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The Starling mechanism of the urinary bladder contractile function and the influence of hyperglycemia on diabetic rats☆

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Abstract

Diabetic cystopathy is one of the common complications of diabetes. Bladder dysfunction in diabetes is attributable to diabetic neuropathy that induces sensory and autonomic nerve dysfunction. **Materials and Methods:** In the present study, the contractile mechanism of the bladder was evaluated both with and without electrical stimulation in normal rats, streptozotocin (STZ)-induced diabetic rats, and diabetic rats with insulin treatment. **Results:** Both the normal and diabetic rats had optimal capacity of bladder and optimal length of detrusor muscle strips. The peak values of the volume–pressure curves of the bladder and length–tension curves of detrusor muscle strips as well as the enhanced values after electrical stimulation in 6- and 10-week diabetic groups were lower than in the 6- and 10-week normal groups and insulin-treated groups. However, there was no significant difference in peak and enhanced values between normal rats and diabetic rats treated with insulin, indicating that voiding function was improved after insulin treatment. **Conclusions:** The contractile function of rat's bladder including normal rats, diabetic rats, and diabetic rats treated with insulin is similar to the 'Starling mechanism.' It can be impaired by hyperglycemia, and insulin treatment is helpful to restore this function.

Keywords: Sprague-Dawley rat; Diabetic neurogenic bladder; Electric stimulus

1. Introduction

Diabetes is a major health concern that is often accompanied with urological complications. About 40–60% patients with diabetes have diabetic cystopathy or diabetic neurogenic bladder (DNB) (Kitami, 1991), which is characterized by impaired bladder sensation, an elevated threshold for initiating the micturition reflex, and an asymptomatic increase in bladder capacity and retention (Vinik, Maser, Mitchell, & Freeman, 2003). The biology of diabetes-associated bladder complications can be due to an alternation in the detrusor smooth muscle, neuronal dysfunction, and urothelial dysfunction (Brown et al., 2005). It has been reported in streptozotocin (STZ)-induced diabetic rats that decreased nerve growth factor (NGF) levels in the bladder and lumbosacral dorsal root ganglia were associated with bladder dysfunction, and herpes simplex virus type 1 vector–mediated NGF gene therapy may prove useful in improving bladder function (Sasaki et al., 2002, 2004). Because diabetic cystopathy is often irreversible, treatment options for diabetic cystopathy are limited, and it has proven to be difficult to restore bladder function in diabetic patients (Sasaki et al., 2002). So it is important to study the mechanism of bladder function.

In our clinic work, we found that a considerable number of patients with DNB had detrusor muscle contraction weakness and dysuresia, because of overfilling of the bladder. We also found that the achievement ratio of voluntary micturition after extubation in the persistent urethral catheter opening of DNB patients was much higher than timing (2−4 h) urethral catheter opening patients.

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Based on these observations, we supposed that the detrusor muscle of the bladder had similar myocardial contractile function and the role is similar to the 'Starling mechanism' or 'balloon principle,' which means the contraction force of the detrusor muscle rises in response to the increased bladder volume within a certain range, then the contraction force of the detrusor muscle declines in response to the increased volume beyond the range.

Furthermore, our department tried to use electrical stimulation in vitro and persistent urethral catheter opening in the treatment of DNB patients. The effect was satisfactory and the treatment significantly decreased, even eliminated, the volume of bladder residual urine (BRU) in DNB patients. However, the mechanism and effect were not fully elucidated; further research is still needed to explore the specific mechanism.

This study proceeded with establishing the model of diabetic rats, to validate the Starling mechanism of the detrusor muscle by the variation measurement of volume–pressure curves of the urinary bladder and length–tension curves of detrusor muscle strips both with and without electrical stimulation. In order to approach the pathophysiological mechanism and pathology basis, we used the detrusor muscle of Sprague-Dawley (SD) rats as research object and studied the changes in pathophysiology and histomorphology, and the influence of electrical stimulation and insulin treatment. Eventually, our work would better understand the function of the detrusor muscle in DNB patients and induce the optimal treatment.

2. Material and methods

2.1. Experimental animals

Ninety-eight female SD rats (230-280 g), purchased from the Experimental Animal Central of Guangzhou Traditional Chinese Medicine University (Guangzhou, China), were housed in a light- and humidity-controlled room and given free access to food and water. All the rats were kept on a 12/12-h light–dark cycle. Twenty-eight of 98 SD rats were picked randomly for the control groups: 14 for the 6-week control group (group 6W.Con) and 14 for the 10-week control group (group 10W.Con). After an overnight fast, SD rats were rendered diabetic (group STZ-D, n=70) by a single intraperitoneal injection of 60 mg/kg body weight STZ (Sigma, St. Louis, MO, USA) dissolved in 0.1 mol/l citrate buffer, pH 4.5. Control groups received the same volume of citrate buffer alone. Animals were studied for 6 weeks (group 6W.STZ-D, n=17) and 10 weeks (group 10W.STZ-D, n=18) after diabetes induction. Three days after STZ injection, diabetic rats received once daily subcutaneous injections of Novolin NPH insulin (Novo Nordisk, Bagsvaerd, Denmark; 2–6 U at 8:00 a.m.) (group STZ-I) for 6 weeks (group 6W.STZ-I, n=16) and 10 weeks (group 10W.STZ-I, n=16). There were three, four, two, and two diabetic rats that died in each group, respectively; it means that 14 rats completed the trial in every group. Seven rats were picked randomly for volume–pressure curve measurement of the urinary bladder, and seven rats were picked randomly for length–tension curve measurement of detrusor muscle strips in every group, respectively. All protocols described in this article were performed according to the rules of our local ethics committee for animal experimentation.

2.2. Measurement of blood glucose

A single drop of tail blood was used to measure glucose via a glucometer (OneTouch SureStep, Johnson & Johnson, Inc., Milpitas, CA, USA). Development of diabetes (blood glucose >250 mg/dl) was verified 3 days and 4 weeks after STZ injection.

2.3. Measurement of volume–pressure curve of the urinary bladder in vivo

After the rats were anesthetized with chloral hydrate (300 mg/kg wt ip; manufacturing laboratory of Shenzhen People's Hospital, Shenzhen, China), the bladder was exposed with a lower midline abdominal incision. The ureter on each side was ligated and a polyethylene catheter (PE-50; Nihon Becton Dickinson, Tokyo, Japan) was inserted into the bladder through the external urethral orifice for the collection of BRU. After the surgery, cystometry was performed under anesthetized condition. The intravesical catheter was connected via a three-way stopcock to a pressure transducer (SJ-1; Space Medico-Engineering Institute of China, Beijing, China) and a syringe for recording intravesical bladder pressure and infusing saline into the bladder, respectively (Sasaki et al., 2002). 0.2 ml saline at room temperature (20–22°C) was infused into the bladder with a syringe every time continuously and the intravesical pressure was recorded with a four-channel physiograph (BL-410; Chengdu TME Technology Co Ltd., Chengdu, China). When 0.4, 0.8, 1.2, …, 2.8 ml saline was injected, respectively, the mean value of intravesical pressure was recorded, double-wire stimulation electrodes were placed in the middle of the bladder, and then electrical stimulation (10 mA, 20 Hz) with a pulse duration of 0.5 ms was applied. It took about 30 s to reach a stable value; the mean and maximum intravesical pressure was recorded after being stimulated continually for 6 s and then the volume–pressure curve of both without and with electrical stimulation was drawn. We also calculated the variance value after stimulation, drew its volume–pressure curve, and recorded the mean and maximum value, too.

2.4. Measurement of initial length–tension curve of isolated detrusor muscle strips

The rats were stunned by a blow to the head. Their urinary bladders were rapidly removed and placed in 4°C Krebs solution (in millimolars: NaCl 118, KCl 4.75, $CaCl_2$ 2.5,