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Effects of a selective beta3 adrenoreceptor agonist (CL-316,243) on cystometric parameters in conscious and anesthetized female rats.

Hypothesis / aims of study

Beta3 adrenoceptors are expressed in the urinary bladder of several species including human and rat. A number of *in vivo* studies have shown that beta3adrenoceptor (beta3-ADR) agonists produce an increase in bladder capacity, but also produce a decrease in amplitude of micturition in anesthetized rats (1-2). However there are fewer reports of the action of beta3-ADR agonists in conscious rats and while there are reported effects on bladder capacity, stimulation of beta3-ADRs does not appear to significantly affect the amplitude of micturition (3). Therefore the aim of the current study was to directly compare the effects of intravenous administrations (i.v.) of a selective beta3-ADR agonist (CL-316,243) on cystometric parameters in conscious and anesthetized rats.

Study design, materials and methods

1) Conscious studies: Rats were anesthetized with isoflurane. The jugular vein and urinary bladder were catheterized for i.v. drug administration and intravesical pressure recording, respectively. Two days after surgery, cystometry in conscious rat was performed. The bladder was continuously infused with saline at a flow rate of 2 ml/hr. After 45 min (stabilization of the basal cystometric values), vehicle (i.v.) or CL-316,243 (0.01, 0.03, or 0.1mg/kg, i.v.) were administered. Then, intravesical pressure was measured for 1 hour post-administration. Amplitude of Micturition (AM), Basal Pressure (BP) and Intercontraction Interval (ICI) were analyzed and averaged for the 60 min period post-administration (n=7-9 per group). For each cystometric parameter, the effects of CL-316,243 were compared to basal values using a paired Student *t*-test.
2) Anesthetized studies: Rats were anesthetized with urethane (1.2 g/kg, s.c.) and intravesical and jugular catheters implanted. The bladder was infused at a flow rate of 2ml/hr. Following a micturition event, the infusion was stopped, the bladder emptied. After 7 micturition cycles (4 for stabilization and 3 for the basal value), vehicle or CL-316,243 (0.1 mg/kg) were administered i.v. AM and ICI were analyzed 60 minutes post-administration (n=6-8 per group).

Results

1) In conscious rats, CL-316,243 (0.01, 0.03 and 0.1 mg/kg) significantly increased ICI and BC, and decreased MF in a dose dependent manner. No effect on AM was observed with low doses of CL-316,243 (0.01 and 0.03 mg/kg), while at the highest dose (0.1 mg/kg) CL-316,243 slightly, but significantly decreased AM (Figure 1). BP was not modified after CL-316,243 administration at any dose (data not shown). No differences in basal values between groups were observed (data not shown).
2) In anesthetized rats, CL-316.243 (0.1 mg/kg, i.v.) significantly increased ICI 60 min post-administration (717.3 ± 111 *versus* 11160 ± 224) (p<0.01 *versus* basal values). AM was also strongly and significantly decreased 60 min post-administration (11.58 ± 1.91 *versus* 3.70 ± 1.24) (p<0.001 *versus* basal values). No differences in basal values between groups were observed (data not shown).

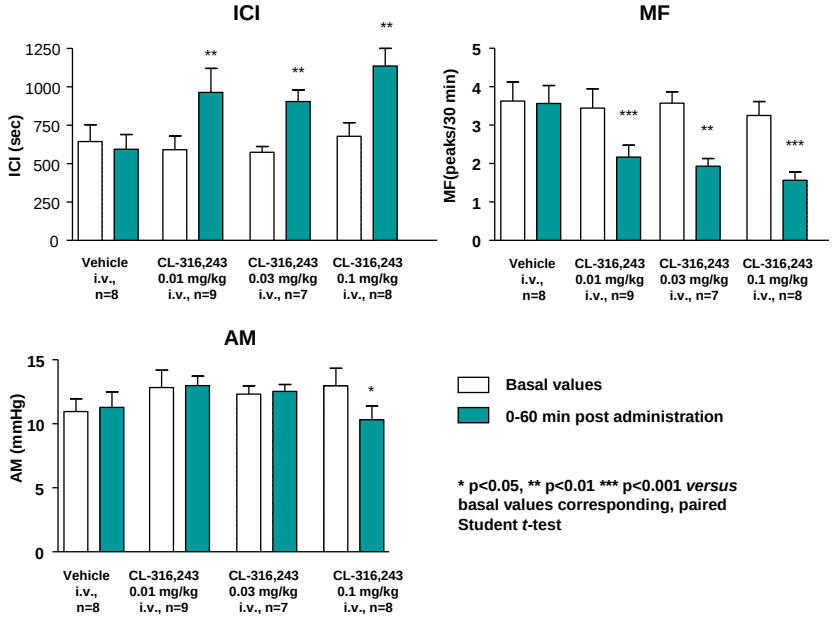

Figure 1: Effects of vehicle and CL-316,243 (0.01, 0.03 and 0.1 mg/kg) on ICI, MF, AM and ThP in conscious female rats.

Interpretation of results

In both experimental conditions CL-316,243 was able to significantly decrease micturition frequency and increase ICI. In conscious rats, low doses of CL-316,243 produced significant effects on MF without affecting the AM. At the highest dose tested, the decrease in MF was associated with a slight decrease in the AM perhaps indicating an effect on efferent neurotransmission at higher doses.

In contrast, in anesthetized rats the increase in ICI after CL-316,243 administration was associated with a strong inhibition of AM, suggesting that this effect is amplified by anesthesia.

Concluding message

It is clear from these studies that the choice of experimental conditions (in this case anesthetized or conscious animals) can affect the interpretation of the effects of potential drugs on cystometric parameters in preclinical species.

In conscious rats, stimulation of beta3-ADRs with CL-316,243 produced a clear positive effect on MF at low doses without deleterious effects on AM, perhaps suggesting an advantage for beta3-ADR agonists, with respect to antimuscarinics, for the treatment of overactive bladder.

References

1. Kullmann et al., J Pharmacol Exp Ther 2009; 330:704-717
2. Takeda et al., J Pharmacol Exp Ther. 2000; 293(3):939-45.
3. Takeda et al., Neurourol Urodyn. 2002; 21(6):558-65

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