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EFFECTS OF LITOXETINE ON URETHRAL PRESSURE AND DETRUSOR OVERACTIVITY IN ANESTHETIZED FEMALE RATS

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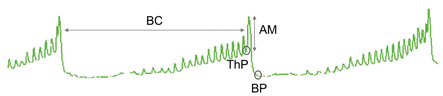
Objectives

Litoxetine (LTX) is a highly selective serotonin (5-HT) reuptake inhibitor and a Multifunctional Serotonin Agonist Antagonist [(1,2)]. To date, the role of 5-HT innervation on urethral and bladder functions in humans and animals is well established. The aims of the current study were to evaluated in two different set of experiments, the effects of intravenous (i.v.) LTX on urethral pressure (UP) and on detrusor overactivity induced by intravesical infusion of acetic acid (AA) in anesthetized rats.

Methods

Two different studies were performed in anesthetized female Wistar rats.

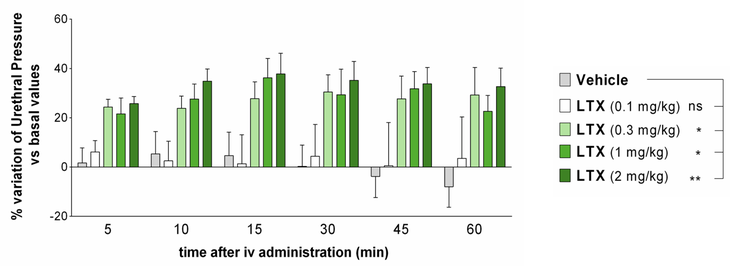
- **Urethral pressure measurement** was performed under pentobarbital anesthesia. A polyethylene catheter was positioned into the urethra. Saline was continuously infused into the urethra (0.5 mL/h) and UP was recorded. After a stabilization period (basal values), a single dose of LTX (0.1, 0.3, 1 or 2 mg/kg) or vehicle (physiological saline) were given i.v. and UP was recorded for 1 hour.
  Maximal increase in UP was calculated in each group. Percentage of variation from basal values was calculated at different time points after administration.
- **Cystometric measurement** was performed under urethane anesthesia. A polyethylene catheter was implanted in the bladder through the dome and secured with a purse-string suture. Saline or 0.3% AA was infused into the bladder at a constant flow rate (3 mL/h). After a stabilization period (basal values), LTX (2 mg/kg) or vehicle, were administered i.v. and vesical pressure was recorded for 1 hour. The following cystometric parameters were analyzed:
  Amplitude of micturition (AM, mmHg), Basal Pressure (BP, mmHg), Threshold Pressure (ThP, mmHg) and Bladder Capacity (BC, mL).



Results

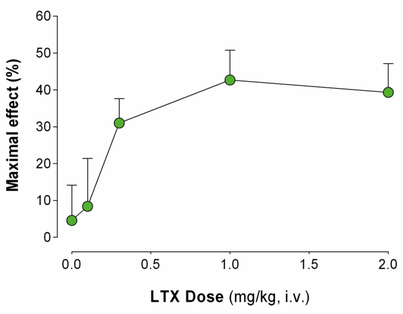
LTX induced a dose-dependent increase of Urethral Pressure

- Basal UP was not statistically different between groups (data not shown).



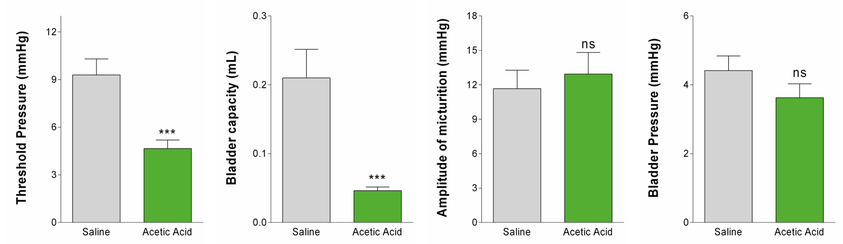
Data represent mean values ± SEM (n=5-9/group). ns p>0.05, * p < 0.05, ** p < 0.01, Two-way RM ANOVA

- Following administration of vehicle small variations of UP were observed (maximal increase in UP was 5±10 %).



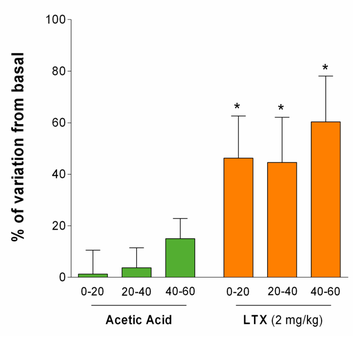
- In contrast, LTX induced a dose-dependent and long lasting (up to 1 hour) increase of UP.
  In comparison to vehicle, LTX effects were significant starting from the dose of 0.3 mg/kg (31±6, 43±8 and 39±8% at 0.3, 1 and 2 mg/kg, i.v., respectively).

LTX increased Bladder Capacity in AA-induced bladder overactivity



Data represent mean values ± SEM (n=8-11/group). ns p>0.05, *** p < 0.001, Mann Whitney test or unpaired *t* test

- In animals with intravesical AA infusion, ThP and BC were markedly and significantly decreased in comparison to saline infused animals. No significant difference was observed for all other cystometric parameters.



Data represent mean values ± SEM (n=8-11/group).
* p < 0.05, unpaired *t* test

- In rats infused with AA, LTX (2 mg/kg, i.v.) significantly increased BC during the 60 min observation period (46±16, 44±18 and 60±18% at 20, 40 and 60 min after administration, respectively). At this dose, LTX was devoid of significant effect on AM, BP and ThP.

Conclusions

In anesthetized rats, LTX increased UP and reduced detrusor overactivity induced by AA. Considering the pharmacological profile of LTX, it is hypothetized that these effects could be related to an increased activity of the urethral sphincter and a decreased activity of the bladder by a 5-HT-mediated mechanism involving spinal or supraspinal structures, as reported for duloxetine [(3)]. However, a direct effect on bladder and/or urethral smooth muscles cannot be ruled out.

Taken together these results suggest that LTX could be useful for treating mixed urinary incontinence.

References

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(3) Thor, K.B. and Katofiasc, M.A., J Pharmacol Exp Ther, **274**:1014-1024, 1995.