THE JOURNAL OF
SEXUAL MEDICINE

Reduced Lordosis and Enhanced Aggression in Paced and Non-Paced Mating in Diabetic Female Rats

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ABSTRACT

Background: Clinical studies have shown altered sexual function in people with diabetes; basic science studies, using the streptozotocin (STZ)-induced animal model of type 1 diabetes mellitus (DM1), have consistently reported decreased sexual behavior in hyperglycemic female animals, but features of sexual motivation and aggressive behavior have not been explored in these animals.

Aim: To study several parameters that denote sexual motivation in STZ-treated female rats and to compare behavioral features of sexual behavior and aggression in non-paced mating (NPM) and paced mating (PM) conditions.

Methods: DM1 was induced by injecting STZ (diluted in citrate buffer) at a dose of 50 mg/kg intraperitoneally over 2 consecutive days into ovariectomized Wistar rats. 10 days later, female rats were treated with estradiol benzoate (10 μg, -24 hours) and progesterone (3 mg, -4 hours); their sexual behavior (including lordosis quotient, lordosis intensity, and proceptivity) and aggression were evaluated under NPM and PM conditions. Body weight, blood glucose levels, and spontaneous ambulatory activity also were measured. A group of STZ-treated animals was administered a long-acting insulin analogue (glargine) every 12 hours for 8 days, and their sexual and aggressive behaviors were evaluated in NPM.

Outcomes: We quantified body weight, blood glucose level, spontaneous ambulatory activity, and sexual and aggressive behaviors in NPM and PM; the time the female rats spent interacting with the male rat or in the male rat's chamber also was registered in PM.

Results: Compared with controls, STZ-treated ovariectomized rats lost body weight, had increased blood glucose levels, and had unchanged spontaneous ambulatory activity. In the PM and NPM conditions, animals showed decreased lordosis quotient and lordosis intensity, increased aggression, and unaltered proceptivity, although in NPM the effects of STZ treatment on aggression were more drastic and were completely prevented by insulin. In PM no differences were found between diabetic and control female rats in the time interacting with the male rat or in the male rat's chamber.

Clinical Translation: These findings support the observation of increased prevalence of sexual dysfunctions and aggression in the clinical setting of DM1.

Strengths and Limitations: The main strength of this study is that it analyzed sexual behavior under PM and NPM conditions and aggression in STZ-treated female rats. Its main limitations are that the model of DM1 represents only 10% of the affected population and that no specific treatment is proposed for the sexual dysfunctions.

Conclusion: These results suggest that STZ-treated rats have decreased sexual receptivity in NPM and PM, accompanied by increased aggressiveness in NPM. **Hernández-Munive AK, Rebolledo-Solleiro D, Ventura-Aquino E, Fernández-Guasti A. Reduced Lordosis and Enhanced Aggression in Paced and Non-Paced Mating in Diabetic Female Rats. J Sex Med 2017;XX:XXX–XXX.**

Key Words: Sexual Dysfunction; Streptozotocin-Induced Diabetes; Female Rats; Paced Mating; Non-Paced Mating; Aggression

Received August 28, 2017. Accepted November 16, 2017.

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https://doi.org/10.1016/j.jsxm.2017.11.018

INTRODUCTION

Type 1 diabetes mellitus (DM1) is a chronic autoimmune disease characterized by high blood glucose levels (BGLs) owing to low or absent insulin pancreatic production.[1] In male animals, including men, there is a large amount of information relating diabetes to sexual dysfunctions.[2,3] In female animals (including women), this information is less abundant, and although some researchers have reported an increase in the incidence of sexual dysfunctions,[2,4,5] others have failed to find alterations.[6–8] The nature of this difference remains unclear but could be related to the diabetes type,[9–11] the difficulties of many women in expressing sexual dysfunctions[3,12] and other factors associated with diabetes, such as depression, importance of a satisfactory sexual life, and marital status.[12–14] In addition, low sexual desire and motivation is a common complaint in women with diabetes[12,15,16] and has been one of the least studied parameter in animal models.

Female rat sexual behavior includes lordosis and proceptivity. Lordosis is defined as the dorsiflexion reflex posture with the consequent pelvic elevation that allows penile intromissions[17–19] and depends mainly on estrogen actions.[20,21] Lordosis is usually preceded by proceptivity, which is composed of a series of behaviors that invite the male animal to initiate and maintain mating. In the rat, proceptivity includes ear wiggling (rapid alternating movements of the head that provokes vibrations of the ears), hopping (a short leap with the female rats landing on all 4 paws followed by the assumption of a crouching posture), and darting (a run of several steps abruptly terminated).[22,23] These behaviors are considered to reflect sexual motivation.[17,24–26] In contrast with lordosis, proceptivity relies on progesterone effects in estrogen-primed animals.[19,22,23]

Various works have experimentally shown that female sexual behavior is decreased in rats treated with streptozotocin (STZ), a pancreotoxin that destroys β-cells producing hypoinsulinemia and hyperglycemia, that is frequently used to model DM1. These reports have consistently shown that STZ-treated female rats display a lower lordosis quotient (LQ) than controls[27–33] and some have suggested that these female rats also have decreased proceptive behaviors.[30,31] The decreased LQ and proceptivity exhibited by hyperglycemic rats is reversed by systemic[31] or central (intracerebroventricular)[32] insulin administration, suggesting an important role for this hormone and its receptors in the brain in modulating sexual behavior.

Most inhibitory effects of STZ on female sexual behavior have been observed in ovariectomized (OVX) female rats exogenously treated with estradiol plus progesterone[27–33] and, to our knowledge, there is a single report that has studied sexual behavior in naturally cycling rats treated with STZ.[34] Most studies use OVX rats because STZ alters the normal sequence of the estrous cycle and drastically decreases the number of natural proestrus cycles (when the female rat is sexually receptive) at the expense of an increase in the number of diestrus cycles.[35] In consequence, STZ administration to intact female rats dramatically decreases their "availability" to display sexual behavior.[34]

It is important to mention that all studies analyzing the effect of diabetes on female rats' sexual behavior have been performed under copulating conditions that are not rewarding for the female rat, such as non-pacing or non-paced mating (NPM).[29–33] In this paradigm, the male rat regulates the timing of copulation and the female rat cannot avoid the male rat's closeness. Therefore, the female rat displays some aggressive behaviors intended to maintain her rhythm of copulation. In contrast, there is another situation in which the female rat regulates copulation that is attained by using laboratory-mating arenas, divided by a wall, with a small opening, through which the female, but not the male rat, can easily pass from one chamber to the other because of its smaller size.[36–38] Under this paradigm, the aggression toward the male rat is decreased compared with that shown in NPM and the rate of copulation is slower. After sexual stimulation (mount, intromission, or ejaculation), the female rat can leave the male rat's compartment through the hole but can return later,[39] resulting in longer intervals between 1 stimulation and another than those found when the male rat regulates mating.[36] This procedure is known as paced mating (PM) or pacing.[36,37,40–42] In this test, in addition, the return latencies to the male rat's compartment after a sexual stimulation generally denote the female rat's motivation to continue copulating, whereas the percentage of exits after each male sexual behavioral parameter is related to the female rat's capacity to discriminate the sensory stimulation it has received.[37,40–42] Thus, pacing permits the analysis of parameters that denote sexual motivation and sensory perception.

The main goal of the present series of experiments was to study several parameters that denote sexual motivation in STZ-treated female rats. Thus, we analyzed and compared the effects of STZ on female sexual behavior, hormonally induced in OVX rats, under NPM and PM. In addition, we examined whether the effects of STZ could be reverted by exogenous insulin. We hypothesized that the inhibitory action of STZ would be milder under pacing than in a situation in which the female rat could not time copulation, and that these effects would be reverted by insulin supplementation.

METHODS

Animals

15 young adult sexually experienced male (350–450 g) and 46 OVX female (250–300 g) Wistar rats were used in this study. All animals were kept in general laboratory conditions and were housed in groups of 7 per cage in a temperature-controlled room under a reversed 12-hour light and 12-hour dark cycle, starting the dark phase at 10:00 AM. Food and water were available ad libitum. All procedures were done in accordance with the guidelines of the Laws and Codes of Mexico (Seventh Title of the Regulations of the General Law of Health Regarding Health Research) following the guidelines of the National Institutes of Health for the use of animals. The institutional animal care and use committee approved all procedures.