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# ASSOCIATIONS BETWEEN LOWER URINARY TRACT SYMPTOMS AND METABOLIC SYNDROME IN OLETTF RATS

Hypothesis / aims of study

The metabolic syndrome (MetS) is a clustering of several metabolic abnormalities or risk factors, including central obesity, dyslipidemia, hypertension, insulin resistance with compensatory hyperinsulinemia and glucose intolerancea. Recent epidemiological surveys demonstrated a significant association between MetS and lower urinary tract symptoms (LUTS). This association has also been suggested in dietary fat rat model with MetS induced by long-term fructose feeding (1).

Recent research indicates that an individual's genetic background can interact with their dietary fat exposure to affect risk of the MetS(2). So far as we known, the genetic animal model resemble human MetS is scare. The OLETF (Otsuka Long-Evans Tokushima Fatty) rat is reported to be a new animal of human MetS that has been established from an outbred Long-Evans strain by selective breeding and subsequently maintained at the Otsuka Pharmaceuticals (Tokushima, Japan) (3). In this study, we tried to investigate the association between MetS and LUTS using this model.

Study design, materials and methods

Forty male OLETF rats and forty control male LETO (Long-Evans Tokushima Otsuka) rats were fed a normal diet from age 4 weeks to 72 weeks in University of Fukui Animal Center. Body weight, systolic blood pressure (tail-cuff method) and urine output were monitored every 8 weeks. Characterization of plasma glucose, triglyceride, cholesterol, and insulin levels were examined at the age of 24 and 56 weeks. Cystometry under waking conditions was also performed at these two ages. The amounts of ATP, PGE2 and NGF released from the stretched bladder epithelium were measured with luciferin-luciferase and ELISA assays at the age of 56 weeks. 8-OHdG amounts were measured to evaluate the oxidizative stress in bladder tissue with ELISA assay at the age of 56 weeks. The mRNA expression of alpha 1A, alpha 1D, M2, M3, P2X1, P2X2, P2Y4, iNOS, EP1, and EP2 receptors were analysed using SYBR green fluorescence Real-time PCR, GAPDH as an internal control.

Results

1. The average body weight of male OLETF rats was significantly increased from the age of 24 weeks to 40 weeks, but significantly decreased from the age of 64 weeks. The systolic blood pressure was gradually increased from the age of 24 weeks. Plasma triglyceride, cholesterol, insulin and glucose were significantly higher in OLETF rats than in LETO rats both at the age of 24 and 56 weeks. These characteristics suggest that OLETF rat could be a model in evaluating the relationship between MetS and LUTS.
2. The urinary frequency for 24 h was significantly greater in OLETF rats from the age of 24 weeks, and the mean voided volume was significantly greater from the age of 56 weeks. This suggests that the male OLETF rats have micturition characteristics of frequent micturition and polyuria from early stage to late stage.
3. On cystometry, non-voiding contractions (NVCs) was observed in OLETF rats at the age of 24 weeks, and markedly increased at the age of 56 weeks. The bladder weight, maximum bladder capacity and residual urine were significantly increased at the age of 56 weeks.
4. The amount of ATP, PGE2 and NGF released from 20 cm $H_2O$ pressure-stretched bladder of OLETF rats was, respectively, significantly increased $3.87 \pm 0.46$, $2.80 \pm 0.34$, $1.37 \pm 0.22$ times as much as those of LETO rats. The amount of 8-OHdG in the bladder of OLETF rats was $4.71 \pm 0.68$ times higher than that of LETO rats.
5. Compared with those of LETO rats, the mRNA expression of M2, M3, P2X3, iNOS, EP1 and EP2 receptors, respectively, increased $2.18 \pm 0.84$, $5.25 \pm 1.09$, $6.87 \pm 1.70$, $21.42 \pm 5.13$, $1.95 \pm 0.64$, $2.42 \pm 0.28$ times in urinary bladder of OLETF rats, while the mRNA expression of alpha 1A, alpha 1D, P2X1 and P2Y4 receptors showed no obvious change.

Interpretation of results

In this study, MetS-associated bladder dysfunction was remarkable in OLETF rat model. It is hypothesized that the increased oxidative stress in MetS stimulates the neurotransmitters, such as ATP, PGE2 and NGF, releasing from the bladder epithelium. Those neurotransmitters were mediated by over-expressed receptors of P2X3, EP1, EP2, M2 and M3 to activate the afferent C-fiber pathway, resulting in the induction of detrusor overactivity and frequency of urination.

Concluding message

The results of our study have shown that there is a significant association between MetS and LUTS in genetic background model OLETF rats.

References

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Disclosures

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