, and timing of copulation (and sometimes the partner as well), and studies that determine if there was reward value to the encounter. Studies such as the bilevel pacing chamber, in which the female rat solicits the male with species specific behaviors demonstrate a type of 'request' for action. Craving can be assessed in a similar way as it has been done in studies of drug addiction and craving, by determining with operant tasks whether an animal will 'work' toward achieving a goal (sexual activity or drug of addiction).

There is a long history in the behavioral psychology literature regarding assessment of motivation, incentives, and reward in the study of sexual function and the interpretation of this data (Agmo et al. 2004; Matthews et al. 1997; Pfaus 1996; Pfaus 2009b). This literature is ultimately relevant to the study of sexual function and interpretation of the studies described herein, but it is beyond the scope of this chapter. What will follow is a short description of current models with potential use in studying both normal and pathological sexual behaviors, what kind of information they provide, and their utility in development of treatments for sexual desire dysfunction.

2.1 Behavioral models assessing sexual motivation

Behavioral models which are used to assess sexual motivation in general fall under two categories: those that measure directly the appetitive or proceptive behaviors used by females to show interest in a partner, and those that measure the reward value of a sexual encounter, providing a measure of the incentive to engage in sexual activity.

2.1.1 Behavioral models assessing appetitive/proceptive behaviors

Pacing chambers: Pacing chambers are experimental boxes designed to allow a female rodent the ability to 'pace' the amount of contact she has with the male. The bi-level chamber is a commonly used design. In this design, the chamber itself consists of two levels with ramps at either end, allowing the female to escape or pursue her partner over both levels (Mendelson et al. 1987; Pfaus et al. 1992). Another type of pacing chamber consists of a plexiglass cage with a barrier in the middle. The barrier contains an opening big enough for the female to pass through, but not the male; alternatively another type of escape route is provided such as a chamber adjacent to a testing arena (Paredes et al. 1999; Peirce et al. 1961). In both of these designs, the female can approach or avoid the male according to her own level of motivation. In these studies behaviors that are meant to 'solicit' the attention of the male (eg ear wiggles, hops and darts, etc.) can be readily measured. In addition, the response to male mounting attempts can be assessed. Pacing chambers are crucial to assessing motivation for sexual contact in a female rodent, as a paradigm that does not allow the female to control the pacing of sexual contact does not induce reward, and therefore decreases motivation (Paredes et al. 1997).

Partner Preference: Partner preference paradigms determine whether the test animal has more attraction to one animal over another. For example, a study examined whether a sexually receptive female rat prefers to spend time investigating another female rat, or a male rat (Clark et al. 2004). The goal of this type of study can be to determine what factors influence motivation for sexual contact as compared to social contact. In another study, female rats were allowed either paced copulation with almond-scented male rats or non-paced copulations with non-scented males. When entered into a partner preference study, the females solicited almond-scented males more than non-scented, suggesting the animals associated the scent with more rewarding sexual contact (Coria-Avila et al. 2005). Clearly there are many variations on partner preference studies that can be utilised, answering different questions related to motivated sexual behavior.

Primate models: Primate sexual behavior models provide an advantage over rodent models in that long-term primate pairs can be studied – mimicing the human situation. The hormone-dependency of primate sexual behavior is less strict than in rodents – again more like humans. Rhesus monkeys have commonly been used to assess proceptive behaviors.

However, primate models also introduce further complexities of social relationships and status, different social structures which can regulate sexual activity. In rhesus monkeys, it is well established that the laboratory setting can substantially alter 'normal' sexual motivation when these relationships cannot be controlled for (Wallen 1990). Marmosets are small primates that form long term pair-bonds and have been successfully utilised for studies of sexual motivation in a laboratory setting. This design has allowed detailed study of hormonal influences and pharmacological manipulations to be assessed for their effects on sexual behavior within the pair (Barnett et al. 2006; Kendrick et al. 1985).

2.1.2 Behavioral models assessing reward value of sexual activity

Place Preference: Place preference is a test in which an animal has a choice between two chambers, and learns to associate one with a rewarding experience (Tzschentke 2007). For example, at the beginning of an experiment, the animal is placed into a cage which is separated in half by a plexiglass divider, but with an opening through which the animal can pass freely. With no conditioned stimulus, the animal will have no preference between the two sides and spends equal time in both. However if an animal is taught to associate a positive experience in one chamber, then the animal will choose to spend time in the chamber in which the positive experience occurred. Alternatively, animals show a preference for a given chamber at the start of the test, and the experimental manipulation is used to change the preference to the alternate chamber. This test has been used to demonstrate a rewarding experience for paced sexual contact (Paredes et al. 1997).

Operant behavior designs: In operant behavior studies, the animal is taught that a sequence of behaviors will lead to a given outcome. For example, a female rat learns that pressing a lever will lead to access to a sexually active male rat (Bermant et al. 1966). In this situation, if the female rat is motivated to engage in sexual behavior, pressing the lever and achieving this access to a male serves as a reinforcer. In one such study, the male was removed following a mount, an intromission, or an ejaculation. The latency for the female to press the level for further contact was recorded. The response latencies were shortest when the females were only mounted, intermediate when intromissions occurred, and longest following ejaculation. These data indicate that the animal was more motivated to continue sexual contact before the male ejaculated than after (Bermant 1961).

2.2 Disorders of desire and potential animal models

Hypoactive sexual desire disorder (HSDD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) as persistent or recurrent deficiency or absence of sexual fantasies and thoughts, and/or desire for, or receptivity to, sexual activity, which causes personal distress or interpersonal difficulties and is not caused by a medical condition or drug (American Psychiatric Association 2000). This disorder has a prevalence of between 6-10% in females assessed from the US population (Johannes et al. 2009; Simon 2010).

In designing preclinical experiments to investigate the biology of HSDD, the ideal would be a population of animals which actually exhibit the symptoms of this disorder with the same underlying neuropathology as patients. Clearly that is not possible. We can measure sexual motivation with the multiple behavioral models mentioned above, and in some situations distress and interpersonal difficulties may even be inferred from animal behavior such as aggressive rejection in rodents or fighting between primate pair-mates, there is no objective

means of assessing thoughts or fantasies in animals. Furthermore, the underlying neuropathology of HSDD is essentially unknown. However, neuroimaging studies indicate that there are clearly differences in brain activation patterns of women suffering from HSDD when compared to healthy volunteers, confirming a neurological basis for symptoms (Arnow, 2009). With the substantial literature from preclinical studies, we are beginning to understand how the neurotransmitter pathways involved in sexual motivation not only function, but also how they can be dysfunctional. Michael Perleman introduced the concept of the 'Sexual Tipping Point'®, which incorporates the myriad of influences on a person when calculating their sexual desire (Perelman 2009). This concept describes the 'excitatory' and 'inhibitory' factors that are imparted by physiological, psychosocial, and cultural influences. Certainly from a neurobiological perspective, this concept holds true (Bancroft et al. 2009). Scientific evidence for this kind of balance in the neurobiology of desire has recently been reviewed, and an evidence based hypothesis generated for the underlying pathology of HSDD (Bancroft et al. 2009; Pfaus 2009b). Neurotransmitters such as dopamine and norepinephrine have a role in stimulating sexual activity, while serotonin plays an inhibitory role. Steroid and stress hormones also play a role in inducing sexual excitation or inhibition. These neurochemical pathways provide the 'balance' which can be tipped towards or away from motivation for sexual contact depending on intrinsic and environmental factors. The basic hypothesis for the neuropathology of HSDD is that either the systems regulating sexual excitation are inefficient, or the systems regulating inhibition are overactive, or both.

Preclinical studies have demonstrated multiple means of making a female animal 'hyposexual' by manipulating the excitatory and inhibitory pathways regulating sexual function. Following are descriptions and suggestions of what might be useful in drug development, for testing of potential compounds to treat HSDD.

Hormone manipulations: The simplest method of achieving low desire in animals is to remove hormone cycling by ovariectomy. Without further manipulation, rodents do not engage in sexual contact and this could potentially be used to assess compounds meant to restore sexual health (Lopez et al. 2007). However, ovariectomised animals are not an ideal model for HSDD since a large proportion of patients are premenopausal and do not show altered hormone status. They may, however, serve to model decreased libido in post-menopausal women. A further option is to exploit a rat's intrinsic hormone cycling. As a female rat moves from estrus into metestrus her physiology adapts by sending a 'stop' signal in the brain. This is hormonally mediated, but with correlated neurophysiological changes (Hawcock et al. 2010; Lopez et al. 2007; Richards et al. 2010). Attempting laboratory studies with only animals in metestrus is not easy, as this stage of their cycle lasts only a few hours, but subhormone priming can induce a steady-state that resembles metestrous behaviorally and in histopathology of vaginal smears (Hawcock et al. 2010). Furthermore, this type of priming has been used to show increases in sexual functioning with both apomorphine and melanotan II (the precursor to bremelanotide)(Allers et al. 2010d; Hawcock et al. 2010). In keeping with this idea, multiple studies using the behavioral paradigms mentioned above have been utilised with sub-estrus hormone primes which induce hyposexual behavior. Further investigation of the potential of sub-estrus hormone primes is certainly warranted.

Pharmacological manipulations: Two models have potential utility that use pharmacological alterations. First is SSRI-induced hyposexuality. Chronic or sub-chronic treatment with SSRIs in rats reduces sexual activity, although the effects on proceptivity compared to

receptivity are unclear (Frye et al. 2010; Guptarak et al. 2010; Matuszczyk et al. 1998). While SSRI-induced sexual dysfunction would not be diagnosed as HSDD in humans, it is still a disorder which requires treatment, and it provides a model of hyposexuality in animals with a well characterised clinical correlate. A further model that was recently presented uses a disruption of early sexual reward which causes animals to 'learn' not to enjoy sexual contact. During her first sexual experiences a female rat is treated with naloxone, which diminishes the reward signal obtained. In further testing this results in a long lasting decrease in sexual contact (Pfaus et al. 2008).

Natural variation in sexual motivation: One study has demonstrated that within a normal population of female laboratory rats, a subgroup can be found which show more avoidance of sexual contact when presented with a male. Hence, when compared to the population as a whole, these animals are hyposexual. Translational relevance remains to be determined however, since apomorphine – a drug that has demonstrated clinical efficacy – does not induce increased sexual behavior in this model (Snoeren et al. 2011)

Marmoset model: A marmoset monkey model of hyposexual activity has been developed that utilises a combination of sub-optimal hormone priming and separation of the male and female pair mates to induce low levels of copulation on reunion. In addition, because the marmoset forms long-term pairs, a study design can include more than one hormone prime in a cross-over design to assess hormone dependence of compounds. This model has recently been used to assess the efficacy of flibanserin, a drug that has demonstrated efficacy in HSDD women in the clinic (Aubert et al. 2009; Tannenbaum et al. 2007).

3. Measuring arousal in animal models

There are two types of arousal that are relevant to sexual function, generalised arousal and peripheral arousal. Generalised arousal is a state of awareness or attention that is given to an organism's surroundings. An animal with a high state of generalised arousal has greater awareness of sensory cues, more motor activity, and a high degree of emotional reactivity. Peripheral arousal during sexual activity is the physiological preparation for sexual contact, such as vaginal and clitoral engorgement and lubrication.

Generalised arousal is relevant to sexual function as varying levels of sensory awareness or attention may be linked to motivation (Schober et al. 2011). In this sense, generalised arousal may be more closely linked to desire, than to peripheral arousal. Indications of decreased general arousal in sexual dysfunction, in particular women with HSDD support this link to desire. Women with HSDD show different brain activation patterns compared to healthy controls when viewing erotic videos, women with HSDD demonstrate differences in attending to sexual cues compared to healthy controls, and also have different electroencphalographic excitability as measured by the P300 wave when compared to both healthy controls and to women with arousal disorder (Arnow et al. 2009; McCall et al. 2006; Vardi et al. 2009). Consequently, it is possible that HSDD results from decreased generalised arousal or is a cause of it. Either way, it is clearly an important part of the sexual cycle. Generalised arousal is thought to be a key feature of an animal preparing to engage in any motivated behavior, not just sexual contact. If generalised arousal is necessary for motivated behavior, and motivated behavior is best measured in the aforementioned models, perhaps these behaviors are a good surrogate for generalised arousal.

Peripheral arousal related to sexual function typically refers to the autonomic response of the body as it prepares for sexual contact. In theory, the possibilities for preclinical research

of the physiological mechanisms of arousal are endless. The circuitry from brainstem autonomic centers to the genitalia has been well studied, as have been the peripheral nerve innervation and structure and function of the genitalia. The understanding of healthy functioning arousal pathways, tissues, and biochemistry has grown substantially in recent years.

Below is a brief description of methods used to investigate peripheral arousal. Rather than review in detail the numerous techniques available, we will give a short description of the methods which can be utilised and the types of data generated.

3.1 Models of peripheral arousal

Lordosis behavior: It is arguable whether a lordosis reflex posture can be used as a measure of arousal. This is a posture adopted by female rats which allows the male access for intromission and ejaculation. The reason for including this here is twofold: female rats will exhibit lordosis even in non-paced mating situations where a 'rewarding' sexual experience does not occur and is therefore distinct from motivation or desire, and female rats will typically resist intromission if they are in a non-receptive hormone state or in pain. For these reasons, possibly lordosis may be a surrogate marker for arousal, in that physiologically, her body may be prepared for sexual contact and it is not uncomfortable to engage in copulation.

Vaginal blood flow models: Typically these types of studies are carried out in aneasthetised animals, usually rats or rabbits (Beharry et al. 2003; Giuliano et al. 2010; Hale et al. 2003). A basic paradigm uses peripheral nerve stimulation (ie pudendal or pelvic) to stimulate blood flow to the clitoris and vagina. These studies have been critical in elucidating the mechanisms by which blood flow to the genitals is regulated, and the neurotransmitters and hormones involved in such regulation. The blood flow itself can be measured by techniques, such as plethysmography or laser doppler flowmetry. In addition to the standard rate or amplitude of flow, further characterisation of blood flow as measured by laser doppler can elicit surrogate measures of autonomic activation to the vagina (Allers et al. 2010d; Allers et al. 2010c). These measures are obtained by fast Fourier transform analysis of the oscillations within blood flow and are similar to those used to assess heart rate variability. Using this type of analysis responses to naturally arousing stimuli (a male rat) and experimental manipulations meant to induce arousal (drugs, nerve section, hormone status) are observed.

In vitro studies: Studies on gential tissues also help to define the intricate biochemical and physiological mechanisms for healthy sexual functioning (Aughton et al. 2008; Wilson et al. 2009). These types of studies may investigate the mechanisms involved in vaginal smooth muscle contraction and relaxation, lubrication, or neurotransmitter release from innervating nerves. In addition, one unique model utilises an ex vivo brain tissue assay which shows responses that are highly predictive of lordosis behavior. In a drug development project where increased lordosis could be predictive of clinical efficacy, this assay provides an ideal tool for early drug screening (Booth et al. 2010).

3.2 Disorders of arousal and potential animal models

Female sexual arousal disorder (FSAD) is defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) as the inability to attain or maintain until completion of sexual activity adequate lubrication in response to sexual excitement (American Psychiatric Association 2000). Unfortunately, this definition does not truly seem to describe many FSAD patients since several studies have now shown that a

patient will rate her subjective feelings of arousal quite low, but tends to show a normal genital response (Laan et al. 2008; Rellini et al. 2006). Classifying patients into subgroups of mainly genital arousal, or subjective arousal dysfunction in studies using VPA begins to show some differences, but subjective assessments remain the best diagnostic tools (Both et al. 2010; Salonia et al. 2010). In healthy women, there is not always agreement between subjective and physiologically measured responses either, perhaps due to interoceptive differences in attending to one's own genital physiology.

Even though there is a wealth of information on healthy arousal responses, there is no evidence based hypothesis for the neuropathology of FSAD. Clear differences in sympathetic responsiveness has been demonstrated in patients as compared to controls using procedures such as hyperventilation or extreme exercise (Brotto et al. 2009; Meston 2000). This points to a pathology in the systemic autonomic nervous system, or central-autonomic interface, rather than in the genitalia.

The majority of models above cannot provide translational disease models for FSAD, since vaginal vasocongestion is not affected in a large number of women with FSAD, and the likely pathology is within the circuitry of the autonomic or central nervous system. Only one technique above has demonstrated that it can actually distinguish between healthy controls and women with FSAD, and has been demonstrated to have predictive utility.

Slow oscillations in vaginal blood flow: In this model, laser Doppler flowmetry or vaginal plethysmograph can be used to record blood flow within the vaginal wall (Allers et al. 2010d; Allers et al. 2010c). Rather than assessing peak amplitudes, rate or other typical measures, the trace is analysed by fast Fourier transform (FFT) to elucidate the oscillatory charactistics of flow. This technique is well established in vascular research and these oscillations are known to reflect autonomic nervous system input to the tissue being studied. In this way, these measures are a surrogate of autonomic input. When measured in the vagina, the changes seen during sexual arousal paradigms are specific to the vagina, meaning they do not occur in other tissues simultaneously. This method has been used to differentiate human patients, correlates highly with subjective arousal in both healthy and FSAD women, and has been used in animals to show arousal inducing effects of apomorphine and melanotan II, in addition to natural arousal (exposure to sexually active male). Upon apomorphine administration animals in metestrus respond with increased slow oscillations in this model, at the same doses that induce restoration of sexual behavior in a partner-preference test (Hawcock et al. 2010). This model has not yet been used clinically to demonstrate restoration of natural arousal in FSAD women with a drug candidate, but has great potential as a translational model for investigation of drugs to treat FSAD.

4. Lessons from drug discovery

The process of drug discovery requires that a target (eg receptor, enzyme, etc.) be identified with a reasonable hypothesis for why it is engaged in a given disease state. This hypothesis is then rigorously tested within the laboratory with tool compounds and drug candidates. Alternatively, and typical of the sexual health field, a prosexual side effect is noticed for a given drug candidate, and this is quickly followed up to assess its potential for therapeutic use in sexual medicine. This process leads to a substantial amount of research into pathways, disease states, and pharmacological mechanisms regarding a particular target being generated. Within sexual health groups in the pharmaceutical industry recent targets have included dopamine receptors, serotonin receptors, and melanocortin receptors. The

following examples demonstrate how the process of drug discovery and new drugs available for testing has contributed substantially to the scientific understanding of sexual function and dysfunction.

4.1 Apomorphine

Drug development teams have adopted multiple strategies for assessing dopamine receptors as a drug target, including assessing the roles of individual dopamine receptor subtypes, dopamine reuptake, or using a classical dopamine receptor agonist (apomorphine) in different formulations. Apomorphine is a non-selective dopamine agonist was first discovered in 1869 and over time has been used as an emetic, a treatment for alcohol and morphine addictions, and to improve symptoms of Parkinson's Disease (Subramony 2006).

Dopamine has long been known to be a modulator of sexual function. There are decades of literature reporting pro-sexual effects of dopamine agonists but also reports of the same paradigms producing reduced sexual behavior. Much research has focussed on elucidating the hormone dependence of effects, the regions of the brain where increased or decreased dopamine occurs during sexual contact in efforts to investigate the real role of dopamine in sexual function and where discrepancies in data may come from. Many review articles have highlighted ongoing questions related to dopamine in sexual function (Meisel et al. 2006; Paredes et al. 2004; Peeters et al. 2008; Pfaus 2009a; Stolzenberg et al. 2011b; Stolzenberg et al. 2011a).

Regardless of the scientific debates over how dopamine regulates sexual function, clinical evidence has indicated that stimulating dopamine receptors may provide help for women with sexual dysfunction (Bechara et al. 2004; Caruso et al. 2004a). For this reason, studies were undertaken to investigate further why apomorphine can have opposing effects on sexual behavior in rodents.

Using a partner preference paradigm in which a rat chooses to actively investigate either a sexually vigorous male or a castrated male, a measure of active investigation can be utilised to determine sexual interest compared to social interest. In this paradigm, female rats that are ovariectomised and given a sub-hormone prime to resemble metestrus do not show a preference for either male rat. Upon apomorphine treatment, a dose dependent increase in preference for the sexually vigorous male is observed. When this study is run with animals that have been fully hormonally primed to resemble behavioral estrous, they show a clear preference for the sexually vigorous male, which is decreased by apomorphine treatment (Hawcock et al. 2010). These data indicate that when ALL other conditions are equal dopamine receptor agonism can have the exact opposite effect simply by artificially placing the animal into different stages of the estrous cycle.

Further investigations suggest that the opposing effects of apomorphine occur in the naturally cycling animal in metestrus compared to estrous. Using the FFT analysis of laser doppler flowmetry in rats, these differential effects of apomorphine are also present. Metestrus animals had a significant increase in slow oscillatory activity of blood flow, which in this model is indicative of sexual arousal (Allers et al. 2010d). Furthermore, this increase could not be blocked by the peripheral antagonist domperidone, but could be attenuated with the centrally acting antagonist haloperidol, indicating apomorphine's actions did originate in the brain (Allers et al. 2010c). In estrous animals, apomorphine elicited a decrease in slow oscillatory activity indicating decreased arousal. The dose ranges in both

metestrus and estrous animals which had effects in this model are the same as those in the partner-preference model.

An electrophysiological study was undertaken to further understand the underlying mechanisms for the observed differences in apomorphine actions. Neurons from the paraventricular nucleus, a nucleus important for sexual function and hormonally regulated, were studied in animals from all four stages of the estrous cycle. Firing rates from this nucleus varied substantially across the estrous cycle, with metestrous rates being the highest. In addition subpopulations of neurons were identified: slow neurons which increase in response to apomorphine, and fast neurons which decrease in response to the drug. A greater proportion of the fast neurons were evident in metestrous, accounting for the higher mean firing rate, and leading to relatively greater decreases upon apomorphine (Richards et al. 2010).

Taken together, these data suggest that during metestrous, a neurological 'stop' signal has been physiologically delivered to the animal which is reflected the animal's behavioral disinterest in a sexual partner. This 'stop' signal is sensitive to, and can be reversed by apomorphine administration. This reversal manifests as increased interest in a sexual partner and increased sexual arousal. An underlying mechanism may be the inhibition of a fast-firing population of neurons within the paraventricular nucleus of the brain.

4.2 Bremelanotide

The peptide α-melanocyte stimulating hormone (MSH) is a product of the proopiomelanocortin pro-hormone. This peptide has long been known to be involved in regulation of energy homeostasis and has been suggested as a target for number medical indications (Hedlund 2004).

In the mid-1980s, a group at the University of Arizona synthesized two highly potent MSH analogues (Hadley et al. 1998). One compound, deemed Melanotan I (MTI) was licensed out and further characterised for utility as a tanning drug, given the known role of MSH in pigmentation. A further analogue, Melanotan II (MTII) was developed which was smaller and the hope was that this would aid in its absorption and tissue distribution. The investigator decided to assess for himself whether this second analogue had the tanning capability seen with MTI and proceeded to dose himself. While it is unclear whether he did achieve a tan, what the investigator reports was an "unrelenting" erection lasting 8 hours. Not long after, this compound was licensed out for further development as a sexual dysfunction treatment candidate. PT-141 is the active metabolite of MTII and ultimately became the drug development lead compound and was renamed bremelanotide.

Clincal trials in women have demonstrated that bremelanotide increases sexual desire and arousal in women with arousal disorders (Diamond et al. 2004; Diamond et al. 2006; Safarinejad 2008). In one study, using vaginal plethysmography to assess vasocongestion, even though subjective scores were increased over placebo, there was no change in vasocongestion measures as compared to controls, confirming that vaginal vasocongestion is not a suitable method for assessing efficacy of compounds (Diamond et al. 2006).

Prior to the discovery and development of bremelanotide, melanocortin receptors were not considered to be of great interest within the sexual medicine field. Since that time, a surge of interest has appeared, and along with it a boost in scientific research investigating the mechanisms involved.

Bremelanotide is an agonist at melanocortin 3 and 4 (MC3 and MC4) receptors, whose primary localisation is in the hypothalamic regions of the brain (Molinoff et al. 2003). The

most evidence currently points to action within either the medial pre-optic area (MPOA) or the paraventricular nuclues (PVN) or both. Behavioral studies in pacing chambers have demonstrated that peripheral administration of bremelanotide increases proceptive behaviors in female rats with different hormone primes. In addition, injection of the drug directly into the MPOA results in the same effect (Pfaus et al. 2007). In keeping with this data, peripheral injection of bremelanotide results in increased activation of MPOA neurons as measured by c-fos. In addition to bremelanotide's actions on proceptivity, the parent compound MTII has also been demonstrated to induce arousal in rats using the laser doppler method with FFT analysis of slow oscillatory activity (Allers et al. 2010d).
In male rats, a similar study demonstrates that following administration of bremelanotide c-fos activation occurs within the PVN of the hypothalamus (Molinoff et al. 2003). To assess if this is a potential pathway in females, further investigation was undertaken in naturally cycling estrus rats. Pseudorabies virus (PRV) injection to the clitoris and vagina resulted in transsynaptic labeling present in both the PVN and the MPOA. Furthermore, neurons that were double-labeled for PRV and the melanocortin 4 receptor were found in both the PVN and MPOA, indicating melanocortin pathways exist from both of these regions to the genitalia (Gelez et al. 2010). Between 4 and 8% of the PRV labeled neurons were triple-labeled for both the melanocortin 4 receptor and oxytocin. These data demonstrate direct pathways from both the PVN and the MPOA to the genitalia that could be part of bremelanotide's mechanism of action through activation of melanocortin 4 receptors on oxytocin neurons.

4.3 Flibanserin

Flibanserin was discovered in 1990 as part of a program investigating targets for depression (Borsini et al. 1997). This compound was developed based on a very sound rationale for why agonist activity at post-synaptic 5-HT1A receptors and antagonism of 5-HT2A receptors combined would be beneficial to patients with major depressive disorder (Borsini et al. 2002). Unfortuantely, during Phase II trials for depression, flibanserin was not superior to the positive control, paroxetine (Kennedy 2010).
Within the Phase II trials, patients were given the ASEX questionnaire to assess sexual function. Flibanserin treatment improved sexual function in 70% of the patients. Development of flibanserin for depression was discontinued but restarted development for the indication of hypoactive sexual desire disorder. Following several Phase III clinical trials with flibanserin in premenopausal women, the data indicating increased desire and decreased distress following chronic flibanserin treatment is substantial (Clayton et al. 2009; Goldfischer et al. 2009; Jolly et al. 2009).
Following the reassignment of this drug, the search for a mechanism of action began. Within sexual function research, 5-HT1A receptor agonism has long been known to reduce sexual behavior (Ahlenius et al. 1989; Mendelson et al. 1986; Uphouse et al. 1991). The finding that a 5-HT1A agonist is prosexual in women was puzzling. Treatment of rats in pacing chambers either at full estrous priming or sub-hormonal priming also indicated that rats increased proceptive behaviors with chronic flibanserin treatment, and hence, sexual motivation – eliminating the possibility of a species difference in 5-HT1A actions (Allers et al. 2010b; Greggain et al. 2010). Acute dosing of flibanserin has no effect on sexual behavior in rodents.
In pair-bonded marmosets, a study was conducted to compare the effects of chronic flibanserin treatment with that of a commonly used 5-HT1A agonist, 8-OH-DPAT. In this study, flibanserin induced increased affiliative behavior in both pair mates, although only

the females were treated. 8-OH-DPAT induced increased aggression between pairmates after treatment of females alone (Aubert et al. 2009). The result is that flibanserin is clearly not a typical 5-HT1A receptor agonist, but has unique properties that contribute to its mechanism of action.

A key to the difference in flibanserin pharmacology is it's ability to act only at post-synaptic 5-HT-1A receptors. A study by Marazziti et al. demonstrated that in human brain, flibanserin has low nanmolar potency at 5-HT1A receptors in the prefrontal cortex, but none at 10μM in the dorsal raphe nucleus (Marazziti et al. 2002). The 5-HT1A receptors in the dorsal raphe nucleus are responsible for regulating serotonin release throughout the brain and typical 5-HT1A agonists will inhibit this release. Post-synaptic receptors are located outside of the dorsal raphe nucleus and have many different functions, including regulating release of all monoamines. To determine how flibanserin administration affects monoamine release two microdialysis studies were undertaken. The first investigated acute dosing while measuring serotonin, dopamine, and norepinephrine in three regions of the brain: the prefrontal cortex, the dorsal raphe, and the hippocampus (Invernizzi et al. 2003). The surprising result was that flibanserin administration decreased serotonin in the prefrontal cortex and dorsal raphe, but not the hippocampus. Recent evidence suggests that hippocampal serotonin is regulated primarily by presynaptic 5-HT1A receptors within the dorsal raphe, so the interpretation for this study is that by acting only at post-synaptic receptors flibanserin can affect serotonin release in selected brain areas. The following microdialysis study indicated that dopamine and norepinephrine are also affected in regionally selective patterns upon chronic dosing (Allers et al. 2010a). Potentially the most significant finding was that within the prefrontal cortex, an area important for general arousal and motivation, basal levels of dopamine and norepinephrine were increased selectively in the prefrontal cortex out of the regions studied (prefrontal cortex, nucleus accumbens, hypothalamic medial preoptic area).

HSDD patients have been shown to have altered cortical reactivity and demonstrate differences in attending to sexual cues (McCall et al. 2006; Vardi et al. 2009). Flibanserin, by increasing two neurotransmitters known to be involved in sexual desire, selectively in regions responsible for attention and awareness, may act to restore these functions (Stahl et al. 2011).

5. Conclusions

In conclusion, the development of centrally acting clinically efficacious drugs (albeit none yet with FDA approval) to treat sexual dysfunction, and the development of new models for assessing drug effects preclinically has given the sexual sexual function research field a much needed boost. New models of dysfunction can now be validated as they are developed and translation to human dysfunction can be better established.

6. References

Agmo, A., Turi, A. L., Ellingsen, E., and Kaspersen, H.2004Preclinical models of sexual desire: conceptual and behavioral analysesPharmacol.Biochem.Behav.783379404

Ahlenius, S., Larsson, K., and Fernandez-Guasti, A.1989Evidence for the involvement of central 5-HT1A receptors in the mediation of lordosis behavior in the female ratPsychopharmacology (Berl).984440444

Allers, K. A., Dremencov, E., Ceci, A., Flik, G., Ferger, B., Cremers, T. I., Ittrich, C., and Sommer, B.2010aAcute and repeated flibanserin administration in female rats modulates monoamines differentially across brain areas: a microdialysis studyJ.Sex Med.7517571767

Allers, K. A., Gelez, H., Sommer, B., and Giuliano, F.2010bEffects of flibanserin on appetitive and consummatory aspects of sexual behavior in ovariectomized female rats primed with estrogen and progesteroneSociety for Neuroscience Meeting Abstracts595

Allers, K. A., Richards, N., Scott, L., Sweatman, C., Cheung, J., Reynolds, D., Casey, J. H., and Wayman, C.2010cII. Slow oscillations in vaginal blood flow: regulation of vaginal blood flow patterns in rat by central and autonomic mechanismsJ.Sex Med.7310881103

Allers, K. A., Richards, N., Sultana, S., Sudworth, M., Dawkins, T., Hawcock, A. B., Buchanon, T., Casey, J. H., and Wayman, C.2010dI. Slow oscillations in vaginal blood flow: alterations during sexual arousal in rodents and humansJ.Sex Med.7310741087

American Psychiatric Association2000Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision.

Arnow, B. A., Millheiser, L., Garrett, A., Lake, Polan M., Glover, G. H., Hill, K. R., Lightbody, A., Watson, C., Banner, L., Smart, T., Buchanan, T., and Desmond, J. E.1-23-2009Women with hypoactive sexual desire disorder compared to normal females: A functional magnetic resonance imaging studyNeuroscience.1582484502

Aubert, Y., converse, A., Sommer, B., Allers, K. A., and Abbott, D. H.2009Comparison of flibanserin with the 5-HT1A agonist (+)-8-OH-DPAT in affecting interactions between male-female marmoset pairsJ.Sex Med.6(suppl 5)422

Aughton, K. L., Hamilton-Smith, K., Gupta, J., Morton, J. S., Wayman, C. P., and Jackson, V. M.2008Pharmacological profiling of neuropeptides on rabbit vaginal wall and vaginal artery smooth muscle in vitroBr.J.Pharmacol.1552236243

Bancroft, J., Graham, C. A., Janssen, E., and Sanders, S. A.2009The dual control model: current status and future directionsJ.Sex Res.462-3121142

Barnett, D. K., Bunnell, T. M., Millar, R. P., and Abbott, D. H.2006Gonadotropin-releasing hormone II stimulates female sexual behavior in marmoset monkeys Endocrinology. 1471615623

Bechara, A., Bertolino, M. V., Casabe, A., and Fredotovich, N.2004A double-blind randomized placebo control study comparing the objective and subjective changes in female sexual response using sublingual apomorphineJ Sex Med12

Beharry, R. K., Hale, T. M., Wilson, E. A., Heaton, J. P., and Adams, M. A.2003Evidence for centrally initiated genital vasocongestive engorgement in the female rat: findings from a new model of female sexual arousal responseInt.J.Impot.Res.152122128

Bermant, G.6-2-1961Response Latencies of Female Rats during Sexual Intercourse Science. 133346617711773

Bermant, G. and Westbrook, W. H.1966Peripheral factors in the regulation of sexual contact by female ratsJ.Comp Physiol Psychol.612244250

Booth, C., Wayman, C. P., and Jackson, V. M.2010An ex vivo multi-electrode approach to evaluate endogenous hormones and receptor subtype pharmacology on evoked

and spontaneous neuronal activity within the ventromedial hypothalamus; translation from female receptivityJ.Sex Med.7724112423

Borsini, F., Cesana, R., Kelly, J., Leonard, B. E., McNamara, M., Richards, J., and Seiden, L.1997BIMT 17: a putative antidepressant with a fast onset of action? Psychopharmacology (Berl). 1344378386

Borsini, F., Evans, K., Jason, K., Rohde, F., Alexander, B., and Pollentier, S. 2002 Pharmacology of flibanserin CNS. Drug Rev. 82117142

Both, S., Laan, E., and Schultz, W. W.2010Disorders in sexual desire and sexual arousal in women, a 2010 state of the artJ.Psychosom.Obstet.Gynaecol.314207218

Brotto, L. A., Klein, C., and Gorzalka, B. B.2009Laboratory-induced hyperventilation differentiates female sexual arousal disorder subtypes Arch. Sex Behav. 384463475

Caruso, S., Agnello, C., Intelisano, G., Farina, M., Di Mari, L., and Cianci, A.2004aPlacebo-controlled study on efficacy and safety of daily apomorphine SL intake in premenopausal women affected by hypoactive sexual desire disorder and sexual arousal disorder Urology 635

Caruso, S., Agnello, C., Intelisano, G., Farina, M., Di, Mari L., and Cianci, A.2004bPlacebo-controlled study on efficacy and safety of daily apomorphine SL intake in premenopausal women affected by hypoactive sexual desire disorder and sexual arousal disorder Urology. 635955959

Clark, A. S., Kelton, M. C., Guarraci, F. A., and Clyons, E. Q.2004Hormonal status and test condition, but not sexual experience, modulate partner preference in female ratsHorm.Behav. 455314323

Clayton, A., jayne, C., Jacobs, M., Kimura, T., Pyke, R., and Lewis-D'Agostino, D.2009Efficacy of flibanserin as a potential treatment for hypoactive sexual desire disorder in North American premenopausal women: Results from the DAHLIA trial. J Sex Med 6 (suppl 5) 408

Clayton, A. H., Dennerstein, L., Pyke, R., and Sand, M.2010Flibanserin: a potential treatment for Hypoactive Sexual Desire Disorder in premenopausal womenWomens Health (Lond Engl.).65639653

Coria-Avila, G. A., Ouimet, A. J., Pacheco, P., Manzo, J., and Pfaus, J. G.2005Olfactory conditioned partner preference in the female ratBehav.Neurosci.11937167250735-7044

DeRogatis, L. R., Clayton, A. H., Rosen, R. C., Sand, M., and Pyke, R. E.2011Should sexual desire and arousal disorders in women be merged?Arch.Sex Behav.402217219

Diamond, L. E., Earle, D. C., Heiman, J. R., Rosen, R. C., Perelman, M. A., and Harning, R.2006An effect on the subjective sexual response in premenopausal women with sexual arousal disorder by bremelanotide (PT-141), a melanocortin receptor agonistJ.Sex Med.346286381743-6095

Diamond, L. E., Earle, D. C., Rosen, R. C., Willett, M. S., and Molinoff, P. B.2004Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction Int. J. Impot. Res. 1615159

Frye, C. A. and Rhodes, M. E.2010Fluoxetine-Induced Decrements in Sexual Responses of Female Rats and Hamsters Are Reversed by 3alpha,5alpha-THPJ.Sex Med.

Gelez, H., Poirier, S., Facchinetti, P., Allers, K. A., Wayman, C., Alexandre, L., and Giuliano, F.2010Neuroanatomical evidence for a role of central melanocortin-4 receptors and oxytocin in the efferent control of the rodent clitoris and vaginaJ.Sex Med.7620562067

Giuliano, F., Pfaus, J., Srilatha, B., Hedlund, P., Hisasue, S., Marson, L., and Wallen, K.2010Experimental models for the study of female and male sexual functionJ.Sex Med.7929702995

Goldfischer, E. R., Breaux, J., Katz, M., Kaufman, J., Smith, W. B., Patel, P., Mikl, J., Sand, M., and Pyke, R.2009Efficacy of continued flibanserin treatment in premenopausal women with hypoactive sexual desire disorder: Results from the ROSE study.J Sex Med20096(suppl 5)114

Greggain, J., Allers, K. A., Sommer, B., and Pfaus, J.2010Effects of repeated flibanserin treatment on appetitive sexual behaviors in male and female ratsJ Sex Med7(suppl 6)395

Guptarak, J., Sarkar, J., Hiegel, C., and Uphouse, L.2010Role of 5-HT(1A) receptors in fluoxetine-induced lordosis inhibitionHorm.Behav.582290296

Hadley, M. E., Hruby, V. J., Blanchard, J., Dorr, R. T., Levine, N., Dawson, B. V., al-Obeidi, F., and Sawyer, T. K.1998Discovery and development of novel melanogenic drugs. Melanotan-I and -IIPharm.Biotechnol.11:575-95.575595

Hale, T. M., Heaton, J. P., and Adams, M. A.2003A framework for the present and future development of experimental models of female sexual dysfunction Int. J. Impot. Res. 15 Suppl 5:S75-9.S75S79

Hawcock, A. B., Dawkins, T. E., and Reynolds, D. S.2010Assessment of 'active investigation' as a potential measure of female sexual incentive motivation in a preclinical non-contact rodent model: observations with apomorphine Pharmacol. Biochem. Behav. 952179186

Hedlund, P.2004PT-141 PalatinCurr.Opin.Investig.Drugs.54456462

Invernizzi, R. W., Sacchetti, G., Parini, S., Acconcia, S., and Samanin, R.2003Flibanserin, a potential antidepressant drug, lowers 5-HT and raises dopamine and noradrenaline in the rat prefrontal cortex dialysate: role of 5-HT(1A) receptorsBr.J.Pharmacol.139712811288

Johannes, C. B., Clayton, A. H., Odom, D. M., Rosen, R. C., Russo, P. A., Shifren, J. L., and Monz, B. U.2009Distressing sexual problems in United States women revisited: prevalence after accounting for depressionJ.Clin.Psychiatry.701216981706

Jolly, E., Clayton, A., Thorp, J., Kimura, T, Sand, M., and Pyke, R.2009Efficacy of flibanserin 100 mg qhs as a potential treatment for hypoactive sexual desire disorder in North American premenopausal womenJ Sex Med6(Supp 5)465

Kendrick, K. M. and Dixson, A. F.1985Effects of oestradiol 17B, progesterone and testosterone upon proceptivity and receptivity in ovariectomized common marmosets (Callithrix jacchus)Physiol Behav.341123128

Kennedy, S.2010Flibanserin: initial evidence of efficacy on sexual dysfunction, in patients with major depressive disorderJ.Sex Med.71034493459

Laan, E., van Driel, E. M., and van Lunsen, R. H.2008Genital responsiveness in healthy women with and without sexual arousal disorderJ.Sex Med.5614241435

Lopez, H. H., Wurzel, G., and Ragen, B.2007The effect of acute bupropion on sexual motivation and behavior in the female ratPharmacol.Biochem.Behav.873369379

Marazziti, D., Palego, L., Giromella, A., Mazzoni, M. R., Borsini, F., Mayer, N., Naccarato, A. G., Lucacchini, A., and Cassano, G. B.2002Region-dependent effects of flibanserin and buspirone on adenylyl cyclase activity in the human brain Int. J. Neuropsychopharmacol.52131140

Matthews, T. J., Grigore, M., Tang, L., Doat, M., Kow, L. M., and Pfaff, D. W.1997Sexual reinforcement in the female ratJ.Exp.Anal.Behav.683399410

Matuszczyk, J. V., Larsson, K., and Eriksson, E.1998Subchronic administration of fluoxetine impairs estrous behavior in intact female rats Neuropsychopharmacology. 196492498

McCall, K. and Meston, C.2006Cues resulting in desire for sexual activity in womenJ.Sex Med.35838852

Meisel, R. L. and Mullins, A. J.12-18-2006Sexual experience in female rodents: cellular mechanisms and functional consequencesBrain Res.112615665

Mendelson, S. D. and Gorzalka, B. B.19865-HT1A receptors: differential involvement in female and male sexual behavior in the ratPhysiol Behav.372345351

Mendelson, S. D. and Gorzalka, B. B.1987An improved chamber for the observation and analysis of the sexual behavior of the female ratPhysiol Behav.3916771

Meston, C. M.2000Sympathetic nervous system activity and female sexual arousal Am. J. Cardiol. 862A30F34F

Molinoff, P. B., Shadiack, A. M., Earle, D., Diamond, L. E., and Quon, C. Y.2003PT-141: a melanocortin agonist for the treatment of sexual dysfunction Ann. N.Y. Acad.Sci.994:96-102.96102

Paredes, R. G. and Agmo, A.2004Has dopamine a physiological role in the control of sexual behavior? A critical review of the evidence Prog.Neurobiol.733179226

Paredes, R. G. and Alonso, A.1997Sexual behavior regulated (paced) by the female induces conditioned place preferenceBehav. Neurosci.1111123128

Paredes, R. G. and Vazquez, B.11-1-1999What do female rats like about sex? Paced matingBehav.Brain Res.1051117127

Peeters, M. and Giuliano, F.2008Central neurophysiology and dopaminergic control of ejaculationNeurosci.Biobehav. Rev.323438453

PEIRCE, J. T. and NUTTALL, R. L.1961Self-paced sexual behavior in the female ratJ.Comp Physiol Psychol.54:310-3.310313

Perelman, M. A.2009The sexual tipping point: a mind/body model for sexual medicineJ.Sex Med.63629632

Pfaus, J., Giuliano, F., and Gelez, H.2007Bremelanotide: an overview of preclinical CNS effects on female sexual functionJ.Sex Med.4 Suppl 42692791743-6095

Pfaus, J. G.1996Frank A. Beach award. Homologies of animal and human sexual behaviorsHorm.Behav.3031872000018-506X

Pfaus, J. G.2009bPathways of sexual desireJ.Sex Med.6615061533

Pfaus, J. G.2009aPathways of sexual desireJ.Sex Med.6615061533

Pfaus, J. G. and Pfaff, D. W.1992Mu-, delta-, and kappa-opioid receptor agonists selectively modulate sexual behaviors in the female rat: differential dependence on progesteroneHorm.Behav.264457473

Pfaus, J. G., serrano, S, and Coria-Avila, G.2008Blockade of optiod receptors during early sexual experience decreases sexual desire in female ratsSociety for Neuroscience Meeting Abstracts97.15

Rellini, A. and Meston, C.2006The sensitivity of event logs, self-administered questionnaires and photoplethysmography to detect treatment-induced changes in female sexual arousal disorder (FSAD) diagnosisJ.Sex Med.32283291

Richards, N., Wayman, C., and Allers, K. A.2010Neuronal activity in the hypothalamic paraventricular nucleus varies across the estrous cycle in anesthetized female rats: effects of dopamine receptor agonismJ.Sex Med.7311041115

Rosen, R., Brown, C., Heiman, J., Leiblum, S., Meston, C., Shabsigh, R., Ferguson, D., and D'Agostino, R., Jr.2000The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual functionJ.Sex Marital Ther.262191208

Safarinejad, M. R.2008Evaluation of the safety and efficacy of bremelanotide, a melanocortin receptor agonist, in female subjects with arousal disorder: a double-blind placebo-controlled, fixed dose, randomized studyJ.Sex Med.54887897

Salonia, A., Giraldi, A., Chivers, M. L., Georgiadis, J. R., Levin, R., Maravilla, K. R., and McCarthy, M. M.5-11-2010Physiology of Women's Sexual Function: Basic Knowledge and New FindingsJ.Sex Med.

Schober, J., Weil, Z., and Pfaff, D.2011How generalized CNS arousal strengthens sexual arousal (and vice versa)Horm.Behav.595689695

Simon, J. A.2010Low sexual desire--is it all in her head? Pathophysiology, diagnosis, and treatment of hypoactive sexual desire disorderPostgrad.Med.1226128136

Snoeren, E. M., Chan, J. S., de Jong, T. R., Waldinger, M. D., Olivier, B., and Oosting, R. S.2011A new female rat animal model for hypoactive sexual desire disorder; behavioral and pharmacological evidenceJ.Sex Med.814456

Stahl, S. M., Sommer, B., and Allers, K. A.2011Multifunctional pharmacology of flibanserin: possible mechanism of therapeutic action in hypoactive sexual desire disorderJ.Sex Med.811527

Stolzenberg, D. S. and Numan, M.2011bHypothalamic interaction with the mesolimbic DA system in the control of the maternal and sexual behaviors in ratsNeurosci.Biobehav.Rev.353826847

Stolzenberg, D. S. and Numan, M.2011aHypothalamic interaction with the mesolimbic DA system in the control of the maternal and sexual behaviors in ratsNeurosci.Biobehav.Rev.353826847

Subramony, J. A.2006Apomorphine in dopaminergic therapyMol.Pharm.34380385

Tannenbaum, P. L., Schultz-Darken, N. J., Woller, M. J., and Abbott, D. H.2007Gonadotrophin-releasing hormone (GnRH) release in marmosets II: pulsatile release of GnRH and pituitary gonadotrophin in adult females J. Neuroendocrinol. 195354363

Tzschentke, T. M.2007Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decadeAddict.Biol.123-4227462

Uphouse, L., Montanez, S., Richards-Hill, R., Caldarola-Pastuszka, M., and Droge, M.1991Effects of the 5-HT1A agonist, 8-OH-DPAT, on sexual behaviors of the proestrous rat Pharmacol. Biochem. Behav. 393635640

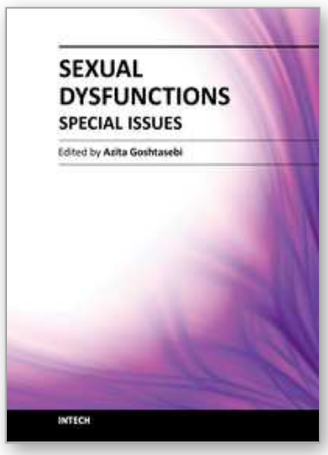
Vardi, Y., Sprecher, E., Gruenwald, I., Yarnitsky, D., Gartman, I., and Granovsky, Y.2009The p300 event-related potential technique for libido assessment in women with hypoactive sexual desire disorder J. Sex Med. 6616881695

Wallen, K.1990Desire and ability: hormones and the regulation of female sexual behaviorNeurosci.Biobehav.Rev.1422332410149-7634

Wilson, L. A., Wayman, C. P., and Jackson, V. M.2009Neuropeptide modulation of a lumbar spinal reflex: potential implications for female sexual functionJ.Sex Med.64947957

IntechOpen

IntechOpen



Sexual Dysfunctions - Special Issues

Edited by Dr. Azita Goshtasebi

ISBN 978-953-307-859-5
Hard cover, 128 pages
Publisher InTech
Published online 22, December, 2011
Published in print edition December, 2011

Sexual dysfunctions have recently recognized as one of the major public health problems. This book enhances our scientific understanding of sexual function and dysfunction from different perspectives. It presents evidence-based interventions for sexual dysfunctions in difficult medical situations such as cancer, and gives a valuable overview of recent experimental researches on the topic. Published in collaboration with InTech - Open Access Publisher, this imperative work will be a practical resource for health care providers and researchers who are involved in the study of sexual health.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Kelly A. Allers and Bernd Sommer (2011). Paradigms for Preclinical Investigations of Female Sexual Function and Dysfunction (HSDD and FSAD), Sexual Dysfunctions - Special Issues, Dr. Azita Goshtasebi (Ed.), ISBN: 978-953-307-859-5, InTech, Available from: http://www.intechopen.com/books/sexual-dysfunctions-special-issues/paradigms-for-preclinical-investigations-of-female-sexual-function-and-dysfunction-hsdd-and-fsad-

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the Creative Commons Attribution 3.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen