Abstract # 224

Experimental evidence of the effect of the inhibition of phosphodiesterase type 4 by rolipram in conscious rat with bladder outlet obstruction.

Julia-Guilloteau V.[1], Mevel K.[1], Oger S.[1], Bernabé J.[1], Denys P.[2], Alexandre L.[1], Giuliano F.[1, 2]

[1] *Pelvipharm, Domaine CNRS, 1 avenue de la terrasse, Bâtiment 5, F-91190 Gif-sur-Yvette, France*

[2] *AP-HP Raymond Poincaré hospital, Neuro-urology unit, physical medecine and rehabilitation department, 104 Bd R. Poincaré, F-92380 Garches, France - giuliano@cyber-sante.org*

PELVI PHARM

OBJECTIVES

Bladder outlet obstruction (BOO) is a common etiology of overactive bladder (OAB). BOO may result from benign prostatic hyperplasia, urethral stricture or congenital abnormality. The functional changes that develop in response to BOO include detrusor instability, elevated voiding pressure and the presence of a residual urine volume. The morphological changes associated with BOO are smooth muscle hyperplasia and hypertrophy developed to produce the elevated pressures necessary to maintain effective bladder emptying .

The BOO model in rats mimics the voiding patterns of patients with severe bladder outlet obstruction in that animals develop an increased bladder capacity, high voiding pressures, residual urine volume and detrusor instability.

The intensity and the duration of the cAMP second messenger signalling within the detrusor smooth cells is partly regulated by phosphodiesterase type 4 (PDE4) enzymes.

Increase in cAMP levels by PDE4 inhibition has been reported to relax various types of smooth muscle cells.

We aimed to investigate the effect of the selective inhibition of PDE4 activity by an archetypal PDE4 inhibitor, rolipram, in an experimental model of OAB induced by partial BOO in conscious rats

MATERIALS & METHODS

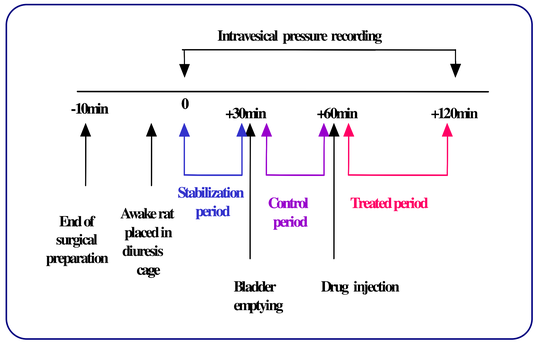
Partial bladder outlet obstruction

Female Wistar rats weighing 200-225 g were anesthetized with isoflurane. The bladder and the proximal urethra of all rats were exposed through a lower midline abdominal incision. An extraurethral metal rod with an external diameter of 1 mm, was placed around the urethra to provide a calibrated loop for a single 4-0 silk suture inducing a partial BOO. The metal rod was removed after calibrated urethral ligation and the abdominal wall was closed. Non-obstructed control rats underwent the same surgical procedure than obstructed rats without inserting a proximal urethral ligature.

Cystometry

Six weeks after the first surgery, animals were anesthetized with isoflurane (1-1.2%). A trumpet tip polyethylene catheter (PE50), filled with saline, was inserted through the dome into the bladder and secured with a suture. The urinary bladder was slowly filled to check eventual leakage. The abdominal wall was then closed. Cystometry was then performed in conscious rats. Rats were placed in a diuresis cage for freely moving animals. The bladder catheter was connected to a pressure transducer (Elcomatic EM 750, UK) and a syringe-pump KDS-200 (Kd Scientific, Phymep, Paris) with a T-tube, allowing simultaneous bladder perfusion and bladder pressure monitoring. The intravesical pressure was recorded continuously using an acquisition card (DAS 1000, Computer Boards, DIPSI, France) and a specific data acquisition software (Elphy, CNRS, France).

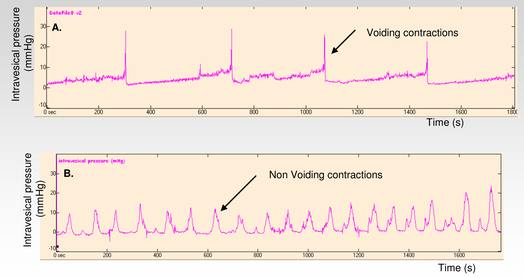
The bladder was continuously infused (50µl/min) with saline (at room temperature). After a stabilization period of 30 min to check the quality of the recording and the frequency of micturition, the bladder was emptied before the 30 min control period cystometry. For each group, the treatment (rolipram, 3 mg/kg or vehicle DMSO 30 % IP) was delivered at the end of the control period and before the beginning of the 60 min cystometry recording.
During cystometry, the animals are continuously observed by the experimenter to discriminate between moving artefacts and bladder contractions. Voiding and non voiding bladder contractions were noted .



Protocol design

RESULTS

Micturition pattern of a BOO rat



Typical cystometric tracings: A. sham rat . B. 6-weeks BOO rat (bladder weight superior to 0.7g)

A. Bladder filling in a sham rat with an infusion rate of 50 µl/min induced a voiding cycle of about 7 min. between each contraction. Bladder filled under low pressure and the animal generated sharp detrusor voiding contractions.

B. Bladder contractions observed in 6-weeks BOO rat were non voiding contractions (absence of micturition) since at the infusion rate used (50 µl/min) the hypertrophied bladder was not filled enough to elicit a micturition reflex. Non voiding contractions were characteristic of bladder outlet obstruction. They were frequent and with a low amplitude (inferior to 10 mmHg).

		Number of non voiding contractions /h	Amplitude of non voiding contractions (mmHg)	Intravesical basal pressure (mmHg)	AUC of non voiding contractions (mmHg.s)	Duration of non voiding contractions (s)
Vehicle group (n=6)	Control period	87.0 ± 17.6	9.5 ± 3.9	2.1 ±1.7	156.0 ± 72.9	26.1 ± 1.7
	Treated period	71.5 ± 20.9	14.3 ± 5.7	2.9 ± 1.9	350.7± 197.7	30.3 ± 3.7
Rolipram group (n=8)	Control period	92.7 ± 16.7	4.3 ±1.3	1.9 ± 0.8	77.3 ± 30.3	26.2 ± 3.6
	Treated period	53.0 ± 9.8 *	3.4 ± 0.4	1.1 ± 0.9	56.2 ± 8.9	31.1 ± 6.5

Effect of rolipram or vehicle on urodynamic parameters in BOO rats with a bladder weight superior to 0.7g.
** p<0.05 paired student's t-test, comparison between control and treated periods*

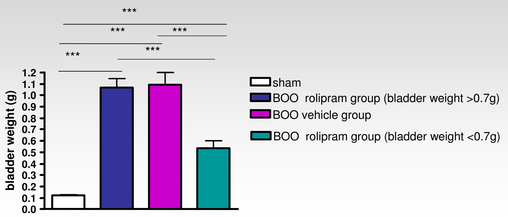
Rolipram decreased the frequency of non voiding contractions when the bladder was hypertrophied

		Number of non voiding contractions /h	Amplitude of non voiding contractions (mmHg)	Intravesical basal pressure (mmHg)	AUC of non voiding contractions (mmHg.s)	Duration of non voiding contractions (s)
Rolipram group (n=6)	Control period	30.0 ± 7.9	34.9 ±10.7	4.3 ± 1.9	560.7 ±175.1	31.5 ± 3.2
	Treated period	35.3 ± 9.6	44.9 ±14.4	3.9 ±1.7	639.3 ±202.6	30.4 ± 1.9

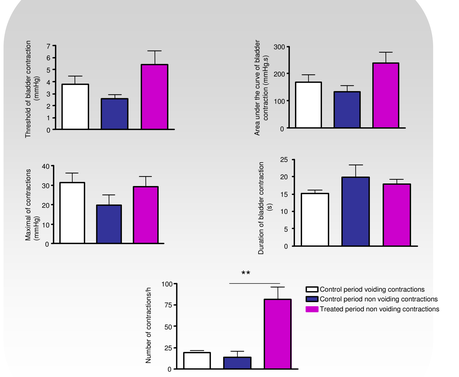
Effect of rolipram on urodynamic parameters in BOO rats with a bladder weight inferior to 0.7g.

No difference in urodynamic parameters was observed after rolipram when the bladder was not hypertrophied.

Bladder weight



Partial BOO elicited bladder hypertrophy characterized by an increase in the bladder weight. Two groups can be differentiated in BOO rats in function of the bladder weight (>0.7g and <0.7g) and micturition patterns



Effect of rolipram on urodynamic parameters in sham rats
p<0.05 paired student's t-test, comparison between control and treated periods

Note: after rolipram administration, no voiding contractions were observed in sham group

CONCLUSIONS

Partial BOO elicited bladder hypertrophy and an increase in non voiding contractions. In BOO rats with a marked bladder hypertrophy, rolipram, a specific PDE4 inhibitor, reduced detrusor hyperactivity. Confirmation of these results would indicate that there is a potential for PDE4 inhibitors in the treatment of OAB.