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Title (type in CAPITAL LETTERS, leave one blank line before the text):

URETHRAL RESISTANCE AND NITRIC OXIDE CONTAINING NERVE IN RATS OF NON-INSULIN DEPENDENT DIABETES MELLITUS MODEL

Introduction: Many patients with diabetic neuropathy have voiding dysfunction manifested by an abnormal cystometrogram and a grossly enlarged bladder and no opened bladder neck on video-images. Previous investigations on bladder innervation and function led to the conclusion that voiding dysfunction in the diabetic patient is resulted from autonomic and sensory neuropathy in bladder only. In contrast, few investigation was focused on urethral mechanism as a cause for voiding dysfunction in the diabetics.

We herein, evaluated whether and how urethral factor is responsible for voiding dysfunction in the diabetic rats.

Materials and Methods: Total, 57 male Sprague-Dawley rats(29 diabetic and 28 control; 200-500g in weights), were included in this study. Diabetes was induced using Weir's method(neonatal streptozotocin injection method; 90 mg/kg) on the second day after birth, which was known as the model of Non-insulin dependant diabetes mellitus (NIDDM). Experiments were done at the age of 12, 24, and 36 weeks for urodynamic study (n=39) and immunohistochemistry (n=18).

To evaluate the urethral resistance, the urodynamic study was performed using the two-channel BIOPAC system, double lumen catheter(16/20/22 G) through bladder dome, PE 10 catheter in the urethra. The detrusor pressure on urethral leaking(detrusor leak point pressure(LPP)) was compared in diabetic and control rats. And the effect of various drugs such as L-nitro-arginine-methyl ester (L-NAME, 20 mg/kg) or sodium nitroprusside(SNP, 2 mg/kg) was also observed.

To evaluate the pathologic state of nitric oxide synthase (NOS) containing nerve, immunohistochemistry was performed using rabbit anti-nNOS in diabetic and control rats. For the statistical analysis of the data, un-paired t test was used.

Results: The DM models were compatible to the finding of NIDDM. On the urodynamic study, the detrusor LPPs of diabetic rats were significantly higher than those of control rats at the age of 12 and 24 weeks. On 36 weeks those were similar between DM and control rats.

After intravenous injection of L-NAME, detrusor LPPs of diabetes were not changed while they were significantly increased in controls. After intravenous injection of SNP, detrusor LPPs were decreased in both diabetics and controls.

Urethral immunohistochemistry showed that the number and immuno-reactivities of nNOS containing nerve fibers in diabetics were significantly decreased, compared to those in controls. Those findings were also prominent in older age within the group of both diabetics and controls

Conclusion: The results indicate that urethral resistance is gradually increased along with the duration of diabetes, which might be resulted from reduction of urethral NOS containing nerve. Urethral factor in DM cystopathy has an important role on the pathogenesis of voiding dysfunction in patients with diabetes

Table. The detrusor leak point pressure in normal and diabetic rats without medication according to the age.

Age(weeks)	Group	Without medication	L-NAME[1]	Sodium Nitroprusside[2]
12	Control	26.05±4.86	29.51±0.87	13.77±3.25
	DM	32.10±12.01	34.26±2.91	19.73±6.76
24	Control	26.84±4.50	37.04±2.14	15.14±5.48
	DM	39.17±5.72**	37.90±7.36	22.15±2.82
36	Control	37.09±3.95	33.64±2.44	21.45±6.67
	DM	34.71±5.69	29.45±1.52	26.04±4.16

Average ±standard deviation(mmHg)
**p<0.01: Each comparison with normal control
1. Detrusor leak point pressure with pre-injection of L-NAME
2. Detrusor leak point pressure with injection of sodium nitroprusside

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Title (type in CAPITAL LETTERS, leave one blank line before the text):

HEPARIN-BINDING EPIDERMAL GROWTH FACTOR-LIKE GROWTH FACTOR EXPRESSION IN BLADDER SMOOTH MUSCLE IN RESPONSE TO PASSIVE AND ACTIVE FORCE.

AIMS OF STUDY: Bladder outlet obstruction produces increased smooth muscle mass and bladder dysfunction. Previous studies have demonstrated that mechanical stretch induces Heparin-binding epidermal growth factor-like growth factor (HB-EGF) expression in cultured bladder smooth muscle cells, mediated by an autocrine release of Angiotensin II (Ang II) [1]. HB-EGF is produced in smooth muscle of the bladder and stimulates smooth muscle proliferation [2]. The peptide hormone Ang II has been implicated in hypertrophic responses in cardiac and smooth muscle cells when it binds and activates angiotensin type 1 (AT1) receptors [3,4]. In this study, the effect of active and passive tension on HB-EGF expression in bladder tissue was determined. We also evaluated whether the stretch induced HB-EGF expression was Ang II dependent.

METHODS: Urinary bladders were removed from anesthetized rats. The bladder body was separated from the bladder base and cut into strips. Bladder tissue was placed in perfusion chambers containing oxygenated Kreb's solution at 37° and placed under 2 grams of tension. Tissue was equilibrated for 45-60 minutes. In some chambers, a continuous train of electric field stimulation (20 volts, 0.4 Hz, 5ms) was delivered to the suspended tissue. In other chambers, the tissue was stretched to a force of 2 grams, but not stimulated. Muscle strips were subjected to passive or active tension for 4, 6, or 8 hours with or without exposure to losartan (AT1 receptor antagonist). After the experiment, tissue was frozen in liquid nitrogen and relative levels of HB-EGF mRNA were measured by semi-quantitative RT-PCR.

RESULTS: Passive stretch of smooth muscle strips resulted in an increase in HB-EGF mRNA expression in a time dependent fashion. Active contraction, induced by electric field stimulation, augmented the passive stretch induced HB-EGF mRNA expression at each time point.
Exposure to losartan decreased the amplituded of contraction and inhibited the HB-EGF mRNA expression induced by electric field stimulation.

CONCLUSION: In the obstructed bladder, hypertrophy of smooth muscle cells is associated with