ORIGINAL RESEARCH—BASIC SCIENCE

Restoration of Female Genital Vasocongestive Arousal Responses in Young and Aged Rats

Rochard K.S. Beharry,* Taben M. Hale,† Jeremy P.W. Heaton,* Rany Shamloul,*‡ and Michael A. Adams*

*Queen's University—Department of Pharmacology and Toxicology, Kingston, Ontario, Canada; †University of Montreal—Department of Pharmacology, Montreal, Quebec, Canada; ‡Department of Andrology, Sexology and STDs, Cairo University, Cairo, Egypt

DOI: 10.1111/j.1743-6109.2007.00750.x

ABSTRACT

Introduction. Treatments of aged, male hypertensive rats that induce vascular remodeling or that normalize endothelial function are known to produce sustained improvements in erectile function. Whether the treatments targeting these processes benefit female genital vasocongestive arousal (GVA) responses is currently not known.

Aim. To determine whether the actions of nitric oxide (NO) are critical to the apomorphine (APO)-generated GVA responses in both intact and ovariectomized OVX young adult female rats (before any aging-associated decreases in the responses). In addition, we also investigated whether the diminished GVA responses in aged rats could be restored, at least in part, using an antihypertensive treatment, which is known to enhance erectile responses and improve general vascular function in male rats.

Methods. In female Wistar rats, APO-induced GVA responses (80 μg/kg, subcutaneously [sc], 30 minutes) were assessed by videomonitoring following various treatments. Young adult females were ovariectomized or were treated with the nitric oxide synthase (NOS) inhibitor N-nitro-L-arginine methyl ester (30 mg/kg, iv), followed by an NO mimetic, sodium nitroprusside (10 μg/kg/minute, intravenous). Aged females (18 months) were treated for 2 weeks with the angiotensin converting enzyme (ACE) inhibitor, enalapril (30 mg/kg/day, orally) plus low sodium (0.04%).

Main Outcome Measures. APO-induced GVA responses in female rats.

Results. There was an age-associated reduction in sexual responses in normotensive rats that was greatly enhanced (fourfold) by brief, aggressive antihypertensive treatment. The enhanced vasocongestive responses persisted for a 5-week off-treatment. Both OVX and NOS inhibition significantly decreased sexual responses by approximately 80% in young female rats. Systemic administration of an NO mimetic recovered vasocongestive responses in the NOS-blocked rats, but not in OVX animals.

Conclusions. Although mechanisms were not established, the major findings were that brief aggressive ACE inhibitor treatment markedly improved sexual responses in aged female rats, and systemic delivery of an NO mimetic recovered sexual responses in globally NOS-blocked animals. **Beharry RKS, Hale TM, Heaton JPW, Shamloul R, and Adams MA. Restoration of female genital vasocongestive arousal responses in young and aged rats. J Sex Med 2008;5:804–812.**

Key Words. Female Sexual Responses; Apomorphine; Genital Vasocongestive Arousal

Introduction

Female sexual dysfunction (FSD), as described in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [1], includes disorders of sexual interest/desire, arousal, orgasm, and pain. Although the measurement instruments of FSD differ between epidemiological studies [2], it is generally agreed that there is some level of dysfunction in approximately 40% of women even between the ages of 18 and 41 [3], and an even higher prevalence in older women [4]. Despite this

prevalence, there are still no approved treatments for this condition.

While FSD research, in general, has expanded substantially in the past decade, there are still insufficient experimental models to facilitate the full understanding of just the physiology and pathophysiology of this condition, never mind the psychological aspects. Pfaus et al. [5] wrote a comprehensive review of the literature pertaining to animal models of the human sexual responses in which they indicated that female arousal responses, in particular, had received much less attention than had erectile responses in men [5]. In that regard, to try to further the understanding of the physiology and pathophysiology of the female response, we recently developed a conscious animal model of female genital vasocongestive arousal (GVA) responses [6]. In this model, a centrally acting, mixed dopaminergic agonist, apomorphine (APO), is administered at low doses to promote the activation of a pathway that links hypothalamus stimulation to peripheral genital responses. In particular, these responses included multiple occurrences of specific behaviors that were temporally coupled with genital vasculogenic engorgement within 30 minutes [6]. Bechara et al. [7] and Caruso et al. [8] both used low-dose APO to enhance various indices of physiological responses (vasculogenic engorgement, vaginal lubrication, and clitoral hemodynamics) in adult women. Thus, APO treatment has been shown to produce both behavioral and physical responses in women and female rats, which are homologous with those obtained with APO-induced erectile responses both in men and male rats [7–9]. This vasculogenic engorgement of the female genital area, herein termed genital vasocongestive arousal (GVA), is a significant physiological component of a sexual arousal response [10,11]. For example, the occurrence of a GVA involves a blood flow-dependent engorgement of the external genitalia and widening of the introitus over a time interval (2–3 seconds) [9] consistent with sexual activity in rats. Furthermore, the ancillary behavioral responses in females that are temporally linked to the GVAs were found to be similar to those in males including the "startle" response, arching of the back, and genital grooming [10].

Although not as well established as it is in males, there is an association between increasing age, the progression of cardiovascular disease (e.g., hypertension), and the incidence and severity of FSD [12,13]. Complicating the issue further, some studies have suggested that similar to men, women may experience diminished sexual function with certain medications used to treat hypertension [13]. In this regard, we previously demonstrated in aged, male hypertensive rats that treatment with antihypertensive drugs that are known to induce vascular remodeling results in a sustained improvement in erectile function [14]. Whether the same treatment benefits occur for female GVA response is currently not known.

While the physiology of a female sexual response has not yet been fully elucidated, evidence to date suggests that nitric oxide (NO) plays a major role, at least in the physiological component of the response [15,16]. Both the vagina and clitoris have been shown to be abundantly innervated by NO-producing neurons [17,18]. During stimulation at the level of the genitalia, NO has been suggested to mediate, at least in part, smooth muscle relaxation via a cyclic guanosine monophosphate-dependent mechanism [19]. In addition to peripheral vasodilation, NO may also be involved in mediating hypothalamic mechanisms of sexual arousal by regulating the release of dopamine and serotonin [20]. Interestingly, previous studies have demonstrated a dependence of the NO pathway on the actions of endogenous hormones [21–23]. For example, estrogen has been shown to increase nitric oxide synthase (NOS) activity both in the hypothalamus [22] and in the periphery (vagina) [23]. Although the critical role of NO for sexual responses has been demonstrated in male rats, where NOS inhibition prevented APO-induced erections [23], similar studies have not been performed in females.

The model of APO-generated GVA responses in female rats has previously been established and shown to be, at least in part, dependent on the hormonal milieu, i.e., varying with the stage of the estrous cycle [6]. In the present study, we have extended this work to test the hypotheses that APO-induced GVA responses in female rats are also dependent, at least in part, on the actions of (i) ovarian hormones, (ii) NO, and (iii) an appropriate circulatory state. To accomplish this assessment, given the recognized significance of NO in mediating penile erections in males, one objective was to examine whether the actions of NO were critical to the APO-generated GVA responses in both intact and ovariectomized (OVX) young adult female rats (before any aging-associated decreases in the responses). In addition, we also investigated whether the decreased GVA responses that are found in aged female rats could be restored, at least in part, using a pharmacological treatment