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UP-REGULATION OF MUSCARINIC RECEPTOR AND PURINERGIC RECEPTOR IN THE FRUCTOSE-FED RAT.

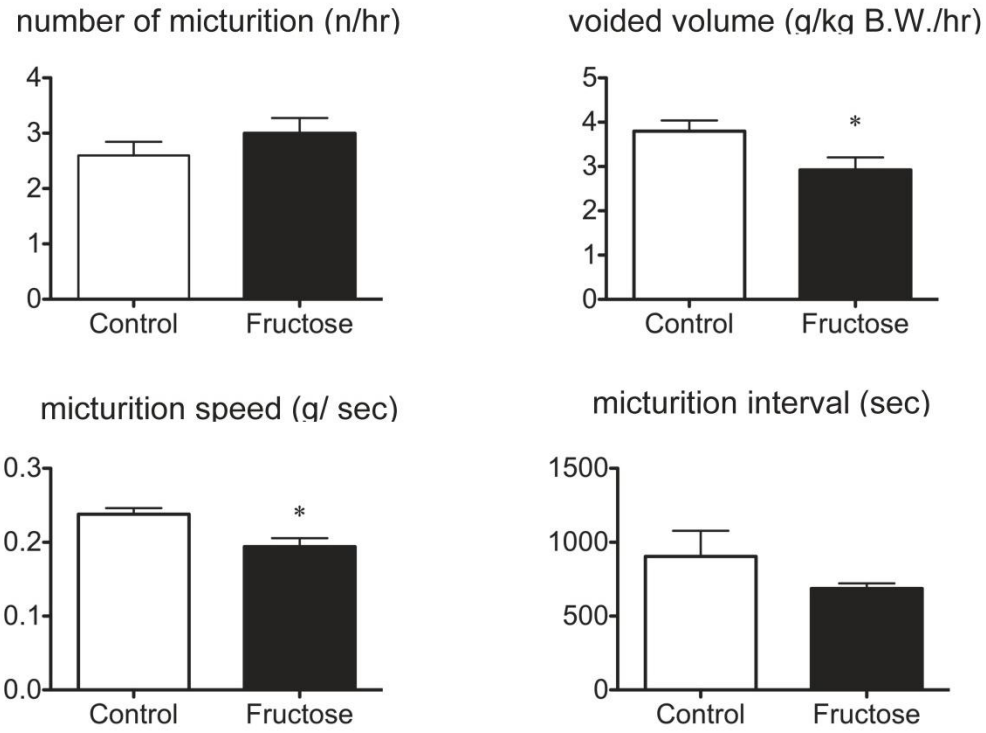
Hypothesis / aims of study

Diabetic cystopathy is a common complication of diabetes mellitus and clinically, up to 80% of patients with diabetes mellitus develop bladder dysfunction. It is known that the symptoms of diabetic cystopathy are characterized by the decreased bladder sensation, increased bladder capacity and impaired detrusor contractility with increased residual urine. However, these symptoms are not always observed in diabetic patients and several studies have shown that urinary frequency and urgency with detrusor hyperactivity also occur. Muscarinic and purinergic receptors in the bladder are significantly involved in the regulation of urination. Previous studies have suggested the possible involvement of these pharmacologically relevant receptors in the pathogenesis of urinary dysfunction of diabetic rats. Thus, the present study was conducted to test whether the development of diabetic state in fructose-fed rats causes the alteration of urodynamic parameters and muscarinic and purinergic receptors in the bladder.

Study design, materials and methods

Male Sprague-Dawley rats (8 weeks old) were divided into fructose-fed group and control group. The fructose-fed group was fed a 60% fructose diet, whereas control group received standard rat chow for 3 months. Following 3 months treatment, plasma glucose and serum insulin were measured for evaluating metabolic syndrome. The time of micturition and micturition volume were recorded after the administration of pure water (30 mL/kg). Micturition frequency, voiding speed, voiding volume and micturition interval were calculated from the recorded data. Muscarinic receptor and purinergic receptor in the bladder were measured by radioligand binding assays using [^{3}H]NMS and [^{3}H]αβ-MeATP, respectively, and binding parameters of apparent dissociation constant (K_d) and maximal number of binding sites (B_{max}) were estimated by nonlinear regression analysis using Graph Pad Prism.

Fig. 1. Micturition parameters of 3-month fructose-fed rats after administration of water (30 mL/kg) for 1.5 hr.
Values are the mean ± S.E. for seven to ten rats. Asterisks show a significant difference from the control values, *P<0.05



Results

Fructose-fed rats displayed significantly higher level of serum insulin, but no difference was observed in the plasma glucose between fructose-fed rats and control rats. Micturition volume and voiding speed were significantly decreased in fructose-fed rats (Fig. 1). The B_{max} for specific binding of [^{3}H]NMS and [^{3}H]αβ-MeATP was significantly increased in the bladder from fructose-fed rats compared with control rats (Table 1). On the other hand, the B_{max} for [^{3}H]NMS in the submaxillary gland was not altered by the fructose treatment.

Interpretation of results

Diabetic cystopathy are generally thought to be induced by hyperglycemia. The rats fed a fructose enriched diet showed insulin resistance, hyperinsulinemia, hypertriglycdmidemia and hypertension [1]. The present study has shown that muscarinic and purinergic receptors were up-regulated in the bladder and micturition volume was significantly decreased in fructose-fed rats

without hyperglycemia. It is indicated that metabolic perturbations induced muscarinic and purinergic recepter up-regulation in the bladder and decreace of the bladder capacity.

Table1. Kd and Bmax for specific binding of [^{3}H]NMS and [^{3}H] $\alpha\beta$ -MeATP in the bladder of 3month fructose-fed rats.

	Kd (pM)		Bmax (fmol/mg tissue)	
	Control	Fructose	Control	Fructose
[^{3}H]NMS	288±12	323±18	6.8±0.3	8.8±0.5*
[^{3}H]$\alpha\beta$-MeATP	0.77±0.08	0.80±0.08	16.7±1.6	21.1±2.6*

Values are the mean ± S.E. for seven to ten rats.
Asterisks show a significant difference from the control values, *P<0.05

Concluding message

Long-term fructose-fed rats induces increased expression of muscarinic and purinergic receptors in the bladder. The receptor alteration is associated with the decrease of the bladder capacity.

References

1. J Urol, 179: 2470-2476 (2008)

Specify source of funding or grant	**No**
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	**The Laboratory Animal Care and Use Committee at University of Shizuoka**