# Exercise Training Improves the Defective Centrally Mediated Erectile Responses in Rats with Type I Diabetes

Hong Zheng, MD, William G. Mayhan, PhD, and Kaushik P. Patel, PhD

Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE, USA

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**ABSTRACT**

***Introduction.*** Erectile dysfunction is a serious and common complication of diabetes mellitus. Apart from the peripheral actions, central mechanisms are also responsible for the penile erection.

***Aim.*** The goal of the present study was to determine the impact of exercise training (ExT) on the centrally mediated erectile dysfunction in streptozotocin (STZ)-induced type I diabetic (T1D) rats.

***Methods.*** Male Sprague–Dawley rats were injected with STZ to induce diabetes mellitus. Three weeks after STZ or vehicle injections, rats were assigned to either ExT (treadmill running for 3–4 weeks) or sedentary groups to produce four experimental groups: control + sedentary, T1D + sedentary, control + ExT, and T1D + ExT.

***Main Outcome Measure.*** After 3–4 weeks ExT, central N-methyl-D-aspartic acid (NMDA) or sodium nitroprusside (SNP)-induced penile erectile responses were measured. Neuronal nitric oxide synthase (nNOS) expression in the paraventricular nucleus (PVN) of the hypothalamus was measured by using histochemistry, real time polymerase chain reaction (PCR) and Western blot approaches.

***Results.*** In rats with T1D, ExT significantly improved the blunted erectile response, and the intracavernous pressure changes to NMDA (50 ng) microinjection within the PVN (T1D + ExT: $3.0 \pm 0.6$ penile erection/rat; T1D + sedentary: $0.5 \pm 0.3$ penile erection/rat within 20 minutes, $P < 0.05$). ExT improved erectile dysfunction induced by central administration of exogenous nitric oxide (NO) donor, SNP in T1D rats. Other behavior responses including yawning and stretching, induced by central NMDA and SNP microinjection were also significantly increased in T1D rats after ExT. Furthermore, we found that ExT restored the nNOS mRNA and protein expression in the PVN in T1D rats.

***Conclusions.*** These results suggest that ExT may have beneficial effects on the erectile dysfunction in diabetes through improvement of NO bioavailability within the PVN. Thus, ExT may be used as therapeutic modality to up-regulate nNOS within the PVN and improve the central component of the erectile dysfunction in diabetes mellitus. **Zheng H, Mayhan WG, and Patel KP. Exercise training improves the defective centrally mediated erectile responses in rats with type I diabetes. J Sex Med 2011;8:3086–3097.**

***Key Words.*** Type I Diabetes; Exercise Training; Central Nervous System; Central Mechanisms of Penile Erection

## Introduction

Sexual dysfunction is a well-known consequence of diabetes mellitus in men [1,2]. Erectile dysfunction, retrograde ejaculation, and loss of seminal emission have been described in male diabetic patients. Approximately 35% to 75% of men with diabetes mellitus have erectile dysfunction [3]. In animal experiments, diabetic rats show significant deficits in mount, intromission, and ejaculatory behaviors, suggesting that both the sexual arousal (libido) and potency components of male sexual behavior are adversely affected by diabetes [4]. The primary therapy for men with diabetes and erectile dysfunction is oral administration of phosphodiesterase type 5 (PDE5) inhibitors, such as Viagra. Consistent with these observations, there is a deceased expression of PDE5 in penile tissue from a diabetic animal model [5]. However, approximately 50% of male patients with diabetes are unresponsive to this treatment [6]. Because the actions of PDE5 inhibitors are thought to affect

the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis, it is possible that other components of the erectile response, including the initiating central mechanisms independent of PDE5, may contribute to the altered erectile dysfunction in diabetic males. The contribution of the central component of the altered erectile dysfunction in diabetes is generally understudied to date.

It is generally accepted that different central and peripheral neural and/or humoral endocrine mechanisms participate in the regulation of sexual response. Penile erection is the result of a complex central and peripheral interaction that induces muscle and vascular changes at the level of the erectile tissues. Regarding the central mechanism, several neurotransmitters and neuropeptides that control erectile function, including excitatory amino acid, N-methyl-D-aspartic acid (NMDA), dopamine, nitric oxide (NO), oxytocin, gamma-amino-butyric acid and opioid, have been identified [7]. These compounds act in several brain areas, including the paraventricular nucleus (PVN) of the hypothalamus [8,9], which convey information to the genitals via projections from the spinal cord.

The PVN of the hypothalamus is involved in numerous functions including feeding, metabolic balance, cardiovascular regulation, as well as erectile function and sexual behavior. Bilateral lesions of the PVN dramatically reduce the erectile effects of several compounds [10]. Activation of the PVN neurons by central components such as NMDA, or by electrical stimulation, leads to penile erection [11,12]. Our previous study demonstrated that penile erection occurs concomitantly in response to administration of NMDA directly into the PVN [13]. Administration of NMDA within the PVN demonstrated a decreased response in penile erection, yawning, and stretching in diabetic rats [13]. It is further observed that the level of neuronal nitric oxide synthase (nNOS) protein is decreased in rats with diabetes compared with control rats. Previously, we also measured penile erection, yawning, and stretching before and after the administration of adenoviral transfection of nNOS gene into the PVN of control and diabetic rats [13]. The results showed that restoration of nNOS within the PVN of diabetic rats with viral transfection corrects the behavioral responses (erection and yawning) mediated by microinjection of NMDA. This suggests an abnormality in NO mechanism in the central nervous system specifically within the PVN, which is involved in the altered erectile responses in diabetic rats.

Clinical and experimental studies have shown the benefits of exercise training (ExT) in type I diabetic (T1D) by insulin sensitivity improvement, reduction in insulin requirement, and an attenuation of autonomic and cardiovascular dysfunction [14,15]. It has been shown that long-term regular ExT benefits the vascular health and erectile function of patients with erectile dysfunction and diabetes [16–18]. However, the mechanisms by which ExT improves the status of diabetic patients and animals remain unclear. Running exercise can enhance the functional response of rats' corpus cavernosum by increasing the NO-cGMP signaling pathway [19,20]. Exercise training also elicits a beneficial effect on the impaired corpus cavernosum, relaxing responses in rats with diabetes [21]. Although ExT has been shown to enhance endothelial function in the patients and animals with T1D [22,23], there are little data on the role of ExT in the modulation of central component of erectile function. In other studies, we have previously demonstrated that ExT restores the levels of nNOS with the PVN of rats with chronic heart failure [24]. Whether ExT improves this central nNOS within the PVN of rats with diabetes remains to be examined.

## Aims

The aims of our study were to test (i) whether ExT improves centrally NMDA-induced erectile dysfunction in rats with T1D; (ii) whether ExT improves centrally mediated sodium nitroprusside (SNP)-induced erectile dysfunction in rats with T1D rats; and (iii) whether the nNOS system is restored in the PVN of ExT T1D rats.

## Methods

### *Animal and Treatment*

This study was approved by the University of Nebraska Medical Center Institutional Animal Care and Use Committee, and conformed to the guidelines for the care and use of laboratory animals of the National Institutes of Health and the American Physiological Society. Male Sprague–Dawley rats (200–220 g, Sasco) were randomly injected with streptozotocin (STZ) (65 mg/kg i.p) to induce diabetes or vehicle (citrate buffer) for controls. The percentage of diabetic animals after STZ injection was about 80%. Onset of diabetes was identified by polydipsia, polyuria, and blood glucose levels of >250 mg/dL. The