

# Abstract N°990: THE SELECTIVE $\beta_3$ -ADRENOCEPTOR AGONIST CL316,243 POTENTLY MODIFIES CYSTOMETRIC PARAMETERS IN ANESTHETIZED MICE: COMPARISON WITH OXYBUTYNYN

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## INTRODUCTION & OBJECTIVES

- Relaxation of detrusor muscle is mainly mediated by beta-adrenoceptors ( $\beta$ -ARs), especially  $\beta_3$ -ARs in humans (1). Therefore, a selective  $\beta_3$ -ARs agonist might be a clinical utility for treatment of patients with overactive bladder (OAB).
- The  $\beta$ -ARs subtypes mediating bladder relaxation differ from species to species (2). A previous *in vitro* study showed a relaxant action of isoproterenol ( $\beta$ -ARs agonist) on KCl-induced contraction of the mice isolated detrusor muscle (3). However, there is no information about the implication of  $\beta_3$ -ARs in bladder relaxation in mice.
- The aims of this study were to evaluate, in anesthetized mice, the effects of CL316,243 (CL), a  $\beta_3$ -ARs selective agonist (4), on micturition reflex, and to compare its effects to oxybutynin (OXY), a drug used for the treatment of OAB.

## MATERIALS & METHODS

- Discontinuous cystometries were performed in female C57Bl6/J mice anesthetized with urethane (1.8 g/kg, i.p.). A catheter connected to a pressure transducer was implanted into the bladder to record intravesical pressure. A jugular vein was catheterized for substances administration.
- Bladder was perfused (NaCl 0.9%, 0.6 mL/h) until a micturition reflex occurs. Then the bladder was manually emptied, and the residual volume measured. After 3 micturition cycles (considered as basal values), 3 increasing doses of CL (0.01, 0.03, 0.1 mg/kg), OXY (0.3, 1, 3 mg/kg) or vehicle (NaCl 0.9%) were administered consecutively. The effects of each dose were observed on two consecutive micturition cycles, 5 min after. Cystometric parameters analyzed are presented on Figure 1.
- The results were expressed as mean  $\pm$  sem of percentage of variation from basal values. The differences between cystometric parameters before and after drugs administration were compared with one-way ANOVA with repeated measures followed by Newman-Keuls test. A  $p < 0.05$  was accepted for statistical significance.

## CONCLUSION

- In anesthetized mice, CL and OXY have similar effects on cystometric parameters. However, CL is about 30 fold more potent than OXY.
- The increase in BC after CL administration suggests the implication of  $\beta_3$ -ARs in the relaxation of mice detrusor muscle.
- The fact that OXY increased BC, supports the view that cholinergic receptors are implicated on the afferent pathway of micturition in accordance with their reported localisation on the bladder urothelium (5).
- Muscarinic receptors and  $\beta_3$ -ARs seems to be implicated on the efferent pathway of micturition as reflected by a decrease of AM by CL and OXY. This effect on AM could explain the increased RV observed.
- Considering that the therapeutic effect of muscarinic receptor antagonists in OAB is due to their ability to increase BC,  $\beta_3$ -ARs agonists could be useful to treat OAB in humans.

**INTRODUCTION AND OBJECTIVE:** Relaxation of detrusor muscle is mainly mediated by beta-adrenoceptors ( $\beta$ -ARs). In humans, the major  $\beta$ -ARs subtype responsible for bladder relaxation is the  $\beta_3$ -ARs. Therefore,  $\beta_3$ -ARs are a potentially important drug target. The aim of the present study was to compare in anesthetized mice, the effects of a selective  $\beta_3$ -ARs agonist, CL316,243 to the effects of a drug for the treatment of overactive bladder, oxybutynin.

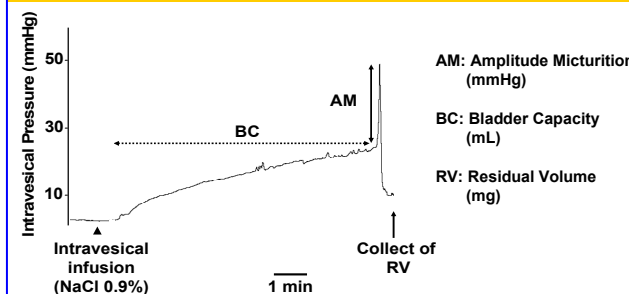
**METHODS:** An intravesical catheter was implanted in female C57BL/6J mice. Bladder was perfused (NaCl 0.9%, 0.6 mL/h) until inducing a micturition cycle, then it was manually emptied, and the residual volume measured. A series of three control micturition cycles (considered as basal values) were obtained. Then, 0.01, 0.03 and 0.1 mg/kg CL316,243 or, 0.3, 1, 3 mg/kg oxybutynin or the solvent (NaCl 0.9%) were administered (i.v. route) consecutively. The effects of each dose were observed on two consecutive micturition cycles, 5 min after drugs administration. Amplitude micturition (AM, mmHg), bladder capacity (BC, mL) and residual volume (RV, mg) were analysed. The results were expressed as mean  $\pm$  sem of % variation from basal values. The differences between cystometric parameters before and after drugs administration were statistically compared.

**RESULTS:** Cystometric basal values between groups were not statistically different (see Table 1). Solvent administration did not modify cystometric parameters. CL316,243 and oxybutynin dose-dependently and significantly decreased AM and increased BC and RV (see Figure 2). Dribbling incontinence was occasionally observed (2/8 with CL and 1/8 with OXY).

**CONCLUSION:** In anesthetized mice, CL316,243 is 30 fold more potent than oxybutynin to modify cystometric parameters. As it is well known that the therapeutic effect of muscarinic receptor antagonists in overactive bladder is due to its ability to increase BC,  $\beta_3$ -ARs agonists could be useful to treat overactive bladder in humans.

## ABSTRACT

Figure 1: Typical recording of a micturition cycle and cystometric parameters analyzed in female anesthetized mice.



## BASAL VALUES

Reproducible control micturition cycles were observed in all groups. Basal values between groups were not statistically different (Table 1).

Table 1: Basal values of cystometric parameters in vehicle, CL316,243 and oxybutynin group.

	Basal values ( $\pm$ sem)		
	AM (mmHg)	BC (mL)	RV (mg)
NaCl 0.9%	32.50 $\pm$ 6.11	0.091 $\pm$ 0.011	75 $\pm$ 12
CL316,243	33.29 $\pm$ 5.98	0.082 $\pm$ 0.016	67 $\pm$ 16
oxybutynin	29.46 $\pm$ 2.98	0.086 $\pm$ 0.012	72 $\pm$ 12

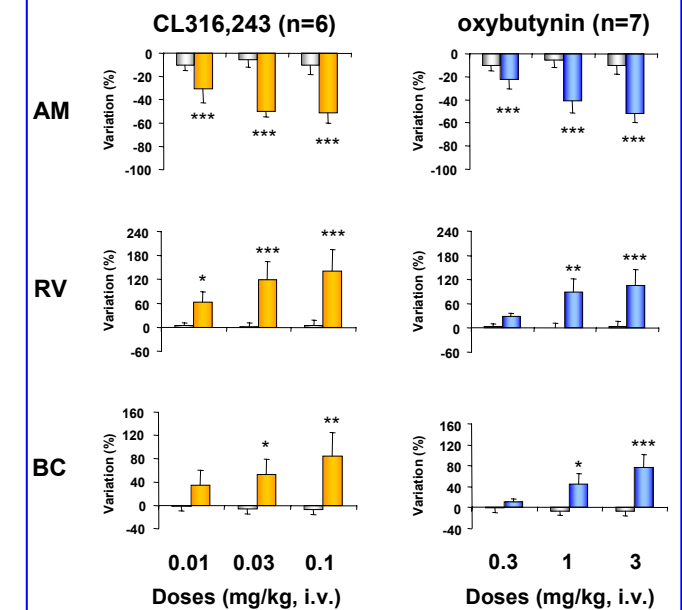
## EFFECTS OF VEHICLE ON CYSTOMETRIC PARAMETERS

Repeated administrations of vehicle (n=8) were without significant effect on AM, BC and RV ( $p > 0.05$ , Figure 2).

## EFFECTS OF CL316,243 AND OXYBUTYNYN ON CYSTOMETRIC PARAMETERS

CL (n=6) and OXY (n=7) dose-dependently and significantly decreased AM and increased RV and BC as compared to basal values (Figure 2). Dribbling incontinence was occasionally observed (2/8 with CL and 1/8 with OXY).

Figure 2: Effect of vehicle, CL316,243 and oxybutynin on AM, RV and BC in anesthetized mice ( $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$  vs basal values).



## REFERENCES

- Igawa et al. Br J Pharmacol. 126: 819-825, 1999.
- Martin et al. Br J Pharmacol. 147: 88-119, 2006.
- Matsui et al. J Pharmacol Exp Ther. 305: 106-113, 2003.
- Yoshida et al. Life Sci. 54: 491-498, 1994.
- Mukerji et al. J Urol. 176: 367-373, 2006.

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