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ANTI-CANCER AGENT, OXALIPLATIN, SHORTENS VOIDING FUNCTION AND WEAKENS DETRUSOR MUSCLE CONTRACTION IN RATS

Hypothesis / aims of study
The incidence of cancer is very high worldwide, and the primary mode of treatment is administration of chemotherapeutic agents. Fortunately, the National Cancer Institute has reported over 12 million cancer survivors in the US. Therefore, it is necessary to develop effective care plans to improve the quality of life of cancer survivors. Few reports exist regarding the influence of anti-cancer agents on voiding function. We reported previously that some anti-cancer agents caused endothelial dysfunction and erectile dysfunction in a study using an animal model. Therefore, we assumed that some anti-cancer agents might also cause voiding dysfunction. In this study, we investigated the chronological change in voiding function after administration of the anti-cancer agent, oxaliplatin (L-OHP), using a rat model.

Study design, materials, and methods
Male Wistar ST rats at 12 weeks of age were used for the study. The rats were categorized into two groups: Control and L-OHP. L-OHP (4 mg/kg) was administered to the rats intraperitoneally for 2 days, while 5% glucose solution (vehicle) was administered to the control rats. After 4 weeks, voiding function and detrusor muscle contraction were evaluated. Cystometrography (CMG) was performed to assess the bladder voiding interval and intravesical pressure. Detrusor muscle contraction was measured by isometric tension using bladder tissue. Contraction was induced by carbachol and electrical field stimulation (EFS). A muscarinic receptor antagonist was also used. Real-time PCR was used to examine variations in the expression of mRNA in the excised bladder tissue.

Results
Based on the CMG (80 μL/min) results (Figure 1A), L-OHP significantly shortened the voiding interval (L-OHP group: 615.0 ± 135.6 s, Control group: 1308.3 ± 263.7 s, Figure 1B). Intravesical pressure was not significantly different between groups (Figure 1C). On the other hand, the L-OHP group showed a significantly weaker contractile force of the detrusor muscle in response to carbachol (L-OHP group: 105.1 ± 4.5 % that of 80 mM high-potassium Krebs solution (High K^+), Control group: 147.8 ± 31.6 % that of 80 mM High K^+, Figure 1D). Similarly, the L-OHP group showed a weaker contractile force against EFS (L-OHP group: 63.6 ± 18.1 % that of 80 mM High K+, Control group: 107.7 ± 10.1 % that of 80 mM High K+, Figure 1E). Muscarinic receptor (M2) mRNA expression was higher in the L-OHP group than in the Control group. However, M3 mRNA expression was lower in the L-OHP group than in the Control group. Rho-associated protein kinase 1 (ROCK-1) mRNA was also lower in the L-OHP group than in the Control group.

Interpretation of results
We showed that L-OHP could change the voiding function and detrusor muscle contraction of rats. A well-known adverse effect of L-OHP is peripheral neuropathy. We had hypothesized that L-OHP would prolong the voiding interval. However, L-OHP shortened the voiding interval in this study. Interestingly, L-OHP also up-regulated M2 mRNA expression, which could explain the shortened voiding interval. On the other hand, L-OHP weakened detrusor muscle contraction. L-OHP decreased not only M3 mRNA but also ROCK-1 mRNA expression. We believe that the down-regulated M3 and ROCK-1 mRNA led to weakened detrusor muscle contraction.

Concluding message
Our findings indicate that anti-cancer agents can change voiding function and detrusor muscle contraction. If anti-cancer agents are repeatedly administered, they can result in an overactive bladder and eventually an underactive bladder. Therefore, follow-up care for cancer survivors should include some form of continence medication.

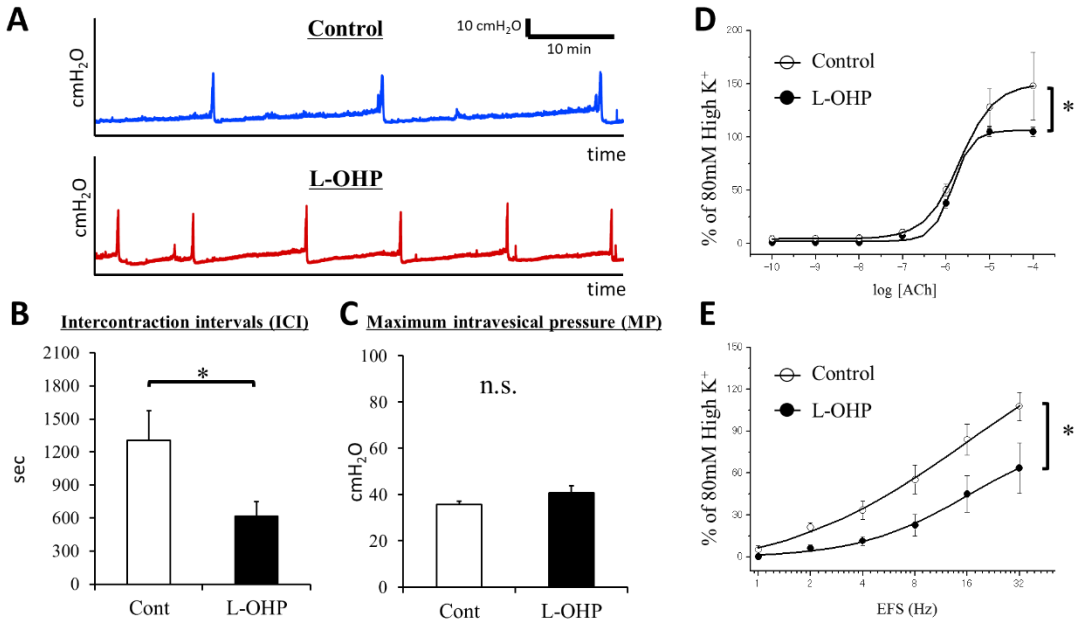

Figure 1. (A-C) Cystometrography after 4 weeks of oxaliplatin (L-OHP) administration. (A) Representative cystometrograms during intravesicular infusion of saline in the control and L-OHP groups. (B) Results of the intercontraction intervals (ICI) analysis. (C) The maximum intravesical pressure (MP) in each group. (D-E) Detrusor muscle contraction was measured by isometric tension using bladder tissue. (D) Carbachol-induced contraction curve for rat bladder strips, showing the contractile effect of increasing concentrations of carbachol (10^{-10}–10^{-4} M) on bladder strips. (E) Electrical field stimulation (EFS)-induced contraction curve for rat bladder strips, showing the contractile effect of increasing hertz of EFS (1−32 Hz) on bladder strips. Each bar indicates mean ± standard error. *P < 0.05 between groups by Student's *t*-test; n.s., not significant.

Disclosures
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