THE EFFECTS OF PEPTIDERIC G NERVE (CALCITONIN GENE-RELATED PEPTIDE, CGRP) AND CALCIUM-RELATED CONTRACTION ON THE VOIDING DYSFUNCTION AND HISTOPATHOLOGICAL ALTERATION IN THE DIABETIC CYSTOPATHY RATS

Hypothesis / aims of study
To investigate the effects of calcitonin gene-related peptide (CGRP) and calcium-related contraction on the urinary bladder voiding dysfunction and histopathological alteration in streptozotocin-induced diabetic rats and reveal the relations between peptidergic nerve and Calcium and diabetic neurogenic bladder.

Study design, materials and methods
Sprague-Dawley male rats were divided randomly into two groups: normal control(NC) and diabetes mellitus (DM). The number of rats in each group is 20. The diabetic rat was induced by intraperitoneal injection of streptozotocin (60 mg/kg). The diabetic rats were successfully accepted by measuring fasting serum glucose concentration more than 12 mmol/L continually three times. All experimental rats received free access to food and water and were reared in SPF environmental. After eight weeks, the bladder wet weight, cystometrogram, contractile responses to electrical field stimulation (EFS) and acetylcholine (ACh). The changes of the detrusor strip contractility in calcium solution(2.5 mmol/L), low calcium solution(0.25mmol/L) and calcium-free solution(0 mmol/L) were detected. The expression of CGRP mRNA in each rats’ dorsal root ganglion(DRG) were measured by RT-PCR and the expression levels of CGRP of bladder and DRG were detected by Western-Blot. Detrusor muscle ultrastructure and histopathological alteration were observed.

Results
Compared with NC group, the bladder wet weight, the volume threshold for micturition and post-voided residual volume and bladder capacity were significantly increased in the diabetic rats. However, maximum intravesical pressure, contractile responses to EFS and Ach in the detrusor strips were dramatically decreased in DM group. The content of the mRNA of CGRP of DRG and bladder in diabetic rats was much lower than that of the controls (DRG: 0.54 ±0.02 vs. 1.13 ±0.01 and bladder: 0.46 ±0.02 vs. 1.07 ±0.04, P<0.01). The relation between thebladder contractility and different concentrations of external environment(extracellular calcium) displayed that contract force produced from DM group was more lower than control rats did. Histopathological studies showed that the detrusor cells expressed compensatively hypertrophy, intracellular collagen fibers increased obviously and mitochondra swelled in the bladder muscle unltrastructure of diabetic rats.

Interpretation of results
Over 8 weeks, diabetic cystopathy in experimental rats came to a discompensatory stage, an impaired sensation of bladder fullness, increased bladder capacity, reduced bladder contractility and increased residual urine were all observed in our study. Urinary bladder dysfunction is a recognized complication of diabetes mellitus (DM) and has been attributed mostly to peripheral autonomic neuropathy and myogenic lesions. CGRP as a non-adrenergic, non-cholinergic neurotransmitter play vital important role in sensation of bladder fullness. The decrease in the content of CGRP can lead to functional alternations in autonomic neurotransmission, especially signal transduction pathways, which followed by enlarged and atomic bladder. Intracellular collagen fibers increased obviously and mitochondra swelled in the bladder muscle unltrastructure of diabetic rats can influence two types of Ca2+ release in the sarcoplasmatic reticulum of smooth muscle cells: ryanodine-receptor mediated Ca2+ release and inositol 1,4,5-trisphosphate-induced Ca2+ release. Our study showed the histopathological alteration in the diabetic bladder and the concentration of extracellular calcium can adjust the contractility in the detrusor strip.

Concluding message
Calcitonin gene-related peptide(CGRP) and calcium-related contraction play an important role in the urinary bladder voiding dysfunction and histopathological alteration in streptozotocin-induced diabetic rats and their relations with each another are closely in our study. How to enhance the contents of CGRP in bladder and DRG and maintain the constant concentration of calcium in diabetic bladder may be a key to solve and treat the diabetic cystopathy.

References

Specify source of funding or grant
| Nanjing Science and Medical Research Council Grant( YKK043, ZKX08016) |

Is this a clinical trial? No

What were the subjects in the study? ANIMAL

Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained? Yes
| Name of ethics committee | Jiangsu Province Animal Research Advisory Committee |