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# CHRONIC TREATMENT WITH ANAGLIPTIN, A DIPEPTIDYL-PEPTIDASE IV INHIBITOR PREVENTED BLADDER DYSFUNCTION AFTER ACUTE ISCHEMIA IN RATS

Hypothesis/aims of study
Dipeptidyl-peptidase 4 inhibitors (DPP-4I) are widely used for diabetes. DPP-4I inhibits the degradation of incretins such as glucagon-like peptide-1 (GLP-1) or GIP and enhances the secretion of insulin. In addition, it has been recently reported that DPP-4I has neuroprotective and angiogenic effects. Bladder ischemia is considered one of the causes of overactive and underactive bladder. In this study, we investigated whether chronic treatment with anagliptin, a DPP-4I, improved the bladder function of rats with acute bladder ischemia.

Study design, materials and methods
Eight-week-old female Wistar-ST rats were divided into four groups: (1) control (n=9), (2) ligation (n=6), (3) ligation plus anagliptin (n=7), (4) ligation plus liraglutide, an agonist of GLP-1 receptor (n=6). Rats in group (2-4) underwent ligature of bilateral internal iliac arteries. Rats in group 1 were subjected to sham surgery. Anagliptin was administered to rats in the form of CE-2 mixed with anagliptin (final conc. 0.3% anagliptin). Liraglutide (300 μg/kg) was injected subcutaneously. After 4 weeks, blood glucose levels were measured and cystometry (80 μL/min) was performed for all rats. Statistical analysis was performed by using an analysis of variance (ANOVA) and Bonferroni's multiple *t*-test.

Results
At 4 weeks after the observation period, blood glucose levels did not change in all the groups. Micturition intervals in the ligation group were significantly longer than those in control group ($P<0.05$, Figure 1). The micturition intervals in the ligation plus anagliptin group were significantly shorter than those in the ligation group ($P<0.05$) while those in the ligation plus liraglutide group were unaltered compared to the values in the ligation group (Figure 1). There were no differences among all the groups in baseline pressure, maximum voiding pressure, and threshold pressure.

Interpretation of results
We found that bilateral ligation of the internal iliac arteries caused bladder ischemia and was impaired the function of the sensory nerve. The treatment with anagliptin normalized the micturition intervals, suggesting that treatment preserved the function of the sensory nerve. However, it is unknown whether anagliptin improved these effects directly or indirectly because we did not measure the blood flow to the bladder or evaluate the sensory nerve in this study. Liraglutide did not affect the micturition intervals, suggesting that the effects of anagliptin were not attributable to GLP-1.

Concluding message
Anagliptin improved the prolongation of micturition intervals in acute ischemic conditions, and the underlying mechanism was not considered to involve GLP-1.

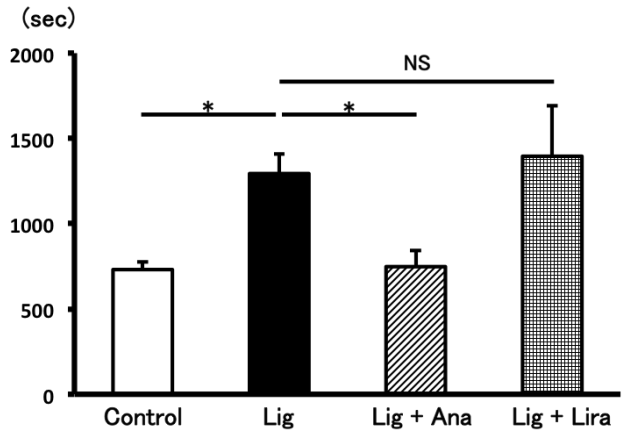


Figure 1 Micturition intervals in each group.
Lig: Ligation, Ana: anagliptin, Lira: liragrutide. n=6-9. *$P<0.05$, analysis of variance (ANOVA) and Bonferroni's multiple t-test. NS: no significance.

Disclosures
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