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Taurine Supplementation Improves Erectile Function in Rats with Streptozotocin-induced Type 1 Diabetes via Amelioration of Penile Fibrosis and Endothelial Dysfunction

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ABSTRACT

Introduction: For patients with diabetes, erectile dysfunction (ED) is common and greatly affects quality of life. However, these patients often exhibit a poor response to first-line oral phosphodiesterase type 5 inhibitors.

Aim: To investigate whether taurine, a sulfur-containing amino acid, affects diabetic ED (DED).

Methods: Type 1 diabetes mellitus was induced in male rats by using streptozotocin. After 12 weeks, an apomorphine test was conducted to confirm DED. Only rats with DED were administered taurine or vehicle for 4 weeks. Age-matched nondiabetic rats were administered saline intraperitoneally for 4 weeks.

Main Outcome Measures: Erectile function was evaluated by electrical stimulation of the cavernous nerve. Histologic and molecular alterations of the corpus cavernosum also were analyzed.

Results: Erectile function was significantly reduced in the diabetic rats compared with in the nondiabetic rats, and was improved in the diabetic rats treated with taurine. The corpus cavernosum of the rats with DED exhibited severe fibrosis and decreased smooth muscle content. Deposition of extracellular matrix proteins was increased in the diabetic rats, while expression of endothelial nitric oxide synthase/cyclic guanosine monophosphate/nitric oxide pathway—related proteins was reduced. Taurine supplementation ameliorated erectile response as well as histologic and molecular alterations.

Conclusion: Taurine supplementation improves erectile function in rats with DED probably by potential antifibrotic activity. This finding provides evidence for a potential new therapy for DED.

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Key Words: Taurine; Diabetes; Erectile Dysfunction; Fibrosis; Extracellular Matrix

INTRODUCTION

Erectile dysfunction (ED), defined as the inability to attain or maintain a penile erection sufficient for successful vaginal intercourse, is becoming more common worldwide.[1] Approximately 15% to 20% of the general male population experiences ED.[2,3] Patients with diabetes are nearly 3 times more likely to suffer from ED compared to patients without diabetes. In addition, ED appears to arise 10 years earlier in patients with diabetes and tends to be more severe, significantly decreasing health-related quality of life.[4] Furthermore, the prevalence of ED is 95% in patients with diabetes above the age of 60.[3]

Introduction of phosphodiesterase type 5 (PDE5) inhibitors revolutionized the treatment of ED. PDE5 inhibitors enhance nitric oxide (NO)-mediated relaxation of the corpus cavernosum by preventing cyclic guanosine monophosphate (cGMP) degradation. Currently, PDE5 inhibitors are the first-line therapy for ED.[5—6] However, because ED is caused by multiple factors, a certain proportion of patients, especially those with diabetes, exhibit a poor response to PDE5 inhibitors.[7] Moreover, the failure rate for all PDE5 inhibitors is higher in men with diabetes than in men without.[8] In addition, diabetes could induce a series of pathophysiologic changes that could contribute to the decreased response to PDE5 inhibitors. Therefore, it is urgent to develop novel treatment modalities for men with diabetic ED (DED).

Taurine (2-aminoethanesulfonic acid), a sulfur-containing amino acid, is one of the most abundant free amino acids in the human body. It plays a role in several physiologic functions, including neuromodulation or neurotransmission, modulation of calcium flow, osmoregulation, stabilization of membranes, and bile formation in the liver.[9] Data from existing studies have

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indicated that taurine might decrease cholesterol level, control high blood pressure, and have protective potential in the cardiovascular system.[10] Previous studies also have shown a beneficial effect of taurine on diabetes-associated complications. Importantly, it has been demonstrated that taurine supplementation can enhance sexual response and mating ability in aged rats.[11] However, whether taurine could mitigate DED has not been investigated.

In the present study, we evaluated the effect of taurine in rats with DED in vivo. Our results show that taurine improves erectile function in diabetic rats and could serve as an alternative therapy for ED.

METHODS

Treatment of Animals

This study was approved by the Animal Care and Use Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei, China. Forty-five 8-week-old male Sprague-Dawley rats were used in the present study. After overnight fasting, the rats were injected with freshly prepared streptozotocin (60 mg/kg; Sigma-Aldrich, St. Louis, MO, USA; n = 37) or vehicle (0.1 mol/L citrate-phosphate buffer; pH, 4.2; n = 8; nondiabetic control group) intraperitoneally. Blood glucose levels were measured 72 hours after streptozotocin injection using a blood glucose meter (ACCU-CHEK Performa; Roche Diagnostics, Shanghai, China). Only rats with a fasting glucose concentration $\geq$16.7 mmol/L were considered as diabetic rats (n = 35).

At 12 weeks, 30 diabetic rats survived. An apomorphine (APO) test was conducted to confirm DED. Eighteen APO-negative rats were used for further experiments.[12,13] Rats with DED were administered taurine (400 mg/kg; Sigma-Aldrich; DED + taurine group) or vehicle (saline, DED group) intraperitoneally daily for another 4 weeks (n = 9 per group). This dose of taurine is within the range used in previous studies.[14–16]

In Vivo Erection Studies

At 12 weeks after diabetes was induced, erectile function was evaluated by observing APO-induced erection in all surviving rats. APO was injected into the loose skin of the cervical vertebra subcutaneously (80 μg/kg). Then a camera was set in the bottom of the cage for 30 minutes, and the number of erections was recorded. The criteria for penile erection were based on previous studies as follows: stretching of the penis with a congested glans, repeated pelvic thrusts immediately followed by an upright position, and complete emergence of an engorged glans penis and distal penile shaft; otherwise, the result was negative.[13,17]

At week 16, following a 2-day washout of taurine, intracavernosal pressure (ICP) was measured in all groups as described previously.[18] Under proper anesthesia (pentobarbital sodium, 40 mg/kg, i.p.), the rats were fixed on the table, and the left carotid artery was exposed. A PE-50 tube filled with heparinized saline (100 IU/mL) was cannulated into the artery and connected to a pressure transducer to monitor mean arterial pressure (MAP) continuously. A 25-G needle was inserted into the left penile crura to monitor ICP. Pressure data were recorded by a data acquisition system (PowerLab/4SP; AD Instruments, Bella Vista, Australia). Erectile response was elicited by electrical stimulation using a bipolar electrode hooked to the cavernous nerve. Stimulation parameters were as follows: 7.5 v, 12 Hz, and 1.2 ms; this was judged to cause a maximal reaction.[18–20] The ratio between maximum ICP and MAP (ICP max/MAP) was calculated to normalize for variations in systemic blood pressure. Total ICP was determined by the area under the curve (AUC, mmHg · s) during stimulation.

After finishing these in vivo studies, the rats were sacrificed by intraperitoneal overdose of pentobarbital. Penile midshafts were maintained in 4% paraformaldehyde overnight and embedded in paraffin for subsequent histologic studies. Remaining penile tissues were snap frozen in liquid nitrogen and stored at −80°C for subsequent molecular detection. Blood samples were obtained from rats via the vena cava. The total testosterone levels were measured in the central laboratory of our institution.

Western Blot Analysis

Equal amounts (40 μg/lane) of protein extracts were electrophoresed on 10% sodium dodecylsulfate–polyacrylamide gels, transferred to polyvinylidene fluoride membranes (Immobilon-P Transfer Membrane; Millipore Corporation, Billerica, MA, USA), and probed with antibodies against endothelial nitric oxide synthase (eNOS; 1:500; BD Biosciences, San Jose, CA, USA), plasminogen activator inhibitor type 1 (PAI-1; 1:2500; BD Biosciences), collagen I (1:500; Boster, Wuhan, China), collagen IV (1:500; Proteintech, Wuhan, China), transforming growth factor β1 (TGF-β1; 1:500; Abcam, Cambridge, UK), α–smooth muscle actin (α-SMA; 1:1000; Abcam), or β-actin (1:500; Boster). Primary antibodies were incubated overnight at 4°C followed by incubation with horseradish peroxidase-labeled secondary antibody (1:10,000; Jackson ImmunoResearch, West Grove, PA, USA), then detected with Bio-Rad Clarity Western ECL Substrate (Bio-Rad Laboratories, CA, USA). The resulting image was analyzed using ImageJ software (http://rsb.info.nih.gov/ij) to determine the integrated density value of each protein band.

cGMP Measurement

cGMP was measured in extracts from penile samples using a commercial cGMP enzyme immunoassay kit (Cayman Chemicals Inc., Ann Arbor, MI, USA) following the manufacturer's instructions. Protein content in each sample was measured using the BCA assay and expressed as range of pmol cGMP/mg protein. All samples were analyzed in triplicate.[20]

Histologic Assessment

Penile tissue sections (5 μm thickness) were processed for immunohistochemistry as described previously.[21] The primary antibody was mouse anti–α-SMA (1:150; Boster). Masson's

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