2010 ISSWSH ABSTRACTS

Selected Paper Session #1

Moderator: Irwin Goldstein, MD

#1

NEW INVESTIGATOR AWARD: BASIC SCIENCE: RECURRENT VULVOVAGINAL CANDIDA ALBICANS INFECTION CAUSES PERSISTENT POST-INFECTION VULVAR PAIN AND ALTERED VULVAR INNERVATION

Melissa Farmer, Anna M. Taylor, Andrea L. Bailey, Leigh C. MacIntyre, Zarah E. Milagrosa, Halley P. Crissman, Gary J. Bennett, Alfredo Ribeiro-da-Silva, Yitzchak M. Binik and Jeffrey S. Mogil
McGill University, Montreal, Canada
(Presented By: Melissa Farmer)

Introduction and Objectives: Provoked vestibulodynia is a highly prevalent idiopathic pain disorder characterized by touch evoked pain (mechanical allodynia) in the vulvar vestibule; women with the disorder often have a history of recurrent candidiasis (yeast infections).
Methods: We evaluated whether the repeated exposure to a common pathogen can lead to the development of chronic pain.
Results: A subset of female mice subjected to recurrent Candida albicans infection developed vulvar mechanical allodynia and hyperinnervation of peptidergic nociceptor and sympathetic fibers, all present long after infection resolution.
Conclusion: These data strongly suggest a causal role for recurrent yeast infections in the pathogenesis of provoked vestibulodynia and demonstrate for the first time that common infections can cause persistent pain states.

#2

CHRONIC FLIBANSERIN TREATMENT INCREASES SOLICITATIONS IN THE FEMALE RAT

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(Presented By: Helene Gelez)

Introduction and Objectives: Flibanserin is being developed for the treatment of hypoactive sexual desire disorder (HSDD) in women, but has not been yet tested in female rat. The aim of this study was to assess the effects of acute and chronic administration of flibanserin on rat female sexual behaviour as a step towards validating the ability of this model to predict compounds potentially useful in treating HSDD.
Methods: Sexually naïve Long Evans female rats (n = 52) were ovariectomized and primed subcutaneously with estradiol benzoate (10 µg) and progesterone (500 µg) 48 h and 4 h, respectively, before a 30–min copulatory test with a sexually vigorous male into the bilevel chamber. After receiving 10 sexual training tests, the females received one of the four treatments (vehicle, flibanserin 5 mg/kg, 15 mg/kg or 45 mg/kg,) administered per oral gavage twice daily for 29–days. Copulatory tests in the bilevel chamber were performed the first day of treatment (acute effect, 2 h after first oral administration) and once a week during 4 weeks (chronic effect). Female proceptive behaviors including number of solicitations and hops and darts, and receptive behaviors including lordosis quotient and intensity were measured and quantified during each 30–min copulatory test. Each behavioural parameter was compared between groups using a One–way ANOVA test.
Results: Acute flibanserin or 8–days of chronic flibanserin treatment, did not modify female proceptive nor receptive behaviors. After 15 days of chronic treatment with flibanserin 45 mg/kg, the females displayed significantly more solicitations than the 3 other groups. Other behavioural parameters did not differ between groups. The significant increase in female solicitations 45 mg/kg was still observed after 22–days of chronic treatment.
Conclusion: This study provides evidence for the first time the prosexual effect of flibanserin in female rats receiving flibanserin 45 mg/kg, twice daily administered for 15 days. These data suggest that assessing the number of solicitations as opposed to other behaviours in this model of female sexual motivation may be useful in predicting compounds for HSDD. This preliminary hypothesis must be confirmed by other compounds with human efficacy in HSDD if those become available, providing further validation for use as a predictive model. Such animal models may allow further investigation regarding flibanserin mechanism of action.

#3 **Not CME Accredited*

COMPARISON OF FLIBANSERIN WITH THE 5-HT1A AGONIST 8-OH-DPAT IN EFFECTING INTERACTIONS BETWEEN MALE-FEMALE MARMOSET PAIRS

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(Presented By: Kelly A. Allers)

Introduction and Objectives: Flibanserin is a 5–HT1A agonist and 5–HT2A antagonist which is currently in development for the treatment of hypoactive sexual desire disorder (HSDD). The objective of this study was to compare how treatment of the female marmoset with flibanserin compares to that of a typical 5–HT1A agonist on the interactions, both sexual and non–sexual, of male–female pairs of marmosets.
Methods: In this study, the female marmosets receiving the test compounds are ovariectomized, primed with either mid–follicular phase estradiol levels, which produces a low level of baseline sexual behavior, or no hormone. Test compounds and vehicle are administered in a cross–over design and estradiol replacement or no hormone are maintained throughout for each individual. Animals are treated with flibanserin (15 mg/kg p.o., n = 8 pairs) or 8–OH–DPAT (0.1 mg/kg s.c., n = 8 pairs) or vehicle for at least 4 weeks prior to behavioral testing. Males and females are separated for 90 min prior to behavioral testing to stimulate interactions upon being reunited.
Results: In pairs in which the female was treated with 8–OH–DPAT, males were more aggressive towards their females and females rejected male-mounting attempts more frequently. In pairs in which the female was treated with flibanserin, the females demonstrated more self-grooming (genital and non-genital) and also increased time spent grooming their male partners. Males of these pairs also increased the amount of time spent grooming their female partners. There was no effect of estradiol replacement on either group. Chronic 8–OH–DPAT increased signs of serotonin behavioral syndrome, while flibanserin did not.

Conclusion: Chronic flibanserin treatment of females has a positive impact on interactions between partners in a marmoset pair. In marmoset pairs in which females are treated chronically with 15 mg/kg flibanserin, there is more affiliative behavior demonstrated between partners, and self–grooming behavior in females. By contrast, chronic treatment of females with a prototypical 5–HT1A agonist (8–OH–DPAT) increases their rejection of mounts by male partners and increases aggression received.

#4

SILDENAFIL AND ROLIPRAM ENHANCE CLITORAL AND VAGINAL BLOOD FLOW RESPONSES TO DORSAL CLITORAL NERVE STIMULATION IN ANESTHETIZED FEMALE RATS

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(Presented By: Fabio Castiglione)

Introduction and Objectives: Nitric oxide and cGMP regulate clitoral and vaginal smooth muscle tonus. Few studies have explored the role of cAMP on genital bloodflow. We evaluated the effect of rolipram (type 4 cAMP–degrading phosphodiesterase inhibitor) and sildenafil on the bloodflow of the vagina and clitoris by dorsal clitoral nerve (DCN) stimulation in the rat. We also evaluated the effect on clitoral or vaginal bloodflow by local administration of prostaglandin E1 (PGE1).

Methods: After ethical approval, 10 female Sprague Dawley rats (250 g) were used. During anesthesia, mean arterial blood pressure (MAP) was monitored via the carotid artery. Clitoral and vaginal bloodflow was registered via laser Doppler probes on the clitoris or inside of the vagina. Sildenafil (2 mg/kg), or rolipram (3 mg/kg) were administered via intraperitoneal route. A bipolar electrode and a Grass S48 were used to stimulate the DCN. PGE1 (2 μg) was applied locally on the external genitalia.

Results: Control stimulations (5 V, 2.5 Hz) of the DCN caused peak flows and filling–rates of the clitoris and vagina of 6.8 ± 0.9 and 5.9 ± 0.5 TPU and 0.32 ± 0.10 and 0.49 ± 0.08 TPU/sec. Sildenafil or rolipram did not per se affect MAP or genital flow. Sildenafil increased DCN–induced peak clitoral flow and filling–rate to 13.9 ± 2.1 TPU ($p < 0.001$) and 1.32 ± 0.54 TPU/sec ($p < 0.05$). Sildenafil increased the flow/MAP ratio from 0.13 ± 0.03 to 0.21 ± 0.03 TPU/cmH2O ($p < 0.05$). Corresponding values for rolipram amounted to 10.2 ± 1.3 TPU (peak flow; $p < 0.05$) and 1.36 ± 0.33 TPU/sec (rate of filling; $p < 0.05$). Rolipram increased the flow/MAP ratio of the clitoris from 0.09 ± 0.001 to 0.15 ± 0.02 TPU/cmH2O ($p < 0.05$). For the vagina, sildenafil increased peak flow and filling–rate to DCN–activation to 11.2 ± 0.7 TPU ($p < 0.01$) and 0.80 ± 0.04 TPU/sec ($p < 0.01$). In comparison, rolipram increased peak flow and rate of filling to DCN–activation to 12.2 ± 1.3 TPU ($p < 0.05$) and 1.60 ± 0.30 TPU/sec ($p < 0.05$). The flow/MAP ratio for the vagina was increased by sildenafil from 0.08 ± 0.001 to 0.17 ± 0.01 TPU/cmH2O ($p < 0.01$) and by rolipram from 0.09 ± 0.01 to 0.18 ± 0.01 TPU/cmH2O ($p < 0.05$). PGE1 caused clitoral or vaginal flows amounting to 20 ± 4 and 24 ± 6 TPU. L–NNA partially reversed DCN–activated responses after sildenafil or rolipram.

Conclusion: Sildenafil and rolipram increased clitoral and vaginal bloodflow during DCN activation. Based on the current results, it appears as if both cGMP and cAMP–mediated responses are of importance for genital responses of the female rat.

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#5

EXPRESSION OF ENOS AND ASSOCIATED REGULATORY PROTEINS IN THE MURINE AND HUMAN CLITORIS

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(Presented By: Janine Oliver)

Introduction and Objectives: Despite extensive studies on the pathophysiology of male erectile dysfunction, the pathophysiology of female sexual dysfunction remains poorly understood and effective treatments are lacking. Little is known about the mechanisms regulating endothelial nitric oxide synthase (eNOS) activity and thus nitric oxide (NO) bioavailability in female sexual function. In this study we investigated the expression and localization of proteins involved in eNOS regulation and downstream targets in the murine and human clitoris.

Methods: Immunohistochemistry and western blotting specific for eNOS, phospho–eNOS (Ser1177), caveolin–1, heat shock protein 90 (Hsp90), phosphodiesterase type 5 (PDE5), soluble guanylate cyclase (sGC), and proliferative cell nuclear antigen (PCNA) were performed on human clitoral tissue obtained from a C57B6 mouse as well as from a 7–month–old female patient with congenital adrenal hyperplasia who underwent feminizing genitoplasty. The main outcome measures include the identification of eNOS and associated regulatory proteins by immunohistochemistry and western blot analysis in human clitoral tissue in a congenital adrenal hyperplasia patient as well as in murine tissue to confirm that the results hold true for clitoral tissue which was not androgenised.

Results: In the human clitoral tissue eNOS, caveolin–1, and Hsp90 were all localized to the endothelium of sinusoids and arterioles of human clitoral corpus cavernosum. PDE5 and sGC were localized to the trabecular smooth muscle. Western blot analysis confirmed their presence. Active, phospho–eNOS (Ser1177) was also detected. PCNA immunostaining revealed that the nuclei of a cell population in the stroma were actively undergoing proliferation. The presence of eNOS and these regulatory proteins was confirmed in the mouse clitoris representing clitoral tissue without androgen effect.

Conclusion: Our results suggest that a pathway consisting of caveolin–1 and Hsp90 may regulate eNOS activity in female clitoral tissue. The downstream targets sGC and PDE5 are present in the smooth muscle cells suggesting contribution to genital tone and sexual arousal. This data demonstrates that similar regulatory pathways may exist in both male and female erectile tissues.

#6

THE HEAT IS ON: EXAMINING THE RELIABILITY OF GENITAL TEMPERATURE MEASUREMENT IN MEN AND WOMEN

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(Presented By: Tuuli M. Kukkonen)

Introduction and Objectives: Recent research has demonstrated that thermography can be used to assess physiological sexual arousal in men and women. Findings indicate that genital temperature change is specific to sexual arousal and significantly correlates with self–report. This study was designed to expand on these previous findings by 1) measuring the test–retest reliability of thermography and 2) examining the effect of male–oriented and female–oriented sexually explicit videos on subjective and physiological arousal in men and women.

Methods: Healthy men (n = 20) and women (n = 20) aged 18–45 attended three testing sessions over a three–month period. During each session, participants viewed neutral film clips followed by three different sexually explicit videos that were counterbalanced across