

Effects of duloxetine on bladder and external urethral sphincter in anesthetized female guinea-pigs with intravesical acetic acid

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Objectives

The anatomy of the urinary tract and urodynamic profile of guinea-pigs is similar to humans ^(1,2). In contrast to rats where the motoneurons innervating the bladder are located in L6-S1, in guinea-pigs they are present in the S1 segment of the spinal cord ⁽³⁾. In addition, external urethral sphincter (EUS) motoneurons in the guinea-pig are located in the region of the ventral horn corresponding to the Onuf nucleus in cats and humans ⁽³⁾. It has been demonstrated in anesthetized cats, that acetic acid (AA) bladder infusion induces bladder overactivity and loss of bladder/EUS coordination, effects that were reversed by duloxetine ⁽⁴⁾.

The aim of this study was to evaluate the effect of duloxetine on both bladder and EUS activity during intravesical AA infusion in anesthetized female guinea-pigs.

Methods

- Female Dunkin-Hartley guinea-pigs were anesthetized with isoflurane (3%) for surgery. Intravesical and jugular catheters were implanted for intravesical pressure recording and drug administration, respectively. Stainless wire electrodes were inserted into the EUS. For cystometry, anesthesia was switched to urethane (1.2 g/kg, i.p.).
- Baseline bladder and EUS activity were determined during a continuous bladder infusion with NaCl 0.9% (12 ml/hr) for 30 min. The bladder was then continuously infused with 0.2% AA for 30 min. The last three micturitions were averaged to obtain basal values.
- Duloxetine (3 mg/kg, i.v., n=6) or vehicle (saline, n=6) was intravenously infused over 5 min at the infusion rate of 0.2 ml/min. Bladder and EUS activity were monitored for one hour post-administration.
- Intercontraction interval (ICI) and maximal EUS amplitude during the voiding and filling phases were measured and averaged for 30 min periods post-administration and compared to basal values (during AA infusion).
- For each parameter, values post-administration were compared to basal values using one way ANOVA with repeated measures followed by Newman-Keul's test. A p value < 0.05 was considered to be statistically significant.

Conclusions

These results demonstrate that in the guinea-pig, intravesical AA 0.2% can induce bladder overactivity characterized by a substantial decrease in ICI together with an increase in EUS activity associated with a loss of bladder/urethra coordination. Duloxetine (NE and 5-HT reuptake inhibitor) partially reversed the effect of AA on ICI and restored bladder/urethra coordination.

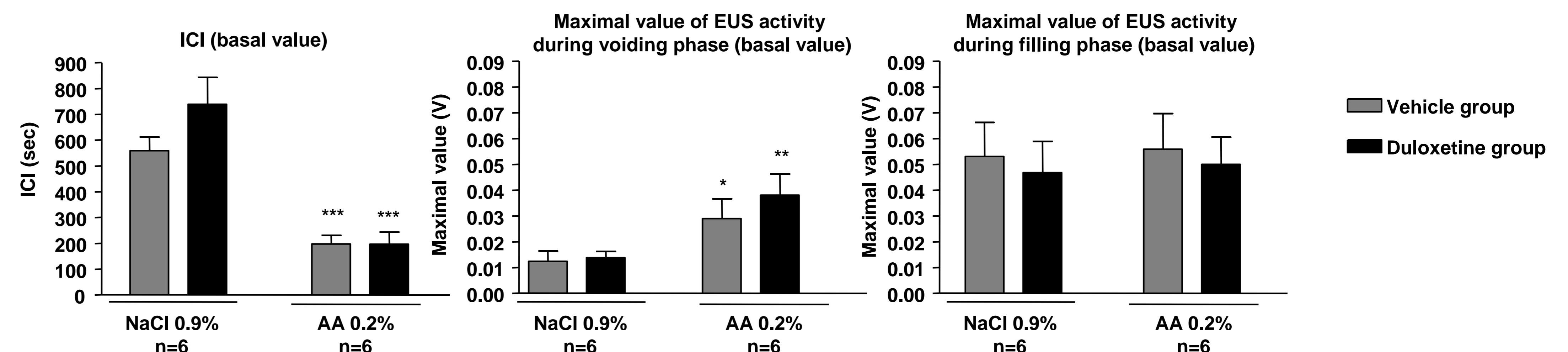
This experimental model in guinea-pigs appears to be useful for investigating bladder and EUS function in normal and pathological conditions and for evaluating potential treatments for bladder and urethral dysfunctions.

References

- (1) Van Asselt *et al*, Am J Physiol, **269**: 98-103, 1995.
- (2) Neuhaus *et al*, Anat Histol Embryol, **30**: 185-192, 2001.
- (3) Kuipers *et al*, Neurosci, **362**: 57-60, 2004.
- (4) Thor *et al*, J Pharmacol Exp Ther, **274**: 1014-1024, 1995.

Results

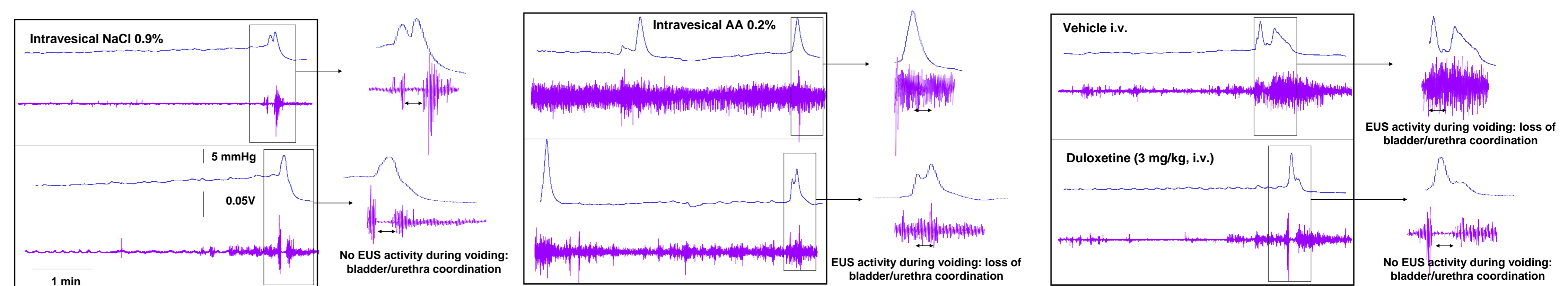
Effects of intravesical AA 0.2% on ICI and EUS activity in anesthetized female guinea-pigs



* p<0.05, ** p<0.01, *** p<0.001 versus NaCl 0.9% values; one way ANOVA with repeated measures followed by Newman-Keul's test

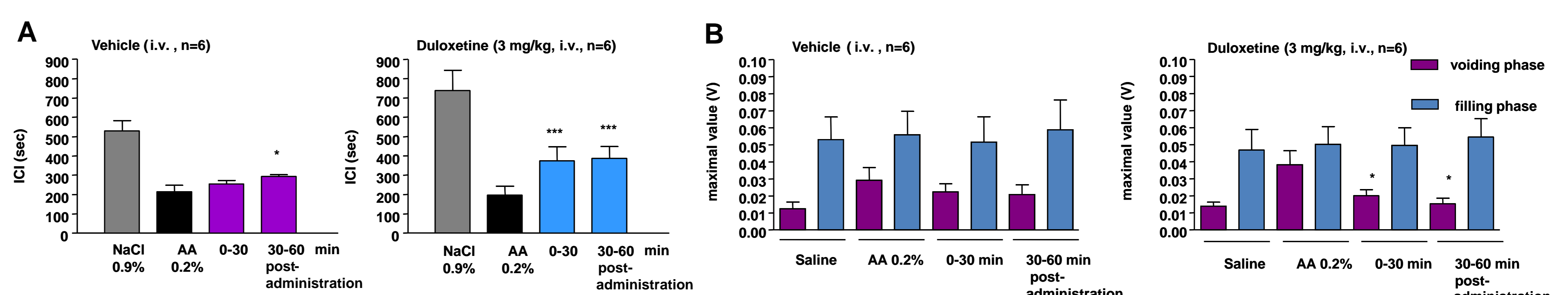
- Intravesical AA 0.2% elicited bladder overactivity characterized by a significant decrease in ICI and an increase in EUS activity during the voiding phase.

Original recordings of bladder and EUS activity in anesthetized female guinea-pigs before and after AA intravesical infusion: effects of vehicle and duloxetine



- Intravesical AA 0.2% elicited an increase in EUS activity mainly during the voiding phase and a loss of bladder/urethra coordination.

Effects of duloxetine (3 mg/kg, i.v.) and its vehicle on ICI (A) and maximal values of EUS activity during voiding and filling phases (B)



* p<0.05, *** p<0.001 versus AA values; one way ANOVA with repeated measures followed by Newman-Keul's test

- In presence of AA, duloxetine (3 mg/kg, i.v.) significantly increased ICI for up to 60 min post-administration while there was only a slight increase in ICI after vehicle treatment.
- Duloxetine also significantly decreased EUS activity during the voiding phase and thus restored bladder/urethra coordination.