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CHRONIC DPP-4 INHIBITION IMPROVED BLADDER DYSFUNCTION AND HEMODYNAMICS IN RATS WITH LIGATION OF INTERNAL ILIAC ARTERIES

Hypothesis / aims of study

Dipeptidyl-peptidase 4 inhibitors (DPP-4Is) are widely used for diabetes. DPP-4Is inhibit the degradation of incretins such as glucagon-like peptide-1 (GLP-1) or glucose-dependent insulinotropic polypeptide and enhance insulin secretion. In addition, DPP-4I has been recently reported to have neuroprotective and angiogenic effects. Bladder ischemia is considered a cause of overactive and underactive bladder. In this study, we investigated whether chronic treatment with anagliptin, a DPP-4I, improved bladder function of rats with acute bladder ischemia and elucidated the mechanisms of the improvement by focusing on bladder blood flow.

Study design, materials and methods

First, 8-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), and (4) ligation plus liraglutide, an agonist of the GLP-1 receptor (n = 6). The rats in groups 2–4 underwent ligature of bilateral internal iliac arteries. The rats in group 1 were subjected to sham surgery. Anagliptin was administered to the rats in the form of CE-2 mixed with anagliptin (final concentration, 0.3% anagliptin). Liraglutide (300 μg/kg) was injected subcutaneously. After 4 weeks, blood glucose levels, DPP-4 activity, and GLP-1 levels were measured, and cystometry (80 μL/min) was performed for all the rats.

Next, under anesthesia induced by isoflurane, the bladder blood flow was measured with the bladder empty by using laser-Doppler flowmetry in the other rats in the control, ligation, and ligation plus anagliptin groups that did not undergo cystometry (n = 8 in each group). The dose and administration period of anagliptin were the same as those in the functional study. In addition, we examined the bladder blood flow before and after injection of anagliptin (1 mg/kg, intravenously) by using intact rats (n = 5) to examine the effect of the acute administration of anagliptin on bladder blood flow.

Statistical analysis was performed by using 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. As expected, the DPP-4 activity in the ligation plus anagliptin group was significantly inhibited in comparison with those in the control, ligation, and ligation plus liraglutide groups ($P < 0.01$). The GLP-1 activity in the ligation plus anagliptin group was significantly higher than that in the control and ligation groups ($P < 0.01$), and that in the ligation plus liraglutide group was significantly higher than that in the other three groups ($P < 0.01$).

The intercontraction intervals (ICIs) in the ligation group were significantly longer than those in the control group ($P < 0.05$, Figure 1). The ICIs in the ligation plus anagliptin group were significantly shorter than those in the ligation group ($P < 0.05$, Figure 1), whereas those in the ligation plus liraglutide group were unaltered in comparison with the values in the ligation group. No significant differences were found among groups in terms of baseline pressure, maximum voiding pressure, and threshold pressure.

The bladder blood flow in the ligation group was significantly lower than that in the control group ($P < 0.01$, Figure 2), whereas that in the ligation plus anagliptin group was significantly higher than that in the ligation group ($P < 0.01$, Figure 2). In the study that used intact rats, acute intravenous injection of anagliptin did not change bladder blood flow.

Interpretation of results

We found that bilateral ligation of the internal iliac arteries caused bladder ischemia and impaired sensory nerve function. The treatment with anagliptin normalized the ICIs, suggesting that treatment preserved sensory nerve function. Liraglutide did not affect the ICIs, suggesting that the effects of anagliptin were not attributable to GLP-1. However, whether anagliptin improved these effects directly or indirectly remains unknown. Thus, we examined the effects of anagliptin on bladder blood flow. Hence, chronic anagliptin treatment improved bladder blood flow in the rats with an ischemic bladder, although acute injection of anagliptin did not change blood flow in the intact rats. These results suggest that chronic treatment with anagliptin improved bladder blood flow indirectly, which led to the improvement of bladder function.

Concluding message

Anagliptin improved the prolongation of micturition intervals with the improvement of bladder hemodynamics in acute ischemic conditions, and the underlying mechanism was not considered to involve GLP-1.
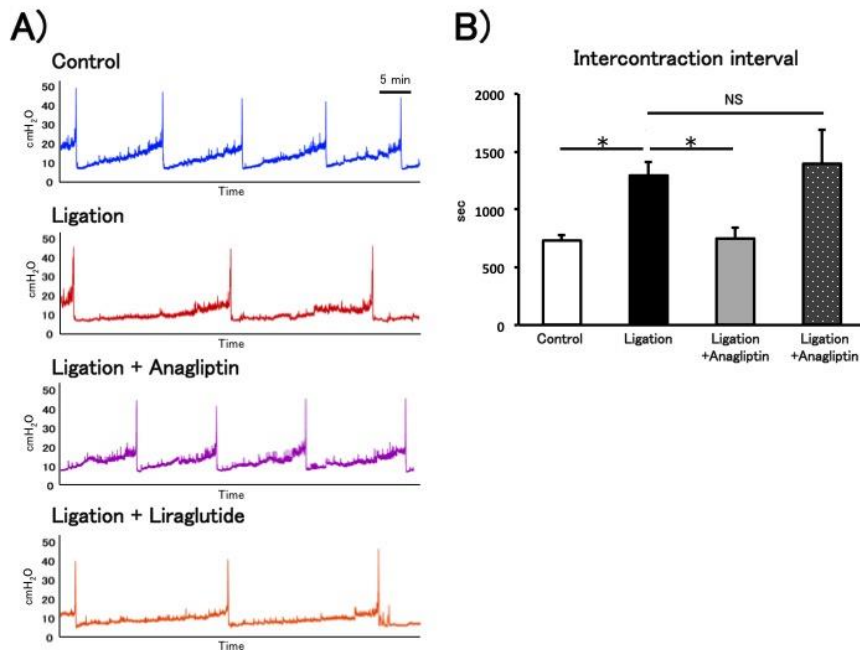
Figure 1. Micturition pattern in each group.
A) Representative chart for each group. B) Intercontraction interval in each group
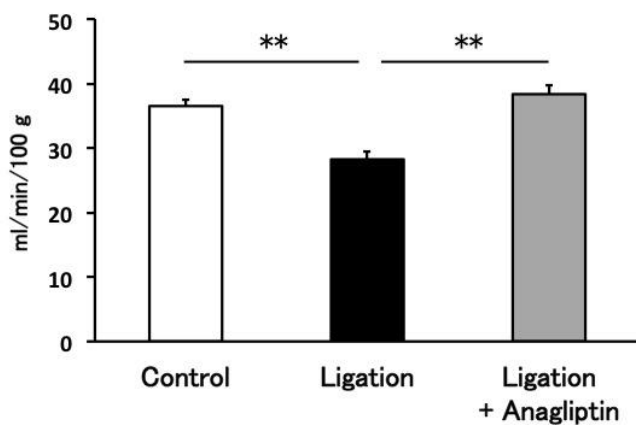n = 6–9. *P < 0.05, analysis of variance (ANOVA) and Bonferroni's multiple t test. NS: no significance.

Figure 2. Bladder blood flow in each group.
n = 8. **P < 0.01, analysis of variance (ANOVA) and Bonferroni's multiple t test.