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ASSOCIATION OF MUSCARINE AND P2X RECEPTOR LEVELS IN URINARY BLADDER TO LOWER URINARY TRACT DYSFUNCTION IN THE INITIAL PHASE OF A STREPTOZOTOCIN (STZ)-TREATED RAT DIABETES MODEL

Hypothesis / aims of study
Lower urinary tract dysfunction is the most common complication in diabetics. Typical lower urinary tract dysfunction related to diabetes is characterized by an increase in the bladder capacity in storage phase, the reduction of voiding efficiency and an increase of residual urine associated with the reduction of detrusor muscle contractility in the voiding phase. However, recent studies have shown that there are significant serial changes in lower urinary tract dysfunction in diabetics. Briefly, in many patients, overactive bladder symptoms such as the urgency and frequency during daytime are observed in the initial phase of diabetes. Furthermore, most patients complain of severe nocturnal pollakisuria due to diabetes-related polydipsia/polyuria, and it is reported that a urinary flow kinetics test identifies detrusor muscle hyperactivity in such patients. However, the pathogenesis remains to be clarified. In this study, we evaluated time course of lower urinary tract dysfunction and receptor levels of muscarine and P2X in urinary bladder in the initial phase of a Streptozotocin (STZ)-treated rat diabetes model.

Study design, materials and methods
Seven-week-old female Wistar rats were used. They were divided into control and STZ-treated (50 mg/kg, i.p.) groups. We performed 24-hour frequency-volume chart, cystometry, contractility assessments of the detrusor muscle with EFS, Carbachol, and $\alpha\ \beta$-methylene ATP ($\alpha\ \beta$-mATP), and measurement of bladder muscarine and P2X receptor levels by radioreceptor assay with [^{3}H]NMS and [^{3}H]$\alpha\ \beta$-MeATP as labeling ligands at Weeks 1, 4, 8, and 12.

Results
In the STZ-treated group, the 24-hour urine volume, frequency of urination, and urine volume per urination were significantly greater than in the control group continuously until Week 12. Cystometry revealed an increase of bladder capacity, residual urine volume, and maximum contractile pressure. Contractile reactions to EFS, Carbachol, and $\alpha\ \beta$-mATP were also significantly enhanced. The radioreceptor assay identified a significant increase in the Bmax of muscarine receptors without Kd changes at Weeks 4, 8, and 12. The Bmax of P2X receptors also significantly increased without Kd changes at Weeks 1, 4, 8, and 12.

Interpretation of results
These results suggested the up-regulation of muscarine and P2X receptors in the initial phase of STZ administration.

Concluding message
The contractile reactions of the detrusor muscle to EFS, Carbachol, and $\alpha\ \beta$-mATP were enhanced in the initial phase of STZ administration. On radioreceptor assay, there were increases in the muscarine and P2X receptor counts, suggesting that this reaction contributes to overactive bladder-like symptoms in the initial phase of diabetes.

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**This study followed the guidelines for care and use of laboratory animals and was approved by guidelines for animal experiments of the Nihon University School of Medicine**