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Tibial Nerve Stimulation to Drive Genital Sexual Arousal in an Anesthetized Female Rat

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ABSTRACT

Background: There is clinical evidence that percutaneous tibial nerve stimulation can positively benefit women with female sexual interest/arousal disorder, yet no studies have explored the potential mechanisms further.

Aim: To investigate the effect of tibial nerve stimulation on vaginal blood perfusion (VBP) in an anesthetized rat model.

Methods: 16 ketamine-anesthetized rats were surgically implanted with a nerve cuff electrode on 1 tibial nerve. The tibial nerve was stimulated for 30 minutes continuously or non-continuously at a frequency of 10 to 25 Hz.

Outcomes: VBP was measured with laser Doppler flowmetry and analyzed using a wavelet transform of time-frequency representations with a focus on the neurogenic energy range (0.076—0.200 Hz).

Results: 25 of 33 (75.8%) stimulation periods had at least a 500% increase in laser Doppler flowmetry neurogenic energy compared with baseline. This increase was most common within 20 to 35 minutes after the start of stimulation. There was no statistically significant difference for frequency used or estrous cycle stage.

Clinical Translation: The results of this study provide further support for percutaneous tibial nerve stimulation as an alternative treatment option for women with genital arousal aspects of female sexual interest/arousal disorder.

Strengths and Limitations: This study successfully demonstrates the ability of tibial nerve stimulation to increase VBP. However, further studies to determine parameter optimization and to illuminate neural mechanisms are needed. Further studies also are necessary to determine effects of repeated stimulation sessions.

Conclusion: Long-duration tibial stimulation was successful at driving increases in the neurogenic component of VBP, providing evidence that tibial nerve stimulation could be used to treat genital arousal aspects of female sexual interest/arousal disorder by improving pelvic blood flow. **Zimmerman LL, Rice IC, Berger MB, Bruns TM. Tibial Nerve Stimulation to Drive Genital Sexual Arousal in an Anesthetized Female Rat. J Sex Med 2018;XX:XXX—XXX.**

Key Words: Electrical Stimulation; Tibial Nerve; Vaginal Blood Flow; Female Sexual Dysfunction; Neuromodulation; Laser Doppler

INTRODUCTION

Female sexual dysfunction (FSD) affects millions of women worldwide.[1] Dysfunction can arise from biological, sociocultural, and psychological factors. FSD has a significant impact on quality of life and interpersonal relationships.[2,3] The prevalence of at least 1 form of sexual dysfunction is 40% to 45% of adult women with 12% of women experiencing sexually related personal distress,[4,5] yet there is no clear treatment option for a wide range of FSD deficits with high efficacy and minimal side effects. Female sexual interest/arousal disorder (FSIAD) and female orgasmic disorder are associated with inadequate genital arousal, which can be caused by decreased genital blood flow.[6]

Flibanserin has had mixed but generally positive results in treating the sexual interest deficit in women with FSIAD[7—9] but fails to treat the physiologic genital arousal aspects. Sildenafil has been shown to improve clitoral and vaginal blood flow in women, with resulting improvements in sexual function.[10] However, there are conflicting reports of clinical benefits and efficacy[11,12] and a high likelihood of moderate adverse events.[13]

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Percutaneous tibial nerve stimulation (PTNS), also referred to as posterior tibial nerve stimulation, has been studied clinically for more than 30 years for decreasing symptoms of overactive bladder and incontinence.[14] Patients typically receive weekly 30-minute stimulation sessions for 12 weeks with periodic maintenance sessions thereafter.[15] The stimulation has a carry-over effect, causing lasting bladder improvements long after the 30-minute stimulation. The mechanisms of PTNS are not well understood, but the tibial nerve enters the spinal cord at some of the sacral roots that innervate pelvic organs.[16] It has been proposed that PTNS works through modulating signals to and from the bladder through the sacral plexus using retrograde afferent stimulation.[17] 1 theory for the mechanism is that PTNS results in improved pelvic blood flow.[18] In studies of patients receiving PTNS for lower urinary tract dysfunction, some women noted significant improvements in sexual functioning, including arousal, desire, lubrication, and ease of orgasm.[19,20] Because bladder dysfunction has been shown to cause decreases in sexual functioning,[21] treating women for bladder dysfunction could improve sexual functioning as a result. However, improvements in sexual functioning after PTNS have not been correlated with improvement in bladder functioning, providing evidence that PTNS has direct effects on sexual functioning. PTNS also has improved sexual functioning in women receiving treatment for chronic pelvic pain.[22] However, these results have not been entirely separated from a secondary effect of treating bladder dysfunction or pain or studied further.

Rats are a standard animal model for the pharmacology, neuroanatomy, and vaso-congestive mechanisms involved in the sexual function of women.[23] Physiologic markers of sexual arousal have been modeled in a few prior limited anesthetized rat studies through pudendal, clitoral, and pelvic nerve stimulation.[24–27] In these experiments, stimulation-driven genital arousal was evaluated through blood engorgement or perfusion of the vagina, measured with laser Doppler flowmetry (LDF). These experiments showed that short-duration pudendal, clitoral, and pelvic nerve electrical stimulation can cause a brief, transient increase in vaginal blood perfusion (VBP). Increases in vaginal blood flow also has been seen in sexually aroused women.[28] These responses can be dependent on the frequency of stimulation.[25] Vaginal luminal diameter in anesthetized rats also has been shown to increase concurrently with blood flow during genital arousal driven by acute nerve stimulation.[29]

There is evidence that the level of genital arousal in female rats can be evaluated through analysis of slow oscillations in vaginal blood flow.[28,30] Numerical computer models and experiments using rat models have shown that the frequency domain analysis of blood flow LDF signals can be segmented into cardiac, respiration, myogenic, neurogenic, and endothelial-related metabolic activities.[31,32] The neurogenic frequency range for micro blood perfusion oscillations is 0.076 to 0.200 Hz. Neurogenic oscillations are associated with sympathetically driven changes in microvascular perfusion, as would be the expected mechanism in sexual arousal.[33] An analysis of this blood flow parameter could yield further insights than prior use of LDF alone.

This exploratory study investigated the ability to drive genital sexual arousal with tibial nerve electrical stimulation. This report also introduces a novel method of analyzing genital blood perfusion as an arousal response through the evaluation of wavelet analysis of neurogenic LDF oscillations. This wavelet analysis was used to determine the ability of long-duration tibial nerve stimulation to drive prolonged increases in VBP. The goal of this study was to further establish PTNS as a potential treatment option for women with sexual dysfunction and investigate the relation between stimulation and VBP.

METHODS

Animals

All procedures were approved by the local institutional animal care and use committee in accordance with the National Institutes of Health's guidelines for the care and use of laboratory animals. Animals were housed under standard conditions. Experiments were conducted in 16 nulliparous female Sprague-Dawley rats (Charles River Breeding Labs, Wilmington, MA, USA) weighing 210 to 310 g. The animals were anesthetized with a cocktail of ketamine, xylazine, and acepromazine (90, 7.5, and 1.5 mg/kg, respectively) during surgery and maintained with ketamine (30 mg/kg every 30 minutes) during testing, because ketamine has been used in similar studies evaluating sexual arousal in sedated rats.[25,34,35] The temperature was maintained at 37°C with a heating pad and monitored with a rectal thermometer. Heart rate, respiration rate, and oxygen saturation levels were monitored and recorded every 15 minutes. A vaginal lavage was performed after anesthesia induction before surgery to determine the estrous stage.[36]

The tibial nerve was accessed on the right hind limb above the ankle on the medial side. A bipolar nerve cuff with stranded stainless steel wire (0.016-inch diameter; Cooner Wire Co, Chatsworth, CA, USA) and silicone elastomer tubing (1-mm inner diameter; Dow Corning, Midland, MI, USA) was placed around the nerve and connected to an Isolated Pulse Generator (Model 2100, AM Systems, Carlsborg, WA, USA). In the last 13 experiments, the bladder was manually drained and a catheter (polyethyline-50) was inserted 3 cm through the urethra into the bladder and connected to pressure transducer (DPT-100, Utah Medical Products, Inc, Midvale, UT, USA) and a Grass amplifier (Model CP511 High Performance AC Preamplifier, Astro-Med, Inc, West Warwick, RI, USA). The bladder drained around the catheter throughout the procedure. VBP was assessed using a laser Doppler probe (MNP110XP, ADInstruments, Colorado Springs, CO, USA) connected to a Blood FlowMeter (50-Hz sampling rate; INL191, ADInstruments). The Blood FlowMeter measures blood perfusion on a scale of 0 to 5,000 arbitrary blood perfusion units. The probe was inserted 1 to 2 cm into the